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(54) **Title**: MALATE SALT OF N- (4- { [6, 7-BIS (METHYLOXY) QUIN0LIN-4-YL] OXY}PHENYL-N' - (4 -FLUOROPHENYL) CYCLOPROPANE-1-DICARBOXAMIDE, AND CRYSTALLINE FORMS THEROF FOR THE TREATMENT OF CANCER

(57) **Abstract**: Disclosed are malate salts of N-(4-{ [6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)- N'-(4-fluorophenyl)cyclopropane-l,l-dicarboxamide, including a (L)-malate salt, a (D)- malate salt, a (DL) malate salt, and mixtures thereof; and crystalline and amorphous forms of the malate salts. Also disclosed are pharmaceutical compositions comprising at least one malate salts of N-(4-{ [6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)- cyclopropane-l,l-dicarboxamide; and methods of treating cancer comprising administering at least one malate salt of N-(4-{ [6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-ffuorophenyl)cyclopropane- 1, 1 -dicarboxamide.

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MALATE SALT OF N-(4-{[6,7-BIS(METHYLOXY) QUINOLIN-4-YL]OXY}PHENYL-N'-(4-FLUOROPHENYL) CYCLOPROPANE-1,1-DICARBOXAMIDE, AND CRYSTALLINE FORMS THEROF FOR THE TREATMENT OF CANCER

Cross-reference to Related Applications

[0001] This application claims priority to U.S. provisional application 61/145,421, filed January 16, 2009, which is incorporated herein by reference.

Technical Field

[0002] This disclosure relates to malate salts of N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and to crystalline and amorphous forms of the malate salts of N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. The malate salts of N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide include one of (1) the (L)-malate salt, (2) the (D)-malate salt, (3) the (D,L)-malate salt, and (4) mixtures therof. The disclosure also relates to pharmaceutical compositions comprising at least one malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-cyclopropane-1,1-dicarboxamide.

[0003] The disclosure also relates to pharmaceutical compositions comprising a crystalline or an amorphous form of at least one malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-cyclopropane-1,1-dicarboxamide.

[0004] The disclosure also relates to methods of treating cancer comprising administering at least one malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

[0005] The disclosure further relates to methods of treating cancer comprising administering a crystalline or an amorphous form of at least one malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

Background

[0006] Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms. One mechanism that can be exploited in cancer treatment is the modulation of protein kinase activity because signal transduction through protein kinase activation is responsible for many of the

characteristics of tumor cells. Protein kinase signal transduction is of particular relevance in, for example, thyroid, gastric, head and neck, lung, breast, prostate, and colorectal cancers, as well as in the growth and proliferation of brain tumor cells.

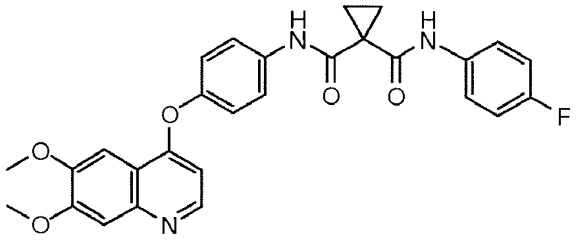
[0007] Protein kinases can be categorized as receptor type or non-receptor type. Receptor-type tyrosine kinases are comprised of a large number of transmembrane receptors with diverse biological activity. For a detailed discussion of the receptor-type tyrosine kinases, see Plowman et al., DN&P 7(6): 334-339, 1994. Since protein kinases and their ligands play critical roles in various cellular activities, deregulation of protein kinase enzymatic activity can lead to altered cellular properties, such as uncontrolled cell growth associated with cancer. In addition to oncological indications, altered kinase signaling is implicated in numerous other pathological diseases, including, for example, immunological disorders, cardiovascular diseases, inflammatory diseases, and degenerative diseases. Therefore, protein kinases are attractive targets for small molecule drug discovery. Particularly attractive targets for small-molecule modulation with respect to antiangiogenic and antiproliferative activity include receptor type tyrosine kinases Ret, c-Met, and VEGFR2.

[0008] The kinase c-Met is the prototypic member of a subfamily of heterodimeric receptor tyrosine kinases (RTKs) which include Met, Ron and Sea. The endogenous ligand for c-Met is the hepatocyte growth factor (HGF), a potent inducer of angiogenesis. Binding of HGF to c-Met induces activation of the receptor via autophosphorylation resulting in an increase of receptor dependent signaling, which promotes cell growth and invasion. Anti-HGF antibodies or HGF antagonists have been shown to inhibit tumor metastasis *in vivo* (See: Maulik et al Cytokine & Growth Factor Reviews 2002 13, 41-59). c-Met, VEGFR2 and/or Ret overexpression has been demonstrated on a wide variety of tumor types including breast, colon, renal, lung, squamous cell myeloid leukemia, hemangiomas, melanomas, astrocytic tumor (which includes glioblastoma,
giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components). The Ret protein is a transmembrane receptor with tyrosine kinase activity. Ret is mutated in most familial forms of medullary thyroid cancer. These mutations activate the kinase function of Ret and convert it into an oncogene product.

[0009] Inhibition of EGF, VEGF and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. Drug Disc. Technol. 2001 6, 1005-1024).Kinase KDR (refers to kinase insert domain receptor tyrosine kinase) and flt-4 (fms-like tyrosine kinase-4) are both vascular endothelial growth factor (VEGF) receptors. Inhibition of EGF, VEGF and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular

processes needed for tumor growth and survival (Matter A. Drug Disc. Technol. 2001 6, 1005-1024). EGF and VEGF receptors are desirable targets for small molecule inhibition.

[0010] Accordingly, small-molecule compounds that specifically inhibit, regulate and/or modulate the signal transduction of kinases, particularly including Ret, c-Met and VEGFR2 described above, are particularly desirable as a means to treat or prevent disease states associated with abnormal cell proliferation and angiogenesis. One such small-molecule is N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, which has the chemical structure:



WO 2005/030140 describes the synthesis of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (Example 12, 37, 38, and 48) and also discloses the therapeutic activity of this molecule to inhibit, regulate and/or modulate the signal transduction of kinases, (Assays, Table 4, entry 289). Example 48 is on paragraph [0353] in WO 2005/030140.

[0011] Besides therapeutic efficacy, the drug developer endeavors to provide a suitable form of the therapeutic agent that has properties relating to processing, manufacturing, storage stability, and/or usefulness as a drug. Accordingly, the discovery of a form that possesses some or all of these desired properties is vital to drug development.

[0012] Applicants have found a salt form of the drug N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide that has suitable properties for use in a pharmaceutical composition for the treatment of a proliferative disease such as cancer. The novel salt form of the invention exists in crystalline and amorphous forms

Summary

[0013] This disclosure relates to malate salts of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as described herein, pharmaceutical compositions thereof as described herein, and uses thereof as described herein.

[0014] Another aspect relates to crystalline and amorphous forms of the malate salts of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as described herein, pharmaceutical compositions thereof as described herein, and uses thereof as described herein.

Brief Description of the Figures

[0015] Figure 1 shows the experimental XRPD pattern for crystalline Compound (I), Form N-1 at 25 °C.

[0016] Figure 2 shows the solid state ^{13}C NMR spectrum of crystalline Compound (I), Form N-1.

[0017] Figure 3 shows the solid state ^{15}N NMR spectrum of crystalline Compound (I), Form N-1.

[0018] Figure 4 shows the solid state ^{19}F NMR spectrum of crystalline Compound (I), Form N-1.

[0019] Figure 5 shows the thermal gravimetric analysis (TGA) of crystalline Compound (I), Form N-1.

[0020] Figure 6 shows the differential scanning calorimetry (DSC) of crystalline Compound (I), Form N-1.

[0021] Figure 7 shows the moisture sorption of crystalline Compound (I), Form N-1.

[0022] Figure 8 shows the experimental XRPD pattern for crystalline Compound (I), Form N-2 at 25 °C.

[0023] Figure 9 shows the solid state ^{13}C NMR spectrum of crystalline Compound (I), Form N-2.

[0024] Figure 10 shows the solid state ^{15}N NMR spectrum of crystalline Compound (I), Form N-2.

[0025] Figure 11 shows the solid state ^{19}F NMR spectrum of crystalline Compound (I), Form N-2.

[0026] Figure 12 shows the thermal gravimetric analysis (TGA) of crystalline Compound (I), Form N-2.

[0027] Figure 13 shows the differential scanning calorimetry (DSC) of crystalline Compound (I), Form N-2.

[0028] Figure 14 shows the moisture sorption of crystalline Compound (I), Form N-2.

[0029] Figure 15 shows the experimental and simulated XRPD patterns for crystalline Compound (III), Form N-1 at room temperature.

[0030] Figure 16 shows the solid state ^{13}C NMR spectrum of crystalline Compound (III), Form N-1.

[0031] Figure 17 shows the solid state ^{15}N NMR spectrum of crystalline Compound (III), Form N-1.

[0032] Figure 18 shows the solid state ^{19}F NMR spectrum of crystalline Compound (III), Form N-1.

[0033] Figure 19 shows the thermal gravimetric analysis (TGA) of crystalline Compound (III), Form N-1.

[0034] Figure 20 shows the differential scanning calorimetry (DSC) of crystalline Compound (III), Form N-1.

[0035] Figure 21 shows the moisture sorption of crystalline Compound (III), Form N-1.

[0036] Figure 22 shows the XRPD pattern of amorphous Compound (I) at room temperature.

[0037] Figure 23 shows the solid state ^{13}C NMR spectrum of amorphous Compound (I).

[0038] Figure 24 shows the solid state ^{15}N NMR spectrum of amorphous Compound (I).

[0039] Figure 25 shows the solid state ^{19}F NMR spectrum of amorphous Compound (I).

[0040] Figure 26 shows the differential scanning calorimetry (DSC) of amorphous Compound (I).

[0041] Figure 27 shows the moisture sorption of amorphous Compound (I).

Detailed Description

[0042] This disclosure relates to improvements of the physiochemical properties of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, whereby this compound may be suitable for drug development. Disclosed herein are malate salts of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. New solid state forms of those salts are also disclosed. The malate salts as well as their crystalline and amorphous forms disclosed herein each represent separate aspects of the disclosure. Although the malate salts and their solid state forms are described herein, the invention also relates to novel compositions containing the disclosed salts and solid state forms. Therapeutic uses of the salts and solid state forms described as well as therapeutic compositions containing them represent separate aspects of the disclosure. The techniques used to characterize the salts and their solid state forms are described in the examples below. These techniques, alone or in combination, may be used to characterize the salts and their solid state forms disclosed herein. The salts and their solid state forms may be also characterized by reference to the disclosed figures.

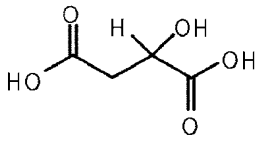
[0043] N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-cyclopropane-1,1-dicarboxamide was found to have an enzyme Ret IC_{50} value of about 5.2 nM (nanomolar) and an enzyme c-Met IC_{50} value of about 1.3 nM (nanomolar). The assay that was used to measure this c-Met activity is described in paragraph [0458] in WO2005-030140.

[0044] RET biochemical activity was assessed using a Luciferase-Coupled Chemiluminescent Kinase assay (LCCA) format as described in WO2005-030140. Kinase activity was measured as the percent ATP remaining following the kinase reaction. Remaining ATP was detected by luciferase-luciferin-coupled chemiluminescence. Specifically, the reaction was initiated by mixing test compounds, 2μM ATP, 1μM poly-EY and 15nM RET (baculovirus expressed human RET kinase domain M700-D1042 with a $(His)_6$ tag on the N-terminus) in a 20uL assay buffer (20mM Tris-HCL pH 7.5, 10mM $MgCl_2$, 0.01% Triton X-100, 1 mM DTT, 3mM $MnCl_2$). The mixture was incubated at ambient temperature for 2hours after which 20uL luciferase-luciferin mix was added and the chemiluminescent signal read using a Wallac Victor^2 reader. The luciferase-luciferin mix consists of 50 mM HEPES, pH 7.8, 8.5ug/mL oxalic acid (pH 7.8), 5 mM DTT, 0.4% Triton X-100, 0.25 mg/mL coenzyme A, 63 μM AMP, 28 μg/mL luciferin and 40,000 units of light/mL luciferase.

Malate Salts of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

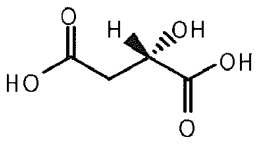
[0045] This disclosure relates to malate salts of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. These malate salts are a combination of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide with malic acid which forms a 1:1 malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

[0046] Malic acid has the following structure:



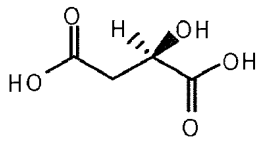
Due to its chiral carbon, two enantiomers of malic acid exist, (L)-malic acid and (D)-malic acid.

[0047] (L)-malic acid has the following structure:



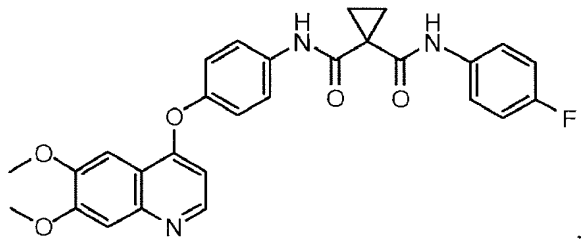
There are various names or designations for the (L)-malic acid that are known in the art. These include butanedioic acid, hydroxy-, (2S)- (9CI); butanedioic acid, hydroxy-, (S)-; malic acid, L- (8CI); malic acid, l- (3CI); (-)-(S)-malic acid; (-)-Hydroxysuccinic acid; (-)-(L)-malic acid; (-)-malic acid; (2S)-2-hydroxybutanedioic acid; (2S)-2-hydroxysuccinic acid; (S)-malic acid; apple acid; L-(-)-malic acid; (L)-malic acid; NSC 9232; S-(-)-malic acid; and S-2-hydroxybutanedioic acid.

[0048] (D) malic acid has the following structure:



There are various names or designations for the (D)-malic acid that are known in the art. These include butanedioic acid, 2-hydroxy-, (2R)-, butanedioic acid, hydroxy-, (2R)- (9CI); butanedioic acid, hydroxy-, (R)-; (+)-malic acid; (2R)-2-hydroxybutanedioic acid; (2R)-malic acid; (R)-(+)-malic acid; (R)-malic acid; D-(+)-2-hydroxysuccinic acid; D-(+)-malic acid; and D-malic acid.

[0049] As discussed above, the chemical structure of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is



There are no chiral carbons in its chemical structure. There are various names for N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide which are publicly known, and some of these various names or designations include 1,1-cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- and 1,1-cyclopropanedicarboxamide, N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)- (9CI).

[0050] N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide can be prepared according to any of several different methodologies, either on a gram scale (<1 kg) or a kilogram scale (>1 kg). A gram-scale method is set forth in WO 2005-030140, which describes the synthesis of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (Examples 25, 37, 38, and 48), which is hereby incorporated by reference. Alternatively, N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, including the active compound(s), can be prepared on a kilogram scale using the procedure set forth in Example 1 below.

[0051] This disclosure relate to malate salts of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide:

the (L)-malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (Compound (I));

the (D)-malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (Compound (II)); and

the (DL)-malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (Compound (III)).

Each has improved properties over N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and its other salts. The names used herein to characterize a specific form, e.g. "N-2" etc., are not to be limited so as to exclude any other substance possessing similar or identical physical and chemical characteristics, but rather such names are used as mere identifiers that are to be interpreted in accordance with the characterization information presented herein.

[0052] The malate salts of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, and particularly Compound (I), have a preferred combination of pharmaceutical properties for development. Under the conditions of 25°C/60% relative humidity (RH) and 40 °C/60%RH, Compound (I) showed no change in assay, purity, moisture and dissolution. The DSC/TGA showed the Compound (I) to be stable up to 185°C. No solvent losses were observed. The uptake of water by the (L)-malate salt was reversible with a slight hysteresis. The amount of water taken up was calculated at about 0.60wt% at 90%RH. The (L)-malate salt was synthesized with good yield and purity >90% and had sufficient solubility for use in a pharmaceutical composition. The amount of water associated with this salt was calculated at about 0.5wt% by Karl Fischer analysis and correlates with TGA and GVS analysis. The (D)-malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-

dicarboxamide) will have the same properties as the (L)-malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide).

[0053] The Compound (I) salt itself, and separately its crystalline and amorphous forms, exhibit beneficial properties over the free base and the other salts of the N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. For example, the hydrochloride salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide exhibits undesirable moisture sensitivity, changing phase upon exposure to high humidity (75% humidity) and high temperature (40°C). The maleate salt had low solubility. The tartrate salt had low crystallinity and low solubility. The phosphate salt exhibited an 8% weight gain due to absorption of H_2O – the highest among the salts tested.

[0054] The water solubility of the various salts was determined using 10 mg solids per mL water. The salts were prepared in a salt screen by reacting an acetone solution of the freebase with stock tetrahydrofuran (THF) solutions of a range of acids in about a 1:1 molar ratio. Table 1 below summarizes the water solubility and other data relating to the free base and each salt.

Table 1

	Solubility (mg/ml)	
Free base	<<0.001	very low solubility
Propionate	<<0.001	no salt formation; mixture of free base and acid
Acetate	<<0.001	no salt formation; mixture of free base and acid
Succinate	0.010	no salt formation; mixture of free base and acid
Benzoate	0.005	no salt formation; mixture of free base and acid
L-Lactate	0.015	Amorphous, salt
Pyrroglutamate	0.44	Amorphous, salt
Glycolate	0.016	Amorphous, salt
L-Ascorbate	0.053	low crystallinity
Sulfate	0.004	Crystalline salt, low solubility
Tosylate	0.007	Crystalline salt, low solubility
Malonate	0.003	Crystalline salt, low solubility
2,5dihydroxybenzoate	<<0.001	Crystalline Salt, low solubility
Fumarate	0.008	Crystalline Salt, low solubility
Citrate	0.002	Crystalline Salt, low solubility
Mesylate	0.175	Crystalline Salt; possible sulfonic acid formation when made with alcohol
Esylate	0.194	Crystalline Salt; possible sulfonic acid formation when made with alcohol
Benzenesulfonate	0.039	Crystalline Salt; possible sulfonic acid formation

	Solubility (mg/ml)	
		when made with alcohol
Chloride	0.070	Crystalline but Hygroscopic; possible hydrate formation. Change in XRPD pattern upon exposure to humidity.
Maleate	0.005	Crystalline salt, possible hydrate formation; low solubility; different XRPD pattern observed upon scale up (possible polymorphism issue)
Phosphate	0.026	Crystalline but Hygroscopic.
L-Tartrate	0.014	Low degree of crystallinity; Hygroscopic.
(L)-Malate	0.059	Crystalline; non-Hygroscopic with no indication of hydrate formation. Suitable solubility, and chemical/physical stability.

[0055] Another aspect of this disclosure relates to crystalline forms of Compound (I), which include the N-1 and/or the N-2 crystalline form of Compound (I) as described herein. Each of form of Compound (I) is a separate aspect of the disclosure. Similarly, another aspect of this disclosure relates to crystalline forms of Compound (II), which include the N-1 and/or the N-2 crystalline form of Compound (II) as described herein. Each of which is also a separate aspect of the disclosure. As is known in the art, the crystalline (D) malate salt will form the same crystalline form and have the same properties as crystalline Compound (I). See WO 2008/083319, which discusses the properties of crystalline enantiomers. Mixtures of the crystalline forms of Compounds (I) and (II) are another aspect of the disclosure.

[0056] The crystalline N-1 forms of Compounds (I) and (II) as described here may be characterized by at least one of the following:

(i) a solid state ^{13}C NMR spectrum with peaks at 18.1, 42.9, 44.5, 70.4, 123.2, 156.2, 170.8, 175.7, and 182.1 ppm, ± 0.2 ppm;

(ii) a solid state ^{13}C NMR spectrum substantially in accordance with the pattern shown in Figure 2;

(iii) an x-ray powder diffraction pattern (CuKα λ=1.5418Å) comprising four or more peaks selected from: 6.4, 9.0, 12.0, 12.8, 13.5, 16.9, 19.4, 21.5, 22.8, 25.1, and 27.6 °2θ ± 0.2 °2θ, wherein measurement of the crystalline form is at an ambient room temperature;

(iv) an x-ray powder diffraction (XRPD) spectrum substantially in accordance with the pattern shown in Figure 1;

(v) a solid state ^{15}N NMR spectrum with peaks at 118.6, 119.6, 120.7, 134.8, 167.1, 176.0, and 180 ppm, ±0.2 ppm; and/or

(vi) a solid state ^{15}N NMR spectrum substantially in accordance with the pattern shown in Figure 3.

[0057] Other solid state properties which may be used to characterize the crystalline N-1 forms of Compounds (I) and (II) are shown in the figures and discussed in the examples below. For crystalline Compound (I), the solid state phase and the degree of crystallinity remained unchanged after exposure to 75%RH at 40°C for 1 week.

[0058] The crystalline N-2 forms of Compounds (I) and (II) as described here may be characterized by at least one of the following:

(i) a solid state ^{13}C NMR spectrum with peaks at 23.0, 25.9, 38.0, 54.4, 56.11, 41.7, 69.7, 102.0, 122.5, 177.3, 179.3, 180.0, and 180.3, ± 0.2 ppm;

(ii) a solid state ^{13}C NMR spectrum substantially in accordance with the pattern shown in Figure 9;

(ii) an x-ray powder diffraction pattern (CuKα λ=1.5418Å) comprising four or more peaks selected from: 6.4, 9.1, 12.0, 12.8, 13.7, 17.1, 20.9, 21.9, 22.6, and 23.7 °2θ ± 0.2 °2θ, wherein measurement of the crystalline form is at an ambient room temperature;

(iv) an x-ray powder diffraction (XRPD) spectrum substantially in accordance with the pattern shown in Figure 8;

(v) a solid state ^{15}N NMR spectrum with peaks at 118.5, 120.8, 135.1, 167.3, and 180.1 ppm; and/or

(vi) a solid state ^{15}N NMR spectrum substantially in accordance with the pattern shown in Figure 10.

Other solid state properties which may be used to characterize the crystalline N-2 forms of Compounds (I) and (II) are shown in the figures and discussed in the examples below.

[0059] In another embodiment, the disclosure relates to a crystalline form of Compound (I), as described herein in any of the aspects and/or embodiments, is substantially pure N-1 form.

[0060] In another embodiment, the disclosure relates to a crystalline form of Compound (I), as described herein in any of the aspects and/or embodiments, is substantially pure N-2 form.

[0061] The disclosure also relates to amorphous forms of Compounds (I) and (II). The preparation and solid state properties and characteristics of the amorphous form of Compound (I) are described in the examples below. The amorphous forms of Compounds (I) and (II) represent another aspect of the disclosure.

[0062] One further aspect of the disclosure relates to mixtures of Compound (I) and Compound (II). The mixtures may have from greater than zero weight % to less than 100 weight % Compound (I) and from less than 100 weight % to greater zero weight % Compound (II), based on the total weight of Compound (I) and Compound (II). In other embodiments, the mixture comprises from about 1 to about 99 weight % Compound (I) and from about 99 to about 1 weight % Compound (II), based on the total weight of Compound (I) and Compound (II) in said mixture. In a further embodiment, the mixture comprises from about 90 weight % to less than 100 weight % Compound (I) and from greater than zero weight % to about 10 weight % Compound (II), based on the total weight of Compound (I) and Compound (II). Accordingly, the mixture may have 1-10% by weight of Compound (I); 11-20% by weight of Compound (I); 21-30% by weight of Compound (I); 31-40% by weight of Compound (I); 41-50% by weight of Compound (I); 51-60% by weight of Compound (I); 61-70% by weight of Compound (I); 71-80% by weight of Compound (I); 81-90% by weight of Compound (I); or 91-99% by weight of Compound (I) with the remaining weight percentage of malate salt being that of Compound (II).

[0063] Another aspect of this disclosure relates to crystalline forms of (DL)-malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, Compound (III). The (DL)-malate salt is prepared from racemic malic acid. The crystalline N-1 form of Compound (III) as described here may be characterized by at least one of the following:

(i) a solid state ^{13}C NMR spectrum with four or more peaks selected from 20.8, 26.2, 44.8, 55.7, 70.7, 100.4, 101.0, 114.7, 115.2, 116.0, 119.7, 120.4, 121.6, 124.4, 136.9, 138.9, 141.1, 145.7, 150.3, 156.5, 157.6, 159.6, 165.2, 167.4, 171.2, 176.3, 182.1 ppm, ± 0.2 ppm;

(ii) a solid state ^{13}C NMR spectrum substantially in accordance with the pattern shown in Figure 16;

(iii) a powder x-ray diffraction pattern (CuKα λ=1.5418Å) comprising four or more 2θ values selected from: 12.8, 13.5, 16.9, 19.4, 21.5, 22.8, 25.1, and 27.6, ±0.2 °2θ, wherein measurement of the crystalline form is at temperature of room temperature;

(iv) an x-ray powder diffraction (XRPD) spectrum substantially in accordance with the pattern shown in Figure 15;

(v) a solid state ^{15}N NMR spectrum with peaks at 119.6, 134,7, and 175.5 ppm, ± 0.2 ppm; and/or

(vi) a solid state ^{15}N NMR spectrum substantially in accordance with the pattern shown in Figure 17.

Other solid state properties which may be used to characterize the crystalline N-1 form of Compound (III) are shown in the figures and discussed in the examples below. In one embodiment, the N-1 Form of Compound (III) is characterized by unit cell parameters approximately equal to the following:

Cell dimensions: a = 14.60 Å
b = 5.20 Å
c = 39.09 Å
α = 90.0°
β = 90.4°
γ = 90.0°

Space group: $P2_1/n$
Molecules of Compound (I)/unit cell: 4
Volume = 2969 $Å^3$
Density (calculated) = 1.422 g/cm^3

The unit cell parameters of Form N-1 of Compound (III) were measured at a temperature of approximately 25°C, *e.g.*, ambient or room temperature.

[0064] Each of the N-1 and N-2 crystalline forms of Compounds (I) and (II) and the crystalline form N-1 of Compound (III) have unique characteristics that can distinguish them one from another. These characteristics can be understood by comparing the physical properties of the solid state forms which are presented in the Examples below. For example, Table 2 lists characteristic XRPD peak positions (°2θ±0.2 °2θ) for crystalline Compound (III), Form N-1 and Forms N-1 and N-2 of crystalline Compound (I). Amorphous forms do not display reflection peaks in their XRPD patterns.

Table 2

Characteristic diffraction peak positions (degrees 2θ±0.2) @ RT, based on pattern collected with a diffractometer (CuKα) with a spinning capillary.

Compound (I) Form N-1	Compound (I) Form N-2	Compound (III) Form N-1
6.4	6.4	6.4
9.0	9.1	9.1
12.0	12.0	12.1
12.8	12.8	12.8
13.5	13.7	13.6
16.9	17.1	17.1
19.4*	20.9*	19.3
21.5*	21.9*	21.4
22.8*	22.6	22.8
25.1*	23.7	25.1
27.6*	--	27.6

*unique reflections between Compound (I), Form N-1 and Compound (I), Form N-2.

The unique reflections between Forms N-1 and N-2 of crystalline Compound (II) are designated by an asterisk (*). As discussed above, Compound (II) is an enantiomer of Compound (I) and thus, Compound (II), Form N-1 will have the same characteristic reflection pattern and unique peaks as those listed in Table 2 for Compound (I), Form N-1. Likewise, Compound (II), Form N-2 will have the same characteristic reflection pattern and unique peaks as those listed in Table 2 for Compound (I), Form N-2. Compounds (I) and (II) are distinct from one another based on their absolute stereochemistry, *i.e.*, the (L)-malate salt versus the (D)-malate salt, respectively. Crystalline Compound (III), Form N-1, is distinct as the (D,L)-malate salt.

[0065] The characteristic peaks from the solid state NMR may also serve to distinguish the crystalline and amorphous forms disclosed herein. For example, Table 3 lists characteristic solid state ^{13}C NMR peaks for crystalline Compound (III), Form N-1; crystalline Compound (I), Forms N-1 and N-2, and the amorphous form of Compound (I).

Table 3

Solid State Carbon-13 NMR Resonances (ppm, ±0.2 ppm)			
(I) Form N-1	(I), Form N-2	(III), Form N-1	(I), Amorphous
18.1	23.0	20.8	27.2
42.9	25.9	26.2	33.8
44.5	38.0	44.8	142.9
54.4	54.4	70.7	--
56.1	56.1	114.7	--
70.4	41.7	141.1	--
123.2	69.7	145.7	--
156.2	102.0	176.3	--
170.8	122.5	182.1	--
175.7	177.3	--	--
182.1	179.3	--	--
--	180.0	--	--
--	180.3	--	--

The solid state ^{19}F and ^{15}N NMR spectra, discussed below, provide data for similar comparison and characterization. As discussed above, being an enantiomer of Compound (I),

crystalline Forms N-1 and N-2 and the amorphous form of Compound (II) will have the same solid state NMR resonances, and unique peaks between them, as those listed in Table 3 for Forms N-1 and N-2 of crystalline Compound (I).

Pharmaceutical Compositions and Methods of Treatment

[0066] Another aspect of this disclosure relates to a pharmaceutical composition comprising at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, and a pharmaceutically acceptable excipient. The amount of Compound (I), Compound (II), Compound (III), or the combinations thereof in the pharmaceutical composition can be a therapeutically effective amount. Compound (I), Compound (II), or Compound (III) may individually be present in the pharmaceutical composition as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms. Accordingly another aspect of this disclosure relates to a solid or dispersion pharmaceutical composition comprising at least one of a therapeutically effective amount of a crystalline form of Compound (I), Compound (II), Compound (III), or combinations thereof, and a pharmaceutically acceptable excipient.

[0067] Another aspect of this disclosure relates to a method of treating cancer comprising administering to a subject in need thereof at least one of Compound (I), Compound (II), Compound (III) or combinations thereof. The amount of Compound (I), Compound (II), or combinations thereof administered can be a therapeutically effective amount. Compound (I), Compound (II), or Compound (III) may be individually administered as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms, with crystalline Compound (I), Form N-1or N-2 being preferred. Accordingly another aspect of this disclosure relates to a method of treating cancer comprising administering to a subject in need thereof a therapeutically effective amount of at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, wherein Compound (I), Compound (II), or Compound (III) is present in a crystalline form. In another aspect of this disclosure, the method of treatment may be practiced by administering a pharmaceutical composition of at least one of Compound (I), Compound (II), Compound (III) or combinations thereof such as discussed above.

[0068] Another aspect of this disclosure relates to a method of treating cancer, as discussed above, where the cancer treated is stomach cancer, esophageal carcinoma, kidney cancer, liver cancer, ovarian carcinoma, cervical carcinoma, large bowel cancer, small bowel cancer, brain cancer (including astrocytic tumor, which includes glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components), lung cancer

(including non-small cell lung cancer), bone cancer, prostate carcinoma, pancreatic carcinoma, skin cancer, bone cancer, lymphoma, solid tumors, Hodgkin's disease, non-Hodgkin's lymphoma or thyroid cancer thyroid cancer (including medullary thyroid cancer).

[0069] Tyrosine kinase inhibitors have also been used to treat non-small cell lung cancer (NSCLC). Gefitinib and erlotinib are angiogenesis inhibitors that target receptors of an epidermal growth factor called tyrosine kinase. Erlotinib and Gefitinib are currently being used for treating NSCLC. Another aspect of this disclosure relates to a method of treating non-small cell lung cancer (NSCLC) in a subject, the method comprising administering to the subject in need of the treatment a therapeutically effective amount of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, or a pharmaceutically acceptable salt thereof, optionally in combination with Erlotinib or Gefitinib. In another embodiment, the combination is with Erlotinib.

[0070] Another aspect of this disclosure relates to a method of treating non-small cell lung cancer (NSCLC) in a subject, the method comprising administering to the subject in need of the treatment a therapeutically effective amount of Erlotinib or Gefitinib in combination with at least one of Compound (I), Compound (II), Compound (III) or combinations thereof. Compound (I), Compound (II), or Compound (III) may be individually administered as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms. Accordingly another aspect of this disclosure relates to a method of treating a method of treating non-small cell lung cancer (NSCLC) in a subject, the method comprising administering to the subject in need of the treatment a therapeutically effective amount of Erlotinib or Gefitinib in combination with at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, wherein Compound (I), Compound (II), or Compound (III) is present in a crystalline form. In another aspect of this disclosure, this method of treatment may be practiced by administering a pharmaceutical composition of at least one of Compound (I), Compound (II), Compound (III) or combinations thereof such as discussed above. In another embodiment, the combination administered in this method is Erlotinib with at least one of Compound (I), Compound (II), Compound (III), or combinations thereof.

[0071] Another aspect of this disclosure relates to a method of treating an astrocytic tumor (which includes glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components in a subject) in a subject, the method comprising administering to the subject in need of the treatment a therapeutically effective amount of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

[0072] Another aspect of this disclosure relates to a method of treating an astrocytic tumor (which includes glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components in a subject) in a subject, the method comprising administering to the subject in need of the treatment a therapeutically effective amount of at least one of Compound (I), Compound (II), Compound (III) or combinations thereof. Compound (I), Compound (II), or Compound (III) may be individually administered as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms. Accordingly another aspect of this disclosure relates to a method of treating an astrocytic tumor comprising administering to a subject in need thereof a therapeutically effective amount of at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, wherein Compound (I), Compound (II), or Compound (III) is present in a crystalline form. In another aspect of this disclosure, this method of treatment may be practiced by administering a pharmaceutical composition of at least one of Compound (I), Compound (II), Compound (III) or combinations thereof such as discussed above.

[0073] Another aspect of this disclosure relates to a method of treating thyroid cancer (including medullary thyroid cancer) in a subject, the method comprising administering to the subject in need of the treatment N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, or a pharmaceutically acceptable salt thereof. The amount administered can be a therapeutically effective amount.

[0074] Another aspect of this disclosure relates to a method of treating thyroid cancer (including medullary thyroid cancer) in a subject, the method comprising administering to the subject in need of the treatment at least one of Compound (I), Compound (II), Compound (III) or combinations thereof. Compound (I), Compound (II), or Compound (III) may be individually administered as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms. Accordingly another aspect of this disclosure relates to a method of treating thyroid cancer comprising administering to a subject in need thereof a therapeutically effective amount of at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, wherein Compound (I), Compound (II), or Compound (III) is present in a crystalline form. In another aspect of this disclosure, this method of treatment may be practiced by administering a pharmaceutical composition of at least one of Compound (I), Compound (II), Compound (III) or combinations thereof such as discussed above.

[0075] Another aspect of this disclosure relates to a method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities. This

method administers, to a subject in need thereof, at least one of Compound (I), Compound (II), Compound (III) or combinations thereof. The amount of Compound (I), Compound (II), or combinations thereof administered can be a therapeutically effective amount. Compound (I), Compound (II), or Compound (III) may be individually administered as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms.

[0076] Accordingly another aspect of this disclosure relates to a method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities comprising administering to a subject in need thereof a therapeutically effective amount of at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, wherein Compound (I), Compound (II), or Compound (III) is present in a crystalline form. In another aspect of this disclosure, this method of treatment may be practiced by administering a pharmaceutical composition of at least one of Compound (I), Compound (II), Compound (III) or combinations thereof such as discussed above. Another aspect of this disclosure relates to a method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities. This method administers, to a subject in need thereof, a crystalline form of Compound (I), Compound (II), or any combination of Compound (I) and (II). The amount of Compound (I), Compound (II), or any combination of Compound (I) and (II) administered can be a therapeutically effective amount.

[0077] Another aspect of this disclosure relates to a use of the N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to any of the above embodiments for the manufacture of a medicament for the treatment of a disease or disorder discussed above. When dissolved, a crystalline or amorphous form according to this disclosure loses its solid state structure, and is therefore referred to as a solution of, for example, Compound (I). At least one crystalline form disclosed herein may be used to prepare at least one liquid formulation in which at least one crystalline form according to the disclosure is dissolved and/or suspended.

[0078] A pharmaceutical composition such as discussed above may be any pharmaceutical form which contains active Compound (I), Compound (II) and/or Compound (III), including the solid state forms thereof (hereinafter referred to as active compound(s). The pharmaceutical composition may be, for example, a tablet, capsule, liquid suspension, injectable, topical, or transdermal. The pharmaceutical compositions generally contain about 1% to about 99% by weight of the active compound(s), or a crystalline form of the active compound(s), and 99% to 1% by weight of a suitable pharmaceutical excipient. In one example, the composition will be between about 5% and about 75% by weight of active

compound, with the rest being suitable pharmaceutical excipients or other adjuvants, as discussed below.

[0079] A "therapeutically effective amount of the active compounds, or a crystalline or amorphous form of the active compound(s), according to this disclosure to inhibit, regulate and/or modulate the signal transduction of kinases (discussed here concerning the pharmaceutical compositions) refers to an amount sufficient to treat a patient suffering from any of a variety of cancers associated with abnormal cell proliferation and angiogenesis. A therapeutically effective amount according to this disclosure is an amount therapeutically useful for the treatment or prevention of the disease states and disorders discussed herein. Compounds (I), (II), and/or (III) (including their solid state forms), possess therapeutic activity to inhibit, regulate and/or modulate the signal transduction of kinases such as described in WO2005-030140. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-cyclopropane-1,1-dicarboxamide.

[0080] The actual amount required for treatment of any particular patient will depend upon a variety of factors including the disease state being treated and its severity; the specific pharmaceutical composition employed; the age, body weight, general health, sex and diet of the patient; the mode of administration; the time of administration; the route of administration; and the rate of excretion of the active compound(s), or a crystalline form of the active compound(s), according to this disclosure; the duration of the treatment; any drugs used in combination or coincidental with the specific compound employed; and other such factors well known in the medical arts. These factors are discussed in Goodman and Gilman's "The Pharmacological Basis of Therapeutics", Tenth Edition, A. Gilman, J.Hardman and L. Limbird, eds., McGraw-Hill Press, 155-173, 2001, which is incorporated herein by reference. The active compound(s) , or a crystalline form of active compound(s), according to this disclosure and pharmaceutical compositions comprising them, may be used in combination with anticancer or other agents that are generally administered to a patient being treated for cancer. They may also be co-formulated with one or more of such agents in a single pharmaceutical composition.

[0081] Depending on the type of pharmaceutical composition, the pharmaceutically acceptable carrier may be chosen from any one or a combination of carriers known in the art. The choice of the pharmaceutically acceptable carrier depends partly upon the desired method of administration to be used. For a pharmaceutical composition of this disclosure, that is, one of the active compound(s), or a crystalline form of the active compound(s), of this disclosure, a carrier should be chosen so as to substantially maintain the particular form of the active compound(s), whether it would be crystalline or not. In other words, the carrier should

not substantially alter the form the active compound(s) are. Nor should the carrier be otherwise incompatible with the form of the active compound(s), such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutical composition.

[0082] The pharmaceutical compositions of this disclosure may be prepared by methods know in the pharmaceutical formulation art, for example, see Remington's Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pa., 1990). In a solid dosage forms Compound (I) is admixed with at least one pharmaceutically acceptable excipient such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, cellulose derivatives, starch, alginates, gelatin, polyvinylpyrrolidone, sucrose, and gum acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, croscarmellose sodium, complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, magnesium stearate and the like (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

[0083] Pharmaceutically acceptable adjuvants known in the pharmaceutical formulation art may also be used in the pharmaceutical compositions of this disclosure. These include, but are not limited to, preserving, wetting, suspending, sweetening, flavoring, perfuming, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. If desired, a pharmaceutical composition of this disclosure may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, and antioxidants, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, and butylalted hydroxytoluene.

[0084] Solid dosage forms as described above can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain pacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedded compositions that can be used are polymeric substances and waxes. The active

compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

[0085] Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

[0086] Compositions for rectal administrations are, for example, suppositories that can be prepared by mixing the active compound(s), or a crystalline form of the active compound(s), with, for example, suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt while in a suitable body cavity and release the active component therein.

[0087] Because the active compound(s), or a crystalline form of the active compound(s), is maintained during their preparation, solid dosage forms are preferred for the pharmaceutical composition of this disclosure. Solid dosage forms for oral administration, which includes capsules, tablets, pills, powders, and granules, are particularly preferred. In such solid dosage forms, the active compound(s) mixed with at least one inert, pharmaceutically acceptable excipient (also known as a pharmaceutically acceptable carrier). Administration of the active compound(s), or a crystalline form of the active compound(s), in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration or agents for serving similar utilities. Thus, administration can be, for example, orally, nasally, parenterally (intravenous, intramuscular, or subcutaneous), topically, transdermally, intravaginally, intravesically, intracistemally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages. One preferable route of administration is oral administration, using a convenient dosage regimen that can be adjusted according to the degree of severity of the disease-state to be treated.

General Preparation Methods of Crystalline Forms

[0088] Crystalline forms may be prepared by a variety of methods including, but not limited to, for example, crystallization or recrystallization from a suitable solvent mixture; sublimation; growth from a melt; solid state transformation from another phase; crystallization from a supercritical fluid; and jet spraying. Techniques for crystallization or recrystallization of crystalline forms of a solvent mixture include, but are not limited to, for

example, evaporation of the solvent; decreasing the temperature of the solvent mixture; crystal seeding of a supersaturated solvent mixture of the compound and/or salt thereof; crystal seeding a supersaturated solvent mixture of the compound and/or a salt from thereof; freeze drying the solvent mixture; and adding antisolvents (countersolvents) to the solvent mixture. High throughput crystallization techniques may be employed to prepare crystalline forms including polymorphs.

[0089] Crystals of drugs, including polymorphs, methods of preparation, and characterization of drug crystals are discussed in *Solid-State Chemistry of Drugs*, S.R. Byrn, R.R. Pfeiffer, and J.G. Stowell, 2nd Edition, SSCI, West Lafayette, Indiana (1999).

[0090] In a crystallization technique in which solvent is employed, the solvent(s) are typically chosen based on one or more factors including, but not limited to, for example, solubility of the compound; crystallization technique utilized; and vapor pressure of the solvent. Combinations of solvents may be employed. For example, the compound may be solubilized in a first solvent to afford a solution to which antisolvent is then added to decrease the solubility of the Compound (I)n the solution and precipitate the formation of crystals. An antisolvent is a solvent in which a compound has low solubility.

[0091] In one method that can be used in preparing crystals, Compound (I), Compound (II) and/or Compound (III) can be suspended and/or stirred in a suitable solvent to afford a slurry, which may be heated to promote dissolution. The term "slurry", as used herein, means a saturated solution of the compound, wherein such solution may contain an additional amount of compound to afford a heterogeneous mixture of compound and solvent at a given temperature.

[0092] Seed crystals may be added to any crystallization mixture to promote crystallization. Seeding may be employed to control growth of a particular polymorph and/or to control the particle size distribution of the crystalline product. Accordingly, calculation of the amount of seeds needed depends on the size of the seed available and the desired size of an average product particle as described, for example, in Programmed Cooling Batch Crystallizers," J.W. Mullin and J. Nyvlt, Chemical Engineering Science, 1971, 26, 3690377. In general, seeds of small size are needed to effectively control the growth of crystals in the batch. Seeds of small size may be generated by sieving, milling, or micronizing large crystals, or by microcrystallizing a solution. In the milling or micronizing of crystals, care should be taken to avoid changing crystallinity from the desired crystalline form (i.e., changing to an amorphous or other polymorphic form).

[0093] A cooled crystallization mixture may be filtered under vacuum and the isolated solid product washed with a suitable solvent, such as, for example, cold recrystallization

solvent. After being washed, the product may be dried under a nitrogen purge to afford the desired crystalline form. The product may be analyzed by a suitable spectroscopic or analytical technique including, but not limited to, for example, differential scanning calorimetry (DSC); x-ray powder diffraction (XRPD); and thermogravimetric analysis (TGA) to assure the crystalline form of the compound has been formed. The resulting crystalline form may be produced in an amount greater than about 70 wt.% isolated yield, based on the weight of the compound originally employed in the crystallization procedure, and preferably greater than about 90 wt.% isolated yield. Optionally, the product may be delumped by being comilled or passed through mesh screen.

[0094] The features and advantages of this disclosure may be more readily understood by those of ordinary skill in the art upon reading the following detailed description. It is to be appreciated that certain features of the invention that are, for clarity reasons, described above and below in the context of separate embodiments, may also be combined to form a single embodiment. Conversely, various features of this disclosure that are, for brevity reasons, described in the context of a single embodiment, may also be combined so as to form sub-combinations thereof. The disclosure is further illustrated by the following examples, which are not to be construed as limiting the disclosure in scope or spirit to the specific procedures described in them.

[0095] The definitions set forth herein take precedence over definitions set forth in any patent, patent application, and/or patent application publication incorporated herein by reference. All measurements are subject to experimental error and are within the spirit of the invention.

[0096] As used herein, "amorphous" refers to a solid form of a molecule and/or ion that is not crystalline. An amorphous solid does not display a definitive X-ray diffraction pattern with sharp maxima.

[0097] As used herein, the term "substantially pure" means the crystalline form of Compound (I) referred to contains at least about 90wt.% based on the weight of such crystalline form. The term "at least about 90 wt.%," while not intending to limit the applicability of the doctrine of equivalents to the scope of the claims, includes, but is not limited to, for example, about 90, about 91, about 92, about 93, about 94, about 95, about 96, about 97, about 98, about 99 and about 100% wt. %, based on the weight of the crystalline form referred to. The remainder of the crystalline form of Compound (I) may comprise other Form(s) of Compound (I) and/or reaction impurities and/or processing impurities that arise, for example, when the crystalline form is prepared. The presence of reaction impurities and/or processing impurities may be determined by analytical techniques known in the art,

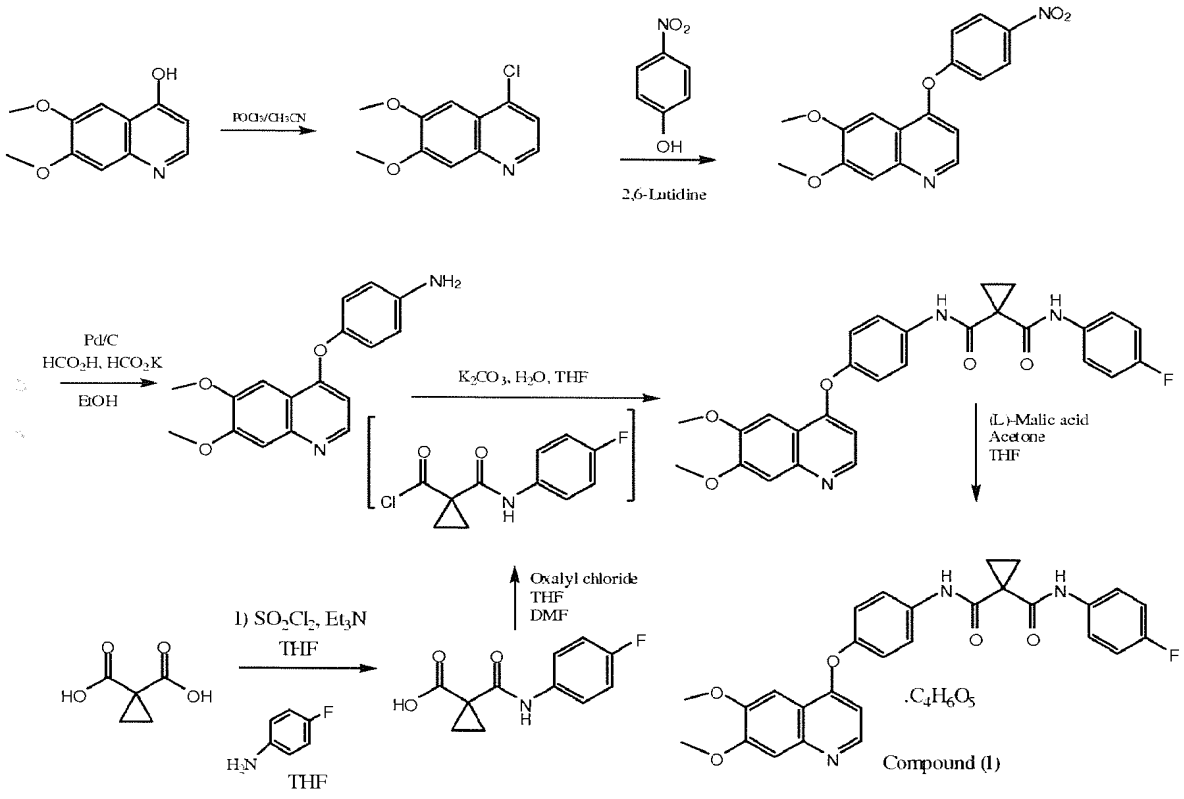
such as, for example, chromatography, nuclear magnetic resonance spectroscopy, mass spectroscopy, and/or infrared spectroscopy.

PREPARATIVE EXAMPLES

[0098] Example 1: Preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof (Compound (I)).

[0099] The synthetic route used for the preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof is depicted in Scheme 1:

SCHEME 1



[00100] The process shown in Scheme 1 is described in more detail below.

[00101] 1.1 Preparation of 4–Chloro–6,7–dimethoxy–quinoline

[00102] A reactor was charged sequentially with 6,7–dimethoxy–quinoline–4–ol (1 L, 10.0 kg) and acetonitrile (64.0 L). The resulting mixture was heated to approximately 65°C and phosphorus oxychloride ($POCl_3$, 50.0 kg) was added. After the addition of $POCl_3$, the

temperature of the reaction mixture was raised to approximately 80°C. The reaction was deemed complete (approximately 9.0 hours) when <2% of the starting material remained (in process high-performance liquid chromatography [HPLC] analysis). The reaction mixture was cooled to approximately 10°C and then quenched into a chilled solution of dichloromethane (DCM, 238.0 kg), 30% NH_4OH (135.0 kg), and ice (440.0 kg). The resulting mixture was warmed to approximately 14°C, and phases were separated. The organic phase was washed with water (40.0 kg) and concentrated by vacuum distillation with the removal of solvent (approximately 190.0 kg). Methyl-t-butyl ether (MTBE, 50.0 kg) was added to the batch, and the mixture was cooled to approximately 10°C, during which time the product crystallized out. The solids were recovered by centrifugation, washed with n-heptane (20.0 kg), and dried at approximately 40°C to afford the title compound (8.0 kg).

[00103] 1.2 Preparation of 6,7–Dimethyl–4–(4-nitro–phenoxy)–quinoline

[00104] A reactor was sequentially charged with 4–chloro–6,7–dimethoxy–quinoline (8.0 kg), 4 nitrophenol (7.0 kg), 4 dimethylaminopyridine (0.9 kg), and 2,6 lutidine (40.0 kg). The reactor contents were heated to approximately 147°C. When the reaction was complete (<5% starting material remaining as determined by in process HPLC analysis, approximately 20 hours), the reactor contents were allowed to cool to approximately 25°C. Methanol (26.0 kg) was added, followed by potassium carbonate (3.0 kg) dissolved in water (50.0 kg). The reactor contents were stirred for approximately 2 hours. The resulting solid precipitate was filtered, washed with water (67.0 kg), and dried at 25°C for approximately 12 hours to afford the title compound (4.0 kg).

[00105] 1.3 Preparation of 4–(6,7 –Dimethoxy–quinoline–4–yloxy)–phenylamine

[00106] A solution containing potassium formate (5.0 kg), formic acid (3.0 kg), and water (16.0 kg) was added to a mixture of 6,7-dimethoxy–4–(4-nitro–phenoxy)–quinoline (4.0 kg), 10% palladium on carbon (50% water wet, 0.4 kg) in tetrahydrofuran (40.0 kg) that had been heated to approximately 60°C. The addition was carried out such that the temperature of the reaction mixture remained approximately 60°C. When the reaction was deemed complete as determined using in-process HPLC analysis (<2% starting material remaining, typically 1 5 hours), the reactor contents were filtered. The filtrate was concentrated by vacuum distillation at approximately 35°C to half of its original volume, which resulted in the precipitation of the product. The product was recovered by filtration, washed with water (12.0 kg), and dried under vacuum at approximately 50°C to afford the title compound (3.0 kg; 97% AUC).

[00107] 1.4 Preparation of 1–(4–Fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid

[00108] Triethylamine (8.0 kg) was added to a cooled (approximately 4°C) solution of commercially available cyclopropane–1,1–dicarboxylic acid (2 1, 10.0 kg) in THF (63.0 kg) at a rate such that the batch temperature did not exceed 10°C. The solution was stirred for approximately 30 minutes, and then thionyl chloride (9.0 kg) was added, keeping the batch temperature below 10°C. When the addition was complete, a solution of 4–fluoroaniline (9.0 kg) in THF (25.0 kg) was added at a rate such that the batch temperature did not exceed 10°C. The mixture was stirred for approximately 4 hours and then diluted with isopropyl acetate (87.0 kg). This solution was washed sequentially with aqueous sodium hydroxide (2.0 kg dissolved in 50.0 L of water), water (40.0 L), and aqueous sodium chloride (10.0 kg dissolved in 40.0 L of water). The organic solution was concentrated by vacuum distillation followed by the addition of heptane, which resulted in the precipitation of solid. The solid was recovered by centrifugation and then dried at approximately 35°C under vacuum to afford the title compound. (10.0 kg).

[00109] 1.5 Preparation of 1–(4–Fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride

[00110] Oxalyl chloride (1.0 kg) was added to a solution of 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid (2.0 kg) in a mixture of THF (11 kg) and N, N-dimethylformamide (DMF; 0.02 kg) at a rate such that the batch temperature did not exceed 30°C. This solution was used in the next step without further processing.

[00111] 1.6 Preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

[00112] The solution from the previous step containing 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride was added to a mixture of 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (3.0 kg) and potassium carbonate (4.0 kg) in THF (27.0 kg) and water (13.0 kg) at a rate such that the batch temperature did not exceed 30°C. When the reaction was complete (in typically 10 minutes), water (74.0 kg) was added. The mixture was stirred at 15–30°C for approximately 10 hours, which resulted in the precipitation of the product. The product was recovered by filtration, washed with a premade solution of THF (11.0 kg) and water (24.0 kg), and dried at approximately 65°C under vacuum for approximately 12 hours to afford the title compound (free base, 5.0 kg). ^{1}H NMR (400 MHz, d_6-DMSO): δ 10.2 (s, 1H), 10.05 (s, 1H), 8.4 (s, 1H), 7.8 (m, 2H), 7.65 (m, 2H), 7.5 (s, 1H), 7.35 (s, 1H), 7.25 (m, 2H), 7.15(m, 2H), 6.4 (s, 1H), 4.0 (d, 6H), 1.5 (s, 4H). LC/MS: M+H= 502.

[00113] 1.7 Preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (L) malate salt (Compound (I))

[00114] A solution of (L)-malic acid (2.0 kg) in water (2.0 kg) was added to a solution of Cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide free base (1 5, 5.0 kg) in ethanol, maintaining a batch temperature of approximately 25°C. Carbon (0.5 kg) and thiol silica (0.1 kg) were then added, and the resulting mixture was heated to approximately 78°C, at which point water (6.0 kg) was added. The reaction mixture was then filtered, followed by the addition of isopropanol (38.0 kg), and was allowed to cool to approximately 25°C. The product was recovered by filtration and washed with isopropanol (20.0 kg) and dried at approximately 65°C to afford Compound (I) (5.0 kg).

[00115] Example 2: Preparation of Crystalline Compound (I), Form N-1

[00116] A solution was prepared by adding tetrahydrofuran (12 mL/g-bulk-LR (limiting reagent); 1.20 L) and N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (100 g; 1.00 equiv; 100.00 g) and (L)-malic acid (1.2 equiv (molar); 32.08 g) to a 1 L reactor. Water (0.5317 mL/g-bulk-LR; 53.17 mL) was added and the solution was heated to 60 °C and maintained at that temperature for one hour until the solids were fully dissolved. The solution was passed through a Polish Filter.

[00117] At 60 °C, acetonitrile (12 mL/g-bulk-LR; 1.20 L) was added over a period of 8 hours. The solution was held at 60 °C for 10 hours. The solution was then cooled to 20 °C and held for 1 hour. The solids were filtered and washed with acetonitrile (12 mL/g-bulk-LR; 1.20 L). The solids were dried at 60 °C (25 mm Hg) for 6 hours to afford Compound (I), Form N-1 (108 g; 0.85 equiv; 108.00 g; 85.22% yield) as a white crystalline solid.

[00118] Example 3: Alternate Preparation of Crystalline Compound (I), Form N-1

[00119] A solution was prepared with 190 mL tetrahydrofuran (110 mL), methyl isobutyl ketone, and 29 mL water. Next, 20 mL of this solution were transferred into an amber bottle, and then saturated by adding N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (L)-malate until a thick slurry formed, and aging for at least 2 h with stirring at room temperature. The solids were removed by filtration through a Buchner funnel, rendering a clear saturated solution.

[00120] Separately, a powder blend was made with known amounts of two batches of Compound (I): (1) 300 mg of batch 1, which contained approximately 41% Compound (I), Form N-1 and 59% Compound (I), Form N-2 by Raman spectroscopy analysis, and (2) 200 mg of batch 2, which had a XPRD pattern similar to Compound (I), Form N-2.

[00121] The Compound (I), Form N-1 and Compound (I), Form N-2 powder blend was added into the saturated solution, and the slurry was aged under magnetic stirring at room temperature for 25 days. The slurry was then sampled and filtered through a Buchner funnel to obtain 162 mg of wet cake. The wet cake was dried in a vacuum oven at 45°C to afford 128 mg of crystalline Compound (I) in the N-1 form.

[00122] Example 4: Preparation of Crystalline Compound (I), Form N-2

[00123] 4.1 Preparation of Crystalline Compound (I), Form N-2 Seed Crystals

[00124] A solution was prepared by combining 20 ml of acetone and 300mg of freebase N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide in a 25ml screw capped vial. Next, 0.758ml of a 0.79M (L)-malic acid stock solution was added to the vial with magnetic stirring. The solution was then left stirring for 24hr at ambient temperature. The sample was then suction filtered with 0.45µm PTFE filter cartridge and dried *in vacuo* at ambient temperature overnight.

[00125] 4.2 Preparation of Crystalline Compound (I), Form N-2.

[00126] To a reactor were added N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (48 g; 1.00 equiv; 48.00 g) and tetrahydrofuran (16.5 mL/g-bulk-LR; 792.00 mL). The water content was adjusted to 1 wt% water. The solution was heated to 60°C. Once dissolved, the solution was passed through a polish filter to provide the first solution.

[00127] In a separate reactor, (L)-malic acid (1.2 equiv (molar); 15.40 g) was dissolved into methyl isobutyl ketone (10 mL/g-bulk-LR; 480.00 mL) and tetrahydrofuran (1 mL/g-bulk-LR; 48.00 mL). Next, 50 mL of the (L)-malic acid solution was added to the first solution at 50°C. Seed crystals were added (1%, 480 mg) and the malic acid solution was added at 50°C dropwise via an addition funnel (1.3 ml/min (3 h)). The slurry was held at 50°C for 18 h and then was cooled to 25°C over 30 min. The solids were filtered, and washed with 20% tetrahydrofuran/methyl isobutyl ketone (10V, 480 mL). The solids were dried under vacuum at 60 °C for 5 h to afford Compound (I) (55.7 g; 0.92 equiv; 55.70 g; 91.56% yield) as an off-white crystalline solid.

[00128] Example 5: Preparation of Crystalline Compound (III), Form N-1

[00129] A one ml aliquot (DL)-malic acid salt of N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, slurried in tetrahydrofuran (THF), was heated to 60 °C on a hot-plate in a half-dram vial. Next,

tetrahydrofuran was added drop-wise until an almost clear solution was obtained. The vial was capped, removed from the hot plate and equilibrated at ambient temperature without agitation. Crystallization was apparent after several hours and the solution was allowed to stand overnight to allow completion. Several droplets of the resulting slurry were placed on a glass slide for microscopic analysis. The crystalline material consisted of many elongated plates ranging up to 60 microns in the longest dimension.

[00130] Alternate Preparation of Crystalline Compound (III), Form N-1

[00131] To a reactor were added N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (15 g; 1.00 equiv; 15.00 g) and tetrahydrofuran (16.5 mL/g-bulk-LR; 792.00 mL). The water content was adjusted to 1 wt % water. The solution was heated to 60 °C. Once dissolved, the solution was passed through a polish filter to provide the first solution.

[00132] In a separate reactor, (DL)-malic acid (1.2 equiv (molar); 4.53 g) was dissolved into methyl isobutyl ketone (8 mL/g-bulk-LR; 120.00 mL) and tetrahydrofuran (1 mL/g-bulk-LR; 15.00 mL). Next, 20 mL of the solution was added to the first solution at 50 °C. The malic acid solution was added at 50 °C dropwise via an addition funnel (1.3 ml/min (3 h)). The slurry was held at 50 °C for 18 h and then was cooled to 25 °C over 30 min. The solids were filtered, and washed with 20 %THF/MIBK (10V, 150 mL). The solids were dried under vacuum at 60 °C for 5 h to afford Compound (III) (15.52 g; 86.68% yield) as an off-white solid.

[00133] Example 6: Preparation of Amorphous Compound (I)

[00134] A solution was prepared with 5 g of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (L)-malate and 250 mL of a 1:1 (v:v) mixture of methanol and dichloromethane. The hazy solution was filtered through a 0.45 micron filter to yield a clear, yellowish solution. The solution was pumped through the spray dryer nozzle at a rate of 12.9 cc/min, and was atomized by nitrogen gas fed at a rate of 10.9 L/min. The temperature at the inlet of the cyclone was set to 65 °C to dry the wet droplets. Dry amorphous powder (1.5 g) was collected (yield = 30%).

CHARACTERIZATION EXAMPLES

[00135] I. NMR Spectra in Dimethyl Sulfoxide Solution

[00136] I.1 Compound (I), Form N-1

[00137] ^{1}H NMR (400 MHz, d_6-DMSO): δ 1.48 (s, 1 H), 2.42-2.48 (m, 1 H), 2.60-2.65 (m, 1 H), 3.93-3.96 (m, 6 H), 4.25-4.30 (dd, 1 H, J = 5, 8 Hz), 6.44 (d, 1H, J = 5 Hz, 1 H), 7.12-7.19 (m, 2 H), 7.22-7.26 (m, 2 H), 7.40 (s, 1 H), 7.51 (s, 1 H), 7.63-7.68 (m, 2 H), 7.76-7.80 (m, 2 H), 8.46-8.49 (m, 1 H), 10.08 (s, 1 H), 10.21 (s, 1 H).

[00138] ^{13}C NMR(d_6-DMSO): 15.36, 31.55, 55.64, 55.67, 66.91, 99.03, 102.95, 107.66, 114.89, 115.07, 115.11, 121.17, 122.11, 122.32, 122.39, 135.15, 136.41, 146.25, 148.7, 149.28,

149.38, 152.54, 157.03, 159.42, 160.02, 168.07, 171.83, 174.68.

[00139] I.2 Compound (I), Form N-2

[00140] ^{1}H NMR (400 MHz, d_6-DMSO): δ 1.48 (s, 1 H), 2.42-2.48 (m, 1 H), 2.60-2.65 (m, 1 H), 3.93-3.96 (m, 6 H), 4.25-4.30 (dd, 1 H, J = 5, 8 Hz), 6.44 (d, J = 5 Hz, 1 H), 7.12-7.19 (m, 2 H), 7.22-7.26 (m, 2 H), 7.40 (s, 1 H), 7.51 (s, 1 H), 7.63-7.68 (m, 2 H), 7.76-7.80 (m, 2 H), 8.46-8.49 (m, 1 H), 10.08 (s, 1 H), 10.21 (s, 1 H).

[00141] ^{13}C NMR(d_6-DMSO): 15.36, 31.55, 55.64, 55.67, 66.91, 99.03, 102.95, 107.66, 114.89, 115.07, 115.11, 121.17, 122.11, 122.32, 122.39, 135.15, 136.41, 146.25, 148.7, 149.28, 149.38, 152.54, 157.03, 159.42, 160.02, 168.07, 171.83, 174.68.

[00142] I.3 Compound (III), Form N-1

[00143] ^{1}H NMR (400 MHz, d_6-DMSO): δ 1.48 (s, 1 H), 2.42-2.48 (m, 1 H), 2.60-2.65 (m, 1 H), 3.93-3.96 (m, 6 H), 4.25-4.30 (dd, 1 H, J = 5, 8 Hz), 6.44 (d, J = 5 Hz, 1 H), 7.12-7.19 (m, 2 H), 7.22-7.26 (m, 2 H), 7.40 (s, 1 H), 7.51 (s, 1 H), 7.63-7.68 (m, 2 H), 7.76-7.80 (m, 2 H), 8.46-8.49 (m, 1 H), 10.08 (s, 1 H), 10.21 (s, 1 H).

[00144] ^{13}C NMR(d_6-DMSO): 15.36, 31.55, 55.64, 55.67, 66.91, 99.03, 102.95, 107.66, 114.89, 115.07, 115.11, 121.17, 122.11, 122.32, 122.39, 135.15, 136.41, 146.25, 148.7, 149.28, 149.38, 152.54, 157.03, 159.42, 160.02, 168.07, 171.83, 174.68.

[00145] Characterization of Solid State Forms of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, malate

[00146] II. Powder X-Ray Diffraction (XRPD) Studies

[00147] X-Ray Powder Diffraction (XRPD) patterns were collected on a Bruker AXS C2 GADDS diffractometer equipped with an automated XYZ stage, laser video microscope for auto-sample positioning and a HiStar 2-dimensional area detector. The radiation source used was copper (Cu Kα = 1.5406 Å), wherein the voltage was set at 40 kV and the current was set at 40 mA, X-ray optics consists of a single Göbel multilayer mirror coupled with a pinhole collimator of 0.3 mm. The beam divergence, *i.e.* the effective size of the X-ray beam on the

sample, was approximately 4 mm. A θ-θ continuous scan mode was employed with a sample - detector distance of 20 cm which gives an effective 2θ range of 3.2 °-29.8 °. Samples run under ambient conditions (from about 18 °C to about 25 °C) were prepared as flat plate specimens using powder as received without grinding. Approximately 1-2 mg of the sample was lightly pressed on a glass slide to obtain a flat surface. Typically the sample would be exposed to the X-ray beam for 120 seconds. Beam divergence (*i.e.*, effective size of X-ray spot, gives a value of approximately 4mm. Alternatively, the powder samples were placed in sealed glass capillaries of 1mm or less in diameter; the capillary was rotated during data collection at a sample-detector distance of 15 cm. Data were collected for $3 \leq 2\theta \leq 35°$ with a sample exposure time of at least 2000 seconds. The resulting two-dimensional diffraction arcs were integrated to create a traditional 1-dimensional XRPD pattern with a step size of 0.02 °2θ in the range of 3 to 35 °2θ ± 0.2 °2θ. The software used for data collection was GADDS for WNT 4.1.16 and the data were analyzed and presented using Diffrac Plus EVA v 9.0.0.2 or v 13.0.0.2.

[00148] II.1 Compound (I), Form N-1

[00149] Figure 1 shows the experimental XRPD pattern of crystalline Compound (I), Form N-1 acquired at room temperature (about 25 °C). A list of the peaks are shown in Table 2, above. The 2θ values at 19.4, 21.5, 22.8, 25.1, and 27.6 (± 0.2 °2θ) are useful for characterizing crystalline Compound (I), Form N-1. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-1.

[00150] II.2 Compound (I), Form N-2

[00151] Figure 8 shows the experimental XRPD pattern of crystalline Compound (I), Form N-2 acquired at room temperature (about 25 °C). A list of the peaks are shown in Table 2, above. The 2θ values at 20.9 and 21.9 (± 0.2 °2θ) are useful for characterizing crystalline Compound (I), Form N-2. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-2.

[00152] II.3 Compound (III), Form N-1

[00153] Figure 15 shows the experimental and the simulated XRPD pattern of crystalline Compound (III), Form N-1, acquired at 25°C using a spinning capillary sample. A list of the peaks are shown in Table 2, above. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (III), Form N-2.

[00154] II.4 Amorphous Compound (I)

[00155] Figure 22 shows the experimental XRPD pattern of amorphous Compound (I) acquired at room temperature (about 25°C). The spectra is characterized a broad peak and the absence of sharp peaks, which is consistent with an amorphous material.

[00156] III. Single Crystal X-Ray Study for Compound (III), Form N-1

[00157] Data were collected on a Bruker-Nonius CAD4 serial diffractometer. Unit cell parameters were obtained through least-squares analysis of the experimental diffractometer settings of 25 high-angle reflections. Intensities were measured using Cu Kα radiation (λ = 1.5418 Å) at a constant temperature with the θ-2θ variable scan technique and were corrected only for Lorentz-polarization factors. Background counts were collected at the extremes of the scan for half of the time of the scan. Alternately, single crystal data were collected on a Bruker-Nonius Kappa CCD 2000 system using Cu Kα radiation (λ = 1.5418 Å). Indexing and processing of the measured intensity data were carried out with the HKL2000 software package (Otwinowski, Z. & Minor, W. (1997) in *Macromolecular Crystallography,* eds. Carter, W.C. Jr & Sweet, R.M. (Academic, NY), Vol. 276, pp.307-326) in the Collect program suite (Collect Data collection and processing user interface: Collect: Data collection software, R. Hooft, Nonius B.V., 1998). Alternately, single crystal data were collected on a Bruker-AXS APEX2 CCD system using Cu Kα radiation (λ = 1.5418 Å). Indexing and processing of the measured intensity data were carried out with the APEX2 software package/program suite (APEX2 Data collection and processing user interface: APEX2 User Manual, v1.27). When indicated, crystals were cooled in the cold stream of an Oxford cryo system (Oxford Cryosystems Cryostream cooler: J. Cosier and A.M. Glazer, J. Appl. Cryst., 1986, 19, 105) during data collection.

[00158] The structures were solved by direct methods and refined on the basis of observed reflections using either the SDP software package (SDP, Structure Determination Package, Enraf-Nonius, Bohemia NY 11716. Scattering factors, including *f'* and *f''*, in the SDP software were taken from the" International Tables for Crystallography", Kynoch Press, Birmingham, England, 1974; Vol IV, Tables 2.2A and 2.3.1) with minor local modifications or the crystallographic packages MAXUS (maXus solution and refinement software suite: S. Mackay, C.J. Gilmore, C. Edwards, M. Tremayne, N. Stewart, K. Shankland. maXus: a computer program for the solution and refinement of crystal structures from diffraction data) or SHELXTL (APEX2 Data collection and processing user interface: APEX2 User Manual, v1.27).

[00159] The derived atomic parameters (coordinates and temperature factors) were refined through full matrix least-squares. The function minimized in the refinements was $\Sigma_w(|F_o| -$

$|F_c|)^2$. R is defined as $\Sigma \; ||F_o| - |F_c||/\Sigma \; |F_o|$ while $R_w = [\Sigma_w(|F_o| - |F_c|)^2/\Sigma_w \; |F_o|^2]^{1/2}$ where w is an appropriate weighting function based on errors in the observed intensities. Difference maps were examined at all stages of refinement. Hydrogens were introduced in idealized positions with isotropic temperature factors, but no hydrogen parameters were varied.

[00160] "Hybrid" simulated powder X-ray patterns were generated as described in the literature (Yin. S.; Scaringe, R. P.; DiMarco, J.; Galella, M. and Gougoutas, J. Z., *American Pharmaceutical Review*, 2003, 6,2, 80). The room temperature cell parameters were obtained by performing a cell refinement using the CellRefine.xls program. Input to the program includes the 2-theta position of *ca.* 10 reflections, obtained from the experimental room temperature powder pattern; the corresponding Miller indices, *hkl*, were assigned based on the single-crystal data collected at low temperature. A new (hybrid) XRPD was calculated (by either of the software programs, Alex or LatticeView) by inserting the molecular structure determined at low temperature into the room temperature cell obtained in the first step of the procedure. The molecules are inserted in a manner that retains the size and shape of the molecule and the position of the molecules with respect to the cell origin, but, allows intermolecular distances to expand with the cell.

[00161] A single crystal, measuring 40 x 30 x 10 microns, was selected from the slurry of crystals described in Example 5 for single crystal diffraction analysis. The selected crystal was affixed to a thin glass fiber with a small amount of a light grease, and mounted at room temperature on a Bruker ApexII single crystal diffractometer equipped with a rotating copper anode.

[00162] Crystalline Compound (III), From N-1 is characterized by unit cell parameters approximately equal to those reported in Table 4. The unit cell parameters were measured at a temperature of about 25°C.

Table 4

a = 14.60 Å
b = 5.20 Å
c = 39.09 Å
α = 90.0°
β = 90.4°
γ = 90.0°
Space group: $P2_1/n$
Molecules of Compound (I)/unit cell: 4
Volume = 2969 $Å^3$

[00163] Structure solution and refinement were routine in the monoclinic space group, $P2_1/n$, with four formula units in the unit cell. The structure contains cations of N-(4-{[6,7-

bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, protonated at the quinoline nitrogen atom, and singly ionized malic acid anions, in a 1:1 ratio. Further, the crystal contained a 1:1 ratio of (L)-malic acid ions to (D)-malic acid ions. Table 5

fractional atomic coordinates for Compound (III), Form N-1 calculated at a temperature of about 25°C.

[00164] Based on the single crystal X-ray data, crystalline Compound (III), Form N-1 may be characterized by a simulated powder x-ray diffraction (XRPD) pattern substantially in accordance with the simulated pattern shown in Figure 15 and/or by an observed XRPD pattern substantially in accordance with the experimental pattern shown in Figure 15.

Table 5

Fractional Atomic Coordinates for Compound (III), Form N-1

Calculated at a Temperature of about 25°C

Atom	X	Y	Z	Atom	X	Y	Z
O1	0.30601	-0.52166	0.22875	C40	0.25712	-0.35516	0.17574
O2	0.29518	0.12504	0.09391	C41	0.63543	0.13842	0.29041
O3	0.19041	-0.53232	0.18147	C42	0.22703	0.46640	0.06306
F5	-0.07307	2.12170	-0.08811	C43	0.34559	1.01717	-0.10021
O6	0.18186	1.20500	-0.03241	C44	0.39312	1.20834	-0.08137
O7	0.57137	0.22739	0.23473	C45	0.48224	0.32340	0.15059
O8	0.58700	-0.17911	0.24998	O46	0.77400	0.04784	0.34652
O9	0.41742	0.76377	-0.04319	C47	0.79349	0.09920	0.31966
N10	0.28649	0.82210	-0.01420	H10	0.22646	0.91057	-0.01479
O11	0.87391	0.22086	0.31241	H16	0.24790	1.42164	-0.10317
N12	0.46887	0.17029	0.17613	H19	-0.04176	1.82973	-0.03893
C13	0.29647	0.64886	0.01247	H20	0.16347	1.73025	-0.13083
C14	0.31416	1.08187	-0.06304	H22	0.43179	-0.17902	0.22447
C15	0.33900	-0.02207	0.14761	H23	0.17093	0.73524	0.03244
N16	0.20651	1.40640	-0.08267	H27	0.21953	-0.24212	0.12962
C17	0.40079	-0.01723	0.17602	H29	0.07954	1.50390	-0.03492
C18	0.29743	0.29956	0.06604	H30	0.04671	2.05817	-0.13354
C19	0.00418	1.80556	-0.05680	H33	0.41851	0.16255	0.04395
C20	0.11925	1.73626	-0.11097	H34	0.43433	0.41859	0.10106
C21	0.22556	1.24019	-0.05791	H38	0.41440	0.45648	-0.00227
C22	0.39150	-0.17467	0.20389	H41	0.61062	0.02238	0.31086
C23	0.22558	0.63870	0.03619	H42	0.17752	0.45794	0.07911
O24	0.62714	0.39565	0.29760	H45	0.53033	0.44239	0.15049
C25	0.34591	0.87438	-0.03961	H31a	0.76754	0.12071	0.26693
C26	0.36467	-0.51389	0.25773	H31b	0.74726	-0.15247	0.28137
C27	0.26562	-0.20277	0.14859	H43a	0.30237	1.06909	-0.12187
C28	0.35380	0.15272	0.12054	H43b	0.36868	0.85693	-0.10836
C29	0.07365	1.60604	-0.05443	H44a	0.45563	1.18725	-0.07495

C30	0.04897	1.92890	-0.11212	H44b	0.38932	1.39942	-0.08846
C31	0.73841	0.04517	0.28641	H26a	0.35958	-0.37184	0.27147
C32	0.32089	-0.35160	0.20385	H26b	0.42813	-0.55605	0.25348
C33	0.36641	0.29052	0.04302	H26c	0.34954	-0.66814	0.27571
C34	0.42458	0.32272	0.12143	H35a	0.08189	-0.39941	0.15398
C35	0.11723	-0.54030	0.15742	H35b	0.06671	-0.68838	0.16269
C36	0.12933	1.59042	-0.08228	H35c	0.13276	-0.61095	0.13323
C37	-0.00344	1.93494	-0.08547	H11	0.88836	0.21926	0.28968
C38	0.36439	0.47245	0.01586	H12	0.50720	0.16494	0.19477
C39	0.59040	0.05797	0.25625	H24	0.61522	0.45898	0.27789

[00165] IV. Solid State Nuclear Magnetic Resonance (SSNMR)

[00166] All solid-state C-13 NMR measurements were made with a Bruker DSX-400, 400 MHz NMR spectrometer. High resolution spectra were obtained using high-power proton decoupling and the TPPM pulse sequence and ramp amplitude cross-polarization (RAMP-CP) with magic-angle spinning (MAS) at approximately 12 kHz (A.E. Bennett et al, *J. Chem. Phys.*,1995, 103, 6951),(G. Metz, X. Wu and S.O. Smith, *J. Magn. Reson. A*,. 1994, 110, 219-227). Approximately 70 mg of sample, packed into a canister-design zirconia rotor was used for each experiment. Chemical shifts (δ) were referenced to external adamantane with the high frequency resonance being set to 38.56 ppm (W.L. Earl and D.L. VanderHart, *J. Magn. Reson.*, 1982, 48, 35-54).

[00167] IV.1 Compound (I), Form N-1

[00168] The solid state ^{13}C NMR spectrum of crystalline Compound (I), Form N-1 is shown in Figure 2. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-1.

[00169] SS ^{13}C NMR Peaks: 18.1, 20.6, 26.0, 42.9, 44.5, 54.4, 55.4, 56.1, 70.4, 99.4, 100.1, 100.6, 114.4, 114.9, 115.8, 119.6, 120.1, 121.6, 123.2, 124.1, 136.4, 138.6, 140.6, 145.4, 150.1, 150.9, 156.2, 157.4, 159.4, 164.9, 167.1, 170.8, 175.7, and 182.1 ppm, ± 0.2 ppm.

[00170] Figure 3 shows the solid state ^{15}N NMR spectrum of crystalline Compound (I), Form N-1. The spectrum shows peaks at 118.6, 119.6, 120.7, 134.8, 167.1, 176.0, and 180 ppm, ± 0.2 ppm. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-1.

[00171] Figure 4 shows the solid state ^{19}F NMR spectrum of crystalline Compound (I), Form N-1. The spectrum shows a peak at -121.6, -120.8, and -118.0 ppm, ± 0.2 ppm.

[00172] IV.2 Compound (I), Form N-2

[00173] The solid state ^{13}C NMR spectrum of crystalline Compound (I), Form N-2 is shown in Figure 9. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-2.

[00174] SS ^{13}C NMR Peaks: 20.5, 21.8, 23.0, 25.9, 26.4, 38.0, 41.7, 54.7, 55.8, 56.2, 56.6, 69.7, 99.4, 100.0, 100.4, 100.8, 102.3, 114.5, 115.5, 116.7, 119.0, 120.2, 121.1, 121.2, 122.1, 122.9, 124.5, 136.0, 137.3, 138.1, 138.9, 139.5, 140.2, 144.9, 145.7, 146.1, 150.7, 156.7, 157.7, 159.6, 159.7, 165.1, 167.0, 168.0, 171.5, 177.3, 179.3, 180.0, and 180.3 ppm, ± 0.2 ppm.

[00175] Figure 10 shows the solid state ^{15}N NMR spectrum of crystalline Compound (I), Form N-2. The spectrum shows peaks at 118.5, 120.8, 135.1, 167.3, and 180.1 ppm, ± 0.2 ppm. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-2.

[00176] Figure 11 shows the solid state ^{19}F NMR spectrum of crystalline Compound (I), Form N-2. The spectrum shows peaks at -121.0 and -119.1 ppm, ± 0.2 ppm. Those peaks, individually or together, may be sufficient to characterize crystalline Compound (I), Form N-2.

[00177] IV.3 Compound (III), Form N-1

[00178] The solid state ^{13}C NMR spectrum of crystalline Compound (III), Form N-1 is shown in Figure 16. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (III), Form N-1.

[00179] SS ^{13}C NMR Peaks: 20.8, 26.2, 44.8, 55.7, 70.7, 100.4, 101.0, 114.7, 115.2, 116.0, 119.7, 120.4, 121.6, 124.4, 136.9, 138.9, 141.1, 145.7, 150.3, 156.5, 157.6, 159.6, 165.2, 167.4, 171.2, 176.3, and 182.1 ppm, ± 0.2 ppm.

[00180] Figure 17 shows the solid state ^{15}N NMR spectrum of crystalline Compound (III), Form N-1. The spectrum shows peaks at 119.6, 134.7, and 175.5 ppm, ± 0.2 ppm. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (III), Form N-1.

[00181] Figure 18 shows the solid state ^{19}F NMR spectrum of crystalline Compound (III), Form N-1. The spectrum shows a peak at -120.5 ppm, ± 0.2 ppm.

[00182] IV.4 Compound (I), Amorphous

[00183] Figure 23 shows the solid state ^{13}C NMR spectrum of amorphous Compound (I). The entire list of peaks, or a subset thereof, may be sufficient to characterize amorphous Compound (I).

[00184] SS ^{13}C NMR Peaks (ppm): 12.2, 17.8, 20.3, 21.8, 27.2, 33.8, 41.7, 56.9, 69.9, 99.9, 102.2, 115.6, 122.2, 134.4, 137.8, 142.9, 149.1, 150.9, 157.3, 159.7, 167.0, 171.7, 173.1, 177.4, and 179.5 ppm, ± 0.2 ppm.

[00185] Figure 24 shows the solid state ^{15}N NMR spectrum of amorphous Compound (I). The spectrum shows peaks at 120.8, 131.8, 174.7, and 178.3 ppm, ± 0.2 ppm. The entire list of peaks, or a subset thereof, may be sufficient to characterize amorphous Compound (I).

[00186] Figure 25 shows the solid state ^{19}F NMR spectrum of amorphous Compound (I). The spectrum shows a peak at -118.9 ppm, ± 0.2 ppm.

[00187] V. Thermal Characterization Measurements

[00188] Thermal Gravimetric Analysis (TGA)

[00189] The TGA measurements were performed in a TA Instruments™ model Q500 or 2950, employing an open pan setup. The sample (about 10-30 mg) was placed in a platinum pan previously tared. The weight of the sample was measured accurately and recorded to a thousand of a milligram by the instrument. The furnace was purged with nitrogen gas at 100mL/min. Data were collected between room temperature and 300°C at 10°C/min heating rate.

[00190] Differential Scanning Calorimetry (DSC) Analysis

[00191] DSC measurements were performed in a TA Instruments™ model Q2000, Q1000 or 2920, employing an open pan setup. The sample (about 2-6 mg) was weighed in an aluminum pan and recorded accurately recorded to a hundredth of a milligram, and transferred to the DSC. The instrument was purged with nitrogen gas at 50mL/min. Data were collected between room temperature and 300°C at 10°C/min heating rate. The plot was made with the endothermic peaks pointing down.

[00192] V.1 Compound (I), Form N-1

[00193] Figure 5 shows the TGA thermogram for crystalline Compound (I), Form N-1, which shows a weight loss of approximately 0.4 weight % at a temperature of 170°C.

[00194] Figure 6 shows the DSC thermogram for crystalline Compound (I), Form N-1, which showed a melting point of approximately 187°C.

[00195] V.2 Compound (I), Form N-2

[00196] Figure 12 shows the TGA thermogram for crystalline Compound (I), Form N-2, which shows a weight loss of approximately 0.1 weight % at a temperature of 170°C.

[00197] Figure 13 shows the DSC thermogram for crystalline Compound (I), Form N-2, which showed a melting point of approximately 186°C.

[00198] V.3 Compound (III), Form N-1

[00199] Figure 19 shows the TGA thermogram for crystalline Compound (III), Form N-1, which shows a weight loss of approximately 0.2 weight % at a temperature of 170°C.

[00200] Figure 20 shows the DSC thermogram for crystalline Compound (III), Form N-1, which showed a melting point of approximately 186°C.

[00201] V.2 Compound (I), Amorphous

[00202] Figure 26 shows the DSC for crystalline Compound (I).

[00203] VI. Moisture Vapor Isotherm Measurements

[00204] Moisture sorption isotherms were collected in a VTI SGA-100 Symmetric Vapor Analyzer using approximately 10 mg of sample. The sample was dried at 60°C until the loss rate of 0.0005 wt %/min was obtained for 10 minutes. The sample was tested at 25°C and 3 or 4, 5, 15, 25, 35, 45, 50, 65, 75, 85, and 95% RH. Equilibration at each RH was reached when the rate of 0.0003 wt%/min for 35 minutes was achieved or a maximum of 600 minutes.

[00205] VI.1 Compound (I), Form N-1

[00206] Figure 7 shows the moisture vapor isotherm of crystalline Compound (I), Form N-1.

[00207] VI.2 Compound (I), Form N-1

[00208] Figure 14 shows the moisture vapor isotherm of crystalline Compound (I), Form N-2.

[00209] VI.3 Compound (III), Form N-1

[00210] Figure 21 shows the moisture vapor isotherm of crystalline Compound (III), Form N-1.

[00211] VI.4 Compound (I), Amorphous

[00212] Figure 27 shows the moisture vapor isotherm of amorphous Compound (I).

[00213] The foregoing disclosure has been described in some detail by way of illustration and example, for purposes of clarity and understanding. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications can be made while remaining within the spirit and scope of the invention. It will be obvious to one of skill in the art that changes and modifications can be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with

reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

Claims

What is claimed is:

1. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt.

2. The N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to claim 1, wherein said salt is the (DL)-malate salt.

3. The N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to claim 1, wherein said salt is a (L)-malate salt or (D)-malate salt.

4. The N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to claim 3, wherein said salt is the (L)-malate salt.

5. The N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to claim 3, wherein said salt is the (D)-malate salt.

6. The N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to any one of claims 3 to 5, wherein said salt is crystalline.

7. The N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to claim 6, wherein said salt is in crystalline Form N-1 and said Form N-1 is characterized by at least one of the following:
(i) a solid state ^{13}C NMR spectrum with four or more peaks selected from 18.1, 42.9, 44.5, 70.4, 123.2, 156.2, 170.8, 175.7, and 182.1, ± 0.2 ppm;
(ii) a powder x-ray diffraction pattern (CuKα λ=1.5418Å) comprising four or more 2θ values selected from: 12.8±0.2 °2θ, 13.5±0.2 °2θ, 16.9±0.2 °2θ, 19.4±0.2 °2θ, 21.5±0.2 °2θ, 22.8±0.2 °2θ, 25.1±0.2 °2θ, 27.6±0.2 °2θ, wherein measurement of the crystalline form is at room temperature; and/or

(iii) an x-ray powder diffraction (XRPD) pattern substantially in accordance with the pattern shown in Figure 1.

8. The N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to claim 7, wherein said salt is least 90 weight % Form N-1, based on weight of said salt.

9. The N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to claim 6, wherein said salt is in crystalline Form N-2 and said Form N-2 is characterized by at least one of the following:
(i) a solid state ^{13}C NMR spectrum with four or more peaks selected from 23.0, 25.9, 38.0, 41.7, 69.7, 102.0, 122.5, 177.3, 179.3, 180.0, and 180.3, ± 0.2 ppm;
(ii) a powder x-ray diffraction pattern (CuKα λ=1.5418Å) comprising 2θ values at 20.9±0.2 °2θ and 21.9±0.2 °2θ, and two or more 2θ values selected from: 6.4±0.2 °2θ, 9.1±0.2 °2θ, 12.0±0.2 °2θ, 12.8±0.2, 13.7±0.2, 17.1±0.2, 22.6±0.2, 23.7±0.2, wherein measurement of the crystalline form is at room temperature; and/or
(iii) an x-ray powder diffraction (XRPD) pattern substantially in accordance with the pattern shown in Figure 8.

10. The N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to claim 9, wherein said salt is least 90 weight % Form N-2, based on weight of said salt.

11. A pharmaceutical composition comprising the N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to any one of claim 4-10; and a pharmaceutically acceptable excipient.

12. Use of the N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to any one of claims 3-10, for the manufacture of a medicament for the treatment of cancer.

13. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to any one of claims 3-10, for use in therapy in treating cancer.

14. The crystalline form of the (L)-malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide according to any one of claims 6-10, for use as a medicament for treating thyroid cancer in a subject.

15. The crystalline form of the (L)-malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide according to any one of claims 6-10, for use as a medicament for treating glioblastoma in a subject.

Figure 1

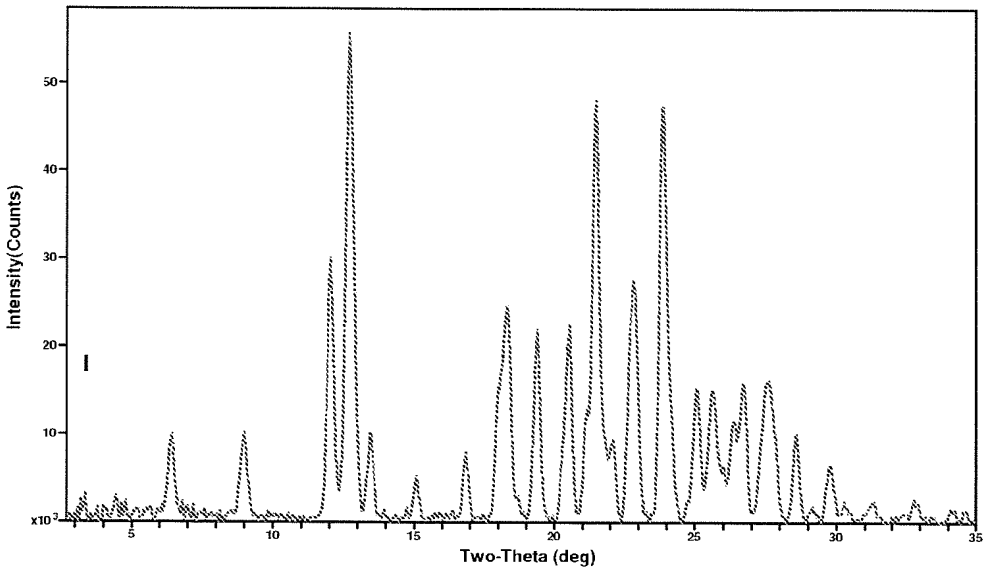

Intensity(Counts)
x10^3
50
40
30
20
10
I
5
10
15
20
25
30
35
Two-Theta (deg)

Figure 2

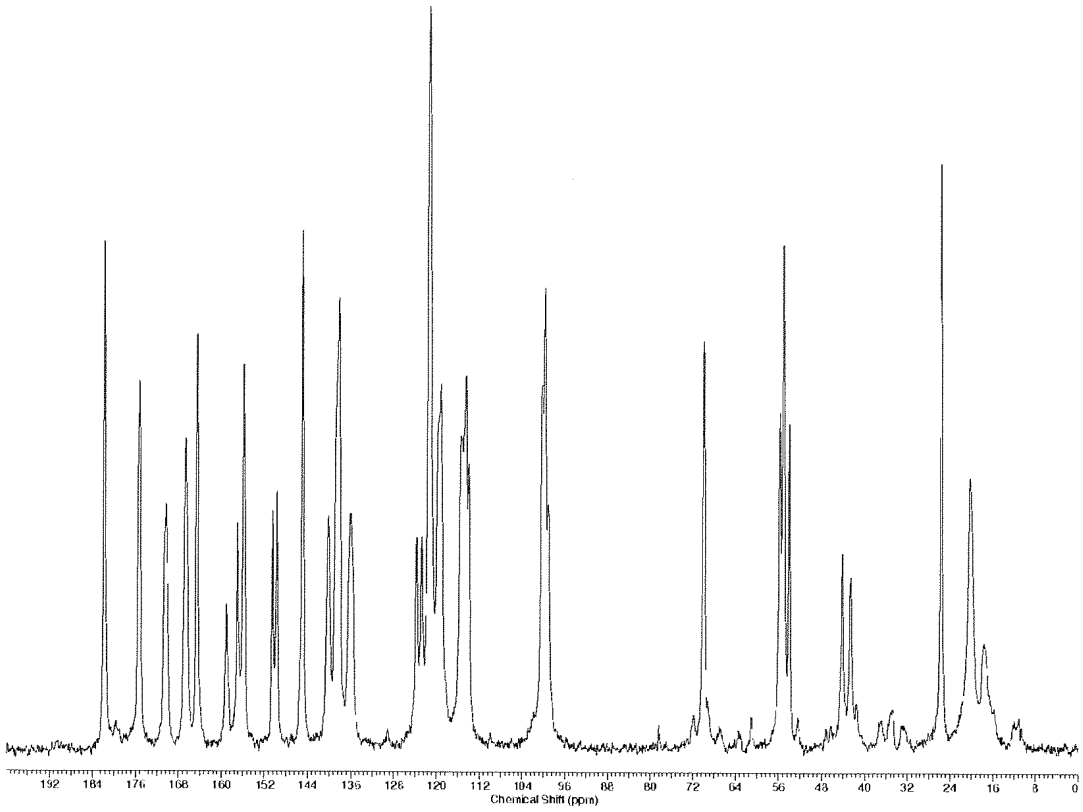

192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

Figure 3

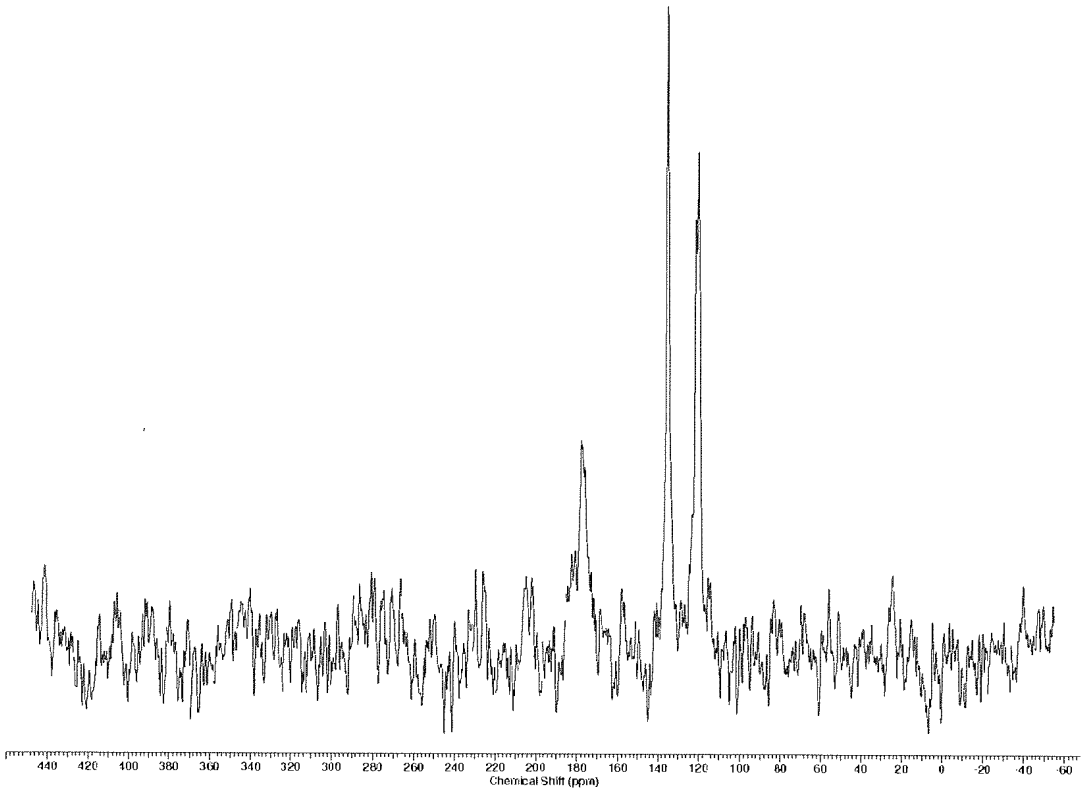

440 420 400 380 360 340 320 300 280 260 240 220 200 180 160 140 120 100 80 60 40 20 0 -20 -40 -60
Chemical Shift (ppm)

Figure 4

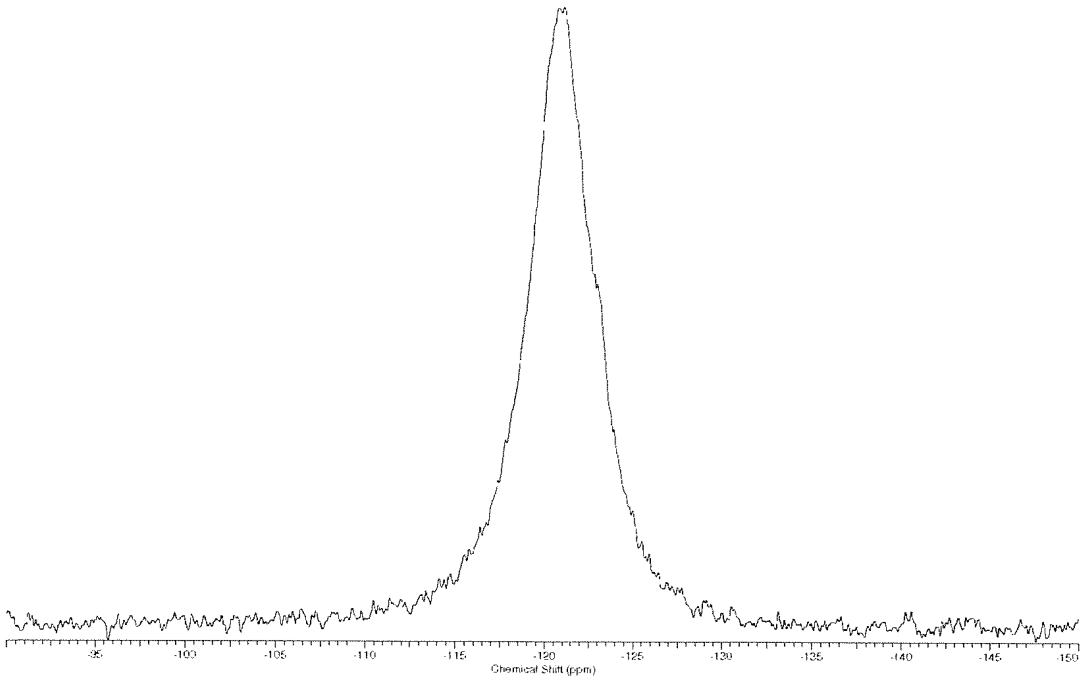

-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
Chemical Shift (ppm)

Figure 5

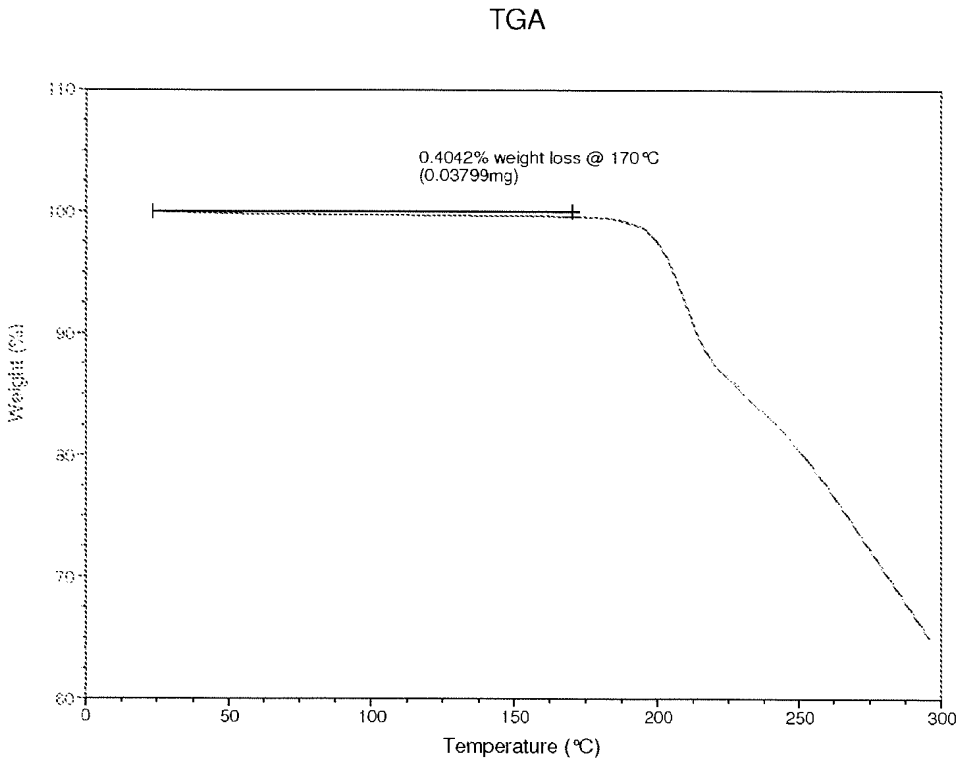

TGA
0.4042% weight loss @ 170°C
(0.03799mg)
Weight (%)
110
100
90
80
70
60
0
50
100
150
200
250
300
Temperature (°C)

Figure 6

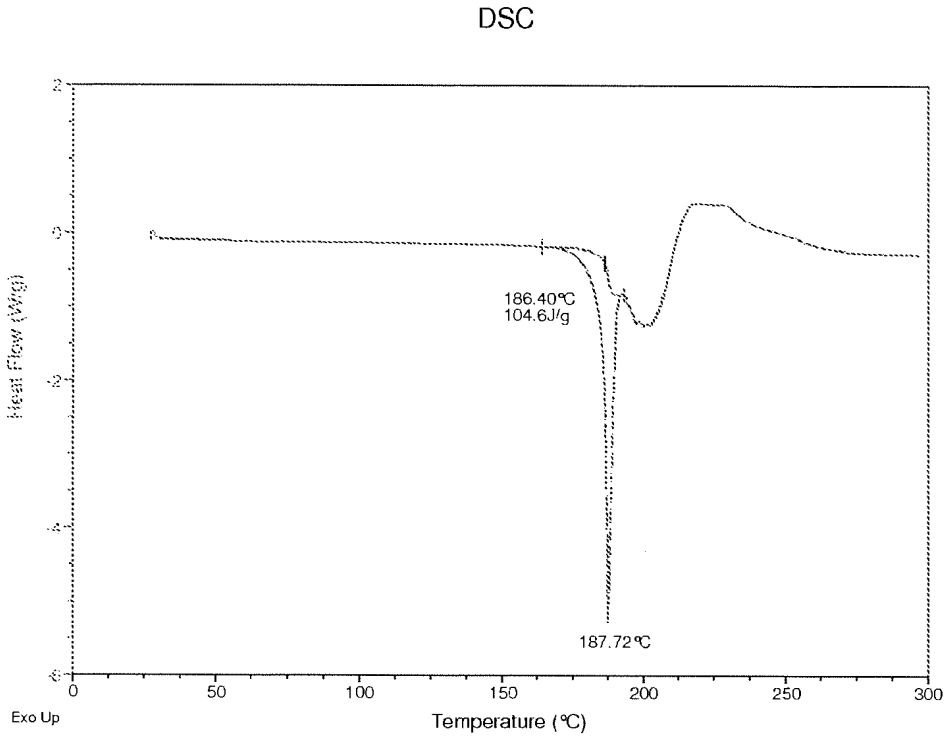
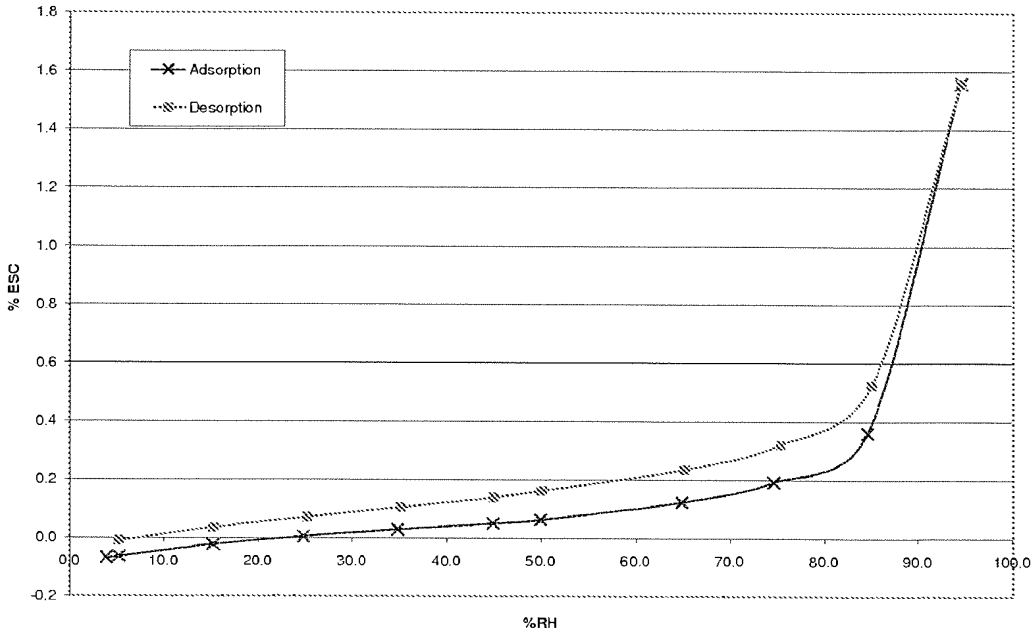

DSC
Heat Flow (W/g)
186.40℃
104.6J/g
187.72℃
Exo Up
Temperature (℃)
0
50
100
150
200
250
300

Figure 7



Moisture Sorption of Compound (I), Form N-1

Figure 8

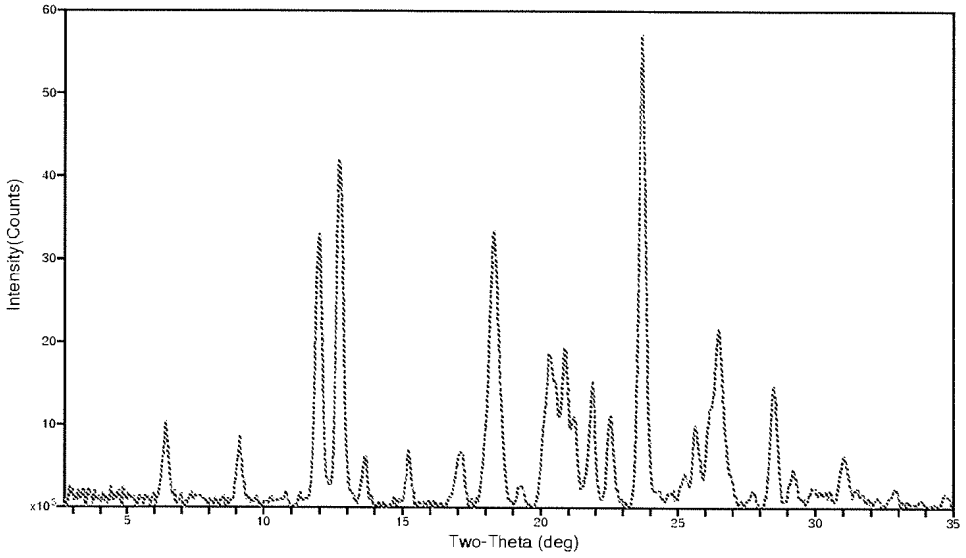

Intensity(Counts)
x10^3
60
50
40
30
20
10
5
10
15
20
25
30
35
Two-Theta (deg)

Figure 9

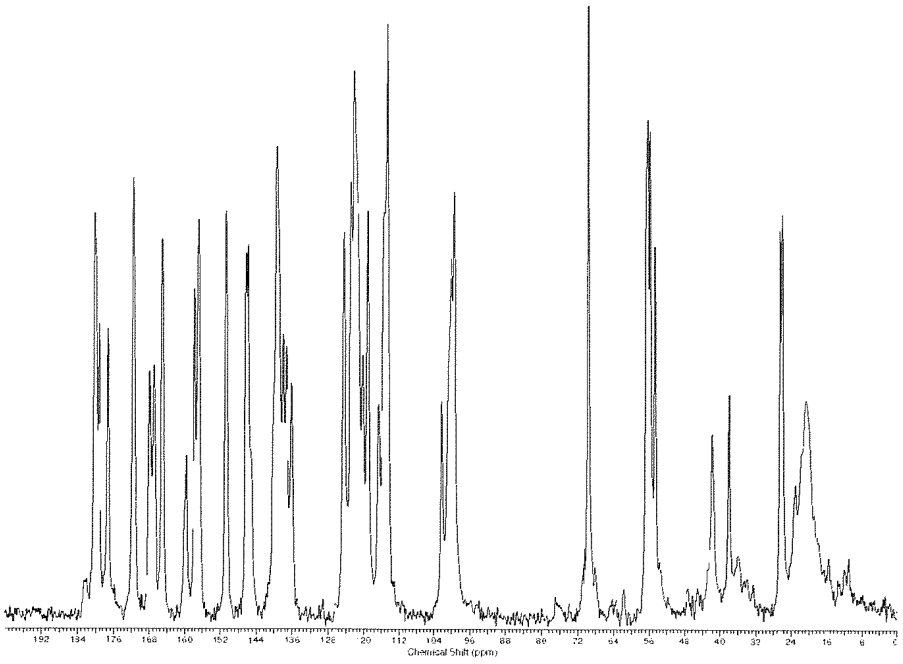

192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

Figure 10

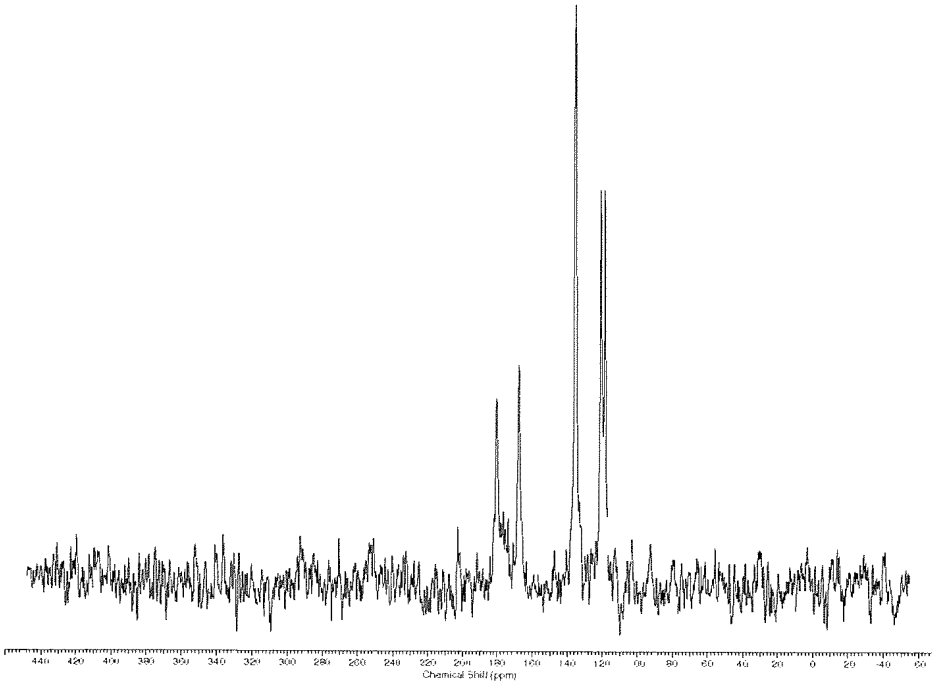

440 420 400 380 360 340 320 300 280 260 240 220 200 180 160 140 120 100 80 60 40 20 0 -20 -40 -60
Chemical Shift (ppm)

Figure 11

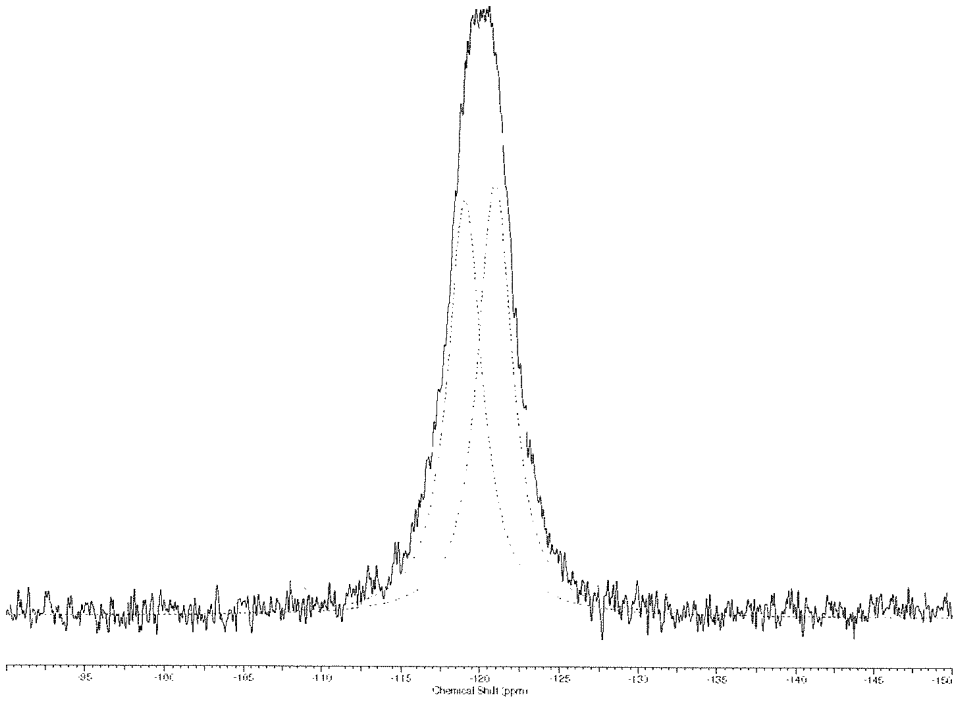

-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
Chemical Shift (ppm)

Figure 12

TGA

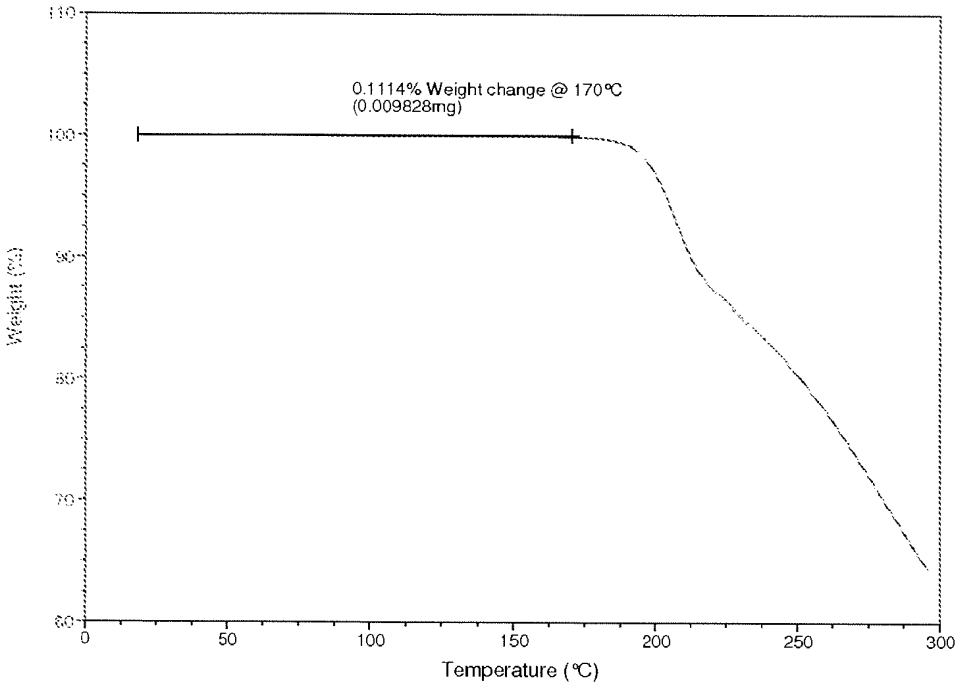


Figure 13

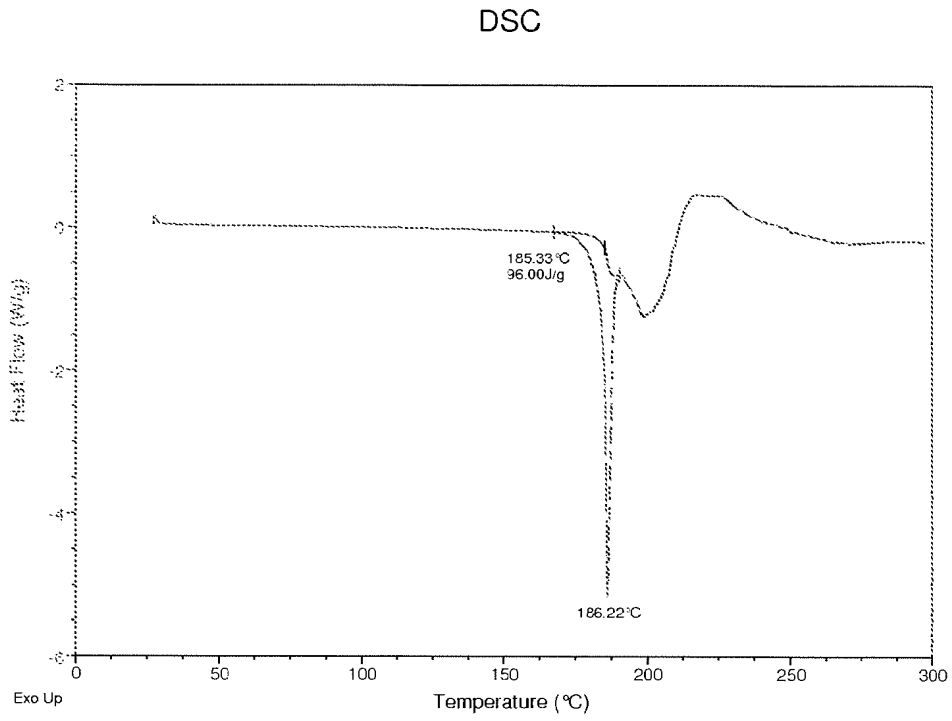

DSC
185.33°C
96.00J/g
186.22°C
Heat Flow (W/g)
Exo Up
Temperature (°C)
0
50
100
150
200
250
300

Figure 14

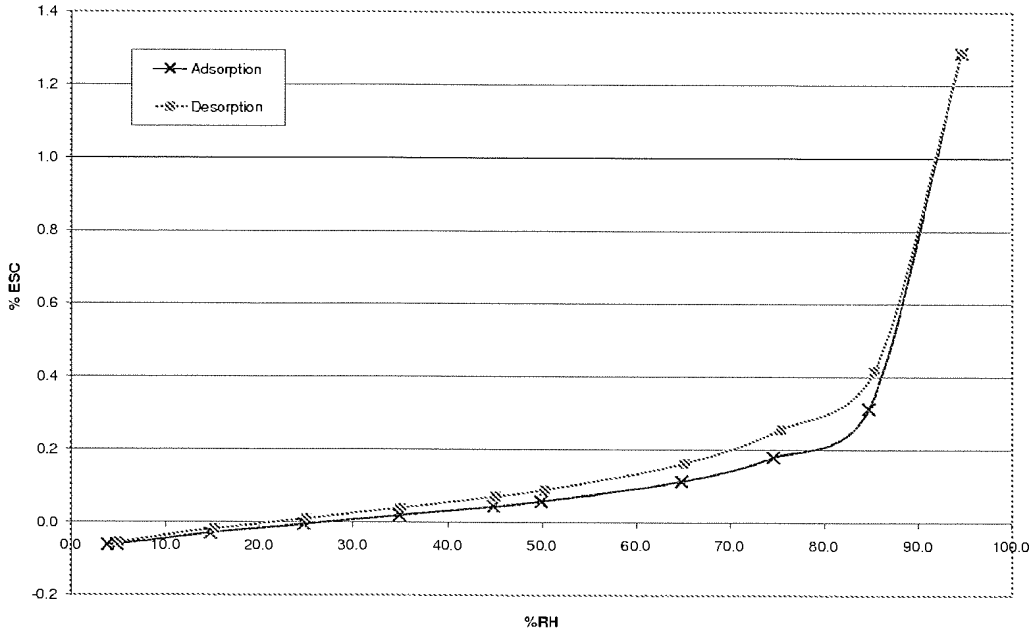

Adsorption
Desorption
% ESC
%RH
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0

Figure 15

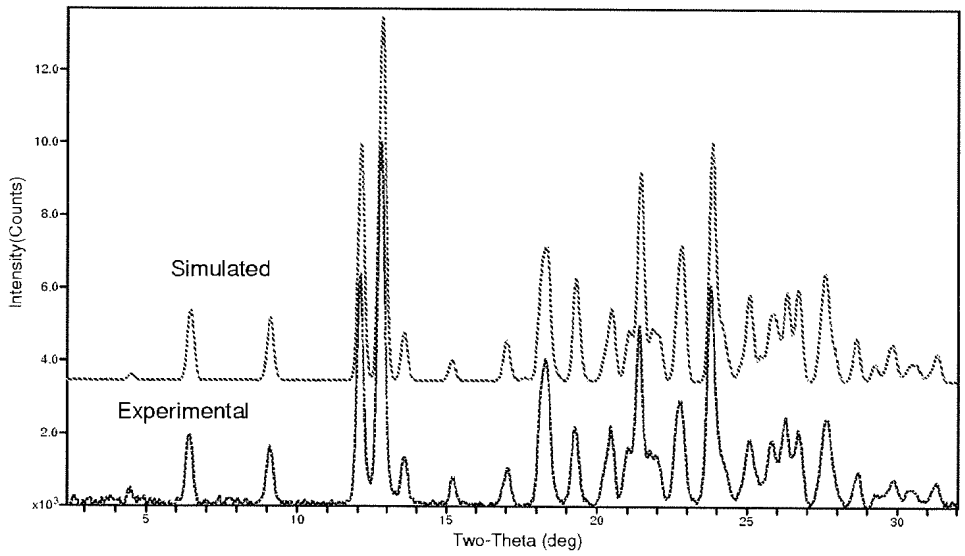

Intensity(Counts)
x10^3
12.0
10.0
8.0
6.0
4.0
2.0
Simulated
Experimental
5
10
15
20
25
30
Two-Theta (deg)

Figure 16

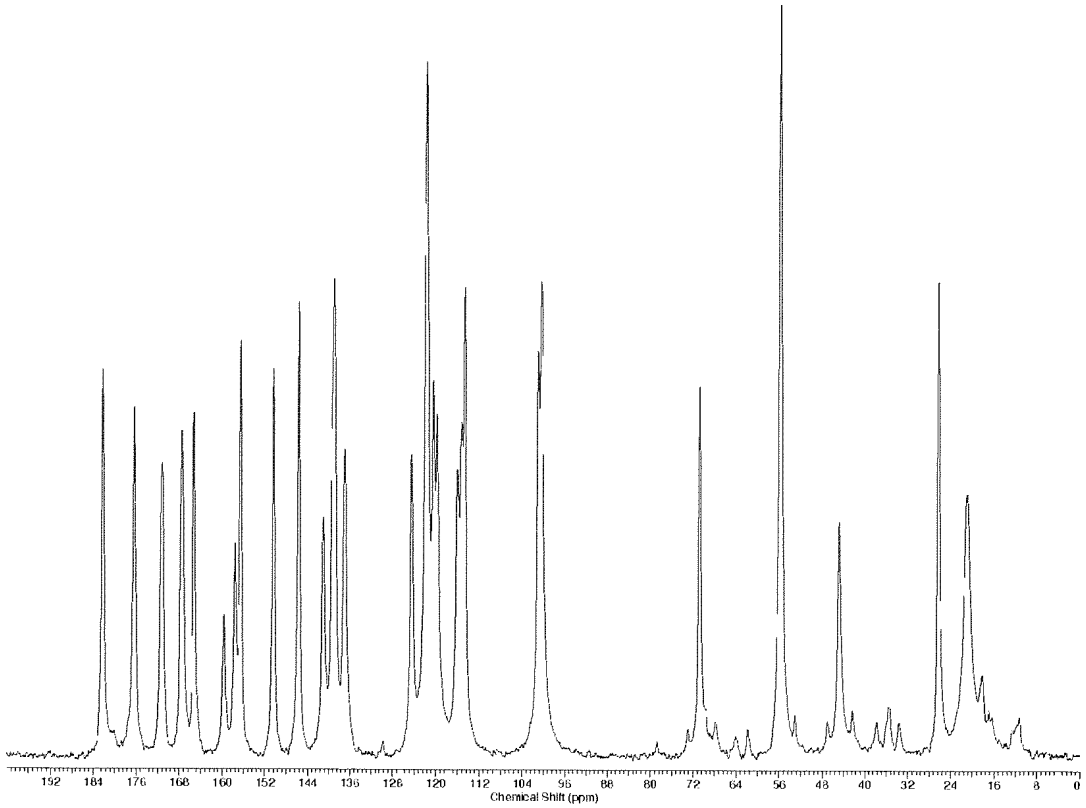

192 184 176 168 160 152 144 136 126 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

Figure 17

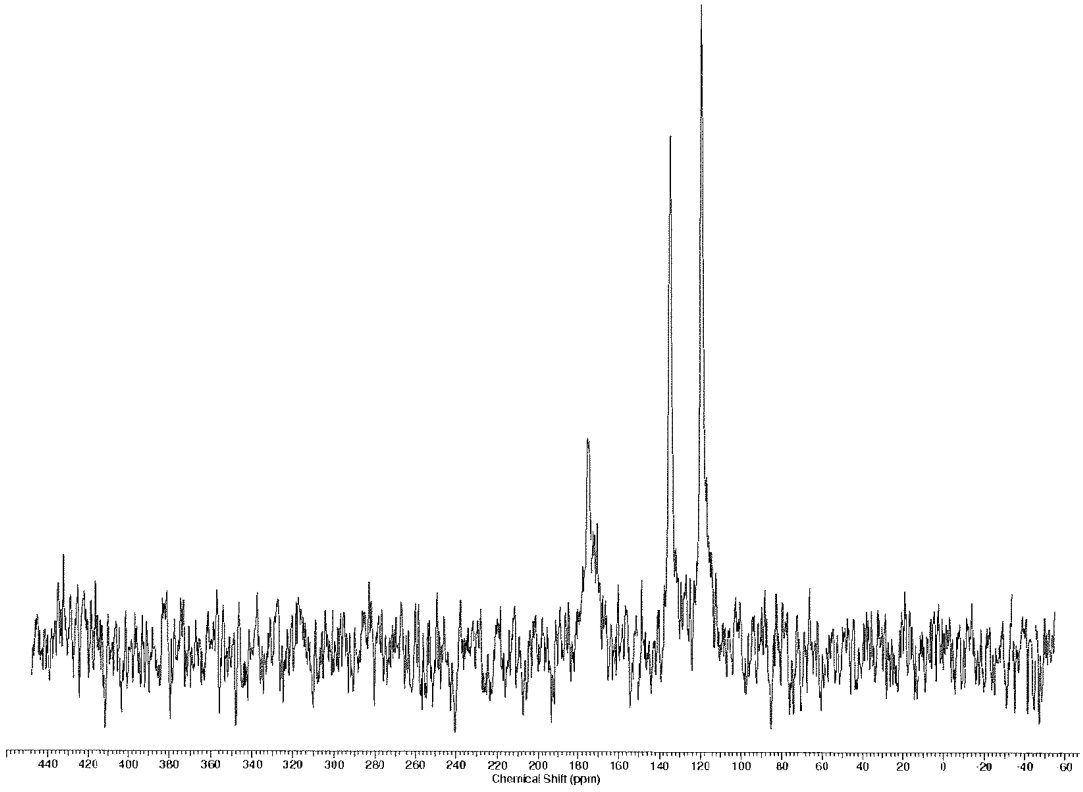

440 420 400 380 360 340 320 300 280 260 240 220 200 180 160 140 120 100 80 60 40 20 0 -20 -40 -60
Chemical Shift (ppm)

Figure 18

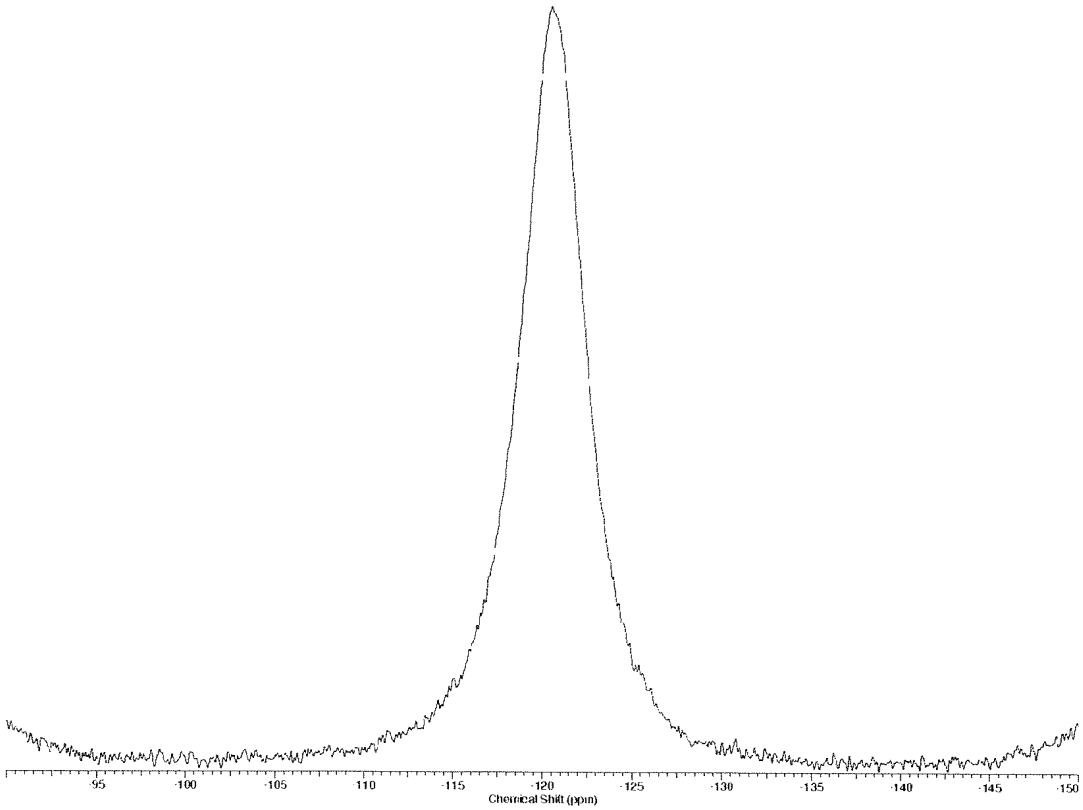

-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
Chemical Shift (ppm)

Figure 19

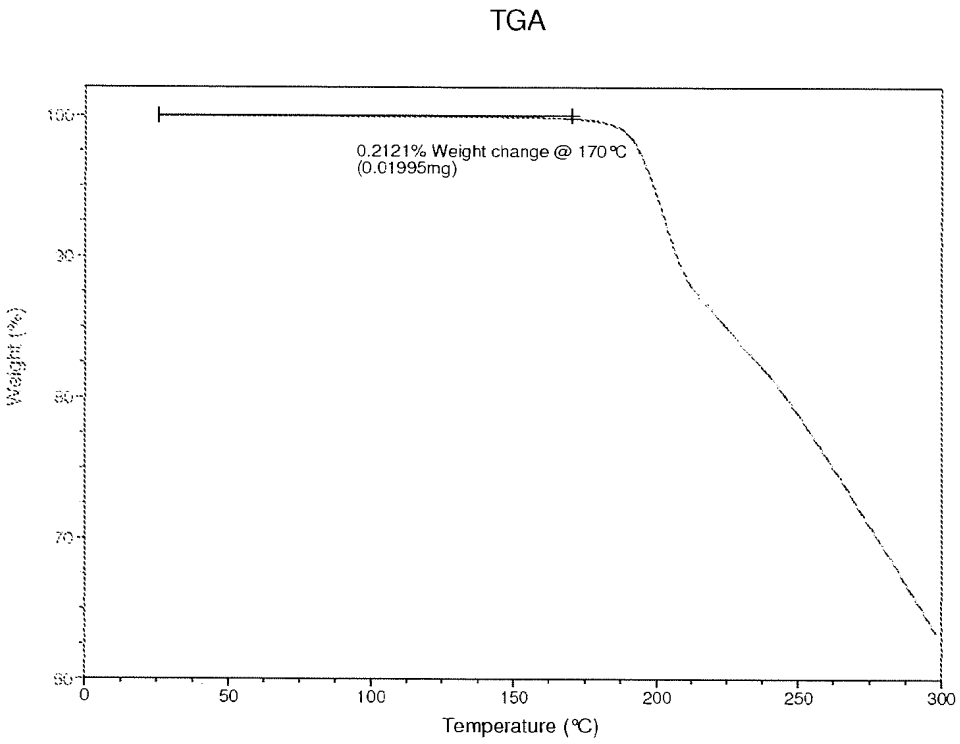

TGA
0.2121% Weight change @ 170°C
(0.01995mg)
Weight (%)
100
90
80
70
60
0
50
100
150
200
250
300
Temperature (°C)

Figure 20

DSC

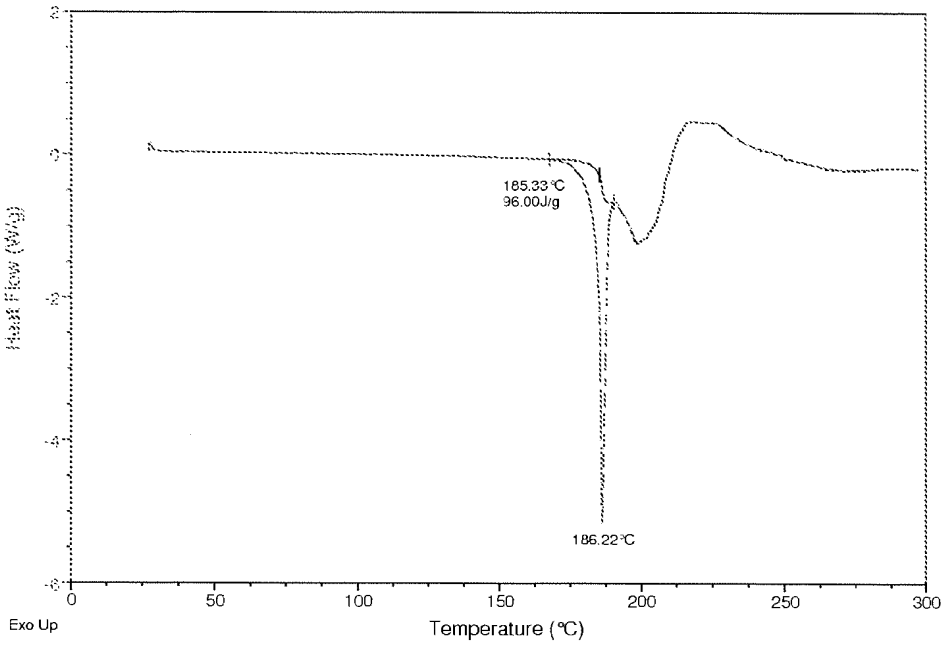


Figure 21

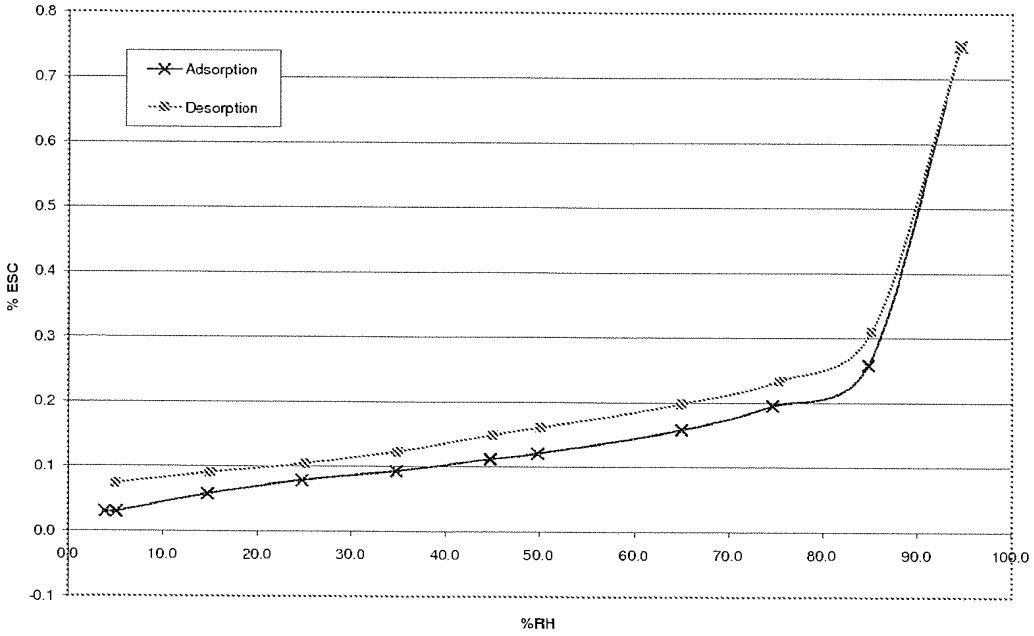

Adsorption
Desorption
% ESC
%RH
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0

Figure 22

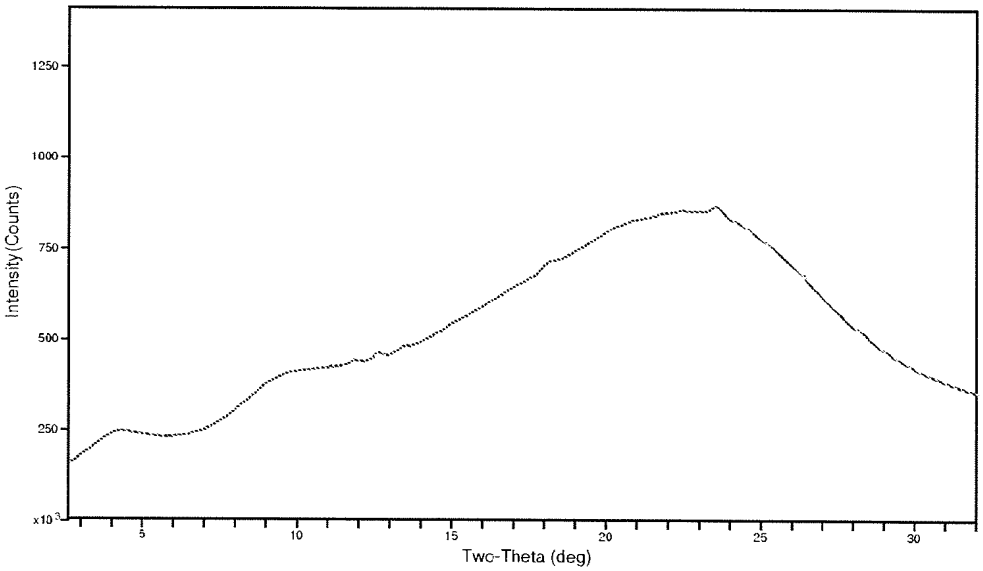

1250
1000
750
500
250
x10 3
Intensity (Counts)
5
10
15
20
25
30
Two-Theta (deg)

Figure 23

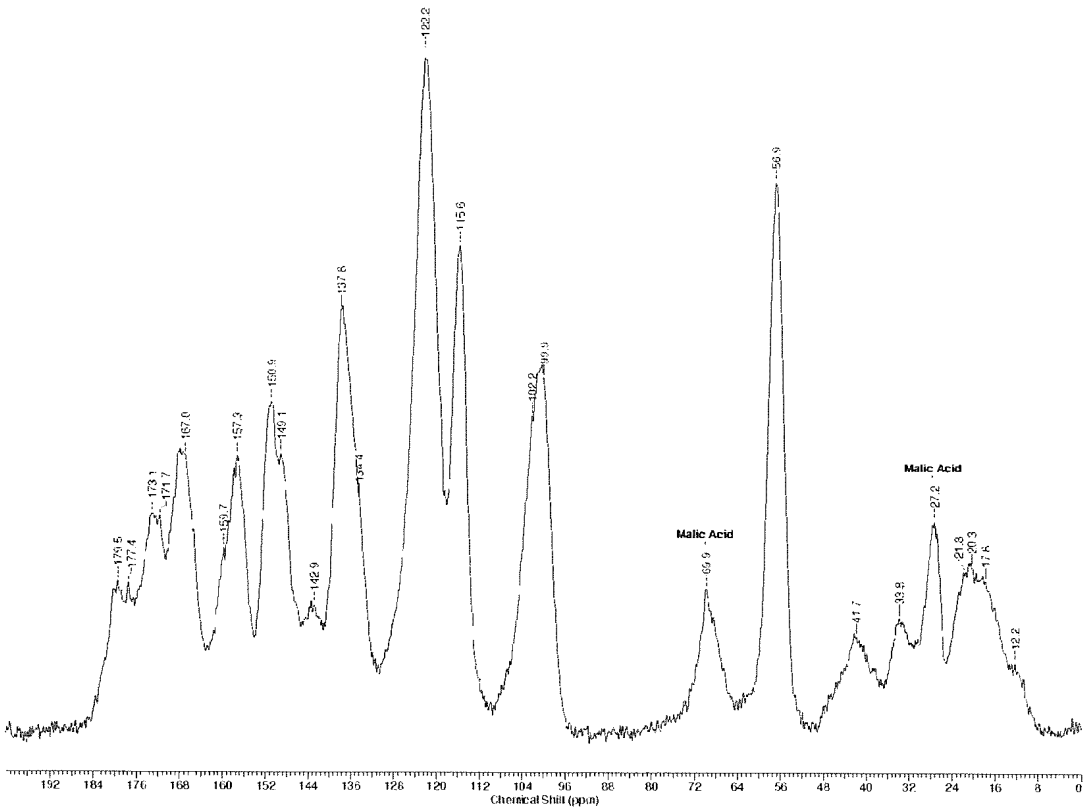


Figure 24

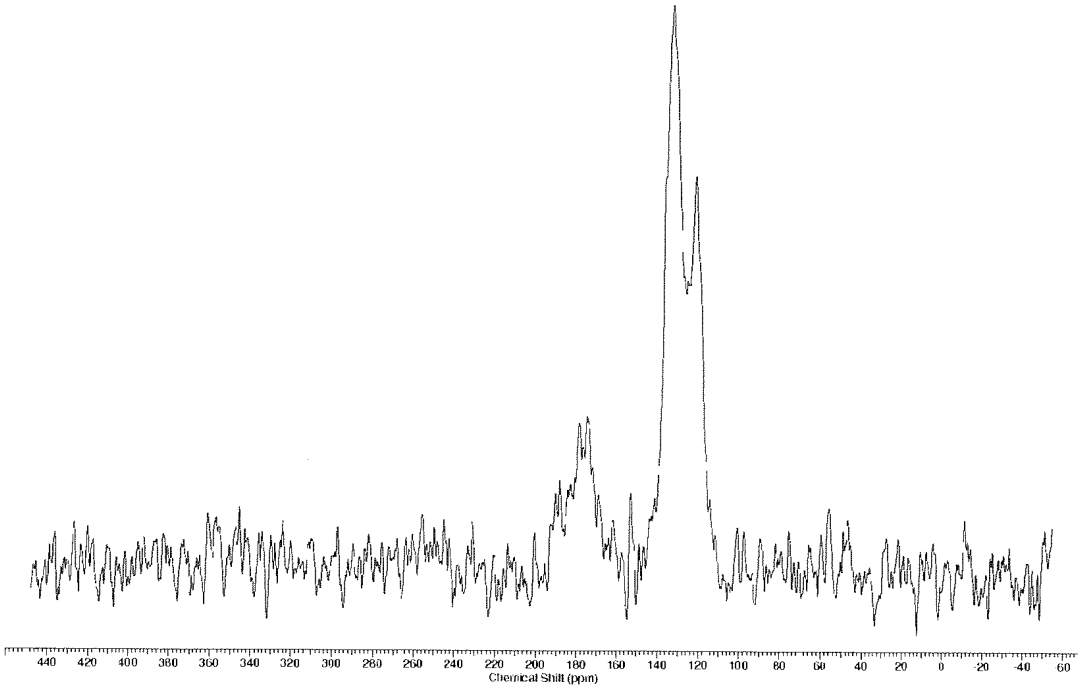

440 420 400 380 360 340 320 300 280 260 240 220 200 180 160 140 120 100 80 60 40 20 0 -20 -40 -60
Chemical Shift (ppm)

Figure 25

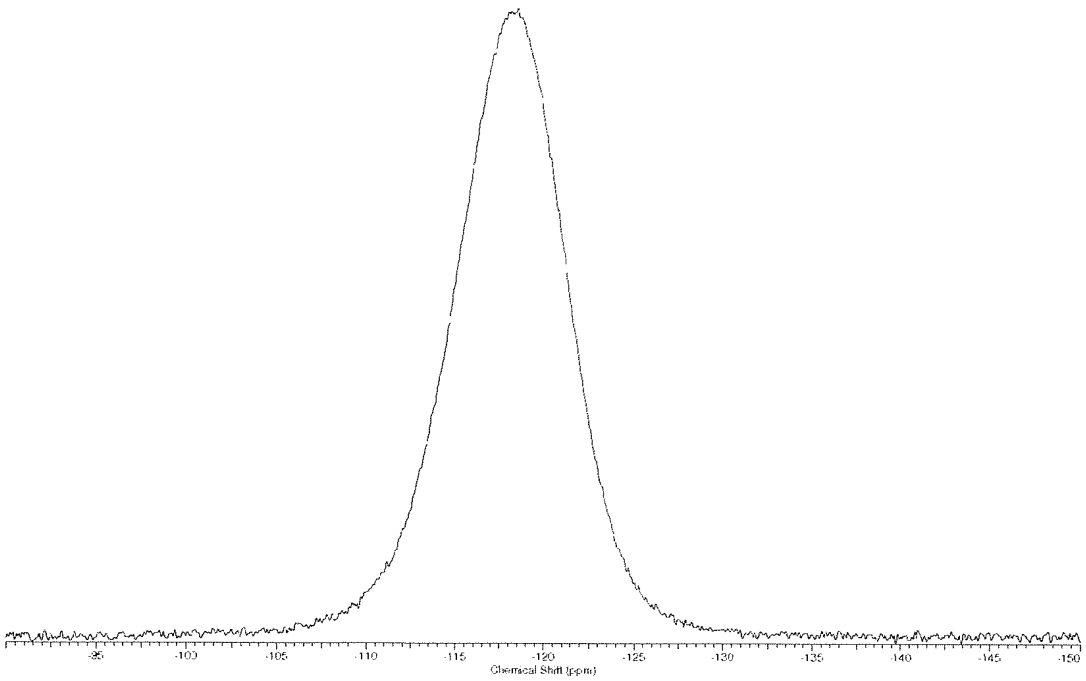

-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
Chemical Shift (ppm)

Figure 26

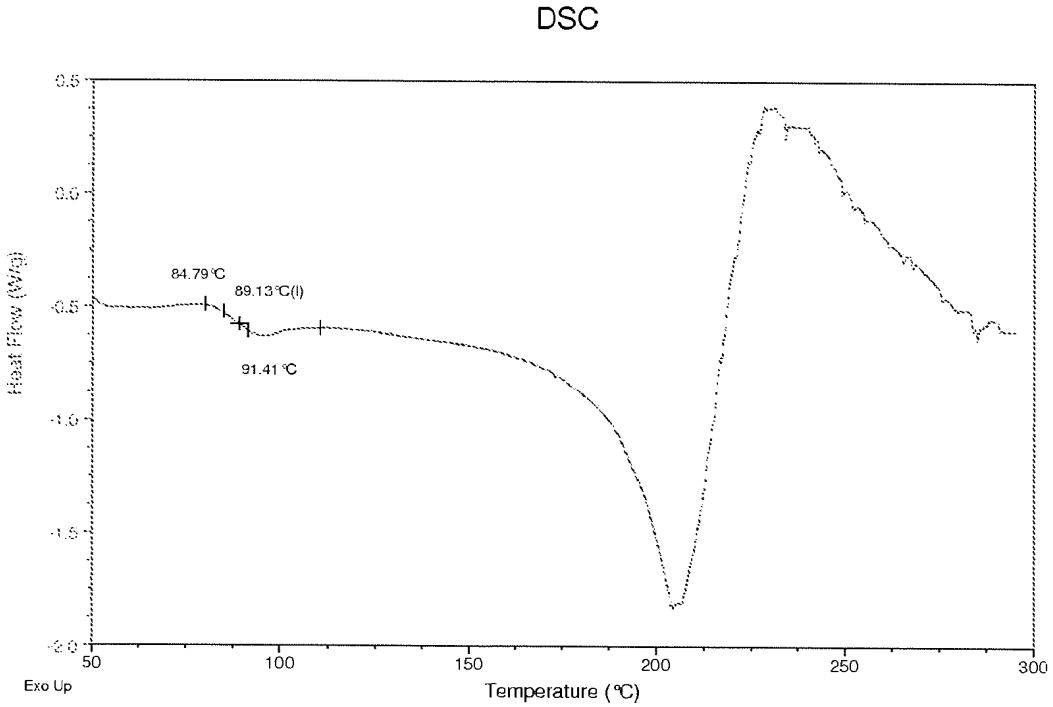
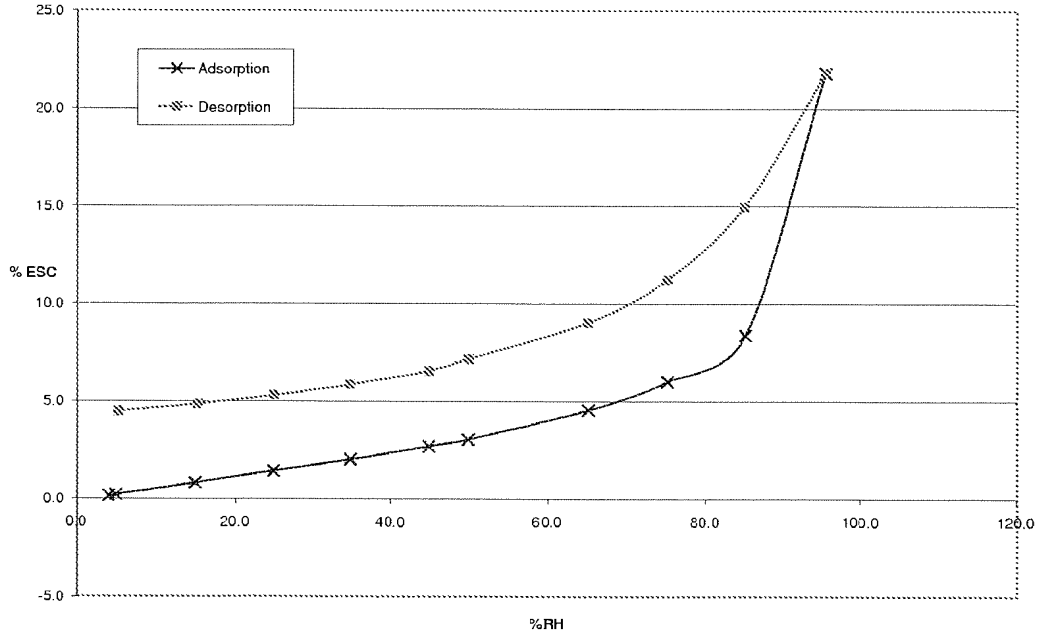

DSC
0.5
0.0
-0.5
-1.0
-1.5
-2.0
Heat Flow (W/g)
84.79°C
89.13°C(I)
91.41°C
50
100
150
200
250
300
Exo Up
Temperature (°C)

Figure 27



KALAMAZOO.46896.1

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/021194

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D215/227 A61K31/47 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/030140 A2 (EXELIXIS INC [US]; BANNEN LYNNE CANNE [US]; CHAN DIVA SZE-MING [US]; C) 7 April 2005 (2005-04-07) cited in the application page 212, paragraph 353 - page 213; example 48 claims 1-168 page 159, paragraph 236	1-15

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 March 2010	24/03/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Marzi, Elena

1

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2010/021194

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005030140 A2	07-04-2005	AU 2004275842 A1	07-04-2005
		CA 2537812 A1	07-04-2005
		EP 1673085 A2	28-06-2006
		JP 2007506777 T	22-03-2007
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		US 2007225307 A1	27-09-2007
		US 2007244116 A1	18-10-2007
		US 2009105299 A1	23-04-2009

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(51) International Patent Classification:
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A61K 31/47 (2006.01)

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(22) International Filing Date:
15 January 2010 (15.01.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/145,421 16 January 2009 (16.01.2009) US

(71) Applicants *(for all designated States except US)*: **EXELIXIS, INC.** [US/US]; P.O. Box 511, 249 East Grand Avenue, South San Francisco, CA 94080 (US). **BRISTOL-MEYERS SQUIBB COMPANY** [US/US]; P.O. Box 4000, Princeton, NJ 08543 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **ST CLAIR BROWN, Adrian** [GB/GB]; 67 Stour Green, Ely, Cambridgeshire CB6 2XJ (GB). **LAMB, Peter** [US/US]; 814 Mandana Blvd., Oakland, CA 94610 (US). **GALLAGHER, William, P.** [US/US]; P.O. Box 4000, Princeton, NJ 08543 (US).

(74) Agent: **BERVEN, Heidi M.**; Honigman Miller Schwartz and Cohn LLP, 350 East Michigan Avenue, Suite 300, Kalamazoo, MI 49007 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

(48) Date of publication of this corrected version:
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(15) Information about Correction:
see Notice of 2 December 2010

(54) Title: MALATE SALT OF N- (4- { [6, 7-BIS (METHYLOXY) QUINOLIN-4-YL] OXY}PHENYL-N' - (4 -FLUOROPHENYL) CYCLOPROPANE-1,1-DICARBOXAMIDE, AND CRYSTALLINE FORMS THEROF FOR THE TREATMENT OF CANCER

(57) Abstract: Disclosed are malate salts of N-(4-{ [6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)- N'-(4-fluorophenyl)cyclopropane-l,l-dicarboxamide, including a (L)-malate salt, a (D)- malate salt, a (DL) malate salt, and mixtures thereof; and crystalline and amorphous forms of the malate salts. Also disclosed are pharmaceutical compositions comprising at least one malate salts of N-(4-{ [6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)- cyclopropane-1,l-dicarboxamide; and methods of treating cancer comprising administering at least one malate salt of N-(4-{ [6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-ffuorophenyl)cyclopropane- 1, 1 -dicarboxamide.

WO 2010/083414 A8

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(43) International Publication Date
22 July 2010 (22.07.2010)

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A61K 31/47 (2006.01)

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PCT/US2010/021194

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(25) Filing Language: English

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(30) Priority Data:
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(75) Inventors/Applicants *(for US only)*: **BROWN, Adrian, St. Clair** [GB/GB]; 67 Stour Green, Ely, Cambridgeshire CB6 2XJ (GB). **LAMB, Peter** [US/US]; 814 Mandana Blvd., Oakland, CA 94610 (US). **GALLAGHER, William, P.** [US/US]; P.O. Box 4000, Princeton, NJ 08543 (US).

(74) Agent: **BERVEN, Heidi, M.**; Honigman Miller Schwartz and Cohn LLP, 350 East Michigan Avenue, Suite 300, Kalamazoo, MI 49007 (US).

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(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

(48) Date of publication of this corrected version:
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(15) Information about Corrections:
see Notice of 17 March 2011

Previous Correction:
see Notice of 2 December 2010

(54) Title: MALATE SALT OF N- (4- { [6, 7-BIS (METHYLOXY) QUIN0LIN-4-YL] OXY}PHENYL)-N' - (4 -FLUOROPHENYL) CYCLOPROPANE-1,1-DICARBOXAMIDE, AND CRYSTALLINE FORMS THEROF FOR THE TREATMENT OF CANCER

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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PCT

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(51) International Patent Classification:
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A61K 31/517 (2006.01) *A61P 35/00* (2006.01)

(21) International Application Number:
PCT/US2010/044749

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(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
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(71) Applicant *(for all designated States except US)*: **EXELIXIS,INC** [US/US]; 210 East Grand Avenue, P.O. Box 511, South San Francisco, CA 94083-0511 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **AFTAB, Dana T.** [US/US]; 736 Tamarack Drive, San Rafael, CA 94903 (US). **MUELLER, Thomas** [DE/US]; 21030 Harrison Street, Unit #26, San Francisco, CA 94110 (US). **WEITZMAN, Aaron** [CA/US]; 492 Arboleda Drive, Los Altos, CA 94024 (US). **HOLLAND, Jaymes** [US/US]; South San Francisco, CA 94083-0511 (US).

(74) Agent: **BERVEN, Heidi M.**; Honigman Miller Schwartz and Cohn LLP, 350 East Michigan Ave., Suite 300, Kalamazoo, MI 49007-3800 (US).

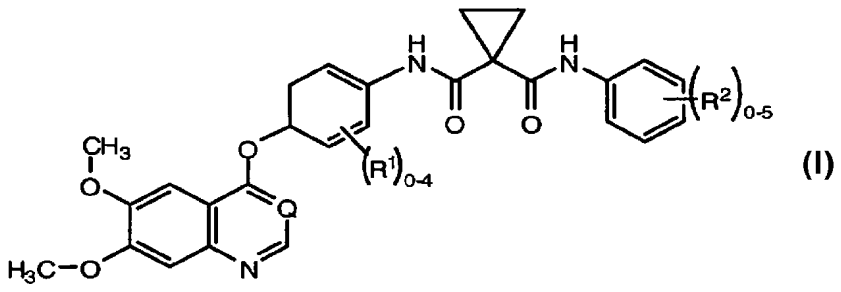
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(54) **Title**: METHODS OF USING C-MET MODULATORS



(I)

(57) **Abstract**: Methods of treating cancer by administering a compound of Formula (I), (Formula I) or a pharmaceutically acceptable salt or solvate thereof, in combination with other cancer treatments are described, wherein R^1 is halo; R^2 is halo; and Q is CH or N.

WO 2011/017639 A1

METHODS OF USING C-MET MODULATORS

FIELD OF THE INVENTION

[0001] This invention relates to methods of using c-Met modulators, and specifically c-Met modulators in combination with other anti-cancer agents and/or radiation, which can be useful for the modulation of various cellular activities and for the treatment of various diseases as described in the specification.

BACKGROUND OF THE INVENTION

[0002] Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms. One mechanism that can be exploited in cancer treatment is the modulation of protein kinase activity because signal transduction through protein kinase activation is responsible for many of the characteristics of tumor cells. Protein kinase signal transduction is of particular relevance in, for example, thyroid, gastric, head and neck, lung, breast, prostate, and colorectal cancers, as well as in the growth and proliferation of brain tumor cells.

[0003] Protein kinases can be categorized as receptor type or non-receptor type. Receptor-type tyrosine kinases are comprised of a large number of transmembrane receptors with diverse biological activity. For a detailed discussion of the receptor-type tyrosine kinases, see Plowman et al., DN&P 7(6): 334-339, 1994. Since protein kinases and their ligands play critical roles in various cellular activities, deregulation of protein kinase enzymatic activity can lead to altered cellular properties, such as uncontrolled cell growth associated with cancer. In addition to oncological indications, altered kinase signaling is implicated in numerous other pathological diseases, including, for example, immunological disorders, cardiovascular diseases, inflammatory diseases, and degenerative diseases. Therefore, protein kinases are attractive targets for small molecule drug discovery. Particularly attractive targets for small-molecule modulation with respect to antiangiogenic and antiproliferative activity include receptor type tyrosine kinases Ret, c-Met, and VEGFR2.

[0004] The kinase c-Met is the prototypic member of a subfamily of heterodimeric receptor tyrosine kinases (RTKs) which include Met, Ron and Sea. The endogenous ligand for c-Met is the hepatocyte growth factor (HGF), a potent inducer of angiogenisis. Binding of HGF to c-Met

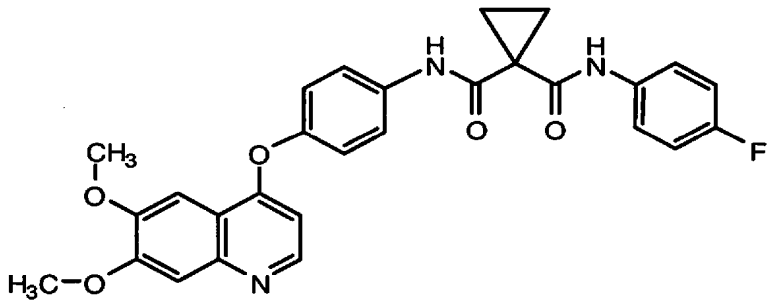
induces activation of the receptor via autophosphorylation resulting in an increase of receptor dependent signaling, which promotes cell growth and invasion. Anti-HGF antibodies or HGF antagonists have been shown to inhibit tumor metastasis in vivo (See: Maulik et al Cytokine & Growth Factor Reviews 2002 13, 41-59). c-Met, VEGFR2 and/or Ret overexpression has been demonstrated on a wide variety of tumor types including breast, colon, renal, lung, squamous cell myeloid leukemia, hemangiomas, melanomas, astrocytomas, and glioblastomas. The Ret protein is a transmembrane receptor with tyrosine kinase activity. Ret is mutated in most familial forms of medullary thyroid cancer. These mutations activate the kinase function of Ret and covert it into an oncogene product.

[0005] Inhibition of EGF, VEGF and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. Drug Disc. Technol. 2001 6, 1005-1024).Kinase KDR (refers to kinase insert domain receptor tyrosine kinase) and flt-4 (fms-like tyrosine kinase-4) are both vascular endothelial growth factor (VEGF) receptors. Inhibition of EGF, VEGF and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. Drug Disc. Technol. 2001 6, 1005-1024). EGF and VEGF receptors are desirable targets for small molecule inhibition.

[0006] Glioblastoma is the most aggressive form of primary brain tumor, with an incidence of 2.3 per 100,000 persons per year in the United Sates. The median survival time following diagnosis is 12-15 months with current standard of care involving surgery followed by radiation. It has been reported that targeting the MET pathway potentiates GBM response to gamma-radiation (Lal et al, 2005). It has also been report that MET expression correlate with high grade GBM tumors (Hirose et al, 1998) and expression of HGF and MET correlate with malignancy (Koochekpour et al, 1995; Abounader et al, 2001, Uchinokura et al, 2006). It has also been reported that the glioma derived stem cell factor induces angiogenesis within the brain. SCF and VEGF may have complementary roles in the robust angiogenic response in GBM (Sun et al, 2006).

[0007] Accordingly, small-molecule compounds that specifically inhibit, regulate and/or modulate the signal transduction of kinases, particularly including Ret, c-Met and VEGFR2 described above, are particularly desirable as a means to treat or prevent disease states associated

with abnormal cell proliferation and angiogenesis. One such small-molecule is N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, which has the chemical structure:



[0008] WO 2005/030140 describes the synthesis of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (Examples 25, 37, 38, and 48) and also discloses the therapeutic activity of this molecule to inhibit, regulate and/or modulate the signal transduction of kinases, (Assays, Table 4, entry 289). Compound (I) has been measured to have an c-Met IC_{50} value of 1.3 nanomolar (nM) and a Ret IC_{50} value of 5.2 nanomolar (nM).

[0009] Thus, finding new uses of compounds for treating diseases by using new combination therapies is desirable.

SUMMARY OF THE INVENTION

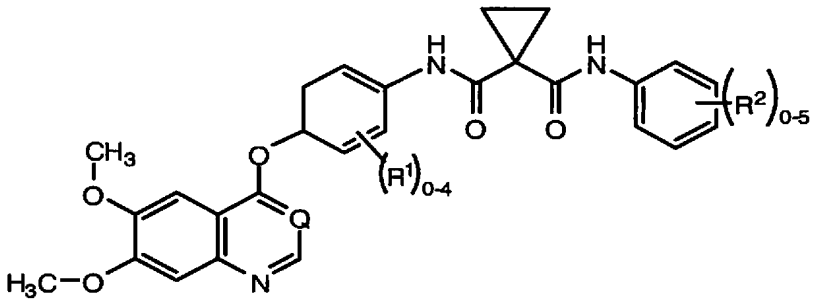
[0010] The summary of the invention only summarizes certain aspects of the invention and is not intended to be limiting in nature. These aspects and other aspects and embodiments are described more fully below. All references cited in this specification are hereby incorporated by reference in their entirety. In the event of a discrepancy between the express disclosure of this specification and the references incorporated by reference, the express disclosure of this specification shall control.

[0011] One aspect of this disclosure relates to methods of treating diseases, as defined in the detailed description herein below. These methods of treatment include administering a Compound of Formula I, wherein the compound of Formula I is as define in the detailed description of the invention, to a patient in need of the treatment, in combination with either

temozolomide (TMZ) and/or radiation therapy (RT) and optionally one or more additional treatment(s), wherein the one or more additional treatment(s) are as described in the detailed description of the invention.

DETAILED DESCRIPTION OF THE INVENTION

[0012] Aspect (I) of this disclosure relates to a method of treating a disease comprising administering to a patient in need of the treatment a compound of Formula I:



I

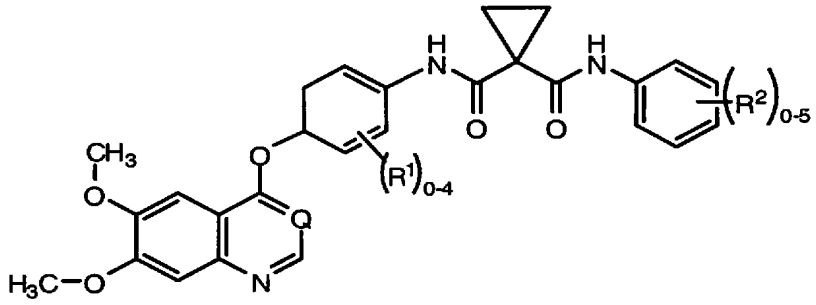
or a pharmaceutically acceptable salt thereof, in combination with temozolomide (TMZ) wherein:

R^1 is halo;

R^2 is halo; and

Q is CH or N.

[0013] Aspect (II) of this disclosure relates to a method of treating a disease comprising administering to a patient in need of the treatment a compound of Formula I:



I

or a pharmaceutically acceptable salt thereof, in combination with radiation therapy (RT) wherein:

R^1 is halo;

R^2 is halo; and

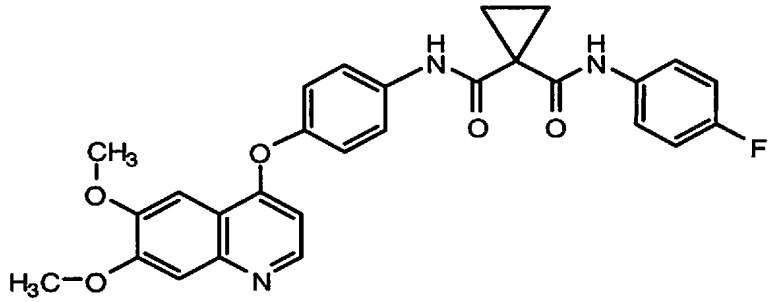
Q is CH or N.

[0014] In other embodiments of aspect (I) and Apsect (II) of this disclosure the compound of Formula I, or a pharmaceutically acceptable salt thereof, is a pharmaceutical composition which further comprises a pharmaceutically acceptable carrier, excipient, or diluent.

[0015] In other embodiments of Aspect (I), the method further comprises administereing to the patient one or more additional treatment(s), wherein the one or more treatment(s) are selected from (1) surgery, (2) one or more additional chemotherapeutic agent(s), (3) one or more hormone therapy(s), (4) one or more antibody(s), and (5) one or more immunotherapy(ies), (6) radioactive iodine therapy, and (7) radiation.

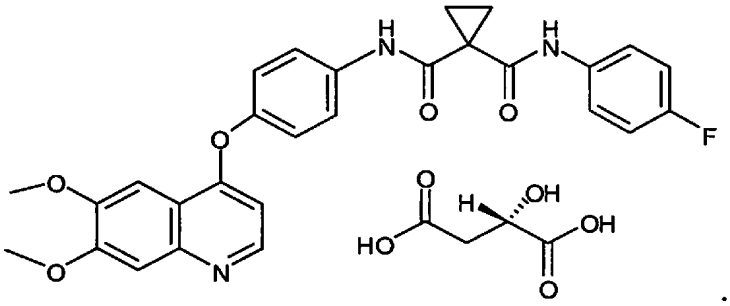
[0016] In other embodiments of Aspect (II), the method further comprises administereing to the patient one or more additional treatment(s), wherein the one or more treatment(s) are selected from (1) surgery, (2) one or more additional chemotherapeutic agent(s), (3) one or more hormone therapy(s), (4) one or more antibody(s), and (5) one or more immunotherapy(ies).

[0017] In other embodiments of Aspect (I) and Apsect (II), the compound of Formula I in any of the above embodiments is the following compound:



or a pharmaceutical salt thereof.

[0018] In other embodiments of Aspect (I) and Apsect (II), the compound of Formula I in any of the above embodiments is the following compound:



[0019] The compound of Formula (I), and all of the embodiments of the compound of Formula (I) as described herein, includes both the recited compounds as well as individual isomers and mixtures of isomers. In each instance, the compound of Formula (I) includes the pharmaceutically acceptable salts, hydrates, and/or solvates of the recited compounds and any individual isomers or mixture of isomers thereof.

Abbreviations and Definitions

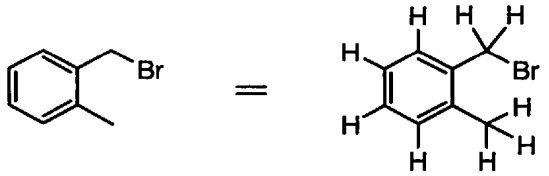
[0020] The following abbreviations and terms have the indicated meanings throughout:

Abbreviation	Meaning
Ac	acetyl
Br	broad
°C	degrees Celsius
c-	cyclo
CBZ	CarboBenZoxy = benzyloxycarbonyl
d	doublet
dd	doublet of doublet
dt	doublet of triplet
DCM	dichloromethane
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphano)ferrocene
EI	Electron Impact ionization

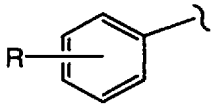
Abbreviation	Meaning
g	gram(s)
Gy	Gray unit
h or hr	hour(s)
HPLC	high pressure liquid chromatography
L	liter(s)
M	molar or molarity
m	Multiplet
mg	milligram(s)
MGMT	O^6-Methylguanine methyltransferase
MHz	megahertz (frequency)
Min	minute(s)
mL	milliliter(s)
µL	microliter(s)
µM	Micromole(s) or micromolar
mM	Millimolar
mmol	millimole(s)
mol	mole(s)
MS	mass spectral analysis
N	normal or normality
nM	Nanomolar
NMR	nuclear magnetic resonance spectroscopy
q	Quartet
RT	Radiation Therapy
s	Singlet
t or tr	Triplet
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography

[0021] The symbol "-" means a single bond, "=" means a double bond.

[0022] When chemical structures are depicted or described, unless explicitly stated otherwise, all carbons are assumed to have hydrogen substitution to conform to a valence of four. For example, in the structure on the left-hand side of the schematic below there are nine hydrogens implied. The nine hydrogens are depicted in the right-hand structure. Sometimes a particular atom in a structure is described in textual formula as having a hydrogen or hydrogens as substitution (expressly defined hydrogen), for example, $-CH_2CH_2-$. It is understood by one of ordinary skill in the art that the aforementioned descriptive techniques are common in the chemical arts to provide brevity and simplicity to description of otherwise complex structures.

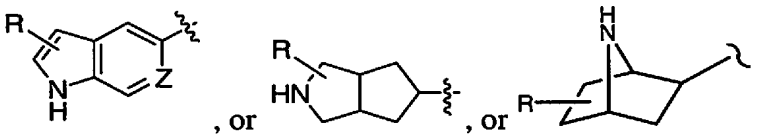


[0023] If a group "R" is depicted as "floating" on a ring system, as for example in the formula:



then, unless otherwise defined, a substituent "R" may reside on any atom of the ring system, assuming replacement of a depicted, implied, or expressly defined hydrogen from one of the ring atoms, so long as a stable structure is formed.

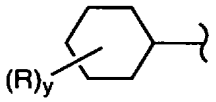
[0024] If a group "R" is depicted as floating on a fused ring system, as for example in the formulae:



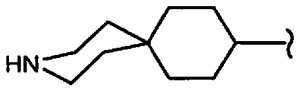
then, unless otherwise defined, a substituent "R" may reside on any atom of the fused ring system, assuming replacement of a depicted hydrogen (for example the -NH- in the formula above), implied hydrogen (for example as in the formula above, where the hydrogens are not shown but understood to be present), or expressly defined hydrogen (for example where in the formula above, "Z" equals =CH-) from one of the ring atoms, so long as a stable structure is

formed. In the example depicted, the "R" group may reside on either the 5-membered or the 6-membered ring of the fused ring system. In the formulas depicted above, there may more than one R group (R_y), wherein y is an integer of 1 or more. When y is 2, for example, then the two "R's" may reside on any two atoms of the ring system, again assuming each replaces a depicted, implied, or expressly defined hydrogen on the ring.

[0025] When a group "R" is depicted as existing on a ring system containing saturated carbons, as for example in the formula:



where, in this example, "y" can be more than one, assuming each replaces a currently depicted, implied, or expressly defined hydrogen on the ring; then, unless otherwise defined, where the resulting structure is stable, two "R's" may reside on the same carbon. A simple example is when R is a methyl group; there can exist a geminal dimethyl on a carbon of the depicted ring (an "annular" carbon). In another example, two R's on the same carbon, including that carbon, may form a ring, thus creating a spirocyclic ring (a "spirocyclyl" group) structure with the depicted ring as for example in the formula:



[0026] "Halogen" or "halo" refers to fluorine, chlorine, bromine or iodine.

[0027] "Yield" for each of the reactions described herein is expressed as a percentage of the theoretical yield.

[0028] "Cancer" refers to cellular-proliferative disease states, including but not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hanlartoma, inesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous

adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis defornians), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastorna multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma], fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; Adrenal Glands: neuroblastoma; and breast cancer. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions.

[0029] "Hormone therapy" or "hormonal therapy" includes, for example, treatment with one or more of the following: steroids (e.g. dexamethasone), finasteride, tamoxifen, and an aromatase inhibitor.

[0030] "Patient" for the purposes of the present invention includes humans and other animals, particularly mammals, and other organisms. Thus the methods are applicable to both human therapy and veterinary applications. In another embodiment the patient is a mammal, and in another embodiment the patient is human.

[0031] A "pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. It is understood that the pharmaceutically acceptable salts are non-toxic. Additional information on suitable pharmaceutically acceptable salts can be found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, which is incorporated herein by reference or S. M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977;66:1-19 both of which are incorporated herein by reference.

[0032] Examples of pharmaceutically acceptable acid addition salts include those formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; as well as organic acids such as acetic acid, trifluoroacetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, 3-(4-hydroxybenzoyl)benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, p-toluenesulfonic acid, and salicylic acid and the like.

[0033] Examples of a pharmaceutically acceptable base addition salts include those formed when an acidic proton present in the parent compound is replaced by a metal ion, such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Specific salts are the ammonium, potassium, sodium, calcium, and magnesium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include, but are not limited to, salts of primary, secondary, and *tert*iary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins. Examples of organic bases include isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol,

dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, tromethamine, *N*-methylglucamine, polyamine resins, and the like. Exemplary organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline, and caffeine.

[0034] "Platin(s)," and "platin-containing agent(s)" include, for example, cisplatin, carboplatin, and oxaliplatin.

[0035] "Prodrug" refers to compounds that are transformed (typically rapidly) *in vivo* to yield the parent compound of the above formulae, for example, by hydrolysis in blood. Common examples include, but are not limited to, ester and amide forms of a compound having an active form bearing a carboxylic acid moiety. Examples of pharmaceutically acceptable esters of the compounds of this invention include, but are not limited to, alkyl esters (for example with between about one and about six carbons) the alkyl group is a straight or branched chain. Acceptable esters also include cycloalkyl esters and arylalkyl esters such as, but not limited to benzyl. Examples of pharmaceutically acceptable amides of the compounds of this invention include, but are not limited to, primary amides, and secondary and tertiary alkyl amides (for example with between about one and about six carbons). Amides and esters of the compounds of the present invention may be prepared according to conventional methods. A thorough discussion of prodrugs is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference for all purposes.

[0036] "Taxane(s)" includes, for example, one or more of the following: Paclitaxel (Taxol®) and Docetaxel (Taxotere®).

[0037] "Therapeutically effective amount" is an amount of a compound of the invention, that when administered to a patient, ameliorates a symptom of the disease. A therapeutically effective amount is intended to include an amount of a compound alone or in combination with other active ingredients effective to modulate Ret, c-Met, and/or VEGFR2, or effective to treat or prevent cancer. The amount of a compound of the invention which constitutes a "therapeutically effective amount" will vary depending on the compound, the disease state and its severity, the age of the patient to be treated, and the like. The therapeutically effective amount can be

determined routinely by one of ordinary skill in the art having regard to their knowledge and to this disclosure.

[0038] "Topoisomerase inhibitor" includes, for example, one or more of the following: amsacrine, camptothecin, etoposide, etoposide phosphate, exatecan, irinotecan, lurtotecan, and teniposide, and topotecan.

[0039] "Treating" or "treatment" of a disease, disorder, or syndrome, as used herein, includes (i) preventing the disease, disorder, or syndrome from occurring in a human, i.e. causing the clinical symptoms of the disease, disorder, or syndrome not to develop in an animal that may be exposed to or predisposed to the disease, disorder, or syndrome but does not yet experience or display symptoms of the disease, disorder, or syndrome; (ii) inhibiting the disease, disorder, or syndrome, *i.e.*, arresting its development; and (iii) relieving the disease, disorder, or syndrome, *i.e.*, causing regression of the disease, disorder, or syndrome. As is known in the art, adjustments for systemic versus localized delivery, age, body weight, general health, sex, diet, time of administration, drug interaction and the severity of the condition may be necessary, and will be ascertainable with routine experimentation by one of ordinary skill in the art.

Additional Embodiments of the Invention

[0040] In another embodiment of Aspect (I) or Aspect (II) of this disclosure, the disease being treated is selected from astocytoma, glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components.

[0041] In another embodiment of Aspect (I) of this disclosure, the method further comprises administering radiation therapy to the patient.

[0042] In another embodiment of Aspect (I) of this disclosure, the disease is selected from astocytoma, glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendrogilial components; and the the method further comprises administering radiation therapy to the patient.

[0043] In another embodiment of Aspect (I) or Aspect (II) of this disclosure, the disease is selected from astocytoma, glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendrogilial components; and the the method further comprises administering surgury to the patient.

[0044] In another embodiment of Aspect (I) of this disclosure, the disease is selected from astocytoma, glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendrogilial components; and the the method further comprises administering radiation therapy and surgery to the patient.

[0045] Non-limiting examples of the additional chemotherapeutic agent(s) that can be used in any of the above embodiments include rapamycin, a rapamycin analogue, an alkylating agent(s), a taxane(s), and a platin(s). In chemotherapeutic agent(s) is selected from rapamycin, temozolomide, paclitaxel, docetaxel, carboplatin, cisplatin, oxaliplatin, gefitinib (Iressa®), erlotinib (Tarceva®), Zactima (ZD6474), HKI-272, pelitinib, canertinib, and lapatinib.

[0046] A non-limiting example of the antibody that can be used as the one or more additional treatments in Aspect (I) or Aspect (II) of this disclosure is panitumumab.

[0047] In another embodiment of Aspect (I) or (II) of this disclosure, the one or more additional treatments is one or more hormone therapy(s). Non-limiting examples of the hormone therapy(s) that can be used in this embodiment include tamoxifen, Toremifene (Fareston), Fulvestrant (Faslodex), Megestrol acetate (Megace), ovarian ablation, Raloxifene, a luteinizing hormone-releasing hormone (LHRH) analog (including goserelin and leuprolide), Megestrol acetate (Megace), and one or more aromatase inhibitor(s); in another embodiment, one or more of the aromatase inhibitor(s) is selected from letrozole (Femara), anastrozole (Arimidex), and exemestane (Aromasin). In another embodiment, one or more of the hormone therapy(s) is selected from tamoxifen and an aromatase inhibitor.

[0048] In another embodiment of Aspect (I) or Aspect (II) of this disclosure, the disease is an astrocytic tumor selected from astocytoma, glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components, and the one or more treatment(s) are selected from (1) surgery, (2) radiation, (3) one or more additional chemotherapeutic agent(s), (4) one or more anti-seizure agent(s), and (5) one or more agent(s) to reduce swelling. Non-limiting examples of the radiation treatment that can be used in this embodiment include external beam radiation, interstitial radiotherapy, and stereotactic radiosurgery. Non-limiting examples of the additional chemotherapeutic agent(s) that can be used in this embodiment include carmustine (BCNU), Erlotinib (Tarceva), bevacizumab, gefitinib (Iressa), rapamycin, cisplatin, BCNU, lomustine, procarbazine, and vincristine. A non-limiting examples of the antiseizure agent(s) that can be used in this embodiment is diphenylhydantoin (Dilantin). A non-limiting example of

the agent that can be used to reduce swelling in this embodiment include dexamethasone (Decadron).

[0049] In another embodiment of Aspect (I) of this disclosure, the one or more additional treatments are radiation and surgery.

[0050] In another embodiment of Aspect (I) of this disclosure, the one or more additional treatments are radiation and one or more additional chemotherapeutic agent(s).

[0051] In another embodiment of Aspect (I) or Aspect (II) of this disclosure, the one or more additional treatments are surgery and one or more additional chemotherapeutic agent(s).

[0052] In another embodiment, treatment for patients with GB comprises a (1) "concurrent phase," which is followed by a (2) "rest phase," which is followed by a (3) "maintenance phase."

[0053] The concurrent phase is followed by a (2) "rest phase which can range from about 2 weeks to about 8 weeks in duration. The rest phase is meant to allow for recovery from delayed toxicity, if present. In another embodiment, the rest phase can range from about 3 weeks to about 6 weeks in duration. In another embodiment, the rest phase is about 4 weeks in duration.

[0054] The rest phase is followed by a (3) "maintenance phase," during which patients receive active pharmaceutical ingredients for approximately twelve 28-day cycles, but can vary from about six to about twenty four 28-day cycles. In various embodiments, patients receive different amounts of the compound of Formula I at different times according to the phase of TMZ and radiation therapy.

Concurrent Phase

[0055] During the concurrent phase, the compound of Formula I, in one embodiment, can be administered to the patient concurrently with RT and TMZ for 3-12 weeks, or 4-10 weeks, or 6-7 weeks. In another embodiment, for patients having a mutation in the MGMT promoter wherein the mutated MGMT promoter is an unmethylated promoter, the compound of Formula I will be administered to the patient concurrently with RT for 6-7 weeks in the concurrent phase. The concurrent phase can range from about 3 weeks to about 12 weeks in duration. In another embodiment, the concurrent phase ranges from about 4 weeks to about 10 weeks in duration. In another embodiment, the concurrent phase ranges from about 6 weeks to about 8 weeks in duration. In another embodiment, the concurrent phase ranges from about 6 weeks to about 7 weeks in duration. During the concurrent phase, active pharmaceutical ingredients are given with (RT). In another embodiment, the active pharmaceutical ingredient(s) in the concurrent phase are TMZ and the compound of Formula I. In another embodiment, the active

pharmaceutical ingredient in the concurrent phase is TMZ provided that the compound of Formula I is at least one of the active pharmaceutical ingredients in the maintenance phase. In another embodiment, the active pharmaceutical ingredient in the concurrent phase is the compound of Formula I.

Rest Phase

[0056] During the rest phase, no RT, compounds of Formula I, or TMZ is administed to the patient. The rest phase can range from about 2 weeks to about 12 weeks. In another embodiment, the rest phase can range from about 3 weeks to about 6 weeks in duration. In another embodiment, the rest phase range is about 4 weeks in duration.

Maintenance Phase

[0057] In one embodiment of the maintenance phase, the compound of Formula I is administered to the patient. In another embodiment of the maintenance phase, temozolomide and the compound of Formula I are both administered to the patient. In another embodiment of the maintenance phase, temozolomide and the compound of Formula I are each administered to the patient for a period of time ranging from about 4 months to about 10 months. In another embodiment of the maintenance phase, temozolomide and the compound of Formula I are each administered to the patient for about 4 months. In another embodiment of the maintenance phase, temozolomide and the compound of Formula I are each administered to the patient for about 5 months. In another embodiment of the maintenance phase, temozolomide and the compound of Formula I are each administered to the patient for about 6 months. In another embodiment of the maintenance phase, temozolomide and the compound of Formula I are each administered to the patient for about 7 months. In another embodiment of the maintenance phase, temozolomide and the compound of Formula I are each administered to the patient for about 8 months. In another embodiment of the maintenance phase, temozolomide and the compound of Formula I are each administered to the patient for about 9 months. In another embodiment of the maintenance phase, temozolomide and the compound of Formula I are each administered to the patient for about 10 months. In another embodiment of the maintenance phase, the compound of Formula I is administered to the patient for period of time ranging from about 4 months to about 10 months. In another embodiment of the maintenance phase, the compound of Formula I is administered for about 4 months. In another embodiment of the maintenance phase, the

compound of Formula I is administered for about 5 months. In another embodiment of the maintenance phase, the compound of Formula I is administered for about 6 months. In another embodiment of the maintenance phase, the compound of Formula I is administered for about 7 months. In another embodiment of the maintenance phase, the compound of Formula I is administered for about 8 months. In another embodiment of the maintenance phase the compound of Formula I is administered for about 9 months. In another embodiment of the maintenance phase, the compound of Formula I is administered for 10 months.

[0058] During the maintenance phase, the compound of Formula I can be administered daily as a single oral agent as a 10-200 mg dosages (which can be in capsules or tablets). In another embodiment of the maintenance phase, the compound of Formula I can be administered daily as a single oral agent as a 25-125 mg dosage, or 25-100 mg dosage, (which can be in a capsule or tablet). Also during the maintenance phase, TMZ can be administered for 5 consecutive days and repeated every 28 days. TMZ, during the maintenance phase, can be administered to the patient as 5-300 mg dosages (which can be in capsules or tablets) to the patient.

[0059] For purposes of this disclosure, for all examples that are disclosed herein that refer to the compound of Formula I or temozolomide in dosage amounts in milligrams (mg), it is to be read as mg of the compound in question, and this dosage amount can be administered in any form, including tablet and capsule form. The examples of capsule or tablet forms, that are within the parenthesis after the dosage amounts, are non-limiting examples of how the dosages can be administered and these examples are meant to be non-limiting. For example, in the above embodiment, TMZ can be administered in other modes in addition to capsules or tablets, which are meant to be only non-limiting examples of how the dosage amount can be administered.

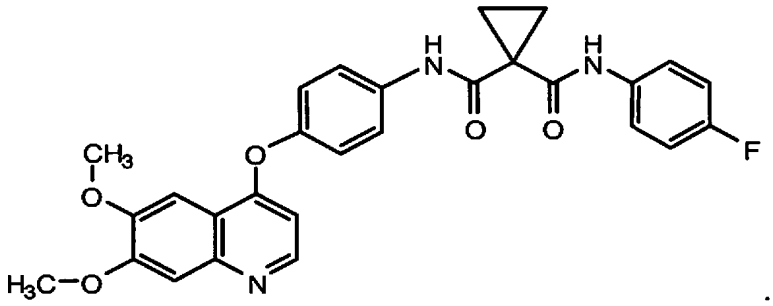
[0060] In non-limiting examples in all of the above embodiments (including the concurrent and maintenance phases), the compound of Formula I can be administered in 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, 150 mg, 155 mg, 160 mg, 165 mg, 170 mg, 175 mg, 180 mg, 185 mg, 190 mg, 195 mg, and 200 mg dosages (which can be in capsules or tablets).

[0061] In non-limiting examples in all of the above embodiments (including the concurrent and maintenance phases), TMZ can be administered in 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg,

150 mg, 155 mg, 160 mg, 165 mg, 170 mg, 175 mg, 180 mg, 185 mg, 190 mg, 195 mg, 200 mg, 205 mg, 210 mg, 215 mg, 220 mg, 225 mg, 230 mg, 235 mg, 240 mg, 245 mg, 250 mg, 255 mg, 260 mg, 265 mg, 260 mg, 275 mg, 280 mg, 285 mg, 290 mg, 295 mg, and 300 mg dosages (which can be in capsules or tablets).

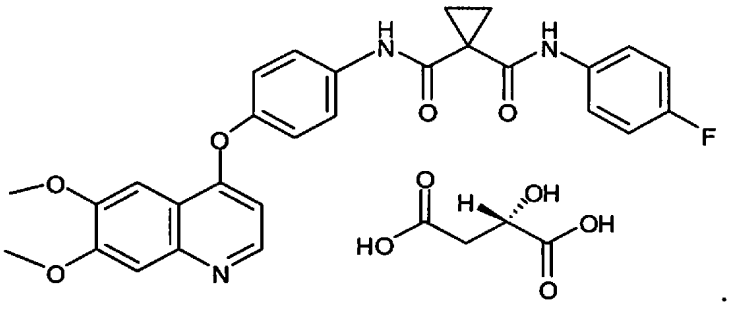
[0062] In another embodiment of Aspect (I) or Aspect (II) of this disclosure, the concurrent phase comprises administereing radiation and the compound of Formula I to the patient; the rest phase comprises not administering the compound of Formula I or radiation to the patient; and the maintenance phase comprises administereing the compound of Formula I to the patient. In one subembodiment of this embodiment, the concurrent phase can be 7-8 weeks in duration, the rest phase can be about 4 weeks in duration; and the maintence phase is of a duration sufficient slow down the cancer growth. In another subembodiment of this embodiment, the compound of Formula I is administered to the patient in 25-100 mg dosages, or 25-125 mg dosages, (which can be in capsules or tablets) daily during the concurrent phase; TMZ is administered to the patient in 5-180 mg dosages (which can be in capsules or tablets) daily to the patient during the concurrent phase; RT is administered to the patient during the concurrent phase using 1.8-2 Gy/fraction, daily for 5 days/week for a total dose of up to 60 Gy; the compound of Formula I is administered to the patient in 25-100 mg dosages, or 25-125 mg dosages, (which can be in capsules or tablets) daily during the maintenance phase; and TMZ is administered to the patient in 5-180 mg dosages (which can be in capsules or tablets) for 5 consecutive days and repeated every 28 days until the cancer growth is slowed down.

[0063] In other embodiments of any of the above embodiments of Aspect (I) and Aspect (II), the Compound of Formula I is the following compound:



or a pharmaceutical salt thereof.

[0064] In another embodiment, the compound of Formula I is the (L)-malate salt form of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide having the following structure:



General Administration

[0065] In one aspect, the invention provides pharmaceutical compositions comprising a compound of Formula I as described above and a pharmaceutically acceptable carrier, excipient, or diluent. In certain other embodiments, administration is by the oral route. Administration of the compound of Formula I, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration or agents for serving similar utilities. Thus, administration can be, for example, orally, nasally, parenterally (intravenous, intramuscular, or subcutaneous), topically, transdermally, intravaginally, intravesically, intracistemally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin dosages (which can be in capsules or tablets), powders, solutions, suspensions, or aerosols, or the like, specifically in unit dosage forms suitable for simple administration of precise dosages.

[0066] The compositions will include a conventional pharmaceutical carrier or excipient and a compound of Formula I as the/an active agent, and, in addition, may include carriers and adjuvants, etc.

[0067] Adjuvants include preserving, wetting, suspending, sweetening, flavoring, perfuming, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars,

sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

[0068] If desired, a pharmaceutical composition of the compound of Formula I may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, antioxidants, and the like, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, butylalted hydroxytoluene, etc.

[0069] The choice of formulation depends on various factors such as the mode of drug administration (e.g., for oral administration, formulations in the form of tablets, pills or capsules) and the bioavailability of the drug substance. Recently, pharmaceutical formulations have been developed especially for drugs that show poor bioavailability based upon the principle that bioavailability can be increased by increasing the surface area i.e., decreasing particle size. For example, U.S. Pat. No. 4,107,288 describes a pharmaceutical formulation having particles in the size range from 10 to 1,000 nm in which the active material is supported on a crosslinked matrix of macromolecules. U.S. Pat. No. 5,145,684 describes the production of a pharmaceutical formulation in which the drug substance is pulverized to nanoparticles (average particle size of 400 nm) in the presence of a surface modifier and then dispersed in a liquid medium to give a pharmaceutical formulation that exhibits remarkably high bioavailability.

[0070] Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

[0071] One specific route of administration is oral, using a convenient daily dosage regimen that can be adjusted according to the degree of severity of the disease-state to be treated.

[0072] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b)

binders, as for example, cellulose derivatives, starch, alignates, gelatin, polyvinylpyrrolidone, sucrose, and gum acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, croscarmellose sodium, complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, magnesium stearate and the like (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

[0073] Solid dosage forms as described above can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain pacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedded compositions that can be used are polymeric substances and waxes. The active compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

[0074] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. Such dosage forms are prepared, for example, by dissolving, dispersing, etc., the compound of Formula I, or a pharmaceutically acceptable salt thereof, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like; solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide; oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols and fatty acid esters of sorbitan; or mixtures of these substances, and the like, to thereby form a solution or suspension.

[0075] Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

[0076] Compositions for rectal administrations are, for example, suppositories that can be prepared by mixing the compound of Formula I with, for example, suitable non-irritating

excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt while in a suitable body cavity and release the active component therein.

[0077] Dosage forms for topical administration of the compound of Formula I include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalmic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this dislcosure.

[0078] Compressed gases may be used to disperse the compound of Formula I in aerosol form. Inert gases suitable for this purpose are nitrogen, carbon dioxide, etc.

[0079] Generally, depending on the intended mode of administration, the pharmaceutically acceptable compositions will contain about 1% to about 99% by weight of a compound(s) of Formula I, or a pharmaceutically acceptable salt thereof, and 99% to 1% by weight of a suitable pharmaceutical excipient. In one example, the composition will be between about 5% and about 75% by weight of a compound(s) of Formula I, or a pharmaceutically acceptable salt thereof, with the rest being suitable pharmaceutical excipients.

[0080] Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pa., 1990). The composition to be administered will, in any event, contain a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for treatment of a disease-state in accordance with the teachings of this disclosure.

[0081] The compounds of this disclosure, or their pharmaceutically acceptable salts or solvates, are administered in a therapeutically effective amount which will vary depending upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of the compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular disease-states, and the host undergoing therapy. The compound of Formula I can be administered to a patient at dosage levels in the range of about 0.1 to about 1,000 mg per day. For a normal human adult having a body weight of about 70 kilograms, a dosage in the range of about 0.01 to about 100 mg per kilogram of body weight per day is an example. The specific dosage used, however, can vary. For example, the dosage can depend on a number of factors

including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well known to one of ordinary skill in the art.

[0082] If formulated as a fixed dose, such combination products employ the compound of Formula I within the dosage range described above and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of Formula I may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

General Synthesis

[0083] Compounds of this invention can be made by the synthetic procedures described below. These procdures are merely illustrative of some methods by which the compounds of Formula I can be synthesized, and various modifications to these procudures can be made. The starting materials and the intermediates of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

[0084] The disclosure is further illustrated by the following examples, which are not to be construed as limiting the disclosure in scope or spirit to the specific procedures described in them.

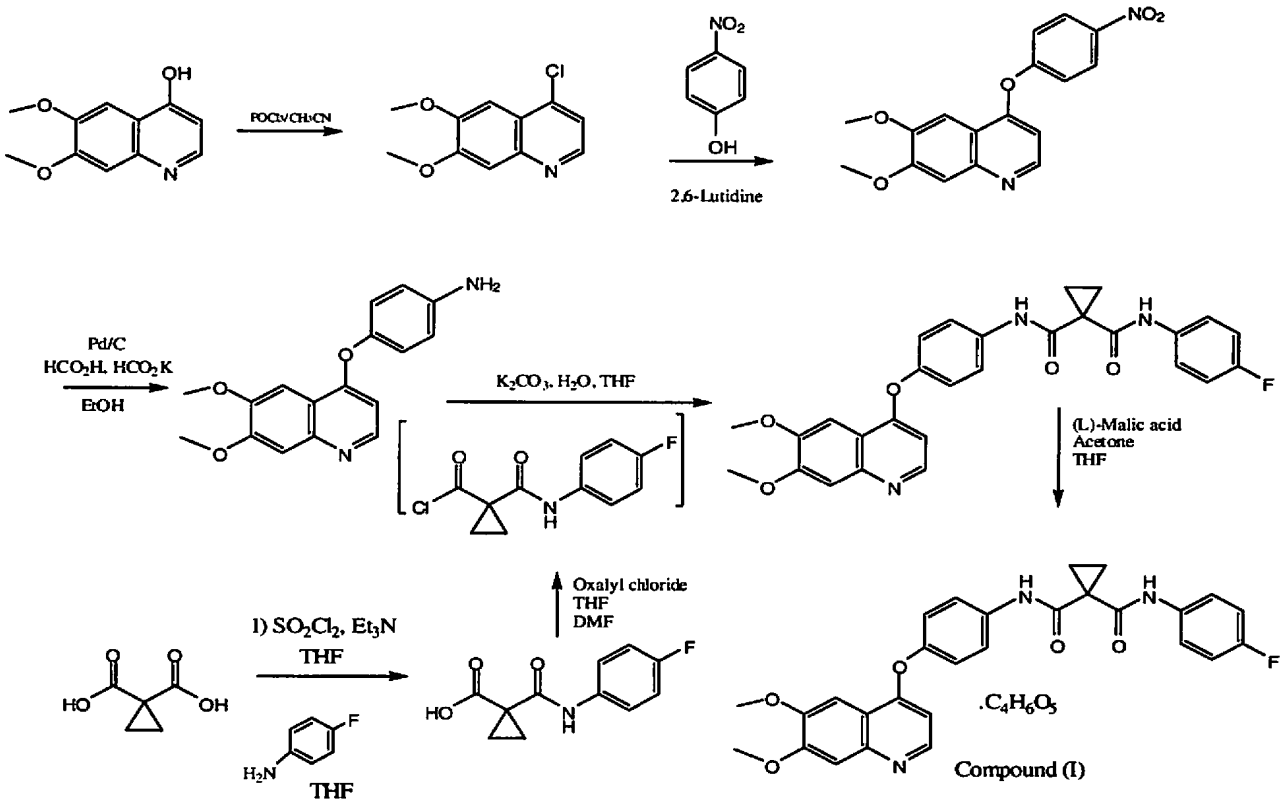
EXAMPLES

Example 1A

Preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof.

[0085] A synthetic route that has been used for the preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof is depicted in Figure 1:

FIGURE 1



[0086] The process above is described in more detail below.

Preparation of 4–Chloro–6,7–dimethoxy–quinoline

[0087] A reactor was charged sequentially with 6,7–dimethoxy–quinoline–4–ol (10.0 kg) and acetonitrile (64.0 L). The resulting mixture was heated to approximately 65°C and phosphorus oxychloride ($POCl_3$, 50.0 kg) was added. After the addition of $POCl_3$, the temperature of the reaction mixture was raised to approximately 80°C. The reaction was deemed complete (approximately 9.0 hours) when <2% of the starting material remained (in process high-performance liquid chromotography [HPLC] analysis). The reaction mixture was cooled to approximately 10°C and then quenched into a chilled solution of dichloromethane (DCM, 238.0 kg), 30% NH_4OH (135.0 kg), and ice (440.0 kg). The resulting mixture was warmed to approximately 14°C, and phases were separated. The organic phase was washed with water (40.0 kg) and concentrated by vacuum distillation with the removal of solvent (approximately 190.0 kg). Methyl-t-butyl ether (MTBE, 50.0 kg) was added to the batch, and the mixture was cooled to approximately 10°C, during which time the product crystallized out. The solids were

recovered by centrifugation, washed with n heptane (20.0 kg), and dried at approximately 40°C to afford the title compound (8.0 kg).

Preparation of 6,7–dimethyl–4–(4-nitro–phenoxy)–quinoline

[0088] A reactor was sequentially charged with 4–chloro–6,7–dimethoxy–quinoline (8.0 kg), 4 nitrophenol (7.0 kg), 4 dimethylaminopyridine (0.9 kg), and 2,6 lutidine (40.0 kg). The reactor contents were heated to approximately 147°C. When the reaction was complete (<5% starting material remaining as determined by in process HPLC analysis, approximately 20 hours), the reactor contents were allowed to cool to approximately 25°C. Methanol (26.0 kg) was added, followed by potassium carbonate (3.0 kg) dissolved in water (50.0 kg). The reactor contents were stirred for approximately 2 hours. The resulting solid precipitate was filtered, washed with water (67.0 kg), and dried at 25°C for approximately 12 hours to afford the title compound (4.0 kg).

Preparation of 4–(6,7 –dimethoxy–quinoline–4–yloxy)–phenylamine

[0089] A solution containing potassium formate (5.0 kg), formic acid (3.0 kg), and water (16.0 kg) was added to a mixture of 6,7-dimethoxy–4–(4-nitro–phenoxy)–quinoline (4.0 kg), 10% palladium on carbon (50% water wet, 0.4 kg) in tetrahydrofuran (40.0 kg) that had been heated to approximately 60°C. The addition was carried out such that the temperature of the reaction mixture remained approximately 60°C. When the reaction was deemed complete as determined using in-process HPLC analysis (<2% starting material remaining, typically 1 5 hours), the reactor contents were filtered. The filtrate was concentrated by vacuum distillation at approximately 35°C to half of its original volume, which resulted in the precipitation of the product. The product was recovered by filtration, washed with water (12.0 kg), and dried under vacuum at approximately 50°C to afford the title compound (3.0 kg).

Preparation of 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid

[0090] Triethylamine (8.0 kg) was added to a cooled (approximately 4°C) solution of commercially available cyclopropane–1,1–dicarboxylic acid (2 1, 10.0 kg) in THF (63.0 kg) at a rate such that the batch temperature did not exceed 10°C. The solution was stirred for approximately 30 minutes, and then thionyl chloride (9.0 kg) was added, keeping the batch temperature below 10°C. When the addition was complete, a solution of 4–fluoroaniline (9.0 kg) in THF (25.0 kg) was added at a rate such that the batch temperature did not exceed 10°C. The mixture was stirred for approximately 4 hours and then diluted with isopropyl acetate (87.0 kg).

This solution was washed sequentially with aqueous sodium hydroxide (2.0 kg dissolved in 50.0 L of water), water (40.0 L), and aqueous sodium chloride (10.0 kg dissolved in 40.0 L of water). The organic solution was concentrated by vacuum distillation followed by the addition of heptane, which resulted in the precipitation of solid. The solid was recovered by centrifugation and then dried at approximately 35°C under vacuum to afford the title compound. (10.0 kg).

Preparation of 1–(4–Fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride

[0091] Oxalyl chloride (1.0 kg) was added to a solution of 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid (2.0 kg) in a mixture of THF (11 kg) and N, N-dimethylformamide (DMF; 0.02 kg) at a rate such that the batch temperature did not exceed 30°C. This solution was used in the next step without further processing.

Preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

[0092] The solution from the previous step containing 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride was added to a mixture of 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (3.0 kg) and potassium carbonate (4.0 kg) in THF (27.0 kg) and water (13.0 kg) at a rate such that the batch temperature did not exceed 30°C. When the reaction was complete (in typically 10 minutes), water (74.0 kg) was added. The mixture was stirred at 15–30°C for approximately 10 hours, which resulted in the precipitation of the product. The product was recovered by filtration, washed with a pre made solution of THF (11.0 kg) and water (24.0 kg), and dried at approximately 65°C under vacuum for approximately 12 hours to afford the title compound (free base, 5.0 kg). ^{1}H NMR (400 MHz, d_6-DMSO): δ 10.2 (s, 1H), 10.05 (s, 1H), 8.4 (s, 1H), 7.8 (m, 2H), 7.65 (m, 2H), 7.5 (s, 1H), 7.35 (s, 1H), 7.25 (m, 2H), 7.15(m, 2H), 6.4 (s, 1H), 4.0 (d, 6H), 1.5 (s, 4H). LC/MS: M+H= 502.

Preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (L) malate salt

[0093] A solution of L-malic acid (2.0 kg) in water (2.0 kg) was added to a solution of cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide free base (1 5, 5.0 kg) in ethanol, maintaining a batch temperature of approximately 25°C. Carbon (0.5 kg) and thiol silica (0.1 kg) were then added, and the resulting mixture was heated to approximately 78°C, at which point water (6.0 kg) was added. The reaction mixture was then filtered, followed by the addition of isopropanol (38.0 kg), and was

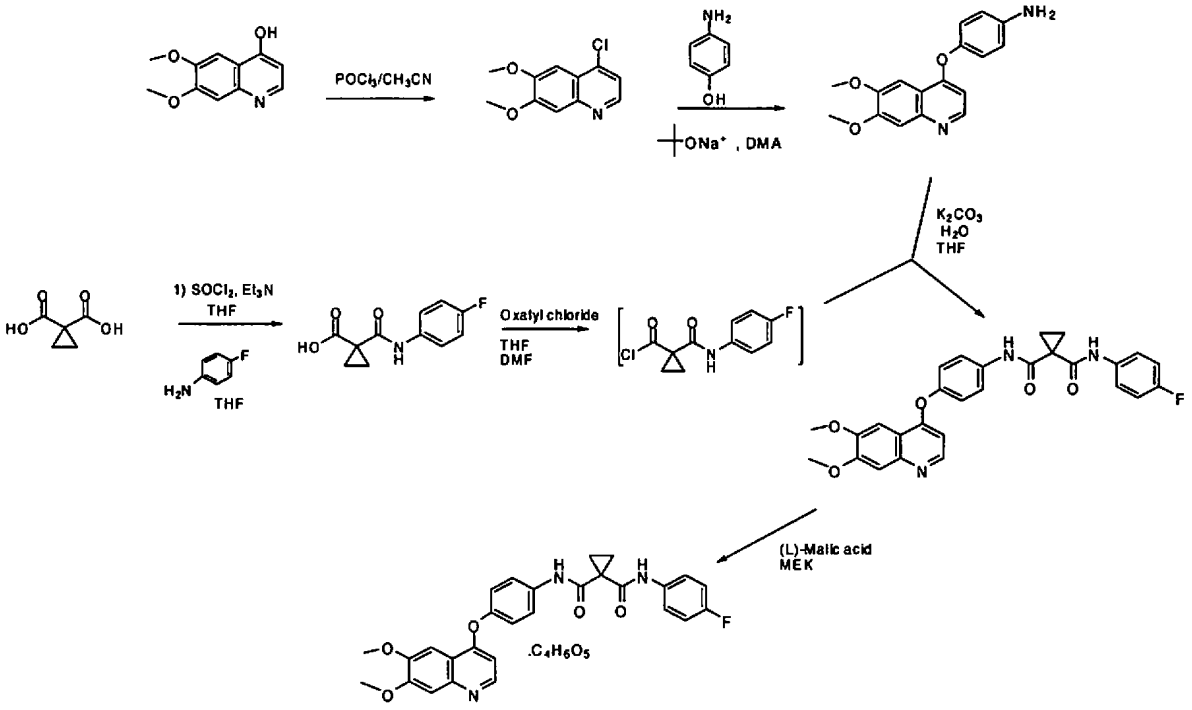
allowed to cool to approximately 25°C. The product was recovered by filtration and washed with isopropanol (20.0 kg) and dried at approximately 65°C to afford the title compound (5.0 kg).

Example 1B

Preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof.

[0094] Another synthetic route that has been used for the preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof is depicted in Figure 2:

Figure 2



Preparation of 4–Chloro–6,7–dimethoxy–quinoline

[0095] A reactor was charged sequentially with 6,7–dimethoxy–quinoline–4–ol (47.0 kg) and acetonitrile (318.8 kg). The resulting mixture was heated to approximately 60 °C and phosphorus oxychloride ($POCl_3$, 130.6 kg) was added. After the addition of $POCl_3$, the temperature of the reaction mixture was raised to approximately 77°C. The reaction was deemed complete (approximately 13 hours) when <3% of the starting material remained (in-process high-

performance liquid chromatography [HPLC] analysis). The reaction mixture was cooled to approximately 2 – 7 °C and then quenched into a chilled solution of dichloromethane (DCM, 482.8 kg), 26 % NH_4OH (251.3 kg), and water (900 L). The resulting mixture was warmed to approximately 20 – 25 °C, and phases were separated. The organic phase was filtered through a bed of AW hyflo super-cel NF (Celite; 5.4 kg) and the filter bed was washed with DCM (118.9 kg). The combined organic phase was washed with brine (282.9 kg) and mixed with water (120 L). The phases were separated and the organic phase was concentrated by vacuum distillation with the removal of solvent (approximately 95 L residual volume). DCM (686.5 kg) was charged to the reactor containing organic phase and concentrated by vacuum distillation with the removal of solvent (approximately 90 L residual volume). Methyl t-butyl ether (MTBE, 226.0 kg) was then charged and the temperature of the mixture was adjusted to – 20 to – 25 °C and held for 2.5 hours resulting in solid precipitate which was then filtered and washed with n-heptane (92.0 kg), and dried on a filter at approximately 25 °C under nitrogen to afford the title compound. (35.6 kg).

Preparation of 4–(6, 7 –Dimethoxy–quinoline–4–yloxy)–phenylamine

[0096] 4-Aminophenol (24.4 kg) dissolved in N,N-dimethylacetamide (DMA, 184.3 kg) was charged to a reactor containing 4-chloro-6,7-dimethoxyquinoline (35.3 kg), sodium t-butoxide (21.4 kg) and DMA (167.2 kg) at 20 – 25 °C. This mixture was then heated to 100 – 105°C for approximately 13 hours. After the reaction was deemed complete as determined using in-process HPLC analysis (<2% starting material remaining), the reactor contents were cooled at 15 to 20 °C and water (pre-cooled, 2 to 7 °C, 587 L) charged at a rate to maintain 15 to 30 °C temperature . The resulting solid precipitate was filtered, washed with a mixture of water (47 L) and DMA (89.1 kg) and finally with water (214 L). The filter cake was then dried at approximately 25°C on filter to yield crude 4–(6, 7 –dimethoxy–quinoline–4–yloxy)–phenylamine (59.4 kg wet, 41.6 kg dry calculated based on LOD). Crude 4–(6, 7 –dimethoxy–quinoline–4–yloxy)–phenylamine was refluxed (approximately 75 °C) in a mixture of tetrahydrofuran (THF, 211.4 kg) and DMA (108.8 kg) for approximately 1h and then cooled to 0 – 5°C and aged for approximately 1 h after which time the solid was filtered, washed with THF (147.6 kg) and dried on a filter under vacuum at approximately 25°C to yield 4–(6, 7 –dimethoxy–quinoline–4–yloxy)–phenylamine (34.0 kg).

Preparation of 1–(4–Fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid

[0097] Triethylamine (19.5 kg) was added to a cooled (approximately 5 C) solution of cyclopropane–1,1–dicarboxylic acid (24.7 kg) in THF (89.6 kg) at a rate such that the batch temperature did not exceed 5°C. The solution was stirred for approximately 1.3 h, and then thionyl chloride (23.1 kg) was added, keeping the batch temperature below 10 C. When the addition was complete, the solution was stirred for approximately 4 h keeping the temperature below 10 °C. A solution of 4–fluoroaniline (18.0 kg) in THF (33.1 kg) was then added at a rate such that the batch temperature did not exceed 10 C. The mixture was stirred for approximately 10 hours after which the reaction was deemed complete. The reaction mixture was then diluted with isopropyl acetate (218.1 kg). This solution was washed sequentially with aqueous sodium hydroxide (10.4 kg, 50 % dissolved in 119 L of water) further diluted with water (415 L), then with water (100 L) and finally with aqueous sodium chloride (20.0 kg dissolved in 100 L of water). The organic solution was concentrated by vacuum distillation (100 L residual volume) below 40 °C followed by the addition of n-heptane (171.4 kg), which resulted in the precipitation of solid. The solid was recovered by filtration and washed with n-Heptane (102.4 kg) resulting in wet crude, 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid (29.0 kg). The crude, 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid was dissolved in methanol (139.7 kg) at approximately 25°C followed by the addition of water (320 L) resulting in slurry which was recovered by filtration, washed sequentially with water (20 L) and n-heptane (103.1 kg) and then dried on the filter at approximately 25 C under nitrogen to afford the title compound (25.4 kg).

Preparation of 1–(4–Fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride

[0098] Oxalyl chloride (12.6 kg) was added to a solution of 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid (22.8 kg) in a mixture of THF (96.1 kg) and N, N-dimethylformamide (DMF; 0.23 kg) at a rate such that the batch temperature did not exceed 25 C. This solution was used in the next step without further processing.

Preparation of cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide

[0099] The solution from the previous step containing 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride was added to a mixture of compound 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (23.5 kg) and potassium carbonate (31.9 kg) in THF (245.7 kg) and water (116 L) at a rate such that the batch temperature did not exceed 30 °C. When the reaction was complete (in approximately 20 minutes), water (653 L) was added. The mixture was stirred at 20–25 C for approximately 10 hours, which resulted in the precipitation of the product.

The product was recovered by filtration, washed with a pre-made solution of THF (68.6 kg) and water (256 L), and dried first on a filter under nitrogen at approximately 25°C and then at approximately 45 C under vacuum to afford the title compound (41.0 kg, 38.1 kg, calculated based on LOD).

Preparation of cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide, (L) malate salt

[00100] Cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide (1-5; 13.3 kg), L-malic acid (4.96 kg), methyl ethyl ketone (MEK; 188.6 kg) and water (37.3 kg) were charged to a reactor and the mixture was heated to reflux (approximately 74°C) for approximately 2 h. The reactor temperature was reduced to 50 to 55°C and the reactor contents were filtered. These sequential steps described above were repeated two more times starting with similar amounts of 1-5 (13.3 kg), L-Malic acid (4.96 kg), MEK (198.6 kg) and water (37.2 kg). The combined filtrate was azeotropically dried at atmospheric pressure using MEK (1133.2 kg) (approximate residual volume 711 L; KF < 0.5 % w/w) at approximately 74°C. The temperature of the reactor contents was reduced to 20 to 25°C and held for approximately 4 hours resulting in solid precipitate which was filtered, washed with MEK (448 kg) and dried under vacuum at 50°C to afford the title compound (45.5 kg).

EXAMPLE 2

Administration of the compound of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide during the Concurrent Phase to patients.

[00101] Example 2A: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 5, 20, 100, 250, 140 and 180 mg dosages (which can be

in capsules or tablets). In another embodiment, the starting dose of TMZ is 75 mg/m^2/day with concurrent RT for 6 weeks. For purposes of this patent application, the term "m^2" refers to body surface area in patients measured in square meters. Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

[00102] Example 2B: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 5 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

[00103] Example 2C: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 50 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 5 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

[00104] Example 2D: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the

mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 75 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 5 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

[00105] Example 2E: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 5 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

[00106] Example 2F: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 100 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 20 mg dosages (which can be in capsules or tablets). Patients receive

RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

[00107] Example 2G: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 50 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 20 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

[00108] Example 2H: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 75 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 20 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

[00109] Example 2I: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-

bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 20 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

[00110] Example 2J: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 100 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 20 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

[00111] Example 2K: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 100 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

[00112] Example 2L: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent

phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 50 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 100 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

[00113] Example 2M: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 75 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 100 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

[00114] Example 2N: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 100 mg dosages (which can be in capsules or tablets).

Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

[00115] Example 2O: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 100 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 100 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

[00116] Example 2P: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 140 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

[00117] Example 2Q: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-

bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 50 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 140 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

[00118] Example 2R: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 75 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 140 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

[00119] Example 2S: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 140 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

[00120] Example 2T: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent

phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 100 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 140 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

[00121] Example 2U: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 180 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

[00122] Example 2V: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 50 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 180 mg dosages (which can be in capsules or tablets). Patients

receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

[00123] Example 2W: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 75 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 180 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

[00124] Example 2X: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 180 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

[00125] Example 2Y: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-

bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 100 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 180 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

[00126] Example 2Z: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 250 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

[00127] Example 2AA: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 50 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 250 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

[00128] Example 2AB: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent

phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 75 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 250 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

[00129] Example 2AC: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 250 mg dosages (which can be in capsules or tablets). Patients receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

[00130] Example 2AD: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is initiated at the start of a 6-7 week concurrent phase of RT and TMZ. Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 100 mg dosages (which can be in capsules or tablets). The concurrent phase is followed by a rest phase that will last for about 4 weeks. TMZ, when given, is supplied as 250 mg dosages (which can be in capsules or tablets). Patients

receive RT consisting of fractional focal irradiation administered using a 1.8-2 Gy/fraction, daily for 5 days/week for 6-7 weeks, for a total dose of up to 60 Gy.

EXAMPLE 3

Administration of the compound of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide during the Concurrent Phase to patients.

[00131] Example 3A: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 25 mg and 100 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 5, 20, 100, 250, 140, 180, and 200 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. In another embodiment, TMZ is administered in the amount of 200 mg/m^2/day given for 5 consecutive days and repeated every 28 days. For purposes of this disclosure, the term m2 is meant to mean body surface area in patients measured in square meters. The maintenance phase in Example 3A can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

[00132] Example 3B: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 25 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 5 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in

Example 3B can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

[00133] Example 3C: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 50 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 5 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3C can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

[00134] Example 3D: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 75 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 5 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3D can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

[00135] Example 3E: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 100 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the

mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 5 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3E can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

[00136] Example 3F: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 25 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 20 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3F can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

[00137] Example 3G: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 50 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 20 mg dosages (which can be in capsules

or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3G can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 82AD.

[00138] Example 3H: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 75 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 20 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3H can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

[00139] Example 3I: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 100 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 20 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3I can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

[00140] Example 3J: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 25 mg dosages (which can be

in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 100 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3J can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

[00141] Example 3K: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 50 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 100 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3K can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

[00142] Example 3L: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 75 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in

capsules or tablets). TMZ, when given, is supplied as 100 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3L can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

[00143] Example 3M: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 100 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 100 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3M can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

[00144] Example 3N: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 25 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 140 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3N can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

[00145] Example 3O: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 50 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 140 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3O can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

[00146] Example 3P: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 75 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 140 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3P can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

[00147] Example 3Q: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 100 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-

bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 140 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3Q can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

[00148] Example 3R: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 25 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 180 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3R can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

[00149] Example 3S: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 50 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 180 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3S can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E,

2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

[00150] Example 3T: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 75 mg dosages (which can be in a capsule or tablet). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 180 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3T can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

[00151] Example 3U: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 100 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 180 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3U can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

[00152] Example 3V: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 25 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead

receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied in doses of 200 mg/m^2/day given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3V can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

[00153] Example 3W: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 50 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied in doses of 200 mg/m^2/day given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3W can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

[00154] Example 3X: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 75 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied in doses of 200 mg/m^2/day given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3X can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

[00155] Example 3Y: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 100 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied in doses of 200 mg/m^2/day given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3Y can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

[00156] Example 3Z: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 25 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 250 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3Z can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

[00157] Example 3AA: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 50 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 250 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3AA can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

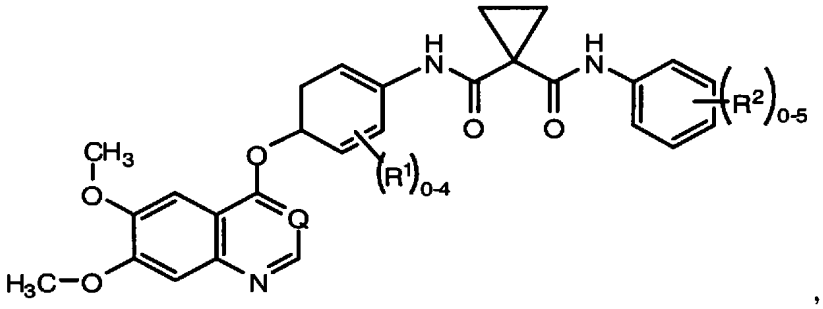
[00158] Example 3AB: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 75 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied in doses of 200 mg/m^2/day given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3AB can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

[00159] Example 3AC: N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as 100 mg dosages (which can be in capsules or tablets). Some patients that have a mutation in the MGMT promoter, wherein the mutated MGMT promoter is an unmethylated promoter, may not receive TMZ and instead receive N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a single agent in combination with RT. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is administered as a single oral agent supplied as 25 mg and 100 mg dosages (which can be in capsules or tablets). TMZ, when given, is supplied as 250 mg dosages (which can be in capsules or tablets) given for 5 consecutive days and repeated every 28 days. The maintenance phase in Example 3AC can be combined with the concurrent phase of any of Examples 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2L, 2M, 2N, 2O, 2P, 2Q, 2R, 2S, 2T, 2U, 2V, 2W, 2X, 2Y, 2Z, 2AA, 2AB, 2AC and 2AD.

[00160] The foregoing disclosure has been described in some detail by way of illustration and example, for purposes of clarity and understanding. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications can be made while remaining within the spirit and scope of the invention. It will be obvious to one of skill in the art that changes and modifications can be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

What is claimed is:

1. A method of treating cancer, wherein the method comprises administering to a patient in need of the treatment a compound of Formula I:



I

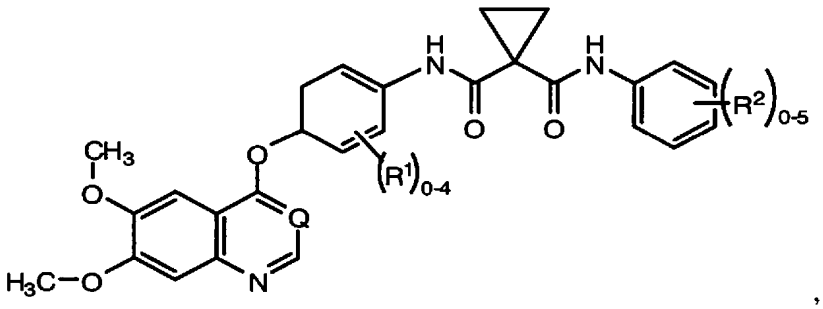
or a pharmaceutically acceptable salt thereof, in combination with temozolomide (TMZ) wherein:

R^1 is halo;

R^2 is halo; and

Q is CH or N.

2. A method of treating cancer, wherein the method comprises administering to a patient in need of the treatment a compound of Formula I:



I

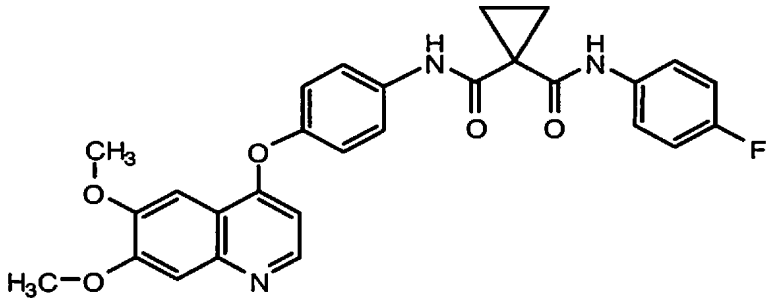
or a pharmaceutically acceptable salt thereof, in combination with radiation therapy (RT) wherein:

R^1 is halo;

R^2 is halo; and

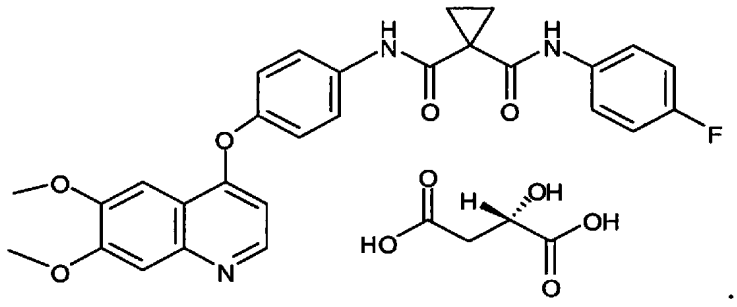
Q is CH or N.

3. The method according to any of claims 1-2, wherein the compound of Formula I is represented by the following structure:



or a pharmaceutically acceptable salt thereof.

4. The method according to any one of claims 1-2, wherein the compound of Formula I is represented by the following structure:



5. The method according to any one of claims 1-3, wherein the the compound of Formula I, or a pharmaceutically acceptable salt thereof, further comprises a pharmaceutically acceptable carrier, excipient, or diluent.

6. The method according to according to any one of claims 1 and 3-5, wherein the one or more additional treatment(s) are selected from (1) surgery, (2) one or more additional chemotherapeutic agent(s), (3) one or more hormone therapy(s), (4) one or more antibody(s), (5) one or more immunotherapy(ies), (6) radioactive iodine therapy, and (7) radiation.

7. The method according to any one of claims 1 and 3-6, wherein the one or more additional treatment(s) is radiation.

8. The method according to any one of claims 1-7 comprising administering a therapeutically effective dose of compound (I) or a pharmaceutically acceptable salt thereof.

9. The method according to any one of claims 1 and 3-8 comprising administering a therapeutically effective dose of TMZ.

10. The method according to any one of claims 2-9 comprising administering a therapeutically effective dose of radiation.

11. The method according to any one of claims 1-10, where the cancer is brain cancer.

12. The method according to any one of claims 1-11, where the cancer is selected from astocytoma, glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components.

13. The method according to any one of claims 1-12, wherein the method comprises (1) a concurrent phase, (2) a rest phase and (3) a maintenance phase, wherein:

the concurrent phase comprises administereing radiation and the compound of Formula I to the patient;

the rest phase comprises not administering the compound of Formula I or radiation to the patient; and

the maintenance phase comprises administereing the compound of Formula I to the patient.

14. The method according to any one of claims 1-13, wherein the concurrent phase is 7-8 weeks in duration, and the rest phase is about 4 weeks in duration; and the maintence phase is of a duration sufficient slow down the cancer growth.

15. The method according to any one of claims 1-14, wherein the compound of Formula I is administered to the patient in 25-125 mg dosages daily during the concurrent phase; TMZ is administered to the patient in 5-180 mg dosages daily to the patient during the concurrent phase; RT is administered to the patient during the concurrent phase using 1.8-2 Gy/fraction, daily for 5 days/week for a total dose of up to 60 Gy; the compound of Formula I is administered to the patient in 25-125 mg dosages daily during the maintenance phase; and TMZ is administered to the patient in 5-180 mg dosages for 5 consecutive days and repeated every 28 days until the cancer growth is slowed down.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/044749

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/47 A61K31/517 A61K45/06 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/076415 A1 (EXELIXIS INC [US]; LAMB PETER [US]) 26 June 2008 (2008-06-26) claim 1, page 472 claims 26, 39	2,3,5-8, 10
Y	WO 2005/030140 A2 (EXELIXIS INC [US]; BANNEN LYNNE CANNE [US]; CHAN DIVA SZE-MING [US]; C) 7 April 2005 (2005-04-07) cited in the application * abstract page 157 claim 45	1-15

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 September 2010	15/09/2010

Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/044749

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2006/014420 A1 (ANGION BIOMEDICA CORP [US]; ZEMBOWER DAVID E [US]; SING JASBIR [US]; M) 9 February 2006 (2006-02-09) page 9 page 136, line 21 - line 24	1-15
Y	US 2006/199843 A1 (ZELDIS JEROME B [US]) 7 September 2006 (2006-09-07) paragraph [0203]	1-15

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2010/044749

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008076415 A1	26-06-2008	AU 2007334402 A1	26-06-2008
		CA 2671982 A1	26-06-2008
		CN 101605540 A	16-12-2009
		EP 2101759 A1	23-09-2009
		JP 2010513288 T	30-04-2010
		US 2008166359 A1	10-07-2008
WO 2005030140 A2	07-04-2005	AU 2004275842 A1	07-04-2005
		AU 2010204459 A1	19-08-2010
		AU 2010204461 A1	19-08-2010
		CA 2537812 A1	07-04-2005
		EP 1673085 A2	28-06-2006
		EP 2210607 A1	28-07-2010
		EP 2213661 A1	04-08-2010
		JP 2007506777 T	22-03-2007
		US 2009170896 A1	02-07-2009
		US 2007054928 A1	08-03-2007
		US 2007225307 A1	27-09-2007
		US 2007244116 A1	18-10-2007
		US 2009105299 A1	23-04-2009
WO 2006014420 A1	09-02-2006	AU 2005269974 A1	09-02-2006
		CA 2573103 A1	09-02-2006
		CN 101031551 A	05-09-2007
		EP 1768964 A1	04-04-2007
		JP 2008505907 T	28-02-2008
		US 2006025406 A1	02-02-2006
US 2006199843 A1	07-09-2006	NONE	

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(74) Agent: **BERVEN, Heidi, M. Ph. D.**; Honigman Miller Schwartz and Cohn LLP, 350 East Michigan Ave., Suite 300, Kalamazoo, MI 49007-3800 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

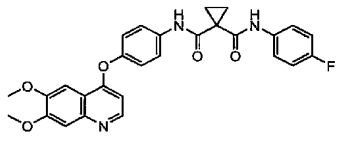
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) Title: C-MET MODULATOR PHARMACEUTICAL COMPOSITIONS



Compound I

(57) Abstract: Pharmaceutical compositions and unit dosage forms comprising Compound (I) are disclosed.

WO 2012/009722 A1

C-MET MODULATOR PHARMACEUTICAL COMPOSITIONS

Cross-Reference to Related Applications

[0001] This application claims priority to U.S. Application Serial Number 61/365,253, filed July 16, 2010, and Application Serial Number 61/370,843, filed August 5, 2010, the entire contents of each of which are incorporated herein by reference.

Field of the Invention

[0002] Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms. One mechanism that can be exploited in cancer treatment is the modulation of protein kinase activity. Signal transduction through protein kinase activation is responsible for many of the characteristics of tumor cells. Protein kinase signal transduction is particularly relevant in, for example, renal cancer, gastric cancer, head and neck cancers, lung cancer, breast cancer, prostate cancer, colorectal cancers, and hepatocellular carcinoma, as well as in the growth and proliferation of brain tumor cells.

[0003] Protein kinases can be categorized as receptor type or non-receptor type. Receptor-type tyrosine kinases are comprised of a large number of transmembrane receptors with diverse biological activity. For a detailed discussion of the receptor-type tyrosine kinases, see Plowman et al., DN&P 7(6): 334-339, 1994. Since protein kinases and their ligands play critical roles in various cellular activities, deregulation of protein kinase enzymatic activity can lead to altered cellular properties, such as uncontrolled cell growth that is associated with cancer. In addition to oncological indications, altered kinase signaling is implicated in numerous other pathological diseases, including, for example, immunological disorders, cardiovascular diseases, inflammatory diseases, and degenerative diseases. Protein kinases are therefore attractive targets for small molecule drug discovery. Particularly attractive targets for small-molecule modulation with respect to antiangiogenic and antiproliferative activity include receptor type tyrosine kinases c-Met, KDR, c-Kit, Axl, flt-3, and flt-4.

[0004] The kinase c-Met is the prototypic member of a subfamily of heterodimeric receptor tyrosine kinases (RTKs), which include Met, Ron, and Sea. The endogenous ligand for c-Met is the hepatocyte growth factor (HGF), a potent inducer of angiogenesis. Binding of HGF to c-Met induces activation of the receptor via autophosphorylation resulting in an increase of receptor dependent signaling, which promotes cell growth and invasion. Anti-HGF antibodies or HGF antagonists have been shown to inhibit tumor metastasis *in vivo* (See

Maulik et al Cytokine & Growth Factor Reviews 2002 13, 41-59). c-Met overexpression has been demonstrated on a wide variety of tumor types, including breast, colon, renal, lung, squamous cell myeloid leukemia, hemangiomas, melanomas, astrocytomas, and glioblastomas. Additionally, activating mutations in the kinase domain of c-Met have been identified in hereditary and sporadic renal papilloma and squamous cell carcinoma. (See, e.g., Maulik et al., Cytokine & growth Factor reviews 2002 13, 41-59; Longati et al., Curr Drug Targets 2001, 2, 41-55; Funakoshi et al., Clinica Chimica Acta 2003 1-23).

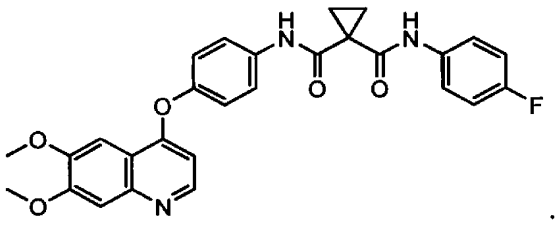
[0005] Inhibition of epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), and ephrin signal transduction will prevent cell proliferation and angiogenesis, both of which are key cellular processes needed for tumor growth and survival (Matter A., Drug Disc. Technol. 2001 6, 1005-1024). Kinase KDR (refers to kinase insert domain receptor tyrosine kinase) and flt-4 (fms-like tyrosine kinase-4) are both VEGF receptors. EGF and VEGF receptors are desirable targets for small molecule inhibition. All members of the VEGF family stimulate cellular responses by binding to tyrosine kinase receptors (the VEGFRs) on the cell surface, which causes them to dimerize and become activated through transphosphorylation. The VEGF receptors have an extracellular portion with immunoglobulin-like domains, a single transmembrane spanning region, and an intracellular portion containing a split tyrosine-kinase domain. VEGF binds to VEGFR-1 and VEGFR-2. VEGFR-2 is known to mediate almost all of the known cellular responses to VEGF.

[0006] Kinase c-Kit (also called stem cell factor receptor or steel factor receptor) is a type 3 receptor tyrosine kinase (RTK) that belongs to the platelet-derived growth factor receptor subfamily. Overexpression of c-Kit and c-Kit ligand has been described in variety of human diseases, including human gastrointestinal stromal tumors, mastocytosis, germ cell tumors, acute myeloid leukemia (AML), NK lymphoma, small-cell lung cancer, neuroblastomas, gynecological tumors, and colon carcinoma. Moreover, elevated expression of c-Kit may also relate to the development of neoplasia associated with neurofibromatosis type 1 (NF-1), mesenchymal tumors GISTs, and mast cell disease, as well as other disorders associated with activated c-Kit.

[0007] Kinase Flt-3 (fms-like tyrosine kinase-3) is constitutively activated via mutation, either in the juxtamembrane region or in the activation loop of the kinase domain, in a large proportion of patients with AML (acute myeloid leukemia) (See Reilly, Leuk. Lymphoma, 2003, 44: 1-7).

[0008] Accordingly, small-molecule compounds that specifically inhibit, regulate, and/or modulate the signal transduction of kinases, including c-Met, VEGFR2, KDR, c-Kit, Axl, flt-

3, and flt-4, are particularly desirable as a means to treat or prevent disease states that are associated with abnormal cell proliferation and angiogenesis. One such small-molecule is Compound I, know also by its chemical name N-[4-[(6,7-Dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide which has the following chemical structure.



I

[0009] Compound I is disclosed and claimed in WO2005/030140, the entire contents of which is herein incorporated by reference. WO2005/030140 describes the synthesis of compound I (Table 2, Compound I2, Example 48) and discloses the therapeutic activity of this molecule to inhibit, regulate, and/or modulate the signal transduction of kinases (Assays, Table 4, entry 289). Compound I may be used as the malate salt.

[0010] Although therapeutic efficacy is the primary concern for a therapeutic agent, the pharmaceutical composition can be equally important to its development. Generally, drug developers endeavor to discover a pharmaceutical composition that possesses desirable properties, such as satisfactory water-solubility (including rate of dissolution), storage stability, hygroscopicity, and reproducibility, all of which can impact the processability, manufacture, and/or bioavailability of the drug. Accordingly, discovery of pharmaceutical compositions that possess some or all of these desired properties is vital to drug development.

Summary of the Invention

[0011] These and other needs are met by the present disclosure, which is directed to a pharmaceutical composition comprising Compound I as provided in Table 1.

Table 1

Ingredient	(% w/w)
Compound I	31.68
Microcrystalline Cellulose	38.85
Lactose anhydrous	19.42
Hydroxypropyl Cellulose	3.00
Croscarmellose Sodium	3.00
Total Intra-granular	**95.95**
Silicon dioxide, Colloidal	0.30
Croscarmellose Sodium	3.00
Magnesium Stearate	0.75
Total	**100.00**

[0012] The disclosure is also directed to a pharmaceutical composition comprising Compound I as provided in Table 2.

Table 2

Ingredient	(% w/w)
Compound I	25.0-33.3
Microcrystalline Cellulose	q.s
Hydroxypropyl Cellulose	3
Poloxamer	0-3
Croscarmellose Sodium	6.0
Colloidal Silicon Dioxide	0.5
Magnesium Stearate	0.5-1.0
Total	100

[0013] The disclosure is further directed to a pharmaceutical composition comprising Compound I as provided in Table 3.

Table 3

Ingredient	**Theoretical Quantity (mg/unit dose)**
Compound I	100.0
Microcrystalline Cellulose PH-102	155.4
Lactose Anhydrous 60M	77.7
Hydroxypropyl Cellulose, EXF	12.0
Croscarmellose Sodium	24
Colloidal Silicon Dioxide	1.2
Magnesium Stearate (Non-Bovine)	3.0
Opadry Yellow	16.0
Total	**416**

[0014] In one aspect, Compound I is present in Tables 1, 2, and 3 as the L-malate salt.

[0015] The disclosure is also directed to a process of preparing a pharmaceutical composition according to Tables 1, 2, or 3.

[0016] The disclosure is further directed to a method for treating cancer, comprising administering to a patient in need of such treatment a pharmaceutical composition according to Tables 1, 2, or 3. The disclosure is also directed to a method for treating cancer, comprising administering to a patient in need of such treatment a pharmaceutical composition according to Tables 1, 2, or 3 in combination with another therapeutic agent.

[0017] In these and other treatment aspects, the cancers to be treated include the cancers disclosed in WO2005/030140, including pancreatic cancer, kidney cancer, liver cancer, prostate cancer, gastric cancer, gastroesophageal cancer, melanoma, lung cancer, breast cancer, thyroid cancer, and astrocytic tumors. More particularly, the cancers include pancreatic cancer, hepatocellular carcinoma (HCC), renal cell carcinoma, castration-resistant prostate cancer (CRPC), gastric or gastroesophageal junction cancer, melanoma, small cell lung cancer (SCLC), ovarian cancer, primary peritoneal or fallopian tube carcinoma, estrogen receptor positive breast cancer, estrogen receptor/progesterone receptor/HER2-negative (triple-negative) breast cancer, inflammatory (regardless of receptor status) breast cancer histology, non-small cell lung cancer (NSCLC), and medullary thyroid cancer.

Detailed Description

[0018] The disclosure is directed to a pharmaceutical formulation comprising Compound I and pharmaceutically acceptable filler, binder, disintegrant, glidant, and lubricant, and optionally a film coating material, each of which are described in greater detail in the following paragraphs. Examples of pharmaceutically acceptable fillers, binders, disintegrants, glidants, lubricants, and film coatings are set forth below and are described in more detail in the Handbook of Pharmaceutical Excipients, Second Edition, Ed. A. Wade and P. J. Weller, 1994, The Pharmaceutical Press, London, England. The term excipient as used herein refers to inert materials which impart satisfactory processing and compression characteristics into the formulation or impart desired physical characteristics to the finished table.

Compound I Pharmaceutical Composition

[0019] The Compound I pharmaceutical composition is a tablet comprising Compound I and excipients selected from the group consisting of a filler, a binder, a disintegrant, a glidant, and a lubricant, and optionally may be coated or uncoated.

Compound I

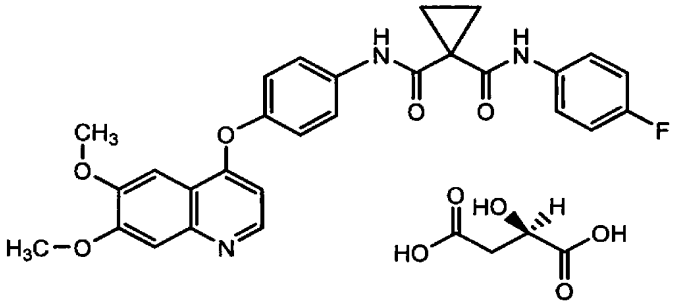
[0020] In one embodiment, the pharmaceutical composition comprises Compound I as the free base.

[0021] In another embodiment, the pharmaceutical composition comprises Compound I as a hydrate.

[0022] In another embodiment, the pharmaceutical composition comprises Compound I as a salt.

[0023] In another embodiment, the salt of Compound I is the malate salt.

[0024] In another embodiment, the malate salt is the L-malate salt of Compound I, which has the following structure.



Compound I, L-Malate Salt

[0025] In a further embodiment, the malate salt is the D-malate salt. In a further embodiment, the malate salt is the D,L-malate salt.

[0026] The malate salts of Compound I, particularly the L malate salt, have a preferred combination of pharmaceutical properties for development. Under the conditions of 25 °C/60 percent relative humidity (RH) and 40 °C/60 percent RH, the L-malate salt of Compound I showed no change in assay, purity, moisture, and dissolution. The DSC/TGA showed the L-malate salt of Compound I to be stable up to 185 °C. No solvent losses were observed. The uptake of water by the L-malate salt was reversible with a slight hysteresis. The amount of water taken up was calculated at about 0.60 weight percent at 90 percent RH. The L-malate salt was synthesized with good yield and purity greater than 90 percent and had sufficient solubility for use in a pharmaceutical composition. The amount of water associated with this salt was calculated at about 0.5 weight percent by Karl Fischer analysis and correlates with TGA and GVS analysis.

[0027] The L-malate salt of Compound I itself, and separately its crystalline and amorphous forms, exhibit beneficial properties over the free base and the other salts of Compound I. For example, the hydrochloride salt of Compound I exhibits undesirable moisture sensitivity, changing phase upon exposure to high humidity (75 percent RH) and high temperature (40°C). The maleate salt had low solubility. The tartrate salt had low crystallinity and low solubility. The phosphate salt exhibited an 8 percent weight gain due to absorption of H_2O, the highest among the salts tested.

[0028] The water solubility of the various salts was determined using 10 mg solids per mL water. The salts were prepared in a salt screen by reacting an acetone solution of the free base with stock tetrahydrofuran (THF) solutions of a range of acids in about a 1:1 molar ratio. The table below summarizes the water solubility and other data relating to the free base and each salt.

	Solubility (mg/ml)	
Free base	<<0.001	very low solubility
Propionate	<<0.001	no salt formation; mixture of free base and acid
Acetate	<<0.001	no salt formation; mixture of free base and acid
Succinate	0.010	no salt formation; mixture of free base and acid
Benzoate	0.005	no salt formation; mixture of free base and acid
L-Lactate	0.015	Amorphous, salt
Pyrroglutamate	0.44	Amorphous, salt
Glycolate	0.016	Amorphous, salt
L-Ascorbate	0.053	low crystallinity
Sulfate	0.004	Crystalline salt, low solubility
Tosylate	0.007	Crystalline salt, low solubility
Malonate	0.003	Crystalline salt, low solubility
2,5dihydroxybenzoate	<<0.001	Crystalline Salt, low solubility
Fumarate	0.008	Crystalline Salt, low solubility
Citrate	0.002	Crystalline Salt, low solubility
Mesylate	0.175	Crystalline Salt; possible sulfonic acid formation when made with alcohol
Esylate	0.194	Crystalline Salt; possible sulfonic acid formation when made with alcohol
Benzenesulfonate	0.039	Crystalline Salt; possible sulfonic acid formation when made with alcohol
Chloride	0.070	Crystalline but Hygroscopic; possible hydrate formation. Change in XRPD pattern upon exposure to humidity.
Maleate	0.005	Crystalline salt, possible hydrate formation; low solubility; different XRPD pattern observed upon scale up (possible polymorphism issue)
Phosphate	0.026	Crystalline but Hygroscopic.
L-Tartrate	0.014	Low degree of crystallinity; Hygroscopic.
L-Malate	0.059	Crystalline; non-Hygroscopic with no indication of hydrate formation. Suitable solubility, and chemical/physical stability.

[0029] In another embodiment, the L-malate salt of Compound I is amorphous or in substantially amorphous form. "Substantially amorphous" means that more than 50 percent of the Compound I L-malate salt is amorphous.

[0030] In another embodiment, the L-malate salt of Compound I is crystalline or in substantially crystalline form. "Substantially crystalline" means that more than 50 percent of the L-malate salt of Compound I is crystalline. Two crystalline forms of the L-malate salt of Compound I are the N-1 and/or the N-2 crystalline forms.

[0031] Similarly, in another embodiment, the D-malate salt of Compound I is amorphous or in substantially amorphous form. "Substantially amorphous" means that more than 50 percent of the D-malate salt of Compound I is amorphous.

[0032] In another embodiment, the D-malate salt of Compound I is crystalline or in substantially crystalline form. "Substantially crystalline" means that more than 50 percent of the D-malate salt of Compound I is crystalline. Two crystalline forms of the D-malate salt of Compound I are the N-1 and/or the N-2 crystalline form.

[0033] Similarly, in another embodiment, the D,L-malate salt of Compound I is amorphous or in substantially amorphous form. "Substantially amorphous" means that more than 50 percent of the D,L-malate salt of Compound I is amorphous.

[0034] In another embodiment, the D,L-malate salt of Compound I is crystalline or in substantially crystalline form. "Substantially crystalline" means that more than 50 percent of the D,L-malate salt of Compound I is crystalline. Two crystalline forms of the D,L-malate salt of Compound I are the N-1 and/or the N-2 crystalline form.

[0035] As is known in the art, the crystalline D malate salt will form the same crystalline form and have the same properties as crystalline Compound I. See WO 2008/083319, which discusses the properties of crystalline enantiomers.

[0036] The crystalline N-1 form of the L-malate salt of Compound I and the N-1 form of the D-malate salt of Compound I may be characterized by at least one of the following:

(i) a solid state ^{13}C NMR spectrum with peaks at 18.1, 42.9, 44.5, 70.4, 123.2, 156.2, 170.8, 175.7, and 182.1 ppm, ± 0.2 ppm;

(ii) an x-ray powder diffraction pattern (CuKα λ=1.5418Å) comprising four or more peaks selected from: 6.4, 9.0, 12.0, 12.8, 13.5, 16.9, 19.4, 21.5, 22.8, 25.1, and 27.6 °2θ ± 0.2 °2θ, wherein measurement of the crystalline form is at an ambient room temperature;

(iii) a solid state ^{15}N NMR spectrum with peaks at 118.6, 119.6, 120.7, 134.8, 167.1, 176.0, and 180 ppm, ±0.2 ppm; and/or

[0037] Other solid state properties which may be used to characterize the crystalline N-1 forms of the L-malate salt of Compound I and the D-malate salt of Compound I are discussed in WO 2010/083414, the entire contents of which are incorporated herein by reference, and as described in the Examples below. For crystalline Compound I L-malate salt, the solid state phase and the degree of crystallinity remained unchanged after exposure to 75 percent RH at 40 °C for 1 week.

[0038] The crystalline N-2 forms of the L- and D-malate salts of Compound I as described here may be characterized by at least one of the following:

(i) a solid state ^{13}C NMR spectrum with peaks at 23.0, 25.9, 38.0, 54.4, 56.11, 41.7, 69.7, 102.0, 122.5, 177.3, 179.3, 180.0, and 180.3, ± 0.2 ppm;

(ii) an x-ray powder diffraction pattern (CuKα λ=1.5418Å) comprising four or more peaks selected from: 6.4, 9.1, 12.0, 12.8, 13.7, 17.1, 20.9, 21.9, 22.6, and 23.7 °2θ ± 0.2 °2θ, wherein measurement of the crystalline form is at an ambient room temperature;

(iii) a solid state ^{15}N NMR spectrum with peaks at 118.5, 120.8, 135.1, 167.3, and 180.1 ppm.

[0039] Other solid state properties may be used to characterize the crystalline N-2 forms of the L- and D-malate salts of Compound I are discussed in WO 2010/083414.

[0040] In another embodiment, the crystalline form of the L-malate salt of Compound I, as described herein in any of the aspects and/or embodiments, is substantially pure N-1 form.

[0041] In another embodiment, the disclosure relates to a crystalline form of the L-malate salt of Compound I in substantially pure N-2 form.

[0042] Another aspect of this disclosure relates to crystalline forms of the D,L-malate salt of Compound I. The D,L-malate salt is prepared from racemic malic acid. The crystalline N-1 form of the D,L malate salt may be characterized by at least one of the following:

(i) a solid state ^{13}C NMR spectrum with four or more peaks selected from 20.8, 26.2, 44.8, 55.7, 70.7, 100.4, 101.0, 114.7, 115.2, 116.0, 119.7, 120.4, 121.6, 124.4, 136.9, 138.9, 141.1, 145.7, 150.3, 156.5, 157.6, 159.6, 165.2, 167.4, 171.2, 176.3, 182.1 ppm, ± 0.2 ppm;

(ii) a powder x-ray diffraction pattern (CuKα λ=1.5418Å) comprising four or more 2θ values selected from: 12.8, 13.5, 16.9, 19.4, 21.5, 22.8, 25.1, and 27.6, ±0.2 °2θ, wherein measurement of the crystalline form is at temperature of room temperature; and/or

(iii) a solid state ^{15}N NMR spectrum with peaks at 119.6, 134,7, and 175.5 ppm, ± 0.2 ppm.

[0043] Other solid state properties may be used to characterize the crystalline N-1 form of the D,L malate salt of Compound I, as discussed in WO 2010/083414. In one embodiment, the N-1 Form of the D,L malate salt of Compound I is characterized by unit cell parameters approximately equal to the following:

Cell dimensions: a = 14.60 Å
b = 5.20 Å
c = 39.09 Å
α = 90.0°
β = 90.4°
γ = 90.0°
Space group: $P2_1/n$
Molecules of Compound I/unit cell: 4
Volume = 2969 $Å^3$
Density (calculated) = 1.422 g/cm^3

[0044] The unit cell parameters of Form N-1 of the D,L malate salt of Compound I were measured at a temperature of approximately 25°C, *e.g.*, ambient or room temperature.

[0045] Each of the N-1 and N-2 crystalline forms of the L-malate salt and the D-malate salt of Compound I and the crystalline form N-1 of the D,L malate salt of Compound I have unique characteristics that can distinguish them one from another. These characteristics can be understood by comparing the physical properties of the solid state forms. For example, Table 4 lists characteristic XRPD peak positions (°2θ±0.2 °2θ) for the crystalline D,L malate salt of Compound I, Form N-1 and Forms N-1 and N-2 of the crystalline L-malate salt of Compound I. Amorphous forms do not display reflection peaks in their XRPD patterns.

Table 4

Characteristic diffraction peak positions (degrees 2θ±0.2) @ RT, based on pattern collected with a diffractometer (CuKα) with a spinning capillary.

Compound I L-Malate Salt Form N-1	Compound I L-Malate Salt Form N-2	Compound (III) D,L Malate Salt Form N-1
6.4	6.4	6.4
9.0	9.1	9.1
12.0	12.0	12.1
12.8	12.8	12.8
13.5	13.7	13.6
16.9	17.1	17.1
19.4*	20.9*	19.3
21.5*	21.9*	21.4
22.8*	22.6	22.8
25.1*	23.7	25.1
27.6*	--	27.6

*unique reflections between Compound I L-Malate Salt, Form N-1 and Compound I, L-Malate Salt, Form N-2.

[0046] The unique reflections between Forms N-1 and N-2 of the crystalline D-malate salt of Compound I are designated by an asterisk (*). As discussed above, the D-malate salt of Compound I is an enantiomer of the L-malate salt of Compound I and thus, Form N-1 of the D-malate salt of Compound I will have the same characteristic reflection pattern and unique peaks as those listed in Table 4 for the L-malate salt of Compound I, Form N-1. Likewise, Form N-2 of the D-malate salt of Compound I will have the same characteristic reflection pattern and unique peaks as those listed in Table 2 for the L-malate salt of Compound I, Form N-2. The L-and D-malate salts of Compound I are distinct from one another based on their absolute stereochemistry, i.e., the L-malate salt versus the D-malate salt, respectively. The crystalline D,L malate salt of Compound I, Form N-1, is distinct as the D,L-malate salt.

[0047] The characteristic peaks from the solid state NMR may also serve to distinguish the crystalline and amorphous forms disclosed herein. For example, Table 5 lists characteristic solid state ^{13}C NMR peaks for the crystalline D,L-malate salt of Compound I, Form N-1, crystalline L-malate salt of Compound I, Forms N-1 and N-2, and the amorphous form of Compound I.

Table 5

Solid State Carbon-13 NMR Resonances (ppm, ±0.2 ppm)			
(I) Form N-1	(I), Form N-2	(III), Form N-1	(I), Amorphous
18.1	23.0	20.8	27.2
42.9	25.9	26.2	33.8
44.5	38.0	44.8	142.9
54.4	54.4	70.7	--
56.1	56.1	114.7	--
70.4	41.7	141.1	--
123.2	69.7	145.7	--
156.2	102.0	176.3	--
170.8	122.5	182.1	--
175.7	177.3	--	--
182.1	179.3	--	--
--	180.0	--	--
--	180.3	--	--

[0048] The solid state ^{19}F and ^{15}N NMR spectra, discussed below, provide data for similar comparison and characterization. As discussed above, being an enantiomer of the L-

malate salt of Compound I, crystalline Forms N-1 and N-2 and the amorphous form of the D-malate salt of Compound I have the same solid state NMR resonances, and unique peaks between them, as those provided for Forms N-1 and N-2 of crystalline L-malate salt of Compound I.

[0049] The crystalline form of the L-malate salt and/or the D-malate salt of Compound I can occur as mixtures. The mixtures may have from greater than zero weight percent to less than 100 weight percent of the L-malate salt form and from less than 100 weight percent to greater than zero weight percent D-malate salt form, based on the total weight of L-malate salt form and D-malate salt form. In another embodiment, the mixture comprises from about 1 to about 99 weight percent of the L-malate salt form and from about 99 to about 1 weight percent of the D-malate salt form, based on the total weight of the L-malate salt form and the D-malate salt form in said mixture. In a further embodiment, the mixture comprises from about 90 weight percent to less than 100 weight percent L-malate salt form and from greater than zero weight percent to about 10 weight percent D-malate salt form, based on the total weight of the L-malate salt form and the D-malate salt form. Accordingly, the mixture may have 1 to 10 percent by weight of the L-malate salt form; 11 to 20 percent by weight of the L-malate salt form; 21 to 30 percent by weight of the L-malate salt form; 31 to 40 percent by weight of the L-malate salt form; 41 to 50 percent by weight of the L-malate salt form; 51 to 60 percent by weight of the L-malate salt form; 61 to 70 percent by weight of the L-malate salt form; 71 to 80 percent by weight of the L-malate salt form; 81 to 90 percent by weight of the L-malate salt form; or 91 to 99 percent by weight of the L-malate salt form with the remaining weight percentage of malate salt being that of the D-malate salt form.

Filler

[0050] As indicated above, the pharmaceutical composition containing Compound I comprises a filler. Fillers are inert ingredients added to adjust the bulk in order to produce a size practical for compression. Examples of fillers include sodium starch glycolate, corn starch, talc, sucrose, dextrose, glucose, lactose, xylitol, fructose, sorbitol, calcium phosphate, calcium sulfate, calcium carbonate, and the like, or mixtures thereof. Microcrystalline cellulose may also be used as a filler and may be any suitable form of microcrystalline cellulose as is known and used in the tabletting art. Preferably, a mixture of lactose and microcrystalline cellulose is used as the filler. In one embodiment, the lactose is anhydrous lactose sold as Lactose 60M, which is readily commercially available from a number of

suppliers. In one embodiment, the microcrystalline cellulose is Avicel PH-102, which is also commercially available.

[0051] Preferably, filler(s) are present in an amount of from about 50 to about 70 percent, and more preferably from about 57 to about 67 percent, by weight on a solids basis of the directly compressible formulation. Preferably, lactose is present in an amount of from about 18 to 22 percent by weight. Preferably, the microcrystalline cellulose is present in an amount of from about 38 to 40 percent by weight.

Binder

[0052] The pharmaceutical composition containing Compound I also comprises a binder. Binders are added to powders to impart cohesive qualities to the powder, which allows the compressed tablet to retain its integrity. The binder can be any pharmaceutically acceptable binder available in the tabletting art, such as acacia, alginic acid, carbomer, carboxymethylcellulose sodium, dextrin, ethylcellulose, gelatin, guar gum, hydrogenated vegetable oil (type I), hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, liquid glucose, magnesium aluminaum silicate, maltodextrin, methylcellulose, polymethacrylates, povidone, pregelatinized starch, sodium alginate, starch, zein, and the like, or mixtures thereof.

[0053] The preferred binder is hydroxypropyl cellulose preferably in an amount of from about 2 to about 4 percent by weight on a solid basis of the directly compressible formulation. In one embodiment, the hydroxypropyl cellulose is commercially available Klucel EXF.

Disintegrant

[0054] The pharmaceutical composition containing Compound I also comprises a disintegrant. A disintegrant is a substance or a mixture of substances added to facilitate breakup or disintegrate after administration. The disintegrant may be any pharmaceutically acceptable disintegrant available in the tabletting art, including alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium, colloidal silicon dioxide, croscarmellose sodium, crospovidone, guar gum, magnesium aluminum silicate, methylcellulose, microcrystalline cellulose, polyacrilin potassium, powdered cellulose, pregelatinized starch, sodium alginate, starch, and the like, or mixtures thereof.

[0055] The preferred disintegrant is croscarmellose sodium, in an amount of from about 4 to about 8 percent by weight, on a solid basis of the directly compressible formulation. In one embodiment, the croscarmellose sodium is commercially available Ac-Di-Sol.

Glidant

[0056] The pharmaceutical composition containing Compound I also comprises a glidant. The glidant may be any pharmaceutically acceptable glidant which contributes to the compressibility, flowability, and homogeneity of the formulation and which minimizes segregation and does not significantly interfere with the release mechanism of the binders as set forth above. Preferably, the glidant is selected to improve the flow of the formulation. Silicon dioxide, particularly colloidal silicon dioxide, is preferred as a glidant.

[0057] The glidant is used in an amount of from about 0.2 to about 0.6 percent by weight on a solid basis of the directly compressible formulation.

Lubricant

[0058] The pharmaceutical composition containing Compound I also comprises a lubricant. Lubricants are employed to prevent adhesion of the tablet material to the surface of dyes and punches. The lubricant may be any pharmaceutically acceptable lubricant which substantially prevents segregation of the powder by contributing to homogeneity of the formulation and which exhibits good flowability. Preferably, the lubricant functions to facilitate compression of the tablets and ejection of the tablets from the die cavity. Such lubricants may be hydrophilic or hydrophobic, and examples include magnesium stearate, Lubritab.RTM., stearic acid, talc, and other lubricants known in the art or to be developed which exhibit acceptable or comparable properties, or mixtures thereof. Examples of lubricants include calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc, zinc stearate, and the like, or mixtures thereof.

[0059] The lubricant should be selected to aid in the flow of the powder in the hopper and into the die. Magnesium stearate exhibits excellent properties in combination with the other preferred excipients of the formulation. Magnesium stearate contributes to reducing friction between the die wall and tablet formulation during compression, as well as to the easy ejection of the Compound I tablets. It also resists adhesion to punches and dies.

[0060] Preferably, the lubricant is magnesium stearate (non-bovine) used in an amount of from about 0.5 to about 1.0 percent by weight on a solid basis of the directly compressible formulation.

Film Coating

[0061] The pharmaceutical composition containing Compound I also comprises an optional film coating. The film coat concentration can be about 1 to about 10 percent by weight on a solid basis of the directly compressible formulation. Film coating suspensions may include combinations of the following components: hypromeollose, carboxymethylcellulose sodium, carnauba wax, cellulose acetate phthalate, cetyl alcohol, confectioner's sugar, ethyl cellulose, gelatin, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, liquid glucose, maltodextrin, methyl cellulose, microcrystalline wax, Opadry and Opadry II, polymethacrylates, polyvinyl alcohol, shellac, sucrose, talc, titanium dioxide, and zein.

[0062] Preferably the film coating comprises commercially available Opadry Yellow. .

[0063] In one embodiment, the tablet composition comprises

30-32 percent by weight of Compound I in at least one of the forms disclosed herein;

50-70 percent by weight of a filler;

2-4 percent by weight of a binder;

4-8 percent by weight a disintegrant; and

0.2-0.6 percent by weight of a glidant; and 0.5-1 percent by weight of a lubricant.

[0064] In another embodiment, the tablet composition comprises:

30-32 percent by weight of Compound I in at least one of the forms disclosed herein;

50-70 percent by weight of a filler;

2-4 percent by weight of a binder;

4-8 percent by weight a disintegrant; and

0.2-0.6 percent by weigh of a glidant; and 0.5-1 percent by weight of a lubricant; wherein the composition is coated.

[0065] In another embodiment, the tablet composition comprises:

Component	Weight/Weight Percent
Compound I	25-29
Microcrystalline Cellulose	q.s.
Lactose Anhydrous	40-44
Hydroxypropyl Cellulose	2-4
Croscarmellose Sodium	2-8
Colloidal Silicon Dioxide	0.1-0.4
Magnesium Stearate	0.7-0.9
Total	100

[0066] In another embodiment, the tablet compositions of this disclosure contain from 10 to about 200 mg of Compound I in at least one of the forms described herein. In another embodiment, the tablet compositions of this disclosure contain from 20 to 100 mg of Compound I. In another embodiment, the tablet compositions contain 20, 25, 50, 60, 75, 80, or 100 mg of Compound I.

[0067] In other embodiments, the tablet compositions are summarized in Tables 1, 2, and 3. The compound I used in these and other compositions disclosed herein is the L-malate salt Compound I. In the tables, the weight of Compound I refers to the amount of N-[4-[(6,7-Dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide in the tablet. The skilled artisan will recognize that a certain amount of the Compound I L-malate salt is required to provide the weights listed in the tables. Thus, for example, in Table 3, 126.7 mg of Compound I L-malate salt is required to provide100 mg of Compound I. Proportionally smaller or larger amounts of Compound I L-malate salt are required for tablet compositions containing less or more of Compound I.

Process

[0068] In another aspect, the disclosure is directed to a process for making pharmaceutical formulations comprising Compound I. In one embodiment, the formulation is a tablet formulation.

[0069] In another embodiment, the process comprises mixing Compound I with one or more of the pharmaceutical excipients. The mixture is then taken up in an aqueous solution containing a binder to form a binder solution. The binder solution is granulated using a granulation technique known in the art. For example, the granulation method may comprise

wet high shear granulation using a wet high shear granulator. The resulting wet granules are then screened and dried using fluid bed drying or the like. The dried granules are then milled. The resulting dry milled granules are then mixed with a glidant and a disintegrant to form an extra-granular blend. A lubricant is then blended into the extraganular blend to form the final blend. The final blend is subsequently compressed to form the compressed tablet, which may be film coated.

[0070] More particularly, the process comprises delumping Compound I as needed prior to mixing with the excipients. Delumping ensures that the Compound I mixes homogeneously with the other excipients during the formulation process. Delumped Compound I is then mixed with microcrystalline cellulose, such as Avicel PH102, lactose (anhydrous, 60M), and croscarmellose sodium. This mixture is then combined with EXF grade hydroxypropoyl cellulose in water to form a binder solution, which is then wet high shear granulated. The resulting wet granules are wet screened and then fluid bed dried according to methods available to the skilled artisan. The resulting dried granules are milled and combined with colloidal silicon dioxide and croscarmellose sodium. Magnesium stearate is added to the mixture. This final blend is then ready for tablet compression. The resulting uncoated core tablets are subsequently film coated. The film coating comprises Opadry Yellow, which contains hypromellose, titanium dioxide, triacetin, and iron oxide yellow.

[0071] More particularly, the formulation process comprises:

a) Delumping unmilled Compound I;

b) Premixing the delumped Compound I with Avicel PH102, lactose anhydrous 60M, and croscarmellose sodium to form a binder solution;

c) Wet high shear granulation of the binder solution to produce wet granules;

d) Wet screening of the wet granules to produce wet screened granules;

e) Fluid bed drying of the wet screened granules to produce dried granules;

f) Dry milling of the dried granules to produce dried milled granules;

g) Blending the dried milled granules with colloidal silicon and croscarmellose to produce an extragranular blend;

h) Lubricant blending of the extragranular blend and magnesium stearate to produce a final blend;

i) Tablet compression of the final blend to form an uncoated core tablet; and

j) Film coating of the uncoated core tablet.

Methods of Treatment

[0072] Another aspect of this disclosure relates to a method of treating cancer, using a pharmaceutical composition containing Compound I in at least one of its forms, either alone or in combination with another therapeutic agent. The cancer being treated is selected from stomach cancer, esophageal carcinoma, kidney cancer, liver cancer, ovarian carcinoma, cervical carcinoma, large bowel cancer, small bowel cancer, brain cancer (including astrocytic tumor, which includes glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components), lung cancer (including non-small cell lung cancer), bone cancer, prostate carcinoma, pancreatic carcinoma, skin cancer, bone cancer, lymphoma, solid tumors, Hodgkin's disease, non-Hodgkin's lymphoma, or thyroid cancer (including medullary thyroid cancer). More particularly, the cancer is pancreatic cancer, hepatocellular carcinoma (HCC), renal cell carcinoma, castration-resistant prostate cancer (CRPC), gastric or gastroesophageal junction cancer, melanoma, small cell lung cancer (SCLC), ovarian cancer, primary peritoneal or fallopian tube carcinoma, estrogen receptor positive breast cancer, estrogen receptor/progesterone receptor/HER2-negative (triple-negative) breast cancer, inflammatory (regardless of receptor status) breast cancer, non-small cell lung cancer (NSCLC), or medullary thyroid cancer.

[0073] Tyrosine kinase inhibitors have also been used to treat non-small cell lung cancer (NSCLC). Gefitinib and erlotinib are angiogenesis inhibitors that target receptors of an epidermal growth factor called tyrosine kinase. Erlotinib and Gefitinib are currently being used for treating NSCLC. Another aspect of this disclosure relates to a method of treating non-small cell lung cancer (NSCLC) comprising administering to the subject in need of the treatment a therapeutically effective amount of Compound I in at least one of the forms described herein, pharmaceutically formulated as described herein, optionally in combination with Erlotinib or Gefitinib. In another embodiment, the combination is with Erlotinib.

[0074] In another embodiment, the cancer is non-small cell lung cancer (NSCLC), and the method comprises administering to the subject in need of the treatment a therapeutically effective amount of Erlotinib or Gefitinib in combination with at least one of the forms of Compound I in at least one of the forms described herein, pharmaceutically formulated as described herein. The method of treatment may be practiced by administering a tablet formulation of at Compound I in at least one of the forms described herein, pharmaceutically formulated as described herein.

[0075] Another aspect of this disclosure relates to a method of treating an astrocytic tumor (which includes glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma

with oligodendroglial components) comprising administering to the subject in need of the treatment a therapeutically effective amount of Compound I in at least one of the forms described herein, pharmaceutically formulated as described herein.

[0076] Another aspect of this disclosure relates to a method of treating thyroid cancer (including medullary thyroid cancer) comprising administering to the subject in need of the treatment a therapeutically effective amount of Compound I in at least one of the forms described herein, pharmaceutically formulated as described herein.

[0077] Another aspect of this disclosure relates to a method of treating hepatocellular carcinoma comprising administering to the subject in need of the treatment a therapeutically effective amount of Compound I in at least one of the forms described herein, pharmaceutically formulated as described herein.

[0078] Another aspect of this disclosure relates to a method of treating renal cell carcinoma comprising administering to the subject in need of the treatment a therapeutically effective amount of Compound I in at least one of the forms described herein, pharmaceutically formulated as described herein.

[0079] Another aspect of this disclosure relates to a method of treating castration resistant prostate cancer comprising administering to the subject in need of the treatment a therapeutically effective amount of Compound I in at least one of the forms described herein, pharmaceutically formulated as described herein. The amount administered can be a therapeutically effective amount.

[0080] Another aspect of this disclosure relates to a method of breast cancer comprising administering to the subject in need of the treatment a therapeutically effective amount of Compound I in at least one of the forms described herein, pharmaceutically formulated as described herein.

[0081] Another aspect of this disclosure relates to a method of treating ovarian cancer comprising administering to the subject in need of the treatment a therapeutically effective amount of Compound I in at least one of the forms described herein, pharmaceutically formulated as described herein.

[0082] Another aspect of this disclosure relates to a method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities. The method comprises administering to the subject in need of the treatment a therapeutically effective amount of Compound I in at least one of the forms described herein, pharmaceutically formulated as described herein.

[0083] A "therapeutically effective amount of the active compounds", or a crystalline or amorphous form of the active compound(s) to inhibit, regulate, and/or modulate the signal transduction of kinases (discussed here concerning the pharmaceutical compositions) refers to an amount sufficient to treat a patient suffering from any of a variety of cancers associated with abnormal cell proliferation and angiogenesis. A therapeutically effective amount according to this disclosure is an amount therapeutically useful for the treatment or prevention of the disease states and disorders discussed herein. Compound I possess therapeutic activity to inhibit, regulate, and/or modulate the signal transduction of kinases such as described in WO 2005/030140.

[0084] The actual amount required for treatment of any particular patient will depend upon a variety of factors, including the disease state being treated and its severity; the specific pharmaceutical composition employed; the age, body weight, general health, sex, and diet of the patient; the mode of administration; the time of administration; the route of administration; the rate of excretion of the active compound(s), or a crystalline form of the active compound(s), according to this disclosure; the duration of the treatment; any drugs used in combination or coincidental with the specific compound employed; and other such factors well known in the medical arts. These factors are discussed in Goodman and Gilman's "The Pharmacological Basis of Therapeutics," Tenth Edition, A. Gilman, J.Hardman and L. Limbird, eds., McGraw-Hill Press, 155-173, 2001, which is incorporated herein by reference. The active compound(s) , or a crystalline form of active compound(s), according to this disclosure, and pharmaceutical compositions comprising them, may be used in combination with anticancer or other agents that are generally administered to a patient being treated for cancer. They may also be co-formulated with one or more of such agents in a single pharmaceutical composition.

EXAMPLES

[0085] The disclosure is illustrated further by the following examples in Scheme 1 and the description thereof, which are not to be construed as limiting the invention in scope or spirit to the specific procedures described in them. Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the invention, as demonstrated by the following examples. Those skilled in the art will also recognize that it may be necessary to utilize different solvents or reagents to achieve some of the above transformations.

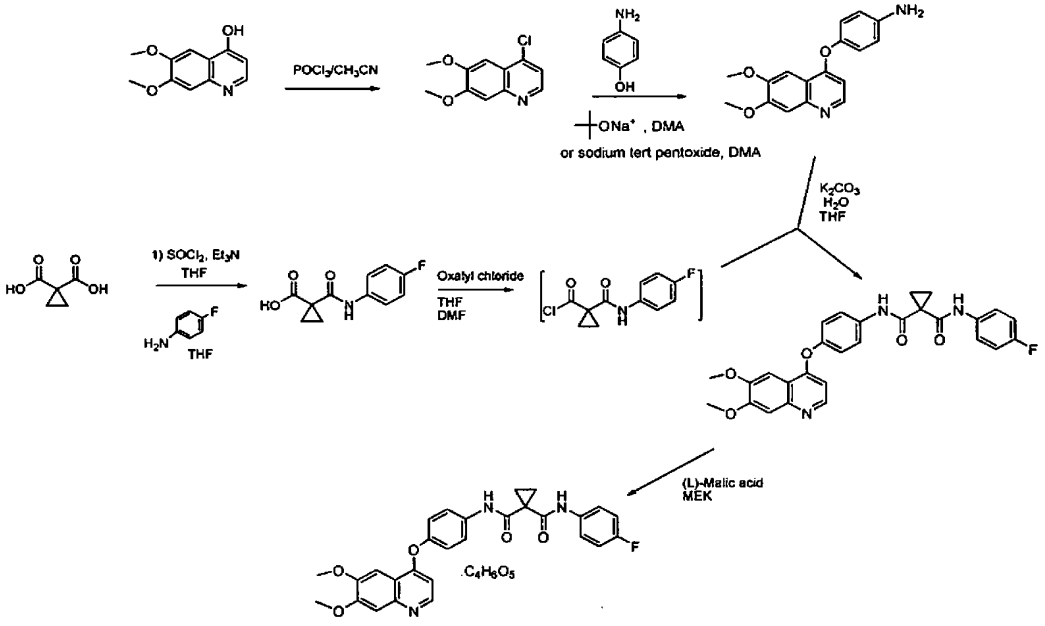
[0086] Unless otherwise specified, all reagents and solvents are of standard commercial grade and are used without further purification. The appropriate atmosphere to run the reaction under, for example, air, nitrogen, hydrogen, argon and the like, will be apparent to those skilled in the art.

Example 1

Preparation of Compound I and Compound I and the L-Malate Salt of Compound I

[0087] A synthetic route that can be used for the preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the L-malate salt thereof is depicted in Scheme 1.

Scheme 1



Preparation of 4–Chloro–6,7–dimethoxy–quinoline

[0088] A reactor was charged sequentially with 6,7–dimethoxy–quinoline–4–ol (47.0 kg) and acetonitrile (318.8 kg). The resulting mixture was heated to approximately 60 °C, and phosphorus oxychloride ($POCl_3$, 130.6 kg) was added. After the addition of $POCl_3$, the temperature of the reaction mixture was raised to approximately 77 °C. The reaction was deemed complete (approximately 13 hours) when less than 3% of the starting material remained (in-process high-performance liquid chromatography [HPLC] analysis). The

reaction mixture was cooled to approximately 2–7 °C and then quenched into a chilled solution of dichloromethane (DCM, 482.8 kg), 26 % NH_4OH (251.3 kg), and water (900 L). The resulting mixture was warmed to approximately 20 – 25 °C, and phases were separated. The organic phase was filtered through a bed of AW hyflo super-cel NF (Celite™; 5.4 kg), and the filter bed was washed with DCM (118.9 kg). The combined organic phase was washed with brine (282.9 kg) and mixed with water (120 L). The phases were separated, and the organic phase was concentrated by vacuum distillation with the removal of solvent (approximately 95 L residual volume). DCM (686.5 kg) was charged to the reactor containing organic phase and concentrated by vacuum distillation with the removal of solvent (approximately 90 L residual volume). Methyl t-butyl ether (MTBE, 226.0 kg) was then charged, and the temperature of the mixture was adjusted to –20 to –25 °C and held for 2.5 hours, resulting in solid precipitate which was then filtered and washed with n-heptane (92.0 kg) and dried on a filter at approximately 25 °C under nitrogen to afford the title compound. (35.6 kg).

Preparation of 4–(6, 7 –Dimethoxy–quinoline–4–yloxy)–phenylamine

[0089] 4-Aminophenol (24.4 kg) dissolved in N,N-dimethylacetamide (DMA, 184.3 kg) was charged to a reactor containing 4-chloro-6,7-dimethoxyquinoline (35.3 kg), sodium t-butoxide (21.4 kg), and DMA (167.2 kg) at 20–25 °C. This mixture was then heated to 100–105 °C for approximately 13 hours. After the reaction was deemed complete as determined using in-process HPLC analysis (less than 2% starting material remaining), the reactor contents were cooled at 15–20 °C, and water (pre-cooled, 2 to 7 °C, 587 L) was charged at a rate to maintain 15-30 °C temperature. The resulting solid precipitate was filtered and washed with a mixture of water (47 L) and DMA (89.1 kg) and again with water (214 L). The filter cake was then dried at approximately 25 °C on filter to yield crude 4–(6, 7 –dimethoxy–quinoline–4–yloxy)–phenylamine (59.4 kg wet, 41.6 kg dry calculated based on LOD). Crude 4–(6, 7 –dimethoxy–quinoline–4–yloxy)–phenylamine was refluxed (approximately 75 °C) in a mixture of tetrahydrofuran (THF, 211.4 kg) and DMA (108.8 kg) for approximately 1 hour, then cooled to 0–5 °C, and aged for approximately 1 hour, after which time the solid was filtered, washed with THF (147.6 kg), and dried on a filter under vacuum at approximately 25 °C to yield 4–(6, 7 –dimethoxy–quinoline–4–yloxy)–phenylamine (34.0 kg).

Alternative Preparation of 4–(6, 7 –Dimethoxy–quinoline–4–yloxy)–phenylamine

[0090] 4-chloro-6,7-dimethoxyquinoline (34.8 kg), 4-Aminophenol (30.8 kg), and sodium tert pentoxide (1.8 equivalents) 88.7 kg, 35 wt percent in THF) were charged to a reactor, followed by N,N-dimethylacetamide (DMA, 293.3 kg). This mixture was then heated to 105 – 115 °C for approximately 9 hours. After the reaction was deemed complete as determined using in-process HPLC analysis (less than 2 percent starting material remaining), the reactor contents were cooled at 15–25 °C, and water (315 kg) was added over a two hour period while maintaining the temperature between 20 and 30 °C. The reaction mixture was then agitated for an additional hour at 20 to 25°C. The crude product was collected by filtration and washed with a mixture of water (88 kg) and DMA (82.1 kg), followed by water (175 kg). The product was dried on a filter drier for 53 hours. The LOD showed less than 1% weight/weight (w/w).

[0091] In an alternative procedure, 1.6 equivalents of sodium tert-pentoxide were used, and the reaction temperature was increased from 110–120 °C. In addition, the cool down temperature was increased to 35-40 °C, and the starting temperature of the water addition was adjusted to 35-40 °C, with an allowed exotherm to 45°C.

Preparation of 1–(4–Fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid

[0092] Triethylamine (19.5 kg) was added to a cooled (approximately 5 °C) solution of cyclopropane–1,1–dicarboxylic acid (24.7 kg) in THF (89.6 kg) at a rate such that the batch temperature did not exceed 5 °C. The solution was stirred for approximately 1.3 hours, and then thionyl chloride (23.1 kg) was added, keeping the batch temperature below 10 °C. When the addition was complete, the solution was stirred for approximately 4 hours, keeping the temperature below 10 °C. A solution of 4–fluoroaniline (18.0 kg) in THF (33.1 kg) was then added at a rate such that the batch temperature did not exceed 10 °C. The mixture was stirred for approximately 10 hours, after which the reaction was deemed complete. The reaction mixture was then diluted with isopropyl acetate (218.1 kg). This solution was washed sequentially with aqueous sodium hydroxide (10.4 kg, 50 percent dissolved in 119 L of water) further diluted with water (415 L), then with water (100 L), and finally with aqueous sodium chloride (20.0 kg dissolved in 100 L of water). The organic solution was concentrated by vacuum distillation (100 L residual volume) below 40 °C, followed by the addition of n-heptane (171.4 kg), which resulted in the precipitation of solid. The solid was recovered by filtration and washed with n-Heptane (102.4 kg), resulting in wet crude, 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid (29.0 kg). The crude, 1–(4–fluoro–

phenylcarbamoyl)–cyclopropanecarboxylic acid was dissolved in methanol (139.7 kg) at approximately 25 °C followed by the addition of water (320 L), resulting in slurry which was recovered by filtration, washed sequentially with water (20 L) and n-heptane (103.1 kg), and then dried on the filter at approximately 25 °C under nitrogen to afford the title compound (25.4 kg).

Preparation of 1–(4–Fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride

[0093] Oxalyl chloride (12.6 kg) was added to a solution of 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid (22.8 kg) in a mixture of THF (96.1 kg) and N, N-dimethylformamide (DMF; 0.23 kg) at a rate such that the batch temperature did not exceed 25 °C. This solution was used in the next step without further processing.

Alternative Preparation of 1–(4–Fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride

[0094] A reactor was charged with 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid (35 kg), DMF (344 g), and THF (175 kg). The reaction mixture was adjusted to 12-17 °C, and then to the reaction mixture was charged with oxalyl chloride (19.9 kg) over a period of 1 hour. The reaction mixture was left stirring at 12-17 °C for 3 to 8 hours. This solution was used in the next step without further processing.

Preparation of cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide

[0095] The solution from the previous step containing 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride was added to a mixture of compound 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (23.5 kg) and potassium carbonate (31.9 kg) in THF (245.7 kg) and water (116 L) at a rate such that the batch temperature did not exceed 30 °C. When the reaction was complete (in approximately 20 minutes), water (653 L) was added. The mixture was stirred at 20–25 °C for approximately 10 hours, which resulted in the precipitation of the product. The product was recovered by filtration, washed with a pre-made solution of THF (68.6 kg) and water (256 L), and dried first on a filter under nitrogen at approximately 25 °C and then at approximately 45 °C under vacuum to afford the title compound (41.0 kg, 38.1 kg, calculated based on LOD).

Alternative Preparation of cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide

[0096] A reactor was charged with 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (35.7 kg, 1 equivalent), followed by 412.9 kg THF. To the reaction mixture was charged a solution of 48.3 K_2CO_3 in 169 kg water. The acid chloride solution described in the Alternative Preparation of 1-(4-Fluoro-phenylcarbamoyl)-cyclopropanecarbonyl chloride above was transferred to the reactor containing 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine while maintaining the temperature between 20-30 °C over a minimum of two hours. The reaction mixture ws stirred at 20-25 °C for a minimum of three hours. The reaction temperature was then adjusted to 30-25 °C, and the mixture was agitated. The agitation was stopped, and the phases of the mixture were allowed to separate. The lower aqueous phase was removed and discarded. To the remaining upper organic phase was added water (804 kg). The reaction was left stirring at 15-25 °C for a minimum of 16 hours.

[0097] The product precipitated. The product was filtered and washed with a mixture of water (179 kg) and THF (157.9 kg) in two portions. The crude product was dried under a vacuum for at least two hours. The dried product was then taken up in THF (285.1 kg). The resulting suspension was transferred to reaction vessel and agitated until the suspension became a clear (dissolved) solution, which required heating to 30-35 °C for approximately 30 minutes. Water (456 kg) was then added to the solution, as well as SDAG-1 ethanol (20 kg) (ethanol denatured with methanol over two hours). The mixture was agitated at 15-25 °C for at least 16 hours. The product was filtered and washed with a mixture of 143 kg water (143 kg) and THF (126.7 kg) in two portions. The product was dried at a maximum temperature set point of 40 °C.

[0098] In an alternative procedure, the reaction temperature during acid chloride formation was adjusted to 10-15 °C. The recrystallization temperature was changed from 15-25 °C to 45-50 °C for 1 hour and then cooled to 15-25 °C over 2 hours.

Preparation of cyclopropane-1,1-dicarboxylic acid [4-(6,7- dimethoxy- quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide, (L) malate salt

[0099] Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy- quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (1-5; 13.3 kg), L-malic acid (4.96 kg), methyl ethyl ketone (MEK; 188.6 kg), and water (37.3 kg) were charged to a reactor, and the mixture was heated to reflux (approximately 74 °C) for approximately 2 hours. The reactor temperature was reduced to 50 to 55 °C, and the reactor contents were filtered. These sequential steps

described above were repeated two more times starting with similar amounts of 1-5 (13.3 kg), L-Malic acid (4.96 kg), MEK (198.6 kg), and water (37.2 kg). The combined filtrate was azeotropically dried at atmospheric pressure using MEK (1133.2 kg) (approximate residual volume 711 L; KF $\leq$ 0.5 % w/w) at approximately 74 °C. The temperature of the reactor contents was reduced to 20 to 25 °C and held for approximately 4 hours, resulting in solid precipitate which was filtered, washed with MEK (448 kg), and dried under vacuum at 50 °C to afford the title compound (45.5 kg).

Alternative Preparation of cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide, (L) malate salt

[00100] Cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide (47.9 kg), L-malic acid (17.2 kg), methyl ethyl ketone (658.2 kg), and water (129.1 kg) were charged to a reactor, and the mixture was heated 50-55 °C for approximately 1-3 hours, and then at 55-60 °C for an additional 4-5 hours. The mixture was clarified by filtration through a 1 μm cartridge. The reactor temperature was adjusted to 20-25 °C and vacuum distilled with a vacuum at 150-200 mm Hg with a maximum jacket temperature of 55 °C to the volume range of 558-731 L.

[00101] The vacuum distillation was performed two more times with the charge of 380 kg and 380.2 kg methyl ethyl ketone, respectively. After the third distillation, the volume of the batch was adjusted to 18 v/w of cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide by charging methyl ethyl ketone (159.9 kg) to give a total volume of 880L. An additional vacuum distillation was carried out by adjusting methyl ethyl ketone (245.7 kg). The reaction mixture was left with moderate agitation at 20-25 °C for at least 24 hours. The product was filtered and washed with methyl ethyl ketone 415.1 kg) in three portions. The product was dried under a vacuum with the jacket temperature set point at 45 °C.

[00102] In an alternative procedure, the order of addition was changes so that a solution of L-malic acid (17.7 kg) dissolved in water (129.9 kg) was added to Cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide (48.7 kg) in methyl ethyl ketone (673.3 kg).

General Methods of Analysis of Crystalline Forms of Compound I and Compound I, Malate Salt

[00103] Crystalline forms may be prepared by a variety of methods including, but not limited to, crystallization or recrystallization from a suitable solvent mixture, sublimation, growth from a melt, solid state transformation from another phase, crystallization from a supercritical fluid, and jet spraying. Techniques for crystallization or recrystallization of crystalline forms of a solvent mixture include, but are not limited to, evaporation of the solvent, decreasing the temperature of the solvent mixture, crystal seeding of a supersaturated solvent mixture of the compound and/or salt thereof, crystal seeding a supersaturated solvent mixture of the compound and/or a salt from thereof, freeze drying the solvent mixture, and adding antisolvents (countersolvents) to the solvent mixture. High throughput crystallization techniques may be employed to prepare crystalline forms including polymorphs.

[00104] Crystals of drugs, including polymorphs, their methods of preparation, and the characterization of drug crystals, are discussed in *Solid-State Chemistry of Drugs*, S.R. Byrn, R.R. Pfeiffer, and J.G. Stowell, 2nd Edition, SSCI, West Lafayette, Indiana (1999).

[00105] In a crystallization technique in which a solvent is employed, the solvent is typically chosen based on one or more factors including, but not limited to, solubility of the compound, crystallization technique utilized, and vapor pressure of the solvent. Combinations of solvents may be employed. For example, the compound may be solubilized in a first solvent to afford a solution, followed by the addition of an antisolvent to decrease the solubility of the compound in the solution and precipitate the formation of crystals. An antisolvent is a solvent in which a compound has low solubility.

[00106] In one method that can be used in preparing crystals, the L-malate salt of Compound I can be suspended and/or stirred in a suitable solvent to afford a slurry, which may be heated to promote dissolution. The term "slurry," as used herein, means a saturated solution of the compound, wherein such solution may contain an additional amount of compound to afford a heterogeneous mixture of compound and solvent at a given temperature.

[00107] Seed crystals may be added to any crystallization mixture to promote crystallization. Seeding may be employed to control growth of a particular polymorph and/or to control the particle size distribution of the crystalline product. Accordingly, calculation of the amount of seeds needed depends on the size of the seed available and the desired size of an average product particle as described, for example, in Programmed Cooling Batch Crystallizers," J.W. Mullin and J. Nyvlt, Chemical Engineering Science, 1971, 26, 3690377.

In general, seeds of small size are needed to effectively control the growth of crystals in the batch. Seeds of small size may be generated by sieving, milling, or micronizing large crystals, or by microcrystallizing a solution. In the milling or micronizing of crystals, care should be taken to avoid changing crystallinity from the desired crystalline form (i.e., changing to an amorphous or other polymorphic form).

[00108] A cooled crystallization mixture may be filtered under vacuum and the isolated solid product washed with a suitable solvent, such as, for example, cold recrystallization solvent. After washing, the product may be dried under a nitrogen purge to afford the desired crystalline form. The product may be analyzed by a suitable spectroscopic or analytical technique including, but not limited to, differential scanning calorimetry (DSC), x-ray powder diffraction (XRPD), and thermogravimetric analysis (TGA), to ensure that the crystalline form of the compound has been formed. The resulting crystalline form may be produced in an amount greater than about 70 weight percent isolated yield, based on the weight of the compound originally employed in the crystallization procedure, and preferably greater than about 90 weight percent isolated yield. Optionally, the product may be delumped by comilling or passing through a mesh screen.

Preparation of Crystalline L-Malate Salt of Compound I

[00109] The preparation of the captioned salt and its characterization is described above and in WO 2010/083414, the entire contents of which is incorporated by reference.

Solid State Nuclear Magnetic Resonance (SSNMR)

[00110] All solid-state ^{13}C NMR measurements were made with a Bruker DSX-400, 400 MHz NMR spectrometer. High resolution spectra were obtained using high-power proton decoupling, the TPPM pulse sequence, and ramp amplitude cross-polarization (RAMP-CP) with magic-angle spinning (MAS) at approximately 12 kHz (A.E. Bennett et al, *J. Chem. Phys.*, 1995, 103, 6951 and G. Metz, X. Wu and S.O. Smith, *J. Magn. Reson. A*,. 1994, 110, 219-227). Approximately 70 mg of sample, packed into a canister-design zirconia rotor, was used for each experiment. Chemical shifts (δ) were referenced to external adamantane with the high frequency resonance being set to 38.56 ppm (W.L. Earl and D.L. VanderHart, *J. Magn. Reson.*, 1982, 48, 35-54).

L-Malate Salt of Compound I

[00111] The solid state ^{13}C NMR spectrum of the crystalline L-malate salt of Compound I provides the following list of peaks, or a subset thereof, may be sufficient to characterize crystalline L-malate salt of Compound I.

[00112] SS ^{13}C NMR Peaks: 18.1, 20.6, 26.0, 42.9, 44.5, 54.4, 55.4, 56.1, 70.4, 99.4, 100.1, 100.6, 114.4, 114.9, 115.8, 119.6, 120.1, 121.6, 123.2, 124.1, 136.4, 138.6, 140.6, 145.4, 150.1, 150.9, 156.2, 157.4, 159.4, 164.9, 167.1, 170.8, 175.7, and 182.1 ppm, ± 0.2 ppm.

[00113] The solid state ^{15}N NMR spectrum of the crystalline L-malate salt of Compound I. provides peaks at 118.6, 119.6, 120.7, 134.8, 167.1, 176.0, and 180 ppm, ± 0.2 ppm. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline L-malate salt of Compound I.

[00114] The solid state ^{19}F NMR spectrum of the crystalline L-malate salt of Compound I. provides peaks at -121.6, -120.8, and -118.0 ppm, ± 0.2 ppm.

Thermal Characterization Measurements

Thermal Gravimetric Analysis (TGA)

[00115] TGA measurements were performed in a TA Instruments™ model Q500 or 2950, employing an open pan setup. The sample (about 10-30 mg) was placed in a previously tared platinum pan. The weight of the sample was measured accurately and recorded to a thousand of a milligram. The furnace was purged with nitrogen gas at 100mL/min. Data were collected between room temperature and 300 °C at 10 °C/min heating rate.

Differential Scanning Calorimetry (DSC) Analysis

[00116] DSC measurements were performed in a TA Instruments™ models Q2000, 1000, or 2920, employing an open pan setup. The sample (about 2-6 mg) was weighed in an aluminum pan, accurately recorded to a hundredth of a milligram, and transferred to the DSC. The instrument was purged with nitrogen gas at 50mL/min. Data were collected between room temperature and 300 °C at a 10 °C/min heating rate. The plot was made with the endothermic peaks pointing down.

L-Malate Salt of Compound I

[00117] The TGA thermogram for the crystalline L-malate salt of Compound I, which shows a weight loss of approximately 0.4 weight percent at a temperature of 170 °C.

[00118] The DSC thermogram for the crystalline L-malate salt of Compound I, which showed a melting point of approximately 187 °C.

Moisture Vapor Isotherm Measurements

[00119] Moisture sorption isotherms were collected in a VTI SGA-100 Symmetric Vapor Analyzer using approximately 10 mg of sample. The sample was dried at 60 °C until the loss rate of less than or equal to 0.0005 weight percent per minute was obtained for 10 minutes. The sample was tested at 25 °C and a relative humidity (RH) of 3, 4, 5, 15, 25, 35, 45, 50, 65, 75, 85, and 95 percent. Equilibration at each RH was reached when the rate of less than or equal to 0.0003 weight percent per minute for 35 minutes was achieved, or at a maximum of 600 minutes.

[00120] All ranges disclosed herein are inclusive of the endpoints, and the endpoints are independently combinable with each other.

[00121] The use of the terms "a", "an", "the", and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Further, it should be noted that the terms "first," "second," and the like herein do not denote any order, quantity, or importance, but rather are used to distinguish one element from another. The modifier "about" used in connection with a quantity is inclusive of the stated value and has the meaning dictated by the context (e.g., it includes the degree of error associated with measurement of the particular quantity).

[00122] The foregoing disclosure has been described in some detail by way of illustration and example, for purposes of clarity and understanding. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications can be made while remaining within the spirit and scope of the invention. It will be obvious to one of skill in the art that changes and modifications can be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

What is claimed is:

1. A pharmaceutical composition comprising:

Ingredient	(% w/w)
Compound I	31.68
Microcrystalline Cellulose	38.85
Lactose anhydrous	19.42
Hydroxypropyl Cellulose	3.00
Croscarmellose Sodium	3.00
Total Intra-granular	**95.95**
Silicon dioxide, Colloidal	0.30
Croscarmellose Sodium	3.00
Magnesium Stearate	0.75
Total	**100.00**

2. A pharmaceutical composition comprising:

Ingredient	(% w/w)
Compound I	25.0-33.3
Microcrystalline Cellulose	q.s
Hydroxypropyl Cellulose	3
Poloxamer	0-3
Croscarmellose Sodium	6.0
Colloidal Silicon Dioxide	0.5
Magnesium Stearate	0.5-1.0
Total	100

3. A pharmaceutical composition comprising:

Ingredient	Theoretical Quantity (mg/unit dose)
Compound I	100.0
Microcrystalline Cellulose PH-102	155.4
Lactose Anhydrous 60M	77.7
Hydroxypropyl Cellulose, EXF	12.0
Croscarmellose Sodium	24
Colloidal Silicon Dioxide	1.2
Magnesium Stearate (Non-Bovine)	3.0
Opadry Yellow	16.0
Total	**416**

4. A pharmaceutical composition comprising:

30-32 percent by weight of Compound I in at least one of the forms disclosed herein;

50-70 percent by weight of a filler;

2-4 percent by weight of a binder;

4-8 percent by weight of a disintegrant; and

0.2-0.6 percent by weight of a glidant; and 0.5-1 percent by weight of a lubricant.

5. The pharmaceutical composition of claim 4, wherein Compound I is the free base.

6. The pharmaceutical composition of claim 4, wherein Compound I is a pharmaceutically acceptable salt.

7. The pharmaceutical composition of claim 4, wherein Compound I is the malate salt.

8. The pharmaceutical composition of claim 4, wherein Compound I is the L-, D-, or D,L malate salt, or mixtures thereof.

9. The pharmaceutical composition of claim 8, wherein the Compound I malate salt is in amorphous, substantially amorphous, crystalline, or substantially crystalline form.

10. The pharmaceutical composition of claim 8, wherein the Compound I malate salt is in crystalline or amorphous form.

11. The pharmaceutical composition of claim 4, wherein the filler is selected from the group consisting of sodium starch glycolate, corn starch, talc, sucrose, dextrose, glucose, lactose, xylitol, fructose, sorbitol, calcium phosphate, calcium sulfate, calcium carbonate, and microcrystalline cellulose, or mixtures thereof.

12. The pharmaceutical composition of claim 11, wherein the filler is comprises lactose and microcrystalline cellulose.

13. The pharmaceutical composition of claim 2, wherein the binder is selected from the group consisting of acacia, alginic acid, carbomer, carboxymethylcellulose sodium, dextrin, ethylcellulose, gelatin, guar gum, hydrogenated vegetable oil (type I), hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, liquid glucose, magnesium aluminaum silicate, maltodextrin, methylcellulose, polymethacrylates, povidone, pregelatinized starch, sodium alginate, starch, and zein, or mixtures thereof.

14. The pharmaceutical composition of claim 13, wherein the binder is hydroxypropyl cellulose.

15 The pharmaceutical composition of claim 14, wherein the disintegrant is selected from the group consisting of alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium, colloidal silicon dioxide, croscarmellose sodium, crospovidone, guar gum, magnesium aluminum silicate, methylcellulose, microcrystalline cellulose, polyacrilin potassium, powdered cellulose, pregelatinized starch, sodium alginate, and starch, or mixtures thereof.

16. The pharmaceutical composition of claim 15, wherein the disintegrant is croscarmellose sodium.

17. The pharmaceutical composition of claim 4, wherein the glidant is colloidal silicon dioxide.

18. The pharmaceutical composition of claim 4, wherein the lubricant is selected from the group consisting of magnesium stearate, Lubritab.RTM., stearic acid, and talc, or mixtures thereof.

19. The pharmaceutical composition of claim 4, wherein the lubricant is magnesium stearate.

20. The pharmaceutical composition of claim 4, further comprising a film coating.

21. The pharmaceutical composition of claim 20, wherein the film coating comprises Opadry Yellow.

22. The pharmaceutical formulation of claims 1-4 which is a tablet formulation.

23. A pharmaceutical composition comprising:

Component	Weight/Weight Percent
Compound I	25-29
Microcrystalline Cellulose	q.s.
Lactose Anhydrous	40-44
Hydroxypropyl Cellulose	2-4
Croscarmellose Sodium	2-8
Colloidal Silicon Dioxide	0.1-0.4
Magnesium Stearate	0.7-0.9
Total	100

24. The pharmaceutical composition of claim 22, further comprising a film coating.

25. The pharmaceutical composition of claim 24, wherein the film coating comprises Opadry yellow.

26. A method for treating cancer, comprising administering to a patient in need of such treatment a pharmaceutical composition of claim 1-4 or 23, alone or in combination with another therapeutic agent.

27. The method of claim 26, wherein the cancer is selected from the group consisting of pancreatic cancer, kidney cancer, liver cancer, prostate cancer, gastric cancer, gastroesophageal cancer, melanoma, lung cancer, breast cancer, thyroid cancer, and astrocytic tumors.

28. The method of claim 27, wherein the cancer is pancreatic cancer, hepatocellular carcinoma (HCC), renal cell carcinoma, castration-resistant prostate cancer (CRPC), gastric or gastroesophageal junction cancer, melanoma, small cell lung cancer (SCLC), ovarian cancer, primary peritoneal or fallopian tube carcinoma, estrogen receptor positive breast cancer, estrogen receptor/progesterone receptor/HER2-negative (triple-negative) breast cancer, inflammatory (regardless of receptor status) breast cancer, non-small cell lung cancer (NSCLC), or medullary thyroid cancer.

29. A process for manufacturing a pharmaceutical composition comprising Compound **I**, comprising the steps of:

a. Delumping unmilled Compound I;
b. Premixing the delumped Compound I with microcrystalline cellulose, anhydrous lactose , and croscarmellose sodium to form a binder solution;
c. Wet high shear granulation of the binder solution to produce wet granules;
d. Wet screening of the wet granules to produce wet screened granules;
e. Fluid bed drying of the wet screened granules to produce dried granules;
f. Dry milling of the dried granules to produce dried milled granules;
g. Blending the dried milled granules with colloidal silicon and croscarmellose to produce an extragranular blend;
h. Lubricant blending of the extragranular blend and magnesium stearate to produce a final blend; and
i. Tablet compression of the final blend to form an uncoated core tablet.

30. The process of claim 29, further comprising the step of film coating of the uncoated core tablet.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/044378

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K31/47
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/030140 A2 (EXELIXIS INC [US]; BANNEN LYNNE CANNE [US]; CHAN DIVA SZE-MING [US]; C) 7 April 2005 (2005-04-07) cited in the application table 2, compound 12 example 48 table 4, entry 289 paragraphs [0025], [0031], [0252], [0253] ----- -/--	1-30

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 October 2011	08/11/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sproll, Susanne

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KURZROCK R ET AL: "379 POSTER A phase I study of XL184, a MET, VEGFR2, and RET kinase inhibitor, administered orally to patients (pts) with advanced malignancies, including a subgroup of pts with medullary thyroid cancer (MTC)", EUROPEAN JOURNAL OF CANCER. SUPPLEMENT, PERGAMON, OXFORD, GB, vol. 6, no. 12, 1 October 2008 (2008-10-01), page 119, XP025534443, ISSN: 1359-6349, DOI: 10.1016/S1359-6349(08)72313-9 [retrieved on 2008-10-01] the whole document -----	1-30
X,P	WO 2010/083414 A1 (EXELIXIS INC [US]; ST CLAIR BROWN ADRIAN [GB]; LAMB PETER [US]; GALLAG) 22 July 2010 (2010-07-22) cited in the application the whole document -----	1-30

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2011/044378

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005030140 A2	07-04-2005	AT 520403 T	15-09-2011
		AT 517091 T	15-08-2011
		AU 2004275842 A1	07-04-2005
		AU 2010204459 A1	19-08-2010
		AU 2010204461 A1	19-08-2010
		CA 2537812 A1	07-04-2005
		CA 2744997 A1	07-04-2005
		DK 2213661 T3	19-09-2011
		EP 1673085 A2	28-06-2006
		EP 2210607 A1	28-07-2010
		EP 2213661 A1	04-08-2010
		JP 4638436 B2	23-02-2011
		JP 2007506777 A	22-03-2007
		JP 2010265302 A	25-11-2010
		JP 2010235631 A	21-10-2010
		JP 2010235632 A	21-10-2010
		JP 2010280674 A	16-12-2010
		JP 2011042686 A	03-03-2011
		US 2009170896 A1	02-07-2009
		US 2007054928 A1	08-03-2007
		US 2007225307 A1	27-09-2007
		US 2007244116 A1	18-10-2007
		US 2009105299 A1	23-04-2009
		US 2011077233 A1	31-03-2011
WO 2010083414 A1	22-07-2010	AR 075025 A1	02-03-2011

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/024591

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D215/227 A61K31/47 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/083414 A1 (EXELIXIS INC [US]; ST CLAIR BROWN ADRIAN [GB]; LAMB PETER [US]; GALLAG) 22 July 2010 (2010-07-22) cited in the application Scheme 1 on page24; claims;claim 11 -----	1-34

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 May 2012	25/05/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Wolf, Claudia

1

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2012/024591

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010083414 A1	22-07-2010	AR 075025 A1	02-03-2011
		AU 2010204619 A1	01-09-2011
		CA 2758030 A1	22-07-2010
		CN 102388024 A	21-03-2012
		EP 2387563 A1	23-11-2011
		KR 20120013301 A	14-02-2012
		SG 173014 A1	29-08-2011
		TW 201036948 A	16-10-2010
		US 2012035212 A1	09-02-2012
		WO 2010083414 A1	22-07-2010

Form PCT/ISA/210 (patent family annex) (April 2005)

Electronic Patent Application Fee Transmittal

Application Number:	15348716
Filing Date:	10-Nov-2016
Title of Invention:	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds
First Named Inventor/Applicant Name:	Jo Ann Wilson
Filer:	Heid Marie Berven/Charles Gregg-Geist
Attorney Docket Number:	224990/10-039C2-US/405045

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
LATE FILING FEE FOR OATH OR DECLARATION	2051	1	70	70
PROCESSING FEE, EXCEPT PROV. APPLS.	2830	1	70	70
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 5 months with $0 paid	2255	1	1500	1500
Miscellaneous:				
		Total in USD ($)		**1640**

Electronic Acknowledgement Receipt

EFS ID:	29579207
Application Number:	15348716
International Application Number:	
Confirmation Number:	5882
Title of Invention:	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds
First Named Inventor/Applicant Name:	Jo Ann Wilson
Customer Number:	91684
Filer:	Heid Marie Berven/Charles Gregg-Geist
Filer Authorized By:	Heid Marie Berven
Attorney Docket Number:	224990/10-039C2-US/405045
Receipt Date:	22-JUN-2017
Filing Date:	10-NOV-2016
Time Stamp:	15:03:30
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1640
RAM confirmation Number	062317INTEFSW00001497503145
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		EX10-039C2-US.pdf	5893791 0e01028d313b404f9f0762383eca1c68d47c6de7	yes	35

Multipart Description/PDF files in .zip description

Document Description	Start	End
Transmittal Letter	35	35
Miscellaneous Incoming Letter	34	34
Extension of Time	33	33
Information Disclosure Statement (IDS) Form (SB08)	25	32
Application Data Sheet	17	24
Request under Rule 48 correcting inventorship	15	16
Applicant Arguments/Remarks Made in an Amendment	10	14
Claims	5	9
Preliminary Amendment	4	4
Applicant Response to Pre-Exam Formalities Notice	3	3
Transmittal Letter	1	2

Warnings:

Information:

2	Foreign Reference	WO2005030140A2_EX04-064C-PC.PDF	18194629 cd297f71e0ed175bfa7dcacdd8588bca052c4a8e	no	428

Warnings:

Information:

3	Foreign Reference	WO2009136663A1.PDF	12623477 4d4b466297604a28fb793626cb651c667601afb5	no	340
Warnings:					
Information:					
4	Foreign Reference	WO2010083414A1_EX09-001C-PC.PDF	1652633 04f165260ce54c53d8d6dc74afd555c3dac568f8	no	74
Warnings:					
Information:					
5	Foreign Reference	WO2011017639A1.PDF	3225484 45126800a9fde12a335d5aef1bf6584dc0ff3b9b	no	61
Warnings:					
Information:					
6	Foreign Reference	WO2012009722_10-011C-PC.PDF	1668309 37012c167e21cf6d9fc4ae9ce6665cfae7df45aa	no	40
Warnings:					
Information:					
7	Non Patent Literature	EMA-EMEA-EuropeanMedicinesAgency-MalateSaltDocument-2008.pdf	183250 47a92c8ce2183914acff0e37bc91e9eaa5e6cc7b	no	10
Warnings:					
Information:					
8	Non Patent Literature	ISR.pdf	52813 cb46f7306b3ef7350ad8c73f27001124a15cf5c4	no	2
Warnings:					
Information:					
9	Non Patent Literature	Kurzrock_Poster.pdf	182875 e25bdda64668a3fb982380c00cc3bf681d7fbfe6	no	1
Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					

10	Non Patent Literature	MSDS_Sigma-Aldrich_67Dimethoxyquinoline.pdf	120183 34242c08349b5873c43a6f4cd007a5a7a37f2f52	no	7
Warnings:					
Information:					
11	Non Patent Literature	US_DHHS_GuidanceForIndustry-StabilityTesting_Nov2003.pdf	280128 b0891b05f0d5103a7b8e1ebee3e57f6157cb1790	no	25
Warnings:					
Information:					
12	Fee Worksheet (SB06)	fee-info.pdf	34631 dad3fa982c00b1c11b5f24250f8f94c8fd4db3bc	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	44112203	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

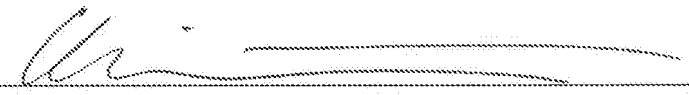
Inventors:	Jo Ann Wilson, et al.	Confirmation No.:	5882
Application No.:	15/348,716	Art Unit:	1629
Filed:	November 10, 2016	Examiner:	TBD
Atty. Docket No.:	224990/10-039C2-US/405045		

Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

CERTIFICATE OF TRANSMISSION UNDER 37 C.F.R. § 1.8(a)

The undersigned hereby certifies that the following documents are being electronically filed in accordance with 37 C.F.R. § 1.6(a)(4) on this 22nd day of June, 2017:

1. Cover Letter to the Commissioner for Patents;
2. Response to the Notice to File Missing Parts of Nonprovisional Application dated November 22, 2016, and Preliminary Amendment;
3. Request to Correct Inventorship under 37 C.F.R. § 1.48;
4. Replacement Application Data Sheet (PTO/AIA/14);
5. Information Disclosure Statement (PTO/SB/08);
6. Foreign Patent Literature Documents (5 documents);
7. Non-Patent Literature Documents (5 documents);
8. Petition for Extension of Time (PTO/AIA/22);
9. Fee Transmittal form (PTO/SB/17); and
10. This Certificate of Transmission under 37 C.F.R. § 1.8(a).



Charles W. Gregg-Geist for Heidi M. Berven, Ph.D., Reg. No. 48,951

PTO/SB/17 (03-13)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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FEE TRANSMITTAL

Complete if known	
Application Number	15/348,716
Filing Date	2016-11-10
First Named Inventor	Jo Ann Wilson
Examiner Name	TBD
Art Unit	1629
Practitioner Docket No.	224990/10-039C2-US/405045

☑ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29. Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

TOTAL AMOUNT OF PAYMENT ($) 1,640.00

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☑ Deposit Account Deposit Account Number: 503145 Deposit Account Name: Honigman Miller Schwartz and Cohn LLP

For the above-identified deposit account, the Director is hereby authorized to (check all that apply):

☑ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☑ Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17 ☑ Credit any overpayment of fee(s)

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES (U = undiscounted fee; S = small entity fee; M = micro entity fee)

	FILING FEES			SEARCH FEES			EXAMINATION FEES			
Application Type	U ($)	S ($)	M ($)	U ($)	S ($)	M ($)	U ($)	S ($)	M ($)	Fees Paid ($)
Utility	280	140*	70	600	300	150	720	360	180	0
Design	180	90	45	120	60	30	460	230	115	
Plant	180	90	45	380	190	95	580	290	145	
Reissue	280	140	70	600	300	150	2,160	1,080	540	
Provisional	260	130	65	0	0	0	0	0	0	

* The $140 small entity status filing fee for a utility application is further reduced to $70 for a small entity status applicant who files the application via EFS-Web.

2. EXCESS CLAIM FEES

Fee Description	Undiscounted Fee ($)	Small Entity Fee ($)	Micro Entity Fee ($)
Each claim over 20 (including Reissues)	80	40	20
Each independent claim over 3 (including Reissues)	420	210	105
Multiple dependent claims	780	390	195

Total Claims		Extra Claims		Fee ($)		Fee Paid ($)
_____	-20 or HP =	_____	x	_____	=	0

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims		Extra Claims		Fee ($)		Fee Paid ($)
_____	-3 or HP =	_____	x	_____	=	0

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims	Fee ($)	Fee Paid ($)
	_____	0

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $400 ($200 for small entity) ($100 for micro entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets		Extra Sheets		Number of each additional 50 or fraction thereof		Fee ($)		Fee Paid ($)
_____	- 100 =	_____	/ 50 =	_____ (round up to a whole number)	x	_____	=	0

4. OTHER FEE(S)

	Fees Paid ($)
Non-English specification, $130 fee (no small or micro entity discount)	0
Non-electronic filing fee under 37 CFR 1.16(t) for a utility application, $400 fee ($200 small or micro entity)	0
Other (e.g., late filing surcharge): Late filing surcharge ($70); Processing Fee ($70); Five Months' Extension of Time ($1,500)	1,640.00

SUBMITTED BY

Signature	/Heidi M. Berven, Ph.D./	Registration No. (Attorney/Agent) 48,951	Telephone 269-337-7710
Name (Print/Type)	Heidi M. Berven, Ph.D.		Date 2017-06-22

This collection of information is required by 37 CFR 1.136. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/22 (03-13)
Approved for use through 7/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)

Docket Number (Optional): 224990/10-039C2-US/405045

Application Number: 15/348,716

Filed: November 10, 2016

For: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

Art Unit: 1629

Examiner: TBD

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	Micro Entity Fee	
☐ One month (37 CFR 1.17(a)(1))	$200	$100	$50	$
☐ Two months (37 CFR 1.17(a)(2))	$600	$300	$150	$
☐ Three months (37 CFR 1.17(a)(3))	$1,400	$700	$350	$
☐ Four months (37 CFR 1.17(a)(4))	$2,200	$1,100	$550	$
☑ Five months (37 CFR 1.17(a)(5))	$3,000	$1,500	$750	$ 1,500.00

☑ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 503145.

☑ Payment made via EFS-Web.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant.

☑ attorney or agent of record. Registration number 48,951.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

Signature — Date: June 22, 2017

Heidi M. Berven, Ph.D. — Typed or printed name

269-337-7710 — Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ * Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.136(a). The information is required to obtain or retain a benefit by the public, which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 6 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

PTO/SB/08a (03-15)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	15348716
Filing Date	2016-11-10
First Named Inventor	Jo Ann Wilson
Art Unit	1629
Examiner Name	TBD
Attorney Docket Number	224990/10-039C2-US/405045

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	7166722		2007-01-23	MATSUNAGA, et al.	
	2	7579473		2011-07-12	BANNEN, et al.	
	3	7977345		2011-08-16	BANNEN, et al.	
	4	7999006		2011-08-16	LAMB, Peter	
	5	8067436		2011-11-29	BANNEN, et al.	
	6	8178532		2012-05-15	BANNEN, et al.	
	7	8314232		2012-11-20	DESCHAMPS, et al.	
	8	8476298		2013-07-02	BANNEN, et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15348716
	Filing Date	2016-11-10
	First Named Inventor	Jo Ann Wilson
	Art Unit	1629
	Examiner Name	TBD
	Attorney Docket Number	224990/10-039C2-US/405045

	9	8497284		2013-07-30	BANNEN, et al.	
	10	8673912		2014-03-18	CANNON, et al.	
	11	8877776		2014-11-04	BROWN, et al.	
	12	9174947		2015-11-03	BANNEN, et al.	
	13	9365516		2016-06-14	WILSON, et al.	

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20050209247		2005-09-22	CAI, et al.	
	2	20070054928		2007-03-08	BANNEN, et al.	
	3	20070078159		2007-04-05	MATSUSHIMA, et al.	
	4	20080161305		2008-07-03	FORSYTH, et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15348716
	Filing Date	2016-11-10
	First Named Inventor	Jo Ann Wilson
	Art Unit	1629
	Examiner Name	TBD
	Attorney Docket Number	224990/10-039C2-US/405045

	5	20090274693		2009-11-05	GILMER, et al.	
	6	20110059081		2011-03-10	BACUS, Sarah	
	7	20110077233		2011-03-31	BANNEN, et al.	
	8	20120070368		2012-03-22	BANNEN, et al.	
	9	20120184523		2012-07-19	BANNEN, et al.	
	10	20120252840		2012-10-04	AFTAB, et al.	
	11	20120282179		2012-11-08	AFTAB, et al.	
	12	20130030172		2013-01-31	WILSON, et al.	
	13	20130142790		2013-06-06	GILMER, et al.	
	14	20130143881		2013-06-06	CANNON, et al.	
	15	20130150363		2013-06-13	GILMER, et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15348716
	Filing Date	2016-11-10
	First Named Inventor	Jo Ann Wilson
	Art Unit	1629
	Examiner Name	TBD
	Attorney Docket Number	224990/10-039C2-US/405045

	16	20130197230		2013-08-01	WILSON, et al.	
	17	20130252940		2013-09-26	BANNEN, et. al.	
	18	20130252956		2013-09-26	KALLENDER, et al.	
	19	20130330377		2013-12-12	WILSON, Jo Ann	
	20	20130337015		2013-12-19	WILSON, et al.	
	21	20140057908		2014-02-27	SMITH, et al.	
	22	20140057943		2014-02-27	SMITH, et al.	
	23	20140066444		2014-03-26	SMITH, et al.	
	24	20140155396		2014-06-05	BANNEN, et. al.	
	25	20140179736		2014-06-26	SCHWAB, et al.	
	26	20140200242		2014-07-17	WILSON, et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15348716
	Filing Date	2016-11-10
	First Named Inventor	Jo Ann Wilson
	Art Unit	1629
	Examiner Name	TBD
	Attorney Docket Number	224990/10-039C2-US/405045

	27	20140228401		2014-08-14	AFTAB, et al.	
	28	20140256938		2014-09-11	WILSON, et al.	
	29	20140302012		2014-10-09	AFTAB, et al.	
	30	20140323522		2014-10-30	AFTAB, et al.	
	31	20150057310		2015-02-26	BROWN, et al.	
	32	20150196545		2015-07-16	AFTAB, et al.	
	33	20150202196		2015-07-23	BANNEN, et al.	
	34	20150376133		2015-12-31	BANNEN, et al.	
	35	20160000772		2016-01-07	AFTAB, et al.	
	36	20160051532		2016-02-25	AFTAB, et al.	
	37	20160185725		2016-06-30	BANNEN, et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15348716
	Filing Date	2016-11-10
	First Named Inventor	Jo Ann Wilson
	Art Unit	1629
	Examiner Name	TBD
	Attorney Docket Number	224990/10-039C2-US/405045

	38	20160220554		2016-08-04	SMITH, et al.	
	39	20160229805		2016-08-11	WILSON, et al.	
	40	20170143689		2017-05-25	WILSON, et al.	

If you wish to add additional U.S. Published Application citation information please click the Add button.

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2005030140	WO		2005-04-07	EXELIXIS, INC.		☐
	2	2009136663	WO		2009-11-12	TAKEDA PHARMACEUTICAL COMPANY LIMITED		☐
	3	2010083414	WO		2010-07-22	EXELIXIS, INC.		☐
	4	2011017639	WO		2011-02-10	EXELIXIS, INC.		☐
	5	2012009722	WO		2012-01-19	EXELIXIS, INC.		☐

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NON-PATENT LITERATURE DOCUMENTS

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15348716
	Filing Date	2016-11-10
	First Named Inventor	Jo Ann Wilson
	Art Unit	1629
	Examiner Name	TBD
	Attorney Docket Number	224990/10-039C2-US/405045

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	European Medicines Agency, "Committee for orphan medicinal products December 2008 plenary meeting monthly report", Doc. Ref. EMEA/666785/2008 Corr. 2, December 22, 2008.	☐
	2	International Search Report for PCT/US2012/024591, mailed May 25, 2012	☐
	3	Kurzrock R et al. "379 POSTER A phase I study of XL 184, a MET, VEGFR2, and RET kinase inhibitor, administered orally to patients (pts) with advanced malignancies, including a subgroup of pts with medullary thyroid cancer (MTC)." Eropean journal of cancer. supplement, vol 6, no 12, 2008-10-01, 119.	☐
	4	SIGMA-ALDRICH CORPORATION, "Safety Data Sheet for 6,7-Dimethoxy-1H-Quinolin-4-One", Version 5.0, October 20, 2014, retrieved from the internet at http://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=US&language=en&productNumber=CDS009101&brand=ALDRICH on October 1, 2015.	☐
	5	United States Department of Health and Human Services, "Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products", Revision 2, November 2003, retrieved from the internet at www.fda.gov/downloads/drugs/guidancecomplianceregulatory information/guidances/ucm073369.pdf on October 1, 2015.	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15348716
Filing Date	2016-11-10
First Named Inventor	Jo Ann Wilson
Art Unit	1629
Examiner Name	TBD
Attorney Docket Number	224990/10-039C2-US/405045

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature		Date (YYYY-MM-DD)	2017-06-22
Name/Print	Heidi M. Berven, Ph.D.	Registration Number	48,951

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	224990/10-039C2-US/405045
	Application Number	15348716
Title of Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Jo Ann		Wilson	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	San Francisco	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	74 Seward Street
Address 2	

City	San Francisco	State/Province	CA
Postal Code	94114	Country	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	~~Khalid~~		~~Shah~~	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

~~City~~	~~South San Francisco~~	~~State/Province~~	~~CA~~	~~Country of Residence~~	~~US~~

Mailing Address of Inventor:

~~Address 1~~	~~12 Amberwood Circle~~
Address 2	

~~City~~	~~South San Francisco~~	~~State/Province~~	~~CA~~
~~Postal Code~~	~~94080~~	~~Country~~	~~US~~

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	224990/10-039C2-US/405045
	Application Number	15348716
Title of Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds	

☐ An Address is being provided for the correspondence Information of this application.			
Customer Number	91684		
Email Address	patent@honigman.com	Add Email	Remove Email

Application Information:

Title of the Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds		
Attorney Docket Number	224990/10-039C2-US/405045	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)		**Suggested Figure for Publication (if any)**	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	224990/10-039C2-US/405045
	Application Number	15348716
Title of Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds	

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	91684		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
~~TBD~~ 15348716	~~Continuation of~~ Divisional of	13984559	~~2013-08-09~~ 2014-03-20
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
13984559	a 371 of international	PCT/US12/24591	2012-02-10
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US12/24591	Claims benefit of provisional	61441520	2011-02-10
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US12/24591	Claims benefit of provisional	61441527	2011-02-10

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	224990/10-039C2-US/405045
	Application Number	15348716
Title of Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds	

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	224990/10-039C2-US/405045
	Application Number	15348716
Title of Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	224990/10-039C2-US/405045
	Application Number	15348716
Title of Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◉ Assignee	○ Legal Representative under 35 U.S.C. 117	○ Joint Inventor
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	Exelixis, Inc.		
Mailing Address Information For Applicant:			
Address 1	210 East Grand Ave.		
Address 2			
City	South San Francisco	**State/Province**	CA
Country	US	Postal Code	94080
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button.

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	224990/10-039C2-US/405045
	Application Number	15348716
Title of Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature				Date (YYYY-MM-DD)	2017-06-22
First Name	Heidi M.	Last Name	Berven	Registration Number	48951

Additional Signature may be generated within this form by selecting the Add button.

PTO/AIA/14 (11-15)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	224990/10-039C2-US/405045
	Application Number	15348716
Title of Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds	

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors:	Jo Ann Wilson, et al.	Confirmation No.:	5882
Application No.:	15/348,716	Art Unit:	1629
Filed:	November 10, 2016	Examiner:	TBD
Atty. Docket No.:	224990/10-039C2-US/405045		

Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST TO CORRECT INVENTORSHIP UNDER 37 C.F.R. § 1.48

Dear Sir or Madam:

The present communication is filed to request correction of the inventorship for U.S. patent application Serial No. 15/348,716 by removing the name of inventor Khalid Shah of South San Francisco, CA. In support of this request, the Applicant hereby submits a marked-up replacement Application Data Sheet (PTO/AIA/14) indicating the correct inventorship for U.S. patent application Serial No. 15/348,716, and the processing fee set forth in § 1.17(i).

Currently, the U.S. Patent and Trademark Office lists the following as inventors for U.S. patent application Serial No. 15/348,716: Jo Ann Wilson; Khalid Shah. The correct inventorship for U.S. patent application Serial No. 15/348,716 is: Jo Ann Wilson. Please remove Khalid Shah as an inventor from U.S. patent application Serial No. 15/348,716. The Applicant respectfully requests issuance of an updated Filing Receipt reflecting the correct inventorship for this application.

The Applicant believes that due for this submission is the $70.00 processing fee set forth in 37 C.F.R. § 1.17(i). The Office is authorized to charge this $70.00 to Deposit Account Number 503145, referencing Attorney Docket Number 224990/10-039C2-US/405045. It is believed that no additional fees are due for this Request; however, if there are any other fees required, or any credits, please apply them to Deposit Account Number 503145, referencing Attorney Docket Number 224990/10-039C2-US/405045.

Inventors:	Jo Ann Wilson, et al.	Confirmation No.:	5882
Application No.:	15/348,716	Art Unit:	1629
Filed:	November 10, 2016	Examiner:	TBD
Atty. Docket No.:	224990/10-039C2-US/405045		

Respectfully submitted,

By: Honigman Miller Schwartz and Cohn LLP

Date: June 22, 2017

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REMARKS

Amendment to the Specification

The Applicant has amended paragraph [0001] of the specification to recite that this application is a divisional application of United States Serial Number 13/984,559, filed March 20, 2014, which claims priority under 35 U.S.C. § 371 to Patent Cooperation Treaty application PCT/US2012/024591, filed February 10, 2012, which claims the benefit of United States provisional application number 61/441,520, filed February 10, 2011, and United States provisional application number 61/441,527, filed February 10, 2011, the entire contents of which are incorporated herein by reference. Submitted herewith is a replacement Application Data Sheet (ADS) (PTO/AIA/14) marked to show the change from the ADS filed in this application on November 10, 2016. The Applicant respectfully requests issuance of an updated Filing Receipt reflecting that this application is a divisional application, and is not a continuation application.

The Applicant notes that the replacement ADS is also marked to show the change to inventorship of this application as set forth in the Request to Correct Inventorship under 37 C.F.R. § 1.48 submitted herewith.

Claim Status

Claims 1-7, 11, and 13 are currently amended. No new matter is added to the currently amended claims.

Claims 8-10 and 12 are original.

Claims 14-34 are cancelled.

Thus, claims 1-13 are currently pending.

Note Regarding Restriction Requirement in Parent Application USSN 13/984,559

The Applicant advises that in an office action dated May 1, 2014, the Examiner of the parent application 13/984,559 (to which this currently pending divisional application claims priority) invoked a restriction requirement. The Groups identified by the Examiner were:

> **Group I**, claims 1-10, 12, and 13, drawn to a process for preparing a compound of formula I.

Group II, claims 14-15, drawn to a process for preparing a compound of formula IB.
Group III, claims 16, 19, 20, 23, and 28-34, drawn to compounds IA or IB and pharmaceutical compositions thereof.

In a response dated July 31, 2014, the Applicant elected Group III. The claims of Groups I and II were cancelled.

The currently amended claims of this divisional application fall within the scope of the Group I claims, and are thus consonant with the restriction requirement. The Applicant has cancelled the Group II and Group III claims.

Notice to File Missing Parts of Nonprovisional Application

The United States Patent and Trademark Office issued a Notice to File Missing Parts of Nonprovisional Application on November 22, 2016. The Notice requires submission of excess claims fees and the surcharge set forth in 37 C.F.R. § 1.16(f) for late submission of fees and/or inventors' declarations. In response, the Applicant submits herewith preliminary claim amendments along with the surcharge of $70.00 set forth in 37 C.F.R. § 1.16(f) for a small entity.

Information Disclosure Statement

The Applicant notes that the filing of the enclosed Information Disclosure Statement shall not be construed to be an admission that the information cited in the statement qualifies as prior art under 35 U.S.C. § § 102 or 103, or is considered to be material to patentability as defined in 37 C.F.R. § 1.56(b). It is believed that no fee is due pursuant to 37 C.F.R. § 1.97(b)(3).

Other C-Met Inhibitor Cases

The Applicant wishes to make the Examiner aware of the Applicant's other applications related to c-Met inhibitors and their use in the treatment of cancer. For the Examiner's convenience, the Applicant is providing a list of the Applicant's applications directed to the treatment of cancer using c-Met inhibitors. The Applicant understands the Examiner has electronic access to these applications and to the Office Actions that have issued in these applications, and has therefore not included copies with this Response. The Applicant will gladly provide the applications and Office Actions to the Examiner, however, upon request.

Application Number	Filing or 371 Date	Patent Number	Examiner	Status
10/573,336	09/18/2006		Koontz, Tammy J.	Abandoned
11/571,140	12/21/2006	7977345	Moore, Susanna	Issued
11/586,751	10/26/2006	9174947	Ward, Paul V.	Issued
11/753,462	05/24/2007	8178532	Ward, Paul V.	Issued
11/753,503	05/24/2007	8476298	Ward, Paul V.	Issued
11/753,514	05/24/2007	8067436	Bernhardt, Emily A.	Issued
12/393,806	02/26/2009	7579473	Seaman, D. Margaret M.	Issued
12/911,442	10/25/2010		Ward, Paul, V.	Abandoned
13/087,094	04/14/2011		Chickos, Sarah, J.	Abandoned
13/129,183	05/13/2011		Seaman, D. Margaret M.	Abandoned
13/132,650	06/03/2011		Seaman, D. Margaret M.	Abandoned
13/145,054	10/20/2011	8877776	Carter, Kendra D	Issued
13/249,815	09/30/2011	8497284	Bernhardt, Emily A.	Issued
13/384,451	07/12/2012	8673912	Anderson, Rebecca L.	Issued
13/389,266	07/12/2012		Perreira, Melissa Jean	Abandoned
13/427,093	03/22/2012		Ward, Paul V.	Abandoned
13/438,964	04/04/2012		Brown-Pettigrew, Angela C.	Abandoned
13/634,275	09/12/2012		Anderson, Rebecca L.	Abandoned
13/753,031	01/29/2013		Pagonakis, Anna	Abandoned
13/753,146	01/29/2013		Pagonakis, Anna	Abandoned
13/810,537	08/26/2013		Pallay, Michael B.	Pending
13/810,546	08/27/2013		Branson, Daniel L.	Abandoned
13/876,290	11/05/2013		Stone, Christopher R.	Abandoned
13/876,306	11/08/2013		Lee, Andrew P.	Abandoned
13/876,318	10/25/2013		Karol, Jody Lynn	Abandoned
13/888,592	05/07/2013		Ward, Paul V.	Abandoned
13/928,977	06/27/2013		Bernhardt, Emily A.	Abandoned
13/984,559	03/20/2014		Rozof, Timothy R.	Pending
14/021,614	09/09/2013		Matos Negron, Taina Del Mar	Pending
14/115,236	02/28/2014		Anderson, James D.	Pending
14/166,545	01/28/2014		Not Yet Assigned	Abandoned
14/173,973	02/06/2014		Johannsen, Diana B.	Abandoned
14/340,871	07/25/2014		Carter, Kendra D.	Pending
14/346,570	03/21/2014		Calvillo, Y. Jeanmarie Z.	Pending
14/353,251	04/21/2014	9365516	Murray, Jeffrey H.	Issued
14/356,927	05/08/2014		Baek, Bong-sook	Pending
14/356,938	05/08/2014		Cerioni, Daniel Lee	Abandoned
14/398,188	10/31/2014		Henley III, Raymond J.	Pending
14/426,580	03/06/2015		Jean-Louis, Samira J.M.	Pending
14/518,733	10/20/2014		Chickos, Sarah J.	Pending
14/668,312	03/25/2015		Brown-Pettigrew, Angela C.	Abandoned

Application Number	Filing or 371 Date	Patent Number	Examiner	Status
14/699,683	04/29/2015		Perreira, Melissa Jean	Pending
14/776,337	09/14/2015		Reese, Heidi L.	Pending
14/782,493	10/05/2015		Grazier, Nyeemah A.	Pending
14/782,537	10/05/2015		Alley, Genevieve S.	Pending
14/843,480	09/02/2015		Stone, Christopher R.	Pending
14/847,801	09/08/2015		Ward, Paul V.	Pending
14/933,801	11/05/2015		Brown-Pettigrew, Angela C.	Pending
15/066,872	03/10/2016		Ward, Paul V.	Pending
15/118,738	08/12/2016		Chandrakumar, Nizal S.	Pending
15/126,767	09/16/2016		Solola, Taofiq A.	Pending
15/133,708	04/20/2016		Murray, Jeffrey H.	Pending
15/305,854	10/21/2016		McMillian, Kara Renita	Pending
15/500,312	01/30/2017		Not Yet Assigned	Pending
15/501,582	02/03/2017		Not Yet Assigned	Pending
15/426,804	02/07/2017		Pallay, Michael B.	Pending
15/612,703	06/02/2017		Not Yet Assigned	Pending
15/617,725	06/08/2017		Not Yet Assigned	Pending
15/618,593	06/09/2017		Not Yet Assigned	Pending
15/621,527	06/13/2017		Not Yet Assigned	Pending

Extension of Time

The Applicant hereby petitions for a five-month extension of time under 37 C.F.R. § 1.136(a) for responding to the Notice to File Missing Parts of Nonprovisional Application in this application dated November 22, 2016. The fee set forth in 37 C.F.R. § 1.17(a)(5) is submitted herewith.

Conclusion

The Applicant believes this submission is fully responsive to the Notice to File Missing Parts of Nonprovisional Application Filed Under 37 C.F.R. § 1.53(b) dated November 22, 2016. The Applicant reserves the right to file divisional applications or take such other appropriate action as deemed necessary to protect the subject matter restricted, canceled, or withdrawn from this application.

It is believed that the fees due for this response are the surcharge of $70.00 set forth in 37 C.F.R. § 1.16(f), the processing fee of $70.00 set forth in § 1.17(i)(1), and the fee of $1,500.00 set forth in § 1.17(a)(5). The Applicant hereby authorizes the Office to charge this total of

$1,640.00 to Deposit Account Number 503145, referencing Attorney Docket Number 224990/10-039C2-US/405045. It is believed that no other fees are due at this time. However, if there are any additional charges for this submission, or any credits, please apply them to Deposit Account Number 503145, referencing Attorney Docket Number 224990/10-039C2-US/405045.

Respectfully submitted,

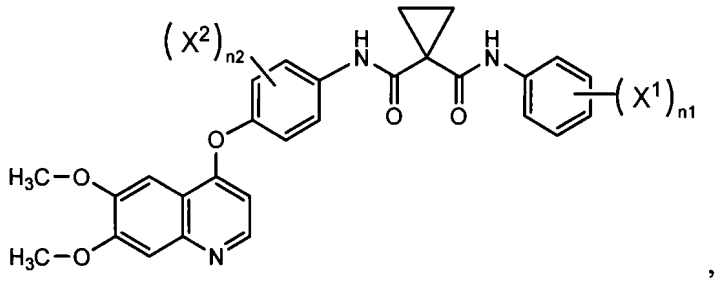
HONIGMAN MILLER SCHWARTZ AND COHN LLP

Dated: June 22, 2017

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Reg. No. 48,951
Honigman Miller Schwartz and Cohn LLP
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Kalamazoo, MI 49007-3800
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CLAIM AMENDMENTS

1. (Currently amended) A process for preparing a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is H, Br, Cl, or F;

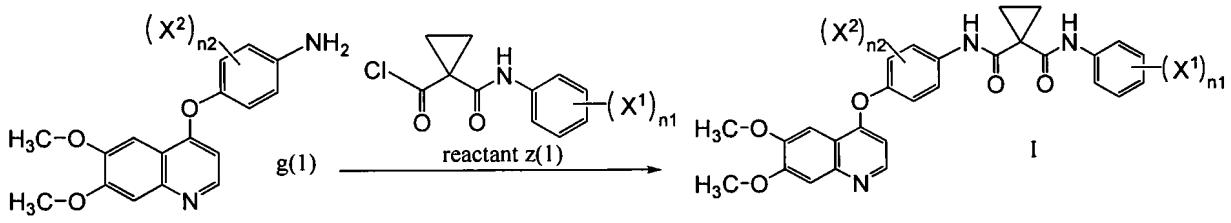
X^2 is H, Br, Cl, or F;

n1 is 1-2; and

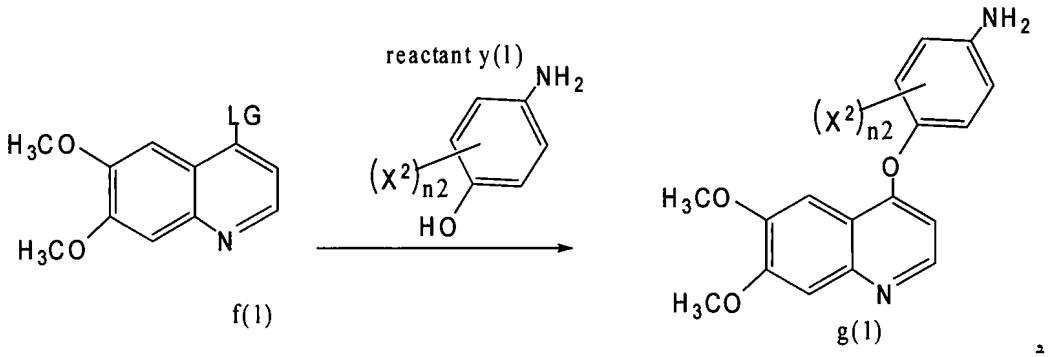
n2 is 1-2;

the process comprising:

contacting a [[the]] compound of formula g(1) with a reactant z(1) to yield the compound of formula I:

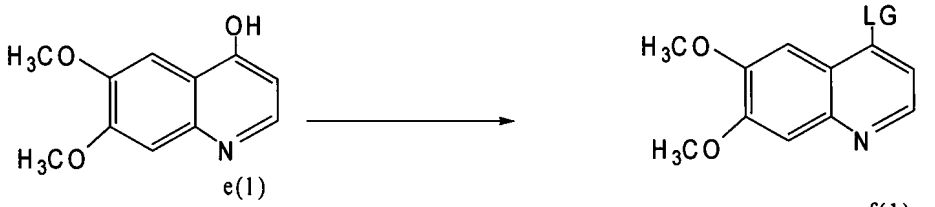


2. (Currently amended) The process according to claim 1, wherein the compound of formula g(1) is made by reacting a compound of formula f(1) with a reactant y(1) to yield the compound of formula g(1):



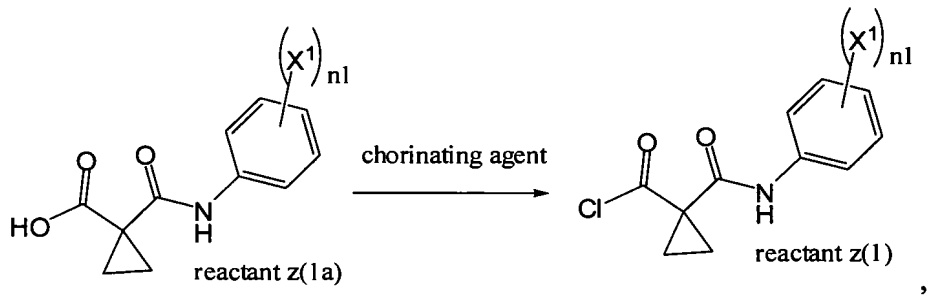
wherein LG represents a leaving group, and each X^2 and n2 are as defined in claim 1.

3. (Currently amended) The process according to claim 2, wherein the compound of formula f(1) is made by converting a compound of formula e(1) to the compound of formula f(1):



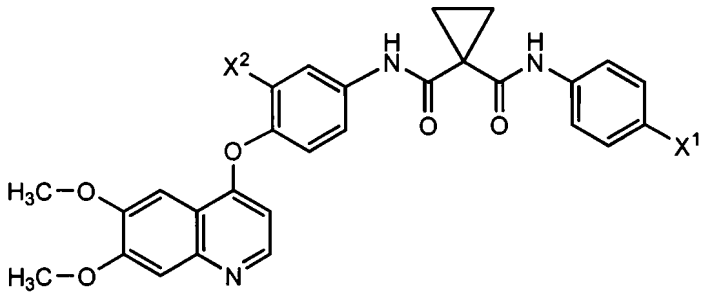
wherein LG represents a leaving group.

4. (Currently amended) The process according to claim 1, wherein the reactant z(1) is made by reacting a reactant z(1a) with a chlorinating agent to yield the reactant z(1):



wherein X^1 is Br, Cl, or F; and n1 is 1-2.

5. (Currently amended) The process according to claim 1, wherein the compound of formula I is a compound of formula IA-1:



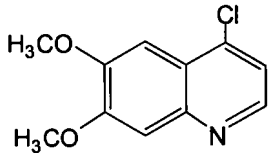
IA-1[[IA]]

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is H, Cl, Br, or F; and

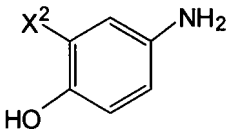
X^2 is H, Cl, Br, or F.

6. (Currently amended) The process according to claim 2[[5]], wherein the compound of formula f(1) is the compound f(2):



f(2) ;

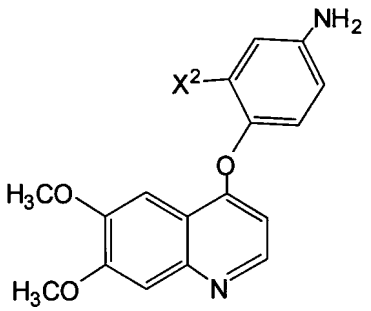
the reactant y(1) is a reactant (y)(2):



reactant (y)(2) ,

wherein X^2 is hydrogen or fluoro; and

the compound of formula g(1) is a compound of formula g(2):



g(2)

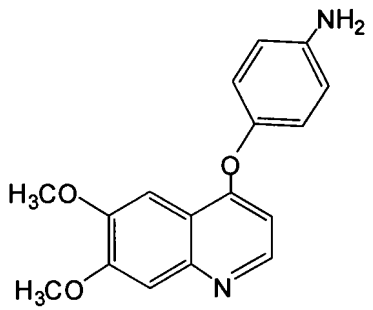
7. (Currently Amended) The process according to claim 6, wherein the reaction of the compound f(2) with the reactant (y)(2) employs a non-nucleophilic base.

8. (Original) The process according to claim 7, wherein the non-nucleophilic base is an alkali metal alkoxide; and the reaction is carried out in a polar solvent.

9. (Original) The process according to claim 8, wherein the alkali metal alkoxide is sodium tert-butoxide, and the polar solvent is DMA.

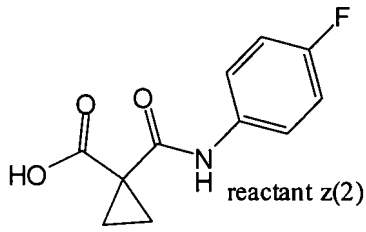
10. (Original) The process according to claim 8, wherein the alkali metal alkoxide is sodium tert-pentoxide, and the polar solvent is DMA.

11. (Currently Amended) The process according to claim [[1]] 4, wherein the compound of formula g(1) is [[of]] the compound g(3):



g(3) ;

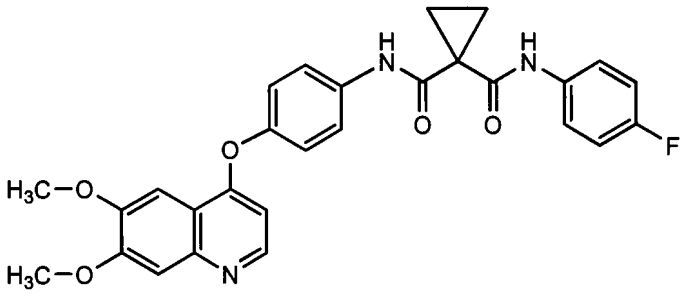
the reactant z(1a) is the reactant (z)(2):



reactant z(2)

; and

the compound of formula I is the compound of formula IA:



IA.

12. (Original) The process according to claim 11, wherein the reaction is carried out in the presence of an inorganic base.

13. (Currently amended) The process according to claim 12, wherein the inorganic base is K_2CO_3, and the ~~solvent employed in this~~ reaction is carried out in a solvent comprising a combination of THF and H_2O.

14-34. Cancelled.

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/348,716	11/10/2016	Jo Ann Wilson	224990/10-039C2-US/405045

CONFIRMATION NO. 5882

91684
JONATHAN P. O'BRIEN, PH.D.
HONIGMAN MILLER SCHWARTZ AND COHN LLP
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Kalamazoo, MI 49007-3800

PUBLICATION NOTICE



Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

Publication No.US-2017-0057921-A1
Publication Date:03/02/2017

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/348,716

APPLICATION AS FILED - PART I

	(Column 1)		(Column 2)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED		NUMBER EXTRA	RATE($)	FEE($)		RATE($)	FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A		N/A	N/A	70		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A		N/A	N/A	300		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A		N/A	N/A	360		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	34	minus 20 =	* 14	x 40 =	560	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	15	minus 3 =	* 12	x 210 =	2520			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				0.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					0.00			
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	3810		TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1)		(Column 2)	(Column 3)					
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/348,716	11/10/2016	1629	730	224990/10-039C2-US/405045	34	15

CONFIRMATION NO. 5882

91684
JONATHAN P. O'BRIEN, PH.D.
HONIGMAN MILLER SCHWARTZ AND COHN LLP
350 EAST MICHIGAN AVENUE, SUITE 300
Kalamazoo, MI 49007-3800

FILING RECEIPT



Date Mailed: 11/22/2016

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Jo Ann Wilson, San Francisco, CA;
Khalid Shah, South San Francisco, CA;

Applicant(s)

Exelixis, Inc., South San Francisco, CA;

Power of Attorney: The patent practitioners associated with Customer Number 91684

Domestic Priority data as claimed by applicant

This application is a CON of 13/984,559 03/20/2014
which is a 371 of PCT/US12/24591 02/10/2012
which claims benefit of 61/441,520 02/10/2011
and claims benefit of 61/441,527 02/10/2011

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 11/18/2016

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/348,716**

Projected Publication Date: 03/02/2017

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****
Title

Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/348,716	11/10/2016	Jo Ann Wilson	224990/10-039C2-US/405045

CONFIRMATION NO. 5882

91684
JONATHAN P. O'BRIEN, PH.D.
HONIGMAN MILLER SCHWARTZ AND COHN LLP
350 EAST MICHIGAN AVENUE, SUITE 300
Kalamazoo, MI 49007-3800

FORMALITIES LETTER

OC000000087322741

Date Mailed: 11/22/2016

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing.

Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- Additional claim fees of $ **3080** as a small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.
- Surcharge as set forth in 37 CFR 1.16(f) must be submitted.
  The surcharge is due for any one of:
  - late submission of the basic filing fee, search fee, or examination fee,
  - late submission of inventor's oath or declaration,
  - filing an application that does not contain at least one claim on filing, or
  - submission of an application filed by reference to a previously filed application.

SUMMARY OF FEES DUE:

The fee(s) required within **TWO MONTHS** from the date of this Notice to avoid abandonment is/are itemized below. Small entity discount is in effect. If applicant is qualified for micro entity status, an acceptable Certification of Micro Entity Status must be submitted to establish micro entity status. (See 37 CFR 1.29 and forms PTO/SB/15A and 15B.)

- $ **70** surcharge.
- $ **2520** for **12** independent claims over 3.
- $ **560** for **14** total claims over 20.
- $(**0**) previous unapplied payment amount.
- $ **3150** TOTAL FEE BALANCE DUE.

Items Required To Avoid Processing Delays:

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  Jo Ann Wilson
  Khalid Shah

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web, including a copy of this Notice and selecting the document description "Applicant response to Pre-Exam Formalities Notice". https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at 1-866-217-9197 or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/mabebe/

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

Substitute for Form PTO-1360
(For use with Form PTO/SB/06)

Application Number	Filing Date
15348716	

Applicant(s) Jo Ann Wilson

* May be used for additional claims or amendments

CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT	
	Indep	Depend	Indep	Depend	Indep	Depend
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Total Claims	34		0		0	

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PTO/AIA/15 (03-13)
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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	224990/10-039C2-US/405045
First Named Inventor	Jo Ann Wilson
Title	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Con
Express Mail Label No.	

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. [✔] **Fee Transmittal Form** (PTO/SB/17 or equivalent)
2. [✔] **Applicant asserts small entity status.** See 37 CFR 1.27
3. [ ] **Applicant certifies micro entity status.** See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
4. [✔] **Specification** [*Total Pages* 47] Both the claims and abstract must start on a new page. *(See MPEP § 608.01(a) for information on the preferred arrangement)*
5. [ ] **Drawing(s)** (35 U.S.C. 113) [*Total Sheets* ____]
6. **Inventor's Oath or Declaration** [*Total Pages* ____] *(including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e))*
   a. [ ] Newly executed (original or copy)
   b. [ ] A copy from a prior application (37 CFR 1.63(d))
7. [✔] **Application Data Sheet** * *See note below.* See 37 CFR 1.76 (PTO/AIA/14 or equivalent)
8. **CD-ROM or CD-R** in duplicate, large table, or Computer Program (*Appendix*)
   [ ] Landscape Table on CD
9. **Nucleotide and/or Amino Acid Sequence Submission** *(if applicable, items a. – c. are required)*
   a. [ ] Computer Readable Form (CRF)
   b. [ ] Specification Sequence Listing on:
      i. [ ] CD-ROM or CD-R (2 copies); or
      ii. [ ] Paper
   c. [ ] Statements verifying identity of above copies

ADDRESS TO:

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ACCOMPANYING APPLICATION PAPERS

10. [ ] **Assignment Papers** (cover sheet & document(s))
    Name of Assignee ____
11. [ ] **37 CFR 3.73(c) Statement** (*when there is an assignee*) [✔] **Power of Attorney**
12. [ ] **English Translation Document** (*if applicable*)
13. [ ] **Information Disclosure Statement** (PTO/SB/08 or PTO-1449)
    [ ] Copies of citations attached
14. [✔] **Preliminary Amendment**
15. [ ] **Return Receipt Postcard** (*MPEP § 503*) (*Should be specifically itemized*)
16. [ ] **Certified Copy of Priority Document(s)** (*if foreign priority is claimed*)
17. [ ] **Nonpublication Request** Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
18. [✔] **Other:** Cover Letter to the Commissioner for Patents
    Certificate of Transmission under 37 C.F.R. § 1.8(a)

*Note: (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 must be included in an Application Data Sheet (ADS).
(2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

19. CORRESPONDENCE ADDRESS

[✔] The address associated with Customer Number: 91684 OR [ ] Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone		Email	

Signature	/Meghan M. Klaric/	Date	2016-11-10
Name (Print/Type)	Meghan M. Klaric	Registration No. (Attorney/Agent)	71226

This collection of information is required by 37 CFR 1.53(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	224990/10-039C2-US/405045
	Application Number	
Title of Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Jo Ann		Wilson	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	San Francisco	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	74 Seward Street		
Address 2			
City	San Francisco	State/Province	CA
Postal Code	94114	Country	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Khalid		Shah	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	South San Francisco	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	12 Amberwood Circle		
Address 2			
City	South San Francisco	State/Province	CA
Postal Code	94080	Country	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

PTO/AIA/14 (11-15)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	224990/10-039C2-US/405045
	Application Number	
Title of Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds	

☐ An Address is being provided for the correspondence Information of this application.			
Customer Number	91684		
Email Address	patent@honigman.com	Add Email	Remove Email

Application Information:

Title of the Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds		
Attorney Docket Number	224990/10-039C2-US/405045	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)		**Suggested Figure for Publication (if any)**	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	224990/10-039C2-US/405045
	Application Number	
Title of Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds	

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	91684		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
TBD	Continuation of	13984559	2013-08-09
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
13984559	a 371 of international	PCT/US12/24591	2012-02-10
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US12/24591	Claims benefit of provisional	61441520	2011-02-10
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US12/24591	Claims benefit of provisional	61441527	2011-02-10

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	224990/10-039C2-US/405045
	Application Number	
Title of Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds	

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	224990/10-039C2-US/405045
		Application Number	
Title of Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds		

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

PTO/AIA/14 (11-15)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	224990/10-039C2-US/405045
	Application Number	
Title of Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◉ Assignee	○ Legal Representative under 35 U.S.C. 117	○ Joint Inventor
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

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Additional Applicant Data may be generated within this form by selecting the Add button.

Assignee Information including Non-Applicant Assignee Information:

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Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

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Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

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Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Meghan M. Klaric/			Date (YYYY-MM-DD)	2016-11-10
First Name	Meghan M.	Last Name	Klaric	Registration Number	71226

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This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

PROCESSES FOR PREPARING QUINOLINE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING SUCH COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Application No. 61/441,520, filed February 10, 2011, and 61/441,527, filed February 10, 2011, which are incorporated herein by reference

FIELD OF THE INVENTION

[0002] This disclosure relates to processes for preparing compounds useful for modulating protein kinase enzymatic activity. More specifically, this disclosure relates to processes for preparing quinolines that are useful for modulating cellular activities such as proliferation, differentiation, programmed cell death, migration, and chemo-invasion and to pharmaceutical compositions containing such compounds.

BACKGROUND OF THE INVENTION

[0003] Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms. One mechanism that can be exploited in cancer treatment is the modulation of protein kinase activity because signal transduction through protein kinase activation is responsible for many of the characteristics of tumor cells. Protein kinase signal transduction is of particular relevance in, for example, renal, gastric, head and neck, lung, breast, prostate, and colorectal cancers; hepatocellular carcinoma; as well as in the growth and proliferation of brain tumor cells.

[0004] Protein kinases can be categorized as receptor type or non-receptor type. Receptor-type tyrosine kinases are comprised of a large number of transmembrane receptors with diverse biological activity. For a detailed discussion of the receptor-type tyrosine kinases, see Plowman et al., DN&P 7(6): 334-339, 1994. Since protein kinases and their ligands play critical roles in various cellular activities, deregulation of protein kinase enzymatic activity can lead to altered cellular properties, such as uncontrolled cell growth associated with cancer. In addition to oncological indications, altered kinase signaling is implicated in numerous other pathological diseases, including, for example, immunological disorders, cardiovascular diseases, inflammatory diseases, and degenerative diseases. Therefore, protein kinases are attractive targets for small molecule drug discovery. Particularly attractive targets for small-molecule modulation with respect to antiangiogenic

and antiproliferative activity include receptor type tyrosine kinases c-Met, KDR, c-Kit, Axl, flt-3, and flt-4.

[0005] The kinase c-Met is the prototypic member of a subfamily of heterodimeric receptor tyrosine kinases (RTKs) which include Met, Ron, and Sea. The endogenous ligand for c-Met is the hepatocyte growth factor (HGF), a potent inducer of angiogenesis. Binding of HGF to c-Met induces activation of the receptor via autophosphorylation, resulting in an increase of receptor dependent signaling, which promotes cell growth and invasion. Anti-HGF antibodies or HGF antagonists have been shown to inhibit tumor metastasis *in vivo* (See: Maulik et al Cytokine & Growth Factor Reviews 2002 13, 41-59). c-Met overexpression has been demonstrated on a wide variety of tumor types including breast, colon, renal, lung, squamous cell myeloid leukemia, hemangiomas, melanomas, astrocytomas, and glioblastomas. Additionally, activating mutations in the kinase domain of c-Met have been identified in hereditary and sporadic renal papilloma and squamous cell carcinoma. (See, e.g., Maulik et al., Cytokine & growth Factor reviews 2002 13, 41-59; Longati et al., Curr Drug Targets 2001, 2, 41-55; Funakoshi et al., Clinica Chimica Acta 2003 1-23).

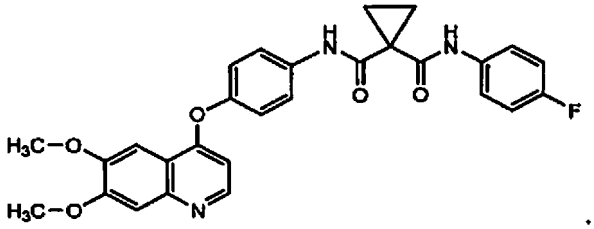
[0006] Inhibition of epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A., Drug Disc. Technol. 2001 6, 1005-1024). Kinase KDR (refers to kinase insert domain receptor tyrosine kinase) and flt-4 (fms-like tyrosine kinase-4) are both VEGF receptors. Inhibition of EGF, VEGF, and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. Drug Disc. Technol. 2001 6, 1005-1024). EGF and VEGF receptors are desirable targets for small molecule inhibition. All members of the VEGF family stimulate cellular responses by binding to tyrosine kinase receptors (the VEGFRs) on the cell surface, causing them to dimerize and become activated through transphosphorylation. The VEGF receptors have an extracellular portion with immunoglobulin-like domains, a single transmembrane spanning region, and an intracellular portion containing a split tyrosine-kinase domain. VEGF binds to VEGFR-1 and VEGFR-2. VEGFR-2 is known to mediate almost all of the known cellular responses to VEGF.

[0007] Kinase c-Kit (also called stem cell factor receptor or steel factor receptor) is a type 3 receptor tyrosine kinase (RTK) belonging to the platelet-derived growth factor receptor subfamily. Overexpression of c-Kit and c-Kit ligand has been described in variety of human

diseases, including human gastrointestinal stromal tumors, mastocytosis, germ cell tumors, acute myeloid leukemia (AML), NK lymphoma, small-cell lung cancer, neuroblastomas, gynecological tumors, and colon carcinoma. Moreover, elevated expression of c-Kit may also relate to the development of neoplasia associated with neurofibromatosis type 1 (NF-1), mesenchymal tumors GISTs, and mast cell disease, as well as other disorders associated with activated c-Kit.

[0008] Kinase Flt-3 (fms-like tyrosine kinase-3) is constitutively activated via mutation, either in the juxtamembrane region or in the activation loop of the kinase domain, in a large proportion of patients with AML (Reilly, Leuk. Lymphoma, 2003, 44: 1-7).

[0009] Small-molecule compounds that specifically inhibit, regulate, and/or modulate the signal transduction of kinases, such as c-Met, VEGFR2, KDR, c-Kit, Axl, flt-3, and flt-4 described above, are particularly desirable as a means to treat or prevent disease states associated with abnormal cell proliferation and angiogenesis. One such small-molecule is compound IA, which has the chemical structure:



IA

WO2005/030140 describes the synthesis of compound IA (Table 2, Compound 12, Example 48) and also discloses the therapeutic activity of this molecule to inhibit, regulate, and/or modulate the signal transduction of kinases (Assays, Table 4, entry 289), the entire contents of which is incorporated herein by reference.

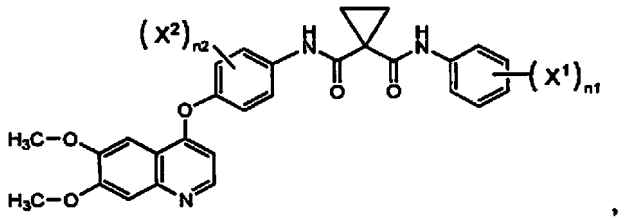
[0010] Although therapeutic efficacy is the primary concern for a therapeutic agent, the pharmaceutical composition can be equally important to its development. Generally, the drug developer endeavors to discover a pharmaceutical composition that possesses desirable properties, such as satisfactory water-solubility (including rate of dissolution), storage stability, hygroscopicity, and reproducibility, all of which can impact the processability, manufacture, and/or bioavailability of the drug.

[0011] Accordingly, there is a need for the discovery of new processes for making quinolines such as compound IA that minimize the formation of undesirable process contaminants or byproducts. There is also a need for new pharmaceutical compositions containing quinolines such as compound IA that are essentially free of process byproducts.

SUMMARY OF THE INVENTION

[0012] These and other needs are met by the present disclosure, which is directed to processes for making and compositions containing quinolines or pharmaceutically acceptable salts thereof.

[0013] In one aspect, the disclosure relates to processes for preparing a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is H, Br, Cl, or F;

X^2 is H, Br, Cl, or F;

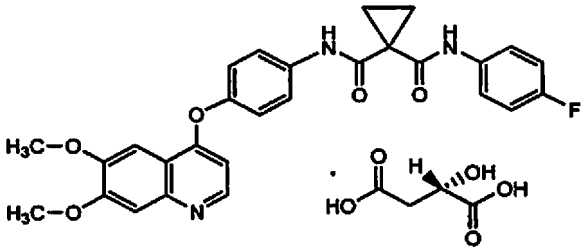
n1 is 1-2; and

n2 is 1-2.

[0014] Intermediates useful in preparing the above compounds are also disclosed.

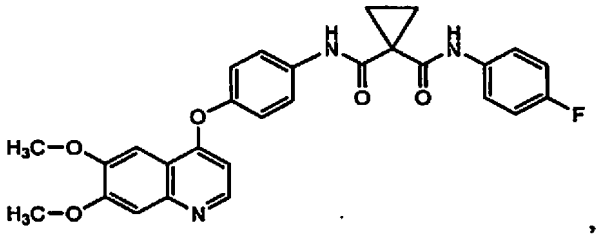
[0015] The compounds of formula I are useful as protein kinase modulators, and they inhibit various protein kinases including Ret and c-Met.

[0016] In another aspect, the disclosure provides a process for preparing compound IB:



IB

from compound IA:



IA,

comprising:

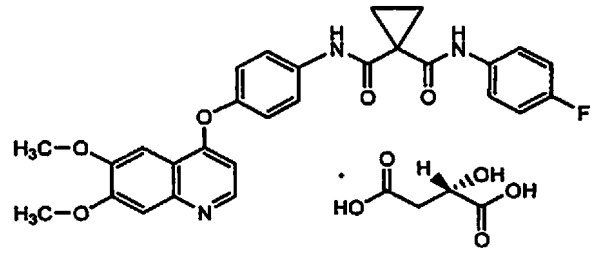
(a) heating and agitating a mixture comprising compound IA and L-malic acid, methylethyl ketone, and water;

(b) cooling the mixture;

(c) vacuum distilling the mixture successively; and

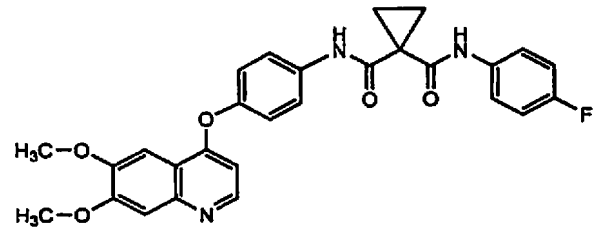
(d) isolating the compound of IB by filtration.

[0017] In another aspect, the disclosure provides a process for preparing compound IB:



IB

from compound IA:



IA,

comprising:

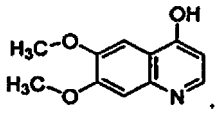
(a) heating and agitating a mixture comprising compound IA and L-malic acid, methylethyl ketone, and water;

(b) cooling the mixture;

(c) seeding the mixture with compound IB;

(d) vacuum distilling the mixture; and

(e) isolating compound IB by filtration.

[0018] In another aspect, the disclosure provides compound I, IA, or IB admixed with less than 100 ppm 6,7-dimethoxy-quinoline-4-ol, the structure of which is  .

[0019] In another aspect, the disclosure provides pharmaceutical compositions containing the compound of formula I, compound IA, or compound IB for oral administration.

[0020] In another aspect, the disclosure provides a pharmaceutical tablet composition according to Table 1.

Table 1

Ingredient	% w/w
Compound I	31.68
Microcrystalline Cellulose (MCC) (Avicel PH102)	38.85
Lactose anhydrous 60 M	19.42
Hydroxypropyl Cellulose, EXF	3.00
Croscarmellose Sodium	3.00
Total Intra-granular	**95.95**
Silicon dioxide, Colloidal PWD	0.30
Croscarmellose Sodium	3.00
Magnesium Stearate	0.75
Total	**100.00**

[0021] In another aspect, the disclosure provides a pharmaceutical tablet composition according to Table 2.

Table 2

Ingredient	(% w/w)
Compound I	25.0-33.3
Microcrystalline Cellulose, NF	q.s
Hydroxypropyl Cellulose, NF	3
Poloxamer, NF	0-3
Croscarmellose Sodium, NF	6.0
Colloidal Silicon Dioxide, NF	0.5
Magnesium Stearate, NF	0.5-1.0
Total	100

[0022] In another aspect, the disclosure provides a pharmaceutical tablet composition according to Table 2A.

Table 2A

Ingredient	% w/w
Compound IB (10 % drug load as Compound IA)	12.67
MCC	51.52
Lactose	25.76
Hydroxypropyl cellulose	3.0
Croscarmellose Sodium	6.0
Colloidal Silicon Dioxide	0.3
Magnesium Stearate	0.75
Total	**100**

[0023] In another aspect, the disclosure provides a pharmaceutical capsule composition according to Table 3.

Table 3

Ingredient	mg/unit dose
Compound IB (10 % drug load as Compound IA)	25
Silicified Microcrystalline Cellulose	196.75
Croscarmellose sodium	12.5
Sodium starch glycolate	12.5
Fumed Silica	0.75
Stearic acid	2.5
Total Fill Weight	250

[0024] In another aspect, the disclosure provides a pharmaceutical capsule composition according to Table 4.

Table 4

Ingredient	mg/unit dose
Compound IB (50 % drug load as Compound IA)	100
Silicified Microcrystalline Cellulose	75.40
Croscarmellose sodium	10.00
Sodium Starch Glycolate	10.00
Fumed silica	0.6
Stearic Acid	4.0
Total Fill Weight	200

[0025] In another aspect, the disclosure provides a pharmaceutical capsule composition according to Table 5, wherein the IB weight equivalents are provided.

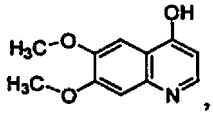
Table 5

	mg/unit dose
Ingredient	**50mg**
Compound IB	63.35
Microcrystalline Cellulose	95.39
Croscarmellose sodium	9.05
Sodium starch glycolate	9.05
Fumed Silica	0.54
Stearic acid	3.62
Total Fill Weight	181.00

[0026] In another aspect, the disclosure provides a pharmaceutical capsule composition according to Table 6, wherein the IB weight equivalents are provided.

Table 6

	mg/unit dose
Ingredient	**60mg**
Compound IB	73.95
Microcrystalline Cellulose	114.36
Croscarmellose sodium	10.85
Sodium starch glycolate	10.85
Fumed Silica	0.65
Stearic acid	4.34
Total Fill Weight	217.00

[0027] In another aspect, the invention is directed to a pharmaceutical composition comprising compound I, IA, or IB admixed with less than 100 ppm 6,7-dimethoxy-quinoline-4-ol, the structure of which is 

, and a pharmaceutically acceptable carrier.

[0028] There are many different aspects and embodiments of the disclosure described herein, and each aspect and each embodiment is non-limiting in regard to the scope of the disclosure. The terms "aspects" and "embodiments" are meant to be non-limiting regardless of where the terms "aspect" or "embodiment" appears in this specification. The transitional term "comprising," as used herein, which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0029] As used herein, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise or they are expressly defined to mean something different.

[0030] The word "can" is used in a non-limiting sense and in contradistinction to the word "must." Thus, for example, in many aspects of the invention a certain element is described as "can" having a specified identity, which is meant to convey that the subject element is permitted to have that identity according to the invention but is not required to have it.

[0031] If a group "R" is depicted as "floating" on a ring system, then unless otherwise defined, the substituent(s) "R" can reside on any atom of the ring system, assuming replacement of a depicted, implied, or expressly defined hydrogen from one of the ring atoms, so long as a stable structure is formed.

[0032] When there are more than one such depicted "floating" groups, such as where there are two groups; then, unless otherwise defined, the "floating" groups can reside on any atoms of the ring system, again assuming each replaces a depicted, implied, or expressly defined hydrogen on the ring.

[0033] "Pharmaceutically acceptable salts" include acid addition salts.

[0034] "Pharmaceutically acceptable acid addition salt" refers to those salts that retain the biological effectiveness of the free bases and that are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, or mixtures thereof, as well as organic acids such as acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like, or mixtures thereof.

[0035] "Essentially free" as used in the phrase "essentially free of process byproducts or contaminants," means that a compound or composition as disclosed here in is admixed with 200 parts per million (ppm) or less of such byproducts or contaminants.

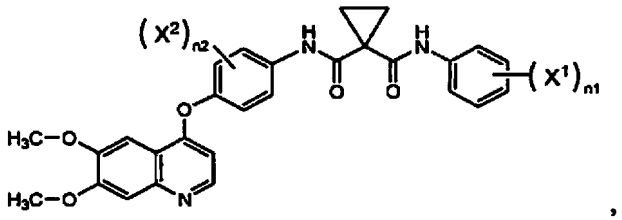
[0036] The disclosure is further illustrated by the following examples, which are not to be construed as limiting the disclosure in scope or spirit to the specific procedures described in them. Unless specified otherwise, the starting materials and various intermediates may be

obtained from commercial sources, prepared from commercially available organic compounds, or prepared using well-known synthetic processes.

Processes

Aspect 1: Processes for Making Compounds of Formula I

[0037] Aspect (1) of the invention relates to a process of preparing a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is H, Br, Cl, or F;

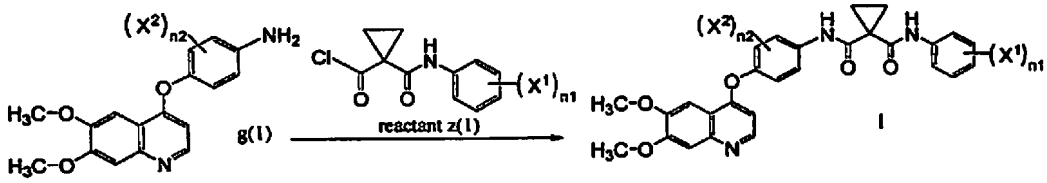
X^2 is H, Br, Cl, or F;

n1 is 1-2; and

n2 is 1-2;

the process comprising:

contacting the compound of formula g(1) with reactant z(1) to yield the compound of formula I:



[0038] The reaction is advantageously carried out under suitable reaction conditions. Non-limiting examples of suitable reaction conditions include using basic conditions. Non-limiting examples of basic conditions that can be used in Aspect (1) include the use of inorganic bases, such as aqueous KOH, NaOH, K_2CO_3, Na_2CO_3, K_3PO_4, Na_3PO_4, K_2HPO_4, Na_2HPO_4, and the like, or mixtures thereof. Other non-limiting examples of suitable reaction conditions include using suitable solvents. Non-limiting examples of suitable solvents that can be used include water miscible solvents, such as THF, acetone, ethanol, and the like, or mixtures thereof. Other non-limiting examples of suitable reaction conditions include using suitable temperatures. Suitable temperatures that may be used for the reaction include a

temperature at a range from about 10 °C to about 30 °C, or alternatively, at a range from about 15 °C to about 28 °C, or alternatively, at a range from about 20 °C to about 25 °C. The product formed by the reaction is in the free base form, and this free base form may be converted into a pharmaceutically acceptable salt thereof by processes known in the art. For example, the compound of formula I can be converted to the L-malate salt by the addition of L-malic acid and a suitable solvent.

[0039] Utilities of the compound of formula I are further described in WO 2005/030140 A2, which is incorporated herein by reference.

Embodiments of Aspect (1) Part A

[0040] In another embodiment of Aspect (1), X^1 is Cl or F.

[0041] In another embodiment of Aspect (1), X^2 is Cl or F.

[0042] In another embodiment of Aspect (1), X^1 is F.

[0043] In another embodiment of Aspect (1), X^2 is F.

[0044] In another embodiment of Aspect (1), X^1 is H.

[0045] In another embodiment of Aspect (1), X^2 is H.

[0046] In another embodiment of Aspect (1), n1 is 1.

[0047] In another embodiment of Aspect (1), n2 is 1.

[0048] In another embodiment of Aspect (1), n1 is 2.

[0049] In another embodiment of Aspect (1), n2 is 2.

[0050] All compounds of formula I for Aspect (1) disclosed above include any of the disclosed alternative embodiments in Part A for each of X^1, X^2, n1 or n2, in combination with any other of the disclosed alternative embodiments in Part A for each of X^1, X^2, n1, or n2, as well as a pharmaceutically acceptable salt of any such combination.

Embodiments of Aspect (1) Part B

[0051] In another embodiment of Aspect (1), n1 and n2 are each 1.

[0052] In another embodiment of Aspect (1), n1 and n2 are each 2.

[0053] In another embodiment of Aspect (1), n1 is 1; and n2 is 2.

[0054] In another embodiment of Aspect (1), n1 is 2 and n2 is 1.

[0055] In another embodiment of Aspect (1), X^1 is H; and X^2 is F.

[0056] In another embodiment of Aspect (1), X^1 is F; and X^2 is H.

[0057] In another embodiment of Aspect (1), X^1 and X^2 are each H.

[0058] In another embodiment of Aspect (1), X^1 and X^2 are each F.

[0059] In another embodiment of Aspect (1), X^1 is Cl; and X^2 is H.

[0060] In another embodiment of Aspect (1), X^1 is H; and X^2 is Cl.

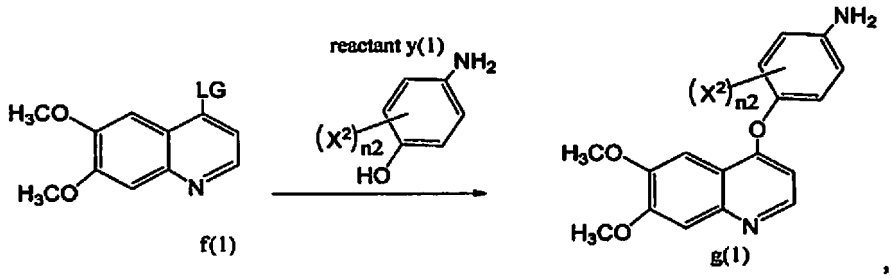
[0061] In another embodiment of Aspect (1), X^1 and X^2 are each Cl.

[0062] In another embodiment of Aspect (1), X^1 is Cl; and X^2 is F.

[0063] In another embodiment of Aspect (1), X^1 is F; and X^2 is Cl.

Embodiments of Aspect (1) Part C

[0064] In an embodiment of Aspect (1), the compound of formula g(1) can be made by reacting a compound of formula f(1) with reactant y(1) to yield the compound of g(1):



wherein LG represents a leaving group, and each of X^2, and n2 are as defined in Aspect (1), or as in any of the embodiments of Aspect (1) Part A. A non-limiting example of a leaving group includes a halo group such as Cl, Br, or F. Various compounds of reactant y(1) are commercially available, such as 2-fluoro-4-aminophenol and 4-aminophenol. Also, the skilled artisan would be able to make any variation of reactant y(1) using commercially available starting materials and by using known techniques to modify these commercially available starting materials to yield various compounds within the scope of reactant y(1).

[0065] The reaction in this embodiment is advantageously carried out under suitable reaction conditions. Non-limiting examples of suitable reaction conditions include using suitable solvents such as polar solvents. Non-limiting examples of polar solvents that can be used include tetrahydrofuran (THF), dimethylacetamide (DMA), dimethylsulfoxide (DMSO), dimethylformamide (DMF), ethyl acetate, N-methyl pyrrolidone (NMP), propylene carbonate, and the like, or mixtures thereof. In another embodiment, the polar solvent is dimethylacetamide (DMA). In another embodiment, the polar solvent is dimethylsulfoxide (DMSO). In another embodiment, the polar solvent is dimethylformamide (DMF). In another embodiment, the polar solvent is ethyl acetate. In another embodiment, the polar solvent is N-methyl pyrrolidone (NMP). In another embodiment, the polar solvent is propylene carbonate. In another embodiment, the solvent is a mixture of solvents, such as a mixture comprising THF and DMA.

[0066] The reactants f(1) and y(1) can be added together at a temperature ranging from about 10 °C to about 30 °C, or alternatively, from about 15 °C to about 28 °C, or alternatively, from about 20 °C to about 25 °C. The mixture is then heated to a temperature ranging from about 80 °C to about 125 °C, or alternatively, from about 95 °C to about 110 °C, or alternatively, from about 100 °C to about 105 °C, and the selected temperature is maintained until the reaction is complete.

[0067] Other non-limiting examples of suitable reaction conditions in this step of Aspect (1) include the use of a suitable base, such as a metal hydroxide or a non-nucleophilic base. Examples of metal hydroxides include sodium hydroxide or potassium hydroxide. Non-limiting examples of non-nucleophilic bases that can be used include lithium diisopropylamide, lithium tetramethylpiperidide, and alkali metal alkoxides such as sodium tert-butoxide, potassium tert-butoxide, sodium-pentoxide, and the like, or mixtures thereof. Preferably, the base is sodium tert-butoxide or sodium tert-pentoxide. In one embodiment, the base is sodium tert-pentoxide. Typically the sodium tert-pentoxide is commercially available as 35 weight percent solution of base in tetrahydrofuran, or as a 95 weight percent solid reagent. Preferably, the sodium tert-pentoxide is a 95 weight percent solid.

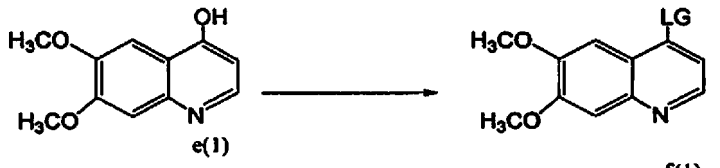
[0068] Typically, approximately 1.1 to 3.0 molar equivalents of base are used relative the moles of f(1) that are used. More preferably, 1.3 to 2.5 molar equivalents of base are used relative the moles of f(1) that are used. More preferably, 1.5 to 2.2 molar equivalents of base are used relative the moles of f(1) that are used. More preferably, 1.7 to 2.1 molar equivalents of base are used relative the moles of f(1) that are used.

[0069] Typically, the amount of molar equivalents of amino phenol that are used exceeds the molar equivalents of base that are used. In one embodiment, 1.1 to 2 molar equivalents of amino phenol are used relative to the molar equivalents of base that are used.

[0070] Once the reaction is substantially complete, the reaction mixture can be cooled to a temperature ranging from about 10 °C to about 25 °C. Precooled water can be charged at a rate to maintain a temperature that ranges from about 5 °C to about 35 °C. Alternatively, the precooled water can be charged at a rate to maintain a temperature that ranges from about 10 °C to about 25 °C. As a non-limiting example, the precooled water can be at a temperature ranging from about 0 °C to about 10 °C. As another non-limiting example, the precooled water can be at a temperature ranging from about 2 °C to about 7 °C. The precipitate can be collected by filtration under standard conditions and purified by standard purification techniques.

Embodiments of Aspect (1) Part D

[0071] In an embodiment of Aspect (1), the compound of formula f(1) can be made by converting a compound of formula e(1) to the compound of formula f(1):



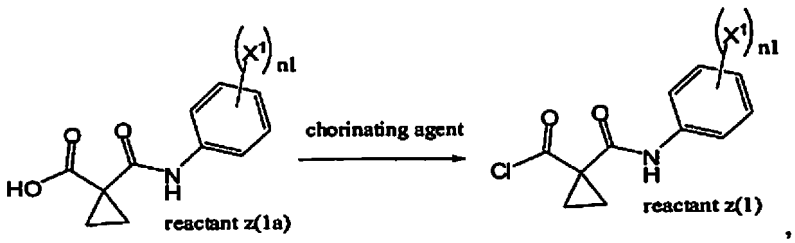
e(1) f(1),

wherein LG represents a leaving group. Non-limiting examples of leaving groups that can be used include halo groups (e.g., Cl, Br, or F) that can be added by halogenating agents. Non-limiting examples of halogenating agents that can be used include chlorinating agents, such as $SOCl_2$, SO_2Cl_2, $COCl_2$, PCl_5, $POCl_3$, and the like.

[0072] The reaction is advantageously carried out under suitable reaction conditions. Non-limiting examples of suitable reaction conditions in Part D of Aspect (1) include the use of suitable solvents. Non-limiting example of suitable solvents that can be used during the halogenation of the compound of formula e(1) include a polar, aprotic solvent, such as CH_3CN, DMF, and the like, or mixtures thereof. In other embodiments, the chlorination can be carried out using $POCl_3$ in acetonitrile, $COCl_2$ in DMF, or $SOCl_2$ in DMF. The addition of the chlorination agent is advantageously carried out at a temperature ranging from about 60 °C to about 90 °C. In another embodiment, the addition of the chlorination agent can be carried out at a temperature ranging from about 70 °C to about 85 °C. In another embodiment, the addition of the chlorination agent can be carried out at a temperature ranging from about 74 °C to about 80 °C. The product can then be collected by filtration and purified using standard techniques.

Embodiments of Aspect (1) Part E

[0073] In an embodiment of Aspect (1), reactant z(1) can be made by reacting reactant z(1a) with a chlorinating agent to yield reactant z(1):



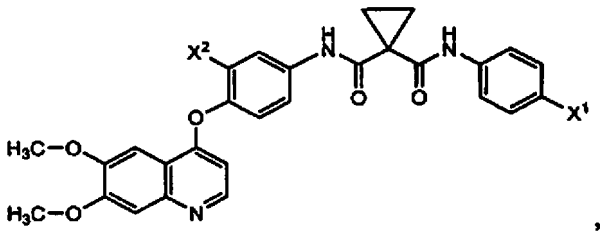
reactant z(1a) reactant z(1),

wherein X^1 is Br, Cl, or F; and n1 is 1-2. Compounds of reactant z(1a) can be made according to the process described in Example 25 of WO 2005/030140 A2, and the skilled artisan would be able to make any necessary substitutions using commercially available starting materials to come up with various compounds within the scope of reactant z(1a). Example 25 in WO 2005/030140 A2 is incorporated herein by reference.

[0074] The reaction is advantageously carried out under suitable reaction conditions. Non-limiting examples of suitable reaction conditions include using a chlorinating agent such as $POCl_3$, oxalyl chloride, and the like. In another embodiment, oxalyl chloride is used as a chlorinating agent. Non-limiting examples of suitable reaction conditions include carrying out the reaction at a temperature in the range from about 0 °C to about 25 °C, or alternatively at a temperature in the range from about 5 °C to about 20 °C. Other non-limiting examples of suitable reaction conditions include carrying out the reaction in a suitable solvent. Non-limiting examples of suitable solvents that can be used include polar aprotic solvents, such as halogenated hydrocarbons (e.g., dichloromethane and chloroform), ethers (e.g., Et_2O), dioxane, tetrahydrofuran (THF) containing catalytic DMF, and the like, or mixtures thereof. The resulting solution containing reactant z(1) can be used, without further processing, to make the compound of formula I.

Other Embodiments of Aspect (1)

[0075] In another embodiment of Aspect (1), the compound of formula I is a compound of formula IA-1:

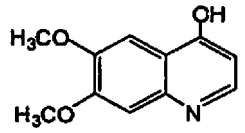


IA-1

or a pharmaceutically acceptable salt thereof, wherein:

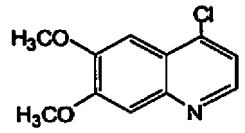
X^1 is H, Cl, Br, or F; and X^2 is H, Cl, Br, or F. Compound IA can be in the free base form or it can converted to a pharmaceutically acceptable salt thereof. Accordingly, compound IA can be converted to its L-malate salt by the addition of L-malic acid and a suitable solvent.

[0076] In another embodiment of Part D of Aspect (1), the compound of formula e(1) is compound e(2):



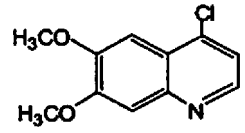
e(2) ;

and the compound of formula f(1) is compound f(2):



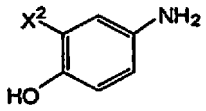
f(2) .

[0077] In another embodiment of Part C of Aspect (1), the compound of formula f(1) is compound f(2):



f(2) ;

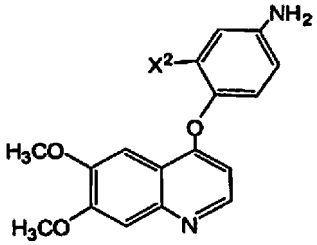
reactant y(1) is reactant (y)(2):



reactant (y)(2) ,

wherein X^2 is hydrogen or fluoro; and

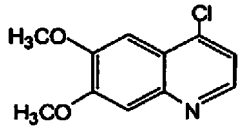
the compound of formula g(1) is of formula g(2):



g(2) .

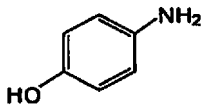
[0078] In a further embodiment, the reaction employs a non-nucleophilic base. In a further embodiment, the non-nucelophilic base is an alkali metal alkoxide; and the reaction is carried out in a polar solvent. In a further embodiment, the alkali metal alkoxide is sodium tert-butoxide, and the polar solvent is DMA.

[0079] In another embodiment of Part C of Aspect (1), the compound of formula f(1) is compound f(2):



f(2) ;

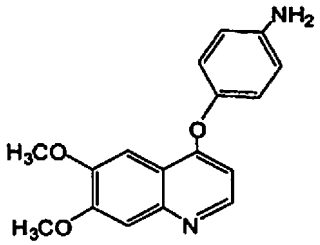
reactant y(1) is reactant (y)(3):



reactant (y)(3) ,

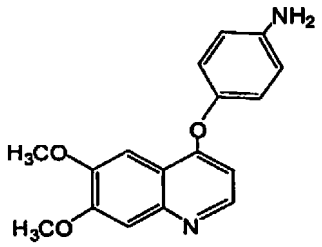
wherein X^2 is hydrogen or fluoro; and

the compound of formula g(1) is compound g(3):



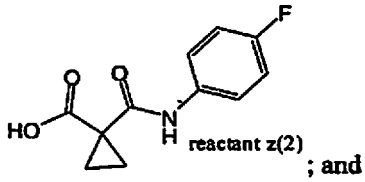
g(3) .

[0080] In another embodiment of Aspect (1) of this disclosure, the compound of formula g(1) is compound g(3):



g(3) ;

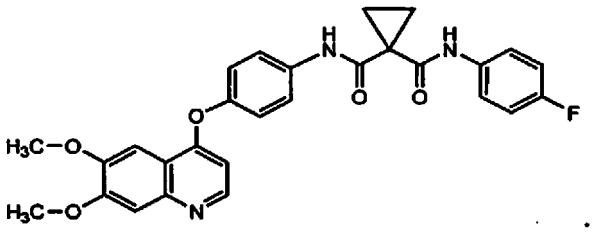
reactant z(1) is reactant (z)(2):



reactant z(2)

; and

the compound of formula I is compound IA:

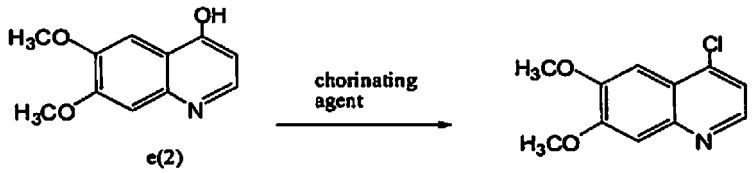


IA

[0081] In a further embodiment, the reaction is carried out in the presence of an inorganic base. In a further embodiment, the inorganic base is K_2CO_3, and the solvent employed in this reaction is a combination of THF and H_2O.

[0082] In another embodiment of Aspect (1) of this disclosure, X^1 and X^2 for each of formula g(1) and reactant z(1) are each selected from Cl or F. In another embodiment, X^1 and X^2 for each of formula g(2), and reactant z(1) are both F.

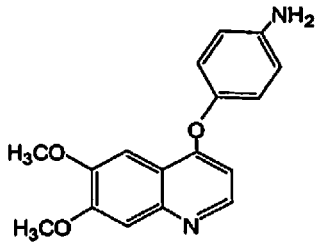
[0083] The compound of formula f(2),or a pharmaceutically acceptable salt thereof, can be made by converting the compound of formula e(2) to a compound of formula f(2) with a chlorinating agent in a suitable solvent:



The compound of formula f(2) can be in its free base form or converted to a pharmaceutically acceptable salt thereof. The reaction conditions that can be used in this aspect include any of the reaction conditions disclosed in Part E of Aspect (1).

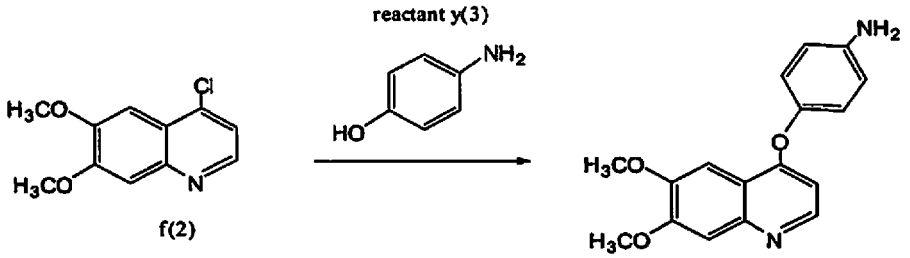
Aspect 2: Processes for Making Compounds of Formula g(2)

[0084] Aspect (2) of the disclosure relates to a process of preparing compound g(2):



g(2)

or a pharmaceutically acceptable salt thereof; the process comprising reacting compound f(2) with reactant y(3) under basic conditions (e.g., using 2,6-lutidine) in an appropriate solvent to yield compound g(3):



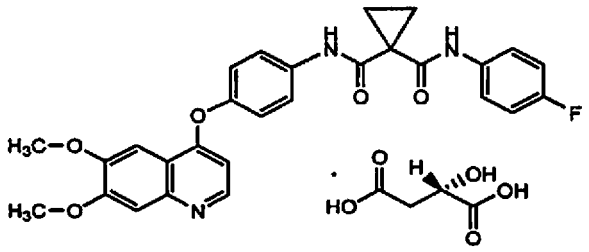
f(2) g(3)

The reaction conditions that can be used in this aspect include any of the reaction conditions disclosed in Part C of Aspect (1).

[0085] Alternative reaction conditions that can be used in this aspect include any of the reaction conditions disclosed in Parts C and D of Aspect (1).

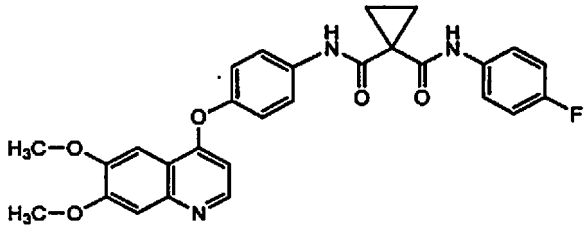
Aspect 3: Processes for Making Compounds of IB

[0086] As indicated above, in one aspect, the invention provides a process for preparing compound IB:



IB

from compound IA:



IA;

comprising:

(a) heating and agitating a mixture comprising compound IA and L-malic acid, methylethyl ketone, and water;

(b) cooling the mixture;

(c) vacuum distilling the mixture successively; and

(d) isolating the compound of IB by filtration.

[0087] In one embodiment of this aspect, compound IA is admixed with a sufficient amount of L-malic acid in a methylethyl ketone (MEK)/water (1:1) mixture. Alternatively, L-malic acid is added as a solution in water to a mixture of compound IA in methyl ethyl ketone. Generally the amount of L-malic is greater than 1 molar equivalent relative to compound IA. The mixture of compound IA and L-malic acid in MEK/water is heated at about 40-70 °C, and preferably at about 50-60 °C, and more preferably at about 55-60 °C with agitation, such as by stirring or the like, for about 1 to about 5 hours. At the end of the heating, the mixture is optionally clarified by filtering to give a clear solution. The resulting clear solution is then vacuum distilled from 1 to about 5 times at 150 to 200 mm Hg and a maximum jacket temperature of 55 °C to provide the desired crystalline compound of IB.

[0088] In one embodiment, L-malic acid is charged as a solution in water to compound IA. Generally the amount of L-malic is greater than 1 molar equivalent relative to compound IA. The mixture of compound IA and L-malic acid in MEK/water is heated at about 40-70 °C, and preferably at about 50-60 °C, and more preferably at about 55-60 °C with agitation, such as by stirring or the like, for about 1 to about 5 hours. At the end of the heating, the mixture is optionally clarified by filtering to give a clear solution which is at a temperature of about 30-40 °C, and more preferably at a temperature of about 33-37 °C. This clear solution is optionally seeded to facilitate crystallization. After seeding, the resulting mixture is vacuum distilled as provided above.

[0089] In one embodiment, compound IB is in the N-1 form. In another embodiment, compound IB is in the N-2 form. In another embodiment, compound IB is a mixture of the N-1 form and the N-2 form. Processes for preparing the N-1 and N-2 forms of compound IB

are disclosed in WO 2010/083414 (PCT/US2010021194), the entire contents of which are incorporated herein by reference.

[0090] In another embodiment, the disclosure relates to compound IA or IB admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment, the compound is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

[0091] In another embodiment, the disclosure relates to compound IA admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment, the compound is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

[0092] In another embodiment, the disclosure relates to compound IB admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment, the compound is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

[0093] In another embodiment, the disclosure relates to compound IB in the N-1 form admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment, the compound is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

[0094] In another embodiment, the disclosure relates to compound IB in the N-2 form admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment, the compound is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

[0095] In another embodiment, the disclosure relates to compound IB as a mixture of the N-1 form and the N-2 form admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment, the compound is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

Pharmaceutical Compositions

[0096] In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound I, IA, or IB. Various carriers used in formulating pharmaceutically acceptable compositions and known techniques for their bulk preparation and subsequent production into unit dosage forms are employed to make the pharmaceutical compositions disclosed herein and are described in Remington: The Science and Practice of Pharmacy, 21st edition, 2005, ed. D. B. Troy, Lippincott Williams & Wilkins, Philadelphia, and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York. The amount of carriers and excipients used in a composition can be varied proportionally according to the amount of active ingredient used (that is, Compound I, IA or IB).

[0097] In one embodiment, the pharmaceutical composition is a tablet.

[0098] In another embodiment, the pharmaceutical composition is a capsule.

[0099] In another embodiment, the pharmaceutical composition comprises Compound IA.

[00100] In another embodiment, the pharmaceutical composition comprises Compound IB.

[00101] In another embodiment, the pharmaceutical composition comprises Compound IB. as the N-1 polymorph.

[00102] In another embodiment, the pharmaceutical composition comprises Compound IB as the N-2 polymorph.

[00103] In another embodiment, the pharmaceutical composition comprises Compound IB as a mixture of the N-1 form and the N-2 form.

[00104] In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; one or more fillers; one or more disintergrants; one or more glidants; and one or more lubricants.

[00105] In this embodiment, the filler comprises microcrystalline cellulose.

[00106] In this embodiment, the disintegrant comprises croscarmellose sodium.

[00107] In this embodiment, the disintegrant comprises croscarmellose sodium and sodium starch glycolate.

[00108] In this embodiment, the glidant comprises fumed silica.

[00109] In this embodiment, the lubricant comprises stearic acid.

[00110] In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; lactose; hydroxypropyl cellulose; croscarmellose sodium; colloidal silicon dioxide; and magnesium stearate.

[00111] In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; hydroxypropyl cellulose; a surfactant; croscarmellose sodium; colloidal silicon dioxide; and magnesium stearate.

[00112] In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; croscarmellose sodium; fumed silica; and stearic acid.

[00113] In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; anhydrous lactose; hydroxypropyl cellulose; croscarmellose sodium; silicon dioxide; and magnesium stearate.

[00114] In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; anhydrous lactose; hydroxypropyl cellulose; a surfactant; croscarmellose sodium; silicon dioxide; and magnesium stearate.

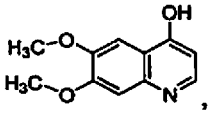
[00115] In another aspect, the disclosure provides a pharmaceutical composition according to Tables 1, 2, 2A, 3, 4, 5, and 6 as provided above. The compositions are prepared according to methods available to the skilled artisan. For example, the Tablet

formulations are prepared by combining, blending, and compacting the components of the tablet compositions. The capsule compositions are prepared by combining and blending the components and then placing the blend in a gelatin capsule.

[00116] For example, the 25 mg capsules (Table 3, 10 percent drug load formulation) are prepared as follows. The drug substance is delumped through a mill. The delumped drug substance is then co-screened with an equal volume Prosolv HD90. The excipients, except for stearic acid, are screened and charged to a blender along with the co-screened drug substance. The mixture is blended in a V-Blender. This process is repeated to manufacture a second sublot of unlubricated blend. The two sublots are then combined together in a V-blender and lubricated with stearic acid which has been co-screened with an equal volume of unlubricated blend. The final blend is then encapsulated into opaque, size 1 gelatin capsules using an automated capsule filling machine. The capsules are then weight sorted through an automatic weight sorter.

[00117] The 100-mg capsules (Table 4, 50% drug load formulation) are manufactured in two equal sublots of 5 kg of blend which are combined prior to lubricant blend The drug substance is delumped through a mill. The excipients, except for stearic acid, are screened and charged to the mixer along with the delumped drug substance. The mixture is blended with a high shear mixer. The process is repeated to manufacture a second sublot of unlubricated blend. The final blend is then encapsulated into Swedish oraopaque, size 1 gelatin capsules using an automated capsule filling machine. The capsuare then weight sorted through an automatic weight sorter.

[00118] The 50 and 60 mg capsules (Tables 5 and 6) are prepared in a similar fashion as the 25 and 100 mg capsules.

[00119] In another aspect, the disclosure relates to a pharmaceutical composition comprising a compound of Formula IA or IB and a pharmaceutically acceptable carrier admixed with less than 100 ppm of 6,7-dimethoxy-quinoline-4-ol. 6,7-dimethoxy-quinoline-4-ol, the structure of which is  , can be used as reagent e(1) to make chloride f(1) and is a byproduct that may form during the synthesis of Compound IA or IB. Minimizing the concentration of contaminants or byproducts such as 6,7-dimethoxy-quinoline-4-ol in pharmaceutical compositions destined for human administration is desirable.

[00120] In one embodiment, the pharmaceutical composition as defined in any of the previous embodiments (for example, the pharmaceutical composition of Tables 1, 2, 2A, 3, 4, 5, and6) is admixed with 100 ppm 6,7-dimethoxy-quinoline-4-ol.

[00121] In another embodiment, the pharmaceutical composition as defined in any of the previous embodiments is admixed with 50 ppm 6,7-dimethoxy-quinoline-4-ol.

[00122] In another embodiment, the pharmaceutical composition as defined in any of the previous embodiments is admixed with 25 ppm 6,7-dimethoxy-quinoline-4-ol.

[00123] In another embodiment, the pharmaceutical composition as defined in any of the previous embodiments is admixed with 15 ppm 6,7-dimethoxy-quinoline-4-ol.

[00124] In another embodiment, the pharmaceutical composition as defined in any of the previous embodiments is admixed with 10 ppm 6,7-dimethoxy-quinoline-4-ol.

[00125] In another embodiment, the pharmaceutical composition as defined in any of the previous embodiments is admixed with 5 ppm 6,7-dimethoxy-quinoline-4-ol.

[00126] In another embodiment, the pharmaceutical composition as defined in any of the previous embodiments is admixed with 2.5 ppm 6,7-dimethoxy-quinoline-4-ol.

[00127] In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; one or more fillers; one or more disintergrants; one or more glidants; and one or more lubricants admixed with 100 ppm or less 6,7-dimethoxy-quinoline-4-ol.

[00128] In this embodiment, the filler comprises microcrystalline cellulose.

[00129] In this embodiment, the disintegrant comprises croscarmellose sodium.

[00130] In this embodiment, the disintegrant comprises croscarmellose sodium and sodium starch glycolate.

[00131] In this embodiment, the glidant comprises fumed silica.

[00132] In this embodiment, the lubricant comprises stearic acid.

[00133] In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; croscarmellose sodium; fumed silica; and stearic acid; admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment of this embodiment, the composition is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with

5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

[00134] In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; anhydrous lactose; hydroxypropyl cellulose; a surfactant; croscarmellose sodium; silicon dioxide; and magnesium stearate; admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment of this embodiment, the composition is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

[00135] In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; croscarmellose sodium; fumed silica; and stearic acid; ; admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment of this embodiment, the composition is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

EXAMPLES

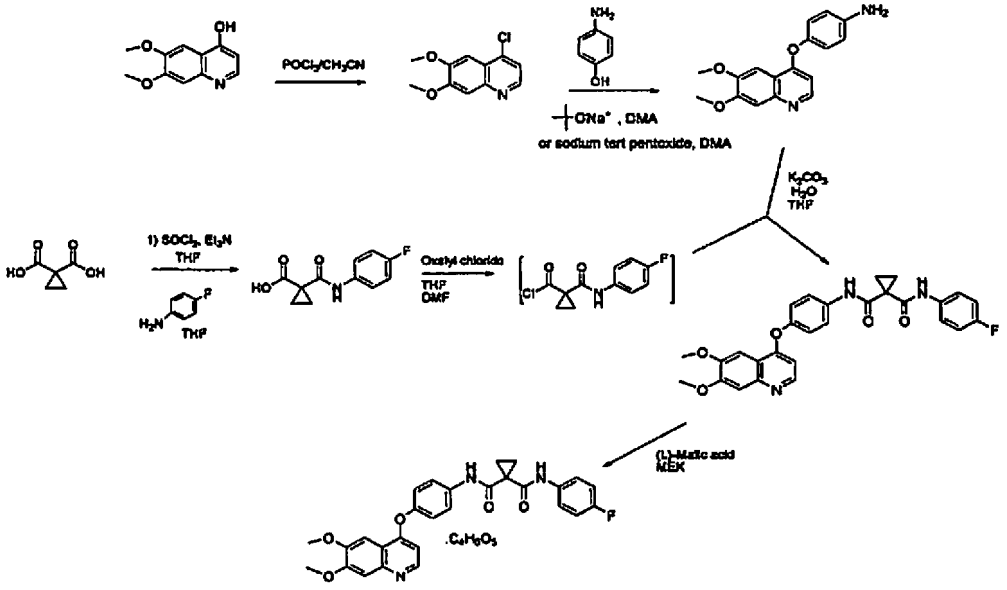
[00136] The invention is illustrated further by the following examples in Scheme 1 and the description thereof, which are not to be construed as limiting the invention in scope or spirit to the specific procedures described in them. Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the invention, as demonstrated by the following examples. Those skilled in the art will also recognize that it may be necessary to utilize different solvents or reagents to achieve some of the above transformations. Unless otherwise specified, all reagents and solvents are of standard commercial grade and are used without further purification. The

appropriate atmosphere to run the reaction under, for example, air, nitrogen, hydrogen, argon, and the like, will be apparent to those skilled in the art.

Preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof.

[00137] A synthetic route that can be used for the preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof is depicted in Figure 1:

Figure 1



Preparation of 4-Chloro-6,7-dimethoxy-quinoline

[00138] A reactor was charged sequentially with 6,7-dimethoxy-quinoline-4-ol (47.0 kg) and acetonitrile (318.8 kg). The resulting mixture was heated to approximately 60 °C, and phosphorus oxychloride ($POCl_3$, 130.6 kg) was added. After the addition of $POCl_3$, the temperature of the reaction mixture was raised to approximately 77 °C. The reaction was deemed complete (approximately 13 hours) when less than 3% of the starting material remained (in-process high-performance liquid chromatography [HPLC] analysis). The reaction mixture was cooled to approximately 2 – 7 °C and then quenched into a chilled solution of dichloromethane (DCM, 482.8 kg), 26 % NH_4OH (251.3 kg), and water (900 L). The resulting mixture was warmed to approximately 20 – 25 °C, and phases were separated.

The organic phase was filtered through a bed of AW hyflo super-cel NF (Celite; 5.4 kg) and the filter bed was washed with DCM (118.9 kg). The combined organic phase was washed with brine (282.9 kg) and mixed with water (120 L). The phases were separated and the organic phase was concentrated by vacuum distillation with the removal of solvent (approximately 95 L residual volume). DCM (686.5 kg) was charged to the reactor containing organic phase and concentrated by vacuum distillation with the removal of solvent (approximately 90 L residual volume). Methyl t-butyl ether (MTBE, 226.0 kg) was then charged and the temperature of the mixture was adjusted to -20 to -25 °C and held for 2.5 hours resulting in solid precipitate which was then filtered and washed with n-heptane (92.0 kg), and dried on a filter at approximately 25 °C under nitrogen to afford the title compound. (35.6 kg).

Preparation of 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine

[00139] 4-Aminophenol (24.4 kg) dissolved in N,N-dimethylacetamide (DMA, 184.3 kg) was charged to a reactor containing 4-chloro-6,7-dimethoxyquinoline (35.3 kg), sodium t-butoxide (21.4 kg) and DMA (167.2 kg) at 20-25 °C. This mixture was then heated to 100-105 °C for approximately 13 hours. After the reaction was deemed complete as determined using in-process HPLC analysis (<2% starting material remaining), the reactor contents were cooled at 15 to 20 °C and water (pre-cooled, 2 to 7 °C, 587 L) charged at a rate to maintain 15 to 30 °C temperature . The resulting solid precipitate was filtered, washed with a mixture of water (47 L) and DMA (89.1 kg) and finally with water (214 L). The filter cake was then dried at approximately 25 °C on filter to yield crude 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (59.4 kg wet, 41.6 kg dry calculated based on LOD). Crude 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine was refluxed (approximately 75 °C) in a mixture of tetrahydrofuran (THF, 211.4 kg) and DMA (108.8 kg) for approximately 1 hour and then cooled to 0-5 °C and aged for approximately 1 h after which time the solid was filtered, washed with THF (147.6 kg) and dried on a filter under vacuum at approximately 25 °C to yield 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (34.0 kg).

Alternative Preparation of 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine

[00140] 4-chloro-6,7-dimethoxyquinoline (34.8 kg) and 4-aminophenol (30.8 kg) and sodium tert pentoxide (1.8 equivalents) 88.7 kg, 35 wt percent in THF) were charged to a reactor, followed by N,N-dimethylacetamide (DMA, 293.3 kg). This mixture was then heated to 105-115 °C for approximately 9 hours. After the reaction was deemed complete as

determined using in-process HPLC analysis (<2% starting material remaining), the reactor contents were cooled at 15 to 25 °C and water (315 kg) was added over a two hour period while maintaining the temperature between 20 and 30 °C. The reaction mixture was then agitated for an additional hour at 20 to 5 °C. The crude product was collected by filtration and washed with a mixture of 88 kg water and 82.1 kg DMA, followed by 175 kg water. The product was dried on a filter drier for 53 hours. The LOD showed less than 1% w/w.

[00141] In an alternative procedure, 1.6 equivalents of sodium tert-pentoxide were used and the reaction temperature was increased from 110-120 °C. In addition , the cool down temperature was increased to 35-40 °C and the starting temperature of the water addition was adjusted to 35-40 °C, with an allowed exotherm to 45 °C.

Preparation of 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid

[00142] Triethylamine (19.5 kg) was added to a cooled (approximately 5 C) solution of cyclopropane-1,1-dicarboxylic acid (24.7 kg) in THF (89.6 kg) at a rate such that the batch temperature did not exceed 5 °C. The solution was stirred for approximately 1.3 hours, and then thionyl chloride (23.1 kg) was added, keeping the batch temperature below 10 °C. When the addition was complete, the solution was stirred for approximately 4 h keeping temperature below 10 °C. A solution of 4–fluoroaniline (18.0 kg) in THF (33.1 kg) was then added at a rate such that the batch temperature did not exceed 10 °C. The mixture was stirred for approximately 10 hours after which the reaction was deemed complete. The reaction mixture was then diluted with isopropyl acetate (218.1 kg). This solution was washed sequentially with aqueous sodium hydroxide (10.4 kg, 50 % dissolved in 119 L of water) further diluted with water (415 L), then with water (100 L) and finally with aqueous sodium chloride (20.0 kg dissolved in 100 L of water). The organic solution was concentrated by vacuum distillation (100 L residual volume) below 40 °C followed by the addition of n-heptane (171.4 kg), which resulted in the precipitation of solid. The solid was recovered by filtration and washed with n-Heptane (102.4 kg) resulting in wet crude, 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (29.0 kg). The crude, 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid was dissolved in methanol (139.7 kg) at approximately 25 °C followed by the addition of water (320 L) resulting in slurry which was recovered by filtration, washed sequentially with water (20 L) and n-heptane (103.1 kg) and then dried on the filter at approximately 25 °C under nitrogen to afford the title compound (25.4 kg).

Preparation of 1-(4-Fluoro-phenylcarbamoyl)-cyclopropanecarbonyl chloride

[00143] Oxalyl chloride (12.6 kg) was added to a solution of 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (22.8 kg) in a mixture of THF (96.1 kg) and N, N-dimethylformamide (DMF; 0.23 kg) at a rate such that the batch temperature did not exceed 25 °C. This solution was used in the next step without further processing.

Alternative Preparation of 1-(4-Fluoro-phenylcarbamoyl)-cyclopropanecarbonyl chloride

[00144] A reactor was charged with 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (35 kg), 344 g DMF, and 175kg THF. The reaction mixture was adjusted to 12-17 °C and then to the reaction mixture was charged 19.9 kg of oxalyl chloride over a period of 1 hour. The reaction mixture was left stirring at 12-17 °C for 3 to 8 hours. This solution was used in the next step without further processing.

Preparation of cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (Compound IA)

[00145] The solution from the previous step containing 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride was added to a mixture of compound 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (23.5 kg) and potassium carbonate (31.9 kg) in THF (245.7 kg) and water (116 L) at a rate such that the batch temperature did not exceed 30 °C. When the reaction was complete (in approximately 20 minutes), water (653 L) was added. The mixture was stirred at 20-25 °C for approximately 10 hours, which resulted in the precipitation of the product. The product was recovered by filtration, washed with a pre-made solution of THF (68.6 kg) and water (256 L), and dried first on a filter under nitrogen at approximately 25 °C and then at approximately 45 °C under vacuum to afford the title compound (41.0 kg, 38.1 kg, calculated based on LOD).

Alternative Preparation of cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide

[00146] A reactor was charged with 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (35.7 kg, 1 equivalent), followed by 412.9 kg THF. To the reaction mixture was charged a solution of 48.3 K_2CO_3 in 169 kg water. The acid chloride solution of described in the Alternative Preparation of 1-(4–Fluoro-phenylcarbamoyl)-cyclopropanecarbonyl chloride above was transferred to the reactor containing 4-(6,7-dimethoxy-quinoline-4-yloxy)-

phenylamine while maintaining the temperature between 20-30 °C over a minimum of two hours. The reaction mixture was stirred at 20-25 °C for a minimum of three hours. The reaction temperature was then adjusted to 30-25 °C and the mixture was agitated. The agitation was stopped and the phases of the mixture were allowed to separate. The lower aqueous phase was removed and discarded. To the remaining upper organic phase was added 804 kg water. The reaction was left stirring at 15-25 °C for a minimum of 16 hours.

[00147] The product precipitated. The product was filtered and washed with a mixture of 179 kg water and 157.9 THF in two portions. The crude product was dried under a vacuum for at least two hours. The dried product was then taken up in 285.1 kg THF. The resulting suspension was transferred to reaction vessel and agitated until the suspension became a clear (dissolved) solution, which required heating to 30-35 °C for approximately 30 minutes. 456 kg water was then added to the solution, as well as 20 kg SDAG-1 ethanol (ethanol denatured with methanol over two hours. The mixture was agitated at 15-25 °C for at least 16 hours. The product was filtered and washed with a mixture of 143 kg water and 126.7 THF in two portions. The product was dried at a maximum temperature set point of 40 °C.

[00148] In an alternative procedure, the reaction temperature during acid chloride formation was adjusted to 10-15 °C. The recrystallization temperature was changed from 15-25 °C to 45-50 °C for 1 hour and then cooled to 15-25 °C over 2 hours.

Preparation of cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy- quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide, (L) malate salt (Compound IB)

[00149] Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (1-5; 13.3 kg), L-malic acid (4.96 kg), methyl ethyl ketone (MEK; 188.6 kg) and water (37.3 kg) were charged to a reactor and the mixture was heated to reflux (approximately 74 °C) for approximately 2 hours. The reactor temperature was reduced to 50 to 55 °C and the reactor contents were filtered. These sequential steps described above were repeated two more times starting with similar amounts of 1-5 (13.3 kg), L-Malic acid (4.96 kg), MEK (198.6 kg) and water (37.2 kg). The combined filtrate was azeotropically dried at atmospheric pressure using MEK (1133.2 kg) (approximate residual volume 711 L; KF $\leq$ 0.5 % w/w) at approximately 74 °C. The temperature of the reactor contents was reduced to 20 to 25 °C and held for approximately 4 hours resulting in solid precipitate which was filtered, washed with MEK (448 kg) and dried under vacuum at 50°C to afford the title compound (45.5 kg).

Alternative Preparation of cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide, (L) malate salt

[00150] Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (47.9 kg), L-malic acid (17.2), 658.2 kg methyl ethyl ketone, and 129.1 kg water (37.3 kg) were charged to a reactor and the mixture was heated 50-55 °C for approximately 1-3 hours, and then at 55-60 °C for an addition al 4-5 hours. The mixture was clarified by filtration through a 1 μm cartridge. The reactor temperature was adjusted to 20-25 °C and vacuum distilled with a vacuum at 150-200 mm Hg with a maximum jacket temperature of 55 °C to the volume range of 558-731 L.

[00151] The vacuum distillation was performed two more times with the charge of 380 kg and 380.2 kg methyl ethyl ketone, respectively. After the third distillation, the volume of the batch was adjusted to 18 v/w of Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide by charging 159.9 kg methyl ethyl ketone to give a total volume of 880L. An addition al vacuum distillation was carried out by adjusting 245.7 methyl ethyl ketone. The reaction mixture was left with moderate agitation at 20-25 °C for at least 24 hours. The product was filtered and washed with 415.1 kg methyl ethyl ketone in three portions. The product was dried under a vacuum with the jacket temperature set point at 45 °C.

[00152] In an alternative procedure, the order of addition was changed so that a solution of 17.7 kg L-malic acid dissolved in 129.9 kg water was added to Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (48.7 kg) in methyl ethyl ketone (673.3 kg).

Preparation of Compound IB, Form N-1

[00153] A solution was prepared by adding tetrahydrofuran (12 mL/g-bulk-LR (limiting reagent); 1.20 L) and N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (100 g; 1.00 equiv; 100.00 g) and (L)-malic acid (1.2 equiv (molar); 32.08 g) to a 1 L reactor. Water (0.5317 mL/g-bulk-LR; 53.17 mL) was added and the solution was heated to 60 °C and maintained at that temperature for one hour until the solids were fully dissolved. The solution was passed through a Polish Filter.

[00154] At 60 °C, acetonitrile (12 mL/g-bulk-LR; 1.20 L) was added over a period of 8 hours. The solution was held at 60 °C for 10 hours. The solution was then cooled to 20 °C and held for 1 hour. The solids were filtered and washed with acetonitrile (12 mL/g-bulk-LR;

1.20 L). The solids were dried at 60 °C (25 mm Hg) for 6 hours to afford compound (I), Form N-1 (108 g; 0.85 equivalent; 108.00 g; 85.22% yield) as a white crystalline solid.

Alternate Preparation of Compound IB, Form N-1

[00155] A solution was prepared with 190 mL tetrahydrofuran (110 mL), methyl isobutyl ketone, and 29 mL water. Next, 20 mL of this solution were transferred into an amber bottle, and then saturated by adding N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (L)-malate until a thick slurry formed, and aging for at least 2 hours with stirring at room temperature. The solids were removed by filtration through a Buchner funnel, rendering a clear saturated solution.

[00156] Separately, a powder blend was made with known amounts of two batches of compound IB: (1) 300 mg of batch 1, which contained approximately 41% compound IB, Form N-1 and 59% compound IB, Form N-2 by Raman spectroscopy analysis, and (2) 200 mg of batch 2, which had a XPRD pattern similar to compound IB, Form N-2.

[00157] The compound IB, Form N-1 and compound (I), Form N-2 powder blend was added into the saturated solution, and the slurry was aged under magnetic stirring at room temperature for 25 days. The slurry was then sampled and filtered through a Buchner funnel to obtain 162 mg of wet cake. The wet cake was dried in a vacuum oven at 45 °C to afford 128 mg of crystalline compound IB in the N-1 form.

Preparation of Crystalline Compound IB, Form N-2

Preparation of Crystalline Componnd IB, Form N-2 Seed Crystals

[00158] A solution was prepared by combining 20 ml of acetone and 300 mg of compound IA (N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide) in a 25ml screw capped vial. Next, 0.758ml of a 0.79M (L)-malic acid stock solution was added to the vial with magnetic stirring. The solution was then left stirring for 24 hours at ambient temperature. The sample was then suction filtered with 0.45μm PTFE filter cartridge and dried *in vacuo* at ambient temperature overnight.

Preparation of Crystalline Compound IB, Form N-2.

[00159] To a reactor were added N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (48 g; 1.00 equiv; 48.00 g) and tetrahydrofuran (16.5 mL/g-bulk-LR; 792.00 mL). The water content was adjusted to 1 wt% water. The solution was heated to 60 °C. Once dissolved, the solution was passed through a polish filter to provide the first solution.

[00160] In a separate reactor, (L)-malic acid (1.2 equiv (molar); 15.40 g) was dissolved into methyl isobutyl ketone (10 mL/g-bulk-LR; 480.00 mL) and tetrahydrofuran (1 mL/g-bulk-LR; 48.00 mL). Next, 50 mL of the (L)-malic acid solution was added to the first solution at 50 °C. Seed crystals were added (1%, 480 mg) and the malic acid solution was added at 50 °C dropwise via an addition funnel (1.3 ml/min over 3 hours). The slurry was held at 50 °C for 18 hours and then was cooled to 25 °C over 30 minutes. The solids were filtered, and washed with 20% tetrahydrofuran/methyl isobutyl ketone (10V, 480 mL). The solids were dried under vacuum at 60 °C for 5 hours to afford compound IB (55.7 g; 0.92 equivalent; 55.70 g; 91.56% yield) as an off-white crystalline solid.

Stability Studies of Pharmaceutical Compositions

[00161] The pharmaceutical capsule compositions of Tables 3 and 4 were prepared by mixing the ingredients according to processes known in the art.

Table 3

Ingredient	mg/unit dose
Compound IB (10 % drug load as Compound IA)	25
Microcrystalline Cellulose	196.75
Croscarmellose sodium	12.5
Sodium starch glycolate	12.5
Fumed Silica	0.75
Stearic acid	2.5
Total Fill Weight	250

Table 4

Ingredient	mg/unit dose
Compound IB (50 % drug load as Compound IA)	100
Silicified Microcrystalline Cellulose	75.40
Croscarmellose sodium	10.00
Sodium Starch Glycolate	10.00
Fumed silica	0.6
Stearic Acid	4.0
Total Fill Weight	200

[00162] The capsule compositions were subjected to stability studies to monitor the formation of 6,7-dimethoxy-quinoline-4-ol at various temperatures and relative humidities over time. The results are summarized in Tables 7A and 7B and Tables 8A and 8B.

Table 7A: Stability of 25 Mg Capsules (Table 3)

	Conditions	Bottle A1	Bottle A2	Bottle A3	Bottle A4
		PPM of 6,7-dimethoxy-quinoline-4-ol			
Initial T=0	25 °C/60% RH	2	2	3	3
1 Month	25 °C/60% RH	3	4	5	NA
	30 °C/75% RH	4	4	NA	NA
	40 °C/75% RH	9	9	10	NA
3 Months	25 °C/60% RH	5	5	7	NA
	30 °C/75% RH	7	6	NA	NA
	40 °C/75% RH	22	23	24	NA
6 Months	25 °C/60% RH	6	6	7	7 (3M in blister)
	30 °C/75% RH	9	9	NA	NA
	40 °C/75% RH	40	44	43	27 (3M in blister)
9 Months	25 °C/60% RH	7	7	9	8 (6M in blister)
	30 °C/75% RH	13	12	NA	NA
	40 °C/75% RH	NA	NA	68	60 (6M in blister)

M=Months; NA=Not Applicable; RH= Relative Humidity; PPM= Parts per Million. A portion of Bottle A4 was repackaged in a blister pack after being stored in bottles for 3 months.

Table 7B: Stability of 25 Mg Capsules (Table 3)

	Conditions	Bottle B1	Bottle B	Bottle B3	Bottle B4
		PPM of 6,7-dimethoxy-quinoline-4-ol			
Initial T=0	25 °C/60% RH	3	1	2	2
1 Month	25 °C/60% RH	<2	<2	<2	NA
	30 °C/75% RH	<2	<2	NA	NA
	40 °C/75% RH	2	<2	<2	NA
3 Months	25 °C/60% RH	2	<2	<2	NA
	30 °C/75% RH	2	<2	NA	NA
	40 °C/75% RH	3	<2	<2	NA
6 Months	25 °C/60% RH	<2	<2	<2	<2 (3M in blister)
	30 °C/75% RH	2	<2	NA	NA
	40 °C/75% RH	4	<2	3	3 (3M in blister)
9 Months	25 °C/60% RH	<2	<2	<2	<2 (6M in blister)
	30 °C/75% RH	3	<2	NA	NA
	40 °C/75% RH	NA	NA	5	4 (6M in blister)

A portion of Bottle B4 was repackaged in a blister pack after being stored in bottles for 3 months.

Table 8A: Stability of 100 Mg Capsules (Table 4)

	Conditions	Bottle A1	Blister A2	Bottle A3
		PPM of 6,7-dimethoxy-quinoline-4-ol		
Initial T=0	25 °C/60% RH	4	4	6
1 Month	25 °C/60% RH	4	4	6
	30 °C/75% RH	4	NA	6
	40 °C/75% RH	6	6	9
3 Months	25 °C/60% RH	5	5	7
	30 °C/75% RH	6	NA	7
	40 °C/75% RH	10	10	12
6 Months	25 °C/60% RH	5	5	
	30 °C/75% RH	6	NA	
	40 °C/75% RH	11	17	

M=Months; NA=Not Applicable; RH= Relative Humidity; PPM= Parts per Million.

Table 8B: Stability of 100 Mg Capsules (Table 4)

	Conditions	Bottle B1	Blister B2	Bottle B3
		PPM of 6,7-dimethoxy-quinoline-4-ol		
Initial T=0	25 °C/60% RH	1	1	2
1 Month	25 °C/60% RH	<2	<2	<2
	30 °C/75% RH	<2	<2	2
	40 °C/75% RH	<2	<2	2
3 Months	25 °C/60% RH	<2	<2	<2
	30 °C/75% RH	<2	NA	<2
	40 °C/75% RH	<2	<2	2
6 Months	25 °C/60% RH	<2	<2	
	30 °C/75% RH	<2	NA	
	40 °C/75% RH	2	2	

M=Months; NA=Not Applicable; RH= Relative Humidity; PPM= Parts per Million.

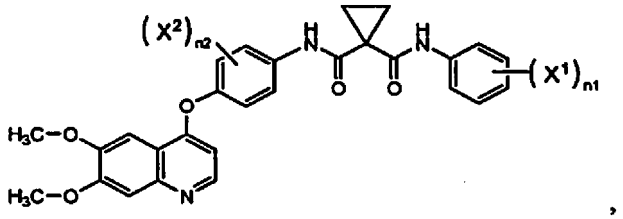
[00163] The results summarized in Tables 7A and 7B and 8A and 8B indicate that formation of 6,7-dimethoxy-quinoline-4-ol was minimized to 50 ppm or less over time in the capsule formulations.

[00164] The foregoing disclosure has been described in some detail by way of illustration and example, for purposes of clarity and understanding. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications can be made while remaining within the spirit and scope of the invention. It will be obvious to one of skill in the art that

changes and modifications can be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled. All references cited herein are incorporated by reference in their entirety.

CLAIMS

1. A process for preparing a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is H, Br, Cl, or F;

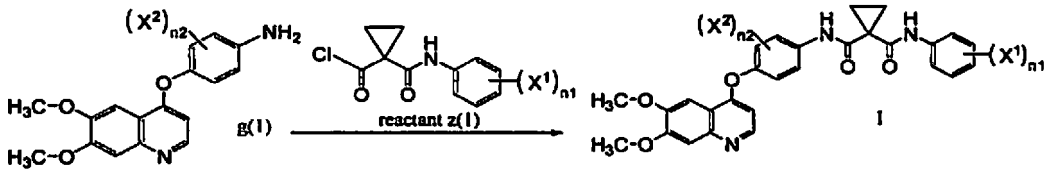
X^2 is H, Br, Cl, or F;

n1 is 1-2; and

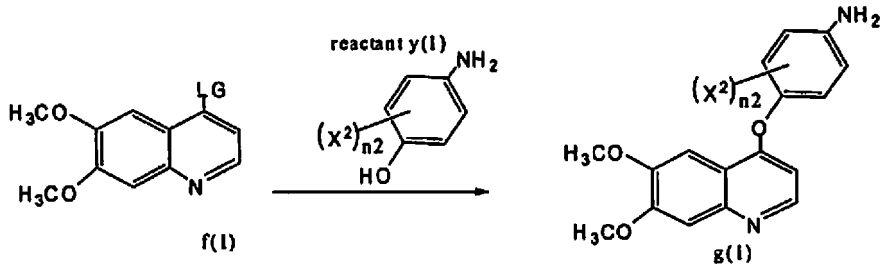
n2 is 1-2;

the process comprising:

contacting the compound of formula g(1) with reactant z(1) to yield the compound of formula I:

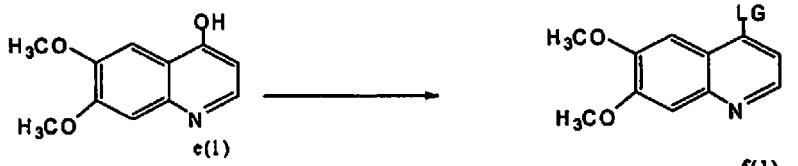


2. The process according to claim 1, wherein the compound of formula g(1) is made by reacting a compound of formula f(1) with reactant y(1) to yield the compound of formula g(1):



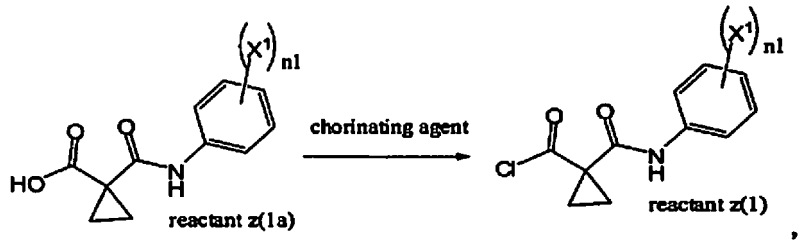
wherein LG represents a leaving group, and each X^2 and n2 are as defined in claim 1.

3. The process according to claim 2, wherein the compound of formula f(1) is made by converting compound e(1) to the compound of formula f(1):



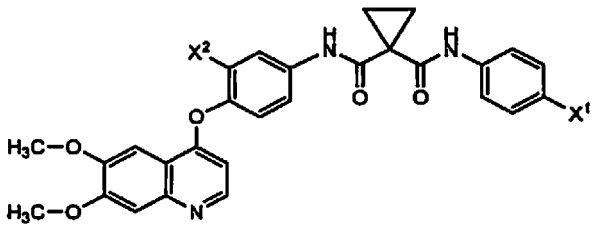
wherein LG represents a leaving group.

4. The process according to claim 1, wherein reactant z(1) is made by reacting reactant z(1a) with a chlorinating agent to yield reactant z(1):



wherein X^1 is Br, Cl, or F; and n1 is 1-2.

5. The process according to claim 1, wherein the compound of formula I is compound IA-1:



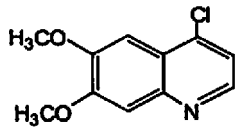
IA

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is H, Cl, Br, or F; and

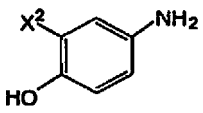
X^2 is H, Cl, Br, or F.

6. The process according to claim 5, wherein the compound of formula f(1) is compound f(2):



f(2) ;

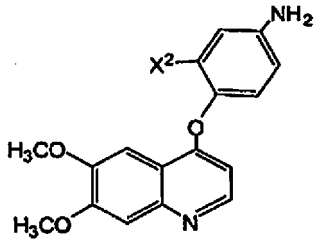
reactant y(1) is reactant (y)(2):



reactant (y)(2) ,

wherein X^2 is hydrogen or fluoro; and

the compound of formula g(1) is of formula g(2):



g(2) .

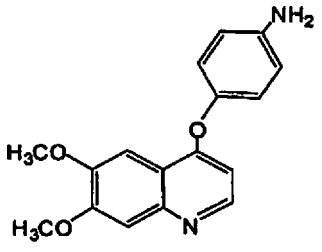
7. The process according to claim 6, wherein the reaction employs a non-nucleophilic base.

8. The process according to claim 7, wherein the non-nucleophilic base is an alkali metal alkoxide; and the reaction is carried out in a polar solvent.

9. The process according to claim 8, wherein the alkali metal alkoxide is sodium tert-butoxide, and the polar solvent is DMA.

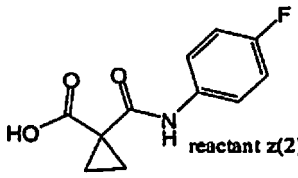
10. The process according to claim 8, wherein the alkali metal alkoxide is sodium tert-pentoxide, and the polar solvent is DMA.

11. The process according to claim 1, wherein the compound of formula g(1) is of compound g(3):



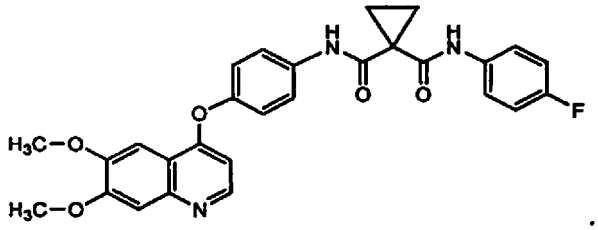
g(3) ;

reactant z(1) is reactant (z)(2):



reactant z(2) ; and

the compound of formula I is compound IA:

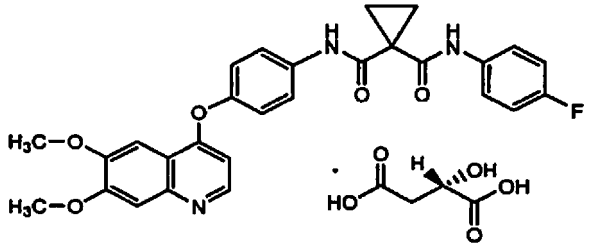


IA

12. The process according to claim 11, wherein the reaction is carried out in the presence of an inorganic base.

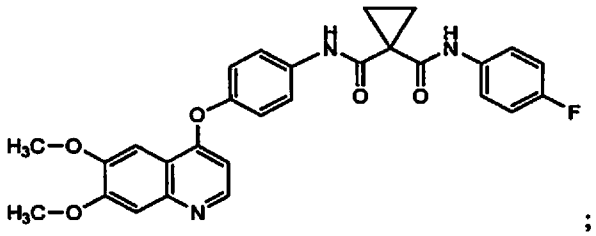
13. The process according to claim 12, wherein the inorganic base is K_2CO_3, and the solvent employed in this reaction is a combination of THF and H_2O.

14. A process for preparing compound IB:



IB

from compound IA:



;

IA

comprising:

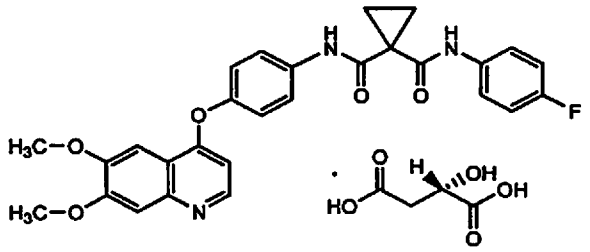
(a) heating and agitating a mixture comprising compound IA and L-malic acid, methylethyl ketone, and water;

(b) cooling the mixture;

(c) vacuum distilling the mixture successively; and

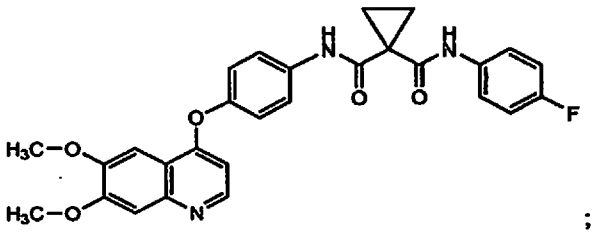
(d) isolating the compound of IB by filtration.

15. A process for preparing compound IB:



IB

from compound IA:



;

IA

comprising:

(a) heating and agitating a mixture comprising compound IA and L-malic acid, methylethyl ketone, and water;
(b) cooling the mixture;
(c) seeding the mixture with the compound of IB;
(d) vacuum distilling the mixture; and
(e) isolating the compound of IB by filtration.

16. Compound IA or IB admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

17. Compound IB admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

18. Compound IB in the N-1 form admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

19. Compound IB in the N-2 form admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

20. Compound IB as a mixture of the N-1 form and N-2 form admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

21. A pharmaceutical composition according to Table 1.

Table 1

Ingredient	% w/w
Compound I	31.68
Microcrystalline Cellulose (Avicel PH102)	38.85
Lactose anhydrous 60 M	19.42
Hydroxypropyl Cellulose, EXF	3.00
Croscarmellose Sodium	3.00
Total Intra-granular	**95.95**
Silicon dioxide, Colloidal PWD	0.30
Croscarmellose Sodium	3.00
Magnesium Stearate	0.75
Total	**100.00**

22. A pharmaceutical composition according to Table 2.

Table 2

Ingredient	(% w/w)
Compound I	25.0-33.3
Microcrystalline Cellulose, NF	q.s
Hydroxypropyl Cellulose, NF	3
Poloxamer, NF	0-3
Croscarmellose Sodium, NF	6.0
Colloidal Silicon Dioxide, NF	0.5
Magnesium Stearate, NF	0.5-1.0
Total	100

23. A pharmaceutical composition according to Table 2A.

Table 2A

Ingredient	% w/w
Compound IB (10 % drug load as Compound IA)	12.67
MCC	51.52
Lactose	25.76
Hydroxypropyl cellulose	3.0
Croscarmellose Sodium	6.0
Colloidal Silicon Dioxide	0.3
Magnesium Stearate	0.75
Total	**100**

24. A pharmaceutical composition according to Table 3.

Table 3

Ingredient	mg/unit dose
Compound IB (10 % drug load as Compound IA)	25
Silicified Microcrystalline Cellulose	196.75
Croscarmellose sodium	12.5
Sodium starch glycolate	12.5
Fumed Silica	0.75
Stearic acid	2.5
Total Fill Weight	250

25. A pharmaceutical composition according to Table 4.

Table 4

Ingredient	mg/unit dose
Compound IB (50 % drug load as Compound IA)	100
Silicified Microcrystalline Cellulose	75.40
Croscarmellose sodium	10.00
Sodium Starch Glycolate	10.00
Fumed silica	0.6
Stearic Acid	4.0
Total Fill Weight	200

26. A pharmaceutical composition according to Table 5.

Table 5

	mg/unit dose
Ingredient	**50mg**
Compound IB (10 % drug load as Compound IA)	63.35
Microcrystalline Cellulose	95.39
Croscarmellose sodium	9.05
Sodium starch glycolate	9.05
Fumed Silica	0.54
Stearic acid	3.62
Total Fill Weight	181.00

27. A pharmaceutical composition according to Table 6.

Table 6

	mg/unit dose
Ingredient	**60mg**
Compound IB	73.95
Microcrystalline Cellulose	114.36
Croscarmellose sodium	10.85
Sodium starch glycolate	10.85
Fumed Silica	0.65
Stearic acid	4.34
Total Fill Weight	217.00

28. The pharmaceutical composition of claims 20-27 admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

29. The pharmaceutical composition of claims 20-27 admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

30. The pharmaceutical composition of claims 20-27 admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

31. The pharmaceutical composition of claims 20-27 admixed with 15 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

32. The pharmaceutical composition of claims 20-27 admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

33. The pharmaceutical composition of claims 20-27 admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

34. The pharmaceutical composition of claims 20-27 admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

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(72) Inventor; and
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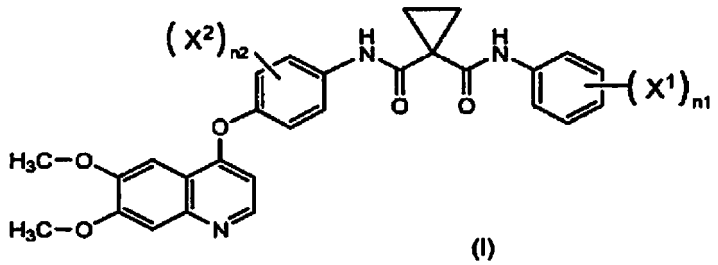
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Published:

— *with international search report (Art. 21(3))*

(54) Title: PROCESSES FOR PREPARING QUINOLINE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING SUCH COMPOUNDS



(I)

(57) Abstract: The present invention is directed to processes for making and compositions containing quinolines such as formula I or pharmaceutically acceptable salts thereof wherein: X1 is H, Br, Cl, or X2 is H, Br, Cl, or n1 is 1-2; and n2 is 1-2.

WO 2012/109510 A1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors:	Jo Ann Wilson, et al.	Art Unit:	TBD
Application No.:	TBD	Examiner:	TBD
Filing Date:	November 10, 2016	Conf. No.:	TBD
Atty. Docket No.:	224990/10-039C2-US/405045		

Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

Commissioner for Patents
United States Patent and Trademark Office
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Alexandria, VA 223313-1450

PRELIMINARY AMENDMENT UNDER 37 C.F.R. § 1.115

Dear Sir or Madam:

Prior to examination of the application, please amend the above-referenced application as follows:

Amendments to the specification begin on page 2.

Remarks begin on page 3.

AMENDMENT TO THE SPECIFICATION

On page 1 of the specification, after the title and header, please replace paragraph [0001] with the following paragraph:

[0001] This application is a continuation application of United States Serial Number 13/984,559, filed March 20, 2014, which claims priority under 35 U.S.C. § 371 to Patent Cooperation Treaty application PCT/US2012/024591, filed February 10, 2012, which claims the benefit of United States provisional application number 61/441,520, filed February 10, 2011, and United States provisional application number 61/441,527, filed February 10, 2011, the entire contents of which are incorporated herein by reference.

REMARKS

Amendments to the Specification

Applicant has amended the application to state that this application is a continuation application of United States Serial Number 13/984,559, filed March 20, 2014, which claims priority under 35 U.S.C. § 371 to Patent Cooperation Treaty application PCT/US2012/024591, filed February 10, 2012, which claims the benefit of United States provisional application number 61/441,520, filed February 10, 2011, and United States provisional application 61/441,527, filed February 10, 2011, the entire contents of which are incorporated herein by reference. It is believed that no new matter is added through the entry of these amendments.

Conclusion and Required Fees

It is believed that the Utility Filing Fee of $70.00, the Utility Search Fee of $300.00, and the Utility Examination Fee of $360.00 are due at this time. The Applicant hereby authorizes the Office to charge this total of $730.00 to Deposit Account No. 503145, referencing Attorney Docket Number 224990/10-039C2-US/405045.

Respectfully submitted,

HONIGMAN MILLER SCHWARTZ AND COHN LLP

/Meghan M. Klaric/

Dated: November 10, 2016

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Application Number	TBD
Filing Date	November 10, 2016
First Named Inventor	Jo Ann Wilson
Title	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds
Art Unit	TBD
Examiner Name	TBD
Attorney Docket Number	224990/10-039C2-US/405045

SIGNATURE of Applicant or Patent Practitioner

Signature	/Meghan M. Klaric/	Date (Optional)	2016-11-10
Name	Meghan M. Klaric	Registration Number	71226
Title (if Applicant is a juristic entity)	Attorney for Applicant		
Applicant Name (if Applicant is a juristic entity)	Exelixis, Inc.		

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☐ *Total of _____ forms are submitted.

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I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

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☑ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 91684

OR

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Country					
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I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Exelixis, Inc.

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

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SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature		Date (Optional)	8/10/16
Name	Jeffrey Hessekiel		
Title	Executive Vice President & General Counsel		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ Total of forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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FEE TRANSMITTAL

Complete if known	
Application Number	TBD
Filing Date	2016-11-10
First Named Inventor	Jo Ann Wilson
Examiner Name	TBD
Art Unit	TBD
Practitioner Docket No.	224990/10-039C2-US/405045

☑ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29. Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

TOTAL AMOUNT OF PAYMENT ($) 730.00

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☑ Deposit Account Deposit Account Number: 503145 Deposit Account Name: Honigman Miller Schwartz and Cohn LLP

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FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES (U = undiscounted fee; S = small entity fee; M = micro entity fee)

	FILING FEES			SEARCH FEES			EXAMINATION FEES			
Application Type	U ($)	S ($)	M ($)	U ($)	S ($)	M ($)	U ($)	S ($)	M ($)	Fees Paid ($)
Utility	280	140*	70	600	300	150	720	360	180	$730.00
Design	180	90	45	120	60	30	460	230	115	
Plant	180	90	45	380	190	95	580	290	145	
Reissue	280	140	70	600	300	150	2,160	1,080	540	
Provisional	260	130	65	0	0	0	0	0	0	

* The $140 small entity status filing fee for a utility application is further reduced to $70 for a small entity status applicant who files the application via EFS-Web.

2. EXCESS CLAIM FEES

Fee Description	Undiscounted Fee ($)	Small Entity Fee ($)	Micro Entity Fee ($)
Each claim over 20 (including Reissues)	80	40	20
Each independent claim over 3 (including Reissues)	420	210	105
Multiple dependent claims	780	390	195

Total Claims		Extra Claims		Fee ($)		Fee Paid ($)
_____	-20 or HP =	_____	x	_____	=	0

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims		Extra Claims		Fee ($)		Fee Paid ($)
_____	-3 or HP =	_____	x	_____	=	0

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims	
Fee ($)	Fee Paid ($)
_____	0

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $400 ($200 for small entity) ($100 for micro entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets		Extra Sheets		Number of each additional 50 or fraction thereof		Fee ($)		Fee Paid ($)
_____	- 100 =	_____	/ 50 =	_____ (round up to a whole number)	x	_____	=	0

4. OTHER FEE(S)

	Fees Paid ($)
Non-English specification, $130 fee (no small or micro entity discount)	
Non-electronic filing fee under 37 CFR 1.16(t) for a utility application, $400 fee ($200 small or micro entity)	
Other (e.g., late filing surcharge): _____	

SUBMITTED BY

Signature	/Meghan M. Klaric/	Registration No. (Attorney/Agent) 71226	Telephone 2693377840
Name (Print/Type)	Meghan M. Klaric		Date 2016-11-10

This collection of information is required by 37 CFR 1.136. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors:	Jo Ann Wilson, et al.	Art Unit:	TBD
Application No.:	TBD	Examiner:	TBD
Filing Date:	November 10, 2016	Conf. No.:	TBD
Atty. Docket No.:	224990/10-039C2-US/405045		

Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

CERTIFICATE OF TRANSMISSION UNDER 37 C.F.R. § 1.8(a)

The undersigned hereby certifies that the following documents are being electronically filed in accordance with 37 C.F.R. § 1.6(a)(4) on this 10th day of November, 2016:

1. Cover Letter to the Commissioner for Patents;
2. Utility Patent Application Transmittal form (PTO/AIA/15);
3. Application Data Sheet (PTO/AIA/14);
4. Specification, Claims, and Abstract (47 pages);
5. Preliminary Amendment;
6. Power of Attorney (PTO/AIA/82);
7. Fee Transmittal form (PTO/SB/17); and
8. This Certificate of Transmission under 37 C.F.R. § 1.8(a).

/Amy L. Peters/

Amy L. Peters (for Meghan M. Klaric., Reg. No.: 71,226)

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds
First Named Inventor/Applicant Name:	Jo Ann Wilson
Filer:	Meghan Mary Klaric/Amy Peters
Attorney Docket Number:	224990/10-039C2-US/405045

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY FILING FEE (ELECTRONIC FILING)	4011	1	70	70
UTILITY SEARCH FEE	2111	1	300	300
UTILITY EXAMINATION FEE	2311	1	360	360
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**730**

Electronic Acknowledgement Receipt

EFS ID:	27479213
Application Number:	15348716
International Application Number:	
Confirmation Number:	5882
Title of Invention:	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds
First Named Inventor/Applicant Name:	Jo Ann Wilson
Customer Number:	91684
Filer:	Meghan Mary Klaric/Amy Peters
Filer Authorized By:	Meghan Mary Klaric
Attorney Docket Number:	224990/10-039C2-US/405045
Receipt Date:	10-NOV-2016
Filing Date:	
Time Stamp:	17:45:14
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$730
RAM confirmation Number	111416INTEFSW00004841503145
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		2016-11-10_EX10-039C2-US_Application.pdf	3350785 dc9a26cd9094f1453922cca488fa67cab1194f9c	yes	65

Multipart Description/PDF files in .zip description

Document Description	Start	End
Miscellaneous Incoming Letter	1	2
Transmittal of New Application	3	3
Application Data Sheet	4	11
Specification	12	48
Claims	49	57
Abstract	58	58
Preliminary Amendment	59	61
Power of Attorney	62	63
Transmittal Letter	64	64
Miscellaneous Incoming Letter	65	65

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	35304 2dd3f4040b8ad5e364c55ee7b7753a08b30e0fce	no	2

Warnings:

Information:

Total Files Size (in bytes):	3386089

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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

HONIGMAN
Honigman Miller Schwartz and Cohn LLP
Attorneys and Counselors

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MKlaric@honigman.com

VIA EFS

November 10, 2016

Commissioner for Patents
United States Patent and Trademark Office
P. O. Box 1450
Alexandria, VA 22313

Re: US Patent Application No.: TBD
Inventors: Jo Ann Wilson, et al.
Filing Date: November 10, 2016
Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds
Attorney Docket No.: 224990/10-039C2-US/405045

Dear Sir or Madam:

Enclosed for filing please find the following documents:

1. This Cover Letter to the Commissioner for Patents;
2. Utility Patent Application Transmittal form (PTO/AIA/15);
3. Application Data Sheet (PTO/AIA/14);
4. Specification, Claims, and Abstract (47 pages);
5. Preliminary Amendment;
6. Power of Attorney (PTO/AIA/82);
7. Fee Transmittal form (PTO/SB/17); and
8. Certificate of Transmission under 37 C.F.R. § 1.8(a).

This application is a continuation application of United States Serial Number 13/984,559, filed March 20, 2014, which claims priority under 35 U.S.C. § 371 to Patent Cooperation Treaty application PCT/US2012/024591, filed February 10, 2012, which claims the benefit of United States provisional application number 61/441,520, filed February 10, 2011, and United States provisional application number 61/441,527, filed February 10, 2011, the entire contents of which are incorporated herein by reference.

It is believed that the Utility Filing Fee of $70.00, the Utility Search Fee of $300.00, and the Utility Examination Fee of $360.00 are due at this time. The Applicant hereby authorizes the Office to charge this total of $730.00 to Deposit Account No. 503145, referencing Attorney Docket Number 224990/10-039C2-US/405045.

Very truly yours,

HONIGMAN MILLER SCHWARTZ AND COHN LLP

/Meghan M. Klaric/

Meghan M. Klaric
Reg. No. 71,226

HMB/ayp

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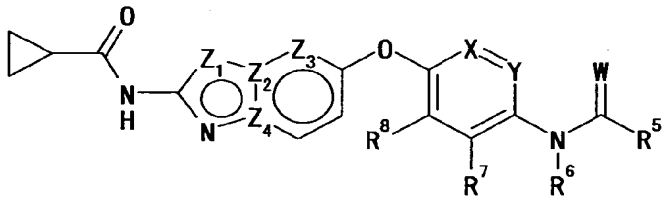
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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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Published:
— *with international search report (Art. 21(3))*
— *with sequence listing part of description (Rule 5.2(a))*

(54) Title: FUSED HETEROCYCLIC DERIVATIVES AND USE THEREOF



(57) Abstract: The present invention provides a fused heterocyclic derivative having a strong kinase inhibitory activity and use thereof. The present invention relates to a compound represented by the formula wherein each symbol is as defined in the present specification, or a salt thereof.

WO 2009/136663 A1

DESCRIPTION

FUSED HETEROCYCLIC DERIVATIVES AND USE THEREOF

Technical Field

The present invention relates to a fused heterocyclic derivative having a potent kinase inhibitory activity and useful for the prophylaxis or treatment of cancer and the like, and use thereof.

(Background of the Invention)

For a solid tumor to grow to a certain size or above, angiogenesis is essential for ensuring sufficient supply of nutrition and oxygen to cancer cell (see, for example, Non Patent Literature 1). One of the important factors causing angiogenesis toward tumor, a vascular endothelial growth factor (VEGF) is known. VEGF is bound to a vascular endothelial growth factor receptor (VEGFR) expressed on vascular endothelial cells and transmits signal for cell proliferation (see, for example, Non Patent Literature 2). Accordingly, inhibition of the VEGF-VEGFR signal transduction system is considered to enable suppression of angiogenesis and tumor growth (see, for example, Non Patent Literature 3). Moreover, since tumor blood vessels are involved in cancer hematogenous metastasis, inhibition of angiogenesis is considered to be effective for suppression of cancer metastasis.

Hepatocyte growth factor (HGF) is known to promote growth of vascular endothelial cell via its receptor (c-Met), and cause angiogenesis (see, for example, Non Patent Literature 4). It has been clarified that c-Met is highly expressed in various types of cancers (colorectal cancer, gastric cancer, lung cancer, kidney cancer, breast cancer, ovary cancer, prostate cancer and the like), and is deeply involved in the growth and survival of cancer cells (see, for example, Non Patent Literature 5). Therefore, cancer cell growth is expected to be suppressed by inhibiting c-Met. Moreover, activation of c-Met is also involved in the invasion

and metastasis of cancer cells (see, for example, Non Patent Literature 6), and inhibition of c-Met is considered to be effective for the prevention of invasion or metastasis of cancer.

Tyrosine Kinase with Immunoglobulin and Epidermal Growth homology domain 2 (TIE2) is a receptor of angiopoietin (angiopoietin 1 and angiopoietin 2), mainly expressed in vascular endothelial cells and is known to be indispensable for the development of blood vessels in the fetal stages (see, for example, Non Patent Literature 7). It has been reported that inhibition of binding of angiopoietin with solubilized form TIE2 etc. decreases tumor blood vessel density and suppresses tumor growth in non-clinical model (see, for example, Non Patent Literature 8). The system of angiopoietin TIE2 is suggested to play a key role in the tumor angiogenesis, along with the VEGF-VEGFR system. Therefore, inhibition of TIE2 is considered to suppress angiogenesis as well as tumor growth.

Fms Like Tyrosine Kinase 3 (FLT3) is mutated most frequently in acute myelocytic leukemia (AML), and is known to be constitutively activated even in the absence of a ligand, by length mutation (FLT3-ITD mutation) of transmembrane portion, which is called Internal Tandem Duplication (ITD), or activated mutation of tyrosine kinase portion (see, for example, Non Patent Literature 9). It is considered that signals from FLT3 activate downstream AKT, extracellular signal regulated kinase (ERK), signal transducer and activator of transcription (STAT5), and are involved in the growth of leukemia cells and suppression of differentiation (see, for example, Non Patent Literature 10). Particularly, the FLT3-ITD mutation observed in 20-30% of AML patients has been reported to correlate with poor life prognosis (see, for example, Non Patent Literature 11). Therefore, inhibition of FLT3 is considered to suppress growth of leukemia cells.

As compounds inhibiting kinase including VEGFR and c-Met, phthalazine derivatives (see, for example, Patent Literature 1), pyrrole-substituted 2-indolinone derivatives (see, for example, Patent Literature 2), quinazoline derivatives (see, for example, Patent Literature 3), ω-carboxyaryl-substituted diphenylurea derivatives (see, for example, Patent Literature 4), quinoline derivatives and quinazoline derivatives (see, for example, Patent Literature 5), nitrogen-containing aromatic ring derivatives (see, for example, Patent Literature 6), quinoline derivative and quinazoline derivative (see, for example, Patent Literature 7) and the like are known.

(Citation List)

Patent Literature

PTL 1: WO98/35958

PTL 2: WO01/60814

PTL 3: WO01/32651

PTL 4: WO00/42012

PTL 5: WO00/43366

PTL 6: WO02/32872

PTL 7: WO03/000660

Non Patent Literature

NPL 1: New England Journal of Medicine, 1971, vol. 285, No. 21, pages 1182-1186

NPL 2: Endocrine Reviews, 1997, vol. 18, No. 1, pages 4-25

NPL 3: Drug Discovery Today, 2001, vol. 6, No. 19, pages 1005-1024

NPL 4: EXS, 1997, vol. 79, pages 193-208

NPL 5: Cytokine & Growth Factor Reviews, 2002, vol. 13, No. 1, pages 41-59

NPL 6: Nature Reviews Molecular Cell Biology, 2003, vol. 4, No. 12, pages 915-925

NPL 7: Genes and Development, 1994, vol. 8, No. 16, pages 1897-1909

NPL 8: The Journal of Clinical investigation, 1997, No. 100,

No. 8, pages 2072-2078
NPL 9: Leukemia, 1996, vol. 10, No. 12, pages 1911-1918
NPL 10: Blood, 2000, vol. 96, No. 12, pages 3907-3914
NPL 11: Blood, 2001, vol. 98, No. 6, pages 1752-1759

Summary of Invention

(Technical Problem)

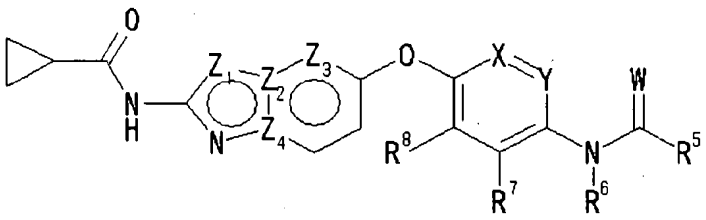
A kinase inhibitor superior in the affinity for kinase, efficacy expression, pharmacokinetics, solubility, interaction with other pharmaceutical products, safety and stability is expected to show a therapeutically superior effect. At present, however, such inhibitor superior in the affinity for kinase, and sufficiently satisfactory in the efficacy expression, pharmacokinetics, solubility, interaction with other pharmaceutical products, safety and stability has not been found. Thus, there is a demand for the development of a compound having a superior kinase inhibitory activity, and sufficiently satisfactory as a pharmaceutical product. Accordingly, an object of the present invention is to provide a compound having a superior kinase inhibitory activity, low toxic and sufficiently satisfactory as a pharmaceutical product.

(Solution to Problem)

The present inventors have conducted intensive studies in an attempt to solve the above-mentioned problems and found that a compound represented by the following formula or a salt thereof has a superior kinase inhibitory activity, which resulted in the completion of the present invention.

Accordingly, the present invention provides the following.

[1] A compound represented by the formula (I):



wherein Z_1, Z_2, Z_3 and Z_4 are in the following combination:

$(Z_1, Z_2, Z_3, Z_4) = (CR^1, N, CR^2, C)$,

(N, N, CR^2, C),

(N, C, CR^2, N),

(S, C, CR^2, C), or

(S, C, N, C);

R^1 and R^2 are the same or different and each is

(1) a hydrogen atom,

(2) a halogen atom,

(3) a group bonded via a carbon atom,

(4) a group bonded via a nitrogen atom,

(5) a group bonded via an oxygen atom, or

(6) a group bonded via a sulfur atom;

W is O or S;

X is CR^3 (R^3 is a hydrogen atom, a halogen atom or C_{1-6} alkyl), or N;

Y is CR^4 (R^4 is a hydrogen atom, a halogen atom or C_{1-6} alkyl), or N;

R^5 is

(1) C_{3-6} cycloalkyl optionally having one C_{6-10} aryl-aminocarbonyl optionally having 1 to 3 substituents selected from a halogen atom and C_{1-6} alkyl,

(2) C_{1-6} alkyl-carbonylamino optionally having one C_{6-10} aryl,

(3) C_{1-6} alkoxy optionally having one C_{6-10} aryl, or

(4) a nitrogen-containing heterocyclic group or an N-oxide thereof optionally having 1 to 4 substituents selected from

(a) C_{6-10} aryl optionally having 1 to 3 substituents selected from a halogen atom and C_{1-6} alkyl,

(b) C_{1-6} alkyl optionally having 1 to 3 halogen atoms, and

(c) oxo;

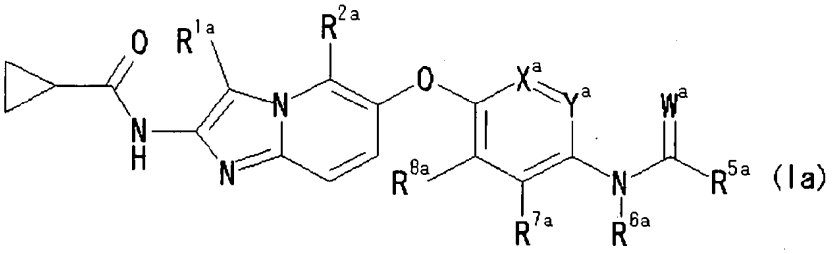
R^6 is a hydrogen atom;

R^7 is a hydrogen atom, a halogen atom or C_{1-6} alkyl; and

R^8 is a hydrogen atom, a halogen atom or C_{1-6} alkyl,

or a salt thereof (to be referred to as "compound (I)" in the present specification);

[2] a compound represented by the formula



(Ia)

wherein R^{1a} and R^{2a} are the same or different and each is

(1) a hydrogen atom,

(2) a halogen atom,

(3) a group bonded via a carbon atom,

(4) a group bonded via a nitrogen atom,

(5) a group bonded via an oxygen atom, or

(6) a group bonded via a sulfur atom;

W^a is O or S;

X^a is CR^{3a} (R^{3a} is a hydrogen atom, a halogen atom or C_{1-6} alkyl), or N;

Y^a is CR^{4a} (R^{4a} is a hydrogen atom, a halogen atom or C_{1-6} alkyl), or N;

R^{5a} is

(1) C_{3-6} cycloalkyl optionally having one C_{6-10} aryl-aminocarbonyl optionally having 1 to 3 substituents selected from a halogen atom and C_{1-6} alkyl,

(2) C_{1-6} alkyl-carbonylamino optionally having one C_{6-10} aryl,

(3) C_{1-6} alkoxy optionally having one C_{6-10} aryl, or

(4) a nitrogen-containing heterocyclic group or an N-oxide thereof optionally having 1 to 4 substituents selected from

(a) C_{6-10} aryl optionally having 1 to 3 substituents selected from a halogen atom and C_{1-6} alkyl,

(b) C_{1-6} alkyl optionally having 1 to 3 halogen atoms, and

(c) oxo;

R^{6a} is a hydrogen atom;

R^{7a} is a hydrogen atom, a halogen atom or C_{1-6} alkyl;
R^{8a} is a hydrogen atom, a halogen atom or C_{1-6} alkyl,
or a salt thereof (to be referred to as "compound (Ia)" in the present specification);

[3] the compound of the above-mentioned [2] wherein
R^{1a} is a hydrogen atom, a fluorine atom or methyl;
R^{2a} is a hydrogen atom;
W^a is O or S;
X^a is CH, CF, CCl, $C(CH_3)$ or N;
Y^a is CH, CF, CCl, $C(CH_3)$ or N;
R^{5a} is
(1) cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,
(2) acetylamino optionally having one phenyl,
(3) methoxy optionally having one phenyl,
(4) tert-butoxy, or
(5) a nitrogen-containing heterocyclic group or an N-oxide thereof optionally having 1 to 4 substituents selected from
(a) phenyl optionally having 1 to 3 substituents selected from a fluorine atom, a chlorine atom, a bromine atom, methyl and isopropyl,
(b) methyl optionally having 1 to 3 fluorine atoms,
(c) ethyl optionally having 1 to 3 fluorine atoms,
(d) isopropyl, and
(e) oxo;
R^{6a} is a hydrogen atom;
R^{7a} is a hydrogen atom; and
R^{8a} is a hydrogen atom;

[4] N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-N'-phenylcyclopropane-1,1-dicarboxamide or a salt thereof;

[5] N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1-phenyl-

1,2-dihydropyridine-3-carboxamide or a salt thereof;
[6] N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide or a salt thereof;
[7] N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)pyridin-2-yl]-6-(4-fluorophenyl)-5-methylpyridine-2-carboxamide 1-oxide or a salt thereof;
[8] a prodrug of the compound of the above-mentioned [1];
[9] a pharmaceutical agent comprising the compound of the above-mentioned [1] or a prodrug thereof;
[10] the pharmaceutical agent of the above-mentioned [9], which is a kinase inhibitor;
[11] the pharmaceutical agent of the above-mentioned [9], which is an agent for the prophylaxis or treatment of cancer;
[12] a method for the prophylaxis or treatment of cancer, which comprises administering an effective amount of the compound of the above-mentioned [1] or a prodrug thereof to the mammal;
[13] use of the compound of the above-mentioned [1] or a prodrug thereof for the production of an agent for the prophylaxis or treatment of cancer;
and the like.

(Advantageous Effects of Invention)

The compound (I) and a prodrug thereof have a strong inhibitory activity against kinases such as vascular endothelial growth factor receptor, hepatocyte growth factor receptor, angiopoietin receptor, Fms Like Tyrosine Kinase 3 (FLT3), platelet-derived growth factor receptor and the like, and have a strong angiogenesis inhibitory activity, cancer cell proliferation inhibitory action and the like. Therefore, they can provide clinically useful agents for the prophylaxis or treatment of cancer, cancer growth inhibitors or cancer invasion and/or metastasis suppressors. Moreover, compound (I) and a prodrug thereof can provide clinically useful agents for the

prophylaxis or treatment of applications to diseases other than cancer, such as chronic rheumatism, diabetic retinopathy and the like, and have excellent efficacy expression, pharmacokinetics, solubility, interaction with other pharmaceutical products, safety and stability.

(Detailed Description of the Invention)

The present invention is explained in detail in the following.

In the present specification, the term "halogen atom" means a fluorine atom, a chlorine atom, a bromine atom or an iodine atom.

In the present specification, the term "C_{1-6} alkyl" means, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl and the like.

In the present specification, the term "C_{3-6} cycloalkyl" means, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

In the present specification, the term "C_{6-10} aryl" means, for example, phenyl, naphthyl and the like.

In the present specification, the term "C_{1-6} alkoxy" means methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy and the like.

In the present specification, the term "C_{1-6} alkyl-carbonylamino" means, for example, acetylamino, ethylcarbonylamino, propylcarbonylamino, isopropylcarbonylamino, butylcarbonylamino, isobutylcarbonylamino, sec-butylcarbonylamino, tert-butylcarbonylamino and the like.

In the present specification, the term "C_{6-10} aryl-aminocarbonyl" means, for example, phenylaminocarbonyl, naphthylaminocarbonyl and the like.

In the present specification, the term "heterocyclic group" means, for example, a monocyclic aromatic heterocyclic group, a fused aromatic heterocyclic group or a nonaromatic

heterocyclic group.

The "monocyclic aromatic heterocyclic group" means, for example, a 5- to 7-membered (preferably 5- or 6-membered) monocyclic aromatic heterocyclic group containing, as a ring constituting atom besides carbon atom, 1 to 4 hetero atoms selected from an oxygen atom, a sulfur atom (optionally oxidized) and a nitrogen atom, and the like. Examples thereof include furyl (e.g., 2-furyl, 3-furyl), thienyl (e.g., 2-thienyl, 3-thienyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl), pyridazinyl (e.g., 3-pyridazinyl, 4-pyridazinyl), pyrazinyl (e.g., 2-pyrazinyl), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), imidazolyl (e.g., 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), isothiazolyl (e.g., 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), isoxazolyl (e.g., 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), oxadiazolyl (e.g., 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl), thiadiazolyl (e.g., 1,3,4-thiadiazol-2-yl), triazolyl (e.g., 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-4-yl), tetrazolyl (e.g., tetrazol-1-yl, tetrazol-5-yl), triazinyl (e.g., 1,3,5-triazin-2-yl) and the like.

The fused aromatic heterocyclic group includes a 9- to 12-membered fused aromatic heterocyclic group formed by fusion of a 5- to 7-membered monocyclic aromatic heterocyclic group containing, as ring-constituting atom besides carbon atom, 1 to 4 heteroatoms selected from an oxygen atom, a sulfur atom (optionally oxidized) and a nitrogen atom, and the like, and C_{6-10} aryl and the like; a 8- to 12-membered fused aromatic heterocyclic group formed by fusion of 5- to 7-membered monocyclic aromatic heterocyclic groups, and the like. Examples thereof include quinolyl (e.g., 2-quinolyl, 3-quinolyl, 4-

quinolyl), isoquinolyl (e.g., 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl), quinazolyl (e.g., 2-quinazolyl, 4-quinazolyl), quinoxalyl (e.g., 2-quinoxalyl), benzofuryl (e.g., 2-benzofuryl, 3-benzofuryl), isobenzofuryl (e.g., 1-isobenzofuryl, 3-isobenzofuryl), benzothienyl (e.g., 2-benzothienyl, 3-benzothienyl), isobenzothienyl (e.g., 1-isobenzothienyl, 3-isobenzothienyl), benzoxazolyl (e.g., 2-benzoxazolyl), benzothiazolyl (e.g., 2-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl), benzimidazolyl (e.g., benzimidazol-1-yl, benzimidazol-2-yl, benzimidazol-5-yl), indolyl (e.g., indol-1-yl, indol-2-yl, indol-3-yl, indol-4-yl, indol-5-yl, indol-6-yl), indazolyl (e.g., 1H-indazol-3-yl), pyrrolopyrazinyl (e.g., 1H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyrazin-6-yl), imidazopyridyl (e.g., 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl), imidazopyrazinyl (e.g., 1H-imidazo[4,5-b]pyrazin-2-yl), benzisoxazolyl (e.g., benzisoxazol-3-yl), benzotriazolyl (e.g., 1H-1,2,3-benzotriazol-5-yl), benzopyrazolyl (e.g., benzopyrazol-5-yl), pyrazolopyridyl (e.g., 1H-pyrazolo[4,3-c]pyridin-3-yl), pyrazolothienyl (e.g., 2H-pyrazolo[3,4-b]thiophen-2-yl), pyrazolotriazinyl (e.g., pyrazolo[5,1-c][1,2,4]triazin-3-yl) and the like.

Examples of the "nonaromatic heterocyclic group" include a 3- to 8-membered nonaromatic heterocyclic group containing, as a ring constituting atom besides carbon atom, 1 to 4 hetero atoms selected from an oxygen atom, a sulfur atom (optionally oxidized) and a nitrogen atom, and the like. Examples thereof include oxiranyl (e.g., 2-oxiranyl), azetidinyl (e.g., 1-azetidinyl, 2-azetidinyl, 3-azetidinyl), oxetanyl (e.g., 2-oxetanyl, 3-oxetanyl), thietanyl (e.g., 2-thietanyl, 3-thietanyl), pyrrolidinyl (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl), tetrahydrofuryl (e.g., 2-tetrahydrofuryl, 3-tetrahydrofuryl), thioranyl (e.g., 2-thioranyl, 3-thioranyl), piperidinyl (e.g., 1-piperidinyl, 2-piperidinyl, 3-piperidinyl,

4-piperidinyl), tetrahydropyranyl (e.g., 2-tetrahydropyranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl), thianyl (e.g., 2-thianyl, 3-thianyl), morpholinyl (e.g., 2-morpholinyl, 3-morpholinyl, 4-morpholinyl), thiomorpholinyl (e.g., 2-thiomorpholinyl, 3-thiomorpholinyl, 4-thiomorpholinyl), piperazinyl (e.g., 1-piperazinyl, 2-piperazinyl), azepanyl (e.g., 1-azepanyl, 3-azepanyl), oxepanyl (e.g., 3-oxepanyl), thiepanyl (e.g., 3-thiepanyl), oxazepanyl (e.g., 1,4-oxazepan-4-yl, 1,4-oxazepan-5-yl), thiazepanyl (e.g., 1,4-thiazepan-4-yl, 1,4-thiazepan-5-yl), azocanyl (e.g., 1-azocanyl, 4-azocanyl), oxocanyl (e.g., 4-oxocanyl), thiocanyl (e.g., 4-thiocanyl), oxazocanyl (e.g., 1,4-oxazocan-5-yl), thioazocanyl (e.g., 1,4-thioazocan-5-yl), dioxinyl (e.g., 1,4-dioxin-2-yl), dihydropyrazolyl (e.g., 2,3-dihydropyrazol-1-yl, 2,3-dihydropyrazol-3-yl, 2,3-dihydropyrazol-4-yl, 2,3-dihydropyrazol-5-yl), hexahydropyrimidinyl (e.g., hexahydropyrimidin-1-yl, hexahydropyrimidin-2-yl, hexahydropyrimidin-4-yl, hexahydropyrimidin-5-yl), tetrahydropyrimidinyl (e.g., 1,2,3,4-tetrahydropyrimidin-1-yl, 1,2,3,4-tetrahydropyrimidin-2-yl, 1,2,5,6-tetrahydropyrimidin-1-yl, 1,2,5,6-tetrahydropyrimidin-2-yl), dihydropyrimidinyl (e.g., 1,2-dihydropyrimidin-1-yl, 1,2-dihydropyrimidin-2-yl), tetrahydropyridyl (e.g., 1,2,3,4-tetrahydropyridin-1-yl, 1,2,3,4-tetrahydropyridin-2-yl, 1,2,5,6-tetrahydropyridin-1-yl, 1,2,5,6-tetrahydropyridin-2-yl), dihydropyridyl (e.g., 1,2-dihydropyridin-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl), tetrahydroimidazolyl (e.g., tetrahydroimidazol-1-yl, tetrahydroimidazol-2-yl, tetrahydroimidazol-4-yl), dihydroimidazolyl (e.g., 4,5-dihydroimidazol-1-yl, 4,5-dihydroimidazol-2-yl, 4,5-dihydroimidazol-4-yl, 4,5-dihydroimidazol-5-yl) and the like.

In the present specification, the term "group bonded via a carbon atom" means, for example, cyano, a hydrocarbon group

optionally having substituent(s), a heterocyclic group bonded via a carbon atom optionally having substituent(s) and the like.

Examples of the "hydrocarbon group optionally having substituent(s)" include alkyl optionally having substituent(s), alkenyl optionally having substituent(s), alkynyl optionally having substituent(s), cycloalkyl optionally having substituent(s), cycloalkenyl optionally having substituent(s), aryl optionally having substituent(s), cycloalkyl-alkyl optionally having substituent(s), cycloalkenyl-alkyl optionally having substituent(s), aryl-alkyl optionally having substituent(s), cycloalkanedienyl optionally having substituent(s) and the like.

In the present specification, the term "alkyl optionally having substituent(s)" means C_{1-6} alkyl optionally having 1 to 3 substituents selected from the following substituent group (hereinafter to be abbreviated as substituent group A).

substituent group A:

(1) a halogen atom;

(2) cyano;

(3) nitro;

(4) hydroxy;

(5) C_{1-6} alkoxy optionally having 1 to 3 halogen atoms;

(6) C_{2-6} alkenyloxy (e.g., ethenyloxy, propenyloxy, butenyloxy, pentenyloxy, hexenyloxy etc.) optionally having 1 to 3 halogen atoms;

(7) C_{2-6} alkynyloxy (e.g., ethynyloxy, propynyloxy, butynyloxy, pentynyloxy, hexynyloxy etc.) optionally having 1 to 3 halogen atoms;

(8) C_{3-6} cycloalkyloxy (e.g., cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy etc.) optionally having 1 to 3 halogen atoms;

(9) C_{3-6} cycloalkenyloxy (e.g., cyclopropenyloxy, cyclobutenyloxy, cyclopentenyloxy, cyclohexenyloxy etc.)

optionally having 1 to 3 halogen atoms;
(10) C_{6-10} aryloxy (e.g., phenyloxy, 1-naphthyloxy, 2-naphthyloxy etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);
(11) C_{3-6} cycloalkyl-C_{1-6} alkoxy (e.g., cyclopropylmethyloxy, cyclopropylethyloxy, cyclobutylmethyloxy, cyclopentylmethyloxy, cyclohexylmethyloxy, cyclohexylethyloxy etc.) optionally having 1 to 3 halogen atoms;
(12) C_{3-6} cycloalkenyl-C_{1-6} alkoxy (e.g., cyclopentenylmethyloxy, cyclohexenylmethyloxy, cyclohexenylethyloxy, cyclohexenylpropyloxy etc.) optionally having 1 to 3 halogen atoms;
(13) C_{6-10} aryl-C_{1-6} alkoxy (e.g., phenylmethyloxy, phenylethyloxy etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);
(14) C_{1-6} alkylsulfamoyl (e.g., methylsulfamoyl, ethylsulfamoyl, propylsulfamoyl etc.);
(15) di-C_{1-6} alkylsulfamoyl (e.g., dimethylsulfamoyl, diethylsulfamoyl, dipropylsulfamoyl etc.);
(16) C_{1-6} alkylamino-carbonyl (e.g., methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl etc.);
(17) di-C_{1-6} alkylamino-carbonyl (e.g., dimethylaminocarbonyl, diethylaminocarbonyl, dipropylaminocarbonyl etc.);
(18) formyl;
(19) C_{1-6} alkyl-carbonyl (e.g., acetyl, ethylcarbonyl, propylcarbonyl, isopropylcarbonyl etc.);
(20) C_{2-6} alkenyl-carbonyl (e.g., ethenylcarbonyl, propenylcarbonyl, butenylcarbonyl, pentenylcarbonyl, hexenylcarbonyl etc.);
(21) C_{2-6} alkynyl-carbonyl (e.g., ethynylcarbonyl, propynylcarbonyl, butynylcarbonyl, pentynylcarbonyl, hexynylcarbonyl etc.);

(22) C_{3-6} cycloalkyl-carbonyl (e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl etc.);

(23) C_{3-6} cycloalkenyl-carbonyl (e.g., cyclopropenylcarbonyl, cyclobutenylcarbonyl, cyclopentenylcarbonyl, cyclohexenylcarbonyl etc.);

(24) C_{6-10} aryl-carbonyl (e.g., benzoyl, 1-naphthylcarbonyl, 2-naphthylcarbonyl etc.);

(25) C_{3-6} cycloalkyl-C_{1-6} alkyl-carbonyl (e.g., cyclopropylmethylcarbonyl, cyclopropylethylcarbonyl, cyclobutylmethylcarbonyl, cyclopentylmethylcarbonyl, cyclohexylmethylcarbonyl, cyclohexylethylcarbonyl etc.);

(26) C_{3-6} cycloalkenyl-C_{1-6} alkyl-carbonyl (e.g., cyclopentenylmethylcarbonyl, cyclohexenylmethylcarbonyl, cyclohexenylethylcarbonyl, cyclohexenylpropylcarbonyl etc.);

(27) C_{6-10} aryl-C_{1-6} alkyl-carbonyl (e.g., benzylcarbonyl, phenylethylcarbonyl etc.);

(28) 5- or 6-membered monocyclic aromatic heterocyclyl-carbonyl (e.g., furylcarbonyl, thienylcarbonyl, pyrrolylcarbonyl, oxazolylcarbonyl, isoxazolylcarbonyl, thiazolylcarbonyl, isothiazolylcarbonyl, imidazolylcarbonyl, pyridylcarbonyl, pyrazolylcarbonyl etc.);

(29) 8- to 12-membered fused aromatic heterocyclyl-carbonyl (e.g., benzofurylcarbonyl, isobenzofurylcarbonyl, benzothienylcarbonyl, isobenzothienylcarbonyl, indolylcarbonyl, isoindolylcarbonyl, 1H-indazolylcarbonyl, benzimidazolylcarbonyl, benzoxazolylcarbonyl etc.);

(30) 3- or 8-membered non-aromatic heterocyclyl-carbonyl (e.g., oxiranylcarbonyl, azetidinylcarbonyl, oxetanylcarbonyl, thietanylcarbonyl, pyrrolidinylcarbonyl, tetrahydrofurylcarbonyl, thiolanylcarbonyl, piperidinylcarbonyl etc.);

(31) C_{1-6} alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl etc.);

(32) C_{2-6} alkenylsulfonyl (e.g., ethenylsulfonyl,

propenylsulfonyl etc.);
(33) C_{2-6} alkynylsulfonyl (e.g., ethynylsulfonyl, propynylsulfonyl, butynylsulfonyl, pentynylsulfonyl, hexynylsulfonyl etc.);
(34) C_{3-6} cycloalkylsulfonyl (e.g., cyclopropylsulfonyl, cyclobutylsulfonyl etc.);
(35) C_{3-6} cycloalkenylsulfonyl (e.g., cyclopropenylsulfonyl, cyclobutenylsulfonyl etc.);
(36) C_{6-10} arylsulfonyl (e.g., phenylsulfonyl etc.);
(37) C_{3-6} cycloalkyl-C_{1-6} alkyl-sulfonyl (e.g., cyclopropylmethylsulfonyl etc.);
(38) C_{3-6} cycloalkenyl-C_{1-6} alkyl-sulfonyl (e.g., cyclopentenylmethylsulfonyl etc.);
(39) C_{6-10} aryl-C_{1-6} alkyl-sulfonyl (e.g., benzylsulfonyl etc.);
(40) 5- or 6-membered monocyclic aromatic heterocyclyl-sulfonyl (e.g., furylsulfonyl, thienylsulfonyl, pyridylsulfonyl etc.);
(41) 8- to 12-membered fused aromatic heterocyclyl-sulfonyl (e.g., benzofurylsulfonyl, isobenzofurylsulfonyl etc.);
(42) 3- to 8-membered non-aromatic heterocyclyl-sulfonyl (e.g., oxiranylsulfonyl, azetidinylsulfonyl etc.);
(43) amino;
(44) mono-C_{1-6} alkylamino (e.g., methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, tert-butylamino etc.) optionally having one substituent selected from

(a) C_{6-10} aryl, and

(b) a 5- or 6-membered monocyclic aromatic heterocyclic group (e.g., furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyridyl, pyrazolyl etc.) optionally having one C_{1-6} alkyl;

(45) di-C_{1-6} alkylamino (e.g., dimethylamino, diethylamino, dipropylamino, diisopropylamino, dibutylamino, diisobutylamino, di-tert-butylamino etc.);
(46) C_{1-6} alkyl-carbonylamino optionally having 1 to 3

substituents selected from

(a) a halogen atom, and

(b) a 5- or 6-membered monocyclic aromatic heterocyclic group (e.g., furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyridyl, pyrazolyl etc.);

(47) C_{3-6} cycloalkyl-carbonylamino (e.g., cyclopropylcarbonylamino, cyclobutylcarbonylamino, cyclopentylcarbonylamino, cyclohexylcarbonylamino etc.);

(48) C_{3-6} cycloalkenyl-carbonylamino (e.g., cyclopropenylcarbonylamino, cyclobutenylcarbonylamino, cyclopentenylcarbonylamino, cyclohexenylcarbonylamino etc.);

(49) C_{6-10} aryl-carbonylamino (e.g., benzoylamino etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);

(50) mono(5- or 6-membered monocyclic aromatic heterocyclyl-carbonyl)amino (e.g., furylcarbonylamino, thienylcarbonylamino, pyrrolylcarbonylamino, oxazolylcarbonylamino, isoxazolylcarbonylamino, thiazolylcarbonylamino, isothiazolylcarbonylamino, imidazolylcarbonylamino, tetrazolylcarbonylamino, pyridylcarbonylamino, pyrazolylcarbonylamino etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);

(51) mono(8- to 12-membered fused aromatic heterocyclyl-carbonyl)amino (e.g., benzofurylcarbonylamino, isobenzofurylcarbonylamino, benzothienylcarbonylamino, isobenzothienylcarbonylamino, benzopyrazolylcarbonylamino etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);

(52) mono(3- to 8-membered non-aromatic heterocyclyl-carbonyl)amino (e.g., oxiranylcarbonylamino, azetidinylcarbonylamino, oxetanylcarbonylamino,

thietanylcarbonylamino, pyrrolidinylcarbonylamino, tetrahydrofurylcarbonylamino, thioranylcarbonylamino, piperidinylcarbonylamino etc.) optionally having 1 to 3 substituents selected from substituent group B and substituent group C (mentioned later);

(53) mono-C_{1-6} alkoxy-carbonylamino (e.g., methoxycarbonylamino, ethoxycarbonylamino, tert-butoxycarbonylamino etc.);

(54) mercapto;

(55) C_{1-6} alkylsulfanyl (e.g., methylsulfanyl, ethylsulfanyl etc.);

(56) C_{2-6} alkenylsulfanyl (e.g., ethenylsulfanyl, propenylsulfanyl etc.);

(57) C_{2-6} alkynylsulfanyl (e.g., ethynylsulfanyl, propynylsulfanyl, butynylsulfanyl, pentynylsulfanyl, hexynylsulfanyl etc.);

(58) C_{3-6} cycloalkylsulfanyl (e.g., cyclopropylsulfanyl, cyclobutylsulfanyl etc.);

(59) C_{3-6} cycloalkenylsulfanyl (e.g., cyclopropenylsulfanyl, cyclobutenylsulfanyl etc.);

(60) C_{6-10} arylsulfanyl (e.g., phenylsulfanyl etc.);

(61) C_{3-6} cycloalkyl-C_{1-6} alkylsulfanyl (e.g., cyclopropylmethylsulfanyl etc.);

(62) C_{3-6} cycloalkenyl-C_{1-6} alkylsulfanyl (e.g., cyclopentenylmethylsulfanyl etc.);

(63) 5- or 6-membered monocyclic aromatic heterocyclic group (e.g., furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyridyl, pyrazolyl etc.);

(64) 8- to 12-membered fused aromatic heterocyclic group (e.g., benzofuryl, isobenzofuryl, benzothienyl, isobenzothienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl etc.);

(65) 3- to 8-membered non-aromatic heterocyclic group (e.g., oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidinyl etc.);

(66) 5- or 6-membered monocyclic aromatic heterocyclyl-oxy (e.g., furyloxy, thienyloxy, pyrrolyloxy, oxazolyloxy, isoxazolyloxy, thiazolyloxy, isothiazolyloxy, imidazolyloxy, pyridyloxy, pyrazolyloxy etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);

(67) 8- to 12-membered fused aromatic heterocyclyl-oxy (e.g., benzofuryloxy, isobenzofuryloxy, benzothienyloxy, isobenzothienyloxy, indolyloxy, isoindolyloxy, 1H-indazolyloxy, benzimidazolyloxy, benzoxazolyloxy etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);

(68) 3- to 8-membered non-aromatic heterocyclyl-oxy (e.g., oxiranyloxy, azetidinyloxy, oxetanyloxy, thietanyloxy, pyrrolidinyloxy, tetrahydrofuryloxy, thiolanyloxy, piperidinyloxy etc.) optionally having 1 to 3 substituents selected from substituent group B and substituent group C (mentioned later);

(69) oxo;

(70) C_{1-6} alkylsulfinyl (e.g., methylsulfinyl, ethylsulfinyl etc.);

(71) C_{2-6} alkenylsulfinyl (e.g., ethenylsulfinyl, propenylsulfinyl etc.);

(72) C_{2-6} alkynylsulfinyl (e.g., ethynylsulfinyl, propynylsulfinyl, butynylsulfinyl, pentynylsulfinyl, hexynylsulfinyl etc.);

(73) C_{3-6} cycloalkylsulfinyl (e.g., cyclopropylsulfinyl, cyclobutylsulfinyl etc.);

(74) C_{3-6} cycloalkenylsulfinyl (e.g., cyclopropenylsulfinyl, cyclobutenylsulfinyl etc.);

(75) C_{6-10} arylsulfinyl (e.g., phenylsulfinyl etc.);

(76) C_{3-6} cycloalkyl-C_{1-6} alkyl-sulfinyl (e.g., cyclopropylmethylsulfinyl etc.);

(77) C_{3-6} cycloalkenyl-C_{1-6} alkyl-sulfinyl (e.g.,

cyclopentenylmethylsulfinyl etc.);
(78) C_{1-6} alkylamino-thiocarbonyl (e.g., methylaminothiocarbonyl, ethylaminothiocarbonyl, propylaminothiocarbonyl etc.);
(79) di-C_{1-6} alkyl-aminothiocarbonyl (e.g., dimethylaminothiocarbonyl, diethylaminothiocarbonyl, dipropylaminothiocarbonyl etc.);
(80) carboxy;
(81) C_{1-6} alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl etc.);
(82) C_{2-6} alkenyloxy-carbonyl (e.g., ethenyloxycarbonyl, propenyloxycarbonyl, butenyloxycarbonyl, pentenyloxycarbonyl, hexenyloxycarbonyl etc.);
(83) C_{2-6} alkynyloxy-carbonyl (e.g., ethynyloxycarbonyl, propynyloxycarbonyl, butynyloxycarbonyl, pentynyloxycarbonyl, hexynyloxycarbonyl etc.);
(84) C_{3-6} cycloalkyl-oxy-carbonyl (e.g., cyclopropyloxycarbonyl, cyclobutyloxycarbonyl, cyclopentyloxycarbonyl, cyclohexyloxycarbonyl etc.);
(85) C_{3-6} cycloalkenyloxy-carbonyl (e.g., cyclopropenyloxycarbonyl, cyclobutenyloxycarbonyl, cyclopentenyloxycarbonyl, cyclohexenyloxycarbonyl etc.);
(86) C_{6-10} aryloxy-carbonyl (e.g., phenyloxycarbonyl, 1-naphthyloxycarbonyl, 2-naphthyloxycarbonyl etc.);
(87) C_{3-6} cycloalkyl-C_{1-6} alkoxy-carbonyl (e.g., cyclopropylmethyloxycarbonyl, cyclopropylethyloxycarbonyl, cyclobutylmethyloxycarbonyl, cyclopentylmethyloxycarbonyl, cyclohexylmethyloxycarbonyl, cyclohexylethyloxycarbonyl etc.);
(88) C_{3-6} cycloalkenyl-C_{1-6} alkoxy-carbonyl (e.g., cyclopentenylmethyloxycarbonyl, cyclohexenylmethyloxycarbonyl, cyclohexenylethyloxycarbonyl, cyclohexenylpropyloxycarbonyl etc.);
(89) C_{6-10} aryl-C_{1-6} alkoxy-carbonyl (e.g.,

phenylmethyloxycarbonyl, phenylethyloxycarbonyl etc.);
(90) sulfamoyl;
(91) carbamoyl;
(92) mono(C_{6-10} aryl-C_{1-6} alkyl-carbonyl)amino (e.g., phenylmethylcarbonylamino etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);
(93) mono(5- or 6-membered monocyclic aromatic heterocyclyl-C_{1-6} alkyl-carbonyl)amino (e.g., furylmethylcarbonylamino, thienylmethylcarbonylamino, pyrrolylmethylcarbonylamino, oxazolylmethylcarbonylamino, isoxazolylmethylcarbonylamino, thiazolylmethylcarbonylamino, isothiazolylmethylcarbonylamino, imidazolylmethylcarbonylamino, tetrazolylmethylcarbonylamino, pyridylmethylcarbonylamino, pyrazolylmethylcarbonylamino etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);
(94) mono(8- to 12-membered fused aromatic heterocyclyl-C_{1-6} alkyl-carbonyl)amino (e.g., benzofurylmethylcarbonylamino, isobenzofurylmethylcarbonylamino, benzothienylmethylcarbonylamino, isobenzothienylmethylcarbonylamino, benzopyrazolylmethylcarbonylamino etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);
(95) mono(3- to 8-membered non-aromatic heterocyclyl-C_{1-6} alkyl-carbonyl)amino (e.g., oxiranylmethylcarbonylamino, azetidinylmethylcarbonylamino, oxetanylmethylcarbonylamino, thietanylmethylcarbonylamino, pyrrolidinylmethylcarbonylamino, tetrahydrofurylmethylcarbonylamino, thioranylmethylcarbonylamino, piperidinylmethylcarbonylamino etc.) optionally having 1 to 3 substituents selected from substituent group B and substituent group C (mentioned later);
(96) mono-C_{6-10} aryl-ureido (e.g., phenylureido etc.)

optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);

(97) mono-5- or 6-membered monocyclic aromatic heterocyclyl-ureido (e.g., furylureido, thienylureido, pyrrolylureido, oxazolylureido, isoxazolylureido, thiazolylureido, isothiazolylureido, imidazolylureido, tetrazolylureido, pyridylureido, pyrazolylureido etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);

(98) mono-8- to 12-membered fused aromatic heterocyclyl-ureido (e.g., benzofurylureido, isobenzofurylureido, benzothienylureido, isobenzothienylureido, benzopyrazolylureido etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);

(99) mono-3- to 8-membered non-aromatic heterocyclyl-ureido (e.g., oxiranylureido, azetidinylureido, oxetanylureido, thietanylureido, pyrrolidinylureido, tetrahydrofurylureido, thioranylureido, piperidinylureido etc.) optionally having 1 to 3 substituents selected from substituent group B and substituent group C (mentioned later);

(100) mono(C_{6-10} aryl-C_{1-6} alkyl)ureido (e.g., phenylmethylureido etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);

(101) mono(5- or 6-membered monocyclic aromatic heterocyclyl-C_{1-6} alkyl)ureido (e.g., furylmethylureido, thienylmethylureido, pyrrolylmethylureido, oxazolylmethylureido, isoxazolylmethylureido, thiazolylmethylureido, isothiazolylmethylureido, imidazolylmethylureido, tetrazolylmethylureido, pyridylmethylureido, pyrazolylmethylureido etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B

and substituent group C (mentioned later);
(102) mono(8- to 12-membered fused aromatic heterocyclyl-C_{1-6} alkyl)ureido (e.g., benzofurylmethylureido, isobenzofurylmethylureido, benzothienylmethylureido, isobenzothienylmethylureido, benzopyrazolylmethylureido etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);
(103) mono(3- to 8-membered non-aromatic heterocyclyl-C_{1-6} alkyl)ureido (e.g., oxiranylmethylureido, azetidinylmethylureido, oxetanylmethylureido, thietanylmethylureido, pyrrolidinylmethylureido, tetrahydrofurylmethylureido, thioranylmethylureido, piperidinylmethylureido etc.) optionally having 1 to 3 substituents selected from substituent group B and substituent group C (mentioned later);
(104) mono-C_{6-10} aryl-aminocarbonyl optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);
(105) mono-5- or 6-membered monocyclic aromatic heterocyclyl-aminocarbonyl (e.g., furylaminocarbonyl, thienylaminocarbonyl, pyrrolylaminocarbonyl, oxazolylaminocarbonyl, isoxazolylaminocarbonyl, thiazolylaminocarbonyl, isothiazolylaminocarbonyl, imidazolylaminocarbonyl, tetrazolylaminocarbonyl, pyridylaminocarbonyl, pyrazolylaminocarbonyl etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);
(106) mono-8- to 12-membered fused aromatic heterocyclyl-aminocarbonyl (e.g., benzofurylaminocarbonyl, isobenzofurylaminocarbonyl, benzothienylaminocarbonyl, isobenzothienylaminocarbonyl, benzopyrazolylaminocarbonyl etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C

(mentioned later);

(107) mono-3- to 8-membered non-aromatic heterocyclyl-aminocarbonyl (e.g., oxiranylaminocarbonyl, azetidinylaminocarbonyl, oxetanylaminocarbonyl, thietanylaminocarbonyl, pyrrolidinylaminocarbonyl, tetrahydrofurylaminocarbonyl, thioranylaminocarbonyl, piperidinylaminocarbonyl etc.) optionally having 1 to 3 substituents selected from substituent group B and substituent group C (mentioned later);

(108) mono(C_{6-10} aryl-C_{1-6} alkyl)aminocarbonyl (e.g., phenylmethylaminocarbonyl etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);

(109) mono(5- or 6-membered monocyclic aromatic heterocyclyl-C_{1-6} alkyl)aminocarbonyl (e.g., furylmethylaminocarbonyl, thienylmethylaminocarbonyl, pyrrolylmethylaminocarbonyl, oxazolylmethylaminocarbonyl, isoxazolylmethylaminocarbonyl, thiazolylmethylaminocarbonyl, isothiazolylmethylaminocarbonyl, imidazolylmethylaminocarbonyl, tetrazolylmethylaminocarbonyl, pyridylmethylaminocarbonyl, pyrazolylmethylaminocarbonyl etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);

(110) mono(8- to 12-membered fused aromatic heterocyclyl-C_{1-6} alkyl)aminocarbonyl (e.g., benzofurylmethylaminocarbonyl, isobenzofurylmethylaminocarbonyl, benzothienylmethylaminocarbonyl, isobenzothienylmethylaminocarbonyl, benzopyrazolylmethylaminocarbonyl etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);

(111) mono(3- to 8-membered non-aromatic heterocyclyl-C_{1-6} alkyl)aminocarbonyl (e.g., oxiranylmethylaminocarbonyl, azetidinylmethylaminocarbonyl, oxetanylmethylaminocarbonyl,

thietanylmethylaminocarbonyl, pyrrolidinylmethylaminocarbonyl, tetrahydrofurylmethylaminocarbonyl, thioranylmethylaminocarbonyl, piperidinylmethylaminocarbonyl etc.) optionally having 1 to 3 substituents selected from substituent group B and substituent group C (mentioned later);

(112) mono-5- or 6-membered monocyclic aromatic heterocyclyl-amino (e.g., furylamino, thienylamino, pyrrolylamino, oxazolylamino, isoxazolylamino, thiazolylamino, isothiazolylamino, imidazolylamino, tetrazolylamino, pyridylamino, pyrazolylamino etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B and substituent group C (mentioned later);

(113) cyclic amino (e.g., pyrrolidino, piperidino, piperazino, morpholino, thiomorpholino etc.) fused with a benzene ring and optionally having one oxo;

(114) C_{2-6} alkynyl-carbonylamino (e.g., ethynylcarbonylamino, propynylcarbonylamino, butynylcarbonylamino, pentynylcarbonylamino, hexynylcarbonylamino etc.) optionally having one C_{6-10} aryl (e.g., phenyl etc.);

(115) C_{6-10} aryl-sulfonylamino (e.g., phenylsulfonylamino, naphthylsulfonylamino etc.) optionally having one substituent selected from

(a) a halogen atom,

(b) C_{1-6} alkyl optionally having 1 to 3 halogen atoms, and

(c) C_{1-6} alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl etc.);

(116) 5- or 6-membered monocyclic aromatic heterocyclyl-sulfonylamino (e.g., furylsulfonylamino, thienylsulfonylamino, pyrrolylsulfonylamino, oxazolylsulfonylamino, isoxazolylsulfonylamino, thiazolylsulfonylamino, isothiazolylsulfonylamino, imidazolylsulfonylamino, tetrazolylsulfonylamino, pyridylsulfonylamino, pyrazolylsulfonylamino etc.) optionally having one C_{1-6} alkyl;

(117) ureido; and

(118) C_{1-6} alkyl-ureido (e.g., methylureido, ethylureido, propylureido etc.).

substituent group B:

(1) a halogen atom;

(2) cyano;

(3) hydroxy;

(4) 3- to 8-membered non-aromatic heterocyclyl-oxy (e.g., oxiranyloxy, azetidinyloxy, oxetanyloxy, thietanyloxy, pyrrolidinyloxy, tetrahydrofuryloxy, thioranyloxy, piperidinyloxy etc.);

(5) amino;

(6) mono-C_{1-6} alkyl-amino (e.g., methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, tert-butylamino etc.);

(7) di-C_{1-6} alkyl-amino (e.g., dimethylamino, diethylamino, dipropylamino, diisopropylamino, dibutylamino, diisobutylamino, di-tert-butylamino, N-ethyl-N-methylamino, N-methyl-N-propylamino, N-ethyl-N-propylamino etc.);

(8) mono-C_{3-6} cycloalkyl-amino (e.g., cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino etc.);

(9) mono(C_{1-6} alkyl-carbonyl)amino (e.g., acetylamino, ethylcarbonylamino, propylcarbonylamino, isobutylcarbonylamino, tert-butylcarbonylamino etc.);

(10) mono(C_{3-6} cycloalkyl-carbonyl)amino (e.g., cyclopropylcarbonylamino, cyclobutylcarbonylamino, cyclopentylcarbonylamino, cyclohexylcarbonylamino etc.);

(11) mercapto;

(12) C_{1-6} alkyl-sulfanyl (e.g., methylsulfanyl, ethylsulfanyl etc.);

(13) C_{3-6} cycloalkyl-sulfanyl (e.g., cyclopropylsulfanyl, cyclobutylsulfanyl etc.);

(14) 3- to 8-membered non-aromatic heterocyclyl-sulfanyl (e.g., oxiranylsulfanyl, azetidinylsulfanyl etc.);

(15) C_{1-6} alkyl-sulfinyl (e.g., methylsulfinyl, ethylsulfinyl etc.);
(16) C_{3-6} cycloalkyl-sulfinyl (e.g., cyclopropylsulfinyl, cyclobutylsulfinyl etc.);
(17) 3- to 8-membered non-aromatic heterocyclyl-sulfinyl (e.g., oxiranylsulfinyl, azetidinylsulfinyl etc.);
(18) C_{1-6} alkyl-sulfonyl (e.g., methylsulfonyl, ethylsulfonyl etc.);
(19) C_{3-6} cycloalkyl-sulfonyl (e.g., cyclopropylsulfonyl, cyclobutylsulfonyl etc.);
(20) 3- to 8-membered non-aromatic heterocyclyl-sulfonyl (e.g., oxiranylsulfonyl, azetidinylsulfonyl etc.);
(21) oxo;
(22) formyl;
(23) C_{1-6} alkyl-carbonyl (e.g., acetyl, ethylcarbonyl, propylcarbonyl, isopropylcarbonyl etc.);
(24) C_{3-6} cycloalkyl-carbonyl (e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl etc.);
(25) 3- to 8-membered non-aromatic heterocyclyl-carbonyl (e.g., oxiranylcarbonyl, azetidinylcarbonyl, oxetanylcarbonyl, thietanylcarbonyl, pyrrolidinylcarbonyl, tetrahydrofurylcarbonyl, thioranylcarbonyl, piperidinylcarbonyl etc.);
(26) carboxy;
(27) carbamoyl;
(28) mono(C_{1-6} alkyl-amino)carbonyl (e.g., methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl etc.);
(29) di-(C_{1-6} alkyl-amino)carbonyl (e.g., dimethylaminocarbonyl, diethylaminocarbonyl, dipropylaminocarbonyl etc.);
(30) sulfo;
(31) sulfamoyl;
(32) mono-C_{1-6} alkylsulfamoyl (e.g., methylsulfamoyl, ethylsulfamoyl, propylsulfamoyl etc.);

(33) di-C_{1-6} alkylsulfamoyl (e.g., dimethylsulfamoyl, diethylsulfamoyl, dipropylsulfamoyl etc.);
(34) a 3- to 8-membered nonaromatic heterocyclic group (e.g., oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thioranyl, piperidinyl etc.);
(35) C_{1-4} alkylenedioxy (e.g., methylenedioxy, ethylenedioxy, trimethylendioxy etc.); and
(36) C_{1-6} alkylsulfanyl (e.g., methylsulfanyl, ethylsulfanyl, propylsulfanyl etc.).

substituent group C:
(1) C_{1-6} alkyl optionally having 1 to 3 substituents selected from substituent group B;
(2) C_{1-6} alkoxy optionally having 1 to 3 substituents selected from substituent group B;
(3) C_{3-6} cycloalkyl optionally having 1 to 3 substituents selected from substituent group B;
(4) C_{3-6} cycloalkyloxy (e.g., cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy etc.) optionally having 1 to 3 substituents selected from substituent group B;
(5) C_{3-6} cycloalkyl-C_{1-6} alkyl (e.g., cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclohexylethyl etc.) optionally having 1 to 3 substituents selected from substituent group B;
(6) C_{3-6} cycloalkyl-C_{1-6} alkoxy (e.g., cyclopropylmethyloxy, cyclopropylethyloxy, cyclobutylmethyloxy, cyclopentylmethyloxy, cyclohexylmethyloxy, cyclohexylethyloxy etc.) optionally having 1 to 3 substituents selected from substituent group B;
(7) C_{6-10} aryl optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B;
(8) C_{6-10} aryloxy (e.g., phenyloxy, 1-naphthyloxy, 2-naphthyloxy etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B;
(9) C_{6-10} aryl-C_{1-6} alkyl (e.g., benzyl, phenylethyl etc.) optionally having 1 to 3 substituents (excluding oxo) selected

from substituent group B;
(10) C_{6-10} aryl-C_{1-6} alkoxy (e.g., phenylmethyloxy, phenylethyloxy etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B;
(11) 5- or 6-membered monocyclic aromatic heterocyclic group (e.g., furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyridyl, pyrazolyl etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B;
(12) 5- or 6-membered monocyclic aromatic heterocyclyl-oxy (e.g., furyloxy, thienyloxy, pyrrolyloxy, oxazolyloxy, isoxazolyloxy, thiazolyloxy, isothiazolyloxy, imidazolyloxy, pyridyloxy, pyrazolyloxy etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B;
(13) 5- or 6-membered monocyclic aromatic heterocyclyl-C_{1-6} alkyl (e.g., furylmethyl, thienylmethyl, pyrrolylmethyl, oxazolylmethyl, isoxazolylmethyl, thiazolylmethyl, isothiazolylmethyl, imidazolylmethyl, pyridylmethyl, pyrazolylmethyl etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B; and
(14) 5- or 6-membered monocyclic aromatic heterocyclyl-C_{1-6} alkoxy (e.g., furylmethyloxy, thienylmethyloxy, pyrrolylmethyloxy, oxazolylmethyloxy, isoxazolylmethyloxy, thiazolylmethyloxy, isothiazolylmethyloxy, imidazolylmethyloxy, pyridylmethyloxy, pyrazolylmethyloxy etc.) optionally having 1 to 3 substituents (excluding oxo) selected from substituent group B.

In the present specification, the term "alkenyl optionally having substituent(s)" means C_{2-6} alkenyl (e.g., ethenyl, propenyl, butenyl, pentenyl, hexenyl, butadienyl etc.) optionally having 1 to 3 substituents selected from substituent group A.

In the present specification, the term "alkynyl

optionally having substituent(s)" means C_{2-6} alkynyl (e.g., ethynyl, propynyl, butynyl, pentynyl, hexynyl etc.) optionally having 1 to 3 substituents selected from substituent group A.

In the present specification, the term "cycloalkyl optionally having substituent(s)" means C_{3-6} cycloalkyl optionally having 1 to 3 substituents selected from

(1) C_{1-6} alkyl optionally having 1 to 3 halogen atoms, and

(2) substituent group A.

In the present specification, the term "cycloalkenyl optionally having substituent(s)" means C_{3-6} cycloalkenyl (e.g., cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl etc.) optionally having 1 to 3 substituents selected from

(1) C_{1-6} alkyl optionally having 1 to 3 halogen atoms, and

(2) substituent group A.

In the present specification, the term "aryl optionally having substituent(s)" means C_{6-10} aryl optionally having 1 to 3 substituents selected from

(1) C_{1-6} alkyl optionally having 1 to 3 halogen atoms, and

(2) substituent group A (excluding oxo).

In the present specification, the term "cycloalkyl-alkyl optionally having substituent(s)" means C_{3-6} cycloalkyl-C_{1-4} alkyl (e.g., cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclohexylethyl etc.) optionally having 1 to 3 substituents selected from

(1) C_{1-6} alkyl optionally having 1 to 3 halogen atoms, and

(2) substituent group A.

In the present specification, the term "cycloalkenyl-alkyl optionally having substituent(s)" means C_{3-6} cycloalkenyl-C_{1-4} alkyl (e.g., cyclopentenylmethyl, cyclohexenylmethyl, cyclohexenylethyl, cyclohexenylpropyl etc.) optionally having 1 to 3 substituents selected from

(1) C_{1-6} alkyl optionally having 1 to 3 halogen atoms, and

(2) substituent group A.

In the present specification, the term "aryl-alkyl optionally having substituent(s)" means C_{6-10} aryl-C_{1-4} alkyl (e.g., benzyl, phenylethyl etc.) optionally having 1 to 3 substituents selected from

(1) C_{1-6} alkyl optionally having 1 to 3 halogen atoms, and

(2) substituent group A (excluding oxo).

In the present specification, the term "cycloalkanedienyl optionally having substituent(s)" means C_{4-6} cycloalkanedienyl (e.g., 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl, 2,5-cyclohexadien-1-yl etc.) optionally having 1 to 3 substituents selected from

(1) C_{1-6} alkyl optionally having 1 to 3 halogen atoms, and

(2) substituent group A.

In the present specification, the term "heterocyclic group bonded via a carbon atom and optionally having substituent(s)" means

(A) a monocyclic aromatic heterocyclic group or fused aromatic heterocyclic group bonded via a carbon atom and optionally having 1 to 3 substituents selected from (1) C_{1-6} alkyl optionally having 1 to 3 halogen atoms, and

(2) substituent group A (excluding oxo), or

(B) a nonaromatic heterocyclic group bonded via a carbon atom and optionally having 1 to 3 substituents selected from (1) C_{1-6} alkyl optionally having 1 to 3 halogen atoms, and

(2) substituent group A.

The "bonded via a carbon atom monocyclic aromatic heterocyclic group" is, for example, a 5- to 7-membered (preferably, 5- or 6-membered) monocyclic aromatic heterocyclic group (having a bond at carbon atom) containing, as a ring constituting atom besides carbon atom, 1 to 4 hetero atoms selected from an oxygen atom, a sulfur atom (optionally oxidized) and a nitrogen atom, and the like. Examples thereof include furyl (e.g., 2-furyl, 3-furyl), thienyl (e.g., 2-thienyl, 3-thienyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-

pyridyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl), pyridazinyl (e.g., 3-pyridazinyl, 4-pyridazinyl), pyrazinyl (e.g., 2-pyrazinyl), pyrrolyl (e.g., 2-pyrrolyl, 3-pyrrolyl), imidazolyl (e.g., 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), pyrazolyl (e.g., 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), isothiazolyl (e.g., 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), isoxazolyl (e.g., 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), oxadiazolyl (e.g., 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl), thiadiazolyl (e.g., 1,3,4-thiadiazol-2-yl), triazolyl (e.g., 1,2,4-triazol-3-yl, 1,2,3-triazol-4-yl), tetrazolyl (e.g., tetrazol-5-yl), triazinyl (e.g., 1,3,5-triazin-2-yl) and the like.

The "fused aromatic heterocyclic group bonded via a carbon atom" is, for example, a 8- to 12-membered fused aromatic heterocyclic group (having a bond at carbon atom) wherein a 5- to 7-membered monocyclic aromatic heterocyclic group containing, as a ring constituting atom besides carbon atom, 1 to 4 hetero atoms selected from an oxygen atom, a sulfur atom (optionally oxidized) and a nitrogen atom, etc. and C_{6-10} aryl and the like are fused; a 8- to 12-membered fused aromatic heterocyclic group (having a bond at carbon atom) wherein 5- to 7-membered monocyclic aromatic heterocyclic groups are fused, and the like. Examples thereof include quinolyl (e.g., 2-quinolyl, 3-quinolyl, 4-quinolyl), isoquinolyl (e.g., 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl), quinazolyl (e.g., 2-quinazolyl, 4-quinazolyl), quinoxalyl (e.g., 2-quinoxalyl), benzofuryl (e.g., 2-benzofuryl, 3-benzofuryl), isobenzofuryl (e.g., 1-isobenzofuryl, 3-isobenzofuryl), benzothienyl (e.g., 2-benzothienyl, 3-benzothienyl), isobenzothienyl (e.g., 1-isobenzothienyl, 3-isobenzothienyl), benzoxazolyl (e.g., 2-benzoxazolyl), benzothiazolyl (e.g., 2-benzothiazolyl, 5-

benzothiazolyl, 6-benzothiazolyl), benzimidazolyl (e.g., benzimidazol-2-yl, benzimidazol-5-yl), indolyl (e.g., indol-2-yl, indol-3-yl, indol-4-yl, indol-5-yl, indol-6-yl), indazolyl (e.g., 1H-indazol-3-yl), pyrrolopyrazinyl (e.g., 1H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyrazin-6-yl), imidazopyridyl (e.g., 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl), imidazopyrazinyl (e.g., 1H-imidazo[4,5-b]pyrazin-2-yl), benzisoxazolyl (e.g., benzisoxazol-3-yl), benzotriazolyl (e.g., 1H-1,2,3-benzotriazol-5-yl), benzopyrazolyl (e.g., benzopyrazol-5-yl), pyrazolopyridyl (e.g., 1H-pyrazolo[4,3-c]pyridin-3-yl), pyrazolothienyl (e.g., 2H-pyrazolo[3,4-b]thiophen-2-yl), pyrazolotriazinyl (e.g., pyrazolo[5,1-c][1,2,4]triazin-3-yl) and the like.

Examples of the "nonaromatic heterocyclic group bonded via a carbon atom" include a 3- to 8-membered nonaromatic heterocyclic group (having a bond at carbon atom) containing, as a ring constituting atom besides carbon atom, 1 to 4 hetero atoms selected from an oxygen atom, a sulfur atom (optionally oxidized) and a nitrogen atom, and the like. Examples thereof include oxiranyl (e.g., 2-oxiranyl), azetidinyl (e.g., 2-azetidinyl, 3-azetidinyl), oxetanyl (e.g., 2-oxetanyl, 3-oxetanyl), thietanyl (e.g., 2-thietanyl, 3-thietanyl), pyrrolidinyl (e.g., 2-pyrrolidinyl, 3-pyrrolidinyl), tetrahydrofuryl (e.g., 2-tetrahydrofuryl, 3-tetrahydrofuryl), thioranyl (e.g., 2-thioranyl, 3-thioranyl), piperidinyl (e.g., 2-piperidinyl, 3-piperidinyl, 4-piperidinyl), tetrahydropyranyl (e.g., 2-tetrahydropyranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl), thianyl (e.g., 2-thianyl, 3-thianyl), morpholinyl (e.g., 2-morpholinyl, 3-morpholinyl), thiomorpholinyl (e.g., 2-thiomorpholinyl, 3-thiomorpholinyl), piperazinyl (e.g., 2-piperazinyl), azepanyl (e.g., 3-azepanyl), oxepanyl (e.g., 3-oxepanyl), thiepanyl (e.g., 3-thiepanyl), oxazepanyl (e.g., 1,4-oxazepane-5-yl),

thiazepanyl (e.g., 1,4-thiazepane-5-yl), azocanyl (e.g., 4-azocanyl), oxocanyl (e.g., 4-oxocanyl), thiocanyl (e.g., 4-thiocanyl), oxazocanyl (e.g., 1,4-oxazocan-5-yl), thioazocanyl (e.g., 1,4-thioazocan5-yl), dioxinyl (e.g., 1,4-dioxin-2-yl), dihydropyrazolyl (e.g., 2,3-dihydropyrazol-3-yl, 2,3-dihydropyrazol-4-yl, 2,3-dihydropyrazol-5-yl), hexahydropyrimidinyl (e.g., hexahydropyrimidin-2-yl, hexahydropyrimidin-4-yl, hexahydropyrimidin-5-yl), tetrahydropyrimidinyl (e.g., 1,2,3,4-tetrahydropyrimidin-2-yl, 1,2,5,6-tetrahydropyrimidin-2-yl), dihydropyrimidinyl (e.g., 1,2-dihydropyrimidin-2-yl), tetrahydropyridyl (e.g., 1,2,3,4-tetrahydropyridin-2-yl, 1,2,5,6-tetrahydropyridin-2-yl), dihydropyridyl (e.g., 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl), tetrahydroimidazolyl (e.g., tetrahydroimidazol-2-yl, tetrahydroimidazol-4-yl), dihydroimidazolyl (e.g., 4,5-dihydroimidazol-2-yl, 4,5-dihydroimidazol-4-yl, 4,5-dihydroimidazol-5-yl) and the like.

In the present specification, the term "a group bonded via a nitrogen atom" means, for example,

(1) nitro,

(2) amino optionally having substituent(s),

(3) a heterocyclic group bonded via a nitrogen atom and optionally having substituent(s),

and the like.

In the present specification, the substituent of amino of the term "amino optionally having substituent(s)" includes, for example, a group bonded via a carbon atom, and the formula $-SO_2R^a$ (R^a is a group bonded via a carbon atom) and the like, wherein the amino is optionally mono- or di-substituted. When it is di-substituted, the substituents may be the same or different.

The "heterocyclic group bonded via a nitrogen atom and optionally having substituent(s)" includes, for example,

(A) a monocyclic aromatic heterocyclic group or fused aromatic heterocyclic group, which is bonded via a nitrogen atom and optionally has 1 to 3 substituents selected from
(1) C_{1-6} alkyl optionally having 1 to 3 halogen atoms, and
(2) substituent group A (excluding oxo), or
(B) a nonaromatic heterocyclic group, which is bonded via a nitrogen atom and optionally has 1 to 3 substituents selected from
(1) C_{1-6} alkyl optionally having 1 to 3 halogen atoms, and
(2) substituent group A.

The "monocyclic aromatic heterocyclic group bonded via a nitrogen atom" includes, for example, a 5- to 7-membered (preferably, 5- or 6-membered) monocyclic aromatic heterocyclic group (having a bond at nitrogen atom) optionally containing, as ring constituting atom besides carbon atom and one nitrogen atom, 1 to 4 hetero atoms selected from an oxygen atom, a sulfur atom (optionally oxidized), and a nitrogen atom, and the like. Examples thereof include pyrrolyl (e.g., 1-pyrrolyl), imidazolyl (e.g., 1-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl), triazolyl (e.g., 1,2,4-triazol-1-yl), tetrazolyl (e.g., tetrazol-1-yl)) and the like.

The "fused aromatic heterocyclic group bonded via a nitrogen atom" is, for example, a 8- to 12-membered fused aromatic heterocyclic group (having a bond at nitrogen atom), wherein a 5- to 7-membered monocyclic aromatic heterocyclic group optionally containing, as ring constituting atom besides carbon atom and one nitrogen atom, 1 to 4 hetero atoms selected from an oxygen atom, a sulfur atom (optionally oxidized), and a nitrogen atom, etc. and C_{6-10} aryl and the like are fused; a 8- to 12-membered fused aromatic heterocyclic group (having a bond at nitrogen atom) wherein 5- to 7-membered monocyclic aromatic heterocyclic groups are fused, and the like. Examples thereof include benzimidazolyl (e.g., benzimidazol-1-yl), indolyl (e.g., indol-1-yl) and the

like.

Examples of the "nonaromatic heterocyclic group bonded via a nitrogen atom" include a 3- to 8-membered nonaromatic heterocyclic group (having a bond at nitrogen atom) optionally containing, as ring constituting atom besides carbon atom and one nitrogen atom, 1 to 4 hetero atoms selected from an oxygen atom, a sulfur atom (optionally oxidized), and a nitrogen atom, and the like. Examples thereof include azetidinyl (e.g., 1-azetidinyl), pyrrolidinyl (e.g., 1-pyrrolidinyl), piperidinyl (e.g., 1-piperidinyl), morpholinyl (e.g., 4-morpholinyl), thiomorpholinyl (e.g., 4-thiomorpholinyl), piperazinyl (e.g., 1-piperazinyl), azepanyl (e.g., 1-azepanyl), oxazepanyl (e.g., 1,4-oxazepan-4-yl), thiazepanyl (e.g., 1,4-thiazepane-4-yl), azocanyl (e.g., 1-azocanyl), dihydropyrazolyl (e.g., 2,3-dihydropyrazol-1-yl), hexahydropyrimidinyl (e.g., hexahydropyrimidin-1-yl), tetrahydropyrimidinyl (e.g., 1,2,3,4-tetrahydropyrimidin-1-yl), 1,2,5,6-tetrahydropyrimidin-1-yl), dihydropyrimidinyl (e.g., 1,2-dihydropyrimidin-1-yl), tetrahydropyridyl (e.g., 1,2,3,4-tetrahydropyridin-1-yl, 1,2,5,6-tetrahydropyridin-1-yl), dihydropyridyl (e.g., 1,2-dihydropyridin-1-yl), tetrahydroimidazolyl (e.g., tetrahydroimidazol-1-yl), dihydroimidazolyl (e.g., 4,5-dihydroimidazol-1-yl) and the like.

In the present specification, the "nitrogen-containing heterocyclic group" is a heterocyclic group containing one or more nitrogen atoms as ring constituting atom. Specific preferable examples include

(1) 5- to 7-membered (preferably, 5- or 6-membered) monocyclic nitrogen-containing aromatic heterocycle containing one or more nitrogen atoms as ring constituting atom, specifically, pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl), pyridazinyl (e.g., 3-pyridazinyl, 4-pyridazinyl), pyrazinyl

(e.g., 2-pyrazinyl), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), imidazolyl (e.g., 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl), triazolyl (e.g., 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-4-yl), tetrazolyl (e.g., tetrazol-1-yl, tetrazol-5-yl) and the like;
(2) a 3- to 8-membered nitrogen-containing nonaromatic heterocyclic group containing one or more nitrogen atoms as ring constituting atom, specifically, azetidinyl (e.g., 1-azetidinyl, 2-azetidinyl, 3-azetidinyl), pyrrolidinyl (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl), piperidinyl (e.g., 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl), morpholinyl (e.g., 2-morpholinyl, 3-morpholinyl, 4-morpholinyl), thiomorpholinyl (e.g., 2-thiomorpholinyl, 3-thiomorpholinyl, 4-thiomorpholinyl), piperazinyl (e.g., 1-piperazinyl, 2-piperazinyl), azepanyl (e.g., 1-azepanyl, 3-azepanyl), dihydropyrazolyl (e.g., 2,3-dihydropyrazol-1-yl, 2,3-dihydropyrazol-3-yl, 2,3-dihydropyrazol-4-yl, 2,3-dihydropyrazol-5-yl), hexahydropyrimidinyl (e.g., hexahydropyrimidin-1-yl, hexahydropyrimidin-2-yl, hexahydropyrimidin-4-yl, hexahydropyrimidin-5-yl), tetrahydropyrimidinyl (e.g., 1,2,3,4-tetrahydropyrimidin-1-yl, 1,2,3,4-tetrahydropyrimidin-2-yl, 1,2,5,6-tetrahydropyrimidin-1-yl, 1,2,5,6-tetrahydropyrimidin-2-yl), dihydropyrimidinyl (e.g., 1,2-dihydropyrimidin-1-yl, 1,2-dihydropyrimidin-2-yl), tetrahydropyridyl (e.g., 1,2,3,4-tetrahydropyridin-1-yl, 1,2,3,4-tetrahydropyridin-2-yl, 1,2,5,6-tetrahydropyridin-1-yl, 1,2,5,6-tetrahydropyridin-2-yl), dihydropyridyl (e.g., 1,2-dihydropyridin-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl), tetrahydroimidazolyl (e.g., tetrahydroimidazol-1-yl, tetrahydroimidazol-2-yl, tetrahydroimidazol-4-yl), dihydroimidazolyl (e.g., 4,5-dihydroimidazol-1-yl, 4,5-dihydroimidazol-2-yl, 4,5-dihydroimidazol-4-yl, 4,5-

dihydroimidazol-5-yl) and the like;
and the like.

In the present specification, "N-oxide of the nitrogen-containing heterocyclic group" is the above-mentioned nitrogen-containing heterocyclic group wherein an oxygen atom is bonded to the nitrogen atom of the ring and, for example, N-oxidepyridyl (e.g., N-oxidepyridin-2-yl, N-oxidepyridin-3-yl, N-oxidepyridin-4-yl), N-oxidepyrazinyl (e.g., N-oxidepyrazin-2-yl), N-oxidepyrimidinyl (e.g., N-oxidepyrimidin-2-yl, N-oxidepyrimidin-4-yl, N-oxidepyrimidin-5-yl), N-oxidepyridazinyl (e.g., N-oxidepyridazin-3-yl, N-oxidepyridazin-4-yl) and the like can be mentioned.

In the present specification, the term "a group bonded via an oxygen atom" means, for example, hydroxy optionally having substituent(s). The substituent of the "hydroxy optionally having substituent(s)" is a group bonded via a carbon atom and the like.

In the present specification, the term "a group bonded via a sulfur atom" means, for example, mercapto, a group represented by the formula $-S(O)_nR^b$ wherein n is an integer of 0 to 2 and R^b is a group bonded via a carbon atom or a group bonded via a nitrogen atom, and the like.

The compound (I) is explained in the following.

R^1 is

(1) a hydrogen atom,
(2) a halogen atom,
(3) a group bonded via a carbon atom,
(4) a group bonded via a nitrogen atom,
(5) a group bonded via an oxygen atom, or
(6) a group bonded via a sulfur atom.

R^1 is a hydrogen atom, a halogen atom (particularly, a fluorine atom), or a C_{1-6} alkyl group (particularly, methyl) is preferable, and a hydrogen atom is more preferable.

R^2 is

(1) a hydrogen atom,
(2) a halogen atom,
(3) a group bonded via a carbon atom,
(4) a group bonded via a nitrogen atom,
(5) a group bonded via an oxygen atom, or
(6) a group bonded via a sulfur atom.

R^2 is preferably a hydrogen atom.

W is O or S.

As W, O is preferable.

X is CR^3 (R^3 is a hydrogen atom, a halogen atom or C_{1-6} alkyl) or N.

X is preferably $CR^{3'}$ wherein $R^{3'}$ is a hydrogen atom, a halogen atom or methyl, or N. Particularly, CH, CF, CCl, $C(CH_3)$ or N is preferable, and CH, CF or N is more preferable.

Y is CR^4 (R^4 is a hydrogen atom, a halogen atom or C_{1-6} alkyl) or N.

Y is preferably $CR^{4'}$ wherein $R^{4'}$ is a hydrogen atom, a halogen atom or methyl, or N. Particularly, CH, CF, CCl, $C(CH_3)$ or N is preferable, and CH, CF or N is more preferable.

R^5 is

(1) C_{3-6} cycloalkyl optionally having one C_{6-10} aryl-aminocarbonyl optionally having 1 to 3 substituents selected from a halogen atom and C_{1-6} alkyl,
(2) C_{1-6} alkyl-carbonylamino optionally having one C_{6-10} aryl,
(3) C_{1-6} alkoxy optionally having one C_{6-10} aryl, or
(4) a nitrogen-containing heterocyclic group or an N-oxide thereof optionally having 1 to 4 substituents selected from

(a) C_{6-10} aryl optionally having 1 to 3 substituents selected from a halogen atom and C_{1-6} alkyl,
(b) C_{1-6} alkyl optionally having 1 to 3 halogen atoms, and
(c) oxo.

R^5 is preferably

(1) cyclopropyl optionally having one phenylaminocarbonyl

optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(2) acetylamino optionally having one phenyl,

(3) methoxy optionally having one phenyl,

(4) tert-butoxy, or,

(5) a nitrogen-containing heterocyclic group or an N-oxide thereof (particularly, pyrazolyl (e.g., 3-pyrazolyl, 5-pyrazolyl), dihydropyrazolyl (e.g., 2,3-dihydropyrazol-4-yl), dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl), N-oxidepyridyl (e.g., N-oxidepyridin-2-yl), hexahydropyrimidinyl (e.g., hexahydropyrimidin-1-yl), tetrahydroimidazolyl (e.g., tetrahydroimidazol-1-yl)) optionally having 1 to 4 substituents selected from

(a) phenyl optionally having 1 to 3 substituents selected from a fluorine atom, a chlorine atom, a bromine atom, methyl and isopropyl,

(b) methyl optionally having 1 to 3 fluorine atoms,

(c) ethyl optionally having 1 to 3 fluorine atoms,

(d) isopropyl, and

(e) oxo.

R^6 is a hydrogen atom.

R^7 is a hydrogen atom, a halogen atom or C_{1-6} alkyl.

R^7 is preferably a hydrogen atom.

R^8 is a hydrogen atom, a halogen atom or C_{1-6} alkyl.

R^8 is preferably a hydrogen atom.

As compound (I), the compounds described in Examples 1 - 38 are preferable, and the compounds described in Examples 1, 3 - 38 are more preferable.

As compound (I), the compounds described in Examples 39 - 85 are also preferable.

In compound (I), Z_1, Z_2, Z_3 and Z_4 are in the following combination.

$(Z_1, Z_2, Z_3, Z_4) = (CR^1, N, CR^2, C)$,

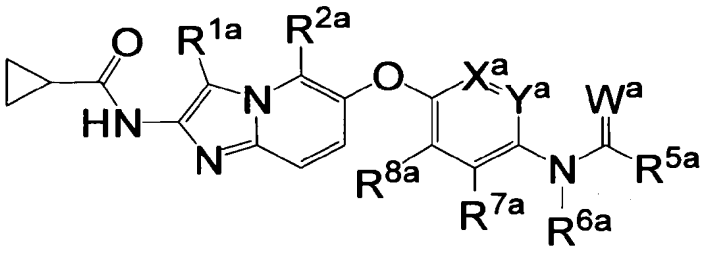
(N, N, CR^2, C),

(N,C,CR^2,N),

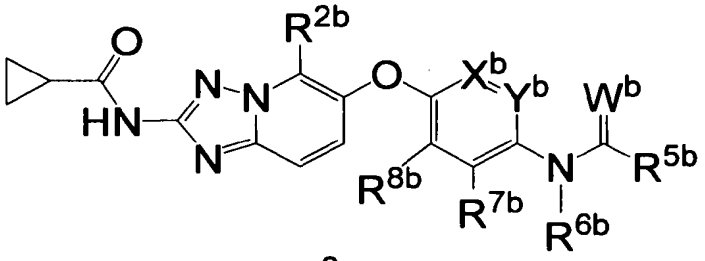
(S,C,CR^2,C) or

(S,C,N,C).

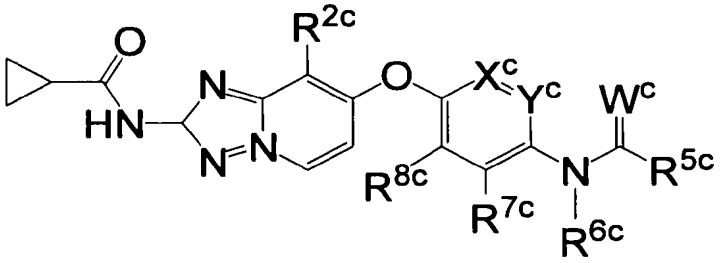
That is, compound (I) can be subdivided into the compounds represented by following formulas (Ia) - (Ie) (hereinafter sometimes to be abbreviated as compounds (Ia) - (Ie)).



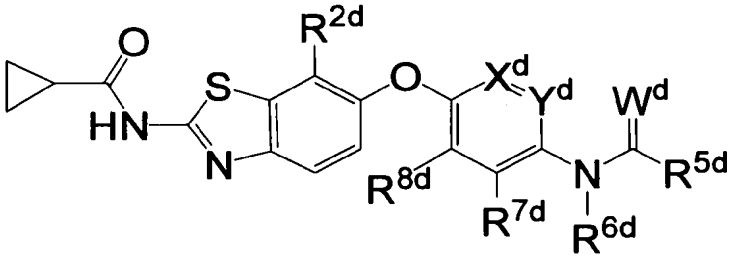
(Ia)



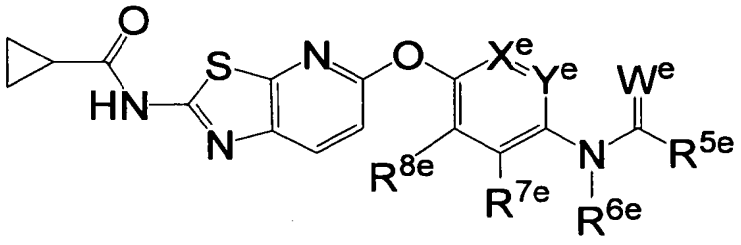
(Ib)



(Ic)



(Id)

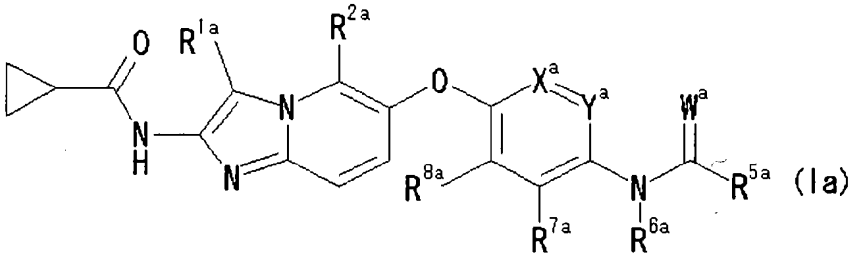


(Ie)

The compounds (Ia) - (Ie) are explained in the following.

[Compound (Ia)]

imidazo[1,2-a]pyridine derivative: a compound represented by the formula



(Ia)

wherein R^{1a} and R^{2a} are the same or different and each is

(1) a hydrogen atom,

(2) a halogen atom,

(3) a group bonded via a carbon atom,

(4) a group bonded via a nitrogen atom,

(5) a group bonded via an oxygen atom, or

(6) a group bonded via a sulfur atom;

W^a is O or S;

X^a is CR^{3a} (R^{3a} is a hydrogen atom, a halogen atom or C_{1-6} alkyl), or N;

Y^a is CR^{4a} (R^{4a} is a hydrogen atom, a halogen atom or C_{1-6} alkyl), or N;

R^{5a} is

(1) C_{3-6} cycloalkyl optionally having one C_{6-10} aryl-aminocarbonyl optionally having 1 to 3 substituents selected from a halogen atom and C_{1-6} alkyl,

(2) C_{1-6} alkyl-carbonylamino optionally having one C_{6-10} aryl,

(3) C_{1-6} alkoxy optionally having one C_{6-10} aryl, or

(4) a nitrogen-containing heterocyclic group or an N-oxide thereof optionally having 1 to 4 substituents selected from

(a) C_{6-10} aryl optionally having 1 to 3 substituents selected from a halogen atom and C_{1-6} alkyl,

(b) C_{1-6} alkyl optionally having 1 to 3 halogen atoms, and

(c) oxo;

R^{6a} is a hydrogen atom;

R^{7a} is a hydrogen atom, a halogen atom or C_{1-6} alkyl; and

R^{8a} is a hydrogen atom, a halogen atom or C_{1-6} alkyl,

or a salt thereof (compound (Ia)).

R^{1a} is preferably a hydrogen atom, a halogen atom (particularly, a fluorine atom), or a C_{1-6} alkyl group (particularly, methyl), and a hydrogen atom is more preferable.

R^{2a} is preferably a hydrogen atom.

W^a is preferably O.

X^a is preferably $CR^{3a'}$ wherein $R^{3a'}$ is a hydrogen atom, a halogen atom or methyl, or N. Particularly, CH, CF, CCl, $C(CH_3)$ or N is preferable, and CH, CF or N is more preferable.

Y^a is preferably $CR^{4a'}$ wherein $R^{4a'}$ is a hydrogen atom, a halogen atom or methyl, or N. Particularly, CH, CF, CCl, $C(CH_3)$ or N is preferable, and CH, CF or N is more preferable.

R^{5a} is preferably

(1) cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(2) acetylamino optionally having one phenyl,

(3) methoxy optionally having one phenyl,

(4) tert-butoxy, or

(5) a nitrogen-containing heterocyclic group or an N-oxide thereof (particularly, pyrazolyl (e.g., 3-pyrazolyl, 5-pyrazolyl), dihydropyrazolyl (e.g., 2,3-dihydropyrazol-4-yl), dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl), N-oxidepyridyl (e.g., N-oxidepyridin-2-yl), hexahydropyrimidinyl (e.g., hexahydropyrimidin-1-yl), tetrahydroimidazolyl (e.g., tetrahydroimidazol-1-yl)) optionally having 1 to 4 substituents selected from

(a) phenyl optionally having 1 to 3 substituents selected from a fluorine atom, a chlorine atom, a bromine atom, methyl and isopropyl,

(b) methyl optionally having 1 to 3 fluorine atoms,

(c) ethyl optionally having 1 to 3 fluorine atoms,

(d) isopropyl, and

(e) oxo.

R^{7a} is preferably a hydrogen atom.

R^{8a} is preferably a hydrogen atom.

Preferable specific examples of compound (Ia) include the following.

[Compound (Ia-A)]

In compound (Ia), a compound wherein

R^{1a} is a hydrogen atom;

R^{2a} is a hydrogen atom;

W^a is O or S;

X^a is $CR^{3a'}$ wherein $R^{3a'}$ is a hydrogen atom or a halogen atom;

Y^a is $CR^{4a'}$ wherein $R^{4a'}$ is a hydrogen atom or a halogen atom;

R^{5a} is

(1) cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(2) acetylamino optionally having one phenyl,

(3) methoxy optionally having one phenyl,

(4) tert-butoxy, or

(5) a nitrogen-containing heterocyclic group or an N-oxide thereof (pyrazolyl (e.g., 3-pyrazolyl, 5-pyrazolyl), dihydropyrazolyl (e.g., 2,3-dihydropyrazol-4-yl), dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl), N-oxidepyridyl (e.g., N-oxidepyridin-2-yl)) optionally having 1 to 4 substituents selected from

(a) phenyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(b) methyl optionally having 1 to 3 fluorine atoms,

(c) ethyl optionally having 1 to 3 fluorine atoms, and

(d) oxo;

R^{6a} is a hydrogen atom;

R^{7a} is a hydrogen atom; and

R^{8a} is a hydrogen atom is preferable.

[Compound (Ia-A1)]

In compound (Ia-A), a compound wherein

R^{1a} is a hydrogen atom;

R^{2a} is a hydrogen atom;

W^a is O;

X^a is CH or CF;

Y^a is CH or CF;

R^{5a} is

(1) cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(2) acetylamino optionally having one phenyl,

(3) methoxy optionally having one phenyl,

(4) tert-butoxy, or

(5) a nitrogen-containing heterocyclic group or an N-oxide thereof (particularly, pyrazolyl (e.g., 3-pyrazolyl, 5-pyrazolyl), dihydropyrazolyl (e.g., 2,3-dihydropyrazol-4-yl), dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl), N-oxidepyridyl (e.g., N-oxidepyridin-2-yl)) optionally having 1 to 4 substituents selected from

(a) phenyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(b) methyl optionally having 1 to 3 fluorine atoms,

(c) ethyl optionally having 1 to 3 fluorine atoms, and

(d) oxo;

R^{6a} is a hydrogen atom;

R^{7a} is a hydrogen atom; and

R^{8a} is a hydrogen atom is preferable.

[Compound (Ia-A2)]

The compounds of Examples 1 - 17, Examples 22 - 33 and Examples 35 - 38, particularly Examples 1, 3 - 17, Examples 22 - 33 and Examples 35 - 38.

[Compound (Ia-B)]

In compound (Ia), a compound wherein

R^{1a} is a hydrogen atom, a halogen atom (particularly, a fluorine atom), or a C_{1-6} alkyl group (particularly, methyl);

R^{2a} is a hydrogen atom;

W^a is O or S (particularly, O);

X^a is $CR^{3a'}$ wherein $R^{3a'}$ is a hydrogen atom, a halogen atom or methyl, or N;

Y^a is $CR^{4a'}$ wherein $R^{4a'}$ is a hydrogen atom, a halogen atom or methyl, or N;

R^{5a} is

(1) cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(2) acetylamino optionally having one phenyl,

(3) methoxy optionally having one phenyl,

(4) tert-butoxy, or

(5) a nitrogen-containing heterocyclic group or an N-oxide thereof (particularly, pyrazolyl (e.g., 3-pyrazolyl, 5-pyrazolyl), dihydropyrazolyl (e.g., 2,3-dihydropyrazol-4-yl), dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl), N-oxidepyridyl (e.g., N-oxidepyridin-2-yl), hexahydropyrimidinyl (e.g., hexahydropyrimidin-1-yl), tetrahydroimidazolyl (e.g., tetrahydroimidazol-1-yl)) optionally having 1 to 4 substituents selected from

(a) phenyl optionally having 1 to 3 substituents selected from a fluorine atom, a chlorine atom, a bromine atom, methyl and isopropyl,

(b) methyl optionally having 1 to 3 fluorine atoms,

(c) ethyl optionally having 1 to 3 fluorine atoms,

(d) isopropyl, and

(e) oxo;

R^{6a} is a hydrogen atom;

R^{7a} is a hydrogen atom; and

R^{8a} is a hydrogen atom is preferable.

[Compound (Ia-B1)]

In compound (Ia-B), a compound wherein

R^{1a} is a hydrogen atom, a fluorine atom or methyl;

R^{2a} is a hydrogen atom;

W^a is O;

X^a is CH, CF, CCl, $C(CH_3)$ or N;

Y^a is CH, CF, CCl, $C(CH_3)$ or N;

R^{5a} is

(1) cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(2) acetylamino optionally having one phenyl,

(3) methoxy optionally having one phenyl,

(4) tert-butoxy, or

(5) a nitrogen-containing heterocyclic group or an N-oxide thereof (particularly, pyrazolyl (e.g., 3-pyrazolyl, 5-pyrazolyl), dihydropyrazolyl (e.g., 2,3-dihydropyrazol-4-yl), dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl), N-oxidepyridyl (e.g., N-oxidepyridin-2-yl), hexahydropyrimidinyl (e.g., hexahydropyrimidin-1-yl), tetrahydroimidazolyl (e.g., tetrahydroimidazol-1-yl)) optionally having 1 to 4 substituents selected from

(a) phenyl optionally having 1 to 3 substituents selected from a fluorine atom, a chlorine atom, a bromine atom, methyl and isopropyl,

(b) methyl optionally having 1 to 3 fluorine atoms,

(c) ethyl optionally having 1 to 3 fluorine atoms,

(d) isopropyl, and

(e) oxo;

R^{6a} is a hydrogen atom;

R^{7a} is a hydrogen atom; and

R^{8a} is a hydrogen atom is preferable.

[Compound (Ia-B2)]

The compounds of Examples 1 - 17, Examples 22 - 33,

Examples 35 - 75 and Examples 77 - 85, particularly Examples 1, 3 - 17, Examples 22 - 33, Examples 35 - 75 and Examples 77 - 85.

[Compound (Ia-B3)]

The compounds of Examples 1 - 17, Examples 22 - 33, Examples 35 - 75 and Examples 77 - 94, particularly Examples 1, 3 - 17, Examples 22 - 33, Examples 35 - 75 and Examples 77 - 94.

[Compound (Ia-C)]

N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-N'-phenylcyclopropane-1,1-dicarboxamide or a salt thereof;

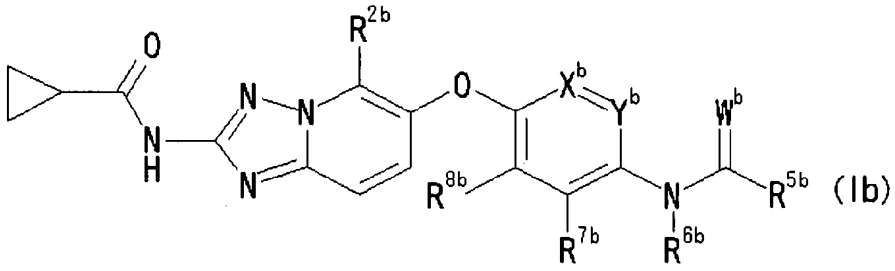
N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide or a salt thereof;

N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide or a salt thereof; or

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)pyridin-2-yl]-6-(4-fluorophenyl)-5-methylpyridine-2-carboxamide 1-oxide or a salt thereof.

[Compound (Ib)]

1,2,4-triazolo[1,5-a]pyridine derivative: a compound represented by the formula



(Ib)

wherein R^{2b} is

(1) a hydrogen atom,

(2) a halogen atom,

(3) a group bonded via a carbon atom,
(4) a group bonded via a nitrogen atom,
(5) a group bonded via an oxygen atom, or
(6) a group bonded via a sulfur atom;
W^b is O or S;
X^b is CR^{3b} (R^{3b} is a hydrogen atom, a halogen atom or C_{1-6} alkyl), or N;
Y^b is CR^{4b} (R^{4b} is a hydrogen atom, a halogen atom or C_{1-6} alkyl), or N;
R^{5b} is
(1) C_{3-6} cycloalkyl optionally having one C_{6-10} aryl-aminocarbonyl optionally having 1 to 3 substituents selected from a halogen atom and C_{1-6} alkyl,
(2) C_{1-6} alkyl-carbonylamino optionally having one C_{6-10} aryl,
(3) C_{1-6} alkoxy optionally having one C_{6-10} aryl, or
(4) a nitrogen-containing heterocyclic group or an N-oxide thereof optionally having 1 to 4 substituents selected from
(a) C_{6-10} aryl optionally having 1 to 3 substituents selected from a halogen atom and C_{1-6} alkyl,
(b) C_{1-6} alkyl optionally having 1 to 3 halogen atoms, and
(c) oxo;
R^{6b} is a hydrogen atom;
R^{7b} is a hydrogen atom, a halogen atom or C_{1-6} alkyl; and
R^{8b} is a hydrogen atom, a halogen atom or C_{1-6} alkyl,
or a salt thereof (compound (Ib)).

R^{2b} is preferably a hydrogen atom.

W^b is preferably O.

X^b is preferably $CR^{3b'}$ wherein $R^{3b'}$ is a hydrogen atom or a halogen atom, and particularly, CF is preferable.

Y^b is preferably $CR^{4b'}$ wherein $R^{4b'}$ is a hydrogen atom or a halogen atom, and particularly, CH is preferable.

R^{5b} is preferably
(1) cyclopropyl optionally having one phenylaminocarbonyl

optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(2) acetylamino optionally having one phenyl,

(3) methoxy optionally having one phenyl,

(4) tert-butoxy, or

(5) a nitrogen-containing heterocyclic group or an N-oxide thereof (particularly, pyrazolyl (e.g., 3-pyrazolyl, 5-pyrazolyl), dihydropyrazolyl (e.g., 2,3-dihydropyrazol-4-yl), dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl), N-oxidepyridyl (e.g., N-oxidepyridin-2-yl)) optionally having 1 to 4 substituents selected from

(a) phenyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(b) methyl optionally having 1 to 3 fluorine atoms,

(c) ethyl optionally having 1 to 3 fluorine atoms, and

(d) oxo,

more preferably,

cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl.

R^{7b} is preferably a hydrogen atom.

R^{8b} is preferably a hydrogen atom.

Preferable specific examples of compound (Ib) include the following.

[Compound (Ib-A)]

In compound (Ib), a compound wherein

R^{2b} is a hydrogen atom;

W^b is O;

X^b is $CR^{3b'}$ wherein $R^{3b'}$ is a hydrogen atom or a halogen atom;

Y^b is $CR^{4b'}$ wherein $R^{4b'}$ is a hydrogen atom or a halogen atom;

R^{5b} is

(1) cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(2) acetylamino optionally having one phenyl,

(3) methoxy optionally having one phenyl,

(4) tert-butoxy, or

(5) a nitrogen-containing heterocyclic group or an N-oxide thereof (pyrazolyl, dihydropyrazolyl, dihydropyridyl, N-oxidepyridyl) optionally having 1 to 4 substituents selected from

(a) phenyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(b) methyl optionally having 1 to 3 fluorine atoms,

(c) ethyl optionally having 1 to 3 fluorine atoms, and

(d) oxo;

R^{6b} is a hydrogen atom;

R^{7b} is a hydrogen atom; and

R^{8b} is a hydrogen atom is preferable.

Particularly, compound (Ib-A) wherein

R^{2b} is a hydrogen atom;

W^b is O;

X^b is CF;

Y^b is CH;

R^{5b} is a cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl;

R^{6b} is a hydrogen atom;

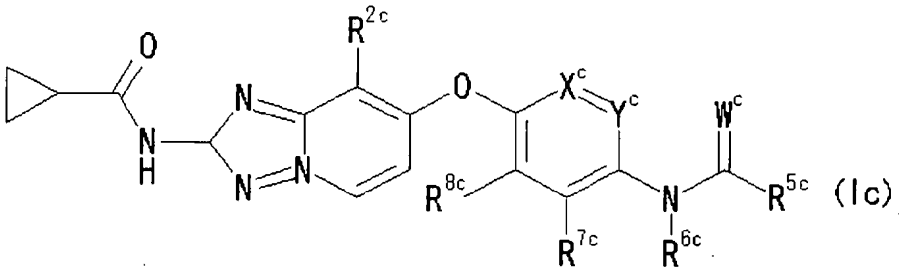
R^{7b} is a hydrogen atom; and

R^{8b} is a hydrogen atom is preferable.

Specifically, compound (Ib-A) is preferably the compound of Example 34.

[Compound (Ic)]

1,2,4-triazolo[1,5-a]pyridine derivative: a compound represented by the formula



(Ic)

wherein R^{2c} is

(1) a hydrogen atom,

(2) a halogen atom,

(3) a group bonded via a carbon atom,

(4) a group bonded via a nitrogen atom,

(5) a group bonded via an oxygen atom, or

(6) a group bonded via a sulfur atom;

W^c is O or S;

X^c is CR^{3c} (R^{3c} is a hydrogen atom, a halogen atom or C_{1-6} alkyl), or N;

Y^c is CR^{4c} (R^{4c} is a hydrogen atom, a halogen atom or C_{1-6} alkyl), or N;

R^{5c} is

(1) C_{3-6} cycloalkyl optionally having one C_{6-10} aryl-aminocarbonyl optionally having 1 to 3 substituents selected from a halogen atom and C_{1-6} alkyl,

(2) C_{1-6} alkyl-carbonylamino optionally having one C_{6-10} aryl,

(3) C_{1-6} alkoxy optionally having one C_{6-10} aryl, or

(4) a nitrogen-containing heterocyclic group or an N-oxide thereof optionally having 1 to 4 substituents selected from

(a) C_{6-10} aryl optionally having 1 to 3 substituents selected from a halogen atom and C_{1-6} alkyl,

(b) C_{1-6} alkyl optionally having 1 to 3 halogen atoms, and

(c) oxo;

R^{6c} is a hydrogen atom;

R^{7c} is a hydrogen atom, a halogen atom or C_{1-6} alkyl; and

R^{8c} is a hydrogen atom, a halogen atom or C_{1-6} alkyl,

or a salt thereof (compound (Ic)).

R^{2c} is preferably a hydrogen atom.

W^c is preferably O.

X^c is preferably $CR^{3c'}$ wherein $R^{3c'}$ is a hydrogen atom or a halogen atom, and particularly preferably CF.

Y^c is preferably $CR^{4c'}$ wherein $R^{4c'}$ is a hydrogen atom or a halogen atom is preferable, and particularly preferably CH.

R^{5c} is preferably

(1) cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(2) acetylamino optionally having one phenyl,

(3) methoxy optionally having one phenyl,

(4) tert-butoxy, or

(5) a nitrogen-containing heterocyclic group or an N-oxide thereof (particularly, pyrazolyl (e.g., 3-pyrazolyl, 5-pyrazolyl), dihydropyrazolyl (e.g., 2,3-dihydropyrazol-4-yl), dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl), N-oxidepyridyl (e.g., N-oxidepyridin-2-yl)) optionally having 1 to 4 substituents selected from

(a) phenyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(b) methyl optionally having 1 to 3 fluorine atoms,

(c) ethyl optionally having 1 to 3 fluorine atoms, and

(d) oxo,

and more preferably

a nitrogen-containing heterocyclic group (particularly, dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl)) optionally having 1 to 4 substituents selected from

(a) phenyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(b) methyl optionally having 1 to 3 fluorine atoms,

(c) ethyl optionally having 1 to 3 fluorine atoms, and

(d) oxo.

R^{7c} is preferably a hydrogen atom.

R^{8c} is preferably a hydrogen atom.

Preferable specific examples of compound (Ic) include the following.

[Compound (Ic-A)]

In compound (Ic), a compound wherein

R^{2c} is a hydrogen atom;

W^c is O;

X^c is $CR^{3c'}$ wherein $R^{3c'}$ is a hydrogen atom or a halogen atom;

Y^c is $CR^{4c'}$ wherein $R^{3c'}$ is a hydrogen atom or a halogen atom;

R^{5c} is

(1) cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(2) acetylamino optionally having one phenyl,

(3) methoxy optionally having one phenyl,

(4) tert-butoxy, or

(5) a nitrogen-containing heterocyclic group or an N-oxide thereof (particularly, pyrazolyl (e.g., 3-pyrazolyl, 5-pyrazolyl), dihydropyrazolyl (e.g., 2,3-dihydropyrazol-4-yl), dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl), N-oxidepyridyl (e.g., N-oxidepyridin-2-yl)) optionally having 1 to 4 substituents selected from

(a) phenyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(b) methyl optionally having 1 to 3 fluorine atoms,

(c) ethyl optionally having 1 to 3 fluorine atoms, and

(d) oxo;

R^{6c} is a hydrogen atom;

R^{7c} is a hydrogen atom; and

R^{8c} is a hydrogen atom, is preferable.

Particularly, compound (Ic-A) wherein

R^{2c} is a hydrogen atom;

W^c is O;

X^c is CF;

Y^c is CH;

R^{5c} is

a nitrogen-containing heterocyclic group (particularly, dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl)) optionally having 1 to 4 substituents selected from

(a) phenyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(b) methyl optionally having 1 to 3 fluorine atoms,

(c) ethyl optionally having 1 to 3 fluorine atoms, and

(d) oxo;

R^{6c} is a hydrogen atom;

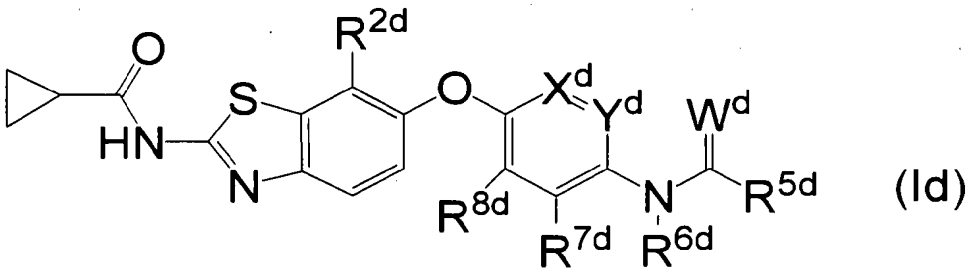
R^{7c} is a hydrogen atom; and

R^{8c} is a hydrogen atom is preferable.

Specifically, compound (Ic-A) is preferably the compound of Example 76.

[Compound (Id)]

1,3-benzothiazole derivative: a compound represented by the formula



(Id)

wherein R^{2d} is

(1) a hydrogen atom,

(2) a halogen atom,

(3) a group bonded via a carbon atom,

(4) a group bonded via a nitrogen atom,

(5) a group bonded via an oxygen atom, or

(6) a group bonded via a sulfur atom;

W^d is O or S;

X^d is CR^{3d} (R^{3d} is a hydrogen atom, a halogen atom or C_{1-6} alkyl),

or N;

Y^d is CR^{4d} (R^{4d} is a hydrogen atom, a halogen atom or C_{1-6} alkyl), or N;

R^{5d} is

(1) C_{3-6} cycloalkyl optionally having one C_{6-10} aryl-aminocarbonyl optionally having 1 to 3 substituents selected from a halogen atom and C_{1-6} alkyl,

(2) C_{1-6} alkyl-carbonylamino optionally having one C_{6-10} aryl,

(3) C_{1-6} alkoxy optionally having one C_{6-10} aryl, or

(4) a nitrogen-containing heterocyclic group or an N-oxide thereof optionally having 1 to 4 substituents selected from

(a) C_{6-10} aryl optionally having 1 to 3 substituents selected from a halogen atom and C_{1-6} alkyl,

(b) C_{1-6} alkyl optionally having 1 to 3 halogen atoms, and

(c) oxo;

R^{6d} is a hydrogen atom;

R^{7d} is a hydrogen atom, a halogen atom or C_{1-6} alkyl; and

R^{8d} is a hydrogen atom, a halogen atom or C_{1-6} alkyl,

or a salt thereof (compound (Id)).

R^{2d} is preferably a hydrogen atom.

W^d is preferably O.

X^d is preferably $CR^{3d'}$ wherein $R^{3d'}$ is a hydrogen atom or a halogen atom, and particularly preferably CF.

Y^d is preferably $CR^{4d'}$ wherein $R^{4d'}$ is a hydrogen atom or a halogen atom, and particularly preferably CH.

R^{5d} is preferably

(1) cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(2) acetylamino optionally having one phenyl,

(3) methoxy optionally having one phenyl,

(4) tert-butoxy, or

(5) a nitrogen-containing heterocyclic group or an N-oxide

thereof (particularly, pyrazolyl (e.g., 3-pyrazolyl, 5-pyrazolyl), dihydropyrazolyl (e.g., 2,3-dihydropyrazol-4-yl), dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl), N-oxidepyridyl (e.g., N-oxidepyridin-2-yl)) optionally having 1 to 4 substituents selected from

(a) phenyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(b) methyl optionally having 1 to 3 fluorine atoms,

(c) ethyl optionally having 1 to 3 fluorine atoms, and

(d) oxo,

and more preferably

cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl.

R^{7d} is preferably a hydrogen atom.

R^{8d} is preferably a hydrogen atom.

Preferable specific examples of compound (Id) include the following.

[Compound (Id-A)]

In compound (Id), a compound wherein

R^{2d} is a hydrogen atom;

W^d is O;

X^d is $CR^{3d'}$ wherein $R^{3d'}$ is a hydrogen atom or a halogen atom;

Y^d is $CR^{4d'}$ wherein $R^{4d'}$ is a hydrogen atom or a halogen atom;

R^{5d} is

(1) cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(2) acetylamino optionally having one phenyl,

(3) methoxy optionally having one phenyl,

(4) tert-butoxy, or

(5) a nitrogen-containing heterocyclic group or an N-oxide thereof (particularly, pyrazolyl (e.g., 3-pyrazolyl, 5-pyrazolyl), dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl), N-

oxidepyridyl (e.g., N-oxidepyridin-2-yl)) optionally having 1 to 4 substituents selected from

(a) phenyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(b) methyl optionally having 1 to 3 fluorine atoms,

(c) ethyl optionally having 1 to 3 fluorine atoms, and

(d) oxo;

R^{6d} is a hydrogen atom;

R^{7d} is a hydrogen atom; and

R^{8d} is a hydrogen atom is preferable.

Particularly, in compound (Id-A), a compound wherein

R^{2d} is a hydrogen atom;

W^d is O;

X^d is CF;

Y^d is CH;

R^{5d} is a cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl;

R^{6d} is a hydrogen atom;

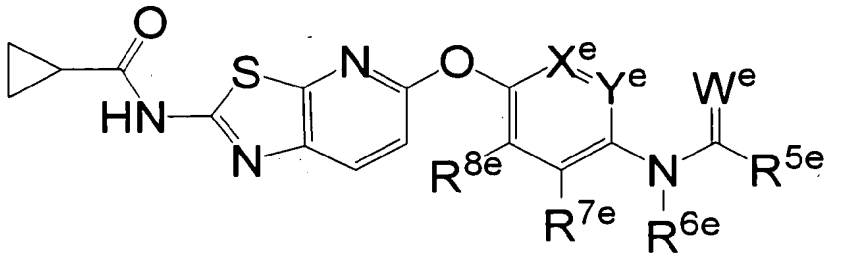
R^{7d} is a hydrogen atom; and

R^{8d} is a hydrogen atom is preferable.

Specifically, as compound (Id-A), the compound of Example 18 is preferable.

[Compound (Ie)]

1,3-thiazolo[5,4-b]pyridine derivative: a compound represented by the formula



(Ie)

wherein

W^e is O or S;

X^e is CR^{3e} (R^{3e} is a hydrogen atom, a halogen atom or C_{1-6} alkyl), or N;

Y^e is CR^{4e} (R^{4e} is a hydrogen atom, a halogen atom or C_{1-6} alkyl), or N;

R^{5e} is

(1) C_{3-6} cycloalkyl optionally having one C_{6-10} aryl-aminocarbonyl optionally having 1 to 3 substituents selected from a halogen atom and C_{1-6} alkyl,

(2) C_{1-6} alkyl-carbonylamino optionally having one C_{6-10} aryl,

(3) C_{1-6} alkoxy optionally having one C_{6-10} aryl, or

(4) a nitrogen-containing heterocyclic group or an N-oxide thereof optionally having 1 to 4 substituents selected from

(a) C_{6-10} aryl optionally having 1 to 3 substituents selected from a halogen atom and C_{1-6} alkyl,

(b) C_{1-6} alkyl optionally having 1 to 3 halogen atoms, and

(c) oxo;

R^{6e} is a hydrogen atom;

R^{7e} is a hydrogen atom, a halogen atom or C_{1-6} alkyl; and

R^{8e} is a hydrogen atom, a halogen atom or C_{1-6} alkyl,

or a salt thereof (compound (Ie)).

W^e is preferably O.

X^e is preferably $CR^{3e'}$ wherein $R^{3e'}$ is a hydrogen atom or a halogen atom, and particularly preferably CF.

Y^e is preferably $CR^{4e'}$ wherein $R^{4e'}$ is a hydrogen atom or a halogen atom, and particularly preferably CH.

R^{5e} is preferably

(1) cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 fluorine atoms,

(2) acetylamino optionally having one phenyl,

(3) methoxy or tert-butoxy optionally having one phenyl, or

(4) a nitrogen-containing heterocyclic group or an N-oxide thereof (particularly, pyrazolyl (e.g., 3-pyrazolyl, 5-pyrazolyl), dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl), N-

oxidepyridyl (e.g., N-oxidepyridin-2-yl)) optionally having 1 to 3 substituents selected from

(a) phenyl optionally having 1 to 3 fluorine atoms,

(b) methyl,

(c) ethyl, and

(d) oxo,

and more preferably, a nitrogen-containing heterocyclic group (particularly, dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl)) optionally having 1 to 3 substituents selected from

(a) phenyl optionally having 1 to 3 fluorine atoms,

(b) methyl,

(c) ethyl, and

(d) oxo.

R^{6e} is a hydrogen atom.

R^{7e} is preferably a hydrogen atom.

R^{8e} is preferably a hydrogen atom.

Preferable specific examples of compound (Ie) include the following.

[Compound (Ie-A)]

In compound (Ie), a compound wherein

W^e is O;

X^e is $CR^{3e'}$ wherein $R^{3e'}$ is a hydrogen atom or a halogen atom;

Y^e is $CR^{4e'}$ wherein $R^{4e'}$ is a hydrogen atom or a halogen atom;

R^{5e} is

(1) cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 fluorine atoms,

(2) acetylamino optionally having one phenyl,

(3) methoxy or tert-butoxy optionally having one phenyl, or

(4) a nitrogen-containing heterocyclic group or an N-oxide thereof (particularly, pyrazolyl (e.g., 3-pyrazolyl, 5-pyrazolyl), dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl), N-oxidepyridyl (e.g., N-oxidepyridin-2-yl)) optionally having 1 to 3 substituents selected from

(a) phenyl optionally having 1 to 3 fluorine atoms,

(b) methyl,

(c) ethyl, and

(d) oxo;

R^{6e} is a hydrogen atom;

R^{7e} is a hydrogen atom; and

R^{8e} is a hydrogen atom is preferable.

Particularly, compound (Ie-A) wherein

W^e is O;

X^e is CF;

Y^e is CH;

R^{5e} is

(1) cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 fluorine atoms,

(2) tert-butoxy optionally having one phenyl, or

(3) a nitrogen-containing heterocyclic group (particularly, dihydropyridyl (e.g., 1,2-dihydropyridin-3-yl)) optionally having 1 to 3 substituents selected from

(a) phenyl optionally having 1 to 3 fluorine atoms,

(b) methyl,

(c) ethyl, and

(d) oxo;

R^{6e} is a hydrogen atom;

R^{7e} is a hydrogen atom; and

R^{8e} is a hydrogen atom is preferable.

Specifically, as compound (Ie-A), compounds of Examples 19 - 21 are preferable.

When compound (I) is a salt, examples of the salt include a metal salt, an ammonium salt, a salt with organic base, a salt with inorganic acid, a salt with organic acid, a salt with basic or acidic amino acid and the like. Preferable examples of the metal salt include alkali metal salt such as sodium salt, potassium salt and the like; alkaline earth metal salt such as calcium salt, magnesium salt, barium salt and the like; aluminum salt and the like. Preferable examples of the salt with the

organic base include a salt with trimethylamine, triethylamine, pyridine, picoline, 2,6-lutidine, ethanolamine, diethanolamine, triethanolamine, cyclohexylamine, dicyclohexylamine, N,N'-dibenzylethylenediamine and the like. Preferable examples of the salt with the inorganic acid include a salt with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like. Preferable examples of the salt with the organic acid include a salt with formic acid, acetic acid, trifluoroacetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like. Preferable examples of the salt with the basic amino acid include a salt with arginine, lysine, ornithine and the like. Preferable examples of the salt with the acidic amino acid include a salt with aspartic acid, glutamic acid and the like.

Of these, pharmaceutically acceptable salt is preferable. For example, where the compound has an acidic functional group, inorganic salt such as alkali metal salt (e.g., sodium salt, potassium salt etc.), alkaline earth metal salt (e.g., calcium salt, magnesium salt etc.) and the like, ammonium salt and the like can be mentioned. Alternatively, where the compound has a basic functional group, for example, a salt with inorganic acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like, or a salt with organic acid such as acetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like can be mentioned.

Hereinafter, the production methods of compound (I) of the present invention are explained.

The compound (I) of the present invention can be obtained, for example, according to the methods shown in the following Schemes or a method analogous thereto and the like.

Each compound in the following Schemes includes salts, and as such salts, for example, those similar to the salts of the compound (I) and the like can be used.

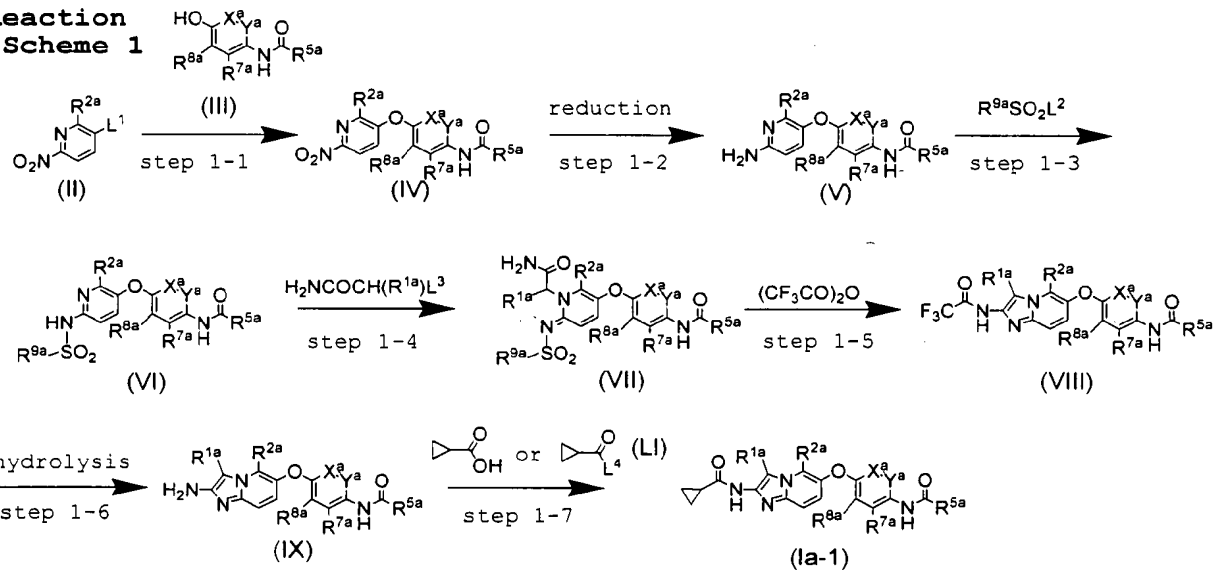
The compound obtained in each step can be used in the form of a reaction mixture or a crude product for the next reaction. In addition, the compound can be isolated from a reaction mixture according to a conventional method, and can be easily purified by a separation means such as recrystallization, distillation, chromatography and the like.

Schematic reaction formulas are shown in the following, wherein each symbol in the compounds is as defined above.

[Production method 1]

In compound (Ia), compound (Ia-1) wherein W^a is an oxygen atom can be produced, for example, by a method shown in Reaction scheme 1. The compound (Ia-1) is encompassed in compound (Ia).

Reaction Scheme 1



wherein L^1 - L^4 are each a leaving group; R^{9a} is (1) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having 1 to 3 substituents selected from (a) a halogen atom and (b) nitro, or (2) C_{6-10} aryl (e.g., phenyl) optionally having 1 to 3 substituents selected from (a) a halogen atom, (b) nitro, and (c) C_{1-6} alkyl

(e.g., methyl, ethyl) optionally having 1 to 3 halogen atoms; and other symbols are as defined above.

Examples of the leaving group for L^1 include (1) a halogen atom, (2) C_{1-6} alkylsulfonyloxy (e.g., methylsulfonyloxy, ethylsulfonyloxy) optionally having 1 to 3 substituents selected from (a) a halogen atom, (b) nitro, and (c) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having 1 to 3 halogen atoms, (3) C_{6-10} arylsulfonyloxy (e.g., phenylsulfonyloxy) optionally having 1 to 3 substituents selected from (a) a halogen atom, (b) nitro, and (c) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having 1 to 3 halogen atoms, and the like.

Examples of the leaving group for L^2 include a halogen atom and the like.

Examples of the leaving group for L^3 include those similar to the leaving group for L^1.

Examples of the leaving group for L^4 include a halogen atom and the like.

(step 1-1):

Compound (IV) can be produced by reacting compound (II) with compound (III).

Compound (III) is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (II).

In this reaction, a base may be added as necessary. As the base, an inorganic base, an organic base and the like are used. Specific examples include sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogen carbonate, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-(dimethylamino)pyridine, N,N-dimethylaniline, sodium methoxide, sodium ethoxide, potassium tert-butoxide, sodium hydride, sodium amide, lithiumdiisopropylamide and the like. The base

is used in a proportion of about 1 mol to about 30 mol, preferably about 1 mol to about 10 mol, per 1 mol of compound (II).

This reaction is advantageously carried out using a solvent inert to the reaction. While the solvent is not particularly limited as long as the reaction proceeds, for example, alcohols such as methanol, ethanol, 2-propanol, 2-methyl-2-propanol and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene, cyclohexane, hexane and the like; esters such as ethyl acetate and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, chlorobenzene, trifluoromethylbenzene and the like; nitriles such as acetonitrile and the like; sulfoxides such as dimethyl sulfoxide and the like; pyridine; acetic acid; water; and the like can be used alone or in a mixture.

While the reaction time varies depending on the kind of reagent and solvent to be used, it is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

This reaction may be performed in a microwave reactor.

(step 1-2):

Compound (V) can be produced by reducing nitro of compound (IV). Nitro can be reduced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock), the fourth series of experimental chemistry, vol. 20, 279-280 and the like, or a method analogous thereto.

(step 1-3):

Compound (VI) can be produced by reacting compound (V)

with a compound represented by the formula $R^{9a}SO_2L^2$ in the presence of a base.

$R^{9a}SO_2L^2$ is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (V).

As the base, those similar to the bases of step 1-1 are used. The base is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (V).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 1-1 are used. Alternatively, an excess amount of a base may be used as a solvent.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

$R^{9a}SO_2L^2$ may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like, or a method analogous thereto.

(step 1-4):

Compound (VII) can be produced by reacting compound (VI) with a compound represented by the formula $H_2NCOCH(R^{1a})L^3$ in the presence of a base.

$H_2NCOCH(R^{1a})L^3$ is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (VI).

As the base, those similar to the bases of step 1-1 are used. The base is used in a proportion of about 0.1 mol to 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (VI).

This reaction is advantageously carried out using a

solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 1-1 are used. Alternatively, an excess amount of a base may be used as a solvent.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

$H_2NCOCH(R^{1a})L^3$ may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like, or a method analogous thereto.

(step 1-5):

Compound (VIII) can be produced by reacting compound (VII) with trifluoroacetic acid anhydride.

Trifluoroacetic acid anhydride is used in a solvent amount for compound (VII).

This reaction is advantageously performed using an additional solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 1-1 are used.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

(step 1-6):

Compound (IX) can be produced by alkalihydrolysis of compound (VIII). This reaction is performed in a water-containing solvent in the presence of a base.

Examples of the base include sodium hydroxide, potassium hydroxide, lithium hydroxide, barium hydroxide, calcium hydroxide, potassium carbonate, sodium carbonate, cesium carbonate, sodium methoxide and the like. The base is used in a proportion of about 1 mol to about 50 mol, preferably about

1 mol to about 10 mol, per 1 mol of compound (VIII).

Examples of the water-containing solvent include mixed solvent of one or more kinds of solvents selected from methanol, ethanol, tetrahydrofuran, 1,4-dioxane and the like and water, and the like.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 100°C.

(step 1-7):

Compound (Ia-1) can be produced by reacting compound (IX) with cyclopropanecarboxylic acid in the presence of a condensation agent, or compound (IX) with compound (LI).

When compound (IX) is reacted with cyclopropanecarboxylic acid in the presence of a condensation agent, cyclopropanecarboxylic acid is used in a proportion of about 1 mol to about 10 mol, preferably about 1 mol to about 3 mol, per 1 mol of compound (IX).

Examples of the condensation agent include 1-ethyl-1-(3-dimethylaminopropyl)carbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide, diethyl cyanophosphate, diphenylphosphoryl azide, 1,1'-carbonyldiimidazole, benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and the like. The condensation agent is used in a proportion of about 1 mol to about 10 mol, preferably about 1 mol to about 5 mol, per 1 mol of compound (IX).

Where necessary, a suitable condensation promoter (e.g., 1-hydroxybenzotriazole, N-hydroxysuccinimide and the like) can be used in this reaction.

Such condensation promoter is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (IX).

This reaction may proceed more smoothly by addition of a base (e.g., triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, 4-(dimethylamino)pyridine and the like). The base is used in a proportion of about 0.01 mol to about 10 mol, preferably about 0.03 mol to about 5 mol, per 1 mol of compound (IX).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 1-1 are used.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

When compound (IX) is reacted with compound (LI), compound (LI) is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (IX).

Generally, this reaction is preferably performed in the presence of a base. However, the presence of a base is not always essential. Examples of the base to be used include sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogen carbonate, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-(dimethylamino)pyridine, N,N-dimethylaniline and the like. The base is used in a proportion of about 0.01 mol to about 10 mol, preferably about 0.03 mol to about 5 mol, per 1 mol of compound (IX).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 1-1 are used.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

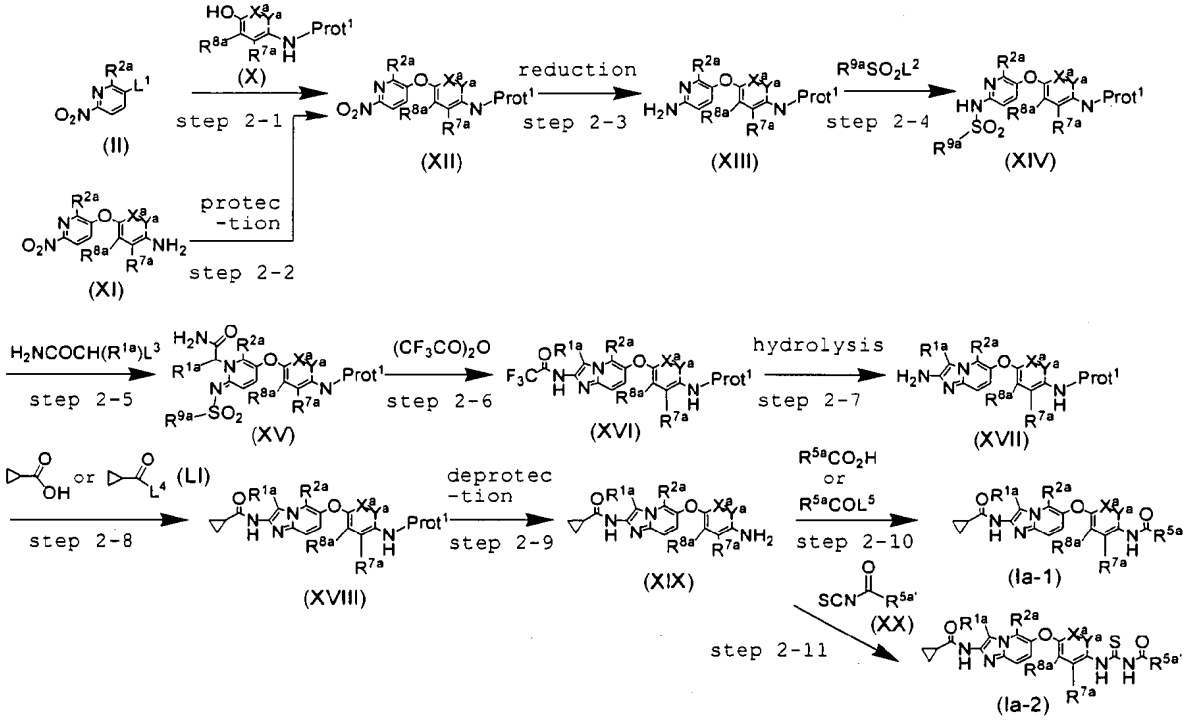
The reaction temperature is generally about -78°C to

about 200°C, preferably about -20°C to about 150°C.

[Production method 2]

In compound (Ia), compound (Ia-2) wherein W^a is a sulfur atom and R^{5a} is C_{1-6} alkyl-carbonylamino optionally having one C_{6-10} aryl can be produced, for example, by a method shown in Reaction scheme 2. The compound (Ia-2) is encompassed in compound (Ia). In addition, compound (Ia-1) can also be produced by a method shown in Reaction scheme 2.

Reaction Scheme 2



wherein $Prot^1$ is an amino-protecting group; L^5 is a leaving group; $R^{5a'}$ is C_{1-6} alkyl optionally having one C_{6-10} aryl; and other symbols are as defined above.

Examples of the amino-protecting group for $Prot^1$ include benzyloxycarbonyl, tert-butoxycarbonyl and the like.

Examples of the leaving group for L^5 include a halogen atom and the like.

The "C_{1-6} alkyl optionally having one C_{6-10} aryl" for $R^{5a'}$ means a group bonded to carbonylamino to form "C_{1-6} alkyl-

carbonylamino optionally having one C_{6-10} aryl" for the above-mentioned R^5.

(step 2-1):

Compound (XII) can be produced by reacting compound (II) with compound (X) in the presence of a base.

Compound (X) is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (II).

As the base, those similar to the bases of step 1-1 are used. The base is used in a proportion of about 1 mol to about 30 mol, preferably about 1 mol to about 10 mol, per 1 mol of compound (II).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 1-1 are used.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

(step 2-2):

Compound (XII) can also be produced by protecting amino of compound (XI). Amino can be protected according to a method known *per se*, for example, the methods described in "Protective Groups in Organic Synthesis, 3rd Ed." (Theodora W. Greene) and the like, or a method analogous thereto.

(steps 2-3 - 2-8):

Compound (XIII), compound (XIV), compound (XV), compound (XVI), compound (XVII) and compound (XVIII) can be synthesized from compound (XII) in the same manner as in steps 1-2 to 1-7, respectively.

(step 2-9):

Compound (XIX) can be produced by removing the amino-protecting group of compound (XVIII). The amino-protecting group can be removed according to a method known *per se*, for

example, the methods described in "Protective Groups in Organic Synthesis, 3rd Ed." (Theodora W. Greene) and the like, or a method analogous thereto.

(step 2-10):

Compound (Ia-1) can be produced by reacting compound (XIX) with carboxylic acid ($R^{5a}CO_2H$) in the presence of a condensation agent.

Carboxylic acid ($R^{5a}CO_2H$) is used in a proportion of about 1 mol to about 10 mol, preferably about 1 mol to about 3 mol, per 1 mol of compound (XIX).

Examples of the condensation agent include 1-ethyl-1-(3-dimethylaminopropyl)carbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide, diethyl cyanophosphate, diphenylphosphoryl azide, 1,1'-carbonyldiimidazole, benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, O-(7-azabenzotriazol-1-yl)-N,N,N,N-tetramethyluronium hexafluorophosphate and the like. The condensation agent is used in a proportion of about 1 mol to about 10 mol, preferably about 1 mol to about 5 mol, per 1 mol of compound (XIX).

Where necessary, a suitable condensation promoter (e.g., 1-hydroxybenzotriazole, N-hydroxysuccinimide etc.) can be used in this reaction. Such condensation promoter is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (XIX).

This reaction may proceed more smoothly by addition of a base. As the base, those similar to the bases of step 1-1 are used. The base is used in a proportion of about 0.01 mol to about 10 mol, preferably about 0.03 mol to about 5 mol, per 1 mol of compound (XIX).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 1-1 are used.

The reaction time is generally about 1 min to about 200 hr, preferably about 10 min to about 100 hr.

The reaction temperature is generally about -100°C to about 250°C, preferably about -78°C to about 200°C.

$R^{5a}CO_2H$ may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like, or a method analogous thereto.

Compound (Ia-1) can also be produced by reacting compound (XIX) with a reactive derivative ($R^{5a}COL^5$) of carboxylic acid in the presence of a base.

The reactive derivative ($R^{5a}COL^5$) of carboxylic acid is used in a proportion of about 1 mol to about 10 mol, preferably about 1 mol to about 3 mol, per 1 mol of compound (XIX).

The base may be used in a proportion of about 0.01 mol to about 10 mol, preferably about 0.03 mol to about 5 mol, per 1 mol of compound (XIX). As the base, those similar to the bases of step 1-1 are used.

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 1-1 are used.

The reaction time is generally about 1 min to about 200 hr, preferably about 10 min to about 100 hr.

The reaction temperature is generally about -100°C to about 250°C, preferably about -78°C to about 200°C.

$R^{5a}COL^5$ may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like, or a method analogous thereto.

(step 2-11):

Compound (Ia-2) can be produced by reacting compound (XIX) with acylthiocyanate derivative (XX).

The acylthiocyanate derivative (XX) is used in a proportion of about 0.1 mol to 10 mol, preferably about 0.5 mol to about 5 mol, per 1 mol of compound (XIX).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 1-1 are used.

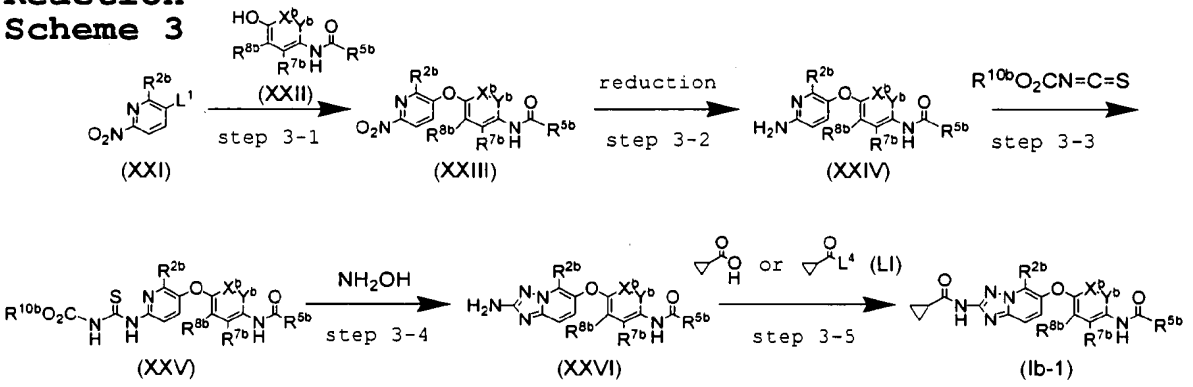
The reaction time is generally about 1 min to about 200 hr, preferably about 10 min to about 100 hr.

The reaction temperature is generally about -100°C to about 250°C, preferably about -78°C to about 200°C.

[Production method 3]

In compound (Ib), compound (Ib-1) wherein W^b is an oxygen atom can be produced, for example, by the method shown in Reaction scheme 3. The compound (Ib-1) is encompassed in compound (Ib).

Reaction Scheme 3



wherein R^{10b} is C_{1-6} alkyl optionally having 1 to 3 substituents selected from (a) a halogen atom and (b) nitro; and other symbols are as defined above.

(step 3-1):

Compound (XXIII) can be produced by reacting compound (XXI) with compound (XXII).

Compound (XXII) is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (XXI).

In this reaction, a base may be added as necessary. As the base, an inorganic base, an organic base and the like are used. Specific examples include sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogen carbonate, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-(dimethylamino)pyridine, N,N-dimethylaniline, sodium methoxide, sodium ethoxide, potassium tert-butoxide, sodium hydride, sodium amide, lithiumdiisopropylamide and the like. The base is used in a proportion of about 1 mol to about 30 mol, preferably about 1 mol to about 10 mol, per 1 mol of compound (XXI).

This reaction is advantageously carried out using a solvent inert to the reaction. The solvent is not particularly limited as long as the reaction proceeds and, for example, alcohols such as methanol, ethanol, 2-propanol, 2-methyl-2-propanol and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene, cyclohexane, hexane and the like; esters such as ethyl acetate and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; nitriles such as acetonitrile and the like; sulfoxides such as dimethyl sulfoxide and the like; pyridine; acetic acid; water; and the like can be used alone or in a mixture.

While the reaction time varies depending on the kind of reagent and solvent to be used, it is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

This reaction may be performed in a microwave reactor.

(step 3-2):

Compound (XXIV) can be produced by reducing nitro of compound (XXIII).

Nitro can be reduced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock), the fourth series of experimental chemistry, vol. 20, 279-280 and the like, or a method analogous thereto.

(step 3-3):

Compound (XXV) can be produced by reacting compound (XXIV) with a compound represented by the formula $R^{10b}O_2C-N=C=S$.

$R^{10b}O_2C-N=C=S$ is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (XXIV).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 3-1 are used.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

$R^{10b}O_2C-N=C=S$ may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like, or a method analogous thereto.

(step 3-4):

Compound (XXVI) can be produced by reacting compound (XXV) with hydroxylamine in the presence of a base.

Hydroxylamine is used in a proportion of about 0.1 mol to about 100 mol, preferably about 0.3 mol to about 30 mol, per 1 mol of compound (XXV).

As the base, those similar to the bases exemplified in step 3-1 are used. The base is used in a proportion of about 0.1 mol to about 100 mol, preferably about 0.3 mol to about 30 mol, per 1 mol of compound (XXV).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 3-1 are used.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

(step 3-5):

Compound (Ib-1) can be produced by reacting compound (XXVI) with cyclopropanecarboxylic acid in the presence of a condensation agent or compound (XXVI) with compound (LI).

When compound (XXVI) is reacted with cyclopropanecarboxylic acid in the presence of a condensation agent, cyclopropanecarboxylic acid is used in a proportion of about 1 mol to about 10 mol, preferably about 1 mol to about 3 mol, per 1 mol of compound (XXVI).

Examples of the condensation agent include 1-ethyl-1-(3-dimethylaminopropyl)carbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide, diethyl cyanophosphate, diphenylphosphoryl azide, 1,1'-carbonyldiimidazole, benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and the like. The condensation agent is used in a proportion of about 1 mol to about 10 mol, preferably about 1 mol to about 5 mol, per 1 mol of compound (XXVI).

Where necessary, a suitable condensation promoter (e.g.,

1-hydroxybenzotriazole, N-hydroxysuccinimide and the like) can be used in this reaction. Such condensation promoter is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (XXVI).

This reaction may proceed more smoothly by addition of a base (e.g., triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene and the like). The base is used in a proportion of about 0.01 mol to about 10 mol, preferably about 0.03 mol to about 5 mol, per 1 mol of compound (XXVI).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 3-1 are used.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

When compound (XXVI) is reacted with compound (LI), compound (LI) is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (XXVI).

Generally, this reaction is preferably performed in the presence of a base. However, the presence of a base is not always essential. Examples of the base include sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogen carbonate, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-(dimethylamino)pyridine, N,N-dimethylaniline and the like. The base is used in a proportion of about 0.01 mol to about 10 mol, preferably about 0.03 mol to about 5 mol, per 1 mol of compound (XXVI).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to

the solvents exemplified in step 3-1 are used.

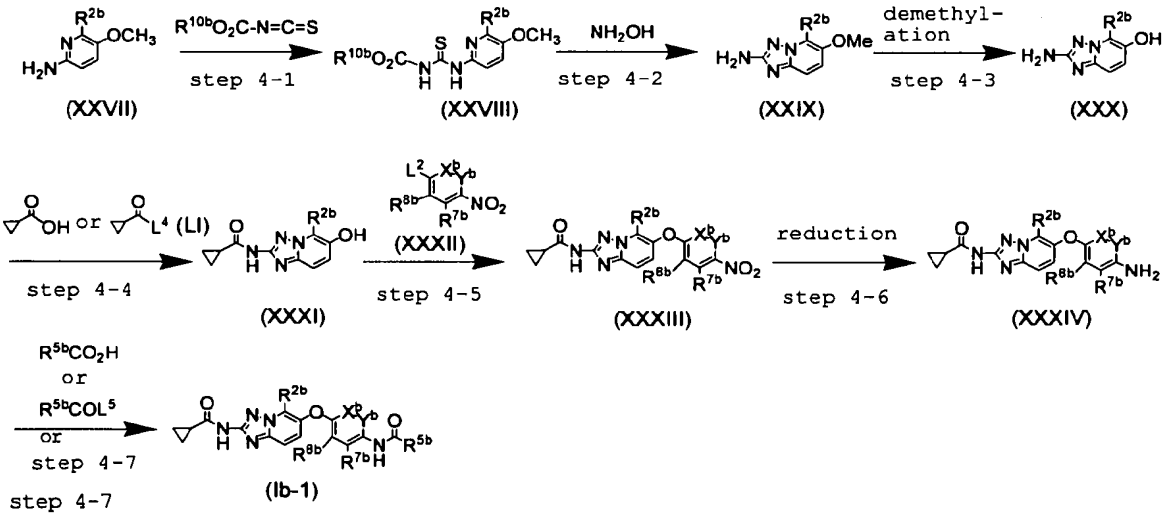
The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

[Production method 4]

Compound (Ib-1) can also be produced, for example, by a method shown in Reaction scheme 4.

Reaction Scheme 4



wherein the symbols are as defined above.

(steps 4-1 and 4-2):

Compound (XXVIII) and compound (XXIX) can be synthesized from compound (XXVII) in the same manner as in steps 3-3 and 3-4, respectively.

(step 4-3):

Compound (XXX) can be produced by demethylation of compound (XXIX).

Demethylation can be performed according to a method known *per se*, for example, the method described in "Protective Groups in Organic Synthesis, 3rd Ed." (Theodora W. Greene) and the like, or a method analogous thereto.

(step 4-4):

Compound (XXXI) can be produced by reacting compound (XXX) with cyclopropanecarboxylic acid in the presence of a condensation agent, or by reacting compound (XXX) with compound (LI) in the same manner as in step 3-5.

(step 4-5):

Compound (XXXIII) can be produced by reacting compound (XXXI) with compound (XXXII) in the presence of a base.

Compound (XXXII) is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (XXXI).

As the base, those similar to the bases exemplified in step 3-1 are used. The base is used in a proportion of about 1 mol to about 30 mol, preferably about 1 mol to about 10 mol, per 1 mol of compound (XXXI).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 3-1 are used.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

(step 4-6):

Compound (XXXIV) can be produced by reducing nitro of compound (XXXIII) in the same manner as in step 3-2.

(step 4-7):

Compound (Ib-1) can be produced by reacting compound (XXXIV) with carboxylic acid ($R^{5b}CO_2H$) in the presence of a condensation agent.

Carboxylic acid ($R^{5b}CO_2H$) is used in a proportion of about 1 mol to about 10 mol, preferably about 1 mol to about 3 mol, per 1 mol of compound (XXXIV).

Examples of the condensation agent include 1-ethyl-1-(3-dimethylaminopropyl)carbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide, diethyl cyanophosphate,

diphenylphosphoryl azide, 1,1'-carbonyldiimidazole, benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, O-(7-azabenzotriazol-1-yl)-N,N,N,N-tetramethyluronium hexafluorophosphate and the like. The condensation agent is used in a proportion of about 1 mol to about 10 mol, preferably about 1 mol to about 5 mol, per 1 mol of compound (XXXIV).

Where necessary, a suitable condensation promoter (e.g., 1-hydroxybenzotriazole, N-hydroxysuccinimide etc.) can be used in this reaction. Such condensation promoter is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (XXXIV).

This reaction may proceed more smoothly by the addition of a base. As the base, those similar to the bases exemplified in step 3-1 are used. The base is used in a proportion of about 0.01 mol to about 10 mol, preferably about 0.03 mol to about 5 mol, per 1 mol of compound (XXXIV).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 3-1 are used.

The reaction time is generally about 1 min to about 200 hr, preferably about 10 min to about 100 hr.

The reaction temperature is generally about -100°C to about 250°C, preferably about -78°C to about 200°C.

$R^{5b}CO_2H$ may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like, or a method analogous thereto.

Compound (Ib-1) can also be produced by reacting compound (XXXIV) with a reactive derivative ($R^{5b}COL^5$) of carboxylic acid.

The reactive derivative ($R^{5b}COL^5$) of carboxylic acid is used in a proportion of about 1 mol to about 10 mol, preferably about 1 mol to about 3 mol, per 1 mol of compound (XXXIV).

This reaction may be performed in the presence of a base. As the base, those similar to the bases exemplified in step 3-1 are used. The base is used in a proportion of about 0.01 mol to about 10 mol, preferably about 0.03 mol to about 5 mol, per 1 mol of compound (XXXIV).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 3-1 are used.

The reaction time is generally about 1 min to about 200 hr, preferably about 10 min to about 100 hr.

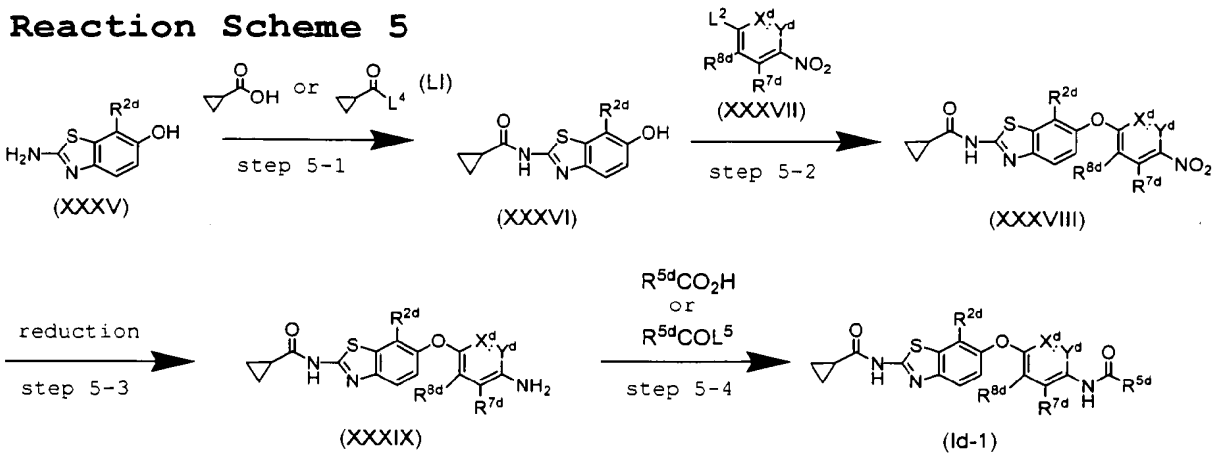
The reaction temperature is generally about -100°C to about 250°C, preferably about -78°C to about 200°C.

$R^{5b}COL^5$ may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like, or a method analogous thereto.

[Production method 5]

In compound (Id), compound (Id-1) wherein W^d is an oxygen atom can also be produced, for example, by a method shown in Reaction scheme 5. The compound (Id-1) is encompassed in compound (Id).

Reaction Scheme 5



wherein the symbols are as defined above.

(step 5-1):

Compound (XXXVI) can be produced by reacting compound (XXXV) with cyclopropanecarboxylic acid in the presence of a condensation agent, or by reacting compound (XXXV) with compound (LI).

When compound (XXXV) is reacted with cyclopropanecarboxylic acid in the presence of a condensation agent, cyclopropanecarboxylic acid is used in a proportion of about 1 mol to about 10 mol, preferably about 1 mol to about 3 mol, per 1 mol of compound (XXXV).

Examples of the condensation agent include 1-ethyl-1-(3-dimethylaminopropyl)carbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide, diethyl cyanophosphate, diphenylphosphoryl azide, 1,1'-carbonyldiimidazole, benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and the like. The condensation agent is used in a proportion of about 1 mol to about 10 mol, preferably about 1 mol to about 5 mol, per 1 mol of compound (XXXV).

Where necessary, a suitable condensation promoter (e.g., 1-hydroxybenzotriazole, N-hydroxysuccinimide and the like) can be used in this reaction. Such condensation promoter is used

in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (XXXV).

This reaction may proceed more smoothly by the addition of a base (e.g., triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene and the like). The base is used in a proportion of about 0.01 mol to about 10 mol, preferably about 0.03 mol to about 5 mol, per 1 mol of compound (XXXV).

This reaction is advantageously carried out using a solvent inert to the reaction. While the solvent is not particularly limited as long as the reaction proceeds, for example, alcohols such as methanol, ethanol, 2-propanol, 2-methyl-2-propanol and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene, cyclohexane, hexane and the like; esters such as ethyl acetate and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; nitriles such as acetonitrile and the like; sulfoxides such as dimethyl sulfoxide and the like; pyridine; acetic acid; water; and the like can be used alone or in a mixture.

While the reaction time varies depending on the kind of reagent and solvent to be used, it is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

This reaction may be performed in a microwave reactor.

When compound (XXXV) is reacted with compound (LI), compound (LI) is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (XXXV).

Generally, this reaction is preferably performed in the

presence of a base. However, the presence of a base is not always essential. Examples of the base include sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogen carbonate, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-(dimethylamino)pyridine, N,N-dimethylaniline and the like. The base is used in a proportion of about 0.01 mol to about 10 mol, preferably about 0.03 mol to about 5 mol, per 1 mol of compound (XXXV).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the aforementioned solvents are used.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

This reaction may be performed in a microwave reactor.

(step 5-2):

Compound (XXXVIII) can be produced by reacting compound (XXXVI) with compound (XXXVII).

Compound (XXXVII) is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (XXXVI).

In this reaction, a base may be added as necessary. As the base, an inorganic base, an organic base and the like are used. Specific examples include sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogen carbonate, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-(dimethylamino)pyridine, N,N-dimethylaniline, sodium methoxide, sodium ethoxide, potassium tert-butoxide, sodium hydride, sodium amide, lithiumdiisopropylamide and the like. The base

is used in a proportion of about 1 mol to about 30 mol, preferably about 1 mol to about 10 mol, per 1 mol of compound (XXXVI).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 5-1 are used.

While the reaction time varies depending on the reagent and solvent to be used, it is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

This reaction may be performed in a microwave reactor.

(step 5-3):

Compound (XXXIX) can be produced by reducing nitro of compound (XXXVIII).

Nitro can be reduced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock), the fourth series of experimental chemistry, vol. 20, 279-280 and the like, or a method analogous thereto.

(step 5-4):

Compound (Id-1) can be produced by reacting compound (XXXIX) with carboxylic acid ($R^{5d}CO_2H$) in the presence of a condensation agent, or by reacting compound (XXXIX) with a reactive derivative of carboxylic acid ($R^{5d}COL^5$).

When compound (XXXIX) is reacted with carboxylic acid ($R^{5d}CO_2H$) in the presence of a condensation agent, carboxylic acid is used in a proportion of about 1 mol to about 10 mol, preferably about 1 mol to about 3 mol, per 1 mol of compound (XXXIX).

Examples of the condensation agent include 1-ethyl-1-(3-dimethylaminopropyl)carbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide, diethyl cyanophosphate,

diphenylphosphoryl azide, 1,1'-carbonyldiimidazole, benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and the like. The condensation agent is used in a proportion of about 1 mol to about 10 mol, preferably about 1 mol to about 5 mol, per 1 mol of compound (XXXIX).

Where necessary, a suitable condensation promoter (e.g., 1-hydroxybenzotriazole, N-hydroxysuccinimide and the like) can be used in this reaction. Such condensation promoter is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (XXXIX).

This reaction may proceed more smoothly by the addition of a base (e.g., triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene and the like). The base is used in a proportion of about 0.01 mol to about 10 mol, preferably about 0.03 mol to about 5 mol, per 1 mol of compound (XXXIX).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 5-1 are used.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

$R^{5d}CO_2H$ may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like, or a method analogous thereto.

When compound (XXXIX) is reacted with a reactive derivative of carboxylic acid ($R^{5d}COL^5$), the reactive derivative of carboxylic acid ($R^{5d}COL^5$) is used in a proportion

of about 1 mol to about 10 mol, preferably about 1 mol to about 3 mol, per 1 mol of compound (XXXIX).

Generally, this reaction is preferably performed in the presence of a base. However, the presence of a base is not always essential. Examples of the base include sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogen carbonate, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-(dimethylamino)pyridine, N,N-dimethylaniline and the like. The base is used in a proportion of about 0.01 mol to about 10 mol, preferably about 0.03 mol to about 5 mol, per 1 mol of compound (XXXIX).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 5-1 are used.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

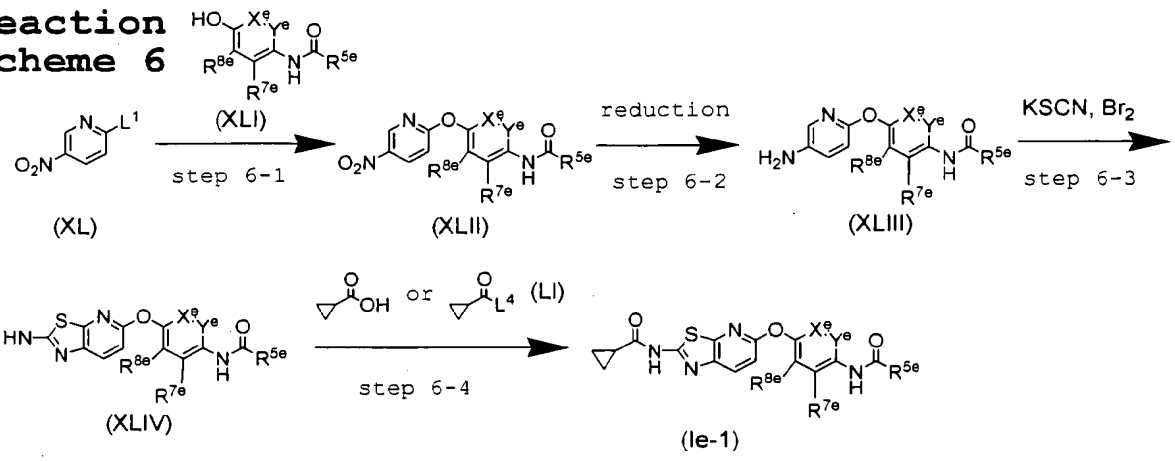
The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

$R^{5d}COL^5$ may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like, or a method analogous thereto.

[Production method 6]

In compound (Ie), compound (Ie-1) wherein W^e is an oxygen atom can be produced, for example, by the method shown in Reaction scheme 6. The compound (Ie-1) is encompassed in compound (Ie).

Reaction Scheme 6



wherein the symbols are as defined above.

(step 6-1):

Compound (XLII) can be produced by reacting compound (XL) with compound (XLI).

Compound (XLI) is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (XL).

Where necessary, a base may be added in this reaction. As the base, an inorganic base, an organic base and the like are used. Specific examples include sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogen carbonate, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-(dimethylamino)pyridine, N,N-dimethylaniline, sodium methoxide, sodium ethoxide, potassium tert-butoxide, sodium hydride, sodium amide, lithiumdiisopropylamide and the like. The base is used in a proportion of about 1 mol to about 30 mol, preferably about 1 mol to about 10 mol, per 1 mol of compound (XL).

This reaction is advantageously carried out using a solvent inert to the reaction. The solvent is not particularly limited as long as the reaction proceeds, and, for example, alcohols such as methanol, ethanol, 2-propanol, 2-methyl-2-

propanol and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene, cyclohexane, hexane and the like; esters such as ethyl acetate and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; nitriles such as acetonitrile and the like; sulfoxides such as dimethyl sulfoxide and the like; pyridine; acetic acid; water; and the like can be used alone or in a mixture.

While the reaction time varies depending on the kind of reagent and solvent to be used, it is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

This reaction may be performed in a microwave reactor.

(step 6-2):

Compound (XLIII) can be produced by reducing nitro of compound (XLII).

Nitro can be reduced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock), the fourth series of experimental chemistry, vol. 20, 279-280 and the like, or a method analogous thereto.

(step 6-3):

Compound (XLIV) can be produced by reacting compound (XLIII) with potassium thiocyanate and bromine.

Potassium thiocyanate is used in a proportion of about 1 mol to about 100 mol, preferably about 1 mol to about 30 mol, per 1 mol of compound (XLIII).

Bromine is used in a proportion of about 1 mol to about 30 mol, preferably about 1 mol to about 10 mol, per 1 mol of

compound (XLIII).

This reaction is advantageously carried out using a solvent inert to the reaction. Examples of the solvent include acetic acid and the like.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

(step 6-4):

Compound (Ie-1) can be produced by reacting compound (XLIV) with cyclopropanecarboxylic acid in the presence of a condensation agent, or by reacting compound (XLIV) with compound (LI).

When compound (XLIV) is reacted with cyclopropanecarboxylic acid in the presence of a condensation agent, cyclopropanecarboxylic acid is used in a proportion of about 1 mol to about 10 mol, preferably about 1 mol to about 3 mol, per 1 mol of compound (XLIV).

Examples of the condensation agent include 1-ethyl-1-(3-dimethylaminopropyl)carbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide, diethyl cyanophosphate, diphenylphosphoryl azide, 1,1'-carbonyldiimidazole, benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and the like. The condensation agent is used in a proportion of about 1 mol to about 10 mol, preferably about 1 mol to about 5 mol, per 1 mol of compound (XLIV).

Where necessary, a suitable condensation promoter (e.g., 1-hydroxybenzotriazole, N-hydroxysuccinimide and the like) can be used in this reaction. Such condensation promoter is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (XLIV).

This reaction may proceed more smoothly by the addition

of a base (e.g., triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene and the like). The base is used in a proportion of about 0.01 mol to about 10 mol, preferably about 0.03 mol to about 5 mol, per 1 mol of compound (XLIV).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 6-1 are used.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

when compound (XLIV) is reacted with compound (LI), compound (LI) is used in a proportion of about 1 to about 10 mol, preferably about 1 to about 3 mol, per 1 mol of compound (XLIV).

Generally, this reaction is preferably performed in the presence of a base. However, the presence of a base is not always essential. Examples of the base include sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogen carbonate, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-(dimethylamino)pyridine, N,N-dimethylaniline and the like. The base is used in a proportion of about 0.01 mol to about 10 mol, preferably about 0.03 mol to about 5 mol, per 1 mol of compound (XLIV).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 6-1 are used.

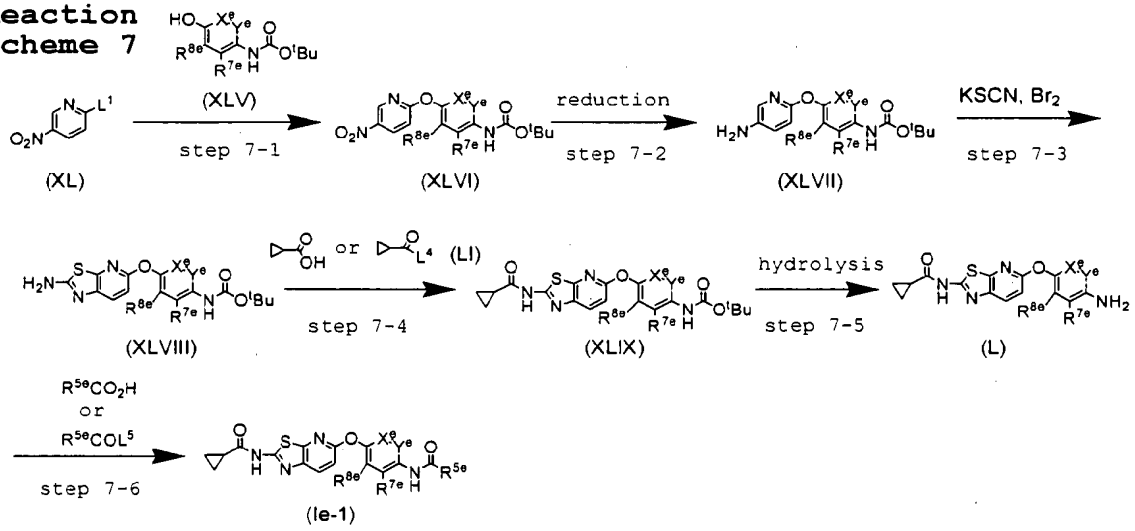
The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

[Production method 7]

Compound (Ie-1) can also be produced, for example, by the method shown in Reaction scheme 7.

Reaction Scheme 7



wherein the symbols are as defined above.

(steps 7-1 to 7-4):

compound (XLVI), compound (XLVII), compound (XLVIII) and compound (XLIX) can be synthesized from compound (XL) and compound (XLV) in the same manner as in steps 6-1 to 6-4, respectively.

(step 7-5):

Compound (L) can be produced by removing the amino-protecting group from compound (XLIX).

The amino-protecting group can be removed according to a method known *per se*, for example, the methods described in "Protective Groups in Organic Synthesis, 3rd Ed." (Theodora W. Greene) and the like, or a method analogous thereto.

(step 7-6):

Compound (Ie-1) can be produced by reacting compound (L) with carboxylic acid ($R^{5e}CO_2H$) in the presence of a condensation agent in the same manner as in step 6-4, or by reacting compound (L) with a reactive derivative ($R^{5e}COL^5$) of carboxylic acid.

$R^{5e}CO_2H$ may be commercially available, or can be produced

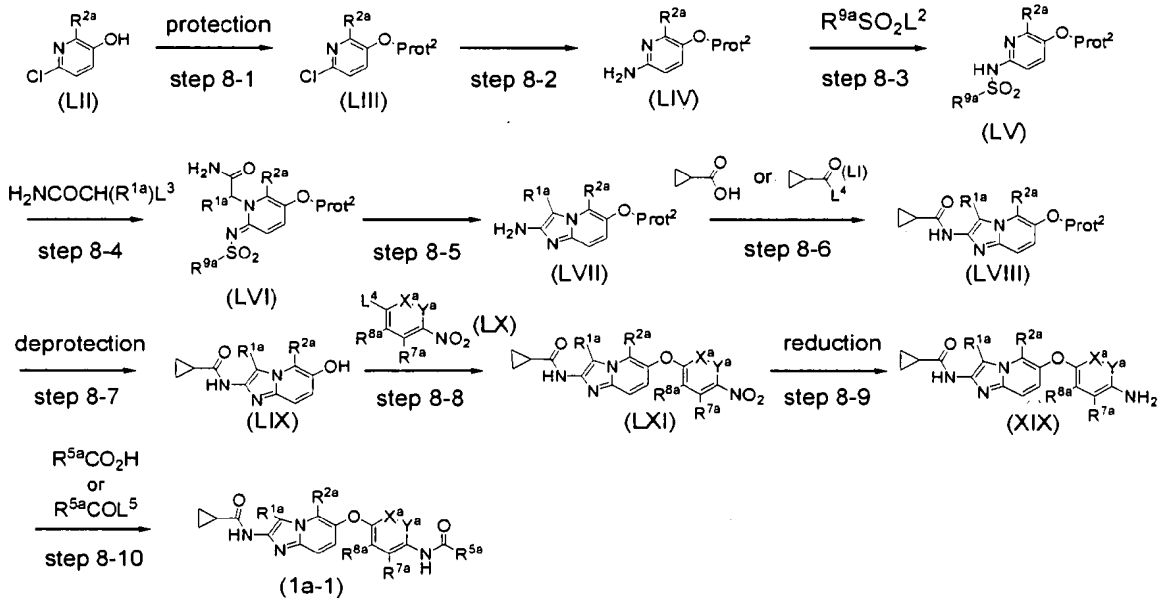
according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like, or a method analogous thereto.

$R^{5e}COL^5$ may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like, or a method analogous thereto.

[Production method 8]

Compound (Ia-1) can also be produced, for example, by the method shown in Reaction scheme 8.

Reaction Scheme 8



wherein $Prot^2$ is a phenolic hydroxyl-protecting group; and other symbols are as defined above.

As the phenolic hydroxyl-protecting group for $Prot^2$, benzyl, 4-methoxybenzyl, 2,4-dimethoxybenzyl and the like are used.

(step 8-1):

Compound (LIII) can be produced by protecting the phenolic hydroxyl group of compound (LII).

The phenolic hydroxyl group can be protected according to a method known *per se*, for example, the methods described in "Protective Groups in Organic Synthesis, 3rd Ed." (Theodora W. Greene) and the like, or a method analogous thereto.

(step 8-2):

Compound (LIV) can be produced using compound (LIII) according to the method described in "ORGANIC LETTERS, 2001, Vol. 3, No. 21, 3417-3419" (Xiaohua Huang), or a method analogous thereto a method.

(steps 8-3 to 8-4):

Compound (LV) and compound (LVI) can be produced from compound (LIV) by steps 8-3 and 8-4 in the same manner as in steps 2-4 and 2-5, respectively.

(step 8-5):

Compound (LVII) can be produced by reacting compound (LVI) with trifluoroacetic acid anhydride and then subjecting the obtained compound to alkalihydrolysis in the presence of a base.

Trifluoroacetic acid anhydride is used in a proportion of about 1 mol to about 30 mol, preferably about 1 mol to about 10 mol, per 1 mol of compound (LVI).

This reaction is advantageously performed by further using a solvent inert to the reaction. The solvent is not particularly limited as long as the reaction proceeds and, for example, alcohols such as methanol, ethanol, 2-propanol, 2-methyl-2-propanol and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene, cyclohexane, hexane and the like; esters such as ethyl acetate and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone and the like; nitriles such as acetonitrile and the

like; sulfoxides such as dimethyl sulfoxide and the like; and the like can be used alone or in a mixture.

While the reaction time varies depending on the reagent and solvent to be used, it is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

This reaction may be performed in a microwave reactor.

Examples of the base to be used for the subsequent alkalihydrolysis include aqueous sodium hydroxide solution, aqueous potassium hydroxide solution, aqueous barium hydroxide solution, aqueous calcium hydroxide solution, aqueous potassium carbonate solution, aqueous sodium carbonate solution, aqueous cesium carbonate solution and the like.

While the reaction time varies depending on the reagent and solvent to be used, it is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

This reaction may be performed in a microwave reactor.

(step 8-6):

Compound (LVIII) can be produced from compound (LVII) in the same manner as in step 2-8.

(step 8-7):

Compound (LIX) can be produced by removing the phenolic hydroxyl-protecting group of compound (LVIII).

The phenolic hydroxyl-protecting group can be removed according to a method known *per se*, for example, the methods described in "Protective Groups in Organic Synthesis, 3rd Ed." (Theodora W. Greene) and the like, or a method analogous thereto.

(step 8-8):

Compound (LXI) can be produced by reacting compound (LIX) with compound (LX) in the presence of a base.

Compound (LX) is used in a proportion of about 0.1 mol to about 30 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (LIX).

As the base, inorganic base or organic base and the like are used. Specifically, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogen carbonate, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-(dimethylamino)pyridine, N,N-dimethylaniline, sodium methoxide, sodium ethoxide, potassium tert-butoxide, sodium hydride, sodium amide, lithium diisopropylamide and the like can be mentioned. The base is used in a proportion of about 1 mol to about 30 mol, preferably about 1 mol to about 10 mol, per 1 mol of compound (LIX).

This reaction is advantageously carried out using a solvent inert to the reaction. The solvent is not particularly limited as long as the reaction proceeds and, for example, ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene, cyclohexane, hexane and the like; esters such as ethyl acetate and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, chlorobenzene, trifluoromethylbenzene and the like; nitriles such as acetonitrile and the like; sulfoxides such as dimethyl sulfoxide and the like; and the like can be used alone or in a mixture.

While the reaction time varies depending on the reagent and solvent to be used, it is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

This reaction may be performed in a microwave reactor.

(step 8-9):

Compound (XIX) can be produced by reducing nitro of compound (LXI). Nitro can be reduced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock), the fourth series of experimental chemistry, vol. 20, 279-280 and the like, or a method analogous thereto.

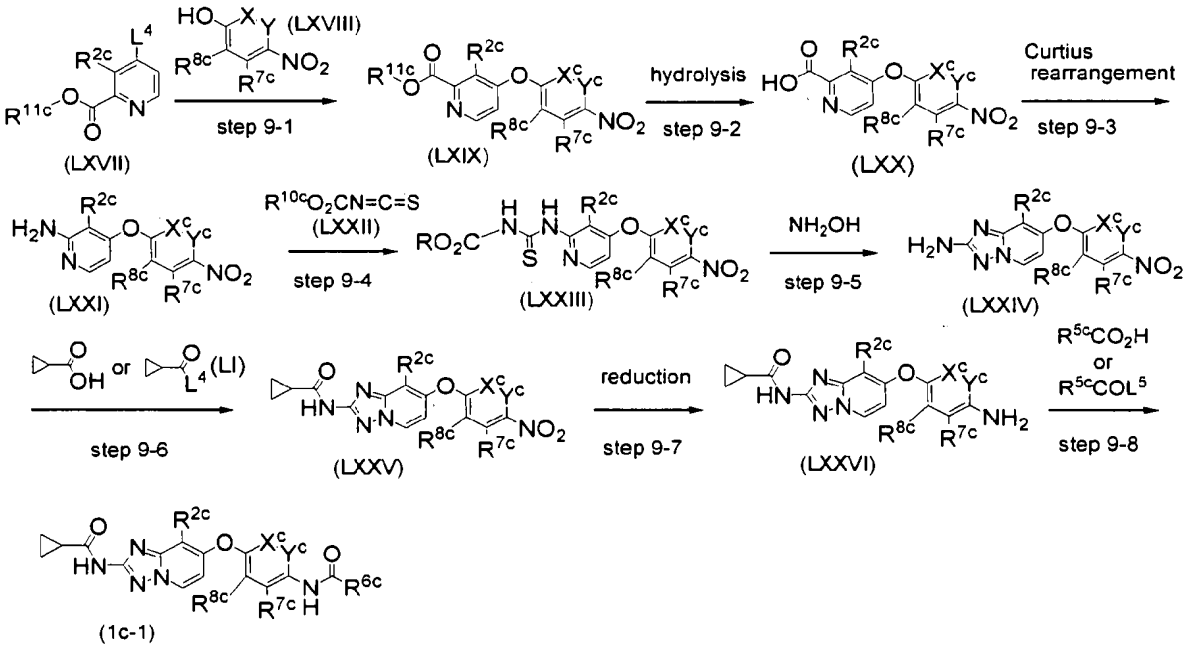
(step 8-10):

Compound (Ia-1) can be synthesized from compound (XIX) in the same manner as in step 2-10.

[Production method 9]

In compound (Ic), compound (Ic-1) wherein W^c is an oxygen atom can be produced, for example, by the method shown in Reaction scheme 9. The compound (Ic-1) is encompassed in compound (Ic).

Reaction Scheme 9



wherein R^{10c} is C_{1-6} alkyl optionally having 1 to 3 substituents selected from (a) a halogen atom and (b) nitro; and other symbols are as defined above.

(step 9-1):

Compound (LXIX) can be produced by reacting compound (LXVII) with compound (LXVIII).

Compound (LXVIII) is used in a proportion of about 0.1 mol to about 30 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (LXVII).

This reaction is advantageously carried out using a solvent inert to the reaction. The solvent is not particularly limited as long as the reaction proceeds and, for example, ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene, cyclohexane, hexane and the like; esters such as ethyl acetate and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, chlorobenzene, trifluoromethylbenzene and the like; nitriles such as acetonitrile and the like; sulfoxides such as dimethyl sulfoxide and the like; and the like can be used alone or in a mixture.

Where necessary, a base may be used in this reaction. Examples of the base include triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-(dimethylamino)pyridine, N,N-dimethylaniline, potassium tert-butoxide, sodium hydride and the like. The base is used in a proportion of about 1 mol to about 30 mol, preferably about 1 mol to about 20 mol, per 1 mol of compound (LXVII).

While the reaction time varies depending on the reagent and solvent to be used, it is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

This reaction may be performed in a microwave reactor.

(step 9-2):

Compound (LXX) can be produced by alkalihydrolysis of

compound (LXIX).

This reaction is performed in a water-containing solvent in the presence of a base. Examples of the base include sodium hydroxide, potassium hydroxide, lithium hydroxide, barium hydroxide, calcium hydroxide, potassium carbonate, sodium carbonate, cesium carbonate, sodium methoxide and the like. The base is used in a proportion of about 1 mol to about 50 mol, preferably about 1 mol to about 10 mol, per 1 mol of compound (LXIX). Examples of the water-containing solvent include a mixed solvent of one or more kinds of solvents selected from methanol, ethanol, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like, and water, and the like.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about 0°C to about 150°C.

(step 9-3):

Compound (LXXI) can be produced by converting carboxyl of compound (LXX) to amino by a method such as Curtius rearrangement and the like.

Carboxyl can be converted to amino according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like, or a method analogous thereto.

(step 9-4):

Compound (LXXIII) can be produced by reacting compound (LXXI) with compound (LXXII).

Compound (LXXII) is used in a proportion of about 0.1 mol to about 10 mol, preferably about 0.3 mol to about 3 mol, per 1 mol of compound (LXXI).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to

the solvents exemplified in step 9-1 are used.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

(step 9-5):

Compound (LXXIV) can be produced by reacting compound (LXXIII) with hydroxylamine in the presence of a base.

Hydroxylamine is used in a proportion of about 0.1 mol to about 100 mol, preferably about 0.3 mol to about 30 mol, per 1 mol of compound (LXXIII).

Examples of the base include triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-(dimethylamino)pyridine, N,N-dimethylaniline and the like. The base is used in a proportion of about 0.1 mol to about 100 mol, preferably about 0.3 mol to about 30 mol, per 1 mol of compound (LXXIII).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in step 9-1 are used.

The reaction time is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

(step 9-6):

Compound (LXXV) can be produced by reacting compound (LXXIV) with cyclopropanecarboxylic acid in the presence of a condensation agent, or reacting compound (LXXIV) with compound (LI) in the same manner as in step 2-8.

(step 9-7):

Compound (LXXVI) can be produced by reducing nitro of compound (LXXV).

Nitro can be reduced according to a method known *per se*,

for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock), the fourth series of experimental chemistry, vol. 20, 279-280 and the like, or a method analogous thereto.

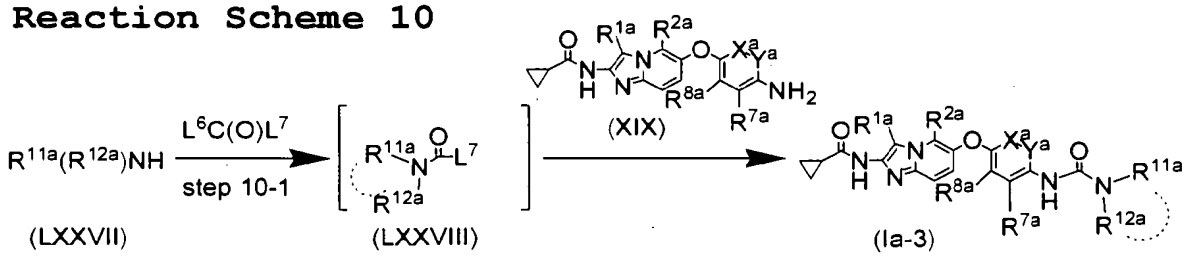
(step 9-8):

Compound (1c-1) can be produced by reacting compound (LXXVI) with $R^{5c}CO_2H$ in the presence of a condensation agent, or reacting compound (LXXVI) with $R^{5c}COL^5$ in the same manner as in step 2-10.

[Production method 10]

In compound (Ia), compound (Ia-3) wherein W^a is an oxygen atom; and R^{5a} is (1) C_{1-6} alkyl-carbonylamino optionally having one C_{6-10} aryl, or (2) a nitrogen-containing heterocyclic group (having a bond on nitrogen atom) optionally having 1 to 4 substituents selected from (a) C_{6-10} aryl optionally having 1 to 3 substituents selected from a halogen atom and C_{1-6} alkyl, (b) C_{1-6} alkyl optionally having 1 to 3 halogen atoms, and (c) oxo can also be produced, for example, by the method shown in Reaction scheme 10. The compound (Ia-3) is encompassed in compound (Ia).

Reaction Scheme 10



wherein R^{11a} is a hydrogen atom, R^{12a} is C_{1-6} alkyl-carbonyl optionally having one C_{6-10} aryl, or R^{11a} and R^{12a} may form, together with the adjacent nitrogen atom, a nitrogen-containing heterocyclic group (having a bond on nitrogen atom) optionally having 1 to 4 substituents selected from (a) C_{6-10} aryl optionally having 1 to 3 substituents selected from a

halogen atom and C_{1-6} alkyl, (b) C_{1-6} alkyl optionally having 1 to 3 halogen atoms, and (c)oxo; L^6 and L^7 are each a leaving group; and other symbols are as defined above.

The leaving groups for L^6 and L^7 are the same or different and each is, for example, (1) a halogen atom, (2) alkoxy optionally having 1 to 3 substituents selected from a halogen atom and C_{1-6} alkyl, (3) aryloxy optionally having 1 to 3 substituents selected from a halogen atom, C_{1-6} alkyl and nitro, and the like.

(step 10-1):

Compound (1a-3) can be produced by first reacting compound (LXXVII) with a compound represented by the formula $L^6C(O)L^7$ to give compound (LXXVIII), and then reacting compound (LXXVIII) with compound (XIX).

$L^6C(O)L^7$ is used in a proportion of 0.1 to 10 mol, preferably 0.3 to 3 mol, per 1 mol of compound (LXXVII).

The reaction may be performed in the presence of a base. As the base, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-(dimethylamino)pyridine, N,N-dimethylaniline and the like can be mentioned. The base is used in a proportion of about 0.1 mol to about 30 mol, preferably about 0.3 mol to about 10 mol, per 1 mol of compound (LXXVII).

This reaction is advantageously carried out using a solvent inert to the reaction. The solvent is not particularly limited as long as the reaction proceeds and, for example, ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene, cyclohexane, hexane and the like; esters such as ethyl acetate and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, chlorobenzene, trifluoromethylbenzene and the like; nitriles such as

acetonitrile and the like; sulfoxides such as dimethyl sulfoxide and the like; pyridine; and the like can be used alone or in a mixture.

While the reaction time varies depending on the reagent and solvent to be used, it is generally about 10 min to about 100 hr, preferably about 30 min to about 50 hr.

The reaction temperature is generally about -78°C to about 200°C, preferably about -20°C to about 150°C.

This reaction may be performed in a microwave reactor.

A compound represented by the formula $L^6C(O)L^7$ may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like, or a method analogous thereto.

The obtained $R^{11a}(R^{12a})NC(O)L^7$ [compound (LXXVIII)] can be used for the next reaction in the form of a reaction mixture or a crude product. It may be isolated and purified from the reaction mixture according to a conventional method and used for the next reaction.

Compound (XIX) is used in a proportion of 0.1 to 10 mol, preferably 0.3 to 3 mol, per 1 mol of compound (LXXVIII).

This reaction may be performed in the presence of a base. As the base, those similar to the bases exemplified above can be used. The base is used in a proportion of 0.1 to 10 mol, preferably 0.3 to 3 mol, per 1 mol of compound (LXXVIII).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified above are used.

The reaction time is generally about 1 min to about 200 hr, preferably about 10 min to about 100 hr.

The reaction temperature is generally about -100°C to about 250°C, preferably about -78°C to about 200°C.

In the aforementioned reactions, compounds (II), (III),

(X), (XI), (XX), (XXI), (XXII), (XXVII), (XXXII), (XXXV), (XXXVII), (XL), (XLI), (XLV), (LI), (LII), (LX), (LXVII), (LXVIII), (LXXII) and (LXXVII) may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like, or a method analogous thereto.

In each of the above-mentioned reactions, when a starting material compound has amino, carboxyl or hydroxyl as a substituent, these groups may be protected by a protecting group generally used for peptide chemistry and the like. In this case, the object compound can be obtained by removing the protecting group after reaction, as necessary. The introduction and removal of these protecting groups can be performed according to a method known *per se*, for example, the methods described in Wiley-Interscience, 1999, "Protective Groups in Organic Synthesis, 3rd Ed." (Theodora W. Greene, Peter G. M. Wuts) and the like.

Examples of the amino-protecting group include formyl group, C_{1-6} alkyl-carbonyl group, C_{1-6} alkoxy-carbonyl group, benzoyl group, C_{7-10} aralkyl-carbonyl group (e.g., benzylcarbonyl), C_{7-14} aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl), trityl group, phthaloyl group, N,N-dimethylaminomethylene group, substituted silyl group (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl), C_{2-6} alkenyl group (e.g., 1-allyl) and the like. These groups are optionally substituted by 1 to 3 substituents selected from a halogen atom, a C_{1-6} alkoxy group and a nitro group.

Examples of the carboxyl-protecting group include C_{1-6} alkyl group, C_{7-11} aralkyl group (e.g., benzyl), phenyl group, trityl group, substituted silyl group (e.g., trimethylsilyl,

triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl), C_{2-6} alkenyl group (e.g., 1-allyl) and the like.

Examples of the hydroxyl-protecting group include C_{1-6} alkyl group, phenyl group, trityl group, C_{7-10} aralkyl group (e.g., benzyl), formyl group, C_{1-6} alkyl-carbonyl group, benzoyl group, C_{7-10} aralkyl-carbonyl group (e.g., benzylcarbonyl), 2-tetrahydropyranyl group, 2-tetrahydrofuranyl group, substituted silyl group (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl), C_{2-6} alkenyl group (e.g., 1-allyl) and the like. These groups are optionally substituted by 1 to 3 substituents selected from a halogen atom, a C_{1-6} alkyl group, a C_{1-6} alkoxy group and a nitro group.

When desired, the above-mentioned reaction may be combined with any one or two or more of known hydrolysis, deprotection, acylation reaction, alkylation reaction, oxidation reaction, cyclization reaction, carbon chain extension reaction, and substituent change reaction, whereby compound (I) can also be produced.

Compound (I) can be isolated and purified by a means known *per se*, such as phase transfer, concentration, solvent extraction, fractionation, liquid conversion, crystallization, recrystallization, chromatography and the like. When compound (I) is obtained as free compounds, they can be converted to desired salts by a method known *per se* or a modification thereof; conversely, when the compounds are obtained as salts, they can be converted to free forms or other desired salts by a method known *per se* or a modification thereof.

Compound (I) may be used as a prodrug. A prodrug of compound (I) and the like means a compound which is converted to compound (I) and the like by a reaction due to an enzyme, a gastric acid, etc. under the physiological condition in the living body, that is, a compound which is converted to

compound (I) and the like by oxidation, reduction, hydrolysis, etc. due to an enzyme; a compound which is converted to compound (I) and the like by hydrolysis etc. due to gastric acid, and the like.

A prodrug of compound (I) may be a compound obtained by subjecting an amino in compound (I) to an acylation, alkylation or phosphorylation (e.g., a compound obtained by subjecting an amino in compound (I) to an eicosanoylation, alanylation, pentylaminocarbonylation, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylation, tetrahydrofuranylation, pyrrolidylmethylation, pivaloyloxymethylation or tert-butylation, etc.); a compound obtained by subjecting a hydroxy in compound (I) to an acylation, alkylation, phosphorylation or boration (e.g., a compound obtained by subjecting an hydroxy in compound (I) to an acetylation, palmitoylation, propanoylation, pivaloylation, succinylation, fumarylation, alanylation or dimethylaminomethylcarbonylation, etc.); a compound obtained by subjecting a carboxy in compound (I) to an esterification or amidation (e.g., a compound obtained by subjecting a carboxy in compound (I) to an ethyl esterification, phenyl esterification, carboxymethyl esterification, dimethylaminomethyl esterification, pivaloyloxymethyl esterification, ethoxycarbonyloxyethyl esterification, phthalidyl esterification, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esterification, cyclohexyloxycarbonylethyl esterification or methylamidation, etc.); and the like. Any one of these compounds can be produced from compound (I) by a method known *per se*.

A prodrug of compound (I) may also be one which is converted into compound (I) under a physiological condition, such as those described in *IYAKUHIN no KAIHATSU* (Development of Pharmaceuticals), Vol. 7, Design of Molecules, p.163-198, Published by HIROKAWA SHOTEN (1990).

When compound (I) has isomers such as optical isomer,

stereoisomer, positional isomer, rotational isomer and the like, any isomers and mixtures are encompassed in compound (I). For example, when compound (I) has an optical isomer, an optical isomer separated from a racemate is also encompassed in compound (I). These isomers can be obtained as independent products by a synthesis means or a separation means (concentration, solvent extraction, column chromatography, recrystallization and the like) known *per se*.

The compound (I) may be a crystal, and both a single crystal and crystal mixtures are encompassed in compound (I). Crystals can be produced by crystallization according to crystallization methods known *per se*.

Compound (I) encompasses hydrate, non-hydrate, solvate and non-solvate within the scope thereof.

A compound labeled with an isotope (e.g., ^{3}H, ^{14}C, ^{35}S, ^{125}I etc.) and the like is also encompassed in compound (I).

Furthermore, compound (I) may be a deuterated compound wherein ^{1}H is converted to $^{2}H(D)$.

Compound (I) of the present invention and a prodrug thereof (hereinafter sometimes to be abbreviated as the compound of the present invention) have, for example, phosphorylation-inhibitory activity against a kinase having such phosphorylating action. As used herein, kinase encompasses not only a substance having a phosphorylating action by itself as a whole, but also a substance a part of which has a phosphorylating action. The phosphorylating action possessed by kinases encompasses both a phosphorylating action on its own and that on other substances.

Examples of kinase include vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), Raf, hepatocyte growth factor receptor (c-Met), angiopoietin receptor, FLT3 and the like.

Examples of vascular endothelial growth factor receptor (VEGFR) include vascular endothelial growth factor receptor 1 (VEGFR1, Flt-1), vascular endothelial growth factor receptor 2

(VEGFR2, KDR, Flk-1), vascular endothelial growth factor receptor 3 (VEGFR3, Flt-4) and the like. Of these, vascular endothelial growth factor receptor 2 (VEGFR2) is preferable.

Examples of platelet-derived growth factor receptor (PDGFR) include platelet-derived growth factor receptor α (PDGFRα), platelet-derived growth factor receptor β (PDGFRβ) and the like.

Examples of Raf include A-Raf, B-Raf, C-Raf and the like.

Examples of angiopoietin receptor include Tyrosine Kinase with Immunoglobulin and Epidermal Growth homology domain 1 (TIE1), TIE2 and the like.

Particularly, as kinase, vascular endothelial growth factor receptor 2 (VEGFR2), platelet-derived growth factor receptor (PDGFR), Raf, hepatocyte growth factor receptor (c-Met), TIE2 and FLT3 are preferable.

Besides these, as kinase, fibroblast growth factor receptor 1 (FGFR1), fibroblast growth factor receptor 2 (FGFR2), fibroblast growth factor receptor 3 (FGFR3), fibroblast growth factor receptor 4 (FGFR4), stem cell factor receptor (c-Kit), Aurora A, Aurora B, Axl, CDK, MEK1, MEK2, Akt, ERK, MAPK, Src, epithelial cell growth factor receptor (EGFR), human epithelial growth factor receptor 2 (HER2), human epithelial growth factor receptor 4 (HER4), Abl, Fgr, Fms, Ron, Ret, Eph, TrkA and the like can also be used.

For example, the vascular endothelial growth factor receptor 2 (VEGFR2) inhibitory activity of the compound of the present invention can be determined according to Test Example 1, the vascular endothelial cell proliferation inhibitory activity can be determined according to Test Example 2, the hepatocyte growth factor receptor (c-Met) inhibitory activity can be determined according to Test Example 3, the human gastric cancer cell line MKN-45 growth inhibitory activity can be determined according to Test Example 4, the human gastric cancer cell line MKN-45 antitumor activity and human blood

cell cancer cell line MV-4-11 antitumor activity can be determined according to Test Example 5, the FLT3 inhibitory activity can be determined according to Test Example 6, the TIE2 inhibitory activity can be determined according to Test Example 7, and the human blood cell cancer cell line MV-4-11 growth inhibitory activity can be determined according to Test Example 8.

The compound of the present invention particularly shows potent inhibitory activity for vascular endothelial growth factor receptor (VEGFR), and specifically high selectivity for vascular endothelial growth factor receptor 2 (VEGFR2, KDR, Flk-1) and potent kinase inhibitory activity for VEGFR1 and PDGFR. In addition, the compound of the present invention shows potent inhibitory action on hepatocyte growth factor receptor (c-Met). The compound of the present invention also shows potent inhibitory action on TIE2. Moreover, the compound of the present invention shows potent inhibitory action on FLT3. Furthermore, since the compound of the present invention is also superior in the efficacy, pharmacokinetics (absorption, distribution, metabolism, excretion etc.), solubility (water-solubility etc.), interaction with other pharmaceutical products, safety (acute toxicity, chronic toxicity, genetic toxicity, reproductive toxicity, cardiotoxicity, carcinogenicity etc.) and stability (chemical stability, stability to enzyme etc.), it is useful as a pharmaceutical agent.

The compound of the present invention is useful as a kinase inhibitor, preferably a vascular endothelial growth factor receptor (VEGFR) inhibitor [preferably a vascular endothelial growth factor receptor 2 (VEGFR2, KDR, Flk-1) inhibitor], a platelet-derived growth factor receptor (PDGFR) inhibitor, hepatocyte growth factor receptor (c-Met) inhibitor, TIE2 inhibitor, FLT3 inhibitor for a mammal (e.g., mouse, rat, hamster, rabbit, cat, dog, bovine, sheep, monkey, human etc.).

Therefore, the compound of the present invention is useful

as an angiogenesis inhibitor, a vascular endothelial cell proliferation inhibitor, cancer cell proliferation inhibitor and the like.

The compound of the present invention is used as a pharmaceutical agent such as an agent for the prophylaxis or treatment of diseases possibly affected by a vascular endothelial growth factor, platelet-derived growth factor, hepatocyte growth factor, angiopoietin, for example, cancer [e.g., colorectal cancer (e.g., familial colorectal cancer, hereditary nonpolyposis colorectal cancer, gastrointestinal stromal tumor etc.), lung cancer (e.g., non-small cell lung cancer, small cell lung cancer, malignant mesothelioma, etc.), mesothelioma, pancreatic cancer (e.g., pancreatic duct cancer, etc.), gastric cancer (e.g., scirrhous gastric cancer, papillary glandular cancer, mucinous glandular cancer, adenosquamous cancer, etc.), breast cancer (e.g., invasive ductal carcinoma, ductal cancer in situ, inflammatory breast cancer, etc.), ovary cancer (e.g., ovarian epithelial cancer, extragonadal germ cell tumor, ovarian germ cell tumor, ovarian low malignant potential tumor etc.), prostate cancer (e.g., hormone-dependent prostate cancer, non-hormone dependent prostate cancer, etc.), liver cancer (e.g., primary liver cancer, extrahepatic bile duct cancer, etc.), thyroid cancer (e.g., medullary thyroid cancer, etc.), head and neck cancer (laryngeal cancer), kidney cancer (e.g., renal cell carcinoma, renal pelvis and ureter transitional cell cancer, etc.), esophagus cancer, testis cancer, uterus cancer, pancreatic endocrine tumor, brain tumor (e.g., pineal astrocytoma, pilocytic astrocytoma, diffuse astrocytoma, anaplastic astrocytoma, etc.), melanoma, sarcoma, urinary bladder cancer, blood cancer including multiple myeloma (e.g., acute myelocytic leukemia, myelodysplastic syndrome) etc.], diabetic retinopathy, rheumatoid arthritis, psoriasis, atherosclerosis, Kaposi's sarcoma, COPD, pain, asthma, endometriosis, nephritis,

osteoarthritis, inflammation such as age-related macular degeneration and the like and hypertension; the above-mentioned cancer growth inhibitor; the above-mentioned cancer metastasis suppressor; an apoptosis promoter; and the like.

Of these, it is effective as an agent for the prophylaxis or treatment of colorectal cancer, lung cancer, pancreatic cancer, gastric cancer, breast cancer, ovary cancer, prostate cancer, liver cancer, thyroid cancer, kidney cancer, brain tumor melanoma, urinary bladder cancer and blood cancer. Particularly, the compound of the present invention is effective as an agent for the prophylaxis or treatment of lung cancer, gastric cancer, colorectal cancer, ovary cancer, prostate cancer, kidney cancer or blood cancer.

In addition, based on the strong hepatocyte growth factor receptor (c-Met) inhibitory action, the compound of the present invention is useful as an agent for suppressing invasion and/or metastasis of cancer (e.g., colorectal cancer, gastric cancer, lung cancer, kidney cancer, breast cancer, ovary cancer, prostate cancer, brain tumor). Based on the strong Fms Like Tyrosine Kinase 3 (FLT3) inhibitory action, moreover, the compound of the present invention is effective as an agent for the prophylaxis or treatment of leukemia (e.g., acute myelocytic leukemia, acute lymphatic leukemia).

The compound of the present invention can be administered orally or parenterally as it is or in a mixture with a pharmacologically acceptable carrier.

The dosage form of the compound of the present invention for oral administration is, for example, tablet (including sugar-coated tablet, film-coated tablet), pill, granule, powder, capsule (including soft capsule, microcapsule), syrup, emulsion, suspension and the like, and the dosage form for parenteral administration is, for example, injection, injecting agent, instillation, suppository and the like. In addition, it is effective to make a sustained release preparation by combining

the compound with a suitable base (e.g., polymer of butyric acid, polymer of glycolic acid, copolymer of butyric acid-glycolic acid, a mixture of a polymer of butyric acid and a polymer of glycolic acid, polyglycerol fatty acid ester etc.).

As a method to produce the compound of the present invention in the above-mentioned dosage form, a known production method generally used in the pertinent field can be employed. When the above-mentioned dosage form is produced, suitable amounts of additives such as excipient, binder, disintegrant, lubricant, sweetening agent, surfactant, suspending agent, emulsifier and the like, generally used in the pertinent field, are appropriately added as necessary for production.

When the compound of the present invention is prepared into a tablet, for example, it can be produced by adding an excipient, a binder, a disintegrant, a lubricant and the like, and when a pill or a granule is to be prepared, it can be produced by adding an excipient, a binder, a disintegrant and the like. When a powder or a capsule is to be prepared, it can be produced by adding an excipient and the like, when a syrup is to be prepared, it can be produced by adding a sweetener and the like, and when an emulsion or a suspension is to be prepared, it can be produced by adding a suspending agent, a surfactant, an emulsifier and the like.

Examples of the excipient include lactose, sucrose, glucose, starch, sucrose, crystalline cellulose, powdered glycyrrhiza, mannitol, sodium hydrogen carbonate, calcium phosphate, calcium sulfate and the like.

Examples of the binder include 5 - 10 wt% starch liquid paste, 10 - 20 wt% gum arabic solution or gelatin solution, 1 - 5 wt% tragacanth solution, carboxymethyl cellulose solution, sodium alginate solution, glycerin and the like.

Examples of the disintegrant include starch, calcium carbonate and the like.

Examples of the lubricant include magnesium stearate,

stearic acid, calcium stearate, purified talc and the like.

Examples of the sweetener include glucose, fructose, invert sugar, sorbitol, xylitol, glycerin, simple syrup and the like.

Examples of the surfactant include sodium lauryl sulfate, polysorbate 80, sorbitan monofatty acid ester, polyoxyl 40 stearate and the like.

Examples of the suspending agent include gum arabic, sodium alginate, sodium carboxymethyl cellulose, methyl cellulose, bentonite and the like.

Examples of the emulsifier include gum arabic, tragacanth, gelatin, polysorbate 80 and the like.

Furthermore, when the compound of the present invention is produced in the above-mentioned dosage form, a suitable amount of a colorant, a preservative, an aromatic, a corrigent, a stabilizer, a thickening agent and the like typically used in the field of preparation can be added on demand.

As the injection, intravenous injection as well as subcutaneous injection, intracutaneous injection, intramuscular injection, instillation and the like are mentioned, and as the sustained release preparation, an iontophoresis transdermal agent and the like are mentioned.

Such injections are prepared by methods known *per se*, or by dissolving, suspending or emulsifying the compound of the present invention in a sterilized aqueous or oily liquid. As an aqueous liquid for injection, physiological saline, isotonic solutions containing glucose or other auxiliary drugs (e.g., D-sorbitol, D-mannitol, sodium chloride and the like) and the like can be mentioned, and they can be used in combination with suitable solubilizing agents, such as alcohols (e.g., ethanol), polyalcohols (e.g., propylene glycol, polyethylene glycol), nonionic surfactants (e.g., polysorbate 80, HCO-50) and the like. As an oily liquid, sesame oil, soybean oil and the like can be mentioned, which may be used in combination with solubilizing

agents such as benzyl benzoate, benzyl alcohol and the like. In addition, buffers (e.g., phosphate buffer, sodium acetate buffer), soothing agents (e.g., benzalkonium chloride, procaine hydrochloride and the like), stabilizers (e.g., human serum albumin, polyethylene glycol and the like), preservatives (e.g., benzyl alcohol, phenol and the like) and the like can be mentioned. A prepared injection is generally filled in an ampoule.

While the content of the compound of the present invention in the pharmaceutical agent of the present invention varies depending on the form of the pharmaceutical preparation, it is generally about 0.01 to 100 wt%, preferably about 2 to 85 wt%, more preferably about 5 to 70 wt%, relative to the entire preparation.

While the content of the additive in the pharmaceutical agent of the present invention varies depending on the form of the pharmaceutical preparation, it is generally about 1 to 99.9 wt%, preferably about 10 to 90 wt%, relative to the entire preparation.

The compound of the present invention is stable and low toxic, and can be used safely. While the daily dose varies depending on the condition and body weight of patients, the kind of compound, administration route and the like, in the case of, for example, oral administration to patients for the treatment of cancer, the daily dose to an adult (body weight about 60 kg) is about 0.1 to 1000 mg, preferably about 0.3 to 300 mg, more preferably about 1 to 200 mg, as an active ingredient (the compound of the present invention), which can be given in a single administration or administered in 2 or 3 portions a day.

When the compound of the present invention is administered parenterally, it is generally administered in the form of a liquid (e.g., injection). While the dose varies depending on the subject of administration, target organ, symptom, administration method and the like, it is, for example, about

0.01 mg to about 100 mg, preferably about 0.01 to about 50 mg, more preferably about 0.01 to about 20 mg, in the form of an injection, relative to 1 kg body weight, which is preferably given by intravenous injection.

The compound of the present invention can be used concurrently with other drugs. To be specific, the compound of the present invention can be used together with medicaments such as hormonal therapeutic agents, chemotherapeutic agents, immunotherapeutic agents, pharmaceutical agents inhibiting the action of cell growth factors or cell growth factor receptors and the like. In the following, the drugs that can be used in combination with the compound of the present invention are abbreviated as concomitant drugs.

Examples of the "hormonal therapeutic agents" include fosfestrol, diethylstylbestrol, chlorotrianisene, medroxyprogesterone acetate, megestrol acetate, chlormadinone acetate, cyproterone acetate, danazol, allylestrenol, gestrinone, mepartricin, raloxifene, ormeloxifene, levormeloxifene, anti-estrogens (e.g., tamoxifen citrate, toremifene citrate, and the like), pill preparations, mepitiostane, testrolactone, aminoglutethimide, LH-RH agonists (e.g., goserelin acetate, buserelin, leuprorelin, and the like), droloxifene, epitiostanol, ethinylestradiol sulfonate, aromatase inhibitors (e.g., fadrozole hydrochloride, anastrozole, retrozole, exemestane, vorozole, formestane, and the like), anti-androgens (e.g., flutamide, bicartamide, nilutamide, and the like), 5α-reductase inhibitors (e.g., finasteride, epristeride, and the like), aderenal cortex hormone drugs (e.g., dexamethasone, prednisolone, betamethasone, triamcinolone, and the like), androgen synthesis inhibitors (e.g., abiraterone, and the like), retinoid and drugs that retard retinoid metabolism (e.g., liarozole, and the like), thyroid gland hormone, and DDS (Drug Delivery System) preparations therefor and the like.

Examples of the "chemotherapeutic agents" include alkylating agents, antimetabolites, anticancer antibiotics, plant-derived anticancer agents, and the like.

Examples of the "alkylating agents" include nitrogen mustard, nitrogen mustard-N-oxide hydrochloride, chlorambutyl, cyclophosphamide, ifosfamide, thiotepa, carboquone, improsulfan tosylate, busulfan, nimustine hydrochloride, mitobronitol, melphalan, dacarbazine, ranimustine, sodium estramustine phosphate, triethylenemelamine, carmustine, lomustine, streptozocin, pipobroman, etoglucid, carboplatin, cisplatin, miboplatin, nedaplatin, oxaliplatin, altretamine, ambamustine, dibrospidium hydrochloride, fotemustine, prednimustine, pumitepa, ribomustin, temozolomide, treosulphan, trophosphamide, zinostatin stimalamer, adozelesin, cystemustine, bizelesin, DDS (Drug Delivery System) preparations thereof, and the like.

Examples of the "antimetabolites" include mercaptopurine, 6-mercaptopurine riboside, thioinosine, methotrexate, pemetrexed, enocitabine, cytarabine, cytarabine ocfosfate, ancitabine hydrochloride, 5-FU drugs (e.g., fluorouracil, tegafur, UFT, doxifluridine, carmofur, gallocitabine, emmitefur, capecitabine, and the like), aminopterine, nelzarabine, leucovorin calcium, tabloid, butocine, folinate calcium, levofolinate calcium, cladribine, emitefur, fludarabine, gemcitabine, hydroxycarbamide, pentostatin, piritrexim, idoxuridine, mitoguazone, thiazophrine, ambamustine, bendamustine, DDS preparations thereof, and the like.

Examples of the "anticancer antibiotics" include actinomycin-D, actinomycin-C, mitomycin-C, chromomycin-A3, bleomycin hydrochloride, bleomycin sulfate, peplomycin sulfate, daunorubicin hydrochloride, doxorubicin hydrochloride, aclarubicin hydrochloride, pirarubicin hydrochloride, epirubicin hydrochloride, neocarzinostatin, mithramycin,

sarcomycin, carzinophilin, mitotane, zorubicin hydrochloride, mitoxantrone hydrochloride, idarubicin hydrochloride, DDS preparations thereof, and the like.

Examples of the "plant-derived anticancer agents" include etoposide, etoposide phosphate, vinblastine sulfate, vincristine sulfate, vindesine sulfate, teniposide, paclitaxel, docetaxel, vinorelbine, DDS preparations thereof, and the like.

Examples of the "immunotherapeutic agents (BRM)" include picibanil, krestin, sizofiran, lentinan, ubenimex, interferons, interleukins, macrophage colony-stimulating factor, granulocyte colony-stimulating factor, erythropoietin, lymphotoxin, BCG vaccine, corynebacterium parvum, levamisole, polysaccharide K, procodazole, anti-CTLA4 antibody, and the like.

Example of the "cell growth factor" in the "pharmaceutical agents inhibiting the action of cell growth factors or cell growth factor receptors" include any substances that promote cell proliferation, which are normally peptides having not more than 20,000 molecular weight that are capable of exhibiting their activity at low concentrations by binding to a receptor including (1) EGF (epidermal growth factor) or substances possessing substantially the same activity as EGF [e.g., TGFα, and the like], (2) insulin or substances possessing substantially the same activity as insulin [e.g., insulin, IGF (insulin-like growth factor)-1, IGF-2, and the like], (3) FGF (fibroblast growth factor) or substances possessing substantially the same activity as FGF [e.g., acidic FGF, basic FGF, KGF (keratinocyte growth factor), FGF-10, and the like], (4) other cell growth factors [e.g., CSF (colony stimulating factor), EPO (erythropoietin), IL-2 (interleukin-2), NGF (nerve growth factor), PDGF (platelet-derived growth factor), TGFβ (transforming growth factor β), HGF (hepatocyte growth factor), VEGF (vascular endothelial growth factor), heregulin, angiopoietin, and the like].

Examples of the "cell growth factor receptors" include any receptors capable of binding to the aforementioned growth factors, including EGF receptor heregulin receptor (HER3, etc.), insulin receptor IGF receptor-1, IGF receptor-2, FGF receptor-1 or FGF receptor-2, VEGF receptor angiopoietin receptor (Tie2 etc.), PDGF receptor HGF receptor (c-Met), NGF receptor (TrkA) and the like.

As the "pharmaceutical agents inhibiting the action of cell growth factors or cell growth factor receptors", EGF inhibitor, TGFα inhibitor, haregulin inhibitor, insulin inhibitor, IGF inhibitor, FGF inhibitor, KGF inhibitor, CSF inhibitor, EPO inhibitor, IL-2 inhibitor, NGF inhibitor, PDGF inhibitor, TGFβ inhibitor, HGF inhibitor, VEGF inhibitor, angiopoietin inhibitor, EGF receptor inhibitor, HER2 inhibitor, HER4 inhibitor, insulin receptor inhibitor, IGF-1 receptor inhibitor, IGF-2 receptor inhibitor, FGF receptor-1 inhibitor, FGF receptor-2 inhibitor, FGF receptor-3 inhibitor, FGF receptor-4 inhibitor, VEGF receptor inhibitor, Tie-2 inhibitor, PDGF receptor inhibitor, Abl inhibitor, Raf inhibitor, FLT3 inhibitor, c-Kit inhibitor, Src inhibitor, PKC inhibitor, Trk inhibitor, Ret inhibitor, mTOR inhibitor, Aurora inhibitor, PLK inhibitor, MEK (MEK1/2) inhibitor, c-MET inhibitor, CDK inhibitor, Akt inhibitor, ERK inhibitor, TrkA inhibitor and the like are used. More specifically, anti-VEGF antibody (Bevacizumab etc.), anti-HER2 antibody (Trastuzumab, Pertuzumab etc.), anti-EGFR antibody (Cetuximab, Panitumumab, Matuzumab, Nimotuzumab etc.), anti-VEGFR antibody, anti-HGF antibody, Imatinib, Erlotinib, Gefitinib, Sorafenib, Sunitinib, Dasatinib, Lapatinib, Vatalanib, 4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxy-7-[3-(1-pyrrolidinyl)propoxy]quinazoline (AZD-2171), Lestaurtinib, Pazopanib, Canertinib, Tandutinib, 3-(4-bromo-2,6-difluorobenzyloxy)-5-[3-[4-(1-pyrrolidinyl)butyl]ureido]isothiazole-4-carboxamide (CP-547632), Axitinib, N-(3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-(pyridin-

4-ylmethylamino)pyridine-3-carboxamide (AMG-706), Nilotinib, 6-[4-(4-ethylpiperazin-1-ylmethyl)phenyl]-N-[1(R)-phenylethyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine (AEE-788), Vandetanib, Temsirolimus, Everolimus, Enzastaurin, N-[4-[4-(4-methylpiperazin-1-yl)-6-(3-methyl-1H-pyrazol-5-ylamino)pyrimidin-2-ylsulfanyl]phenyl]cyclopropanecarboxamide (VX-680), phosphoric acid 2-[N-[3-[4-[5-[N-(3-fluorophenyl)carbamoylmethyl]-1H-pyrazol-3-ylamino]quinazolin-7-yloxy]propyl]-N-ethylamino]ethyl ester (AZD-1152), 4-[9-chloro-7-(2,6-difluorophenyl)-5H-pyrimido[5,4-d][2]benzazepin-2-ylamino]benzoic acid (MLN-8054), N-[2-methoxy-5-[(E)-2-(2,4,6-trimethoxyphenyl)vinylsulfonylmethyl]phenyl]glycine sodium salt (ON-1910Na), 4-[8-cyclopentyl-7(R)-ethyl-5-methyl-6-oxo-5,6,7,8-tetrahydropteridin-2-ylamino]-3-methoxy-N-(1-methylpiperidin-4-yl)benzamide (BI-2536), 5-(4-bromo-2-chlorophenylamino)-4-fluoro-1-methyl-1H-benzimidazole-6-carbohydroxamic acid 2-hydroxyethyl ester (AZD-6244), N-[2(R),3-dihydroxypropoxy]-3,4-difluoro-2-(2-fluoro-4-iodophenylamino)benzamide (PD-0325901) and the like are used.

In addition to the aforementioned drugs, L-asparaginase, aceglatone, procarbazine hydrochloride, protoporphyrin-cobalt complex salt, mercuric hematoporphyrin-sodium, topoisomerase I inhibitors (e.g., irinotecan, topotecan, and the like), topoisomerase II inhibitors (e.g., sobuzoxane, and the like), differentiation inducers (e.g., retinoid, vitamin D, and the like), other angiogenesis inhibitors (e.g., humagillin, shark extract, COX-2 inhibitor and the like), α-blockers (e.g., tamsulosin hydrochloride, and the like), bisphosphonic acids (e.g., pamidronate, zoledronate), thalidomide, 5 azacytidine, decitabine, proteasome inhibitor (e.g., bortezomib), antitumor antibody such as anti-CD20 antibody and the like, toxin labeled antibody and the like can also be used.

By combining the compound of the present invention and a concomitant drug, a superior effect such as

(1) the dose can be reduced as compared to single administration of the compound of the present invention or a concomitant drug,
(2) the drug to be combined with the compound of the present invention can be selected according to the condition of patients (mild case, severe case and the like),
(3) the period of treatment can be set longer,
(4) a sustained treatment effect can be designed,
(5) a synergistic effect can be afforded by a combined use of the compound of the present invention and a concomitant drug, and the like, can be achieved.

In the present specification, the compound of the present invention and a concomitant drug used in combination are referred to as the "combination agent of the present invention".

For use of the combination agent of the present invention, the administration time of the compound of the present invention and the concomitant drug is not restricted, and the compound of the present invention and the concomitant drug can be administered to an administration subject simultaneously, or may be administered at different times. The dosage of the concomitant drug may be determined according to the dose clinically set, and can be appropriately selected depending on the administration subject, administration route, disease, combination and the like.

Examples of the administration mode of the combined use of the compound of the present invention and the concomitant drug include the following methods:
(1) The compound of the present invention and the concomitant drug are simultaneously produced to give a single preparation, which is then administered. (2) The compound of the present invention and the concomitant drug are separately produced to give two kinds of preparations which are administered simultaneously by the same administration route. (3) The compound of the present invention and the concomitant drug are separately produced to give two kinds of preparations which are

administered by the same administration route at different times. (4) The compound of the present invention and the concomitant drug are separately produced to give two kinds of preparations which are administered simultaneously by different administration routes. (5) The compound of the present invention and the concomitant drug are separately produced to give two kinds of preparations which are administered by different administration routes at different times (e.g., the compound of the present invention and the concomitant drug are administered in this order, or in the reverse order). The dose of the concomitant drug is determined in accordance with its clinical dose, and the ratio of the compound of the present invention and the concomitant drug is determined depending on the subject, administration route, disease, symptom, combination, and the like. For example, when the subject is human, the concomitant drug is used in 0.01 to 100 (w/w), relative to the compound of the present invention.

The combination agent of the present invention has low toxicity and, for example, the compound of the present invention and/or the above-mentioned concomitant drug can be mixed, according to a method known *per se*, with a pharmacologically acceptable carrier to give pharmaceutical compositions, such as tablets (including sugar-coated tablet, film-coated tablet), powders, granules, capsules (including soft capsule), solutions, injections, suppositories, sustained release agents and the like, which can be safely administered orally or parenterally (e.g., local, rectum, venous, and the like). An injection can be administered directly to the lesion or administered by intravenous, intramuscular, subcutaneous or intra-tissue administration.

As a pharmacologically acceptable carrier which may be used for preparing a preparation of the combination agent of the present invention, those similar to the aforementioned pharmacologically acceptable carriers, that can be used for the

production of the pharmaceutical agent of the present invention, can be mentioned. Where necessary, the aforementioned additives that can be used for the production of the pharmaceutical agent of the present invention, such as preservatives, antioxidants, colorants, sweetening agents, adsorbents, wetting agents and the like can also be used in appropriate amounts.

The compounding ratio of the compound of the present invention to the concomitant drug in the combination agent of the present invention can be appropriately set depending on the administration subject, administration route, diseases and the like.

For example, the content of the compound of the present invention in the combination agent of the present invention varies depending on the dosage form, and is usually from about 0.01 to 100% by weight, preferably from about 0.1 to 50% by weight, further preferably from about 0.5 to 20% by weight, based on the preparation.

The content of the concomitant drug in the combination agent of the present invention varies depending on the dosage form, and is usually from about 0.01 to 90% by weight, preferably from about 0.1 to 50% by weight, further preferably from about 0.5 to 20% by weight, based on the preparation.

The content of additives in the combination agent of the present invention varies depending on the dosage form, and is usually from about 1 to 99.99% by weight, preferably from about 10 to 90% by weight, based on the preparation.

When the compound of the present invention and the concomitant drug are separately prepared, the same content may be adopted.

These preparations can be produced by a method known *per se*, which is generally employed in the preparation process.

For example, the compound of the present invention and the concomitant drug can be made into an aqueous injection together with a dispersing agent (e.g., Tween 80 (manufactured by Atlas

Powder, US), HCO 60 (manufactured by Nikko Chemicals), polyethylene glycol, carboxymethylcellulose, sodium alginate, hydroxypropylmethylcellulose, dextrin and the like), a stabilizer (e.g., ascorbic acid, sodium pyrosulfite, and the like), a surfactant (e.g., Polysorbate 80, macrogol and the like), a solubilizer (e.g., glycerin, ethanol and the like), a buffer (e.g., phosphoric acid and alkali metal salt thereof, citric acid and alkali metal salt thereof, and the like), an isotonizing agent (e.g., sodium chloride, potassium chloride, mannitol, sorbitol, glucose and the like), a pH adjuster (e.g., hydrochloric acid, sodium hydroxide and the like), a preservative (e.g., ethyl parahydroxybenzoate, benzoic acid, methylparaben, propylparaben, benzyl alcohol and the like), a dissolving agent (e.g., conc. glycerin, meglumine and the like), a solubilizing agent (e.g., propylene glycol, sucrose and the like), a soothing agent (e.g., glucose, benzyl alcohol and the like), and the like, or can be dissolved, suspended or emulsified in a vegetable oil such as olive oil, sesame oil, cotton seed oil, corn oil and the like or a solubilizing agent such as propylene glycol and the like and prepared into an oily injection, whereby an injection is afforded.

In addition, an excipient (e.g., lactose, sucrose, starch and the like), a disintegrating agent (e.g., starch, calcium carbonate and the like), a binder (e.g., starch, gum arabic, carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose and the like), a lubricant (e.g., talc, magnesium stearate, polyethylene glycol 6000 and the like) and the like may be added to the compound of the present invention or the concomitant drug according to a method known *per se*, and the mixture can be compression-molded, then if desirable, the molded product can be coated by a method known *per se* for the purpose of masking of taste, enteric property or durability, to give a preparation for oral administration. As the coating agent, for example, hydroxypropylmethylcellulose, ethylcellulose,

hydroxymethylcellulose, hydroxypropylcellulose, polyoxyethylene glycol, Tween 80, Pluronic F68, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, Eudoragit (methacrylic acid·acrylic acid copolymer, manufactured by Rohm, Germany), pigment (e.g., iron oxide red, titanium dioxide, etc.) and the like can be used. The preparation for oral administration may be any of an immediate-release preparation and a sustained release preparation.

Moreover, the compound of the present invention and the concomitant drug can be made into an oily or aqueous solid, semisolid or liquid suppository according to a method known *per se*, by mixing them with an oily substrate, aqueous substrate or aqueous gel substrate. As the above-mentioned oily substrate, for example, glycerides of higher fatty acids [e.g., cacao butter, Witepsols (manufactured by Dynamit Nobel, Germany), etc.], glycerides of medium chain fatty acid [e.g., Miglyols (manufactured by Dynamit Nobel, Germany), etc.], or vegetable oils (e.g., sesame oil, soybean oil, cotton seed oil and the like), and the like are mentioned. Furthermore, as the aqueous substrate, for example, polyethylene glycol, propylene glycol and the like are mentioned, and as the aqueous gel substrate, for example, natural gums, cellulose derivatives, vinyl polymers, acrylic acid polymers and the like are mentioned.

As the above-mentioned sustained release preparation, sustained release microcapsules and the like are mentioned. The sustained release microcapsule can be produced by a method known *per se*.

The compound of the present invention is preferably molded into a preparation for oral administration such as a solid preparation (e.g., powder, granule, tablet, capsule) and the like, or molded into a preparation for rectal administration such as a suppository and the like. Particularly, a preparation for oral administration is preferable.

The concomitant drug can be made into the above-mentioned drug form depending on the kind of the drug.

The dosage of a combination agent of the present invention differs depending on the kind of a compound of the present invention, age, body weight, condition, drug form, administration method, administration period and the like, and for example, for one cancer patient (adult, body weight: about 60 kg), the combination agent is administered intravenously, at a dose of about 0.01 to about 1000 mg/kg/day, preferably about 0.01 to about 100 mg/kg/day, more preferably about 0.1 to about 100 mg/kg/day, particularly about 0.1 to about 50 mg/kg/day, especially about 1.5 to about 30 mg/kg/day, in terms of the compound of the present invention or the concomitant drug, respectively, once or several times in division a day. Of course, since the dose as described above varies depending on various conditions, amounts smaller than the above-mentioned dosage may sometimes be sufficient, further, amounts over that range sometimes have to be administered.

The amount of the concomitant drug can be set at any value unless side effects are problematical. The daily dosage in terms of the concomitant drug differs depending on the severity of the symptom, age, sex, body weight, sensitivity difference of the subject, administration period, interval, and nature, pharmacy, kind of the pharmaceutical preparation, kind of effective ingredient, and the like, and not particularly restricted, and the amount of a drug is, in the case of oral administration for example, usually from about 0.001 to 2000 mg, preferably from about 0.01 to 500 mg, further preferably from about 0.1 to 100 mg, per 1 kg of a mammal and this is usually administered once to 4-times in division a day.

In administration of a combination agent of the present invention, the compound of the present invention may be administered after administration of the concomitant drug or the concomitant drug may be administered after administration of the

compound of the present invention, though they may be administered simultaneously. When administered at a time interval, the interval differs depending on the effective ingredient to be administered, drug form and administration method, and for example, when the concomitant drug is administered first, a method in which the compound of the present invention is administered within time range of from 1 min to 3 days, preferably from 10 min to 1 day, more preferably from 15 min to 1 hr after administration of the concomitant drug is exemplified. When the compound of the present invention is administered first, a method in which the concomitant drug is administered within time range of from 1 min to 1 day, preferably from 10 min to 6 hrs, more preferably from 15 min to 1 hr after administration of the compound of the present invention is exemplified.

In a preferable administration method, for example, the concomitant drug which has been molded into an oral administration preparation is administered orally at a daily dose of about 0.001 to 200 mg/kg, and about 15 min later, the compound of the present invention which has been molded into an oral administration preparation is administered orally at a daily dose of about 0.005 to 100 mg/kg.

Furthermore, the compound of the present invention or the combination agent of the present invention can be used concurrently with a non-drug therapy. To be precise, the compound of the present invention and the combination agent of the present invention can be combined with a non-drug therapy such as (1) surgery, (2) hypertensive chemotherapy using angiotensin II etc., (3) gene therapy, (4) thermotherapy, (5) cryotherapy, (6) laser cauterization, (7) radiotherapy, and the like.

For example, by using the compound of the present invention or the combination agent of the present invention before or after an surgery and the like, or before or after a

combined treatment of two or three kinds thereof, effects such as prevention of emergence of resistance, prolongation of Disease-Free Survival, suppression of cancer metastasis or recurrence, prolongation of life and the like can be afforded.

In addition, it is possible to combine a treatment with the compound of the present invention or the combination agent of the present invention with a supportive therapy [(i) administration of antibiotic (e.g., β-lactam type such as pansporin and the like, macrolide type such as clarithromycin and the like etc.) for the complication with various infectious diseases, (ii) administration of total parenteral nutrition, amino acid preparation or general vitamin preparation for the improvement of malnutrition, (iii) administration of morphine for pain mitigation, (iv) administration of a pharmaceutical agent for ameliorating side effects such as nausea, vomiting, anorexia, diarrhea, leucopenia, thrombocytopenia, decreased hemoglobin concentration, hair loss, hepatopathy, renopathy, DIC, fever and the like and (v) administration of a pharmaceutical agent for suppressing multiple drug resistance of cancer and the like].

Preferably, the compound of the present invention or the combination agent of the present invention is administered orally (including sustained-release preparations), intravenously (including boluses, infusions and clathrates), subcutaneously and intramuscularly (including boluses, infusions and sustained-release preparations), transdermally, intratumorally or proximally before or after the above-described treatment is conducted.

As a period for administering the compound of the present invention or the combination agent of the present invention before the surgery, etc., for example, it can be administrated 1-time about 30 min to 24 hrs before the surgery, etc., or in 1 to 3 cycles about 3 months to 6 months before the surgery, etc. In this way, the surgery, etc. can be conducted easily because,

for example, a cancer tissue would be reduced by administering the compound of the present invention or the combination agent of the present invention before the surgery, and the like.

As a period for administering the compound of the present invention or the combination agent of the present invention after the surgery, etc., for example, it can be administrated repeatedly per a few weeks to 3 months, about 30 min to 24 hrs after the surgery, and the like. In this way, it enhances the effect of the surgery, etc. by administering the compound of the present invention or the combination agent of the present invention after the surgery, and the like.

Examples

The present invention is specifically explained in the following by way of Reference Examples, Examples, Formulation Examples, Experimental Examples and Test Examples, which are not to be construed as limitative.

In the Examples, preparative HPLC was performed as in the following.

Preparative HPLC tools: Gilson, Inc. High-Throughput purification system

column: YMC Combiprep ODS-A S-5 5 μm, 12 nM. 50 X 20 mm

detection method: UV 220 nm

Unless otherwise specified, the elution by column chromatography was performed under observation by TLC (thin layer chromatography) in Reference Examples and Examples. For TLC observation, 60F254 manufactured by Merck, or NH TLC plate manufactured by Fuji Silysia Chemical Ltd. was used as a TLC plate, and the solvent used as an elution solvent in column chromatography was used as a eluent. For detection, moreover, a UV detector was employed. As the silica gel for column chromatography, silica gel 60 (70-230 mesh) manufactured by Merck, silica gel manufactured by Fuji Silysia Chemical Ltd. or NH silica gel manufactured by Fuji Silysia Chemical Ltd. and the like were used. The room temperature generally means from

about 10°C to 35°C. For drying the extract, anhydrous sodium sulfate or anhydrous magnesium sulfate was used.

In Formulation Examples, the Japanese Pharmacopoeia 15th Edition (hereinafter to be referred to as The Japanese Pharmacopoeia) or Japanese Pharmaceutical Excipients 2003 compatible products were used as the preparation additives (e.g., lactose, cornstarch, magnesium stearate, crystalline cellulose).

Abbreviations in the Examples and Reference Examples mean the following.

NMR: nuclear magnetic resonance spectra

Hz: hertz

J: coupling constant

m: multiplet

q: quartet

t: triplet

d: doublet

s: singlet

br: broad

dt: double triplet

brs: broad singlet

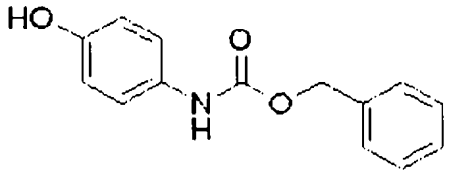
wt%: weight percent

DMSO: dimethyl sulfoxide

HATU: O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate

Reference Example 1

Production of benzyl (4-hydroxyphenyl)carbamate



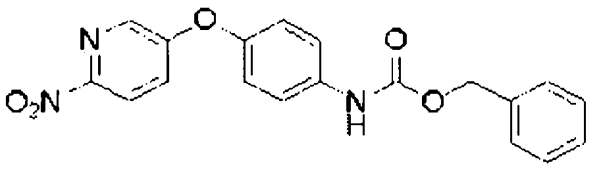
To a suspension of p-aminophenol (7.0 g, 63.9 mmol) in tetrahydrofuran (105 mL) was added saturated aqueous sodium hydrogen carbonate (70 mL), and benzyl chloroformate (12.0 g, 70.3 mmol) was added dropwise at 0°C. After stirring at room

temperature for 16 hr, the reaction mixture was extracted with ethyl acetate (200 mL). The organic layer was washed with saturated brine (100 mL) and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was washed with hexane/ethyl acetate (=4/1) and collected by filtration to give the title compound (8.2 g, 53%).

^{1}H-NMR ($CDCl_3$, 300MHz) δ 4.78 (1H, s), 5.19 (2H, s), 6.52 (1H, br s), 6.77 (2H, d, J = 9.2 Hz), 7.22 - 7.26 (2H, d, J = 8.1 Hz), 7.30 - 7.42 (5H, m).

Reference Example 2

Production of benzyl {4-[(6-nitropyridin-3-yl)oxy]phenyl}carbamate



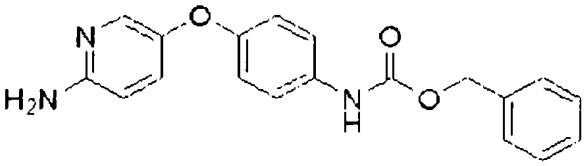
To a solution of benzyl (4-hydroxyphenyl)carbamate (1.44 g, 5.91 mmol) in N,N-dimethylformamide (10 mL) were added cesium carbonate (2.41 g, 7.39 mmol) and 5-bromo-2-nitropyridine (1.0 g, 4.93 mmol), and the mixture was stirred at room temperature for 16 hr. Water (40 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran (=2/1, 120 mL). The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (NH silica gel, hexane/ethyl acetate=3/1→1/3) to give the title compound (1.01 g, 56%).

^{1}H-NMR ($CDCl_3$, 300MHz) δ 5.22 (2H, s), 6.90 (1H, s), 7.07 (2H, d, J = 8.9 Hz), 7.34 - 7.43 (6H, m), 7.50 (2H, d, J = 8.9 Hz), 8.22 (1H, d, J = 8.7 Hz), 8.31 (1H, d, J = 2.7 Hz).

Reference Example 3

Production of benzyl {4-[(6-aminopyridin-3-

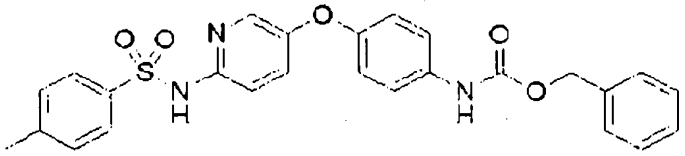
yl)oxy]phenyl}carbamate



To a solution of benzyl {4-[(6-nitropyridin-3-yl)oxy]phenyl}carbamate (5.99 g, 16.4 mmol) in ethanol (80 mL)/water (16 mL) were added reduced iron (5.8 g, 98.4 mmol) and calcium chloride (1.42 g, 11.5 mmol), and the mixture was heated under reflux for 16 hr. The reaction mixture was cooled to room temperature, filtered through celite, and washed with ethanol. The solvent was evaporated under reduced pressure, saturated aqueous sodium hydrogen carbonate (50 mL) was added to the residue, and the mixture was extracted with ethyl acetate (150 mL). The organic layer was washed with water and saturated brine in this order, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, a solid was precipitated with hexane/ethyl acetate (=2/1, 30 mL) and collected by filtration to give the title compound (4.43 g, 81%). The solvent of the filtrate was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (NH silica, hexane/ethyl acetate=3/1→1/3) to give the title compound (0.43 mg, 8%). ^{1}H-NMR (DMSO-d_6, 300MHz) δ 5.13 (2H, s), 5.82 (2H, s), 6.47 (1H, d, J = 8.9 Hz), 6.85 (2H, ddd, J = 10.3, 3.4, 2.2 Hz), 7.15 (1H, dd, J = 8.9, 2.8 Hz), 7.27 - 7.50 (7H, m), 7.71 (1H, d, J = 2.8 Hz), 9.67 (1H, br s).

Reference Example 4

Production of benzyl {4-[(6-{[(4-methylphenyl)sulfonyl]amino}pyridin-3-yl)oxy]phenyl}carbamate

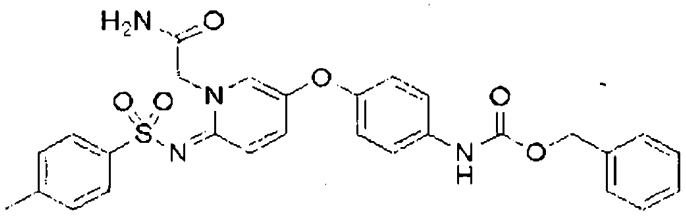


To a solution of benzyl {4-[(6-aminopyridin-3-

yl)oxy]phenyl}carbamate (20.0 g, 59.6 mmol) in pyridine (100 mL) was added p-toluenesulfonyl chloride (13.6 g, 71.6 mmol), and the mixture was stirred at room temperature for 16 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with 0.5N hydrochloric acid, water and saturated brine in this order, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with hexane/ethyl acetate and collected by filtration to give the title compound (23.8 g, 82%).
^{1}H-NMR (DMSO-d_6, 300MHz) δ 2.35 (3H, s), 5.14 (2H, s), 6.94 (2H, d, J = 9.0 Hz), 7.09 (1H, d, J = 9.0 Hz), 7.32 - 7.47 (10H, m), 7.76 (2H, d, J = 8.4 Hz), 7.91 (1H, d, J = 2.4 Hz), 9.76 (1H, s), 10.96 (1H, br s).

Reference Example 5

Production of benzyl (4-{[1-(2-amino-2-oxoethyl)-6-{[(4-methylphenyl)sulfonyl]imino}-1,6-dihydropyridin-3-yl]oxy}phenyl)carbamate



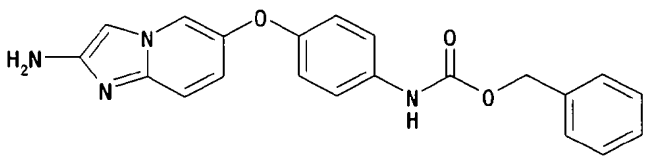
To a solution of benzyl {4-[(6-{[(4-methylphenyl)sulfonyl]amino}pyridin-3-yl)oxy]phenyl}carbamate (23.8 g, 48.6 mmol) in N,N-dimethylformamide (238 mL) were added N,N-diisopropylethylamine (11.0 mL, 63.2 mmol) and iodoacetamide (11.7 g, 63.2 mmol), and the mixture was stirred at room temperature for 24 hr. Water was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate/tetrahydrofuran. The combined organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with

hexane/ethyl acetate and collected by filtration to give the title compound (20.6 g, 78%).

^{1}H-NMR (DMSO-d_6, 300MHz) δ 2.34 (3H, s), 4.81 (2H, s), 5.14 (2H, s), 6.97 (2H, d, J = 9.0 Hz), 7.27 (2H, d, J = 8.1 Hz), 7.31 - 7.48 (9H, m), 7.63 - 7.68 (3H, m), 7.74 (1H, br s), 7.99 (1H, d, J = 3.0 Hz), 9.76 (1H, br s).

Reference Example 6

Production of benzyl {4-[(2-aminoimidazo[1,2-a]pyridin-6-yl)oxy]phenyl}carbamate

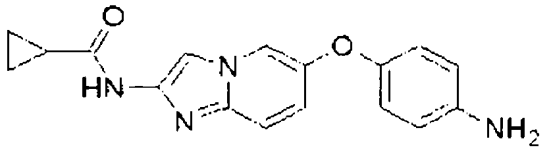


To a solution of benzyl (4-{[1-(2-amino-2-oxoethyl)-6-{[(4-methylphenyl)sulfonyl]imino}-1,6-dihydropyridin-3-yl]oxy}phenyl)carbamate (20.6 g, 37.7 mmol) in tetrahydrofuran (206 mL) was added trifluoroacetic acid anhydride (144 mL), and the mixture was stirred at room temperature for 48 hr. The solvent was evaporated under reduced pressure, ethyl acetate/tetrahydrofuran was added to the residue, washed with saturated aqueous sodium hydrogen carbonate and saturated brine in this order, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, ethanol (200 mL) and 4N aqueous sodium hydroxide solution (50 mL) were added to the residue, and the mixture was stirred at 45°C for 10 hr. The solvent was concentrated to about half under reduced pressure, water was added to the residue, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate→ethyl acetate/methanol=10/1) to give the title compound (9.0 g, 64%).

^{1}H-NMR (DMSO-d_6, 300MHz) δ 5.14 (2H, s), 5.28 (2H, br s), 6.84 (1H, dd, J = 9.5, 2.3 Hz), 6.93 - 7.01 (3H, m), 7.19 (1H, d, J = 9.5 Hz), 7.30 - 7.49 (7H, m), 8.19 (1H, d, J = 2.3 Hz), 9.73 (1H, s).

Reference Example 7

Production of N-[6-(4-aminophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide

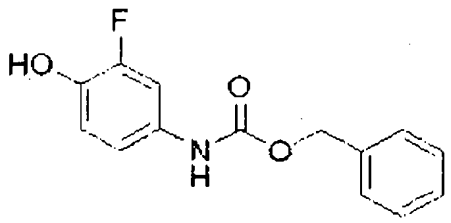


To a solution of benzyl [4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)phenyl]carbamate (500 mg, 1.13 mmol) in 1,2-dimethoxyethane (15 mL) was added 0.15 mol/L aqueous barium hydroxide solution (10 mL), and the mixture was stirred at 90°C for 36 hr. After cooling to room temperature, the reaction mixture was adjusted to pH about 5 with citric acid, and to pH about 10 with saturated aqueous sodium hydrogen carbonate. The mixture was extracted with ethyl acetate/tetrahydrofuran, and the organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=50/50→0/100) to give the title compound (223 g, 64%).

^{1}H-NMR (DMSO-d_6, 300MHz) δ 0.76 - 0.82 (4H, m), 1.85 - 1.96 (1H, m), 4.95 (2H, m), 6.57 (2H, d, J = 8.7 Hz), 6.79 (2H, d, J = 8.7 Hz), 6.96 - 7.11 (1H, m), 7.38 (1H, d, J = 9.6 Hz), 7.99 (1H, s), 8.25 (1H, d, J = 1.8 Hz), 10.89 (1H, s).

Reference Example 8

Production of benzyl (3-fluoro-4-hydroxyphenyl)carbamate

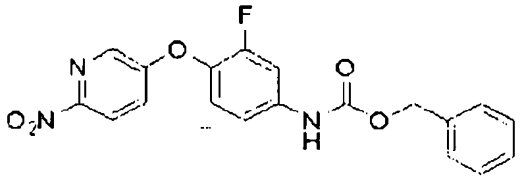


To a suspension of 4-amino-2-fluorophenol (60 g, 472 mmol) in tetrahydrofuran/water (=1/1, 600 mL) was added sodium hydrogen carbonate (43.6 g, 519 mmol), and benzyl chloroformate (74.1 mL, 519 mmol) was added dropwise at 0°C. The mixture was stirred at room temperature for 16 hr, 2N hydrochloric acid (150 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, the residue was washed with hexane/diethyl ether(=1/1) and collected by filtration to give the title compound (82.5 g, 67%). The solvent of the filtrate was evaporated under reduced pressure, and the residue was washed with hexane/diethyl ether(=1/1) and collected by filtration to give the title compound (17.7 g, 14%).

^{1}H-NMR (DMSO-d_6, 300MHz) δ 5.12 (2H, s), 6.85 (1H, t, J = 9.3 Hz), 6.97 - 7.04 (1H, m), 7.25 - 7.45 (6H, m), 9.48 (1H, br s), 9.64 (1H, br s).

Reference Example 9

Production of benzyl {3-fluoro-4-[(6-nitropyridin-3-yl)oxy]phenyl}carbamate



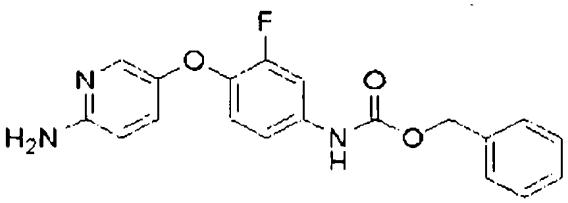
To a solution of benzyl (3-fluoro-4-hydroxyphenyl)carbamate (80 g, 252 mmol) in dimethyl sulfoxide (600 mL) were added cesium carbonate (123 g, 378 mmol) and 5-chloro-2-nitropyridine (40 g, 252 mmol), and the mixture was

stirred at room temperature for 3 hr. Saturated aqueous sodium hydrogen carbonate (1000 mL) and water (1000 mL) were added to the reaction mixture, and the mixture was extracted twice with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with hexane/ethyl acetate(=3/1) and collected by filtration to give the title compound (79.8 g, 83%).

^{1}H-NMR ($CDCl_3$, 300MHz) δ 5.23 (2H, S), 6.82 (1H, s), 7.05 - 7.19 (2H, m), 7.31 - 7.44 (6H, m), 7.59 (1H, dd, J = 12.3, 2.4 Hz), 8.24 (1H, d, J = 9.0 Hz), 8.32 (1H, d, J = 2.7 Hz).

Reference Example 10

Production of benzyl {4-[(6-aminopyridin-3-yl)oxy]-3-fluorophenyl}carbamate



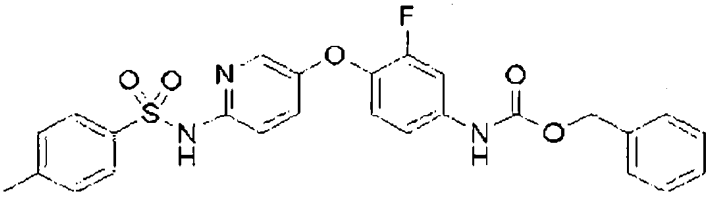
To a solution of benzyl {4-[(6-nitropyridin-3-yl)oxy]phenyl}carbamate (40 g, 104 mmol) in ethanol (1020 mL)/water (180 mL) were added reduced iron (29.1 g, 522 mmol) and calcium chloride (5.8 g, 52 mmol), and the mixture was heated under reflux for 8 hr. The reaction mixture was cooled to room temperature, filtered through celite, and washed with ethanol. The solvent was evaporated under reduced pressure, water (200 mL) was added to the residue, and the mixture was extracted with ethyl acetate (800 mL). The organic layer was washed with water and saturated brine in this order, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and a solid was precipitated with hexane/ethyl acetate (=3/1) and collected by filtration to give the title compound (28.2 g, 76%).

^{1}H-NMR (DMSO-d_6, 300MHz) δ 5.15 (2H, s), 5.82 (2H, s), 6.45 (1H,

d, J = 8.7 Hz), 6.96 (1H, t, J = 9.0 Hz), 7.11 - 7.19 (2H, m), 7.30 - 7.53 (6H, m), 7.70 (1H, d, J = 2.7 Hz), 9.94 (1H, s).

Reference Example 11

Production of benzyl {3-fluoro-4-[(6-{[(4-methylphenyl)sulfonyl]amino}pyridin-3-yl)oxy]phenyl}carbamate

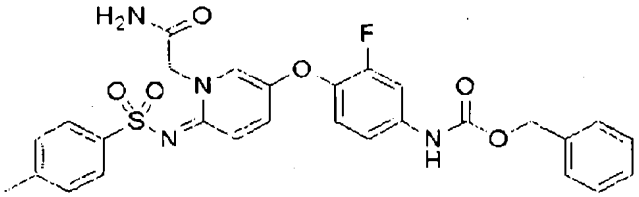


To a solution of benzyl {4-[(6-aminopyridin-3-yl)oxy]-3-fluorophenyl}carbamate (28.2 g, 79.8 mmol) in pyridine (141 mL) was added p-toluenesulfonyl chloride (18.3 g, 98.5 mmol), and the mixture was stirred at room temperature for 16 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with 0.5N hydrochloric acid, water and saturated brine in this order, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with hexane/ethyl acetate and collected by filtration to give the title compound (29.2 g, 72%).

^{1}H-NMR (DMSO-d_6, 300MHz) δ 2.35 (3H, s), 5.16 (2H, s), 7.05 - 7.24 (2H, m), 7.28 - 7.46 (9H, m), 7.50 - 7.58 (1H, m), 7.75 (2H, d, J = 8.4 Hz), 7.91 (1H, d, J = 2.7 Hz), 10.03 (1H, s), 10.95 (1H, br s).

Reference Example 12

Production of benzyl (4-{[(6Z)-1-(2-amino-2-oxoethyl)-6-{[(4-methylphenyl)sulfonyl]imino}-1,6-dihydropyridin-3-yl]oxy}-3-fluorophenyl)carbamate



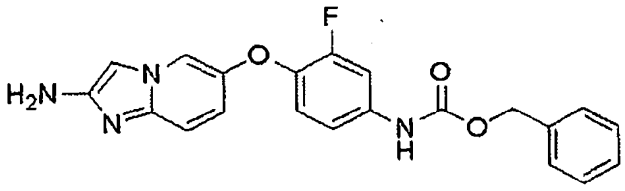
To a solution of benzyl {3-fluoro-4-[(6-{[(4-methylphenyl)sulfonyl]amino}pyridin-3-yl)oxy]phenyl}carbamate

(35.0 g, 69.0 mmol) in N,N-dimethylformamide (350 mL) were added N,N-diisopropylethylamine (15.6 mL, 89.6mmol) and iodoacetamide (16.6 g, 89.6 mmol), and the mixture was stirred at room temperature for 24 hr. Water was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate/tetrahydrofuran. The combined organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with hexane/ethyl acetate and collected by filtration to give the title compound (28.0 g, 72%).

^{1}H-NMR (DMSO-d_6, 300MHz) δ 2.34 (3H, s), 4.80 (2H, s), 5.16 (2H, s), 7.08 - 7.46 (12H, m), 7.50 - 7.58 (1H, m), 7.64 - 7.74 (3H, m), 7.95 (1H, d, J = 3.0 Hz), 10.03 (1H, s).

Reference Example 13

Production of benzyl {4-[(2-aminoimidazo[1,2-a]pyridin-6-yl)oxy]-3-fluorophenyl}carbamate



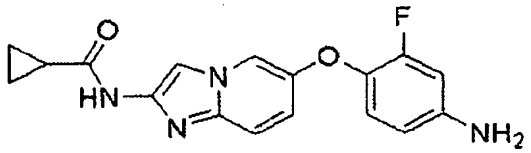
To a solution of benzyl (4-{[1-(2-amino-2-oxoethyl)-6-{[(4-methylphenyl)sulfonyl]imino}-1,6-dihydropyridin-3-yl]oxy}-3-fluorophenyl)carbamate (28.0 g, 49.6 mmol) in tetrahydrofuran (280 mL) was added trifluoroacetic acid anhydride (196 mL), and the mixture was stirred at room temperature for 3 hr. The solvent was evaporated under reduced pressure, ethyl acetate/tetrahydrofuran was added to the residue, and the mixture was washed with saturated aqueous sodium hydrogen carbonate and saturated brine in this order, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, ethanol(140 mL) and 4N aqueous sodium hydroxide solution (40 mL) were added to

the residue, and the mixture was stirred at room temperature for 4 hr. The solvent was concentrated under reduced pressure to about 1/3, water was added to the residue, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/methanol=10/0→9/1) to give the title compound (10.0 g, 51%).

^{1}H-NMR (DMSO-d_6, 300MHz) δ 5.03 (2H, s), 5.16 (2H, s), 6.85 (1H, dd, J = 9.5, 2.3 Hz), 6.97 (1H, s), 7.08 - 7.23 (3H, m), 7.32 - 7.45 (5H, m), 7.54 (1H, dd, J = 13.5, 2.4 Hz), 8.14 (1H, d, J = 1.8 Hz), 9.99 (1H, s).

Reference Example 14

Production of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide



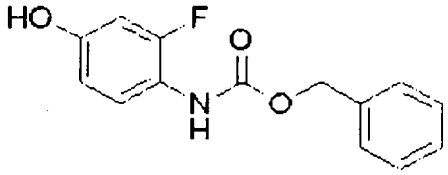
To a suspension of benzyl [4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]carbamate (18.0 g, 39.1 mmol) in 1,2-dimethoxyethane (360 mL) was added 0.15 mol/L aqueous barium hydroxide solution (240 mL), and the mixture was stirred at 90°C for 16 hr. After cooling to room temperature, the reaction mixture was adjusted to about pH 8 with 2N hydrochloric acid, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with ethyl acetate and collected by filtration to give the title compound (9.1 g, 71%).

^{1}H-NMR (DMSO-d_6, 300MHz) δ 0.74 - 0.81 (4H, m), 1.85 - 1.94 (1H,

m), 5.34 (2H, s), 6.38 (1H, dd, J = 8.7 1.2 Hz), 6.49 (1H, dd, J = 13.5, 2.4 Hz), 6.90 - 7.05 (2H, m), 7.38 (1H, d, J = 9.6 Hz), 8.00 (1H, s), 8.22 (1H, d, J = 2.1 Hz), 10.88 (1H, s).

Reference Example 15

Production of benzyl (2-fluoro-4-hydroxyphenyl)carbamate

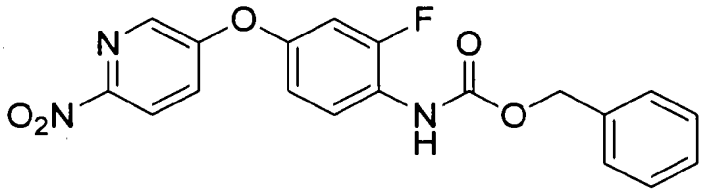


To a suspension of 4-amino-3-fluorophenol (50 g, 39.3 mmol) in tetrahydrofuran/water (=1/1, 500 mL) was added sodium hydrogen carbonate (36.3 g, 39.3 mmol), and benzyl chloroformate (62 mL, 43.3 mmol) was added dropwise at room temperature. The mixture was stirred at room temperature for 16 hr, and extracted with ethyl acetate (1000 mL). The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with hexane/diethyl ether(=1/1) and collected by filtration to give the title compound (94.5 g, 92%).

^{1}H-NMR (DMSO-d_6, 300MHz) δ 5.10 (2H, s), 6.53 - 6.64 (2H, m), 7.10 - 7.26 (1H, m), 7.30 - 7.43 (5H, m), 9.02 (1H, br s), 9.76 (1H, s).

Reference Example 16

Production of benzyl {2-fluoro-4-[(6-nitropyridin-3-yl)oxy]phenyl}carbamate



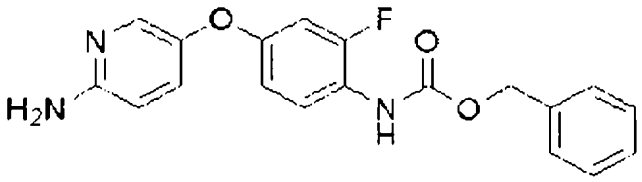
To a solution of benzyl (2-fluoro-4-hydroxyphenyl)carbamate (79 g, 303 mmol) in dimethyl sulfoxide (480 mL) were added cesium carbonate (123 g, 378 mmol) and 5-chloro-2-nitropyridine (40 g, 252 mmol), and the mixture was

stirred at room temperature for 6 hr. Water (1000 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with hexane/ethyl acetate(=3/1) and collected by filtration to give the title compound (74 g, 77%).

^{1}H-NMR (DMSO-d_6, 300MHz) δ 5.17 (2H, s), 7.05 - 7.12 (1H, m), 7.27 - 7.46 (6H, m), 7.66 - 7.78 (2H, m), 8.34 (1H, d, J = 8.6 Hz), 8.46 (1H, d, J = 2.9 Hz), 9.57 (1H, s).

Reference Example 17

Production of benzyl {4-[(6-aminopyridin-3-yl)oxy]-2-fluorophenyl}carbamate



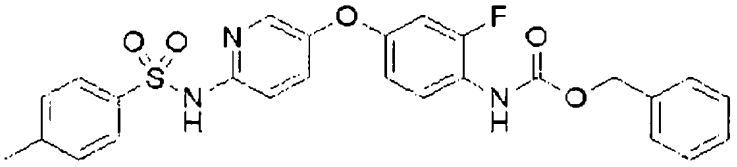
To a solution of benzyl {2-fluoro-4-[(6-nitropyridin-3-yl)oxy]phenyl}carbamate (40 g, 104.3 mmol) in ethanol (1020 mL)/water (180 mL) were added reduced iron (29.1 g, 521.7 mmol) and calcium chloride (5.8 g, 52.2 mmol), and the mixture was heated under reflux for 8 hr. The reaction mixture was cooled to room temperature, filtered through celite, and washed with ethanol. The solvent was evaporated under reduced pressure, water (200 mL) was added to the residue, and the mixture was extracted with ethyl acetate (800 mL). The organic layer was washed with water and saturated brine in this order, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, hexane/ethyl acetate (=3/1) was added, and the precipitate was collected by filtration to give the title compound (28.2 g, 76%).

^{1}H-NMR (DMSO-d_6, 300MHz) δ 5.13 (2H, s), 5.92 (2H, s), 6.49 (1H, d, J = 9.0 Hz), 6.63 - 6.68 (1H, m), 6.81 (1H, dd, J = 11.9,

2.9 Hz), 7.22 (1H, dd, J = 8.7, 2.9 Hz), 7.30 - 7.48 (6H, m), 7.76 (1H, d, J = 2.9 Hz), 9.28 (1H, br s).

Reference Example 18

Production of benzyl {2-fluoro-4-[(6-{[(4-methylphenyl)sulfonyl]amino}pyridin-3-yl)oxy]phenyl}carbamate

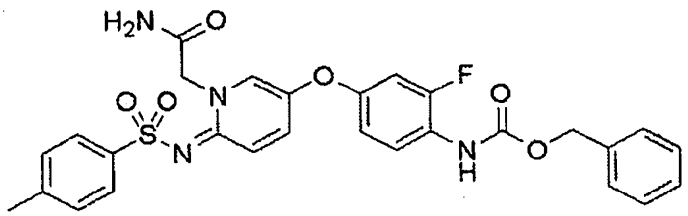


To a solution of benzyl {4-[(6-aminopyridin-3-yl)oxy]-2-fluorophenyl}carbamate (32 g, 90.6 mmol) in pyridine (141 mL) was added p-toluenesulfonyl chloride (18.3 g, 108.7 mmol), and the mixture was stirred at 80°C for 3 hr. After cooling to room temperature, pyridine was evaporated under reduced pressure, water was added to the residue, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with hexane/ethyl acetate and collected by filtration to give the title compound (32.0 g, 70%).

^{1}H-NMR (DMSO-d_6, 300MHz) δ 2.36 (3H, s), 5.13 (2H, s), 6.73 - 6.79 (1H, m), 6.95 (1H, dd, J = 11.6, 2.9 Hz), 7.12 (1H, d, J = 9.0 Hz), 7.30 - 7.56 (9H, m), 7.78 (2H, d, J = 8.4 Hz), 8.00 (1H, d, J = 2.7 Hz), 9.37 (1H, s), 11.04 (1H, br s).

Reference Example 19

Production of benzyl (4-{[(6Z)-1-(2-amino-2-oxoethyl)-6-{[(4-methylphenyl)sulfonyl]imino}-1,6-dihydropyridin-3-yl]oxy}-2-fluorophenyl)carbamate

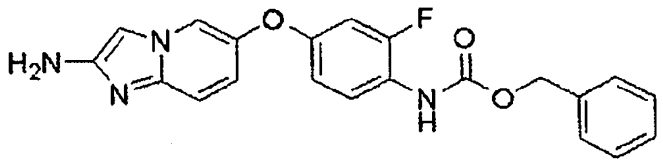


To a solution of benzyl {2-fluoro-4-[(6-{[(4-methylphenyl)sulfonyl]amino}pyridin-3-yl)oxy]phenyl}carbamate (32.0 g, 63.1 mmol) in N,N-dimethylformamide (320 mL) were added N,N-diisopropylethylamine (14.3 mL, 82.0 mmol) and iodoacetamide (15.2 g, 82.0 mmol), and the mixture was stirred at room temperature for 24 hr. Water was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate/tetrahydrofuran. The combined organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with hexane/ethyl acetate and collected by filtration to give the title compound (34.2 g, 96%).

^{1}H-NMR (DMSO-d_6, 300MHz) δ 2.34 (3H, s), 4.81 (2H, s), 5.13 (2H, s), 6.79 - 6.87 (1H, m), 7.02 (1H, dd, J = 11.7, 2.9 Hz), 7.28 (1H, d, J = 7.8 Hz), 7.30 - 7.43 (8H, m), 7.53 - 7.59 (1H, m), 7.65 - 7.75 (4H, m), 8.12 (1H, d, J = 3.0 Hz), 9.38 (1H, br s).

Reference Example 20

Production of benzyl {4-[(2-aminoimidazo[1,2-a]pyridin-6-yl)oxy]-2-fluorophenyl}carbamate



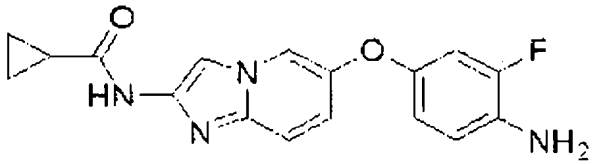
To a solution of benzyl (4-{[1-(2-amino-2-oxoethyl)-6-{[(4-methylphenyl)sulfonyl]imino}-1,6-dihydropyridin-3-yl]oxy}-2-fluorophenyl)carbamate (28.0 g) in tetrahydrofuran (280 mL) was added trifluoroacetic acid anhydride (196 mL), and the mixture was stirred at room temperature for 3 hr. The solvent was evaporated under reduced pressure, ethyl acetate/tetrahydrofuran was added to the residue, and the mixture was washed with saturated aqueous sodium hydrogen carbonate and saturated brine in this order, dried over

anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, ethanol (140 mL) and 4N aqueous sodium hydroxide solution (40 mL) were added to the residue, and the mixture was stirred at room temperature for 4 hr. The solvent was concentrated under reduced pressure to 1/3, water was added to the residue, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/methanol=10/1→9/1) to give the title compound (12.1 g, 51%).

^{1}H-NMR (DMSO-d_6, 300MHz) δ 5.13 (4H, s), 6.76 - 6.82 (1H, m), 6.87 (1H, dd, J = 9.5, 2.3 Hz), 6.91 - 6.96 (1H, m), 7.00 (1H, s), 7.20 (1H, d, J = 9.3 Hz), 7.33 - 7.44 (6H, m), 7.46 - 7.55 (1H, m), 8.32 (1H, d, J = 1.8 Hz), 9.34 (1H, br s).

Reference Example 21

Production of N-[6-(4-amino-3-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide



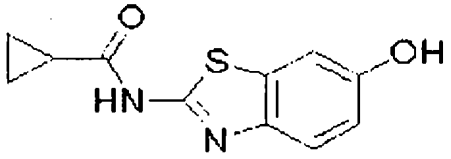
To a suspension of benzyl [4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-2-fluorophenyl]carbamate (9.7 g, 21.1 mmol) in 1,2-dimethoxyethane (291 mL) was added 0.15 mol/L aqueous barium hydroxide solution (194 mL), and the mixture was stirred at 90°C for 16 hr. After cooling to room temperature, the reaction mixture was adjusted to about pH 8 with 2N hydrochloric acid, and extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and filtered. The solvent was evaporated under reduced pressure,

and the residue was washed with ethyl acetate and collected by filtration to give the title compound (4.3 g, 63%).

^{1}H-NMR (DMSO-d_6, 300MHz) δ 0.78 - 0.82 (4H, m), 1.86 - 1.94 (1H, m), 4.98 (2H, s), 6.64 - 6.90 (3H, m), 7.02 (1H, dd, J = 9.6, 2.4 Hz), 7.40 (1H, d, J = 9.9 Hz), 8.01 (1H, s), 8.34 (1H, d, J = 1.5 Hz), 10.92 (1H, s).

Reference Example 22

Production of N-(6-hydroxy-1,3-benzothiazol-2-yl)cyclopropanecarboxamide

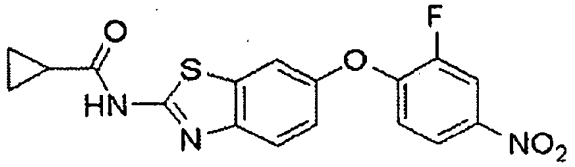


To a solution of 2-amino-1,3-benzothiazol-6-ol (4.99 g, 30.0 mmol) in N,N-dimethylacetamide (20 mL) was added cyclopropanecarbonyl chloride (4.08 mL, 45.0 mmol) at 0°C, and the mixture was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed 3 times with water, dried over anhydrous sodium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with ethyl acetate/diisopropyl ether and collected by filtration to give the title compound (3.22 g, 13.7 mmol) as a white solid.

^{1}H-NMR (DMSO-d_6, 300MHz) δ 0.87 - 0.97 (4H, m), 1.92 - 2.01 (1H, m), 6.87 (1H, dd, J = 8.7, 2.3 Hz), 7.25 (1H, d, J = 2.3 Hz), 7.52 (1H, d, J = 8.7 Hz), 9.53 (1H, br s), 12.41 (1H, br s).

Reference Example 23

Production of N-[6-(2-fluoro-4-nitrophenoxy)-1,3-benzothiazol-2-yl]cyclopropanecarboxamide

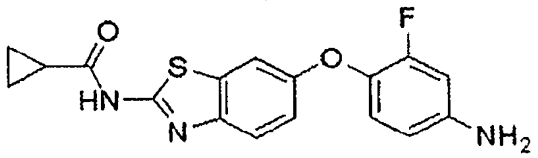


A suspension of N-(6-hydroxy-1,3-benzothiazol-2-yl)cyclopropanecarboxamide (1.17 g, 5.00 mmol), 1,2-difluoro-4-nitrobenzene (0.96 g, 6.00 mmol) and cesium carbonate (3.26 g, 10.0 mmol) in dimethyl sulfoxide (10 mL) was stirred at 50°C for 5 hr. After cooling to room temperature, water was added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate/tetrahydrofuran. The organic layer was washed with water, dried over anhydrous sodium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with ethyl acetate and collected by filtration to give the title compound (1.22 g, 65%) as a pale-yellow solid.

^{1}H-NMR (DMSO-d_6, 300MHz) δ 0.92 - 0.99 (4H, m), 1.96 - 2.03 (1H, m), 7.10 - 7.17 (1H, m), 7.30 (1H, dd, J = 8.9, 2.6 Hz), 7.82 (1H, d, J = 8.9 Hz), 7.90 (1H, d, J = 2.6 Hz), 8.04 - 8.09 (1H, m), 8.36 (1H, dd, J = 10.8, 2.7 Hz), 12.71 (1H, br s).

Reference Example 24

Production of N-[6-(4-amino-2-fluorophenoxy)-1,3-benzothiazol-2-yl]cyclopropanecarboxamide



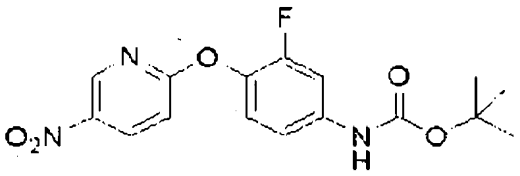
To a suspension of N-[6-(2-fluoro-4-nitrophenoxy)-1,3-benzothiazol-2-yl]cyclopropanecarboxamide (1.15 g, 3.07 mmol) in ethanol (50 mL)/water (10 mL) were added ammonium chloride (1.64 g, 30.7 mmol) and reduced iron (856 g, 15.3 mmol), and the mixture was heated under reflux for 4 hr. The reaction mixture was cooled to room temperature, filtered through celite, and washed with a mixed solution of ethanol/water. The solvent was evaporated under reduced pressure, 1N aqueous sodium hydroxide solution was added to the residue, and the mixture was extracted 3 times with ethyl acetate/tetrahydrofuran. The combined organic layer was dried

over anhydrous sodium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with ethyl acetate/diisopropyl ether and collected by filtration to give the title compound (644 mg, 61%) as a pale-yellow solid.

^{1}H-NMR (DMSO-d_6, 300MHz) δ 0.89 - 0.95 (4H, m), 1.92 - 2.02 (1H, m), 5.35 (2H, s), 6.35 - 6.43 (1H, m), 6.49 (1H, dd, J = 13.2, 2.7 Hz), 6.90 - 7.02 (2H, m), 7.40 (1H, d, J = 2.6 Hz), 7.65 (1H, d, J = 8.7 Hz), 12.54 (1H, br s).

Reference Example 25

Production of tert-butyl {3-fluoro-4-[(5-nitropyridin-2-yl)oxy]phenyl}carbamate

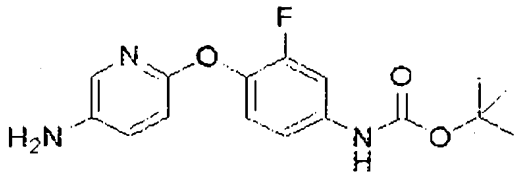


To a solution of tert-butyl (3-fluoro-4-hydroxyphenyl)carbamate (17.2 g, 75.7 mmol) in dimethyl sulfoxide (100 mL) were added 2-chloro-5-nitropyridine (10 g, 63.1 mmol) and cesium carbonate (30.8 g, 94.6 mmol), and the mixture was stirred at room temperature for 4 hr. Water was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with hexane/ethyl acetate(=5/1) and collected by filtration to give the title compound (17.0 g, 77%).

^{1}H-NMR ($CDCl_3$, 300MHz) δ 1.53 (9H, s), 6.57 (1H, s), 7.00 - 7.16 (3H, m), 7.52 (1H, dd, J = 12.3, 2.1 Hz), 8.49 (1H, dd, J = 9.0, 2.9 Hz), 9.00 (1H, d, J = 2.9 Hz).

Reference Example 26

Production of tert-butyl {4-[(5-aminopyridin-2-yl)oxy]-3-fluorophenyl}carbamate

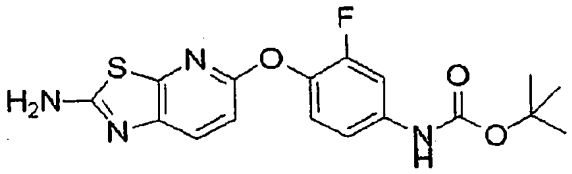


To a suspension of tert-butyl {3-fluoro-4-[(5-nitropyridin-2-yl)oxy]phenyl}carbamate (15 g, 42.9 mmol) in methanol (300 mL) was added 5 wt% palladium/carbon (3.0 g), and the mixture was stirred at room temperature for 8 hr under a hydrogen atmosphere. After nitrogen substitution, insoluble material was collected by filtration and washed with methanol. The solvent of the filtrate was evaporated under reduced pressure, water was added to the residue, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure to give the title compound (12.3 g, 90%).

^{1}H-NMR (DMSO-d_6, 300MHz) δ 1.48 (9H, s), 4.98 (2H, s), 6.76 (1H, d, J = 9.0 Hz), 7.04 - 7.10 (2H, m), 7.13 - 7.19 (1H, m), 7.40 - 7.47 (2H, m), 9.51 (1H, s).

Reference Example 27

Production of tert-butyl {4-[(2-amino[1,3]thiazolo[5,4-b]pyridin-5-yl)oxy]-3-fluorophenyl}carbamate



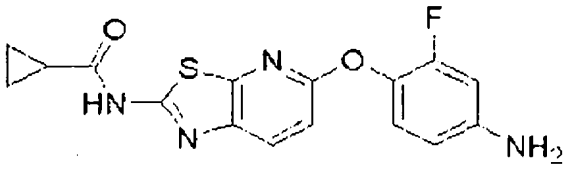
To a solution of potassium thiocyanate (6.1 g, 62.6 mmol) in acetic acid (60 mL) was added a solution of tert-butyl {4-[(5-aminopyridin-2-yl)oxy]-3-fluorophenyl}carbamate (5.0 g, 15.7 mmol) in acetic acid (40 mL) at 0°C. A solution of bromine (3.25 g, 20.4 mmol) in acetic acid (20 mL) was added at 0°C, and the mixture was stirred at room temperature

for 6 hr. Acetic acid was evaporated under reduced pressure, saturated aqueous sodium hydrogen carbonate was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate alone) to give the title compound (2.07 g, 35%).

^{1}H-NMR (DMSO-d_6, 300MHz) δ 1.49 (9H, s), 6.92 (1H, d, J = 8.7 Hz), 7.17 - 7.23 (2H, m), 7.46 - 7.53 (1H, m), 7.57 (2H, s), 7.70 (1H, d, J = 8.7 Hz), 9.59 (1H, s).

Reference Example 28

Production of N-[5-(4-amino-2-fluorophenoxy)[1,3]thiazolo[5,4-b]pyridin-2-yl]cyclopropanecarboxamide



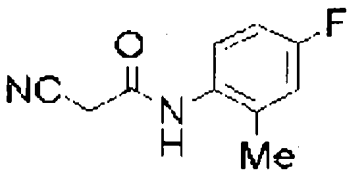
To a solution of tert-butyl [4-({2-[(cyclopropylcarbonyl)amino][1,3]thiazolo[5,4-b]pyridin-5-yl}oxy)-3-fluorophenyl]carbamate (0.50 g, 1.12 mmol) in trifluoroacetic acid (10 mL) was added anisole (0.5 mL), and the mixture was stirred at 0°C for 2 hr. Trifluoroacetic acid was evaporated under reduced pressure, ethyl acetate was added to the residue, and the mixture was washed with saturated aqueous sodium hydrogen carbonate and saturated brine in this order, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=1/1→1/9) to give the title compound (294 mg, 76%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300MHz) δ 0.90 - 0.99 (4H, m), 1.95 - 2.05 (1H, m), 5.34 (2H, s), 6.36 - 6.51 (2H, m), 6.97 (1H, t, J = 8.7 Hz), 7.06 (1H, d, J = 8.7 Hz), 8.11 (1H, d, J = 8.7 Hz), 12.64

(1H, br s).

Reference Example 29

Production of 2-cyano-N-(4-fluoro-2-methylphenyl)acetamide

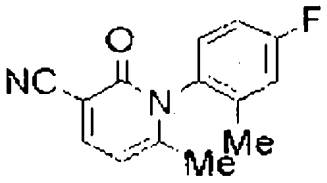


4-Fluoro-2-methylaniline (3.9 g, 31 mmol) was added to ethyl cyanoacetate (5.3 g, 46 mmol) and the mixture was stirred at 150°C for 4 hr. After cooling to room temperature, hexane-ethyl acetate was added to the reaction mixture, and the precipitate was collected by filtration to give the title compound (4.0 g, 67%) as a pale-yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.20 (3H, s), 3.91 (2H, d, J = 10.2 Hz), 7.02 (1H, td, J=8.6, 2.9 Hz), 7.11 (1H, dd, J=9.7, 2.9 Hz), 7.36 (1H, dd, J = 8.8, 5.6 Hz), 9.69 (1H, s).

Reference Example 30

Production of 1-(4-fluoro-2-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile



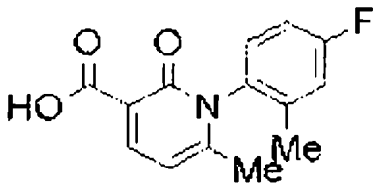
2-Cyano-N-(4-fluoro-2-methylphenyl)acetamide (2.0 g, 10 mmol) and 4-methoxybut-3-en-2-one (1.4 mL, 13 mmol) were suspended in 2-(2-methoxyethoxy)ethanol (20 mL), and 1,4-diazabicyclo[2.2.2]octane (1.2 g, 10 mmol) was added. The mixture was stirred at 120°C for 6 hr, and cooled to room temperature. The mixture was diluted with ethyl acetate (40 mL), and washed with saturated aqueous sodium hydrogen carbonate solution. Then the organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. Hexane-ethyl acetate was added to the residue, and the resulting precipitate was collected by

filtration to give the title compound (630 mg, 25%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.97 (3H, s), 1.98 (3H, s), 6.53 (1H, d, J=7.6 Hz), 7.17 - 7.28 (1H, m), 7.29 - 7.40 (2H, m), 8.19 (1H, d, J=7.4 Hz).

Reference Example 31

Production of 1-(4-fluoro-2-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid

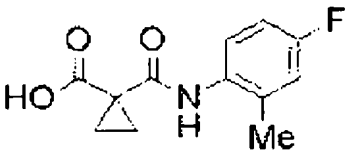


1-(4-fluoro-2-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (590 mg, 2.9 mmol) was suspended in water (3.0 mL), conc. sulfuric acid (3.0 mL) was slowly added dropwise. The mixture was stirred overnight at 100°C, and allowed to cool to room temperature. The reaction system was basified with aqueous sodium hydroxide solution (8N) and washed with ethyl acetate. The aqueous layer was acidified with hydrochloric acid (1N), and extracted twice with ethyl acetate. The mixed organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. Hexane-ethyl acetate was added to the residue, and the resulting precipitate was collected by filtration to give the title compound (480 mg, 75%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.99 (3H, s), 2.06 (3H, s), 6.84 (1H, d, J=7.6 Hz), 7.22 - 7.32 (1H, m), 7.38 (1H, dd, J=9.6, 3.0 Hz), 7.44 (1H, dd, J=8.7, 5.5 Hz), 8.44 (1H, d, J=7.6 Hz), 14.14 (1H, s).

Reference Example 32

Production of 1-[(4-fluoro-2-methylphenyl)carbamoyl]cyclopropanecarboxylic acid

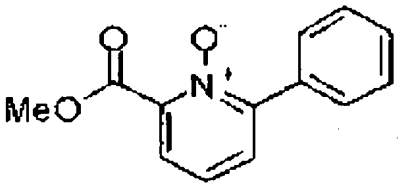


Cyclopropane-1,1-dicarboxylic acid (1.0 g, 8.0 mmol) was suspended in tetrahydrofuran (20 mL), and triethylamine (1.1 mL, 8.0 mmol) was added. After stirring at room temperature for 1 hr, the mixture was cooled in an ice bath. Under ice-cooling, thionyl chloride (0.58 mL, 8.0 mmol) was added dropwise, and the mixture was stirred as it was for 30 min. To this mixture was dropwise added a solution of 4-fluoro-2-methylaniline (3.9 g, 31 mmol) in tetrahydrofuran (2.0 mL) under ice-cooling, and the reaction mixture was warmed to room temperature and stirred overnight. An aqueous sodium hydroxide solution (1N, 50 mL) was added, and the mixture was washed twice with ethyl acetate. The aqueous layer was acidified with hydrochloric acid (1N), and the mixture was extracted twice with ethyl acetate. The mixed organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. Hexane-ethyl acetate was added to the residue, and the precipitate was collected by filtration to give the title compound (1.1 g, 60%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.52 (4H, s), 2.27 (3H, s), 6.99 (1H, td, J=8.7, 3.0 Hz), 7.10 (1H, dd, J=9.7, 2.9 Hz), 7.77 (1H, dd, J=8.9, 5.7 Hz), 10.66 (1H, s), 13.35 (1H, br s).

Reference Example 33

Production of methyl 6-phenylpyridine-2-carboxylate 1-oxide



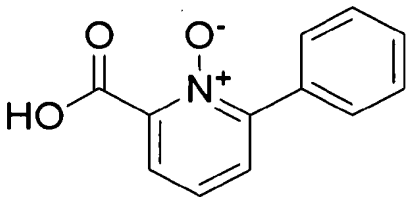
To a solution of methyl 6-phenylpyridine-2-carboxylate (509 mg, 6.24 mmol) in dichloromethane (5 mL) was added m-chloroperbenzoic acid (purity: 69-75%, 2.87 g, 12.5 mmol), and

the mixture was stirred at room temperature for 3 days. Saturated sodium thiosulfate aqueous solution was added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (NH silica gel, ethyl acetate/hexane=1/2→1/1) to give the title compound (142 mg, 10%) as a colorless oil.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 3.88 (3H, s), 7.45 - 7.55 (4H, m), 7.69 (1H, dd, J = 7.8, 2.1 Hz), 7.76 (1H, dd, J = 7.8, 2.1 Hz), 7.78 - 7.84 (2H, m).

Reference Example 34

Production of 6-phenylpyridine-2-carboxylic acid 1-oxide

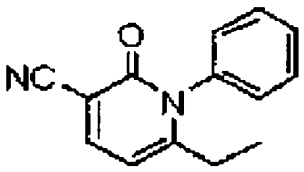


To a solution of methyl 6-phenylpyridine-2-carboxylate 1-oxide in methanol (2 mL) was added 1N aqueous sodium hydroxide solution (1 mL), and the mixture was stirred at room temperature for 3 hr. The reaction mixture was concentrated, 1N hydrochloric acid was added, the precipitate was collected by filtration, and washed with water to give the title compound (120 mg, 90%) as white crystals.

^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.52 - 7.63 (3H, m), 7.76 - 7.85 (2H, m), 7.91 - 8.09 (2H, m), 8.35 (1H, dd, J = 7.7, 2.3 Hz).

Reference Example 35

Production of 6-ethyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carbonitrile

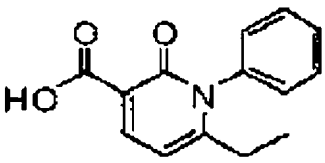


A solution of 2-cyano-N-phenylacetamide (1.08 g, 6.73 mmol), (1E)-1-methoxypent-1-en-3-one (1.0 g, 8.76 mmol) and 1,4-diazabicyclo[2.2.2]octane (755 mg, 6.73 mmol) in 2-(2-methoxyethoxy)ethanol (10 mL) was stirred with heating at 120°C for 7 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (NH silica gel, ethyl acetate/hexane=2/1→4/1) to give the title compound (412 mg, 27%) as a pale-brown solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.00 (3H, t, J = 7.5 Hz), 2.24 (2H, q, J = 7.5 Hz), 6.44 (1H, d, J = 7.7 Hz), 7.31 - 7.39 (2H, m), 7.43 - 7.62 (3H, m), 8.20 (1H, d, J = 7.7 Hz).

Reference Example 36

Production of 6-ethyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylic acid

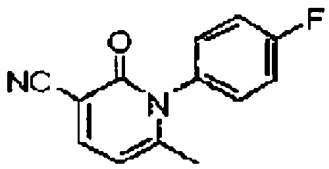


6-Ethyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carbonitrile (395 mg, 1.76 mmol) was dissolved in conc. sulfuric acid (0.4 mL) and water (0.4 mL), and the mixture was stirred with heating at 120°C for 7 hr. 1N Aqueous sodium hydroxide solution was added to the reaction solution, and the mixture was washed with ethyl acetate. 1N Hydrochloric acid was added to the aqueous layer, and the mixture was extracted 3 times with ethyl acetate. The combined organic layer was

washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The residue was washed with ethyl acetate to give the title compound (310 mg, 72%) as a colorless solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.04 (3H, t, J = 7.5 Hz), 2.32 (2H, q, J = 7.5 Hz), 6.77 (1H, d, J = 7.7 Hz), 7.38 - 7.49 (2H, m), 7.51 - 7.67 (3H, m), 8.46 (1H, d, J = 7.7 Hz), 14.28 (1H, s).

Reference Example 37

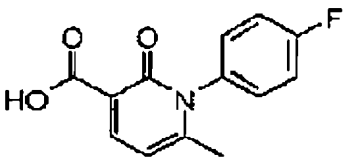
Production of 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile



A solution of 2-cyano-N-(4-fluorophenyl)acetamide (15 g, 84.2 mmol), 4-methoxybut-3-en-2-one (12.6 g, 125.9 mmol) and 1,4-diazabicyclo[2.2.2]octane (9.4 g, 84.2 mmol) in 2-(2-methoxyethoxy)ethanol (150 mL) was stirred with heating at 120°C for 5 hr. (3E)-4-Methoxybut-3-en-2-one (4.2 g, 41.9 mmol) and 1,4-diazabicyclo[2,2,2]octane (4.7 g, 41.9 mmol) were further added to the reaction mixture, and the mixture was stirred with heating at 120°C for 1 hr. 2N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained solid was washed with ethyl acetate to give the title compound (6 g, 31%) as a pale-brown solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.01 (3H, s), 6.45 - 6.52 (1H, m), 7.35 - 7.48 (4H, m), 8.15 (1H, d, J = 7.4 Hz).

Reference Example 38

Production of 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid

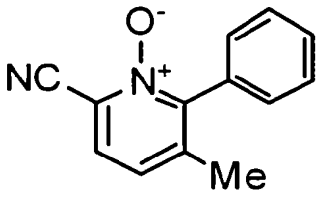


1-(4-Fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (3 g, 13.1 mmol) was dissolved in conc. sulfuric acid (6.0 mL) and water (6.0 mL), and the mixture was stirred with heating at 120°C for 20 hr. 8N Aqueous sodium hydroxide solution was added to the reaction solution, and the mixture was washed with ethyl acetate. 2N hydrochloric acid was added to the aqueous layer, and the mixture was extracted twice with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The residue was washed with diethyl ether and collected by filtration to give the title compound (2.41 g, 74%) as a pale-brown solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.10 (3H, s), 6.80 (1H, d, J = 7.9 Hz), 7.37 - 7.58 (4H, m), 8.41 (1H, d, J = 7.9 Hz), 14.21 (1H, s).

Reference Example 39

Production of 5-methyl-6-phenylpyridine-2-carbonitrile 1-oxide



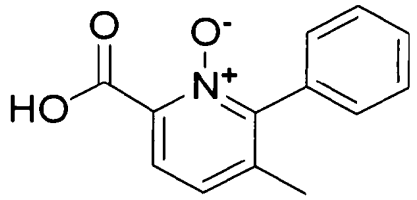
A solution of 6-(4-fluorophenyl)-5-methylpyridine-2-carbonitrile (750 mg, 3.86 mmol) and m-chloroperbenzoic acid (purity 69%, 2.4 g, 96.5 mmol) in tetrahydrofuran (8 mL) was stirred with heating at 50°C for 3 days. Saturated aqueous sodium thiosulfate solution was added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The combined organic layer was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent

was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane=1/3→1/2) to give the title compound (74.8 mg, 9%) as white crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.10 (3H, s), 7.32 - 7.41 (2H, m), 7.45 - 7.59 (4H, m), 8.03 (1H, d, J = 8.3 Hz).

Reference Example 40

Production of 5-methyl-6-phenylpyridine-2-carboxylic acid 1-oxide

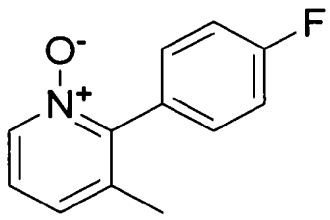


In the same manner as in Reference Example 38 and using 5-methyl-6-phenylpyridine-2-carbonitrile 1-oxide (74.8 mg, 0.356 mmol), conc. sulfuric acid (0.3 mL) and water (0.3 mL), the title compound (83.1 mg, 99%) was obtained as colorless crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.16 (3H, s), 7.43 - 7.49 (2H, m), 7.51 - 7.62 (3H, m), 7.92 (1H, d, J = 8.5 Hz), 8.28 (1H, d, J = 8.5 Hz).

Reference Example 41

Production of 2-(4-fluorophenyl)-3-methylpyridine 1-oxide



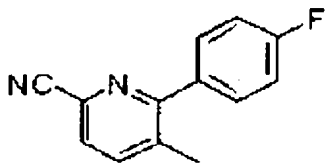
A solution of 2-(4-fluorophenyl)-3-methylpyridine (26.8 g, 0.143 mol) and m-chloroperbenzoic acid (purity 69%, 39 g, 0.157 mol) in tetrahydrofuran (100 mL) was stirred with heating at 50°C for 5 hr. The solvent was evaporated under reduced pressure, and the obtained residue was purified 3

times by silica gel column chromatography (NH silica gel, ethyl acetate) to give a white solid. The obtained solid was washed with ethyl acetate to give the title compound (24.7 g, 85%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.04 (3H, s), 7.21 - 7.46 (6H, m), 8.16 - 8.24 (1H, m).

Reference Example 42

Production of 6-(4-fluorophenyl)-5-methylpyridine-2-carbonitrile



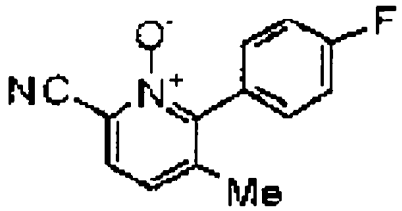
To a solution of 2-(4-fluorophenyl)-3-methylpyridine 1-oxide (24 g, 0.118 mol) in tetrahydrofuran (200 mL) were added trimethylsilyl cyanide (19.2 mL, 0.153 mol) and dimethylcarbamoyl chloride (14.1 mL, 0.153 mmol), and the mixture was heated under reflux for 2 hr. Ethyl acetate and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was washed with diethyl ether and collected by filtration to give the title compound (16.7 g, 67%) as a white solid. Under reduced pressure, the filtrate was concentrated, and the obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane=1/9) to give the title compound (3.0 g, 12%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.41 (3H, s), 7.07 - 7.43 (2H, m), 7.53 - 7.76 (2H, m), 7.90 - 8.07 (2H, m).

Reference Example 43

Production of 6-(4-fluorophenyl)-5-methylpyridine-2-

carbonitrile 1-oxide

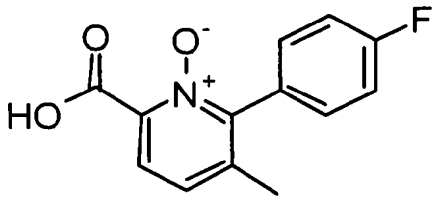


To a solution of 6-(4-fluorophenyl)-5-methylpyridine-2-carbonitrile (16.76 g, 79 mmol) and sodium percarbonate (24.8 g, 158 mmol) in acetonitrile (200 mL) was added dropwise trifluoromethanesulfonic acid anhydride (66.8 g, 237 mmol) at 0°C, and the mixture was stirred at 0°C for 1 hr and further at room temperature overnight. Saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane=1/2→1/1) to give the title compound (6.2 g, 40%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.11 (3H, s), 7.30 - 7.42 (2H, m), 7.42 - 7.53 (3H, m), 8.03 (1H, d, J = 8.3 Hz).

Reference Example 44

Production of 6-(4-fluorophenyl)-5-methylpyridine-2-carboxylic acid 1-oxide



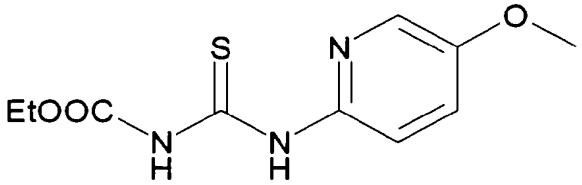
In the same manner as in Reference Example 38 and using 6-(4-fluorophenyl)-5-methylpyridine-2-carbonitrile 1-oxide (6.07 g, 26.6 mmol), conc. sulfuric acid (18 mL) and water (18 mL), the title compound (5.72 g, 87%) was obtained as a white

solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.18 (3H, s), 7.35 - 7.47 (2H, m), 7.50 - 7.62 (2H, m), 7.93 (1H, d, J = 8.9 Hz), 8.30 (1H, d, J = 8.1 Hz).

Reference Example 45

Production of ethyl [(5-methoxypyridin-2-yl)carbamothioyl]carbamate

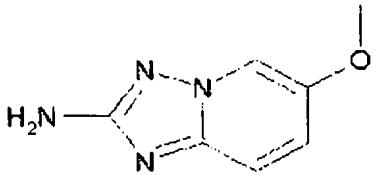


To a solution of 5-methoxypyridin-2-amine (1.05 g, 8.43 mmol) in dimethyl sulfoxide (5 mL) was added ethyl isothiocyanatoformate (1.44 g, 11.0 mmol), and the mixture was stirred for 15 hr. The reaction mixture was diluted with water, and extracted with ethyl acetate (×3). The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the residue was dried to give the title compound (1.34 g, 62%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.26 (3H, t, J = 7.2 Hz), 3.84 (3H, s), 4.22 (2H, q, J = 7.2 Hz), 7.51 (1H, dd, J = 9.0, 3.0 Hz), 8.12 (1H, d, J = 3.0 Hz), 8.54 (1H, br s), 11.38 (1H, br s), 12.04 (1H, br s).

Reference Example 46

Production of 6-methoxy[1,2,4]triazolo[1,5-a]pyridin-2-amine



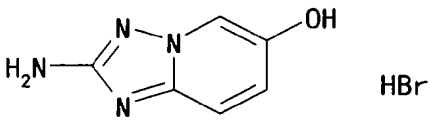
A mixture of ethyl [(5-methoxypyridin-2-yl)carbamothioyl]carbamate (1.34 g, 5.25 mmol), hydroxylammonium chloride (2.55 g, 36.7 mmol), N,N-diisopropylethylamine (4.57 mL, 26.2 mmol), ethanol (15 mL)

and methanol (15 mL) was stirred at 80°C for 8 hr. The reaction mixture was diluted with water, and extracted with ethyl acetate (×3). The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the residue was collected by filtration, and washed with ethyl acetate-hexane to give the title compound (790 mg, 92%) as a yellow oil.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 3.78 (3H, s), 5.79 (2H, br s), 7.18 (1H, dd, J = 9.6, 2.4 Hz), 7.27 (1H, d, J = 9.6 Hz), 8.28 (1H, d, J = 2.4 Hz).

Reference Example 47

Production of 2-amino[1,2,4]triazolo[1,5-a]pyridin-6-ol hydrobromide

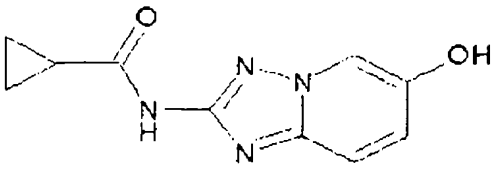


A mixture of 6-methoxy[1,2,4]triazolo[1,5-a]pyridin-2-amine (780 mg, 4.75 mmol), 48% hydrobromic acid (3 mL) was stirred under refluxing conditions for 7 hr. 48% Hydrobromic acid (2 mL) was further added and the mixture was stirred under refluxing conditions for 3 hr. The mixture was concentrated under reduced pressure, and diisopropyl ether (2 mL) and ethanol (1 mL) were added to the residue. The precipitate was collected by filtration, and washed with diisopropyl ether to give the title compound (984 mg, 89%) as a brown solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 7.53 - 7.61 (2H, m), 8.34 (1H, dd, J = 1.8, 0.9 Hz), 10.57 (1H, br s).

Reference Example 48

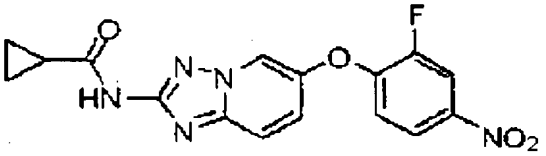
Production of N-(6-hydroxy[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide



To a solution of 2-amino[1,2,4]triazolo[1,5-a]pyridin-6-ol hydrobromide (1.50 g, 4.22 mmol) in N,N-dimethylacetamide (5 mL) was added cyclopropanecarbonyl chloride (1.15 mL, 12.7 mmol) with stirring under ice-cooling, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with water, and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the residue was collected by filtration, and washed with ethyl acetate-hexane to give the title compound (1.59 g, 89%) as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.79 - 0.82 (4H, m), 1.96 - 2.05 (1H, m), 7.28 (1H, dd, J = 9.4, 2.4 Hz), 7.52 (1H, d, J = 9.4 Hz), 8.20 (1H, d, J = 2.4 Hz), 10.01 (1H, br s), 10.82 (1H, s).

Reference Example 49

Production of N-[6-(2-fluoro-4-nitrophenoxy)[1,2,4]triazolo[1,5-a]pyridin-2-yl]cyclopropanecarboxamide



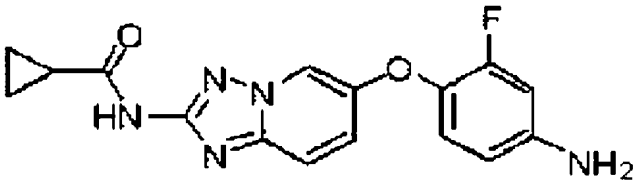
To a solution of N-(6-hydroxy[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide (2 g, 9.16 mmol) and 1,2-difluoro-4-nitrobenzene (1.46 g, 9.16 mmol) in dimethyl sulfoxide (20 mL) was added cesium carbonate (4.48 g, 13.7 mmol), and the mixture was stirred at room temperature for 17 hr. The reaction mixture was filtered through celite, and the filtrate was diluted with water and ethyl acetate, and extracted twice with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous

magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate to give the title compound (1.5 g, 46%) as a white solid.

^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.77 - 0.87 (4H, m), 2.04 (1H, br s), 7.23 - 7.35 (1H, m), 7.64 - 7.73 (1H, m), 7.78 - 7.84 (1H, m), 8.05 (1H, dd, J = 9.1, 1.1 Hz),8.35 (1H, d, J = 10.8 Hz), 9.17 (1H, s), 11.10 (1H, br s).

Reference Example 50

Production of N-[6-(4-amino-2-fluorophenoxy)[1,2,4]triazolo[1,5-a]pyridin-2-yl]cyclopropanecarboxamide



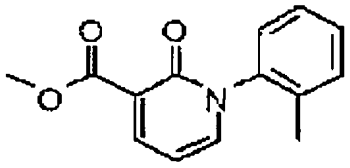
A solution of N-[6-(2-fluoro-4-nitrophenoxy)[1,2,4]triazolo[1,5-a]pyridin-2-yl]cyclopropanecarboxamide (400 mg, 1.12 mmol), reduced iron (312 mg, 5.59 mmol) and ammonium chloride (600 mg, 11.2 mmol) in ethanol (8 mL) and water (2 mL) was heated under reflux for 1.5 hr. The reaction mixture was filtered through celite, and the filtrate was diluted with water and ethyl acetate and extracted 3 times with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane=1/2→ethyl acetate/methanol=9/1) to give the title compound (125 mg, 34%) as a white solid.

^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.72 - 0.90 (4H, m), 1.93 - 2.13 (1H, m), 5.41 (2H, s), 6.33 - 6.44 (1H, m), 6.50 (1H, dd, J = 13.4, 2.5 Hz), 6.92 - 7.05 (1H, m), 7.44 (1H, dd, J = 9.6, 2.5 Hz), 7.66 (1H, dd, J = 9.6, 0.8 Hz), 8.45 (1H, d, J = 1.9 Hz),

10.98 (1H, s).

Reference Example 51

Production of methyl 1-(2-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate

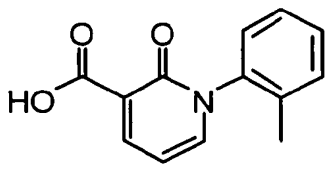


To a solution of methyl 2-oxo-2H-pyran-3-carboxylate (3 g, 19.5 mmol) in tetrahydrofuran (30 mL) and N,N-dimethylformamide (10 mL) was added 2-methylaniline (2.09 g, 19.5 mmol), and the mixture was stirred at room temperature for 7 hr. 4-Dimethylaminopyridine (119 mg, 0.974 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (4.48 g, 23.4 mmol) were added to the reaction mixture, and the mixture was further stirred at room temperature for 17 hr. 1N Hydrochloric acid was added to the reaction solution, and the mixture was extracted 3 times with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (NH silica gel, ethyl acetate/hexane=1/1) to give the title compound (882 mg, 19%) as yellow crystals.

^{1}H-NMR (300 MHz, DMSO-d_6) δ 2.04 (3H, s), 3.75 (3H, s), 6.36 - 6.47 (1H, m), 7.17 - 7.45 (4H, m), 7.86 (1H, dd, J = 6.6, 2.3 Hz), 8.16 (1H, dd, J = 7.2, 2.3 Hz).

Reference Example 52

Production of 1-(2-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid

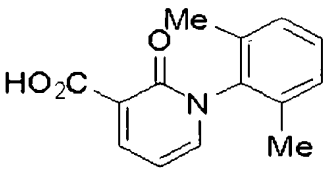


To a solution (9 mL) of methyl 1-(2-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (880 mg, 3.62 mmol) in methanol was added 1N aqueous sodium hydroxide solution (5 mL), and the mixture was stirred at room temperature for 4 hr. The reaction mixture was adjusted to pH<7 with 1N hydrochloric acid and concentrated under reduced pressure. The precipitate was collected by filtration and washed with water to give the title compound (704 mg, 85%) as yellow crystals.

^{1}H-NMR (300 MHz, DMSO-d_6) δ 2.07 (3H, s), 6.74 - 6.88 (1H, m), 7.35 - 7.51 (4H, m), 8.14 (1H, dd, J = 6.6, 2.1 Hz), 8.52 (1H, dd, J = 7.4, 2.1 Hz), 14.25 (1H, br s).

Reference Example 53

Production of 1-(2,6-dimethylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid

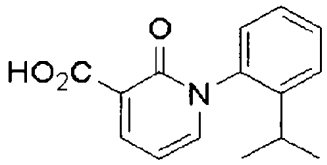


Dimethyl [(3-methoxyprop-2-en-1-ylidene)propanedionate (1.1 g, 5.6 mmol) and 2,6-dimethylaniline (0.69 mL, 5.6 mmol) were dissolved in N,N-dimethylacetamide (1.2 mL), and the mixture was stirred at 130°C overnight. After cooling to room temperature, the reaction system was diluted with ethyl acetate and washed with saturated sodium hydrogen carbonate. The organic layer was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was dissolved in methanol (15 mL), 60% sodium hydride (1.1 g, 28 mmol) was slowly added with stirring, and the mixture was further stirred at room temperature for 3 hr. Distilled water (10 mL) was added, and the mixture was further stirred at room temperature for 1 hr. 1N Aqueous sodium hydroxide solution (10 mL) was added to the reaction system and the mixture was washed with ethyl acetate. The aqueous layer was acidified with 1N hydrochloric acid (20 mL) and extracted twice with

ethyl acetate. The collected organic layer was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. Hexane/ethyl acetate (=2/1) was added, and the resulting precipitate was collected by filtration to give the title compound (220 mg, 16%) as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.00 (6H, s), 6.88 (1H, d, J = 7.2 Hz), 7.26-7.41 (3H, m), 8.10 (1H, dd, J = 6.6, 2.1 Hz), 8.56 (1H, dd, J = 7.2, 2.1 Hz), 14.20 (1H, s).

Reference Example 54

Production of 1-[2-(1-methylethyl)phenyl]-2-oxo-1,2-dihydropyridine-3-carboxylic acid



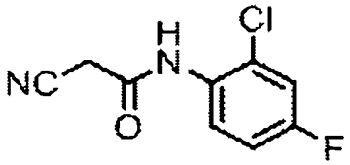
Methyl 2-oxo-2H-pyran-3-carboxylate (3.0 g, 19 mmol) was dissolved in a mixed solvent of tetrahydrofuran (40 mL) and N,N-dimethylformamide (10 mL), and 2-(1-methylethyl)aniline (2.7 mL, 19 mmol) was added. After stirring overnight at room temperature, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (4.5 g, 23 mmol) and 4-(N,N-dimethylamino)pyridine (120 mg, 1.0 mmol) were added, and the mixture was further stirred overnight at room temperature. The reaction system was diluted with ethyl acetate and washed with saturated aqueous sodium hydrogen carbonate solution, and the organic layer was dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=40/60→60/40) to give methyl 1-[2-(1-methylethyl)phenyl]-2-oxo-1,2-dihydropyridine-3-carboxylate (800 mg). Methyl 1-[2-(1-methylethyl)phenyl]-2-oxo-1,2-dihydropyridine-3-carboxylate (800 mg) was dissolved in a mixed solvent of tetrahydrofuran (5 mL) and methanol (5 mL), 1N aqueous sodium hydroxide solution (5 mL) was added, and the

mixture was stirred at room temperature for 2 hr. The mixture was diluted with distilled water (20 mL) and washed with ethyl acetate. The aqueous layer was acidified with 1N hydrochloric acid (7 mL) and extracted twice with ethyl acetate. The collected organic layer was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. A small amount of hexane/ethyl acetate was added to the residue, and the resulting precipitate was collected by filtration to give 1-[2-(1-methylethyl)phenyl]-2-oxo-1,2-dihydropyridine-3-carboxylic acid (760 mg, 15%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.07 - 1.18 (6H, m), 2.51 - 2.57 (1H, m), 6.76 - 6.87 (1H, m), 7.32 - 7.43 (2H, m), 7.50 - 7.62 (2H, m), 8.19 (1H, dd, J = 6.6, 2.1 Hz), 8.53 (1H, dd, J = 7.2, 2.1 Hz), 14.25 (1H, s).

Reference Example 55

Production of N-(2-chloro-4-fluorophenyl)-2-cyanoacetamide

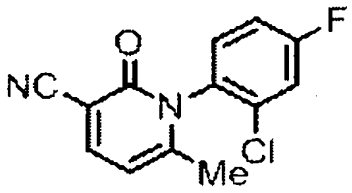


A mixture of 2-chloro-4-fluoroaniline (3.55 g, 24.3 mmol), cyanoacetic acid (2.48 g, 29.2 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide·hydrochloride (7.01 g, 36.5 mmol), 1H-1,2,3-benzotriazol-1-ol (4.94 g, 36.5 mmol), triethylamine (5.10 mL, 36.5 mmol) and N,N-dimethylformamide (50 mL) was stirred at room temperature for 16 hr. The mixture was diluted with ethyl acetate, washed with water, saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over anhydrous magnesium sulfate, and filtered through a basic silica gel pad. The solvent was evaporated under reduced pressure, and the obtained residue was washed with hexane and collected by filtration to give the title compound (2.84 g, 54%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 3.98 (2H, s), 7.21 - 7.30 (1H, m), 7.49 - 7.58 (1H, m), 7.61 - 7.71 (1H, m), 10.00 (1H, s).

Reference Example 56

Production of 1-(2-chloro-4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile

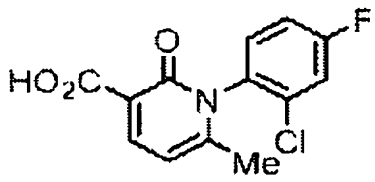


A mixture of N-(2-chloro-4-fluorophenyl)-2-cyanoacetamide (2.00 g, 9.40 mmol), (3E)-4-methoxybut-3-en-2-one (1.13 g, 11.2 mmol), 1,4-diazabicyclo[2.2.2]octane (1.05 g, 9.40 mmol) and 2-(2-methoxyethoxy)ethanol (20 mL) was stirred at 130°C for 3 hr. After cooling to room temperature, the mixture was diluted with ethyl acetate, washed with 1N hydrochloric acid, water (×2) and saturated brine, dried over anhydrous magnesium sulfate, and filtered through a silica gel pad. The solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (100 g, ethyl acetate/hexane=2/98→50/50). The obtained residue was washed with ethyl acetate/hexane and collected by filtration to give the title compound (0.75 g, 30%) as a pale-yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.01 (3H, s), 6.51 - 6.61 (1H, m), 7.42 - 7.55 (1H, m), 7.63 - 7.73 (1H, m), 7.77 - 7.85 (1H, m), 8.18 - 8.27 (1H, m).

Reference Example 57

Production of 1-(2-chloro-4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid



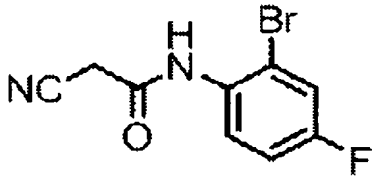
To a mixture of 1-(2-chloro-4-fluorophenyl)-6-methyl-2-

oxo-1,2-dihydropyridine-3-carbonitrile, 1-(2-chloro-4-fluorophenyl)-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (0.75 g, 3.80 mmol) and water (5 mL) was added conc. sulfuric acid (5 mL) at 0°C, and the mixture was stirred at 100°C for 18 hr. After cooling to 0°C, the mixture was basified (pH 11) with 8N aqueous sodium hydroxide solution and washed with ethyl acetate. The aqueous layer was acidified (pH 4) with 5N hydrochloric acid and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was washed with diethyl ether and collected by filtration to give the title compound (588 mg, 55%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.09 (3H, s), 6.85 (1H, d, J = 7.5 Hz), 7.48 - 7.57 (1H, m), 7.72 - 7.89 (2H, m), 8.46 (1H, d, J = 7.5 Hz), 13.84 (1H, br s).

Reference Example 58

Production of N-(2-bromo-4-fluorophenyl)-2-cyanoacetamide



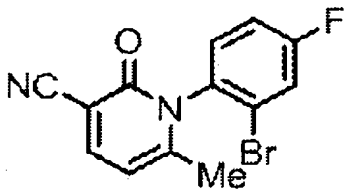
A mixture of 2-bromo-4-fluoroaniline (10.0 g, 52.6 mmol), cyanoacetic acid (5.36 g, 63.1 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide·hydrochloride (15.1 g, 78.9 mmol), 1H-1,2,3-benzotriazol-1-ol (10.6 g, 78.9 mmol), triethylamine (10.9 mL, 78.9 mmol) and N,N-dimethylformamide (150 mL) was stirred at room temperature for 16 hr. The mixture was diluted with ethyl acetate, washed with water, saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over anhydrous magnesium sulfate, and filtered through a pad packed with NH silica gel. The solvent was evaporated under reduced pressure, and the obtained residue was washed with hexane and collected by

filtration to give the title compound (8.04 g, 59%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 3.96 (2H, s), 7.26 - 7.34 (1H, m), 7.54 - 7.61 (1H, m), 7.64 - 7.70 (1H, m), 9.97 (1H, s).

Reference Example 59

Production of 1-(2-bromo-4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile

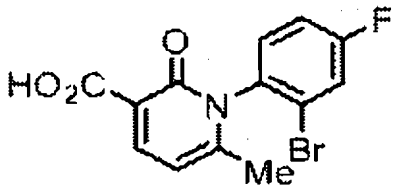


A mixture of N-(2-bromo-4-fluorophenyl)-2-cyanoacetamide (5.00 g, 19.4 mmol), (3E)-4-methoxybut-3-en-2-one (2.33 g, 23.3 mmol), 1,4-diazabicyclo[2.2.2]octane (2.18 g, 19.4 mmol) and 2-(2-methoxyethoxy)ethanol (50 mL) was stirred at 130°C for 5 hr. After cooling to room temperature, the mixture was diluted with ethyl acetate, washed with 1N hydrochloric acid, water (×2) and saturated brine, dried over anhydrous magnesium sulfate, and filtered through a silica gel pad. The solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (100 g, ethyl acetate/hexane=2/98→50/50), washed with ethyl acetate-hexane and collected by filtration to give the title compound (1.78 g, 29%) as a pale-brown powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.99 (3H, s), 6.51 - 6.59 (1H, m), 7.46 - 7.56 (1H, m), 7.63 - 7.70 (1H, m), 7.87 - 7.95 (1H, m), 8.21 - 8.26 (1H, m).

Reference Example 60

Production of 1-(2-bromo-4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid

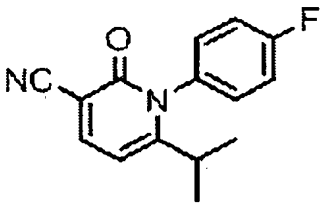


To a mixture of 1-(2-bromo-4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile, 1-(2-bromo-4-fluorophenyl)-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (2.00 g, 6.51 mmol) and water (10 mL) was added conc. sulfuric acid (10 mL) at 0°C, and the mixture was stirred at 100°C for 16 hr. After cooling to 0°C, the mixture was basified (pH 11) with 8N aqueous sodium hydroxide solution and washed with ethyl acetate. The aqueous layer was acidified (pH 4) with 5N hydrochloric acid and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was washed with diethyl ether and collected by filtration to give the title compound (1.12 g, 53%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.08 (3H, s), 6.85 (1H, d, J = 7.6 Hz), 7.52 - 7.60 (1H, m), 7.71 - 7.78 (1H, m), 7.91 - 7.98 (1H, m), 8.46 (1H, d, J = 7.6 Hz), 13.87 (1H, br s).

Reference Example 61

Production of 1-(4-fluorophenyl)-6-(1-methylethyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile



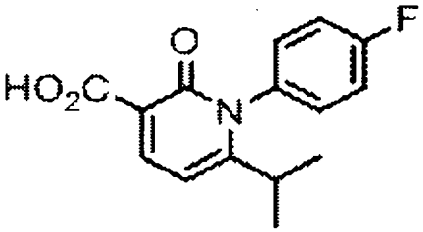
A mixture of (1E)-1-methoxy-4-methylpenta-1-en-3-one (508 mg, 3.96 mmol), 2-cyano-N-(4-fluorophenyl)acetamide (847 mg, 4.75 mmol), 1,4-diazabicyclo[2.2.2]octane (444 mg, 3.96 mmol) and 2-(2-methoxyethoxy)ethanol (10 mL) was stirred at 130°C for 6 hr. After cooling to room temperature, the mixture was diluted with ethyl acetate, washed with 1N hydrochloric acid, water (×2) and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (ethyl

acetate/hexane=0/100→60/40) and silica gel column chromatography (NH silica gel, ethyl acetate/hexane=0/100→60/40) to give the title compound (604 mg, 59%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.08 (6H, d, J = 6.8 Hz), 2.34 - 2.45 (1H, m), 6.52 (1H, d, J = 7.7 Hz), 7.34 - 7.57 (4H, m), 8.21 (1H, d, J = 7.7 Hz).

Reference Example 62

Production of 1-(4-fluorophenyl)-6-(1-methylethyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid

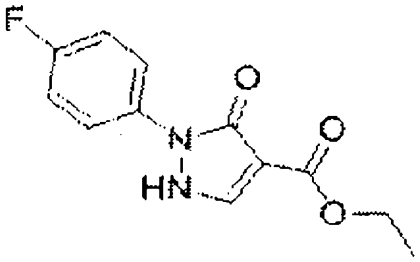


To a mixture of 1-(4-fluorophenyl)-6-(1-methylethyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (604 mg, 2.35 mmol) and water (5 mL) was added conc. sulfuric acid (5 mL) at 0°C, and the mixture was stirred at 100°C for 14 hr. After cooling to 0°C, the mixture was basified (pH 11) with 8N aqueous sodium hydroxide solution and washed with ethyl acetate. The aqueous layer was acidified (pH 4) with 5N hydrochloric acid and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure to give the title compound (425 mg, 65%) as a pale-yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.12 (6H, d, J = 6.8 Hz), 2.42 - 2.53 (1H, m), 6.85 (1H, d, J = 7.7 Hz), 7.40 - 7.49 (2H, m), 7.53 - 7.61 (2H, m), 8.46 (1H, d, J = 7.7 Hz), 14.22 (1H, s).

Reference Example 63

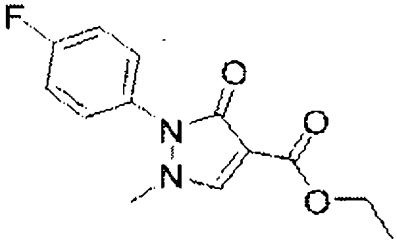
Production of ethyl 2-(4-fluorophenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate



To a suspension of (4-fluorophenyl)hydrazine·hydrochloride (3 g, 18 mmol) and water (75 mL) were added potassium carbonate (5.6 g, 40 mmol) and diethyl ethoxymethylenemalonate (4.8 g, 22 mmol), and the mixture was heated under reflux for 7 hr. After cooling to room temperature, the mixture was washed with ethyl acetate. 6N Aqueous hydrochloric acid solution was added to the separated aqueous layer under ice-cooling. The precipitated solid was collected by filtration, washed with water and ethyl acetate/hexane (1/10), and dried under reduced pressure to give the title compound (2.2 g, 48%) as a yellow solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.28 (3H, t, J = 6.5 Hz), 4.10 - 4.34 (2H, m), 7.25 - 7.44 (2H, m), 7.71 (2H, br s), 7.82 (1H, br s), 12.31 (1H, br s).

Reference Example 64

Production of ethyl 2-(4-fluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate



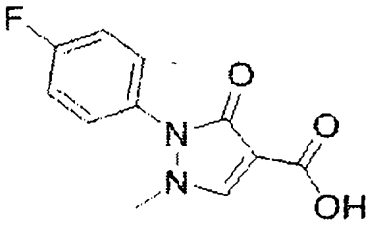
A mixture of ethyl 2-(4-fluorophenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (2.2 g, 8.9 mmol) and methyl trifluoromethanesulfonate (3 mL) was stirred at 80°C for 40 min. The mixture was purified by silica gel column chromatography (NH silica gel, ethyl acetate/hexane=70/30→100/0) to give the title compound (1.6 g,

67%) as a pale-yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.23 (3H, t, J = 7.1 Hz), 3.39 (3H, s), 4.15 (2H, q, J = 7.2 Hz), 7.34 - 7.47 (4H, m), 8.51 (1H, s).

Reference Example 65

Production of 2-(4-fluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid

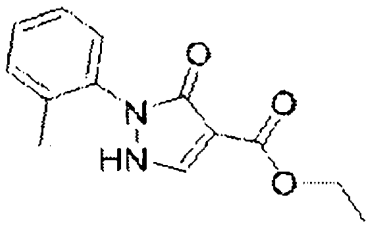


To a solution of ethyl 2-(4-fluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (1.6 g, 5.9 mmol) in tetrahydrofuran (6 mL)/methanol (5 mL) was added 4N aqueous sodium hydroxide solution (9 mL), and the mixture was stirred at 60°C for 1 hr. Tetrahydrofuran and methanol were evaporated under reduced pressure. 6N Aqueous hydrochloric acid solution was added to the residue with stirring, and the precipitated solid was collected by filtration. The filtrate was washed with water and ethyl acetate/hexane (1/5), and dried under reduced pressure to give the title compound (1.1 g, 79%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 3.41 (3H, s), 7.35 - 7.54 (4H, m), 8.52 (1H, s), 11.85 (1H, br s).

Reference Example 66

Production of ethyl 2-(2-methylphenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate



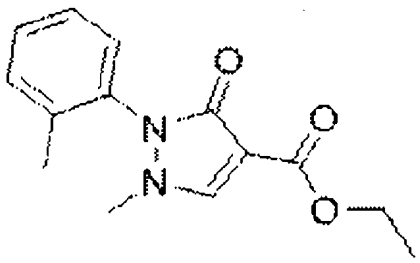
In the same manner as in Reference Example 63 and using

(2-methylphenyl)hydrazine·hydrochloride (5 g, 32 mmol), water (100 mL), potassium carbonate (9.7 g, 70 mmol) and diethyl ethoxymethylenemalonate (8.3 g, 38 mmol) as starting materials, the title compound (6.8 g, 87%) was obtained as a brown solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.28 (3H, t, J = 7.2 Hz), 2.07 (3H, s), 4.22 (2H, q, J = 7.2 Hz), 7.23 - 7.43 (4H, m), 7.79 (1H, s).

Reference Example 67

Production of ethyl 1-methyl-2-(2-methylphenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate

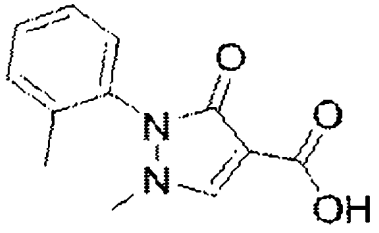


In the same manner as in Reference Example 64 and using ethyl 2-(2-methylphenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (3.1 g, 12 mmol) and methyl trifluoromethanesulfonate (2.5 mL) as starting materials, the title compound (2.1 g, 66%) was obtained as a pale-yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.23 (3H, t, J = 7.1 Hz), 2.10 (3H, s), 3.29 (3H, s), 4.09 - 4.20 (2H, m), 7.27 (1H, d, J = 7.6 Hz), 7.33 - 7.46 (3H, m), 8.49 (1H, s).

Reference Example 68

Production of 1-methyl-2-(2-methylphenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid



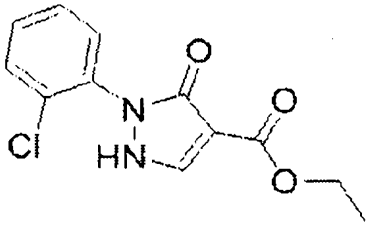
In the same manner as in Reference Example 65 and using

ethyl 1-methyl-2-(2-methylphenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (2.1 g, 8.2 mmol), tetrahydrofuran (6 mL), methanol (4 mL) and 4N aqueous sodium hydroxide solution (9 mL) as starting materials, the title compound (750 mg, 40%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.11 (3H, s), 3.29 (3H, s), 7.26 - 7.48 (4H, m), 8.42 (1H, s).

Reference Example 69

Production of ethyl 2-(2-chlorophenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate

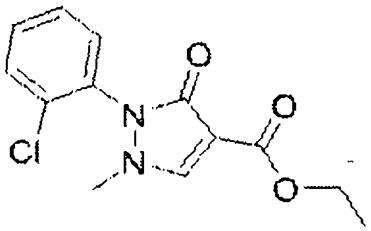


In the same manner as in Reference Example 63 and using (2-chlorophenyl)hydrazine·hydrochloride (5 g, 28 mmol), water (100 mL), potassium carbonate (8.5 g, 62 mmol) and diethyl ethoxymethylenemalonate (7.3 g, 34 mmol) as starting materials, the title compound (5.8 g, 78%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.28 (3H, t, J = 7.0 Hz), 4.22 (2H, q, J = 7.0 Hz), 7.48 - 7.60 (3H, m), 7.65 - 7.70 (1H, m), 7.81 (1H, s), 12.13 (1H, br s).

Reference Example 70

Production of ethyl 2-(2-chlorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate

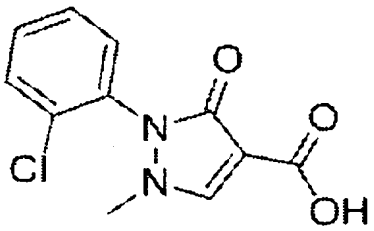


In the same manner as in Reference Example 64 and using ethyl 2-(2-chlorophenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (3.4 g, 12 mmol) and methyl

trifluoromethanesulfonate (3 mL) as starting materials, the title compound (2.8 g, 81%) was obtained as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.23 (3H, t, J = 7.1 Hz), 3.32 (3H, s), 4.15 (2H, q, J = 7.1 Hz), 7.51 - 7.66 (3H, m), 7.70 - 7.75 (1H, m), 8.53 (1H, s).

Reference Example 71

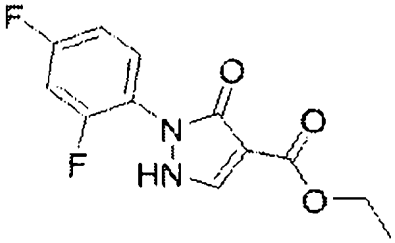
Production of 2-(2-chlorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid



In the same manner as in Reference Example 65 and using ethyl 2-(2-chlorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (2.8 g, 9.9 mmol), tetrahydrofuran (6 mL), methanol (5 mL) and 4N aqueous sodium hydroxide solution (8 mL) as starting materials, the title compound (2.3 g, 91%) was obtained as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 3.34 (3H, s), 7.52 - 7.68 (3H, m), 7.72 - 7.77 (1H, m), 8.53 (1H, s), 11.75 (1H, s).

Reference Example 72

Production of ethyl 2-(2,4-difluorophenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate



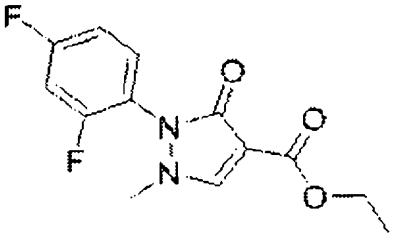
In the same manner as in Reference Example 63 and using (2,4-difluorophenyl)hydrazine·hydrochloride (5.1 g, 28 mmol), water (100 mL), potassium carbonate (8.6 g, 62 mmol) and diethyl ethoxymethylenemalonate (7.4 g, 34 mmol) as starting materials, the title compound (5.0 g, 66%) was obtained as a

pale-yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.27 (3H, t, J = 7.0 Hz), 4.22 (2H, q, J = 7.0 Hz), 7.22 - 7.31 (1H, m), 7.49 - 7.66 (2H, m), 7.83 (1H, s), 12.26 (1H, br s).

Reference Example 73

Production of ethyl 2-(2,4-difluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate

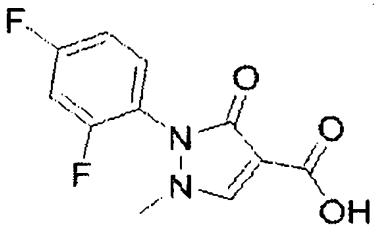


In the same manner as in Reference Example 64 and using ethyl 2-(2,4-difluorophenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (3.6 g, 13 mmol) and methyl trifluoromethanesulfonate (3 mL) as starting materials, the title compound (2.4 g, 65%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.23 (3H, t, J = 7.1 Hz), 3.38 (3H, s), 4.09 - 4.20 (2H, m), 7.26 - 7.35 (1H, m), 7.54 - 7.70 (2H, m), 8.54 (1H, s).

Reference Example 74

Production of 2-(2,4-difluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid

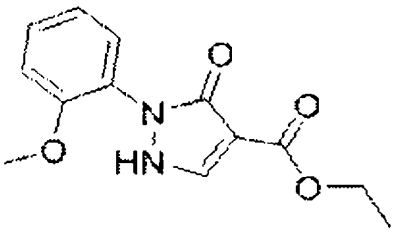


In the same manner as in Reference Example 65 and using ethyl 2-(2,4-difluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (2.4 g, 8.7 mmol), tetrahydrofuran (6 mL), methanol (5 mL) and 4N aqueous sodium hydroxide solution (8 mL) as starting materials, the title compound (1.8 g, 83%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 3.38 (3H, s), 7.26 - 7.37 (1H, m), 7.54 - 7.74 (2H, m), 8.53 (1H, s), 11.77 (1H, br s).

Reference Example 75

Production of ethyl 2-(2-methoxyphenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate

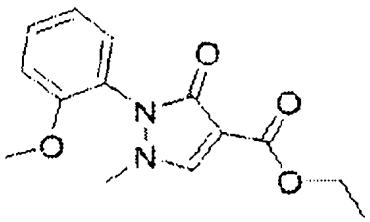


In the same manner as in Reference Example 63 and using (2-methoxyphenyl)hydrazine·hydrochloride (5.3 g, 30 mmol), water (100 mL), potassium carbonate (9.1 g, 66 mmol) and diethyl ethoxymethylenemalonate (7.8 g, 36 mmol) as starting materials, the title compound (6.1 g, 78%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.27 (3H, t, J = 7.0 Hz), 3.75 (3H, s), 4.21 (2H, q, J = 7.0 Hz), 7.02 - 7.09 (1H, m), 7.20 (1H, dd, J = 8.3, 1.1 Hz), 7.29 (1H, dd, J = 7.7, 1.7 Hz), 7.44 - 7.52 (1H, m), 7.74 (1H, s), 11.56 (1H, br s).

Reference Example 76

Production of ethyl 2-(2-methoxyphenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate

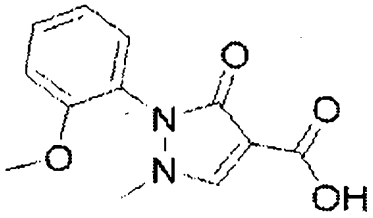


In the same manner as in Reference Example 64 and using ethyl 2-(2-methoxyphenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (3.6 g, 14 mmol) and methyl trifluoromethanesulfonate (3 mL) as starting materials, the title compound (2.5 g, 66%) was obtained as a pale-yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.22 (3H, t, J = 7.1 Hz), 3.28 (3H, s), 3.77 (3H, s), 4.08 - 4.18 (2H, m), 7.06 - 7.15 (1H, m), 7.23 (1H, dd, J = 8.4, 1.0 Hz), 7.34 (1H, dd, J = 7.7, 1.7 Hz), 7.49 - 7.58 (1H, m), 8.41 (1H, s).

Reference Example 77

Production of 2-(2-methoxyphenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid

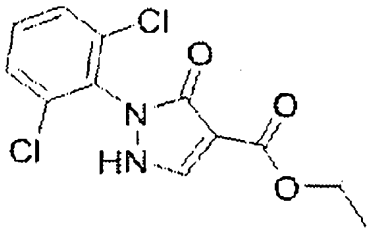


In the same manner as in Reference Example 65 and using ethyl 2-(2-methoxyphenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (2.5 g, 9.2 mmol), tetrahydrofuran (6 mL), methanol (5 mL) and 4N aqueous sodium hydroxide solution (8 mL) as starting materials, the title compound (1.9 g, 85%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 3.33 (3H, s), 3.79 (3H, s), 7.08 - 7.16 (1H, m), 7.26 (1H, dd, J = 8.4, 1.0 Hz), 7.41 (1H, dd, J = 7.7, 1.7 Hz), 7.53 - 7.62 (1H, m), 8.47 (1H, s), 11.79 (1H, s).

Reference Example 78

Production of ethyl 2-(2,6-dichlorophenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate



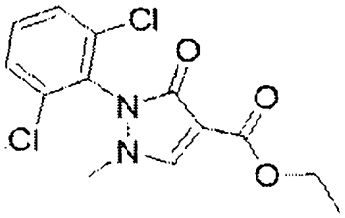
In the same manner as in Reference Example 63 and using (2,6-dichlorophenyl)hydrazine·hydrochloride (4.8 g, 23 mmol), water (100 mL), potassium carbonate (6.9 g, 50 mmol) and diethyl ethoxymethylenemalonate (5.9 g, 27 mmol) as starting

materials, the title compound (5.0 g, 73%) was obtained as a pale-yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.28 (3H, t, J = 7.0 Hz), 4.22 (2H, q, J = 7.0 Hz), 7.57 - 7.63 (1H, m), 7.68 - 7.73 (2H, m), 7.87 (1H, s), 12.37 (1H, br s).

Reference Example 79

Production of ethyl 2-(2,6-dichlorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate

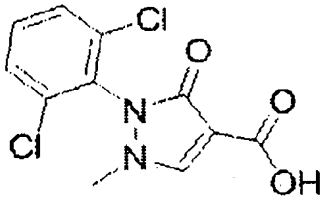


In the same manner as in Reference Example 64 and using ethyl 2-(2,6-dichlorophenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (3.7 g, 12 mmol) and methyl trifluoromethanesulfonate (3 mL) as starting materials, the title compound (3.4 g, 87%) was obtained as a pale-yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.24 (3H, t, J = 7.2 Hz), 3.35 (3H, s), 4.15 (2H, q, J = 7.2 Hz), 7.63 - 7.70 (1H, m), 7.74 - 7.78 (2H, m), 8.59 (1H, s).

Reference Example 80

Production of 2-(2,6-dichlorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid



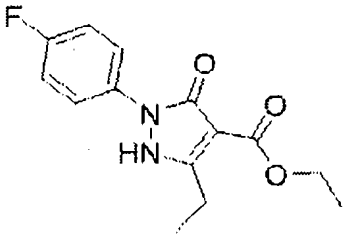
In the same manner as in Reference Example 65 and using ethyl 2-(2,6-dichlorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (3.4 g, 11 mmol), tetrahydrofuran (6 mL), methanol (5 mL) and 4N aqueous sodium hydroxide solution (8 mL) as starting materials, the title compound (2.8 g, 90%)

was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 3.35 (3H, s), 7.63 - 7.71 (1H, m), 7.74 - 7.80 (2H, m), 8.57 (1H, s), 11.79 (1H, br s).

Reference Example 81

Production of ethyl 5-ethyl-2-(4-fluorophenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate

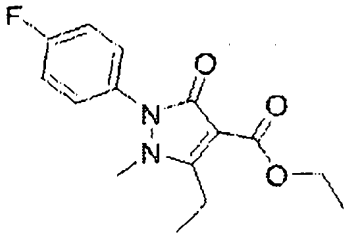


To a solution of (4-fluorophenyl)hydrazine (5.5 g, 43 mmol) in acetic acid (70 mL) was added diethylpropanoylpropanedionate (11 g, 52 mmol), and the mixture was stirred at 60°C for 3.5 hr. The solvent was evaporated under reduced pressure, and hexane was added to the residue. The mixture was filtered to remove insoluble materials. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=10/90→50/50) to give the title compound (3.7 g, 31%) as a pale-yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.19 (3H, t, J = 7.6 Hz), 1.29 (3H, t, J = 7.2 Hz), 2.74 (2H, q, J = 7.6 Hz), 4.24 (2H, q, J = 7.2 Hz), 7.26 - 7.40 (2H, m), 7.64 - 7.75 (2H, m).

Reference Example 82

Production of ethyl 5-ethyl-2-(4-fluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate



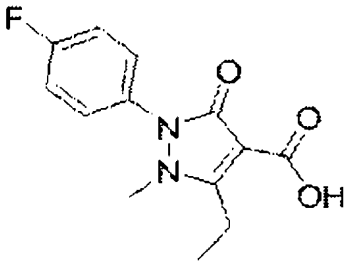
In the same manner as in Reference Example 64 and using ethyl 5-ethyl-2-(4-fluorophenyl)-3-oxo-2,3-dihydro-1H-

pyrazole-4-carboxylate (3.1 g, 11 mmol) and methyl trifluoromethanesulfonate (3.7 mL) as starting materials, the title compound (1.9 g, 57%) was obtained as a pale-yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.14 - 1.26 (6H, m), 2.99 (2H, q, J = 7.6 Hz), 3.31 (3H, s), 4.15 (2H, q, J = 7.1 Hz), 7.38 (4H, d, J = 6.8 Hz).

Reference Example 83

Production of 5-ethyl-2-(4-fluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid

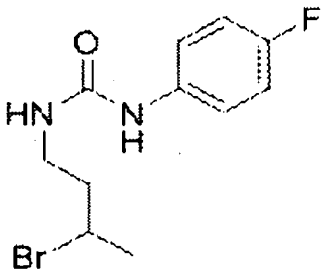


In the same manner as in Reference Example 65 and using ethyl 5-ethyl-2-(4-fluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (1.9 g, 6.4 mmol), tetrahydrofuran (4 mL), methanol (4 mL) and 4N aqueous sodium hydroxide solution (5 mL) as starting materials, the title compound (1.5 g, 92%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.20 (3H, t, J = 7.6 Hz), 3.02 (2H, q, J = 7.6 Hz), 3.39 (3H, s), 7.37 - 7.49 (2H, m), 7.49 - 7.59 (2H, m), 12.23 (1H, br s).

Reference Example 84

Production of 1-(3-bromobutyl)-3-(4-fluorophenyl)urea



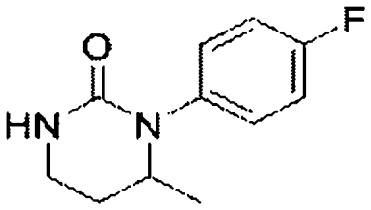
To a solution of 3-bromobutane-1-aminehydrobromide (2270

mg, 9.7 mmol) in pyridine (18 mL) was slowly added 1-fluoro-4-isocyanatobenzene (1600 mg, 12 mmol) under ice-cooling, and the mixture was stirred at room temperature for 2 hr. The solvent was evaporated under reduced pressure, ethyl acetate/tetrahydrofuran and 0.5N aqueous hydrochloric acid solution were added to the residue, and the aqueous layer was extracted with ethyl acetate/tetrahydrofuran (×3). The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the residue was washed with ethyl acetate/hexane (=1/1) to give the title compound (1750 mg, 62%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.70 (3H, d, J = 6.6 Hz), 1.89 - 2.01 (2H, m), 3.06 - 3.19 (1H, m), 3.22 - 3.32 (1H, m), 4.25 - 4.37 (1H, m), 6.23 (1H, t, J = 5.8 Hz), 7.00 - 7.08 (2H, m), 7.35 - 7.42 (2H, m), 8.47 (1H, s).

Reference Example 85

Production of 1-(4-fluorophenyl)-6-methyltetrahydropyrimidin-2(1H)-one



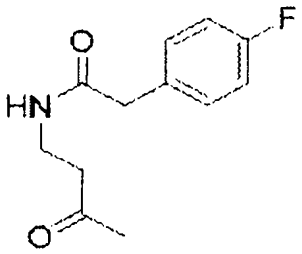
To a solution of 1-(3-bromobutyl)-3-(4-fluorophenyl)urea (1750 mg, 6.1 mmol) in N,N-dimethylformamide (30 mL) was added potassium tert-butoxide (920 mg, 7.0 mmol), and the mixture was stirred at 50°C for 6 hr. The solvent was evaporated under reduced pressure, and ethyl acetate/tetrahydrofuran and 6N aqueous hydrochloric acid solution were added to the residue. The aqueous layer was extracted with ethyl acetate/tetrahydrofuran (×3). The combined organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica

gel column chromatography (NH silica gel, ethyl acetate/hexane=50/50→100/0) to give the title compound (490 mg, 39%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.02 (3H, d, J = 6.4 Hz), 1.66 - 1.81 (1H, m), 1.96 - 2.13 (1H, m), 3.14 - 3.31 (2H, m), 3.85 - 3.96 (1H, m), 6.57 (1H, br s), 7.10 - 7.26 (4H, m).

Reference Example 86

Production of 2-(4-fluorophenyl)-N-(3-oxobutyl)acetamide

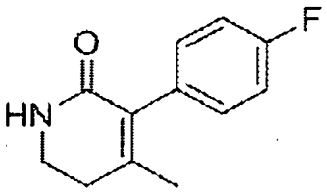


To a solution of 4-aminobutan-2-one hydrochloride (2.95 g, 24 mmol) in N,N-dimethylacetamide (50 mL) was slowly added (4-fluorophenyl)acetylchloride (4.90 g, 29 mmol) under ice-cooling, and the mixture was stirred at room temperature for 2 hr. Triethylamine (4.80 g, 48 mmol) was added to the mixture, and the mixture was stirred at room temperature for 17 hr. Ethyl acetate/tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution were added to the mixture, and the aqueous layer was extracted with ethyl acetate/tetrahydrofuran (×3). The combined organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=50/50→100/0) to give the title compound (2.10 g, 39%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.07 (3H, s), 2.58 (2H, t, J = 6.7 Hz), 3.17 - 3.25 (2H, m), 3.36 (2H, s), 7.05 - 7.16 (2H, m), 7.21 - 7.30 (2H, m), 8.04 (1H, br. s.).

Reference Example 87

Production of 3-(4-fluorophenyl)-4-methyl-5,6-dihydropyridin-2(1H)-one

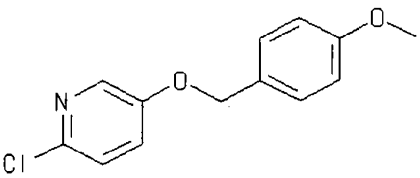


To a solution of 2-(4-fluorophenyl)-N-(3-oxobutyl)acetamide (1.95 g, 8.7 mmol) in ethanol (120 mL) was added 20 wt% sodium ethoxide/ethanol solution (6.54 g, 19 mmol), and the mixture was stirred at 80°C for 8 hr. The solvent was evaporated under reduced pressure, ethyl acetate/tetrahydrofuran and 1N aqueous hydrochloric acid solution were added to the residue, and the aqueous layer was extracted with ethyl acetate/tetrahydrofuran (×3). The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the residue was washed with ethyl acetate/hexane (1/10) to give the title compound (1.36 g, 76%) as a brown solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.73 (3H, s), 2.39 (2H, t, J = 7.0 Hz), 3.28 (2H, td, J = 7.0, 2.7 Hz), 7.14 (4H, d, J = 7.6 Hz), 7.45 (1H, br s).

Reference Example 88

Production of 2-chloro-5-[(4-methoxybenzyl)oxy]pyridine



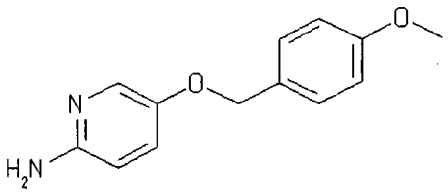
To a solution of 2-chloro-5-hydroxypyridine (50 g, 0.386 mol) and potassium carbonate (80 g, 0.579 mol) in N,N-dimethylformamide (300 mL) was added p-methoxybenzyl chloride (66.5 g, 0.425 mol), and the mixture was stirred at 80°C for 4 hr. Ethyl acetate and water were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and

filtered. The solvent was evaporated under reduced pressure, and the obtained residue was washed with methanol to give the title compound (61.3 g, 64%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 3.76 (3H, s), 5.10 (2H, s), 6.82 - 7.06 (2H, m), 7.34 - 7.46 (3H, m), 7.50 - 7.59 (1H, m), 8.17 (1H, d, J = 2.6 Hz).

Reference Example 89

Production of 5-[(4-methoxybenzyl)oxy]pyridin-2-amine

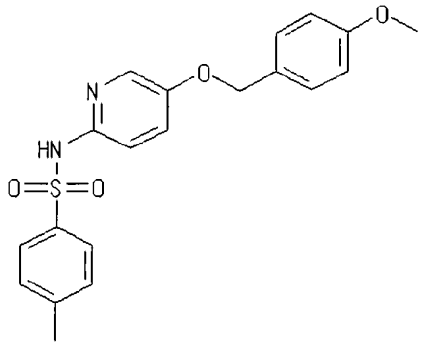


To a solution of 2-chloro-5-[(4-methoxybenzyl)oxy]pyridine (45 g, 180 mmol), tris(dibenzylideneacetone)dipalladium(0) (5 g, 5.46 mmol) and (2-biphenyl)dicyclohexylphosphine (5.1 g, 14.56 mmol) in tetrahydrofuran (500 mL) was added dropwise bis(trimethylsilyl)amidelithium (1.6 mol/L tetrahydrofuran solution, 170 mL, 273.2 mmol) at room temperature, and the mixture was stirred at 80°C for 4 hr under a nitrogen atmosphere. 2N Hydrochloric acid (300 mL, 600 mmol) was added to the reaction mixture, and the mixture was stirred at room temperature for 1 hr. Ethyl acetate and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with water and twice with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the obtained residue was washed with methanol to give the title compound (34.4 g, 82%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 3.75 (3H, s), 4.90 (2H, s), 5.45 (2H, s), 6.40 (1H, d, J = 8.9 Hz), 6.86 - 6.98 (2H, m), 7.14 (1H, dd, J = 8.9, 3.0 Hz), 7.28 - 7.38 (2H, m), 7.67 (1H, d, J = 2.6 Hz).

Reference Example 90

Production of N-{5-[(4-methoxybenzyl)oxy]pyridin-2-yl}-4-methylbenzenesulfonamide

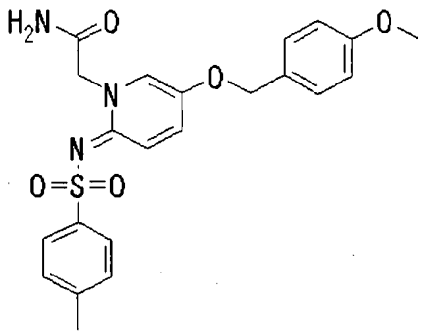


To a solution of 5-[(4-methoxybenzyl)oxy]pyridin-2-amine (24 g, 104 mmol) in pyridine (210 mL) was added 4-methylbenzenesulfonyl chloride (20.9 g, 110 mmol) at 0°C, and the mixture was stirred at room temperature for 4 hr. The reaction mixture was concentrated, the residue was washed with saturated aqueous sodium hydrogen carbonate solution and ethyl acetate to give the title compound (37 g, 93%) as a pale-red solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.34 (3H, s), 3.75 (3H, s), 4.98 (2H, s), 6.82 - 7.00 (2H, m), 7.07 (1H, d, J = 8.9 Hz), 7.26 - 7.46 (5H, m), 7.66 - 7.77 (2H, m), 7.91 (1H, d, J = 2.6 Hz), 10.74 (1H, br s).

Reference Example 91

Production of 2-[5-[(4-methoxybenzyl)oxy]-2-{[(4-methylphenyl)sulfonyl]imino}pyridin-1(2H)-yl]acetamide



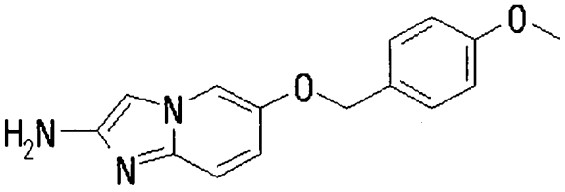
To a suspension of N-{5-[(4-methoxybenzyl)oxy]pyridin-2-yl}-4-methylbenzenesulfonamide (10.0 g, 26.0 mmol) in N,N-

dimethylformamide (85 mL) were added N,N-diisopropylethylamine (6.8 mL, 39.0 mmol) and iodoacetamide (5.77 g, 31.0 mmol), and the mixture was stirred at 60°C for 5 hr. After cooling to room temperature, ethyl acetate and water were added, and the mixture was extracted 3 times with a mixed solution of ethyl acetate and tetrahydrofuran. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (34.4 g, 75%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.33 (3H, s), 3.75 (3H, s), 4.82 (2H, s), 4.89 (2H, s), 6.81 - 7.03 (2H, m), 7.20 - 7.41 (6H, m), 7.60 - 7.69 (3H, m), 7.76 (1H, d), 7.92 (1H, d, J = 3.0 Hz).

Reference Example 92

Production of 6-[(4-methoxybenzyl)oxy]imidazo[1,2-a]pyridin-2-amine



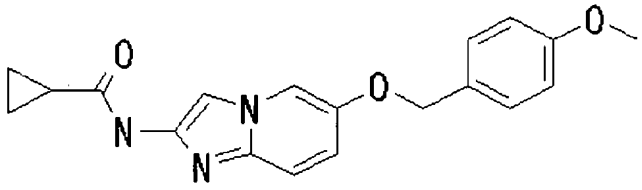
To a suspension of 2-[5-[(4-methoxybenzyl)oxy]-2-{[(4-methylphenyl)sulfonyl]imino}pyridin-1(2H)-yl]acetamide (20.8 g, 47.1 mmol) in tetrahydrofuran (200 mL) was added trifluoroacetic acid anhydride (49.5 g, 235.5 mmol) at 0°C, and the mixture was stirred for 1 hr. Methanol (100 mL) was added to the reaction mixture, 8N aqueous sodium hydroxide solution was added until pH reached 12 to 13, and the mixture was stirred at room temperature for 3 hr. Water and ethyl acetate were added to the reaction mixture, and the mixture was extracted 4 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated

under reduced pressure. The obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (8.6 g, 68%) as a brown solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 3.76 (3H, s), 4.90 (2H, s), 4.93 (2H, s), 6.81 (1H, dd, J = 9.5, 2.4 Hz), 6.88 - 7.00 (3H, m), 7.08 (1H, d, J = 9.6 Hz), 7.32 - 7.44 (2H, m), 8.12 (1H, d, J = 1.7 Hz).

Reference Example 93

Production of N-{6-[(4-methoxybenzyl)oxy]imidazo[1,2-a]pyridin-2-yl}cyclopropanecarboxamide

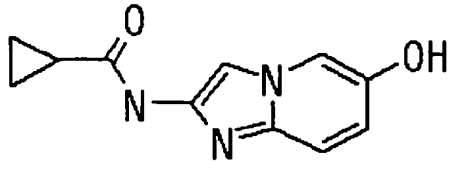


To a solution of 6-[(4-methoxybenzyl)oxy]imidazo[1,2-a]pyridin-2-amine (8.5 g, 31.6 mmol) in N,N-dimethylacetamide (80 mL) was added a solution of cyclopropanecarbonyl chloride (3.43 mL, 37.9 mmol) in N,N-dimethylacetamide (20 mL) at 0°C, and the mixture was stirred at 0°C for 3 hr. The reaction mixture was diluted with water, and the precipitate was collected by filtration and washed with water and ethyl acetate to give the title compound (8.9 g, 83%) as a gray solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.62 - 0.89 (4H, m), 1.87 - 1.96 (1H, m), 3.76 (3H, s), 4.96 (2H, s), 6.89 - 6.99 (2H, m), 7.02 (1H, dd, J = 9.6, 2.3 Hz), 7.32 (1H, d, J = 9.6 Hz), 7.37 - 7.45 (2H, m), 7.96 (1H, s), 8.36 (1H, d, J = 1.7 Hz), 10.88 (1H, s).

Reference Example 94

Production of N-(6-hydroxyimidazo[1,2-a]pyridin-2-yl)cyclopropanecarboxamide

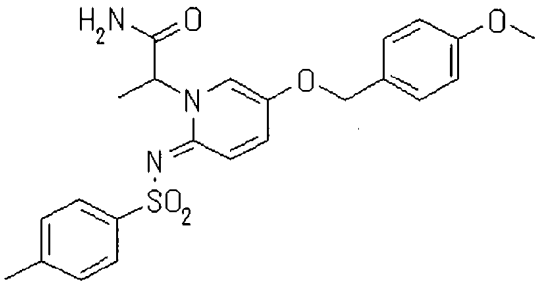


To a solution of N-{6-[(4-methoxybenzyl)oxy]imidazo[1,2-a]pyridin-2-yl}cyclopropanecarboxamide (10.1 g, 29.9 mmol) and anisole (25.97 mL, 239.2 mmol) in trifluoromethylbenzene (200 mL) was added trifluoroacetic acid (40.4 mL), and the mixture was stirred at room temperature for 3 hr. Saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was extracted 5 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (5.7 g, 88%) as a pale-brown solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.67 - 0.86 (4H, m), 1.83 - 1.97 (1H, m), 6.89 (1H, dd, J = 9.6, 2.3 Hz), 7.25 (1H, d, J = 9.4 Hz), 7.91 (1H, s), 7.96 - 8.00 (1H, m), 9.43 (1H, br s), 10.81 (1H, s).

Reference Example 95

Production of 2-[5-[(4-methoxybenzyl)oxy]-2-{[(4-methylphenyl)sulfonyl]imino}pyridin-1(2H)-yl]propanamide



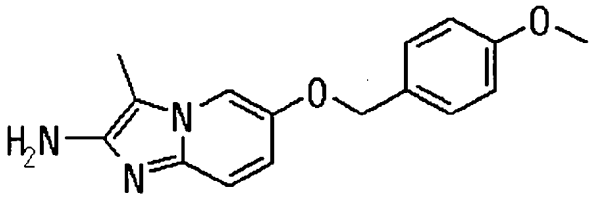
To a solution of N-{5-[(4-methoxybenzyl)oxy]pyridin-2-yl}-4-methylbenzenesulfonamide (3 g, 7.80 mmol) in N,N-dimethylformamide (30 mL) were added 2-bromopropanamide (2.82 g, 18.4 mmol) and N,N-diisopropylethylamine (4.04 mL, 23.4 mmol), and the mixture was stirred at room temperature for 2 days. Ethyl acetate and water were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine,

dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane=3/1→ethyl acetate alone) to give the title compound (2.64 g, 74%) as a colorless oil.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.65 (3H, d, J = 7.4 Hz), 2.33 (3H, s), 3.75 (3H, s), 4.83 - 5.12 (2H, m), 5.80 (1H, q, J = 7.2 Hz), 6.86 - 6.98 (2H, m), 7.19 - 7.47 (6H, m), 7.59 - 7.83 (5H, m).

Reference Example 96

Production of 6-[(4-methoxybenzyl)oxy]-3-methylimidazo[1,2-a]pyridin-2-amine



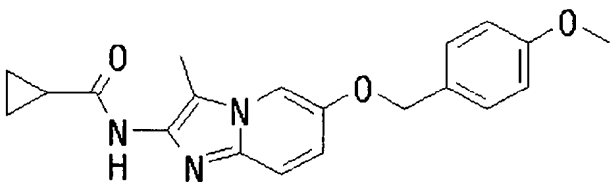
To a suspension of 2-[5-[(4-methoxybenzyl)oxy]-2-{[(4-methylphenyl)sulfonyl]imino}pyridin-1(2H)-yl]propanamide (2.6 g, 5.71 mmol) in tetrahydrofuran (25 mL) was added trifluoroacetic acid anhydride (2.35 mL, 17.1 mmol) at 0°C, and the mixture was stirred at room temperature for 1 hr. 8N Aqueous sodium hydroxide solution was added to the reaction mixture until it reached pH 12 to 13, and the mixture was stirred at 50°C for 5 hr. Water and ethyl acetate were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (1.0 g, 68%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.26 (3H, s), 3.76 (3H, s), 4.81 (2H, s), 5.01 (2H, s), 6.80 (1H, dd, J = 9.4, 2.3 Hz), 6.91 - 6.99 (2H, m), 7.09 (1H, d, J = 9.4 Hz), 7.31 - 7.48 (2H, m),

7.67 (1H, d, J = 2.1 Hz).

Reference Example 97

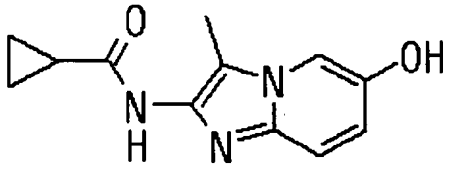
Production of N-{6-[(4-methoxybenzyl)oxy]-3-methylimidazo[1,2-a]pyridin-2-yl}cyclopropanecarboxamide



To a solution of 6-[(4-methoxybenzyl)oxy]-3-methylimidazo[1,2-a]pyridin-2-amine (1.0 g, 3.53 mmol) in N,N-dimethylacetamide (10 mL) was added cyclopropanecarbonyl chloride (352 μL, 3.88 mmol), and the mixture was stirred at 0°C for 2 hr. Ethyl acetate and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (750 mg, 60%) as a slightly-yellow solid. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.64 - 0.93 (4H, m), 1.80 - 1.89 (1H, m), 2.28 (3H, s), 3.76 (3H, s), 5.06 (2H, s), 6.91 - 7.08 (3H, m), 7.34 - 7.48 (3H, m), 7.91 (1H, d, J = 1.9 Hz), 10.12 (1H, s).

Reference Example 98

Production of N-(6-hydroxy-3-methylimidazo[1,2-a]pyridin-2-yl)cyclopropanecarboxamide



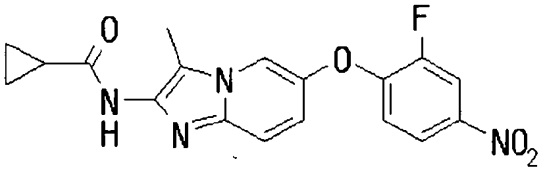
To a solution of N-{6-[(4-methoxybenzyl)oxy]-3-methylimidazo[1,2-a]pyridin-2-yl}cyclopropanecarboxamide (700 mg, 1.99 mmol) and anisole (1.73 mL, 15.9 mmol) in

trifluoromethylbenzene (7 mL) was added trifluoroacetic acid (1.4 mL), and the mixture was stirred at room temperature for 2 hr. Saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was extracted 4 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate to give the title compound (65 mg, 14%) as a slightly-yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.70 - 0.82 (4H, m), 1.73 - 1.90 (1H, m), 2.21 (3H, s), 6.87 - 6.98 (1H, m), 7.32 (1H, d, J = 9.6 Hz), 7.58 (1H, d, J = 1.9 Hz), 9.51 (1H, br s), 10.06 (1H, s).

Reference Example 99

Production of N-[6-(2-fluoro-4-nitrophenoxy)-3-methylimidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide



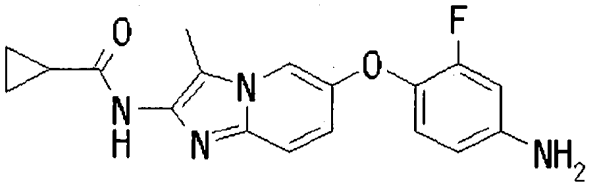
To a solution of N-(6-hydroxy-3-methylimidazo[1,2-a]pyridin-2-yl)cyclopropanecarboxamide (65 mg, 0.281 mmol) and 1,2-difluoro-4-nitrobenzene (37 μL, 0.337 mmol) in dimethyl sulfoxide (1 mL) was added cesium carbonate (137 mg, 0.422 mmol), and the mixture was stirred overnight at room temperature. Ethyl acetate and saturated aqueous ammonium chloride solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane=1/1→ethyl acetate alone) to give the title

compound (80 mg, 77%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.68 - 0.91 (4H, m), 1.76 - 1.92 (1H, m), 2.29 (3H, s), 7.12 - 7.28 (2H, m), 7.60 (1H, d, J = 9.4 Hz), 7.96 - 8.11 (1H, m), 8.37 (1H, dd, J = 10.9, 2.7 Hz), 8.53 (1H, d, J = 1.9 Hz), 10.27 (1 H, br s).

Reference Example 100

Production of N-[6-(4-amino-2-fluorophenoxy)-3-methylimidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide

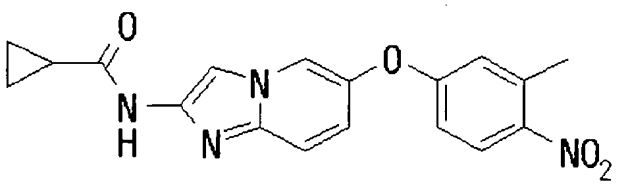


A mixed solution of N-[6-(2-fluoro-4-nitrophenoxy)-3-methylimidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (80 mg, 0.216 mmol), reduced iron (64 mg, 1.08 mmol) and ammonium chloride (116 mg, 2.16 mmol) in ethanol (2 mL)/water (0.5 mL) was stirred at 80°C for 3 hr. The reaction mixture was diluted with ethyl acetate and filtered through celite. Water was added to the filtrate, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure to give the title compound (60 mg, 82%) as a slightly yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.77 (4H, d, J = 5.9 Hz), 1.80 - 1.91 (1H, m), 2.22 (3H, s), 5.33 (2H, s), 6.33 - 6.42 (1H, m), 6.49 (1H, dd, J = 13.4, 2.6 Hz), 6.88 - 7.04 (2H, m), 7.45 (1H, d, J = 9.8 Hz), 7.85 (1H, d, J = 2.1 Hz), 10.17 (1H, br s).

Reference Example 101

Production of N-[6-(3-methyl-4-nitrophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide

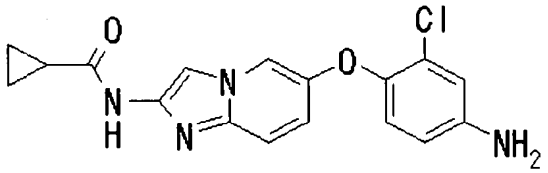


To a solution of N-(6-hydroxyimidazo[1,2-a]pyridin-2-yl)cyclopropanecarboxamide (200 mg, 0.92 mmol) and 4-fluoro-2-methyl-1-nitrobenzene (171.3 mg, 1.1 mmol) in dimethyl sulfoxide (2 mL) was added cesium carbonate (450 mg, 1.38 mmol), and the mixture was stirred at room temperature for 6 hr. Ethyl acetate and saturated aqueous ammonium chloride solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The residue was washed with ethyl acetate and collected by filtration to give the title compound (232 mg, 72%) as a brown solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.88 (4H, m), 1.88 - 1.97 (1H, m), 2.52 (3H, s), 7.03 (1H, dd, J = 9.1, 2.8 Hz), 7.09 - 7.18 (2H, m), 7.52 (1H, d, J = 9.4 Hz), 7.99 - 8.16 (2H, m), 8.68 (1H, dd, J = 2.5, 0.8 Hz), 11.02 (1H, s).

Reference Example 102

Production of N-[6-(4-amino-2-chlorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide

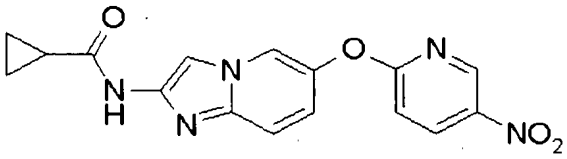


To a solution of N-(6-hydroxyimidazo[1,2-a]pyridin-2-yl)cyclopropanecarboxamide (200 mg, 0.921 mmol) and 4-fluoro-3-chloro-1-nitrobenzene (193 mg, 1.11 mmol) in dimethyl sulfoxide (2 mL) was added cesium carbonate (450 mg, 1.38 mmol), and the mixture was stirred at room temperature for 6 hr. Ethyl acetate and saturated aqueous ammonium chloride

solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, and the solvent was evaporated under reduced pressure. A mixed solution of the obtained residue, reduced iron (271 mg, 4.61 mmol) and ammonium chloride (493 mg, 9.21 mmol) in ethanol (2 mL)/tetrahydrofuran (2 mL)/water (1 mL) was stirred at 80°C for 7 hr. The reaction mixture was diluted with ethyl acetate and tetrahydrofuran, and filtered through celite. Water was added to the filtrate, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane=2/1→ethyl acetate alone) to give the title compound (177.5 mg, 56%) as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.67 - 0.89 (4H, m), 1.82 - 1.96 (1H, m), 5.33 (2H, s), 6.54 (1H, dd, J = 8.7, 2.6 Hz), 6.72 (1H, d, J = 2.6 Hz), 6.93 (1H, d, J = 8.7 Hz), 6.99 (1H, dd, J = 9.6, 2.5 Hz), 7.38 (1H, d, J = 9.6 Hz), 8.00 (1H, s), 8.17 (1H, d, J = 1.9 Hz), 10.89 (1H, s).

Reference Example 103

Production of N-{6-[(5-nitropyridin-2-yl)oxy]imidazo[1,2-a]pyridin-2-yl}cyclopropanecarboxamide



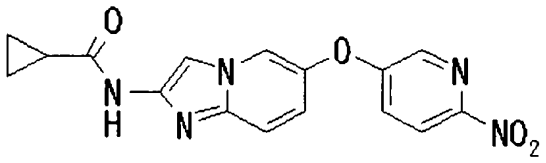
To a solution of N-(6-hydroxyimidazo[1,2-a]pyridin-2-yl)cyclopropanecarboxamide (200 mg, 0.921 mmol) and 2-chloro-5-nitropyridine (175 mg, 1.1 mmol) in dimethyl sulfoxide (3 mL) was added cesium carbonate (450 mg, 1.38 mmol), and the mixture was stirred at room temperature for 3 hr. Ethyl acetate, tetrahydrofuran and water were added to the reaction mixture, and the mixture was extracted 3 times with ethyl

acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (111 mg, 36%) as a brown solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.67 - 0.91 (4H, m), 1.90 - 1.98 (1H, m), 7.19 (1H, dd, J = 9.6, 2.3 Hz), 7.37 (1H, d, J = 9.1 Hz), 7.50 (1H, d, J = 9.6 Hz), 8.08 (1H, s), 8.65 (1H, dd, J = 9.1, 2.8 Hz), 8.69 - 8.74 (1H, m), 9.05 (1H, d, J = 2.3 Hz), 11.02 (1H, s).

Reference Example 104

Production of N-{6-[(6-nitropyridin-3-yl)oxy]imidazo[1,2-a]pyridin-2-yl}cyclopropanecarboxamide

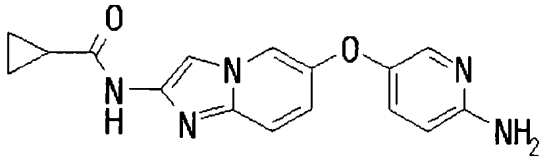


Using N-(6-hydroxyimidazo[1,2-a]pyridin-2-yl)cyclopropanecarboxamide (200 mg, 0.921 mmol), 5-chloro-2-nitropyridine (218.8 mg, 1.38 mmol), dimethyl sulfoxide (5 mL) and cesium carbonate (450 mg, 1.38 mmol), and in the same manner as in the production method of N-[6-(3-methyl-4-nitrophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (Reference Example 101), the title compound (190 mg, 61%) was obtained as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.70 - 0.88 (4H, m), 1.88 - 1.98 (1H, m), 7.22 (1H, dd, J = 9.6, 2.3 Hz), 7.55 (1H, d, J = 9.6 Hz), 7.74 (1H, dd, J = 9.0, 2.9 Hz), 8.09 (1H, s), 8.33 (1H, d, J = 9.4 Hz), 8.50 (1H, d, J = 2.5 Hz), 8.76 (1H, dd, J = 2.5, 0.8 Hz), 11.02 (1H, s).

Reference Example 105

Production of N-{6-[(6-aminopyridin-3-yl)oxy]imidazo[1,2-a]pyridin-2-yl}cyclopropanecarboxamide

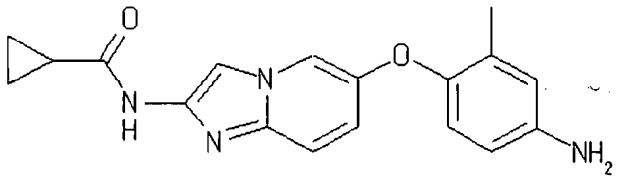


A mixed solution of N-{6-[(6-nitropyridin-3-yl)oxy]imidazo[1,2-a]pyridin-2-yl}cyclopropanecarboxamide (184 mg, 0.542 mmol), reduced iron (173 mg, 2.95 mmol) and ammonium chloride (315 mg, 5.89 mmol) in ethanol (2 mL) and water (0.5 mL) was stirred at 80°C for 1 hr. The reaction mixture was diluted with ethyl acetate, and filtered through celite. Water was added to the filtrate, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate→ethyl acetate/methanol=95/5) to give the title compound (75 mg, 45%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.70 - 0.87 (4H, m), 1.84 - 1.94 (1H, m), 5.87 (2H, s), 6.48 (1H, d, J = 8.9 Hz), 7.04 (1H, dd, J = 9.6, 2.5 Hz), 7.24 (1H, dd, J = 8.9, 3.0 Hz), 7.39 (1H, d, J = 9.6 Hz), 7.79 (1H, d, J = 2.5 Hz), 8.00 (1H, s), 8.29 (1H, dd, J = 2.5, 0.8 Hz), 10.91 (1H, s).

Reference Example 106

N-[6-(4-amino-2-methylphenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide



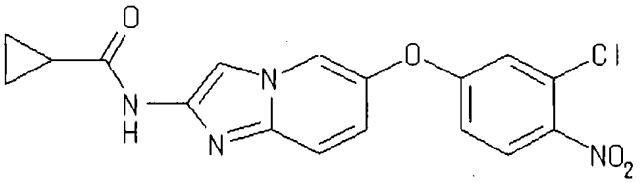
To a solution of N-(6-hydroxyimidazo[1,2-a]pyridin-2-yl)cyclopropanecarboxamide (300 mg, 1.38 mmol) and 4-fluoro-3-methyl-1-nitrobenzene (279 mg, 1.80 mmol) in dimethyl sulfoxide (3 mL) was added cesium carbonate (674 mg, 2.07 mmol), and the mixture was stirred at room temperature for 24

hr. Ethyl acetate, tetrahydrofuran and water were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, and the solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate and collected by filtration. A mixed solution of the obtained solid, reduced iron (406 mg, 6.9 mmol) and ammonium chloride (738 mg, 13.8 mmol) in ethanol (5 mL)/tetrahydrofuran (3 mL)/water (2 mL) was stirred at 80°C for 6 hr. The reaction mixture was diluted with ethyl acetate and tetrahydrofuran, and filtered through celite. Water was added to the filtrate, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane=2/1→ethyl acetate alone) to give the title compound (190 mg, 43%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.60 - 0.92 (4H, m), 1.79 - 1.93 (1H, m), 2.06 (3H, s), 4.93 (2H, s), 6.35 - 6.44 (1H, m), 6.48 (1H, d, J = 2.3 Hz), 6.69 (1H, d, J = 8.5 Hz), 6.97 (1H, dd, J = 9.6, 2.3 Hz), 7.36 (1H, d, J = 9.6 Hz), 7.97 (1H, s), 8.03 - 8.06 (1H, m), 10.87 (1H, s).

Reference Example 107

Production of N-[6-(3-chloro-4-nitrophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide



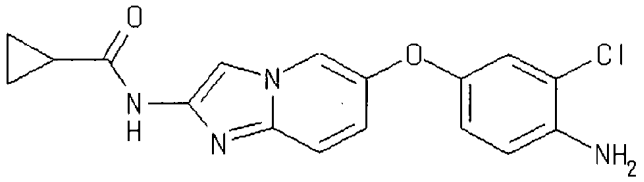
Using N-(6-hydroxyimidazo[1,2-a]pyridin-2-yl)cyclopropanecarboxamide (200 mg, 0.92 mmol), 4-fluoro-2-chloro-1-nitrobenzene (315 mg, 1.79 mmol), dimethyl sulfoxide (4 mL) and cesium carbonate (675 mg, 2.07 mmol), and in the

same manner as in Reference Example 101, the title compound (382 mg, 74%) was obtained as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.68 - 0.92 (4H, m), 1.88 - 1.97 (1H, m), 7.13 - 7.24 (2H, m), 7.44 (1H, d, J = 2.6 Hz), 7.53 (1H, d), 8.04 - 8.20 (2H, m), 8.64 - 8.81 (1H, m), 11.02 (1H, s).

Reference Example 108

Production of N-[6-(4-amino-3-chlorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide

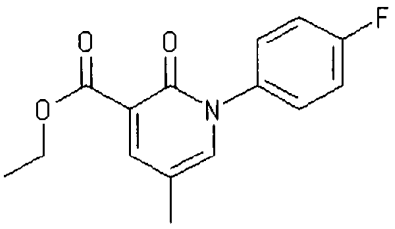


Using N-[6-(3-chloro-4-nitrophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (300 mg, 0.805 mmol), reduced iron (237 mg, 4.02 mmol), ammonium chloride (430 mg, 8.05 mmol), ethanol (2 mL), tetrahydrofuran (2 mL) and water (0.5 mL), and in the same manner as in Reference Example 105, the title compound (166 mg, 60%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.58 - 0.94 (4H, m), 1.85 - 1.97 (1H, m), 5.20 (2H, s), 6.73 - 6.91 (2H, m), 6.96 - 7.06 (2H, m), 7.40 (1H, d, J = 9.6 Hz), 8.01 (1H, s), 8.34 (1H, d, J = 1.5 Hz), 10.91 (1H, s).

Reference Example 109

Production of ethyl 1-(4-fluorophenyl)-5-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate



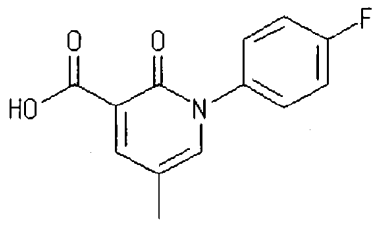
To a solution (30 mL) of diethyl[(2E)-3-ethoxy-2-methylprop-2-en-1-ylidene]propanedionate (160 mg, 0.467 mmol) and piperidine (0.2 mL) in ethanol was added 4-fluoroaniline

(1.12 mL, 11.7 mmol) was added, and the mixture was stirred at 80°C for 17 hr. The reaction mixture was concentrated, and the obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane=1/2→1/1) to give a brown solid. The brown solid was washed with diethyl ether and collected by filtration to give the title compound (1.2 g, 37%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.25 (3H, t, J = 7.1 Hz), 2.09 (3H, s), 4.21 (2H, q, J = 7.2 Hz), 7.26 - 7.41 (2H, m), 7.43 - 7.54 (2H, m), 7.76 (1H, dd, J = 2.6, 0.9 Hz), 7.98 (1H, d, J = 2.6 Hz).

Reference Example 110

Production of 1-(4-fluorophenyl)-5-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid

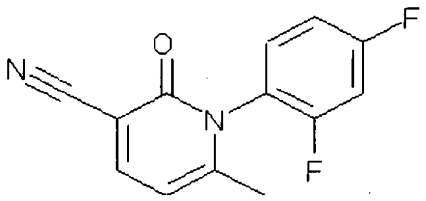


To a solution of ethyl 1-(4-fluorophenyl)-5-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate (1.2 g, 4.36 mmol) in methanol (12 mL) was added 1N aqueous sodium hydroxide solution (10 mL, 10 mmol), and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated, and the obtained residue was diluted with ethyl acetate and water and extracted with water. The aqueous layer was treated with 1N hydrochloric acid (20 mL, 20 mmol), and the precipitate was collected by filtration to give a white solid. The white solid was washed with water to give the title compound (730 mg, 68%).

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.20 (3H, s), 7.31 - 7.52 (2H, m), 7.55 - 7.67 (2H, m), 8.07 (1H, dd, J = 2.6, 0.9 Hz), 8.39 (1H, d, J = 2.5 Hz), 14.48 (1H, br s).

Reference Example 111

Production of 1-(2,4-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile

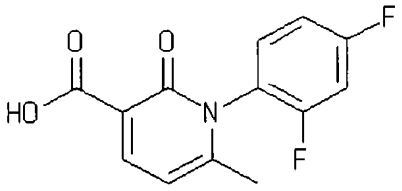


To a solution of 2-cyano-N-(2,4-difluorophenyl)acetamide (5.5 g, 28 mmol) and (3E)-4-methoxybut-3-en-2-one (3.65 g, 36.5 mmol) in dimethyleneglycol monomethylether (50 mL) was added 1,4-diazabicyclo[2.2.2]octane (3.14 g, 28 mmol), and the mixture was stirred at 120°C for 12 hr. The reaction mixture was diluted with 2N hydrochloric acid, tetrahydrofuran and ethyl acetate, and extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate to give a slightly yellow solid. The slightly yellow solid was suspended in tetrahydrofuran at 80°C, and the suspension was stirred for 30 min. The suspension was filtrated, and the obtained solid was washed with tetrahydrofuran to give the title compound (650 mg, 9.4%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.07 (3H, s), 6.38 - 6.75 (1H, m), 7.17 - 7.39 (1H, m), 7.53 - 7.74 (2H, m), 8.05 - 8.39 (1H, m).

Reference Example 112

Production of 1-(2,4-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid



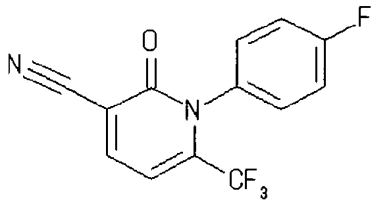
A solution of 1-(2,4-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (600 mg, 2.44 mmol) in conc. sulfuric acid (3 mL)/water (3 mL) was stirred at 120°C for 17

hr. The reaction solution was allowed to cool to room temperature, and alkalified with 8N aqueous sodium hydroxide solution. The aqueous layer was washed with ethyl acetate. The aqueous layer was acidified with 2N hydrochloric acid and the precipitate was collected by filtration and washed with water to give the title compound (600 mg, 93%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.15 (3H, s), 6.83 (1H, d, J = 8.1 Hz), 7.28 - 7.43 (1H, m), 7.56 - 7.82 (2H, m), 8.44 (1H, d, J = 7.6 Hz), 13.74 (1 H, br s).

Reference Example 113

Production of 1-(4-fluorophenyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

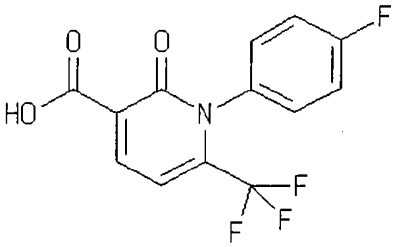


To a solution of 2-cyano-N-(4-fluorophenyl)acetamide (2 g, 11.2 mmol) and (3E)-4-ethoxy-1,1,1-trifluorobut-3-en-2-one (2.26 g, 13.4 mmol) in dimethyleneglycol monomethylether (20 mL) was added 1,4-diazabicyclo[2.2.2]octane (1.26 g, 11.2 mmol), and the mixture was stirred at 120°C for 6 hr. The reaction mixture was diluted with 1N hydrochloric acid and ethyl acetate, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (NH silica gel, ethyl acetate/hexane=1/2→1/1) to give a white solid. The white solid was washed with ethyl acetate and collected by filtration to give the title compound (230 mg, 7.2%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 7.13 (1H, d, J = 7.6 Hz), 7.32 - 7.46 (2H, m), 7.49 - 7.60 (2H, m), 8.44 (1H, d, J = 7.4 Hz).

Reference Example 114

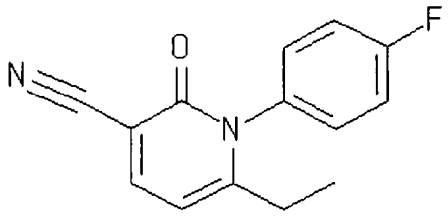
Production of 1-(4-fluorophenyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydropyridine-3-carboxylic acid



A solution of 1-(4-fluorophenyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile (200 mg, 0.709 mmol) in conc. sulfuric acid (1.5 mL)/water (1.5 mL) was stirred at 120°C for 17 hr. The reaction solution was allowed to cool to room temperature, 6N aqueous sodium hydroxide solution was added, and the aqueous layer was washed with ethyl acetate. 1N Hydrochloric acid was added to the aqueous layer, and the precipitate was filtered and washed with water to give the title compound (160 mg, 75%) as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 7.24 (1H, d, J = 7.6 Hz), 7.35 - 7.48 (2H, m), 7.51 - 7.65 (2H, m), 8.40 (1H, d, J = 7.6 Hz), 13.62 (1H, br s).

Reference Example 115

Production of 6-ethyl-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile



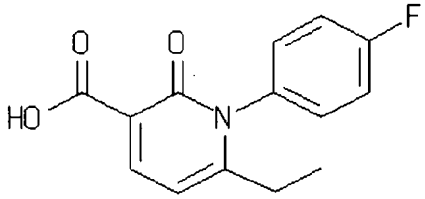
To a solution of 2-cyano-N-(4-fluorophenyl)acetamide (1.7 g, 10.6 mmol) in dimethyleneglycol monomethylether (20 mL) were added 1,4-diazabicyclo[2.2.2]octane (1.2 g, 10.6 mmol) and (1E)-1-methoxypent-1-en-3-one (1.82 g, 15.9 mmol), and the mixture was stirred at 120°C for 12 hr. The reaction mixture was diluted with 1N hydrochloric acid and ethyl

acetate, and extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (NH silica gel, ethyl acetate/hexane=50/50→100/0) to give a white solid. The white solid was washed with ethyl acetate to give the title compound (410 mg, 16%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.00 (3H, t, J = 7.4 Hz), 2.25 (2H, q, J = 7.4 Hz), 6.44 (1H, d, J = 7.6 Hz), 7.35 - 7.49 (4H, m), 8.20 (1H, d, J = 7.6 Hz).

Reference Example 116

Production of 6-ethyl-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid

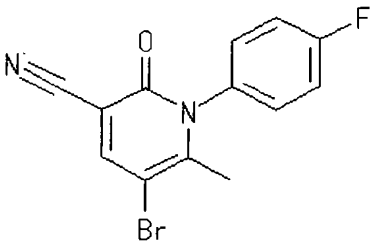


A solution of 6-ethyl-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (410 mg, 1.69 mmol) in conc. sulfuric acid (2 mL)/water (2 mL) was stirred at 120°C for 17 hr. The reaction solution was allowed to cool to room temperature, 6N aqueous sodium hydroxide solution was added, and the aqueous layer was washed with ethyl acetate. 1N Hydrochloric acid was added to the aqueous layer, and the precipitate was collected by filtration and washed with water to give the title compound (345 mg, 78%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.05 (3H, t, J = 7.4 Hz), 2.33 (2 H, q, J = 7.4 Hz), 6.76 (1H, d, J = 7.7 Hz), 7.37 - 7.62 (4H, m), 8.45 (1H, d, J = 7.7 Hz), 14.17 (1H, br s).

Reference Example 117

Production of 5-bromo-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile

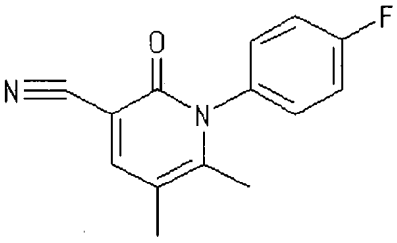


To a solution of 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (1 g, 4.05 mmol) in acetonitrile (10 mL)/tetrahydrofuran (5 mL) was added N-bromosuccinimide (792 mg, 4.46 mmol), and the mixture was stirred at 60°C overnight. After cooling to room temperature, saturated aqueous sodium hydrogen carbonate solution and ethyl acetate were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was washed with diethyl ether and collected by filtration to give the title compound (1.07 g, 86%) as a slightly yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.12 (3H, s), 6.95 - 7.77 (4H, m), 8.55 (1H, s).

Reference Example 118

Production of 1-(4-fluorophenyl)-5,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile



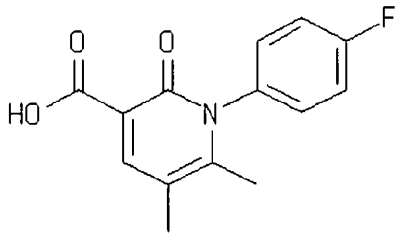
To a solution of 5-bromo-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (200 mg, 0.651 mmol) in N,N-dimethylformamide (2 mL) were added tetramethyltin (582 mg, 3.255 mmol) and tetrakistriphenylphosphinepalladium(0) (22.3 mg, 0.019 mmol), and the mixture was stirred at 120°C for 17 hr. Water and ethyl acetate were added to the reaction

mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, and the solvent was evaporated under reduced pressure. The obtained residue was washed with diethyl ether and collected by filtration to give the title compound (94 mg, 60%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.94 (3H, s), 2.10 (3H, s), 7.27 - 7.52 (4H, m), 8.13 (1H, s).

Reference Example 119

Production of 1-(4-fluorophenyl)-5,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid

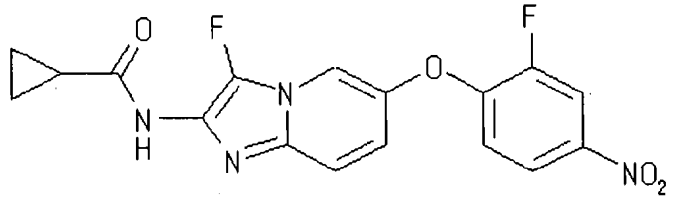


A solution of 1-(4-fluorophenyl)-5,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (90 mg, 0.324 mmol) in conc. sulfuric acid (0.5 mL) and water (0.5 mL) was stirred at 120°C for 8 hr. The reaction solution was allowed to cool to room temperature and diluted with water. The precipitate was collected by filtration and washed with water to give the title compound (90 mg, 93%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.03 (3H, s), 2.23 (3H, s), 7.37 - 7.52 (4H, m), 8.37 (1H, s), 14.44 (1H, br s).

Reference Example 120

Production of N-[3-fluoro-6-(2-fluoro-4-nitrophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide



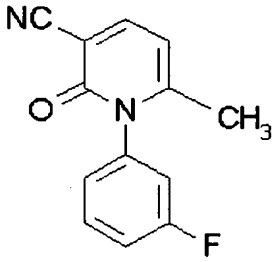
To a solution of N-[6-(2-fluoro-4-

nitrophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (121.6 mg, 0.341 mmol) in acetonitrile (0.5 mL)/tetrahydrofuran (0.5 mL) was added 1-fluoro-2,6-dichloropyridine triflate (129 mg, 0.409 mmol), and the mixture was stirred at room temperature for 2 hr. Tetrahydrofuran, ethyl acetate and 1N hydrochloric acid were added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (NH silica gel, ethyl acetate/hexane=1/2→1/1) to give the title compound (15.2 mg, 12%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.69 - 0.89 (4H, m), 1.77 - 1.94 (1H, m), 7.10 - 7.37 (2H, m), 7.58 (1H, d, J = 1.9 Hz), 7.94 - 8.16 (1H, m), 8.37 (1H, dd, J = 10.9, 2.7 Hz), 8.56 (1H, d, J = 2.3 Hz), 10.58 (1H, s).

Reference Example 121

1-(3-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile



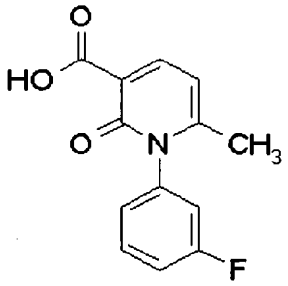
A solution (50 mL) of 2-cyano-N-(3-fluorophenyl)acetamide (6.60 g, 37.0 mmol), (3E)-4-methoxybut-3-en-2-one (5.60 g, 56.0 mmol) and 1,4-diazabicyclo[2.2.2]octane (6.20 g, 56.0 mmol) in 2-(2-methoxyethoxy)ethanol was stirred at 120°C for 12 hr. The reaction solution was divided into two layers with ethyl acetate and water and subjected to extraction (3 times) with ethyl acetate. The organic layer was washed with water and

saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (2.60 g, 31%) as a brown solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.03 (3H, s), 6.50 (1H, d, J = 7.6 Hz), 7.24 (1H, ddd, J = 7.4, 1.1 0.9 Hz), 7.34 - 7.46 (2H, m), 7.54 - 7.71 (1H, m), 8.17 (1H, d, J = 7.6 Hz).

Reference Example 122

1-(3-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid

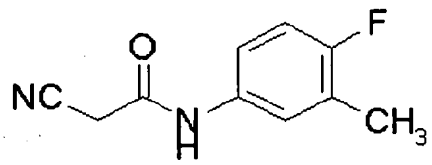


1-(3-Fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (2.60 g, 11.0 mmol) was suspended in aqueous sulfuric acid solution (98% sulfuric acid 13 mL, water 13 mL), and the mixture was stirred at 130°C for 10 hr. The reaction solution was allowed to cool to room temperature, water was added, and the precipitate was collected by filtration. The obtained solid was washed with ethyl acetate to give the title compound (2.20 g, 78%) as a brown solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.12 (3H, s), 6.81 (1H, dd, J = 7.6, 0.8 Hz), 7.32 (1H, ddd, J = 7.9, 1.9, 0.9 Hz), 7.38 - 7.53 (2H, m), 7.66 (1H, td, J = 8.1, 6.4 Hz), 8.41 (1H, d, J = 7.6 Hz).

Reference Example 123

2-cyano-N-(4-fluoro-3-methylphenyl)acetamide

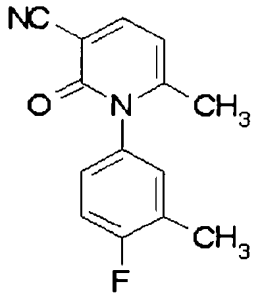


A mixture of 4-fluoro-3-methylaniline (2.50 g, 20.0 mmol) and ethyl cyanoacetate (2.70 g, 24.0 mmol) was stirred at 180°C for 14 hr. After cooling to room temperature, the obtained solid was washed with hexane and collected by filtration to give the title compound (3.60 g, 95%) as a brownish-red solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.22 (3H, s), 3.88 (2H, s), 7.10 (1H, t, J = 9.2 Hz), 7.28 - 7.55 (2H, m), 10.27 (1H, br s).

Reference Example 124

1-(4-fluoro-3-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile

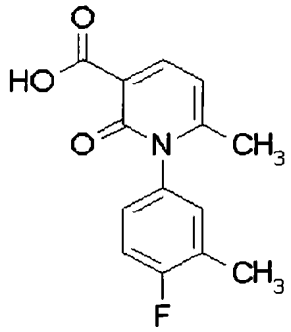


A solution (30 mL) of 2-cyano-N-(4-fluoro-3-methylphenyl)acetamide (3.60 g, 19.0 mmol), (3E)-4-methoxybut-3-en-2-one (2.80 g, 28.0 mmol) and 1,4-diazabicyclo[2.2.2]octane (3.20 g, 28.0 mmol) in 2-(2-methoxyethoxy)ethanol was stirred at 120°C for 12 hr. After cooling to room temperature, the reaction solution was divided into two layers with ethyl acetate and water and subjected to extraction (3 times) with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (1.60 g, 34%) as a brown solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.02 (3H, s), 2.27 (3H, d, J = 1.9 Hz), 6.43 - 6.53 (1H, m), 7.17 - 7.38 (3H, m), 8.14 (1H, d, J = 7.4 Hz).

Reference Example 125

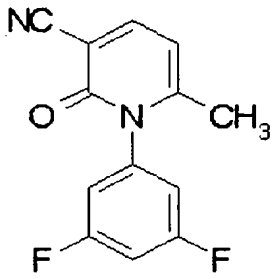
1-(4-fluoro-3-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid



1-(4-Fluoro-3-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (1.60 g, 6.60 mmol) was suspended in aqueous sulfuric acid solution (98% sulfuric acid 8 mL, water 8 mL), and the mixture was stirred at 130°C for 10 hr. The reaction solution was cooled to room temperature, water was added, and the precipitated solid was collected by filtration. The obtained solid was washed with ethyl acetate to give the title compound (1.00 g, 58%) as a brown solid. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.11 (3H, s), 2.29 (3H, d, J = 1.9 Hz), 6.80 (1H, d, J = 7.6 Hz), 7.27 - 7.48 (3H, m), 8.40 (1H, d, J = 7.6 Hz).

Reference Example 126

1-(3,5-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile



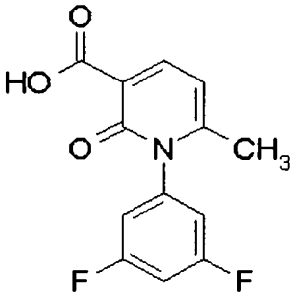
A solution (30 mL) of 2-cyano-N-(3,5-difluorophenyl)acetamide (3.10 g, 16.0 mmol), (3E)-4-methoxybut-3-en-2-one (2.40 g, 24.0 mmol) and 1,4-diazabicyclo[2.2.2]octane (2.70 g, 24.0 mmol) in 2-(2-methoxyethoxy)ethanol was stirred at 130°C for 12 hr. After

cooling to room temperature, the reaction solution was divided into two layers with ethyl acetate and water and subjected to extraction (3 times) with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (1.60 g, 40%) as a brown solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.07 (3H, s), 6.51 (1H, dd, J = 7.6, 0.8 Hz), 7.24 - 7.42 (2H, m), 7.49 (1H, tt, J = 9.4, 2.4 Hz), 8.18 (1H, d, J = 7.6 Hz).

Reference Example 127

1-(3,5-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid

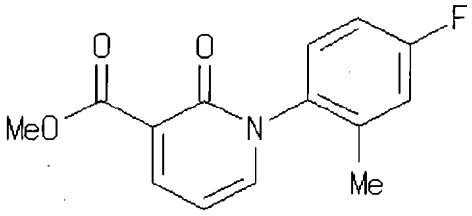


1-(3,5-Difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (1.50 g, 6.20 mmol) was suspended in aqueous sulfuric acid solution (98% sulfuric acid 8 mL, water 8 mL), and the mixture was stirred at 120°C for 10 hr. The reaction solution was cooled to room temperature and poured into water, and the precipitate was collected by filtration. The obtained solid was washed with ethyl acetate to give the title compound (1.00 g, 61%) as a brown solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.15 (3H, s), 6.80 (1H, dd, J = 7.6, 0.8 Hz), 7.35 - 7.47 (2H, m), 7.53 (1H, tt, J = 9.4, 2.4 Hz), 8.42 (1H, d, J = 7.6).

Reference Example 128

Production of methyl 1-(4-fluoro-2-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate

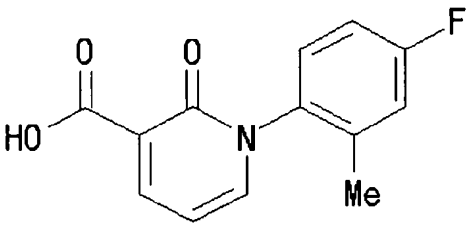


To a solution of methyl 2-oxo-2H-pyran-3-carboxylate (3 g, 19.5 mmol) in N,N-dimethylformamide (18 mL) was added 4-fluoro-2-methylaniline (2.44 g, 19.5 mmol), and the mixture was stirred at room temperature for 3 hr. 4-Dimethylaminopyridine (119 mg, 0.974 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (4.48 g, 23.4 mmol) were added to the reaction mixture, and the mixture was further stirred at room temperature for 16 hr. 2N Hydrochloric acid was added to the reaction solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane=1/1), and the obtained solid was washed with hexane/ethyl acetate (=1/1) and collected by filtration to give the title compound (0.40 g, 8%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.04 (3H, s), 3.75 (3H, s), 6.43 (1H, t, J = 6.9 Hz), 7.15 - 7.23 (1H, m), 7.27 - 7.37 (2H, m), 7.86 (1H, dd, J = 7.1, 2.4 Hz) 8.16 (1H, dd, J = 7.1, 2.4 Hz).

Reference Example 129

Production of 1-(4-fluoro-2-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid



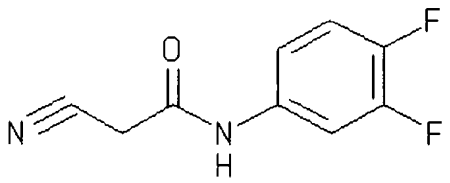
To a suspension of methyl 1-(4-fluoro-2-methylphenyl)-2-

oxo-1,2-dihydropyridine-3-carboxylate (0.40 g, 1.53 mmol) in methanol (9 mL) was added 2N aqueous sodium hydroxide solution (1.15 mL), and the mixture was stirred at room temperature for 3 hr. 6N Hydrochloric acid (0.5 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the obtained residue was washed with hexane/ethyl acetate (=1/1) to give the title compound (704 mg, 85%) as a yellow solid.

^{1}H-NMR (300 MHz, DMSO-d_6) δ 2.07 (3H, s), 6.81 (1H, t, J = 6.9 Hz), 7.20 - 7.29 (1H, m), 7.32 - 7.38 (1H, m), 7.46 - 7.52 (1H, m), 8.13 (1H, dd, J = 6.9, 2.1 Hz), 8.51 (1H, dd, J= 6.9, 2.1 Hz), 14.16 (1H, br s).

Reference Example 130

Production of 2-cyano-N-(3,4-difluorophenyl)acetamide



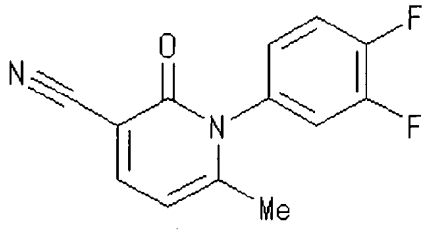
A mixed solution of 3,4-difluoroaniline (10 g, 77.5 mmol) and ethyl cyanoacetate (10.5 g, 92.9 mmol) was heated to 180°C and stirred for 8 hr. After cooling to room temperature, the mixture was dissolved in ethyl acetate/tetrahydrofuran and washed with water and saturated brine in this order. The mixture was dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (7.6 g, 56%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 3.92 (2H, s), 7.22 - 7.28 (1H, m), 7.36 - 7.47 (1H, m), 7.68 - 7.75 (1H, m), 10.53 (1H, s).

Reference Example 131

Production of 1-(3,4-difluorophenyl)-6-methyl-2-oxo-1,2-

dihydropyridine-3-carbonitrile

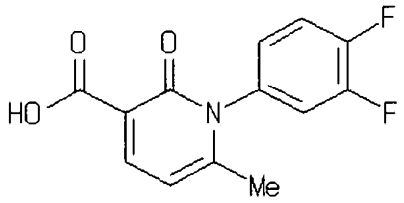


A mixture of 2-cyano-N-(3,4-difluorophenyl)acetamide (6.0 g, 30.6 mmol), (3E)-4-methoxybut-3-en-2-one (4.29 g, 42.8 mmol) and 2-(2-methoxyethoxy)ethanol (60 mL) was stirred at 90°C for 20 min. 1,4-Diazabicyclo[2.2.2]octane (3.77 g, 33.6 mmol) was added, and the mixture was stirred at 125°C for 5 hr. After cooling to room temperature, the mixture was adjusted to pH 5 with 2N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the obtained residue was washed with ethyl acetate/hexane (=1/1) and collected by filtration to give the title compound (3.69 g, 49%) as a pale-yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.05 (3H, s), 6.48 - 6.51 (1H, m), 7.25 - 7.35 (1H, m), 7.61 - 7.73 (2H, m), 8.17 (1H, d, J = 7.5 Hz).

Reference Example 132

Production of 1-(3,4-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid



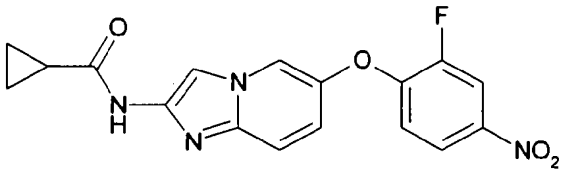
Water (7.2 mL) and conc. sulfuric acid (7.2 mL) were added to 1-(3,4-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (3.6 g, 14.6 mmol), and the mixture was stirred at 100°C for 20 hr. The mixture was basified (pH 10) with 8N aqueous sodium hydroxide solution at

0°C and washed with ethyl acetate. The aqueous layer was acidified (pH 3) with 6N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the obtained residue was washed with ethyl acetate/hexane (=1/1) and collected by filtration to give the title compound (2.49 g, 64%) as a thin-yellow powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.13 (3H, s), 6.80 (1H, d, J = 8.1 Hz), 7.34 - 7.43 (1H, m), 7.65 - 7.80 (2H, m), 8.41 (1H, d, J = 7.5 Hz), 14.06 (1H, br s).

Reference Example 133

Production of N-[6-(2-fluoro-4-nitrophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide

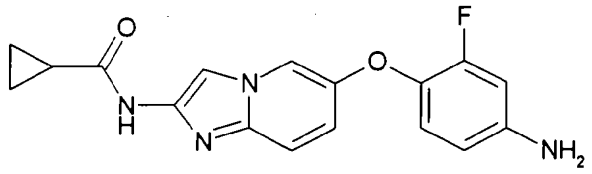


To a solution of N-(6-hydroxyimidazo[1,2-a]pyridin-2-yl)cyclopropanecarboxamide (30 g, 138 mmol) and 1,2-difluoro-4-nitrobenzene (24.2 g, 152 mmol) in dimethyl sulfoxide (180 mL) was added cesium carbonate (58.5 g, 180 mmol), and the mixture was stirred at room temperature for 5 hr under an argon atmosphere. Water (1080 mL) was added to the reaction mixture, and the mixture was stirred for 20 min. The precipitate was collected by filtration and washed with water and ethyl acetate. After air drying for one day, the mixture was dried under reduced pressure at 100°C for 5 hr to give the title compound (46.5 g, 95%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.84 (4H, m), 1.88 - 1.99 (1H, m), 7.22 (1H, d, J = 9.5 Hz), 7.21 - 7.27 (1H, m), 7.54 (1H, d, J = 9.5 Hz), 8.01 - 8.08 (1H, m), 8.08 (1H, s), 8.36 (1H, dd, J = 11.1, 2.9 Hz), 8.74 (1H, d, J = 1.8 Hz), 11.02 (1H, s).

Reference Example 134

Production of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide

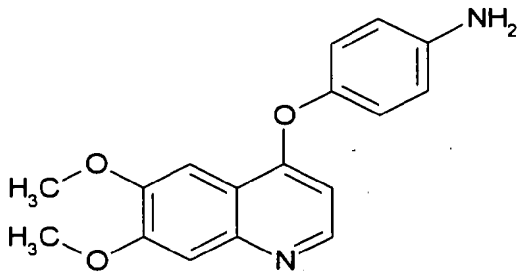


To a suspension of N-[6-(2-fluoro-4-nitrophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (10 g, 28.1 mmol) in tetrahydrofuran (80 mL)/methanol (80 mL) were added iron chloride·hexahydrate (0.5 g), hydrazine·monohydrate (8.2 mL, 168 mmol) and activated carbon (1.0 g), and the mixture was heated under reflux for 16 hr. After cooling to 40°C, the mixture was filtered through celite and washed with methanol. The solvent of the filtrate was evaporated under reduced pressure, and the precipitate was washed with water/methanol (=10/1) and collected by filtration to give the title compound (8.4 g, 92%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.81 (4H, m), 1.85 - 1.96 (1H, m), 5.34 (2H, s), 6.34 - 6.40 (1H, m), 6.49 (1H, dd, J = 135.5, 2.7 Hz), 7.00 - 7.05 (1H, m), 7.38 (1H, d, J = 9.5 Hz), 8.00 (1H, s), 8.21 (1H, d, J = 2.1 Hz), 10.88 (1H, s).

Reference Example 135

Production of 4-[(6,7-dimethoxyquinolin-4-yl)oxy]aniline

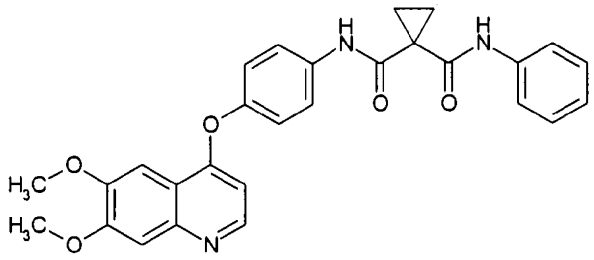


A suspension of 4-chloro-6,7-dimethoxyquinoline (1566 mg, 7.00 mmol), 4-aminophenol (917 mg, 8.40 mmol) and cesium carbonate (4561 mg, 14.0 mmol) in dimethyl sulfoxide (14 ml)

was stirred at 100°C for 18 hr. Water was added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate/tetrahydrofuran (=1/1). The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate→ethyl acetate/methanol=60/40). Ethyl acetate was added to the obtained residue and the mixture was filtrated to give the title compound (1267 mg, 61%) as a white powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 3.93 (6H, s), 5.16 (2H, s), 6.37 (1H, d, J = 5.4 Hz), 6.67 (2H, d, J = 8.7 Hz), 6.93 (2H, d, J = 8.7 Hz), 7.36 (1H, s), 7.50 (1H, s), 8.43 (1H, d, J = 5.4 Hz).

Reference Example 136

Production of N-{4-[(6,7-dimethoxyquinolin-4-yl]phenyl}-N'-phenylcyclopropanedicarboxamide



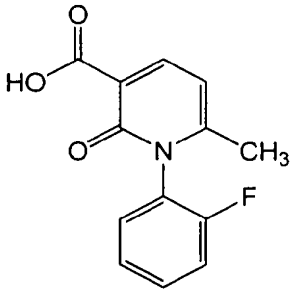
To a solution of 1-(phenylcarbamoyl)cyclopropanecarboxylic acid (237 mg, 1.04 mmol) in tetrahydron (10 mL) were added N,N-dimethylformamide (1 drop) and oxalyl chloride (178 μL, 2.08 mmol), and the mixture was stirred at room temperature for 2 hr. The solvent was evaporated under reduced pressure, N,N-dimethylacetamide (3 ml) and 4-[(6,7-dimethoxyquinolin-4-yl)oxy]aniline (213 mg, 1.04 mmol) were added to the obtained residue, and the mixture was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (ethyl acetate→ethyl

acetate/methanol=75/25). The obtained powder was recrystallized from ethyl acetate/diisopropyl ether to give the title compound (286 mg, 74%) as white crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.49 (4H, s), 3.93 (3H, s), 3.95 (3H, s), 6.43 (1H, d, J = 5.3 Hz), 7.07 (1H, t, J = 7.4 Hz), 7.23 (2H, d, J = 9.2 Hz), 7.27 - 7.35 (2H, m), 7.39 (1H, s), 7.51 (1H, s), 7.63 (2H, d, J = 7.4 Hz), 8.47 (1H, d, J = 5.3 Hz), 10.05(1H, brs), 10.26 (1H, brs).

Reference Example 137

Production of 1-(2-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid

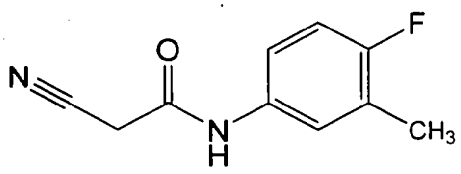


An aqueous solution (98% sulfuric acid 3 mL, water 3 mL) of 1-(2-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (660 mg, 3.08 mmol) in sulfuric acid was stirred at 130°C for 6 hr. The reaction solution was cooled to room temperature, water was added, and the precipitated solid was collected by filtration. The obtained solid was washed with ethyl acetate to give the title compound (550 mg, 72%) as a brown solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.14 (3H, s), 6.84 (1H, d, J = 8.1 Hz), 7.41 - 7.70 (4H, m), 8.45 (1H, d, J = 7.6 Hz), 13.87 (1H, br s).

Reference Example 138

Production of 2-cyano-N-(4-fluoro-3-methylphenyl)acetamide

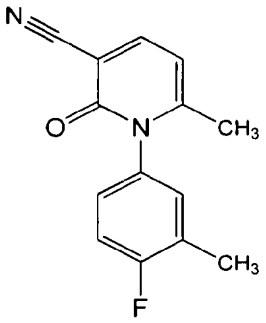


A mixture of 4-fluoro-3-methylaniline (2.50 g, 20.0 mmol) and ethyl cyanoacetate (2.70 g, 24.0 mmol) was stirred at 180°C for 14 hr. After the reaction, the mixture was cooled to room temperature, and the obtained solid was washed with hexane and collected by filtration to give the title compound (3.60 g, 95%) as a brownish-red solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.22 (3H, s), 3.88 (2H, s), 7.10 (1H, t, J = 9.2 Hz), 7.28 - 7.55 (2H, m), 10.27 (1H, br s).

Reference Example 139

Production of 1-(4-fluoro-3-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile

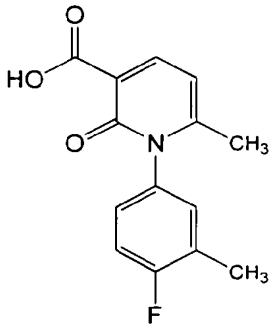


A solution (30 mL) of 2-cyano-N-(4-fluoro-3-methylphenyl)acetamide (3.60 g, 19.0 mmol), (3E)-4-methoxybut-3-en-2-one (2.80 g, 28.0 mmol) and 1,4-diazabicyclo[2.2.2]octane (3.20 g, 28.0 mmol) in 2-(2-methoxyethoxy)ethanol was stirred at 120°C for 12 hr. After cooling to room temperature, the reaction solution was divided into two layers with ethyl acetate and water and subjected to extraction (3 times) with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (1.60 g, 34%) as a brown solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.02 (3H, s), 2.27 (3H, d, J = 1.9 Hz), 6.43 - 6.53 (1H, m), 7.17 - 7.38 (3H, m), 8.14 (1H, d, J = 7.4 Hz).

Reference Example 140

Production of 1-(4-fluoro-3-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid

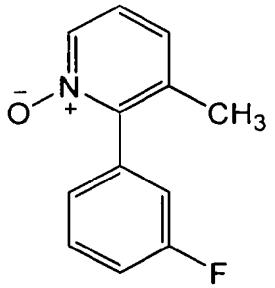


An aqueous solution (98% sulfuric acid 8 mL, water 8 mL) of 1-(4-fluoro-3-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (1.60 g, 6.60 mmol) in sulfuric acid was stirred at 130°C for 10 hr. The reaction solution was cooled to room temperature, water was added, and the precipitated solid was collected by filtration. The obtained solid was washed with ethyl acetate to give the title compound (1.00 g, 58%) as a brown solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.11 (3H, s), 2.29 (3H, d, J = 1.9 Hz), 6.80 (1H, d, J = 7.6 Hz), 7.27 - 7.48 (3H, m), 8.40 (1H, d, J = 7.6 Hz).

Reference Example 141

Production of 2-(3-fluorophenyl)-3-methylpyridine 1-oxide



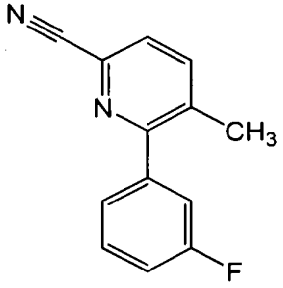
To a solution (100 mL) of 2-(3-fluorophenyl)-3-methylpyridine (4.83 g, 25.8 mmol) in ethyl acetate was added 3-chloroperbenzoic acid (7.1 g, 28.4 mmol), and the mixture was stirred at 50°C for 5 hr. The disappearance of 3-chloroperbenzoic acid was confirmed using potassium iodide

starch paper (manufactured by ADVANTEC MFS, INC), and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (4.26 g, 81%).

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.05 (3H, s), 7.17 (1H, dt, J = 7.6, 1.2 Hz), 7.21 - 7.40 (4H, m), 7.54 (1H, td, J = 7.8, 5.9 Hz), 8.20 (1H, dd, J = 5.4, 1.6 Hz).

Reference Example 142

Production of 6-(3-fluorophenyl)-5-methylpyridine-2-carbonitrile



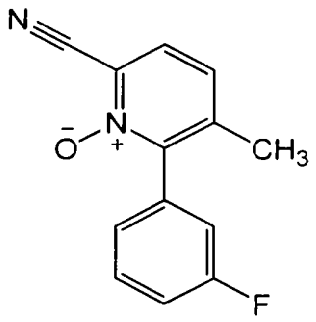
A solution (40 mL) of 2-(3-fluorophenyl)-3-methylpyridine 1-oxide (4.26 g, 21.0 mmol), dimethylcarbamic acid chloride (2.94 g, 27.3 mmol) and trimethylsilanecarbonitrile (2.71 g, 27.3 mmol) in tetrahydrofuran was heated under reflux, and the mixture was stirred for 2 hr. After cooling to room temperature, the reaction solution was divided into two layers with ethyl acetate and saturated aqueous sodium hydrogen carbonate solution and subjected to extraction (3 times) with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography to give the title compound (4.42 g, 99%).

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.41 (3H, s), 7.27 - 7.39 (1H, m), 7.39 - 7.48 (2H, m), 7.50 - 7.62 (1H, m), 7.93 - 8.09 (2H, m).

Reference Example 143

Production of 6-(3-fluorophenyl)-5-methylpyridine-2-

carbonitrile 1-oxide

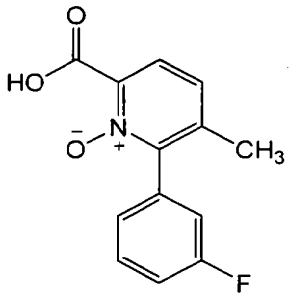


To a solution (50 mL) of 6-(3-fluorophenyl)-5-methylpyridine-2-carbonitrile (4.42 g, 20.8 mmol) in acetonitrile were added trifluoroacetic acid anhydride (17.6 g, 62.4 mmol) and sodium percarbonate (6.5 g, 41.6 mmol) at 0°C, and the mixture was stirred at 0°C for 1 hr and at room temperature overnight. The reaction solution was divided into two layers with ethyl acetate and saturated aqueous sodium hydrogen carbonate solution and subjected to extraction (3 times) with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The disappearance of sodium percarbonate was confirmed, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography to give the title compound (1.4 g, 29%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.11 (3H, s), 7.23 (1H, dt, J = 7.7, 1.2 Hz), 7.29 - 7.39 (2H, m), 7.48 - 7.53 (1H, m), 7.53 - 7.64 (1H, m), 8.05 (1H, d, J = 8.3 Hz).

Reference Example 144

Production of 6-(3-fluorophenyl)-5-methylpyridine-2-carboxylic acid 1-oxide

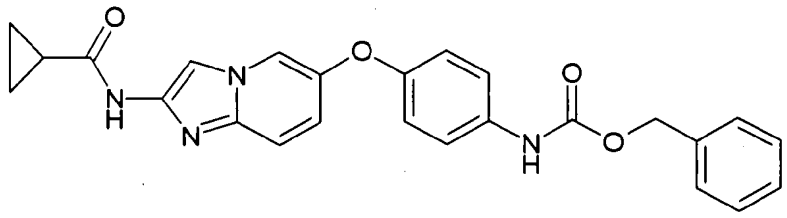


An aqueous solution (98% sulfuric acid 6 mL, water 6 mL) of 6-(3-fluorophenyl)-5-methylpyridine-2-carbonitrile 1-oxide (1.4 g, 6.13 mmol) in sulfuric acid was stirred at 120°C for 10 hr. The reaction solution was cooled to room temperature and added to water, and the precipitated solid was collected by filtration. The obtained solid was washed with ethyl acetate to give the title compound (1.07 g, 71%) as a brown solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.18 (3H, s), 7.26 - 7.47 (3H, m), 7.54 - 7.73 (1H, m), 7.87 - 8.01 (1H, m), 8.31 (1H, d, J = 8.3 Hz).

Example 1

Production of benzyl [4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)phenyl]carbamate



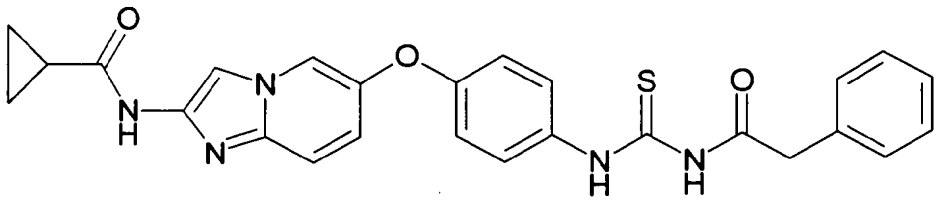
To a solution of benzylcarbamate {4-[(2-aminoimidazo[1,2-a]pyridin-6-yl)oxy]phenyl}carbamate (8.7 g, 22.2 mmol) in N,N-dimethylacetamide (70 mL) was added cyclopropanecarbonyl chloride (2.21 mL, 24.4 mmol) at room temperature, and the mixture was stirred at room temperature for 1 hr. Saturated aqueous sodium hydrogen carbonate was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was

washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with hexane/ethyl acetate (=1/1) and collected by filtration to give the title compound (8.5 g, 87%) as a thin-brown solid.

^{1}H-NMR (DMSO-d_6, 300MHz) δ 0.76 - 0.82 (4H, m), 1.85 - 1.95 (1H, m), 5.14 (2H, s), 6.97 - 7.09 (3H, m), 7.27 - 7.50 (8H, m), 8.03 (1H, s), 8.44 (1H, d, J = 1.8 Hz), 9.75 (1H, s), 10.97 (1H, s).

Example 2

Production of N-[6-(4-{[(phenylacetyl)carbamothioyl]amino}phenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide



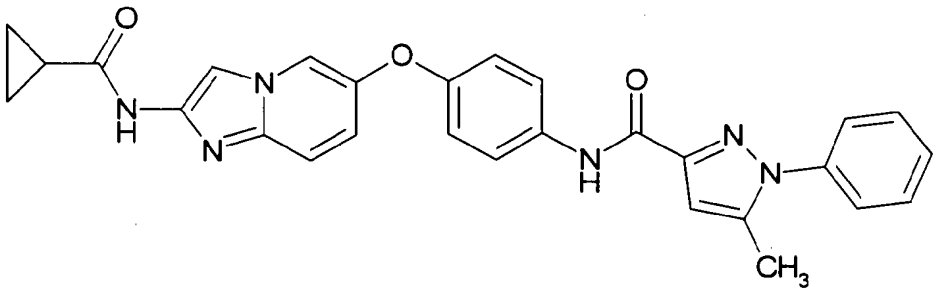
To a solution of phenylacetyl chloride (422 mg, 2.59 mmol) in acetonitrile (8 mL) was added potassium thiocyanate (317 mg, 3.24 mmol), and the mixture was stirred at 50°C for 1 hr. The reaction solution was cooled to room temperature, saturated aqueous sodium hydrogen carbonate was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogen carbonate and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The obtained residue was dissolved in toluene (2 mL)/ethanol (2 mL), N-[6-(4-aminophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (200 mg, 649 μmol) was added, and the mixture was stirred at room temperature for 1 hr. Saturated aqueous sodium hydrogen carbonate was added to the reaction solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with 1N aqueous sodium

hydroxide solution, water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane) and recrystallized from ethanol/water to give the title compound (98 mg, 31%) as a pale-yellow powder.

^{1}H-NMR (DMSO-d_6, 300MHz) δ 0.68-0.93 (4H, m), 1.82 - 2.05 (1H, m), 3.81 (2H, s), 7.02 (2H, d, J = 8.9 Hz), 7.08 (1H, dd, J = 9.6, 2.1 Hz), 7.22 - 7.41 (5H, m), 7.46 (1H, d, J = 9.6 Hz), 7.57 (2H, d, J = 8.9 Hz), 8.05 (1H, s), 8.57 (1H, d, J = 2.1 Hz), 10.97 (1H, s), 11.69 (1H, s), 12.30 (1H, s).

Example 3

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)phenyl]-5-methyl-1-phenyl-1H-pyrazole-3-carboxamide



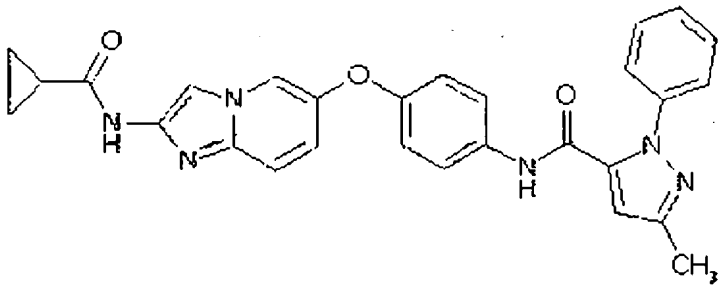
To a solution of 5-methyl-1-phenyl-1H-pyrazole-3-carboxylic acid (197 mg, 973 μmol) in tetrahydrofuran (2 mL) were added oxalyl chloride (80 μL, 973 μmol) and N,N-dimethylformamide (2 drops) under ice-cooling, and the mixture was stirred at room temperature for 1 hr. A solution of N-[6-(4-aminophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (200 mg, 649 μmol) in N,N-dimethylacetamide (2 mL) was added to the reaction solution, and the mixture was stirred at room temperature for 2 hr. Saturated aqueous sodium hydrogen carbonate was added to the reaction solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with 1N aqueous sodium

hydroxide solution, water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The obtained residue was recrystallized from ethanol/water to give the title compound (187 mg, 39%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300MHz) δ 0.75 - 0.86 (4H, m), 1.86 - 1.98 (1H, m), 2.30 (3H, s), 6.83 (1H, s), 7.03 (2H, d, J = 9.1 Hz), 7.02 - 7.08 (1H, m), 7.31 - 7.50 (6H, m), 7.65 (2H, d, J = 9.1 Hz), 8.04 (1H, s), 8.48 (1H, d, J = 1.7 Hz), 10.53 (1H, s), 10.95 (1H, s).

Example 4

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)phenyl]-3-methyl-1-phenyl-1H-pyrazole-5-carboxamide



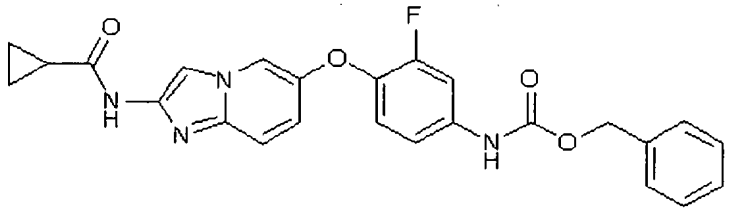
To a solution of 3-methyl-1-phenyl-1H-pyrazole-5-carboxylic acid (197 mg, 973 μmol) in tetrahydrofuran (2 mL) were added oxalyl chloride (80 μL, 973 μmol) and N,N-dimethylformamide under ice-cooling, and the mixture was stirred at room temperature for 1 hr. A solution of N-[6-(4-aminophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (200 mg, 649 μmol) in N,N-dimethylacetamide (2 mL) was added to the reaction solution, and the mixture was stirred at room temperature for 2 hr. Saturated aqueous sodium hydrogen carbonate was added to the reaction solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with 1N aqueous sodium hydroxide solution, water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The obtained

residue was recrystallized from ethanol/water to give the title compound (138 mg, 29%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300MHz) δ 0.74 - 0.87 (4H, m), 1.83 - 2.05 (1H, m), 2.36 (3H, s), 6.79 (1H, s), 7.02 (2H, d, J = 9.1 Hz), 7.07 (1H, dd, J = 9.6, 2.2 Hz), 7.45 (1H, d, J = 9.6 Hz), 7.47 - 7.68 (5H, m), 7.82 (2H, d, J = 8.9 Hz), 8.05 (1H, s), 8.49 (1H, d, J = 1.7 Hz), 10.08 (1H, s), 10.95 (1H, s).

Example 5

Production of benzyl [4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]carbamate

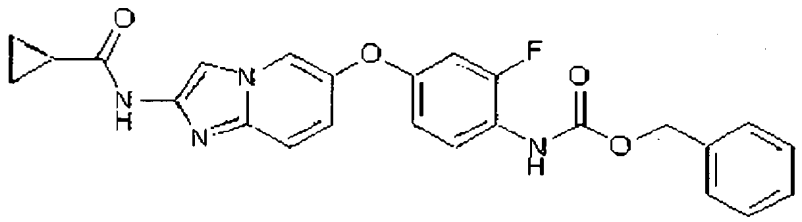


To a solution of benzyl {4-[(2-aminoimidazo[1,2-a]pyridin-6-yl)oxy]-3-fluorophenyl}carbamate (10.0 g, 25.5 mmol) in N,N-dimethylacetamide (100 mL) was added cyclopropanecarbonyl chloride (2.77 mL, 30.6 mmol) at 0°C, and the mixture was stirred at room temperature for 2 hr. Water and saturated aqueous sodium hydrogen carbonate were added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with ethyl acetate and collected by filtration to give the title compound (9.2 g, 78%) as a thin-brown solid.

^{1}H-NMR (DMSO-d_6, 300MHz) δ 0.76 - 0.81 (4H, m), 1.85 - 1.96 (1H, m), 5.17 (2H, s), 7.05 - 7.25 (4H, m), 7.30 - 7.45 (5H, m), 7.52 - 7.60 (1H, m), 8.01 (1H, s), 8.38 (1H, d, J = 2.1 Hz), 10.02 (1H, s), 10.93 (1H, s).

Example 6

Production of benzyl [4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-2-fluorophenyl]carbamate

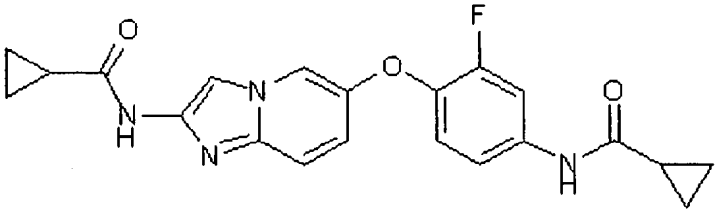


To a solution of benzyl {4-[(2-aminoimidazo[1,2-a]pyridin-6-yl)oxy]-2-fluorophenyl}carbamate (12.1 g, 30.9 mmol) in N,N-dimethylacetamide (84.7 mL) was added cyclopropanecarbonyl chloride (3.36 mL, 37.0 mmol) at 0°C, and the mixture was stirred at room temperature for 2 hr. Water and saturated aqueous sodium hydrogen carbonate were added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with ethyl acetate and collected by filtration to give the title compound (9.7 g, 68%) as a thin-brown solid.

^{1}H-NMR (DMSO-d_6, 300MHz) δ 0.77 - 0.83 (4H, m), 1.86 - 1.96 (1H, m), 5.14 (2H, s), 6.81 - 6.86 (1H, m), 6.97 - 7.11 (2H, m), 7.31 - 7.56 (7H, m), 8.05 (1H, s), 8.57 (1H, d, J = 1.5 Hz), 9.37 (1H, br s), 10.97 (1H, s).

Example 7

Production of N-(6-{4-[(cyclopropylcarbonyl)amino]-2-fluorophenoxy}imidazo[1,2-a]pyridin-2-yl)cyclopropanecarboxamide

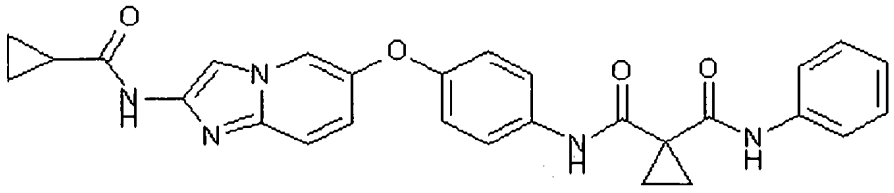


To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (150 mg, 0.46 mmol) in N,N-dimethylacetamide (1.5 mL) was added cyclopropanecarbonyl chloride (50.1 μL, 0.55 mmol) at room temperature, and the mixture was stirred at room temperature for 30 min. Saturated aqueous sodium hydrogen carbonate was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=40/60→0/100). The obtained powder was washed with ethyl acetate and collected by filtration to give the title compound (150 mg, 83%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300MHz) δ 0.76 - 0.84 (8H, m), 1.71 - 1.80 (1H, m), 1.86 - 1.96 (1H, m), 7.09 (1H, dd, J = 9.6, 2.4 Hz), 7.16 (1H, d, J = 9.0 Hz), 7.24 - 7.30 (1H, m), 7.43 (1H, d, J = 9.6 Hz), 7.78 (1H, dd, J = 13.5, 2.4 Hz), 8.02 (1H, s), 8.41 (1H, d, J = 2.1 Hz), 10.41 (1H, s), 10.93 (1H, s).

Example 8

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)phenyl]-N'-phenylcyclopropane-1,1-dicarboxamide



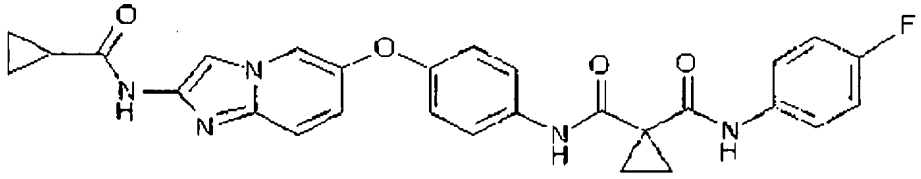
To a solution of N-[6-(4-aminophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (142 mg, 0.461 mmol) in N,N-dimethylacetamide (2.8 mL) were added 1-(phenylcarbamoyl)cyclopropanecarboxylic acid (142 mg, 0.691

mmol), HATU (263 mg, 0.691 mmol) and N,N-diisopropylethylamine (120 μL, 0.691 mmol), and the mixture was stirred at room temperature for 4 hr. Saturated aqueous sodium hydrogen carbonate was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=40/60→0/100), washed with hexane/ethyl acetate and collected by filtration to give the title compound (130 mg, 57%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300MHz) δ 0.75 - 0.82 (4H, m), 1.46 (4H, s), 1.86 - 1.96 (1H, m), 6.96 - 7.09 (4H, m), 7.27 - 7.33 (2H, m), 7.44 (1H, d, J = 9.6 Hz), 7.57 - 7.62 (4H, m), 8.04 (1H, s), 8.47 (1H, d, J = 1.5 Hz), 10.00 (1H, br s), 10.07 (1H, br s), 10.94 (1H, s).

Example 9

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide



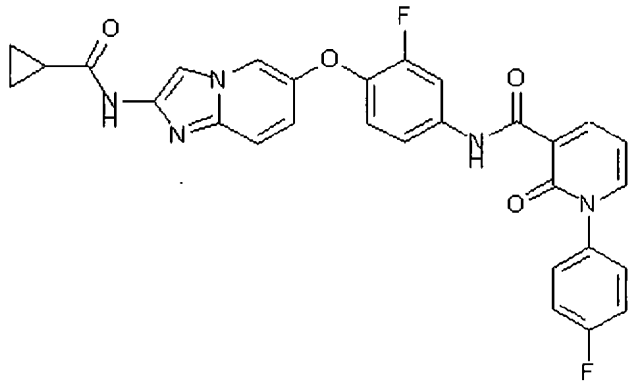
Using N-[6-(4-aminophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (150 mg, 0.486 mmol), N,N-dimethylacetamide (3.0 mL), 1-[(4-fluorophenyl)carbamoyl]cyclopropanecarboxylic acid (163 mg, 0.730 mmol), HATU (277 mg, 0.730 mmol) and N,N-diisopropylethylamine (127 μL, 0.730 mmol) and in the same manner as in Example 8, the title compound (111 mg, 44%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300MHz) δ 0.75 - 0.82 (4H, m), 1.44 (4H, s),

1.86 - 1.96 (1H, m), 6.96 - 7.17 (5H, m), 7.44 (1H, d, J = 9.6 Hz), 7.57 - 7.65 (4H, m),8.03 (1H, s), 8.47 (1H, d, J = 1.8 Hz), 10.03 (1H, br s), 10.06 (1H, br s), 10.94 (1H, s).

Example 10

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide



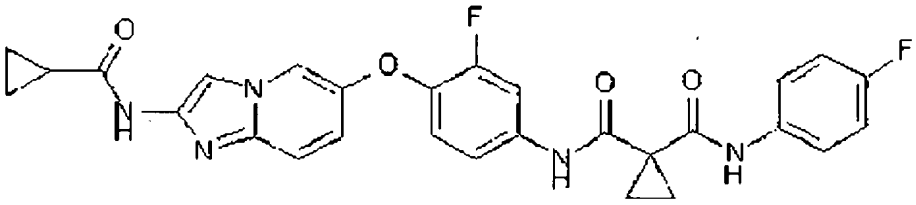
To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (150 mg, 0.460 mmol) in N,N-dimethylacetamide (3.0 mL) were added 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (161 mg, 0.689 mmol), HATU (262 mg, 0.689 mmol) and N,N-diisopropylethylamine (120 μL, 0.689 mmol), and the mixture was stirred at room temperature for 2 hr. Water and saturated aqueous sodium hydrogen carbonate were added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with ethyl acetate and collected by filtration to give the title compound (269 mg, 81%) as a pale-yellow solid.

^{1}H-NMR (DMSO-d_6, 300MHz) δ 0.76 - 0.81 (4H, m), 1.85 - 1.96 (1H, m), 6.69 - 6.75 (1H, m), 7.08 - 7.19 (2H, m), 7.34 - 7.45 (4H, m), 7.58 - 7.63 (2H, m), 7.94 - 7.99 (1H, m),8.03 (1H, s),

8.10 - 8.14 (1H, m), 8.47 (1H, d, J = 1.8 Hz), 8.57 (1H, dd, J = 7.4, 2.3 Hz), 10.94 (1H, br s), 12.03 (1H, s).

Example 11

N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

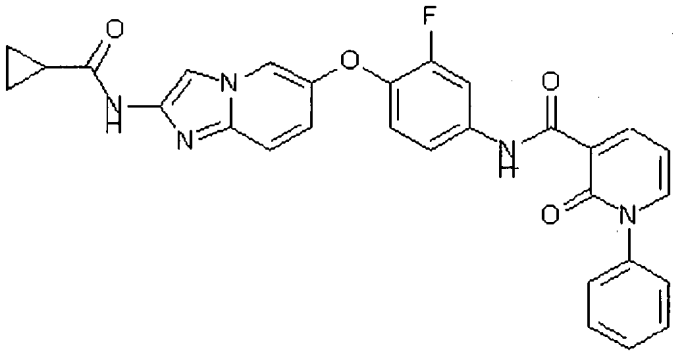


To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (150 mg, 0.460 mmol) in N,N-dimethylacetamide (3.0 mL) were added 1-[(4-fluorophenyl)carbamoyl]cyclopropanecarboxylic acid (154 mg, 0.689 mmol), HATU (262 mg, 0.689 mmol) and N,N-diisopropylethylamine (120 μL, 0.689 mmol), and the mixture was stirred at room temperature for 4 hr. Saturated aqueous sodium hydrogen carbonate was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=40/60→0/100), washed with hexane/ethyl acetate and collected by filtration to give the title compound (99 mg, 41%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300MHz) δ 0.76 - 0.81 (4H, m), 1.42 - 1.47 (4H, m), 1.86 - 1.96 (1H, m), 7.05 - 7.18 (4H, m), 7.33 - 7.45 (2H, m), 7.60 - 7.66 (2H, m), 7.81 (1H, dd, J = 13.8, 2.4 Hz),8.02 (1H, s), 8.43 (1H, d, J = 2.1 Hz), 9.99 (1H, br s), 10.24 (1H, br s), 10.93 (1H, s).

Example 12

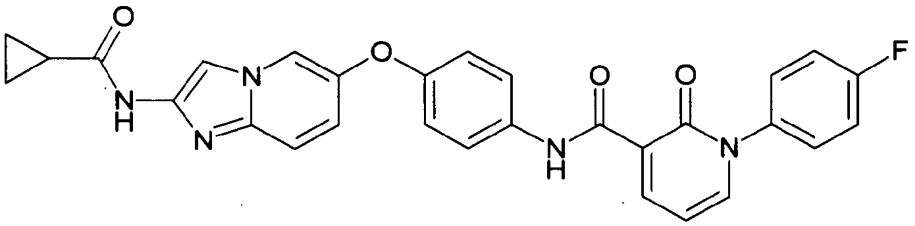
Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide



Using N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (150 mg, 0.460 mmol), N,N-dimethylacetamide (3.0 mL), 2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylic acid (138 mg, 0.644 mmol), HATU (262 mg, 0.689 mmol) and N,N-diisopropylethylamine (120 μL, 0.689 mmol) and in the same manner as in Example 10, the title compound (171 mg, 71%) was obtained as a pale-yellow solid. ^{1}H-NMR (DMSO-d_6, 300MHz) δ 0.75 - 0.82 (4H, m), 1.85 - 1.96 (1H, m), 6.70 - 6.75 (1H, m), 7.08 - 7.20 (2H, m), 7.34 - 7.61 (7H, m), 7.94 - 8.00 (1H, m), 8.02 (1H, s), 8.10 - 8.15 (1H, m), 8.46 (1H, d, J = 1.8 Hz), 8.56 - 8.60 (1H, m), 10.93 (1H, s), 12.06 (1H, s).

Example 13

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)phenyl]-2-oxo-1-(4-fluorophenyl)-1,2-dihydropyridine-3-carboxamide

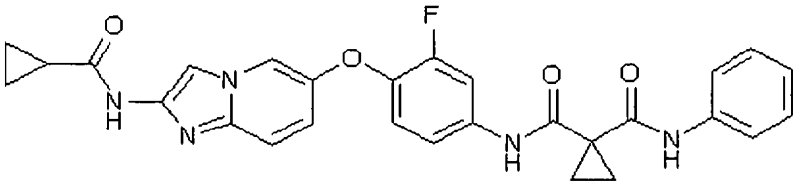


Using N-[6-(4-aminophenoxy)imidazo[1,2-a]pyridin-2-

yl]cyclopropanecarboxamide (150 mg, 0.486 mmol), N,N-dimethylacetamide (3.0 mL), 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (170 mg, 0.729 mmol), HATU (277 mg, 0.729 mmol) and N,N-diisopropylethylamine (127 μL, 0.729 mmol) and in the same manner as in Example 10, the title compound (181 mg, 71%) was obtained as a white solid.
^{1}H-NMR (DMSO-d_6, 300MHz) δ 0.76 - 0.82 (4H, m), 1.85 - 1.96 (1H, m), 6.68 - 6.74 (1H, m), 7.00 - 7.10 (3H, m), 7.37 - 7.48 (3H, m), 7.56 - 7.72 (4H, m), 8.04 (1H, s), 8.08 - 8.12 (1H, m), 8.50 - 8.51 (1H, m), 8.54 - 8.58 (1H, m), 10.95 (1H, s), 11.89 (1H, s).

Example 14

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-N'-phenylcyclopropane-1,1-dicarboxamide



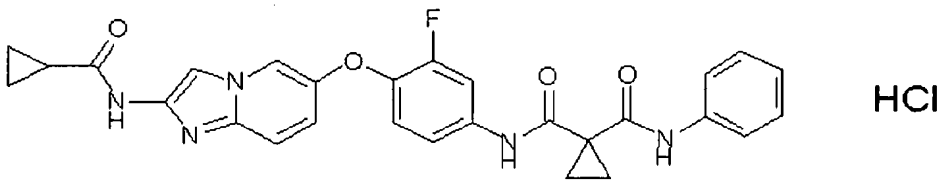
To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (400 mg, 1.23 mmol) in N,N-dimethylacetamide (4.0 mL) were added 1-(phenylcarbamoyl)cyclopropanecarboxylic acid (352 mg, 1.72 mmol), HATU (699 mg, 1.84 mmol) and N,N-diisopropylethylamine (320 μL, 1.84 mmol), and the mixture was stirred at room temperature for 3 hr. Water and saturated aqueous sodium hydrogen carbonate were added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl

acetate=40/60→0/100). The obtained powder was recrystallized from methyl ethyl ketone/water (=20/1) to give the title compound (294 mg, 47%) as white crystals.

^{1}H-NMR (DMSO-d_6, 300MHz) δ 0.75 - 0.83 (4H, m), 1.43 - 1.48 (4H, m), 1.85 - 1.96 (1H, m), 7.02 - 7.18 (3H, m), 7.26 - 7.46 (4H, m), 7.62 (2H, dd, J = 8.6, 1.1 Hz), 7.81 (1H, dd, J = 13.5, 2.7 Hz), 8.03 (1H, s), 8.42 - 8.44 (1H, m), 9.98 (1H, br s), 10.22 (1H, s), 10.94 (1H, s).

Example 15

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-N'-phenylcyclopropane-1,1-dicarboxamide hydrochloride



HCl

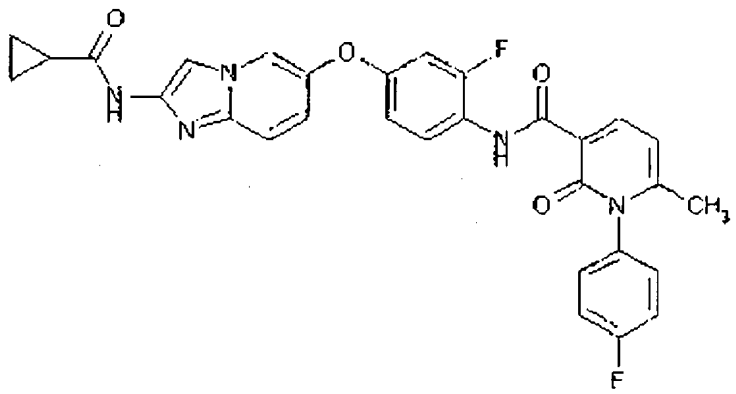
A suspension of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-N'-phenylcyclopropane-1,1-dicarboxamide (960 mg, 1.87 mmol) in methyl ethyl ketone (9.6 mL) was stirred with heating at 60°C, and 6N hydrochloric acid was added. The mixture was cooled to room temperature and left standing for 20 hr. The precipitate was filtered and washed with methyl ethyl ketone to give the title compound (697 mg, 68%) as white crystals.

^{1}H-NMR (DMSO-d_6, 300MHz) δ 0.85 - 0.94 (4H, m), 1.44 - 1.51 (4H, m), 1.90 - 1.99 (1H, m), 7.03 - 7.10 (1H, m), 7.21 - 7.34 (3H, m), 7.41 - 7.52 (2H, m), 7.60 - 7.64 (2H, m), 7.70 (1H, d, J = 9.6 Hz), 7.82 - 7.87 (1H, m), 8.06 (1H, s), 8.57 (1H, d, J = 1.8 Hz), 9.99 (1H, s), 10.32 (1H, s), 11.66 (1H, s).

Example 16

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-2-

fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



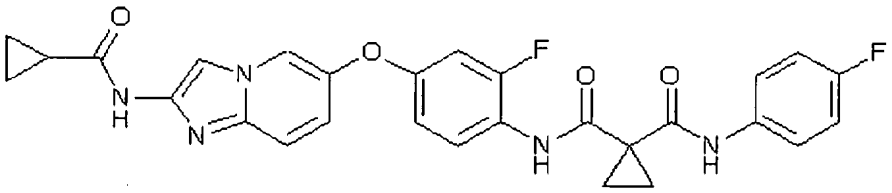
To a solution of N-[6-(4-amino-3-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (150 mg, 0.46 mmol) in N,N-dimethylacetamide (3.0 mL) were added 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (170 mg, 0.689 mmol), HATU (262 mg, 0.689 mmol) and N,N-diisopropylethylamine (120 μL, 0.689 mmol), and the mixture was stirred at room temperature for 20 hr. Saturated aqueous sodium hydrogen carbonate was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with ethyl acetate and collected by filtration to give the title compound (208 mg, 81%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300MHz) δ 0.77 - 0.81 (4H, m), 1.86 - 1.96 (1H, m), 2.07 (3H, s), 6.70 (1H, d, J = 8.1 Hz), 6.86 - 6.92 (1H, m), 7.06 - 7.12 (2H, m), 7.40 - 7.52 (5H, m), 8.04 (1H, s), 8.37 - 8.56 (3H, m), 10.97 (1H, s), 12.04 (1H, s).

Example 17

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-2-

fluorophenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

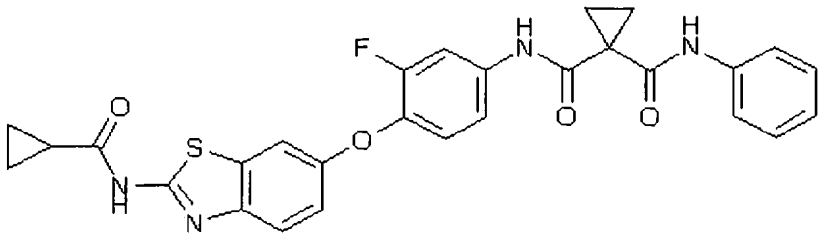


To a solution of N-[6-(4-amino-3-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (150 mg, 0.46 mmol) in N,N-dimethylacetamide (3.0 mL) were added 1-[(4-fluorophenyl)carbamoyl]cyclopropanecarboxylic acid (170 mg, 0.689 mmol), HATU (262 mg, 0.689 mmol) and N,N-diisopropylethylamine (120 μL, 0.689 mmol), and the mixture was stirred at room temperature for 20 hr. Saturated aqueous sodium hydrogen carbonate was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (NH silica gel, ethyl acetate alone). The obtained powder was washed with hexane/ethyl acetate and collected by filtration to give the title compound (115 mg, 47%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300MHz) δ 0.77 - 0.82 (4H, m), 1.51 - 1.59 (4H, s), 1.87 - 1.96 (1H, m), 6.82 - 6.88 (1H, m), 7.00 - 7.20 (4H, m), 7.47 (1H, d, J = 9.6 Hz), 7.56 - 7.63 (2H, m), 7.72 - 7.80 (1H, m), 8.05 (1H, s), 8.57 (1H, d, J = 1.5 Hz), 10.00 (1H, s), 10.37 (1H, s), 10.97 (1H, s).

Example 18

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]-1,3-benzothiazol-6-yl}oxy)-3-fluorophenyl]-N'-phenylcyclopropane-1,1-dicarboxamide

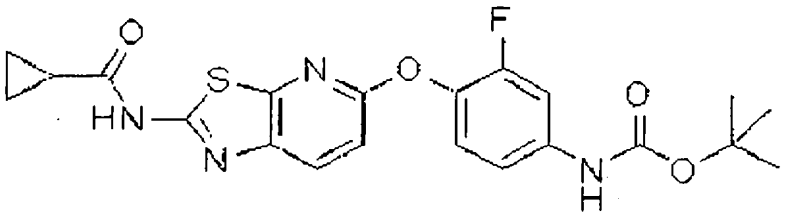


To a solution of 1-(phenylcarbamoyl)cyclopropanecarboxylic acid (214 mg, 1.04 mmol) in tetrahydrofuran (2 mL) were added oxalyl chloride (178 μL, 2.08 μmol) and N,N-dimethylformamide (2 drops) under ice-cooling, and the mixture was stirred at room temperature for 3 hr. The solvent was evaporated under reduced pressure. To a solution of the obtained residue in N,N-dimethylacetamide (5 mL) was added N-[6-(4-amino-2-fluorophenoxy)-1,3-benzothiazol-2-yl]cyclopropanecarboxamide (275 mg, 0.80 mmol), and the mixture was stirred at room temperature for 18 hr. Water was added to the reaction solution, and the mixture was extracted with ethyl acetate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=80/20→20/80, NH silica gel, hexane/ethyl acetate=50/50→0/100) and recrystallized from ethyl acetate to give the title compound (241 mg, 57%) as white crystals.

^{1}H-NMR (DMSO-d_6, 300MHz) δ 0.89 - 0.97 (4H, m), 1.44 - 1.47 (4H, m), 1.95 - 2.06 (1H, m), 7.03 - 7.19 (3H, m), 7.25 - 7.43 (3H, m), 7.56 (1H, d, J = 2.7 Hz), 7.60 - 7.64 (2H, m), 7.70 (1H, d, J = 8.7 Hz), 7.81 (1H, dd, J = 13.5, 2.4 Hz), 9.99 (1H, s), 10.24 (1H, s), 12.59 (1H, s).

Example 19

Production of tert-butyl [4-({2-[(cyclopropylcarbonyl)amino][1,3]thiazolo[5,4-b]pyridin-5-yl}oxy)-3-fluorophenyl]carbamate

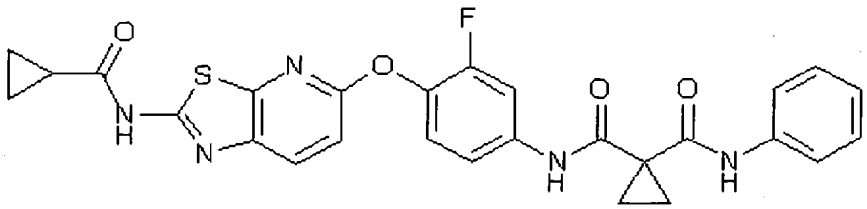


To a solution of tert-butyl {4-[(2-amino[1,3]thiazolo[5,4-b]pyridin-5-yl)oxy]-3-fluorophenyl}carbamate (2.02 g, 5.37 mmol) in N,N-dimethylacetamide (20.2 mL) were added cyclopropanecarbonyl chloride (0.97 mL, 10.7 mmol) and triethylamine (2.24 mL, 16.1 mmol), and the mixture was stirred at room temperature for 24 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, methanol (20 mL) and 5% aqueous sodium carbonate solution (10 mL) were added to the residue, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with hexane/ethyl acetate(=1/1) and collected by filtration to give the title compound (1.33 g, 56%).

^{1}H-NMR (DMSO-d_6, 300MHz) δ 0.92 - 0.99 (4H, m), 1.49 (9H, s), 1.85 - 1.95 (1H, m), 7.16 (1H, d, J = 8.7 Hz), 7.24 - 7.27 (2H, m), 7.50 - 7.58 (1H, m), 8.16 (1H, d, J = 8.7 Hz), 9.63 (1H, s), 12.67 (1H, br s).

Example 20

Production of N-[4-({2-[(cyclopropylcarbonyl)amino][1,3]thiazolo[5,4-b]pyridin-5-yl}oxy)-3-fluorophenyl]-N'-phenylcyclopropane-1,1-dicarboxamide

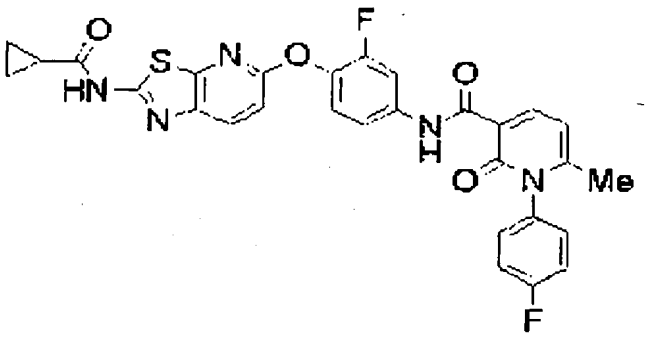


To a solution of N-[5-(4-amino-2-fluorophenoxy)[1,3]thiazolo[5,4-b]pyridin-2-yl]cyclopropanecarboxamide (150 mg, 0.436 mmol) in N,N-dimethylacetamide (3.0 mL) were added 1-(phenylcarbamoyl)cyclopropanecarboxylic acid (134 mg, 0.653 mmol), HATU (248 mg, 0.653 mmol) and N,N-diisopropylethylamine (114 μL, 0.653 mmol), and the mixture was stirred at room temperature for 2 hr. Saturated aqueous sodium hydrogen carbonate was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate alone). The obtained powder was washed with hexane/ethyl acetate and collected by filtration to give the title compound (175 mg, 76%).

^{1}H-NMR (DMSO-d_6, 300MHz) δ 0.89 - 0.98 (4H, m), 1.47 (4H, s), 1.94 - 2.03 (1H, m), 7.03 - 7.09 (1H, m), 7.18 (1H, d, J = 8.9 Hz), 7.25 - 7.34 (3H, m), 7.40 - 7.46 (1H, m), 7.61 - 7.65 (2H, m), 7.79 (1H, dd, J = 13.1, 2.3 Hz), 8.17 (1H, d, J = 8.9 Hz), 10.01 (1H, s), 10.26 (1H, s), 12.68 (1H, br s).

Example 21

Production of N-[4-({2-[(cyclopropylcarbonyl)amino][1,3]thiazolo[5,4-b]pyridin-5-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide

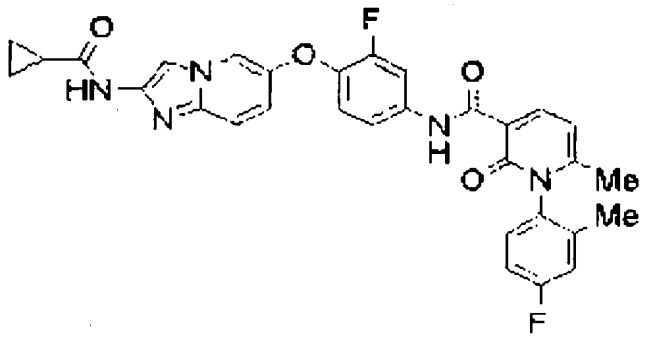


N-[5-(4-Amino-2-fluorophenoxy)[1,3]thiazolo[5,4-b]pyridin-2-yl]cyclopropanecarboxamide (240 mg, 0.70 mmol), 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (190 mg, 0.77 mmol) and HATU (340 mg, 0.91 mmol) were suspended in N,N'-dimethylformamide (3.0 mL), and N,N-diisopropylethylamine (0.24 mL, 1.4 mmol) was added. After stirring at room temperature for 8 hr, the mixture was diluted with ethyl acetate (5.0 mL) and tetrahydrofuran (5.0 mL). The mixture was washed twice with saturated aqueous sodium hydrogen carbonate solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and ethyl acetate was added to the residue. The resulting precipitate was collected by filtration to give the title compound (350 mg, 0.61 mmol, 88%) as a pale-yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.89 - 0.99 (4H, m), 1.93 - 2.03 (1H, m), 2.08 (3H, s), 6.71 (1H, d, J=8.3 Hz), 7.19 (1H, d, J=8.7 Hz), 7.32 (1H, t, J=8.8 Hz), 7.40 - 7.55 (5H, m), 7.95 (1H, dd, J=12.9, 2.4 Hz), 8.17 (1H, d, J=8.7 Hz), 8.50 (1H, d, J=7.6 Hz), 12.03 (1H, s), 12.69 (1H, s).

Example 22

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluoro-2-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide

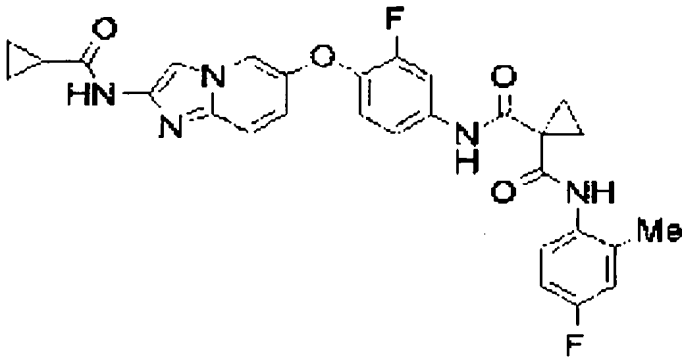


N-[6-(4-Amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (150 mg, 0.46 mmol), 1-(4-fluoro-2-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (130 mg, 0.51 mmol) and HATU (230 mg, 0.60 mmol) were suspended in N,N-dimethylformamide (3.0 mL), and N,N-diisopropylethylamine (0.16 mL, 0.92 mmol) was added. After stirring at room temperature for 8 hr, the reaction mixture was diluted with ethyl acetate (5.0 mL) and tetrahydrofuran (5.0 mL). The mixture was washed twice with saturated aqueous sodium hydrogen carbonate solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, ethyl acetate was added to the residue, and the resulting precipitate was collected by filtration. The obtained precipitate was recrystallized from ethanol/water to give the title compound (130 mg, 50%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74-0.83 (4H, m), 1.86 - 1.97 (1H, m), 2.00 (3H, s), 2.03 (3H, s), 6.75 (1H, d, J = 8.1 Hz), 7.07 - 7.18 (2H, m), 7.21 - 7.30 (1H, m), 7.33 - 7.47 (4H, m), 7.97 (1H, dd, J = 13.3, 2.4 Hz), 8.02 (1H, s), 8.45 (1H, d, J = 1.9 Hz), 8.51 (1H, d, J = 7.6 Hz), 10.93 (1H, s), 11.97 (1H, s).

Example 23

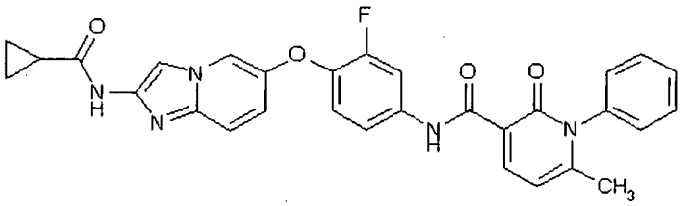
Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-N'-(4-fluoro-2-methylphenyl)cyclopropane-1,1-dicarboxamide



N-[6-(4-Amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (150 mg, 0.46 mmol), 1-[(4-fluoro-2-methylphenyl)carbamoyl]cyclopropanecarboxylic acid (120 mg, 0.51 mmol) and HATU (230 mg, 0.60 mmol) were suspended in N,N-dimethylformamide (3.0 mL), and N,N-diisopropylethylamine (0.16 mL, 0.92 mmol) was added. After stirring at room temperature for 8 hr, the reaction mixture was diluted with ethyl acetate (5.0 mL) and tetrahydrofuran (5.0 mL). The mixture was washed twice with saturated aqueous sodium hydrogen carbonate solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, ethyl acetate was added to the residue, and the resulting precipitate was collected by filtration. The obtained precipitate was recrystallized from ethanol/water to give the title compound (110 mg, 45%) as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.84 (4H, m), 1.52 (4H, s), 1.85 - 1.97 (1H, m), 2.20 (3H, s), 6.97 - 7.19 (4H, m), 7.34 - 7.40 (1H, m), 7.41 - 7.50 (2H, m), 7.75 - 7.85 (1H, m), 8.03 (1H, s), 8.44 (1H, d, J=1.9 Hz), 9.73 (1H, s), 10.41 (1H, s), 10.94 (1H, s).

Example 24

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide

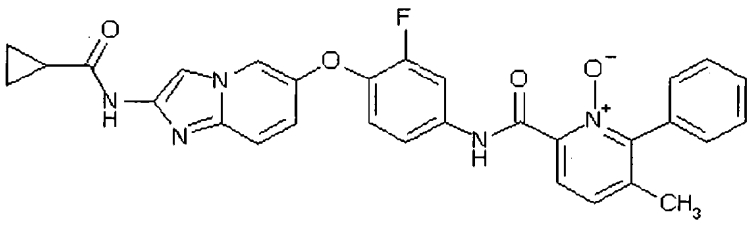


To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (70 mg, 0.215 mmol) and 6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylic acid (59.1 mg, 0.258 mmol) in N,N-dimethylformamide (1.0 mL) were added HATU (98 mg, 0.258 mmol) and N,N-diisopropylethylamine (74 μL, 0.43 mmol), and the mixture was stirred at room temperature for 17 hr. Ethyl acetate and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate) to give a pale-yellow solid. The obtained pale-yellow solid was washed with ethyl acetate and collected by filtration to give the title compound (66 mg, 57%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.70 - 0.85 (4H, m), 1.86 - 1.96 (1H, m), 2.06 (3H, s), 6.71 (1H, d, J = 8.3 Hz), 7.07 - 7.17 (2H, m), 7.32 - 7.65 (7H, m), 7.96 (1H, dd, J = 13.4, 2.5 Hz), 8.02 (1H, s), 8.42 - 8.52 (2H, m), 10.93 (1H, s), 12.02 (1H, s).

Example 25

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-5-methyl-6-phenylpyridine-2-carboxamide 1-oxide

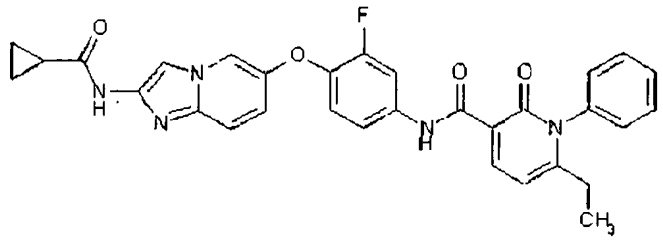


To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (98.8 mg, 0.303 mmol) and 5-methyl-6-phenylpyridine-2-carboxylic acid 1-oxide (83.1 mg, 0.363 mmol) in N,N-dimethylformamide (1.0 mL) were added HATU (150 mg, 0.394 mmol) and N,N-diisopropylethylamine (104 μL, 0.606 mmol), and the mixture was stirred at room temperature for 3.5 hr. Ethyl acetate and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (NH silica gel, ethyl acetate) to give a white solid. The obtained solid was washed with ethyl acetate to give the title compound (100 mg, 61%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.72 - 0.86 (4H, m), 1.85 - 1.98 (1H, m), 2.12 (3H, s), 7.05 - 7.21 (2H, m), 7.36 - 7.61 (7H, m), 7.70 (1H, d, J = 8.9 Hz), 7.98 (1H, dd, J = 13.0, 2.5 Hz), 8.03 (1H, s), 8.31 (1H, d, J = 8.3 Hz), 8.49 (1 H, d, J = 1.7 Hz), 10.94 (1H, s), 13.79 (1H, s).

Example 26

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-ethyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide

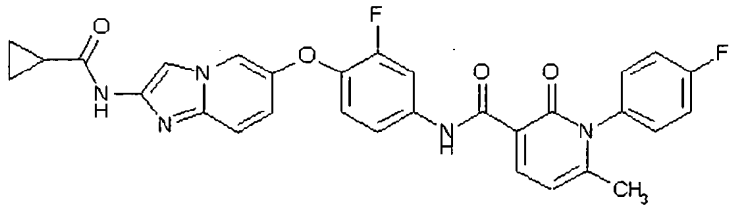


To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (100 mg, 0.306 mmol) and 6-ethyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylic acid (89 mg, 0.366 mmol) in N,N-dimethylformamide (1.0 mL) were added HATU (151 mg, 0.397 mmol) and N,N-diisopropylethylamine (105 μL, 0.612 mmol), and the mixture was stirred at room temperature for 17 hr. Ethyl acetate and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate) to give a white solid. The obtained white solid was washed with ethyl acetate to give the title compound (100 mg, 59%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.85 (4H, m), 1.05 (3H, t, J = 7.4 Hz), 1.82 - 2.01 (1H, m), 2.30 (2H, q, J= 7.4 Hz), 6.68 (1H, d, J = 7.7 Hz), 7.05 - 7.21 (2H, m), 7.31 - 7.48 (4H, m), 7.49 - 7.66 (3H, m), 7.97 (1H, dd, J = 13.2, 2.5 Hz), 8.02 (1H, s), 8.45 (1H, d, J = 1.7 Hz), 8.53 (1H, d, J = 7.7 Hz), 10.94 (1H, s), 12.02 (1H, s).

Example 27

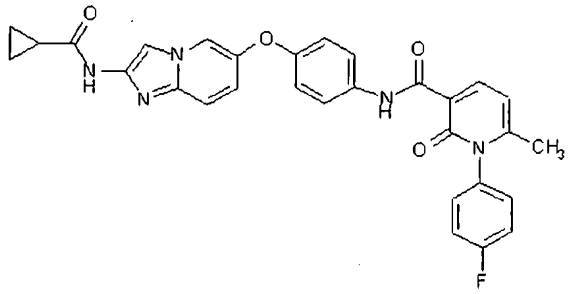
Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (100 mg, 0.306 mmol) and 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (90.8 mg, 0.367 mmol) in N,N-dimethylformamide (1.0 mL) were added HATU (151 mg, 0.397 mmol) and N,N-diisopropylethylamine (105 μL, 0.612 mmol), and the mixture was stirred at room temperature for 20 hr. Ethyl acetate and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate) to give a white solid. The obtained white solid was washed with ethyl acetate to give the title compound (131 mg, 77%) as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.66 - 0.92 (4H, m), 1.87 - 1.93 (1H, m), 2.07 (3H, s), 6.70 (1H, d, J = 7.6 Hz), 7.01 - 7.18 (2H, m), 7.26 - 7.56 (6H, m), 7.97 (1H, d, J = 13.4 Hz), 8.02 (1H, s), 8.40 - 8.54 (2H, m), 10.93 (1H, s), 11.98 (1H, s).

Example 28

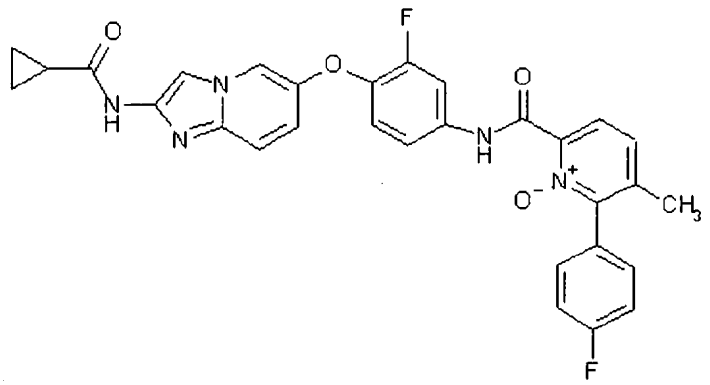
Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



To a solution of N-[6-(4-aminophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (100 mg, 0.324 mmol) and 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (96.1 mg, 0.389 mmol) in N,N-dimethylformamide (1.0 mL) were added HATU (147.8 mg, 0.389 mmol) and N,N-diisopropylethylamine (111.6 μL, 0.648 mmol), and the mixture was stirred at room temperature for 20 hr. Tetrahydrofuran, ethyl acetate and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was washed with tetrahydrofuran and collected by filtration to give the title compound (154 mg, 88%) as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.68 - 0.86 (4H, m), 1.89 - 1.95 (1H, m), 2.06 (3H, s), 6.60 - 6.76 (1H, m), 6.93 - 7.12 (3H, m), 7.37 - 7.53 (5H, m), 7.63 - 7.73 (2H, m), 8.03 (1H, s), 8.40 - 8.54 (2H, m), 10.94 (1H, s), 11.83 (1H, s).

Example 29

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-(4-fluorophenyl)-5-methylpyridine-2-carboxamide 1-oxide



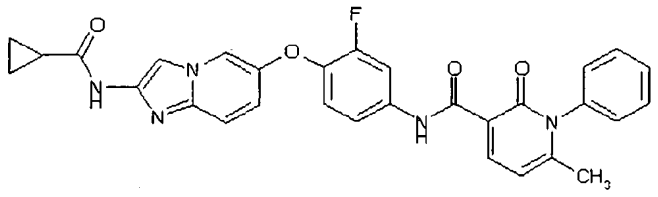
To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (100 mg, 0.306 mmol) and 6-(4-fluorophenyl)-5-methylpyridine-2-carboxylic acid 1-oxide (98.9 mg, 0.367 mmol) in N,N-dimethylformamide (1.0 mL) were added HATU (140 mg, 0.368 mmol) and N,N-diisopropylethylamine (105 μL, 0.612 mmol), and the mixture was stirred at room temperature for 3 hr. Ethyl acetate and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted twice with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate) to give a white solid. The obtained white solid was washed with ethyl acetate to give the title compound (80 mg, 47%) as white crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.66 - 0.89 (4H, m), 1.87 - 1.97 (1H, m), 2.13 (3H, s), 7.07 - 7.22 (2H, m), 7.33 - 7.55 (6H, m), 7.69 (1H, d, J = 8.9 Hz), 7.98 (1H, dd, J = 13.0, 2.5 Hz), 8.03 (1H, s), 8.31 (1H, d, J = 8.3 Hz), 8.48 (1H, d, J = 1.7 Hz), 10.94 (1H, s), 13.73 (1H, s).

Example 30

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-

carboxamide hydrochloride



To a suspension of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide (464 mg, 0,864 mmol) in ethanol was added and dissolved therein 6N hydrochloric acid (86.4 μL, 1.04 mmol). The solution was concentrated to a half amount, and left standing for 17 hr. The precipitate was collected by filtration and washed with ethanol to give a pale-yellow solid (458 mg).

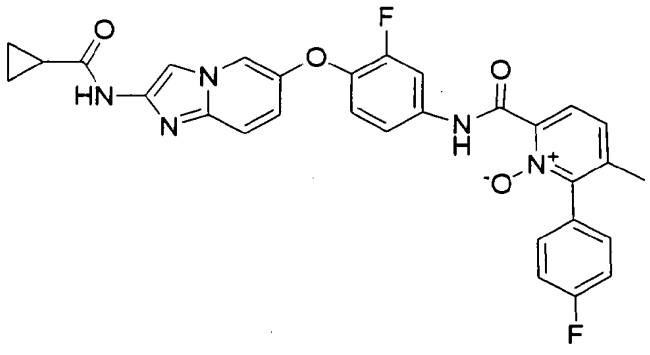
A suspension of pale-yellow solid (100 mg) in methyl ethyl ketone (10 mL) was stirred at 60°C for 17 hr. The precipitate was filtered, washed with methyl ethyl ketone and collected by filtration to give the title compound (80 mg).

To the title compound (80 mg) was added a pale-yellow solid (358 mg), after which methyl ethyl ketone (4 mL) was added, and the mixture was stirred at 60°C for 6 hr. The precipitate was collected by filtration to give the title compound (330 mg, 67%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.80 - 0.93 (4H, m), 1.88 - 2.00 (1H, m), 2.07 (3H, s), 6.72 (1H, d, J= 8.3 Hz), 7.24 (1H, t, J = 9.1 Hz), 7.37 - 7.75 (8H, m), 8.01 (1H, dd, J = 13.2, 2.5 Hz), 8.06 (1H, s), 8.49 (1H, d, J = 7.6 Hz), 8.59 (1H, d, J = 2.1 Hz), 11.65 (1 H, br s), 12.07 (1H, s).

Example 31

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-(4-fluorophenyl)-5-methylpyridine-2-carboxamide 1-oxide hydrochloride



HC l

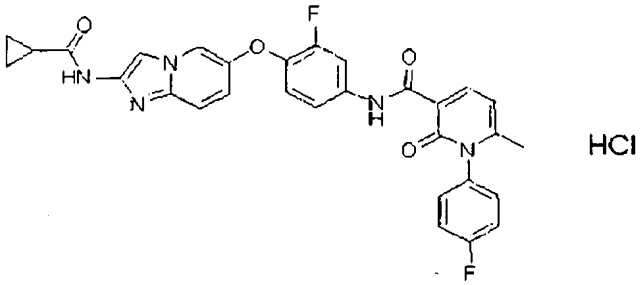
To a suspension of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-(4-fluorophenyl)-5-methylpyridine-2-carboxamide 1-oxide (1.54 g, 2.77 mmol) in ethanol (15 mL) was added and dissolved therein 6N hydrochloric acid (554 μL, 3.32 mmol), and the mixture was left standing at room temperature overnight. The precipitate was collected by filtration and washed with ethanol to give a white powder. The white powder was dissolved in ethyl acetate, tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted twice with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The residue was suspended in ethanol (30 mL) and heated to 80°C. 6N Hydrochloric acid (370 μL, 2.22 mmol) was added dropwise and dissolved therein. The solution was allowed to gradually cool to 50°C, and the mixture was stirred for 6 hr. The precipitate was collected by filtration and washed with ethanol to give a white solid. The white solid was suspended in methyl ethyl ketone (10 mL), and the suspension was stirred at 50°C overnight. The precipitate was collected by filtration and washed with methyl ethyl ketone to give the title compound (747 mg, 46%) as white crystals.

^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.80 - 0.97 (4H, m), 1.88 - 2.06 (1H, m), 2.13 (3H, s), 7.20 - 7.44 (3H, m), 7.46 - 7.82 (6H, m), 8.03 (1H, dd, J = 13.1, 2.4 Hz), 8.09 (1H, s), 8.31 (1H, d,

J= 8.3 Hz), 8.66 (1H, d, J = 1.7 Hz), 11.91 (1H, s), 13.77 (1H, s).

Example 32

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide hydrochloride



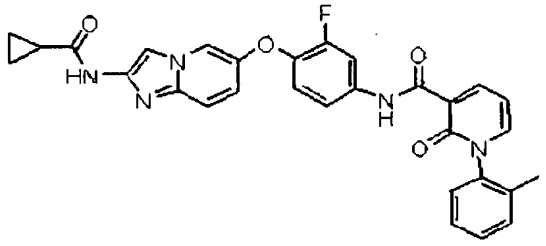
To a suspension of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide (1.42 g, 2.55 mmol) in ethanol (14 mL) and water (2 mL) was added and dissolved therein 6N hydrochloric acid (510 μL, 3.06 mmol), and the solution was concentrated to a half amount, and left standing for 1 hr. The precipitate was collected by filtration to give white crystals. The white crystals were suspended in ethanol (50 mL) again, 6N hydrochloric acid (205 μL, 1.53 mmol) was added, and the mixture was dissolved at 70°C. The solution was left standing at room temperature for 6 hr. The precipitate was collected by filtration to give a white solid. The white solid (850 mg) was dissolved in ethyl acetate, tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted 3 times with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The residue was suspended in ethanol (20 mL), heated to 80°C and dissolved by dropwise addition of 6N hydrochloric acid (358 μL, 2.15 mmol).

The solution was allowed to gradually cool to 50°C, and the mixture was stirred overnight. The precipitate was collected by filtration and washed with ethanol to give a white solid. The white solid was suspended in methyl ethyl ketone (10 mL), and the mixture was stirred at 50°C overnight. The precipitate was collected by filtration and washed with methyl ethyl ketone to give the title compound (590 mg, 39%) as white crystals.

^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.83 - 0.97 (4H, m), 1.90 - 2.03 (1H, m), 2.08 (3H, s), 6.71 (1H, d, J = 8.1 Hz), 7.25 (1H, t, J = 9.1 Hz), 7.35 - 7.61 (6H, m), 7.75 (1H, d, J = 9.8 Hz), 8.02 (1H, dd, J = 13.2, 2.5 Hz), 8.08 (1H, s), 8.49 (1H, d, J= 7.6 Hz), 8.62 (1H, d, J = 1.9 Hz), 11.85 (1H, s), 12.03 (1H, s).

Example 33

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(2-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide



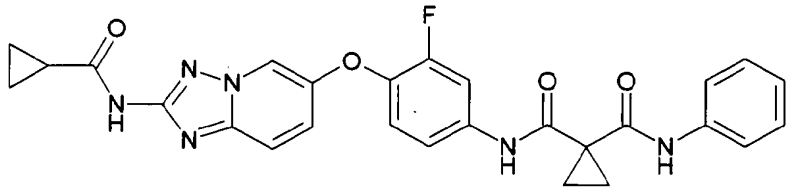
Using N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (200 mg, 0.613 mmol), 1-(2-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (169 mg, 0.735 mmol), N,N-dimethylformamide (2 mL), N,N-diisopropylethylamine(211 μL, 1.23 mmol) and HATU (280 mg, 0.735 mmol) and in the same manner as in Example 24, the title compound (177 mg, 54%) was obtained as pale-yellow crystals.

^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.61 - 0.95 (4H, m), 1.87 - 1.95 (1H, m), 2.08 (3H, s), 6.64 - 6.83 (1H, m), 7.04 - 7.24 (2H, m), 7.33 - 7.53 (6H, m), 7.91 - 8.09 (3H, m), 8.46 (1H, d, J =

1.7 Hz), 8.61 (1H, dd, J = 7.3, 2.2 Hz), 10.94 (1H, s), 12.07 (1H, s).

Example 34

Production of N-[4-({2-[(cyclopropylcarbonyl)amino][1,2,4]triazolo[1,5-a]pyridin-6-yl}oxy)-3-fluorophenyl]-N'-phenylcyclopropane-1,1-dicarboxamide

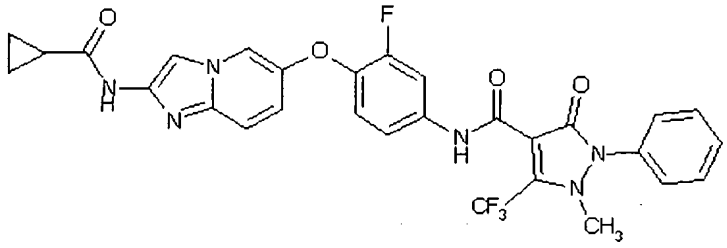


Using N-[6-(4-amino-2-fluorophenoxy)[1,2,4]triazolo[1,5-a]pyridin-2-yl]cyclopropanecarboxamide (120 mg, 0.367 mmol), 1-(phenylcarbamoyl)cyclopropanecarboxylic acid (90.4 mg, 0.440 mmol), N,N-dimethylformamide (1 mL), N,N-diisopropylethylamine (126 μL, 0.733 mmol) and HATU (209 mg, 0.550 mmol) and in the same manner as in Example 24, the title compound (151 mg, 80%) was obtained as white crystals.

^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.71 - 0.86 (4H, m), 1.43 - 1.50 (4H, m), 1.97 - 2.09 (1H, m), 7.03 - 7.10 (1H, m), 7.19 (1H, t, J = 9.2 Hz), 7.26 - 7.41 (3H, m), 7.51 (1H, dd, J = 9.6, 2.3 Hz), 7.58 - 7.65 (2H, m), 7.71 (1H, d, J = 9.6 Hz), 7.82 (1H, dd, J = 13.5, 2.4 Hz), 8.78 (1H, d, J = 1.7 Hz), 9.98 (1H, s), 10.24 (1H, s), 11.03 (1H, s).

Example 35

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-methyl-3-oxo-2-phenyl-5-(trifluoromethyl)-2,3-dihydro-1H-pyrazole-4-carboxamide

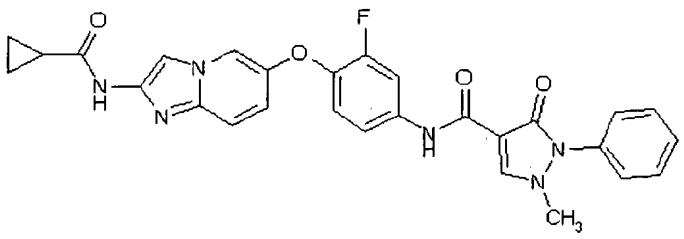


A mixture of 1-methyl-3-oxo-2-phenyl-5-(trifluoromethyl)-2,3-dihydro-1H-pyrazole-4-carboxylic acid (450 mg, 1.6 mmol), N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (360 mg, 1.1 mmol), HATU (590 mg, 1.6 mmol), diisopropylethylamine (430 mg, 3.3 mmol) and N,N-dimethylformamide (7 mL) was stirred at room temperature for 13 hr. Ethyl acetate/tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution were added to the mixture, and the aqueous layer was extracted 4 times with ethyl acetate/tetrahydrofuran. The combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (NH silica gel, ethyl acetate/hexane=40/60→100/0) to give the title compound (320 mg, 48%) as a pale-yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.84 (4H, m), 1.85 - 1.97 (1H, m), 3.52 (3H, s), 7.11 (1H, dd, J = 9.6, 2.5 Hz), 7.17 (1H, t, J = 9.0 Hz), 7.26 - 7.32 (1H, m), 7.44 (1H, d, J = 9.6 Hz), 7.53 - 7.69 (5H, m), 7.88 (1H, dd, J = 13.1, 2.4 Hz), 8.03 (1H, s), 8.45 (1H, d, J = 1.7 Hz), 10.93 (1H, s), 10.97 (1H, s).

Example 36

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide

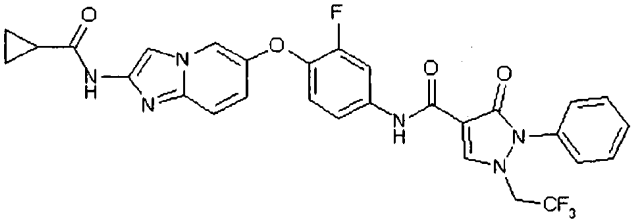


Using 1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylic acid (220 mg, 0.99 mmol), N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (220 mg, 0.66 mmol), HATU (380 mg, 0.99 mmol), diisopropylethylamine (260 mg, 2.0 mmol) and N,N-dimethylformamide (6 mL) as starting materials and in the same manner as in Example 35, the title compound (50 mg, 15%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.84 (4H, m), 1.86 - 1.97 (1H, m), 3.48 (3H, s), 7.11 (1H, dd, J = 9.6, 2.5 Hz), 7.16 (1H, t, J = 9.0 Hz), 7.21 - 7.27 (1H, m), 7.43 (1H, d, J = 9.6 Hz), 7.46 - 7.64 (5H, m), 7.90 (1H, dd, J = 13.3, 2.5 Hz), 8.02 (1H, s), 8.44 (1H, d, J = 1.9 Hz), 8.62 (1H, s), 10.45 (1H, s), 10.93 (1H, s).

Example 37

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-3-oxo-2-phenyl-1-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-pyrazole-4-carboxamide



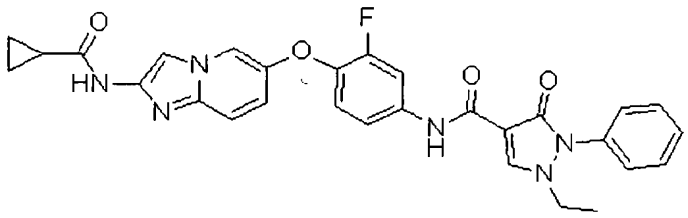
Using 3-oxo-2-phenyl-1-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-pyrazole-4-carboxylic acid (210 mg, 0.72 mmol), N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (170 mg, 0.52 mmol), HATU (280 mg, 0.72 mmol), diisopropylethylamine (200 mg, 1.6 mmol) and N,N-

dimethylformamide (6 mL) as starting materials and in the same manner as in Example 35, the title compound (240 mg, 77%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.84 (4H, m), 1.87 - 1.97 (1H, m), 4.90 (2H, q, J = 8.5 Hz), 7.11 (1H, dd, J = 9.6, 2.3 Hz), 7.17 (1H, t, J = 9.0 Hz), 7.27 - 7.33 (1H, m), 7.40 - 7.46 (3H, m), 7.50 - 7.65 (3H, m), 7.89 (1H, dd, J = 13.1, 2.3 Hz), 8.03 (1H, s), 8.46 (1H, d, J = 1.9 Hz), 8.87 (1H, s), 10.26 (1H, s), 10.94 (1H, s).

Example 38

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-ethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide

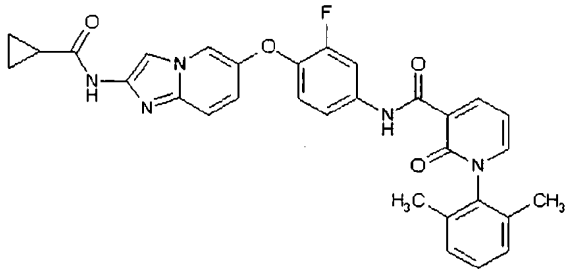


Using 1-ethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylic acid (270 mg, 1.2 mmol), N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (260 mg, 0.79 mmol), HATU (450 mg, 1.2 mmol), diisopropylethylamine (300 mg, 2.4 mmol) and N,N-dimethylformamide (6 mL) as starting materials and in the same manner as in Example 35, the title compound (140 mg, 34%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.83 (4H, m), 1.07 (3H, t, J = 7.2 Hz), 1.87 - 1.96 (1H, m), 3.88 (2H, q, J = 7.2 Hz), 7.11 (1H, dd, J = 9.7, 2.4 Hz), 7.16 (1H, t, J = 8.9 Hz), 7.22 - 7.28 (1H, m), 7.40 - 7.66 (6H, m), 7.90 (1H, dd, J = 13.3, 2.4 Hz), 8.02 (1H, s), 8.44 (1H, d, J = 1.7 Hz), 8.71 (1H, s), 10.43 (1H, s), 10.93 (1H, s).

Example 39

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(2,6-dimethylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide

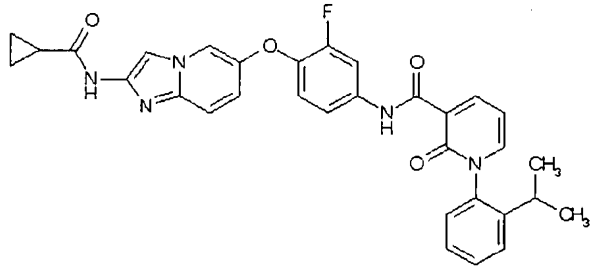


1-(2,6-Dimethylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (120 mg, 0.51 mmol), N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (150 mg, 0.46 mmol) and HATU (340 mg, 0.91 mmol) were suspended in N,N-dimethylformamide (3.0 mL), and N,N-diisopropylethylamine (0.16 mL, 0.92 mmol) was added. After stirring at room temperature overnight, the mixture was diluted with ethyl acetate (5.0 mL) and tetrahydrofuran (5.0 mL). The mixture was washed twice with saturated aqueous sodium hydrogen carbonate solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=65/35→85/15). The fractions containing the object product were mixed. The solvent was evaporated under reduced pressure, and a small amount of hexane/ethyl acetate was added. The resulting precipitate was collected by filtration to give the title compound (130 mg, 49%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.80 (4H, d, J = 2.3 Hz), 1.86 - 1.97 (1H, m), 2.02 (6H, s), 6.81 (1H, d, J = 7.0 Hz), 7.07 - 7.19 (2H, m), 7.24 - 7.41 (4H, m), 7.44 (1H, d, J = 9.6 Hz), 7.93-8.04 (3H, m), 8.46 (1H, d, J = 1.9 Hz), 8.64 (1H, dd, J = 7.3, 2.2 Hz), 10.94 (1H, s), 12.07 (1H, s).

Example 40

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-[2-(1-methylethyl)phenyl]-2-oxo-1,2-dihydropyridine-3-carboxamide



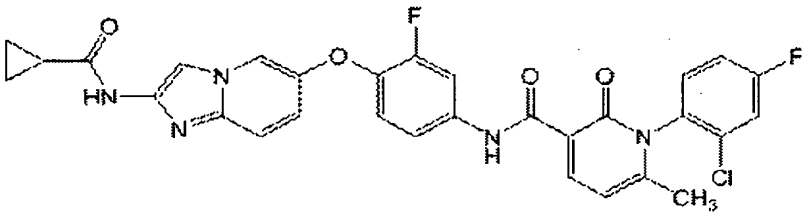
1-[2-(1-Methylethyl)phenyl]-2-oxo-1,2-dihydropyridine-3-carboxylic acid (100 mg, 0.39 mmol), N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (120 mg, 0.35 mmol) and HATU (170 mg, 0.45 mmol) were suspended in N,N-dimethylformamide (3.0 mL), and N,N-diisopropylethylamine (0.12 mL, 0.71 mmol) was added. After stirring at room temperature overnight, the mixture was diluted with ethyl acetate (5.0 mL) and tetrahydrofuran (5.0 mL). The mixture was washed twice with saturated aqueous sodium hydrogen carbonate solution, and the organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=65/35→85/15). The fractions containing the object product were mixed. The solvent was evaporated under reduced pressure, and a small amount of hexane/ethyl acetate (=2/1) was added. The resulting precipitate was collected by filtration to give the title compound (53 mg, 27%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.79 (4H, d, J = 2.5 Hz), 1.12 (3H, d, J = 6.8 Hz), 1.16 (3H, d, J=7.2 Hz), 1.86 - 1.97 (1H, m), 2.52 - 2.62 (1H, m), 6.75 (1H, d, J = 7.2 Hz), 7.06 - 7.21 (2H, m), 7.31 - 7.47 (4H, m), 7.48 - 7.60 (2H, m), 7.97 (1H, dd, J

= 13.2, 2.5 Hz), 8.02 (1H, s,), 8.10 (1H, dd, J = 6.5, 2.2 Hz,), 8.45 (1H, d, J = 1.9 Hz), 8.62 (1H, dd, J = 7.3, 2.2 Hz), 10.94 (1H, s), 12.08 (1H, s).

Example 41

Production of 1-(2-chloro-4-fluorophenyl)-N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



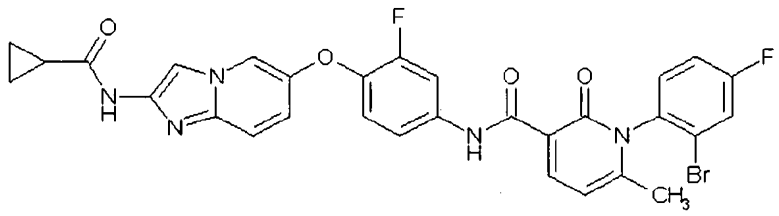
A mixture of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (150 mg, 0.459 mmol), 1-(2-chloro-4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (168 mg, 0.597 mmol), HATU (262 mg, 0.689 mmol), N,N-diisopropylethylamine (160 μL, 0.919 mmol) and N,N-dimethylformamide (3 mL) was stirred at room temperature for 18 hr. After dilution with ethyl acetate, the mixture was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (NH silica gel, 30 g, ethyl acetate/hexane=2/98→100/0), silica gel column chromatography (30 g, ethyl acetate/hexane=0/100→100/0) and preparative HPLC (acetonitrile/water=40/60→50/50, containing 0.1% trifluoroacetic acid) to give the title compound (101 mg, 37%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.83 (4H, m), 1.86 - 1.97 (1H, m), 2.07 (3H, s), 6.75 - 6.80 (1H, m), 7.07 - 7.18 (2H, m), 7.35 - 7.41 (1H, m), 7.44 (1H, d, J = 9.6 Hz), 7.47 - 7.55 (1H, m), 7.71 - 7.78 (1H, m), 7.83 (1H, dd, J = 8.5, 2.8 Hz), 7.97 (1H, dd, J = 13.4, 2.4 Hz), 8.02 (1H, s), 8.46 (1H, dd, J

= 2.4, 0.6 Hz), 8.54 (1H, d, J = 7.5 Hz), 10.95 (1H, s), 11.81 (1H, s).

Example 42

Production of 1-(2-bromo-4-fluorophenyl)-N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



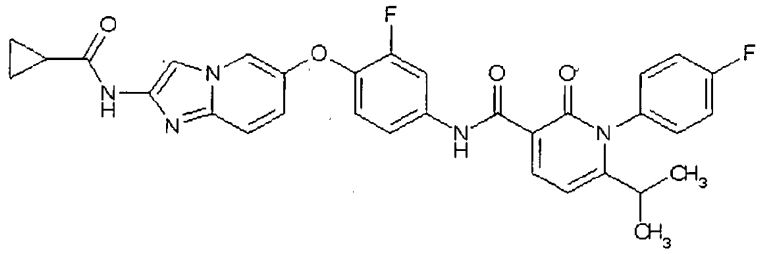
A mixture of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (150 mg, 0.459 mmol), 1-(2-bromo-4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (146 mg, 0.448 mmol), HATU (262 mg, 0.689 mmol), N,N-diisopropylethylamine (160 μL, 0.919 mmol) and N,N-dimethylformamide (3 mL) was stirred at room temperature for 3 days. After dilution with ethyl acetate, the mixture was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (NH silica gel, 30 g, ethyl acetate/hexane=2/98→100/0) and preparative HPLC (acetonitrile/water =40/60→50/50, containing 0.1% trifluoroacetic acid) to give the title compound (152 mg, 52%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.82 (4H, m), 1.86 - 1.97 (1H, m), 2.06 (3H, s), 6.75 - 6.80 (1H, m), 7.07 - 7.18 (2H, m), 7.35 - 7.47 (2H, m), 7.50 - 7.58 (1H, m), 7.69 - 7.76 (1H, m), 7.90 - 8.01 (2H, m), 8.02 (1H, s), 8.44 - 8.47 (1H, m), 8.54 (1H, d, J = 7.5 Hz), 10.94 (1H, s), 11.84 (1H, s).

Example 43

Production of N-[4-({2-

[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-6-(1-methylethyl)-2-oxo-1,2-dihydropyridine-3-carboxamide

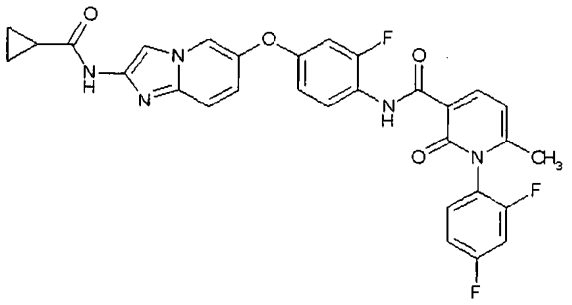


A mixture of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (150 mg, 0.459 mmol), 1-(4-fluorophenyl)-6-(1-methylethyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (151 mg, 0.551 mmol), HATU (262 mg, 0.689 mmol), N,N-diisopropylethylamine (240 μL, 1.37 mmol) and N,N-dimethylformamide (3 mL) was stirred at room temperature for 4 days. After dilution with ethyl acetate, the mixture was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (NH silica gel, 30 g, ethyl acetate/hexane=2/98→80/20) to give the title compound (157 mg, 58%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.82 (4H, m), 1.12 (6H, d, J = 6.8 Hz), 1.87 - 1.97 (1H, m), 2.44 - 2.56 (1H, m), 6.76 (1H, d, J = 7.9 Hz), 7.07 - 7.18 (2H, m), 7.33 - 7.39 (1H, m), 7.39 - 7.49 (3H, m), 7.49 - 7.57 (2H, m), 7.97 (1H, dd, J = 13.2, 2.4 Hz), 8.02 (1H, s), 8.45 (1H, dd, J = 2.4, 0.6 Hz), 8.54 (1H, d, J = 7.9 Hz), 10.93 (1H, s), 11.97 (1H, s).

Example 44

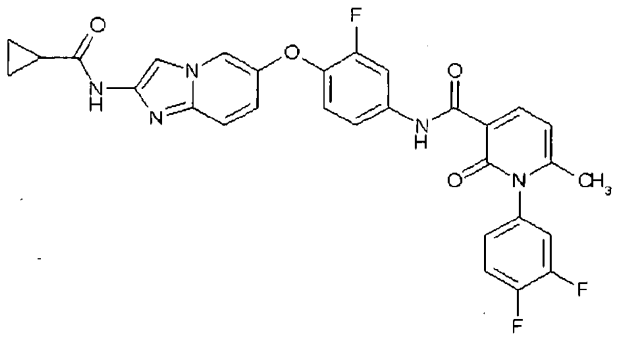
Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-2-fluorophenyl]-1-(2,4-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (200 mg, 0.613 mmol) and 1-(2,4-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (244 mg, 0.919 mmol) in N,N-dimethylacetamide (2.0 mL) were added HATU (350 mg, 0.919 mmol) and N,N-diisopropylethylamine (160 μL, 0.919 mmol), and the mixture was stirred at room temperature for 3 hr. Saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (284 mg, 81%) as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.77 - 0.81 (4H, m), 1.86 - 1.99 (1H, m), 2.12 (3H, s), 6.76 (1H, d, J = 8.4 Hz), 6.87 - 6.94 (1H, m), 7.07 - 7.13 (2H, m), 7.31 - 7.40 (1H, m), 7.46 (1H, d, J = 9.9 Hz), 7.58 - 7.76 (2H, m), 8.04 (1H, s), 8.39 (1H, t, J = 9.2 Hz), 8.51 - 8.56 (2H, m), 10.96 (1H, s), 11.84 (1H, d, J = 1.8Hz).

Example 45

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(3,4-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide

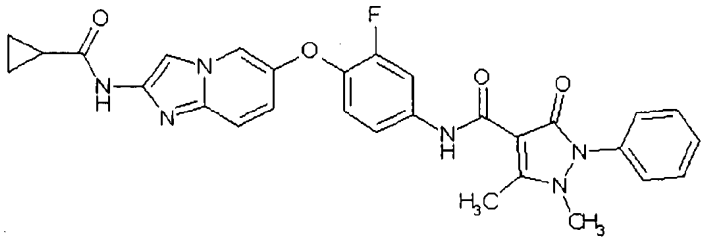


Using a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (200 mg, 0.613 mmol) and 1-(3,4-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (244 mg, 0.919 mmol) in N,N-dimethylacetamide (2.0 mL), HATU (350 mg, 0.919 mmol) and N,N-diisopropylethylamine (160 μL, 0.919 mmol) and in the same manner as in Example 44, the title compound (301 mg, 86%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.80 (4H, m), 1.87 - 1.97 (1H, m), 2.10 (3H, s), 6.71 (1H, d, J = 7.8 Hz), 7.08 - 7.14 (2H, m), 7.33 - 7.46 (3H, m), 7.64 - 7.74 (2H, m), 7.94 - 7.97 (1H, m), 8.02 (1H, s), 8.44 - 8.50 (2H, m), 10.93 (1H, s), 11.91 (1H, d, J = 1.8Hz).

Example 46

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide



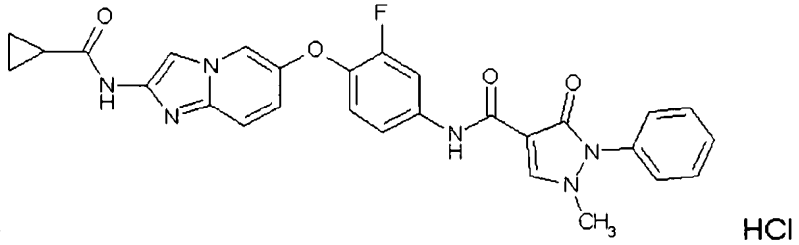
A mixture of 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylic acid (279 mg, 1.2 mmol), N-[6-(4-amino-

2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (265 mg, 0.81 mmol), HATU (460 mg, 1.2 mmol), N,N-diisopropylethylamine (320 mg, 2.4 mmol) and N,N-dimethylformamide (9 mL) was stirred at room temperature for 18 hr. Ethyl acetate/tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution were added to the mixture, and the aqueous layer was extracted with ethyl acetate/tetrahydrofuran (×3). The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (NH silica gel, ethyl acetate/hexane=40/60→100/0) to give the title compound (300 mg, 69%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.83 (4H, m), 1.86 - 1.97 (1H, m), 2.70 (3H, s), 3.36 (3H, s), 7.07 - 7.24 (3H, m), 7.40 - 7.46 (3H, m), 7.47 - 7.63 (3H, m), 7.90 (1H, dd, J = 13.4, 2.3 Hz), 8.03 (1H, s), 8.44 (1H, d, J = 1.9 Hz), 10.86 (1H, s), 10.93 (1H, s).

Example 47

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide·hydrochloride



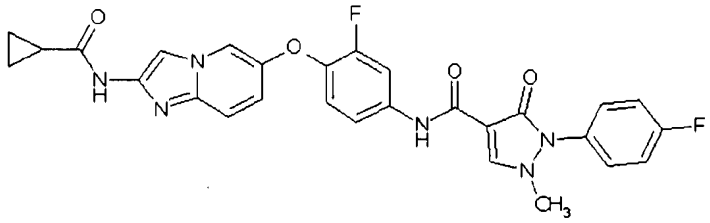
To a suspension of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (480 mg, 0.92 mmol) in methyl ethyl ketone (7

mL) was slowly added 6N aqueous hydrochloric acid solution (4 mL) and then water (4 mL), and the mixture was stirred at 80°C for 5 min. The mixture was cooled to room temperature and stirred at room temperature for 3 hr. The precipitated solid was collected by filtration, washed with methyl ethyl ketone and dried under reduced pressure to give the title compound (410 mg, 79%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.83 - 0.93 (4H, m), 1.90 - 2.00 (1H, m), 3.49 (3H, s), 7.22 - 7.33 (2H, m), 7.45 - 7.64 (6H, m), 7.70 (1H, d, J = 9.6 Hz), 7.95 (1H, dd, J = 13.4, 1.9 Hz), 8.06 (1H, s), 8.57 (1H, d, J = 1.9 Hz), 8.64 (1H, s), 10.50 (1H, s), 11.65 (1H, s).

Example 48

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-2-(4-fluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxamide



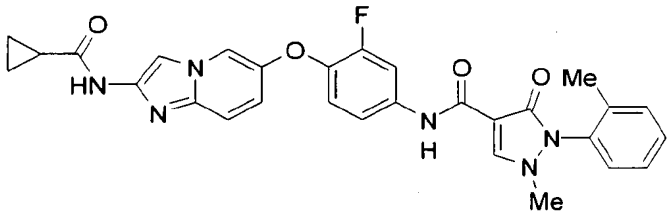
In the same manner as in Example 46 and using 2-(4-fluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid (280 mg, 1.2 mmol), N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (260 mg, 0.80 mmol), HATU (460 mg, 1.2 mmol), N,N-diisopropylethylamine (310 mg, 2.4 mmol) and N,N-dimethylformamide (6 mL) as starting materials, the title compound (350 mg, 81%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.72 - 0.85 (4H, m), 1.86 - 1.97 (1H, m), 3.48 (3H, s), 7.11 (1H, dd, J = 9.6, 2.3 Hz), 7.16 (1H, t, J = 8.9 Hz), 7.21 - 7.27 (1H, m), 7.40 - 7.50 (3H, m), 7.52 - 7.60 (2H, m), 7.90 (1H, dd, J = 13.2, 2.3 Hz), 8.02 (1H,

s), 8.44 (1H, d, J = 1.9 Hz), 8.62 (1H, s), 10.43 (1H, s), 10.94 (1H, s).

Example 49

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-methyl-2-(2-methylphenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxamide

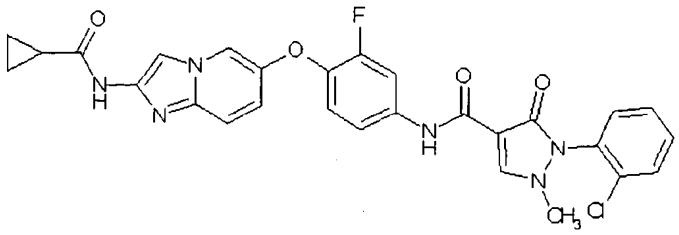


In the same manner as in Example 46 and using 1-methyl-2-(2-methylphenyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid (370 mg, 1.6 mmol), N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (260 mg, 0.80 mmol), HATU (610 mg, 1.6 mmol), N,N-diisopropylethylamine (410 mg, 3.2 mmol) and N,N-dimethylformamide (12 mL) as starting materials, the title compound (300 mg, 70%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.72 - 0.84 (4H, m), 1.86 - 1.96 (1H, m), 2.14 (3H, s), 3.38 (3H, s), 7.08 - 7.19 (2H, m), 7.20 - 7.25 (1H, m), 7.38 - 7.54 (5H, m), 7.91 (1H, dd, J = 13.3, 2.4 Hz), 8.02 (1H, s), 8.44 (1H, d, J = 1.7 Hz), 8.62 (1H, s), 10.47 (1H, s), 10.94 (1H, s).

Example 50

Production of 2-(2-chlorophenyl)-N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxamide

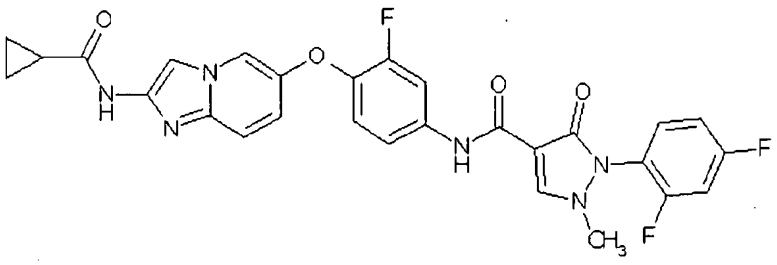


In the same manner as in Example 46 and using 2-(2-chlorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid (330 mg, 1.3 mmol), N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (250 mg, 0.77 mmol), HATU (490 mg, 1.3 mmol), N,N-diisopropylethylamine (340 mg, 2.6 mmol) and N,N-dimethylformamide (15 mL) as starting materials, the title compound (260 mg, 60%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.71 - 0.85 (4H, m), 1.86 - 1.96 (1H, m), 3.41 (3H, s), 7.08 - 7.20 (2H, m), 7.21 - 7.27 (1H, m), 7.44 (1H, d, J = 9.6 Hz), 7.57 - 7.73 (3H, m), 7.78 (1H, dd, J = 7.8, 1.4 Hz), 7.90 (1H, dd, J = 13.2, 2.5 Hz), 8.03 (1H, s), 8.44 (1H, d, J = 1.9 Hz), 8.66 (1H, s), 10.33 (1H, s), 10.93 (1H, s).

Example 51

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-2-(2,4-difluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxamide



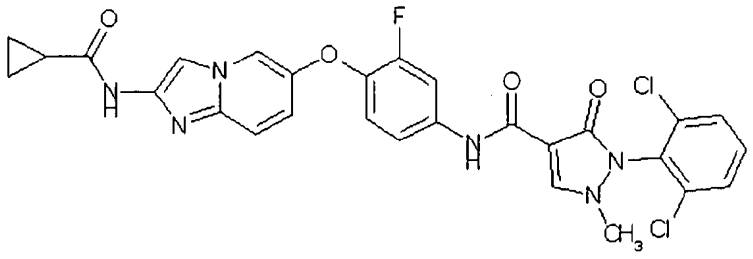
In the same manner as in Example 46 and using 2-(2,4-difluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid (330 mg, 1.3 mmol), N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-

yl]cyclopropanecarboxamide (250 mg, 0.77 mmol), HATU (490 mg, 1.3 mmol), N,N-diisopropylethylamine (340 mg, 2.6 mmol) and N,N-dimethylformamide (15 mL) as starting materials, the title compound (330 mg, 76%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.72 - 0.84 (4H, m), 1.87 - 1.97 (1H, m), 3.47 (3H, s), 7.08 - 7.20 (2H, m), 7.22 - 7.28 (1H, m), 7.33 - 7.41 (1H, m), 7.44 (1H, d, J = 9.6 Hz), 7.61 - 7.70 (1H, m), 7.72 - 7.81 (1H, m), 7.89 (1H, dd, J = 13.2, 2.5 Hz), 8.02 (1H, s), 8.44 (1H, d, J = 1.7 Hz), 8.66 (1H, s), 10.27 (1H, s), 10.93 (1H, s).

Example 52

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-2-(2,6-dichlorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxamide



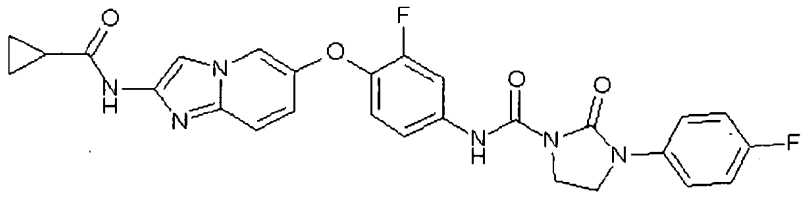
In the same manner as in Example 46 and using 2-(2,6-dichlorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid (370 mg, 1.3 mmol), N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (250 mg, 0.77 mmol), HATU (490 mg, 1.3 mmol), N,N-diisopropylethylamine (340 mg, 2.6 mmol) and N,N-dimethylformamide (15 mL) as starting materials, the title compound (330 mg, 72%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.71 - 0.84 (4H, m), 1.86 - 1.98 (1H, m), 3.44 (3H, s), 7.07 - 7.20 (2H, m), 7.23 - 7.29 (1H, m), 7.44 (1H, d, J = 9.6 Hz), 7.69 - 7.76 (1H, m), 7.79 - 7.84 (2H, m), 7.89 (1H, dd, J = 13.3, 2.4 Hz), 8.03 (1H, s), 8.44 (1H, d, J = 1.9 Hz), 8.73 (1H, s), 10.18 (1H, s), 10.94 (1H,

s).

Example 53

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-3-(4-fluorophenyl)-2-oxoimidazolidine-1-carboxamide



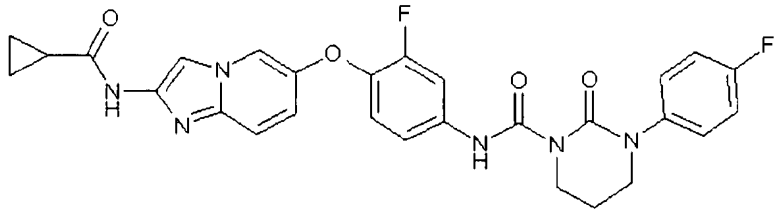
To a solution of 1-(4-fluorophenyl)imidazolidin-2-one (280 mg, 1.5 mmol) in tetrahydrofuran (5 mL) was added bis(trichloromethyl) carbonate (270 mg, 0.92 mmol), and the mixture was stirred at 70°C for 5 hr. The mixture was cooled to room temperature, a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (250 mg, 0.77 mmol) in tetrahydrofuran (5 mL) and N,N-diisopropylethylamine (300 mg, 2.3 mmol) were added to the mixture, and the mixture was stirred at room temperature for 40 min. Ethyl acetate/tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution were added to the mixture, and the aqueous layer was extracted with ethyl acetate/tetrahydrofuran (×3). The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (NH silica gel, ethyl acetate/hexane=50/50→90/10) to give the title compound (120 mg, 30%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.84 (4H, m), 1.85 - 1.97 (1H, m), 3.86 - 4.00 (4H, m), 7.10 (1H, dd, J = 9.6, 2.5 Hz), 7.16 (1H, t, J = 9.1 Hz), 7.23 - 7.32 (3H, m), 7.44 (1H, d, J = 9.6 Hz), 7.61 - 7.67 (2H, m), 7.75 (1H, dd, J = 13.2, 2.5

Hz), 8.03 (1H, s), 8.45 (1H, d, J = 1.7 Hz), 10.42 (1H, s), 10.93 (1H, s).

Example 54

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-3-(4-fluorophenyl)-2-oxotetrahydropyrimidine-1(2H)-carboxamide



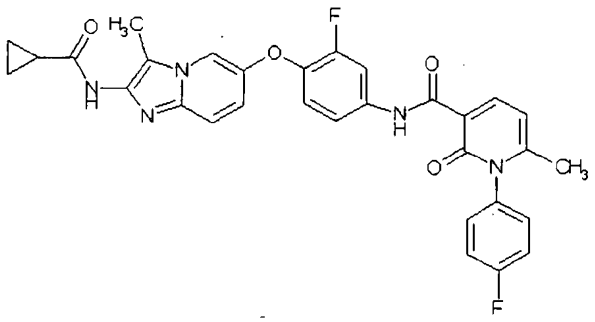
To a solution of 1-(4-fluorophenyl)tetrahydropyrimidin-2(1H)-one (360 mg, 1.8 mmol) in tetrahydrofuran (5 mL) was added bis(trichloromethyl) carbonate (330 mg, 1.1 mmol), and the mixture was stirred at 70°C for 3.5 hr. The mixture was cooled to room temperature, a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (300 mg, 0.92 mmol) in tetrahydrofuran (8 mL) and N,N-diisopropylethylamine (360 mg, 2.8 mmol) were added to the mixture, and the mixture was stirred at room temperature for 30 min. Ethyl acetate/tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution were added to the mixture, and the aqueous layer was extracted with ethyl acetate/tetrahydrofuran (×3). The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (NH silica gel, ethyl acetate/hexane=40/60→90/10) to give the title compound (250 mg, 49%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.85 (4H, m), 1.86 - 1.98 (1H, m), 2.06 - 2.16 (2H, m), 3.66 (2H, t, J = 5.9 Hz), 3.85 - 3.96 (2H, m), 7.06 - 7.15 (2H, m), 7.15 - 7.32 (3H, m), 7.38 -

7.48 (3H, m), 7.71 (1H, dd, J = 13.3, 2.4 Hz), 8.02 (1H, s), 8.44 (1H, d, J = 1.7 Hz), 10.94 (1H, s), 11.78 (1H, s).

Example 55

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]-3-methylimidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



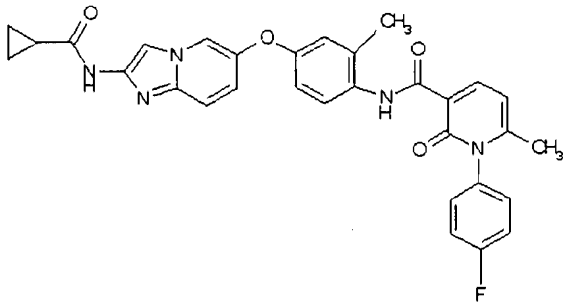
To a solution of 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (56.7 mg, 0.229 mmol) and N-[6-(4-amino-2-fluorophenoxy)-3-methylimidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (60 mg, 0.176 mmol) in N,N-dimethylformamide (1 mL) were added N,N-diisopropylethylamine (61 μL, 0.352 mmol) and HATU (87 mg, 0.229 mmol), and the mixture was stirred at room temperature for 17 hr. Ethyl acetate and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate alone) to give a yellow oil. The obtained oil was dissolved in ethyl acetate (1 mL) and left standing at room temperature for 17 hr. The precipitated solid was collected by filtration, washed with diethyl ether and collected by filtration to give the title compound (76 mg, 75%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.78 (4H, m), 1.74 - 1.91 (1H, m), 2.07 (3H, s), 2.26 (3H, s), 6.61 - 6.79 (1H, m), 7.01 - 7.15

(2H, m), 7.28 - 7.37 (1H, m), 7.38 - 7.54 (5H, m), 7.97 (1H, dd, J = 13.2, 2.5 Hz), 8.19 (1H, d, J = 1.9 Hz), 8.48 (1 H, d, J = 7.6 Hz), 10.21 (1H, br s), 11.97 (1H, s).

Example 56

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-2-methylphenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



A mixed solution of N-[6-(3-methyl-4-nitrophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (200 mg, 0.568 mmol), reduced iron (166.9 mg, 2.84 mmol) and ammonium chloride (303 mg, 5.68 mmol) in ethanol (2 mL) and water (0.5 mL) was stirred at 80°C for 6 hr. The reaction mixture was diluted with ethyl acetate and tetrahydrofuran, and filtered through celite. Water was added to the filtrate, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane=50/50→100/0) to give a white solid.

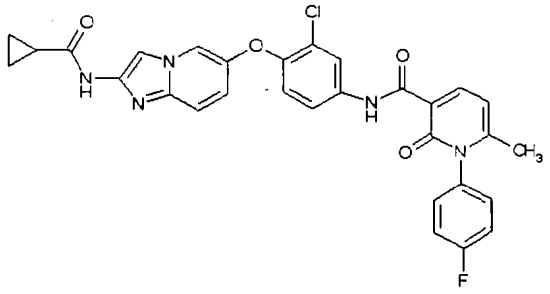
To a solution of the obtained white solid and 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (45 mg, 0.182 mmol) in N,N-dimethylformamide (1 mL) were added N,N-diisopropylethylamine (48 μL, 0.28 mmol) and HATU (69 mg, 0.182 mmol), and the mixture was stirred at room

temperature for 2 hr. Ethyl acetate, tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate alone) to give a yellow solid. The obtained solid was washed with ethyl acetate and collected by filtration to give the title compound (33 mg, 41%) as a slightly yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.68 - 0.91 (4H, m), 1.89 - 1.96 (1H, m), 2.06 (3H, s), 2.19 (3H, s), 6.70 (1H, d, J = 8.3 Hz), 6.83 - 6.97 (2H, m), 7.05 (1H, dd, J = 9.6, 2.3 Hz), 7.35 - 7.56 (5H, m), 8.03 (1H, s), 8.23 (1H, d, J = 8.9 Hz), 8.45 - 8.53 (2H, m), 10.94 (1H, s), 11.67 (1H, s).

Example 57

Production of N-[3-chloro-4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



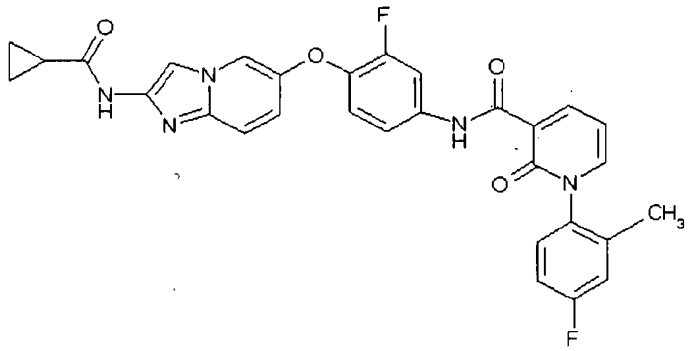
To a solution of N-[6-(4-amino-2-chlorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (100 mg, 0.292 mmol) and 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (94 mg, 0.38 mmol) in N,N-dimethylformamide (1 mL) were added N,N-diisopropylethylamine (100 μL, 0.583 mmol) and HATU

(144 mg, 0.380 mmol), and the mixture was stirred at 60°C for 4 hr. Ethyl acetate, tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate alone) to give a white solid. The obtained solid was washed with ethyl acetate and collected by filtration to give the title compound (120.2 mg, 72%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.67 - 0.90 (4H, m), 1.85 - 1.96 (1H, m), 2.07 (3H, s), 6.71 (1H, d, J = 8.3 Hz), 6.99 - 7.14 (2H, m), 7.35 - 7.57 (6H, m), 8.02 (1H, s), 8.16 (1H, d, J = 2.5 Hz), 8.40 - 8.51 (2H, m), 10.94 (1H, s), 11.96 (1H, s).

Example 58

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluoro-2-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide



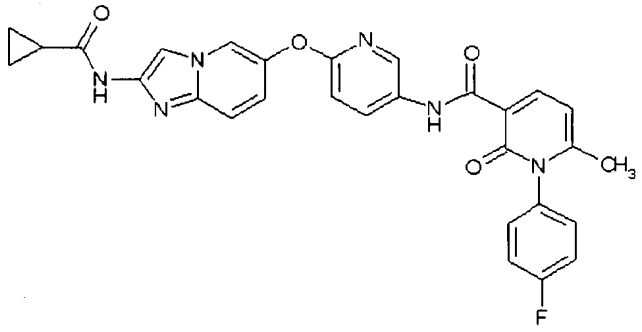
To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (100 mg, 0.306 mmol) and 1-(4-fluoro-2-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (98 mg, 0.398 mmol) in N,N-dimethylformamide (2 mL) were

added N,N-diisopropylethylamine (105 μL, 0.612 mmol) and HATU (151 mg, 0.398 mmol), and the mixture was stirred at room temperature for 4 hr. Ethyl acetate, tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (140 mg, 82%) as a slightly yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.69 - 0.85 (4H, m), 1.86 - 1.96 (1H, m), 2.08 (3H, s), 6.67 - 6.81 (1H, m), 7.06 - 7.52 (7H, m), 7.88 - 8.11 (3H, m), 8.46 (1H, d, J = 1.7 Hz), 8.61 (1 H, dd, J = 7.3, 2.2 Hz), 10.94 (1H, s), 12.02 (1H, s).

Example 59

Production of N-[6-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)pyridin-3-yl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



A mixed solution of N-{6-[(5-nitropyridin-2-yl)oxy]imidazo[1,2-a]pyridin-2-yl}cyclopropanecarboxamide (111 mg, 0.327 mmol), reduced iron (96 mg, 1.64 mmol) and ammonium chloride (175 mg, 3.27 mmol) in ethanol (2 mL) and water (0.5 mL) was stirred at 70°C for 1.5 hr. The reaction mixture was diluted with ethyl acetate and filtered through celite. Water was added to the filtrate, and the mixture was extracted twice

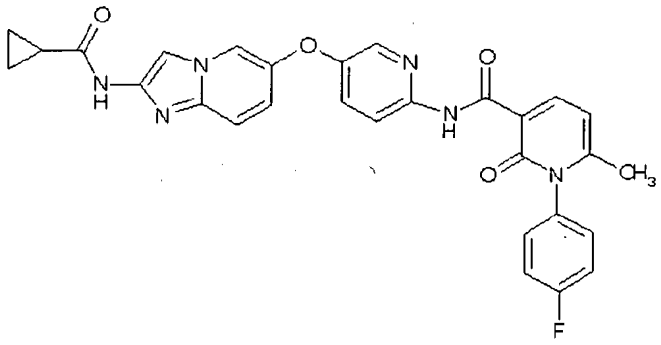
with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate and collected by filtration to give a yellow solid.

To a solution of the obtained yellow solid and 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (76.8 mg, 0.311 mmol) in N,N-dimethylformamide (1 mL) were added N,N-diisopropylethylamine (89 μL, 0.518 mmol) and HATU (128 mg, 0.337 mmol), and the mixture was stirred at room temperature for 7 hr. Ethyl acetate, tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (70 mg, 40%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.64 - 0.91 (4H, m), 1.87 - 1.96 (1H, m), 2.08 (3H, s), 6.70 (1H, d, J = 8.3 Hz), 7.03 - 7.18 (2H, m), 7.34 - 7.56 (5H, m), 8.04 (1H, s), 8.24 (1H, dd, J = 8.9, 2.8 Hz), 8.42 (1H, d, J = 2.3 Hz), 8.47 (1H, d, J = 7.6 Hz), 8.56 - 8.61 (1H, m), 10.96 (1H, s), 11.85 (1H, s).

Example 60

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)pyridin-2-yl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide

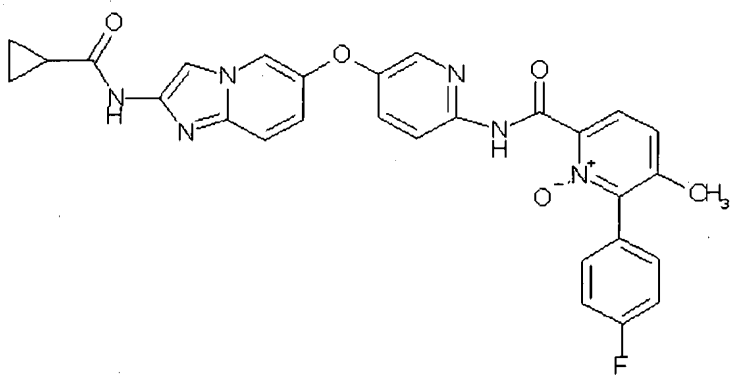


To a solution of N-{6-[(6-aminopyridin-3-yl)oxy]imidazo[1,2-a]pyridin-2-yl}cyclopropanecarboxamide (75 mg, 0.242 mmol) and 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (78 mg, 0.315 mmol) in N,N-dimethylformamide (1 mL) were added N,N-diisopropylethylamine (83 μL, 0.484 mmol) and HATU (120 mg, 0.315 mmol), and the mixture was stirred at room temperature for 17 hr. Ethyl acetate, tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (116 mg, 89%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.70 - 0.88 (4H, m), 1.85 - 1.96 (1H, m), 2.07 (3H, s), 6.66 - 6.75 (1H, m), 7.12 (1H, dd, J = 9.6, 2.5 Hz), 7.38 - 7.52 (5H, m), 7.58 (1H, dd, J = 9.1, 3.0 Hz), 8.03 (1H, s), 8.16 (1H, d, J = 2.5 Hz), 8.29 (1 H, d, J = 9.6 Hz), 8.46 - 8.56 (2H, m), 10.95 (1H, s), 12.22 (1H, s).

Example 61

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)pyridin-2-yl]-6-(4-fluorophenyl)-5-methylpyridine-2-carboxamide 1-oxide

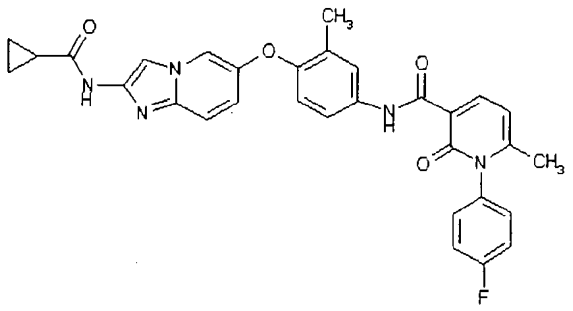


To a solution of N-{6-[(6-aminopyridin-3-yl)oxy]imidazo[1,2-a]pyridin-2-yl}cyclopropanecarboxamide (100 mg, 0.323 mmol) and 6-(4-fluorophenyl)-5-methylpyridine-2-carboxylic acid 1-oxide (103.8 mg, 0.42 mmol) in N,N-dimethylformamide (1 mL) were added N,N-diisopropylethylamine (111 μL, 0.646 mmol) and HATU (160 mg, 0.42 mmol), and the mixture was stirred at room temperature for 4 hr. Ethyl acetate, tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (140 mg, 80%) as a slightly yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.60 - 0.87 (4H, m), 1.86 - 1.96 (1H, m), 2.13 (3H, s), 7.14 (1H, dd, J = 9.5, 2.4 Hz), 7.33 - 7.55 (5H, m), 7.62 (1H, dd, J = 9.1, 3.0 Hz), 7.69 (1H, d, J = 8.9 Hz), 8.04 (1H, s), 8.21 (1H, d, J = 2.5 Hz), 8.26 - 8.37 (2H, m), 8.57 (1H, dd, J = 2.5, 0.8 Hz), 10.97 (1H, s), 13.99 (1H, s).

Example 62

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-methylphenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide

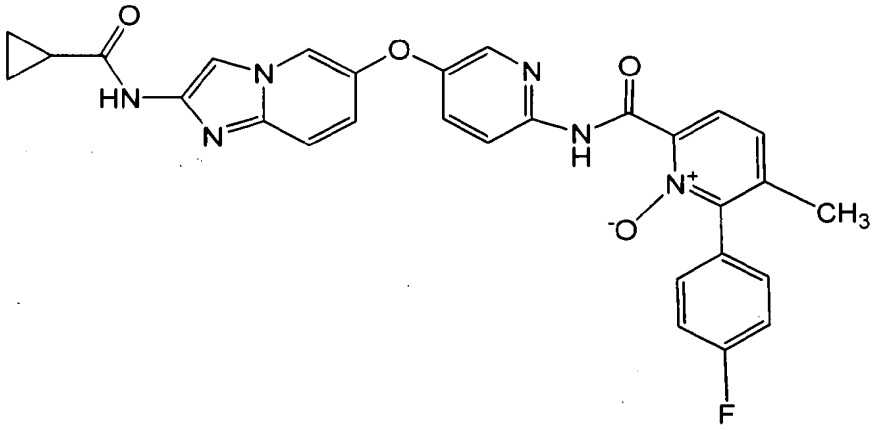


Using N-[6-(4-amino-2-methylphenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (100 mg, 0.31 mmol), 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (99.7mg,0.403 mmol), N,N-dimethylformamide (1 mL), N,N-diisopropylethylamine (107 μL, 0.620 mmol) and HATU (153 mg, 0.403 mmol) and in the same manner as in Example 57, the title compound (125.7 mg, 74%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.67 - 0.88 (4H, m), 1.86 - 1.95 (1H, m), 2.07 (3H, s), 2.23 (3H, s), 6.69 (1H, d, J = 8.1 Hz), 6.85 (1H, d, J = 8.9 Hz), 7.03 (1H, dd, J = 9.6, 2.3 Hz), 7.37 - 7.68 (7H, m), 8.01 (1H, s), 8.32 (1H, d, J = 1.7 Hz), 8.46 (1H, d, J = 7.6 Hz), 10.92 (1H, s), 11.85 (1H, s).

Example 63

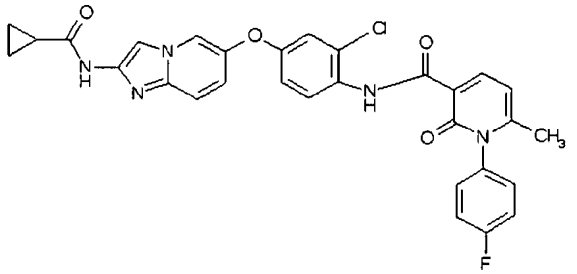
Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)pyridin-2-yl]-6-(4-fluorophenyl)-5-methylpyridine-2-carboxamide 1-oxide·hydrochloride·monohydrate



To a suspension of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)pyridin-2-yl]-6-(4-fluorophenyl)-5-methylpyridine-2-carboxamide 1-oxide (530 mg, 0.984 mmol) in ethanol (8 mL) were added 6N hydrochloric acid (0.984 mL, 5.9 mmol) and water (0.984 mL) at 80°C. The reaction solution was stirred at 70°C for 7 hr, and the precipitate was collected by filtration to give the title compound (197.6 mg, 34%) as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.79 - 0.98 (4H, m), 1.86 - 2.01 (1H, m), 2.14 (3H, s), 7.28 - 7.57 (5H, m), 7.61 - 7.77 (3H, m), 8.06 (1H, s), 8.26 (1H, d, J = 2.5 Hz), 8.29 - 8.37 (2H, m), 8.67 (1H, d, J = 1.7 Hz), 11.48 (1H, br s), 14.02 (1H, s).

Example 64

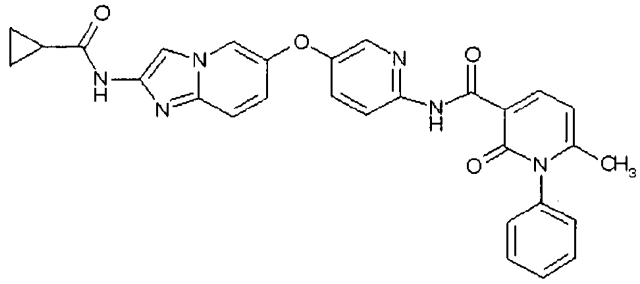
Production of N-[2-chloro-4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



Using N-[6-(4-amino-3-chlorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (160 mg, 0.467 mmol), 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (150 mg, 0.607 mmol), N,N-dimethylformamide (2 mL), N,N-diisopropylethylamine (161 μL, 0.934 mmol) and HATU (230.8 mg, 0.607 mmol) and in the same manner as in Example 60, the title compound (250 mg, 94%) was obtained as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.86 (4H, m), 1.86 - 1.97 (1H, m), 2.06 (3H, s), 6.64 - 6.77 (1H, m), 7.02 - 7.14 (2H, m), 7.24 (1H, d, J = 3.0 Hz), 7.38 - 7.54 (5H, m), 8.04 (1H, s), 8.43 - 8.58 (3H, m), 10.96 (1H, s), 12.15 (1H, s).

Example 65

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)pyridin-2-yl]-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide

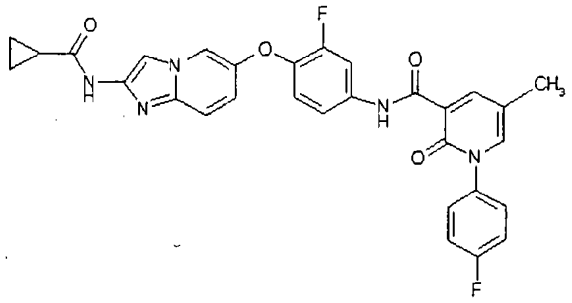


To a solution of N-{6-[(6-aminopyridin-3-yl)oxy]imidazo[1,2-a]pyridin-2-yl}cyclopropanecarboxamide (200 mg, 0.647 mmol) and 6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylic acid (178 mg, 0.776 mmol) in N,N-dimethylformamide (3 mL) were added N,N-diisopropylethylamine (233 μL, 1.29 mmol) and HATU (320 mg, 0.841 mmol), and the mixture was stirred at room temperature for 6 hr. Ethyl acetate, tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate and collected by filtration. The obtained white solid was suspended in methyl ethyl ketone (2 mL), and the mixture was stirred at 80°C for 17 hr. The suspension was collected by filtration to give the title compound (175 mg, 52%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.72 - 0.84 (4H, m), 1.86 - 1.98 (1H, m), 2.06 (3H, s), 6.70 (1H, d, J = 8.3 Hz), 7.12 (1H, dd, J = 9.6, 2.5 Hz), 7.29 - 7.70 (7H, m), 8.03 (1H, s), 8.16 (1H, d, J = 2.5 Hz), 8.29 (1H, d, J = 9.1 Hz), 8.45 - 8.55 (2H, m), 10.95 (1H, s), 12.24 (1H, s).

Example 66

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-5-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



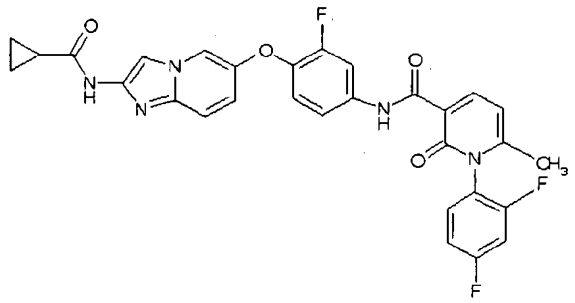
To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (100 mg, 0.306 mmol) and 1-(4-fluorophenyl)-5-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (90.8 mg, 0.367 mmol) in N,N-dimethylformamide (1 mL) were added N,N-diisopropylethylamine (105 μL, 0.612 mmol) and HATU (151 mg, 0.40 mmol), and the mixture was stirred at room temperature for 6 hr. Ethyl acetate, tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate and collected by filtration. The obtained slightly yellow solid was suspended in methanol (3 mL), and the mixture was stirred at 70°C for 10 min. The suspension was collected by filtration, and the obtained solid was washed with methanol to give the title compound (122 mg, 72%) as a slightly yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.71 - 0.85 (4H, m), 1.92 (1H, m), 2.20 (3H, s), 7.02 - 7.23 (2H, m), 7.30 - 7.50 (4H, m), 7.53 -

7.67 (2H, m), 7.88 - 8.06 (3H, m), 8.46 (2H, s), 10.93 (1H, s), 12.16 (1H, s).

Example 67

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(2,4-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide

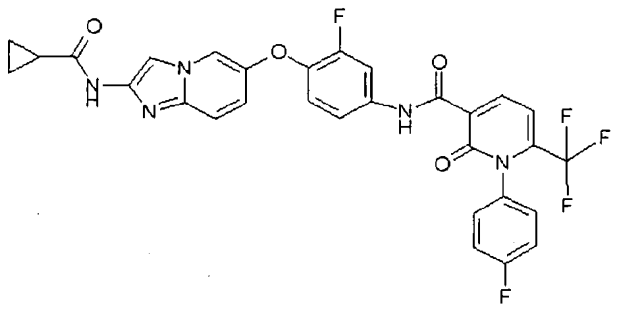


Using N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide(100mg, 0.306 mmol), 1-(2,4-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (97.4 mg, 0.367 mmol), N,N-dimethylformamide (1 mL), N,N-diisopropylethylamine (105 μL, 0.612 mmol) and HATU (151 mg, 0.40 mmol) and in the same manner as in Example 65, the title compound (115 mg, 66%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.67 - 0.83 (4H, m), 1.85 - 1.96 (1H, m), 2.13 (3H, s), 6.71 - 6.86 (1H, m), 7.04 - 7.22 (2H, m), 7.30 - 7.48 (3H, m), 7.57 - 7.79 (2H, m), 7.96 (1H, dd, J = 13.2, 2.5 Hz), 8.02 (1H, s), 8.46 (1H, d, J = 1.9 Hz), 8.52 (1H, d, J = 7.6 Hz), 10.93 (1H, s), 11.76 (1H, s).

Example 68

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydropyridine-3-carboxamide

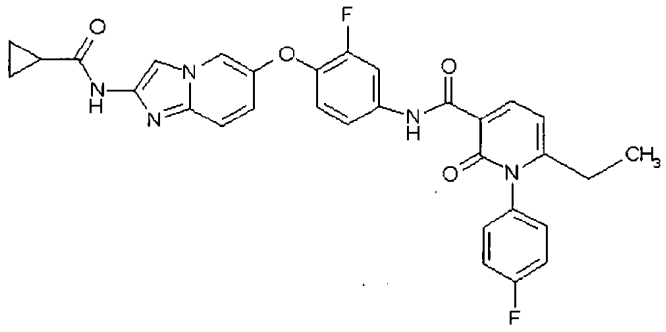


To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (90 mg, 0.276 mmol) and 1-(4-fluorophenyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydropyridine-3-carboxylic acid (100 mg, 0.331 mmol) in N,N-dimethylformamide (2 mL) were added N,N-diisopropylethylamine (95 μL, 0.552 mmol) and HATU (126 mg, 0.331 mmol), and the mixture was stirred at room temperature for 6 hr. Ethyl acetate, tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate and collected by filtration. The obtained slightly yellow solid was suspended in ethanol (3 mL), and the mixture was stirred at 70°C for 17 hr. The suspension was collected by filtration and washed with ethanol to give the title compound (32.7 mg, 19%) as a slightly yellow solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.61 - 0.91 (4H, m), 1.86 - 1.97 (1H, m), 7.04 - 7.20 (2H, m), 7.31 (1H, d, J = 7.7 Hz), 7.38 - 7.48 (4H, m), 7.57 (2H, d, J = 4.5 Hz), 7.97 (1H, dd, J = 13.0, 2.5 Hz), 8.02 (1H, s), 8.47 (1H, d, J = 1.7 Hz), 8.63 (1H, d, J = 7.6 Hz), 10.93 (1H, s), 11.66 (1H, s).

Example 69

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-

fluorophenyl]-6-ethyl-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide

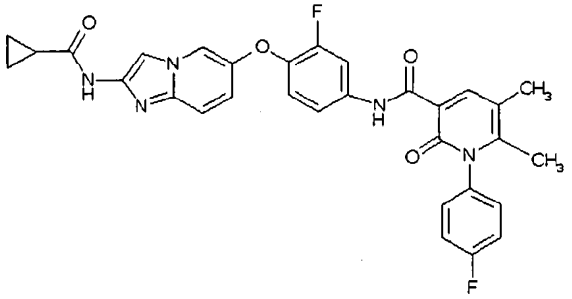


Using N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (100 mg, 0.306 mmol), 6-ethyl-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (95.9mg,0.367 mmol), N,N-dimethylformamide (1 mL), N,N-diisopropylethylamine (105 μL, 0.612 mmol) and HATU (151 mg, 0.40 mmol) and in the same manner as in Example 68, the title compound (64.1 mg, 37%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.70 - 0.87 (4H, m), 1.06 (3H, t, J = 7.3 Hz), 1.81 - 2.01 (1H, m), 2.30 (2H, q, J = 7.5 Hz), 6.68 (1H, d, J = 7.7 Hz), 7.01 - 7.22 (2H, m), 7.30 - 7.56 (6H, m), 7.87 - 8.06 (2H, m), 8.45 (1H, d, J = 1.7 Hz), 8.53 (1H, d, J = 7.7 Hz), 10.93 (1H, s), 11.98 (1H, s).

Example 70

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-5,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxamide

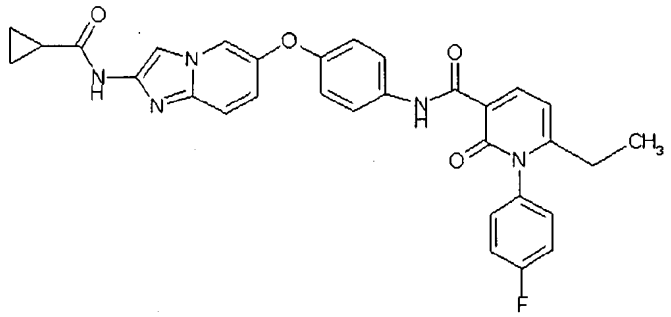


To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (83 mg, 0.255 mmol) and 1-(4-fluorophenyl)-5,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (80 mg, 0.306 mmol) in N,N-dimethylformamide (1 mL) were added N,N-diisopropylethylamine (88 μL, 0.51 mmol) and HATU (116 mg, 0.306 mmol), and the mixture was stirred at room temperature for 6 hr. Ethyl acetate, tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate alone) to give a white solid. The obtained solid was suspended in methyl ethyl ketone, stirred at 80°C and collected by filtration to give the title compound (90 mg, 62%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.69 - 0.85 (4H, m), 1.82 - 1.96 (1H, m), 2.01 (3H, s), 2.23 (3H, s), 7.05 - 7.20 (2H, m), 7.30 - 7.50 (6H, m), 7.91 - 8.08 (2H, m), 8.35 - 8.48 (2H, m), 10.93 (1H, s), 12.11 (1H, s).

Example 71

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)phenyl]-6-ethyl-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide

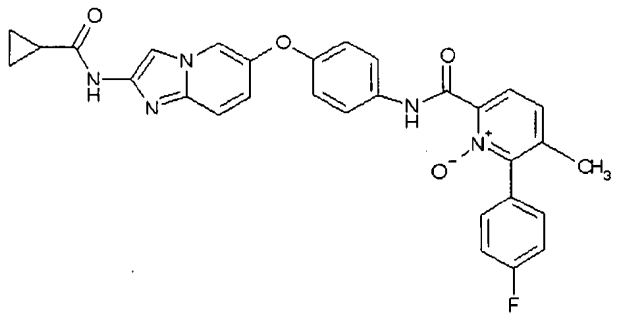


Using N-[6-(4-aminophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (100 mg, 0.324 mmol), 6-ethyl-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (101.5mg,0.389 mmol), N,N-dimethylformamide (1 mL), N,N-diisopropylethylamine (111 μL, 0.648 mmol) and HATU (148 mg, 0.389 mmol) and in the same manner as in Example 57, the title compound (133 mg, 74%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.68 - 0.87 (4H, m), 1.05 (3H, t, J = 7.4 Hz), 1.86 - 1.96 (1H, m), 2.30 (2H, q, J = 7.4 Hz), 6.66 (1H, d, J = 7.9 Hz), 6.93 - 7.16 (3H, m), 7.36 - 7.55 (5H, m), 7.63 - 7.75 (2H, m), 8.03 (1H, s), 8.44 - 8.59 (2H, m), 10.94 (1H, s), 11.83 (1H, s).

Example 72

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)phenyl]-6-(4-fluorophenyl)-5-methylpyridine-2-carboxamide 1-oxide



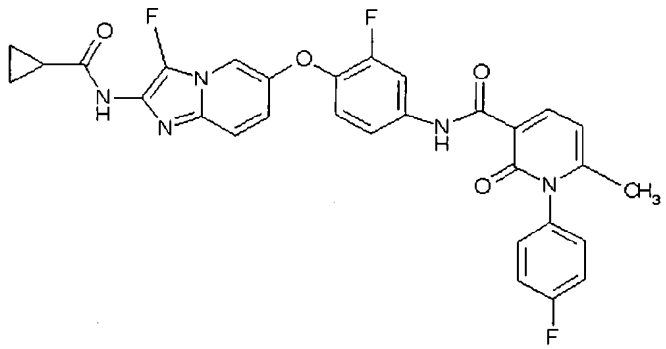
Using N-[6-(4-aminophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (200 mg, 0.649 mmol), 6-(4-fluorophenyl)-5-methylpyridine-2-carboxylic acid 1-oxide (192.5 mg, 0.779 mmol), N,N-dimethylformamide (2 mL), N,N-diisopropylethylamine (224 μL, 1.30 mmol) and HATU (296 mg, 0.779 mmol) and in the same manner as in Example 58, the title compound (254 mg, 73%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.70 - 0.87 (4H, m), 1.86 - 1.98 (1H, m), 2.12 (3H, s), 6.94 - 7.15 (3H, m), 7.32 - 7.56 (5H, m), 7.65 - 7.80 (3H, m), 8.04 (1H, s), 8.31 (1H, d, J = 8.3

Hz), 8.50 - 8.56 (1H, m), 10.95 (1H, s), 13.60 (1H, s).

Example 73

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]-3-fluoroimidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



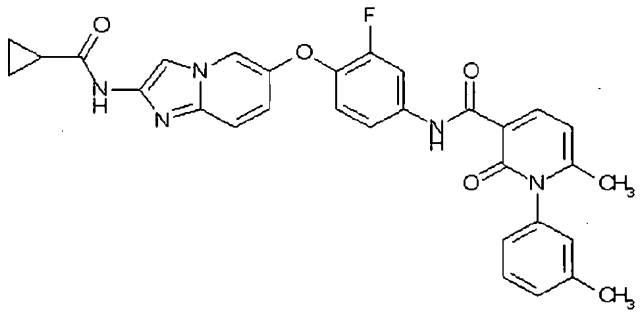
A mixed solution of N-[3-fluoro-6-(2-fluoro-4-nitrophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (15.2 mg, 0.041 mmol), reduced iron (12.1 mg, 0.205 mmol) and ammonium chloride (21.9 mg, 0.41 mmol) in ethanol (1 mL) and water (0.2 mL) was stirred at 90°C for 5 hr. The reaction mixture was diluted with ethyl acetate and saturated aqueous ammonium chloride solution and extracted twice with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. To a solution of the obtained residue and 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (12.2 mg, 0.0492 mmol) in N,N-dimethylformamide (1 mL) were added N,N-diisopropylethylamine (14 μL, 0.082 mmol) and HATU (18.7 mg, 0.0492 mmol), and the mixture was stirred at room temperature for 17 hr. Ethyl acetate and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The

obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane=2/1→ethyl acetate alone) to give a white solid. The obtained solid was washed with ethyl acetate and collected by filtration to give the title compound (8 mg, 34%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.68 - 0.90 (4H, m), 1.77 - 1.93 (1H, m), 2.07 (3H, s), 6.66 - 6.78 (1H, m), 7.07 - 7.25 (2H, m), 7.32 - 7.59 (6H, m), 7.97 (1H, dd, J = 13.3, 2.4 Hz), 8.13 (1H, d, J = 2.3 Hz), 8.48 (1H, d, J = 7.6 Hz), 10.51 (1H, s), 11.99 (1H, s).

Example 74

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-1-(3-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide



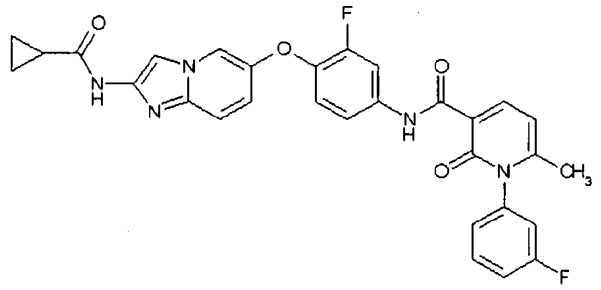
To a solution (3 mL) of 6-methyl-1-(3-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (120 mg, 0.50 mmol) in tetrahydrofuran were added oxalyl dichloride (130 mg,1.0 mmol) and N,N-dimethylformamide (1 drop), and the mixture was stirred at room temperature for 1 hr. The mixture was concentrated under reduced pressure, and the solvent was evaporated. N,N-Dimethylformamide (3,0 mL) and a solution (2.0 mL) of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (130 mg, 0.40 mmol) in N,N-dimethylformamide were successively added, and the mixture was stirred at room temperature for 5 hr. Saturated aqueous sodium hydrogen carbonate solution was added to the reaction

solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (150 mg, 69%) as a brown solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.70 - 0.86 (4H, m), 1.85 - 1.96 (1H, m), 2.07 (3H, s), 2.38 (3H, s), 6.69 (1H, d, J = 8.1 Hz), 7.05 - 7.55 (8H, m), 7.96 (1H, dd, J = 13.2, 2.5 Hz), 8.02 (1H, s), 8.43 - 8.53 (2H, m), 10.93 (1H, s), 12.03 (1H, s).

Example 75

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(3-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



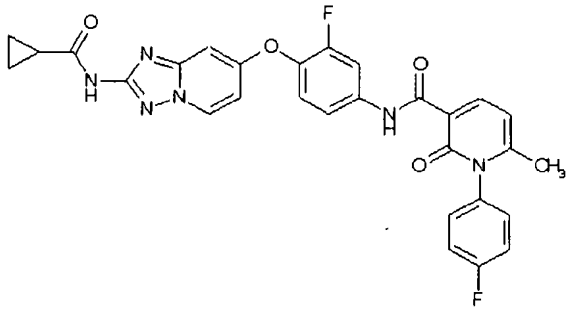
A solution (5 mL) of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (130 mg, 0.40 mmol), 1-(3-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (120 mg, 0.48 mmol), HATU (180 mg, 0.48 mmol) and N,N-diisopropylethylamine (100 mg, 0.80 mmol) in N,N-dimethylformamide was stirred at room temperature for 5 hr. The reaction solution was divided into two layers with tetrahydrofuran (10 mL) and saturated aqueous sodium hydrogen carbonate solution (10 mL) and the aqueous layer was subjected to extraction (3 times) with ethyl acetate (15 mL). The combined organic layer was washed with water (15 mL) and

saturated brine (15 mL), dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the obtained residue was washed with ethyl acetate and collected by filtration to give the title compound (80 mg, 35%) as a brown solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.77 - 0.93 (4H, m), 1.88 - 1.98 (1H, m), 2.10 (3H, s), 6.72 (1H, d, J = 8.3 Hz), 7.22 (1H, t, J = 9.1 Hz), 7.30 (1H, dt, J = 7.8, 1.0 Hz), 7.35 - 7.52 (4H, m), 7.65 (2H, d, J = 8.7 Hz), 8.00 (1H, dd, J = 13.2, 2.5 Hz), 8.05 (1H, s), 8.49 (1H, d, J = 7.6 Hz), 8.57 (1H, d, J = 2.1 Hz), 11.52 (1H, br s), 11.98 (1H, s).

Example 76

Production of N-[4-({2-[(cyclopropylcarbonyl)amino][1,2,4]triazolo[1,5-a]pyridine-7-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



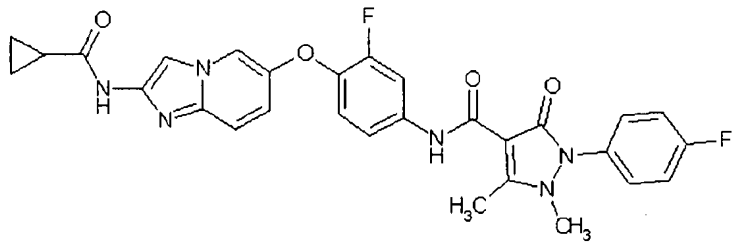
To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (150 mg, 0.458 mmol) and 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (170 mg, 0.687 mmol) in N,N-dimethylacetamide (3.0 mL) were added HATU (261 mg, 0.687 mmol) and N,N-diisopropylethylamine (120 μL, 0.687 mmol), and the mixture was stirred at room temperature for 16 hr. Saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The extract was washed with

saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane=25/75→100/0) and the obtained solid was washed with ethyl acetate and collected by filtration to give the title compound (111 mg, 44%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.78 - 0.83 (4H, m), 1.98 - 2.07 (1H, m), 2.08 (3H, s), 6.72 (1H, d, J = 8.4 Hz), 6.84 (1H, d, J = 2.7 Hz), 6.91 - 6.96 (1H, m), 7.34 - 7.54 (6H, m), 8.03 (1H, dd, J = 12.9, 2.4 Hz), 8.50 (1H, d, J = 7.5 Hz), 8.80 (1H, d, J = 6.9 Hz), 10.99 (1H, s), 12.08 (1H, s).

Example 77

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-2-(4-fluorophenyl)-1,5-dimethyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxamide



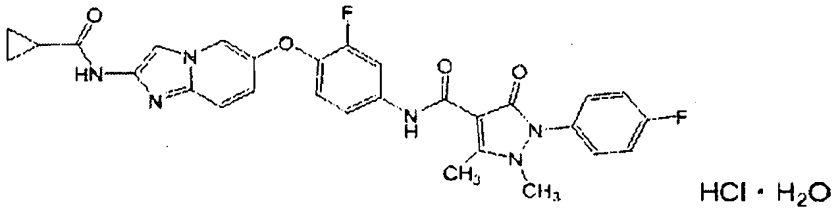
To a solution of 2-(4-fluorophenyl)-1,5-dimethyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid (1130 mg, 4.5 mmol) in tetrahydrofuran (75 mL) were added N,N-dimethylformamide (6 drops) and oxalyl dichloride (780 μL, 9.1 mmol), and the mixture was stirred at room temperature for 1 hr. The solvent was evaporated under reduced pressure, and the obtained residue was dissolved in N,N-dimethylacetamide (10 mL). The solution was added to a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (1230 mg, 3.8 mmol) in N,N-dimethylacetamide (30 mL), and the mixture was stirred at room

temperature for 4 hr. Ethyl acetate/tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution were added to the mixture, and the aqueous layer was extracted 4 times with ethyl acetate/tetrahydrofuran. The combined organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was washed with ethyl acetate and collected by filtration to give the title compound (1640 mg, 67%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.84 (4H, m), 1.86 - 1.97 (1H, m), 2.69 (3H, s), 3.35 (3H, s), 7.05 - 7.24 (3H, m), 7.38 - 7.55 (5H, m), 7.90 (1H, dd, J = 13.4, 2.3 Hz), 8.02 (1H, s), 8.44 (1H, d, J = 1.9 Hz), 10.84 (1H, s), 10.94 (1H, s).

Example 78

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-2-(4-fluorophenyl)-1,5-dimethyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxamide hydrochloride monohydrate



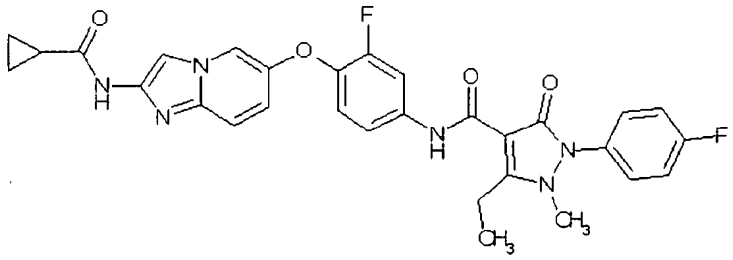
To a suspension of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-2-(4-fluorophenyl)-1,5-dimethyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxamide (400 mg, 0.72 mmol) in methyl ethyl ketone (7 mL) and water (5 mL) was slowly added 6N aqueous hydrochloric acid solution (240 μL), and the mixture was stirred at room temperature for 1 hr. The precipitated solid was collected by filtration, washed with methyl ethyl ketone and suspended in ethanol (5 mL), and the suspension was stirred at 70°C for 10 min. The solid was collected by filtration, washed with ethanol and dried under

reduced pressure to give the title compound (120 mg, 27%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.84 - 0.95 (4H, m), 1.90 - 2.01 (1H, m), 2.69 (3H, s), 3.36 (3H, s), 7.25 - 7.28 (2H, m), 7.41 - 7.54 (4H, m), 7.57 (1H, dd, J = 9.6, 2.1 Hz), 7.75 (1H, d, J = 9.6 Hz), 7.90 - 7.99 (1H, m), 8.08 (1H, s), 8.61 (1H, d, J = 2.1 Hz), 10.89 (1H, s), 11.85 (1H, s).

Example 79

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-5-ethyl-2-(4-fluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxamide



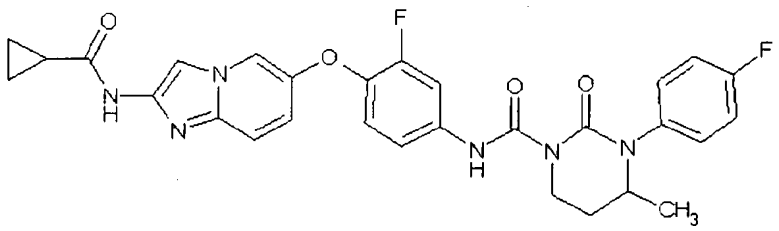
In the same manner as in Example 77 and using 5-ethyl-2-(4-fluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid (250 mg, 0.94 mmol), tetrahydrofuran (9 mL), N,N-dimethylformamide (1 drop), oxalyl dichloride (160 μL, 1.9 mmol), N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (250 mg, 0.78 mmol) and N,N-dimethylacetamide (12 mL) as starting materials, the title compound (210 mg, 47%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.83 (3H, m), 1.20 - 1.29 (4H, m), 1.85 - 1.96 (1H, m), 3.15 (2H, q, J = 7.5 Hz), 3.39 (3H, s), 7.06 - 7.23 (3H, m), 7.39 - 7.48 (3H, m), 7.49 - 7.58 (2H, m), 7.91 (1H, dd, J = 13.4, 2.3 Hz), 8.03 (1H, s), 8.42 - 8.47 (1H, m), 10.87 (1H, s), 10.94 (1H, s).

Example 80

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-

fluorophenyl]-3-(4-fluorophenyl)-4-methyl-2-oxotetrahydropyrimidine-1(2H)-carboxamide



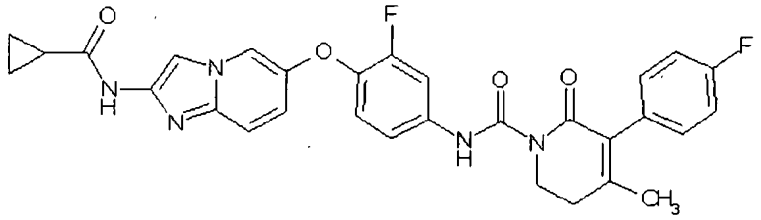
To a solution of 1-(4-fluorophenyl)-6-methyltetrahydropyrimidin-2(1H)-one (240 mg, 1.1 mmol) in tetrahydrofuran (5 mL) was added bis(trichloromethyl) carbonate (170 mg, 0.57 mmol), and the mixture was stirred at 70°C for 3.5 hr. The mixture was cooled to room temperature, a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (250 mg, 0.76 mmol) in tetrahydrofuran (8 mL) and N,N-diisopropylethylamine (300 mg, 2.3 mmol) were added to the mixture, and the mixture was stirred at room temperature for 1 hr. Ethyl acetate/tetrahydrofuran and saturated aqueous sodium hydrogen carbonate solution were added to the mixture, and the aqueous layer was extracted 3 times with ethyl acetate/tetrahydrofuran. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (NH silica gel, ethyl acetate/hexane=50/50→100/0) to give the title compound (29 mg, 7%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.69 - 0.86 (4H, m), 1.07 (3H, d, J = 6.4 Hz), 1.84 - 1.97 (2H, m), 2.19 - 2.36 (1H, m), 3.74 - 3.88 (1H, m), 3.91 - 4.13 (2H, m), 7.04 - 7.15 (2H, m), 7.17 - 7.31 (3H, m), 7.33 - 7.46 (3H, m), 7.65 - 7.77 (1H, m), 8.02 (1H, s), 8.41 - 8.47 (1H, m), 10.94 (1H, s), 11.81 (1H, s).

Example 81

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-

fluorophenyl]-5-(4-fluorophenyl)-4-methyl-6-oxo-3,6-dihydropyridine-1(2H)-carboxamide



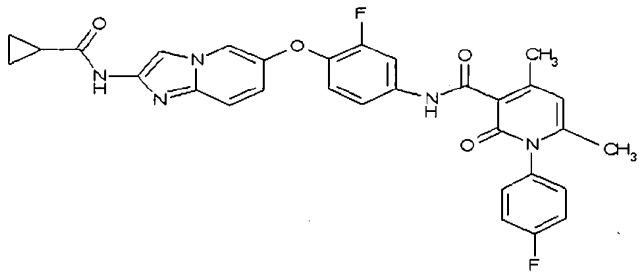
To a solution of bis(trichloromethyl) carbonate (127 mg, 0.43 mmol) in tetrahydrofuran (4 mL) were slowly added a solution of 3-(4-fluorophenyl)-4-methyl-5,6-dihydropyridin-2(1H)-one (240 mg, 1.2 mmol) and triethylamine (240 mg, 2.3 mmol) in tetrahydrofuran (2 mL) under ice-cooling, and the mixture was stirred at 0°C for 40 min and at room temperature for 15 min. A solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (250 mg, 0.78 mmol) in tetrahydrofuran (4 mL) and triethylamine (79 mg, 0.78 mmol) were added to the mixture, and the mixture was stirred at room temperature for 2 hr. Ethyl acetate/tetrahydrofuran and saturated brine were added to the mixture, and the aqueous layer was extracted 3 times with ethyl acetate/tetrahydrofuran. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (NH silica gel, ethyl acetate/hexane=40/60→90/10) to give the title compound (170 mg, 39%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.72 - 0.85 (4H, m), 1.82 (3H, s), 1.87 - 1.96 (1H, m), 2.60 (2H, t, J = 6.5 Hz), 4.02 (2H, t, J = 6.5 Hz), 7.06 - 7.17 (2H, m), 7.19 - 7.32 (5H, m), 7.43 (1H, d, J = 9.6 Hz), 7.74 (1H, dd, J = 13.3, 2.5 Hz), 8.02 (1H, s), 8.45 (1H, d, J = 1.7 Hz), 10.94 (1H, s), 11.51 (1H, s).

Example 82

Production of N-[4-({2-

[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxamide



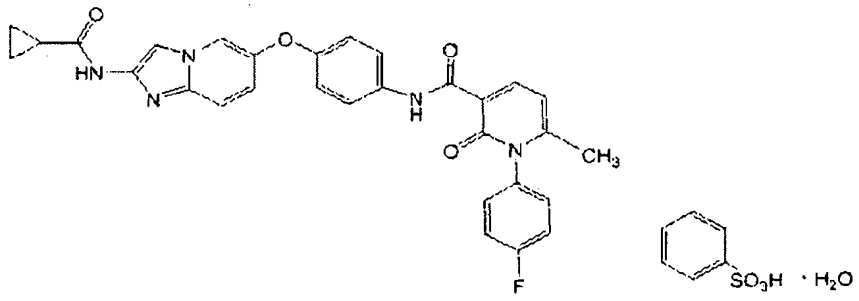
To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (116 mg, 0.357 mmol) and 1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (112 mg, 0.429 mmol) in N,N-dimethylformamide (1 mL) were added N,N-diisopropylethylamine (123 μL, 0.714 mmol) and HATU (163 mg, 0.428 mmol), and the mixture was stirred at room temperature for 4 hr. Ethyl acetate and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate) to give a white solid. The obtained solid was washed with ethyl acetate and collected by filtration to give the title compound (110 mg, 54%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.38 - 1.08 (4H, m), 1.54 - 2.17 (4H, m), 2.36 (3H, s), 6.37 (1H, s), 6.91 - 7.24 (2H, m), 7.24 - 7.58 (6H, m), 7.88 (1H, dd, J = 13.4, 2.5 Hz), 8.02 (1H, s), 8.42 (1H, d, J = 1.9 Hz), 10.93 (1H, s), 11.11 (1H, s).

Example 83

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-

yl}oxy)phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide benzenesulfonate monohydrate

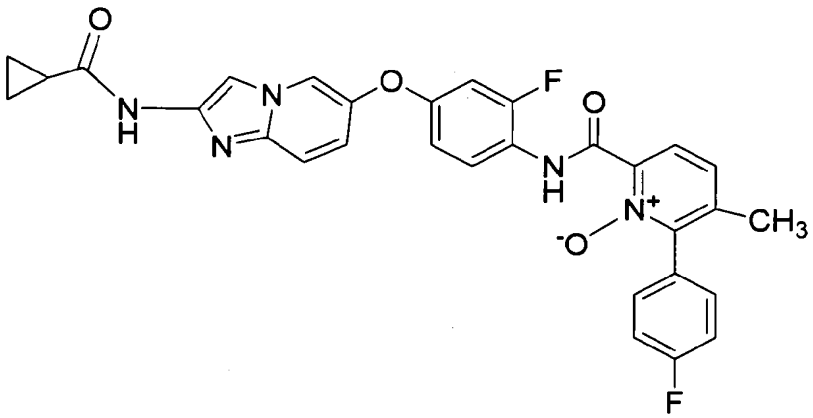


To a solution (90 mL) of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide (400 mg, 0.744 mmol) in tetrahydrofuran was added benzenesulfonic acid monohydrate (197 mg, 1.12 mmol) at 80°C. The mixture was filtered, and the filtrate was gradually cooled to room temperature. The solution at room temperature was distilled off at 110°C to evaporate tetrahydrofuran to about half, and gradually cooled again to room temperature. The precipitate was collected by filtration, and the solid was washed with tetrahydrofuran and dried to give the title compound (309 mg, 58%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.78 - 0.99 (4H, m), 1.90 (1H, s), 2.07 (3H, s), 6.70 (1H, d, J = 8.3 Hz), 7.01 - 7.16 (2H, m), 7.25 - 7.35 (3H, m), 7.38 - 7.53 (5H, m), 7.56 - 7.64 (2H, m), 7.65 - 7.78 (3H, m), 8.05 (1H, s), 8.48 (1H, d, J = 7.6 Hz), 8.60 (1H, d, J = 1.7 Hz), 11.43 (1H, s), 11.88 (1H, s).

Example 84

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-2-fluorophenyl]-6-(4-fluorophenyl)-5-methylpyridine-2-carboxamide 1-oxide

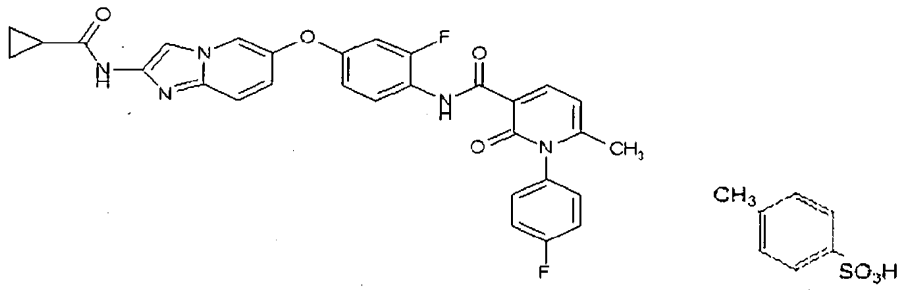


To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (200 mg, 0.613 mmol) and 6-(4-fluorophenyl)-5-methylpyridine-2-carboxylic acid 1-oxide (212 mg, 0.858 mmol) in N,N-dimethylacetamide (2.0 mL) were added HATU (350 mg, 0.919 mmol) and N,N-diisopropylethylamine (160 μL, 0.919 mmol), and the mixture was stirred at room temperature for 6 hr. Ethyl acetate/tetrahydrofuran was added and the mixture was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure and the obtained residue was recrystallized from tetrahydrofuran to give the title compound (109 mg, 32%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.78 - 0.82 (4H, m), 1.88 - 1.97 (1H, m), 2.13 (3H, s), 6.90 - 6.95 (1H, m), 7.08 - 7.16 (2H, m), 7.28 - 7.52 (5H, m), 7.70 - 7.73 (1H, m), 8.05 (1H, s), 8.30 - 8.40 (2H, m), 8.58 (1H, s), 10.97 (1H, s), 14.01 (1H, s).

Example 85

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-2-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide p-toluenesulfonate

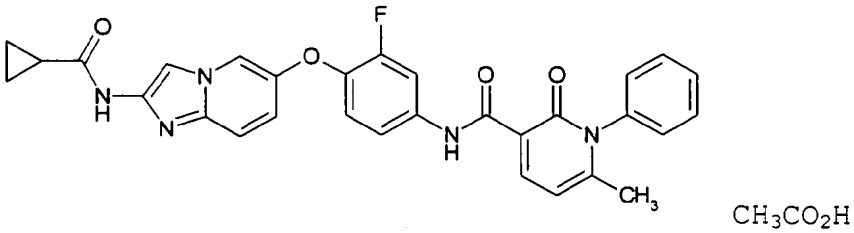


To N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-2-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide (300 mg, 0.54 mmol) was added tetrahydrofuran (15 mL), and the mixture was dissolved by heating at 60°C. p-Toluenesulfonic acid monohydrate (123.3 mg, 0.65 mmol) was added. The mixture was stirred at 50°C for 1 hr and at 40°C for 12 hr. After cooling to room temperature, the precipitate was collected by filtration, washed with tetrahydrofuran and dried at 100°C for 3 hr under reduced pressure to give the title compound (259 mg, 66%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.85 - 0.90 (4H, m), 1.86 - 1.94 (1H, m), 2.07 (3H, s), 2.29 (3H, s), 6.71 (1H, d, J = 8.1 Hz), 6.95 - 7.00 (1H, m), 7.11 (2H, d, J = 7.8 Hz), 7.13 - 7.18 (1H, m), 7.40 - 7.52 (7H, m), 7.66 (1H, d, J = 9.6Hz), 8.05 (1H, s), 8.42 - 8.50 (2H, m), 8.66 (1H, s), 11.35 (1H, s), 12.09 (1H, s).

Example 86

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide acetate



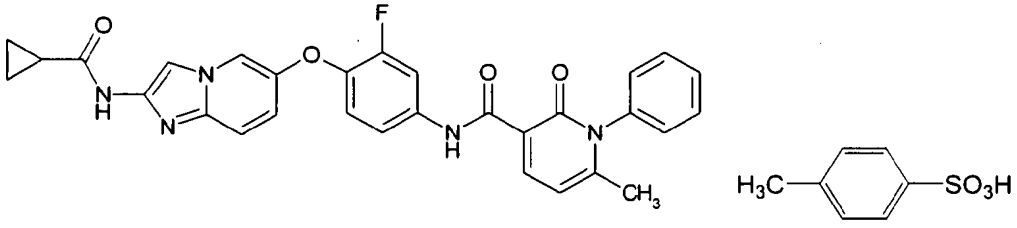
To a solution of N-[4-({2-

[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide (500 mg, 0.93 mmol) in acetic acid (3 ml) was added diisopropyl ether (15 ml) at room temperature. The reaction solution was stirred at 70°C for 3 hr, and the precipitate was collected by filtration and washed with diisopropyl ether to give a white solid (420 mg). To a solution (4 ml) of the white solid (400 mg) in acetic acid was added water (3 ml) at 80°C, and the mixture was cooled to room temperature and stirred for 17 hr. The precipitate was collected by filtration and washed with water to give the title compound (330 mg, 59%) as white crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.80 (4H, m), 1.91 (4H, s), 2.06 (3H, s), 6.71 (1H, d, J = 7.4 Hz), 6.89 - 7.25 (2H, m), 7.25 - 7.48 (4H, m), 7.48 - 7.74 (3H, m), 7.74 - 8.15 (2H, m), 8.15 - 8.66 (2H, m), 10.93 (1H, s), 12.02 (2H, s).

Example 87

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide p-toluenesulfonate



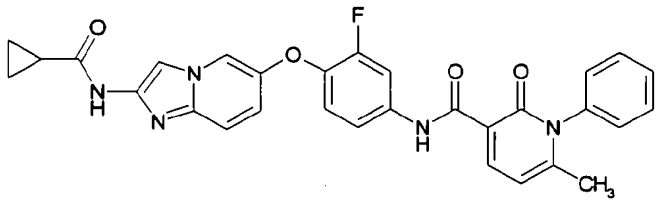
To a suspension of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide (650 mg, 1.21 mmol) in ethanol (6.5 ml) was added p-toluenesulfonic acid monohydrate (276 mg, 1.45 mmol) at 70°C. The reaction solution was stirred at 70°C for 1 hr, and the precipitate was collected by filtration and washed with ethanol to give the title compound (702 mg, 82%) as white

crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.48 - 0.96 (4H, m), 1.90 (1H, br s), 2.07 (3H, s), 2.29 (3H, s), 6.71 (1H, d, J = 7.9 Hz), 6.98 - 7.26 (3H, m), 7.27 - 7.73 (10H, m), 7.83 - 8.15 (2H, m), 8.27 - 8.69 (2H, m), 11.23 (1H, br s), 12.05 (1H, s).

Example 88

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide hydrochloride



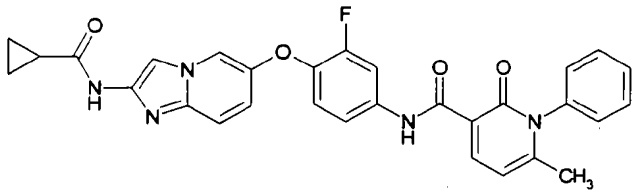
HCl

A solution (5 to 10%) of hydrogen chloride/methanol was heated to 50°C, and N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide (500 mg, 0.93 mmol) was added. The mixture was stirred for 5 min and at room temperature for 30 min. The precipitate was collected by filtration and washed with methanol to give the title compound (420 mg, 79%) as white crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.35 - 1.61 (4H, m), 1.77 - 2.04 (1H, m), 2.07 (3H, s), 6.72 (1H, d, J = 8.3 Hz), 7.04 - 7.36 (1H, m), 7.36 - 7.49 (4H, m), 7.49 - 7.80 (4H, m), 7.93 - 8.26 (2H, m), 8.49 (1H, d, J = 7.6 Hz), 8.56 (1H, d, J = 1.9 Hz), 11.49 (1H, br s), 12.06 (1H, s).

Example 89

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide methanesulfonate



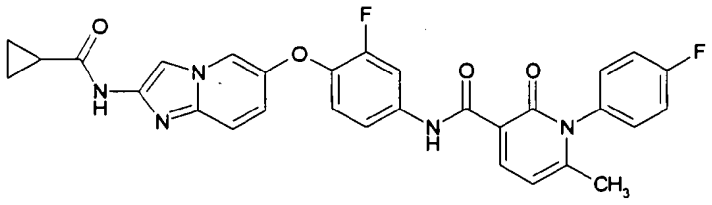
CH_3SO_3H

A suspension (3 mL) of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide (500 mg, 0.93 mmol) in ethanol was heated to 80°C, and a solution (1 mL) of methanesulfonic acid (107 mg, 1.12 mmol) in ethanol was added. The mixture was cooled to room temperature, diethyl ether was added dropwise, and the obtained solid was collected by filtration to give the title compound (550mg, 93%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.82 - 0.98 (4H, m), 1.83 - 1.97 (1H, m), 2.07 (3H, s), 2.37 (3H, s), 6.72 (1H, d, J = 8.1 Hz), 7.27 (1H, t, J = 9.0 Hz), 7.36 - 7.47 (3H, m), 7.50 - 7.66 (4H, m), 7.75 (1H, d, J = 1.2 Hz), 7.96 - 8.13 (2H, m), 8.49 (1H, d, J = 7.6 Hz), 8.61 (1H, d, J = 1.9 Hz), 11.56 (1H, s), 12.08 (1H, s).

Example 90

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide acetate



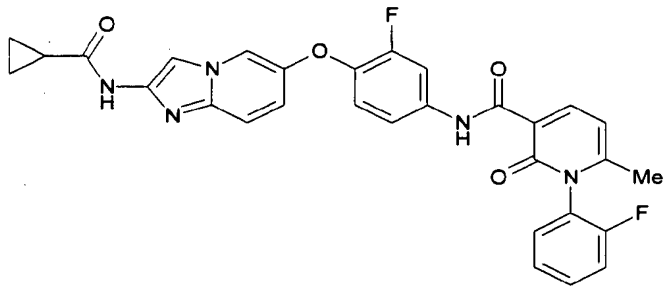
CH_3CO_2H

To N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide (700 mg, 1.26 mmol) was added acetic acid (3.5 mL), and the mixture was

heated to 60°C. Methylethylketone (2.1 mL) and water (3.5 mL) were added, and the mixture was cooled to room temperature and stirred at room temperature for 16 hr. The precipitate was collected by filtration and washed with water to give the title compound (512 mg, 66%) as white crystals.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.82 (4H, m), 1.85 - 1.96 (1H, m), 1.91 (3H, s), 2.07 (3H, s), 6.75 (1H, d, J = 8.1 Hz), 7.10 - 7.17 (2H, m), 7.34 - 7.53 (6H, m), 7.97 (1H, dd, J = 13.2, 2.7 Hz), 8.02 (1H, s), 8.45 - 8.50 (2H, m), 10.94 (1H, s), 11.99 (1H, s).

Example 91

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(2-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



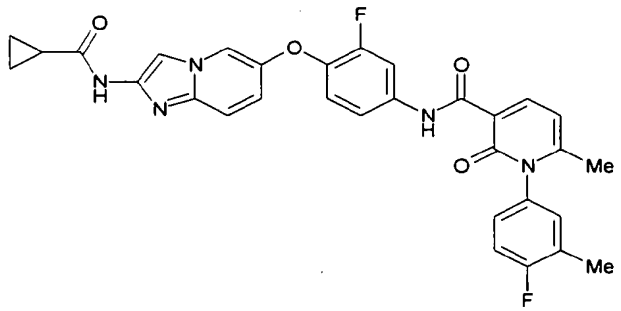
A solution (5 mL) of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (131 mg, 0.40 mmol), 1-(2-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (119 mg, 0.48 mmol), HATU (183 mg, 0.48 mmol) and N,N-diisopropylethylamine (103 mg, 0.80 mmol) in N,N-dimethylformamide was stirred at room temperature for 5 hr. The reaction solution was divided into two layers with tetrahydrofuran and sodium hydrogen carbonate saturated aqueous solution and the aqueous layer was subjected to extraction (3 times) with ethyl acetate. The combined organic layer was washed with water and saturated brine, dried over

anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (basic silica) and recrystallized from ethanol to give the title compound (80 mg, 36%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.68 - 0.89 (4H, m), 1.83 - 1.98 (1H, m), 2.12 (3H, s), 6.71 - 6.82 (1H, m), 7.07 - 7.19 (2H, m), 7.35 - 7.68 (6H, m), 7.96 (1H, dd, J = 13.2, 2.5 Hz), 8.02 (1H, s), 8.46 (1H, d, J = 1.7 Hz), 8.53 (1H, d, J = 7.6 Hz), 10.94 (1H, s), 11.81 (1H, s).

Example 92

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluoro-3-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



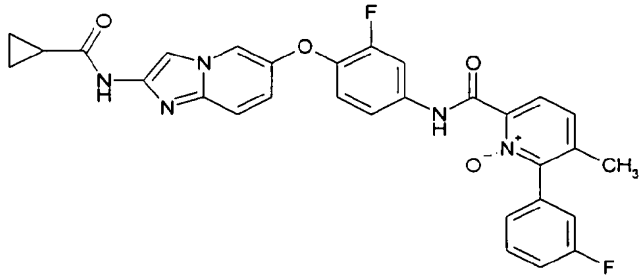
A solution (5 mL) of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (131 mg, 0.40 mmol), 1-(4-fluoro-3-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (125 mg, 0.48 mmol), HATU (183 mg, 0.48 mmol) and N,N-diisopropylethylamine (103 mg, 0.80 mmol) in N,N-dimethylformamide was stirred at room temperature for 5 hr. The reaction solution was divided into two layers with tetrahydrofuran and sodium hydrogen carbonate saturated aqueous solution and the aqueous layer was subjected to extraction (3 times) with ethyl acetate. The combined organic layer was washed with water and saturated brine, dried over

anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (basic silica) and recrystallized from ethanol to give the title compound (100 mg, 44%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.69 - 0.87 (4H, m), 1.84 - 1.98 (1H, m), 2.09(3H, s), 2.29 (3H, d, J = 1.5 Hz), 6.70 (1H, d, J = 8.3 Hz), 7.05 - 7.19 (2H, m), 7.24 - 7.41 (4H, m), 7.43 (1H, d, J = 9.6 Hz), 7.97 (1H, dd, J = 13.2, 2.5 Hz), 8.02 (1H, s), 8.35 - 8.57 (2H, m), 10.94 (1H, s), 12.00 (1H, s)

Example 93

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-(3-fluorophenyl)-5-methylpyridine-2-carboxamide 1-oxide



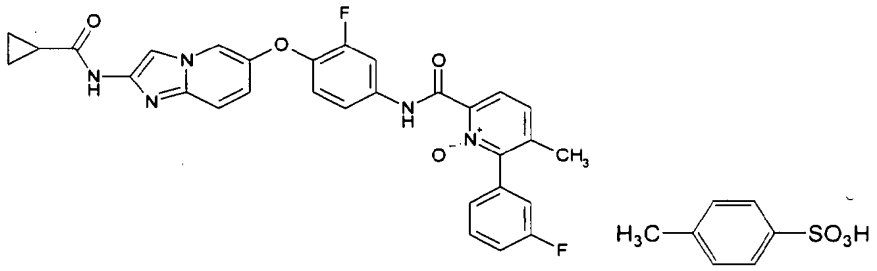
A solution (5 mL) of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (196 mg, 0.60 mmol), 6-(3-fluorophenyl)-5-methylpyridine-2-carboxylic acid 1-oxide (178 mg, 0.72 mmol), HATU (273 mg, 0.72 mmol) and N,N-diisopropylethylamine (155 mg, 1.20 mmol) in N,N-dimethylformamide was stirred at room temperature for 5 hr. The reaction solution was divided into two layers with tetrahydrofuran and sodium hydrogen carbonate saturated aqueous solution and the aqueous layer was subjected to extraction (3 times) with ethyl acetate. The combined organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and filtered. The solvent was

evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (basic silica) and recrystallized from ethanol/water to give the title compound (250 mg, 75%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.85 (4H, m), 1.85 - 1.98 (1H, m), 2.13 (3H, s), 7.08 - 7.21 (2H, m), 7.24 - 7.30 (1H, m), 7.30 - 7.40 (2H, m), 7.41 - 7.52 (2H, m), 7.54 - 7.65 (1H, m), 7.71 (1H, d, J = 9.1 Hz), 7.98 (1H, dd, J = 13.0, 2.5 Hz), 8.03 (1H, s), 8.32 (1H, d, J = 8.3 Hz), 8.49 (1H, d, J = 1.7 Hz), 10.94 (1H, s), 13.69 (1H, s).

Example 94

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-(3-fluorophenyl)-5-methylpyridine-2-carboxamide 1-oxide p-toluenesulfonate



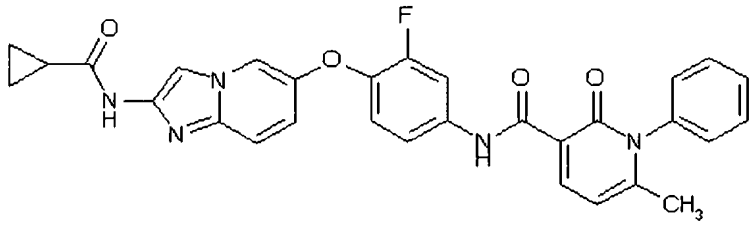
An ethanol (20 mL) suspension containing N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-(3-fluorophenyl)-5-methylpyridine-2-carboxamide 1-oxide (833 mg, 1.50 mmol) was heated to 90°C, and p-toluenesulfonic acid monohydrate (314 mg, 1.65 mmol) was added. When the mixture became a uniform transparent solution, the precipitated solid was collected by filtration and washed with ethanol to give the title compound (870 mg, 80%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.79 - 0.96 (4H, m), 1.83 - 1.97 (1H, m), 2.14 (3H, s), 2.29 (3H, s), 7.11 (2H, d, J = 7.7 Hz), 7.21 - 7.41 (4H, m), 7.43 - 7.66 (5H, m), 7.66 - 7.76 (2H, m), 7.96 - 8.10 (2H, m), 8.33 (1H, d, J = 8.3 Hz), 8.60 (1H, d, J

= 1.9 Hz), 11.42 (1H, s), 13.73 (1H, s).

Example 95

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide



To a solution of N-[6-(4-amino-2-fluorophenoxy)imidazo[1,2-a]pyridin-2-yl]cyclopropanecarboxamide (1.0 g, 3.06 mmol) and 6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylic acid (843 mg, 3.68 mmol) in N,N-dimethylacetamide (10 mL) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (822 mg, 4.29 mmol), 1-hydroxybenzotriazole (580 mg, 4.29 mmol) and triethylamine (854 μL, 6.13 mmol), and the mixture was stirred at room temperature for 16 hr. Water (60 mL) was added to the reaction mixture, and the mixture was stirred for 20 min. The precipitate was collected by filtration and washed with water and ethyl acetate. The obtained powder was recrystallized from methyl ethyl ketone/water to give the title compound (1.08 g, 66%) as white crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.70 - 0.85 (4H, m), 1.86 - 1.96 (1H, m), 2.06 (3H, s), 6.71 (1H, d, J = 8.3 Hz), 7.07 - 7.17 (2H, m), 7.32 - 7.65 (7H, m), 7.96 (1H, dd, J = 13.4, 2.5 Hz), 8.02 (1H, s), 8.42 - 8.52 (2H, m), 10.93 (1H, s), 12.02 (1H, s).

Formulation Example 1

A pharmaceutical agent containing the compound of the present invention as an active ingredient can be produced, for example, according to the following formulation.

1. capsule

(1) compound obtained in Example 2	40 mg
(2) lactose	70 mg
(3) crystalline cellulose	9 mg
(4) magnesium stearate	1 mg
1 capsule	120 mg

(1), (2), (3) and 1/2 of (4) are blended, granulated and the rest of (4) is added thereto. The whole mixture is sealed in a gelatin capsule.

2. tablet

(1) compound obtained in Example 2	40 mg
(2) lactose	58 mg
(3) cornstarch	18 mg
(4) crystalline cellulose	3.5 mg
(5) magnesium stearate	0.5 mg
1 tablet	120 mg

(1), (2), (3), 2/3 of (4), and 1/2 of (5) are blended and granulated. The rest of (4) and (5) are added to the granules. The mixture is compression-formed into a tablet.

Formulation Example 2

The compound (50 mg) obtained Example 2 is dissolved in Japanese Pharmacopoeia distilled water for injection (50 mL), and the Japanese Pharmacopoeia distilled water for injection is added to 100 mL. This solution is filtrated under sterile conditions. The solution (1 mL) is taken, filled in a vial for injection under sterile conditions, freeze-dried and sealed.

Experimental Example 1

Cloning of human vascular endothelial growth factor receptor 2 (VEGFR2) gene and preparation of recombinant baculovirus

Human vascular endothelial growth factor receptor 2 (hereinafter to be referred to as VEGFR2) gene was cloned by PCR using cDNA Libraries Human Placenta (Clontech) as a template. The primer used for PCR was prepared from base sequence (Genbank Accession AF035121) information of VEGFR2 gene by adding a base

sequence encoding flag peptide and a recognition sequence of the restriction enzyme to a base sequence (2671-4374 of Genbank Accession AF035121) encoding the VEGFR2 intracellular domain region, so that the protein contains an N-terminal Flag tag. The primer base sequence is shown below.

VEGFR2-U:

5′-
AATTAAGTCGACATGGACTACAAGGATGACGATGACAAGAAGCGGGCCAATGGAGGGGAACTGA
AGACA-3′ (SEQ ID NO: 1)

and

VEGFR2-L:

5′-AATTAAGCATGCTTAAACAGGAGGAGAGCTCAGTGTGGTCCC-3′ (SEQ ID NO: 2)

The base sequence of primer VEGFR2-U is shown in SEQUENCE LISTING SEQ ID NO: 1, and the base sequence of primer VEGFR2-L is shown in SEQUENCE LISTING SEQ ID NO: 2.

The PCR reaction was conducted using a KOD-plus kit (TOYOBO). The obtained PCR product was electrophoresed on agarose gel (1%), the DNA fragment amplified by PCR was recovered from the gel, and then digested with restriction enzymes Sal I and Sph I. The DNA treated with the restriction enzymes was electrophoresed on agarose gel (1%), and the obtained DNA fragment was recovered and ligated to plasmid pFASTBAC1 (Invitrogen) digested with restriction enzymes Sal I and Sph I to give expression plasmid pFB-VEGFR2. The base sequence of the insert fragment was confirmed and found to be identical with the base sequence (2671-4374 of Genbank Accession AF035121) of VEGFR2 intracellular domain. Furthermore, using BAC-TO-BAC Baculovirus Expression System (Invitrogen), virus stock BAC-VEGFR2 of recombinant baculovirus was prepared.

Experimental Example 2

Preparation of vascular endothelial growth factor receptor 2 (VEGFR2) intracellular domain protein

SF-21 cells were sown at 1×10^6 cells/mL to Sf-900II SFM medium (1 L, Invitrogen) containing 10% fetal bovine serum

(trace), 50 mg/L Gentamicin (Invitrogen) and 0.1% Pluronic F-68 (Invitrogen), and shaking culture was performed using a 2 L volume Erlenmeyer flask at 27°C, 100 rpm. After culturing for 24 hrs, recombinant baculovirus BAC-VEGFR2 (13.4 mL) was added to the mixture, and the mixture was further cultured for 3 days. The culture medium was centrifuged at 2,000 rpm for 5 min to give virus-infected cells. The infected cells were washed with a phosphate buffered saline (Invitrogen), centrifuged under the same conditions, and the cells were preserved at -80°C. The cryopreserved cells were thawed in ice, suspended in buffer A (50 mM Tris buffer (30 mL, pH 7.4) containing 20% glycerol, 0.15 M NaCl) supplemented with Complete Protease Inhibitor (Boehringer), and ruptured 3 times with a Polytron homogenizer (Kinematica) at 20,000 rpm for 30 sec. The ruptured medium was clarified by centrifugation at 40,000 rpm for 30 min and filtered with a 0.45 μm filter. The filtrate was passed through a column packed with Anti-FLAG M2 Affinity Gel (4 mL, Sigma) at a flow rate of about 0.5 mL/min. The column was washed with buffer A, and eluted with buffer A containing 100 μg/mL of FLAG peptide. The eluate was concentrated with Vivaspin 20 (Vivascience) having a molecular weight cut off of 30K. The buffer of this concentrate was exchanged using NAP™ 25 column (Amersham Bioscience) equilibrated with buffer A. The fractions containing intracellular domain protein of VEGFR2 were collected, glycerol was added to the final concentration of 50% and cryopreserved at -80°C.

Test Example 1

Determination of vascular endothelial growth factor receptor 2 (VEGFR2) kinase inhibitory activity

A test compound dissolved in dimethyl sulfoxide (DMSO) was diluted with a buffer (50 mM Tris-HCl (pH 7.5), 5 mM $MgCl_2$, 5 mM $MnCl_2$, 2 mM dithiothreitol, 0.01% Tween-20). To this compound solution (5 μL) was added a buffer (10 μL) containing 50 ng/mL of VEGFR2 intracellular domain protein and 250 ng/mL of biotin

labeled polypeptide biotinyl-poly-Glu:Tyr (4:1) (CIS bio International). To the obtained mixture was added a buffer (10 μL) containing ATP (25 μM), the mixture was allowed to react at 25°C for 5 min and the reaction was quenched with 25 μL of a stop solution (100 mM EDTA disodium salt, 62.5 mM HEPES buffer (pH 7.4), 250 mM NaCl, 0.1% bovine serum albumin, 10 μg/mL AlphaScreen assay streptavidin donor beads (Streptavidin Donor beads: PerkinElmer), 10 μg/mL AlphaScreen assay anti-phosphotyrosine recognition antibody PY-100 binding acceptor beads (Anti-phosphotyrosine (P-Tyr-100) Acceptor beads: PerkinElmer)). The reaction solution was allowed to stand at 25°C for 16 hrs, and the wells were counted using a plate reader (Fusion™ (PerkinElmer)). The kinase inhibitory rate (%) of the test compound was calculated by the following formula:

Inhibitory rate (%)=(1-(count of test compound - blank)÷(control - blank))×100

The count of the solution reacted without addition of the compound was used as a "control", and the count of the solution without the compound and ATP was used as a "blank".

As shown in Table 1, the inhibitory rates of the compounds of Examples 10, 11, 14, 18, 20, 24, 27, 28, 29, 32, 45, 46, 53, 57, 60, 61, 66, 70, 72, 75, 76, 77, 80, 81, 82, 84, 86, 87, 88, 90, 93 and 94 at 1 μM were not less than 70%.

In addition, the IC_{50} values of the compounds of Examples 10, 11, 14, 18, 20, 24, 27, 28, 29, 32, 45, 46, 53, 57, 60, 61, 66, 70, 72, 75, 76, 77, 80, 81, 82, 84, 86, 87, 88, 90, 93 and 94 were not more than 1 μM.

Table 1

Example	inhibitory rate (%) at 1 μM
10	97
11	99
14	99
18	91
20	73
24	100
27	100
28	96
29	100
32	100
45	99
46	100
53	92
57	100
60	98
61	99
66	100
70	99
72	100
75	100
76	99
77	100
80	100
81	99
82	100
84	99
86	100
87	100
88	100
90	100
93	100
94	100

Test Example 2

Vascular endothelial cell proliferation inhibitory test

Human umbilical vein-derived vascular endothelial cells (HUVEC purchased from KURABO INDUSTRIES LTD.) were cultured in an incubator at 37°C, 5% carbon dioxide in a vascular endothelial cell medium (Invitrogen) containing 3% bovine fetal serum and 2.5 ng/mL basic fibroblast growth factor. To be specific, HUVEC was suspended in a vascular endothelial cell medium containing the aforementioned 3% bovine fetal serum and plated on a 96 well flat bottom plate by 50 μL (3000 cells) each well. After culture overnight, various concentrations of the test substance and 120 ng/mL of vascular endothelial growth factor (VEGF) were dissolved in a vascular endothelial cell medium containing 3% bovine fetal serum and added to each well by 50 μL. After 5 days of culture, a Cell counting kit-8 reagent (DOJINDO LABORATORIES) was added to each well by 10 μL, and the mixture was reacted in an incubator at 37°C, 5% carbon dioxide for 2-3 hr. The absorbance at 450 nm was measured by a microtiter plate reader and the cell proliferation inhibitory activity was determined. Using the absorbance with addition of a test substance at each concentration and based on the nonlinear least-squares analysis using a logistic curve of SAS system NLIN procedure, the concentration of the test substance (IC_{50} value) necessary for showing 50% of the value obtained without addition of the test substance was calculated.

The inhibitory rates of the compounds of Example 10, 11, 14, 18, 20, 24, 27, 28, 29, 32, 45, 46, 53, 57, 60, 61, 66, 70, 72, 75, 76, 77, 80, 81, 82, 84, 86, 87, 88, 90, 93 and 94 at 1 μM were not less than 40%.

In addition, the IC_{50} values of the compounds of Examples 10, 11, 14, 18, 20, 24, 27, 28, 29, 32, 45, 46, 53, 57, 60, 61, 66, 70, 72, 75, 76, 77, 80, 81, 82, 84, 86, 87, 88, 90, 93 and 94 were not more than 2 μM.

Table 2

Example	inhibitory rate (%) at 1 μM
10	92
11	92
14	92
18	87
20	48
24	83
27	89
28	85
29	87
32	87
45	89
46	80
53	89
57	83
60	89
61	89
66	94
70	90
72	91
75	91
76	83
77	91
80	88
81	88
82	88
84	91
86	88
87	88
88	99
90	89
93	91
94	86

Test Example 3

Determination of hepatocyte growth factor receptor (c-Met) kinase inhibitory activity

A test compound dissolved in dimethyl sulfoxide (DMSO) was diluted with a buffer (50 mM Tris-HCl (pH 7.5), 5 mM $MgCl_2$, 5 mM $MnCl_2$, 2 mM dithiothreitol, 0.01% Tween-20). To this compound solution (5 μL) was added a buffer (10 μL) containing 2.5 ng/ml of c-Met intracellular domain protein (Millipore) and 250 ng/mL of biotin labeled polypeptide biotinyl-poly-Glu:Tyr (4:1) (CIS bio International). At 5 min after mixing kinase enzyme and the compound and biotin labeled polypeptide, to the obtained mixture was added a buffer (10 μL) containing ATP (5 μM), the mixture was allowed to react at 25°C for 10 min and the reaction was quenched with 25 μL of a stop solution (100 mM EDTA disodium salt, 62.5 mM HEPES buffer (pH 7.4), 250 mM NaCl, 0.1% bovine serum albumin, 10 μg/mL AlphaScreen assay streptavidin donor beads (Streptavidin Donor beads: PerkinElmer), 10 μg/mL AlphaScreen assay anti-phosphotyrosine recognition antibody PT-66 binding acceptor beads (Anti-phosphotyrosine (PT-66) Acceptor beads: PerkinElmer)). The reaction solution was allowed to stand at 25°C for 16 hrs, and the wells were counted using a plate reader (Fusion™ (PerkinElmer)). The kinase inhibitory rate (%) of the test compound was calculated by the following formula:

Inhibitory rate (%)=(1-(count of test compound - blank)÷(control - blank))×100

The count of the solution reacted without addition of the compound was used as a "control", and the count of the solution without the compound and ATP was used as a "blank".

As shown in Table 3, the inhibitory rates of the compounds of Examples 10, 11, 14, 18, 20, 24, 27, 28, 29, 32, 45, 46, 53, 57, 60, 61, 66, 70, 72, 75, 76, 77, 80, 81, 82, 84, 86, 87, 88, 90, 93, and 94 at 1 μM were not less than 80%.

In addition, the IC_{50} values of the compounds of Examples

10, 11, 14, 18, 20, 24, 27, 28, 29, 32, 45, 46, 53, 57, 60, 61, 66, 70, 72, 75, 76, 77, 80, 81, 82, 84, 86, 87, 88, 90, 93 and 94 were not more than 1 μM.

Table 3

Example	inhibitory rate (%) at 1 μM
10	99
11	100
14	100
18	100
20	98
24	100
27	100
28	100
29	100
32	100
45	100
46	100
53	100
57	100
60	99
61	100
66	100
70	100
72	100
75	100
76	100
77	100
80	100
81	100
82	100
84	100
86	100
87	100
88	100
90	100
93	100
94	100

Test Example 4

Human gastric cancer cell line MKN-45 growth inhibitory test

Human gastric cancer cell line MKN-45 (RIKEN BioResource Center) was cultured in RPMI1640 (Invitrogen) containing 10% bovine fetal serum in a gas incubator at 37°C, 5% CO_2. MKN-45 cells were treated with trypsin/EDTA and recovered. The cells were suspended in RPMI1640 containing 0.3% bovine fetal serum, plated on a 96 well flat bottom plate at a cells density of 3000 cells/50 μL per well. After culturing overnight, various concentrations of test substance were dissolved in RPMI1640 containing 0.3% bovine fetal serum and added to each well by 50 μL. After culture for 3 days, a Cell counting kit-8 reagent (DOJINDO LABORATORIES) was added to each well by 10 μL, and reacted in an incubator at 37°C, 5% CO_2 for 2-3 hr. After the reaction, the absorbance of each well at 450 nm was measured by a microtiter plate reader. The concentration of a test substance necessary for inhibiting the growth by 50% (IC_{50} value) was calculated using a cell proliferation rate with addition of the test substance at each concentration and according to the nonlinear regression analysis using GraphPad Prism [Sigmoidal dose response (variable slope)]. The cell proliferation rate (%) with addition of a test substance at each concentration was calculated by the following formula. As a positive control (100% growth), dimethyl sulfoxide was added instead of a test substance. As a negative control (0% growth), the compound of Reference Example 136 (WO2005/030140, Entry 104), which is a known c-Met inhibitor, was added in large excess (10 μM) instead of a test substance.

As shown in Table 4, the inhibitory rates of the compounds of Examples 10, 11, 14, 18, 20, 24, 27, 28, 29, 32, 45, 46, 53, 57, 60, 61, 66, 70, 72, 75, 76, 77, 80, 81, 82, 84, 86, 87, 88, 90, 93 and 94 at 1 μM were not less than 80%.

In addition, the IC_{50} values of the compounds of Examples

10, 11, 14, 18, 20, 24, 27, 28, 29, 32, 45, 46, 53, 57, 60, 61, 66, 70, 72, 75, 76, 77, 80, 81, 82, 84, 86, 87, 88, 90, 93 and 94 were not more than 1 μM.

Table 4

Example	inhibitory rate (%) at 1 μM
10	100
11	100
14	100
18	96
20	99
24	91
27	100
28	100
29	100
32	97
45	99
46	100
53	97
57	98
60	100
61	100
66	88
70	97
72	99
75	96
76	99
77	92
80	82
81	89
82	100
84	93
86	100
87	100
88	93
90	95
93	99
94	99

Test Example 5

Antitumor test (MKN-45 and MV-4-11)

Cancer cells were cultured in a culture medium containing 10% bovine fetal serum in an incubator at 37°C, 5% CO_2. MKN-45 cells were treated with trypsin/EDTA and isolated. MKN-45 and MV-4-11 cells were washed with HBSS (HANK's Balanced Saline Solution). When MKN-45 cells were transplanted, they were adjusted with HBSS to a cell density of 1.2×10^8 cells/mL, and transplanted by subcutaneous injection of 0.05 mL of a mixed suspension (3×10^6 cells) of the cell suspension and the same amount of Matrigel into the abdomen of 6 or 7-week-old female nude mouse (BALB/c nu/nu, CLEA Japan, Inc.). When MV-4-11 cells were transplanted, they were adjusted with HBSS to a cell density of 1.2×10^8 cells/mL, and transplanted by subcutaneous injection of 0.05 mL of a mixed suspension (3×10^6 cells) of the cell suspension and the same amount of Matrigel into the abdomen of 7-week-old female nude mouse (BALB/c nu/nu, CLEA Japan, Inc.). When the average tumor volume reached 100-250 mm^3, the mice were grouped, and various doses of test substance were orally administered for 14 consecutive days starting from the next day. The length of the major axis and the length of the minor axis of the tumor were measured over time and the tumor volume was calculated by tumor volume = major axis length × minor axis length × minor axis length × 0.5. The ratio of an increase in the average tumor volume of the control group to an increase in the average tumor volume of the drug administration group was taken as the tumor growth rate (%) of the drug administration group. Table 5 showned MKN-45 tumor growth rate (%) and table 6 showned MV-4-11 tumor growth rate (%).

Table 5

Example	dose (mg/kg)	tumor growth rate(%)
15	2	85
32	2	14
63	1	24
87	2	17
88	2	17

Table 6

Example	dose (mg/kg)	tumor growth rate (%)
15	2	17
32	2	<0
63	2	<0
87	2	<0
88	2	<0

Test Example 6

Determination of Fms Like Tyrosine Kinase 3 (FLT3) kinase inhibitory activity

A test compound dissolved in dimethyl sulfoxide (DMSO) was diluted with a buffer (50 mM Tris-HCl (pH 7.5), 5 mM $MgCl_2$, 5 mM $MnCl_2$, 2 mM dithiothreitol, 0.01% Tween-20). To this compound solution (5 μL) was added a buffer (10 μL) containing 7.5 ng/ml of FLT3 intracellular domain protein (Millipore) and 250 ng/mL of biotin labeled polypeptide biotinyl-poly-Glu:Tyr (4:1) (CIS bio International). At 5 min after mixing kinase enzyme and the compound and biotin labeled polypeptide, to the obtained mixture was added a buffer (10 μL) containing ATP (5 μM), the mixture was allowed to react at 25°C for 10 min and the reaction was quenched with 25 μL of a stop solution (100 mM EDTA disodium salt, 62.5 mM HEPES buffer (pH 7.4), 250 mM NaCl, 0.1% bovine serum albumin, 10 μg/mL AlphaScreen assay streptavidin donor beads (Streptavidin Donor Beads: PerkinElmer), 10 μg/mL AlphaScreen assay anti-phosphotyrosine recognition antibody Y-

100 binding acceptor beads (Anti-phosphotyrosine (P-Tyr-100) Acceptor beads: PerkinElmer)). The reaction solution was allowed to stand at 25°C for 16 hrs, and the wells were counted using a plate reader (Envision™ (PerkinElmer)). The kinase inhibitory rate (%) of the test compound was calculated by the following formula:

Inhibitory rate (%)=(1-(count of test compound - blank)÷(control - blank))×100

The count of the solution reacted without addition of the compound was used as a "control", and the count of the solution without the compound and ATP was used as a "blank".

As shown in Table 7, the inhibitory rates of the compounds of Examples 10, 11, 14, 18, 24, 27, 28, 29, 32, 45, 46, 53, 57, 60, 61, 66, 70, 72, 75, 76, 77, 80, 81, 82, 84, 86, 87, 88, 90, 93 and 94 at 1 μM were not less than 50%.

In addition, the IC_{50} values of the compounds of Examples 10, 11, 14, 18, 24, 27, 28, 29, 32, 45, 46, 53, 57, 60, 61, 66, 70, 72, 75, 76, 77, 80, 81, 82, 84, 86, 87, 88, 90, 93 and 94 were not more than 1 μM.

Table 7

Example	inhibitory rate (%) at 1 μM
10	63
11	88
14	88
18	55
24	87
27	73
28	63
29	96
32	75
45	93
46	92
53	66
57	93
60	89
61	71
66	75
70	94
72	91
75	92
76	86
77	96
80	93
81	90
82	79
84	96
86	97
87	96
88	96
90	69
93	93
94	94

Test Example 7

Determination of TIE2 kinase inhibitory activity

A test compound dissolved in dimethyl sulfoxide (DMSO) was diluted with a buffer (50 mM Tris-HCl (pH 7.5), 5 mM $MgCl_2$, 5 mM $MnCl_2$, 2 mM dithiothreitol, 0.01% Tween-20). A buffer (10 μL) containing 50 ng/mL of Tie2 intracellular domain protein (Millipore) and 250 ng/mL of biotin labeled polypeptide biotinyl-poly-Glu:Tyr (4:1) (CIS bio International) was added to the compound solution (5 μL). At 5 min from the mixing of the kinase enzyme, the compound and the biotin labeled polypeptide, a buffer (10 μL) containing 5 μM ATP was added, and the mixture was reacted at 25°C for 10 min. The reaction was quenched by the addition of 25 μL of a stop solution (100 mM EDTA disodium salt, 62.5 mM HEPES buffer (pH 7.4), 250 mM NaCl, 0.1% bovine serum albumin, 10 μg/mL AlphaScreen assay streptavidin donor beads (Streptavidin Donor beads: PerkinElmer), 10 μg/mL AlphaScreen assay anti-phosphotyrosine recognition antibody PT-66 binding acceptor beads (Anti-phosphotyrosine (PT-66) Acceptor beads: PerkinElmer)). The reaction solution was allowed to stand at 25°C for 16 hrs, and the cells were counted using a plate reader (Fusion™ (PerkinElmer)). The kinase inhibitory rate (%) of the test compound was calculated by the following formula:

Inhibitory rate (%)=(1-(count of test compound - blank)÷(control - blank))×100

The count of the solution reacted without addition of the compound was used as a "control", and the count of the solution without the compound and ATP was used as a "blank".

As shown in Table 8, the inhibitory rates of the compounds of Examples 10, 11, 14, 18, 24, 27, 28, 29, 32, 45, 46, 53, 57, 60, 61, 66, 70, 72, 75, 76, 77, 80, 81, 82, 84, 86, 87, 88, 90, 93 and 94 at 1 μM were not less than 50%.

In addition, the IC_{50} values of the compounds of Examples

10, 11, 14, 18, 24, 27, 28, 29, 32, 45, 46, 53, 57, 60, 61, 66, 70, 72, 75, 76, 77, 80, 81, 82, 84, 86, 87, 88, 90, 93 and 94 were not more than 1 μM.

Table 8

Example	inhibitory rate (%) at 1 μM
10	99
11	100
14	98
18	77
24	100
27	100
28	100
29	100
32	99
45	100
46	100
53	56
57	100
60	100
61	99
66	100
70	99
72	100
75	100
76	100
77	100
80	100
81	100
82	100
84	100
86	100
87	100
88	100
90	100
93	100
94	100

Test Example 8

Human blood cell cancer cell line MV-4-11 growth inhibitory test

Human blood cell cancer cell line MV-4-11 (ATCC) was cultured in IMDM (Invitrogen) containing 10% bovine fetal serum in an incubator at 37°C, 5% CO_2. MV-4-11 cells were treated with trypsin/EDTA and recovered. The cells were suspended in IMDM containing 10% bovine fetal serum, plated on a 96 well flat bottom plate at a cells density of 30,000 cells/50 μL per well. After culturing overnight, various concentrations of test substance were dissolved in IMDM containing 10% bovine fetal serum and added to each well by 50 μL. After culture for 3 days, a Cell counting kit-8 reagent (DOJINDO LABORATORIES) was added to each well by 10 μL, and reacted in an incubator at 37°C, 5% CO_2 for 2-3 hr. After the reaction, the absorbance of each well at 450 nm was measured by a microtiter plate reader. The concentration of a test substance necessary for inhibiting the growth by 50% (IC_{50} value) was calculated using a cell proliferation rate with addition of the test substance at each concentration and according to the nonlinear regression analysis using GraphPad Prism [Sigmoidal dose response (variable slope)].

As shown in Table 9, the inhibitory rates of the compounds of Examples 10, 11, 14, 18, 20, 24, 27, 28, 29, 32, 45, 46, 53, 57, 60, 61, 66, 70, 72, 75, 76, 77, 80, 81, 82, 84, 86, 87, 88, 90, 93 and 94 at 1 μM were not less than 90%.

The IC_{50} values of the compounds of Examples 10, 11, 14, 18, 20, 24, 27, 28, 29, 32, 45, 46, 53, 57, 60, 61, 66, 70, 72, 75, 76, 77, 80, 81, 82, 84, 86, 87, 88, 90, 93 and 94 were not more than 1 μM.

Table 9

Example	inhibitory rate (%) at 1 μM
10	96
11	97
14	97
18	96
20	96
24	98
27	96
28	97
29	97
32	92
45	97
46	97
53	97
57	97
60	97
61	97
66	98
70	98
72	97
75	97
76	97
77	97
80	97
81	98
82	97
84	98
86	91
87	92
88	91
90	92
93	91
94	92

SEQUENCE LISTING free text

[SEQ ID NO: 1]

Designed oligonucleotide primer to amplify DNA encoding human VEGFR2

[SEQ ID NO: 2]

Designed oligonucleotide primer to amplify DNA encoding human VEGFR2

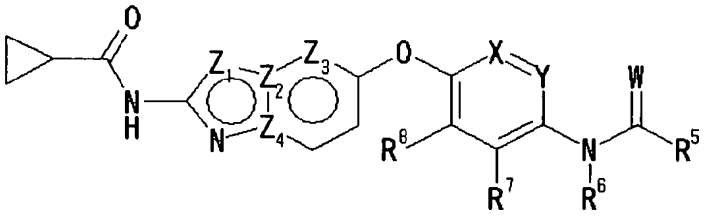
Industrial Applicability

The compound of the present invention show superior inhibitory activity on kinases such as vascular endothelial growth factor receptor, hepatocyte growth factor receptor, angiopoietin receptor (TIE2), Fms Like Tyrosine Kinase 3 (FLT3) and the like. Therefore, a clinically useful agent for the prophylaxis or treatment of diseases related to the action of vascular endothelial growth factor, hepatocyte growth factor, angiopoietin, FLT3 ligand (FL) in the living body (e.g., cancer etc.) can be provided. Moreover, since the compound of the present invention are also superior in efficacy expression, pharmacokinetics, solubility, interaction with other pharmaceutical products, safety and stability, they are useful as pharmaceutical agents.

This application is based on patent application Nos. 2008-122789 and 2008-306661 filed in Japan, the contents of which are incorporated in full herein by this reference.

CLAIMS

1. A compound represented by the formula (I):



wherein Z_1, Z_2, Z_3 and Z_4 are in the following combination:

$(Z_1, Z_2, Z_3, Z_4) = (CR^1, N, CR^2, C)$,

(N, N, CR^2, C),

(N, C, CR^2, N),

(S, C, CR^2, C), or

(S, C, N, C);

R^1 and R^2 are the same or different and each is

(1) a hydrogen atom,

(2) a halogen atom,

(3) a group bonded via a carbon atom,

(4) a group bonded via a nitrogen atom,

(5) a group bonded via an oxygen atom, or

(6) a group bonded via a sulfur atom;

W is O or S;

X is CR^3 (R^3 is a hydrogen atom, a halogen atom or C_{1-6} alkyl), or N;

Y is CR^4 (R^4 is a hydrogen atom, a halogen atom or C_{1-6} alkyl), or N;

R^5 is

(1) C_{3-6} cycloalkyl optionally having one C_{6-10} aryl-aminocarbonyl optionally having 1 to 3 substituents selected from a halogen atom and C_{1-6} alkyl,

(2) C_{1-6} alkyl-carbonylamino optionally having one C_{6-10} aryl,

(3) C_{1-6} alkoxy optionally having one C_{6-10} aryl, or

(4) a nitrogen-containing heterocyclic group or an N-oxide thereof optionally having 1 to 4 substituents selected from

(a) C_{6-10} aryl optionally having 1 to 3 substituents selected from a halogen atom and C_{1-6} alkyl,

(b) C_{1-6} alkyl optionally having 1 to 3 halogen atoms, and

(c) oxo;

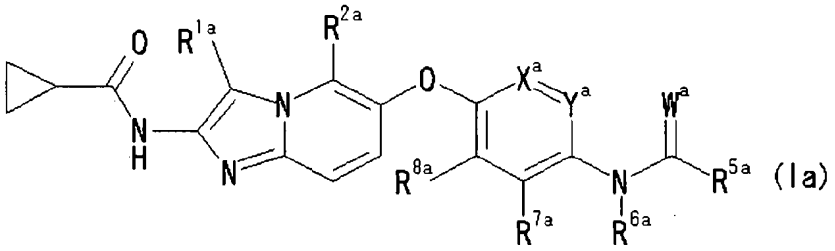
R^6 is a hydrogen atom;

R^7 is a hydrogen atom, a halogen atom or C_{1-6} alkyl; and

R^8 is a hydrogen atom, a halogen atom or C_{1-6} alkyl,

or a salt thereof.

2. A compound represented by the formula



(Ia)

wherein R^{1a} and R^{2a} are the same or different and each is

(1) a hydrogen atom,

(2) a halogen atom,

(3) a group bonded via a carbon atom,

(4) a group bonded via a nitrogen atom,

(5) a group bonded via an oxygen atom, or

(6) a group bonded via a sulfur atom;

W^a is O or S;

X^a is CR^{3a} (R^{3a} is a hydrogen atom, a halogen atom or C_{1-6} alkyl), or N;

Y^a is CR^{4a} (R^{4a} is a hydrogen atom, a halogen atom or C_{1-6} alkyl), or N;

R^{5a} is

(1) C_{3-6} cycloalkyl optionally having one C_{6-10} aryl-aminocarbonyl optionally having 1 to 3 substituents selected from a halogen atom and C_{1-6} alkyl,

(2) C_{1-6} alkyl-carbonylamino optionally having one C_{6-10} aryl,

(3) C_{1-6} alkoxy optionally having one C_{6-10} aryl, or

(4) a nitrogen-containing heterocyclic group or an N-oxide thereof optionally having 1 to 4 substituents selected from

(a) C_{6-10} aryl optionally having 1 to 3 substituents selected from a halogen atom and C_{1-6} alkyl,

(b) C_{1-6} alkyl optionally having 1 to 3 halogen atoms, and

(c) oxo;

R^{6a} is a hydrogen atom;

R^{7a} is a hydrogen atom, a halogen atom or C_{1-6} alkyl;

R^{8a} is a hydrogen atom, a halogen atom or C_{1-6} alkyl,

or a salt thereof.

3. The compound of claim 2 wherein

R^{1a} is a hydrogen atom, a fluorine atom or methyl;

R^{2a} is a hydrogen atom;

W^a is O or S;

X^a is CH, CF, CCl, $C(CH_3)$ or N;

Y^a is CH, CF, CCl, $C(CH_3)$ or N;

R^{5a} is

(1) cyclopropyl optionally having one phenylaminocarbonyl optionally having 1 to 3 substituents selected from a fluorine atom and methyl,

(2) acetylamino optionally having one phenyl,

(3) methoxy optionally having one phenyl,

(4) tert-butoxy, or

(5) a nitrogen-containing heterocyclic group or an N-oxide thereof optionally having 1 to 4 substituents selected from

(a) phenyl optionally having 1 to 3 substituents selected from a fluorine atom, a chlorine atom, a bromine atom, methyl and isopropyl,

(b) methyl optionally having 1 to 3 fluorine atoms,

(c) ethyl optionally having 1 to 3 fluorine atoms,

(d) isopropyl, and

(e) oxo;

R^{6a} is a hydrogen atom;
R^{7a} is a hydrogen atom; and
R^{8a} is a hydrogen atom.

4. N-[4-({2-[(Cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-N'-phenylcyclopropane-1,1-dicarboxamide or a salt thereof.

5. N-[4-({2-[(Cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide or a salt thereof.

6. N-[4-({2-[(Cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)-3-fluorophenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide or a salt thereof.

7. N-[5-({2-[(Cyclopropylcarbonyl)amino]imidazo[1,2-a]pyridin-6-yl}oxy)pyridin-2-yl]-6-(4-fluorophenyl)-5-methylpyridine-2-carboxamide 1-oxide or a salt thereof.

8. A prodrug of the compound of claim 1.

9. A pharmaceutical agent comprising the compound of claim 1 or a prodrug thereof.

10. The pharmaceutical agent of claim 9, which is a kinase inhibitor.

11. The pharmaceutical agent of claim 9, which is an agent for the prophylaxis or treatment of cancer.

12. A method for the prophylaxis or treatment of cancer, which comprises administering an effective amount of the compound of claim 1 or a prodrug thereof to the mammal.

13. Use of the compound of claim 1 or a prodrug thereof for the production of an agent for the prophylaxis or treatment of cancer.

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2009/058962

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D277/82 C07D471/04 C07D513/04 A61P35/00 A61K31/429
A61K31/437 A61K31/496 A61K31/444

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/44156 A (GLAXO GROUP LTD [GB]; GLAXOSMITHKLINE K K [JP]; CHEUNG MUI [US]; HARRI) 6 June 2002 (2002-06-06) claims 1,74	1-13
Y	WO 2008/016192 A (TAKEDA PHARMACEUTICAL [JP]; SAKAI NOZOMU [JP]; IMAMURA SHINICHI [JP];) 7 February 2008 (2008-02-07) claims 1,10,15,21	1-13
P,X	WO 2008/150015 A (TAKEDA PHARMACEUTICAL [JP]; OGURO YUYA [JP]; IMAMURA SHINICHI [JP]; CA) 11 December 2008 (2008-12-11) claims 1,21,32	1-13

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 July 2009	29/07/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Miniejew, Catherine

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/JP2009/058962

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0244156 A	06-06-2002	AU 3243902 A	11-06-2002
		EP 1341771 A2	10-09-2003
		JP 2004517080 T	10-06-2004
WO 2008016192 A	07-02-2008	AR 062207 A1	22-10-2008
		AU 2007279595 A1	07-02-2008
		CA 2659971 A1	07-02-2008
		CL 22612007 A1	02-05-2008
		CR 10607 A	12-03-2009
		EP 2049541 A2	22-04-2009
		US 2009137595 A1	28-05-2009
WO 2008150015 A	11-12-2008	US 2009163488 A1	25-06-2009

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15348716
Filing Date	2016-11-10
First Named Inventor	Jo Ann Wilson
Art Unit	1625
Examiner Name	Timothy R. Rozof
Attorney Docket Number	224990/10-039C2-US/405045

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	9724342		2017-08-08	WILSON, et al.	
	2	9809549		2017-11-07	BROWN, et al.	

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20080161305		2008-07-03	FORSYTH, et al.	
	2	20110077233		2011-03-31	BANNEN, et al.	
	3	20120252840		2012-10-04	AFTAB, et al.	
	4	20140066444		2014-03-26	SMITH, et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15348716
	Filing Date	2016-11-10
	First Named Inventor	Jo Ann Wilson
	Art Unit	1625
	Examiner Name	Timothy R. Rozof
	Attorney Docket Number	224990/10-039C2-US/405045

	5	20150057310		2015-02-26	BROWN, et al.	
	6	20150202196		2015-07-23	BANNEN, et al.	
	7	20160000772		2016-01-07	AFTAB, et al.	
	8	20160051532		2016-02-25	AFTAB, et al.	
	9	20160229805		2016-08-11	WILSON, et al.	
	10	20170143689		2017-05-25	WILSON, et al.	
	11	20170266178		2017-09-21	WILSON, et al.	
	12	20170275251		2017-09-28	BROWN, et al.	
	13	20180002289		2018-01-04	BROWN, et al.	
	14	20180037552		2018-02-08	BROWN, et al.	

If you wish to add additional U.S. Published Application citation information please click the Add button.

FOREIGN PATENT DOCUMENTS

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15348716
	Filing Date	2016-11-10
	First Named Inventor	Jo Ann Wilson
	Art Unit	1625
	Examiner Name	Timothy R. Rozof
	Attorney Docket Number	224990/10-039C2-US/405045

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1		☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15348716
Filing Date	2016-11-10
First Named Inventor	Jo Ann Wilson
Art Unit	1625
Examiner Name	Timothy R. Rozof
Attorney Docket Number	224990/10-039C2-US/405045

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature		Date (YYYY-MM-DD)	2018-04-17
Name/Print	Heidi M. Berven, Ph.D.	Registration Number	48,951

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

PTO/AIA/22 (03-13)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)

Docket Number (Optional): 224990/10-039C2-US/405045

Application Number: 15/348,716

Filed: November 10, 2016

For: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

Art Unit: 1625

Examiner: Timothy R. Rozof

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	Micro Entity Fee	
☐	One month (37 CFR 1.17(a)(1))	$200	$100	$50	$
☐	Two months (37 CFR 1.17(a)(2))	$600	$300	$150	$
☑	Three months (37 CFR 1.17(a)(3))	$1,400	$700	$350	$ 700.00
☐	Four months (37 CFR 1.17(a)(4))	$2,200	$1,100	$550	$
☐	Five months (37 CFR 1.17(a)(5))	$3,000	$1,500	$750	$

☑ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 503145.

☑ Payment made via EFS-Web.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant.

☑ attorney or agent of record. Registration number 48,951.

☑ attorney or agent acting under 37 CFR 1.34. Registration number _____.

Signature

April 17, 2018
Date

Heidi M. Berven, Ph.D.
Typed or printed name

269-337-7710
Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ * Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.136(a). The information is required to obtain or retain a benefit by the public, which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 6 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

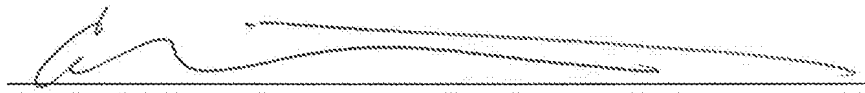
Inventors:	Jo Ann Wilson, et al.	Confirmation No.:	5882
Application No.:	15/348,716	Art Unit:	1625
Filed:	November 10, 2016	Examiner:	Timothy R. Rozof
Atty. Docket No.:	224990/10-039C2-US/405045		

Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

CERTIFICATE OF TRANSMISSION UNDER 37 C.F.R. § 1.8(a)

The undersigned hereby certifies that the following documents are being electronically filed in accordance with 37 C.F.R. § 1.6(a)(4) on this 17th day of April, 2018:

1. Cover Letter to the Commissioner for Patents;
2. Response to the Non-Final Office Action dated October 17, 2017;
3. Information Disclosure Statement (PTO/SB/08);
4. Petition for Extension of Time (PTO/AIA/22); and
5. This Certificate of Transmission under 37 C.F.R. § 1.8(a).



Charles W. Gregg-Geist, for Heidi M. Berven, Ph.D., Reg. No. 48,951

Electronic Patent Application Fee Transmittal

Application Number:	15348716
Filing Date:	10-Nov-2016
Title of Invention:	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds
First Named Inventor/Applicant Name:	Jo Ann Wilson
Filer:	Heid Marie Berven/Charles Gregg-Geist
Attorney Docket Number:	224990/10-039C2-US/405045

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 3 months with $0 paid	2253	1	700	700
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	2806	1	120	120
		Total in USD ($)		**820**

Electronic Acknowledgement Receipt

EFS ID:	32363089
Application Number:	15348716
International Application Number:	
Confirmation Number:	5882
Title of Invention:	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds
First Named Inventor/Applicant Name:	Jo Ann Wilson
Customer Number:	91684
Filer:	Heid Marie Berven/Charles Gregg-Geist
Filer Authorized By:	Heid Marie Berven
Attorney Docket Number:	224990/10-039C2-US/405045
Receipt Date:	17-APR-2018
Filing Date:	10-NOV-2016
Time Stamp:	15:36:48
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$820
RAM confirmation Number	041818INTEFSW00002047503145
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		EX10-039C2-US.pdf	3035867 e9bc700c7647bd556cc69bc63bf3d33978ab3c0c	yes	19

Multipart Description/PDF files in .zip description

Document Description	Start	End
Miscellaneous Incoming Letter	1	2
Amendment/Req. Reconsideration-After Non-Final Reject	3	3
Claims	4	8
Applicant Arguments/Remarks Made in an Amendment	9	13
Information Disclosure Statement (IDS) Form (SB08)	14	17
Extension of Time	18	18
Transmittal Letter	19	19

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	32978 23f69bda0f818135631cd65c11c619b99be25fa3	no	2

Warnings:

Information:

Total Files Size (in bytes):	3068845

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

HONIGMAN

Honigman Miller Schwartz and Cohn LLP
Attorneys and Counselors

Heidi M. Berven

(269) 337-7710
Fax: (269) 337-7711
HBerven@honigman.com

Via EFS Web

April 17, 2018

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313

Re: US Application No.: 15/348,716
Inventors: Jo Ann Wilson, et al.
Filing Date: November 10, 2016
Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds
Confirmation No.: 5882
Attorney Docket No.: 224990/10-039C2-US/405045

Dear Sir or Madam:

Enclosed for filing please find the following documents:

1. This Cover Letter to the Commissioner for Patents;
2. Response to the Non-Final Office Action dated October 17, 2017;
3. Information Disclosure Statement (PTO/SB/08);
4. Petition for Extension of Time (PTO/AIA/22); and
5. Certificate of Transmission under 37 C.F.R. § 1.8(a).

The Applicant notes that the filing of the enclosed Information Disclosure Statement shall not be construed to be an admission that the information cited in the statement qualifies as prior art under 35 U.S.C. § § 102 or 103, or is considered to be material to patentability as defined in 37 C.F.R. § 1.56(b). The fee set forth in 37 C.F.R. § 1.17(p) is submitted in support.

The Applicant hereby petitions for a three-month extension of time under 37 C.F.R. § 1.136(a) for responding to the Non-Final Office Action in this application dated October 17, 2017. The fee set forth in 37 C.F.R. § 1.17(a)(3) is submitted herewith.

It is believed that due for this response are the $120.00 fee set forth in 37 C.F.R. § 1.17(p) for submission of the enclosed Information Disclosure Statement and the $700.00 fee set forth in § 1.17(a)(3) for a three-month extension of time. The Applicant hereby authorizes the Office to charge this total of $820.00 to Deposit Account Number 503145, referencing Attorney Docket Number 224990/10-039C2-US/405045. It is believed that no other fees are due at this time. However, if there are any additional charges for this submission, or any credits,

please apply them to Deposit Account Number 503145, referencing Attorney Docket Number 224990/10-039C2-US/405045.

Very truly yours,

HONIGMAN MILLER SCHWARTZ AND COHN LLP

Heidi M. Berven, Ph.D.
Reg. No. 48,951

HMB/cwg

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/348,716	Filing Date 11/10/2016	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☒ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	**140**
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	**140**

APPLICATION AS AMENDED – PART II

AMENDMENT **04/17/2018**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 11	Minus	** 20	= 0	X $50 =	0
Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $230 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	**0**

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
GLORIA J. TRAMMELL

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                                                        ENTRY    SESSION
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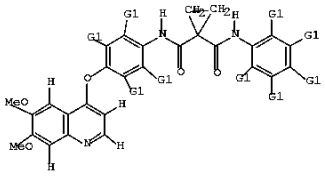
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(10.12.17)

L1      STRUCTURE UPLOADED

=>  d
L1 HAS NO ANSWERS
L1              STR
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G1:H,Cl,Br,F

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Structure attributes must be viewed using the Structure Drawing program.


=> s l1 sss sam
SAMPLE SEARCH INITIATED 15:09:54 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -       30 TO ITERATE

100.0% PROCESSED          30 ITERATIONS                                3 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:          272 TO      928
PROJECTED ANSWERS:               3 TO      163

L2             3 SEA SSS SAM L1

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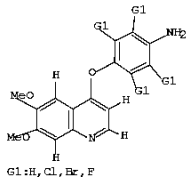
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SEARCH TIME: 00.00.01

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g(1) (10.12.17)

L4      STRUCTURE UPLOADED

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L4 HAS NO ANSWERS
L4              STR
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G1:H,Cl,Br,F

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Structure attributes must be viewed using the Structure Drawing program.


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SEARCH TIME: 00.00.01

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                        BATCH   **COMPLETE**
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PROJECTED ANSWERS:               0 TO        0

L5             0 SEA SSS SAM L4

=> s l4 sss full
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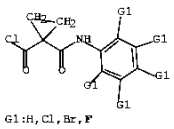
L6            12 SEA SSS FUL L4

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g(1) (10.12.17)


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z(1) (10.12.17)

L7      STRUCTURE UPLOADED

=> d
L7 HAS NO ANSWERS
L7              STR
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G1:H,Cl,Br,F

Structure attributes must be viewed using the Structure Drawing program.

=> s l7 sss sam
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SAMPLE SCREEN SEARCH COMPLETED - 85 TO ITERATE

100.0% PROCESSED 85 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 1147 TO 2253
PROJECTED ANSWERS: 0 TO 0

L8 0 SEA SSS SAM L7

=> s l7 sss full
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FULL SCREEN SEARCH COMPLETED - 1764 TO ITERATE

100.0% PROCESSED 1764 ITERATIONS 12 ANSWERS
SEARCH TIME: 00.00.01

L9 12 SEA SSS FUL L7

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COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 863.25 863.54

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USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Dec 2015

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CAplus now includes the comprehensive Cooperative Patent Classification (CPC). See HELP CPC for details.

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L3 50 S L1 SSS FULL
L4 STRUCTURE UPLOADED
L5 0 S L4 SSS SAM
L6 12 S L4 SSS FULL
L7 STRUCTURE UPLOADED
L8 0 S L7 SSS SAM
L9 12 S L7 SSS FULL

FILE 'CAPLUS' ENTERED AT 15:12:15 ON 12 OCT 2017

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567 L3
119 L6
45 L9
L10 33 L3 AND L6 AND L9

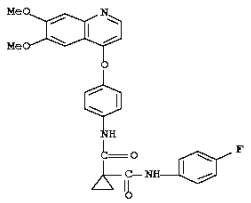
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L10 ANSWER 1 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:2078753 CAPLUS Full-text
TITLE: C-met modulator pharmaceutical compositions comprising N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide
INVENTOR(S): Wilson, Jo Ann
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., No pp. given
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20130337015	A1	20131219	US 2013-13810537	20130826
US 9724342	B2	20170808		
WO 2012009722	A1	20120119	WO 2011-US44378	20110718
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
CN 106420743	A	20170222	CN 2016-10157218	20110718
JP 2016188215	A	20161104	JP 2016-93433	20160506
AU 2016247044	A1	20161103	AU 2016-247044	20161018
US 20170143689	A1	20170525	US 2017-15426804	20170207
US 20170266178	A1	20170921	US 2017-15612703	20170602
PRIORITY APPLN. INFO.:			US 2010-61365253	P 20100716
			US 2010-61370843	P 20100805
			WO 2011-US44378	W 20110718
			AU 2011-278950	A3 20110718
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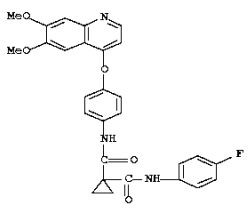
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB Pharmaceutical compns. and unit dosage forms comprising Compd. I are disclosed.
IT 849217-68-1P 1140909-48-3P, Cabozantinib S-malate
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(C-met modulator pharmaceutical compns. comprising dimethoxyquinolinyloxyphenyl(fluorophenyl)cyclopropanedicarboxamide)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

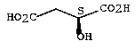
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CMF C28 H24 F N3 O5



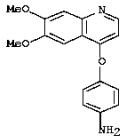
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CRN 97-67-6
CMF C4 H6 O5

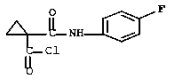
Absolute stereochemistry. Rotation (-).



IT 190728-25-7P 1219937-98-0P,
1-(4-Fluorophenylcarbamoylcyclopropanecarbonyl chloride
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(C-met modulator pharmaceutical compns. comprising dimethoxyquinolinyloxyphenyl(fluorophenyl)cyclopropanedicarboxamide)
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



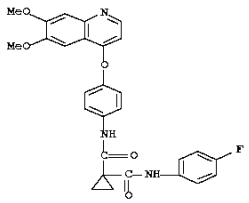
RN 1219937-98-0 CAPLUS
CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)



IT 1235470-36-6 1235470-38-8
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(C-met modulator pharmaceutical compns. comprising dimethoxyquinolinyloxyphenyl(fluorophenyl)cyclopropanedicarboxamide)
RN 1235470-36-6 CAPLUS
CN Butanedioic acid, 2-hydroxy-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:?) (CA INDEX NAME)

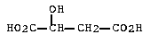
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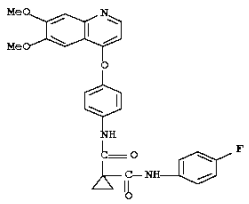
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CMF C4 H6 O5



RN 1235470-38-8 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2R)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:?) (CA INDEX NAME)

CM 1

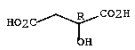
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CM 2

CRN 636-61-3
CMF C4 H6 O5

Absolute stereochemistry. Rotation (+).



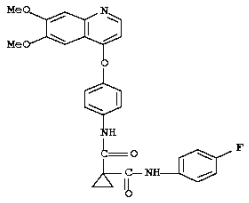
L10 ANSWER 2 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:2059943 CAPLUS Full-text
TITLE: Preparation of cabozantinib and dosage forms for treatment of cancer
INVENTOR(S): Decillis, Arthur
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., No pp. given
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20160022662	A1	20160128	US 2015-14782537	20151005
WO 2014165786	A1	20141009	WO 2014-US33016	20140404

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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2013-61808511 P 20130404
WO 2014-US33016 W 20140404

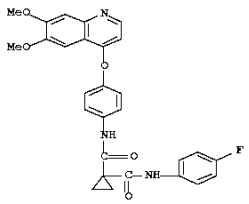
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB This invention relates to a dosage form of cabozantinib and a method of employing the dosage form to treat cancer.
IT 849217-68-1P, Cabozantinib 1140909-48-3P,
Cabozantinib S-malate 1365530-43-3P
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of cabozantinib and dosage forms for treatment of cancer)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

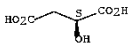
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

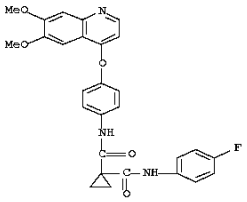
Absolute stereochemistry. Rotation (-).



RN 1365530-43-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2R)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

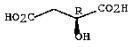
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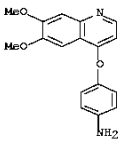
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CRN 636-61-3
CMF C4 H6 O5

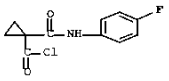
Absolute stereochemistry. Rotation (+).



IT 190728-25-7P 1219937-98-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of cabozantinib and dosage forms for treatment of cancer)
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



RN 1219937-98-0 CAPLUS
CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)



L10 ANSWER 3 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:2055777 CAPLUS Full-text
DOCUMENT NUMBER: 167:390609
TITLE: Method of treating cancer and bone cancer pain
INVENTOR(S): Schwab, Gisela; Aftab, Dana T.
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., No pp. given
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20140179736	A1	20140626	US 2014-14115236	20140228
WO 2012151326	A1	20121108	WO 2012-US36191	20120502

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

JP 2017105751	A	20170615	JP 2016-159543	20160816

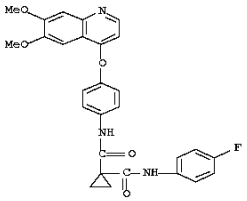
PRIORITY APPLN. INFO.:

US 2011-61481682	P	20110502
US 2011-61557366	P	20111108
WO 2012-US36191	W	20120502
JP 2014-509417	A3	20120502

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB This invention is directed to the treatment of cancer, particularly lung cancer, breast cancer, melanoma, renal cell carcinoma, thyroid cancer that has metastasized to the bone. The invention is also directed to a method for treating bone cancer pain in an individual in need of such treatment comprising administering to the individual an effective amount of a compound of Formula I.

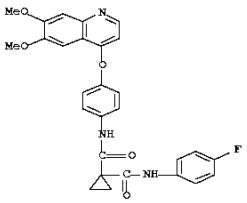
IT 849217-68-1P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(method of treating cancer and bone cancer pain)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



IT 1140909-48-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(method of treating cancer and bone cancer pain)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

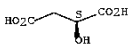
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

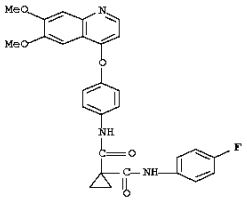
Absolute stereochemistry. Rotation (-).



IT 1365530-43-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method of treating cancer and bone cancer pain)
RN 1365530-43-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2R)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

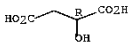
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CMF C28 H24 F N3 O5



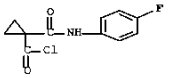
CM 2

CRN 636-61-3
CMF C4 H6 O5

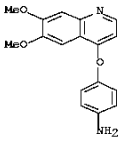
Absolute stereochemistry. Rotation (+).



IT 1219937-98-0P, 1-(4-Fluorophenylcarbamoyl)cyclopropanecarbonyl chloride
RL: PRPH (Prophetic); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(method of treating cancer and bone cancer pain)
RN 1219937-98-0 CAPLUS
CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)



IT 190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(method of treating cancer and bone cancer pain)
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)

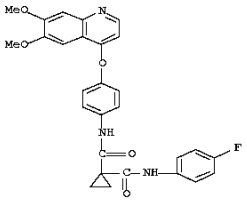


L10 ANSWER 4 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:2051291 CAPLUS Full-text
DOCUMENT NUMBER: 167:390605
TITLE: Method of treating cancer
INVENTOR(S): Aftab, Dana T.; Schimmoller, Frauke
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., No pp. given
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20140323522	A1	20141030	US 2014-14356927	20140508
WO 2013070890	A1	20130516	WO 2012-US64116	20121108

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

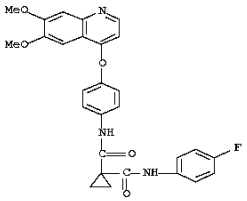
PRIORITY APPLN. INFO.: US 2011-61557358 P 20111108
WO 2012-US64116 W 20121108
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB This invention is directed to the treatment of cancer, particularly castration-resistant prostate cancer and bone metastases, with a dual inhibitor of MET and VEGF.
IT 849217-68-1P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(dual inhibitor of Met and VEGF for treating cancer)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



IT 1140909-48-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(dual inhibitor of Met and VEGF for treating cancer)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

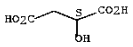
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

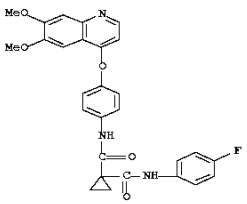
Absolute stereochemistry. Rotation (-).



IT 1365530-43-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dual inhibitor of Met and VEGF for treating cancer)
RN 1365530-43-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2R)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

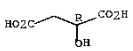
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CMF C28 H24 F N3 O5



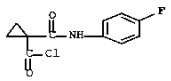
CM 2

CRN 636-61-3
CMF C4 H6 O5

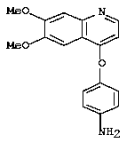
Absolute stereochemistry. Rotation (+).



IT 1219937-98-0P
RL: PRPH (Prophetic); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(dual inhibitor of Met and VEGF for treating cancer)
RN 1219937-98-0 CAPLUS
CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)



IT 190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(dual inhibitor of Met and VEGF for treating cancer)
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



L10 ANSWER 5 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:2041767 CAPLUS Full-text
DOCUMENT NUMBER: 167:324798
TITLE: Method of treating cancer
INVENTOR(S): Aftab, Dana T.
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., No pp. given
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20150133494	A1	20150514	US 2014-14398188	20141031
WO 2013166296	A1	20131107	WO 2013-US39284	20130502

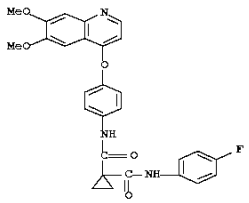
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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2012-61641837 P 20120502
WO 2013-US39284 W 20130502

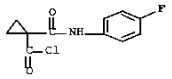
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB This invention is directed to the treatment of cancer, particularly castration-resistant prostate cancer and osteolytic bone metastases, with a dual inhibitor of MET and VEGF.

IT 849217-68-1P 1219937-98-0P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(dual MET-VEGF modulator for treating osteolytic bone metastases)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



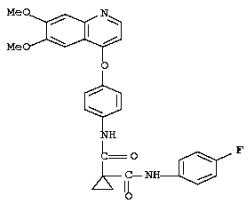
RN 1219937-98-0 CAPLUS
CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)



IT 1140909-48-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(dual MET-VEGF modulator for treating osteolytic bone metastases)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

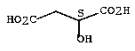
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

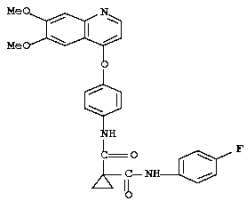
Absolute stereochemistry. Rotation (-).



IT 1365530-43-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dual MET-VEGF modulator for treating osteolytic bone metastases)
RN 1365530-43-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2R)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

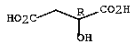
CRN 849217-68-1
CMF C28 H24 F N3 O5



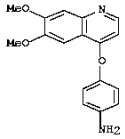
CM 2

CRN 636-61-3
CMF C4 H6 O5

Absolute stereochemistry. Rotation (+).



IT 190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(dual MET-VEGF modulator for treating osteolytic bone metastases)
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



L10 ANSWER 6 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:2037951 CAPLUS Full-text
DOCUMENT NUMBER: 167:302546
TITLE: Method of treating lung adenocarcinoma
INVENTOR(S): Aftab, Dana T.
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., No pp. given
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20150238477	A1	20150827	US 2015-14426580	20150306
WO 2014039971	A1	20140313	WO 2013-US58768	20130909

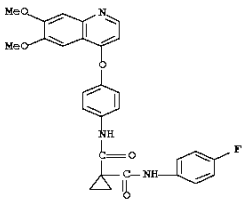
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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2012-61698143 P 20120907
WO 2013-US58768 W 20130909

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB This invention is directed to the treatment of cancer in a patient, particularly a patient with lung adenocarcinoma, and more particularly a patient with KIF5B-RET fusion-pos. non-small cell lung cancer, with an inhibitor of MET, VEGF, and RET which is a compound of Formula I:or a pharmaceutically acceptable salt thereof.

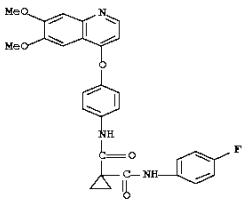
IT 849217-68-1P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(inhibitors of Met, VEGFR and Ret for use in treatment of lung adenocarcinoma)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



IT 1140909-48-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(inhibitors of Met, VEGFR and Ret for use in treatment of lung adenocarcinoma)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

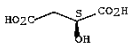
CRN 849217-68-1
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CM 2

CRN 97-67-6
CMF C4 H6 O5

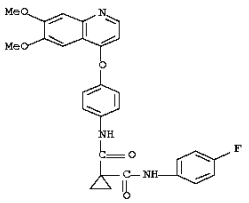
Absolute stereochemistry. Rotation (-).



IT 1365530-43-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitors of Met, VEGFR and Ret for use in treatment of lung adenocarcinoma)
RN 1365530-43-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2R)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

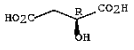
CRN 849217-68-1
CMF C28 H24 F N3 O5



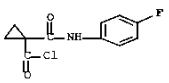
CM 2

CRN 636-61-3
CMF C4 H6 O5

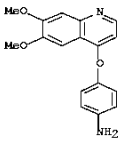
Absolute stereochemistry. Rotation (+).



IT 1219937-98-0P
RL: PRPH (Prophetic); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(inhibitors of Met, VEGFR and Ret for use in treatment of lung adenocarcinoma)
RN 1219937-98-0 CAPLUS
CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)



IT 190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(inhibitors of Met, VEGFR and Ret for use in treatment of lung adenocarcinoma)
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



L10 ANSWER 7 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:2032410 CAPLUS Full-text
DOCUMENT NUMBER: 167:245203
TITLE: (L)-malate salt of N-(4-{[6,7-bis(methyloxy) quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
INVENTOR(S): Brown, Adrian St. Clair; Lamb, Peter; Gallagher, William P.
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: U.S., No pp. given
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

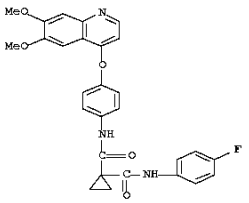
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US 20120035212	A1	20120209			
WO 2010083414	A1	20100722	WO 2010-US21194		20100115
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CN 106083714	A	20161109	CN 2016-10140984		20100115
AU 2013203780	A1	20130502	AU 2013-203780		20130411
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US 20150057310	A1	20150226	US 2014-14340871		20140725
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JP 2017014232	A	20170119	JP 2016-146934		20160727
AU 2016262732	A1	20161215	AU 2016-262732		20161124
US 20170275251	A1	20170928	US 2017-15621527		20170613
PRIORITY APPLN. INFO.:			US 2009-61145421	P	20090116
			WO 2010-US21194	W	20100115
			AU 2010-204619	A3	20100115
			CN 2010-80012656	A3	20100115
			JP 2011-546390	A3	20100115
			NZ 2010-594594	A3	20100115
			US 2011-13145054	A3	20111020
			AU 2013-203780	A3	20130411
			US 2014-14340871	A1	20140725
			JP 2014-264071	A3	20141226
			US 2017-15617725	A1	20170608
			US 2017-15618593	A1	20170609

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB Disclosed are malate salts of N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane -1,1-dicarboxamide, including a (L)-malate salt, a (D)-malate salt, a (DL) malate salt, and mixts. thereof; and crystalline and amorphous forms of the malate salts. Also disclosed are pharmaceutical compns. comprising at least one malate salts of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-cyclopropane-1,1-dicarboxamide; and methods of treating cancer comprising administering at least one malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-ffuorophenyl)cyclopropane-1,1-dicarboxamide.

IT 1235470-36-6P
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of malate salts of bismethoxyquinolinyloxyphenylfluorophenylcyclopropanedicarboxamide and crystalline forms thereof for the treatment of cancer)

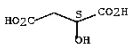
RN 1235470-36-6 CAPLUS



CM 2

CRN 97-67-6
CMF C4 H6 O5

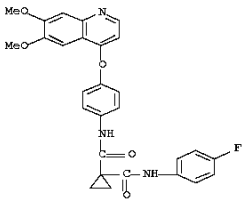
Absolute stereochemistry. Rotation (-).



RN 1235470-38-8 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2R)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:?) (CA INDEX NAME)

CM 1

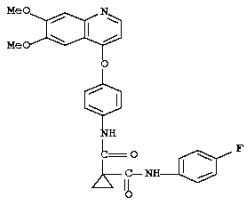
CRN 849217-68-1
CMF C28 H24 F N3 O5



CN Butanedioic acid, 2-hydroxy-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:?) (CA INDEX NAME)

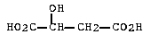
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CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 6915-15-7
CMF C4 H6 O5



IT 1235470-37-7P 1235470-38-8P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of malate salts of bismethoxyquinolinyloxyphenylfluorophenylcyclopropanedicarboxamide and crystalline forms thereof for the treatment of cancer)

RN 1235470-37-7 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:?) (CA INDEX NAME)

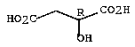
CM 1

CRN 849217-68-1
CMF C28 H24 F N3 O5

CM 2

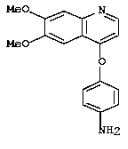
CRN 636-61-3
CMF C4 H6 O5

Absolute stereochemistry. Rotation (+).

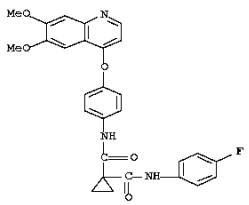


IT 190728-25-7P 849217-68-1P 1219937-98-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of malate salts of bismethoxyquinolinyloxyphenylfluorophenylcyclopropanedicarboxamide and crystalline forms thereof for the treatment of cancer)

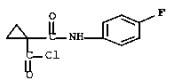
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



RN 1219937-98-0 CAPLUS
CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 246 THERE ARE 246 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 8 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:2003465 CAPLUS Full-text
DOCUMENT NUMBER: 167:175951
TITLE: Process for preparing quinoline derivatives
INVENTOR(S): Wilson, Jo Ann; Naganathan, Sriram; Andersen, Neil G.; Pfeiffer, Matthew
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., No pp. given
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20140256938	A1	20140911	US 2014-14353251	20140421
US 9365516	B2	20160614		
WO 2013059788	A1	20130425	WO 2012-US61320	20121022

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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

US 20160229805 A1 20160811 US 2016-15133708 20160420
PRIORITY APPLN. INFO.: US 2011-61549312 P 20111020
WO 2012-US61320 W 20121022
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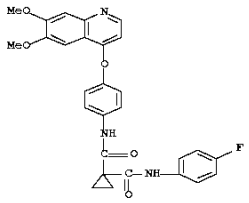
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB A process for prepg. a compd. of Formula I is disclosed, comprising the steps:wherein: R1 is halo; R2 is halo; R3 is (C1-C6)alkyl or (C1-C6)alkyl optionally substituted with heterocycloalkyl; R4 is (C1-C6)alkyl; and Q is CH or N;comprising: (a) contacting 1,1-cyclopropane dicarboxylic acid with thionyl chloride in a polar aprotic solvent; (b) adding and a tertiary amine base to the mixture of step (a) to form a compound of Formula A; and (c) coupling a compound of Formula A with an amine of Formula B to form a compound of Formula I.

IT 1140909-48-3P
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(process for preparing quinoline derivs.)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

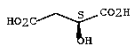
CRN 849217-68-1
CMF C28 H24 F N3 O5



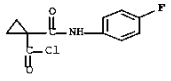
CM 2

CRN 97-67-6
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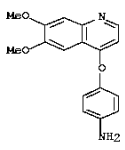
Absolute stereochemistry. Rotation (-).



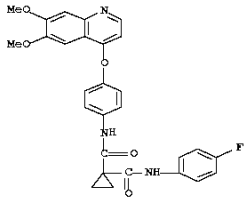
IT 1219937-98-0P
RL: PRPH (Prophetic); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparing quinoline derivs.)
RN 1219937-98-0 CAPLUS
CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)



IT 190728-25-7P 849217-68-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparing quinoline derivs.)
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



L10 ANSWER 9 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:1974375 CAPLUS Full-text
DOCUMENT NUMBER: 167:747
TITLE: Methods of using c-met modulators
INVENTOR(S): Aftab, Dana T.; Mueller, Thomas; Weitzman, Aaron; Holland, Jaymes
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., No pp. given
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20120282179	A1	20121108	US 2012-13389266	20120712
WO 2011017639	A1	20110210	WO 2010-US44749	20100806

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

NZ 624643	A	20151127	NZ 2010-624643	20100806
US 20160000772	A1	20160107	US 2015-14699683	20150429
JP 2016106141	A	20160616	JP 2016-45205	20160309
JP 2017082007	A	20170518	JP 2017-22961	20170210

PRIORITY APPLN. INFO.:
US 2009-61232382 P 20090807
WO 2010-US44749 W 20100806
JP 2012-523982 A3 20100806
NZ 2010-598055 A3 20100806
US 2012-13389266 B1 20120712
JP 2016-45205 A3 20160309

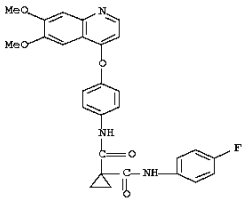
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB Methods of treating cancer by administering a compd. of Formula I,or a pharmaceutically acceptable salt or solvate thereof, in combination with other cancer treatments are described, wherein R1 is halo; R2 is halo; and Q is CH or N.

IT 849217-68-1P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(methods of using c-met modulators)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



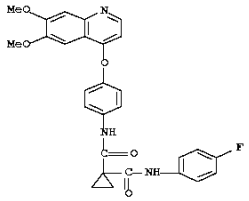
IT 1140909-48-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(methods of using c-met modulators)

RN 1140909-48-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

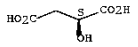
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

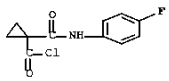
Absolute stereochemistry. Rotation (-).



IT 1219937-98-0P
RL: PRPH (Prophetic); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(methods of using c-met modulators)

RN 1219937-98-0 CAPLUS

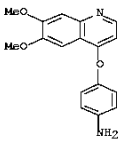
CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)



IT 190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(methods of using c-met modulators)

RN 190728-25-7 CAPLUS

CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L10 ANSWER 10 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN

ACCESSION NUMBER: 2016:1941702 CAPLUS Full-text

DOCUMENT NUMBER: 166:490458

TITLE: Processes for preparing quinoline compounds and pharmaceutical compositions containing such compounds

INVENTOR(S): Wilson, Jo Ann

PATENT ASSIGNEE(S): Exelixis, Inc., USA

SOURCE: U.S. Pat. Appl. Publ., No pp. given
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20140200242	A1	20140717	US 2014-13984559	20140320
US 9717720	B2	20170801		
WO 2012109510	A1	20120816	WO 2012-US24591	20120210
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
NZ 712808	A	20170331	NZ 2012-712808	20120210
JP 2016188216	A	20161104	JP 2016-94411	20160510
US 20170057921	A1	20170302	US 2016-15348716	20161110

PRIORITY APPLN. INFO.:

US 2011-61441520	P	20110210
US 2011-61441527	P	20110210
WO 2012-US24591	W	20120210
JP 2013-553580	A3	20120210
NZ 2012-614130	A3	20120210
US 2014-13984559	A1	20140320

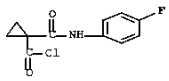
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The present invention is directed to processes for making and compns. containing quinolines such as formula I or pharmaceutically acceptable salts thereof wherein: X1 is H, Br, Cl, or X2 is H, Br, Cl, or n1 is 1-2; and n2 is 1-2.

IT 1219937-98-0P
RL: IMF (Industrial manufacture); PRPH (Prophetic); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(process for preparing quinoline derivs. and pharmaceutical compns. thereof)

RN 1219937-98-0 CAPLUS

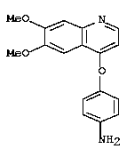
CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)



IT 190728-25-7P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparing quinoline derivs. and pharmaceutical compns. thereof)

RN 190728-25-7 CAPLUS

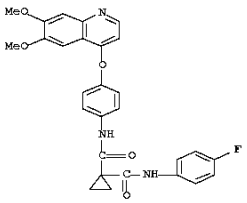
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



IT 849217-68-1P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(process for preparing quinoline derivs. and pharmaceutical compns. thereof)

RN 849217-68-1 CAPLUS

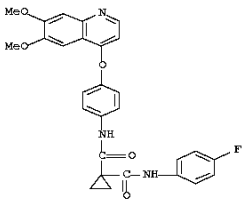
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



IT 1140909-48-3P
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(process for preparing quinoline derivs. and pharmaceutical compns. thereof)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

CRN 849217-68-1
CMF C28 H24 F N3 O5



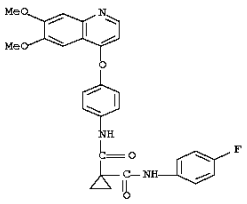
CM 2

CRN 97-67-6
CMF C4 H6 O5

HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM
PRIORITY APPLN. INFO.: US 2013-61808516 P 20130404
WO 2014-US33008 W 20140404

AB This invention relates to the combination of cabozantinib and abiraterone to treat cancer, particularly castration resistant prostate cancer.

IT 849217-68-1P
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(drug combinations to treat cancer)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)

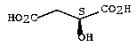


IT 1140909-48-3P
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug combinations to treat cancer)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

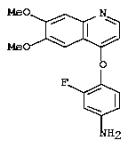
CM 1

CRN 849217-68-1
CMF C28 H24 F N3 O5

Absolute stereochemistry. Rotation (-).



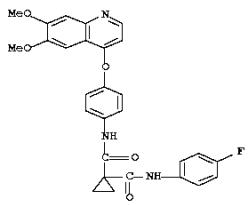
IT 347161-74-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparing quinoline derivs. and pharmaceutical compns. thereof)
RN 347161-74-4 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]-3-fluoro- (CA INDEX NAME)



L10 ANSWER 11 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:1874511 CAPLUS Full-text
DOCUMENT NUMBER: 166:300776
TITLE: Drug combinations to treat cancer
INVENTOR(S): Sweeney, Christopher J.; Kantoff, Phili W.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., No pp. given
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20160082019	A1	20160324	US 2015-14782493	20151005
WO 2014165779	A1	20141009	WO 2014-US33008	20140404

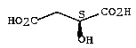
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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR,



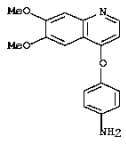
CM 2

CRN 97-67-6
CMF C4 H6 O5

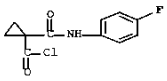
Absolute stereochemistry. Rotation (-).



IT 190728-25-7P 1219937-98-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(drug combinations to treat cancer)
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



RN 1219937-98-0 CAPLUS
CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)



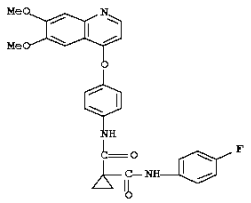
L10 ANSWER 12 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:224790 CAPLUS Full-text
DOCUMENT NUMBER: 164:293822
TITLE: Drug combinations to treat multiple myeloma
INVENTOR(S): Aftab, Dana T.; Lamb, Peter
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 49pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2016022697	A1	20160211	WO 2015-US43825	20150805
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
CA 2957466	A1	20160211	CA 2015-2957466	20150805
AU 2015301097	A1	20170302	AU 2015-301097	20150805
KR 2017031786	A	20170321	KR 2017-7006288	20150805
CN 106573042	A	20170419	CN 2015-80042010	20150805
EP 3177311	A1	20170614	EP 2015-750223	20150805
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JP 2017526662	T	20170914	JP 2017-506390	20150805
MX 2017001490	A	20170511	MX 2017-1490	20170201
US 20170224672	A1	20170810	US 2017-15501582	20170203

PRIORITY APPLN. INFO.: US 2014-62033386 P 20140805
WO 2015-US43825 W 20150805
OTHER SOURCE(S): CASREACT 164:293822; MARPAT 164:293822

AB This invention relates to the combination of a C-Met inhibitor and a proteasome inhibitor to treat cancer, particularly multiple myeloma.

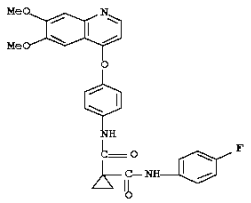
IT 849217-68-1P
RL: PAC (Pharmacological activity); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(drug combinations to treat multiple myeloma)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



IT 1140909-48-3P 1365530-43-3P 1634653-27-2P
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug combinations to treat multiple myeloma)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

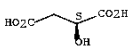
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

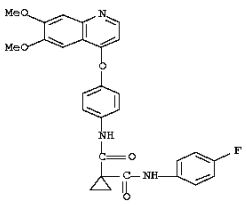
Absolute stereochemistry. Rotation (-).



RN 1365530-43-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2R)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

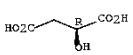
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 636-61-3
CMF C4 H6 O5

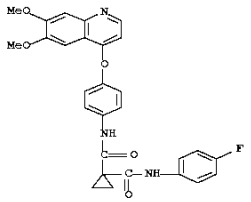
Absolute stereochemistry. Rotation (+).



RN 1634653-27-2 CAPLUS
CN Butanedioic acid, 2-hydroxy-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

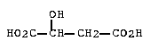
CM 1

CRN 849217-68-1
CMF C28 H24 F N3 O5

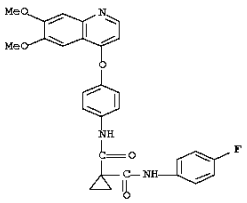


CM 2

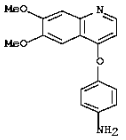
CRN 6915-15-7
CMF C4 H6 O5



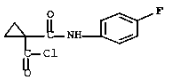
IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drug combinations to treat multiple myeloma)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



IT 190728-25-7P 1219937-98-0P,
1-(4-Fluoro-phenylcarbamoyl)-cyclopropanecarbonyl chloride
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(drug combinations to treat multiple myeloma)
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[[6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)

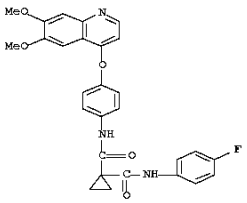


RN 1219937-98-0 CAPLUS
CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

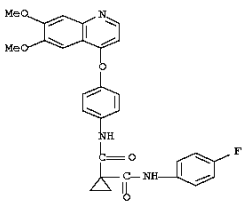
L10 ANSWER 13 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2015:1726025 CAPLUS Full-text



IT 1140909-48-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(treating lung adenocarcinoma)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

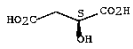
CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).

DOCUMENT NUMBER: 163:628844
TITLE: Method of treating lung adenocarcinoma
INVENTOR(S): Aftab, Dana T.; Yu, Peiwen
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 92pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2015164869	A1	20151029	WO 2015-US27800	20150427
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
CA 2946416	A1	20151029	CA 2015-2946416	20150427
AR 100191	A1	20160914	AR 2015-101255	20150427
AU 2015249232	A1	20161110	AU 2015-249232	20150427
KR 2016147934	A	20161223	KR 2016-7033010	20150427
IL 248408	A	20161229	IL 2015-248408	20150427
EP 3134084	A1	20170301	EP 2015-721100	20150427
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
CN 106488768	A	20170308	CN 2015-80022580	20150427
JP 2017513908	T	20170601	JP 2016-564236	20150427
MX 2016013600	A	20170427	MX 2016-13600	20161017
US 20170042880	A1	20170216	US 2016-15305854	20161021
PRIORITY APPLN. INFO.:			US 2014-61984599 P	20140425
			WO 2015-US27800 W	20150427

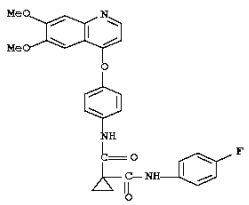
OTHER SOURCE(S): CASREACT 163:628844; MARPAT 163:628844
AB This invention is directed to the treatment of cancer in a patient, particularly a patient with lung adenocarcinoma, and more particularly a patient with SLC34A2-ROS1, CD74-ROS1, or FIG-ROS1 fusion-pos. non-small cell lung cancer, with an inhibitor of MET, VEGFR2, and ROS1.
IT 849217-68-1P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(treating lung adenocarcinoma)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



IT 1365530-43-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treating lung adenocarcinoma)
RN 1365530-43-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2R)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

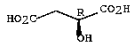
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 636-61-3
CMF C4 H6 O5

Absolute stereochemistry. Rotation (+).

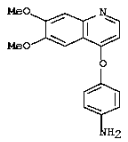


IT 190728-25-7P 1219937-98-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(treating lung adenocarcinoma)

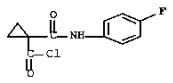
RN 190728-25-7 CAPLUS

CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



RN 1219937-98-0 CAPLUS

CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 14 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN

ACCESSION NUMBER: 2015:1213912 CAPLUS Full-text

DOCUMENT NUMBER: 163:271103

TITLE: Preparation of deuterated cabozantinib derivatives and their application as anticancer agents

INVENTOR(S): Chen, Xinghai; Peng, Wei; Parker, Omar; Zheng, Peiming; Fu, Yong

PATENT ASSIGNEE(S): Shanghai Shengkao Pharmaceutical Technology Co., Ltd., Peop. Rep. China

SOURCE: Faming Zhuanli Shenqing, 35pp.
CODEN: CNXXEV

DOCUMENT TYPE: Patent

LANGUAGE: Chinese

FAMILY ACC. NUM. COUNT: 1

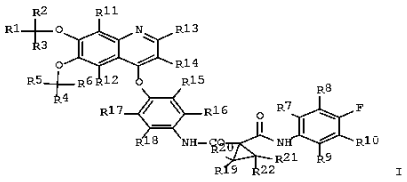
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 104788372	A	20150722	CN 2014-10361351	20140725

PRIORITY APPLN. INFO.: CN 2014-10361351 20140725

OTHER SOURCE(S): CASREACT 163:271103; MARPAT 163:271103

GI



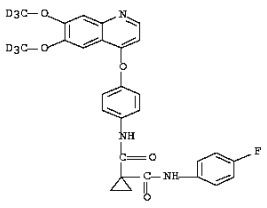
I

AB The invention is related to the prepn. of deuterated cabozantinib derivs. I and their application as anticancer agents. The invention compound I, wherein R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11, R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, and R22 are H or D independently and contain at least one D and their pharmaceutically acceptable salts, crystalline hydrates, solvates, prodrugs, single crystal or polymorph are claimed. Compound I was prepared by multi-step procedure (procedure given). The deuterated cabozantinib derivs. have slow decomposition in vivo, thereby reducing adverse metabolism of drugs. The invention compds. were evaluated for their anticancer activity.

IT 1802168-46-2P 1802168-48-4P 1802168-49-5P
1802168-50-8P 1802168-51-9P 1802168-52-0P
1802168-53-1P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of deuterated cabozantinib derivs. and their application as anticancer agents)

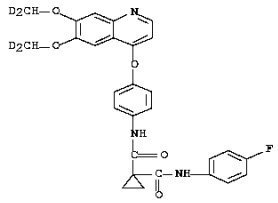
RN 1802168-46-2 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N-[4-[[6,7-di(methoxy-d3)-4-quinolinyl]oxy]phenyl]-N'-(4-fluorophenyl)- (CA INDEX NAME)



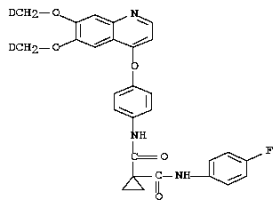
RN 1802168-48-4 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N-[4-[[6,7-di(methoxy-d2)-4-quinolinyl]oxy]phenyl]-N'-(4-fluorophenyl)- (CA INDEX NAME)



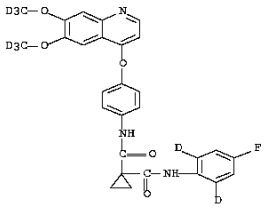
RN 1802168-49-5 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N-[4-[[6,7-di(methoxy-d)-4-quinolinyl]oxy]phenyl]-N'-(4-fluorophenyl)- (CA INDEX NAME)



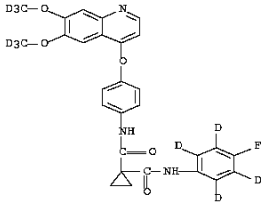
RN 1802168-50-8 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N-[4-[[6,7-di(methoxy-d3)-4-quinolinyl]oxy]phenyl]-N'-(4-fluorophenyl-2,6-d2)- (CA INDEX NAME)



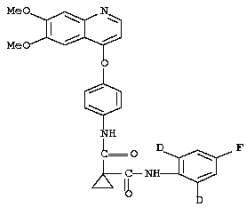
RN 1802168-51-9 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N-[4-[[6,7-di(methoxy-d3)-4-quinolinyl]oxy]phenyl]-N'-(4-fluorophenyl-2,3,5,6-d4)- (CA INDEX NAME)

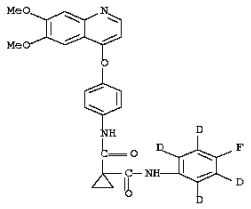


RN 1802168-52-0 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl-2,6-d2)- (CA INDEX NAME)



RN 1802168-53-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl-2,3,5,6-d4)- (CA INDEX NAME)

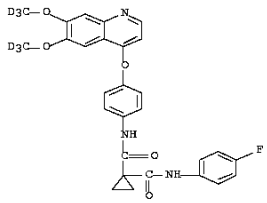


IT 1802168-54-2P 1802168-55-3P 1802168-56-4P
1802168-57-5P 1802168-58-6P 1802168-59-7P
1802168-60-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of deuterated cabozantinib derivs. and their application as anticancer agents)
RN 1802168-54-2 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with

N-[4-[[6,7-di(methoxy-d3)-4-quinolinyl]oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:?) (CA INDEX NAME)

CM 1

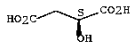
CRN 1802168-46-2
CMF C28 H18 D6 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).

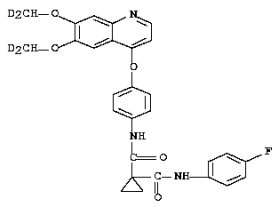


RN 1802168-55-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with

N-[4-[[6,7-di(methoxy-d2)-4-quinolinyl]oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:?) (CA INDEX NAME)

CM 1

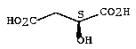
CRN 1802168-48-4
CMF C28 H20 D4 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).

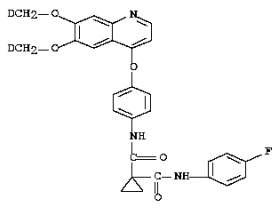


RN 1802168-56-4 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with

N-[4-[[6,7-di(methoxy-d)-4-quinolinyl]oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:?) (CA INDEX NAME)

CM 1

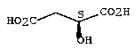
CRN 1802168-49-5
CMF C28 H22 D2 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).

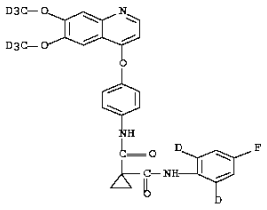


RN 1802168-57-5 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with

N-[4-[[6,7-di(methoxy-d3)-4-quinolinyl]oxy]phenyl]-N'-(4-fluorophenyl-2,6-d2)-1,1-cyclopropanedicarboxamide (1:?) (CA INDEX NAME)

CM 1

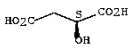
CRN 1802168-50-8
CMF C28 H16 D8 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

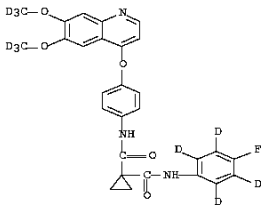
Absolute stereochemistry. Rotation (-).

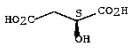


RN 1802168-58-6 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[[6,7-di(methoxy-d3)-4-quinolinyl]oxy]phenyl]-N'-(4-fluorophenyl-2,3,5,6-d4)-1,1-cyclopropanedicarboxamide (1:?) (CA INDEX NAME)

CM 1

CRN 1802168-51-9
CMF C28 H14 D10 F N3 O5

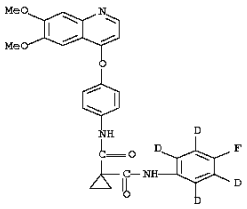




RN 1802168-60-0 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl-2,3,5,6-d4)-1,1-cyclopropanedicarboxamide (1:?) (CA INDEX NAME)

CM 1

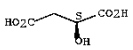
CRN 1802168-53-1
CMF C28 H20 D4 F N3 O5



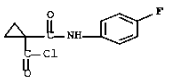
CM 2

CRN 97-67-6
CMF C4 H6 O5

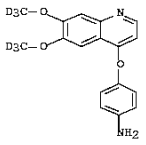
Absolute stereochemistry. Rotation (-).



IT 1219937-98-0P 1802168-63-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of deuterated cabozantinib derivs. and their application as anticancer agents)
RN 1219937-98-0 CAPLUS
CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)



RN 1802168-63-3 CAPLUS
CN Benzenamine, 4-[[6,7-di(methoxy-d3)-4-quinolinyl]oxy]- (CA INDEX NAME)



L10 ANSWER 15 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2015:316867 CAPLUS Full-text
DOCUMENT NUMBER: 162:399931
TITLE: Novel crystal form of quinoline compound and preparation method thereof
INVENTOR(S): Tang, Dongjun; Liu, Yanping; Kou, Jingping
PATENT ASSIGNEE(S): Sunshine Lake Pharma Co., Ltd., Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 15pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 104370811	A	20150225	CN 2014-10399795	20140814
PRIORITY APPLN. INFO.:			CN 2013-10356174 A	20130815

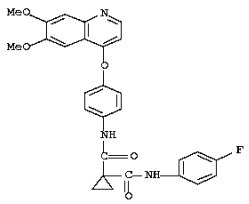
OTHER SOURCE(S): CASREACT 162:399931

AB The present invention relates to a novel crystal form of quinoline compd. N-(4-[[6,7-dimethoxyquinolin-4-yl]oxy]phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarbonamide and preparation method thereof, and belongs to medicinal chemical field. The crystal form is basically pure crystal form I or crystal form II. In the X-ray powder diffraction pattern of crystal form I, there are peaks at 2θ angles of about 11.9, 12.9, 14.4, 16.0, 22.1 and 26.0 degrees. In the X-ray powder diffraction pattern of crystal form II, there are peaks at 2θ angles of about 11.6, 14.1, 18.5, 21.1, 22.2, 23.2, 24.1 and 29.0 degrees. The novel crystal

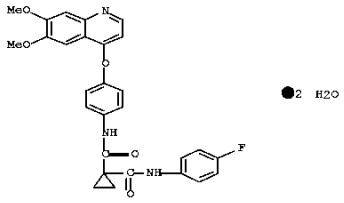
form possesses good stability and mobility, which is conducive to operate in storage, transfer and production, and the novel crystal form can be used for preparing pharmaceutically acceptable salt thereof for application in pharmaceutics.

IT 849217-68-1P 1669412-61-6P 1669412-63-8P
RL: IMF (Industrial manufacture); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(crystal forms of quinoline compound by using three-component coupling and/or condensation as the key steps)

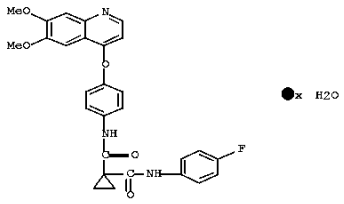
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



RN 1669412-61-6 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-, hydrate (1:2) (CA INDEX NAME)

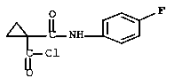


RN 1669412-63-8 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-, hydrate (1:?) (CA INDEX NAME)



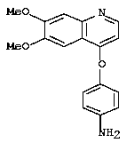
IT 1219937-98-0P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(crystal forms of quinoline compound by using three-component coupling and/or condensation as the key steps)

RN 1219937-98-0 CAPLUS
CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)



IT 190728-25-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(crystal forms of quinoline compound by using three-component coupling and/or condensation as the key steps)

RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)

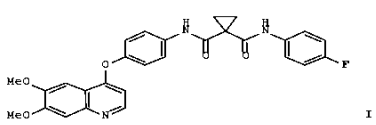


OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L10 ANSWER 16 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2014:1716754 CAPLUS Full-text
DOCUMENT NUMBER: 161:582215
TITLE: Preparation of cabozantinib and dosage forms for treatment of cancer
INVENTOR(S): Decillis, Arthur
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 48pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2014165786	A1	20141009	WO 2014-US33016	20140404
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
EP 2981263	A1	20160210	EP 2014-724909	20140404
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
US 20160022662	A1	20160128	US 2015-14782537	20151005
PRIORITY APPLN. INFO.:			US 2013-61808511 P	20130404
			WO 2014-US33016 W	20140404

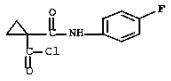
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 161:582215
GI



AB This invention relates to a dosage form of cabozantinib (I) and a method of employing the dosage form to treat cancer. I was prepared starting with 6,7-dimethoxy-4-quinolinol through a number of steps. I S-maleate was also prepared and tablets containing I were prepared

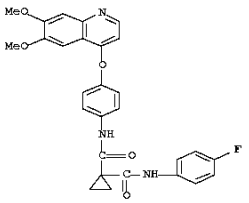
IT 1219937-98-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of)

RN 1219937-98-0 CAPLUS
CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)



IT 849217-68-1P, Cabozantinib 1140909-48-3P, Cabozantinib S-malate 1365530-43-3P
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of cabozantinib and dosage forms for treatment of cancer)

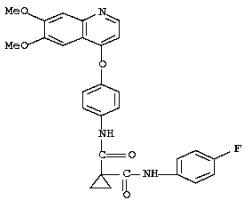
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

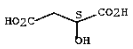
CRN 849217-68-1
CMF C28 H24 F N3 O5

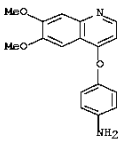


CM 2

CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).





OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

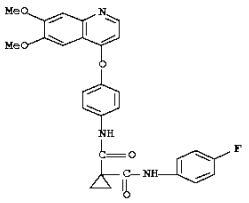
L10 ANSWER 17 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2014:1710486 CAPLUS Full-text
DOCUMENT NUMBER: 161:577829
TITLE: Drug combinations to treat cancer
INVENTOR(S): Sweeney, Christopher J.; Kantoff, Philip W.
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 78pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2014165779	A1	20141009	WO 2014-US33008	20140404
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
CA 2908815	A1	20141009	CA 2014-2908815	20140404
AU 2014248001	A1	20151119	AU 2014-248001	20140404
IL 241868	A	20151130	IL 2014-241868	20140404
KR 2015138268	A	20151209	KR 2015-7030445	20140404
EP 2983639	A1	20160217	EP 2014-724594	20140404
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
JP 2016515628	T	20160530	JP 2016-506653	20140404
US 20160082019	A1	20160324	US 2015-14782493	20151005
MX 2015014046	A	20160516	MX 2015-14046	20151005

RN 1365530-43-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2R)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

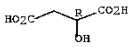
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

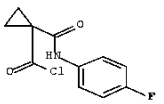
CRN 636-61-3
CMF C4 H6 O5

Absolute stereochemistry. Rotation (+).

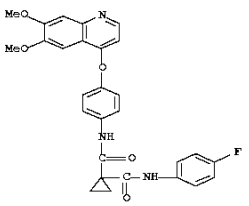


IT 190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of cabozantinib and dosage forms for treatment of cancer)
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)

IN 2015KN03651 A 20160318 IN 2015-KN3651 20151103
PRIORITY APPLN. INFO.: US 2013-61808516 P 20130404
WO 2014-US33008 W 20140404
OTHER SOURCE(S): CASREACT 161:577829; MARPAT 161:577829
GI



AB This invention relates to the combination of cabozantinib and abiraterone to treat cancer, particularly castration resistant prostate cancer.
IT 849217-68-1P, Cabozantinib
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(drug combinations to treat cancer)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)

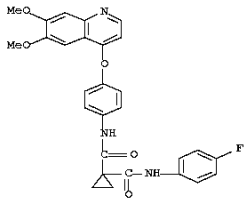


IT 1140909-48-3P
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug combinations to treat cancer)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with

N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

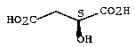
CRN 849217-68-1
CMF C28 H24 F N3 O5



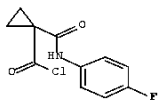
CM 2

CRN 97-67-6
CMF C4 H6 O5

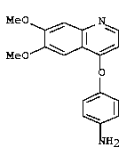
Absolute stereochemistry. Rotation (-).



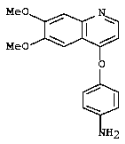
IT 190728-25-7P 1219937-98-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(drug combinations to treat cancer)
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



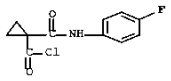
AB The invention discloses a synthesis method of antitumor therapeutic drug of cabozantinib., comprising: using 4-(6, 7- dimethoxy quinoline -4- oxy)-phenylamine to react with 1-((4- fluorophenyl) carbamoyl) cyclopropyl acyl halide, an acid-binding agent in organic solvent at -5~20 °C for 0.5~2h to obtain cabozantinib; the inventive method uses cheap raw materials, has mild conditions, simple and convenient operation, stable process, good repeatability, high molar yield, low cost, so invention is an applicable method for com. production of cabozantinib. Cabozantinib was prepared via chlorination of 6,7-dimethoxyquinolin-4-ol; the resulting 4-chloro-6,7-dimethoxyquinoline underwent condensation with 4-aminophenol or 4-nitrophenol to give the corresponding ethers, which underwent redn and/or acylation with 1-[(4-fluorophenyl)carbamoyl]cyclopropylcarbonyl halides to give cabozantinib. The said 1-[(4-fluorophenyl)carbamoyl]cyclopropylcarbonyl halides were prepared via condensation of 1,1-cyclopropanedicarboxylic acid with p-fluoroaniline followed by halogenation. The inventive method uses cheap raw materials, has mild conditions, simple and convenient operation, stable process, good repeatability, high molar yield, low cost, so invention is an applicable method for com. production of cabozantinib.
IT 190728-25-7P 1219937-98-0P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of antitumor drug cabozantinib starting from (dimethoxy)quinolinol and cyclopropanedicarboxylic acid by using etherification and amidation as the key steps)
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



RN 1219937-98-0 CAPLUS
CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)



RN 1219937-98-0 CAPLUS
CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)

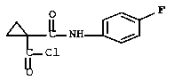


OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

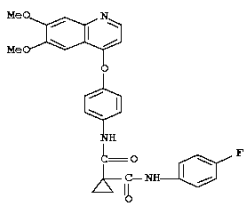
L10 ANSWER 18 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2014:479457 CAPLUS Full-text
DOCUMENT NUMBER: 160:515456
TITLE: Synthesis method of antitumor therapeutic drug of cabozantinib
INVENTOR(S): Cai, Jianping; Chen, Zengfei; Zhang, Lifeng; Fang, Ying
PATENT ASSIGNEE(S): Suzhou Moer Pharmaceutical Co., Ltd., Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 9pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 103664778	A	20140326	CN 2013-10631287	20131127
CN 103664778	B	20170405		
PRIORITY APPLN. INFO.:			CN 2013-10631287	20131127

OTHER SOURCE(S): CASREACT 160:515456; MARPAT 160:515456
GI



IT 849217-68-1P, Cabozantinib
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of antitumor drug cabozantinib starting from (dimethoxy)quinolinol and cyclopropanedicarboxylic acid by using etherification and amidation as the key steps)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



L10 ANSWER 19 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2014:410366 CAPLUS Full-text
DOCUMENT NUMBER: 160:451706
TITLE: Inhibitors of Met, VEGFR and Ret for use in the treatment of lung adenocarcinoma
INVENTOR(S): Aftab, Dana T.
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 80pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

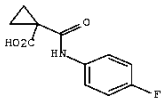
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2014039971	A1	20140313	WO 2013-US58768	20130909
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE,				

EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

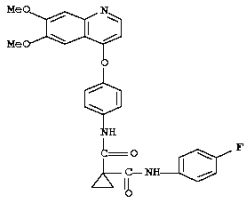
US 20140121239	A1	20140501	US 2013-14021614		20130909
CN 104703600	A	20150610	CN 2013-80052164		20130909
EP 2892532	A1	20150715	EP 2013-765886		20130909
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME					
JP 2015530389	T	20151015	JP 2015-531283		20130909
US 20150238477	A1	20150827	US 2015-14426580		20150306
PRIORITY APPLN. INFO.:			US 2012-61698143	P	20120907
			WO 2013-US58768	W	20130909

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 160:451706; MARPAT 160:451706
GI



AB This invention is directed to the treatment of cancer in a patient, particularly a patient with lung adenocarcinoma, and more particularly a patient with KIF5B-RET fusion-pos. non-small cell lung cancer, with an inhibitor of MET, VEGF, and RET.

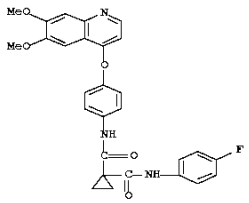
IT 849217-68-1P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(inhibitors of Met, VEGFR and Ret for use in treatment of lung adenocarcinoma)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



IT 1140909-48-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(inhibitors of Met, VEGFR and Ret for use in treatment of lung adenocarcinoma)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

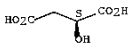
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

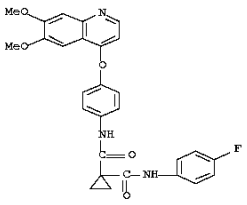
Absolute stereochemistry. Rotation (-).



IT 1365530-43-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitors of Met, VEGFR and Ret for use in treatment of lung adenocarcinoma)
RN 1365530-43-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2R)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

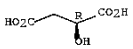
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CMF C28 H24 F N3 O5



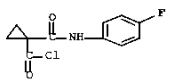
CM 2

CRN 636-61-3
CMF C4 H6 O5

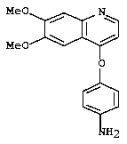
Absolute stereochemistry. Rotation (+).



IT 1219937-98-0P
RL: PRPH (Prophetic); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(inhibitors of Met, VEGFR and Ret for use in treatment of lung adenocarcinoma)
RN 1219937-98-0 CAPLUS
CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)



IT 190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(inhibitors of Met, VEGFR and Ret for use in treatment of lung adenocarcinoma)
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 20 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN

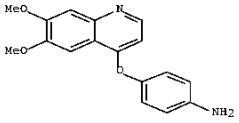
ACCESSION NUMBER:	2013:1734775 CAPLUS Full-text
DOCUMENT NUMBER:	159:691817
TITLE:	A dual MET-VEGF modulator for treating osteolytic bone metastases
INVENTOR(S):	Aftab, Dana T.
PATENT ASSIGNEE(S):	Exelixis, Inc., USA
SOURCE:	PCT Int. Appl., 44pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	2
PATENT INFORMATION:	

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2013166296	A1	20131107	WO 2013-US39284	20130502
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
EP 2844254	A1	20150311	EP 2013-722238	20130502
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
JP 2015515988	T	20150604	JP 2015-510456	20130502
US 20150133494	A1	20150514	US 2014-14398188	20141031
PRIORITY APPLN. INFO.:			US 2012-61641837 P	20120502
			WO 2013-US39284 W	20130502

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASREACT 159:691817; MARPAT 159:691817

GI



AB This invention is directed to the treatment of cancer, particularly castration-resistant prostate cancer and osteolytic bone metastases, with a dual inhibitor of MET and VEGF.

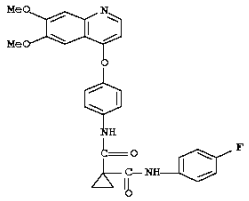
IT 849217-68-1P 1219937-98-0P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(dual MET-VEGF modulator for treating osteolytic bone metastases)

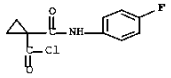
RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



RN 1219937-98-0 CAPLUS

CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)



IT 1140909-48-3P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(dual MET-VEGF modulator for treating osteolytic bone metastases)

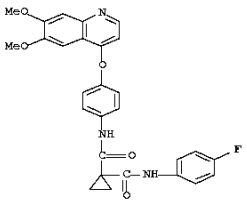
RN 1140909-48-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

CRN 849217-68-1

CMF C28 H24 F N3 O5

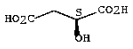


CM 2

CRN 97-67-6

CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



IT 1365530-43-3

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(dual MET-VEGF modulator for treating osteolytic bone metastases)

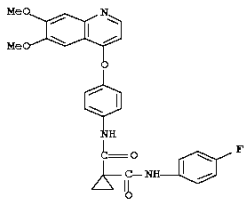
RN 1365530-43-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2R)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

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CRN 849217-68-1

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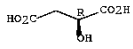


CM 2

CRN 636-61-3

CMF C4 H6 O5

Absolute stereochemistry. Rotation (+).



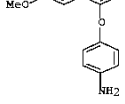
IT 190728-25-7P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(dual MET-VEGF modulator for treating osteolytic bone metastases)

RN 190728-25-7 CAPLUS

CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

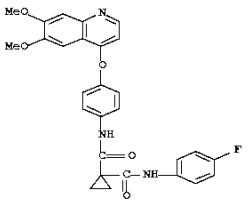
L10 ANSWER 21 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2013:761990 CAPLUS Full-text
DOCUMENT NUMBER: 158:704608
TITLE: Method of quantifying cancer treatment
INVENTOR(S): Holland, Jaymes
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 50pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2013070903	A1	20130516	WO 2012-US64134	20121108
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
CA 2854664	A1	20130516	CA 2012-2854664	20121108
AU 2012335750	A1	20140605	AU 2012-335750	20121108
AR 88813	A1	20140710	AR 2012-104223	20121108
CN 104039226	A	20140910	CN 2012-80066413	20121108
EP 2775921	A1	20140917	EP 2012-795939	20121108
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
JP 2015505360	T	20150219	JP 2014-541261	20121108
BR 112014011008	A2	20170613	BR 2014-112014011008	20121108
IN 2014CN03674	A	20150703	IN 2014-CN3674	20140515

PRIORITY APPLN. INFO.: US 2011-61557362 P 20111108
WO 2012-US64134 W 20121108
OTHER SOURCE(S): CASREACT 158:704608

AB This invention is directed to a method for quantifying cancer treatment response in patients with bone metastases using computer aided bone scan assessment, comprising: (a) obtaining a bone scan image; (b) normalizing the obtained bone scan image to identify normalized bone scan lesions; and (c) quant. assessing the normalized bone scan lesions using bone scan lesion area, bone scan intensity, or bone scan lesion count.

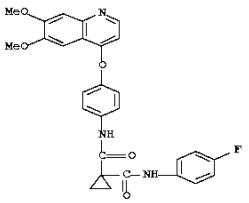
IT 849217-68-1P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(quantifying cancer treatment)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



IT 1140909-48-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(quantifying cancer treatment)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

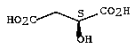
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CRN 849217-68-1
CMF C28 H24 F N3 O5

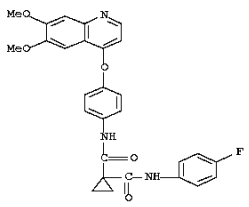


CM 2

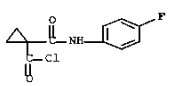
CRN 97-67-6
CMF C4 H6 O5



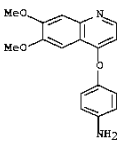
IT 849217-68-1, Cabozantinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(quantifying cancer treatment)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



IT 1219937-98-0P
RL: PRPH (Prophetic); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(quantifying cancer treatment)
RN 1219937-98-0 CAPLUS
CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)



IT 190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(quantifying cancer treatment)
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



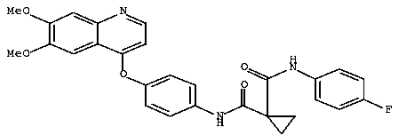
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 22 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2013:761969 CAPLUS Full-text
DOCUMENT NUMBER: 158:704607
TITLE: Dual inhibitor of Met and VEGF for treating cancer
INVENTOR(S): Aftab, Dana T.; Schimmoller, Frauke
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 56pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2013070890	A1	20130516	WO 2012-US64116	20121108
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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
CA 2854336	A1	20130516	CA 2012-2854336	20121108
AU 2012335737	A1	20140605	AU 2012-335737	20121108
IL 232421	A	20140630	IL 2012-232421	20121108
KR 2014088610	A	20140710	KR 2014-7015127	20121108
EP 2776033	A1	20140917	EP 2012-787328	20121108
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
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JP 2014532766	T	20141208	JP 2014-541256	20121108

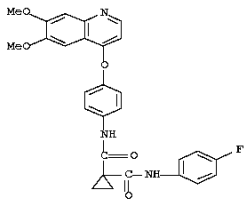
BR 112014011009	A2	20170606	BR 2014-112014011009		20121108
MX 2014005458	A	20150416	MX 2014-5458		20140506
US 20140323522	A1	20141030	US 2014-14356927		20140508
ZA 2014003331	A	20151223	ZA 2014-3331		20140508
IN 2014CN04067	A	20151023	IN 2014-CN4067		20140530
PRIORITY APPLN. INFO.:			US 2011-61557358	P	20111108
			WO 2012-US64116	W	20121108

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 158:704607; MARPAT 158:704607
GI

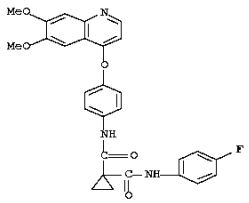


AB This invention is directed to the treatment of cancer, particularly castration-resistant prostate cancer and bone metastases, with a dual inhibitor of MET and VEGF.

IT 849217-68-1P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(dual inhibitor of Met and VEGF for treating cancer)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



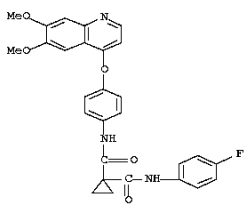
IT 1140909-48-3P



RN 1365530-43-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2R)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

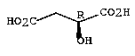
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 636-61-3
CMF C4 H6 O5

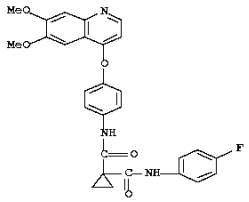
Absolute stereochemistry. Rotation (+).



RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(dual inhibitor of Met and VEGF for treating cancer)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

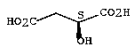
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CM 2

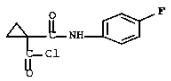
CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).

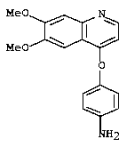


IT 849217-68-1, Cabozantinib 1365530-43-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dual inhibitor of Met and VEGF for treating cancer)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)

IT 1219937-98-0P
RL: PRPH (Prophetic); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(dual inhibitor of Met and VEGF for treating cancer)
RN 1219937-98-0 CAPLUS
CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)



IT 190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(dual inhibitor of Met and VEGF for treating cancer)
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



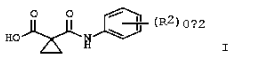
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 23 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2013:644308 CAPLUS Full-text
DOCUMENT NUMBER: 158:620790
TITLE: Process for preparing quinoline derivatives
INVENTOR(S): Wilson, Jo Ann; Naganathan, Sriram; Pfeiffer, Matthew; Andersen, Neil G.
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 47pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

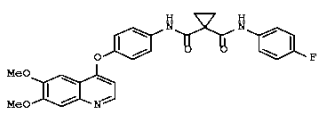
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2013059788	A1	20130425	WO 2012-US61320		20121022
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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM					
CA 2852771	A1	20130425	CA 2012-2852771		20121022
AU 2012325768	A1	20140522	AU 2012-325768		20121022
AU 2012325768	B2	20170810			
IL 232139	A	20140528	IL 2012-232139		20121022
AR 88483	A1	20140611	AR 2012-103944		20121022
KR 2014088874	A	20140711	KR 2014-7012435		20121022
EP 2768796	A1	20140827	EP 2012-783763		20121022
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JP 2014530880	T	20141120	JP 2014-537359		20121022
JP 6208140	B2	20171004			
CN 104395284	A	20150304	CN 2012-80054241		20121022
NZ 624328	A	20161028	NZ 2012-624328		20121022
BR 112014009302	A2	20170523	BR 2014-112014009302		20121022
ZA 2014002579	A	20150325	ZA 2014-2579		20140409
MX 2014004583	A	20141006	MX 2014-4583		20140415
US 20140256938	A1	20140911	US 2014-14353251		20140421
US 9365516	B2	20160614			
IN 2014CN02971	A	20150703	IN 2014-CN2971		20140421
US 20160229805	A1	20160811	US 2016-15133708		20160420
PRIORITY APPLN. INFO.:			US 2011-61549312	P	20111020
			WO 2012-US61320	W	20121022
			US 2014-14353251	A1	20140421

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 158:620790; MARPAT 158:620790
GI



I



II

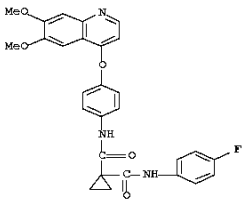
AB The invention is directed to processes for prepg. compds. of formula I (R2 is H, F, Cl and Br) by activation of 1,1-cyclopropanedicarboxylic acid with thionyl chloride followed by amidation with substituted aniline derivative Example compound II L-malate was prepared by chlorination of 6,7-dimethoxyquinolin-4-ol followed by etherification of 4-chloro-6,7-dimethoxyquinoline with 4-aminophenol; the resulting 4-(6,7-dimethoxyquinolin-4-yloxy)phenylamine underwent acylation with 1-[(4-fluorophenyl)carbamoyl]cyclopropanecarbonyl chloride to give compound II, which underwent addition of L-malic acid to give the desired product.

IT 1140909-48-3P
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(process for preparing quinoline derivs.)

RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

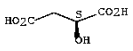
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

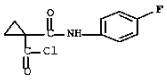
CRN 97-67-6
CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



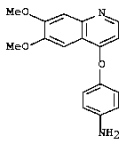
IT 1219937-98-0P, 1-(4-Fluoro-phenylcarbamoyl)-cyclopropanecarbonyl chloride
RL: PRPH (Prophetic); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparing quinoline derivs.)

RN 1219937-98-0 CAPLUS
CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)

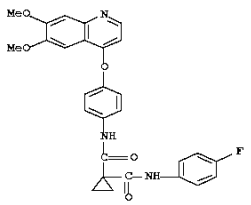


IT 190728-25-7P 849217-68-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparing quinoline derivs.)

RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

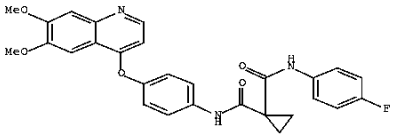
L10 ANSWER 24 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2013:466384 CAPLUS Full-text
DOCUMENT NUMBER: 158:494085
TITLE: Method for treating osteoporosis
INVENTOR(S): Aftab, Dana T.; Clary, Douglas
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 73pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2013043840	A1	20130328	WO 2012-US56281	20120920
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,				

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EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS,
JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY,
MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM,
PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK,
SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VC, VN, ZA, ZM, ZW
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR,
HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS,
SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD,
SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

CA 2848512	A1	20130328	CA 2012-2848512		20120920
AU 2012312364	A1	20140410	AU 2012-312364		20120920
IL 231495	A	20140430	IL 2012-231495		20120920
KR 2014069133	A	20140609	KR 2014-7009534		20120920
CN 103957915	A	20140730	CN 2012-80051094		20120920
EP 2758057	A1	20140730	EP 2012-770368		20120920
EP 2758057	B1	20170531			
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME					
JP 2014527984	T	20141023	JP 2014-531955		20120920
NZ 622722	A	20160930	NZ 2012-622722		20120920
BR 112014006702	A2	20170613	BR 2014-112014006702		20120920
AR 87995	A1	20140430	AR 2012-103501		20120921
TW I564009	B	20170101	TW 2012-134829		20120921
ZA 2014001728	A	20160127	ZA 2014-1728		20140310
MX 2014003027	A	20141024	MX 2014-3027		20140313
IN 2014CN02093	A	20141010	IN 2014-CN2093		20140319
US 20140228401	A1	20140814	US 2014-14346570		20140321
PRIORITY APPLN. INFO.:			US 2011-61538039	P	20110922
			WO 2012-US56281	W	20120920

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 158:494085; MARPAT 158:494085
GI

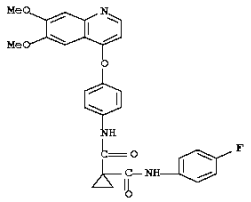


AB This invention is directed to the treatment of osteoporosis using N-(4-[[6,7-bis(methyloxy)quinolin-4-yl]oxy]phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

IT 1140909-48-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(method for treating osteoporosis)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

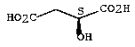
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

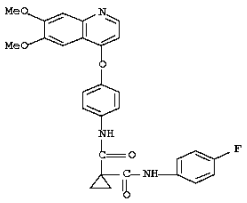
Absolute stereochemistry. Rotation (-).



IT 1365530-43-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method for treating osteoporosis)
RN 1365530-43-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2R)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

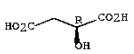
CRN 849217-68-1
CMF C28 H24 F N3 O5



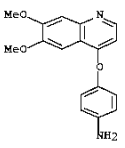
CM 2

CRN 636-61-3
CMF C4 H6 O5

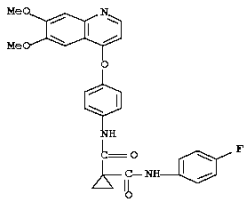
Absolute stereochemistry. Rotation (+).



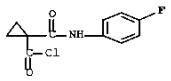
IT 190728-25-7P 849217-68-1P 1219937-98-0P,
1-(4-Fluorophenylcarbamoyl)-cyclopropanecarbonyl chloride
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(method for treating osteoporosis)
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



RN 1219937-98-0 CAPLUS
CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 25 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2012:1630842 CAPLUS Full-text
DOCUMENT NUMBER: 157:699601
TITLE: Method of treating cancer and bone cancer pain
INVENTOR(S): Schwab, Gisela; Aftab, Dana T.
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 52pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2012151326	A1	20121108	WO 2012-US36191	20120502

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP,

KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

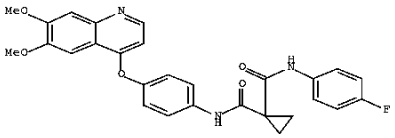
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CA 2834778	A1	20121108	CA 2012-2834778		20120502
AR 86242	A1	20131127	AR 2012-101544		20120502
AU 2012250759	A1	20131128	AU 2012-250759		20120502
AU 2012250759	B2	20170615			
IL 229094	A	20131231	IL 2012-229094		20120502
KR 2014025496	A	20140304	KR 2013-7031635		20120502
EP 2704717	A1	20140312	EP 2012-720754		20120502
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME					
CN 103717221	A	20140409	CN 2012-80026424		20120502
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BR 212013028314	U2	20151103	BR 2013-212013028314		20120502
NZ 617508	A	20160429	NZ 2012-617508		20120502
MX 2013012695	A	20140327	MX 2013-12695		20131030
ZA 2013008206	A	20140730	ZA 2013-8206		20131101
IN 2013KN03259	A	20140221	IN 2013-KN3259		20131105
US 20140179736	A1	20140626	US 2014-14115236		20140228
JP 2017105751	A	20170615	JP 2016-159543		20160816
PRIORITY APPLN. INFO.:			US 2011-61481682	P	20110502
			US 2011-61557366	P	20111108
			JP 2014-509417	A3	20120502
			WO 2012-US36191	W	20120502

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASREACT 157:699601; MARPAT 157:699601

GI



AB This invention is directed to the treatment of cancer, particularly lung cancer, breast cancer, melanoma, renal cell carcinoma, thyroid cancer that has metastasized to the bone. The invention is also directed to a method for treating bone cancer pain in an individual in need of such treatment comprising administering to the individual an effective amount of a compound of Formula I.

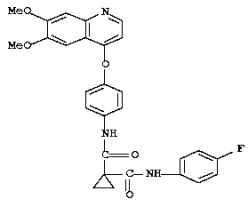
IT 849217-68-1P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(method of treating cancer and bone cancer pain)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



IT 1140909-48-3P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(method of treating cancer and bone cancer pain)

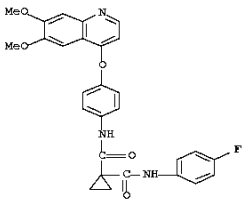
RN 1140909-48-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

CRN 849217-68-1

CMF C28 H24 F N3 O5

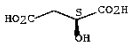


CM 2

CRN 97-67-6

CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



IT 1365530-43-3

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(method of treating cancer and bone cancer pain)

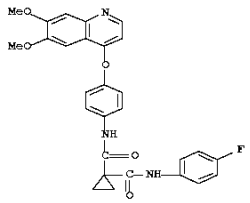
RN 1365530-43-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2R)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

CRN 849217-68-1

CMF C28 H24 F N3 O5

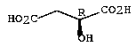


CM 2

CRN 636-61-3

CMF C4 H6 O5

Absolute stereochemistry. Rotation (+).



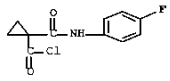
IT 1219937-98-0P, 1-(4-Fluorophenylcarbamoyl)cyclopropanecarbonyl chloride

RL: PRPH (Prophetic); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(method of treating cancer and bone cancer pain)

RN 1219937-98-0 CAPLUS

CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)



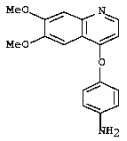
IT 190728-25-7P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(method of treating cancer and bone cancer pain)

RN 190728-25-7 CAPLUS

CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)

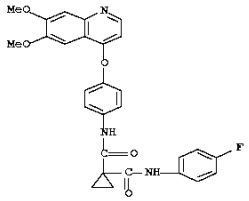


OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 26 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2012:1450760 CAPLUS Full-text
DOCUMENT NUMBER: 157:567006
TITLE: Method of treating cancer
INVENTOR(S): Aftab, Dana T.; Schimmoller, Frauke
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 17pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20120252840	A1	20121004	US 2012-13438964	20120404
US 20150196545	A1	20150716	US 2015-14668312	20150325
US 20160051532	A1	20160225	US 2015-14933801	20151105
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			US 2012-13438964 A1	20120404
			US 2015-14668312 A1	20150325

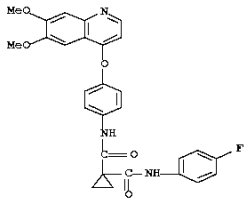
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 157:567006
AB This invention is directed to the treatment of cancer, particularly ocular melanoma, with a dual inhibitor of MET and VEGF such as Compound 1.
IT 849217-68-1P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(method of treating cancer)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



IT 1140909-48-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(method of treating cancer)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

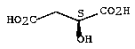
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

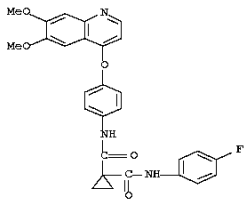
Absolute stereochemistry. Rotation (-).



IT 1365530-43-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method of treating cancer)
RN 1365530-43-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2R)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

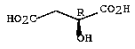
CRN 849217-68-1
CMF C28 H24 F N3 O5



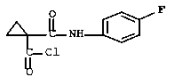
CM 2

CRN 636-61-3
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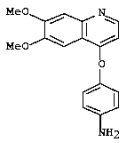
Absolute stereochemistry. Rotation (+).



IT 1219937-98-0P, 1-(4-Fluorophenylcarbamoyl)cyclopropanecarbonyl chloride
RL: PRPH (Prophetic); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(method of treating cancer)
RN 1219937-98-0 CAPLUS
CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)



IT 190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(method of treating cancer)
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L10 ANSWER 27 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2012:1201570 CAPLUS Full-text
DOCUMENT NUMBER: 157:382704
TITLE: Processes for preparing quinoline compounds and pharmaceutical compositions containing such compounds
INVENTOR(S): Wilson, Jo Ann
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 49pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2012109510	A1	20120816	WO 2012-US24591	20120210
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG,				

ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

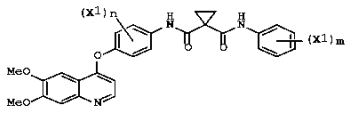
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

CA 2826751	A1	20120816	CA 2012-2826751		20120210
AU 2012214322	A1	20130829	AU 2012-214322		20120210
AU 2012214322	B2	20170427			
AR 85155	A1	20130911	AR 2012-100446		20120210
IL 227848	A	20130930	IL 2012-227848		20120210
CN 103459373	A	20131218	CN 2012-80017723		20120210
EP 2673262	A1	20131218	EP 2012-704492		20120210
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME					
JP 2014505109	T	20140227	JP 2013-553580		20120210
KR 2014044782	A	20140415	KR 2013-7023174		20120210
NZ 614130	A	20151030	NZ 2012-614130		20120210
NZ 712808	A	20170331	NZ 2012-712808		20120210
MX 2013009116	A	20140131	MX 2013-9116		20130807
ZA 2013006072	A	20140430	ZA 2013-6072		20130813
IN 2013KN02666	A	20140103	IN 2013-KN2666		20130903
US 20140200242	A1	20140717	US 2014-13984559		20140320
US 9717720	B2	20170801			
JP 2016188216	A	20161104	JP 2016-94411		20160510
US 20170057921	A1	20170302	US 2016-15348716		20161110
AU 2017204877	A1	20170803	AU 2017-204877		20170714
PRIORITY APPLN. INFO.:			US 2011-61441520	P	20110210
			US 2011-61441527	P	20110210
			AU 2012-214322	A3	20120210
			JP 2013-553580	A3	20120210
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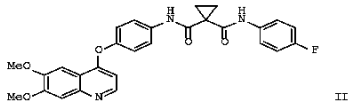
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASREACT 157:382704; MARPAT 157:382704

GI



I



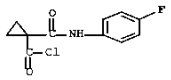
II

AB The invention is directed to processes for prepg. quinoline compds. of formula I wherein X1 is H, Br, Cl and F; X2 is H, Br, Cl and F; n is 1-2 and m is 1-2; and pharmaceutically acceptable salts thereof. Example compound II L-malate was prepared by chlorination of 6,7-dimethoxyquinolin-4-ol followed by etherification of 4-chloro-6,7-dimethoxyquinoline with 4-aminophenol; the resulting 4-(6,7-dimethoxyquinolin-4-yloxy)phenylamine underwent acylation with 1-[(4-fluorophenyl)carbamoyl]cyclopropanecarbonyl chloride to give compound II, which underwent addition of L-malic acid to give the desired product.

IT 1219937-98-0P, 1-[(4-Fluorophenyl)carbamoyl]cyclopropanecarbonyl chloride
RL: IMF (Industrial manufacture); PRPH (Prophetic); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(process for preparing quinoline derivs. and pharmaceutical compns. thereof)

RN 1219937-98-0 CAPLUS

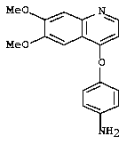
CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)



IT 190728-25-7P, [4-[(6,7-Dimethoxyquinolin-4-yl)oxy]phenyl]amine
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparing quinoline derivs. and pharmaceutical compns. thereof)

RN 190728-25-7 CAPLUS

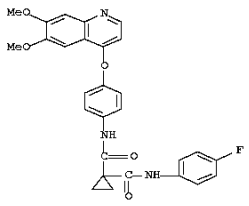
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



IT 849217-68-1P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(process for preparing quinoline derivs. and pharmaceutical compns. thereof)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



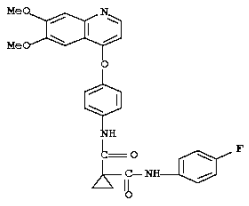
IT 1140909-48-3P
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(process for preparing quinoline derivs. and pharmaceutical compns. thereof)

RN 1140909-48-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

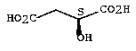
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

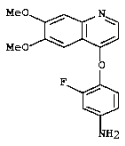
Absolute stereochemistry. Rotation (-).



IT 347161-74-4P, [4-[(6,7-Dimethoxyquinolin-4-yl)oxy]-3-fluorophenyl]amine
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparing quinoline derivs. and pharmaceutical compns. thereof)

RN 347161-74-4 CAPLUS

CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]-3-fluoro- (CA INDEX NAME)



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

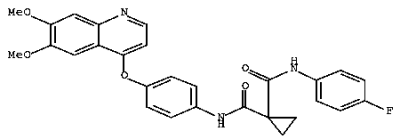
L10 ANSWER 28 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2012:495814 CAPLUS Full-text
DOCUMENT NUMBER: 156:469436
TITLE: Dual inhibitors of Met and VEGF for the treatment of castration- resistant prostate cancer and osteoblastic bone metastases
INVENTOR(S): Smith, David; Hussain, Maha
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 47pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2012044572	A1	20120405	WO 2011-US53233	20110926
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
CA 2812750	A1	20120405	CA 2011-2812750	20110926
AU 2011307304	A1	20130502	AU 2011-307304	20110926
AU 2011307304	B2	20160414		
IL 225507	A	20130530	IL 2011-225507	20110926
EP 2621481	A1	20130807	EP 2011-764655	20110926
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
JP 2013537916	T	20131007	JP 2013-530386	20110926
JP 6158705	B2	20170705		
CN 103402505	A	20131120	CN 2011-80056580	20110926
KR 2014025304	A	20140304	KR 2013-7010372	20110926
NZ 707930	A	20160930	NZ 2011-707930	20110926
EA 27476	B1	20170731	EA 2013-90465	20110926
MX 2013003594	A	20130801	MX 2013-3594	20130327
ZA 2013002422	A	20131223	ZA 2013-2422	20130404
IN 2013KN00998	A	20130906	IN 2013-KN998	20130409
US 20140057943	A1	20140227	US 2013-13876290	20131105
US 20160220554	A1	20160804	US 2015-14843480	20150902
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JP 2017149714	A	20170831	JP 2017-36322	20170228

PRIORITY APPLN. INFO.:

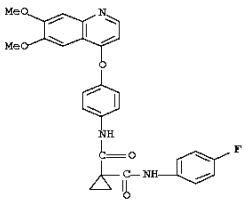
US 2010-61386959	P	20100927
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AU 2011-307304	A3	20110926
JP 2013-530386	A3	20110926
NZ 2011-609212	A3	20110926
WO 2011-US53233	W	20110926
US 2013-13876290	B1	20131105

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 156:469436; MARPAT 156:469436
GI



AB This invention is directed to the treatment of cancer, particularly castration-resistant prostate cancer and osteoblastic bone metastases, with a dual inhibitor of MET and VEGF.

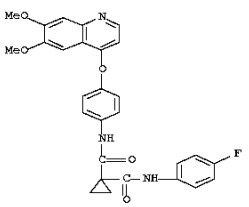
IT 849217-68-1P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(dual inhibitors of Met and VEGF for treatment of castration resistant prostate cancer and osteoblastic bone metastases)
RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



IT 1140909-48-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(dual inhibitors of Met and VEGF for treatment of castration resistant prostate cancer and osteoblastic bone metastases)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

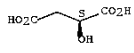
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

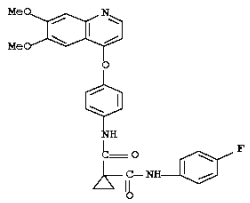
Absolute stereochemistry. Rotation (-).



IT 1365530-43-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dual inhibitors of Met and VEGF for treatment of castration resistant prostate cancer and osteoblastic bone metastases)
RN 1365530-43-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2R)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

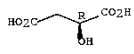
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

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CMF C4 H6 O5

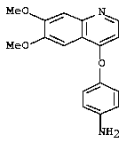
Absolute stereochemistry. Rotation (+).



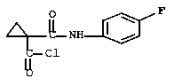
IT 190728-25-7P, 4-(6,7-Dimethoxyquinolin-4-yloxy)phenylamine

1219937-98-0P, 1-(4-Fluorophenylcarbamoyl)cyclopropanecarbonyl chloride
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(dual inhibitors of Met and VEGF for treatment of castration resistant prostate cancer and osteoblastic bone metastases)

RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



RN 1219937-98-0 CAPLUS
CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)



OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 29 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2012:495788 CAPLUS Full-text
DOCUMENT NUMBER: 156:469435
TITLE: Dual inhibitors of Met and VEGF for the treatment of castration resistant prostate cancer and osteoblastic bone metastases
INVENTOR(S): Smith, David; Hussain, Maha
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 70pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2012044577	A1	20120405	WO 2011-US53245	20110926
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
CA 2812744	A1	20120405	CA 2011-2812744	20110926
AU 2011307309	A1	20130502	AU 2011-307309	20110926
EP 2621483	A1	20130807	EP 2011-764657	20110926
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR				
JP 2013537918	T	20131007	JP 2013-530392	20110926
CN 103391773	A	20131113	CN 2011-80056999	20110926
US 20140057908	A1	20140227	US 2013-13876306	20131108

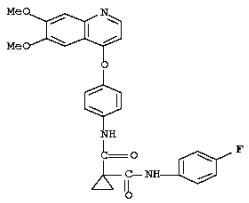
PRIORITY APPLN. INFO.:

US 2010-61386971	P	20100927
US 2010-61386983	P	20100927
US 2010-61386993	P	20100927
WO 2011-US53245	W	20110926

OTHER SOURCE(S): CASREACT 156:469435; MARPAT 156:469435
AB This invention discloses compds. directed at the treatment of cancer, particularly castration- resistant prostate cancer and osteoblastic bone metastases, with a dual inhibitor of MET and VEGF.
IT 1140909-48-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(dual inhibitors of Met and VEGF for treatment of castration resistant prostate cancer and osteoblastic bone metastases)
RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

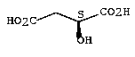
CRN 849217-68-1
CMF C28 H24 F N3 O5



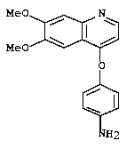
CM 2

CRN 97-67-6
CMF C4 H6 O5

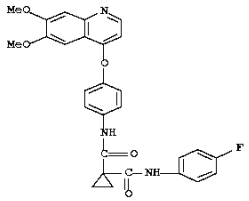
Absolute stereochemistry. Rotation (-).



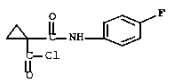
IT 190728-25-7P, 4-(6,7-Dimethoxyquinolin-4-yloxy)phenylamine
849217-68-1P 1219937-98-0P,
1-(4-Fluorophenylcarbamoyl)cyclopropanecarbonyl chloride
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(dual inhibitors of Met and VEGF for treatment of castration resistant prostate cancer and osteoblastic bone metastases)
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



RN 849217-68-1 CAPLUS
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



RN 1219937-98-0 CAPLUS
CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)

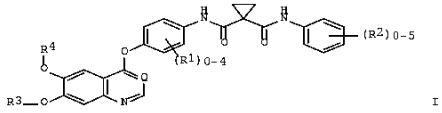


OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 30 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2012:425741 CAPLUS Full-text
DOCUMENT NUMBER: 156:412018
TITLE: Methods of using C-met modulators as Anticancer agents
INVENTOR(S): Bannen, Lynne Canne; Chan, Diva Sze-Ming; Forsyth, Timothy Patrick; Khoury, Richard George; Leahy, James William; Mac, Morrison B.; Mann, Larry W.; Nuss, John M.; Parks, Jason Jevious; Wang, Yong; Xu, Wei; Simeone, Diane
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 25pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20120070368	A1	20120322	US 2011-13087094	20110414

US 20150202196 A1 20150723 US 2014-14518733 20141020
PRIORITY APPLN. INFO.: US 2010-61325095 P 20100416
US 2011-13087094 B1 20110414
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 156:412018; MARPAT 156:412018
GI



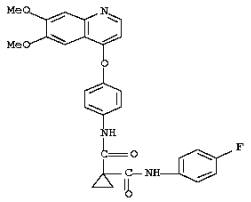
I

AB Disclosed are methods of treating cancer by administering a compd. of Formula I (wherein R1, R2 = independently, halo; R3, R4 = independently, (C1-C6)-alkyl; Q = CH, N) in combination with gemcitabine (GEM).

IT 849217-68-1P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(c-met modulators as antitumor agents)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



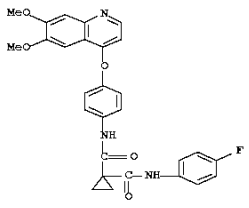
IT 1365530-43-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(c-met modulators as antitumor agents)

RN 1365530-43-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2R)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

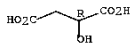
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 636-61-3
CMF C4 H6 O5

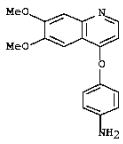
Absolute stereochemistry. Rotation (+).



IT 190728-25-7P, 4-(6,7-Dimethoxyquinolin-4-yloxy)phenylamine
1219937-98-0P, 1-(4-Fluorophenylcarbamoyl)cyclopropanecarbonyl chloride
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(c-met modulators as antitumor agents)

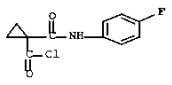
RN 190728-25-7 CAPLUS

CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



RN 1219937-98-0 CAPLUS

CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L10 ANSWER 31 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2012:90800 CAPLUS Full-text
DOCUMENT NUMBER: 156:186804
TITLE: C-met modulator pharmaceutical compositions comprising N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide
INVENTOR(S): Wilson, Jo Ann
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 40pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2012009722	A1	20120119	WO 2011-US44378	20110718

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

CA 2805645	A1	20120119	CA 2011-2805645	20110718
AR 82252	A1	20121121	AR 2011-102584	20110718
AU 2011278950	A1	20130307	AU 2011-278950	20110718
AU 2011278950	B2	20160721		
IL 224189	A	20130324	IL 2011-224189	20110718
EP 2593090	A1	20130522	EP 2011-740764	20110718
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
CN 103221035	A	20130724	CN 2011-80044602	20110718
JP 2013531045	T	20130801	JP 2013-519870	20110718
JP 5934204	B2	20160615		
KR 2013137586	A	20131217	KR 2013-7003043	20110718
NZ 607118	A	20150529	NZ 2011-607118	20110718
TW I516477	B	20160111	TW 2011-125336	20110718
SG 10201609324	A1	20170127	SG 2016-10201609324	20110718
CN 106420743	A	20170222	CN 2016-10157218	20110718
IN 2013KN00112	A	20130705	IN 2013-KN112	20130114
MX 2013000567	A	20130501	MX 2013-567	20130115
ZA 2013000458	A	20130925	ZA 2013-458	20130117
US 20130337015	A1	20131219	US 2013-13810537	20130826
US 9724342	B2	20170808		
JP 2016188215	A	20161104	JP 2016-93433	20160506
AU 2016247044	A1	20161103	AU 2016-247044	20161018
US 20170143689	A1	20170525	US 2017-15426804	20170207
US 20170266178	A1	20170921	US 2017-15612703	20170602

PRIORITY APPLN. INFO.:

US 2010-61365253	P	20100716
US 2010-61370843	P	20100805
AU 2011-278950	A3	20110718
CN 2011-80044602	A3	20110718
JP 2013-519870	A3	20110718
WO 2011-US44378	W	20110718
US 2013-13810537	A3	20130826
US 2017-15426804	A3	20170207

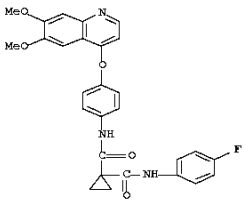
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 156:186804

AB Pharmaceutical compns. and unit dosage forms comprising N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (I) are disclosed. Thus, 6,7-dimethoxyquinolin-4-ol was converted to 4-chloro-6,7-dimethoxyquinoline followed by reaction with 4-aminphenol to give 4-(6,7-dimethoxy-quinolin-4-yloxy)-phenylamine. This was further allowed to react with 1-(4-fluorophenylcarbamoyl)cyclopropanecarbonyl chloride to give I. A tablet composition comprised 31.68% along with excipients such as microcryst. cellulose 38.85, lactose, HPC, and Croscarmellose sodium.

IT 849217-68-1P 1140909-48-3P, Cabozantinib S-malate
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(C-met modulator pharmaceutical compns. comprising dimethoxyquinolinyloxyphenyl(fluorophenyl)cyclopropanedicarboxamide)

RN 849217-68-1 CAPLUS

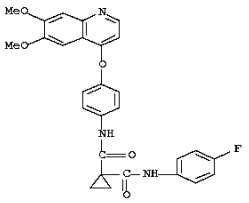
CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



RN 1140909-48-3 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

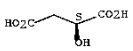
CRN 849217-68-1
CMF C28 H24 F N3 O5

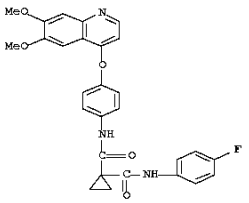


CM 2

CRN 97-67-6
CMF C4 H6 O5

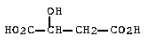
Absolute stereochemistry. Rotation (-).





CM 2

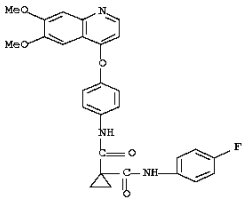
CRN 6915-15-7
CMF C4 H6 O5



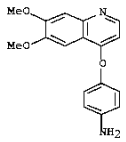
RN 1235470-38-8 CAPLUS
CN Butanedioic acid, 2-hydroxy-, (2R)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:?) (CA INDEX NAME)

CM 1

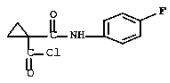
CRN 849217-68-1
CMF C28 H24 F N3 O5



IT 190728-25-7P 1219937-98-0P,
1-(4-Fluorophenylcarbamoylcyclopropanecarbonyl chloride
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(C-met modulator pharmaceutical compns. comprising dimethoxyquinolinyloxyphenyl(fluorophenyl)cyclopropanedicarboxamide)
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



RN 1219937-98-0 CAPLUS
CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)



IT 1235470-36-6 1235470-38-8
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(C-met modulator pharmaceutical compns. comprising dimethoxyquinolinyloxyphenyl(fluorophenyl)cyclopropanedicarboxamide)
RN 1235470-36-6 CAPLUS
CN Butanedioic acid, 2-hydroxy-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:?) (CA INDEX NAME)

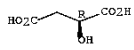
CM 1

CRN 849217-68-1
CMF C28 H24 F N3 O5

CM 2

CRN 636-61-3
CMF C4 H6 O5

Absolute stereochemistry. Rotation (+).



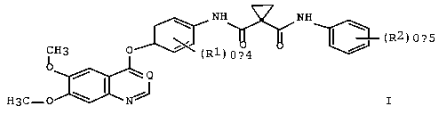
OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 32 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2011:174316 CAPLUS Full-text
DOCUMENT NUMBER: 154:225400
TITLE: C-met modulators as antitumor agents
INVENTOR(S): Aftab, Dana T.; Mueller, Thomas; Weitzman, Aaron; Holland, Jaymes
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 61pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2011017639	A1	20110210	WO 2010-US44749	20100806
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
CA 2770100	A1	20110210	CA 2010-2770100	20100806
AU 2010279234	A1	20120301	AU 2010-279234	20100806
AU 2010279234	B2	20161020		
KR 20120059540	A	20120608	KR 2012-7006111	20100806
KR 1761380	B1	20170725		
EP 2461810	A1	20120613	EP 2010-742985	20100806
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CN 102647985	A	20120822	CN 2010-80045677		20100806
JP 2013501731	T	20130117	JP 2012-523982		20100806
JP 5933435	B2	20160608			
IL 217889	A	20130228	IL 2010-217889		20100806
NZ 598055	A	20140530	NZ 2010-598055		20100806
IL 238849	A	20150630	IL 2010-238849		20100806
NZ 624643	A	20151127	NZ 2010-624643		20100806
EA 24563	B1	20160930	EA 2012-70247		20100806
KR 2017087966	A	20170731	KR 2017-7020220		20100806
IN 2012MN00278	A	20120824	IN 2012-MN278		20120203
ZA 2012000842	A	20121128	ZA 2012-842		20120203
MX 2012001654	A	20120314	MX 2012-1654		20120207
US 20120282179	A1	20121108	US 2012-13389266		20120712
US 20160000772	A1	20160107	US 2015-14699683		20150429
JP 2016106141	A	20160616	JP 2016-45205		20160309
AU 2017200269	A1	20170202	AU 2017-200269		20170116
JP 2017082007	A	20170518	JP 2017-22961		20170210
PRIORITY APPLN. INFO.:			US 2009-61232382	P	20090807
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			IL 2010-217889	A3	20100806
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			KR 2012-7006111	A3	20100806
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			WO 2010-US44749	W	20100806
			US 2012-13389266	B1	20120712
			JP 2016-45205	A3	20160309

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 154:225400; MARPAT 154:225400
GI



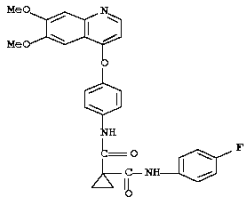
I

AB Methods of treating cancer by administering a compd. of Formula I (wherein R1 = halo; R2 = halo; Q = CH, N; n = 0-4; m = 0-5) or a pharmaceutically acceptable salt or solvate thereof, in combination with other cancer treatments are described.

IT 849217-68-1P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(methods of using c-met modulators)

RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



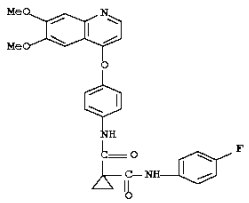
IT 1140909-48-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(methods of using c-met modulators)

RN 1140909-48-3 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) (CA INDEX NAME)

CM 1

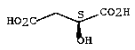
CRN 849217-68-1
CMF C28 H24 F N3 O5



CM 2

CRN 97-67-6
CMF C4 H6 O5

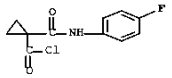
Absolute stereochemistry. Rotation (-).



IT 1219937-98-0P
RL: PRPH (Prophetic); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(methods of using c-met modulators)

RN 1219937-98-0 CAPLUS

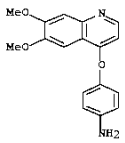
CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)



IT 190728-25-7P, 4-(6,7-Dimethoxyquinolin-4-yloxy)phenylamine
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(methods of using c-met modulators)

RN 190728-25-7 CAPLUS

CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 33 OF 33 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2010:912816 CAPLUS Full-text
DOCUMENT NUMBER: 153:204211
TITLE: Preparation of malate salts of N-[4-[[6,7-bis(methyloxy)quinolin-4-yl]oxy]phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and crystalline forms thereof for the treatment of cancer.
INVENTOR(S): St Clair Brown, Adrian; Lamb, Peter; Gallagher, William P.
PATENT ASSIGNEE(S): Exelixis, Inc., USA; Bristol-Meyers Squibb Company
SOURCE: PCT Int. Appl., 72pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2010083414	A1	20100722	WO 2010-US21194	20100115
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
CA 2758030	A1	20100722	CA 2010-2758030	20100115
AR 75025	A1	20110302	AR 2010-100098	20100115
AU 2010204619	A1	20110901	AU 2010-204619	20100115
AU 2010204619	B2	20160811		
EP 2387563	A1	20111123	EP 2010-701175	20100115
EP 2387563	B1	20130306		
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KR 2012013301	A	20120214	KR 2011-7018924	20100115
KR 1733773	B1	20170510		
CN 102388024	A	20120321	CN 2010-80012656	20100115
JP 2012515220	T	20120705	JP 2011-546390	20100115
JP 5677318	B2	20150225		
IL 214086	A	20130131	IL 2010-214086	20100115
PT 2387563	E	20130325	PT 2010-701175	20100115
ES 2402524	T3	20130506	ES 2010-701175	20100115
NZ 594594	A	20131129	NZ 2010-594594	20100115
EA 19959	B1	20140730	EA 2011-70941	20100115
TW I447108	B	20140801	TW 2010-101140	20100115
IL 234097	A	20140930	IL 2010-234097	20100115
NZ 618004	A	20150626	NZ 2010-618004	20100115
TW I511956	B	20151211	TW 2014-115685	20100115
CN 106083714	A	20161109	CN 2016-10140984	20100115
TW I577664	B	20170411	TW 2015-129563	20100115
EA 26425	B1	20170428	EA 2014-110	20100115
KR 2017052702	A	20170512	KR 2017-7011913	20100115
ZA 2011005167	A	20120328	ZA 2011-5167	20110713
MX 2011007620	A	20111104	MX 2011-7620	20110715
IN 2011KN03402	A	20121102	IN 2011-KN3402	20110811

US 8877776	B2	20141104	US 2011-13145054		20111020
US 20120035212	A1	20120209			
HK 1164305	A1	20131108	HK 2012-104893		20120518
AU 2013203780	A1	20130502	AU 2013-203780		20130411
AU 2013203780	B2	20160901			
JP 2015096543	A	20150521	JP 2014-264071		20141226
JP 5980894	B2	20160831			
JP 2017014232	A	20170119	JP 2016-146934		20160727
AU 2016262732	A1	20161215	AU 2016-262732		20161124
US 20170275251	A1	20170928	US 2017-15621527		20170613
PRIORITY APPLN. INFO.:			US 2009-61145421	P	20090116
			AU 2010-204619	A3	20100115
			CN 2010-80012656	A3	20100115
			IL 2010-214086	A3	20100115
			JP 2011-546390	A3	20100115
			KR 2011-7018924	A3	20100115
			NZ 2010-594594	A3	20100115
			WO 2010-US21194	W	20100115
			US 2011-13145054	A3	20111020
			AU 2013-203780	A3	20130411
			US 2014-14340871	A1	20140725
			JP 2014-264071	A3	20141226
			US 2017-15617725	A1	20170608
			US 2017-15618593	A1	20170609

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASREACT 153:204211

AB N-[4-[[6,7-bis(methyloxy)quinolin-4-yl]oxy]phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide malate salts were prepared Thus, 1-(4-fluorophenylcarbamoyl)cyclopropanecarboxylic acid (preparation given) was stirred with (COCl)2 in THF/DMF at ≤30° and the mixture was added to 4-(6,7-dimethoxyquinolin-4-yloxy)phenylamine (preparation given) and K2CO3 in THF/H2O followed by addition of H2O and stirring for 10 h to give N-[4-[[6,7-bis(methyloxy)quinolin-4-yl]oxy]phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. The latter in EtOH was treated with malic acid in H2O followed by addition of C, thiol silica, heating to 78°, and addition of H2O followed by filtration, addition of Me2CHOH, cooling, and filtration to give N-[4-[[6,7-bis(methyloxy)quinolin-4-yl]oxy]phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide malate.

IT 1235470-36-6P

RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of malate salts of bismethoxyquinolinyloxyphenylfluorophenylcyclopropanedicarboxamide and crystalline forms thereof for the treatment of cancer)

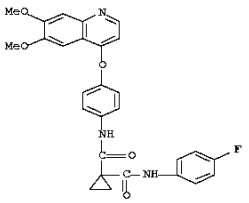
RN 1235470-36-6 CAPLUS

CN Butanedioic acid, 2-hydroxy-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:?) (CA INDEX NAME)

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CRN 849217-68-1

CMF C28 H24 F N3 O5

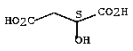


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CRN 97-67-6

CMF C4 H6 O5

Absolute stereochemistry. Rotation (-).



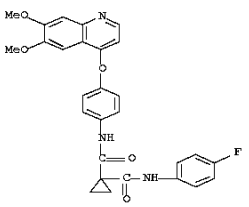
RN 1235470-38-8 CAPLUS

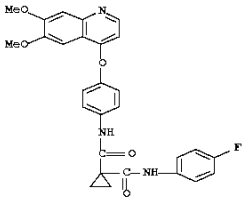
CN Butanedioic acid, 2-hydroxy-, (2R)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:?) (CA INDEX NAME)

CM 1

CRN 849217-68-1

CMF C28 H24 F N3 O5

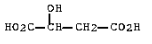




CM 2

CRN 6915-15-7

CMF C4 H6 O5



IT 1235470-37-7P 1235470-38-8P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of malate salts of bismethoxyquinolinyloxyphenylfluorophenylcyclopropanedicarboxamide and crystalline forms thereof for the treatment of cancer)

RN 1235470-37-7 CAPLUS

CN Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:?) (CA INDEX NAME)

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CRN 849217-68-1

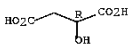
CMF C28 H24 F N3 O5

CM 2

CRN 636-61-3

CMF C4 H6 O5

Absolute stereochemistry. Rotation (+).



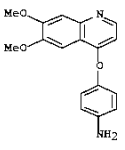
IT 190728-25-7P, 4-(6,7-Dimethoxyquinolin-4-yloxy)phenylamine 849217-68-1P 1219937-98-0P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of malate salts of bismethoxyquinolinyloxyphenylfluorophenylcyclopropanedicarboxamide and crystalline forms thereof for the treatment of cancer)

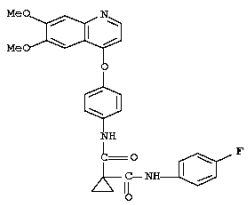
RN 190728-25-7 CAPLUS

CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)

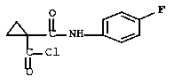


RN 849217-68-1 CAPLUS

CN 1,1-Cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- (CA INDEX NAME)



RN 1219937-98-0 CAPLUS
CN Cyclopropanecarbonyl chloride, 1-[[(4-fluorophenyl)amino]carbonyl]- (CA INDEX NAME)



OS.CITING REF COUNT: 9 THERE ARE 9 CAPLUS RECORDS THAT CITE THIS RECORD (9 CITINGS)
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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FILE 'REGISTRY' ENTERED AT 15:09:03 ON 12 OCT 2017
L1 STRUCTURE UPLOADED
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L2 3 SEA FILE=REGISTRY SSS SAM L1
L3 50 SEA FILE=REGISTRY SSS FUL L1
L4 STRUCTURE UPLOADED
D
L5 0 SEA FILE=REGISTRY SSS SAM L4
L6 12 SEA FILE=REGISTRY SSS FUL L4
L7 STRUCTURE UPLOADED
D
L8 0 SEA FILE=REGISTRY SSS SAM L7
L9 12 SEA FILE=REGISTRY SSS FUL L7

FILE 'CAPLUS' ENTERED AT 15:12:15 ON 12 OCT 2017
L10 33 SEA FILE=CAPLUS SPE=ON ABB=ON PLU=ON L3 AND L6 AND L9
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COST IN U.S. DOLLARS SINCE FILE ENTRY 285.28 TOTAL SESSION 1148.82

STN INTERNATIONAL LOGOFF AT 15:13:21 ON 12 OCT 2017

Connecting via Winsock to STN at pto-stn on port 23

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PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

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NEWS 3 JAN 11 PatentPak Now available to STN Express 8.6 and STN on the Web customers
NEWS 4 JAN 11 CAplus Family of Files Updated with New Data to Support PatentPak in STN
NEWS 5 JAN 14 The Derwent World Patents Index (DWPI): Latest Manual Code Revision is now live
NEWS 6 MAR 23 CHEMLIST Content Expanded with the Addition of Information from Vermont
NEWS 7 JUL 21 Non-conventional Patent Families for Chinese Dual Filings in INPADOC on STN
NEWS 8 NOV 10 Latest New STN Release Extends Export to Excel Support to 28 More Databases and Includes New Structure Search Enhancements.
NEWS 9 NOV 22 Critical information for users of Embase on STN
NEWS 10 FEB 2 Data Quality Improved in CNFULL and FRFULL
NEWS 11 FEB 10 The 2017 version of MEDLINE now available on STN
NEWS 12 MAR 29 A Fresh Look for the ADIS Databases on STN
NEWS 13 MAR 29 New Version of Dissertation Abstracts Database Launched on STN
NEWS 14 APR 19 Additional Medline Unique Records Being Added to Embase
NEWS 15 APR 20 Latest Release of New STN Enhances Search History and Expands Database Coverage
NEWS 16 MAY 12 INPADOC/INPAFAM: New Chinese Legal Status Codes
NEWS 17 JUL 13 Now available, STNext(TM) elevates your classic STN experience
NEWS 18 JUL 26 Embase(TM) Updated to Include Author Identifiers and Links to Retractions and Errata
NEWS 19 AUG 30 Log into STNext(TM) for a chance to win!
NEWS 20 SEP 13 Taiwanese Chemical Substance Inventory Now Included in CHEMLIST
NEWS 21 SEP 15 New Emtree Thesaurus Version in Embase Expands Cell Line

Names

NEWS EXPRESS 06 JUN 2017 CURRENT WINDOWS VERSION IS V8.6,
AND CURRENT DISCOVER FILE IS DATED 06 JUN 2017.

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FILE 'HOME' ENTERED AT 17:25:32 ON 12 OCT 2017

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COST IN U.S. DOLLARS SINCE FILE ENTRY 0.29 TOTAL SESSION 0.29

FILE 'REGISTRY' ENTERED AT 17:26:10 ON 12 OCT 2017
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TSCA INFORMATION NOW CURRENT THROUGH MAY 22, 2017

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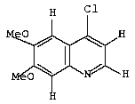
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=>
Uploading C:\Users\trozof\Documents\STN Express 8.4\Queries\15348716 Formula f(1) (10.12.17)

L1 STRUCTURE UPLOADED

=> d
L1 HAS NO ANSWERS
L1 STR



Structure attributes must be viewed using the Structure Drawing program.

=> s l1 sss sam
SAMPLE SEARCH INITIATED 17:26:39 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 78 TO ITERATE

100.0% PROCESSED 78 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 1031 TO 2089
PROJECTED ANSWERS: 0 TO 0

L2 0 SEA SSS SAM L1

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FULL SCREEN SEARCH COMPLETED - 1233 TO ITERATE

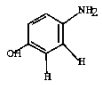
100.0% PROCESSED 1233 ITERATIONS 2 ANSWERS
SEARCH TIME: 00.00.01

L3 2 SEA SSS FUL L1

=>
Uploading C:\Users\trozof\Documents\STN Express 8.4\Queries\15348716 Formula y(1) (10.12.17)

L4 STRUCTURE UPLOADED

=> d
L4 HAS NO ANSWERS
L4 STR



Structure attributes must be viewed using the Structure Drawing program.

=> s l4 sss sam
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SAMPLE SCREEN SEARCH COMPLETED - 228082 TO ITERATE

100.0% PROCESSED 228082 ITERATIONS 50 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 4533311 TO 4589969
PROJECTED ANSWERS: 10343 TO 13257

L5 50 SEA SSS SAM L4

=> s l4 sss full
FULL SEARCH INITIATED 17:27:05 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 4566834 TO ITERATE

100.0% PROCESSED 4566834 ITERATIONS 11320 ANSWERS
SEARCH TIME: 00.00.02

L6 11320 SEA SSS FUL L4

=> file caplus
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 574.54 574.83

FILE 'CAPLUS' ENTERED AT 17:27:09 ON 12 OCT 2017
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FILE COVERS 1907 - 12 Oct 2017 VOL 167 ISS 17
FILE LAST UPDATED: 11 Oct 2017 (20171011/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Dec 2015
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Dec 2015

CAplus includes complete International Patent Classification (IPC) reclassification data for the third quarter of 2017.

CAplus now includes the comprehensive Cooperative Patent Classification (CPC). See HELP CPC for details.

CAS Information Use Policies apply and are available at:

http://www.cas.org/legal/infopolicy

This file contains CAS Registry Numbers for easy and accurate substance identification.

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(FILE 'HOME' ENTERED AT 17:25:32 ON 12 OCT 2017)

FILE 'REGISTRY' ENTERED AT 17:26:10 ON 12 OCT 2017
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L3 2 S L1 SSS FULL
L4 STRUCTURE UPLOADED
L5 50 S L4 SSS SAM
L6 11320 S L4 SSS FULL

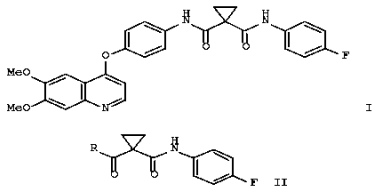
FILE 'CAPLUS' ENTERED AT 17:27:09 ON 12 OCT 2017

=> s l3 and l6
138 L3
30057 L6
L7 70 L3 AND L6

=> d ibib abs hitstr -70

L7 ANSWER 1 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2017:1102508 CAPLUS Full-text
DOCUMENT NUMBER: 167:278884
TITLE: Crystal structures of intermediates in a new synthesis of antitumor drug cabozantinib
AUTHOR(S): Laus, Gerhard; Schreiner, Erwin; Nerdinger, Sven; Kahlenberg, Volker; Wurst, Klaus; Vergeiner, Stefan; Schottenberger, Herwig
CORPORATE SOURCE: Faculty of Chemistry and Pharmacy, Leopold-Franzens University, Innsbruck, 6020, Austria
SOURCE: Heterocycles (2016), 93(1, Spec. Issue), 323-332
CODEN: HTCYAM; ISSN: 1881-0942
DIGITAL OBJECT ID: 10.3987/com-15-s(t)45
PUBLISHER: Japan Institute of Heterocyclic Chemistry
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
OTHER SOURCE(S): CASREACT 167:278884

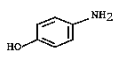
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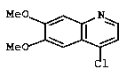
I

II

AB The heterocyclic antitumor drug cabozantinib (I) was synthesized by condensation of 4-(6,7-dimethoxyquinolin-4-yl-oxy)aniline and Me 1-(4-fluorophenylcarbamoyl)cyclopropanecarboxylate II [R = OMe] in the presence of two equivalent of sodium methoxide and azeotropic removal of methanol. In turn, the intermediate Me 1-(4-fluorophenylcarbamoyl)cyclopropanecarboxylate II [R = OMe] was prepared from 4-fluoroaniline and di-Me 1,1-cyclopropanedicarboxylate in the presence of one equivalent of sodium methoxide. Crystal structures of 6,7-dimethoxyquinolin-4(1H)-one, 4-(6,7-dimethoxyquinolin-4-yl-oxy)aniline and compds. II [R = OMe, 4-FC6H4NH] were determined
IT 123-30-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(crystal structures of intermediates in new synthesis of antitumor drug cabozantinib)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



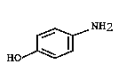
IT 35654-56-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(crystal structures of intermediates in new synthesis of antitumor drug cabozantinib)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



L7 ANSWER 2 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2017:720961 CAPLUS Full-text
DOCUMENT NUMBER: 167:5585
TITLE: Preparation method of Cabozantinib from diethyl malonate and 4-fluoroaniline
INVENTOR(S): Wang, Zhiguo; Song, Yanhong; Ma, Xiujuan; Tian, Beibei; Li, Shijiang; Li, Chao; Li, Tao; Zhang, Xin
PATENT ASSIGNEE(S): Shanghai Zaiqi Bio-Tech Co., Ltd., Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 10pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

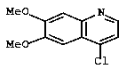
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 106632028	A	20170510	CN 2016-11199311	20161222
PRIORITY APPLN. INFO.:			CN 2016-11199311	20161222

AB The invention has simple operation, is environmentally friendly, the comprehensive yield is more than 50%, is obviously improved, greatly reduces the current medicine production cost, and is suitable for industrial scale production The method comprises: (1) reacting di-Et malonate and 4-fluoroaniline to obtain Et 3-(4-fluoro Ph amino)-3-oxopropionate; (2) hydrolysis of of Et 3-(4-fluoro Ph amino)-3-oxopropionate to obtain 3-(4-fluoro Ph amino)-3-oxopropionic acid; (3) reacting of 4-chloro-6,7-dimethoxy quinoline and 4-aminophenol to obtain 4-[(6,7-dimethoxy quinolin-4-yl)oxo] aniline; (4) reacting of 3-(4-fluoro Ph amino)-3-oxopropionic acid and 1-(3-dimethylamino propyl)-3-Et carbodiimide hydrochloride and 4-[(6,7-dimethoxy quinolin-4-yl)oxo] aniline to obtain N-(4-(6,7-dimethoxy quinolin-4-yl)oxophenyl)-N'-(4-fluorophenyl)malonamide; (5) reacting of N-(4-(6,7-dimethoxy quinolin-4-yl)oxophenyl)-N'-(4-fluorophenyl)malonamide and 1,2-dibromoethane to give Cabozantinib.
IT 123-30-8 35654-56-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of Cabozantinib from di-Et malonate and 4-fluoroaniline)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



RN 35654-56-9 CAPLUS

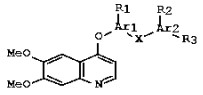
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



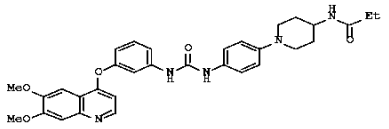
L7 ANSWER 3 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2017:531946 CAPLUS Full-text
DOCUMENT NUMBER: 166:419333
TITLE: Process for preparation of FLT3 kinase inhibitor and application
INVENTOR(S): Liu, Qingsong; Liu, Jing; Li, Binhua; Wang, Aoli; Wu, Hong; Chen, Cheng; Wang, Wenchao; Hu, Chen; Zhao, Zheng; Yu, Kailin; Wang, Beilei; Wang, Li
PATENT ASSIGNEE(S): Hefei Zhongke Precedo Biomedical Technology Co., Ltd., Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 92pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 106543143	A	20170329	CN 2015-10608850	20150922

PRIORITY APPLN. INFO.: CN 2015-10608850 20150922
OTHER SOURCE(S): CASREACT 166:419333; MARPAT 166:419333
GI

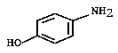


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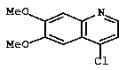


II

AB The invention relates to prepn. of FLT3 kinase inhibitor, comprising compound, its pharmaceutically acceptable salt, solvate, isomer, ester, acid, metabolite or prodrug. of formula I, wherein Ar1 and Ar2 are independently selected from aryl or heteroaryl; and R1 and R2 are independently selected from H, halogen, alkyl, etc. Compound II was prepared via multi step synthesis starting from. The synthesized compds. are applied in the prevention or treatment of cell proliferative diseases and/or FLT3- and c-Kit-related diseases, and in the inhibition of FLT3 kinase activity especially mutated FLT3/ITD kinase.
IT 123-30-8, 4-Aminophenol 35654-56-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of FLT3 kinase inhibitor and application)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

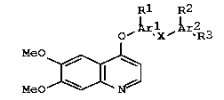


L7 ANSWER 4 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2017:518744 CAPLUS Full-text
DOCUMENT NUMBER: 166:384949
TITLE: Preparation of quinoline derivatives useful as FLT3 kinase inhibitors for the treatment of cancer
INVENTOR(S): Liu, Qingsong; Liu, Jing; Li, Binhua; Wang, Aoli; Wu, Hong; Chen, Cheng; Wang, Wenchao; Hu, Chen; Zhao, Zheng; Yu, Kailin; Wang, Beilei; Wang, Li
PATENT ASSIGNEE(S): Precedo Pharmaceuticals Co., Ltd., Peop. Rep. China
SOURCE: PCT Int. Appl., 115pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

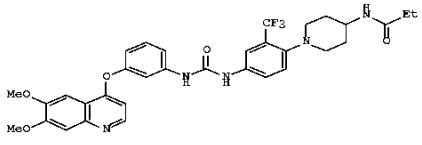
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2017049462	A1	20170330	WO 2015-CN90306	20150922

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MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM
PRIORITY APPLN. INFO.: WO 2015-CN90306 20150922
OTHER SOURCE(S): CASREACT 166:384949; MARPAT 166:384949
GI

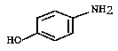


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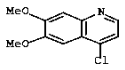


II

AB The invention relates to quinoline derivs. of formula I, method for their preparation and their use as FLT3 kinase inhibitors for the treatment of cell proliferative diseases and diseases related to FLT3 and c-Kit kinase. Compds. of formula I, wherein Ar1 and Ar2 are independently (hetero)aryl; X is NHCONH, NHCOCH2CONH, NH, etc.; R1 and R2 are independently H, halo and (halo)alkyl; R3 is piperazinyl, 4-(acylamino)piperidinyl, alkylsulfonylamino, etc., and their pharmaceutically acceptable salts, are claimed. Example compound II was prepared via a multistep procedure (procedure given). The invention compds. were evaluated for their FLT3 kinase and cKIT kinase inhibitory activity and anticancer activity. From the assay, it was determined that example compound II exhibited TC50 value of 0.055 μM and 0.258 μM towards FLT3 kinase and cKIT kinase resp.
IT 123-30-8 35654-56-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of quinoline derivs. useful as FLT3 kinase inhibitors for the treatment of cancer)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)

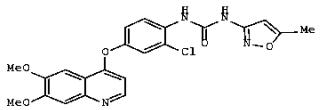


RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 5 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2017:230411 CAPLUS Full-text
DOCUMENT NUMBER: 166:327296
TITLE: A new and practical synthesis of tivozanib
AUTHOR(S): Zhu, Chunping; Mao, Yongjun; Wang, Han; Xu, Jingli
CORPORATE SOURCE: College of Chemistry and Chemical Engineering, Shanghai University of Engineering Science, Shanghai, 201620, Peop. Rep. China
SOURCE: Heterocycles (2016), 92(10), 1882-1887
CODEN: HTCYAM; ISSN: 1881-0942
DIGITAL OBJECT ID: 10.3987/COM-16-13555
PUBLISHER: Japan Institute of Heterocyclic Chemistry
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
OTHER SOURCE(S): CASREACT 166:327296
GI



I

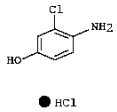
AB New and improved synthetic route of tivozanib (I) was described on a hectogram scale. Reduction cyclization process to prepare the key intermediate 6,7-dimethoxyquinolin-4-ol from the 3-(dimethylamino)-1-(2-nitrophenyl)prop-2-en-1-one compound at H2/Ni condition was adopted in good result. Com. available materials, simple reaction and operation were used, including nitration, condensation,

hydrogenation, chlorination and so on, to give the final product in 28.7% yield over six steps and 98.9% purity (HPLC).

IT 52671-64-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of tivozanib via dimethoxyquinolinol as key intermediate)

RN 52671-64-4 CAPLUS

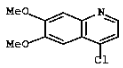
CN Phenol, 4-amino-3-chloro-, hydrochloride (1:1) (CA INDEX NAME)



IT 35654-56-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of tivozanib via dimethoxyquinolinol as key intermediate)

RN 35654-56-9 CAPLUS

CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



L7 ANSWER 6 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN

ACCESSION NUMBER: 2016:2078753 CAPLUS Full-text

TITLE: C-met modulator pharmaceutical compositions comprising N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide

INVENTOR(S): Wilson, Jo Ann

PATENT ASSIGNEE(S): Exelixis, Inc., USA

SOURCE: U.S. Pat. Appl. Publ., No pp. given
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20130337015	A1	20131219	US 2013-13810537	20130826
US 9724342	B2	20170808		
WO 2012009722	A1	20120119	WO 2011-US44378	20110718

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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2013-61808511 P 20130404
WO 2014-US33016 W 20140404

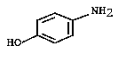
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB This invention relates to a dosage form of cabozantinib and a method of employing the dosage form to treat cancer.

IT 123-30-8, 4-Aminophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of cabozantinib and dosage forms for treatment of cancer)

RN 123-30-8 CAPLUS

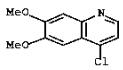
CN Phenol, 4-amino- (CA INDEX NAME)

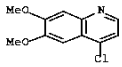


IT 35654-56-9P, 4-Chloro-6,7-dimethoxyquinoline
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of cabozantinib and dosage forms for treatment of cancer)

RN 35654-56-9 CAPLUS

CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

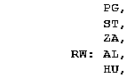




IT 35654-56-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(C-met modulator pharmaceutical compns. comprising dimethoxyquinolinyloxyphenyl(fluorophenyl)cyclopropanedicarboxamide)

RN 35654-56-9 CAPLUS

CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



L7 ANSWER 8 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN

ACCESSION NUMBER: 2016:2055777 CAPLUS Full-text

DOCUMENT NUMBER: 167:390609

TITLE: Method of treating cancer and bone cancer pain

INVENTOR(S): Schwab, Gisela; Aftab, Dana T.

PATENT ASSIGNEE(S): Exelixis, Inc., USA

SOURCE: U.S. Pat. Appl. Publ., No pp. given
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20140179736	A1	20140626	US 2014-14115236	20140228
WO 2012151326	A1	20121108	WO 2012-US36191	20120502

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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

JP 2017105751	A	20170615	JP 2016-159543	20160816

PRIORITY APPLN. INFO.:
US 2011-61481682 P 20110502
US 2011-61557366 P 20111108
WO 2012-US36191 W 20120502
JP 2014-509417 A3 20120502

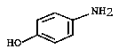
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB This invention is directed to the treatment of cancer, particularly lung cancer, breast cancer, melanoma, renal cell carcinoma, thyroid cancer that has metastasized to the bone. The invention is also directed to a method for treating bone cancer pain in an individual in need of such treatment comprising administering to the individual an effective amount of a compound of Formula I.

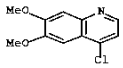
IT 123-30-8, 4-Aminophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(method of treating cancer and bone cancer pain)

RN 123-30-8 CAPLUS

CN Phenol, 4-amino- (CA INDEX NAME)



IT 35654-56-9P, 4-Chloro-6,7-dimethoxyquinoline
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(method of treating cancer and bone cancer pain)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



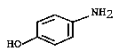
L7 ANSWER 9 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:2051291 CAPLUS Full-text
DOCUMENT NUMBER: 167:390605
TITLE: Method of treating cancer
INVENTOR(S): Aftab, Dana T.; Schimmoller, Frauke
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., No pp. given
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20140323522	A1	20141030	US 2014-14356927	20140508
WO 2013070890	A1	20130516	WO 2012-US64116	20121108

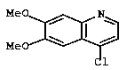
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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2011-61557358 P 20111108
WO 2012-US64116 W 20121108

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB This invention is directed to the treatment of cancer, particularly castration-resistant prostate cancer and bone metastases, with a dual inhibitor of MET and VEGF.
IT 123-30-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(dual inhibitor of Met and VEGF for treating cancer)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



IT 35654-56-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(dual inhibitor of Met and VEGF for treating cancer)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



L7 ANSWER 10 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:2041767 CAPLUS Full-text
DOCUMENT NUMBER: 167:324798
TITLE: Method of treating cancer
INVENTOR(S): Aftab, Dana T.
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., No pp. given
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20150133494	A1	20150514	US 2014-14398188	20141031
WO 2013166296	A1	20131107	WO 2013-US39284	20130502

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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2012-61641837 P 20120502
WO 2013-US39284 W 20130502

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB This invention is directed to the treatment of cancer, particularly castration-resistant prostate cancer and osteolytic bone metastases, with a dual inhibitor of MET and VEGF.
IT 123-30-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(dual MET-VEGF modulator for treating osteolytic bone metastases)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)

IT 35654-56-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(dual MET-VEGF modulator for treating osteolytic bone metastases)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

L7 ANSWER 11 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:2037951 CAPLUS Full-text
DOCUMENT NUMBER: 167:302546
TITLE: Method of treating lung adenocarcinoma
INVENTOR(S): Aftab, Dana T.
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., No pp. given
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20150238477	A1	20150827	US 2015-14426580	20150306
WO 2014039971	A1	20140313	WO 2013-US58768	20130909

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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2012-61698143 P 20120907
WO 2013-US58768 W 20130909

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB This invention is directed to the treatment of cancer in a patient, particularly a patient with lung adenocarcinoma, and more particularly a patient with KIF5B-RET fusion-pos. non-small cell lung cancer, with an inhibitor of MET, VEGF, and RET which is a compound of Formula I:or a pharmaceutically acceptable salt thereof.
IT 123-30-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(inhibitors of Met, VEGFR and Ret for use in treatment of lung adenocarcinoma)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)

IT 35654-56-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(inhibitors of Met, VEGFR and Ret for use in treatment of lung adenocarcinoma)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

L7 ANSWER 12 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:2003465 CAPLUS Full-text
DOCUMENT NUMBER: 167:175951
TITLE: Process for preparing quinoline derivatives

INVENTOR(S): Wilson, Jo Ann; Naganathan, Sriram; Andersen, Neil G.; Pfeiffer, Matthew
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., No pp. given
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20140256938	A1	20140911	US 2014-14353251	20140421
US 9365516	B2	20160614		
WO 2013059788	A1	20130425	WO 2012-US61320	20121022

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US 20160229805	A1	20160811	US 2016-15133708	20160420

PRIORITY APPLN. INFO.:

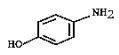
US 2011-61549312	P	20111020
WO 2012-US61320	W	20121022
US 2014-14353251	A1	20140421

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

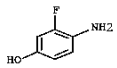
AB A process for prepg. a compd. of Formula I is disclosed, comprising the steps:wherein: R1 is halo; R2 is halo; R3 is (C1-C6)alkyl or (C1-C6)alkyl optionally substituted with heterocycloalkyl; R4 is (C1-C6)alkyl; and Q is CH or N;comprising: (a) contacting 1,1-cyclopropane dicarboxylic acid with thionyl chloride in a polar aprotic solvent; (b) adding and a tertiary amine base to the mixture of step (a) to form a compound of Formula A; and (c) coupling a compound of Formula A with an amine of Formula B to form a compound of Formula I.

IT 123-30-8 399-95-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for preparing quinoline derivs.)

RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)

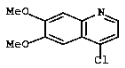


RN 399-95-1 CAPLUS
CN Phenol, 4-amino-3-fluoro- (CA INDEX NAME)



IT 35654-56-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparing quinoline derivs.)

RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



L7 ANSWER 13 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:1941702 CAPLUS Full-text
DOCUMENT NUMBER: 166:490458
TITLE: Processes for preparing quinoline compounds and pharmaceutical compositions containing such compounds
INVENTOR(S): Wilson, Jo Ann
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., No pp. given
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20140200242	A1	20140717	US 2014-13984559	20140320
US 9717720	B2	20170801		
WO 2012109510	A1	20120816	WO 2012-US24591	20120210

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NZ 712808	A	20170331	NZ 2012-712808	20120210
JP 2016188216	A	20161104	JP 2016-94411	20160510
US 20170057921	A1	20170302	US 2016-15348716	20161110

PRIORITY APPLN. INFO.:

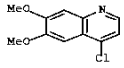
US 2011-61441520	P	20110210
US 2011-61441527	P	20110210
WO 2012-US24591	W	20120210
JP 2013-553580	A3	20120210
NZ 2012-614130	A3	20120210
US 2014-13984559	A1	20140320

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The present invention is directed to processes for making and compns. containing quinolines such as formula I or pharmaceutically acceptable salts thereof wherein: X1 is H, Br, Cl, or X2 is H, Br, Cl, or n1 is 1-2; and n2 is 1-2.

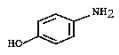
IT 35654-56-9P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparing quinoline derivs. and pharmaceutical compns. thereof)

RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

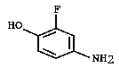


IT 123-30-8 399-96-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for preparing quinoline derivs. and pharmaceutical compns. thereof)

RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



RN 399-96-2 CAPLUS
CN Phenol, 4-amino-2-fluoro- (CA INDEX NAME)



L7 ANSWER 14 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN

ACCESSION NUMBER: 2016:1874511 CAPLUS Full-text
DOCUMENT NUMBER: 166:300776
TITLE: Drug combinations to treat cancer
INVENTOR(S): Sweeney, Christopher J.; Kantoff, Phili W.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., No pp. given
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20160082019	A1	20160324	US 2015-14782493	20151005
WO 2014165779	A1	20141009	WO 2014-US33008	20140404

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

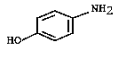
PRIORITY APPLN. INFO.:

US 2013-61808516	P	20130404
WO 2014-US33008	W	20140404

AB This invention relates to the combination of cabozantinib and abiraterone to treat cancer, particularly castration resistant prostate cancer.

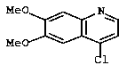
IT 123-30-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(drug combinations to treat cancer)

RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



IT 35654-56-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(drug combinations to treat cancer)

RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

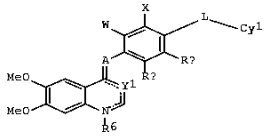


L7 ANSWER 15 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:1695752 CAPLUS Full-text
DOCUMENT NUMBER: 165:522607
TITLE: Preparation of quinazolinamines and quinolinamines as KSR antagonists useful in mono- and combination therapy of cancer
INVENTOR(S): Dar, Arvin; Dhawan, Neil; Scopton, Alex P.
PATENT ASSIGNEE(S): Icahn School of Medicine at Mount Sinai, USA
SOURCE: PCT Int. Appl., 161pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2016168704	A1	20161020	WO 2016-US27899	20160415

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

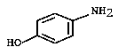
PRIORITY APPLN. INFO.: US 2015-62148591 P 20150416
OTHER SOURCE(S): CASREACT 165:522607; MARPAT 165:522607
GI



I

AB The invention relates to prepn. of quinazolinamines and quinolinamines of the exemplary formula I wherein all the variables are as defined in the disclosure, as antagonists of Kinase Suppressor of Ras (KSR). Compds. I and pharmaceutical compns. comprising I, the KSR inhibitors can be used in mono- and combination therapy of cancer.

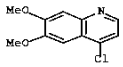
IT 123-30-8, 4-Aminophenol 2835-99-6, 4-Amino-3-methylphenol 35654-56-9, 4-Chloro-6,7-dimethoxyquinoline
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of quinazolinamines and quinolinamines as KSR antagonists useful in mono- and combination therapy of cancer)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



RN 2835-99-6 CAPLUS
CN Phenol, 4-amino-3-methyl- (CA INDEX NAME)



RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

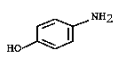


REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 16 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:1425466 CAPLUS Full-text
DOCUMENT NUMBER: 165:385748
TITLE: Small molecule stabilization of the KSR inactive state antagonizes oncogenic Ras signalling
AUTHOR(S): Dhawan, Neil S.; Scopton, Alex P.; Dar, Arvin C.
CORPORATE SOURCE: Department of Oncological Sciences, The Tisch Cancer Institute, The Icahn School of Medicine at Mount Sinai, New York, NY, 10029, USA
SOURCE: Nature (London, United Kingdom) (2016), 537(7618), 112-116
CODEN: NATUAS; ISSN: 0028-0836
DIGITAL OBJECT ID: 10.1038/nature19327
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
OTHER SOURCE(S): CASREACT 165:385748

AB Deregulation of the Ras-mitogen activated protein kinase (MAPK) pathway is an early event in many different cancers and a key driver of resistance to targeted therapies. Sustained signalling through this pathway is caused most often by mutations in K-Ras, which biochem. favors the stabilization of active RAF signalling complexes. Kinase suppressor of Ras (KSR) is a MAPK scaffold that is subject to allosteric regulation through dimerization with RAF. Direct targeting of KSR could have important therapeutic implications for cancer; however, testing this hypothesis has been difficult owing to a lack of small-mol. antagonists of KSR function. Guided by KSR mutations that selectively suppress oncogenic, but not wild-type, Ras signalling, we developed a class of compds. that stabilize a previously unrecognized inactive state of KSR. These compds., exemplified by APS-2-79, modulate KSR-dependent MAPK signalling by antagonizing RAF heterodimerization as well as the conformational changes required for phosphorylation and activation of KSR-bound MEK (mitogen-activated protein kinase kinase). Furthermore, APS-2-79 increased the potency of several MEK inhibitors specifically within Ras-mutant cell lines by antagonizing release of neg. feedback signalling, demonstrating the potential of targeting KSR to improve the efficacy of current MAPK inhibitors. These results reveal conformational switching in KSR as a druggable regulator of oncogenic Ras, and further suggest co-targeting of enzymic and scaffolding activities within Ras-MAPK signalling complexes as a therapeutic strategy for overcoming Ras-driven cancers.

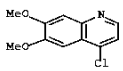
IT 123-30-8 2835-99-6 35654-56-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(small mol. stabilization of KSR inactive state antagonizes oncogenic Ras signalling)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



RN 2835-99-6 CAPLUS
CN Phenol, 4-amino-3-methyl- (CA INDEX NAME)



RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 17 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:702303 CAPLUS Full-text
DOCUMENT NUMBER: 164:602041
TITLE: Preparation of quinoline derivatives as multitarget kinase inhibitor useful for the treatment of cancer
INVENTOR(S): Zhou, Youjun; Zhou, Hao; Zheng, Canhui; Zhu, Ju; Lv, Jiaguo; Sun, Nannan; Chen, Shana
PATENT ASSIGNEE(S): The Second Military Medical University, PLA, Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 36pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 105541798	A	20160504	CN 2016-10077368	20160203

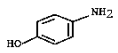
PRIORITY APPLN. INFO.: CN 2016-10077368 20160203
OTHER SOURCE(S): CASREACT 164:602041; MARPAT 164:602041
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

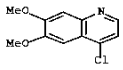
AB The invention relates to quinoline derivs. of formula I, method for their preparation and their use as multitarget kinase inhibitor for the treatment of cancer. Compds. of formula I, wherein R1 is H and halo; R2 is H, alkyl, halo, OH and amino; R3 is H and C1-5alkyl; X is N and O, are claimed. Example compound II was prepared by a multistep procedure (procedure given). The invention compds. were evaluated for their anticancer activity and inhibitory activity towards kinase KDR and MET. From the assay, it was determined that example compound II exhibited IC50 value in the range of 1.48 μM to 11.6 μM.

IT 123-30-8 35654-56-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of quinoline derivs. as multitarget kinase inhibitor useful

for
the treatment of cancer)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



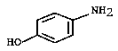
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



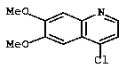
L7 ANSWER 18 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:224790 CAPLUS Full-text
DOCUMENT NUMBER: 164:293822
TITLE: Drug combinations to treat multiple myeloma
INVENTOR(S): Aftab, Dana T.; Lamb, Peter
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 49pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2016022697	A1	20160211	WO 2015-US43825	20150805
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
CA 2957466	A1	20160211	CA 2015-2957466	20150805
AU 2015301097	A1	20170302	AU 2015-301097	20150805
KR 2017031786	A	20170321	KR 2017-7006288	20150805
CN 106573042	A	20170419	CN 2015-80042010	20150805
EP 3177311	A1	20170614	EP 2015-750223	20150805
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
JP 2017526662	T	20170914	JP 2017-506390	20150805
MX 2017001490	A	20170511	MX 2017-1490	20170201
US 20170224672	A1	20170810	US 2017-15501582	20170203

PRIORITY APPLN. INFO.: US 2014-62033386 P 20140805
WO 2015-US43825 W 20150805
OTHER SOURCE(S): CASREACT 164:293822; MARPAT 164:293822
AB This invention relates to the combination of a C-Met inhibitor and a proteasome inhibitor to treat cancer, particularly multiple myeloma.
IT 123-30-8, 4-Aminophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(drug combinations to treat multiple myeloma)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



IT 35654-56-9P, 4-Chloro-6,7-dimethoxyquinoline
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(drug combinations to treat multiple myeloma)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

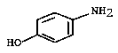


REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

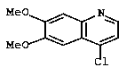
L7 ANSWER 19 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2015:1726025 CAPLUS Full-text
DOCUMENT NUMBER: 163:628844
TITLE: Method of treating lung adenocarcinoma
INVENTOR(S): Aftab, Dana T.; Yu, Peiwen
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 92pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2015164869	A1	20151029	WO 2015-US27800	20150427
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
CA 2946416	A1	20151029	CA 2015-2946416	20150427
AR 100191	A1	20160914	AR 2015-101255	20150427
AU 2015249232	A1	20161110	AU 2015-249232	20150427
KR 2016147934	A	20161223	KR 2016-7033010	20150427
IL 248408	A	20161229	IL 2015-248408	20150427
EP 3134084	A1	20170301	EP 2015-721100	20150427
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
CN 106488768	A	20170308	CN 2015-80022580	20150427
JP 2017513908	T	20170601	JP 2016-564236	20150427
MX 2016013600	A	20170427	MX 2016-13600	20161017
US 20170042880	A1	20170216	US 2016-15305854	20161021

PRIORITY APPLN. INFO.: US 2014-61984599 P 20140425
WO 2015-US27800 W 20150427
OTHER SOURCE(S): CASREACT 163:628844; MARPAT 163:628844
AB This invention is directed to the treatment of cancer in a patient, particularly a patient with lung adenocarcinoma, and more particularly a patient with SLC34A2-ROS1, CD74-ROS1, or FIG-ROS1 fusion-pos. non-small cell lung cancer, with an inhibitor of MET, VEGFR2, and ROS1.
IT 123-30-8, p-Aminophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(treating lung adenocarcinoma)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



IT 35654-56-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(treating lung adenocarcinoma)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

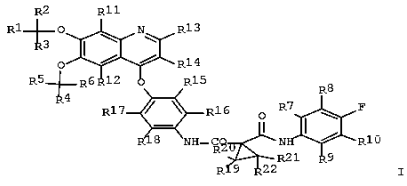


REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 20 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2015:1213912 CAPLUS Full-text
DOCUMENT NUMBER: 163:271103
TITLE: Preparation of deuterated cabozantinib derivatives and their application as anticancer agents
INVENTOR(S): Chen, Xinghai; Peng, Wei; Parker, Omar; Zheng, Feiming; Fu, Yong
PATENT ASSIGNEE(S): Shanghai Shengkao Pharmaceutical Technology Co., Ltd., Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 35pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 104788372	A	20150722	CN 2014-10361351	20140725

PRIORITY APPLN. INFO.: CN 2014-10361351 20140725
OTHER SOURCE(S): CASREACT 163:271103; MARPAT 163:271103
GI

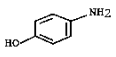


AB The invention is related to the prepn. of deuterated cabozantinib derivs. I and their application as anticancer agents. The invention compound I, wherein R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11, R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, and R22 are H or D independently and contain at least one D and their pharmaceutically acceptable salts, crystalline hydrates, solvates, prodrugs, single crystal or polymorph are claimed. Compound I was prepared by multi-step procedure (procedure given). The deuterated cabozantinib derivs. have slow decomposition in vivo, thereby

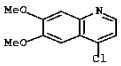
reducing adverse metabolism of drugs. The invention compds. were evaluated for their anticancer activity.

IT 123-30-8 35654-56-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of deuterated cabozantinib derivs. and their application as anticancer agents)

RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)

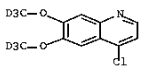


RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



IT 1714998-85-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of deuterated cabozantinib derivs. and their application as anticancer agents)

RN 1714998-85-2 CAPLUS
CN Quinoline, 4-chloro-6,7-di(methoxy-d3)- (CA INDEX NAME)



L7 ANSWER 21 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2015:191731 CAPLUS Full-text
DOCUMENT NUMBER: 162:299963
TITLE: Preparation of Tivozanib intermediate
INVENTOR(S): Hao, Guiyun; Huang, Wei; Cen, Junda
PATENT ASSIGNEE(S): Shanghai Institute of Pharmaceutical Industry, Peop. Rep. China; China State Institute of Pharmaceutical Industry
SOURCE: Faming Zhuanli Shenqing, 12pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese

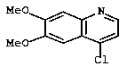
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 104326924	A	20150204	CN 2013-10310007	20130722

PRIORITY APPLN. INFO.: CN 2013-10310007 20130722
OTHER SOURCE(S): CASREACT 162:299963
AB The invention relates to prepn. of Tivozanib intermediate 3-chloro-4-aminophenol. 3-Chloro-4-aminophenol was prepared by reaction of p-aminobenzenesulfonic acid and 3-chlorophenol; the resulting 4-[(2-chloro-4-hydroxyphenyl)azo]-benzenesulfonic acid underwent underwent reduction to give product.

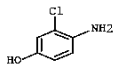
IT 35654-56-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of Tivozanib intermediate 3-chloro-4-aminophenol)

RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



IT 17609-80-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of Tivozanib intermediate 3-chloro-4-aminophenol)

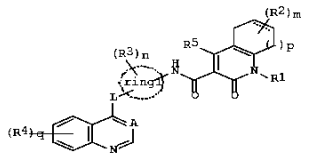
RN 17609-80-2 CAPLUS
CN Phenol, 4-amino-3-chloro- (CA INDEX NAME)



L7 ANSWER 22 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2015:161573 CAPLUS Full-text
DOCUMENT NUMBER: 162:258994
TITLE: Preparation of quinolinecarboxamide compounds, their medical compositions, and preventive and/or therapeutic method for Axl-related disorders
INVENTOR(S): Inukai, Takayuki; Takeuchi, Jun; Yasuhiro, Tomoko
PATENT ASSIGNEE(S): Ono Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 141pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2015012298	A1	20150129	WO 2014-JP69419	20140723
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
CA 2918888	A1	20150129	CA 2014-2918888	20140723
AU 2014294109	A1	20160211	AU 2014-294109	20140723
CN 105408312	A	20160316	CN 2014-80041780	20140723
KR 2016033707	A	20160328	KR 2016-7002008	20140723
IL 243743	A	20160331	IL 2014-243743	20140723
EP 3026045	A1	20160601	EP 2014-828976	20140723
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
MX 2016000989	A	20160516	MX 2016-989	20160122
US 20160168121	A1	20160616	US 2016-14906993	20160122
US 9573935	B2	20170221		
IN 201647002406	A	20160831	IN 2016-47002406	20160122
US 20170088542	A1	20170330	US 2016-15373091	20161208

PRIORITY APPLN. INFO.: JP 2013-153350 A 20130724
WO 2014-JP69419 W 20140723
US 2016-14906993 A1 20160122
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 162:258994; MARPAT 162:258994
GI

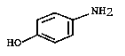


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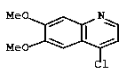
AB The compds., their salts, their solvates, their N-oxides, and their prodrugs are represented by formula I [R1 = (un)substituted C1-8 alkyl, (un)substituted C3-7 carbocycle; (un)substituted 4- to 7-membered heterocycle; R2 = C1-4 (halo)alkyl, halo, oxo, etc.; R3 = C1-4 (halo)alkyl, halo; R4 = C1-4 alkoxy, C1-4 haloalkyl, C2-4 alkenyloxy, etc.; R5 = H, C1-4 (halo)alkyl, halo, etc.; A = CH, N; L = O, NH, CO, S, etc.; ring1 = 5- to 7-membered cyclic group; double bond comprising solid and broken lines represent C-C single or double bond; m, n = 0-5; p = 0-2; q = 0-4]. Thus, amidating 5-[(6,7-dimethoxy-4-quinolinyl)oxy]-2- pyridineamine (preparation given) with 2,5-dioxo-1-phenyl-1,2,5,6,7,8-hexahydro-3-quinolinecarboxylic acid (preparation given), gave N-[5-[(6,7-dimethoxy-4-quinolinyl)oxy]-2-pyridinyl]-2,5-dioxo-1-phenyl-1,2,5,6,7,8-hexahydro-3-quinolinecarboxamide with Axl inhibitory activity (IC50) 0.0022 μM. Formulations containing I are given.

IT 123-30-8, 4-Aminophenol 35654-56-9, 4-Chloro-6,7-dimethoxyquinoline
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of quinolinecarboxamides for preventive and/or therapeutic method for Axl-related disorders)

RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

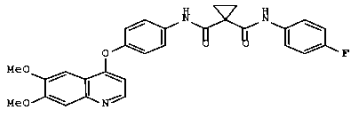


OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 23 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2014:1716754 CAPLUS Full-text
DOCUMENT NUMBER: 161:582215
TITLE: Preparation of cabozantinib and dosage forms for treatment of cancer
INVENTOR(S): Decillis, Arthur
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 48pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2014165786 A1 20141009 WO 2014-US33016 20140404
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM
EP 2981263 A1 20160210 EP 2014-724909 20140404
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME
US 20160022662 A1 20160128 US 2015-14782537 20151005
PRIORITY APPLN. INFO.: US 2013-61808511 P 20130404
WO 2014-US33016 W 20140404
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 161:582215
GI

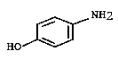


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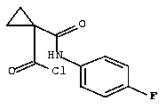
AB This invention relates to a dosage form of cabozantinib (I) and a method of employing the dosage form to treat cancer. I was prepared starting with 6,7-dimethoxy-4-quinolinol through a number of steps. I S-maleate was also prepared and tablets containing I were prepared

IT 123-30-8, 4-Aminophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of cabozantinib and dosage forms for treatment of cancer)

RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



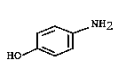
JP 2016515628 T 20160530 JP 2016-506653 20140404
US 20160082019 A1 20160324 US 2015-14782493 20151005
MX 2015014046 A 20160516 MX 2015-14046 20151005
IN 2015KN03651 A 20160318 IN 2015-KN3651 20151103
PRIORITY APPLN. INFO.: US 2013-61808516 P 20130404
WO 2014-US33008 W 20140404
OTHER SOURCE(S): CASREACT 161:577829; MARPAT 161:577829
GI



AB This invention relates to the combination of cabozantinib and abiraterone to treat cancer, particularly castration resistant prostate cancer.

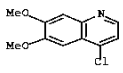
IT 123-30-8, 4-Aminophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(drug combinations to treat cancer)

RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



IT 35654-56-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(drug combinations to treat cancer)

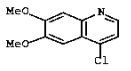
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS

IT 35654-56-9P, 4-Chloro-6,7-dimethoxyquinoline
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of cabozantinib and dosage forms for treatment of cancer)

RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



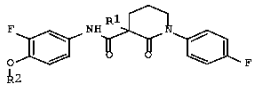
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 24 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2014:1710486 CAPLUS Full-text
DOCUMENT NUMBER: 161:577829
TITLE: Drug combinations to treat cancer
INVENTOR(S): Sweeney, Christopher J.; Kantoff, Philip W.
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 78pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2014165779	A1	20141009	WO 2014-US33008	20140404
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
CA 2908815	A1	20141009	CA 2014-2908815	20140404
AU 2014248001	A1	20151119	AU 2014-248001	20140404
IL 241868	A	20151130	IL 2014-241868	20140404
KR 2015138268	A	20151209	KR 2015-7030445	20140404
EP 2983639	A1	20160217	EP 2014-724594	20140404
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 25 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2014:484709 CAPLUS Full-text
DOCUMENT NUMBER: 161:186431
TITLE: Discovery of novel c-Met inhibitors bearing a 3-carboxylpiperidin-2-one scaffold
AUTHOR(S): Zhang, Wei; Ai, Jing; Shi, Dakuo; Peng, Xia; Ji, Yinchun; Liu, Jian; Geng, Meiyu; Li, Yingxia
CORPORATE SOURCE: School of Pharmacy, Fudan University, Shanghai, 201203, Peop. Rep. China
SOURCE: Molecules (2014), 19(2), 2655-2673, 19 pp.
CODEN: MOLEFW; ISSN: 1420-3049
DIGITAL OBJECT ID: 10.3390/molecules19022655
PUBLISHER: MDPI AG
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
OTHER SOURCE(S): CASREACT 161:186431
GI

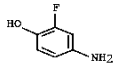


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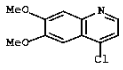
AB A series of compds. contg. a novel 3-carboxypiperidin-2-one scaffold I [R1 = H, Me, Et, n-Bu, Cl; R2 = 2-amino-3-chloropyridin-4-yl, 7H-pyrrolo[2,3-d]pyrimidin-4-yl, 6,7-dimethoxyquinolin-4-yl, etc.], based on the lead structure BMS-777607 were designed, synthesized and evaluated for their c-Met kinase inhibition and cytotoxicity against MKN45 human gastric cancer cell line. The results indicated that compound I [R1 = Cl, R2 = 6,7-dimethoxyquinolin-4-yl] exhibited significant inhibitory effect on c-Met with IC50 value of 8.6 nM and MKN45 cell proliferation with IC50 value of 0.57μM.

IT 399-96-2 35654-56-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of carboxypiperidinone scaffolds and evaluation of their c-Met kinase inhibition, SAR and cytotoxicity against MKN45 cancer cell lines)

RN 399-96-2 CAPLUS
CN Phenol, 4-amino-2-fluoro- (CA INDEX NAME)



RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

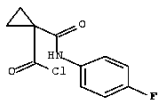


REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

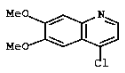
L7 ANSWER 26 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2014:479457 CAPLUS Full-text
DOCUMENT NUMBER: 160:515456
TITLE: Synthesis method of antitumor therapeutic drug of cabozantinib
INVENTOR(S): Cai, Jianping; Chen, Zengfei; Zhang, Lifeng; Fang, Ying
PATENT ASSIGNEE(S): Suzhou Moer Pharmaceutical Co., Ltd., Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 9pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 103664778	A	20140326	CN 2013-10631287	20131127
CN 103664778	B	20170405		

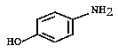
PRIORITY APPLN. INFO.: CN 2013-10631287 20131127
OTHER SOURCE(S): CASREACT 160:515456; MARPAT 160:515456
GI



AB The invention discloses a synthesis method of antitumor therapeutic drug of cabozantinib., comprising: using 4-(6, 7- dimethoxy quinoline -4- oxy)-phenylamine to react with 1-((4- fluorophenyl) carbamoyl) cyclopropyl acyl halide, an acid-binding agent in organic solvent at -5~20 °C for 0.5~2h to obtain cabozantinib; the inventive method uses cheap raw materials, has mild conditions, simple and convenient operation, stable process, good repeatability, high molar yield, low cost, so invention is an applicable method for com. production of cabozantinib. Cabozantinib was prepared via chlorination of 6,7-dimethoxyquinolin-4-ol; the resulting 4-chloro-6,7-dimethoxyquinoline underwent condensation with 4-aminophenol or 4-nitrophenol to give the corresponding ethers, which underwent redn and/or acylation with 1-[(4-fluorophenyl)carbamoyl]cyclopropylcarbonyl halides to give cabozantinib. The said 1-[(4-fluorophenyl)carbamoyl]cyclopropylcarbonyl halides were prepared via condensation of 1,1-cyclopropanedicarboxylic acid with p-fluoroaniline followed by halogenation. The inventive method uses cheap raw materials, has mild conditions, simple and convenient operation, stable process, good repeatability, high molar yield, low cost, so invention is an applicable method for com. production of cabozantinib.
IT 35654-56-9P, 4-Chloro-6,7-dimethoxyquinoline
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of antitumor drug cabozantinib starting from (dimethoxy)quinolinol and cyclopropanedicarboxylic acid by using etherification and amidation as the key steps)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



IT 123-30-8, 4-Aminophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of antitumor drug cabozantinib starting from (dimethoxy)quinolinol and cyclopropanedicarboxylic acid by using etherification and amidation as the key steps)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)

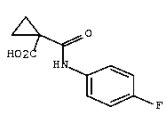


L7 ANSWER 27 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2014:410366 CAPLUS Full-text
DOCUMENT NUMBER: 160:451706
TITLE: Inhibitors of Met, VEGFR and Ret for use in the treatment of lung adenocarcinoma
INVENTOR(S): Aftab, Dana T.
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 80pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

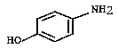
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2014039971	A1	20140313	WO 2013-US58768	20130909
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
US 20140121239	A1	20140501	US 2013-14021614	20130909
CN 104703600	A	20150610	CN 2013-80052164	20130909
EP 2892532	A1	20150715	EP 2013-765886	20130909
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
JP 2015530389	T	20151015	JP 2015-531283	20130909
US 20150238477	A1	20150827	US 2015-14426580	20150306

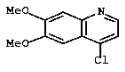
PRIORITY APPLN. INFO.: US 2012-61698143 P 20120907
WO 2013-US58768 W 20130909
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 160:451706; MARPAT 160:451706
GI



AB This invention is directed to the treatment of cancer in a patient, particularly a patient with lung adenocarcinoma, and more particularly a patient with KIF5B-RET fusion-pos. non-small cell lung cancer, with an inhibitor of MET, VEGF, and RET.
IT 123-30-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(inhibitors of Met, VEGFR and Ret for use in treatment of lung adenocarcinoma)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)

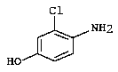


IT 35654-56-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(inhibitors of Met, VEGFR and Ret for use in treatment of lung adenocarcinoma)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



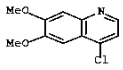
OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 28 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2013:1967223 CAPLUS Full-text
DOCUMENT NUMBER: 162:205137
TITLE: Synthesis of tivozanib
AUTHOR(S): Wang, Jing; Wang, Yalou; Qin, Yuyan
CORPORATE SOURCE: School of Pharmacy, China Pharmaceutical University, Nanjing, Jiangsu Province, 210009, Peop. Rep. China
SOURCE: Zhongguo Yiyao Gongye Zazhi (2013), 44(6), 541-544
CODEN: ZYGZEA; ISSN: 1001-8255
PUBLISHER: Zhongguo Yiyao Gongye Zazhi Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
OTHER SOURCE(S): CASREACT 162:205137
AB 4-Chloro-6,7-dimethoxyquinoline (6) was synthesized from 3,4-dimethoxyaniline (2) and ethoxymethylenemalonic acid di-Et ester by substitution, cyclization, hydrolysis, decarboxylation and chlorination. In another route, 6 was synthesized from 2, Meldrum's acid and tri-Me orthoformate by substitution, cyclization and chlorination. Then 6 was etherized with 4-amino-3-chlorophenol hydrochloride (7) and coupled with 3-amino-5methylisoxazole by ureapoiesis to yield the antitumor drug tivozanib with an overall yield of 35%-37% (based on compound 2).
IT 52671-64-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis of tivozanib)
RN 52671-64-4 CAPLUS
CN Phenol, 4-amino-3-chloro-, hydrochloride (1:1) (CA INDEX NAME)



● HCl

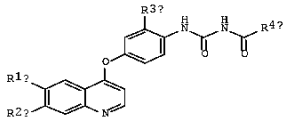
IT 35654-56-9P, 4-Chloro-6,7-dimethoxyquinoline
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of tivozanib)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



L7 ANSWER 29 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2013:1877350 CAPLUS Full-text
DOCUMENT NUMBER: 160:53747
TITLE: Preparation of 4-[4-(5-membered aromatic heterocyclic carbonyl ureido)phenyloxy]quinoline derivatives having inhibitory activity on CSF-1R and/or TrkA
INVENTOR(S): Kawai, Ryohei; Yamanouchi, Maasa; Saku, Osamu; Nakagawa, Hiroshi; Nakoji, Masayoshi; Kubo, Kazuo
PATENT ASSIGNEE(S): Kyowa Hakko Kirin Co., Ltd., Japan
SOURCE: PCT Int. Appl., 144pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

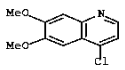
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2013180128	A1	20131205	WO 2013-JP64765	20130528

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM
PRIORITY APPLN. INFO.: JP 2012-120458 A 20120528
OTHER SOURCE(S): CASREACT 160:53747; MARPAT 160:53747
GI



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AB Title compds. I [R1A, R2A = independently hydroxy, (un)substituted alkoxy or (un)substituted aliphatic heterocyclyloxy; R3A = alkoxy; R4A = 5-membered aromatic heterocyclyl (optionally substituted with (un)substituted alkyl, halo, cycloalkyl (optionally substituted with alkyl), etc.); or pharmaceutically acceptable salts thereof] were prepared For example, reaction of 4-amino-3-methoxyphenol with NaH/4-chloro-6,7-dimethoxyquinoline, treatment with triphosgene/phenol and exposure to 2-methyloxazole-4-carboxamide afforded compound I [R1A = R2A = R3A = OMe; R4A = 2-methyloxazol-4-yl] (II). The selected invention compds., e.g., II, showed IC50 values of <100 nmol/L for phosphorylation of CSF-1R (colony stimulating factor-1 receptor) and TrkA (tropomyosin-related kinase A). Of note, compds. I are useful for the treatment of cancer metastasis, rheumatoid arthritis, osteoporosis, etc.
IT 35654-56-9, 4-Chloro-6,7-dimethoxyquinoline 61638-01-5, 4-Amino-3-methoxyphenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of 4-[4-(5-membered aromatic heterocyclic carbonyl ureido)phenyloxy]quinoline derivs. having inhibitory activity on CSF-1R and/or TrkA)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



RN 61638-01-5 CAPLUS
CN Phenol, 4-amino-3-methoxy- (CA INDEX NAME)

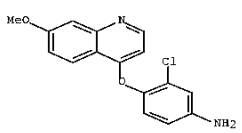


REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

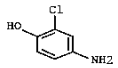
L7 ANSWER 30 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2013:1873443 CAPLUS Full-text
DOCUMENT NUMBER: 160:50465
TITLE: Substituted quinoline compounds and use as Antitumor agents
INVENTOR(S): Xi, Ning; Wang, Tingjin; Zeng, Shan; Sun, Mingming; Wang, Kunrui
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 80pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2013180949	A1	20131205	WO 2013-US41036	20130515

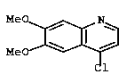
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM
PRIORITY APPLN. INFO.: US 2012-61652210 P 20120527
OTHER SOURCE(S): CASREACT 160:50465; MARPAT 160:50465
GI



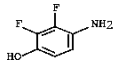
AB The present invention provides novel substituted quinoline compds., pharmaceutical acceptable salts and formulations thereof useful in modulating the protein tyrosine kinase activity, and in modulating cellular activities such as proliferation, differentiation, apoptosis, migration and invasion. The invention also provides pharmaceutically acceptable compns. comprising such compds. and methods of using the compns. in the treatment of hyperproliferative disorders in mammals, especially humans.
IT 3964-52-1, 4-Amino-2-chlorophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(substituted quinoline compds. and methods of use)
RN 3964-52-1 CAPLUS
CN Phenol, 4-amino-2-chloro- (CA INDEX NAME)



IT 35654-56-9P, 4-Chloro-6,7-dimethoxyquinoline
163733-99-1P, 4-Amino-2,3-difluorophenol
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(substituted quinoline compds. and methods of use)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



RN 163733-99-1 CAPLUS
CN Phenol, 4-amino-2,3-difluoro- (CA INDEX NAME)



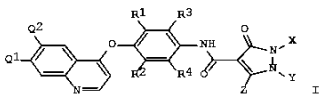
OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 31 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN

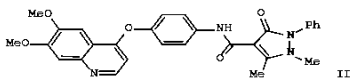
ACCESSION NUMBER: 2013:1866363 CAPLUS Full-text
DOCUMENT NUMBER: 160:33885
TITLE: Substituted quinoline compound useful in treatment of hyperproliferative diseases and its preparation
INVENTOR(S): Xi, Ning; Wang, Tingjin; Zeng, Shan; Sun, Mingming; Wang, Kunrui
PATENT ASSIGNEE(S): HEC Pharm Co., Ltd., Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 57pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
CN 103420986	A	20131204	CN 2013-10179608		20130515
PRIORITY APPLN. INFO.:			CN 2012-10154478	A	20120518
			CN 2013-10118880	A	20130403

OTHER SOURCE(S): CASREACT 160:33885; MARPAT 160:33885
GI

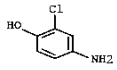


I

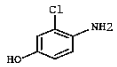


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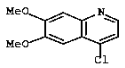
AB The invention relates to substituted quinoline compds. of formula I as protein kinase regulator useful in treatment of proliferative diseases and their preparation Compound I, wherein R1, R2, R3, and R4 are independently H, D, F, Cl, or Br; Q1 and Q2 are independently H, D, C1-6 alkyl, etc.; X and Z are independently H, D, C1-6 alkyl, etc.; Y is H, D, C2-6 alkynyl, etc.; their stereoisomers, N-oxides, solvates, pharmaceutically acceptable salts, are claimed. Compound II was prepared by multi-step procedure (procedure given). The present invention also relates to the pharmaceutical compns. containing the inventive compds., and method of application of the pharmaceutical composition for treatment of a mammal, especially hyperproliferative disease.
IT 3964-52-1 17609-80-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of substituted quinoline compound useful in treatment of hyperproliferative diseases)
RN 3964-52-1 CAPLUS
CN Phenol, 4-amino-2-chloro- (CA INDEX NAME)



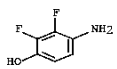
RN 17609-80-2 CAPLUS
CN Phenol, 4-amino-3-chloro- (CA INDEX NAME)



IT 35654-56-9P 163733-99-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of substituted quinoline compound useful in treatment of hyperproliferative diseases)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



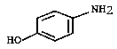
RN 163733-99-1 CAPLUS
CN Phenol, 4-amino-2,3-difluoro- (CA INDEX NAME)



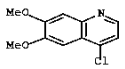
L7 ANSWER 32 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2013:1734775 CAPLUS Full-text
DOCUMENT NUMBER: 159:691817
TITLE: A dual MET-VEGF modulator for treating osteolytic bone metastases
INVENTOR(S): Aftab, Dana T.
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 44pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

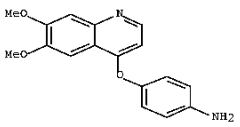
PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2013166296	A1	20131107	WO 2013-US39284		20130502
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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM					
EP 2844254	A1	20150311	EP 2013-722238		20130502
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME					
JP 2015515988	T	20150604	JP 2015-510456		20130502
US 20150133494	A1	20150514	US 2014-14398188		20141031
PRIORITY APPLN. INFO.:			US 2012-61641837	P	20120502
			WO 2013-US39284	W	20130502

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 159:691817; MARPAT 159:691817
GI



IT 35654-56-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(dual MET-VEGF modulator for treating osteolytic bone metastases)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

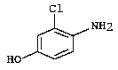




AB This invention is directed to the treatment of cancer, particularly castration-resistant prostate cancer and osteolytic bone metastases, with a dual inhibitor of MET and VEGF.
IT 123-30-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(dual MET-VEGF modulator for treating osteolytic bone metastases)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)

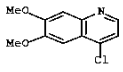
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 33 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2013:1241241 CAPLUS Full-text
DOCUMENT NUMBER: 159:364231
TITLE: Synthesis of tivozanib hydrochloride monohydrate
AUTHOR(S): Fu, Ying; Zhang, Qing-wen
CORPORATE SOURCE: State Key Laboratory of New Drug and Pharmaceutical Process, Shanghai Institute of Pharmaceutical Industry, China State Institute of Pharmaceutical Industry, Shanghai, 200437, Peop. Rep. China
SOURCE: Zhongguo Xinyao Zazhi (2013), 22(1), 26-29
CODEN: ZXZHA6; ISSN: 1003-3734
PUBLISHER: Zhongguo Xinyao Zazhi Youxian Gongsi
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
OTHER SOURCE(S): CASREACT 159:364231
AB The synthetic process of tivozanib hydrochloride monohydrate (1) was investigated. Tivozanib hydrochloride monohydrate (1) was prepared from 3,4-dimethoxyacetophenone (2), via nitration, reduction, cyclization, chlorination, condensation, urea formation, and salification. The structures of intermediates and target compound 1 were confirmed by 1H-NMR, ESI-MS and/or element anal. The overall yield was 35%. This process boasts readily available raw materials, mild condition, simple operation and stable yield.
IT 52671-64-4, 4-Amino-3-chlorophenol hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis of tivozanib hydrochloride monohydrate)
RN 52671-64-4 CAPLUS
CN Phenol, 4-amino-3-chloro-, hydrochloride (1:1) (CA INDEX NAME)



● HCl

IT 35654-56-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of tivozanib hydrochloride monohydrate)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



L7 ANSWER 34 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2013:793171 CAPLUS Full-text
DOCUMENT NUMBER: 159:9214
TITLE: Preparation of uracil derivatives as AXL and c-MET kinase inhibitors
INVENTOR(S): Dandu, Reddeppareddy; Hudkins, Robert L.; Josef, Kurt A.; Prouty, Catherine P.; Tripathy, Rabindranath
PATENT ASSIGNEE(S): Cephalon, Inc., USA
SOURCE: PCT Int. Appl., 174pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2013074633	A1	20130523	WO 2012-US65019	20121114
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
CA 2852697	A1	20130523	CA 2012-2852697	20121114
AU 2012339640	A1	20140605	AU 2012-339640	20121114
AU 2012339640	B2	20170105		
IL 232405	A	20140630	IL 2012-232405	20121114
AR 88872	A1	20140716	AR 2012-104293	20121114
KR 2014090678	A	20140717	KR 2014-7015807	20121114
CN 103958497	A	20140730	CN 2012-80055840	20121114
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EP 2780338	A1	20140924	EP 2012-798087	20121114
EP 2780338	B1	20161109		
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JP 2014533287	T	20141211	JP 2014-541416	20121114
JP 6051434	B2	20161227		
NZ 624945	A	20150925	NZ 2012-624945	20121114
SG 10201510307	A1	20160128	SG 2015-10201510307	20121114
NZ 712194	A	20160527	NZ 2012-712194	20121114
EA 23521	B1	20160630	EA 2014-90971	20121114
IL 245658	A	20160630	IL 2012-245658	20121114
EP 3045453	A1	20160720	EP 2016-153088	20121114
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TW I562989	B	20161221	TW 2012-142365	20121114
PH 12014500883	B1	20170407	PH 2014-12014500883	20121114
BR 112014011548	A2	20170509	BR 2014-112014011548	20121114
PH 12016501535	A	20170522	PH 2016-12016501535	20121114
ES 2614824	T3	20170602	ES 2012-798087	20121114
IL 252517	A	20170731	IL 2012-252517	20121114
ZA 2014002940	A	20170830	ZA 2014-2940	20121114
MX 2014005766	A	20140530	MX 2014-5766	20140513
US 20140275077	A1	20140918	US 2014-14276138	20140513
US 9029538	B2	20150512		
IN 2014CN04308	A	20160122	IN 2014-CN4308	20140611
US 20150209358	A1	20150730	US 2015-14681974	20150408
US 9522902	B2	20161220		
US 20150210670	A1	20150730	US 2015-14681981	20150408
US 9120778	B2	20150901		
JP 2017071612	A	20170413	JP 2016-215753	20161104
US 20170050949	A1	20170223	US 2016-15346582	20161108
US 9745283	B2	20170829		
AU 2017201042	A1	20170309	AU 2017-201042	20170216

PRIORITY APPLN. INFO.:

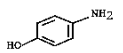
US 2011-61559312	P	20111114
AU 2012-339640	A3	20121114
EP 2012-798087	A3	20121114
IL 2012-232405	A3	20121114
IL 2012-245658	A3	20121114
JP 2014-541416	A3	20121114
NZ 2012-624945	A3	20121114
PH 2014-12014500883	A3	20121114
WO 2012-US65019	W	20121114
US 2014-14276138	A1	20140513
US 2015-14681974	A1	20150408

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 159:9214; MARPAT 159:9214

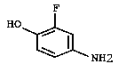
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

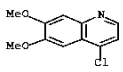
AB The invention relates to uracil derivs. of formula I and their prepn., useful as AXL and c-MET kinase inhibitors in the treatment of disease. Compds. of formula I, in which R is each independently H, (un)substituted C1-6 alkyl, C2-6 alkenyl, etc.; D is O, S, SO, SO2, CO, CHOH, CH2, NH, and N-C1-6 alkyl; E and G are independently H, (un)substituted C1-6 alkyl, C2-6 alkenyl, etc.; W is CH and N; X and Y are independently N and (un)substituted CH; R3 is H and C1-6 alkyl; or salt form thereof, are claimed. Example compound II was prepared by amidation of 1-ethyl-3-(4-fluorophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid with 4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluorophenylamine. Invention compds. were evaluated for their AXL and c-MET inhibitory activity. From the assay, it was determined that compound II exhibited IC50 value for AXL and c-MET of <10 nM.
IT 123-30-8, 4-Aminophenol 399-96-2,
4-Amino-2-fluorophenol 35654-56-9,
4-Chloro-6,7-dimethoxyquinoline 163733-99-1,
4-Amino-2,3-difluorophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of uracil derivs. as AXL and c-MET kinase inhibitors)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



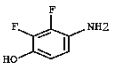
RN 399-96-2 CAPLUS
CN Phenol, 4-amino-2-fluoro- (CA INDEX NAME)



RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



RN 163733-99-1 CAPLUS
CN Phenol, 4-amino-2,3-difluoro- (CA INDEX NAME)



OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 35 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2013:761990 CAPLUS Full-text
DOCUMENT NUMBER: 158:704608
TITLE: Method of quantifying cancer treatment
INVENTOR(S): Holland, Jaymes
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 50pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2013070903	A1	20130516	WO 2012-US64134	20121108
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
CA 2854664	A1	20130516	CA 2012-2854664	20121108
AU 2012335750	A1	20140605	AU 2012-335750	20121108
AR 88813	A1	20140710	AR 2012-104223	20121108
CN 104039226	A	20140910	CN 2012-80066413	20121108
EP 2775921	A1	20140917	EP 2012-795939	20121108
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
JP 2015505360	T	20150219	JP 2014-541261	20121108
BR 112014011008	A2	20170613	BR 2014-112014011008	20121108

IN 2014CN03674	A	20150703	IN 2014-CN3674		20140515
PRIORITY APPLN. INFO.:			US 2011-61557362	P	20111108
			WO 2012-US64134	W	20121108

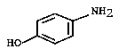
OTHER SOURCE(S): CASREACT 158:704608

AB This invention is directed to a method for quantifying cancer treatment response in patients with bone metastases using computer aided bone scan assessment, comprising: (a) obtaining a bone scan image; (b) normalizing the obtained bone scan image to identify normalized bone scan lesions; and (c) quant. assessing the normalized bone scan lesions using bone scan lesion area, bone scan intensity, or bone scan lesion count.

IT 123-30-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(quantifying cancer treatment)

RN 123-30-8 CAPLUS

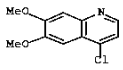
CN Phenol, 4-amino- (CA INDEX NAME)



IT 35654-56-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(quantifying cancer treatment)

RN 35654-56-9 CAPLUS

CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 36 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN

ACCESSION NUMBER: 2013:761969 CAPLUS Full-text

DOCUMENT NUMBER: 158:704607

TITLE: Dual inhibitor of Met and VEGF for treating cancer

INVENTOR(S): Aftab, Dana T.; Schimmoller, Frauke

PATENT ASSIGNEE(S): Exelixis, Inc., USA

SOURCE: PCT Int. Appl., 56pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

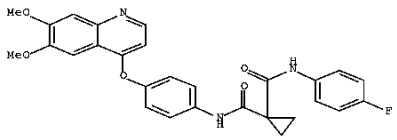
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2013070890	A1	20130516	WO 2012-US64116	20121108
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
CA 2854336	A1	20130516	CA 2012-2854336	20121108
AU 2012335737	A1	20140605	AU 2012-335737	20121108
IL 232421	A	20140630	IL 2012-232421	20121108
KR 2014088610	A	20140710	KR 2014-7015127	20121108
EP 2776033	A1	20140917	EP 2012-787328	20121108
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
CN 104159585	A	20141119	CN 2012-80066410	20121108
JP 2014532766	T	20141208	JP 2014-541256	20121108
BR 112014011009	A2	20170606	BR 2014-112014011009	20121108
MX 2014005458	A	20150416	MX 2014-5458	20140506
US 20140323522	A1	20141030	US 2014-14356927	20140508
ZA 2014003331	A	20151223	ZA 2014-3331	20140508
IN 2014CN04067	A	20151023	IN 2014-CN4067	20140530
PRIORITY APPLN. INFO.:			US 2011-61557358	P 20111108
			WO 2012-US64116	W 20121108

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASREACT 158:704607; MARPAT 158:704607

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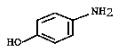


AB This invention is directed to the treatment of cancer, particularly castration-resistant prostate cancer and bone metastases, with a dual inhibitor of MET and VEGF.

IT 123-30-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(dual inhibitor of Met and VEGF for treating cancer)

RN 123-30-8 CAPLUS

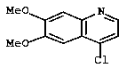
CN Phenol, 4-amino- (CA INDEX NAME)



IT 35654-56-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(dual inhibitor of Met and VEGF for treating cancer)

RN 35654-56-9 CAPLUS

CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 37 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN

ACCESSION NUMBER: 2013:644308 CAPLUS Full-text

DOCUMENT NUMBER: 158:620790

TITLE: Process for preparing quinoline derivatives

INVENTOR(S): Wilson, Jo Ann; Naganathan, Sriram; Pfeiffer, Matthew; Andersen, Neil G.

PATENT ASSIGNEE(S): Exelixis, Inc., USA

SOURCE: PCT Int. Appl., 47pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

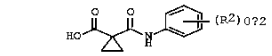
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2013059788	A1	20130425	WO 2012-US61320	20121022
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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
CA 2852771	A1	20130425	CA 2012-2852771	20121022
AU 2012325768	A1	20140522	AU 2012-325768	20121022
AU 2012325768	B2	20170810		
IL 232139	A	20140528	IL 2012-232139	20121022
AR 88483	A1	20140611	AR 2012-103944	20121022
KR 2014088874	A	20140711	KR 2014-7012435	20121022
EP 2768796	A1	20140827	EP 2012-783763	20121022
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
JP 2014530880	T	20141120	JP 2014-537359	20121022
JP 6208140	B2	20171004		
CN 104395284	A	20150304	CN 2012-80054241	20121022
NZ 624328	A	20161028	NZ 2012-624328	20121022
BR 112014009302	A2	20170523	BR 2014-112014009302	20121022
ZA 2014002579	A	20150325	ZA 2014-2579	20140409
MX 2014004583	A	20141006	MX 2014-4583	20140415
US 20140256938	A1	20140911	US 2014-14353251	20140421
US 9365516	B2	20160614		
IN 2014CN02971	A	20150703	IN 2014-CN2971	20140421
US 20160229805	A1	20160811	US 2016-15133708	20160420
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			WO 2012-US61320	W 20121022
			US 2014-14353251	A1 20140421

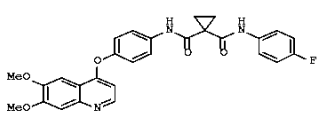
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASREACT 158:620790; MARPAT 158:620790

GI



I

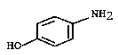


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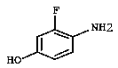
AB The invention is directed to processes for prepg. compds. of formula I (R2 is H, F, Cl and Br) by activation of 1,1-cyclopropanedicarboxylic acid with thionyl chloride followed by amidation with substituted aniline derivative Example compound II L-malate was prepared by chlorination of 6,7-dimethoxyquinolin-4-ol followed by etherification of 4-chloro-6,7-dimethoxyquinoline with 4-aminophenol; the resulting 4-(6,7-dimethoxyquinolin-4-yloxy)phenylamine underwent acylation with 1-[(4-fluorophenyl)carbamoyl]cyclopropanecarbonyl chloride to give compound II, which underwent addition of L-malic acid to give the desired product.

IT 123-30-8 399-95-1

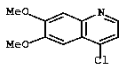
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for preparing quinoline derivs.)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



RN 399-95-1 CAPLUS
CN Phenol, 4-amino-3-fluoro- (CA INDEX NAME)



IT 35654-56-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparing quinoline derivs.)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

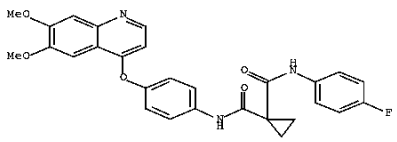


OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

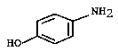
L7 ANSWER 38 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2013:466384 CAPLUS Full-text
DOCUMENT NUMBER: 158:494085
TITLE: Method for treating osteoporosis
INVENTOR(S): Aftab, Dana T.; Clary, Douglas
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 73pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2013043840	A1	20130328	WO 2012-US56281	20120920
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
CA 2848512	A1	20130328	CA 2012-2848512	20120920
AU 2012312364	A1	20140410	AU 2012-312364	20120920
IL 231495	A	20140430	IL 2012-231495	20120920
KR 2014069133	A	20140609	KR 2014-7009534	20120920
CN 103957915	A	20140730	CN 2012-80051094	20120920
EP 2758057	A1	20140730	EP 2012-770368	20120920
EP 2758057	B1	20170531		
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
JP 2014527984	T	20141023	JP 2014-531955	20120920
NZ 622722	A	20160930	NZ 2012-622722	20120920
BR 112014006702	A2	20170613	BR 2014-112014006702	20120920
AR 87995	A1	20140430	AR 2012-103501	20120921
TW I564009	B	20170101	TW 2012-134829	20120921
ZA 2014001728	A	20160127	ZA 2014-1728	20140310
MX 2014003027	A	20141024	MX 2014-3027	20140313
IN 2014CN02093	A	20141010	IN 2014-CN2093	20140319
US 20140228401	A1	20140814	US 2014-14346570	20140321
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			WO 2012-US56281 W	20120920

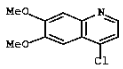
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 158:494085; MARPAT 158:494085
GI



AB This invention is directed to the treatment of osteoporosis using N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.
IT 123-30-8, 4-Aminophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(method for treating osteoporosis)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



IT 35654-56-9P, 4-Chloro-6,7-dimethoxyquinoline
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(method for treating osteoporosis)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

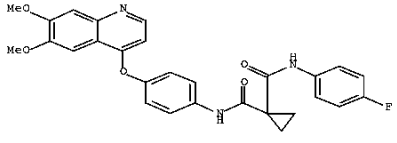


REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 39 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2012:1630842 CAPLUS Full-text
DOCUMENT NUMBER: 157:699601
TITLE: Method of treating cancer and bone cancer pain
INVENTOR(S): Schwab, Gisela; Aftab, Dana T.
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 52pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

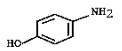
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2012151326	A1	20121108	WO 2012-US36191	20120502
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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
CA 2834778	A1	20121108	CA 2012-2834778	20120502
AR 86242	A1	20131127	AR 2012-101544	20120502
AU 2012250759	A1	20131128	AU 2012-250759	20120502
AU 2012250759	B2	20170615		
IL 229094	A	20131231	IL 2012-229094	20120502
KR 2014025496	A	20140304	KR 2013-7031635	20120502
EP 2704717	A1	20140312	EP 2012-720754	20120502
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CN 103717221	A	20140409	CN 2012-80026424	20120502
JP 2014513129	T	20140529	JP 2014-509417	20120502
BR 212013028314	U2	20151103	BR 2013-212013028314	20120502
NZ 617508	A	20160429	NZ 2012-617508	20120502
MX 2013012695	A	20140327	MX 2013-12695	20131030
ZA 2013008206	A	20140730	ZA 2013-8206	20131101
IN 2013KN03259	A	20140221	IN 2013-KN3259	20131105
US 20140179736	A1	20140626	US 2014-14115236	20140228
JP 2017105751	A	20170615	JP 2016-159543	20160816
PRIORITY APPLN. INFO.:			US 2011-61481682 P	20110502
			US 2011-61557366 P	20111108
			JP 2014-509417 A3	20120502
			WO 2012-US36191 W	20120502

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 157:699601; MARPAT 157:699601
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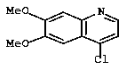


AB This invention is directed to the treatment of cancer, particularly lung cancer, breast cancer, melanoma, renal cell carcinoma, thyroid cancer that has metastasized to the bone. The invention is also directed to a method for treating bone cancer pain in an individual in need of such treatment comprising administering to the individual an effective amount of a compound of Formula I.
IT 123-30-8, 4-Aminophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(method of treating cancer and bone cancer pain)

RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



IT 35654-56-9P, 4-Chloro-6,7-dimethoxyquinoline
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(method of treating cancer and bone cancer pain)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

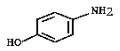


OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

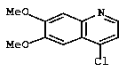
L7 ANSWER 40 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2012:1450760 CAPLUS Full-text
DOCUMENT NUMBER: 157:567006
TITLE: Method of treating cancer
INVENTOR(S): Aftab, Dana T.; Schimmoller, Frauke
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 17pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20120252840	A1	20121004	US 2012-13438964	20120404
US 20150196545	A1	20150716	US 2015-14668312	20150325
US 20160051532	A1	20160225	US 2015-14933801	20151105
PRIORITY APPLN. INFO.:			US 2011-61471367 P	20110404
			US 2012-13438964 A1	20120404
			US 2015-14668312 A1	20150325

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 157:567006
AB This invention is directed to the treatment of cancer, particularly ocular melanoma, with a dual inhibitor of MET and VEGF such as Compound 1.
IT 123-30-8, 4-Aminophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(method of treating cancer)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



IT 35654-56-9P, 4-Chloro-6,7-dimethoxyquinoline
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(method of treating cancer)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L7 ANSWER 41 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2012:1201570 CAPLUS Full-text
DOCUMENT NUMBER: 157:382704
TITLE: Processes for preparing quinoline compounds and pharmaceutical compositions containing such compounds
INVENTOR(S): Wilson, Jo Ann
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 49pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2012109510	A1	20120816	WO 2012-US24591	20120210

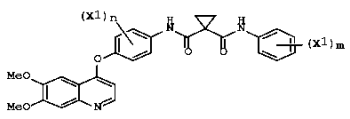
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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

CA 2826751	A1	20120816	CA 2012-2826751	20120210
AU 2012214322	A1	20130829	AU 2012-214322	20120210
AU 2012214322	B2	20170427		
AR 85155	A1	20130911	AR 2012-100446	20120210
IL 227848	A	20130930	IL 2012-227848	20120210
CN 103459373	A	20131218	CN 2012-80017723	20120210
EP 2673262	A1	20131218	EP 2012-704492	20120210

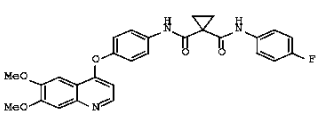
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME

JP 2014505109	T	20140227	JP 2013-553580	20120210
KR 2014044782	A	20140415	KR 2013-7023174	20120210
NZ 614130	A	20151030	NZ 2012-614130	20120210
NZ 712808	A	20170331	NZ 2012-712808	20120210
MX 2013009116	A	20140131	MX 2013-9116	20130807
ZA 2013006072	A	20140430	ZA 2013-6072	20130813
IN 2013KN02666	A	20140103	IN 2013-KN2666	20130903
US 20140200242	A1	20140717	US 2014-13984559	20140320
US 9717720	B2	20170801		
JP 2016188216	A	20161104	JP 2016-94411	20160510
US 20170057921	A1	20170302	US 2016-15348716	20161110
AU 2017204877	A1	20170803	AU 2017-204877	20170714
PRIORITY APPLN. INFO.:			US 2011-61441520 P	20110210
			US 2011-61441527 P	20110210
			AU 2012-214322 A3	20120210
			JP 2013-553580 A3	20120210
			NZ 2012-614130 A3	20120210
			WO 2012-US24591 W	20120210
			US 2014-13984559 A1	20140320

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 157:382704; MARPAT 157:382704
GI

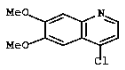


I

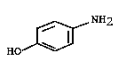


II

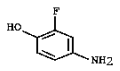
AB The invention is directed to processes for prepg. quinoline compds. of formula I wherein X1 is H, Br, Cl and F; X2 is H, Br, Cl and F; n is 1-2 and m is 1-2; and pharmaceutically acceptable salts thereof. Example compound II L-malate was prepared by chlorination of 6,7-dimethoxyquinolin-4-ol followed by etherification of 4-chloro-6,7-dimethoxyquinoline with 4-aminophenol; the resulting 4-(6,7-dimethoxyquinolin-4-yloxy)phenylamine underwent acylation with 1-[(4-fluorophenyl)carbamoyl]cyclopropanecarbonyl chloride to give compound II, which underwent addition of L-malic acid to give the desired product.
IT 35654-56-9P, 4-Chloro-6,7-dimethoxyquinoline
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparing quinoline derivs. and pharmaceutical compns. thereof)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



IT 123-30-8, 4-Aminophenol 399-96-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for preparing quinoline derivs. and pharmaceutical compns. thereof)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



RN 399-96-2 CAPLUS
CN Phenol, 4-amino-2-fluoro- (CA INDEX NAME)

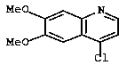


OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

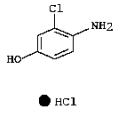
L7 ANSWER 42 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2012:975643 CAPLUS Full-text
DOCUMENT NUMBER: 157:198195
TITLE: Method for synthesizing antitumor targeting drug tivozanib
INVENTOR(S): Liu, Mingxing; Hu, Lixiu; Wu, Jianhong; Zhang, Zhixiang; Liu, Junan
PATENT ASSIGNEE(S): Wuhan Maidesen Pharmaceutical Science and Technology Co., Ltd., Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 8pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 102532116	A	20120704	CN 2011-10226114	20110809
CN 102532116	B	20150121		
PRIORITY APPLN. INFO.:			CN 2011-10226114	20110809

OTHER SOURCE(S): CASREACT 157:198195
AB The invention relates to a process for the prepn. of antitumor targeting drug tivozanib. For instance, Friedel-Crafts reaction of 1,2-dimethoxybenzene with acetyl chloride followed by nitration, reduction, and heterocyclization with Et formate gave 6,7-dimethoxy-4(1H)-quinolinone. Tivozanib was then prepared by chlorination of 6,7-dimethoxy-4(1H)-quinolinone followed by substitution with 4-amino-3-chloro-phenol hydrochloride and condensation with Ph chloroformate and 5-methyl-3-isoxazolamine.
IT 35654-56-9P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of tivozanib)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



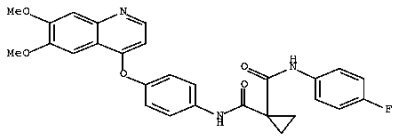
IT 52671-64-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of tivozanib)
RN 52671-64-4 CAPLUS
CN Phenol, 4-amino-3-chloro-, hydrochloride (1:1) (CA INDEX NAME)



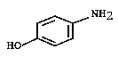
L7 ANSWER 43 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2012:495814 CAPLUS Full-text
DOCUMENT NUMBER: 156:469436
TITLE: Dual inhibitors of Met and VEGF for the treatment of castration- resistant prostate cancer and osteoblastic bone metastases
INVENTOR(S): Smith, David; Hussain, Maha
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 47pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2012044572	A1	20120405	WO 2011-US53233	20110926
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
CA 2812750	A1	20120405	CA 2011-2812750	20110926
AU 2011307304	A1	20130502	AU 2011-307304	20110926
AU 2011307304	B2	20160414		
IL 225507	A	20130530	IL 2011-225507	20110926
EP 2621481	A1	20130807	EP 2011-764655	20110926
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JP 2013537916	T	20131007	JP 2013-530386	20110926
JP 6158705	B2	20170705		
CN 103402505	A	20131120	CN 2011-80056580	20110926
KR 2014025304	A	20140304	KR 2013-7010372	20110926
NZ 707930	A	20160930	NZ 2011-707930	20110926
EA 27476	B1	20170731	EA 2013-90465	20110926
MX 2013003594	A	20130801	MX 2013-3594	20130327
ZA 2013002422	A	20131223	ZA 2013-2422	20130404
IN 2013KN00998	A	20130906	IN 2013-KN998	20130409
US 20140057943	A1	20140227	US 2013-13876290	20131105
US 20160220554	A1	20160804	US 2015-14843480	20150902
AU 2016204747	A1	20160728	AU 2016-204747	20160708
JP 2017149714	A	20170831	JP 2017-36322	20170228
PRIORITY APPLN. INFO.:			US 2010-61386959	P 20100927
			US 2011-61481671	P 20110502
			AU 2011-307304	A3 20110926
			JP 2013-530386	A3 20110926
			NZ 2011-609212	A3 20110926
			WO 2011-US53233	W 20110926
			US 2013-13876290	B1 20131105

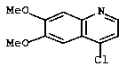
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 156:469436; MARPAT 156:469436
GI



AB This invention is directed to the treatment of cancer, particularly castration-resistant prostate cancer and osteoblastic bone metastases, with a dual inhibitor of MET and VEGF.
IT 123-30-8, 4-Aminophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(dual inhibitors of Met and VEGF for treatment of castration resistant prostate cancer and osteoblastic bone metastases)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



IT 35654-56-9P, 4-Chloro-6,7-dimethoxyquinoline
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(dual inhibitors of Met and VEGF for treatment of castration resistant prostate cancer and osteoblastic bone metastases)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

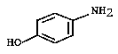


OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

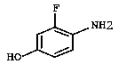
L7 ANSWER 44 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2012:495788 CAPLUS Full-text
DOCUMENT NUMBER: 156:469435
TITLE: Dual inhibitors of Met and VEGF for the treatment of castration resistant prostate cancer and osteoblastic bone metastases
INVENTOR(S): Smith, David; Hussain, Maha
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 70pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2012044577	A1	20120405	WO 2011-US53245	20110926
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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
CA 2812744	A1	20120405	CA 2011-2812744	20110926
AU 2011307309	A1	20130502	AU 2011-307309	20110926
EP 2621483	A1	20130807	EP 2011-764657	20110926
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR				
JP 2013537918	T	20131007	JP 2013-530392	20110926
CN 103391773	A	20131113	CN 2011-80056999	20110926
US 20140057908	A1	20140227	US 2013-13876306	20131108
PRIORITY APPLN. INFO.:			US 2010-61386971	P 20100927
			US 2010-61386983	P 20100927
			US 2010-61386993	P 20100927
			WO 2011-US53245	W 20110926

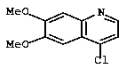
OTHER SOURCE(S): CASREACT 156:469435; MARPAT 156:469435
AB This invention discloses compds. directed at the treatment of cancer, particularly castration- resistant prostate cancer and osteoblastic bone metastases, with a dual inhibitor of MET and VEGF.
IT 123-30-8, 4-Aminophenol 399-95-1, 2-Fluoro-4-hydroxyaniline
RL: RCT (Reactant); RACT (Reactant or reagent)
(dual inhibitors of Met and VEGF for treatment of castration resistant prostate cancer and osteoblastic bone metastases)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



RN 399-95-1 CAPLUS
CN Phenol, 4-amino-3-fluoro- (CA INDEX NAME)

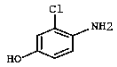


IT 35654-56-9P, 4-Chloro-6,7-dimethoxyquinoline
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(dual inhibitors of Met and VEGF for treatment of castration resistant prostate cancer and osteoblastic bone metastases)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

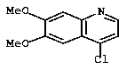


OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 45 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2012:247673 CAPLUS Full-text
DOCUMENT NUMBER: 156:533720
TITLE: Synthesis of anticancer targeted therapies drug tivozanib
AUTHOR(S): Liu, Mingxing; Hu, Lixiu; Wang, Xianwen; Zhu, Hongda
CORPORATE SOURCE: Department of Pharmacy, College of Bioengineering, Hubei University of Technology, Wuhan, 430068, Peop. Rep. China
SOURCE: Advanced Materials Research (Durnten-Zurich, Switzerland) (2012), 396-398(Pt. 2, Advances in Chemical Engineering), 1490-1492
CODEN: AMREFI; ISSN: 1022-6680
DIGITAL OBJECT ID: 10.4028/www.scientific.net/AMR.396-398.1490
PUBLISHER: Trans Tech Publications Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 156:533720
AB Tivozanib was synthesized through the cyclization, chlorinated, condensation reaction with 2-amino-4,5-dimethoxyacetophenone as the starting material. All synthetic compds. were analyzed by FT-IR, 1H-NMR, MS and HPLC. The purity of tivozanib was more than 98.5%. Synthetic routes and methods of tivozanib are feasible to industrial production owing to the cheap raw materials, mild reaction conditions, stable technol. and high yield.
IT 17609-80-2, 4-Amino-3-chlorophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of anticancer tivozanib starting from dimethoxy-o-aminoacetophenone Et formate via cyclization, chlorination, condensations)
RN 17609-80-2 CAPLUS
CN Phenol, 4-amino-3-chloro- (CA INDEX NAME)



IT 35654-56-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of anticancer tivozanib starting from dimethoxy-o-aminoacetophenone Et formate via cyclization, chlorination, condensations)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



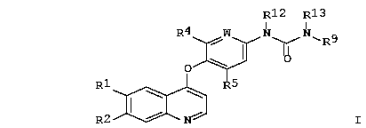
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 46 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2012:96895 CAPLUS Full-text
DOCUMENT NUMBER: 156:175266
TITLE: Preparation of nitrogenated aromatic heterocyclic compounds as FGFR (fibroblast growth factor receptor) inhibitors
INVENTOR(S): Furuta, Takayuki; Kubo, Kazuo; Nakoji, Masayoshi; Kawai, Ryohei
PATENT ASSIGNEE(S): Kyowa Hakko Kirin Co., Ltd., Japan
SOURCE: PCT Int. Appl., 113pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

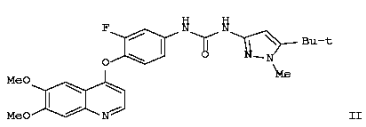
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2012008564	A1	20120119	WO 2011-JP66186	20110715

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: JP 2010-161272 A 20100716
OTHER SOURCE(S): CASREACT 156:175266; MARPAT 156:175266
GI

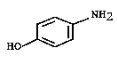


I



II

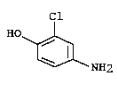
AB Disclosed are compds. I [R1, R2 = H, hydroxy, (un)substituted alkylsulfonyloxy, etc.; W = CR3 or nitrigen atom; R3 = H, alkoxy or halo; R4, R5 = H or halo; R9 = (un)substituted pyrazolyl or (un)substituted isoxazolyl; R12, R13 = H or alkyl; or pharmaceutically acceptable salts thereof]. Thus, compound II was prepared via cyclocondensation of Et 5,5-dimethyl-2,4-dioxohexanoate with methylhydrazine sulfate, hydrolysis and treatment with (PhO)2PON3/4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluoroaniline. In inhibition assay of FGFR2-phosphorylation, the selected invention compds., e.g., II, exhibited IC50 of <100 nmol/L. Compds. I are claimed useful for the treatment of stomach cancer.
IT 123-30-8, 4-Aminophenol 3096-69-3, 4-Amino-2,3-dimethylphenol 7248-09-1, 4-Amino-2-chlorophenol hydrochloride 35654-56-9, 4-Chloro-6,7-dimethoxyquinoline
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of nitrogenated aromatic heterocyclic compds. as FGFR inhibitors)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



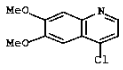
RN 3096-69-3 CAPLUS
CN Phenol, 4-amino-2,3-dimethyl- (CA INDEX NAME)



RN 7248-09-1 CAPLUS
CN Phenol, 4-amino-2-chloro-, hydrochloride (1:1) (CA INDEX NAME)



RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

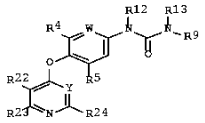


REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 47 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2012:96817 CAPLUS Full-text
DOCUMENT NUMBER: 156:167650
TITLE: Nitrogen-containing heteroaromatic compounds, and pharmaceuticals, fibroblast growth factor receptor inhibitors, and antitumor agents containing them
INVENTOR(S): Furuta, Takayuki; Kubo, Kazuo; Atsumi, Toshiyuki; Yamanouchi, Maasa
PATENT ASSIGNEE(S): Kyowa Hakko Kirin Co., Ltd., Japan
SOURCE: PCT Int. Appl., 103pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

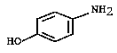
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2012008563	A1	20120119	WO 2011-JP66185	20110715
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
CN 103003262	A	20130327	CN 2011-80035144	20110715
EP 2594566	A1	20130522	EP 2011-806893	20110715
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR				
KR 2013091331	A	20130816	KR 2013-7003633	20110715
JP 5789259	B2	20151007	JP 2012-524602	20110715
US 20130225581	A1	20130829	US 2013-13810568	20130328

PRIORITY APPLN. INFO.: JP 2010-161272 A 20100716
WO 2011-JP66185 W 20110715
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 156:167650; MARPAT 156:167650
GI

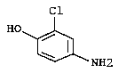


I

AB N-contg. heteroarom. compds. I [W = CR3 (R3 = H, lower alkyl, lower alkoxy, halo), N; R4 = H, lower alkyl, halo; R5 = H, lower alkyl; R9 = substituted imidazolyl; R12, R13 = H, (un)substituted aryl, (un)substituted heteroaryl, CONR26R27 (R26, R27 = H, lower alkyl, heteroaryl); R26 and R27 may be bonded to form a (un)substituted benzene or thiophene ring; R24 = H, lower alkyl; Y = CR25 (R25 = H, lower alkyl), N] or their pharmacol. acceptable salts, are useful for therapy and/or prophylaxis of FGF receptor-related diseases and neoplasm, especially gastric cancer. Thus, IC50 of 1-[2-tert-butyl-4-(1-methyl-1H-pyrazol-5-yl)-1H-imidazol-5-yl]-3-[4-(6,7-dimethoxyquinolin-4-yloxy)phenyl]urea (II; preparation given) against human FGFR2 activity was <100 nmol/L. IC50 of II against proliferation of OCUM-2MD3 human scirrhous gastric cancer cell was <30 nmol/L.
IT 123-30-8, 4-Aminophenol 7248-09-1, 4-Amino-2-chlorophenol hydrochloride 35654-56-9, 4-Chloro-6,7-dimethoxyquinoline
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of nitrogen-containing heteroarom. compds. for treatment of FGF receptor-related diseases and neoplasm, especially gastric cancer)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)

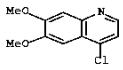


RN 7248-09-1 CAPLUS
CN Phenol, 4-amino-2-chloro-, hydrochloride (1:1) (CA INDEX NAME)



● HCl

RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

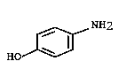


REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

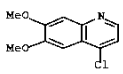
L7 ANSWER 48 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2012:90800 CAPLUS Full-text
DOCUMENT NUMBER: 156:186804
TITLE: C-met modulator pharmaceutical compositions comprising N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide
INVENTOR(S): Wilson, Jo Ann
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 40pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2012009722	A1	20120119	WO 2011-US44378	20110718
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
CA 2805645	A1	20120119	CA 2011-2805645	20110718
AR 82252	A1	20121121	AR 2011-102584	20110718
AU 2011278950	A1	20130307	AU 2011-278950	20110718
AU 2011278950	B2	20160721		
IL 224189	A	20130324	IL 2011-224189	20110718
EP 2593090	A1	20130522	EP 2011-740764	20110718
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
CN 103221035	A	20130724	CN 2011-80044602	20110718
JP 2013531045	T	20130801	JP 2013-519870	20110718
JP 5934204	B2	20160615		
KR 2013137586	A	20131217	KR 2013-7003043	20110718
NZ 607118	A	20150529	NZ 2011-607118	20110718
TW I516477	B	20160111	TW 2011-125336	20110718
SG 10201609324	A1	20170127	SG 2016-10201609324	20110718
CN 106420743	A	20170222	CN 2016-10157218	20110718
IN 2013KN00112	A	20130705	IN 2013-KN112	20130114
MX 2013000567	A	20130501	MX 2013-567	20130115
ZA 2013000458	A	20130925	ZA 2013-458	20130117
US 20130337015	A1	20131219	US 2013-13810537	20130826
US 9724342	B2	20170808		
JP 2016188215	A	20161104	JP 2016-93433	20160506
AU 2016247044	A1	20161103	AU 2016-247044	20161018
US 20170143689	A1	20170525	US 2017-15426804	20170207
US 20170266178	A1	20170921	US 2017-15612703	20170602

PRIORITY APPLN. INFO.: US 2010-61365253 P 20100716
US 2010-61370843 P 20100805
AU 2011-278950 A3 20110718
CN 2011-80044602 A3 20110718
JP 2013-519870 A3 20110718
WO 2011-US44378 W 20110718
US 2013-13810537 A3 20130826
US 2017-15426804 A3 20170207
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 156:186804
AB Pharmaceutical compns. and unit dosage forms comprising N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (I) are disclosed. Thus, 6,7-dimethoxyquinolin-4-ol was converted to 4-chloro-6.7-dimethoxyquinoline followed by reaction with 4-aminphenol to give 4-(6,7-dimethoxy-quinolin-4-yloxy)-phenylamine. This was further allowed to react with 1-(4-fluorophenylcarbamoyl)cyclopropanecarbonyl chloride to give I. A tablet composition comprised 31.68% along with excipients such as microcryst. cellulose 38.85, lactose, HPC, and Croscarmellose sodium.
IT 123-30-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(C-met modulator pharmaceutical compns. comprising dimethoxyquinolinyloxyphenyl(fluorophenyl)cyclopropanedicarboxamide)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)

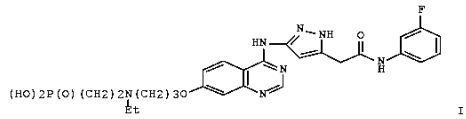


IT 35654-56-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(C-met modulator pharmaceutical compns. comprising dimethoxyquinolinyloxyphenyl(fluorophenyl)cyclopropanedicarboxamide)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



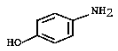
OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 49 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2012:28810 CAPLUS Full-text
DOCUMENT NUMBER: 156:175215
TITLE: Discovery of AZD2932, a new Quinazoline Ether Inhibitor with high affinity for VEGFR-2 and PDGFR tyrosine kinases
AUTHOR(S): Ple, Patrick A.; Jung, Frederic; Ashton, Sue; Hennequin, Laurent; Laine, Romuald; Morgentin, Remy; Pasquet, Georges; Taylor, Sian
CORPORATE SOURCE: Centre de Recherches, AstraZeneca, Reims, 51689, Fr.
SOURCE: Bioorganic & Medicinal Chemistry Letters (2012), 22(1), 262-266
CODEN: BMCLE8; ISSN: 0960-894X
DIGITAL OBJECT ID: 10.1016/j.bmcl.2011.11.019
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
OTHER SOURCE(S): CASREACT 156:175215
GI

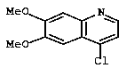


I

AB A new series of quinazolinyloxy- and quinazolinylamonopyrazoleacetamides which inhibits VEGFR-2 and PDGFR tyrosine kinases is described here. In vitro, pharmacokinetics and in vivo evaluations led to the selection of AZD2932 (I).
IT 123-30-8, 4-Aminophenol 35654-56-9, 4-Chloro-6,7-dimethoxyquinoline
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of N-aryl-5-(quinazolin-4-ylamino)pyrazole-3-acetamides with high affinity for VEGFR-2 and PDGFR tyrosine kinases)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



OS.CITING REF COUNT: 9 THERE ARE 9 CAPLUS RECORDS THAT CITE THIS RECORD (9 CITINGS)
REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 50 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2009:1402348 CAPLUS Full-text
DOCUMENT NUMBER: 151:550574
TITLE: Preparation of fused heterocyclic derivatives as kinase inhibitors
INVENTOR(S): Miyamoto, Naoki; Matsumoto, Shigemitsu; Imamura, Shinichi
PATENT ASSIGNEE(S): Takeda Pharmaceutical Company Limited, Japan
SOURCE: PCT Int. Appl., 340pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

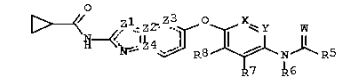
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009136663	A1	20091112	WO 2009-JP58962	20090507

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE,

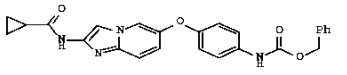
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RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

US 20110046169	A1	20110224	US 2010-990760	20101102
US 8445509	B2	20130521		

PRIORITY APPLN. INFO.: JP 2008-122789 A 20080508
JP 2008-306661 A 20081201
WO 2009-JP58962 W 20090507
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 151:550574; MARPAT 151:550574
GI

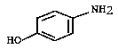


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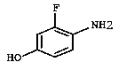


II

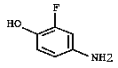
AB The title compds. I [(Z1,Z2,Z3,Z4) = (CR1,N,CR2,C), (N,N,CR2,C), (N,C,CR2,N), (S,C,CR2,C) or (S,C,N,C); R1, R2 = H, halo, etc.; W = O, S; X = CR3, N (wherein R3 = H, halo, alkyl); Y = CR4, N (R4 = H, halo, alkyl); R5 = cycloalkyl optionally having one aryl-aminocarbonyl, alkyl-carbonylamino optionally having one aryl, alkoxy optionally having one aryl, etc.; R6 = H; R7, R8 = H, halo, alkyl] having a strong kinase inhibitory activity, were prepared and formulated. Thus, reacting benzyl [4-[(2-aminoimidazo[1,2-a]pyridin-6-yl)oxy]phenyl]carbamate with cyclopropanecarbonyl chloride in N,N-dimethylacetamide afforded 87% II. Exemplified compds. I were tested against various kinases and in antitumor tests (data given for representative compds. I).
IT 123-30-8, 4-Aminophenol 399-95-1, 4-Amino-3-fluorophenol 399-96-2, 4-Amino-2-fluorophenol 35654-56-9, 4-Chloro-6,7-dimethoxyquinoline
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of fused heterocyclic derivs. as kinase inhibitors for treating cancer)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



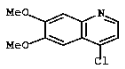
RN 399-95-1 CAPLUS
CN Phenol, 4-amino-3-fluoro- (CA INDEX NAME)



RN 399-96-2 CAPLUS
CN Phenol, 4-amino-2-fluoro- (CA INDEX NAME)



RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

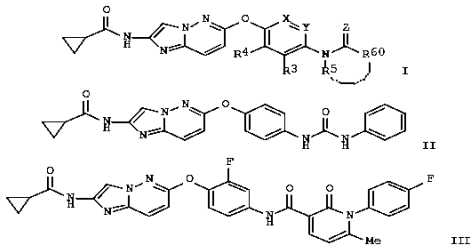
L7 ANSWER 51 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2009:944300 CAPLUS Full-text
DOCUMENT NUMBER: 151:245679
TITLE: Preparation of 6-(imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide derivatives as protein kinase inhibitors and anticancer agents
INVENTOR(S): Miyamoto, Naoki; Matsumoto, Shigemitsu; Imamura, Shinichi; Hirayama, Takaharu
PATENT ASSIGNEE(S): Takeda Pharmaceutical Company Limited, Japan

SOURCE: PCT Int. Appl., 184pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009096435	A1	20090806	WO 2009-JP51383	20090128

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: JP 2008-18367 A 20080129
JP 2008-276354 A 20081028
OTHER SOURCE(S): CASREACT 151:245679; MARPAT 151:245679
GI



I

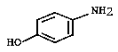
II

III

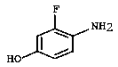
AB This invention pertains to condensed heterocyclic compds. represented by formula [I; X = N, CR1; Y = N, CR2; R1-R4 = H, halo, C1-6 alkyl; R60 = each (un)substituted C6-10 arylamino, N-containing 5- or 6-membered ring group, or aromatic heterocyclyl, C7-12 aralkylcarbonylamino, C7-12 aralkyloxy; Z = O, S] and salts thereof. These compds. are potent kinase inhibitors with reduced toxicity and useful for preventing and/or treating cancer. Thus, a suspension of N-[6-(4-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide in 12.0 mL toluene was heated to 100°, treated with 84.3 μL Ph isocyanate, and stirred at 110° for 1 h to give 76% N-(6-(4-[(phenylcarbamoyl)amino]phenoxy)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (II). The compound (III) inhibited 100% VEGFR-2 (Vascular endothelial growth factor receptor type VEGFR-2) kinase and c-Met kinase, 90% the proliferation of human umbilical vein endothelial cells (HUVEC), and 93% the proliferation of human stomach cancer MKN45 cells. A capsule, a tablet, and a injection vial formulation containing II were prepared

IT 123-30-8, 4-Aminophenol 399-95-1, 4-Amino-3-fluorophenol 399-96-2, 4-Amino-2-fluorophenol 2835-96-3, 4-Amino-2-methylphenol 2835-99-6, 4-Amino-3-methylphenol 3964-52-1, 4-Amino-2-chlorophenol 17609-80-2, 4-Amino-3-chlorophenol 35654-56-9, 4-Chloro-6,7-dimethoxyquinoline
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of 6-(imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide derivs. as protein kinase inhibitors and anticancer agents)

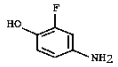
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



RN 399-95-1 CAPLUS
CN Phenol, 4-amino-3-fluoro- (CA INDEX NAME)



RN 399-96-2 CAPLUS
CN Phenol, 4-amino-2-fluoro- (CA INDEX NAME)



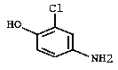
RN 2835-96-3 CAPLUS
CN Phenol, 4-amino-2-methyl- (CA INDEX NAME)



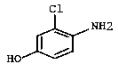
RN 2835-99-6 CAPLUS
CN Phenol, 4-amino-3-methyl- (CA INDEX NAME)



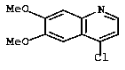
RN 3964-52-1 CAPLUS
CN Phenol, 4-amino-2-chloro- (CA INDEX NAME)



RN 17609-80-2 CAPLUS
CN Phenol, 4-amino-3-chloro- (CA INDEX NAME)



RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 52 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2009:576501 CAPLUS Full-text
DOCUMENT NUMBER: 150:515173
TITLE: Preparation of fused azoles such as 2,5-disubstituted benzimidazoles, benzoxazoles and benzothiazoles as kinase inhibitors
INVENTOR(S): Di Pietro, Lucian V.; Harmange, Jean-Christophe; Askew, Benny C., Jr.; Elbaum, Daniel; Germain, Julie; Habgood, Gregory J.; Kim, Joseph L.; Patel, Vinod F.; Potashman, Michele; Van Der Plas, Simon
PATENT ASSIGNEE(S): Amgen Inc., USA
SOURCE: U.S., 95pp.; Chemical Indexing Equivalent to 141:332190 (WO)
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 7531553	B2	20090512	US 2004-804915	20040319
US 20040209892	A1	20041021		
AU 2004223827	A1	20041007	AU 2004-223827	20040322
AU 2004223827	B2	20080306		
CA 2518909	A1	20041007	CA 2004-2518909	20040322
WO 2004085425	A1	20041007	WO 2004-US8809	20040322

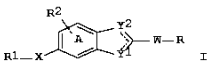
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RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1638954	A1	20060329	EP 2004-758050	20040322
JP 2006520805	T	20060914	JP 2006-507472	20040322
MX 2005010086	A	20060210	MX 2005-10086	20050921

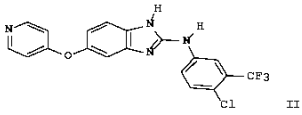
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PRIORITY APPLN. INFO.:	US 2003-60456691	P	20030321
	US 2004-804915	A	20040319
	WO 2004-US8809	A	20040322

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 150:515173
GI



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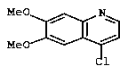


II

AB Title compds. I [W, X, Y1 and Y2 independently = O, S(O)n and NR3; ring A optionally contains a N atom at a non-fused, non-substituted ring position; n = 0-2; R = (un)substituted-aryl, -heterocyclyl, -fused heterocyclyl, etc.; R1 = (un)substituted-aryl, -arylalkyl, -heterocyclyl, etc.; R2 = H, halo, alkoxy, etc.; R3 = H or alkyl] are prepared and disclosed as having kinase inhibitory activity, such as VEGFR/KDR inhibitory activity. Thus, e.g., II was prepared by cyclocondensation of 4-(pyridin-4-yloxy)benzene-1,2-diamine with 1-chloro-4-isothiocyanato-2-trifluoromethylbenzene. In human umbilical vein endothelial cell proliferation assay, selected I inhibited VEGF-stimulated proliferation at a level below 100 nM. Accordingly, I would be useful in the prevention and treatment of angiogenesis related disorders, ophthalmol. conditions, proliferative diseases, inflammatory diseases, and other pathol. conditions as described in the specification.

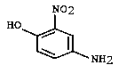
IT 35654-56-9P
RL: PRPH (Prophetic); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of benzimidazole, benzoxazole and benzothiazole derivs. as kinase inhibitors)

RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

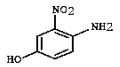


IT 119-34-6 610-81-1, 4-Amino-3-nitrophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of benzimidazole, benzoxazole and benzothiazole derivs. as kinase inhibitors)

RN 119-34-6 CAPLUS
CN Phenol, 4-amino-2-nitro- (CA INDEX NAME)



RN 610-81-1 CAPLUS
CN Phenol, 4-amino-3-nitro- (CA INDEX NAME)



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

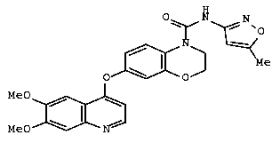
L7 ANSWER 53 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2009:549474 CAPLUS Full-text
DOCUMENT NUMBER: 150:494882
TITLE: Preparation of isoxazolyl quinolinylmethoxymethylbenzoxazinecarboxamides for treatment of VEGF mediated disease.
INVENTOR(S): Harmange, Jean-Christophe; William, Matthew W.; Teffera, Yohannes; Subramanian, Raju; White, Ryan; Zanon, Roger; Larrow, Jay; Payack, Joseph F.; Dilmeghani Seran, Mina
PATENT ASSIGNEE(S): Amgen Inc., USA
SOURCE: PCT Int. Appl., 62pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009058267	A2	20090507	WO 2008-US12224	20081028
WO 2009058267	A3	20100610		

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

AU 2008319366	A1	20090507	AU 2008-319366		20081028
AU 2008319366	B2	20120301			
CA 2703257	A1	20090507	CA 2008-2703257		20081028
CA 2703257	C	20130219			
US 20090149454	A1	20090611	US 2008-290223		20081028
US 7795254	B2	20100914			
EP 2220078	A2	20100825	EP 2008-845711		20081028
EP 2220078	B1	20130522			
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JP 2011502147	T	20110120	JP 2010-532037		20081028
JP 5343082	B2	20131113			
ES 2417009	T3	20130805	ES 2008-845711		20081028
MX 2010004620	A	20100728	MX 2010-4620		20100427
PRIORITY APPLN. INFO.:			US 2007-61000948	P	20071029
			WO 2008-US12224	W	20081028

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 150:494882
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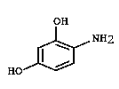


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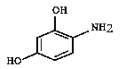
AB Title compd. (I) and 4 metabolites thereof were prepd. Thus, 7-(6,7-dimethoxyquinolin-4-yloxy)-3,4-dihydro-2H-benzo[b][1,4]oxazine (preparation given), Ph 5-methylisoxazol-3-ylcarbamate (preparation given) and KOCMe3 were heated in N-methylpyrrolidone/EtOAc at 65° to give 92% I. I inhibited VEGF induced proliferation of HUVEC cells with IC50 = 2 nM.

IT 13066-95-0 34781-86-7, 4-Aminoresorcinol hydrochloride 35654-56-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of isoxazolyl quinolinylmethoxymethylbenzoxazinecarboxamides for treatment of VEGF mediated disease)

RN 13066-95-0 CAPLUS
CN 1,3-Benzenediol, 4-amino- (CA INDEX NAME)

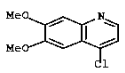


RN 34781-86-7 CAPLUS
CN 1,3-Benzenediol, 4-amino-, hydrochloride (1:1) (CA INDEX NAME)



● HCl

RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L7 ANSWER 54 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2008:501397 CAPLUS Full-text
DOCUMENT NUMBER: 148:495976
TITLE: Preparation of pyridonecarboxamide derivatives for treating hyper-proliferative and angiogenesis disorders
INVENTOR(S): Boyer, Stephen; Cantin, David; Liang, Sidney X.
PATENT ASSIGNEE(S): Bayer Healthcare A.-G., Germany
SOURCE: PCT Int. Appl., 72pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

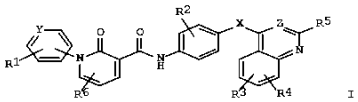
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008048375	A1	20080424	WO 2007-US11981	20070518

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW,

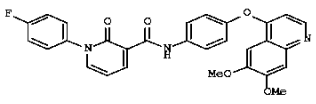
GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

CA 2652417	A1	20080424	CA 2007-2652417	20070518
EP 2023926	A1	20090218	EP 2007-861312	20070518
EP 2023926	B1	20111012		
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, RS				
JP 2009537632	T	20091029	JP 2009-512061	20070518
AT 528002	T	20111015	AT 2007-861312	20070518
US 20090306103	A1	20091210	US 2009-300751	20090520
PRIORITY APPLN. INFO.:			US 2006-60801700 P	20060519
			WO 2007-US11981 W	20070518

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 148:495976; MARPAT 148:495976
GI



I

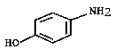


II

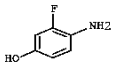
AB The title compds. I [X = O or S; Y and Z = CH or N; R1 = H, halo, CN, etc.; R2 = H, halo, alkoxy, etc.; R3, R4 = H, halo, CN, etc.; R5 = H, (un)substituted OH, NH2, etc.; R6 = H, alkoxy, (un)substituted NH2, etc.], useful for treating hyper-proliferative disorders and angiogenesis disorders, were prepared and formulated. E.g., a multi-step synthesis of II, starting from 2-amino-4,5-dimethoxyacetophenone, was given. Compds. I were tested in Flk-1, c-Met and Bcr-Abl assays and showed IC50 of <3 μM in one or more of the these assays.

IT 123-30-8, 4-Aminophenol 399-95-1, 4-Amino-3-fluorophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of novel pyridonecarboxamides for use in mono- and combination therapy of hyperproliferative and angiogenesis disorders)

RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)

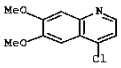


RN 399-95-1 CAPLUS
CN Phenol, 4-amino-3-fluoro- (CA INDEX NAME)



IT 35654-56-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of novel pyridonecarboxamides for use in mono- and combination therapy of hyperproliferative and angiogenesis disorders)

RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

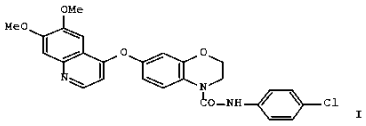


REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 55 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN

ACCESSION NUMBER:	2008:244482 CAPLUS Full-text
DOCUMENT NUMBER:	148:417251
TITLE:	Novel 2,3-Dihydro-1,4-Benzoxazines as Potent and Orally Bioavailable Inhibitors of Tumor-Driven Angiogenesis
AUTHOR(S):	La, Daniel S.; Belzile, Julie; Bready, James V.; Coxon, Angela; DeMelfi, Thomas; Doerr, Nicholas; Estrada, Juan; Flynn, Julie C.; Flynn, Shaun R.; Graceffa, Russell F.; Harriman, Shawn P.; Larrow, Jay F.; Long, Alexander M.; Martin, Matthew W.; Morrison, Michael J.; Patel, Vinod F.; Roveto, Philip M.; Wang, Ling; Weiss, Matthew M.; Whittington, Douglas A.; Teffera, Yohannes; Zhao, Zhiyang; Polverino, Anthony J.; Harmange, Jean-Christophe
CORPORATE SOURCE:	Chemistry Research and Discovery, Amgen Inc., Cambridge, MA, 02139, USA
SOURCE:	Journal of Medicinal Chemistry (2008), 51(6), 1695-1705
	CODEN: JMCMAR; ISSN: 0022-2623
DIGITAL OBJECT ID:	10.1021/jm701129j
PUBLISHER:	American Chemical Society
DOCUMENT TYPE:	Journal
LANGUAGE:	English
OTHER SOURCE(S):	CASREACT 148:417251

GI

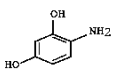


I

AB Angiogenesis is vital for solid tumor growth, and its prevention is a proven strategy for the treatment of disease states such as cancer. The vascular endothelial growth factor (VEGF) pathway provides several opportunities by which small mols. can act as inhibitors of endothelial proliferation and migration. Critical to these processes is signaling through VEGFR-2 or the kinase insert domain receptor (KDR) upon stimulation by its ligand VEGF. Herein, the authors report the discovery of 2,3-dihydro-1,4-benzoxazines as inhibitors of intrinsic KDR activity (IC50 < 0.1 μM) and human umbilical vein endothelial cell (HUVEC) proliferation with IC50 < 0.1 μM. More specifically, compound (I) was identified as a potent (KDR: < 1 nM and HUVEC: 4 nM) and selective inhibitor that exhibited efficacy in angiogenic in vivo models. In addition, this series of mols. is typically well-absorbed orally, further demonstrating the 2,3-dihydro-1,4-benzoxazine moiety as a promising platform for generating kinase-based antiangiogenic therapeutic agents.

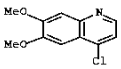
IT 34781-86-7 35654-56-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(novel 2,3-dihydro-1,4-benzoxazines as potent and orally bioavailable inhibitors of tumor-driven angiogenesis)

RN 34781-86-7 CAPLUS
CN 1,3-Benzenediol, 4-amino-, hydrochloride (1:1) (CA INDEX NAME)



● HCl

RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



OS.CITING REF COUNT: 44 THERE ARE 44 CAPLUS RECORDS THAT CITE THIS RECORD (44 CITINGS)
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

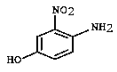
L7 ANSWER 56 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN

ACCESSION NUMBER:	2008:70351 CAPLUS Full-text
DOCUMENT NUMBER:	148:205324
TITLE:	Design, synthesis, and evaluation of orally active benzimidazoles and benzoxazoles as vascular endothelial growth factor-2 receptor tyrosine kinase inhibitors. [Erratum to document cited in CA147:439495]
AUTHOR(S):	Potashman, Michele H.; Bready, James; Coxon, Angela; DeMelfi, Thomas M.; DiPietro, Lucian; Doerr, Nicholas; Elbaum, Daniel; Estrada, Juan; Gallant, Paul; Germain, Julie; Gu, Yan; Harmange, Jean-Christophe; Kaufman, Stephen A.; Kendall, Rick; Kim, Joseph L.; Kumar, Gondi N.; Long, Alexander M.; Neervannan, Seshadri; Patel, Vinod F.; Polverino, Anthony; Rose, Paul; van der Plas, Simon; Whittington, Douglas; Zanon, Roger; Zhao, Huilin
CORPORATE SOURCE:	Department of Medicinal Chemistry, Amgen Inc., Cambridge, MA, 02139, USA
SOURCE:	Journal of Medicinal Chemistry (2008), 51(3), 699
	CODEN: JMCMAR; ISSN: 0022-2623
DIGITAL OBJECT ID:	10.1021/jm800006z
PUBLISHER:	American Chemical Society
DOCUMENT TYPE:	Journal
LANGUAGE:	English

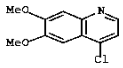
AB On page 4351, coauthor Roger Zanon is incorrectly listed as a corresponding author with an asterisk by his name; That symbol should be an open circle indicating his affiliation with the Department of Pharmaceutics.

IT 610-81-1, 4-Amino-3-nitrophenol 35654-56-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(Design, Synthesis, and Evaluation of Orally Active Benzimidazoles and Benzoxazoles as Vascular Endothelial Growth Factor-2 Receptor Tyrosine Kinase Inhibitors (Erratum))

RN 610-81-1 CAPLUS
CN Phenol, 4-amino-3-nitro- (CA INDEX NAME)



RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

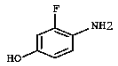


OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

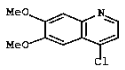
L7 ANSWER 57 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2007:1311820 CAPLUS Full-text
DOCUMENT NUMBER: 148:135016
TITLE: Synthesis and structure-activity relationships of potent antitumor active quinoline and naphthyridine derivatives
AUTHOR(S): Srivastava, Sanjay K.; Jha, Amrita; Agarwal, Shiv K.; Mukherjee, Rama; Burman, Anand C.
CORPORATE SOURCE: Medicinal Chemistry, Dabur Research Foundation, Ghaziabad, 201 010, India
SOURCE: Anti-Cancer Agents in Medicinal Chemistry (2007), 7(6), 685-709
CODEN: AAMCE4; ISSN: 1871-5206
DIGITAL OBJECT ID: 10.2174/187152007784111313
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The disease of cancer has been ranked second after cardiovascular diseases and plant-derived mols. have played an important role for the treatment of cancer. Nine cytotoxic plant-derived mols. such as vinblastine, vincristine, navelbine, etoposide, teniposide, taxol, taxotere, topotecan and irinotecan have been approved as anticancer drugs. Recently, epothilones are being emerging as future potential anti-tumor agents. However, targeted cancer therapy has now been rapidly expanding and small organic mols. are being exploited for this purpose. Amongst target specific small organic mols., quinazoline was found as one of the most successful chemical class in cancer chemotherapy as three drugs namely Gefitinib, Erlotinib and Canertinib belong to this series. Now, quinazoline related chemical classes such as quinolines and naphthyridines are being exploited in cancer chemotherapy and a number of mols. such as compds. EKB-569 (52), HKI-272 (78) and SNS-595 (127a) are in different phases of clin. trials. This review presents the synthesis of quinolines and naphthyridines derivs., screened for anticancer activity since year 2000. The synthesis of most potent derivs. in each prototype has been delineated. A brief structure activity relationship for each prototype has also been discussed. It has been observed that aniline group at C-4, aminoacrylamide substituents at C-6, cyano group at C-3 and alkoxy groups at C-7 in the quinoline ring play an important role for optimal activity. While aminopyrrolidine functionality at C-7, 2'-thiazolyl at N-1 and carboxy group at C-3 in 1,8-naphthyridine ring are essential for eliciting the cytotoxicity. This review would help the medicinal chemist to design and synthesize mols. for targeted cancer chemotherapy.

IT 399-95-1, 4-Amino-3-fluorophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(Synthesis and structure-activity relationships of potent antitumor active quinoline and naphthyridine derivs.)
RN 399-95-1 CAPLUS
CN Phenol, 4-amino-3-fluoro- (CA INDEX NAME)



IT 35654-56-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(Synthesis and structure-activity relationships of potent antitumor active quinoline and naphthyridine derivs.)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



OS.CITING REF COUNT: 32 THERE ARE 32 CAPLUS RECORDS THAT CITE THIS RECORD (32 CITINGS)
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

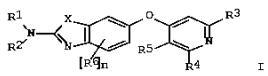
L7 ANSWER 58 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2007:1209424 CAPLUS Full-text
DOCUMENT NUMBER: 147:486428
TITLE: Preparation of 6-O-substituted benzoxazole and benzothiazole compounds for inhibiting CSF-1R signaling
INVENTOR(S): Sutton, James C.; Wiesmann, Marion; Wang, Weibo; Lindvall, Mika K.; Lan, Jiong; Ramurthy, Savithri; Sharma, Anu; Mieuli, Elizabeth J.; Klivansky, Liana M.; Lenahan, William P.; Kaufman, Susan; Yang, Hong; Ng, Simon C.; Pfister, Keith; Wagman, Allan; Sung, Victoria; Sendzik, Martin
PATENT ASSIGNEE(S): Novartis AG, Switz.
SOURCE: PCT Int. Appl., 280 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007121484	A2	20071025	WO 2007-US66898	20070418
WO 2007121484	A3	20080207		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA				
AU 2007237904	A1	20071025	AU 2007-237904	20070418
AU 2007237904	B2	20110303		
CA 2649288	A1	20071025	CA 2007-2649288	20070418
CA 2649288	C	20151124		
US 20080045528	A1	20080221	US 2007-737069	20070418
US 7553854	B2	20090630		
KR 2008112388	A	20081224	KR 2008-7028138	20070418
KR 1464385	B1	20141121		
EP 2010528	A2	20090107	EP 2007-797244	20070418
EP 2010528	B1	20171004		
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CN 101432281	A	20090513	CN 2007-80013974	20070418
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JP 2009534410	T	20090924	JP 2009-506754	20070418
JP 5328640	B2	20131030		
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AR 60545	A1	20080625	AR 2007-101682	20070419
ZA 2008008105	A	20090624	ZA 2008-8105	20080922
IN 2008DN08410	A	20090522	IN 2008-DN8410	20081006
IN 286774	A1	20170901		
CR 10365	A	20090107	CR 2008-10365	20081015
MX 2008013427	A	20081104	MX 2008-13427	20081017
NO 2008004800	A	20081117	NO 2008-4800	20081113
US 20100280006	A1	20101104	US 2009-387946	20090508
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US 8710048	B2	20140429		

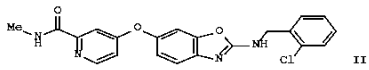
PRIORITY APPLN. INFO.:

US 2006-60793517	P	20060419
US 2007-60893857	P	20070308
US 2007-737069	A3	20070418
WO 2007-US66898	W	20070418
US 2009-387946	A1	20090508

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 147:486428; MARPAT 147:486428
GI



I



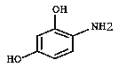
II

AB The title compds. I [X = O, S, SO; R1, R2 = H, alkyl, acyl, etc.; or NR1R2 = heterocyclyl, heteroaryl; R3 = H, halo, alkyl, etc.; R6 = alkyl, alkoxy, amino, halo; n = 0-2; when X = O, R4 = H, alkyl, alkenyl or alkynyl, and R5 = H, alkyl, alkenyl, etc., or R4 and R5 are taken together to form hetreocyclyl, cycloalkyl, aryl or heteroaryl; when X = S or SO, R4 = H, alkyl, alkenyl or alkynyl, and R5 = H, alkyl, alkenyl, etc.; and their stereoisomers, tautomers, solvates, oxides, esters, and their prodrugs and pharmaceutically acceptable salts], useful for inhibiting cellular proliferation, inhibiting the growth and/or metathesis of tumors, treating or preventing cancer, treating or preventing degenerating bone diseases such as rheumatoid arthritis, and/or inhibiting mols. such as CSF-1R, were prepared and disclosed. E.g., a multi-step synthesis of II, starting from 4-aminoresorcinol and ethylxanthic acid, was given. II showed 99% inhibition of CSR-1R at about 1 μM. Compns. of the compds. I, either alone or in combination with at least one addnl. therapeutic agent, with a pharmaceutically acceptable carrier, and uses of the compds., either alone or in combination with at least one addnl. therapeutic agent are also disclosed.

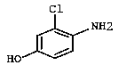
IT 2835-99-6, 4-Amino-m-cresol 13066-95-0, 4-Aminoresorcinol 17609-80-2 35654-56-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of 6-O-substituted benzoxazole and benzothiazole compds. for inhibiting CSF-1R signaling)
RN 2835-99-6 CAPLUS
CN Phenol, 4-amino-3-methyl- (CA INDEX NAME)



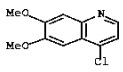
RN 13066-95-0 CAPLUS
CN 1,3-Benzenediol, 4-amino- (CA INDEX NAME)



RN 17609-80-2 CAPLUS
CN Phenol, 4-amino-3-chloro- (CA INDEX NAME)

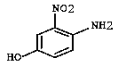


RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

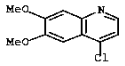


OS.CITING REF COUNT: 10 THERE ARE 10 CAPLUS RECORDS THAT CITE THIS RECORD (13 CITINGS)

L7 ANSWER 59 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2007:899544 CAPLUS Full-text
DOCUMENT NUMBER: 147:439495
TITLE: Design, Synthesis, and Evaluation of Orally Active Benzimidazoles and Benzoxazoles as Vascular Endothelial Growth Factor-2 Receptor Tyrosine Kinase Inhibitors
AUTHOR(S): Potashman, Michele H.; Bready, James; Coxon, Angela; DeMelfi, Thomas M., Jr.; DiPietro, Lucian; Doerr, Nicholas; Elbaum, Daniel; Estrada, Juan; Gallant, Paul; Germain, Julie; Gu, Yan; Harmange, Jean-Christophe; Kaufman, Stephen A.; Kendall, Rick; Kim, Joseph L.; Kumar, Gondi N.; Long, Alexander M.; Neervannan, Seshadri; Patel, Vinod F.; Polverino, Anthony; Rose, Paul; Van der Plas, Simon; Whittington, Douglas; Zanon, Roger; Zhao, Huilin
CORPORATE SOURCE: Department of Medicinal Chemistry, Amgen Inc., Cambridge, MA, 02139, USA
SOURCE: Journal of Medicinal Chemistry (2007), 50(18), 4351-4373
CODEN: JMCMAR; ISSN: 0022-2623
DIGITAL OBJECT ID: 10.1021/jm070034i
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 147:439495
AB inhibition of the VEGF signaling pathway has become a valuable approach in the treatment of cancers. guided by X-ray crystallog. and mol. modeling, a series of 2-aminobenzimidazoles and 2-aminobenzoxazoles were identified as potent inhibitors of the vascular endothelial growth factor-2 receptor tyrosine kinase VEGFR-2 (also known as KDR, kinase insert domain receptor) in both enzymic and HUVEC cellular proliferation assays. in this report we describe the synthesis and structure-activity relationship of a series of 2-aminobenzimidazoles and benzoxazoles, culminating in the identification of a nonracemic pyrrolidinylmethoxyphenylaminobenzoxazolyloxy pyridinecarboxamide as a potent and selective VEGFR-2 inhibitor displaying a good pharmacokinetic profile. the nonracemic pyrrolidinylmethoxyphenylaminobenzoxazolyloxy pyridinecarboxamide also demonstrated efficacy in both the murine matrigel model for vascular permeability (79% inhibition observed at 100 mg/kg) and the rat corneal angiogenesis model (ED50 = 16.3 mg/kg).
IT 610-81-1, 4-Amino-3-nitrophenol 35654-56-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of arylamino- and aryloxy-substituted benzimidazoles and benzoxazoles as potential orally active inhibitors of VEGFR-2/KDR and of angiogenesis for use as anticancer agents)
RN 610-81-1 CAPLUS
CN Phenol, 4-amino-3-nitro- (CA INDEX NAME)



RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



OS.CITING REF COUNT: 87 THERE ARE 87 CAPLUS RECORDS THAT CITE THIS RECORD (87 CITINGS)
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

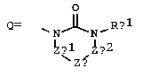
L7 ANSWER 60 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2007:863627 CAPLUS Full-text
DOCUMENT NUMBER: 147:235192
TITLE: Preparation of urea derivatives containing nitrogenous aromatic ring compounds as inhibitors of angiogenesis
INVENTOR(S): Funahashi, Yasuhiro; Tsuruoka, Akihiko; Matsukura, Masayuki; Haneda, Toru; Fukuda, Yoshio; Kamata, Junichi; Takahashi, Keiko; Matsushima, Tomohiro; Miyazaki, Kazuki; Nomoto, Ken-Ichi; Watanabe, Tatsuo; Obaishi, Hiroshi; Yamaguchi, Atsumi; Suzuki, Sachi; Nakamura, Katsuji; Mimura, Fusayo; Yamamoto, Yuji; Matsui, Junji; Matsui, Kenji; Yoshiba, Takako; Suzuki, Yasuyuki; Arimoto, Itaru
PATENT ASSIGNEE(S): Eisai Co., Ltd, Japan
SOURCE: U.S., 458pp., Cont.-in-part of Appl. No. PCT/JP01/09221.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 7253286	B2	20070807	US 2003-420466	20030418
US 20040053908	A1	20040318		
WO 2002032872	A1	20020425	WO 2001-JP9221	20011019
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1506962	A2	20050216	EP 2004-25700	20011019
EP 1506962	A3	20050302		
EP 1506962	B1	20080702		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
EP 1777218	A1	20070425	EP 2006-23078	20011019
EP 1777218	B1	20081231		
R: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE, TR				
CN 101024627	A	20070829	CN 2007-10007096	20011019
CN 101029022	A	20070905	CN 2007-10007097	20011019
CN 101029022	B	20110112		
ES 2282299	T3	20071016	ES 2001-976786	20011019
ZA 2003003567	A	20040810	ZA 2003-3567	20030508
JP 2005272474	A	20051006	JP 2005-124034	20050421
JP 4354929	B2	20091028		
US 20060247259	A1	20061102	US 2005-293785	20051202
US 7612092	B2	20091103		
US 20060160832	A1	20060720	US 2006-347749	20060203
AU 2006203099	A1	20060810	AU 2006-203099	20060719
AU 2006236039	A1	20061207	AU 2006-236039	20061116
AU 2006236039	B2	20080522		
US 20100197911	A1	20100805	US 2008-244227	20081002
US 7973160	B2	20110705		
JP 2009215313	A	20090924	JP 2009-123432	20090521
JP 5086304	B2	20121128		
US 20110118470	A1	20110519	US 2011-986638	20110107
US 8372981	B2	20130212		

PRIORITY APPLN. INFO.:

JP 2000-320420	A	20001020
JP 2000-386195	A	20001220
JP 2001-46685	A	20010222
WO 2001-JP9221	A2	20011019
AU 2001-295986	A3	20011019
AU 2001-95986	TO	20011019
CN 2001-819710	A3	20011019
EP 2001-976786	A3	20011019
JP 2002-536056	A3	20011019
US 2003-420466	A3	20030418
JP 2005-124034	A3	20050421
US 2005-293785	A1	20051202
US 2008-244227	A3	20081002

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 147:235192; MARPAT 147:235192
GI

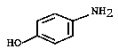


AB N-aryl or N-heteroarylurea derivs. represented by the general formula Ag-Xg-Yg-Tg1 or salts thereof, or hydrates of both [wherein Ag = (un)substituted C6-14 aryl or 5- to 14-membered heterocyclic group; Xg = single bond, O, S, C1-6 alkylene, SO, SO2, (un)substituted NH; Yg = (un)substituted C6-14 aryl, 5- to 14-membered heterocyclic group, C1-8 alkyl, C3-8 alicyclic hydrocarbyl, C6-14 aryl-C1-6 alkyl, 5- to 14-membered heteroaryl-C1-6 alkyl, (CH2)gSO2 (g = 1-8), (CH2)faCH:CH(CH2)fb (fa, fb = 0, 1,2,3), etc.; and Tg1 = a group of the general formula -Eg-CO-NRg1(Zg) or Q; wherein Eg = a single bond, (un)substituted NH; Rg1 = H, (un)substituted C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C3-8 aliphatic hydrocarbyl, etc.; Zg = C1-8 alkyl, C3-8 alicyclic hydrocarbyl, C6-14 aryl, etc.; Zg1, Zg2 = (a) a single bond, (b) C1-6 alkylene optionally having ≥1 atoms selected from O, S, and N in the middle or the terminus of the chain and optionally substituted with oxo, (c) (un)substituted C2-6 alkenyl] are prepared These compds. are also inhibitors of vascular endothelial growth factor receptor kinase (VEGFR2 kinase) and are useful as antitumor agents against hemangioma, pancreatic cancer, stomach cancer, colon cancer, breast cancer, prostate cancer, lung cancer, brain tumor, leukemia, or ovarian cancer, as cancer metastasis inhibitors, and for the treatment of retina neovascularization, diabetic retinopathy, atherosclerosis, or inflammatory diseases such as osteoarthritis, rheumatoid arthritis, psoriasis, or delayed hypersensitivity. Thus, to solution of 334 mg 4-[6-(4-benzyloxyphenyl)-7-(2-trimethylsilylethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy]-2-chlorophenylamine in 4 mL DMF were added 0.066 mL pyridine and 0.102 mL Ph chlorocarbonate and stirred at room temperature for 2.5 h to give 330 mg N-[4-[6-(4-benzyloxyphenyl)-7-(2-

trimethylsilylethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy]-2-chlorophenyl]-N'-cyclopropylurea which (260 mg) was hydrogenolyzed over platinum oxide in ethanol overnight to give 160 mg N-[4-[6-(4-hydroxyphenyl)-7-(2-trimethylsilylethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy]-2-chlorophenyl]-N'-cyclopropylurea (I). I showed IC50 of 0.02 nM for inhibiting the vascular endothelial growth factor (VEGF)-stimulated sandwich tube formation in vascular endothelial cell.

IT 123-30-8 2835-96-3 2835-99-6
3096-69-3 17609-80-2 35654-56-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of urea derivs. containing nitrogenous aromatic ring compds. as
angiogenesis inhibitors for prevention or treatment of diseases)

RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



RN 2835-96-3 CAPLUS
CN Phenol, 4-amino-2-methyl- (CA INDEX NAME)



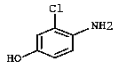
RN 2835-99-6 CAPLUS
CN Phenol, 4-amino-3-methyl- (CA INDEX NAME)



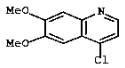
RN 3096-69-3 CAPLUS
CN Phenol, 4-amino-2,3-dimethyl- (CA INDEX NAME)



RN 17609-80-2 CAPLUS
CN Phenol, 4-amino-3-chloro- (CA INDEX NAME)

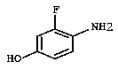


RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



IT 399-95-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of urea derivs. containing nitrogenous aromatic ring compds. as
angiogenesis inhibitors for prevention or treatment of diseases)

RN 399-95-1 CAPLUS
CN Phenol, 4-amino-3-fluoro- (CA INDEX NAME)



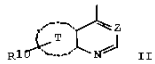
OS.CITING REF COUNT: 36 THERE ARE 36 CAPLUS RECORDS THAT CITE THIS RECORD (47 CITINGS)
REFERENCE COUNT: 117 THERE ARE 117 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 61 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2006:542661 CAPLUS Full-text

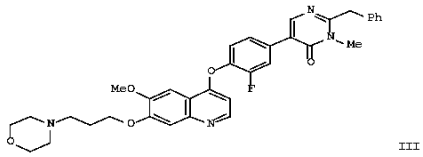
DOCUMENT NUMBER: 145:46082
TITLE: Preparation of substituted heterocycles for treating HGF mediated diseases
INVENTOR(S): Kim, Tae-Seong; Bellon, Steven; Booker, Shon; D'Angelo, Noel; Dominguez, Celia; Fellows, Ingrid; Lee, Matthew; Liu, Longbin; Rainbeau, Elizabeth; Siegmund, Aaron C.; Tasker, Andrew; Xi, Ning; Cheng, Yuan
PATENT ASSIGNEE(S): Amgen Inc., USA
SOURCE: PCT Int. Appl., 228 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006060318	A2	20060608	WO 2005-US42935	20051129
WO 2006060318	A3	20060720		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
AU 2005312048	A1	20060608	AU 2005-312048	20051129
AU 2005312048	B2	20120802		
CA 2587642	A1	20060608	CA 2005-2587642	20051129
CA 2587642	C	20130409		
US 20060252777	A1	20061109	US 2005-289659	20051129
US 7652009	B2	20100126		
EP 1827434	A2	20070905	EP 2005-848812	20051129
EP 1827434	B1	20140115		
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, YU				
JP 2008521900	T	20080626	JP 2007-544417	20051129
ES 2450566	T3	20140325	ES 2005-848812	20051129
MX 2007006230	A	20070725	MX 2007-6230	20070524

PRIORITY APPLN. INFO.: US 2004-60632271 P 20041130
WO 2005-US42935 W 20051129
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 145:46082; MARPAT 145:46082
GI



II

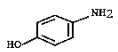


III

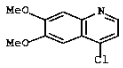
AB The title compds. R1XWAYR [I; R = (un)substituted aryl, heterocyclyl, cycloalkyl, etc.; R1 = II (wherein ring T = Ph, 5-6 membered heteroaryl; Z = N or CH; R10 = alkoxy, haloalkoxy, arylalkoxy, etc.); W = (un)substituted aryl, 5-6 membered heteroaryl; A = (un)substituted 5-7 membered N-containing heterocyclyl; X = O, S, NR2, CR3R4; Y = a bond, CO, CONH, etc.; R2 = H, alkyl, haloalkyl, etc.; R3, R4 = H, alkyl, aryl, etc.] which are effective for prophylaxis and treatment of diseases, such as HGF mediated diseases, were prepared E.g., a multi-step synthesis of III, starting from 2-benzyl-3H-pyrimidin-4-one, was given. Compds. I showed inhibition of c-Met kinase at doses less than 2 μM. The invention encompasses novel compds. I, analogs, prodrugs and pharmaceutically acceptable salts thereof, pharmaceutical compns. and methods for prophylaxis and treatment of diseases and other maladies or conditions involving, cancer and the like. The subject invention also relates to processes for making such compds. as well as to intermediates useful in such processes.

IT 123-30-8, 4-Aminophenol 35654-56-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of substituted heterocycles for treating HGF mediated diseases)

RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

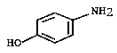


OS.CITING REF COUNT: 8 THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (8 CITINGS)
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

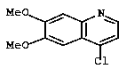
L7 ANSWER 62 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2006:192537 CAPLUS Full-text
DOCUMENT NUMBER: 144:362578
TITLE: Identification of Potent and Selective Inhibitors of PDGF Receptor Autophosphorylation
AUTHOR(S): Furuta, Takayuki; Sakai, Teruyuki; Senga, Terufumi; Osawa, Tatsushi; Kubo, Kazuo; Shimizu, Toshiyuki; Suzuki, Rika; Yoshino, Tetsuya; Endo, Megumi; Miwa, Atsushi
CORPORATE SOURCE: Pharmaceutical Research Laboratories, Kirin Brewery Co. Ltd., Takasaki, Gunma, 370-1295, Japan
SOURCE: Journal of Medicinal Chemistry (2006), 49(7), 2186-2192
CODEN: JMCMAR; ISSN: 0022-2623
DIGITAL OBJECT ID: 10.1021/jm0506423
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 144:362578

AB We report the structure-activity relationship of quinoline and quinazoline derivs., which include urea, thiourea, urethane, and acylthiourea groups, as inhibitors of the platelet-derived growth factor (PDGF) receptor autophosphorylation. Our previous studies showed that the quinoline and quinazoline derivs. including urea, thiourea, and carbamate groups were highly potent compds. as the PDGF receptor autophosphorylation inhibitor, but these compds. did not exhibit receptor selectivity between the PDGF receptor and the c-kit receptor. As a result of further synthesis and biol. evaluation, we have found that the quinoline and quinazoline-acylthiourea derivs. showed not only good inhibitory activity for the PDGF receptor but also receptor selectivity between the PDGF receptor and the c-kit receptor. Furthermore N-{4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(2-methylbenzoyl)thiourea exhibited potent oral efficacy in in vivo assay using the rat carotid balloon injury model. Therefore, the quinoline and quinazoline-acylthiourea derivs. may be expected to have potential as therapeutic agents for the treatment of restenosis.

IT 123-30-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(Identification of Potent and Selective Inhibitors of PDGF Receptor Autophosphorylation)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



IT 35654-56-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(Identification of Potent and Selective Inhibitors of PDGF Receptor Autophosphorylation)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



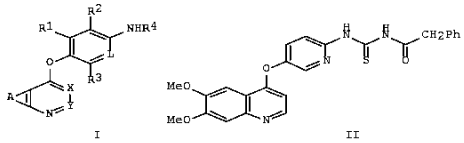
OS.CITING REF COUNT: 36 THERE ARE 36 CAPLUS RECORDS THAT CITE THIS RECORD (36 CITINGS)
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 63 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2005:1331145 CAPLUS Full-text
DOCUMENT NUMBER: 144:69740
TITLE: Preparation of ether-linked quinoline and thienopyridine derivatives as c-MET/HGFR inhibitors
INVENTOR(S): Kung, Pei-Pei
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: PCT Int. Appl., 81 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005121125	A1	20051222	WO 2005-IB1849	20050530

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

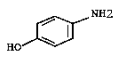
PRIORITY APPLN. INFO.: US 2004-60579993 P 20040609
US 2005-60665321 P 20050325
OTHER SOURCE(S): CASREACT 144:69740; MARPAT 144:69740
GI



I II

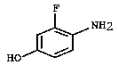
AB Title compds. represented by the formula I [wherein L = N or CR5; A = fused (hetero)aryl; X, Y = independently N or CR7; R1-R3, R5, R7 = independently H, halo, (cyclo)alkyl, aryl, etc.; R4 = H, (cyclo)alkyl, (hetero)aryl, etc.; and pharmaceutically acceptable salts, solvates or hydrates thereof] were prepared as hepatocyte growth factor receptor (c-MET or HGFR) inhibitors. For example, II was provided in a multi-step synthesis starting from 4-chloro-6,7-dimethoxyquinoline. II showed inhibition of HGFR with IC50 value of 0.030 μM in the cellular HGFR autophosphorylation assay. Thus, I and their pharmaceutical comps. are useful as c-MET/HGFR inhibitors for the treatment of a variety of HGFR-mediated disorders, including cancers.

IT 51-78-5, 4-Aminophenol hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of ether-linked quinoline and thienopyridine derivs. as HGFR inhibitors)
RN 51-78-5 CAPLUS
CN Phenol, 4-amino-, hydrochloride (1:1) (CA INDEX NAME)

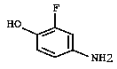


● HCl

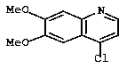
IT 399-95-1P, 4-Amino-3-fluorophenol 399-96-2P, 4-Amino-2-fluorophenol 35654-56-9P, 4-Chloro-6,7-dimethoxyquinoline
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of ether-linked quinoline and thienopyridine derivs. as HGFR inhibitors)
RN 399-95-1 CAPLUS
CN Phenol, 4-amino-3-fluoro- (CA INDEX NAME)



RN 399-96-2 CAPLUS
CN Phenol, 4-amino-2-fluoro- (CA INDEX NAME)



RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



OS.CITING REF COUNT: 8 THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (8 CITINGS)
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

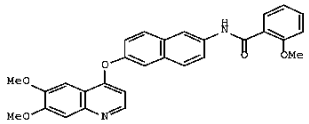
L7 ANSWER 64 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2005:696877 CAPLUS Full-text
DOCUMENT NUMBER: 143:211847
TITLE: Preparation of heteroaryl substituted naphthalenes as inhibitors of Lck, VEGFR and/or HGF related activity
INVENTOR(S): Potashman, Michele; Kim, Tae-Seong; Bellon, Steven; Booker, Shon; Cheng, Yuan; Kim, Joseph L.; Tasker, Andrew; Xi, Ning; Xu, Shimin; Harmange, Jean-Christophe; Borg, George; Weiss, Matthew; Hodous, Brian L.; Graceffa, Russell; Buckner, Willian H.; Masse, Craig E.; Choquette, Deborah; Martin, Matthew W.; Germain, Julie; Dipietro, Lucian V.; Chaffee, Stuart C.; Nunes, Joseph J.; Buchanan, John L.; Habgood, Gregory J.; McGowan, David C.; Whittington, Douglas A.
PATENT ASSIGNEE(S): Amgen Inc., USA
SOURCE: PCT Int. Appl., 444 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005070891	A2	20050804	WO 2005-US2326	20050124
WO 2005070891	A3	20051020		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, SM				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2005206571	A1	20050804	AU 2005-206571	20050124
AU 2005206571	B2	20100812		
CA 2553423	A1	20050804	CA 2005-2553423	20050124
CA 2553423	C	20120320		
EP 1713484	A2	20061025	EP 2005-722533	20050124
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, BA, HR, IS, YU				
US 20060241115	A1	20061026	US 2005-42634	20050124
US 7435823	B2	20081014		
CN 1933839	A	20070321	CN 2005-80006839	20050124
BR 2005007373	A	20070710	BR 2005-7373	20050124
JP 2007518824	T	20070712	JP 2006-551404	20050124
JP 4932495	B2	20120516		
EA 11402	B1	20090227	EA 2006-1350	20050124
MX 2006008327	A	20060929	MX 2006-8327	20060721
IN 2006CN02683	A	20070608	IN 2006-CN2683	20060721
CR 8531	A	20070608	CR 2006-8531	20060725
NO 2006003693	A	20061023	NO 2006-3693	20060817
ZA 2006006941	A	20080227	ZA 2006-6941	20060821
US 20090176774	A1	20090709	US 2008-157303	20080609
US 8178557	B2	20120515		

PRIORITY APPLN. INFO.:	US 2004-60538691	P	20040123
	US 2005-42634	A3	20050124
	WO 2005-US2326	W	20050124

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 143:211847; MARPAT 143:211847
GI

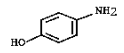


II

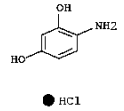
AB The title compds. I [R1XAYR; R = (un)substituted aryl, heterocyclyl, cycloalkyl, etc.; R1 = (un)substituted quinolinyl, quinazolinyl, pyrimidinyl, etc.; A = (un)substituted naphthalenediyl, etc.; X = O, S, (un)substituted NH, CH2; Y = NHCO, CONH, etc.] which are effective for prophylaxis and treatment of diseases, such as HGF mediated diseases, were prepared E.g., a multi-step synthesis of II, starting from 6-hydroxy-2-naphthoic acid, was given. The compds. I showed inhibition of LcK kinase, c-Met kinase, and VEGFR kinase at less than 10 μM. The invention encompasses novel compds. I, analogs, prodrugs and pharmaceutically acceptable salts thereof, pharmaceutically compns. and methods for prophylaxis and treatment of diseases and other maladies or conditions involving, cancer and the like.

IT 123-30-8, 4-Hydroxyaniline 34781-86-7, 4-Aminoresorcinol hydrochloride 35654-56-9, 4-Chloro-6,7-dimethoxyquinoline
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of heteroaryl substituted naphthalenes as inhibitors of Lck, VEGFR and/or HGF related activity)

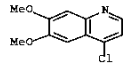
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



RN 34781-86-7 CAPLUS
CN 1,3-Benzenediol, 4-amino-, hydrochloride (1:1) (CA INDEX NAME)



RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



OS.CITING REF COUNT: 20 THERE ARE 20 CAPLUS RECORDS THAT CITE THIS RECORD (21 CITINGS)

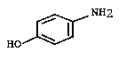
L7 ANSWER 65 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN

ACCESSION NUMBER:	2005:128342 CAPLUS Full-text
DOCUMENT NUMBER:	142:411203
TITLE:	Novel Potent Orally Active Selective VEGFR-2 Tyrosine Kinase Inhibitors: Synthesis, Structure-Activity Relationships, and Antitumor Activities of N-Phenyl-N'-{4-(4-quinolyloxy)phenyl}ureas
AUTHOR(S):	Kubo, Kazuo; Shimizu, Toshiyuki; Ohyama, Shin-Ichi; Murooka, Hideko; Iwai, Akemi; Nakamura, Kazuhide; Hasegawa, Kazumasa; Kobayashi, Yoshiko; Takahashi, Noriko; Takahashi, Kazumi; Kato, Shinichiro; Izawa, Toshio; Isoe, Toshiyuki
CORPORATE SOURCE:	Pharmaceutical Research and Development Laboratories, Kirin Brewery Co., Ltd., Gunma, 370-1295, Japan
SOURCE:	Journal of Medicinal Chemistry (2005), 48(5), 1359-1366 CODEN: JMCMAR; ISSN: 0022-2623
DIGITAL OBJECT ID:	10.1021/jm030427r
PUBLISHER:	American Chemical Society
DOCUMENT TYPE:	Journal
LANGUAGE:	English
OTHER SOURCE(S):	CASREACT 142:411203

AB N-Phenyl-N'-{4-(4-quinolyloxy)phenyl}ureas were found to be a novel class of potent inhibitors for the vascular endothelial growth factor receptor 2 (VEGFR-2) tyrosine kinase through synthetic modifications of a lead compound and structure-activity relationship studies. A representative compound N-(2,4-difluorophenyl)-N'-4-[[(6,7-dimethoxy-4-quinolyl)oxy]-2-fluorophenyl]urea, termed Ki8751, inhibited VEGFR-2 phosphorylation at an IC50 value of 0.90 nM, and also inhibited the PDGFR family members such as PDGFRα and c-Kit at 67 nM and 40 nM, resp. However, Ki8751 did not have any inhibitory activity against other kinases such as EGFR, HGFR, InsulinR and others even at 10000 nM. Ki8751 suppressed the growth of the VEGF-stimulated human umbilical vein endothelial cell (HUVEC) on a nanomolar level. Ki8751 showed significant antitumor activity against five human tumor xenografts such as GL07 (glioma), St-4 (stomach carcinoma), LC6 (lung carcinoma), DLD-1 (colon carcinoma) and A375 (melanoma) in nude mice and also showed complete tumor growth inhibition with the LC-6 xenograft in nude rats following oral administration once a day for 14 days at 5 mg/kg without any body weight loss.

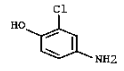
IT 123-30-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of N-phenyl-N'-{4-(4-quinolyloxy)phenyl}ureas and their antitumor activity)

RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)

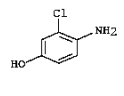


IT 3964-52-1, 2-Chloro-4-aminophenol 52671-64-4, 3-Chloro-4-aminophenol hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of N-phenyl-N'-{4-(4-quinolyloxy)phenyl}ureas as inhibitors for
the vascular endothelial growth factor receptor 2 (VEGFR-2) tyrosine kinase)

RN 3964-52-1 CAPLUS
CN Phenol, 4-amino-2-chloro- (CA INDEX NAME)

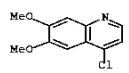


RN 52671-64-4 CAPLUS
CN Phenol, 4-amino-3-chloro-, hydrochloride (1:1) (CA INDEX NAME)



IT 35654-56-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of N-phenyl-N'-{4-(4-quinolyloxy)phenyl}ureas as inhibitors for
the vascular endothelial growth factor receptor 2 (VEGFR-2) tyrosine kinase)

RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



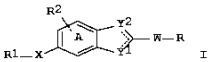
OS.CITING REF COUNT: 73 THERE ARE 73 CAPLUS RECORDS THAT CITE THIS RECORD (75 CITINGS)
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 66 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2004:817883 CAPLUS Full-text

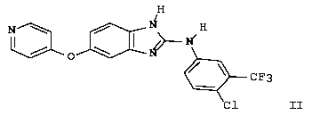
DOCUMENT NUMBER: 141:332190
TITLE: Preparation of fused azoles such as 2,5-disubstituted benzimidazoles, benzoxazoles and benzothiazoles as kinase inhibitors
INVENTOR(S): Dipietro, Lucian V.; Harmange, Jean-Christophe; Askew, Benny C., Jr.; Elbaum, Daniel; Germain, Julie; Habgood, Gregory J.; Kim, Joseph L.; Patel, Vinod F.; Potashman, Michele; Van der Plas, Simon
PATENT ASSIGNEE(S): Amgen Inc., USA
SOURCE: PCT Int. Appl., 289 pp., Chemical Indexing Equivalent to 150:515173 (US)
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004085425	A1	20041007	WO 2004-US8809	20040322
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 7531553	B2	20090512	US 2004-804915	20040319
US 20040209892	A1	20041021		
AU 2004223827	A1	20041007	AU 2004-223827	20040322
AU 2004223827	B2	20080306		
CA 2518909	A1	20041007	CA 2004-2518909	20040322
EP 1638954	A1	20060329	EP 2004-758050	20040322
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK				
JP 2006520805	T	20060914	JP 2006-507472	20040322
MX 2005010086	A	20060210	MX 2005-10086	20050921

PRIORITY APPLN. INFO.: US 2003-60456691 P 20030321
US 2004-804915 A 20040319
WO 2004-US8809 A 20040322
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 141:332190; MARPAT 141:332190
GI



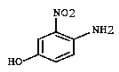
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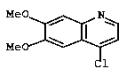
II

AB Title compds. I [W, X, Y1 and Y2 independently = O, S(O)n and NR3; ring A optionally contains a N atom at a non-fused, non-substituted ring position; n = 0-2; R = (un)substituted-aryl, -heterocyclyl, -fused heterocyclyl, etc.; R1 = (un)substituted-aryl, -arylalkyl, -heterocyclyl, etc.; R2 = H, halo, alkoxy, etc.; R3 = H or alkyl] are prepared and disclosed as having kinase inhibitory activity, such as VEGFR/KDR inhibitory activity. Thus, e.g., II was prepared by cyclocondensation of 4-(pyridin-4-yloxy)benzene-1,2-diamine with 1-chloro-4-isothiocyanato-2-trifluoromethylbenzene. In human umbilical vein endothelial cell proliferation assay, selected I inhibited VEGF-stimulated proliferation at a level below 100 nM. Accordingly, I would be useful in the prevention and treatment of angiogenesis related disorders, ophthalmol. conditions, proliferative diseases, inflammatory diseases, and other pathol. conditions as described in the specification.

IT 610-81-1 35654-56-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of benzimidazole, benzoxazole and benzothiazole derivs. as kinase inhibitors)
RN 610-81-1 CAPLUS
CN Phenol, 4-amino-3-nitro- (CA INDEX NAME)



RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



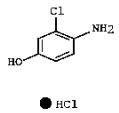
OS.CITING REF COUNT: 15 THERE ARE 15 CAPLUS RECORDS THAT CITE THIS RECORD (16 CITINGS)
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 67 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2004:354935 CAPLUS Full-text
DOCUMENT NUMBER: 140:363009
TITLE: N-[2-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-N'-(5-methyl-3-isoxazolyl)urea salt crystals
INVENTOR(S): Matsunaga, Naoki; Yoshida, Satoshi; Yoshino, Ayako; Nakajima, Tatsuo
PATENT ASSIGNEE(S): Kirin Beer Kabushiki Kaisha, Japan
SOURCE: PCT Int. Appl., 115 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004035572	A1	20040429	WO 2003-JP13439	20031021
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003301430	A1	20040504	AU 2003-301430	20031021
EP 1559715	A1	20050803	EP 2003-756734	20031021
EP 1559715	B1	20070926		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 3763414	B2	20060405	JP 2004-544999	20031021
AT 374199	T	20071015	AT 2003-756734	20031021
PT 1559715	E	20071024	PT 2003-756734	20031021
ES 2294317	T3	20080401	ES 2003-756734	20031021
US 20060052415	A1	20060309	US 2005-532104	20050421
US 7166722	B2	20070123		

PRIORITY APPLN. INFO.: JP 2002-306101 A 20021021
WO 2003-JP13439 W 20031021
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB This invention provides crystals of pharmaceutically acceptable salts of N-[2-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-N'-(5-methyl-3-isoxazolyl)urea. The salt crystals are used in treating a disease selected from the group consisting of tumor, diabetic retinopathy, rheumatoid arthritis, psoriasis, atheroma arteriosclerosis, Kaposi's sarcoma and exudative age-related macular degeneration. The salt crystals have properties appropriate for prepns. for oral administration.

IT 52671-64-4, 4-Amino-3-chlorophenol hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(N-[2-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-N'-(5-methyl-3-isoxazolyl)urea salt crystals for treatment of tumor, diabetic retinopathy, rheumatoid arthritis, psoriasis)
RN 52671-64-4 CAPLUS
CN Phenol, 4-amino-3-chloro-, hydrochloride (1:1) (CA INDEX NAME)



● HCl

IT 35654-56-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(N-[2-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-N'-(5-methyl-3-isoxazolyl)urea salt crystals for treatment of tumor, diabetic retinopathy, rheumatoid arthritis, psoriasis)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

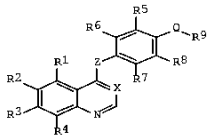
OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 68 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2003:319877 CAPLUS Full-text
DOCUMENT NUMBER: 138:338162
TITLE: Preparation of quinoline or quinazoline derivatives inhibiting auto-phosphorylation of fibroblast growth factor receptors
INVENTOR(S): Miwa, Atsushi; Yoshino, Tetsuya; Osawa, Tatsushi; Sakai, Teruyuki; Shimizu, Toshiyuki; Fujiwara, Yasunari
PATENT ASSIGNEE(S): Kirin Beer Kabushiki Kaisha, Japan

SOURCE: PCT Int. Appl., 264 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003033472	A1	20030424	WO 2002-JP10803	20021017
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002343997	A1	20030428	AU 2002-343997	20021017
EP 1447405	A1	20040818	EP 2002-775365	20021017
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
JP 4383870	B2	20091216	JP 2003-536212	20021017
US 20050049264	A1	20050303	US 2004-491898	20040920
US 7495104	B2	20090224		

PRIORITY APPLN. INFO.: JP 2001-319826 A 20011017
JP 2002-167652 A 20020607
WO 2002-JP10803 W 20021017
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 138:338162
GI

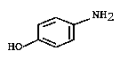


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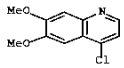
AB The invention provides novel compds. represented by the general formula (I) or pharmaceutically acceptable salts or solvates thereof [wherein X = CH, N; Z = O, S; Q = R10, CR11R12, CO, O, S(O)m (wherein m is 0 to 2), NHCONH (wherein R10 = H, C1-10 alkyl; R11, R12 = H, C1-6 alkylcarbonyloxy); R1, R2, R3 = H, OH, halogeno, nitro, amino, C1-6 alkyl or alkoxy or C2-6 alkenyl or alkynyl like (with the proviso that the alkyl and the alkoxy may be further substituted); R4 = H; R5, R6, R7, R8 = H, halogeno, C1-4 alkyl or alkoxy; R9 = C1-10 alkyl, (un)saturated 3- to 8-membered carbocyclic or heterocyclic group which may be substituted]. These compds. exhibit an inhibitory activity against autophosphorylation of fibroblast growth factor receptor (FGFR) family, in particular FGFR2 (Bek), can inhibit the proliferation of cancer cells through oral or i.v. administration, and are useful for the treatment of malignant tumors such as stomach cancer, brain tumor, large intestine cancer, pancreatic carcinoma, lung cancer, kidney cancer, ovarian cancer, and prostate cancer. Thus, 103 mg 1-(3,3-dimethylbutyl)-3-[2-fluoro-4-(7-hydroxy-6-methoxyquinolin-4-yloxy)phenyl]urea (preparation given), 166 mg K2CO3, and 69 mg 4-(2-chloroethyl)morpholine hydrochloride were stirred in 2 mL DMF at 75-80° for 16 h to give 37% 1-(3,3-dimethylbutyl)-3-[2-fluoro-4-[6-methoxy-7-(2-morpholin-4-ylethoxy)quinolin-4-yloxy]phenyl]urea (II). II and 1-(3,3-dimethylbutyl)-3-[2-chloro-4-[6-methoxy-7-[2-(2,6-dimethylmorpholin- 4-yl)ethoxy]quinolin-4-yloxy]phenyl]urea showed IC50 of <0.0100 and 0.0094 μM, resp., for inhibiting the autophosphorylation of Bek prepared from human Scirrhous stomach cancer OCUM-2MD3.

IT 123-30-8, 4-Aminophenol 35654-56-9, 4-Chloro-6,7-dimethoxyquinoline
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of quinoline or quinazoline derivs. inhibiting auto-phosphorylation of fibroblast growth factor receptors as antitumor agents)

RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

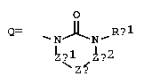


OS.CITING REF COUNT: 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (28 CITINGS)
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 69 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2002:314913 CAPLUS Full-text
DOCUMENT NUMBER: 136:340689
TITLE: Preparation of urea derivatives containing nitrogenous aromatic ring compounds as inhibitors of angiogenesis
INVENTOR(S): Funahashi, Yasuhiro; Tsuruoka, Akihiko; Matsukura, Masayuki; Haneda, Toru; Fukuda, Yoshio; Kamata, Junichi; Takahashi, Keiko; Matsushima, Tomohiro; Miyazaki, Kazuki; Nomoto, Kenichi; Watanabe, Tatsuo; Obaishi, Hiroshi; Yamaguchi, Atsumi; Suzuki, Sachi; Nakamura, Katsuji; Mimura, Fusayo; Yamamoto, Yuji; Matsui, Junji; Matsui, Kenji; Yoshiba, Takako; Suzuki, Yasuyuki; Arimoto, Itaru
PATENT ASSIGNEE(S): Eisai Co., Ltd., Japan
SOURCE: PCT Int. Appl., 699 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002032872	A1	20020425	WO 2001-JP9221	20011019
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2426461	A1	20020425	CA 2001-2426461	20011019
CA 2426461	C	20110412		
AU 2001095986	A	20020429	AU 2001-95986	20011019
AU 2001295986	A1	20020704	AU 2001-295986	20011019
AU 2001295986	B2	20060817		
HU 2003002603	A2	20031128	HU 2003-2603	20011019
HU 2003002603	A3	20100329		
HU 230302	B1	20151228		
CN 1478078	A	20040225	CN 2001-819710	20011019
CN 1308310	C	20070404		
EP 1415987	A1	20040506	EP 2001-976786	20011019
EP 1415987	B1	20070228		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
EP 1506962	A2	20050216	EP 2004-25700	20011019
EP 1506962	A3	20050302		
EP 1506962	B1	20080702		
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NZ 525324	A	20050324	NZ 2001-525324	20011019
JP 3712393	B2	20051102	JP 2002-536056	20011019
RU 2264389	C2	20051120	RU 2003-114740	20011019
AT 355275	T	20060315	AT 2001-976786	20011019
EP 1777218	A1	20070425	EP 2006-23078	20011019
EP 1777218	B1	20081231		
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PT 1415987	E	20070531	PT 2001-976786	20011019
CN 101024627	A	20070829	CN 2007-10007096	20011019
CN 101029022	A	20070905	CN 2007-10007097	20011019
CN 101029022	B	20110112		
ES 2282299	T3	20071016	ES 2001-976786	20011019
IL 155447	A	20080605	IL 2001-155447	20011019
AT 399766	T	20080715	AT 2004-25700	20011019
TW I304061	B	20081211	TW 2001-125928	20011019
AT 419239	T	20090115	AT 2006-23078	20011019
ES 2318649	T3	20090501	ES 2006-23078	20011019
IL 189677	A	20101031	IL 2001-189677	20011019
NO 2003001731	A	20030619	NO 2003-1731	20030414
NO 326781	B1	20090216		
MX 2003003362	A	20030801	MX 2003-3362	20030415
US 7253286	B2	20070807	US 2003-420466	20030418
US 20040053908	A1	20040318		
ZA 2003003567	A	20040810	ZA 2003-3567	20030508
JP 2005272474	A	20051006	JP 2005-124034	20050421
JP 4354929	B2	20091028		
US 20060247259	A1	20061102	US 2005-293785	20051202
US 7612092	B2	20091103		
US 20060160832	A1	20060720	US 2006-347749	20060203
AU 2006203099	A1	20060810	AU 2006-203099	20060719
AU 2006236039	A1	20061207	AU 2006-236039	20061116
AU 2006236039	B2	20080522		
NO 2007004657	A	20030619	NO 2007-4657	20070912
US 20100197911	A1	20100805	US 2008-244227	20081002
US 7973160	B2	20110705		
JP 2009215313	A	20090924	JP 2009-123432	20090521
JP 5086304	B2	20121128		
US 20110118470	A1	20110519	US 2011-986638	20110107
US 8372981	B2	20130212		

PRIORITY APPLN. INFO.: JP 2000-320420 A 20001020
JP 2000-386195 A 20001220
JP 2001-46685 A 20010222
AU 2001-295986 A3 20011019
AU 2001-95986 TO 20011019
CN 2001-819710 A3 20011019
EP 2001-976786 A3 20011019
IL 2001-155447 A3 20011019
JP 2002-536056 A3 20011019
WO 2001-JP9221 W 20011019
US 2003-420466 A3 20030418
JP 2005-124034 A3 20050421
US 2005-293785 A1 20051202
US 2008-244227 A3 20081002
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 136:340689
GI



AB N-aryl or N-heteroarylurea derivs. represented by the general formula Ag-Xg-Yg-Tg1 or salts thereof, or hydrates of both [wherein Ag = (un)substituted C6-14 aryl or 5- to 14-membered heterocyclic group; Xg = single bond, O, S, C1-6 alkylene, SO, SO2, (un)substituted NH; Yg = (un)substituted C6-14 aryl, 5- to 14-membered heterocyclic group, C1-8 alkyl, C3-8 alicyclic hydrocarbyl, C6-14 aryl-C1-6 alkyl, 5- to 14-membered heteroaryl-C1-6 alkyl, (CH2)gSO2 (g = 1-8), (CH2)faCH:CH(CH2)fb (fa, fb = 0, 1,2,3), etc.; and Tg1 = a group of the general formula -Eg-CO-NRg1(Zg) or Q; wherein Eg = a single bond, (un)substituted NH; Rg1 = H, (un)substituted C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C3-8 aliphatic hydrocarbyl, etc.; Zg = C1-8 alkyl, C3-8 alicyclic hydrocarbyl, C6-14 aryl, etc.; Zg1, Zg2 = (a) a single bond, (b) C1-6 alkylene optionally having ≥1 atoms selected from O, S, and N in the middle or the terminus of the chain and optionally substituted with oxo, (c) (un)substituted C2-6 alkenyl] are prepared These compds. are also inhibitors of vascular endothelial growth factor receptor kinase (VEGFR2 kinase) and are useful as antitumor agents against hemangioma, pancreatic cancer, stomach cancer, colon cancer, breast cancer, prostate cancer, lung cancer, brain tumor, leukemia, or ovarian cancer, as cancer metastasis inhibitors, and for the treatment of retina neovascularization, diabetic retinopathy, atherosclerosis, or inflammatory diseases such as osteoarthritis, rheumatoid arthritis, psoriasis, or delayed hypersensitivity. Thus, to solution of 334 mg 4-[6-(4-benzyloxyphenyl)-7-(2-trimethylsilylethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy]-2-chlorophenylamine in 4 mL DMF were added 0.066 mL pyridine and 0.102 mL Ph chlorocarbonate and stirred at room temperature for 2.5 h to give 330 mg N-[4-[6-(4-benzyloxyphenyl)-7-(2-trimethylsilylethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy]-2-chlorophenyl]-N'-cyclopropylurea which (260 mg) was hydrogenolyzed over platinum oxide in ethanol overnight to give 160 mg N-[4-[6-(4-hydroxyphenyl)-7-(2-trimethylsilylethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy]-2-chlorophenyl]-N'-cyclopropylurea (I). I showed IC50 of 0.02 nM for inhibiting the vascular endothelial growth factor (VEGF)-stimulated sandwich tube formation in vascular endothelial cell.

IT 2835-96-3, 4-Amino-2-methylphenol 2835-99-6, 4-Amino-3-methylphenol 3096-69-3, 4-Amino-2,3-dimethylphenol 17609-80-2, 4-Amino-3-chlorophenol 35654-56-9, 4-Chloro-6,7-dimethoxyquinoline
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of urea derivs. containing nitrogenous aromatic ring compds. as angiogenesis inhibitors for prevention or treatment of diseases)

RN 2835-96-3 CAPLUS
CN Phenol, 4-amino-2-methyl- (CA INDEX NAME)



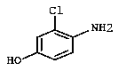
RN 2835-99-6 CAPLUS
CN Phenol, 4-amino-3-methyl- (CA INDEX NAME)



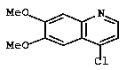
RN 3096-69-3 CAPLUS
CN Phenol, 4-amino-2,3-dimethyl- (CA INDEX NAME)



RN 17609-80-2 CAPLUS
CN Phenol, 4-amino-3-chloro- (CA INDEX NAME)

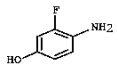


RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



IT 399-95-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of urea derivs. containing nitrogenous aromatic ring compds. as angiogenesis inhibitors for prevention or treatment of diseases)

RN 399-95-1 CAPLUS
CN Phenol, 4-amino-3-fluoro- (CA INDEX NAME)



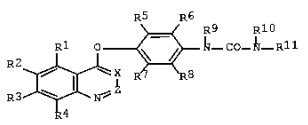
OS.CITING REF COUNT: 62 THERE ARE 62 CAPLUS RECORDS THAT CITE THIS RECORD (161 CITINGS)
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 70 OF 70 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2000:513673 CAPLUS Full-text
DOCUMENT NUMBER: 133:135235
TITLE: Preparation and anti-tumor, anti-atherosclerosis, anti-psoriasis, anti-diabetes, and anti-arthritis activities of quinolines and quinazolines
INVENTOR(S): Kubo, Kazuo; Fujiwara, Yasunari; Isoe, Toshiyuki
PATENT ASSIGNEE(S): Kirin Beer Kabushiki Kaisha, Japan
SOURCE: PCT Int. Appl., 208 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000043366	A1	20000727	WO 2000-JP255	20000120
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2361057	A1	20000727	CA 2000-2361057	20000120
CA 2361057	C	20100406		
AU 2000030748	A	20000807	AU 2000-30748	20000120
AU 771504	B2	20040325		
BR 2000007656	A	20011030	BR 2000-7656	20000120
EP 1153920	A1	20011114	EP 2000-900841	20000120
EP 1153920	B1	20031029		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
TR 2001002090	T2	20020121	TR 2001-2090	20000120
HU 2001005133	A2	20020729	HU 2001-5133	20000120
HU 2001005133	A3	20020930		
JP 2003286263	A	20031010	JP 2003-128216	20000120
NZ 513006	A	20031031	NZ 2000-513006	20000120
AT 253051	T	20031115	AT 2000-900841	20000120
EP 1384712	A1	20040128	EP 2003-24911	20000120
EP 1384712	B1	20070307		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
JP 3519368	B2	20040412	JP 2000-594782	20000120
ES 2208261	T3	20040616	ES 2000-900841	20000120
CN 1183114	C	20050105	CN 2000-805428	20000120
RU 2256654	C2	20050720	RU 2001-123434	20000120
AT 356117	T	20070315	AT 2003-24911	20000120
IL 144461	A	20070704	IL 2000-144461	20000120
ES 2281591	T3	20071001	ES 2003-24911	20000120
PL 204856	B1	20100226	PL 2000-349036	20000120
PL 206627	B1	20100930	PL 2000-388667	20000120
TW I229667	B	20050321	TW 2000-100998	20000121
NO 2001002617	A	20010914	NO 2001-2617	20010529
NO 321295	B1	20060418		
MX 2001007251	A	20011101	MX 2001-7251	20010717
KR 787254	B1	20071220	KR 2001-7009144	20010720
US 6797823	B1	20040928	US 2001-889858	20010723
HK 1043792	A1	20050630	HK 2002-105360	20020719
US 20040209905	A1	20041021	US 2004-842009	20040510
US 7169789	B2	20070130		
US 20070027318	A1	20070201	US 2006-526739	20060926

PRIORITY APPLN. INFO.:
JP 1999-14858 A 19990122
JP 1999-26691 A 19990203
JP 1999-142493 A 19990521
JP 1999-253624 A 19990907
EP 2000-900841 A3 20000120
JP 2000-594782 A3 20000120
WO 2000-JP255 W 20000120
US 2001-889858 A3 20010723
US 2004-842009 A3 20040510

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 133:135235
GI



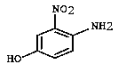
I

AB Title compds. [I; X and Z represent each CH or N; R1-3 represent each H, optionally substituted alkoxy, etc.; R4 represents H; R5-8 represent each H, halogeno, alkyl, alkoxy, alkylthio, nitro or amino, provided that all of R5-8 do not represent H simultaneously; R9 and R10 represent each H, alkyl or alkylcarbonyl; and R11 represents alkyl, alkenyl, alkynyl or aralkyl], pharmaceutically acceptable salts and solvates, and medicinal compns. containing the same are prepared and tested having antitumor activity and causing no morphol. change in cells. Thus, the title compound I (X = CH; Z = CH; R1, R4, R5,R7-R10 each an H; R11 = 3,5-F2C6H3) was prepared and tested.

IT 610-81-1, 4-Amino-3-nitrophenol 3096-69-3,

4-Amino-2,3-dimethylphenol 35654-56-9,
4-Chloro-6,7-dimethoxyquinoline 52671-64-4
94276-04-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation and antitumor activity of quinolines and quinazolines)

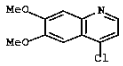
RN 610-81-1 CAPLUS
CN Phenol, 4-amino-3-nitro- (CA INDEX NAME)



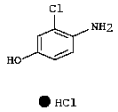
RN 3096-69-3 CAPLUS
CN Phenol, 4-amino-2,3-dimethyl- (CA INDEX NAME)



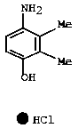
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



RN 52671-64-4 CAPLUS
CN Phenol, 4-amino-3-chloro-, hydrochloride (1:1) (CA INDEX NAME)



RN 94276-04-7 CAPLUS
CN Phenol, 4-amino-2,3-dimethyl-, hydrochloride (1:1) (CA INDEX NAME)



OS.CITING REF COUNT: 36 THERE ARE 36 CAPLUS RECORDS THAT CITE THIS RECORD (69 CITINGS)
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 602.74 1177.57

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DICTIONARY FILE UPDATES: 11 OCT 2017 HIGHEST RN 2147485-70-7

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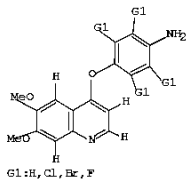
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Uploading C:\Users\trozof\Documents\STN Express 8.4\Queries\15348716 Formula g(1) (10.12.17)

L8 STRUCTURE UPLOADED

=> d
L8 HAS NO ANSWERS
L8 STR



G1:H,Cl,Br,F

Structure attributes must be viewed using the Structure Drawing program.

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FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
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FILE COVERS 1907 - 12 Oct 2017 VOL 167 ISS 17
FILE LAST UPDATED: 11 Oct 2017 (20171011/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Dec 2015
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Dec 2015

CAplus includes complete International Patent Classification (IPC) reclassification data for the third quarter of 2017.

CAplus now includes the comprehensive Cooperative Patent Classification (CPC). See HELP CPC for details.

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http://www.cas.org/legal/infopolicy

This file contains CAS Registry Numbers for easy and accurate substance identification.

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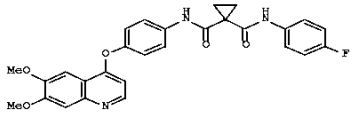
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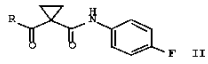
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L11 ANSWER 1 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2017:1102508 CAPLUS Full-text
DOCUMENT NUMBER: 167:278884
TITLE: Crystal structures of intermediates in a new synthesis of antitumor drug cabozantinib
AUTHOR(S): Laus, Gerhard; Schreiner, Erwin; Nerdinger, Sven; Kahlenberg, Volker; Wurst, Klaus; Vergeiner, Stefan; Schottenberger, Herwig
CORPORATE SOURCE: Faculty of Chemistry and Pharmacy, Leopold-Franzens University, Innsbruck, 6020, Austria
SOURCE: Heterocycles (2016), 93(1, Spec. Issue), 323-332
CODEN: HTCYAM; ISSN: 1881-0942
DIGITAL OBJECT ID: 10.3987/com-15-s(t)45
PUBLISHER: Japan Institute of Heterocyclic Chemistry
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
OTHER SOURCE(S): CASREACT 167:278884
GI

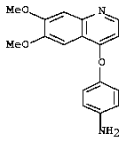


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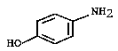


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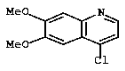
AB The heterocyclic antitumor drug cabozantinib (I) was synthesized by condensation of 4-(6,7-dimethoxyquinolin-4-yl-oxy)aniline and Me 1-(4-fluorophenylcarbamoyl)cyclopropanecarboxylate II [R = OMe] in the presence of two equivalent of sodium methoxide and azeotropic removal of methanol. In turn, the intermediate Me 1-(4-fluorophenylcarbamoyl)cyclopropanecarboxylate II [R = OMe] was prepared from 4-fluoroaniline and di-Me 1,1-cyclopropanedicarboxylate in the presence of one equivalent of sodium methoxide. Crystal structures of 6,7-dimethoxyquinolin-4(1H)-one, 4-(6,7-dimethoxyquinolin-4-yl-oxy)aniline and compds. II [R = OMe, 4-FC6H4NH] were determined
IT 190728-25-7P
RL: PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(crystal and mol. structure; crystal structures of intermediates in new synthesis of antitumor drug cabozantinib)
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



IT 123-30-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(crystal structures of intermediates in new synthesis of antitumor drug cabozantinib)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



IT 35654-56-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(crystal structures of intermediates in new synthesis of antitumor drug cabozantinib)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

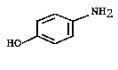


L11 ANSWER 2 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2017:720961 CAPLUS Full-text
DOCUMENT NUMBER: 167:5585
TITLE: Preparation method of Cabozantinib from diethyl malonate and 4-fluoroaniline
INVENTOR(S): Wang, Zhiguo; Song, Yanhong; Ma, Xiujuan; Tian, Beibei; Li, Shijiang; Li, Chao; Li, Tao; Zhang, Xin
PATENT ASSIGNEE(S): Shanghai Zaiqi Bio-Tech Co., Ltd., Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 10pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese

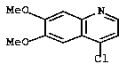
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 106632028	A	20170510	CN 2016-11199311	20161222

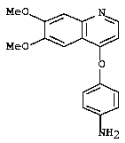
PRIORITY APPLN. INFO.: CN 2016-11199311 20161222
AB The invention has simple operation, is environmentally friendly, the comprehensive yield is more than 50%, is obviously improved, greatly reduces the current medicine production cost, and is suitable for industrial scale production The method comprises: (1) reacting di-Et malonate and 4-fluoroaniline to obtain Et 3-(4-fluoro Ph amino)-3-oxopropionate; (2) hydrolysis of of Et 3-(4-fluoro Ph amino)-3-oxopropionate to obtain 3-(4-fluoro Ph amino)-3-oxopropionic acid; (3) reacting of 4-chloro-6,7-dimethoxy quinoline and 4-aminophenol to obtain 4-[(6,7-dimethoxy quinolin-4-yl)oxo] aniline; (4) reacting of 3-(4-fluoro Ph amino)-3-oxopropionic acid and 1-(3-dimethylamino propyl)-3-Et carbodiimide hydrochloride and 4-[(6,7-dimethoxy quinolin-4-yl)oxo] aniline to obtain N-(4-(6,7-dimethoxy quinolin-4-yl)oxophenyl)-N'-(4-fluorophenyl)malonamide; (5) reacting of N-(4-(6,7-dimethoxy quinolin-4-yl)oxophenyl)-N'-(4-fluorophenyl)malonamide and 1,2-dibromoethane to give Cabozantinib.
IT 123-30-8 35654-56-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of Cabozantinib from di-Et malonate and 4-fluoroaniline)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



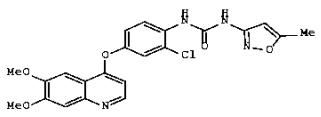
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



IT 190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of Cabozantinib from di-Et malonate and 4-fluoroaniline)
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)

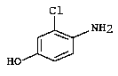


L11 ANSWER 3 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2017:230411 CAPLUS Full-text
DOCUMENT NUMBER: 166:327296
TITLE: A new and practical synthesis of tivozanib
AUTHOR(S): Zhu, Chunping; Mao, Yongjun; Wang, Han; Xu, Jingli
CORPORATE SOURCE: College of Chemistry and Chemical Engineering, Shanghai University of Engineering Science, Shanghai, 201620, Peop. Rep. China
SOURCE: Heterocycles (2016), 92(10), 1882-1887
CODEN: HTCYAM; ISSN: 1881-0942
DIGITAL OBJECT ID: 10.3987/COM-16-13555
PUBLISHER: Japan Institute of Heterocyclic Chemistry
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
OTHER SOURCE(S): CASREACT 166:327296
GI



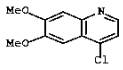
I

AB New and improved synthetic route of tivozanib (I) was described on a hectogram scale. Reduction cyclization process to prepare the key intermediate 6,7-dimethoxyquinolin-4-ol from the 3-(dimethylamino)-1-(2-nitrophenyl)prop-2-en-1-one compound at H2/Ni condition was adopted in good result. Com. available materials, simple reaction and operation were used, including nitration, condensation, hydrogenation, chlorination and so on, to give the final product in 28.7% yield over six steps and 98.9% purity (HPLC).
IT 52671-64-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of tivozanib via dimethoxyquinolinol as key intermediate)
RN 52671-64-4 CAPLUS
CN Phenol, 4-amino-3-chloro-, hydrochloride (1:1) (CA INDEX NAME)

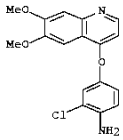


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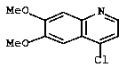
IT 35654-56-9P 286371-44-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of tivozanib via dimethoxyquinolinol as key intermediate)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



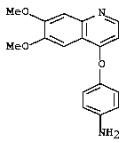
RN 286371-44-6 CAPLUS
CN Benzenamine, 2-chloro-4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



L11 ANSWER 4 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:2078753 CAPLUS Full-text
TITLE: C-met modulator pharmaceutical compositions comprising N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide
INVENTOR(S): Wilson, Jo Ann
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., No pp. given
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English



RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



L11 ANSWER 5 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:2059943 CAPLUS Full-text
TITLE: Preparation of cabozantinib and dosage forms for treatment of cancer
INVENTOR(S): Decillis, Arthur
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., No pp. given
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

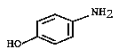
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20160022662	A1	20160128	US 2015-14782537	20151005
WO 2014165786	A1	20141009	WO 2014-US33016	20140404

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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2013-61808511 P 20130404
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

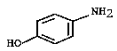
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20130337015	A1	20131219	US 2013-13810537	20130826
US 9724342	B2	20170808		
WO 2012009722	A1	20120119	WO 2011-US44378	20110718

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CN 106420743 A 20170222 CN 2016-10157218 20110718
JP 2016188215 A 20161104 JP 2016-93433 20160506
AU 2016247044 A1 20161103 AU 2016-247044 20161018
US 20170143689 A1 20170525 US 2017-15426804 20170207
US 20170266178 A1 20170921 US 2017-15612703 20170602
PRIORITY APPLN. INFO.: US 2010-61365253 P 20100716
US 2010-61370843 P 20100805
WO 2011-US44378 W 20110718
AU 2011-278950 A3 20110718
CN 2011-80044602 A3 20110718
JP 2013-519870 A3 20110718
US 2013-13810537 A3 20130826
US 2017-15426804 A3 20170207
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB Pharmaceutical compns. and unit dosage forms comprising Compd. I are disclosed.
IT 123-30-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(C-met modulator pharmaceutical compns. comprising dimethoxyquinolinyloxyphenyl(fluorophenyl)cyclopropanedicarboxamide)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)

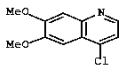


IT 35654-56-9P 190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(C-met modulator pharmaceutical compns. comprising dimethoxyquinolinyloxyphenyl(fluorophenyl)cyclopropanedicarboxamide)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

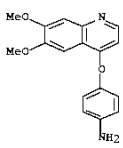
WO 2014-US33016 W 20140404
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB This invention relates to a dosage form of cabozantinib and a method of employing the dosage form to treat cancer.
IT 123-30-8, 4-Aminophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of cabozantinib and dosage forms for treatment of cancer)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



IT 35654-56-9P, 4-Chloro-6,7-dimethoxyquinoline
190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of cabozantinib and dosage forms for treatment of cancer)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



L11 ANSWER 6 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:2055777 CAPLUS Full-text
DOCUMENT NUMBER: 167:390609
TITLE: Method of treating cancer and bone cancer pain
INVENTOR(S): Schwab, Gisela; Aftab, Dana T.
PATENT ASSIGNEE(S): Exelixis, Inc., USA

SOURCE: U.S. Pat. Appl. Publ., No pp. given
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

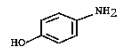
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20140179736	A1	20140626	US 2014-14115236	20140228
WO 2012151326	A1	20121108	WO 2012-US36191	20120502
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JP 2017105751	A	20170615	JP 2016-159543	20160816

PRIORITY APPLN. INFO.:
US 2011-61481682 P 20110502
US 2011-61557366 P 20111108
WO 2012-US36191 W 20120502
JP 2014-509417 A3 20120502

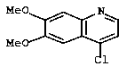
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB This invention is directed to the treatment of cancer, particularly lung cancer, breast cancer, melanoma, renal cell carcinoma, thyroid cancer that has metastasized to the bone. The invention is also directed to a method for treating bone cancer pain in an individual in need of such treatment comprising administering to the individual an effective amount of a compound of Formula I.

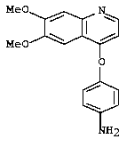
IT 123-30-8, 4-Aminophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(method of treating cancer and bone cancer pain)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



IT 35654-56-9P, 4-Chloro-6,7-dimethoxyquinoline
190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(method of treating cancer and bone cancer pain)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



L11 ANSWER 7 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:2051291 CAPLUS Full-text
DOCUMENT NUMBER: 167:390605
TITLE: Method of treating cancer
INVENTOR(S): Aftab, Dana T.; Schimmoller, Frauke
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., No pp. given
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

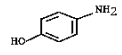
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20140323522	A1	20141030	US 2014-14356927	20140508
WO 2013070890	A1	20130516	WO 2012-US64116	20121108
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PRIORITY APPLN. INFO.:
US 2011-61557358 P 20111108
WO 2012-US64116 W 20121108

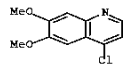
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB This invention is directed to the treatment of cancer, particularly castration-resistant prostate cancer and bone metastases, with a dual inhibitor of MET and VEGF.

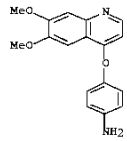
IT 123-30-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(dual inhibitor of Met and VEGF for treating cancer)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



IT 35654-56-9P 190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(dual inhibitor of Met and VEGF for treating cancer)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



L11 ANSWER 8 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:2041767 CAPLUS Full-text
DOCUMENT NUMBER: 167:324798
TITLE: Method of treating cancer
INVENTOR(S): Aftab, Dana T.
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., No pp. given
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

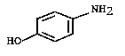
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20150133494	A1	20150514	US 2014-14398188	20141031
WO 2013166296	A1	20131107	WO 2013-US39284	20130502
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PRIORITY APPLN. INFO.:
US 2012-61641837 P 20120502
WO 2013-US39284 W 20130502

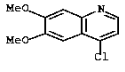
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB This invention is directed to the treatment of cancer, particularly castration-resistant prostate cancer and osteolytic bone metastases, with a dual inhibitor of MET and VEGF.

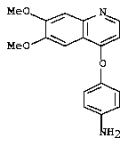
IT 123-30-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(dual MET-VEGF modulator for treating osteolytic bone metastases)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



IT 35654-56-9P 190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(dual MET-VEGF modulator for treating osteolytic bone metastases)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)

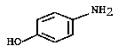


L11 ANSWER 9 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:2037951 CAPLUS Full-text
DOCUMENT NUMBER: 167:302546
TITLE: Method of treating lung adenocarcinoma
INVENTOR(S): Aftab, Dana T.
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., No pp. given
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

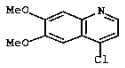
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20150238477	A1	20150827	US 2015-14426580	20150306
WO 2014039971	A1	20140313	WO 2013-US58768	20130909

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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

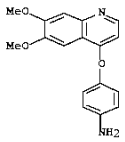
PRIORITY APPLN. INFO.: US 2012-61698143 P 20120907
WO 2013-US58768 W 20130909
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB This invention is directed to the treatment of cancer in a patient, particularly a patient with lung adenocarcinoma, and more particularly a patient with KIF5B-RET fusion-pos. non-small cell lung cancer, with an inhibitor of MET, VEGF, and RET which is a compound of Formula I:or a pharmaceutically acceptable salt thereof.
IT 123-30-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(inhibitors of Met, VEGFR and Ret for use in treatment of lung adenocarcinoma)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



IT 35654-56-9P 190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(inhibitors of Met, VEGFR and Ret for use in treatment of lung adenocarcinoma)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)

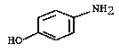


L11 ANSWER 10 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:2003465 CAPLUS Full-text
DOCUMENT NUMBER: 167:175951
TITLE: Process for preparing quinoline derivatives
INVENTOR(S): Wilson, Jo Ann; Naganathan, Sriram; Andersen, Neil G.; Pfeiffer, Matthew
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., No pp. given
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

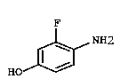
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US 20140256938	A1	20140911	US 2014-14353251	20140421
US 9365516	B2	20160614		
WO 2013059788	A1	20130425	WO 2012-US61320	20121022

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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

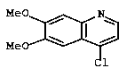
US 20160229805 A1 20160811 US 2016-15133708 20160420
PRIORITY APPLN. INFO.: US 2011-61549312 P 20111020
WO 2012-US61320 W 20121022
US 2014-14353251 A1 20140421
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB A process for prepg. a compd. of Formula I is disclosed, comprising the steps:wherein: R1 is halo; R2 is halo; R3 is (C1-C6)alkyl or (C1-C6)alkyl optionally substituted with heterocycloalkyl; R4 is (C1-C6)alkyl; and Q is CH or N;comprising: (a) contacting 1,1-cyclopropane dicarboxylic acid with thionyl chloride in a polar aprotic solvent; (b) adding and a tertiary amine base to the mixture of step (a) to form a compound of Formula A; and (c) coupling a compound of Formula A with an amine of Formula B to form a compound of Formula I.
IT 123-30-8 399-95-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for preparing quinoline derivs.)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



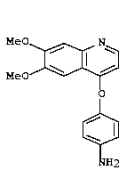
RN 399-95-1 CAPLUS
CN Phenol, 4-amino-3-fluoro- (CA INDEX NAME)



IT 35654-56-9P 190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparing quinoline derivs.)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



L11 ANSWER 11 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:1941702 CAPLUS Full-text
DOCUMENT NUMBER: 166:490458
TITLE: Processes for preparing quinoline compounds and pharmaceutical compositions containing such compounds
INVENTOR(S): Wilson, Jo Ann
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., No pp. given
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20140200242	A1	20140717	US 2014-13984559	20140320
US 9717720	B2	20170801		
WO 2012109510	A1	20120816	WO 2012-US24591	20120210

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PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

NZ 712808	A	20170331	NZ 2012-712808	20120210
JP 2016188216	A	20161104	JP 2016-94411	20160510
US 20170057921	A1	20170302	US 2016-15348716	20161110

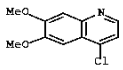
PRIORITY APPLN. INFO.:
US 2011-61441520 P 20110210
US 2011-61441527 P 20110210
WO 2012-US24591 W 20120210
JP 2013-553580 A3 20120210
NZ 2012-614130 A3 20120210
US 2014-13984559 A1 20140320

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

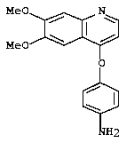
AB The present invention is directed to processes for making and compns. containing quinolines such as formula I or pharmaceutically acceptable salts thereof wherein: X1 is H, Br, Cl, or X2 is H, Br, Cl, or n1 is 1-2; and n2 is 1-2.

IT 35654-56-9P 190728-25-7P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparing quinoline derivs. and pharmaceutical compns. thereof)

RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

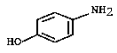


RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)

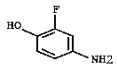


IT 123-30-8 399-96-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for preparing quinoline derivs. and pharmaceutical compns. thereof)

RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)

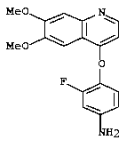


RN 399-96-2 CAPLUS
CN Phenol, 4-amino-2-fluoro- (CA INDEX NAME)



IT 347161-74-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparing quinoline derivs. and pharmaceutical compns. thereof)

RN 347161-74-4 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]-3-fluoro- (CA INDEX NAME)



L11 ANSWER 12 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN

ACCESSION NUMBER:	2016:1874511 CAPLUS Full-text
DOCUMENT NUMBER:	166:300776
TITLE:	Drug combinations to treat cancer
INVENTOR(S):	Sweeney, Christopher J.; Kantoff, Phili W.
PATENT ASSIGNEE(S):	USA
SOURCE:	U.S. Pat. Appl. Publ., No pp. given CODEN: USXXCO
DOCUMENT TYPE:	Patent
LANGUAGE:	English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20160082019	A1	20160324	US 2015-14782493	20151005
WO 2014165779	A1	20141009	WO 2014-US33008	20140404

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

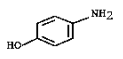
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

PRIORITY APPLN. INFO.:
US 2013-61808516 P 20130404
WO 2014-US33008 W 20140404

AB This invention relates to the combination of cabozantinib and abiraterone to treat cancer, particularly castration resistant prostate cancer.

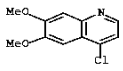
IT 123-30-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(drug combinations to treat cancer)

RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)

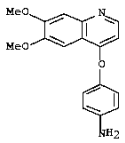


IT 35654-56-9P 190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(drug combinations to treat cancer)

RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



L11 ANSWER 13 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN

ACCESSION NUMBER:	2016:702303 CAPLUS Full-text
DOCUMENT NUMBER:	164:602041
TITLE:	Preparation of quinoline derivatives as multitarget kinase inhibitor useful for the treatment of cancer
INVENTOR(S):	Zhou, Youjun; Zhou, Hao; Zheng, Canhui; Zhu, Ju; Lv, Jiaguo; Sun, Nannan; Chen, Shana
PATENT ASSIGNEE(S):	The Second Military Medical University, PLA, Peop. Rep. China
SOURCE:	Faming Zhuanli Shenqing, 36pp. CODEN: CNXXEV
DOCUMENT TYPE:	Patent
LANGUAGE:	Chinese
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 105541798	A	20160504	CN 2016-10077368	20160203

PRIORITY APPLN. INFO.:
CN 2016-10077368 20160203

OTHER SOURCE(S): CASREACT 164:602041; MARPAT 164:602041

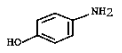
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

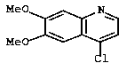
AB The invention relates to quinoline derivs. of formula I, method for their preparation and their use as multitarget kinase inhibitor for the treatment of cancer. Compds. of formula I, wherein R1 is H and halo; R2 is H, alkyl, halo, OH and amino; R3 is H and C1-5alkyl; X is N and O, are claimed. Example compound II was prepared by a multistep procedure (procedure given). The invention compds. were evaluated for their anticancer activity and inhibitory activity towards kinase KDR and MET. From the assay, it was determined that example compound II exhibited IC50 value in the range of 1.48 μM to 11.6 μM.

IT 123-30-8 35654-56-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of quinoline derivs. as multitarget kinase inhibitor useful for the treatment of cancer)

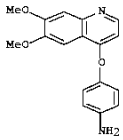
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



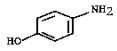
IT 190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of quinoline derivs. as multitarget kinase inhibitor useful for
the treatment of cancer)
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



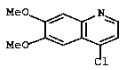
L11 ANSWER 14 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:224790 CAPLUS Full-text
DOCUMENT NUMBER: 164:293822
TITLE: Drug combinations to treat multiple myeloma
INVENTOR(S): Aftab, Dana T.; Lamb, Peter
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 49pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2016022697	A1	20160211	WO 2015-US43825	20150805
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
CA 2957466	A1	20160211	CA 2015-2957466	20150805
AU 2015301097	A1	20170302	AU 2015-301097	20150805
KR 2017031786	A	20170321	KR 2017-7006288	20150805
CN 106573042	A	20170419	CN 2015-80042010	20150805
EP 3177311	A1	20170614	EP 2015-750223	20150805
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
JP 2017526662	T	20170914	JP 2017-506390	20150805
MX 2017001490	A	20170511	MX 2017-1490	20170201
US 20170224672	A1	20170810	US 2017-15501582	20170203
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			WO 2015-US43825 W	20150805

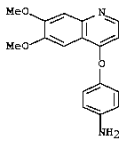
OTHER SOURCE(S): CASREACT 164:293822; MARPAT 164:293822
AB This invention relates to the combination of a C-Met inhibitor and a proteasome inhibitor to treat cancer, particularly multiple myeloma.
IT 123-30-8, 4-Aminophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(drug combinations to treat multiple myeloma)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



IT 35654-56-9P, 4-Chloro-6,7-dimethoxy-quinoline
190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(drug combinations to treat multiple myeloma)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)

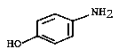


REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

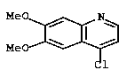
L11 ANSWER 15 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2015:1726025 CAPLUS Full-text
DOCUMENT NUMBER: 163:628844
TITLE: Method of treating lung adenocarcinoma
INVENTOR(S): Aftab, Dana T.; Yu, Peiwen
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 92pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2015164869	A1	20151029	WO 2015-US27800	20150427
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
CA 2946416	A1	20151029	CA 2015-2946416	20150427
AR 100191	A1	20160914	AR 2015-101255	20150427
AU 2015249232	A1	20161110	AU 2015-249232	20150427
KR 2016147934	A	20161223	KR 2016-7033010	20150427
IL 248408	A	20161229	IL 2015-248408	20150427
EP 3134084	A1	20170301	EP 2015-721100	20150427
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
CN 106488768	A	20170308	CN 2015-80022580	20150427
JP 2017513908	T	20170601	JP 2016-564236	20150427
MX 2016013600	A	20170427	MX 2016-13600	20161017
US 20170042880	A1	20170216	US 2016-15305854	20161021
PRIORITY APPLN. INFO.:			US 2014-61984599 P	20140425
			WO 2015-US27800 W	20150427

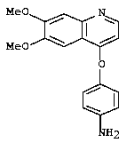
OTHER SOURCE(S): CASREACT 163:628844; MARPAT 163:628844
AB This invention is directed to the treatment of cancer in a patient, particularly a patient with lung adenocarcinoma, and more particularly a patient with SLC34A2-ROS1, CD74-ROS1, or FIG-ROS1 fusion-pos. non-small cell lung cancer, with an inhibitor of MET, VEGFR2, and ROS1.
IT 123-30-8, p-Aminophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(treating lung adenocarcinoma)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



IT 35654-56-9P 190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(treating lung adenocarcinoma)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)

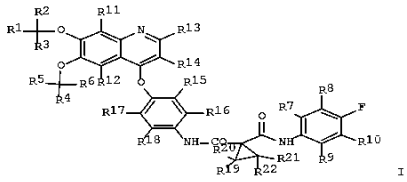


REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 16 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2015:1213912 CAPLUS Full-text
DOCUMENT NUMBER: 163:271103
TITLE: Preparation of deuterated cabozantinib derivatives and their application as anticancer agents
INVENTOR(S): Chen, Xinghai; Peng, Wei; Parker, Omar; Zheng, Feiming; Fu, Yong
PATENT ASSIGNEE(S): Shanghai Shengkao Pharmaceutical Technology Co., Ltd., Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 35pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

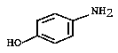
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 104788372	A	20150722	CN 2014-10361351	20140725

PRIORITY APPLN. INFO.: CN 2014-10361351 20140725
OTHER SOURCE(S): CASREACT 163:271103; MARPAT 163:271103
GI

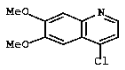


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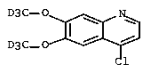
AB The invention is related to the prepn. of deuterated cabozantinib derivs. I and their application as anticancer agents. The invention compound I, wherein R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11, R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, and R22 are H or D independently and contain at least one D and their pharmaceutically acceptable salts, crystalline hydrates, solvates, prodrugs, single crystal or polymorph are claimed. Compound I was prepared by multi-step procedure (procedure given). The deuterated cabozantinib derivs. have slow decomposition in vivo, thereby reducing adverse metabolism of drugs. The invention compds. were evaluated for their anticancer activity.
IT 123-30-8 35654-56-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of deuterated cabozantinib derivs. and their application as anticancer agents)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



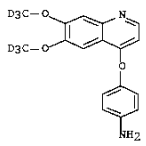
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



IT 1714998-85-2P 1802168-63-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of deuterated cabozantinib derivs. and their application as anticancer agents)
RN 1714998-85-2 CAPLUS
CN Quinoline, 4-chloro-6,7-di(methoxy-d3)- (CA INDEX NAME)



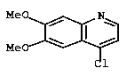
RN 1802168-63-3 CAPLUS
CN Benzenamine, 4-[[6,7-di(methoxy-d3)-4-quinolinyl]oxy]- (CA INDEX NAME)



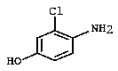
L11 ANSWER 17 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2015:191731 CAPLUS Full-text
DOCUMENT NUMBER: 162:299963
TITLE: Preparation of Tivozanib intermediate
INVENTOR(S): Hao, Guiyun; Huang, Wei; Cen, Junda
PATENT ASSIGNEE(S): Shanghai Institute of Pharmaceutical Industry, Peop. Rep. China; China State Institute of Pharmaceutical Industry
SOURCE: Faming Zhuanli Shenqing, 12pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 104326924	A	20150204	CN 2013-10310007	20130722

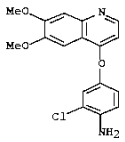
PRIORITY APPLN. INFO.: CN 2013-10310007 20130722
OTHER SOURCE(S): CASREACT 162:299963
AB The invention relates to prepn. of Tivozanib intermediate 3-chloro-4-aminophenol. 3-Chloro-4-aminophenol was prepared by reaction of p-aminobenzenesulfonic acid and 3-chlorophenol; the resulting 4-[(2-chloro-4-hydroxyphenyl)azo]-benzenesulfonic acid underwent underwent reduction to give product.
IT 35654-56-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of Tivozanib intermediate 3-chloro-4-aminophenol)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



IT 17609-80-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of Tivozanib intermediate 3-chloro-4-aminophenol)
RN 17609-80-2 CAPLUS
CN Phenol, 4-amino-3-chloro- (CA INDEX NAME)



IT 286371-44-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of Tivozanib intermediate 3-chloro-4-aminophenol)
RN 286371-44-6 CAPLUS
CN Benzenamine, 2-chloro-4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



L11 ANSWER 18 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2015:161573 CAPLUS Full-text
DOCUMENT NUMBER: 162:258994
TITLE: Preparation of quinolinecarboxamide compounds, their medical compositions, and preventive and/or therapeutic method for Axl-related disorders
INVENTOR(S): Inukai, Takayuki; Takeuchi, Jun; Yasuhiro, Tomoko
PATENT ASSIGNEE(S): Ono Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 141pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

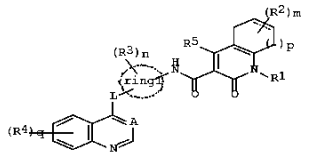
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2015012298	A1	20150129	WO 2014-JP69419	20140723

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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

CA 2918888	A1	20150129	CA 2014-2918888		20140723
AU 2014294109	A1	20160211	AU 2014-294109		20140723
CN 105408312	A	20160316	CN 2014-80041780		20140723
KR 2016033707	A	20160328	KR 2016-7002008		20140723
IL 243743	A	20160331	IL 2014-243743		20140723
EP 3026045	A1	20160601	EP 2014-828976		20140723
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME					
MX 2016000989	A	20160516	MX 2016-989		20160122
US 20160168121	A1	20160616	US 2016-14906993		20160122
US 9573935	B2	20170221			
IN 201647002406	A	20160831	IN 2016-47002406		20160122
US 20170088542	A1	20170330	US 2016-15373091		20161208
PRIORITY APPLN. INFO.:			JP 2013-153350	A	20130724
			WO 2014-JP69419	W	20140723
			US 2016-14906993	A1	20160122

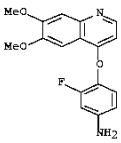
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 162:258994; MARPAT 162:258994
GI



I

AB The compds., their salts, their solvates, their N-oxides, and their prodrugs are represented by formula I [R1 = (un)substituted C1-8 alkyl, (un)substituted C3-7 carbocycle; (un)substituted 4- to 7-membered heterocycle; R2 = C1-4 (halo)alkyl, halo, oxo, etc.; R3 = C1-4 (halo)alkyl, halo; R4 = C1-4 alkoxy, C1-4 haloalkyl, C2-4 alkenyloxy, etc.; R5 = H, C1-4 (halo)alkyl, halo, etc.; A = CH, N; L = O, NH, CO, S, etc.; ring1 = 5- to 7-membered cyclic group; double bond comprising solid and broken lines represent C-C single or double bond; m, n = 0-5; p = 0-2; q = 0-4]. Thus, amidating 5-[(6,7-dimethoxy-4-quinolinyl)oxy]-2- pyridineamine (preparation given) with 2,5-dioxo-1-phenyl-1,2,5,6,7,8-hexahydro-3-quinolinecarboxylic acid (preparation given), gave N-[5-[(6,7-dimethoxy-4-quinolinyl)oxy]-2-pyridinyl]-2,5-dioxo-1-phenyl-1,2,5,6,7,8-hexahydro-3-quinolinecarboxamide with Axl inhibitory activity (IC50) 0.0022 μM. Formulations containing I are given.

IT 123-30-8, 4-Aminophenol 35654-56-9,



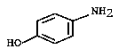
OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 19 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2014:1716754 CAPLUS Full-text
DOCUMENT NUMBER: 161:582215
TITLE: Preparation of cabozantinib and dosage forms for treatment of cancer
INVENTOR(S): Decillis, Arthur
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 48pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

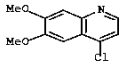
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2014165786	A1	20141009	WO 2014-US33016	20140404
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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
EP 2981263	A1	20160210	EP 2014-724909	20140404
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
US 20160022662	A1	20160128	US 2015-14782537	20151005
PRIORITY APPLN. INFO.:			US 2013-61808511 P	20130404
			WO 2014-US33016 W	20140404

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 161:582215
GI

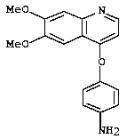
4-Chloro-6,7-dimethoxyquinoline
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of quinolinecarboxamides for preventive and/or therapeutic method for Axl-related disorders)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



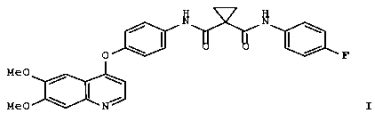
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



IT 190728-25-7P 347161-74-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of quinolinecarboxamides for preventive and/or therapeutic method for Axl-related disorders)
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



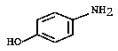
RN 347161-74-4 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]-3-fluoro- (CA INDEX NAME)



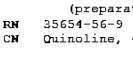
I

AB This invention relates to a dosage form of cabozantinib (I) and a method of employing the dosage form to treat cancer. I was prepared starting with 6,7-dimethoxy-4-quinolinol through a number of steps. I S-maleate was also prepared and tablets containing I were prepared

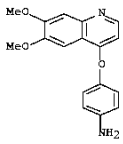
IT 123-30-8, 4-Aminophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of cabozantinib and dosage forms for treatment of cancer)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



IT 35654-56-9P, 4-Chloro-6,7-dimethoxyquinoline
190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of cabozantinib and dosage forms for treatment of cancer)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)

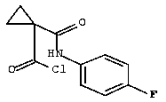


OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

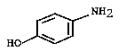
L11 ANSWER 20 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2014:1710486 CAPLUS Full-text
DOCUMENT NUMBER: 161:577829
TITLE: Drug combinations to treat cancer
INVENTOR(S): Sweeney, Christopher J.; Kantoff, Philip W.
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 78pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2014165779	A1	20141009	WO 2014-US33008	20140404
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
CA 2908815	A1	20141009	CA 2014-2908815	20140404
AU 2014248001	A1	20151119	AU 2014-248001	20140404
IL 241868	A	20151130	IL 2014-241868	20140404
KR 2015138268	A	20151209	KR 2015-7030445	20140404
EP 2983639	A1	20160217	EP 2014-724594	20140404
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
JP 2016515628	T	20160530	JP 2016-506653	20140404
US 20160082019	A1	20160324	US 2015-14782493	20151005
MX 2015014046	A	20160516	MX 2015-14046	20151005
IN 2015KN03651	A	20160318	IN 2015-KN3651	20151103

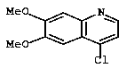
PRIORITY APPLN. INFO.: US 2013-61808516 P 20130404
WO 2014-US33008 W 20140404
OTHER SOURCE(S): CASREACT 161:577829; MARPAT 161:577829
GI



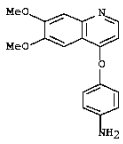
AB This invention relates to the combination of cabozantinib and abiraterone to treat cancer, particularly castration resistant prostate cancer.
IT 123-30-8, 4-Aminophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(drug combinations to treat cancer)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



IT 35654-56-9P 190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(drug combinations to treat cancer)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

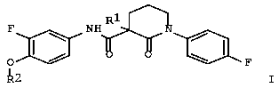


RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



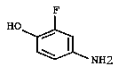
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 21 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2014:484709 CAPLUS Full-text
DOCUMENT NUMBER: 161:186431
TITLE: Discovery of novel c-Met inhibitors bearing a 3-carboxylpiperidin-2-one scaffold
AUTHOR(S): Zhang, Wei; Ai, Jing; Shi, Dakuo; Peng, Xia; Ji, Yinchun; Liu, Jian; Geng, Meiyu; Li, Yingxia
CORPORATE SOURCE: School of Pharmacy, Fudan University, Shanghai, 201203, Peop. Rep. China
SOURCE: Molecules (2014), 19(2), 2655-2673, 19 pp.
CODEN: MOLEFW; ISSN: 1420-3049
DIGITAL OBJECT ID: 10.3390/molecules19022655
PUBLISHER: MDPI AG
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
OTHER SOURCE(S): CASREACT 161:186431
GI

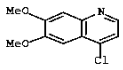


I

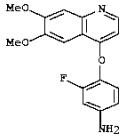
AB A series of compds. contg. a novel 3-carboxypiperidin-2-one scaffold I [R1 = H, Me, Et, n-Bu, Cl; R2 = 2-amino-3-chloropyridin-4-yl, 7H-pyrrolo[2,3-d]pyrimidin-4-yl, 6,7-dimethoxyquinolin-4-yl, etc.], based on the lead structure BMS-777607 were designed, synthesized and evaluated for their c-Met kinase inhibition and cytotoxicity against MKN45 human gastric cancer cell line. The results indicated that compound I [R1 = Cl, R2 = 6,7-dimethoxyquinolin-4-yl] exhibited significant inhibitory effect on c-Met with IC50 value of 8.6 nM and MKN45 cell proliferation with IC50 value of 0.57μM.
IT 399-96-2 35654-56-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of carboxypiperidinone scaffolds and evaluation of their c-Met kinase inhibition, SAR and cytotoxicity against MKN45 cancer cell lines)
RN 399-96-2 CAPLUS
CN Phenol, 4-amino-2-fluoro- (CA INDEX NAME)



RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



IT 347161-74-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of carboxypiperidinone scaffolds and evaluation of their c-Met kinase inhibition, SAR and cytotoxicity against MKN45 cancer cell lines)
RN 347161-74-4 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]-3-fluoro- (CA INDEX NAME)



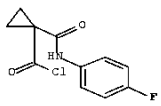
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 22 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2014:479457 CAPLUS Full-text

DOCUMENT NUMBER: 160:515456
TITLE: Synthesis method of antitumor therapeutic drug of cabozantinib
INVENTOR(S): Cai, Jianping; Chen, Zengfei; Zhang, Lifeng; Fang, Ying
PATENT ASSIGNEE(S): Suzhou Moer Pharmaceutical Co., Ltd., Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 9pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 103664778	A	20140326	CN 2013-10631287	20131127
CN 103664778	B	20170405		
PRIORITY APPLN. INFO.:			CN 2013-10631287	20131127

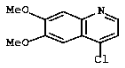
OTHER SOURCE(S): CASREACT 160:515456; MARPAT 160:515456
GI



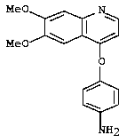
AB The invention discloses a synthesis method of antitumor therapeutic drug of cabozantinib., comprising: using 4-(6, 7- dimethoxy quinoline -4- oxy)-phenylamine to react with 1-((4- fluorophenyl) carbamoyl) cyclopropyl acyl halide, an acid-binding agent in organic solvent at -5~20 °C for 0.5~2h to obtain cabozantinib; the inventive method uses cheap raw materials, has mild conditions, simple and convenient operation, stable process, good repeatability, high molar yield, low cost, so invention is an applicable method for com. production of cabozantinib. Cabozantinib was prepared via chlorination of 6,7-dimethoxyquinolin-4-ol; the resulting 4-chloro-6,7-dimethoxyquinoline underwent condensation with 4-aminophenol or 4-nitrophenol to give the corresponding ethers, which underwent redn and/or acylation with 1-[(4-fluorophenyl)carbamoyl]cyclopropylcarbonyl halides to give cabozantinib. The said 1-[(4-fluorophenyl)carbamoyl]cyclopropylcarbonyl halides were prepared via condensation of 1,1-cyclopropanedicarboxylic acid with p-fluoroaniline followed by halogenation. The inventive method uses cheap raw materials, has mild conditions, simple and convenient operation, stable process, good repeatability, high molar yield, low cost, so invention is an applicable method for com. production of cabozantinib.

IT 35654-56-9P, 4-Chloro-6,7-dimethoxyquinoline
190728-25-7P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of antitumor drug cabozantinib starting from (dimethoxy)quinolinol and cyclopropanedicarboxylic acid by using etherification and amidation as the key steps)

RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

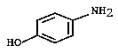


RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



IT 123-30-8, 4-Aminophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of antitumor drug cabozantinib starting from (dimethoxy)quinolinol and cyclopropanedicarboxylic acid by using etherification and amidation as the key steps)

RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)

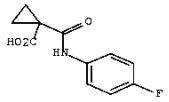


L11 ANSWER 23 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2014:410366 CAPLUS Full-text
DOCUMENT NUMBER: 160:451706
TITLE: Inhibitors of Met, VEGFR and Ret for use in the treatment of lung adenocarcinoma
INVENTOR(S): Aftab, Dana T.
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 80pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2014039971	A1	20140313	WO 2013-US58768	20130909
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
US 20140121239	A1	20140501	US 2013-14021614	20130909
CN 104703600	A	20150610	CN 2013-80052164	20130909
EP 2892532	A1	20150715	EP 2013-765886	20130909
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
JP 2015530389	T	20151015	JP 2015-531283	20130909
US 20150238477	A1	20150827	US 2015-14426580	20150306
PRIORITY APPLN. INFO.:			US 2012-61698143 P	20120907
			WO 2013-US58768 W	20130909

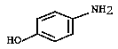
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 160:451706; MARPAT 160:451706
GI



AB This invention is directed to the treatment of cancer in a patient, particularly a patient with lung adenocarcinoma, and more particularly a patient with KIF5B-RET fusion-pos. non-small cell lung cancer, with an inhibitor of MET, VEGF, and RET.

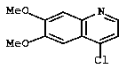
IT 123-30-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(inhibitors of Met, VEGFR and Ret for use in treatment of lung adenocarcinoma)

RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)

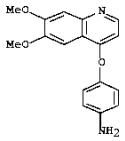


IT 35654-56-9P 190728-25-7P
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(inhibitors of Met, VEGFR and Ret for use in treatment of lung adenocarcinoma)

RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



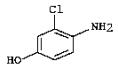
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



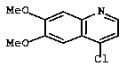
OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 24 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2013:1967223 CAPLUS Full-text
DOCUMENT NUMBER: 162:205137
TITLE: Synthesis of tivozanib
AUTHOR(S): Wang, Jing; Wang, Yalou; Qin, Yuyan
CORPORATE SOURCE: School of Pharmacy, China Pharmaceutical University, Nanjing, Jiangsu Province, 210009, Peop. Rep. China
SOURCE: Zhongguo Yiyao Gongye Zazhi (2013), 44(6), 541-544
CODEN: ZYGZEA; ISSN: 1001-8255
PUBLISHER: Zhongguo Yiyao Gongye Zazhi Bianjibu
DOCUMENT TYPE: Journal

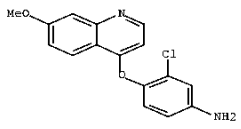
LANGUAGE: Chinese
OTHER SOURCE(S): CASREACT 162:205137
AB 4-Chloro-6,7-dimethoxyquinoline (6) was synthesized from 3,4-dimethoxyaniline (2) and ethoxymethylenemalonic acid di-Et ester by substitution, cyclization, hydrolysis, decarboxylation and chlorination. In another route, 6 was synthesized from 2, Meldrum's acid and tri-Me orthoformate by substitution, cyclization and chlorination. Then 6 was etherizied with 4-amino-3-chlorophenol hydrochloride (7) and coupled with 3-amino-5methylisoxazole by ureapoiesis to yield the antitumor drug tivozanib with an overall yield of 35%-37% (based on compound 2).
IT 52671-64-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis of tivozanib)
RN 52671-64-4 CAPLUS
CN Phenol, 4-amino-3-chloro-, hydrochloride (1:1) (CA INDEX NAME)



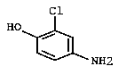
IT 35654-56-9P, 4-Chloro-6,7-dimethoxyquinoline
286371-44-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of tivozanib)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



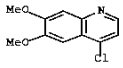
RN 286371-44-6 CAPLUS
CN Benzenamine, 2-chloro-4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



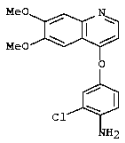
AB The present invention provides novel substituted quinoline compds., pharmaceutical acceptable salts and formulations thereof useful in modulating the protein tyrosine kinase activity, and in modulating cellular activities such as proliferation, differentiation, apoptosis, migration and invasion. The invention also provides pharmaceutically acceptable compns. comprising such compds. and methods of using the compns. in the treatment of hyperproliferative disorders in mammals, especially humans.
IT 3964-52-1, 4-Amino-2-chlorophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(substituted quinoline compds. and methods of use)
RN 3964-52-1 CAPLUS
CN Phenol, 4-amino-2-chloro- (CA INDEX NAME)



IT 35654-56-9P, 4-Chloro-6,7-dimethoxyquinoline
163733-99-1P, 4-Amino-2,3-difluorophenol 190728-25-7P,
4-((6,7-Dimethoxyquinolin-4-yl)oxy)aniline 286371-44-6P
1426312-64-2P 1437323-99-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(substituted quinoline compds. and methods of use)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



RN 163733-99-1 CAPLUS
CN Phenol, 4-amino-2,3-difluoro- (CA INDEX NAME)

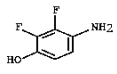


L11 ANSWER 25 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2013:1873443 CAPLUS Full-text
DOCUMENT NUMBER: 160:50465
TITLE: Substituted quinoline compounds and use as Antitumor agents
INVENTOR(S): Xi, Ning; Wang, Tingjin; Zeng, Shan; Sun, Mingming; Wang, Kunrui
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 80pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

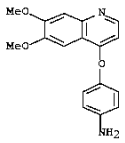
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2013180949	A1	20131205	WO 2013-US41036	20130515

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

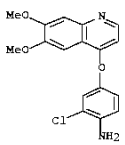
PRIORITY APPLN. INFO.: US 2012-61652210 P 20120527
OTHER SOURCE(S): CASREACT 160:50465; MARPAT 160:50465
GI



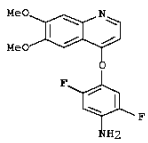
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



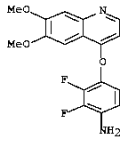
RN 286371-44-6 CAPLUS
CN Benzenamine, 2-chloro-4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



RN 1426312-64-2 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]-2,5-difluoro- (CA INDEX NAME)



RN 1437323-99-3 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]-2,3-difluoro- (CA INDEX NAME)

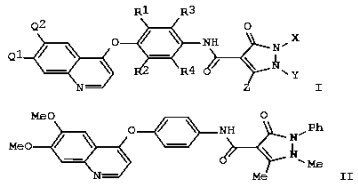


OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

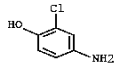
L11 ANSWER 26 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2013:1866363 CAPLUS Full-text
DOCUMENT NUMBER: 160:33885
TITLE: Substituted quinoline compound useful in treatment of hyperproliferative diseases and its preparation
INVENTOR(S): Xi, Ning; Wang, Tingjin; Zeng, Shan; Sun, Mingming; Wang, Kunrui
PATENT ASSIGNEE(S): HEC Pharm Co., Ltd., Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 57pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
CN 103420986	A	20131204	CN 2013-10179608		20130515
PRIORITY APPLN. INFO.:			CN 2012-10154478	A	20120518
			CN 2013-10118880	A	20130403

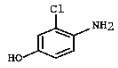
OTHER SOURCE(S): CASREACT 160:33885; MARPAT 160:33885
GI



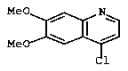
AB The invention relates to substituted quinoline compds. of formula I as protein kinase regulator useful in treatment of proliferative diseases and their preparation Compound I, wherein R1, R2, R3, and R4 are independently H, D, F, Cl, or Br; Q1 and Q2 are independently H, D, C1-6 alkyl, etc.; X and Z are independently H, D, C1-6 alkyl, etc.; Y is H, D, C2-6 alkynyl, etc.; their stereoisomers, N-oxides, solvates, pharmaceutically acceptable salts, are claimed. Compound II was prepared by multi-step procedure (procedure given). The present invention also relates to the pharmaceutical compns. containing the inventive compds., and method of application of the pharmaceutical composition for treatment of a mammal, especially hyperproliferative disease.
IT 3964-52-1 17609-80-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of substituted quinoline compound useful in treatment of hyperproliferative diseases)
RN 3964-52-1 CAPLUS
CN Phenol, 4-amino-2-chloro- (CA INDEX NAME)



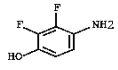
RN 17609-80-2 CAPLUS
CN Phenol, 4-amino-3-chloro- (CA INDEX NAME)



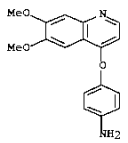
IT 35654-56-9P 163733-99-1P 190728-25-7P
286371-44-6P 1426312-64-2P 1437323-99-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of substituted quinoline compound useful in treatment of hyperproliferative diseases)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



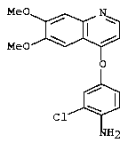
RN 163733-99-1 CAPLUS
CN Phenol, 4-amino-2,3-difluoro- (CA INDEX NAME)



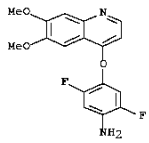
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



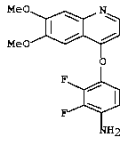
RN 286371-44-6 CAPLUS
CN Benzenamine, 2-chloro-4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



RN 1426312-64-2 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]-2,5-difluoro- (CA INDEX NAME)



RN 1437323-99-3 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]-2,3-difluoro- (CA INDEX NAME)

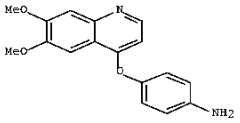


L11 ANSWER 27 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2013:1734775 CAPLUS Full-text
DOCUMENT NUMBER: 159:691817
TITLE: A dual MET-VEGF modulator for treating osteolytic bone metastases
INVENTOR(S): Aftab, Dana T.
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 44pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

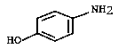
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2013166296	A1	20131107	WO 2013-US39284	20130502
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
EP 2844254	A1	20150311	EP 2013-722238	20130502
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
JP 2015515988	T	20150604	JP 2015-510456	20130502
US 20150133494	A1	20150514	US 2014-14398188	20141031

PRIORITY APPLN. INFO.: US 2012-61641837 P 20120502
WO 2013-US39284 W 20130502
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 159:691817; MARPAT 159:691817
GI

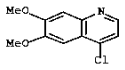


AB This invention is directed to the treatment of cancer, particularly castration-resistant prostate cancer and osteolytic bone metastases, with a dual inhibitor of MET and VEGF.

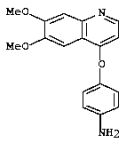
IT 123-30-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(dual MET-VEGF modulator for treating osteolytic bone metastases)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



IT 35654-56-9P 190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(dual MET-VEGF modulator for treating osteolytic bone metastases)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



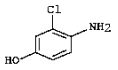
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 28 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2013:1241241 CAPLUS Full-text
DOCUMENT NUMBER: 159:364231
TITLE: Synthesis of tivozanib hydrochloride monohydrate
AUTHOR(S): Fu, Ying; Zhang, Qing-wen
CORPORATE SOURCE: State Key Laboratory of New Drug and Pharmaceutical Process, Shanghai Institute of Pharmaceutical Industry, China State Institute of Pharmaceutical Industry, Shanghai, 200437, Peop. Rep. China
SOURCE: Zhongguo Xinyao Zazhi (2013), 22(1), 26-29
CODEN: ZXZHA6; ISSN: 1003-3734
PUBLISHER: Zhongguo Xinyao Zazhi Youxian Gongsi

DOCUMENT TYPE: Journal
LANGUAGE: Chinese
OTHER SOURCE(S): CASREACT 159:364231

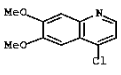
AB The synthetic process of tivozanib hydrochloride monohydrate (1) was investigated. Tivozanib hydrochloride monohydrate (1) was prepared from 3,4-dimethoxyacetophenone (2), via nitration, reduction, cyclization, chlorination, condensation, urea formation, and salification. The structures of intermediates and target compound 1 were confirmed by 1H-NMR, ESI-MS and/or element anal. The overall yield was 35%. This process boasts readily available raw materials, mild condition, simple operation and stable yield.

IT 52671-64-4, 4-Amino-3-chlorophenol hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis of tivozanib hydrochloride monohydrate)
RN 52671-64-4 CAPLUS
CN Phenol, 4-amino-3-chloro-, hydrochloride (1:1) (CA INDEX NAME)

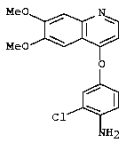


● HCl

IT 35654-56-9P 286371-44-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of tivozanib hydrochloride monohydrate)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



RN 286371-44-6 CAPLUS
CN Benzenamine, 2-chloro-4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



L11 ANSWER 29 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2013:793171 CAPLUS Full-text
DOCUMENT NUMBER: 159:9214
TITLE: Preparation of uracil derivatives as AXL and c-MET kinase inhibitors
INVENTOR(S): Dandu, Reddepparedy; Hudkins, Robert L.; Josef, Kurt A.; Prouty, Catherine P.; Tripathy, Rabindranath
PATENT ASSIGNEE(S): Cephalon, Inc., USA
SOURCE: PCT Int. Appl., 174pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2013074633	A1	20130523	WO 2012-US65019	20121114
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
CA 2852697	A1	20130523	CA 2012-2852697	20121114
AU 2012339640	A1	20140605	AU 2012-339640	20121114
AU 2012339640	B2	20170105		
IL 232405	A	20140630	IL 2012-232405	20121114
AR 88872	A1	20140716	AR 2012-104293	20121114
KR 2014090678	A	20140717	KR 2014-7015807	20121114
CN 103958497	A	20140730	CN 2012-80055840	20121114
CN 103958497	B	20170901		
EP 2780338	A1	20140924	EP 2012-798087	20121114
EP 2780338	B1	20161109		
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JP 2014533287	T	20141211	JP 2014-541416	20121114
JP 6051434	B2	20161227		
NZ 624945	A	20150925	NZ 2012-624945	20121114
SG 10201510307	A1	20160128	SG 2015-10201510307	20121114
NZ 712194	A	20160527	NZ 2012-712194	20121114
EA 23521	B1	20160630	EA 2014-90971	20121114
IL 245658	A	20160630	IL 2012-245658	20121114
EP 3045453	A1	20160720	EP 2016-153088	20121114
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
TW I562989	B	20161221	TW 2012-142365	20121114
PH 12014500883	B1	20170407	PH 2014-12014500883	20121114
BR 112014011548	A2	20170509	BR 2014-112014011548	20121114
PH 12016501535	A	20170522	PH 2016-12016501535	20121114
ES 2614824	T3	20170602	ES 2012-798087	20121114
IL 252517	A	20170731	IL 2012-252517	20121114
ZA 2014002940	A	20170830	ZA 2014-2940	20121114
MX 2014005766	A	20140530	MX 2014-5766	20140513
US 20140275077	A1	20140918	US 2014-14276138	20140513
US 9029538	B2	20150512		
IN 2014CN04308	A	20160122	IN 2014-CN4308	20140611
US 20150209358	A1	20150730	US 2015-14681974	20150408
US 9522902	B2	20161220		
US 20150210670	A1	20150730	US 2015-14681981	20150408
US 9120778	B2	20150901		
JP 2017071612	A	20170413	JP 2016-215753	20161104
US 20170050949	A1	20170223	US 2016-15346582	20161108
US 9745283	B2	20170829		
AU 2017201042	A1	20170309	AU 2017-201042	20170216

PRIORITY APPLN. INFO.:

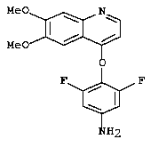
US 2011-61559312	P	20111114
AU 2012-339640	A3	20121114
EP 2012-798087	A3	20121114
IL 2012-232405	A3	20121114
IL 2012-245658	A3	20121114
JP 2014-541416	A3	20121114
NZ 2012-624945	A3	20121114
PH 2014-12014500883	A3	20121114
WO 2012-US65019	W	20121114
US 2014-14276138	A1	20140513
US 2015-14681974	A1	20150408

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 159:9214; MARPAT 159:9214
GI

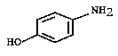
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to uracil derivs. of formula I and their prepn., useful as AXL and c-MET kinase inhibitors in the treatment of disease. Compds. of formula I, in which R is each independently H, (un)substituted C1-6 alkyl, C2-6 alkenyl, etc.; D is O, S, SO, SO2, CO, CHOH, CH2, NH, and N-C1-6 alkyl; E and G are independently H, (un)substituted C1-6 alkyl, C2-6 alkenyl, etc.; W is CH and N; X and Y are independently N and (un)substituted CH; R3 is H and C1-6 alkyl; or salt form thereof, are claimed. Example compound II was prepared by amidation of 1-ethyl-3-(4-fluorophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid with 4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluorophenylamine. Invention compds. were evaluated for their AXL and c-MET inhibitory activity. From the assay, it was determined that compound II exhibited IC50 value for AXL and c-MET of <10 nM.

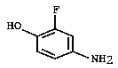
IT 1437324-09-8P
RL: PRPH (Prophetic); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of uracil derivs. as AXL and c-MET kinase inhibitors)
RN 1437324-09-8 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]-3,5-difluoro- (CA INDEX NAME)



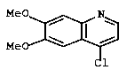
IT 123-30-8, 4-Aminophenol 399-96-2, 4-Amino-2-fluorophenol 35654-56-9, 4-Chloro-6,7-dimethoxyquinoline 163733-99-1, 4-Amino-2,3-difluorophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of uracil derivs. as AXL and c-MET kinase inhibitors)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



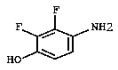
RN 399-96-2 CAPLUS
CN Phenol, 4-amino-2-fluoro- (CA INDEX NAME)



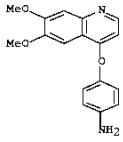
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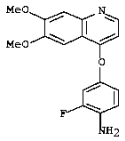
RN 163733-99-1 CAPLUS
CN Phenol, 4-amino-2,3-difluoro- (CA INDEX NAME)



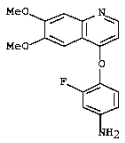
IT 190728-25-7P 228559-74-8P 347161-74-4P 347161-75-5P 1437323-99-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of uracil derivs. as AXL and c-MET kinase inhibitors)
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



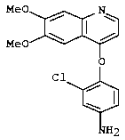
RN 228559-74-8 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]-2-fluoro- (CA INDEX NAME)



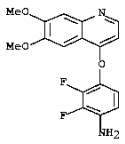
RN 347161-74-4 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]-3-fluoro- (CA INDEX NAME)



RN 347161-75-5 CAPLUS
CN Benzenamine, 3-chloro-4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



RN 1437323-99-3 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]-2,3-difluoro- (CA INDEX NAME)

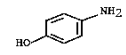


OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

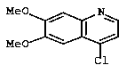
L11 ANSWER 30 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2013:761990 CAPLUS Full-text
DOCUMENT NUMBER: 158:704608
TITLE: Method of quantifying cancer treatment
INVENTOR(S): Holland, Jaymes
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 50pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2013070903	A1	20130516	WO 2012-US64134	20121108
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
CA 2854664	A1	20130516	CA 2012-2854664	20121108
AU 2012335750	A1	20140605	AU 2012-335750	20121108
AR 88813	A1	20140710	AR 2012-104223	20121108
CN 104039226	A	20140910	CN 2012-80066413	20121108
EP 2775921	A1	20140917	EP 2012-795939	20121108
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
JP 2015505360	T	20150219	JP 2014-541261	20121108
BR 112014011008	A2	20170613	BR 2014-112014011008	20121108
IN 2014CN03674	A	20150703	IN 2014-CN3674	20140515

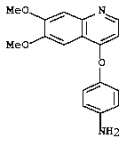
PRIORITY APPLN. INFO.: US 2011-61557362 P 20111108
WO 2012-US64134 W 20121108
OTHER SOURCE(S): CASREACT 158:704608
AB This invention is directed to a method for quantifying cancer treatment response in patients with bone metastases using computer aided bone scan assessment, comprising: (a) obtaining a bone scan image; (b) normalizing the obtained bone scan image to identify normalized bone scan lesions; and (c) quant. assessing the normalized bone scan lesions using bone scan lesion area, bone scan intensity, or bone scan lesion count.
IT 123-30-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(quantifying cancer treatment)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



IT 35654-56-9P 190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(quantifying cancer treatment)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)

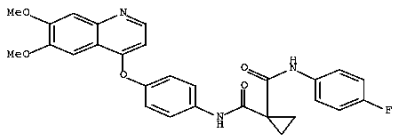


REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

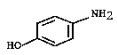
L11 ANSWER 31 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2013:761969 CAPLUS Full-text
DOCUMENT NUMBER: 158:704607
TITLE: Dual inhibitor of Met and VEGF for treating cancer
INVENTOR(S): Aftab, Dana T.; Schimmoller, Frauke
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 56pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2013070890	A1	20130516	WO 2012-US64116	20121108
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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
CA 2854336	A1	20130516	CA 2012-2854336	20121108
AU 2012335737	A1	20140605	AU 2012-335737	20121108
IL 232421	A	20140630	IL 2012-232421	20121108
KR 2014088610	A	20140710	KR 2014-7015127	20121108
EP 2776033	A1	20140917	EP 2012-787328	20121108
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CN 104159585	A	20141119	CN 2012-80066410	20121108
JP 2014532766	T	20141208	JP 2014-541256	20121108
BR 112014011009	A2	20170606	BR 2014-112014011009	20121108
MX 2014005458	A	20150416	MX 2014-5458	20140506
US 20140323522	A1	20141030	US 2014-14356927	20140508
ZA 2014003331	A	20151223	ZA 2014-3331	20140508
IN 2014CN04067	A	20151023	IN 2014-CN4067	20140530

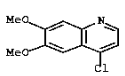
PRIORITY APPLN. INFO.: US 2011-61557358 P 20111108
WO 2012-US64116 W 20121108
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 158:704607; MARPAT 158:704607
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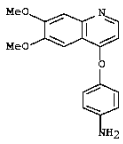
AB This invention is directed to the treatment of cancer, particularly castration-resistant prostate cancer and bone metastases, with a dual inhibitor of MET and VEGF.
IT 123-30-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(dual inhibitor of Met and VEGF for treating cancer)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



IT 35654-56-9P 190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(dual inhibitor of Met and VEGF for treating cancer)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

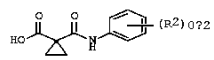
L11 ANSWER 32 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2013:644308 CAPLUS Full-text
DOCUMENT NUMBER: 158:620790
TITLE: Process for preparing quinoline derivatives
INVENTOR(S): Wilson, Jo Ann; Naganathan, Sriram; Pfeiffer, Matthew; Andersen, Neil G.
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 47pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2013059788	A1	20130425	WO 2012-US61320	20121022
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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
CA 2852771	A1	20130425	CA 2012-2852771	20121022
AU 2012325768	A1	20140522	AU 2012-325768	20121022
AU 2012325768	B2	20170810		
IL 232139	A	20140528	IL 2012-232139	20121022
AR 88483	A1	20140611	AR 2012-103944	20121022
KR 2014088874	A	20140711	KR 2014-7012435	20121022
EP 2768796	A1	20140827	EP 2012-783763	20121022
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
JP 2014530880	T	20141120	JP 2014-537359	20121022
JP 6208140	B2	20171004		
CN 104395284	A	20150304	CN 2012-80054241	20121022
NZ 624328	A	20161028	NZ 2012-624328	20121022
BR 112014009302	A2	20170523	BR 2014-112014009302	20121022
ZA 2014002579	A	20150325	ZA 2014-2579	20140409
MX 2014004583	A	20141006	MX 2014-4583	20140415
US 20140256938	A1	20140911	US 2014-14353251	20140421
US 9365516	B2	20160614		
IN 2014CN02971	A	20150703	IN 2014-CN2971	20140421
US 20160229805	A1	20160811	US 2016-15133708	20160420

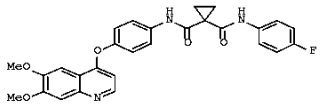
PRIORITY APPLN. INFO.:

US 2011-61549312	P	20111020
WO 2012-US61320	W	20121022
US 2014-14353251	A1	20140421

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 158:620790; MARPAT 158:620790
GI

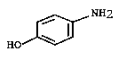


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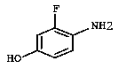


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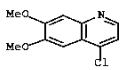
AB The invention is directed to processes for prepg. compds. of formula I (R2 is H, F, Cl and Br) by activation of 1,1-cyclopropanedicarboxylic acid with thionyl chloride followed by amidation with substituted aniline derivative Example compound II L-malate was prepared by chlorination of 6,7-dimethoxyquinolin-4-ol followed by etherification of 4-chloro-6,7-dimethoxyquinoline with 4-aminophenol; the resulting 4-(6,7-dimethoxyquinolin-4-yloxy)phenylamine underwent acylation with 1-[(4-fluorophenyl)carbamoyl]cyclopropanecarbonyl chloride to give compound II, which underwent addition of L-malic acid to give the desired product.
IT 123-30-8 399-95-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for preparing quinoline derivs.)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



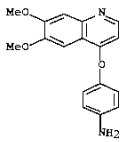
RN 399-95-1 CAPLUS
CN Phenol, 4-amino-3-fluoro- (CA INDEX NAME)



IT 35654-56-9P 190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparing quinoline derivs.)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

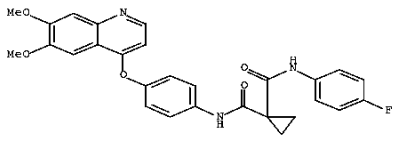
L11 ANSWER 33 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2013:466384 CAPLUS Full-text
DOCUMENT NUMBER: 158:494085
TITLE: Method for treating osteoporosis
INVENTOR(S): Aftab, Dana T.; Clary, Douglas
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 73pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2013043840	A1	20130328	WO 2012-US56281	20120920
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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
CA 2848512	A1	20130328	CA 2012-2848512	20120920
AU 2012312364	A1	20140410	AU 2012-312364	20120920
IL 231495	A	20140430	IL 2012-231495	20120920
KR 2014069133	A	20140609	KR 2014-7009534	20120920
CN 103957915	A	20140730	CN 2012-80051094	20120920
EP 2758057	A1	20140730	EP 2012-770368	20120920
EP 2758057	B1	20170531		
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
JP 2014527984	T	20141023	JP 2014-531955	20120920
NZ 622722	A	20160930	NZ 2012-622722	20120920
BR 112014006702	A2	20170613	BR 2014-112014006702	20120920
AR 87995	A1	20140430	AR 2012-103501	20120921
TW I564009	B	20170101	TW 2012-134829	20120921
ZA 2014001728	A	20160127	ZA 2014-1728	20140310
MX 2014003027	A	20141024	MX 2014-3027	20140313
IN 2014CN02093	A	20141010	IN 2014-CN2093	20140319
US 20140228401	A1	20140814	US 2014-14346570	20140321

PRIORITY APPLN. INFO.:

US 2011-61538039	P	20110922
WO 2012-US56281	W	20120920

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 158:494085; MARPAT 158:494085
GI

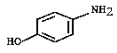


AB This invention is directed to the treatment of osteoporosis using N-(4-[[6,7-bis(methyloxy)quinolin-4-yl]oxy]phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

IT 123-30-8, 4-Aminophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(method for treating osteoporosis)

RN 123-30-8 CAPLUS

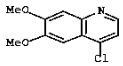
CN Phenol, 4-amino- (CA INDEX NAME)



IT 35654-56-9P, 4-Chloro-6,7-dimethoxyquinoline
190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(method for treating osteoporosis)

RN 35654-56-9 CAPLUS

CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



RN 190728-25-7 CAPLUS

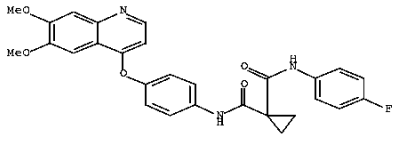
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)

NZ 617508	A	20160429	NZ 2012-617508		20120502
MX 2013012695	A	20140327	MX 2013-12695		20131030
ZA 2013008206	A	20140730	ZA 2013-8206		20131101
IN 2013KN03259	A	20140221	IN 2013-KN3259		20131105
US 20140179736	A1	20140626	US 2014-14115236		20140228
JP 2017105751	A	20170615	JP 2016-159543		20160816
PRIORITY APPLN. INFO.:			US 2011-61481682	P	20110502
			US 2011-61557366	P	20111108
			JP 2014-509417	A3	20120502
			WO 2012-US36191	W	20120502

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASREACT 157:699601; MARPAT 157:699601

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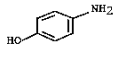


AB This invention is directed to the treatment of cancer, particularly lung cancer, breast cancer, melanoma, renal cell carcinoma, thyroid cancer that has metastasized to the bone. The invention is also directed to a method for treating bone cancer pain in an individual in need of such treatment comprising administering to the individual an effective amount of a compound of Formula I.

IT 123-30-8, 4-Aminophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(method of treating cancer and bone cancer pain)

RN 123-30-8 CAPLUS

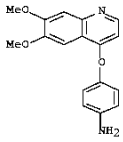
CN Phenol, 4-amino- (CA INDEX NAME)



IT 35654-56-9P, 4-Chloro-6,7-dimethoxyquinoline
190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(method of treating cancer and bone cancer pain)

RN 35654-56-9 CAPLUS

CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 34 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN

ACCESSION NUMBER: 2012:1630842 CAPLUS Full-text

DOCUMENT NUMBER: 157:699601

TITLE: Method of treating cancer and bone cancer pain

INVENTOR(S): Schwab, Gisela; Aftab, Dana T.

PATENT ASSIGNEE(S): Exelixis, Inc., USA

SOURCE: PCT Int. Appl., 52pp.
CODEN: PIXXD2

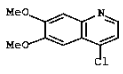
DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

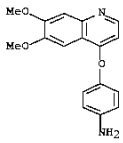
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2012151326	A1	20121108	WO 2012-US36191	20120502
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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
CA 2834778	A1	20121108	CA 2012-2834778	20120502
AR 86242	A1	20131127	AR 2012-101544	20120502
AU 2012250759	A1	20131128	AU 2012-250759	20120502
AU 2012250759	B2	20170615		
IL 229094	A	20131231	IL 2012-229094	20120502
KR 2014025496	A	20140304	KR 2013-7031635	20120502
EP 2704717	A1	20140312	EP 2012-720754	20120502
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
CN 103717221	A	20140409	CN 2012-80026424	20120502
JP 2014513129	T	20140529	JP 2014-509417	20120502
BR 112013028314	U2	20151103	BR 2013-112013028314	20120502



RN 190728-25-7 CAPLUS

CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 35 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN

ACCESSION NUMBER: 2012:1450760 CAPLUS Full-text

DOCUMENT NUMBER: 157:567006

TITLE: Method of treating cancer

INVENTOR(S): Aftab, Dana T.; Schimmoller, Frauke

PATENT ASSIGNEE(S): Exelixis, Inc., USA

SOURCE: U.S. Pat. Appl. Publ., 17pp.
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 20120252840	A1	20121004	US 2012-13438964		20120404
US 20150196545	A1	20150716	US 2015-14668312		20150325
US 20160051532	A1	20160225	US 2015-14933801		20151105
PRIORITY APPLN. INFO.:			US 2011-61471367	P	20110404
			US 2012-13438964	A1	20120404
			US 2015-14668312	A1	20150325

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

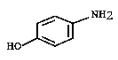
OTHER SOURCE(S): CASREACT 157:567006

AB This invention is directed to the treatment of cancer, particularly ocular melanoma, with a dual inhibitor of MET and VEGF such as Compound 1.

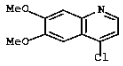
IT 123-30-8, 4-Aminophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(method of treating cancer)

RN 123-30-8 CAPLUS

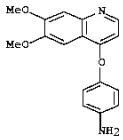
CN Phenol, 4-amino- (CA INDEX NAME)



IT 35654-56-9P, 4-Chloro-6,7-dimethoxyquinoline
190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(method of treating cancer)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L11 ANSWER 36 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2012:1201570 CAPLUS Full-text
DOCUMENT NUMBER: 157:382704
TITLE: Processes for preparing quinoline compounds and pharmaceutical compositions containing such compounds
INVENTOR(S): Wilson, Jo Ann
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 49pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2

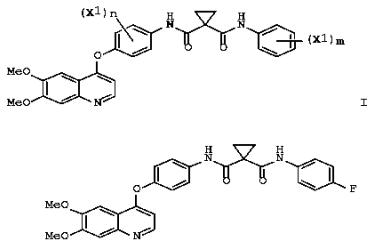
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2012109510	A1	20120816	WO 2012-US24591	20120210
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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
CA 2826751	A1	20120816	CA 2012-2826751	20120210
AU 2012214322	A1	20130829	AU 2012-214322	20120210
AU 2012214322	B2	20170427		
AR 85155	A1	20130911	AR 2012-100446	20120210
IL 227848	A	20130930	IL 2012-227848	20120210
CN 103459373	A	20131218	CN 2012-80017723	20120210
EP 2673262	A1	20131218	EP 2012-704492	20120210
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
JP 2014505109	T	20140227	JP 2013-553580	20120210
KR 20140044782	A	20140415	KR 2013-7023174	20120210
NZ 614130	A	20151030	NZ 2012-614130	20120210
NZ 712808	A	20170331	NZ 2012-712808	20120210
MX 2013009116	A	20140131	MX 2013-9116	20130807
ZA 2013006072	A	20140430	ZA 2013-6072	20130813
IN 2013KN02666	A	20140103	IN 2013-KN2666	20130903
US 20140200242	A1	20140717	US 2014-13984559	20140320
US 9717720	B2	20170801		
JP 2016188216	A	20161104	JP 2016-94411	20160510
US 20170057921	A1	20170302	US 2016-15348716	20161110
AU 2017204877	A1	20170803	AU 2017-204877	20170714

PRIORITY APPLN. INFO.:

US 2011-61441520	P	20110210
US 2011-61441527	P	20110210
AU 2012-214322	A3	20120210
JP 2013-553580	A3	20120210
NZ 2012-614130	A3	20120210
WO 2012-US24591	W	20120210
US 2014-13984559	A1	20140320

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 157:382704; MARPAT 157:382704
GI

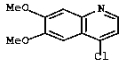


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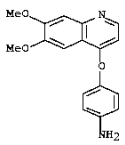
II

AB The invention is directed to processes for prepg. quinoline compds. of formula I wherein X1 is H, Br, Cl and F; X2 is H, Br, Cl and F; n is 1-2 and m is 1-2; and pharmaceutically acceptable salts thereof. Example compound II L-malate was prepared by chlorination of 6,7-dimethoxyquinolin-4-ol followed by etherification of 4-chloro-6,7-dimethoxyquinoline with 4-aminophenol; the resulting 4-(6,7-dimethoxyquinolin-4-yloxy)phenylamine underwent acylation with 1-[(4-fluorophenyl)carbamoyl]cyclopropanecarbonyl chloride to give compound II, which underwent addition of L-malic acid to give the desired product.

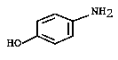
IT 35654-56-9P, 4-Chloro-6,7-dimethoxyquinoline
190728-25-7P, [4-[(6,7-Dimethoxyquinolin-4-yl)oxy]phenyl]amine
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparing quinoline derivs. and pharmaceutical compns. thereof)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



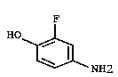
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



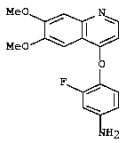
IT 123-30-8, 4-Aminophenol 399-96-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for preparing quinoline derivs. and pharmaceutical compns. thereof)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



RN 399-96-2 CAPLUS
CN Phenol, 4-amino-2-fluoro- (CA INDEX NAME)



IT 347161-74-4P, [4-[(6,7-Dimethoxyquinolin-4-yl)oxy]-3-fluorophenyl]amine
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparing quinoline derivs. and pharmaceutical compns. thereof)
RN 347161-74-4 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]-3-fluoro- (CA INDEX NAME)

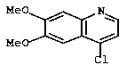


OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

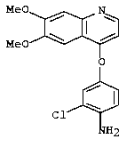
L11 ANSWER 37 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2012:975643 CAPLUS Full-text
DOCUMENT NUMBER: 157:198195
TITLE: Method for synthesizing antitumor targeting drug tivozanib
INVENTOR(S): Liu, Mingxing; Hu, Lixiu; Wu, Jianhong; Zhang, Zhixiang; Liu, Junan
PATENT ASSIGNEE(S): Wuhan Maidesen Pharmaceutical Science and Technology Co., Ltd., Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 8pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 102532116	A	20120704	CN 2011-10226114	20110809
CN 102532116	B	20150121		
PRIORITY APPLN. INFO.:			CN 2011-10226114	20110809

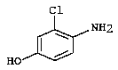
OTHER SOURCE(S): CASREACT 157:198195
AB The invention relates to a process for the prepn. of antitumor targeting drug tivozanib. For instance, Friedel-Crafts reaction of 1,2-dimethoxybenzene with acetyl chloride followed by nitration, reduction, and heterocyclization with Et formate gave 6,7-dimethoxy-4(1H)-quinolinone. Tivozanib was then prepared by chlorination of 6,7-dimethoxy-4(1H)-quinolinone followed by substitution with 4-amino-3-chloro-phenol hydrochloride and condensation with Ph chloroformate and 5-methyl-3-isoxazolamine.
IT 35654-56-9P 286371-44-6P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of tivozanib)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



RN 286371-44-6 CAPLUS
CN Benzenamine, 2-chloro-4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



IT 52671-64-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of tivozanib)
RN 52671-64-4 CAPLUS
CN Phenol, 4-amino-3-chloro-, hydrochloride (1:1) (CA INDEX NAME)



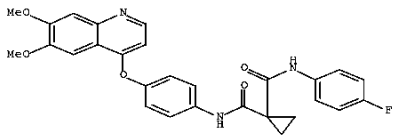
● HCl

L11 ANSWER 38 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2012:495814 CAPLUS Full-text
DOCUMENT NUMBER: 156:469436
TITLE: Dual inhibitors of Met and VEGF for the treatment of castration- resistant prostate cancer and osteoblastic bone metastases
INVENTOR(S): Smith, David; Hussain, Maha
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 47pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2

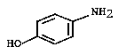
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2012044572	A1	20120405	WO 2011-US53233	20110926
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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
CA 2812750	A1	20120405	CA 2011-2812750	20110926
AU 2011307304	A1	20130502	AU 2011-307304	20110926
AU 2011307304	B2	20160414		
IL 225507	A	20130530	IL 2011-225507	20110926
EP 2621481	A1	20130807	EP 2011-764655	20110926
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JP 2013537916	T	20131007	JP 2013-530386	20110926
JP 6158705	B2	20170705		
CN 103402505	A	20131120	CN 2011-80056580	20110926
KR 20140025304	A	20140304	KR 2013-7010372	20110926
NZ 707930	A	20160930	NZ 2011-707930	20110926
EA 27476	B1	20170731	EA 2013-90465	20110926
MX 2013003594	A	20130801	MX 2013-3594	20130327
ZA 2013002422	A	20131223	ZA 2013-2422	20130404
IN 2013KN00998	A	20130906	IN 2013-KN998	20130409
US 20140057943	A1	20140227	US 2013-13876290	20131105
US 20160220554	A1	20160804	US 2015-14843480	20150902
AU 2016204747	A1	20160728	AU 2016-204747	20160708
JP 2017149714	A	20170831	JP 2017-36322	20170228
PRIORITY APPLN. INFO.:			US 2010-61386959	P 20100927
			US 2011-61481671	P 20110502
			AU 2011-307304	A3 20110926
			JP 2013-530386	A3 20110926
			NZ 2011-609212	A3 20110926
			WO 2011-US53233	W 20110926
			US 2013-13876290	B1 20131105

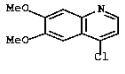
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 156:469436; MARPAT 156:469436
GI



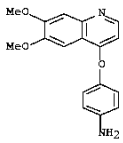
AB This invention is directed to the treatment of cancer, particularly castration-resistant prostate cancer and osteoblastic bone metastases, with a dual inhibitor of MET and VEGF.
IT 123-30-8, 4-Aminophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(dual inhibitors of Met and VEGF for treatment of castration resistant prostate cancer and osteoblastic bone metastases)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



IT 35654-56-9P, 4-Chloro-6,7-dimethoxyquinoline
190728-25-7P, 4-(6,7-Dimethoxyquinolin-4-yloxy)phenylamine
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(dual inhibitors of Met and VEGF for treatment of castration resistant prostate cancer and osteoblastic bone metastases)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)

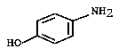


OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

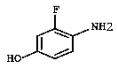
L11 ANSWER 39 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2012:495788 CAPLUS Full-text
DOCUMENT NUMBER: 156:469435
TITLE: Dual inhibitors of Met and VEGF for the treatment of castration resistant prostate cancer and osteoblastic bone metastases
INVENTOR(S): Smith, David; Hussain, Maha
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 70pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2012044577	A1	20120405	WO 2011-US53245	20110926
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
CA 2812744	A1	20120405	CA 2011-2812744	20110926
AU 2011307309	A1	20130502	AU 2011-307309	20110926
EP 2621483	A1	20130807	EP 2011-764657	20110926
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JP 2013537918	T	20131007	JP 2013-530392	20110926
CN 103391773	A	20131113	CN 2011-80056999	20110926
US 20140057908	A1	20140227	US 2013-13876306	20131108

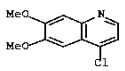
PRIORITY APPLN. INFO.: US 2010-61386971 P 20100927
US 2010-61386983 P 20100927
US 2010-61386993 P 20100927
WO 2011-US53245 W 20110926
OTHER SOURCE(S): CASREACT 156:469435; MARPAT 156:469435
AB This invention discloses compds. directed at the treatment of cancer, particularly castration- resistant prostate cancer and osteoblastic bone metastases, with a dual inhibitor of MET and VEGF.
IT 123-30-8, 4-Aminophenol 399-95-1, 2-Fluoro-4-hydroxyaniline
RL: RCT (Reactant); RACT (Reactant or reagent)
(dual inhibitors of Met and VEGF for treatment of castration resistant prostate cancer and osteoblastic bone metastases)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



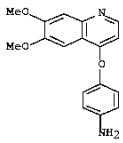
RN 399-95-1 CAPLUS
CN Phenol, 4-amino-3-fluoro- (CA INDEX NAME)



IT 35654-56-9P, 4-Chloro-6,7-dimethoxyquinoline
190728-25-7P, 4-(6,7-Dimethoxyquinolin-4-yloxy)phenylamine
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(dual inhibitors of Met and VEGF for treatment of castration resistant prostate cancer and osteoblastic bone metastases)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

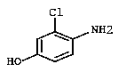


RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)

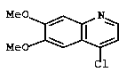


OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

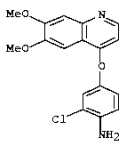
L11 ANSWER 40 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2012:247673 CAPLUS Full-text
DOCUMENT NUMBER: 156:533720
TITLE: Synthesis of anticancer targeted therapies drug tivozanib
AUTHOR(S): Liu, Mingxing; Hu, Lixiu; Wang, Xianwen; Zhu, Hongda
CORPORATE SOURCE: Department of Pharmacy, College of Bioengineering, Hubei University of Technology, Wuhan, 430068, Peop. Rep. China
SOURCE: Advanced Materials Research (Durnten-Zurich, Switzerland) (2012), 396-398(Pt. 2, Advances in Chemical Engineering), 1490-1492
CODEN: AMREFI; ISSN: 1022-6680
DIGITAL OBJECT ID: 10.4028/www.scientific.net/AMR.396-398.1490
PUBLISHER: Trans Tech Publications Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 156:533720
AB Tivozanib was synthesized through the cyclization, chlorinated, condensation reaction with 2-amino-4,5-dimethoxyacetophenone as the starting material. All synthetic compds. were analyzed by FT-IR, 1H-NMR, MS and HPLC. The purity of tivozanib was more than 98.5%. Synthetic routes and methods of tivozanib are feasible to industrial production owing to the cheap raw materials, mild reaction conditions, stable technol. and high yield.
IT 17609-80-2, 4-Amino-3-chlorophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of anticancer tivozanib starting from dimethoxy-o-aminoacetophenone Et formate via cyclization, chlorination, condensations)
RN 17609-80-2 CAPLUS
CN Phenol, 4-amino-3-chloro- (CA INDEX NAME)



IT 35654-56-9P 286371-44-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of anticancer tivozanib starting from dimethoxy-o-aminoacetophenone Et formate via cyclization, chlorination, condensations)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



RN 286371-44-6 CAPLUS
CN Benzenamine, 2-chloro-4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)

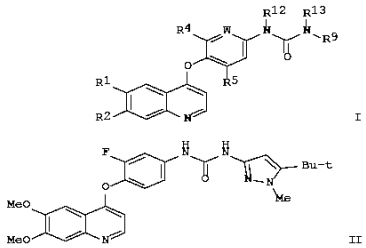


REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 41 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2012:96895 CAPLUS Full-text
DOCUMENT NUMBER: 156:175266
TITLE: Preparation of nitrogenated aromatic heterocyclic compounds as FGFR (fibroblast growth factor receptor) inhibitors
INVENTOR(S): Furuta, Takayuki; Kubo, Kazuo; Nakoji, Masayoshi; Kawai, Ryohei
PATENT ASSIGNEE(S): Kyowa Hakko Kirin Co., Ltd., Japan
SOURCE: PCT Int. Appl., 113pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2012008564 A1 20120119 WO 2011-JP66186 20110715
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
PRIORITY APPLN. INFO.: JP 2010-161272 A 20100716
OTHER SOURCE(S): CASREACT 156:175266; MARPAT 156:175266
GI



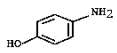
I

II

AB Disclosed are compds. I [R1, R2 = H, hydroxy, (un)substituted alkylsulfonyloxy, etc.; W = CR3 or nitrigen atom; R3 = H, alkoxy or halo; R4, R5 = H or halo; R9 = (un)substituted pyrazolyl or (un)substituted isoxazolyl; R12, R13 = H or alkyl; or pharmaceutically acceptable salts thereof]. Thus, compound II was prepared via cyclocondensation of Et 5,5-dimethyl-2,4-dioxohexanoate with methylhydrazine sulfate, hydrolysis and treatment with (PhO)2PON3/4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluoroaniline. In inhibition assay of FGFR2-phosphorylation, the selected invention compds., e.g., II, exhibited IC50 of <100 nmol/L. Compds. I are claimed useful for the treatment of stomach cancer.

IT 123-30-8, 4-Aminophenol 3096-69-3, 4-Amino-2,3-dimethylphenol 7248-09-1, 4-Amino-2-chlorophenol hydrochloride 35654-56-9, 4-Chloro-6,7-dimethoxyquinoline 190728-25-7 228559-74-8 286371-44-6 347161-74-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of nitrogenated aromatic heterocyclic compds. as FGFR inhibitors)

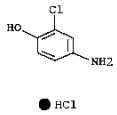
RN 123-30-8 CAPLUS
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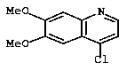
RN 3096-69-3 CAPLUS
CN Phenol, 4-amino-2,3-dimethyl- (CA INDEX NAME)



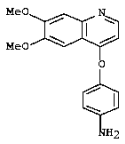
RN 7248-09-1 CAPLUS
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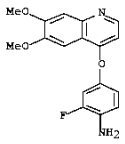
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



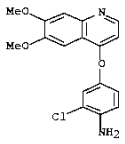
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



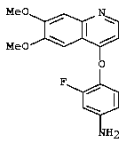
RN 228559-74-8 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]-2-fluoro- (CA INDEX NAME)



RN 286371-44-6 CAPLUS
CN Benzenamine, 2-chloro-4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)

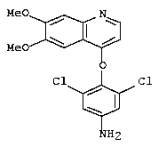


RN 347161-74-4 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]-3-fluoro- (CA INDEX NAME)

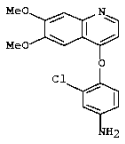


IT 286371-47-9P 347161-75-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of nitrogenated aromatic heterocyclic compds. as FGFR inhibitors)

RN 286371-47-9 CAPLUS
CN Benzenamine, 3,5-dichloro-4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



RN 347161-75-5 CAPLUS
CN Benzenamine, 3-chloro-4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



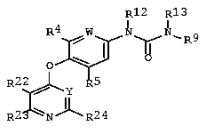
REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 42 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN

ACCESSION NUMBER: 2012:96817 CAPLUS Full-text
DOCUMENT NUMBER: 156:167650
TITLE: Nitrogen-containing heteroaromatic compounds, and pharmaceuticals, fibroblast growth factor receptor inhibitors, and antitumor agents containing them
INVENTOR(S): Furuta, Takayuki; Kubo, Kazuo; Atsumi, Toshiyuki; Yamanouchi, Maasa
PATENT ASSIGNEE(S): Kyowa Hakko Kirin Co., Ltd., Japan
SOURCE: PCT Int. Appl., 103pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2012008563	A1	20120119	WO 2011-JP66185	20110715
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
CN 103003262	A	20130327	CN 2011-80035144	20110715
EP 2594566	A1	20130522	EP 2011-806893	20110715
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR				
KR 2013091331	A	20130816	KR 2013-7003633	20110715
JP 5789259	B2	20151007	JP 2012-524602	20110715
US 20130225581	A1	20130829	US 2013-13810568	20130328

PRIORITY APPLN. INFO.: JP 2010-161272 A 20100716
WO 2011-JP66185 W 20110715
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 156:167650; MARPAT 156:167650
GI

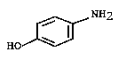


I

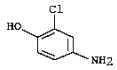
AB N-contg. heteroarom. compds. I [W = CR3 (R3 = H, lower alkyl, lower alkoxy, halo), N; R4 = H, lower alkyl, halo; R5 = H, lower alkyl; R9 = substituted imidazolyl; R12, R13 = H, (un)substituted aryl, (un)substituted heteroaryl, CONR26R27 (R26, R27 = H, lower alkyl, heteroaryl); R26 and R27 may be bonded to form a (un)substituted benzene or thiophene ring; R24 = H, lower alkyl; Y = CR25 (R25 = H, lower alkyl), N] or their pharmacol. acceptable salts, are useful for therapy and/or prophylaxis of FGF receptor-related diseases and neoplasm, especially gastric cancer. Thus, IC50 of 1-[2-tert-butyl-4-(1-methyl-1H-pyrazol-5-yl)-1H-imidazol-5-yl]-3-[4-(6,7-dimethoxyquinolin-4-yloxy)phenyl]urea (II; preparation given) against human FGFR2 activity was <100 nmol/L. IC50 of II against proliferation of OCUM-2MD3 human scirrhous gastric cancer cell was <30 nmol/L.

IT 123-30-8, 4-Aminophenol 7248-09-1, 4-Amino-2-chlorophenol hydrochloride 35654-56-9, 4-Chloro-6,7-dimethoxyquinoline 190728-25-7, 4-(6,7-Dimethoxyquinolin-4-yloxy)aniline 228559-74-8 286371-44-6 347161-74-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of nitrogen-containing heteroarom. compds. for treatment of FGF receptor-related diseases and neoplasm, especially gastric cancer)

RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)

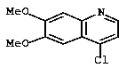


RN 7248-09-1 CAPLUS
CN Phenol, 4-amino-2-chloro-, hydrochloride (1:1) (CA INDEX NAME)

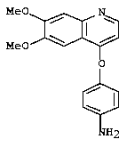


● HCl

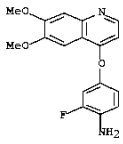
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



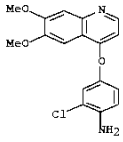
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



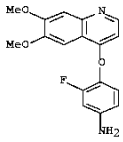
RN 228559-74-8 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]-2-fluoro- (CA INDEX NAME)



RN 286371-44-6 CAPLUS
CN Benzenamine, 2-chloro-4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)

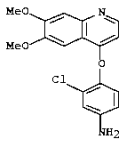


RN 347161-74-4 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]-3-fluoro- (CA INDEX NAME)



IT 347161-75-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of nitrogen-containing heteroarom. compds. for treatment of FGF receptor-related diseases and neoplasm, especially gastric cancer)

RN 347161-75-5 CAPLUS
CN Benzenamine, 3-chloro-4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 43 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2012:90800 CAPLUS Full-text
DOCUMENT NUMBER: 156:186804
TITLE: C-met modulator pharmaceutical compositions comprising N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide
INVENTOR(S): Wilson, Jo Ann
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 40pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2012009722	A1	20120119	WO 2011-US44378	20110718

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

CA 2805645	A1	20120119	CA 2011-2805645		20110718
AR 82252	A1	20121121	AR 2011-102584		20110718
AU 2011278950	A1	20130307	AU 2011-278950		20110718
AU 2011278950	B2	20160721			
IL 224189	A	20130324	IL 2011-224189		20110718
EP 2593090	A1	20130522	EP 2011-740764		20110718
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CN 103221035	A	20130724	CN 2011-80044602		20110718
JP 2013531045	T	20130801	JP 2013-519870		20110718
JP 5934204	B2	20160615			
KR 2013137586	A	20131217	KR 2013-7003043		20110718
NZ 607118	A	20150529	NZ 2011-607118		20110718
TW I516477	B	20160111	TW 2011-125336		20110718
SG 10201609324	A1	20170127	SG 2016-10201609324		20110718
CN 106420743	A	20170222	CN 2016-10157218		20110718
IN 2013KN00112	A	20130705	IN 2013-KN112		20130114
MX 2013000567	A	20130501	MX 2013-567		20130115
ZA 2013000458	A	20130925	ZA 2013-458		20130117
US 20130337015	A1	20131219	US 2013-13810537		20130826
US 9724342	B2	20170808			
JP 2016188215	A	20161104	JP 2016-93433		20160506
AU 2016247044	A1	20161103	AU 2016-247044		20161018
US 20170143689	A1	20170525	US 2017-15426804		20170207
US 20170266178	A1	20170921	US 2017-15612703		20170602

PRIORITY APPLN. INFO.:

US 2010-61365253	P	20100716
US 2010-61370843	P	20100805
AU 2011-278950	A3	20110718
CN 2011-80044602	A3	20110718
JP 2013-519870	A3	20110718
WO 2011-US44378	W	20110718
US 2013-13810537	A3	20130826
US 2017-15426804	A3	20170207

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASREACT 156:186804

AB Pharmaceutical compns. and unit dosage forms comprising N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (I) are disclosed. Thus, 6,7-dimethoxyquinolin-4-ol was converted to 4-chloro-6,7-dimethoxyquinoline followed by reaction with 4-aminphenol to give 4-(6,7-dimethoxy-quinolin-4-yloxy)-phenylamine. This was further allowed to react with 1-(4-fluorophenylcarbamoyl)cyclopropanecarbonyl chloride to give I. A tablet composition comprised 31.68% along with excipients such as microcryst. cellulose 38.85, lactose, HPC, and Croscarmellose sodium.

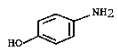
IT 123-30-8

RL: RCT (Reactant); RACT (Reactant or reagent)

(C-met modulator pharmaceutical compns. comprising dimethoxyquinolinyloxyphenyl(fluorophenyl)cyclopropanedicarboxamide)

RN 123-30-8 CAPLUS

CN Phenol, 4-amino- (CA INDEX NAME)



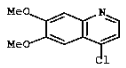
IT 35654-56-9P 190728-25-7P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(C-met modulator pharmaceutical compns. comprising dimethoxyquinolinyloxyphenyl(fluorophenyl)cyclopropanedicarboxamide)

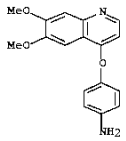
RN 35654-56-9 CAPLUS

CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



RN 190728-25-7 CAPLUS

CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 44 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN

ACCESSION NUMBER: 2009:1402348 CAPLUS Full-text

DOCUMENT NUMBER: 151:550574

TITLE: Preparation of fused heterocyclic derivatives as kinase inhibitors

INVENTOR(S): Miyamoto, Naoki; Matsumoto, Shigemitsu; Imamura, Shinichi

PATENT ASSIGNEE(S): Takeda Pharmaceutical Company Limited, Japan

SOURCE: PCT Int. Appl., 340pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009136663	A1	20091112	WO 2009-JP58962	20090507

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

US 20110046169	A1	20110224	US 2010-990760	20101102
US 8445509	B2	20130521		

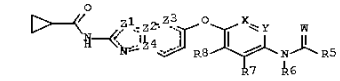
PRIORITY APPLN. INFO.:

JP 2008-122789	A	20080508
JP 2008-306661	A	20081201
WO 2009-JP58962	W	20090507

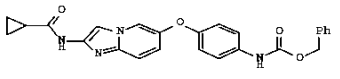
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASREACT 151:550574; MARPAT 151:550574

GI



I



II

AB The title compds. I [(Z1,Z2,Z3,Z4) = (CR1,N,CR2,C), (N,N,CR2,C), (N,C,CR2,N), (S,C,CR2,C) or (S,C,N,C); R1, R2 = H, halo, etc.; W = O, S; X = CR3, N (wherein R3 = H, halo, alkyl); Y = CR4, N (R4 = H, halo, alkyl); R5 = cycloalkyl optionally having one aryl-aminocarbonyl, alkyl-carbonylamino optionally having one aryl, alkoxy optionally having one aryl, etc.; R6 = H; R7, R8 = H, halo, alkyl] having a strong kinase inhibitory activity, were prepared and formulated. Thus, reacting benzyl [4-[(2-aminoimidazo[1,2-a]pyridin-6-yl)oxy]phenyl]carbamate with cyclopropanecarbonyl chloride in N,N-dimethylacetamide afforded 87% II. Exemplified compds. I were tested against various kinases and in antitumor tests (data given for representative compds. I).

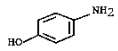
IT 123-30-8, 4-Aminophenol 399-95-1, 4-Amino-3-fluorophenol 399-96-2, 4-Amino-2-fluorophenol 35654-56-9, 4-Chloro-6,7-dimethoxyquinoline

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of fused heterocyclic derivs. as kinase inhibitors for treating cancer)

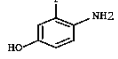
RN 123-30-8 CAPLUS

CN Phenol, 4-amino- (CA INDEX NAME)



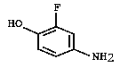
RN 399-95-1 CAPLUS

CN Phenol, 4-amino-3-fluoro- (CA INDEX NAME)



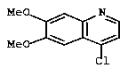
RN 399-96-2 CAPLUS

CN Phenol, 4-amino-2-fluoro- (CA INDEX NAME)

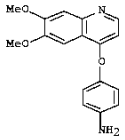


RN 35654-56-9 CAPLUS

CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



IT 190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of fused heterocyclic derivs. as kinase inhibitors for treating cancer)
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



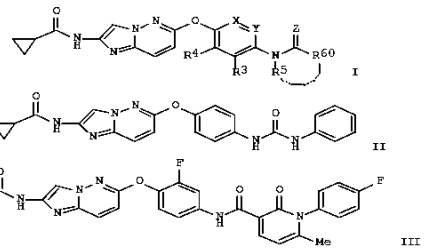
OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 45 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2009:944300 CAPLUS Full-text
DOCUMENT NUMBER: 151:245679
TITLE: Preparation of 6-(imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide derivatives as protein kinase inhibitors and anticancer agents
INVENTOR(S): Miyamoto, Naoki; Matsumoto, Shigemitsu; Imamura, Shinichi; Hirayama, Takaharu
PATENT ASSIGNEE(S): Takeda Pharmaceutical Company Limited, Japan
SOURCE: PCT Int. Appl., 184pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009096435	A1	20090806	WO 2009-JP51383	20090128

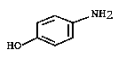
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: JP 2008-18367 A 20080129
JP 2008-276354 A 20081028
OTHER SOURCE(S): CASREACT 151:245679; MARPAT 151:245679
GI

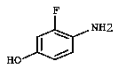


AB This invention pertains to condensed heterocyclic compds. represented by formula [I; X = N, CR1; Y = N, CR2; R1-R4 = H, halo, C1-6 alkyl; R60 = each (un)substituted C6-10 arylamino, N-containing 5- or 6-membered ring group, or aromatic heterocyclyl, C7-12 aralkylcarbonylamino, C7-12 aralkyloxy; Z = O, S] and salts thereof. These compds. are potent kinase inhibitors with reduced toxicity and useful for preventing and/or treating cancer. Thus, a suspension of N-[6-(4-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide in 12.0 mL toluene was heated to 100°, treated with 84.3 μL Ph isocyanate, and stirred at 110° for 1 h to give 76% N-(6-(4-[(phenylcarbamoyl)amino]phenoxy)imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (II). The compound (III) inhibited 100% VEGFR-2 (Vascular endothelial growth factor receptor type VEGFR-2) kinase and c-Met kinase, 90% the proliferation of human umbilical vein endothelial cells (HUVEC), and 93% the proliferation of human stomach cancer MKN45 cells. A capsule, a tablet, and a injection vial formulation containing II were prepared
IT 123-30-8, 4-Aminophenol 399-95-1, 4-Amino-3-fluorophenol 399-96-2, 4-Amino-2-fluorophenol 2835-96-3, 4-Amino-2-methylphenol 2835-99-6, 4-Amino-3-methylphenol 3964-52-1, 4-Amino-2-chlorophenol 17609-80-2, 4-Amino-3-chlorophenol 35654-56-9, 4-Chloro-6,7-dimethoxyquinoline
RL: RCT (Reactant); RACT (Reactant or reagent)

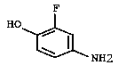
(preparation of 6-(imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide derivs. as protein kinase inhibitors and anticancer agents)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



RN 399-95-1 CAPLUS
CN Phenol, 4-amino-3-fluoro- (CA INDEX NAME)



RN 399-96-2 CAPLUS
CN Phenol, 4-amino-2-fluoro- (CA INDEX NAME)



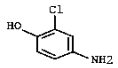
RN 2835-96-3 CAPLUS
CN Phenol, 4-amino-2-methyl- (CA INDEX NAME)



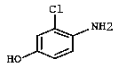
RN 2835-99-6 CAPLUS
CN Phenol, 4-amino-3-methyl- (CA INDEX NAME)



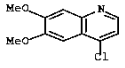
RN 3964-52-1 CAPLUS
CN Phenol, 4-amino-2-chloro- (CA INDEX NAME)



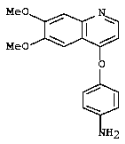
RN 17609-80-2 CAPLUS
CN Phenol, 4-amino-3-chloro- (CA INDEX NAME)



RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



IT 190728-25-7P, 4-[(6,7-Dimethoxyquinolin-4-yl)oxy]aniline
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of 6-(imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide derivs. as protein kinase inhibitors and anticancer agents)
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



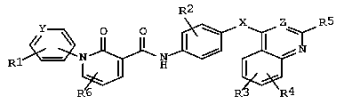
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 46 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2008:501397 CAPLUS Full-text
DOCUMENT NUMBER: 148:495976
TITLE: Preparation of pyridonecarboxamide derivatives for treating hyper-proliferative and angiogenesis disorders
INVENTOR(S): Boyer, Stephen; Cantin, David; Liang, Sidney X.
PATENT ASSIGNEE(S): Bayer Healthcare A.-G., Germany
SOURCE: PCT Int. Appl., 72pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

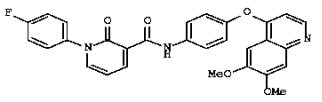
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008048375	A1	20080424	WO 2007-US11981	20070518
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
CA 2652417	A1	20080424	CA 2007-2652417	20070518
EP 2023926	A1	20090218	EP 2007-861312	20070518
EP 2023926	B1	20111012		
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JP 2009537632	T	20091029	JP 2009-512061	20070518
AT 528002	T	20111015	AT 2007-861312	20070518
US 20090306103	A1	20091210	US 2009-300751	20090520
PRIORITY APPLN. INFO.:			US 2006-60801700 P	20060519
			WO 2007-US11981 W	20070518

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASREACT 148:495976; MARPAT 148:495976
GI



I

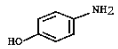


II

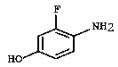
AB The title compds. I [X = O or S; Y and Z = CH or N; R1 = H, halo, CN, etc.; R2 = H, halo, alkoxy, etc.; R3, R4 = H, halo, CN, etc.; R5 = H, (un)substituted OH, NH2, etc.; R6 = H, alkoxy, (un)substituted NH2, etc.], useful for treating hyper-proliferative disorders and angiogenesis disorders, were prepared and formulated. E.g., a multi-step synthesis of II, starting from 2-amino-4,5-dimethoxyacetophenone, was given. Compds. I were tested in Flk-1, c-Met and Bcr-Abl assays and showed IC50 of <3 μM in one or more of the these assays.

IT 123-30-8, 4-Aminophenol 399-95-1, 4-Amino-3-fluorophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of novel pyridonecarboxamides for use in mono- and combination therapy of hyperproliferative and angiogenesis disorders)

RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)

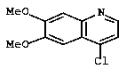


RN 399-95-1 CAPLUS
CN Phenol, 4-amino-3-fluoro- (CA INDEX NAME)

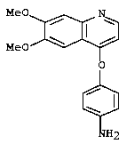


IT 35654-56-9P 190728-25-7P 228559-74-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of novel pyridonecarboxamides for use in mono- and combination therapy of hyperproliferative and angiogenesis disorders)

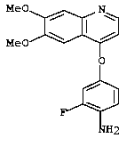
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



RN 228559-74-8 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]-2-fluoro- (CA INDEX NAME)



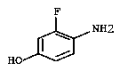
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 47 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2007:1311820 CAPLUS Full-text
DOCUMENT NUMBER: 148:135016
TITLE: Synthesis and structure-activity relationships of potent antitumor active quinoline and naphthyridine derivatives
AUTHOR(S): Srivastava, Sanjay K.; Jha, Amrita; Agarwal, Shiv K.; Mukherjee, Rama; Burman, Anand C.
CORPORATE SOURCE: Medicinal Chemistry, Dabur Research Foundation, Ghaziabad, 201 010, India
SOURCE: Anti-Cancer Agents in Medicinal Chemistry (2007), 7(6), 685-709
CODEN: AAMCE4; ISSN: 1871-5206
DIGITAL OBJECT ID: 10.2174/187152007784111313
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

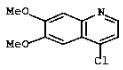
AB The disease of cancer has been ranked second after cardiovascular diseases and plant-derived mols. have played an important role for the treatment of cancer. Nine cytotoxic plant-derived mols. such as vinblastine, vincristine, navelbine, etoposide, teniposide, taxol, taxotere, topotecan and irinotecan have been approved as anticancer drugs. Recently, epothilones are being emerging as future potential anti-tumor agents. However, targeted cancer therapy has now been rapidly expanding and small organic mols. are being exploited for this purpose. Amongst target specific small organic mols., quinazoline was found as one of the most successful chemical class in cancer chemotherapy as three drugs namely Gefitinib, Erlotinib and Canertinib belong to this series. Now, quinazoline related chemical classes such as quinolines and naphthyridines are being exploited in cancer chemotherapy and a number of mols. such as compds. EKB-569 (52), HKI-272 (78) and SNS-595 (127a) are in different phases of clin. trials. This review presents the synthesis of quinolines and naphthyridines derivs., screened for anticancer activity since year 2000. The synthesis of most potent derivs. in each prototype has been delineated. A brief structure activity relationship for each prototype has also been discussed. It has been observed that aniline group at C-4, aminoacrylamide substituents at C-6, cyano group at C-3 and alkoxy groups at C-7 in the quinoline ring play an important role for optimal activity. While aminopyrrolidine functionality at C-7, 2'-thiazolyl at N-1 and carboxy group at C-3 in 1,8-naphthyridine ring are essential for eliciting the cytotoxicity. This review would help the medicinal chemist to design and synthesize mols. for targeted cancer chemotherapy.

IT 399-95-1, 4-Amino-3-fluorophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(Synthesis and structure-activity relationships of potent antitumor active quinoline and naphthyridine derivs.)

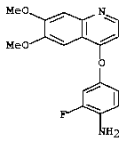
RN 399-95-1 CAPLUS
CN Phenol, 4-amino-3-fluoro- (CA INDEX NAME)



IT 35654-56-9P 228559-74-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(Synthesis and structure-activity relationships of potent antitumor active quinoline and naphthyridine derivs.)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



RN 228559-74-8 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]-2-fluoro- (CA INDEX NAME)



OS.CITING REF COUNT: 32 THERE ARE 32 CAPLUS RECORDS THAT CITE THIS RECORD (32 CITINGS)
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

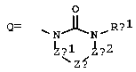
L11 ANSWER 48 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2007:863627 CAPLUS Full-text
DOCUMENT NUMBER: 147:235192
TITLE: Preparation of urea derivatives containing nitrogenous aromatic ring compounds as inhibitors of angiogenesis
INVENTOR(S): Funahashi, Yasuhiro; Tsuruoka, Akihiko; Matsukura, Masayuki; Haneda, Toru; Fukuda, Yoshio; Kamata, Junichi; Takahashi, Keiko; Matsushima, Tomohiro; Miyazaki, Kazuki; Nomoto, Ken-Ichi; Watanabe, Tatsuo; Obaishi, Hiroshi; Yamaguchi, Atsumi; Suzuki, Sachi; Nakamura, Katsuji; Mimura, Fusayo; Yamamoto, Yuji; Matsui, Junji; Matsui, Kenji; Yoshiba, Takako; Suzuki, Yasuyuki; Arimoto, Itaru
PATENT ASSIGNEE(S): Eisai Co., Ltd, Japan
SOURCE: U.S., 458pp., Cont.-in-part of Appl. No. PCT/JP01/09221.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 7253286	B2	20070807	US 2003-420466	20030418
US 20040053908	A1	20040318		
WO 2002032872	A1	20020425	WO 2001-JP9221	20011019
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1506962	A2	20050216	EP 2004-25700	20011019
EP 1506962	A3	20050302		
EP 1506962	B1	20080702		
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EP 1777218	A1	20070425	EP 2006-23078	20011019
EP 1777218	B1	20081231		
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CN 101024627	A	20070829	CN 2007-10007096	20011019
CN 101029022	A	20070905	CN 2007-10007097	20011019
CN 101029022	B	20110112		
ES 2282299	T3	20071016	ES 2001-976786	20011019
ZA 2003003567	A	20040810	ZA 2003-3567	20030508
JP 2005272474	A	20051006	JP 2005-124034	20050421
JP 4354929	B2	20091028		
US 20060247259	A1	20061102	US 2005-293785	20051202
US 7612092	B2	20091103		
US 20060160832	A1	20060720	US 2006-347749	20060203
AU 2006203099	A1	20060810	AU 2006-203099	20060719
AU 2006236039	A1	20061207	AU 2006-236039	20061116
AU 2006236039	B2	20080522		
US 20100197911	A1	20100805	US 2008-244227	20081002
US 7973160	B2	20110705		
JP 2009215313	A	20090924	JP 2009-123432	20090521
JP 5086304	B2	20121128		
US 20110118470	A1	20110519	US 2011-986638	20110107
US 8372981	B2	20130212		

PRIORITY APPLN. INFO.:

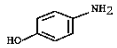
JP 2000-320420	A	20001020
JP 2000-386195	A	20001220
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AU 2001-295986	A3	20011019
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US 2003-420466	A3	20030418
JP 2005-124034	A3	20050421

US 2005-293785 A1 20051202
US 2008-244227 A3 20081002
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 147:235192; MARPAT 147:235192
GI



AB N-aryl or N-heteroarylurea derivs. represented by the general formula Ag-Xg-Yg-Tg1 or salts thereof, or hydrates of both [wherein Ag = (un)substituted C6-14 aryl or 5- to 14-membered heterocyclic group; Xg = single bond, O, S, C1-6 alkylene, SO, SO2, (un)substituted NH; Yg = (un)substituted C6-14 aryl, 5- to 14-membered heterocyclic group, C1-8 alkyl, C3-8 alicyclic hydrocarbyl, C6-14 aryl-C1-6 alkyl, 5- to 14-membered heteroaryl-C1-6 alkyl, (CH2)gSO2 (g = 1-8), (CH2)faCH:CH(CH2)fb (fa, fb = 0, 1,2,3), etc.; and Tg1 = a group of the general formula -Eg-CO-NRg1(Zg) or Q; wherein Eg = a single bond, (un)substituted NH; Rg1 = H, (un)substituted C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C3-8 aliphatic hydrocarbyl, etc.; Zg = C1-8 alkyl, C3-8 alicyclic hydrocarbyl, C6-14 aryl, etc.; Zg1, Zg2 = (a) a single bond, (b) C1-6 alkylene optionally having ≥1 atoms selected from O, S, and N in the middle or the terminus of the chain and optionally substituted with oxo, (c) (un)substituted C2-6 alkenyl] are prepared These compds. are also inhibitors of vascular endothelial growth factor receptor kinase (VEGFR2 kinase) and are useful as antitumor agents against hemangioma, pancreatic cancer, stomach cancer, colon cancer, breast cancer, prostate cancer, lung cancer, brain tumor, leukemia, or ovarian cancer, as cancer metastasis inhibitors, and for the treatment of retina neovascularization, diabetic retinopathy, atherosclerosis, or inflammatory diseases such as osteoarthritis, rheumatoid arthritis, psoriasis, or delayed hypersensitivity. Thus, to solution of 334 mg 4-[6-(4-benzyloxyphenyl)-7-(2-trimethylsilylethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy]-2-chlorophenylamine in 4 mL DMF were added 0.066 mL pyridine and 0.102 mL Ph chlorocarbonate and stirred at room temperature for 2.5 h to give 330 mg N-[4-[6-(4-benzyloxyphenyl)-7-(2-trimethylsilylethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy]-2-chlorophenyl]-N'-cyclopropylurea which (260 mg) was hydrogenolyzed over platinum oxide in ethanol overnight to give 160 mg N-[4-[6-(4-hydroxyphenyl)-7-(2-trimethylsilylethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy]-2-chlorophenyl]-N'-cyclopropylurea (I). I showed IC50 of 0.02 nM for inhibiting the vascular endothelial growth factor (VEGF)-stimulated sandwich tube formation in vascular endothelial cell.
IT 123-30-8 2835-96-3 2835-99-6
3096-69-3 17609-80-2 35654-56-9
190728-25-7 228559-74-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of urea derivs. containing nitrogenous aromatic ring compds. as
angiogenesis inhibitors for prevention or treatment of diseases)

RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



RN 2835-96-3 CAPLUS
CN Phenol, 4-amino-2-methyl- (CA INDEX NAME)



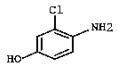
RN 2835-99-6 CAPLUS
CN Phenol, 4-amino-3-methyl- (CA INDEX NAME)



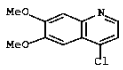
RN 3096-69-3 CAPLUS
CN Phenol, 4-amino-2,3-dimethyl- (CA INDEX NAME)



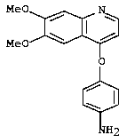
RN 17609-80-2 CAPLUS
CN Phenol, 4-amino-3-chloro- (CA INDEX NAME)



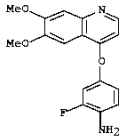
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



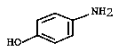
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



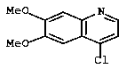
RN 228559-74-8 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]-2-fluoro- (CA INDEX NAME)



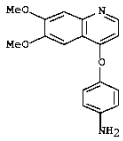
IT 399-95-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of urea derivs. containing nitrogenous aromatic ring compds. as
angiogenesis inhibitors for prevention or treatment of diseases)
RN 399-95-1 CAPLUS
CN Phenol, 4-amino-3-fluoro- (CA INDEX NAME)



IT 35654-56-9P 190728-25-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(Identification of Potent and Selective Inhibitors of PDGF Receptor Autophosphorylation)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

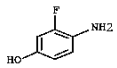


RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 36 THERE ARE 36 CAPLUS RECORDS THAT CITE THIS RECORD (36 CITINGS)
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

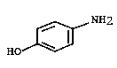
L11 ANSWER 50 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2005:128342 CAPLUS Full-text
DOCUMENT NUMBER: 142:411203
TITLE: Novel Potent Orally Active Selective VEGFR-2 Tyrosine Kinase Inhibitors: Synthesis, Structure-Activity Relationships, and Antitumor Activities of N-Phenyl-N'-[4-(4-quinolyloxy)phenyl]ureas
AUTHOR(S): Kubo, Kazuo; Shimizu, Toshiyuki; Ohyama, Shin-Ichi; Murooka, Hideko; Iwai, Akemi; Nakamura, Kazuhide; Hasegawa, Kazumasa; Kobayashi, Yoshiko; Takahashi, Noriko; Takahashi, Kazumi; Kato, Shinichiro; Izawa,



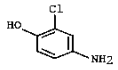
OS.CITING REF COUNT: 36 THERE ARE 36 CAPLUS RECORDS THAT CITE THIS RECORD (47 CITINGS)
REFERENCE COUNT: 117 THERE ARE 117 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 49 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2006:192537 CAPLUS Full-text
DOCUMENT NUMBER: 144:362578
TITLE: Identification of Potent and Selective Inhibitors of PDGF Receptor Autophosphorylation
AUTHOR(S): Furuta, Takayuki; Sakai, Teruyuki; Senga, Terufumi; Osawa, Tatsushi; Kubo, Kazuo; Shimizu, Toshiyuki; Suzuki, Rika; Yoshino, Tetsuya; Endo, Megumi; Miwa, Atsushi
CORPORATE SOURCE: Pharmaceutical Research Laboratories, Kirin Brewery Co. Ltd., Takasaki, Gunma, 370-1295, Japan
SOURCE: Journal of Medicinal Chemistry (2006), 49(7), 2186-2192
CODEN: JMCMAR; ISSN: 0022-2623
DIGITAL OBJECT ID: 10.1021/jm0506423
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 144:362578
AB We report the structure-activity relationship of quinoline and quinazoline derivs., which include urea, thiourea, urethane, and acylthiourea groups, as inhibitors of the platelet-derived growth factor (PDGF) receptor autophosphorylation. Our previous studies showed that the quinoline and quinazoline derivs. including urea, thiourea, and carbamate groups were highly potent compds. as the PDGF receptor autophosphorylation inhibitor, but these compds. did not exhibit receptor selectivity between the PDGF receptor and the c-kit receptor. As a result of further synthesis and biol. evaluation, we have found that the quinoline and quinazoline-acylthiourea derivs. showed not only good inhibitory activity for the PDGF receptor but also receptor selectivity between the PDGF receptor and the c-kit receptor. Furthermore N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-N'-(2-methylbenzoyl)thiourea exhibited potent oral efficacy in in vivo assay using the rat carotid balloon injury model. Therefore, the quinoline and quinazoline-acylthiourea derivs. may be expected to have potential as therapeutic agents for the treatment of restenosis.
IT 123-30-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(Identification of Potent and Selective Inhibitors of PDGF Receptor Autophosphorylation)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)

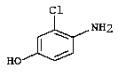
Toshio; Isoe, Toshiyuki
CORPORATE SOURCE: Pharmaceutical Research and Development Laboratories, Kirin Brewery Co., Ltd., Gunma, 370-1295, Japan
SOURCE: Journal of Medicinal Chemistry (2005), 48(5), 1359-1366
CODEN: JMCMAR; ISSN: 0022-2623
DIGITAL OBJECT ID: 10.1021/jm030427r
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 142:411203
AB N-Phenyl-N'-{4-(4-quinolyloxy)phenyl}ureas were found to be a novel class of potent inhibitors for the vascular endothelial growth factor receptor 2 (VEGFR-2) tyrosine kinase through synthetic modifications of a lead compound and structure-activity relationship studies. A representative compound N-(2,4-difluorophenyl)-N'-4-[[(6,7-dimethoxy-4-quinolyl)oxy]-2-fluorophenyl]urea, termed Ki8751, inhibited VEGFR-2 phosphorylation at an IC50 value of 0.90 nM, and also inhibited the PDGFR family members such as PDGFRα and c-Kit at 67 nM and 40 nM, resp. However, Ki8751 did not have any inhibitory activity against other kinases such as EGFR, HGFR, InsulinR and others even at 10000 nM. Ki8751 suppressed the growth of the VEGF-stimulated human umbilical vein endothelial cell (HUVEC) on a nanomolar level. Ki8751 showed significant antitumor activity against five human tumor xenografts such as GL07 (glioma), St-4 (stomach carcinoma), LC6 (lung carcinoma), DLD-1 (colon carcinoma) and A375 (melanoma) in nude mice and also showed complete tumor growth inhibition with the LC-6 xenograft in nude rats following oral administration once a day for 14 days at 5 mg/kg without any body weight loss.
IT 123-30-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of N-phenyl-N'-{4-(4-quinolyloxy)phenyl}ureas and their antitumor activity)
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



IT 3964-52-1, 2-Chloro-4-aminophenol 52671-64-4, 3-Chloro-4-aminophenol hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of N-phenyl-N'-{4-(4-quinolyloxy)phenyl}ureas as inhibitors for
the vascular endothelial growth factor receptor 2 (VEGFR-2) tyrosine kinase)
RN 3964-52-1 CAPLUS
CN Phenol, 4-amino-2-chloro- (CA INDEX NAME)

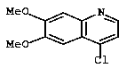


RN 52671-64-4 CAPLUS
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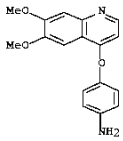


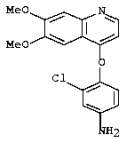
● HCl

IT 35654-56-9P 190728-25-7P 228559-74-8P
286371-44-6P 347161-74-4P 347161-75-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of N-phenyl-N'-{4-(4-quinolyloxy)phenyl}ureas as inhibitors for
the vascular endothelial growth factor receptor 2 (VEGFR-2) tyrosine kinase)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



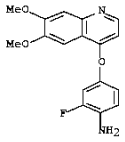


OS.CITING REF COUNT: 73 THERE ARE 73 CAPLUS RECORDS THAT CITE THIS RECORD (75 CITINGS)
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

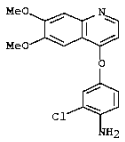
L11 ANSWER 51 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2004:354935 CAPLUS Full-text
DOCUMENT NUMBER: 140:363009
TITLE:
N-[2-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-N'-(5-methyl-3-isoxazolyl)urea salt crystals
INVENTOR(S): Matsunaga, Naoki; Yoshida, Satoshi; Yoshino, Ayako; Nakajima, Tatsuo
PATENT ASSIGNEE(S): Kirin Beer Kabushiki Kaisha, Japan
SOURCE: PCT Int. Appl., 115 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004035572	A1	20040429	WO 2003-JP13439	20031021
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003301430	A1	20040504	AU 2003-301430	20031021
EP 1559715	A1	20050803	EP 2003-756734	20031021
EP 1559715	B1	20070926		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 3763414	B2	20060405	JP 2004-544999	20031021
AT 374199	T	20071015	AT 2003-756734	20031021
PT 1559715	E	20071024	PT 2003-756734	20031021
ES 2294317	T3	20080401	ES 2003-756734	20031021

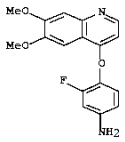
RN 228559-74-8 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]-2-fluoro- (CA INDEX NAME)



RN 286371-44-6 CAPLUS
CN Benzenamine, 2-chloro-4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)

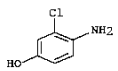


RN 347161-74-4 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]-3-fluoro- (CA INDEX NAME)



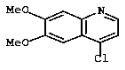
RN 347161-75-5 CAPLUS
CN Benzenamine, 3-chloro-4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)

US 20060052415 A1 20060309 US 2005-532104 20050421
US 7166722 B2 20070123
PRIORITY APPLN. INFO.: JP 2002-306101 A 20021021
WO 2003-JP13439 W 20031021
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB This invention provides crystals of pharmaceutically acceptable salts of N-[2-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-N'-(5-methyl-3-isoxazolyl)urea. The salt crystals are used in treating a disease selected from the group consisting of tumor, diabetic retinopathy, rheumatoid arthritis, psoriasis, atheroma arteriosclerosis, Kaposi's sarcoma and exudative age-related macular degeneration. The salt crystals have properties appropriate for prepns. for oral administration.
IT 52671-64-4, 4-Amino-3-chlorophenol hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(N-[2-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-N'-(5-methyl-3-isoxazolyl)urea salt crystals for treatment of tumor, diabetic retinopathy, rheumatoid arthritis, psoriasis)
RN 52671-64-4 CAPLUS
CN Phenol, 4-amino-3-chloro-, hydrochloride (1:1) (CA INDEX NAME)

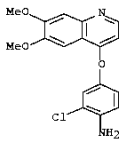


● HCl

IT 35654-56-9P 286371-44-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(N-[2-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-N'-(5-methyl-3-isoxazolyl)urea salt crystals for treatment of tumor, diabetic retinopathy, rheumatoid arthritis, psoriasis)
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



RN 286371-44-6 CAPLUS
CN Benzenamine, 2-chloro-4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



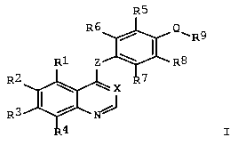
OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 52 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2003:319877 CAPLUS Full-text
DOCUMENT NUMBER: 138:338162
TITLE: Preparation of quinoline or quinazoline derivatives inhibiting auto-phosphorylation of fibroblast growth factor receptors
INVENTOR(S): Miwa, Atsushi; Yoshino, Tetsuya; Osawa, Tatsushi; Sakai, Teruyuki; Shimizu, Toshiyuki; Fujiwara, Yasunari
PATENT ASSIGNEE(S): Kirin Beer Kabushiki Kaisha, Japan
SOURCE: PCT Int. Appl., 264 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003033472	A1	20030424	WO 2002-JP10803	20021017
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002343997	A1	20030428	AU 2002-343997	20021017
EP 1447405	A1	20040818	EP 2002-775365	20021017
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
JP 4383870	B2	20091216	JP 2003-536212	20021017
US 20050049264	A1	20050303	US 2004-491898	20040920
US 7495104	B2	20090224		

PRIORITY APPLN. INFO.: JP 2001-319826 A 20011017
JP 2002-167652 A 20020607
WO 2002-JP10803 W 20021017

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 138:338162
GI

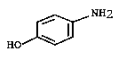


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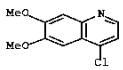
AB The invention provides novel compds. represented by the general formula (I) or pharmaceutically acceptable salts or solvates thereof [wherein X = CH, N; Z = O, S; Q = R10, CR11R12, CO, O, S(O)m (wherein m is 0 to 2), NHCONH (wherein R10 = H, C1-10 alkyl; R11, R12 = H, C1-6 alkylcarbonyloxy); R1, R2, R3 = H, OH, halogeno, nitro, amino, C1-6 alkyl or alkoxy or C2-6 alkenyl or alkynyl like (with the proviso that the alkyl and the alkoxy may be further substituted); R4 = H; R5, R6, R7, R8 = H, halogeno, C1-4 alkyl or alkoxy; R9 = C1-10 alkyl, (un)saturated 3- to 8-membered carbocyclic or heterocyclic group which may be substituted]. These compds. exhibit an inhibitory activity against autophosphorylation of fibroblast growth factor receptor (FGFR) family, in particular FGFR2 (Bek), can inhibit the proliferation of cancer cells through oral or i.v. administration, and are useful for the treatment of malignant tumors such as stomach cancer, brain tumor, large intestine cancer, pancreatic carcinoma, lung cancer, kidney cancer, ovarian cancer, and prostate cancer. Thus, 103 mg 1-(3,3-dimethylbutyl)-3-[2-fluoro-4-(7-hydroxy-6-methoxyquinolin-4-yloxy)phenyl]urea (preparation given), 166 mg K2CO3, and 69 mg 4-(2-chloroethyl)morpholine hydrochloride were stirred in 2 mL DMF at 75-80° for 16 h to give 37% 1-(3,3-dimethylbutyl)-3-[2-fluoro-4-[6-methoxy-7-(2-morpholin-4-ylethoxy)quinolin-4-yloxy]phenyl]urea (II). II and 1-(3,3-dimethylbutyl)-3-[2-chloro-4-[6-methoxy-7-[2-(2,6-dimethylmorpholin- 4-yl)ethoxy]quinolin-4-yloxy]phenyl]urea showed IC50 of <0.0100 and 0.0094 μM, resp., for inhibiting the autophosphorylation of Bek prepared from human Scirrhous stomach cancer OCUM-2MD3.

IT 123-30-8, 4-Aminophenol 35654-56-9, 4-Chloro-6,7-dimethoxyquinoline 190728-25-7 228559-74-8 286371-44-6 347161-74-4 347161-75-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of quinoline or quinazoline derivs. inhibiting auto-phosphorylation of fibroblast growth factor receptors as antitumor agents)

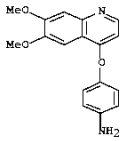
RN 123-30-8 CAPLUS
CN Phenol, 4-amino- (CA INDEX NAME)



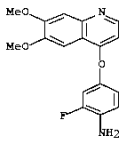
RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



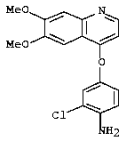
RN 190728-25-7 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



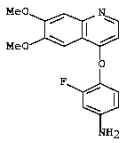
RN 228559-74-8 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]-2-fluoro- (CA INDEX NAME)



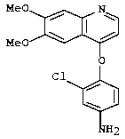
RN 286371-44-6 CAPLUS
CN Benzenamine, 2-chloro-4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



RN 347161-74-4 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]-3-fluoro- (CA INDEX NAME)



RN 347161-75-5 CAPLUS
CN Benzenamine, 3-chloro-4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (28 CITINGS)
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 53 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2002:314913 CAPLUS Full-text
DOCUMENT NUMBER: 136:340689
TITLE: Preparation of urea derivatives containing nitrogenous

aromatic ring compounds as inhibitors of angiogenesis

INVENTOR(S): Funahashi, Yasuhiro; Tsuruoka, Akihiko; Matsukura, Masayuki; Haneda, Toru; Fukuda, Yoshio; Kamata, Junichi; Takahashi, Keiko; Matsushima, Tomohiro; Miyazaki, Kazuki; Nomoto, Kenichi; Watanabe, Tatsuo; Obaishi, Hiroshi; Yamaguchi, Atsumi; Suzuki, Sachi; Nakamura, Katsuji; Mimura, Fusayo; Yamamoto, Yuji; Matsui, Junji; Matsui, Kenji; Yoshiba, Takako; Suzuki, Yasuyuki; Arimoto, Itaru

PATENT ASSIGNEE(S): Eisai Co., Ltd., Japan

SOURCE: PCT Int. Appl., 699 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002032872	A1	20020425	WO 2001-JP9221	20011019
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2426461	A1	20020425	CA 2001-2426461	20011019
CA 2426461	C	20110412		
AU 2001095986	A	20020429	AU 2001-95986	20011019
AU 2001295986	A1	20020704	AU 2001-295986	20011019
AU 2001295986	B2	20060817		
HU 2003002603	A2	20031128	HU 2003-2603	20011019
HU 2003002603	A3	20100329		
HU 230302	B1	20151228		
CN 1478078	A	20040225	CN 2001-819710	20011019
CN 1308310	C	20070404		
EP 1415987	A1	20040506	EP 2001-976786	20011019
EP 1415987	B1	20070228		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
EP 1506962	A2	20050216	EP 2004-25700	20011019
EP 1506962	A3	20050302		
EP 1506962	B1	20080702		
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NZ 525324	A	20050324	NZ 2001-525324	20011019
JP 3712393	B2	20051102	JP 2002-536056	20011019
RU 2264389	C2	20051120	RU 2003-114740	20011019
AT 355275	T	20060315	AT 2001-976786	20011019
EP 1777218	A1	20070425	EP 2006-23078	20011019
EP 1777218	B1	20081231		
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PT 1415987	E	20070531	PT 2001-976786	20011019
CN 101024627	A	20070829	CN 2007-10007096	20011019
CN 101029022	A	20070905	CN 2007-10007097	20011019
CN 101029022	B	20110112		
ES 2282299	T3	20071016	ES 2001-976786	20011019
IL 155447	A	20080605	IL 2001-155447	20011019
AT 399766	T	20080715	AT 2004-25700	20011019
TW I304061	B	20081211	TW 2001-125928	20011019
AT 419239	T	20090115	AT 2006-23078	20011019
ES 2318649	T3	20090501	ES 2006-23078	20011019
IL 189677	A	20101031	IL 2001-189677	20011019
NO 2003001731	A	20030619	NO 2003-1731	20030414
NO 326781	B1	20090216		
MX 2003003362	A	20030801	MX 2003-3362	20030415
US 7253286	B2	20070807	US 2003-420466	20030418
US 20040053908	A1	20040318		
ZA 2003003567	A	20040810	ZA 2003-3567	20030508
JP 2005272474	A	20051006	JP 2005-124034	20050421
JP 4354929	B2	20091028		
US 20060247259	A1	20061102	US 2005-293785	20051202
US 7612092	B2	20091103		
US 20060160832	A1	20060720	US 2006-347749	20060203
AU 2006203099	A1	20060810	AU 2006-203099	20060719
AU 2006236039	A1	20061207	AU 2006-236039	20061116
AU 2006236039	B2	20080522		
NO 20070004657	A	20030619	NO 2007-4657	20070912
US 20100197911	A1	20100805	US 2008-244227	20081002
US 7973160	B2	20110705		
JP 2009215313	A	20090924	JP 2009-123432	20090521
JP 5086304	B2	20121128		
US 20110118470	A1	20110519	US 2011-986638	20110107
US 8372981	B2	20130212		

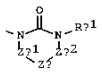
PRIORITY APPLN. INFO.:

JP 2000-320420	A	20001020
JP 2000-386195	A	20001220
JP 2001-46685	A	20010222
AU 2001-295986	A3	20011019
AU 2001-95986	TO	20011019
CN 2001-819710	A3	20011019
EP 2001-976786	A3	20011019
IL 2001-155447	A3	20011019
JP 2002-536056	A3	20011019
WO 2001-JP9221	W	20011019
US 2003-420466	A3	20030418
JP 2005-124034	A3	20050421
US 2005-293785	A1	20051202
US 2008-244227	A3	20081002

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): MARPAT 136:340689

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AB N-aryl or N-heteroarylurea derivs. represented by the general formula Ag-Xg-Yg-Tg1 or salts thereof, or hydrates of both [wherein Ag = (un)substituted C6-14 aryl or 5- to 14-membered heterocyclic group; Xg = single bond, O, S, C1-6 alkylene, SO, SO2, (un)substituted NH; Yg = (un)substituted C6-14 aryl, 5- to 14-membered heterocyclic group, C1-8 alkyl, C3-8 alicyclic hydrocarbyl, C6-14 aryl-C1-6 alkyl, 5- to 14-membered heteroaryl-C1-6 alkyl, (CH2)gSO2 (g = 1-8), (CH2)faCH:CH(CH2)fb (fa, fb = 0, 1,2,3), etc.; and Tg1 = a group of the general formula -Eg-CO-NRg1(Zg) or Q; wherein Eg = a single bond, (un)substituted NH; Rg1 = H, (un)substituted C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C3-8 aliphatic hydrocarbyl, etc.; Zg = C1-8 alkyl, C3-8 alicyclic hydrocarbyl, C6-14 aryl, etc.; Zg1, Zg2 = (a) a single bond, (b) C1-6 alkylene optionally having ≥1 atoms selected from O, S, and N in the middle or the terminus of the chain and optionally substituted with oxo, (c) (un)substituted C2-6 alkenyl] are prepared These compds. are also inhibitors of vascular endothelial growth factor receptor kinase (VEGFR2 kinase) and are useful as antitumor agents against hemangioma, pancreatic cancer, stomach cancer, colon cancer, breast cancer, prostate cancer, lung cancer, brain tumor, leukemia, or ovarian cancer, as cancer metastasis inhibitors, and for the treatment of retina neovascularization, diabetic retinopathy, atherosclerosis, or inflammatory diseases such as osteoarthritis, rheumatoid arthritis, psoriasis, or delayed hypersensitivity. Thus, to solution of 334 mg 4-[6-(4-benzyloxyphenyl)-7-(2-trimethylsilylethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy]-2-chlorophenylamine in 4 mL DMF were added 0.066 mL pyridine and 0.102 mL Ph chlorocarbonate and stirred at room temperature for 2.5 h to give 330 mg N-[4-[6-(4-benzyloxyphenyl)-7-(2-trimethylsilylethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy]-2-chlorophenyl]-N'-cyclopropylurea which (260 mg) was hydrogenolyzed over platinum oxide in ethanol overnight to give 160 mg N-[4-[6-(4-hydroxyphenyl)-7-(2-trimethylsilylethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy]-2-chlorophenyl]-N'-cyclopropylurea (I). I showed IC50 of 0.02 nM for inhibiting the vascular endothelial growth factor (VEGF)-stimulated sandwich tube formation in vascular endothelial cell.

IT 2835-96-3, 4-Amino-2-methylphenol 2835-99-6, 4-Amino-3-methylphenol 3096-69-3, 4-Amino-2,3-dimethylphenol 17609-80-2, 4-Amino-3-chlorophenol 35654-56-9, 4-Chloro-6,7-dimethoxyquinoline 190728-25-7, 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline 228559-74-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of urea derivs. containing nitrogenous aromatic ring compds. as angiogenesis inhibitors for prevention or treatment of diseases)

RN 2835-96-3 CAPLUS
CN Phenol, 4-amino-2-methyl- (CA INDEX NAME)



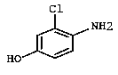
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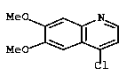
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CN Phenol, 4-amino-2,3-dimethyl- (CA INDEX NAME)



RN 17609-80-2 CAPLUS
CN Phenol, 4-amino-3-chloro- (CA INDEX NAME)

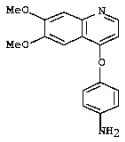


RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)

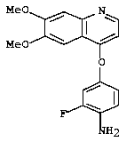


RN 190728-25-7 CAPLUS

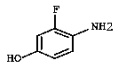
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



RN 228559-74-8 CAPLUS
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]-2-fluoro- (CA INDEX NAME)



IT 399-95-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of urea derivs. containing nitrogenous aromatic ring compds. as
angiogenesis inhibitors for prevention or treatment of diseases)
RN 399-95-1 CAPLUS
CN Phenol, 4-amino-3-fluoro- (CA INDEX NAME)



OS.CITING REF COUNT: 62 THERE ARE 62 CAPLUS RECORDS THAT CITE THIS RECORD (161 CITINGS)
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 54 OF 54 CAPLUS COPYRIGHT 2017 ACS on STN

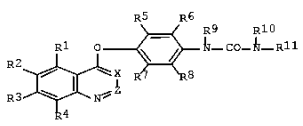
ACCESSION NUMBER: 2000:513673 CAPLUS Full-text
DOCUMENT NUMBER: 133:135235
TITLE: Preparation and anti-tumor, anti-atherosclerosis, anti-psoriasis, anti-diabetes, and anti-arthritis activities of quinolines and quinazolines
INVENTOR(S): Kubo, Kazuo; Fujiwara, Yasunari; Isoe, Toshiyuki
PATENT ASSIGNEE(S): Kirin Beer Kabushiki Kaisha, Japan
SOURCE: PCT Int. Appl., 208 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000043366	A1	20000727	WO 2000-JP255	20000120
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2361057	A1	20000727	CA 2000-2361057	20000120
CA 2361057	C	20100406		
AU 2000030748	A	20000807	AU 2000-30748	20000120
AU 771504	B2	20040325		
BR 2000007656	A	20011030	BR 2000-7656	20000120
EP 1153920	A1	20011114	EP 2000-900841	20000120
EP 1153920	B1	20031029		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
TR 2001002090	T2	20020121	TR 2001-2090	20000120
HU 2001005133	A2	20020729	HU 2001-5133	20000120
HU 2001005133	A3	20020930		
JP 2003286263	A	20031010	JP 2003-128216	20000120
NZ 513006	A	20031031	NZ 2000-513006	20000120
AT 253051	T	20031115	AT 2000-900841	20000120
EP 1384712	A1	20040128	EP 2003-24911	20000120
EP 1384712	B1	20070307		
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JP 3519368	B2	20040412	JP 2000-594782	20000120
ES 2208261	T3	20040616	ES 2000-900841	20000120
CN 1183114	C	20050105	CN 2000-805428	20000120
RU 2256654	C2	20050720	RU 2001-123434	20000120
AT 356117	T	20070315	AT 2003-24911	20000120
IL 144461	A	20070704	IL 2000-144461	20000120
ES 2281591	T3	20071001	ES 2003-24911	20000120
PL 204856	B1	20100226	PL 2000-349036	20000120
PL 206627	B1	20100930	PL 2000-388667	20000120
TW I229667	B	20050321	TW 2000-100998	20000121
NO 2001002617	A	20010914	NO 2001-2617	20010529
NO 321295	B1	20060418		
MX 2001007251	A	20011101	MX 2001-7251	20010717
KR 787254	B1	20071220	KR 2001-7009144	20010720
US 6797823	B1	20040928	US 2001-889858	20010723
HK 1043792	A1	20050630	HK 2002-105360	20020719
US 20040209905	A1	20041021	US 2004-842009	20040510
US 7169789	B2	20070130		
US 20070027318	A1	20070201	US 2006-526739	20060926

PRIORITY APPLN. INFO.:

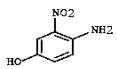
JP 1999-14858	A	19990122
JP 1999-26691	A	19990203
JP 1999-142493	A	19990521
JP 1999-253624	A	19990907
EP 2000-900841	A3	20000120
JP 2000-594782	A3	20000120
WO 2000-JP255	W	20000120
US 2001-889858	A3	20010723
US 2004-842009	A3	20040510

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 133:135235
GI



I

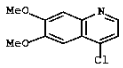
AB Title compds. [I; X and Z represent each CH or N; R1-3 represent each H, optionally substituted alkoxy, etc.; R4 represents H; R5-8 represent each H, halogeno, alkyl, alkoxy, alkylthio, nitro or amino, provided that all of R5-8 do not represent H simultaneously; R9 and R10 represent each H, alkyl or alkylcarbonyl; and R11 represents alkyl, alkenyl, alkynyl or aralkyl], pharmaceutically acceptable salts and solvates, and medicinal compns. containing the same are prepared and tested having antitumor activity and causing no morphol. change in cells. Thus, the title compound I (X = CH; Z = CH; R1, R4, R5,R7-R10 each an H; R11 = 3,5-F2C6H3) was prepared and tested.
IT 610-81-1, 4-Amino-3-nitrophenol 3096-69-3, 4-Amino-2,3-dimethylphenol 35654-56-9, 4-Chloro-6,7-dimethoxyquinoline 52671-64-4 94276-04-7 228559-74-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation and antitumor activity of quinolines and quinazolines)
RN 610-81-1 CAPLUS
CN Phenol, 4-amino-3-nitro- (CA INDEX NAME)



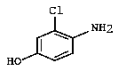
RN 3096-69-3 CAPLUS
CN Phenol, 4-amino-2,3-dimethyl- (CA INDEX NAME)



RN 35654-56-9 CAPLUS
CN Quinoline, 4-chloro-6,7-dimethoxy- (CA INDEX NAME)



RN 52671-64-4 CAPLUS
CN Phenol, 4-amino-3-chloro-, hydrochloride (1:1) (CA INDEX NAME)



● HCl

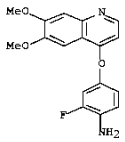
RN 94276-04-7 CAPLUS
CN Phenol, 4-amino-2,3-dimethyl-, hydrochloride (1:1) (CA INDEX NAME)



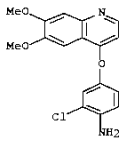
● HCl

RN 228559-74-8 CAPLUS

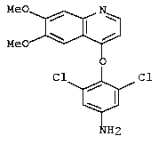
CN Benzenamine, 4-[(6,7-dimethoxy-4-quinolinyl)oxy]-2-fluoro- (CA INDEX NAME)



IT 286371-44-6P 286371-47-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and antitumor activity of quinolines and quinazolines)
RN 286371-44-6 CAPLUS
CN Benzenamine, 2-chloro-4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



RN 286371-47-9 CAPLUS
CN Benzenamine, 3,5-dichloro-4-[(6,7-dimethoxy-4-quinolinyl)oxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 36 THERE ARE 36 CAPLUS RECORDS THAT CITE THIS RECORD (69 CITINGS)
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L2 0 SEA FILE=REGISTRY SSS SAM L1
L3 2 SEA FILE=REGISTRY SSS FUL L1
L4 STRUCTURE UPLOADED
D
L5 50 SEA FILE=REGISTRY SSS SAM L4
L6 11320 SEA FILE=REGISTRY SSS FUL L4

FILE 'CAPLUS' ENTERED AT 17:27:09 ON 12 OCT 2017
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FILE 'REGISTRY' ENTERED AT 17:27:49 ON 12 OCT 2017
L8 STRUCTURE UPLOADED
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L11 54 SEA FILE=CAPLUS SPE=ON ABB=ON PLU=ON L3 AND L6 AND L10
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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	466.62	1931.46

STN INTERNATIONAL LOGOFF AT 17:30:15 ON 12 OCT 2017

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United States Patent and Trademark Office
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www.uspto.gov

BIB DATA SHEET

CONFIRMATION NO. 5882

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
15/348,716	11/10/2016 RULE	514	1625	224990/10-039C2-US/405045

APPLICANTS
Exelixis, Inc., South San Francisco, CA;

INVENTORS
Jo Ann Wilson, San Francisco, CA;

**** CONTINUING DATA ***************************
This application is a DIV of 13/984,559 03/20/2014 PAT 9717720
which is a 371 of PCT/US12/24591 02/10/2012
which claims benefit of 61/441,520 02/10/2011
and claims benefit of 61/441,527 02/10/2011

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **
11/18/2016

Foreign Priority claimed	35 USC 119(a-d) conditions met	Verified and Acknowledged	Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐ Yes ☑ No	☐ Yes ☐ No	/TIMOTHY R ROZOF/ Examiner's Signature	☐ TRR Initials	CA	0	13	1

ADDRESS

JONATHAN P. O'BRIEN, PH.D.
HONIGMAN MILLER SCHWARTZ AND COHN LLP
350 EAST MICHIGAN AVENUE, SUITE 300
Kalamazoo, MI 49007-3800
UNITED STATES

TITLE

Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

FILING FEE RECEIVED	FEES: Authority has been given in Paper	
800	No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/348,716	Wilson, Jo Ann
	Examiner	Art Unit
	TIMOTHY R ROZOF	1625

CPC - Searched*		
Symbol	Date	Examiner
C07D215/233	10/12/2017	TRR
A61K31/47	10/12/2017	TRR

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
EAST and STN search(s) (please see attached search reports)	10/12/2017	TRR

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/TIMOTHY R ROZOF/ Primary Examiner, Art Unit 1625	

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1	("20120035212").PN.	US-PGPUB; USPAT	OR	OFF	2017/10/12 17:17
L2	1	("7169789").PN.	USPAT	OR	OFF	2017/10/12 17:35
S1	1868	546/153	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2014/10/04 13:11
S2	6107	((546/153) or (514/312)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2014/10/04 13:12
S3	4920	S2 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2014/10/04 13:12
S4	476	S3 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2014/10/04 13:14
S5	88	S4 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2014/10/04 13:14
S6	2	("20070054928").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2014/10/04 13:14
S7	735	S3 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2014/10/04 15:14
S8	11	S5 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2014/10/04 15:15
S10	1907	546/153	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2015/06/03 13:56
S11	6748	((546/153) or (514/312)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2015/06/03 13:56
S12	5294	S11 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2015/06/03 13:56
S13	492	S12 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2015/06/03 13:56
S14	96	S13 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2015/06/03 13:56
S15	2	("20070054928").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2015/06/03 13:56
S16	748	S12 and (compound near3	US-PGPUB; USPAT;	OR	ON	2015/06/03

		(IA or IB))	USOCR; EPO; JPO; DERWENT			13:56
S17	12	S14 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2015/06/03 13:56
S19	1924	546/153	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/01/07 13:23
S20	7064	((546/153) or (514/312)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/01/07 13:23
S21	5473	S20 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/01/07 13:23
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S23	96	S22 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/01/07 13:23
S24	2	("20070054928").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/01/07 13:23
S25	755	S21 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/01/07 13:23
S26	12	S23 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/01/07 13:23
S27	1924	546/153	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/01/07 13:23
S28	7064	((546/153) or (514/312)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/01/07 13:23
S29	5473	S28 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/01/07 13:23
S30	494	S29 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/01/07 13:23
S31	96	S30 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/01/07 13:23
S32	2	("20070054928").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/01/07 13:23
S33	755	S29 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/01/07 13:23
S34	12	S31 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/01/07 13:23
S35	0	((A61K31/47.cpc.) or (C07D215/233.cpc.)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/01/07 13:33
S36	5706	A61K31/47.cpc.	US-PGPUB; USPAT;	OR	ON	2016/01/07

		C07D215/233.cpc.	USOCR; EPO; JPO; DERWENT			13:33
S37	4165	S36 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/01/07 13:33
S38	546	S37 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/01/07 13:34
S39	81	S38 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/01/07 13:34
S42	1925	546/153	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S43	7164	((546/153) or (514/312)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/04/28 12:34
S44	5481	S43 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S45	494	S44 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S46	96	S45 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S47	2	("20070054928").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/04/28 12:34
S48	756	S44 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S49	12	S46 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S50	1925	546/153	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S51	7164	((546/153) or (514/312)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/04/28 12:34
S52	5481	S51 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S53	494	S52 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S54	96	S53 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S55	2	("20070054928").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/04/28 12:34
S56	756	S52 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S57	12	S54 and (compound near3	US-PGPUB; USPAT;	OR	ON	2016/04/28

		(IA or IB))	USOCR; EPO; JPO; DERWENT			12:34
S58	1925	546/153	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S59	7164	((546/153) or (514/312)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/04/28 12:34
S60	5481	S59 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S61	494	S60 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S62	96	S61 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S63	2	("20070054928").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/04/28 12:34
S64	756	S60 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S65	12	S62 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S66	1925	546/153	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S67	7164	((546/153) or (514/312)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/04/28 12:34
S68	5481	S67 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S69	494	S68 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S70	96	S69 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S71	2	("20070054928").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/04/28 12:34
S72	756	S68 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S73	12	S70 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S74	0	((A61K31/47.cpc.) or (C07D215/233.cpc.)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/04/28 12:34
S75	5906	A61K31/47.cpc. C07D215/233.cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S76	4191	S75 and	US-PGPUB; USPAT;	OR	ON	2016/04/28

		@ad<="20110210"	USOCR; EPO; JPO; DERWENT			12:34
S77	550	S76 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S78	81	S77 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S79	1927	546/153	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S80	7246	((546/153) or (514/312)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:36
S81	5493	S80 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S82	495	S81 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S83	96	S82 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S84	2	("20070054928").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:36
S85	757	S81 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S86	12	S83 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S87	1927	546/153	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S88	7246	((546/153) or (514/312)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:36
S89	5493	S88 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S90	495	S89 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S91	96	S90 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S92	2	("20070054928").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:36
S93	757	S89 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S94	12	S91 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S95	1927	546/153	US-PGPUB; USPAT;	OR	ON	2016/08/05

			USOCR; EPO; JPO; DERWENT			11:36
S96	7246	((546/153) or (514/312)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:36
S97	5493	S96 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S98	495	S97 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S99	96	S98 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S100	2	("20070054928").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:36
S101	757	S97 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S102	12	S99 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S103	1927	546/153	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S104	7246	((546/153) or (514/312)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:36
S105	5493	S104 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S106	495	S105 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S107	96	S106 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S108	2	("20070054928").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:36
S109	757	S105 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S110	12	S107 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S111	0	((A61K31/47.cpc.) or (C07D215/233.cpc.)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:37
S112	6123	A61K31/47.cpc. C07D215/233.cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S113	4231	S112 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S114	566	S113 and (protein near3	US-PGPUB; USPAT;	OR	ON	2016/08/05

		kinase)	USOCR; EPO; JPO; DERWENT			11:37
S115	82	S114 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S116	1927	546/153	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S117	7246	((546/153) or (514/312)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:37
S118	5493	S117 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S119	495	S118 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S120	96	S119 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S121	2	("20070054928").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:37
S122	757	S118 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S123	12	S120 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S124	1927	546/153	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S125	7246	((546/153) or (514/312)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:37
S126	5493	S125 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S127	495	S126 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S128	96	S127 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S129	2	("20070054928").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:37
S130	757	S126 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S131	12	S128 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S132	1927	546/153	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S133	7246	((546/153) or	US-PGPUB; USPAT;	OR	OFF	2016/08/05

		(514/312)).CCLS.	USOCR; EPO; JPO; DERWENT			11:37
S134	5493	S133 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S135	495	S134 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S136	96	S135 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S137	2	("20070054928").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:37
S138	757	S134 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S139	12	S136 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S140	1927	546/153	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S141	7246	((546/153) or (514/312)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:37
S142	5493	S141 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S143	495	S142 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S144	96	S143 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S145	2	("20070054928").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:37
S146	757	S142 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S147	12	S144 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S148	0	((A61K31/47.cpc.) or (C07D215/233.cpc.)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:37
S149	6123	A61K31/47.cpc. C07D215/233.cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S150	4231	S149 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S151	566	S150 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S152	82	S151 and (compound near3	US-PGPUB; USPAT;	OR	ON	2016/08/05

		(IA or IB))	USOCR; EPO; JPO; DERWENT			11:37
S153	6433	A61K31/47.cpc. C07D215/233.cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2017/01/17 13:35
S154	4302	S153 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2017/01/17 13:35
S155	573	S154 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2017/01/17 13:35
S156	83	S155 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2017/01/17 13:35
S157	7130	A61K31/47.cpc. C07D215/233.cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2017/05/23 14:41
S158	4682	S157 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2017/05/23 14:41
S159	580	S158 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2017/05/23 14:41
S160	83	S159 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2017/05/23 14:41
S161	1	("20120035212").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2017/06/26 14:37
S162	7223	A61K31/47.cpc. C07D215/233.cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2017/06/28 15:15
S163	1	("20120035212").PN.	US-PGPUB; USPAT	OR	OFF	2017/10/12 15:31

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S9	1	((546/153) or (514/312)).CCLS.		OR	OFF	2014/10/04 13:43
S18	1	((546/153) or (514/312)).CCLS.		OR	OFF	2015/06/03 13:56
S40	0	((546/153) or (514/312)).CCLS.		OR	OFF	2016/01/07 13:23
S41	0	((546/153) or (514/312)).CCLS.		OR	OFF	2016/01/07 13:23

10/12/2017 5:57:31 PM
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The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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	Examiner TIMOTHY R ROZOF	Art Unit 1625	AIA Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on June 22, 2017 .

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____ .

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☑ Claim(s) 1-13 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☑ Claim(s) 1-13 is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____ .

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____ .

4) ☐ Other: _____ .

DETAILED CORRESPONDENCE

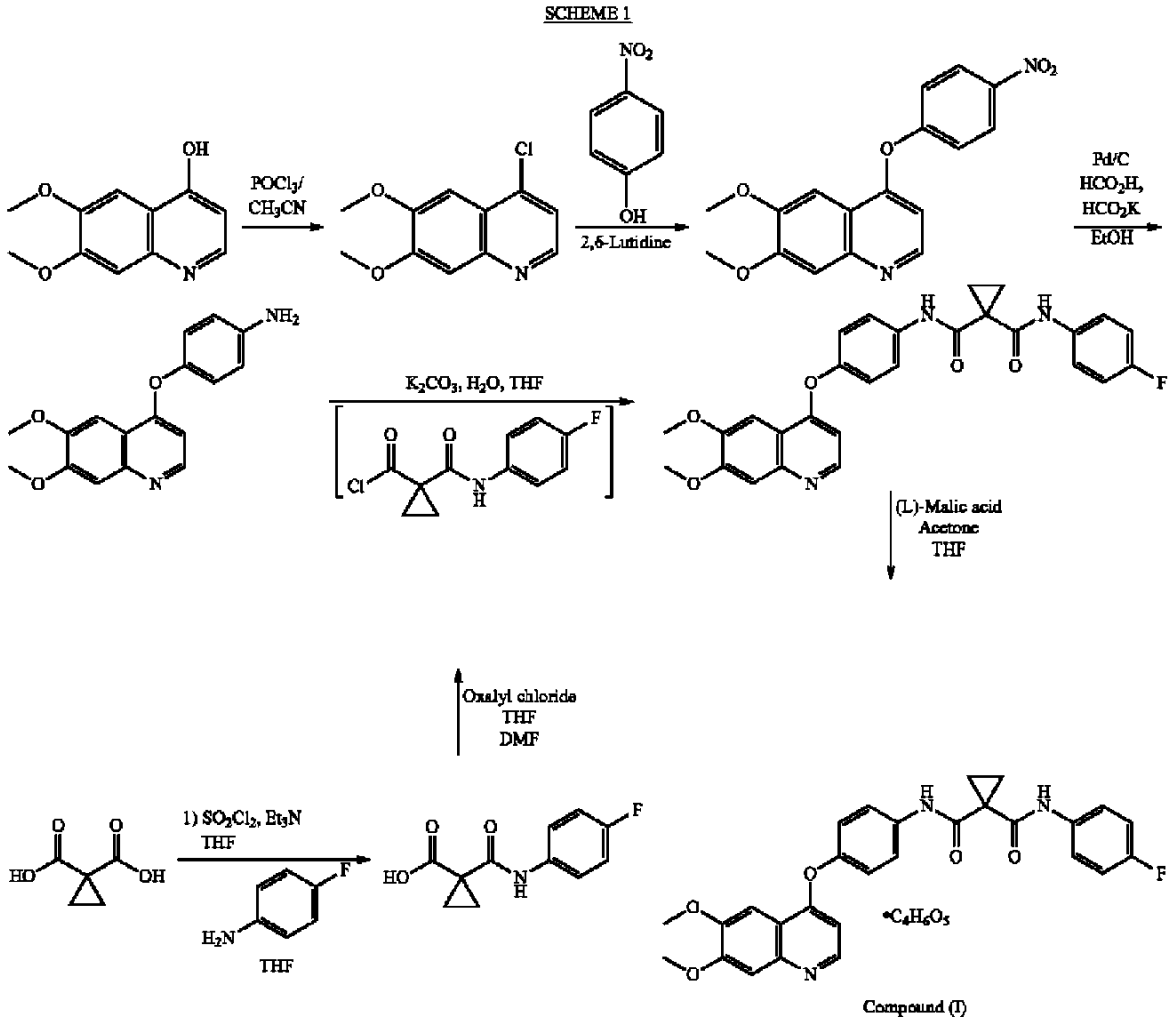
This is a response to Applicant's communication filed on June 22, 2017. Application No. 15/348,716 is a Divisional of U.S. Nonprovisional Application No. 13/984,559, filed March 20, 2014, (now issued U.S. Patent No. 9,717,720) which is a 371 of PCT/US12/24591, filed February 10, 2012, which claims the benefit of U.S. Provisional Applications Nos.: 61/441,520 and 61/441,527, both filed February 10, 2011. Claims 1-13 are pending.

Claim Rejections - 35 USC § 102(e)

The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 4, 5, and 11-13 are rejected under pre-AIA 35 U.S.C. 102(e) as being anticipated by Brown et al., US2012/0035212 A1. Brown discloses the following process for preparing a compound of formula I:



(Brown et al., Specification, p. 10; see also Id., p. 10-13, Examples 1-6.)

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was

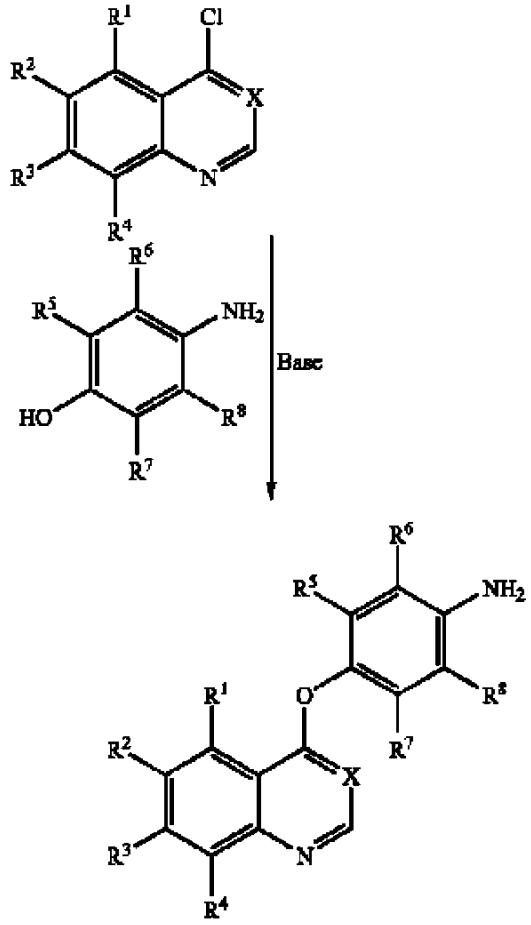
made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-13 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Brown et al., US2010/0035212 (see in the 102(e) rejection above) in view of Kubo et al., 7,169,789. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The difference between the process of the prior art and present invention is that Brown does not disclose the step of preparing the amine substituted compound of formula g(1) as in claim 2. Rather the prior art teaches preparing the nitro substituted derivative of formula g(1), first, which is then subsequently reduced to the amine substituted group of the compound of formula g(1).

Nonetheless, Kubo teaches the process of preparing the amine substituted compound of formula g(1) from a compound formula f(1) and formula y(1) as follows:



(Kudo et al., '789 patent, Specification, Cols. 11-12; see specification, Id., Col. 12, ln. 60 – Col. 14, ln. 5.) Accordingly, all the elements of the present invention were known in the art at the time of the invention.

It would have been obvious to the ordinary artisan at the time of the invention to combine prior art elements according to known methods to yield predictable results. The step of preparing the reduced amine compound of formula g(1) from the compounds of formulas f(1) and y(1) were known in the art at the time of the invention. The ordinary artisan would have been motivated by the desire in the art to reduce unnecessary steps. In this case, the compounds are generally of sufficiently close structural similarity that there is a presumed expectation that

such compounds possess similar properties. MPEP 2144.09. The similarity between the chemical structures and properties is sufficiently close that one of ordinary skill in the art would have been motivated to make the claimed compounds in searching for new compounds for treating or preventing neurodegenerative diseases. Known work in one field of endeavor may prompt variations of it for use in the same field based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art.

Contact Information

No claims are allowed.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY R ROZOF whose telephone number is (571)270-5992. The examiner can normally be reached on Monday - Friday, 9:00 a.m. -5:00 p.m..

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Kosar can be reached on (571) 272-0913. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/TIMOTHY R ROZOF/
Primary Examiner, Art Unit 1625

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/348,716	Wilson, Jo Ann
	Examiner	Art Unit
	TIMOTHY R ROZOF	1625

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	10/12/2017								
	1	✓								
	2	✓								
	3	✓								
	4	✓								
	5	✓								
	6	✓								
	7	✓								
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	33	-								
	34	-								

Notice of References Cited	Application/Control No. 15/348,716	Applicant(s)/Patent Under Reexamination Wilson, Jo Ann	
	Examiner TIMOTHY R ROZOF	Art Unit 1625	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-20120035212-A1	02-2012	Brown; Adrian St. Clair	C07D215/233	514/312
*	B	US-7169789-B2	01-2007	Kubo; Kazuo	C07D215/233	514/266.3
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (03-15)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	15348716
Filing Date	2016-11-10
First Named Inventor	Jo Ann Wilson
Art Unit	1629
Examiner Name	TBD
Attorney Docket Number	224990/10-039C2-US/405045

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	7166722		2007-01-23	MATSUNAGA, et al.	
	2	7579473		2011-07-12	BANNEN, et al.	
	3	7977345		2011-08-16	BANNEN, et al.	
	4	7999006		2011-08-16	LAMB, Peter	
	5	8067436		2011-11-29	BANNEN, et al.	
	6	8178532		2012-05-15	BANNEN, et al.	
	7	8314232		2012-11-20	DESCHAMPS, et al.	
	8	8476298		2013-07-02	BANNEN, et al.	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /T.R.R/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Attorney Docket Number	224990/10-039C2-US/405045

	9	8497284		2013-07-30	BANNEN, et al.	
	10	8673912		2014-03-18	CANNON, et al.	
	11	8877776		2014-11-04	BROWN, et al.	
	12	9174947		2015-11-03	BANNEN, et al.	
	13	9365516		2016-06-14	WILSON, et al.	

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20050209247		2005-09-22	CAI, et al.	
	2	20070054928		2007-03-08	BANNEN, et al.	
	3	20070078159		2007-04-05	MATSUSHIMA, et al.	
	4	20080161305		2008-07-03	FORSYTH, et al.	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /T.R.R/

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	5	20090274693		2009-11-05	GILMER, et al.	
	6	20110059081		2011-03-10	BACUS, Sarah	
	7	20110077233		2011-03-31	BANNEN, et al.	
	8	20120070368		2012-03-22	BANNEN, et al.	
	9	20120184523		2012-07-19	BANNEN, et al.	
	10	20120252840		2012-10-04	AFTAB, et al.	
	11	20120282179		2012-11-08	AFTAB, et al.	
	12	20130030172		2013-01-31	WILSON, et al.	
	13	20130142790		2013-06-06	GILMER, et al.	
	14	20130143881		2013-06-06	CANNON, et al.	
	15	20130150363		2013-06-13	GILMER, et al.	

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	Attorney Docket Number	224990/10-039C2-US/405045

	16	20130197230		2013-08-01	WILSON, et al.	
	17	20130252940		2013-09-26	BANNEN, et. al.	
	18	20130252956		2013-09-26	KALLENDER, et al.	
	19	20130330377		2013-12-12	WILSON, Jo Ann	
	20	20130337015		2013-12-19	WILSON, et al.	
	21	20140057908		2014-02-27	SMITH, et al.	
	22	20140057943		2014-02-27	SMITH, et al.	
	23	20140066444		2014-03-26	SMITH, et al.	
	24	20140155396		2014-06-05	BANNEN, et. al.	
	25	20140179736		2014-06-26	SCHWAB, et al.	
	26	20140200242		2014-07-17	WILSON, et al.	

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	27	20140228401		2014-08-14	AFTAB, et al.	
	28	20140256938		2014-09-11	WILSON, et al.	
	29	20140302012		2014-10-09	AFTAB, et al.	
	30	20140323522		2014-10-30	AFTAB, et al.	
	31	20150057310		2015-02-26	BROWN, et al.	
	32	20150196545		2015-07-16	AFTAB, et al.	
	33	20150202196		2015-07-23	BANNEN, et al.	
	34	20150376133		2015-12-31	BANNEN, et al.	
	35	20160000772		2016-01-07	AFTAB, et al.	
	36	20160051532		2016-02-25	AFTAB, et al.	
	37	20160185725		2016-06-30	BANNEN, et al.	

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	38	20160220554		2016-08-04	SMITH, et al.	
	39	20160229805		2016-08-11	WILSON, et al.	
	40	20170143689		2017-05-25	WILSON, et al.	

If you wish to add additional U.S. Published Application citation information please click the Add button.

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2005030140	WO		2005-04-07	EXELIXIS, INC.		☐
	2	2009136663	WO		2009-11-12	TAKEDA PHARMACEUTICAL COMPANY LIMITED		☐
	3	2010083414	WO		2010-07-22	EXELIXIS, INC.		☐
	4	2011017639	WO		2011-02-10	EXELIXIS, INC.		☐
	5	2012009722	WO		2012-01-19	EXELIXIS, INC.		☐

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NON-PATENT LITERATURE DOCUMENTS

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /T.R.R/

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T5
	1	European Medicines Agency, "Committee for orphan medicinal products December 2008 plenary meeting monthly report", Doc. Ref. EMEA/666785/2008 Corr. 2, December 22, 2008.	☐
	2	International Search Report for PCT/US2012/024591, mailed May 25, 2012	☐
	3	Kurzrock R et al. "379 POSTER A phase I study of XL 184, a MET, VEGFR2, and RET kinase inhibitor, administered orally to patients (pts) with advanced malignancies, including a subgroup of pts with medullary thyroid cancer (MTC)." Eropean journal of cancer. supplement, vol 6, no 12, 2008-10-01, 119.	☐
	4	SIGMA-ALDRICH CORPORATION, "Safety Data Sheet for 6,7-Dimethoxy-1H-Quinolin-4-One", Version 5.0, October 20, 2014, retrieved from the internet at http://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=US&language=en&productNumber=CDS009101&brand=ALDRICH on October 1, 2015.	☐
	5	United States Department of Health and Human Services, "Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products", Revision 2, November 2003, retrieved from the internet at www.fda.gov/downloads/drugs/guidancecomplianceregulatory information/guidances/ucm073369.pdf on October 1, 2015.	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature	/TIMOTHY R ROZOF/	Date Considered	10/12/2017

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /T.R.R/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15348716
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First Named Inventor	Jo Ann Wilson
Art Unit	1629
Examiner Name	TBD
Attorney Docket Number	224990/10-039C2-US/405045

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature		Date (YYYY-MM-DD)	2017-06-22
Name/Print	Heidi M. Berven, Ph.D.	Registration Number	48,951

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /T.R.R/

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/348,716	11/10/2016	1629	800	224990/10-039C2-US/405045	13	1

CONFIRMATION NO. 5882

UPDATED FILING RECEIPT

91684
JONATHAN P. O'BRIEN, PH.D.
HONIGMAN MILLER SCHWARTZ AND COHN LLP
350 EAST MICHIGAN AVENUE, SUITE 300
Kalamazoo, MI 49007-3800



Date Mailed: 06/26/2017

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Jo Ann Wilson, San Francisco, CA;

Applicant(s)

Exelixis, Inc., South San Francisco, CA;

Power of Attorney: The patent practitioners associated with Customer Number 91684

Domestic Priority data as claimed by applicant

This application is a DIV of 13/984,559 03/20/2014
which is a 371 of PCT/US12/24591 02/10/2012
which claims benefit of 61/441,520 02/10/2011
and claims benefit of 61/441,527 02/10/2011

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 11/18/2016

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/348,716**

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****
Title

Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

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No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/348,716	11/10/2016	Jo Ann Wilson	224990/10-039C2-US/405045

CONFIRMATION NO. 5882

91684
JONATHAN P. O'BRIEN, PH.D.
HONIGMAN MILLER SCHWARTZ AND COHN LLP
350 EAST MICHIGAN AVENUE, SUITE 300
Kalamazoo, MI 49007-3800

INFORMAL NOTICE

OC000000092340729

Date Mailed: 06/26/2017

INFORMATIONAL NOTICE TO APPLICANT

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  Jo Ann Wilson

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/hkquach/

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/348,716

APPLICATION AS FILED - PART I

	(Column 1)	(Column 2)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE($)	FEE($)		RATE($)	FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	70		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	300		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	360		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	13 minus 20 =	*	x 40 =	0.00	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*	x 210 =	0.00			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			0.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	730		TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1)		(Column 2)	(Column 3)					
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/348,716	Filing Date 11/10/2016	☐ To be Mailed

ENTITY: ☐ LARGE ☑ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $40 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $210 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

AMENDMENT	06/22/2017	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 13	Minus	** 20	= 0		x $40 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $210 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	tina J barden
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

AMENDMENT TO THE SPECIFICATION

On page 1 of the specification, after the title and header, please replace paragraph [0001] with the following paragraph:

Marked-up Version

[0001] This application is a ~~continuation~~ divisional application of United States Serial Number 13/984,559, filed March 20, 2014, which claims priority under 35 U.S.C. § 371 to Patent Cooperation Treaty application PCT/US2012/024591, filed February 10, 2012, which claims the benefit of United States provisional application number 61/441,520, filed February 10, 2011, and United States provisional application number 61/441,527, filed February 10, 2011, the entire contents of which are incorporated herein by reference.

Clean Version

[0001] This application is a divisional application of United States Serial Number 13/984,559, filed March 20, 2014, which claims priority under 35 U.S.C. § 371 to Patent Cooperation Treaty application PCT/US2012/024591, filed February 10, 2012, which claims the benefit of United States provisional application number 61/441,520, filed February 10, 2011, and United States provisional application number 61/441,527, filed February 10, 2011, the entire contents of which are incorporated herein by reference.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors:	Jo Ann Wilson, et al.	Confirmation No.:	5882
Application No.:	15/348,716	Art Unit:	1629
Filed:	November 10, 2016	Examiner:	TBD
Atty. Docket No.:	224990/10-039C2-US/405045		

Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

Mail Stop Missing Parts
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 223313-1450

RESPONSE TO NOTICE TO FILE MISSING PARTS MAILED NOVEMBER 22, 2016 AND PRELIMINARY AMENDMENT UNDER 37 C.F.R. § 1.115

Dear Sir or Madam:

This submission is responsive to the Notice To File Missing Parts of Nonprovisional Application Filed under 37 C.F.R. § 1.53(b) dated November 22, 2016.

Amendments to the specification begin on page 2.

Amendments to the claims under 37 C.F.R. § 1.115 begin on page 3.

Remarks begin on page 8.

HONIGMAN

Honigman Miller Schwartz and Cohn LLP
Attorneys and Counselors

Heidi M. Berven

(269) 337-7710
Fax: (269) 337-7711
HBerven@honigman.com

Via EFS Web

June 22, 2017

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313

Re: ***US Patent Application No.: 15/348,716***
Inventors: Jo Ann Wilson, et al.
Filing Date: November 10, 2016
Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds
Confirmation No.: 5882
Attorney Docket No.: 224990/10-039C2-US/405045

Dear Sir or Madam:

Enclosed for filing please find the following documents:

1. This Cover Letter to the Commissioner for Patents;
2. Response to the Notice to File Missing Parts of Nonprovisional Application dated November 22, 2016, and Preliminary Amendment;
3. Request to Correct Inventorship under 37 C.F.R. § 1.48;
4. Replacement Application Data Sheet (PTO/AIA/14);
5. Information Disclosure Statement (PTO/SB/08);
6. Foreign Patent Literature Documents (5 documents);
7. Non-Patent Literature Documents (5 documents);
8. Petition for Extension of Time (PTO/AIA/22);
9. Fee Transmittal form (PTO/SB/17); and
10. Certificate of Transmission under 37 C.F.R. § 1.8(a).

The Applicant notes that the filing of the enclosed Information Disclosure Statement shall not be construed to be an admission that the information cited in the statement qualifies as prior art under 35 U.S.C. § § 102 or 103, or is considered to be material to patentability as defined in 37 C.F.R. § 1.56(b). It is believed that no fee is due pursuant to 37 C.F.R. § 1.97(b)(3).

The Applicant hereby petitions for a five-month extension of time under 37 C.F.R. § 1.136(a) for responding to the Notice to File Missing Parts of Nonprovisional Application in this application dated November 22, 2016. The fee set forth in 37 C.F.R. § 1.17(a)(5) is submitted herewith.

It is believed that the fees due for this response are the surcharge of $70.00 set forth in 37 C.F.R. § 1.16(f), the processing fee of $70.00 set forth in § 1.17(i)(1), and the fee of $1,500.00 set forth in § 1.17(a)(5). The Applicant hereby authorizes the Office to charge this total of $1,640.00 to Deposit Account Number 503145, referencing Attorney Docket Number 224990/10-039C2-US/405045. It is believed that no other fees are due at this time. However, if there are any additional charges for this submission, or any credits, please apply them to Deposit Account Number 503145, referencing Attorney Docket Number 224990/10-039C2-US/405045.

Very truly yours,

HONIGMAN MILLER SCHWARTZ AND COHN LLP

Heidi M. Berven, Ph.D.
Reg. No. 48,951

HMB/cwg

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 April 2005 (07.04.2005)

PCT

(10) International Publication Number
WO 2005/030140 A2

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24 September 2004 (24.09.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/506,181	26 September 2003 (26.09.2003)	US
60/535,377	9 January 2004 (09.01.2004)	US
60/577,384	4 June 2004 (04.06.2004)	US

(71) Applicant *(for all designated States except US)*: **EXELIXIS, INC.** [US/US]; 170 Harbor Way, P.O. Box 511, South San Francisco, CA 94083-0511 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BANNEN, Lynne Canne** [US/US]; 801 St. Lawrence Drive, Pacifica, CA 94044 (US). **CHAN, Diva Sze-Ming** [US/US]; 1775 46th Avenue, San Francisco, CA 94122 (US). **CHEN, Jeff** [US/US]; 140 South Van Ness Avenue, Apt. #407, San Francisco, CA 94103 (US). **DALRYMPLE, Lisa Esther** [US/US]; 387 17th Avenue, San Francisco, CA 94121 (US). **FORSYTH, Timothy Patrick** [US/US]; 1928 Wingate Way, Hayward, CA 94541 (US). **HUYNH, Tai Phat** [US/US]; 1530 6th Avenue #2, Oakland, CA 94606 (US). **JAMMALAMADAKA, Vasu** [US/US]; 2806 Maria Street, Pleasanton, CA 94588 (US). **KHOURY, Richard George** [US/US]; 225 Poseidon Lane, Redwood City, CA 94065 (US). **LEAHY, James William** [US/US]; 1185 Camellia Court, San Leandro, CA 94577 (US). **MAC, Morrison B.** [US/US]; 2567 30th Avenue, San Francisco, CA 94116 (US). **MANN, Grace** [US/US]; 231 CAllippe Court, Brisbane, CA 94005 (US). **MANN, Larry W.** [US/US]; 780 Blair Island Road, Apt. #304, Redwood City, CA 94063 (US). **NUSS, John M.** [US/US]; 16 Woodranch Circle, Danville, CA 94506 (US). **PARKS, Jason Jevious** [US/US]; 4005 Cowell Blvd., Apt. 506, Davis, CA 95616 (US). **TAKEUCHI, Craig Stacy** [CA/US]; 1090 Carolan Avenue, Apt. 302, Burlingame, CA 94010 (US). **WANG, Yong** [CN/US]; 170 Harbor Way, South San Francisco, CA 94080 (US). **XU, Wei** [US/US]; 327 Glasgow Circle, Danville, CA 94526 (US).

(74) Agents: **GRIEDEL, Brian D.?** et al.; 170 Harbor Way, P.O. Box 511, South San Francisco, CA 94083-0511 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: C-MET MODULATORS AND METHODS OF USE

(57) Abstract: The present invention provides compounds for modulating protein kinase enzymatic activity for modulating cellular activities such as proliferation, differentiation, programmed cell death, migration and chemoinvasion. More specifically, the invention provides quinazolines and quinolines which inhibit, regulate and/or modulate kinase receptor, particularly c-Met, KDR, c-Kit, flt-3 and flt-4, signal transduction pathways related to the changes in cellular activities as mentioned above, compositions which contain these compounds, and methods of using them to treat kinase-dependent diseases and conditions. The present invention also provides methods for making compounds as mentioned above, and compositions which contain these compounds.

WO 2005/030140 A2

c-Met Modulators and Method of Use

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. provisional patent applications 60/506,181 filed on September 26, 2003, entitled "c-Met Modulators and Method of Use," naming Bannen, Lynne *et. al* as inventors, 60/535,377 filed on January 9, 2004, entitled "c-Met Modulators and Method of Use," naming Bannen, Lynne *et. al* as inventors and 60/577,384 filed on June 4, 2004, entitled "Synthesis of Quinoline and Quinazoline Kinase Modulators," naming Bannen, Lynne *et. al* as inventors; each of which is hereby incorporated by reference in its entirety for all purposes.

FIELD OF THE INVENTION

[0002] This invention relates to compounds for modulating protein kinase enzymatic activity for modulating cellular activities such as proliferation, differentiation, programmed cell death, migration and chemoinvasion. Even more specifically, the invention relates to quinazolines and quinolines which inhibit, regulate and/or modulate kinase receptor signal transduction pathways related to the changes in cellular activities as mentioned above, compositions which contain these compounds, methods of using them to treat kinase-dependent diseases and conditions, synthesis of the compounds as well as processes for formulating the compounds for pharmaceutical purposes.

BACKGROUND OF THE INVENTION

[0003] Improvements in the specificity of agents used to treat cancer is of considerable interest because of the therapeutic benefits which would be realized if the side effects associated with the administration of these agents could be reduced. Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms.

[0004] Protein kinases are enzymes that catalyze the phosphorylation of proteins, in particular, hydroxy groups on tyrosine, serine and threonine residues of proteins. The consequences of this seemingly simple activity are staggering; cell differentiation and proliferation; i.e., virtually all aspects of cell life in one-way or another depend on protein kinase activity. Furthermore, abnormal protein kinase activity has been related to a host of

disorders, ranging from relatively non-life threatening diseases such as psoriasis to extremely virulent diseases such as glioblastoma (brain cancer).

[0005] Protein kinases can be categorized as receptor type or non-receptor type. Receptor-type tyrosine kinases have an extracellular, a transmembrane, and an intracellular portion, while non-receptor type tyrosine kinases are wholly intracellular.

[0006] Receptor-type tyrosine kinases are comprised of a large number of transmembrane receptors with diverse biological activity. In fact, about 20 different subfamilies of receptor-type tyrosine kinases have been identified. One tyrosine kinase subfamily, designated the HER subfamily, is comprised of EGFR (HER1), HER2, HER3, and HER4. Ligands of this subfamily of receptors identified so far include epithelial growth factor, TGF-alpha, amphiregulin, HB-EGF, betacellulin and heregulin. Another subfamily of these receptor-type tyrosine kinases is the insulin subfamily, which includes INS-R, IGF-IR, and IR-R. The PDGF subfamily includes the PDGF-alpha and beta receptors, CSFIR, c-Kit and FLK-II. Then there is the FLK family, which is comprised of the kinase insert domain receptor (KDR), fetal liver kinase-1 (FLK-1), fetal liver kinase-4 (FLK-4) and the fms-like tyrosine kinase-1 (flt-1). The PDGF and FLK families are usually considered together due to the similarities of the two groups. For a detailed discussion of the receptor-type tyrosine kinases, see Plowman et al., DN&P 7(6): 334-339, 1994, which is hereby incorporated by reference.

[0007] The non-receptor type of tyrosine kinases is also comprised of numerous subfamilies, including Src, Frk, Btk, Csk, Abl, Zap70, Fes/Fps, Fak, Jak, Ack, and LIMK. Each of these subfamilies is further sub-divided into varying receptors. For example, the Src subfamily is one of the largest and includes Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr, and Yrk. The Src subfamily of enzymes has been linked to oncogenesis. For a more detailed discussion of the non-receptor type of tyrosine kinases, see Bolen, Oncogene, 8:2025-2031 (1993), which is hereby incorporated by reference.

[0008] Since protein kinases and their ligands play critical roles in various cellular activities, deregulation of protein kinase enzymatic activity can lead to altered cellular properties, such as uncontrolled cell growth associated with cancer. In addition to oncological indications, altered kinase signaling is implicated in numerous other pathological diseases. These include, but are not limited to: immunological disorders, cardiovascular diseases, inflammatory diseases, and degenerative diseases. Therefore,

both receptor and non-receptor protein kinases are attractive targets for small molecule drug discovery.

[0009] One particularly attractive goal for therapeutic use of kinase modulation relates to oncological indications. For example, modulation of protein kinase activity for the treatment of cancer has been demonstrated successfully with the FDA approval of Gleevec® (imatinib mesylate, produced by Novartis Pharmaceutical Corporation of East Hanover, NJ) for the treatment of Chronic Myeloid Leukemia (CML) and gastrointestinal stroma cancers (GIST). Gleevec is a c-Kit and Abl kinase inhibitor.

[0010] Modulation (particularly inhibition) of cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. Drug Disc Technol 2001 6, 1005-1024), is an attractive goal for development of small-molecule drugs. Anti-angiogenic therapy represents a potentially important approach for the treatment of solid tumors and other diseases associated with dysregulated vascularization, including ischemic coronary artery disease, diabetic retinopathy, psoriasis and rheumatoid arthritis. As well, cell antiproliferative agents are desirable to slow or stop the growth of tumors.

[0011] One particularly attractive target for small-molecule modulation, with respect to antiangiogenic and antiproliferative activity is c-Met. The kinase, c-Met, is the prototypic member of a subfamily of heterodimeric receptor tyrosine kinases (RTKs) which include Met, Ron and Sea. Expression of c-Met occurs in a wide variety of cell types including epithelial, endothelial and mesenchymal cells where activation of the receptor induces cell migration, invasion, proliferation and other biological activities associated with "invasive cell growth." As such, signal transduction through c-Met receptor activation is responsible for many of the characteristics of tumor cells.

[0012] The endogenous ligand for c-Met is the hepatocyte growth factor (HGF), a potent inducer of angiogenisis, also known as "scatter factor" (SF). Binding of HGF to c-Met induces activation of the receptor via autophosphorylation resulting in an increase of receptor dependent signaling, which promotes cell growth and invasion. Anti-HGF antibodies or HGF antagonists have been shown to inhibit tumor metastasis *in vivo* (See: Maulik et al Cytokine & Growth Factor Reviews 2002 13, 41-59).

[0013] Tumor growth progression requires the recruitment of new blood vessels into the tumor from preexisting vessels as well as invasion, adhesion and proliferation of malignant cells. Accordingly, c-Met overexpression has been demonstrated on a wide

variety of tumor types including breast, colon, renal, lung, squamous cell myeloid leukemia, hemangiomas, melanomas, astrocytomas, and glioblastomas. Additionally activating mutations in the kinase domain of c-Met have been identified in hereditary and sporadic renal papilloma and squamous cell carcinoma. (See: Maulik et al Cytokine & growth Factor reviews 2002 13, 41-59; Longati et al Curr Drug Targets 2001, 2, 41-55; Funakoshi et al Clinica Chimica Acta 2003 1-23). Thus modulation of c-Met is desirable as a means to treat cancer and cancer-related disease.

[0014] The Eph receptors comprise the largest family of receptor tyrosine kinases and are divided into two groups, EphA and EphB, based on their sequence homology. The ligands for the Eph receptors are ephrin, which are membrane anchored. Ephrin A ligands bind preferentially to EphA receptors whilst ephrin B ligands bind to EphB receptors. Binding of ephrin to Eph receptors causes receptor autophosphorylation and typically requires a cell-cell interaction since both receptor and ligand are membrane bound.

[0015] Overexpression of Eph receptors has been linked to increased cell proliferation in a variety of tumors (Zhou R 1998 Pharmacol Ther. 77, 151-181; Kiyokawa E, Takai S, Tanaka M et al 1994 Cancer Res 54, 3645-3650; Takai N Miyazaki T, Fujisawa K, Nasu K and Miyakawa. 2001 Oncology reports 8, 567-573). The family of Eph receptor tyrosine kinases and their ephrin ligands play important roles in a variety of processes during embryonic development and also in pathological angiogenesis and potentially metastasis. Therefore modulation of Eph receptor kinase activity should provide means to treat or prevent disease states associated with abnormal cell proliferation such as those described above.

[0016] Inhibition of EGF, VEGF and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. Drug Disc. Technol. 2001 6, 1005-1024). EGF and VEGF receptors are previously described targets for small molecule inhibition. KDR and flt-4 are both VEGF receptors

[0017] One particularly attractive target for small-molecule modulation is c-Kit. The proto-oncogene *c-Kit* was first identified as the oncogenic component of the acutely transforming Hardy-Zuckerman 4-feline sarcoma virus (Besmer et al Nature 1986 320:415-421). c-Kit (also called stem cell factor receptor or steel factor receptor) is a type 3 receptor tyrosine kinase (RTK) belonging to the platelet-derived growth factor receptor subfamily. c-Kit binds the ligand stem cell factor (SCF), and triggers its multiple signal

transduction pathways including Src family kinases, phosphatidyl-inositol 3 kinase, the Ras-Raf-Map kinase cascade, and phospholipase C (Broudy et al Blood 1999 94: 1979-1986; Lennartsson et al Oncogene 1999 18: 5546-5553 ; Timokhina et al EMBO J 1998 17;6250-6262; Chian et al Blood 2001 98(5)1365-1373; Blume-Jensen et al Curr Biol 1998 8:779-782; Kissel et al EMBO J 2000 19:1312-1326; Lennartsson et al. Oncogene 1999 18: 5546-5553; Sue et al Blood, 199892:1242-1149; Lev etal EMBO J 1991 10:647-654). c-Kit is required for normal hematopoiesis, melanonogenesis, and gametogenesis. c-Kit is expressed in mast cells, immature myeloid cells, melanocytes, epithelial breast cells and the interstitial cells of Cajal (ICC). In mast cells, it is required not only for the differentiation, maturation, chemotaxis, and haptotaxis but also for the promotion of survival and proliferation.

[0018] Mutations in c-Kit have been implicated in human disease. Mutations in the juxtamembrane domain are found in many human gastrointestinal stromal tumors, and mutations in the kinase domain are found in mastocytosis, germ cell tumors, acute myeloid leukemia (AML), NK lymphoma, and other hematologic disorders (Hirota et al Science 1998 279:577-580; Singer et al J Clin Oncol 2002 203898-3905; Longley et al Proc Natl Aca Sci USA 1999: 1609-1614; Tian et al Am J Pathol 1999 154: 1643-1647; Beghini et al Blood 2000 95:726-727; Hongyo et al Cancer Res 2000 60:2345-2347). These mutations result in ligand-independent tyrosine kinase activity, autophosphorylation of c-Kit, uncontrolled cell proliferation, and stimulation of downstream signaling pathways. Overexpression of c-Kit and c-Kit ligand have also been described in other tumors including small-cell lung cancer, neuroblastomas, gynecological tumors, and colon carcinoma, which might result in autocrine or paracrine c-Kit activation.

[0019] The overexpression of c-Kit has also been implicated in the development of neoplasia associated with neurofibromatosis type 1 (NF1). Mutations in the tumor suppressor gene *NF1* lead to a deficiency in neurofibromin, a GTPase-activating protein for Ras. This deficiency results in abnormal proliferation of Schwann cells in the peripheral nervous system, and predisposes affected individuals to peripheral nerve sheath tumors (neurofibromas), astrocytomas (optic pathway gliomas), learning disabilities, seizures, strokes, macrocephaly, vascular abnormalities, and juvenile myelomonocytic leukemia (Lynch & Gutmann Neurol Clin 2002 20:841-865). Genetic experiments in mice demonstrate that haploinsufficiency at *NF1* partially rescues some of the phenotypes associated with mutations in the gene for c-Kit, indicating that these genes function along

a common developmental pathway (Ingram, et al. J. Exp Med 2000 191:181-187). Also, c-Kit is expressed in schwannoma cells from NF1 patients, but not in normal schwann cells (Ryan et al. J Neurosci Res 1994 37:415-432). These data indicate that elevated c-Kit expression and sensitivity to stem cell factor may play important roles in the development of proliferative disorders associated with NF-1. Therefore, c-Kit inhibitors may be effective chemotherapeutic agents for treating patients with NF-1.

[0020] GISTs are the most common mesenchymal tumors of the gastrointestinal tract, and they are generally resistant to chemotherapy and radiation therapy. However, recent results with the c-Kit/BCR-Abl inhibitor STI571 indicate that targeting c-Kit may be an effective therapeutic strategy for this disease (Eisenberg & Mehren Expert Opin Pharmacother 2003 4:869-874). Malignant mast cell disease often suggests an extremely poor prognosis, and no reliable effective chemotherapeutic agents have been identified (Marone et al Leuk Res 2001 25:583-594). Systemic mast cell disorders have been treated with interferon-alpha, although the effectiveness of this therapy has been variable (Lehmann & Lammle Ann Hematol 1999 78:483-484; Butterfield Br J Dermatol 1998 138: 489-495). Therefore, activated c-Kit might serve as a therapeutic target in GISTs and mast cell disease, as well as other disorders associated with activated c-Kit.

[0021] Flt-3 is normally expressed on hematopoietic progenitor cells and a subset of mature myeloid and lymphoid cells, where it modulates cell survival and proliferation. Flt-3 is constitutively activated via mutation, either in the juxtamembrane region or in the activation loop of the kinase domain, in a large proportion of patients with AML (Reilly Leuk Lymphoma 2003 44: 1-7). Also, mutations in flt-3 are significantly correlated with poor prognosis in AML patients (Sawyers Cancer Cell 2002 1: 413-415).

[0022] Accordingly, the identification of small-molecule compounds that specifically inhibit, regulate and/or modulate the signal transduction of kinases, particularly including c-Met, KDR, c-Kit, flt-3, and flt-4, is desirable as a means to treat or prevent disease states associated with abnormal cell proliferation and angiogenesis, and is an object of this invention.

[0023] Quinolines and quinazolines bearing substitution, for example at the two, four, six and seven positions of their fused ring system have been shown to be particularly attractive targets for kinase inhibition by a number of groups. Conventional quinoline and quinazoline kinase inhibitors typically have fairly simple substitution about the quinoline or quinazoline fused ten-membered ring system, but recently more complex molecules are

being disclosed. For example, we have previously disclosed, in U.S. provisional patent applications 60/506,181 and 60/535,377 which are both incorporated by reference herein in their entirety for all purposes, that certain quinolines and quinazolines are particularly well suited as kinase modulators, more particularly inhibitors of for example c-Met, KDR, c-Kit, flt-3, and flt-4. These molecules in some cases are particularly complex and although they can be made via conventional methods, more efficient routes are desirable, especially in a pharmaceutical setting.

[0024] Conventional methods of making quinolines and quinazolines with the aforementioned substitution patterns usually involve linear construction of a quinoline or quinazoline template upon which relatively simple substitutions are appended. With the advent of more complex substitution about such quinolines and quinazolines (*vide supra*), for example side chains containing cyclic and bicyclic systems with multiple functional groups, conventional methods of synthesis become problematic due to the linear or serial reactions used. Indeed, as such molecules become more complex and the utility of such complex groups is realized, the quinoline and quinazoline ring system becomes more of a sub-structure than a main structure of such inhibitors. Thus it is desirable to find more efficient methods of synthesis, particularly convergent syntheses which are an object of this invention.

SUMMARY OF THE INVENTION

[0025] In one aspect, the present invention provides compounds for modulating kinase activity and methods of treating diseases mediated by kinase activity utilizing the compounds and pharmaceutical compositions thereof. Diseases mediated by kinase activity include, but are not limited to, diseases characterized in part by migration, invasion, proliferation and other biological activities associated with invasive cell growth. In particular to this invention is modulation, even more particularly inhibition, of c-Met, KDR, c-Kit, flt-3, and flt-4.

[0026] In another aspect, the invention provides methods of screening for modulators of c-Met, KDR, c-Kit, flt-3, and flt-4 activity. The methods comprise combining a composition of the invention, a kinase, e.g. c-Met, KDR, c-Kit, flt-3, or flt-4, and at least one candidate agent and determining the effect of the candidate agent on the c-Met, KDR, c-Kit, flt-3, or flt-4, activity.

[0027] In yet another aspect, the invention also provides pharmaceutical kits comprising one or more containers filled with one or more of the ingredients of pharmaceutical

compounds and/or compositions of the present invention, including, one or more kinase, e.g. c-Met, KDR, c-Kit, flt-3, or flt-4, enzyme activity modulators as described herein. Such kits can also include, for example, other compounds and/or compositions (e.g., diluents, permeation enhancers, lubricants, and the like), a device(s) for administering the compounds and/or compositions, and written instructions in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which instructions can also reflects approval by the agency of manufacture, use or sale for human administration.

[0028] In another aspect, the invention also provides a diagnostic agent comprising a compound of the invention and, optionally, pharmaceutically acceptable adjuvants and excipients.

[0029] In still yet another aspect, the present invention provides processes for making compounds, and pharmaceutical compositions thereof, for modulating kinase activity and treating diseases mediated by kinase activity. In particular to this invention are methods for making quinolines and quinazolines used for modulation of kinase activity, even more particularly inhibition of kinase activity, and yet even more particularly inhibition of c-Met, KDR, c-Kit, flt-3, and flt-4.

[0030] These and other features and advantages of the present invention will be described in more detail below with reference to the associated drawings.

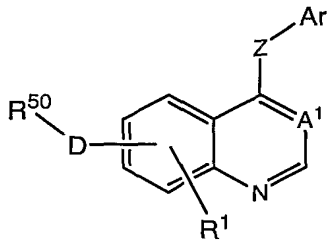
DETAILED DESCRIPTION OF THE INVENTION

[0031] The compositions of the invention are used to treat diseases associated with abnormal and or unregulated cellular activities. Disease states which can be treated by the methods and compositions provided herein include, but are not limited to, cancer (further discussed below), immunological disorders such as rheumatoid arthritis, graft-host diseases, multiple sclerosis, psoriasis; cardiovascular diseases such as artheroscrosis, myocardioinfarction, ischemia, stroke and restenosis; other inflammatory and degenerative diseases such as interbowel diseases, osteoarthritus, macular degeneration, diabetic retinopathy.

[0032] It is appreciated that in some cases the cells may not be in a hyper- or hypo-proliferative and/or migratory state (abnormal state) and still require treatment. For example, during wound healing, the cells may be proliferating "normally", but

proliferation and migration enhancement may be desired. Alternatively, reduction in "normal" cell proliferation and/or migration rate may be desired.

[0033] Thus, in one aspect the present invention comprises a compound for modulating kinase activity according to Formula **I**,



I

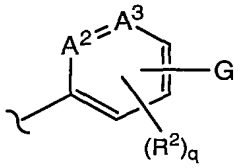
or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein,

R^1 is selected from -H, halogen, $-OR^3$, $-NO_2$, $-NH_2$, $-NR^3R^4$, and optionally substituted lower alkyl;

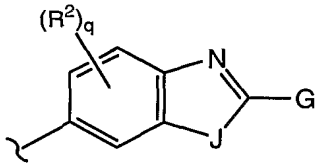
A^1 is selected from =N-, =C(H)-, and =C(CN)-;

Z is selected from $-S(O)_{0-2}-$, -O-, and $-NR^5-$;

Ar is either a group of formula **II**, or of formula **III**,



II



III

wherein,

R^2 is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted lower alkyl;

q is 0 to 4;

G is a group -B-L-T, wherein

B is selected from absent, $-N(R^{13})-$, $-N(SO_2R^{13})-$, -O-, $-S(O)_{0-2}-$, and -C(=O)-;

L is selected from absent, $-C(=S)N(R^{13})-$, $-C(=NR^{14})N(R^{13})-$, $-SO_2N(R^{13})-$, $-SO_2-$, $-C(=O)N(R^{13})-$, $-N(R^{13})-$, $-C(=O)C_{1-2}alkylN(R^{13})-$, $-N(R^{13})C_{1-2}alkylC(=O)-$, $-C(=O)C_{0-1}alkylC(=O)N(R^{13})-$, $-C_{0-4}alkylene-$, $-C(=O)C_{0-1}alkylC(=O)OR^3-$,

$-C(=NR^{14})C_{0-1}alkylC(=O)-$, $-C(=O)-$, $-C(=O)C_{0-1}alkylC(=O)-$, and an optionally substituted four to six-membered heterocyclyl containing between one and three annular heteroatoms including at least one nitrogen; and

T is selected from -H, $-R^{13}$, $-C_{0-4}alkyl$, $-C_{0-4}alkylQ$, $-OC_{0-4}alkylQ$, $-C_{0-4}alkylOQ$, $-N(R^{13})C_{0-4}alkylQ$, $-SO_2C_{0-4}alkylQ$, $-C(=O)C_{0-4}alkylQ$, $-C_{0-4}alkylN(R^{13})Q$, and $-C(=O)N(R^{13})C_{0-4}alkylQ$, wherein each of the aforementioned $C_{0-4}alkyl$ is optionally substituted;

J is selected from $-S(O)_{0-2}-$, -O-, and $-NR^{15}-$;

R^3 is -H or R^4;

R^4 is selected from optionally substituted lower alkyl, optionally substituted aryl, optionally substituted lower arylalkyl, optionally substituted heterocyclyl, and optionally substituted lower heterocyclylalkyl; or

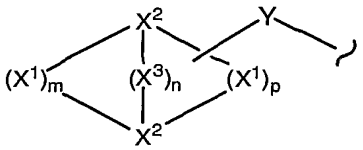
R^3 and R^4, when taken together with a common nitrogen to which they are attached, form an optionally substituted five- to seven-membered heterocyclyl, said optionally substituted five- to seven-membered heterocyclyl optionally containing at least one additional annular heteroatom selected from N, O, S, and P;

A^2 and A^3 are each independently selected from $=N-$, $=C(R^2)-$;

R^5 is -H or optionally substituted lower alkyl;

D is selected from -O-, $-S(O)_{0-2}-$, and $-NR^{15}-$;

R^{50} is either R^3, or according to formula **IV**;



IV

wherein X^1, X^2, and optionally X^3, represent the atoms of a saturated bridged ring system, said saturated bridged ring system comprising up to four annular heteroatoms represented by any of X^1, X^2, and X^3; wherein,

each X^1 is independently selected from $-C(R^6)R^7-$, -O-, $-S(O)_{0-2}-$, and $-NR^8-$;

each X^2 is independently an optionally substituted bridgehead methine or a bridgehead nitrogen;

each X^3 is independently selected from $-C(R^6)R^7-$, -O-, $-S(O)_{0-2}-$, and $-NR^8-$;

Y is either:

an optionally substituted lower alkylene linker, between D and either 1) any annular atom of the saturated bridged ring system, except X^2 when X^2 is a bridgehead nitrogen, or 2) any heteroatom, represented by any of R^6 or R^7; provided there are at least two carbon atoms between D and any annular heteroatom of the saturated bridged ring system or any heteroatom represented by any of R^6 or R^7;

or Y is absent, when Y is absent, said saturated bridged ring system, is directly attached to D via an annular carbon of said saturated bridged ring system, unless D is $-SO_2-$, in which case said saturated bridged ring system, is directly attached to D via an any annular atom of said saturated bridged ring system;

m and p are each independently 1-4;

n is 0-2, when n = 0, then there is a single bond between the two bridgehead X^2's;

R^6 and R^7 are each independently selected from -H, halogen, trihalomethyl, -CN, $-NH_2$, $-NO_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^4$, $-SO_2NR^3R^4$, $-CO_2R^3$, $-C(O)NR^3R^4$, $-N(R^3)SO_2R^4$, $-N(R^3)C(O)R^3$, $-NCO_2R^3$, $-C(O)R^3$, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted lower arylalkyl, optionally substituted heterocyclyl, optionally substituted lower heterocyclylalkyl, and a bond to either Y or D; or

R^6 and R^7, when taken together are oxo; or

R^6 and R^7, when taken together with a common carbon to which they are attached, form a optionally substituted three- to seven-membered spirocyclyl, said optionally substituted three- to seven-membered spirocyclyl optionally containing at least one additional annular heteroatom selected from N, O, S, and P;

R^8 is selected from $-R^3$, Y, $-SO_2NR^3R^4$, $-CO_2R^4$, $-C(O)NR^3R^3$, $-SO_2R^4$, and $-C(O)R^3$;

R^{13} is selected from -H, $-C(=O)R^3$, $-C(=O)OR^3$, $-C(=O)SR^3$, $-SO_2R^4$, $-C(=O)N(R^3)R^3$, and optionally substituted lower alkyl,

two R^{13}, together with the atom or atoms to which they are attached, can combine to form a heteroalicyclic optionally substituted with between one and four of R^{60}, said heteroalicyclic can have up to four annular heteroatoms, and said heteroalicyclic can have an aryl or heteroaryl fused thereto, in which case said aryl or heteroaryl is optionally substituted with an additional one to four of R^{60};

R^{14} is selected from -H, $-NO_2$, $-NH_2$, $-N(R^3)R^4$, -CN, $-OR^3$, optionally substituted lower alkyl, optionally substituted heteroalicyclylalkyl, optionally substituted aryl, optionally substituted arylalkyl and optionally substituted heteroalicyclic;

R^{15} is a group $-M^1-M^2$, wherein M^1 is selected from absent, $-C(=S)N(R^{13})-$, $-C(=NR^{14})N(R^{13})-$, $-SO_2N(R^{13})-$, $-SO_2-$, $-C(=O)N(R^{13})-$, $-C(=O)C(=O)N(R^{13})-$, $-C_{0-4}$alkylene-, -C(=O)-, and an optionally substituted four to six-membered hetercyclyl annular containing between one and three heteratoms including at least one nitrogen; and M^2 is selected from -H, $-C_{0-6}$alkyl, alkoxy, $-C(=O)C_{0-4}$alkylQ, $-C_{0-4}$alkylQ, $-OC_{0-4}$alkylQ-, $-N(R^{13})C_{0-4}$alkylQ-, and $-C(=O)N(R^{13})C_{0-4}$alkylQ; and

Q is a five- to ten-membered ring system, optionally substituted with between zero and four of R^{20};

R^{20} is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted lower alkyl;

R^{60} is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted heteroarylalkyl, and optionally substituted arylalkyl;

two of R^{60}, when attached to a non-aromatic carbon, can be oxo;

with the proviso, only when Ar is according to formula **II**, if Y is a C_{1-6} alkylene; Z is -NH- or $-N(CH_3)-$; R^1 is a C_{1-6}alkyl optionally substituted in the 2-position by -OH or a C_{1-4}alkoxy group; R^2 is -H or halogen; n = 0; and the atoms, X^1, of one bridge of the saturated bridged ring system, when combined with both bridgehead atoms, X^2, of the saturated bridged ring system, represent:

1) either a pyrrolidine or a piperidine, and any atom, X^1 or X^2, of either of said pyrrolidine or said piperidine is attached to Y, then the other bridge of said saturated bridged ring system cannot be any one of $-OC(O)CH_2-$,

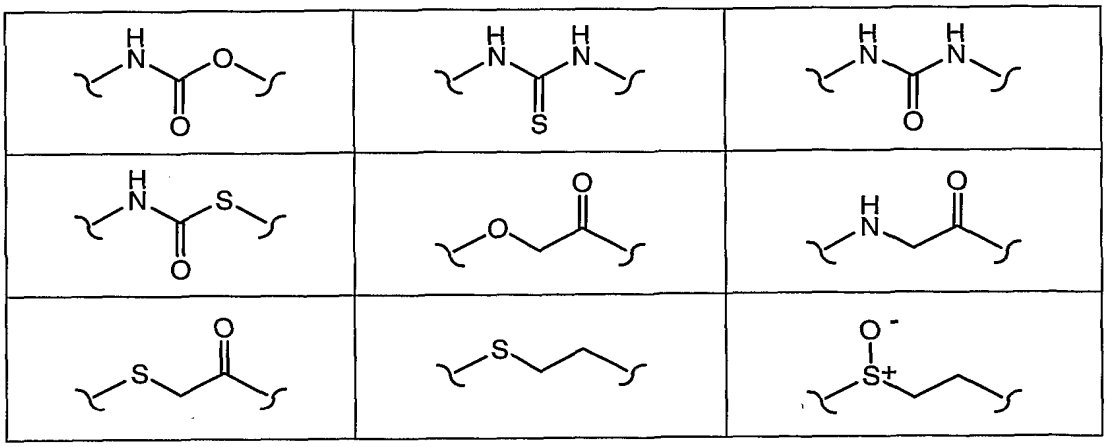
$-CH_2OC(O)-$, $-OC(O)CH_2CH_2-$, $-CH_2OC(O)CH_2-$, $-CH_2CH_2OC(O)-$, $-OC(O)CH_2NH-$, $-OC(O)CH_2N(C_{1-4}alkyl)-$, and $-OC(O)CH_2O-$; or

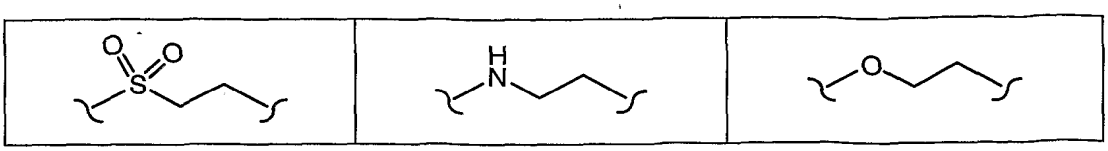
2) either a piperazine or a 4-(C_{1-4}alkyl)-piperazine, and any atom, X^1 or X^2, of either of said piperazine or said 4-(C_{1-4}alkyl)-piperazine is attached to Y, then the other bridge of said saturated bridged ring system, only when attached via the 2- and the 3-position of either of said piperazine or said 4-(C_{1-4}alkyl)-piperazine, cannot be one of $-CH_2OC(O)CH_2-$, $-CH_2CH_2OC(O)-$, and either of the two aforementioned bridges optionally substituted by one or two C_{1-2}alkyl groups; or

3) a piperazine, and any atom, X^1 or X^2, of said piperazine is attached to Y, then the other bridge of said saturated bridged ring system, only when attached via the 3- and the 4-position of said piperazine, cannot be one of $-C(O)OCH_2CH_2-$, $-CH_2OC(O)CH_2-$, and either of the two aforementioned bridges optionally substituted by one or two C_{1-2}alkyl groups, and only when either of the two aforementioned bridges are attached to the 3-position of said piperazine via their left-hand end as depicted above; or

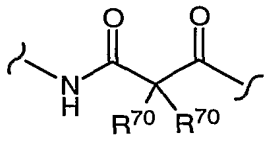
4) a 2-oxomorpholine, said 2-oxomorpholine attached to Y via its 4-position, then the other bridge of said saturated bridged ring system, only when attached via the 5- and the 6-position of said 2-oxomorpholine, cannot be one of $-(CH_2)_g-$, $-CH_2WCH_2-$, $-CH_2WCH_2CH_2-$, and $-CH_2CH_2WCH_2-$, wherein W is -O-, $-S(O)_{0-2}-$, -NH-, or $-N(C_{1-4}alkyl)-$ wherein g is 2, 3, or 4;

and with the proviso that when Z is-O-, Ar is according to formula **II**, and the portion of G directly attached to Ar is selected from:



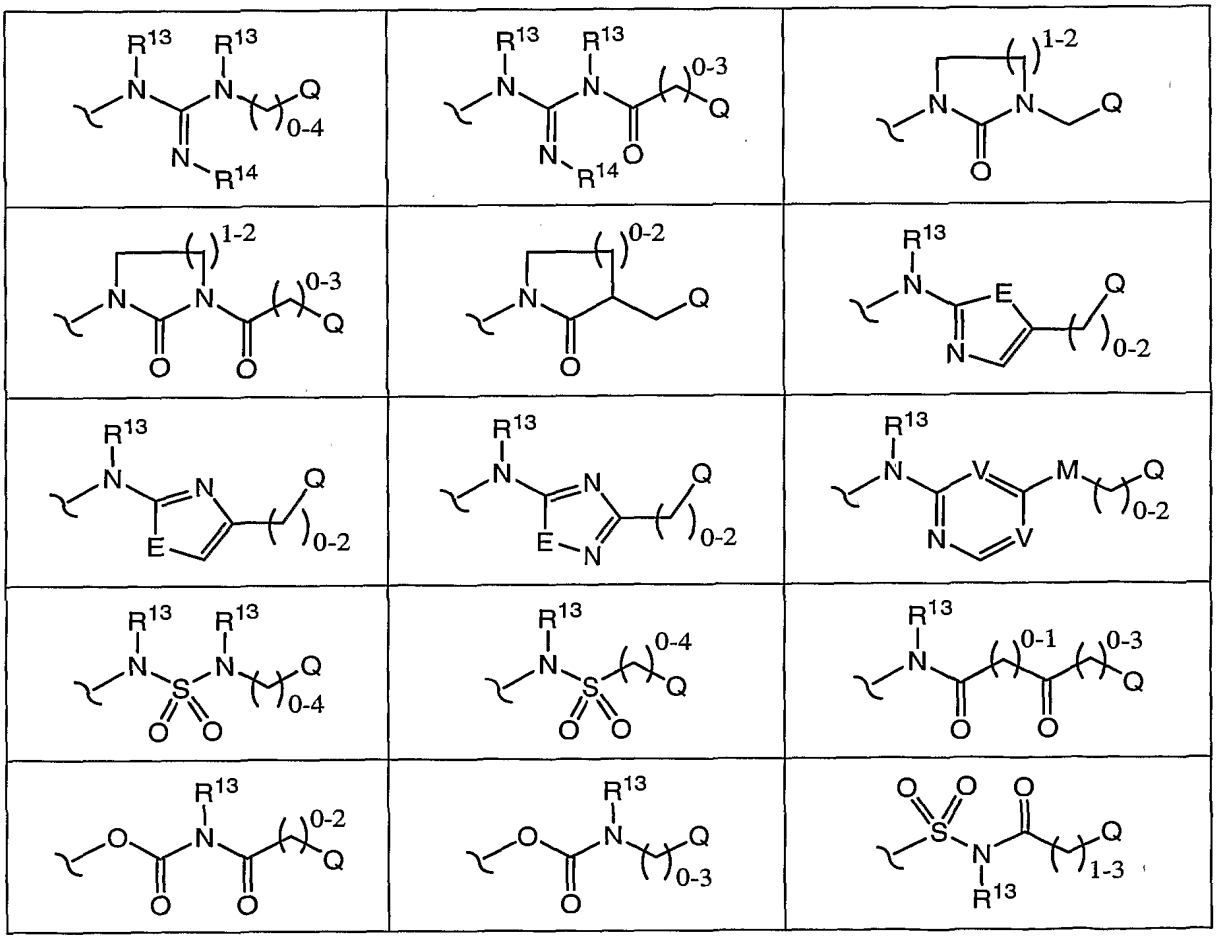


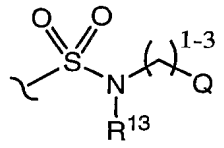
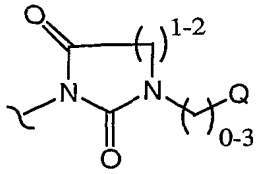
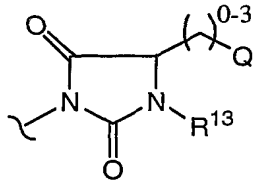
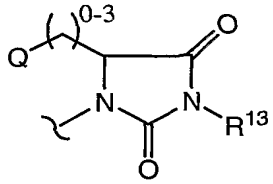
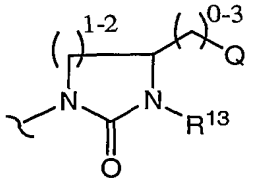
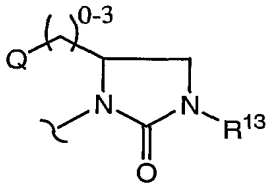
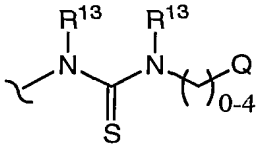
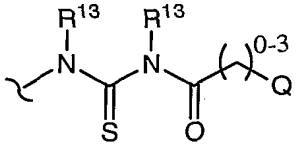
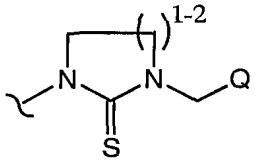
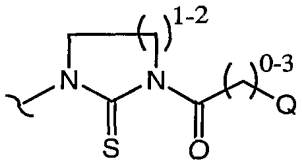
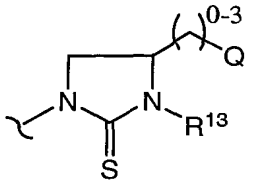
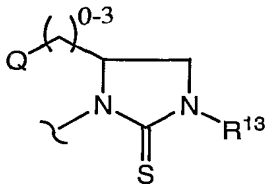
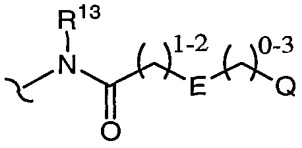
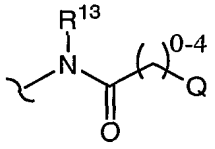
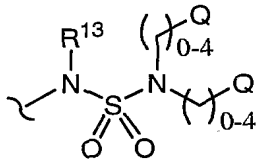
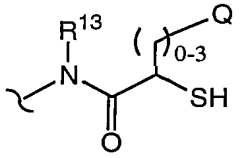
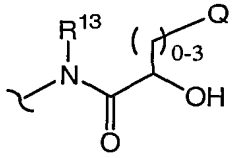
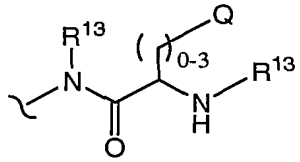
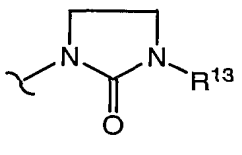
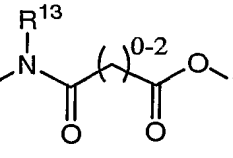
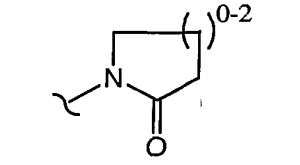
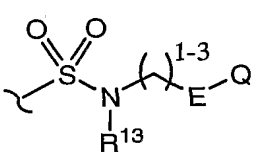
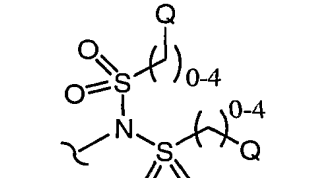
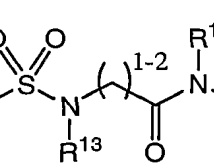
then R^{50} must be of formula **IV**;

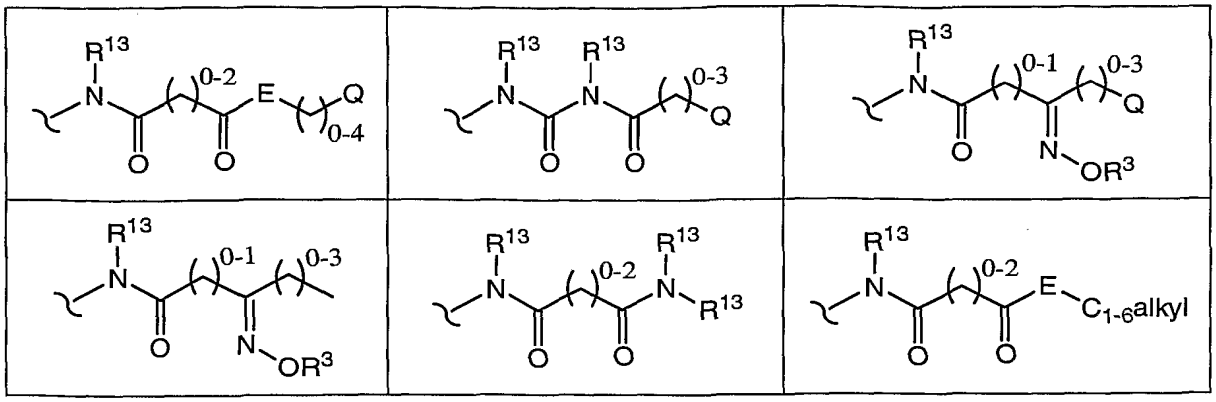
and with the proviso that when Ar is phenylene or substituted phenylene, Z is $-S(O)_{0-2}-$ or -O-, then the portion of G directly attached to Ar cannot contain  , when R^{70} is selected from -H, C_{1-4}alkyl, and C_{1-4}alkoxyl.

[0034] In one example, the compound is according to paragraph [0033], wherein Z is either -O- or $-NR^5-$.

[0035] In another example, the compound is according to paragraph [0034], wherein G is selected from the following:

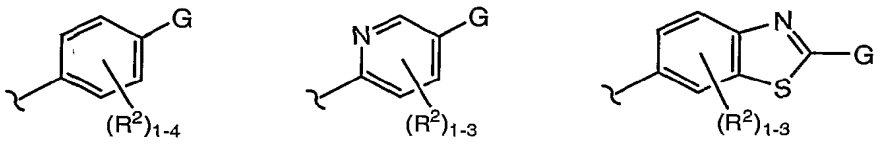




wherein wherein Q, R^{20}, and R^{13} are as defined above; each E is selected from -O-, -N(R^{13})-, -CH_2-, and -S(O)$_{0-2}$-; M is selected from -O-, -N(R^{13})-, -CH_2-, and -C(=O)N(R^{13})-; each V is independently either =N- or =C(H)-; each methylene in any of the above formulae is independently optionally substituted with R^{25}; and R^{25} is selected from halogen, trihalomethyl, -CN, -NO_2, -NH_2, -OR^3, -NR^3R^4, -S(O)$_{0-2}R^3$, -$SO_2NR^3R^3$, -CO_2R^3, -C(O)NR^3R^3, -N(R^3)SO_2R^3, -N(R^3)C(O)R^3, -N(R^3)CO_2R^3, -C(O)R^3, optionally substituted aryl, optionally substituted arylalkyl, heteroarylalkyl, and optionally substituted lower alkyl; two of R^{25}, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered alicyclic or heteroalicyclic, two of R^{25} on a single carbon can be oxo.

[0036] In another example, the compound is according to paragraph [0035], wherein Ar is according to one of formula **IIa**, **IIb**, and **IIIa**.



IIa **IIb** **IIIa**

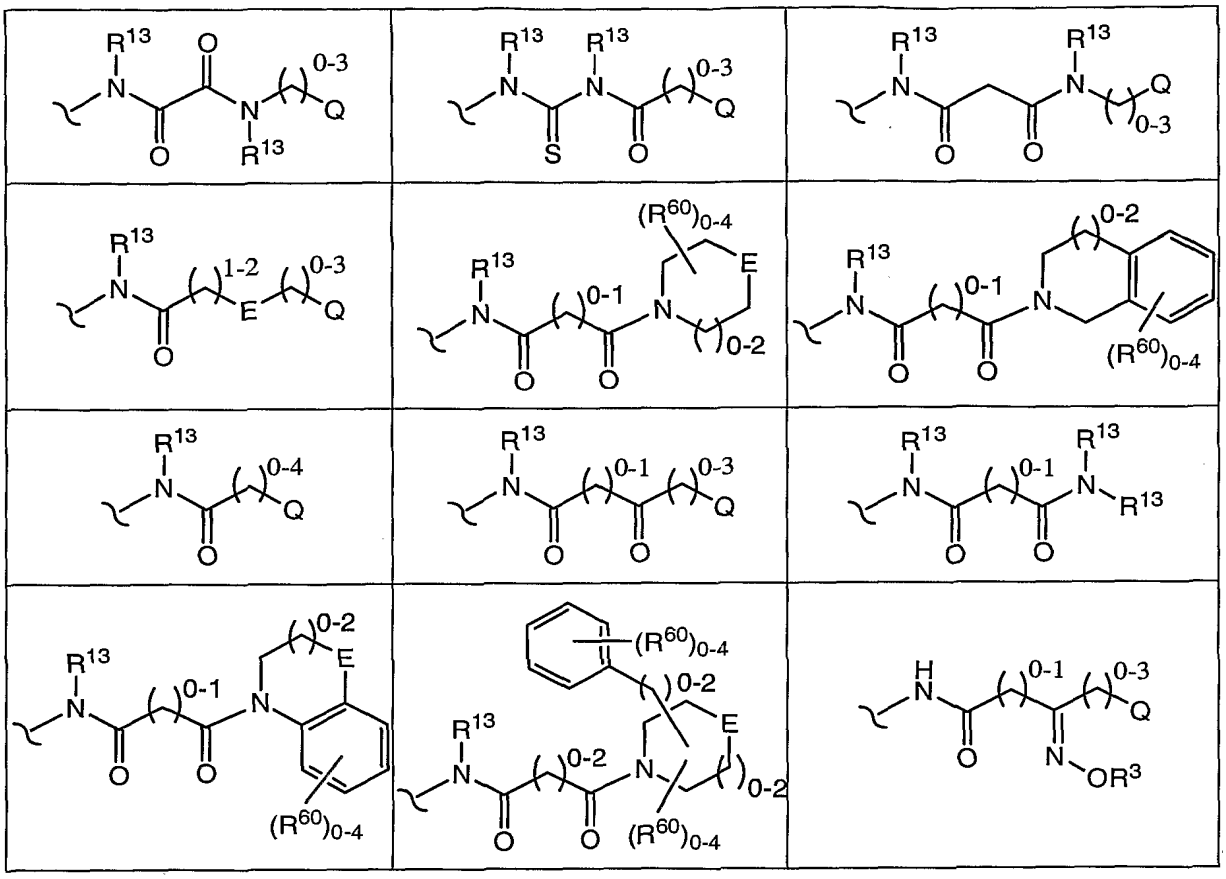
[0037] In another example, the compound is according to paragraph [0036], wherein D is -O- and R^1 is -OR^3.

[0038] In another example, the compound is according to paragraph [0037], wherein -O-R^{50} and R^1 are interchangeably located at the 6-position and 7-position of the quinazoline or quinoline according to formula **I**.

[0039] In another example, the compound is according to paragraph [0038], wherein R^1 is -OH or -OC_{1-6}alkyl.

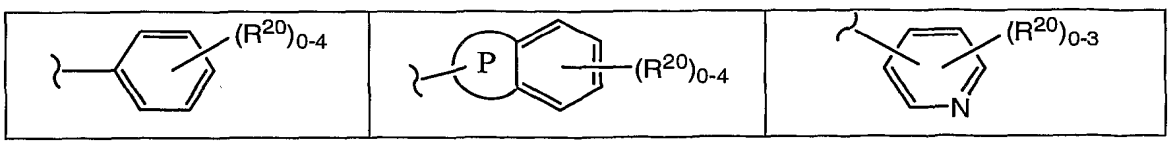
[0040] In another example, the compound is according to paragraph [0039], wherein A^1 is =N- or =C(H)-.

[0041] In another example, the compound is according to paragraph [0040], wherein G is selected from:



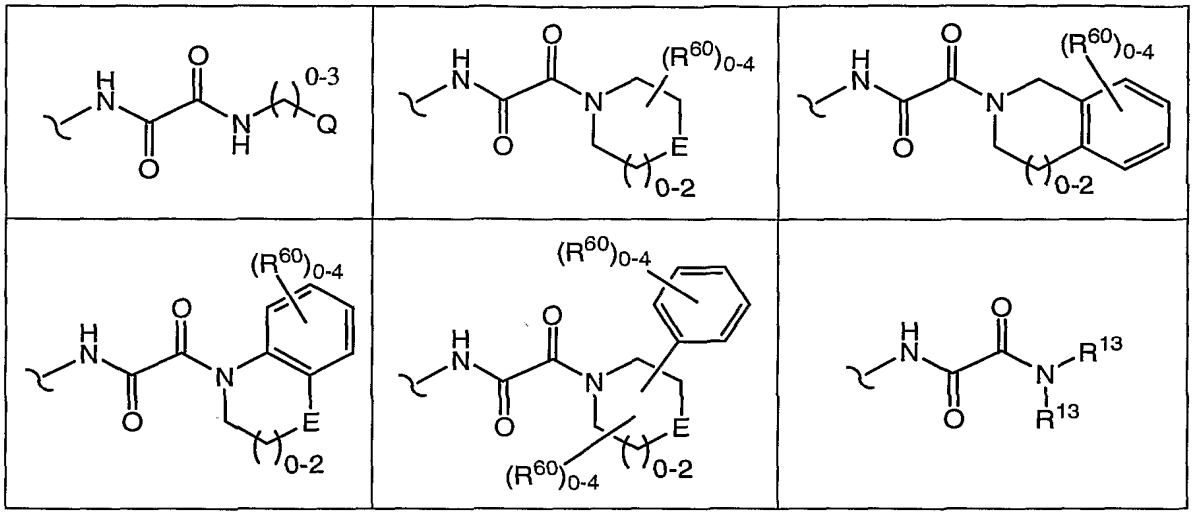
wherein Q, R^{20}, R^{13}, E, and R^{60} are as defined above; each methylene in any of the above formulae, other than those in a depicted ring, is independently optionally substituted with R^{25}; and R^{25} is selected from halogen, trihalomethyl, oxo, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted arylalkyl, heteroarylalkyl, and optionally substituted lower alkyl; two of R^{25}, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered alicyclic or heteroalicyclic.

[0042] In another example, the compound is according to paragraph [0041], wherein Q is selected from:



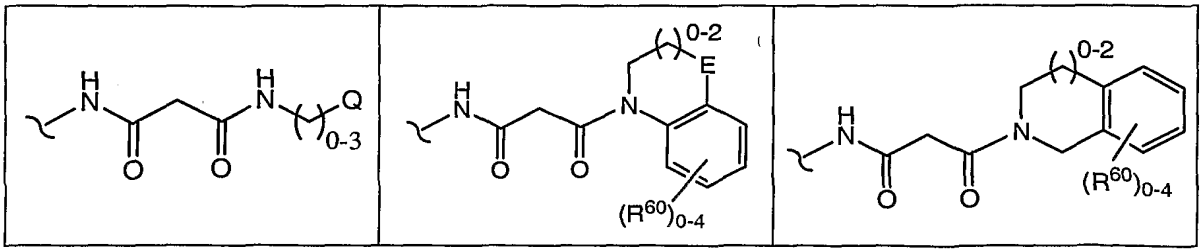
wherein R^{20} is defined as above, and P is a five- to seven-membered ring, including the two shared carbons of the aromatic ring to which P is fused, P optionally containing between one and three heteroatoms.

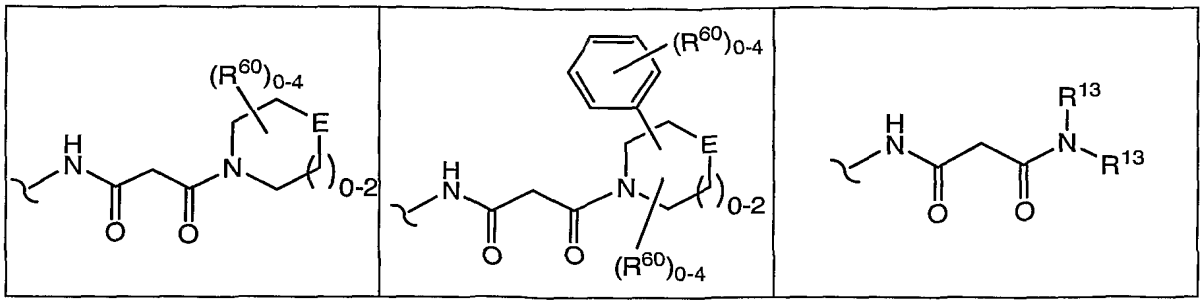
[0043] In another example, the compound is according to paragraph [0042], wherein Ar is according to formula **IIa**, and G is selected from:



wherein Q, R^{20}, R^{13}, E, and R^{60} are as defined above, and each methylene in any of the above formulae, other than those in a depicted ring, is independently optionally substituted with R^{25}; and R^{25} is selected from halogen, trihalomethyl, oxo, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted arylalkyl, heteroarylalkyl, and optionally substituted lower alkyl; two of R^{25}, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered alicyclic or heteroalicyclic.

[0044] In another example, the compound is according to paragraph [0042], wherein Ar is according to formula **IIb**, and G is selected from:





wherein Q, R^{20}, R^{13}, E, and R^{60} are as defined above, and each methylene in any of the above formulae, other than those depicted in a ring, is independently optionally substituted with R^{25}; and R^{25} is selected from halogen, trihalomethyl, oxo, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted arylalkyl, heteroarylalkyl, and optionally substituted lower alkyl; two of R^{25}, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered alicyclic or heteroalicyclic.

[0045] In another example, the compound is according to paragraph [0044], wherein the methylene between the two carbonyls of the depicted formulae is di-substituted with either optionally substituted lower alkyl, or an optionally substituted spirocycle.

[0046] In another example, the compound is according to either [0043] or paragraph [0044], wherein R^{50} is a heteroalicylic or a C_{1-6}alkyl-heteroalicylic.

[0047] In another example, the compound is according to paragraph [0046], wherein at least one of R^2 is halogen.

[0048] In another example, the compound is according to paragraph [0046], wherein R^{50} is according to formula **IV**.

[0049] In another example, the compound is according to paragraph [0048], wherein the saturated bridged ring system according to formula **IV** has a geometry selected from the group consisting of [4.4.0], [4.3.0], [4.2.0], [4.1.0], [3.3.0], [3.2.0], [3.1.0], [3.3.3], [3.3.2], [3.3.1], [3.2.2], [3.2.1], [2.2.2], and [2.2.1].

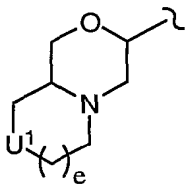
[0050] In another example, the compound is according to paragraph [0049], wherein Y is selected from $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2-$, $-CH_2-$, and absent.

[0051] In another example, the compound is according to paragraph [0050], wherein n is 0 and the saturated bridged ring system according to formula **IV** has a geometry selected from the group consisting of [4.4.0], [4.3.0], [4.2.0], [4.1.0], [3.3.0], [3.2.0], and [3.1.0].

[0052] In another example, the compound is according to paragraph [0051], wherein said saturated bridged ring system contains at least one annular nitrogen or at least one annular oxygen.

[0053] In another example, the compound is according to paragraph [0052], wherein said saturated bridged ring system contains $-NR^8-$, wherein R^8 is selected from -H, optionally substituted lower alkyl, $-CO_2R^3$, $-C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$.

[0054] In another example, the compound is according to paragraph [0052], wherein said saturated bridged ring system is of formula **V**,



V

wherein U^1 is selected from -O-, $-S(O)_{0-2}-$, $-NR^8-$, $-CR^6R^7-$, and absent; and e is 0 or 1.

[0055] In another example, the compound is according to paragraph [0054], wherein Y is $-CH_2-$.

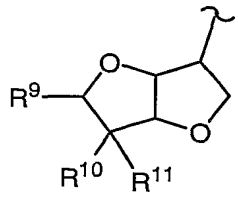
[0056] In another example, the compound is according to paragraph [0055], wherein U^1 is $-NR^8-$, wherein R^8 is selected from -H, optionally substituted lower alkyl, $-CO_2R^3$, $-C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$.

[0057] In another example, the compound is according to paragraph [0055], wherein U^1 is -O-.

[0058] In another example, the compound is according to paragraph [0055], wherein U^1 is absent.

[0059] In another example, the compound is according to paragraph [0052], wherein Y is selected from $-CH_2CH_2-$, $-CH_2-$, and absent.

[0060] In another example, the compound is according to paragraph [0059], wherein said saturated bridged ring system is of formula **VI**,



VI

wherein R^9, R^{10}, and R^{11} are each independently selected from -H, and $-OR^{12}$; or

R^9 is selected from -H, and $-OR^{12}$, and R^{10} and R^{11}, when taken together, are either an optionally substituted alkylidene or an oxo;

R^{12} is selected from -H, $-C(O)R^3$, optionally substituted lower alkylidyne, optionally substituted lower arylalkylidyne, optionally substituted lower heterocyclylalkylidyne, optionally substituted lower alkylidene, optionally substituted lower alkylidenearyl, optionally substituted lower alkylideneheterocyclyl, optionally substituted lower alkyl, optionally substituted lower alkylaryl, optionally substituted aryl, optionally substituted lower heterocyclylalkyl, and optionally substituted heterocyclyl;

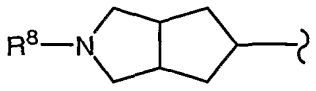
or two R^{12}'s, when taken together, form 1) a corresponding spirocyclic ketal when said two R^{12}'s stem from R^{10} and R^{11}, or 2) a corresponding cyclic ketal when said two R^{12}'s stem from R^9 and one of R^{10} and R^{11}.

[0061] In another example, the compound is according to paragraph [0060], wherein one of R^{10} and R^{11} is $-OR^{12}$, wherein R^{12} is selected from -H, $-C(O)R^3$, and optionally substituted lower alkyl; and R^9 and the other of R^{10} and R^{11} are both -H.

[0062] In another example, the compound is according to paragraph [0061], wherein Y is either $-CH_2-$ or absent.

[0063] In another example, the compound is according to paragraph [0062], wherein R^9 is an alkyl group containing at least one fluorine substitution thereon.

[0064] In another example, the compound is according to paragraph [0053], wherein said saturated bridged ring system is of formula **VII**.

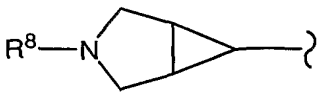


VII

[0065] In another example, the compound is according to paragraph [0064], wherein Y is either $-CH_2-$ or absent.

[0066] In another example, the compound is according to paragraph [0065], wherein R^8 is methyl or ethyl.

[0067] In another example, the compound is according to paragraph [0053], wherein said saturated bridged ring system is of formula **VIII**.

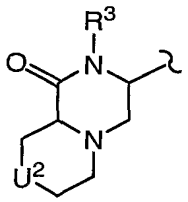


VIII

[0068] In another example, the compound is according to paragraph [0067], wherein Y is $-CH_2-$.

[0069] In another example, the compound is according to paragraph [0068], wherein R^8 is methyl or ethyl.

[0070] In another example, the compound is according to paragraph [0052], wherein said saturated bridged ring system is of formula **IX**



IX

wherein U^2 is selected from -O-, $-S(O)_{0-2}-$, $-NR^8-$, $-CR^6R^7-$, and absent.

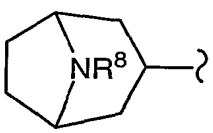
[0071] In another example, the compound is according to paragraph [0070], wherein R^3 of formula **IX** is selected from -H and optionally substituted alkyl.

[0072] In another example, the compound is according to paragraph [0071], wherein U^2 is either $-CR^6R^7-$ or absent.

[0073] In another example, the compound is according to paragraph [0072], wherein U^2 is either $-CH_2-$ or absent.

[0074] In another example, the compound is according to paragraph [0073], wherein Y is $-CH_2-$.

[0075] In another example, the compound is according to paragraph [0053], wherein said saturated bridged ring system is according to formula **X**.



X

[0076] In another example, the compound is according to paragraph [0075], wherein R^8 is methyl or ethyl.

[0077] In another example, the compound is according to paragraph [0033], selected from Table 1.

Table 1

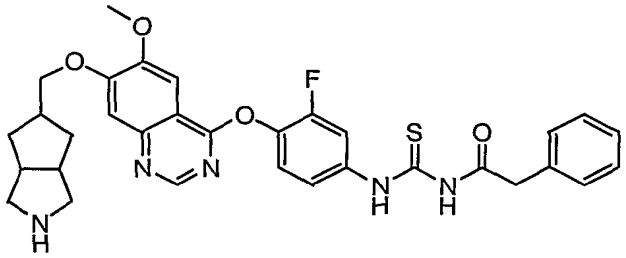
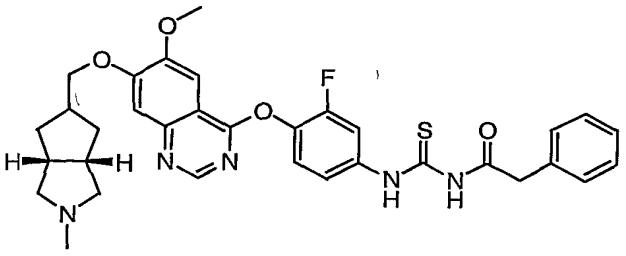
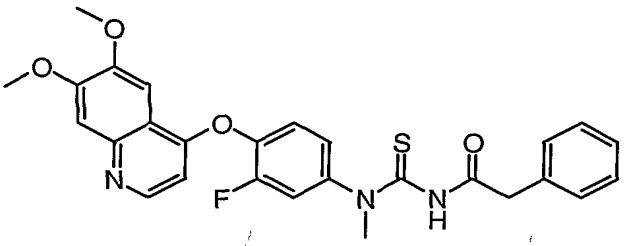
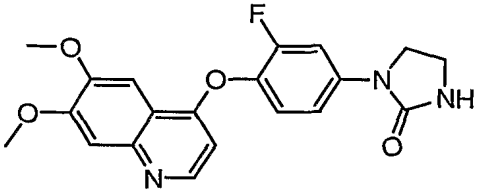
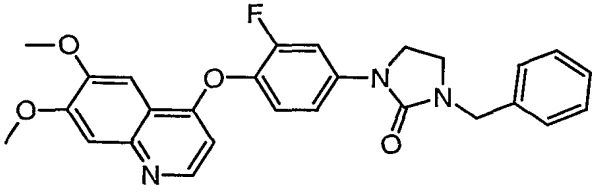
Entry	Name	Structure
1	N-[({3-fluoro-4-[(6-(methyloxy)-7-{[(3aR,6aS)-octahydrocyclopenta[c]pyrrol-5-ylmethyl]oxy}quinazolin-4-yl)oxy]phenyl}amino)carbonothioyl]-2-phenylacetamide	
2	N-{[(3-fluoro-4-{[7-({[(3aR,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-yl]oxy}phenyl)amino]carbonothioyl}-2-phenylacetamide	
3	N-{[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)(methyl)amino]carbonothioyl}-2-phenylacetamide	
4	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)imidazolidin-2-one	
5	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylmethyl)imidazolidin-2-one	

Table 1

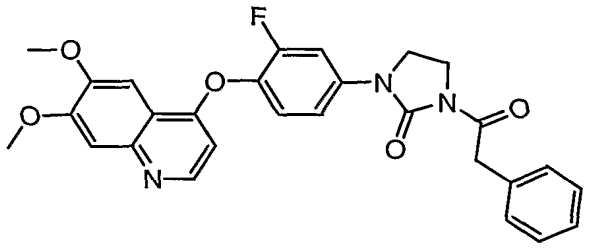
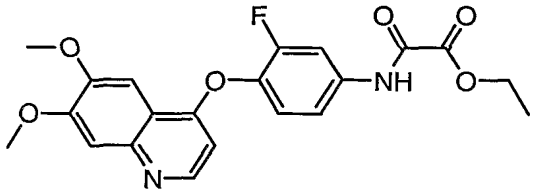
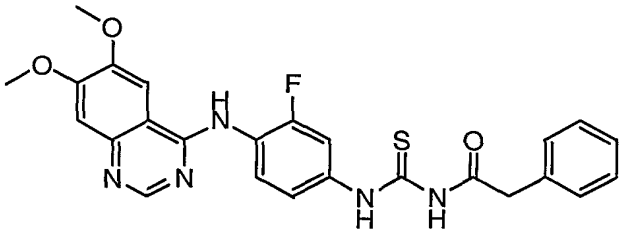
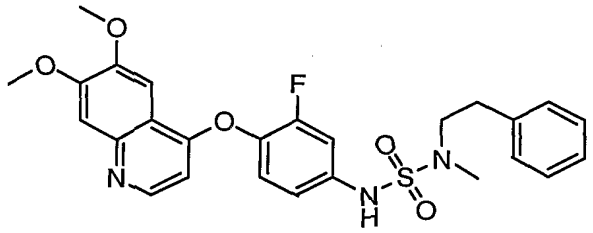
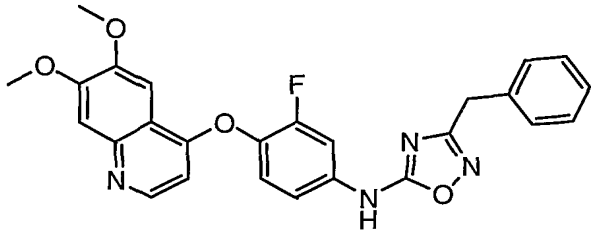
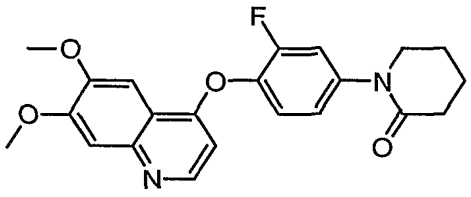
Entry	Name	Structure
6	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylacetyl)imidazolidin-2-one	
7	ethyl [(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)amino](oxo)acetate	
8	N-{[(4-{[6,7-bis(methyloxy)quinazolin-4-yl]amino}-3-fluorophenyl)amino]carbonothioyl}-2-phenylacetamide	
9	N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N-methyl-N-(2-phenylethyl)sulfamide	
10	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylmethyl)-1,2,4-oxadiazol-5-amine	
11	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)piperidin-2-one	

Table 1

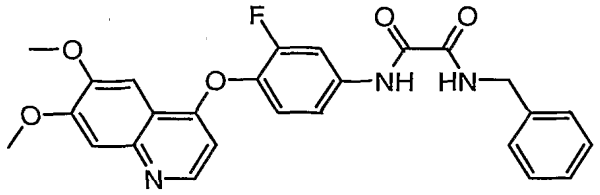
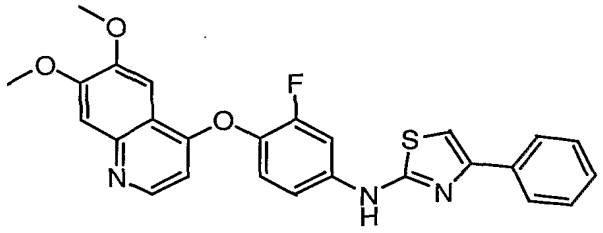
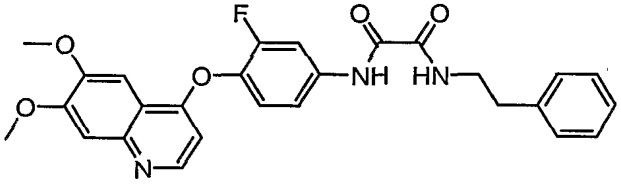
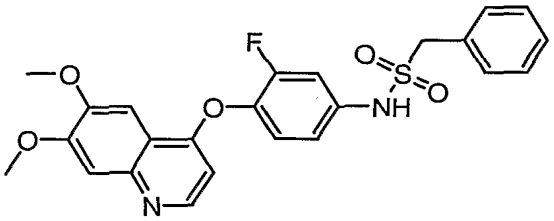
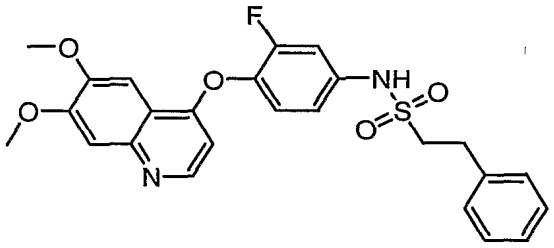
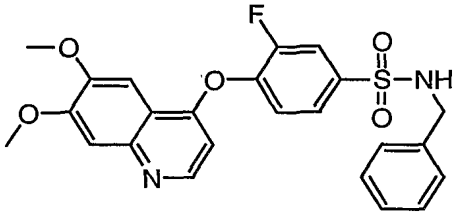
Entry	Name	Structure
12	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(phenylmethyl)ethanediamide	
13	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-4-phenyl-1,3-thiazol-2-amine	
14	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-phenylethyl)ethanediamide	
15	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-1-phenylmethanesulfonamide	
16	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-2-phenylethanesulfonamide	
17	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-(phenylmethyl)benzenesulfonamide	

Table 1

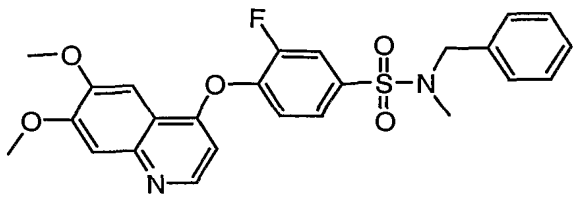
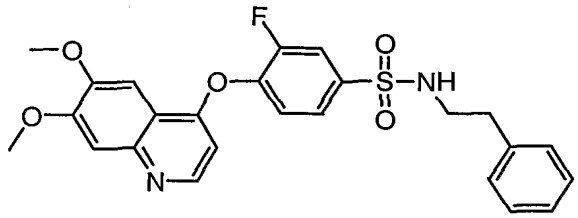
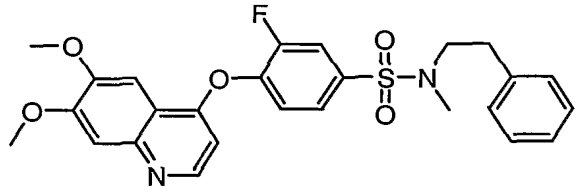
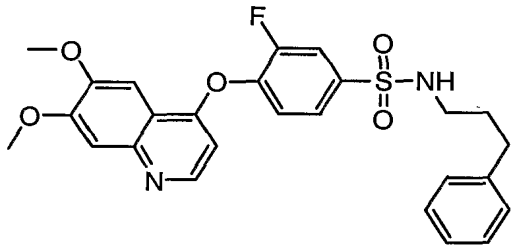
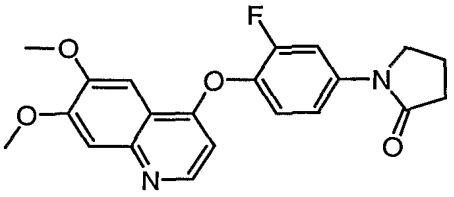
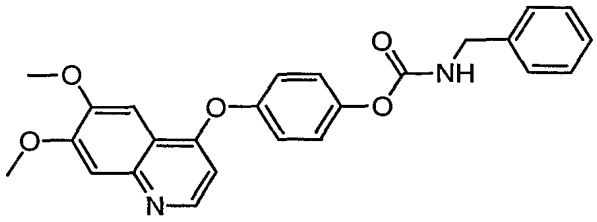
Entry	Name	Structure
18	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(phenylmethyl)benzenesulfonamide	
19	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-(2-phenylethyl)benzenesulfonamide	
20	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(2-phenylethyl)benzenesulfonamide	
21	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-(3-phenylpropyl)benzenesulfonamide	
22	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)pyrrolidin-2-one	
23	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl (phenylmethyl)carbamate	

Table 1

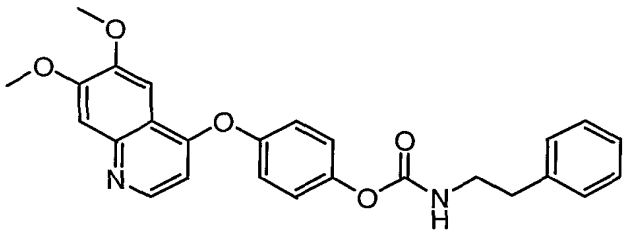
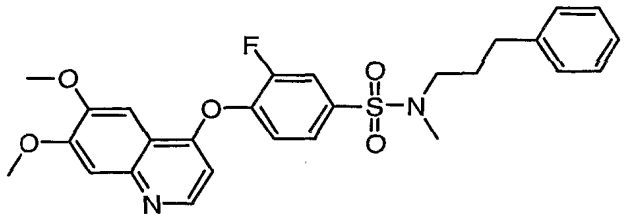
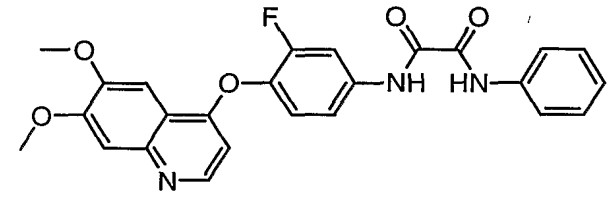
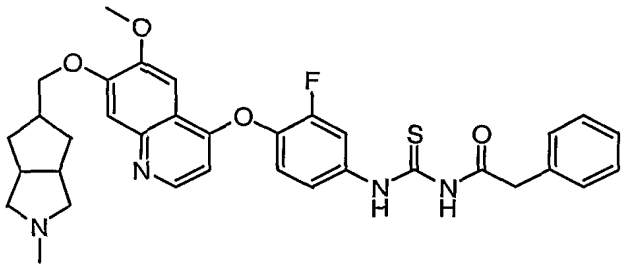
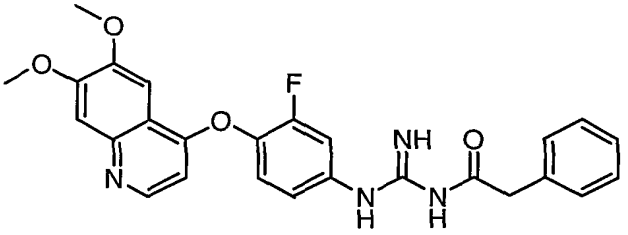
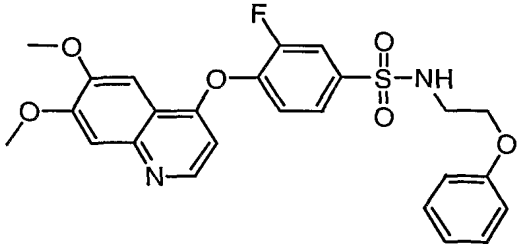
Entry	Name	Structure
24	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl (2-phenylethyl)carbamate	
25	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(3-phenylpropyl)benzenesulfonamide	
26	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-phenylethanediamide	
27	N-{[(3-fluoro-4-{[7-{[(2-methyloctahydrocyclopenta[c]pyrrol-5-yl)methyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}phenyl)amino]carbonothioyl}-2-phenylacetamide	
28	N-[(Z)-[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)amino](imino)methyl]-2-phenylacetamide	
29	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-[2-(phenyloxy)ethyl]benzenesulfonamide	

Table 1

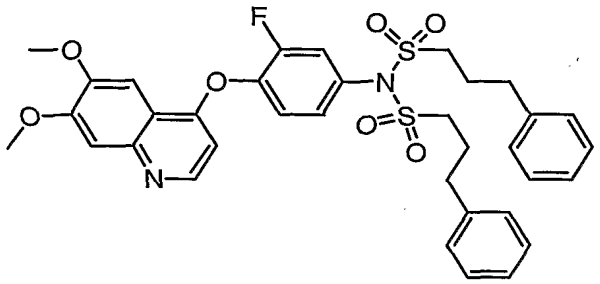
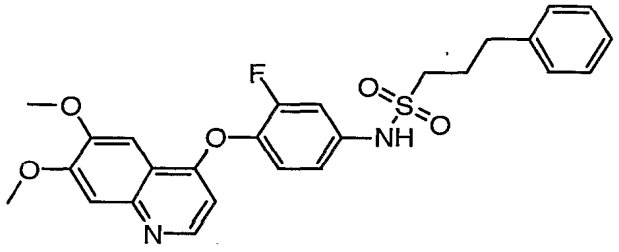
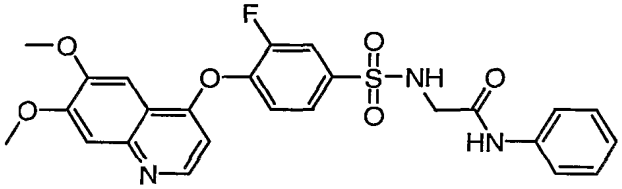
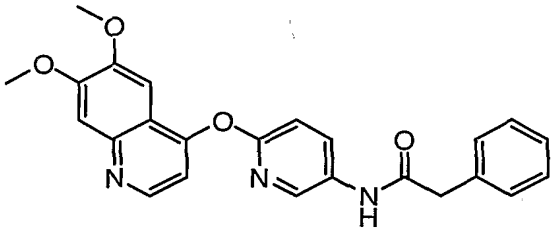
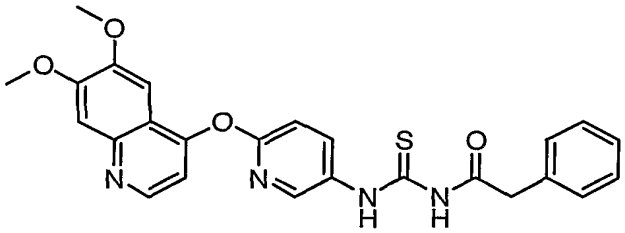
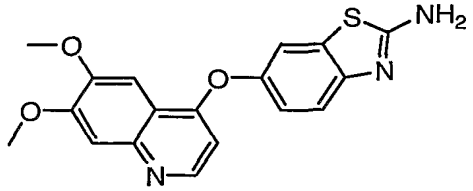
Entry	Name	Structure
30	N,N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-bis-(3-phenylpropane-1-sulfonamide)	
31	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-phenylpropane-1-sulfonamide	
32	N2-[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)sulfonyl]-N1-phenylglycinamide	
33	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-2-phenylacetamide	
34	N-{[(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)amino]carbonothioyl}-2-phenylacetamide	
35	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-1,3-benzothiazol-2-amine	

Table 1

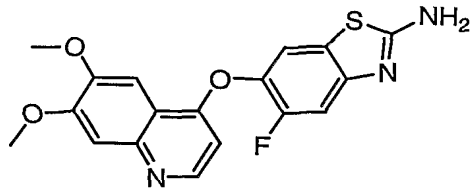
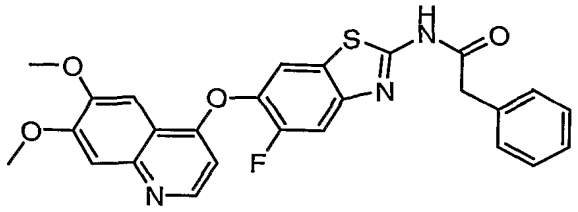
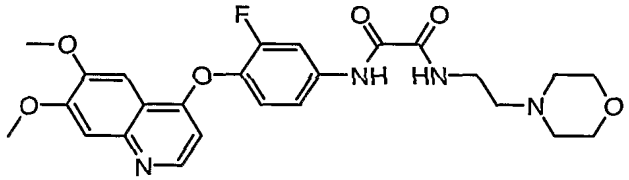
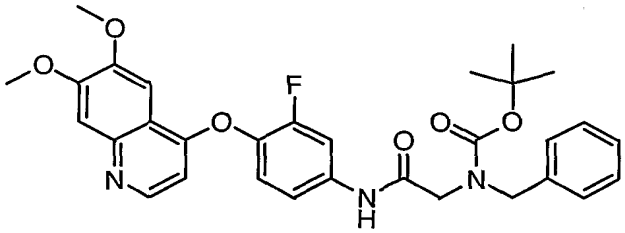
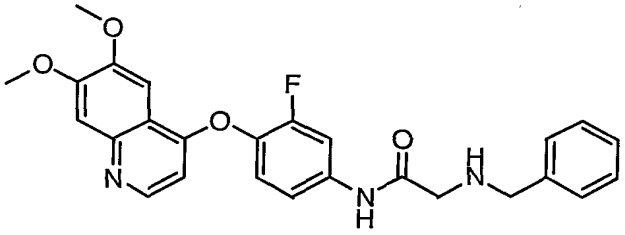
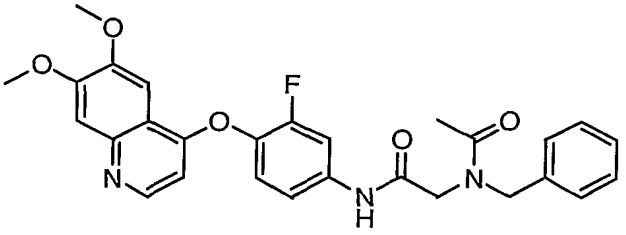
Entry	Name	Structure
36	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-amine	
37	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-phenylacetamide	
38	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-morpholin-4-ylethyl)ethanediamide	
39	benzyl-{[4-(6,7-dimethoxy-quinolin-4-yloxy)-3-fluoro-phenylcarbamoyl]-methyl}-carbamic acid tert-butyl ester	
40	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(phenylmethyl)glycinamide	
41	N2-acetyl-N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(phenylmethyl)glycinamide	

Table 1

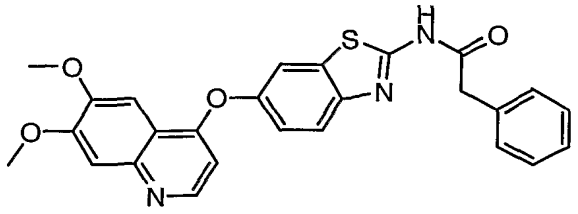
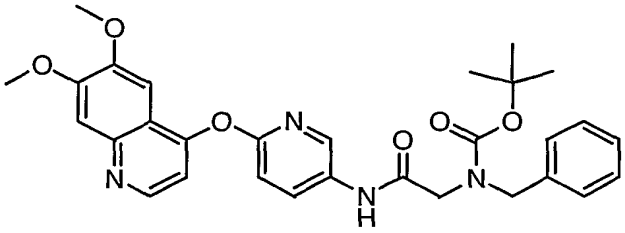
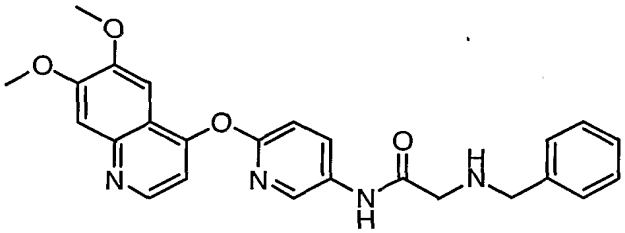
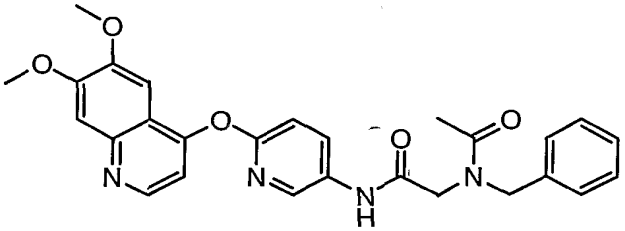
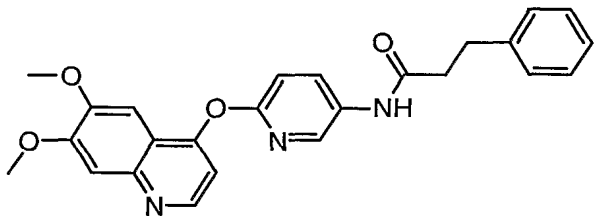
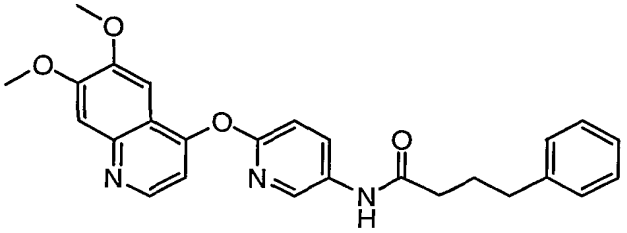
Entry	Name	Structure
42	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-1,3-benzothiazol-2-yl)-2-phenylacetamide	
43	benzyl-{[6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-ylcarbamoyl]-methyl}-carbamic acid tert-butyl ester	
44	N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N2-(phenylmethyl)glycinamide	
45	N2-acetyl-N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N2-(phenylmethyl)glycinamide	
46	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-3-phenylpropanamide	
47	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-4-phenylbutanamide	

Table 1

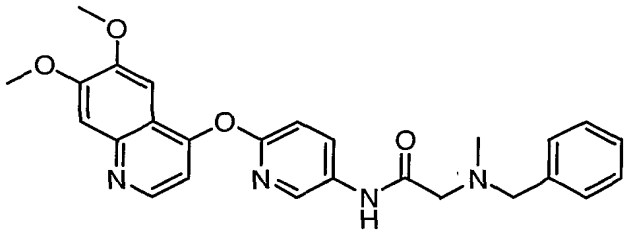
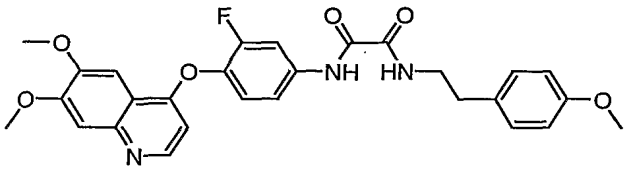
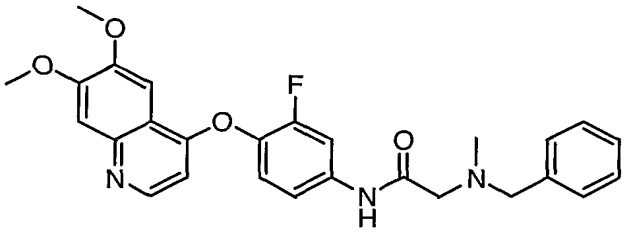
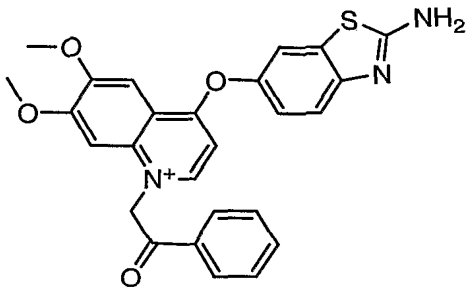
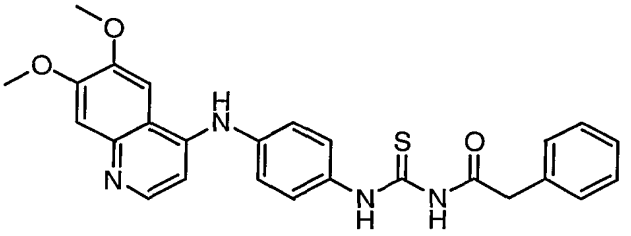
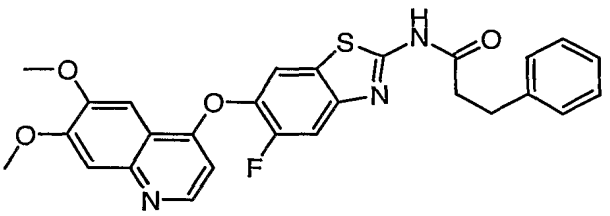
Entry	Name	Structure
48	N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N2-methyl-N2-(phenylmethyl)glycinamide	
49	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{2-[4-(methyloxy)phenyl]ethyl}ethanediamide	
50	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-methyl-N2-(phenylmethyl)glycinamide	
51	4-[(2-amino-1,3-benzothiazol-6-yl)oxy]-6,7-bis(methyloxy)-1-(2-oxo-2-phenylethyl)quinolinium	
52	N-{[(4-{[6,7-bis(methyloxy)quinolin-4-yl]amino}phenyl)amino]carbonothioyl}-2-phenylacetamide	
53	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-3-phenylpropanamide	

Table 1

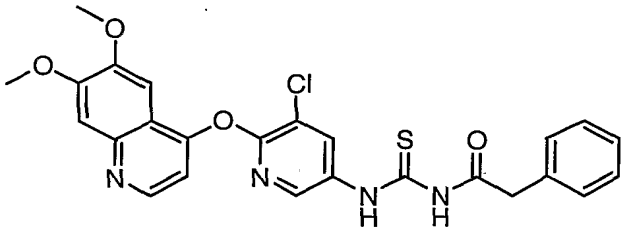
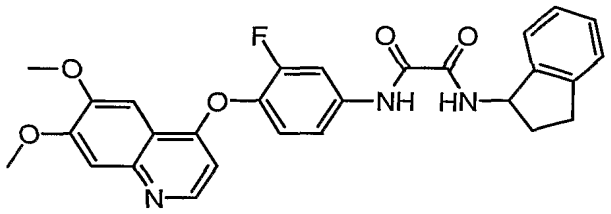
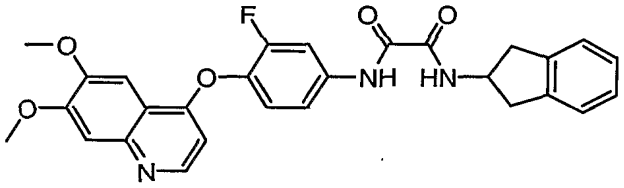
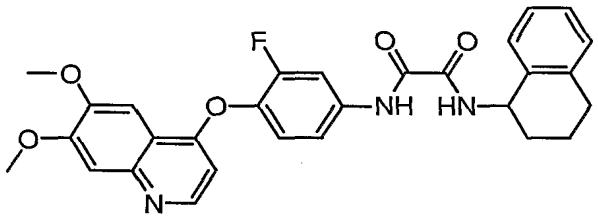
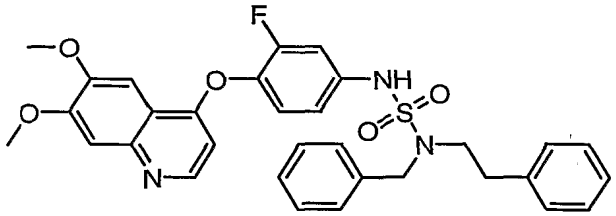
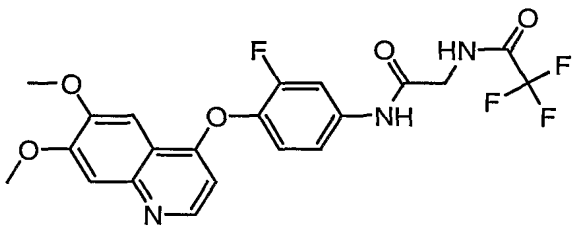
Entry	Name	Structure
54	N-{[(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)amino]carbonothioyl}-2-phenylacetamide	
55	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2,3-dihydro-1H-inden-1-yl)ethanediamide	
56	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2,3-dihydro-1H-inden-2-yl)ethanediamide	
57	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(1,2,3,4-tetrahydronaphthalen-1-yl)ethanediamide	
58	N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N-(2-phenylethyl)-N-(phenylmethyl)sulfamide	
59	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(trifluoroacetyl)glycinamide	

Table 1

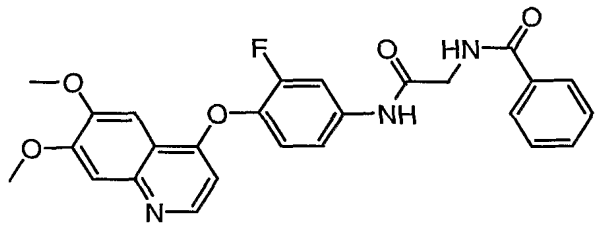
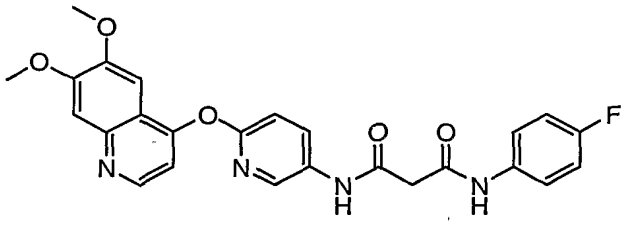
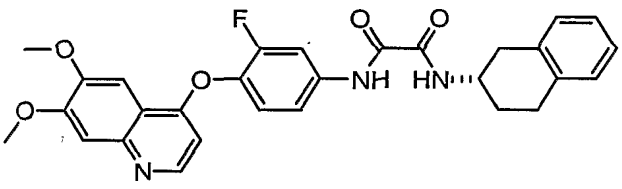
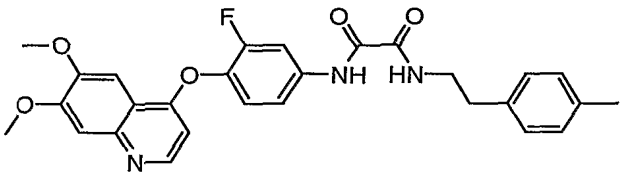
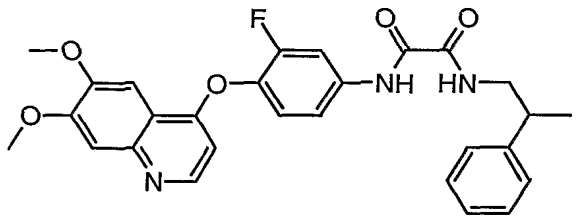
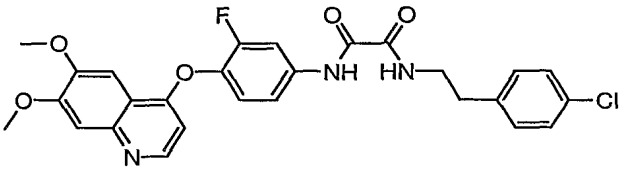
Entry	Name	Structure
60	N-{[4-(6,7-dimethoxy-quinolin-4-yloxy)-3-fluoro-phenylcarbamoyl]-methyl}-benzamide	
61	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N'-(4-fluorophenyl)propanediamide	
62	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[(2S)-1,2,3,4-tetrahydronaphthalen-2-yl]ethanediamide	
63	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(4-methylphenyl)ethyl]ethanediamide	
64	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-phenylpropyl)ethanediamide	
65	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(4-chlorophenyl)ethyl]ethanediamide	

Table 1

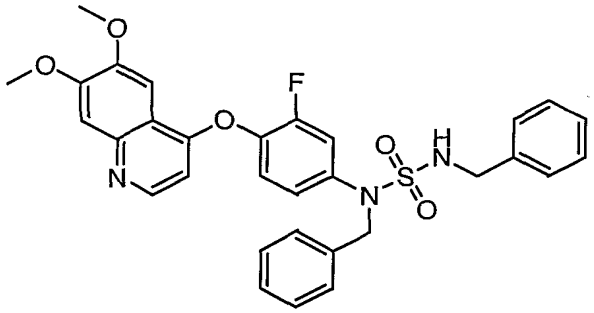
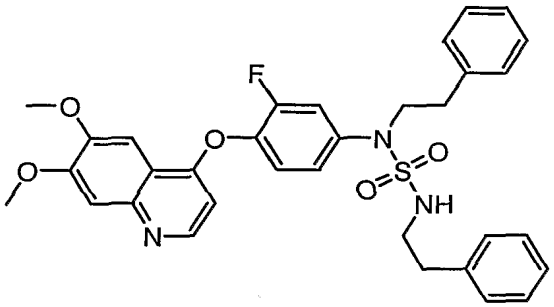
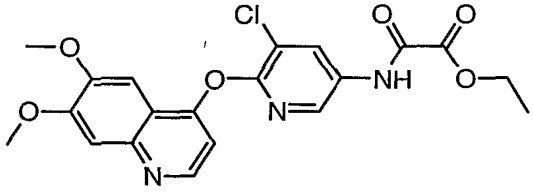
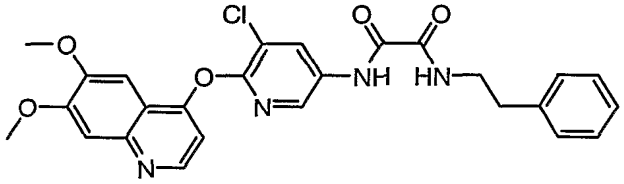
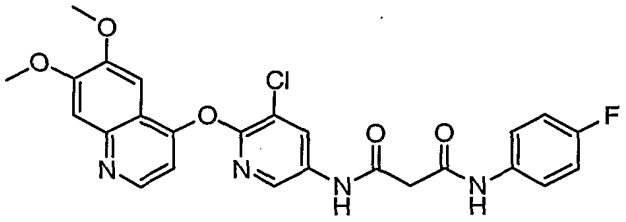
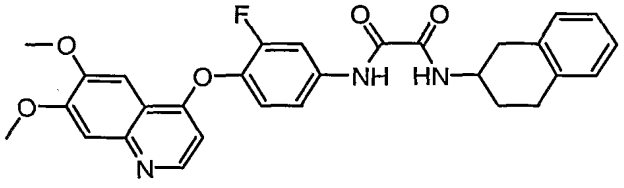
Entry	Name	Structure
66	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N,N'-bis(phenylmethyl)sulfamide	
67	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N,N'-bis(2-phenylethyl)sulfamide	
68	ethyl [(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)amino](oxo)acetate	
69	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-phenylethyl)ethanediamide	
70	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)propanediamide	
71	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(1,2,3,4-tetrahydronaphthalen-2-yl)ethanediamide	

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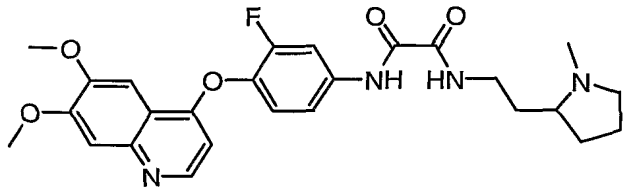
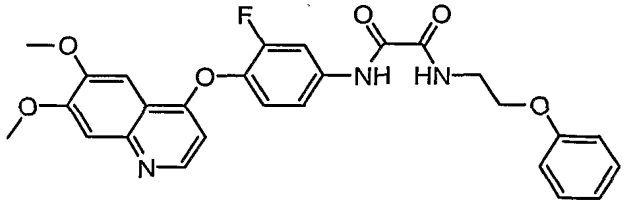
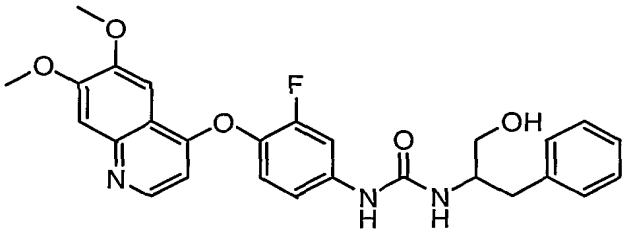
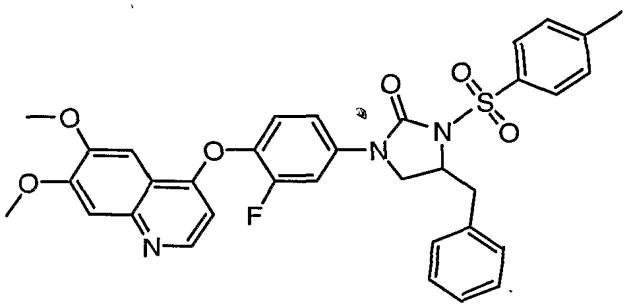
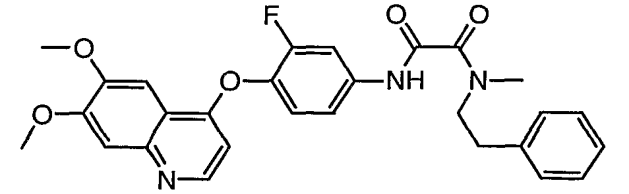
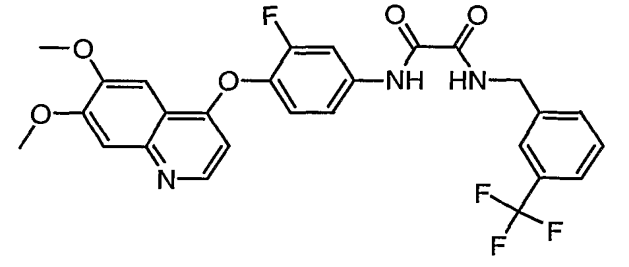
Entry	Name	Structure
72	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(1-methylpyrrolidin-2-yl)ethyl]ethanediamide	
73	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(phenyloxy)ethyl]ethanediamide	
74	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-hydroxy-1-(phenylmethyl)ethyl]urea	
75	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-[(4-methylphenyl)sulfonyl]-4-(phenylmethyl)imidazolidin-2-one	
76	N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N-methyl-N-(2-phenylethyl)ethanediamide	
77	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{[3-(trifluoromethyl)phenyl]methyl}ethanediamide	

Table 1

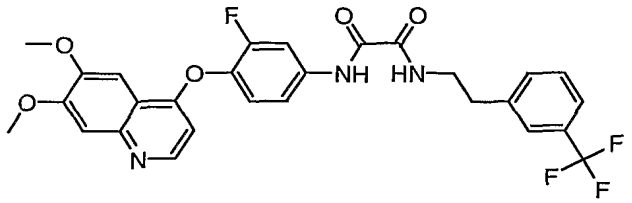
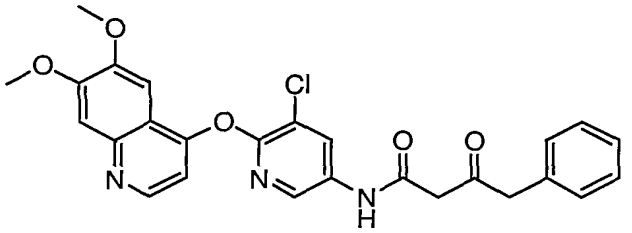
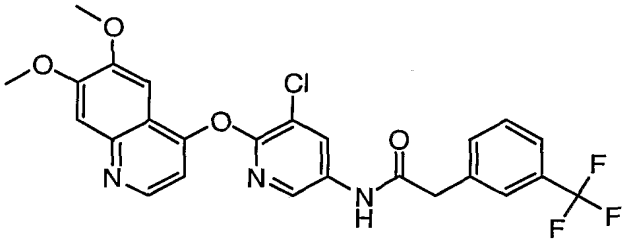
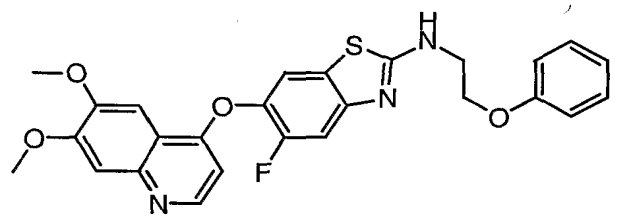
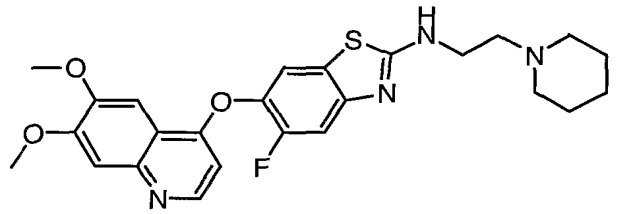
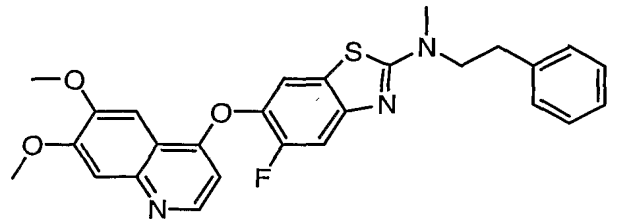
Entry	Name	Structure
78	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{2-[3-(trifluoromethyl)phenyl]ethyl}ethanediamide	
79	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-3-oxo-4-phenylbutanamide	
80	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-2-[3-(trifluoromethyl)phenyl]acetamide	
81	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-[2-(phenyloxy)ethyl]-1,3-benzothiazol-2-amine	
82	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-(2-piperidin-1-ylethyl)-1,3-benzothiazol-2-amine	
83	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-methyl-N-(2-phenylethyl)-1,3-benzothiazol-2-amine	

Table 1

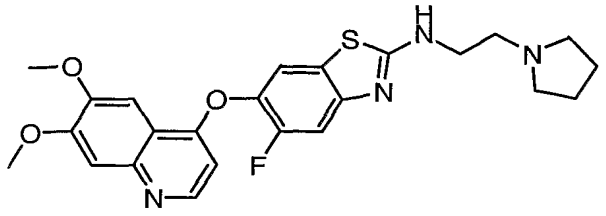
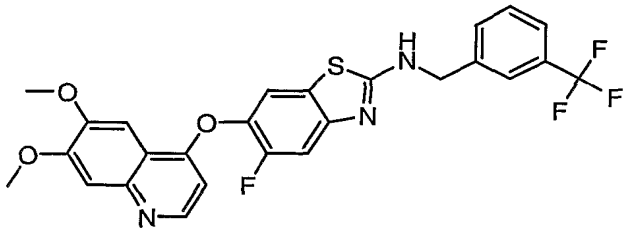
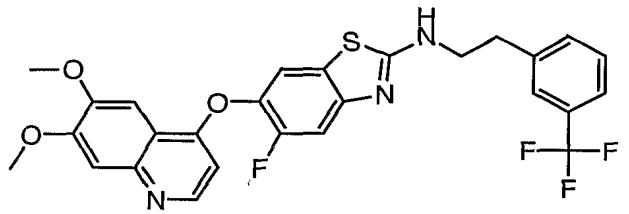
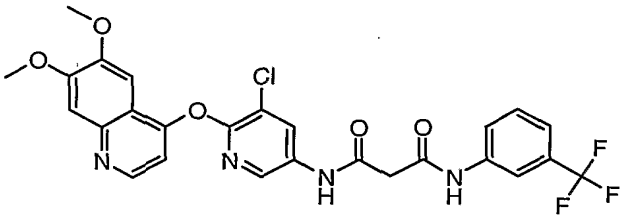
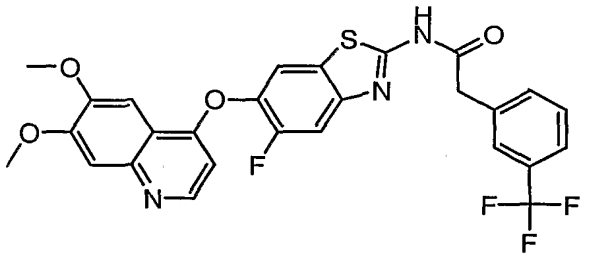
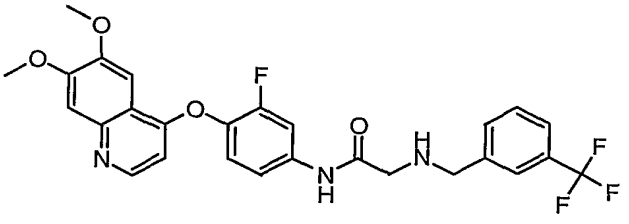
Entry	Name	Structure
84	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-(2-pyrrolidin-1-ylethyl)-1,3-benzothiazol-2-amine	
85	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-{[3-(trifluoromethyl)phenyl]methyl}-1,3-benzothiazol-2-amine	
86	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-{2-[3-(trifluoromethyl)phenyl]ethyl}-1,3-benzothiazol-2-amine	
87	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-[3-(trifluoromethyl)phenyl]propanediamide	
88	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[3-(trifluoromethyl)phenyl]acetamide	
89	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-{[3-(trifluoromethyl)phenyl]methyl}glycinamide	

Table 1

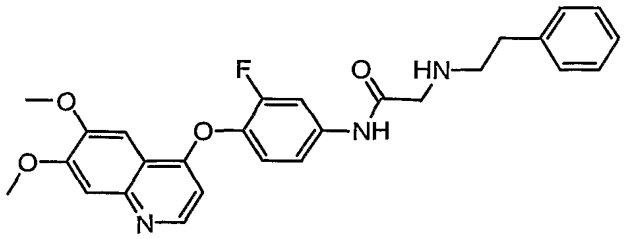
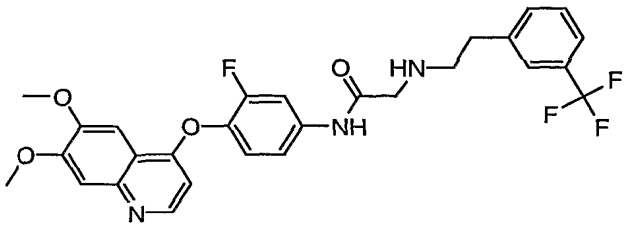
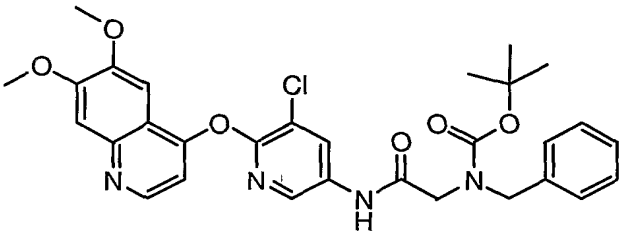
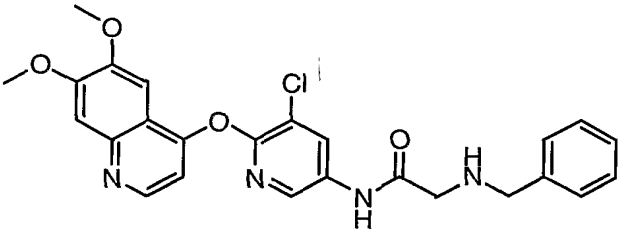
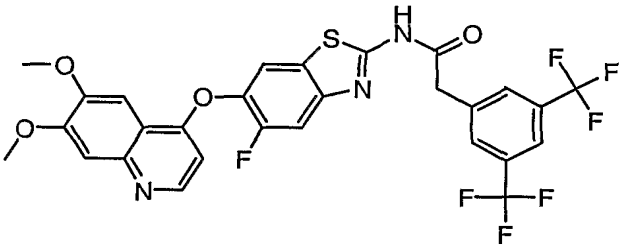
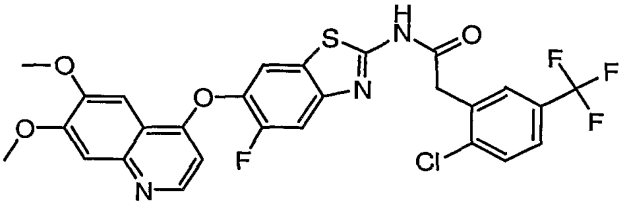
Entry	Name	Structure
90	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(2-phenylethyl)glycinamide	
91	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-{2-[3-(trifluoromethyl)phenyl]ethyl}glycinamide	
92	benzyl-{[5-chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-ylcarbamoyl]-methyl}-carbamic acid tert-butyl ester	
93	N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N2-(phenylmethyl)glycinamide	
94	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[3,5-bis(trifluoromethyl)phenyl]acetamide	
95	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[2-chloro-5-(trifluoromethyl)phenyl]acetamide	

Table 1

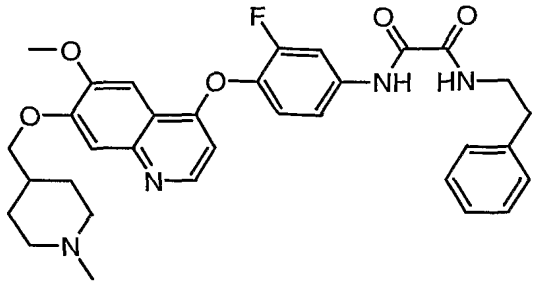
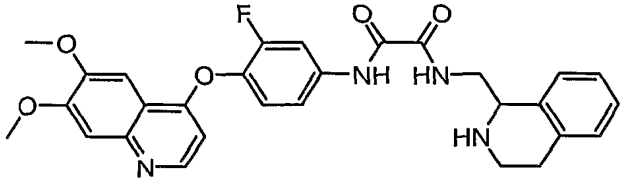
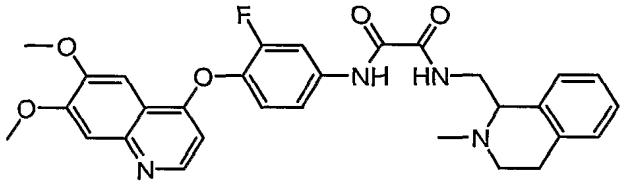
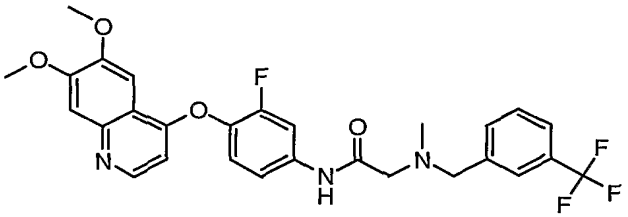
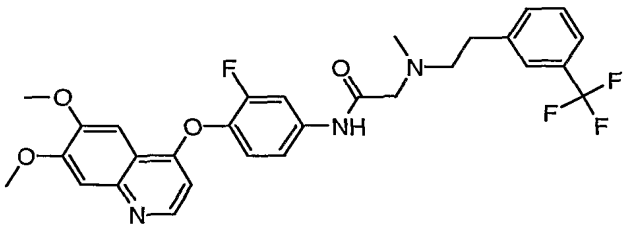
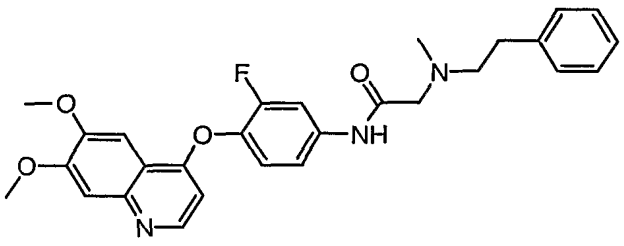
Entry	Name	Structure
96	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(2-phenylethyl)ethanediamide	
97	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(1,2,3,4-tetrahydroisoquinolin-1-ylmethyl)ethanediamide	
98	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[(2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl]ethanediamide	
99	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-methyl-N2-{[3-(trifluoromethyl)phenyl]methyl}glycinamide	
100	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-methyl-N2-{2-[3-(trifluoromethyl)phenyl]ethyl}glycinamide	
101	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-methyl-N2-(2-phenylethyl)glycinamide	

Table 1

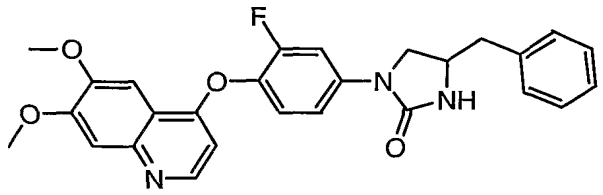
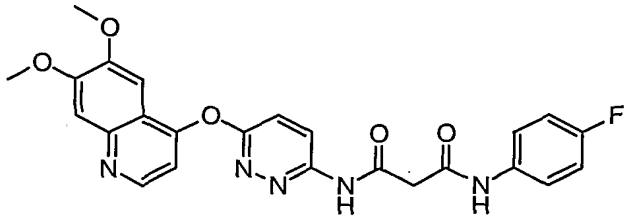
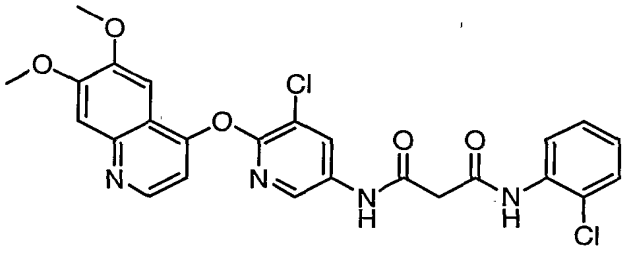
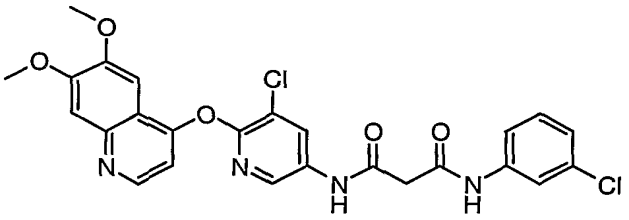
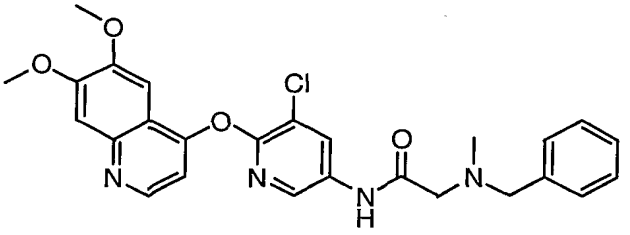
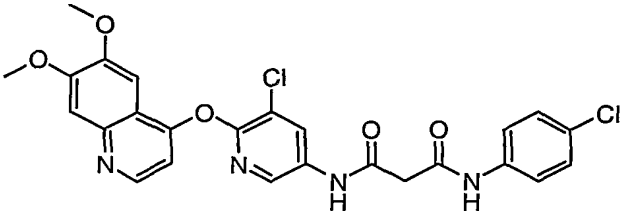
Entry	Name	Structure
102	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-4-(phenylmethyl)imidazolidin-2-one	
103	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridazin-3-yl)-N'-(4-fluorophenyl)propanediamide	
104	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-chlorophenyl)propanediamide	
105	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(3-chlorophenyl)propanediamide	
106	N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N2-methyl-N2-(phenylmethyl)glycinamide	
107	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-chlorophenyl)propanediamide	

Table 1

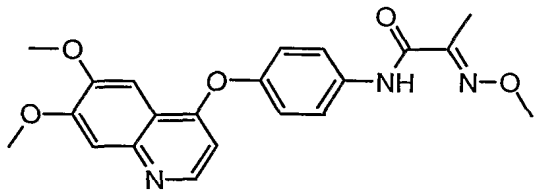
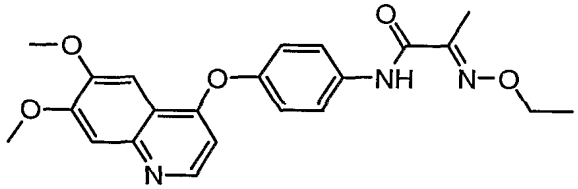
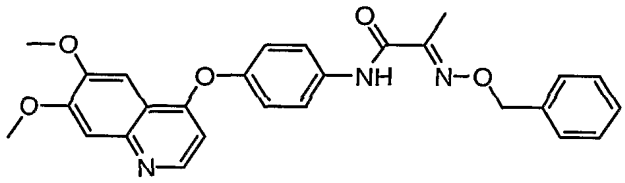
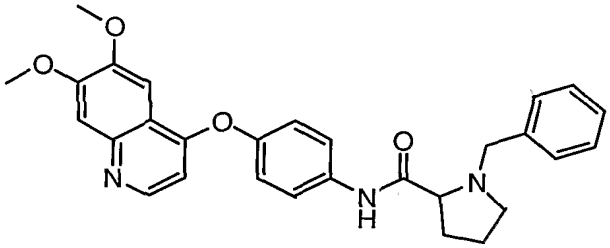
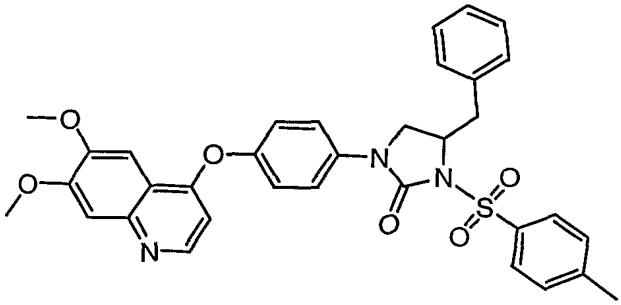
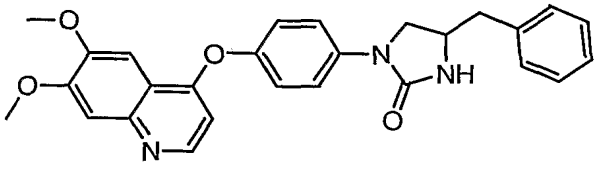
Entry	Name	Structure
108	(2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-[(methyloxy)imino]propanamide	
109	(2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-[(ethyloxy)imino]propanamide	
110	(2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-{[(phenylmethyl)oxy]imino}propanamide	
111	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-1-(phenylmethyl)prolinamide	
112	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-3-[(4-methylphenyl)sulfonyl]-4-(phenylmethyl)imidazolidin-2-one	
113	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)imidazolidin-2-one	

Table 1

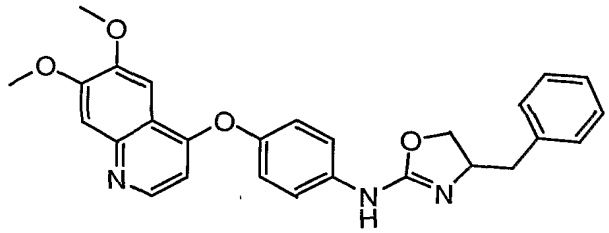
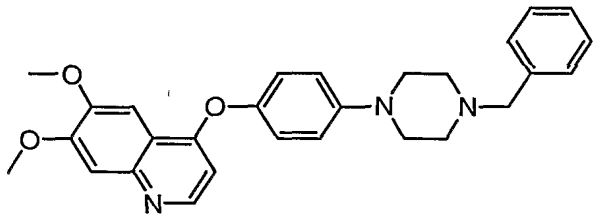
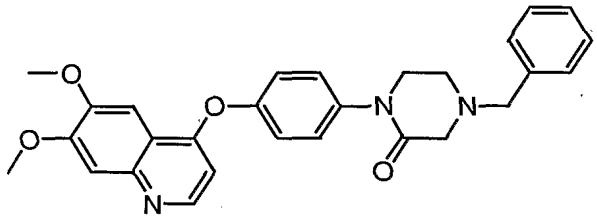
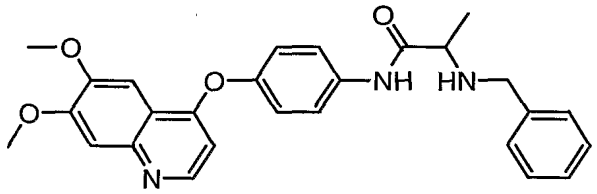
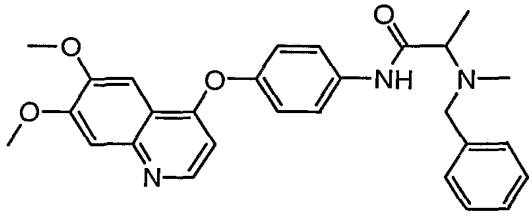
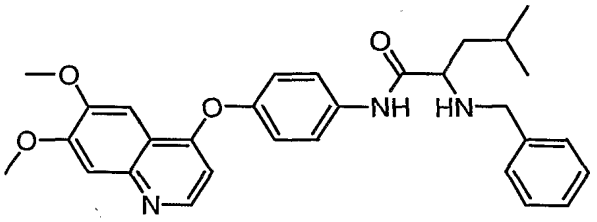
Entry	Name	Structure
114	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)-4,5-dihydro-1,3-oxazol-2-amine	
115	6,7-bis(methyloxy)-4-({4-[4-(phenylmethyl)piperazin-1-yl]phenyl}oxy)quinoline	
116	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)piperazin-2-one	
117	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-(phenylmethyl)alaninamide	
118	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-methyl-N2-(phenylmethyl)alaninamide	
119	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-(phenylmethyl)leucinamide	

Table 1

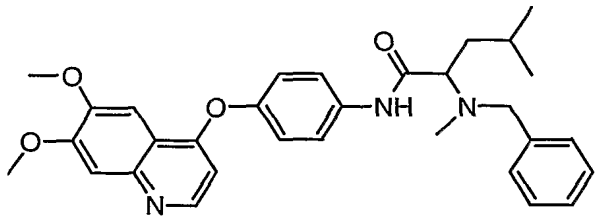
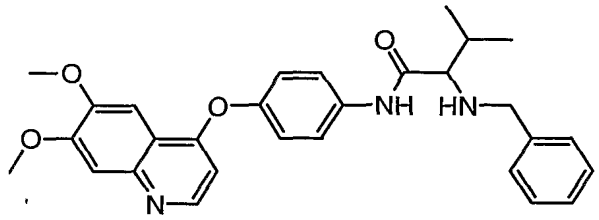
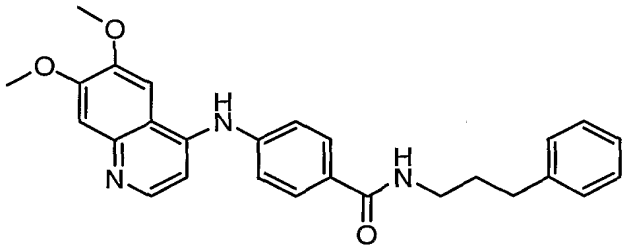
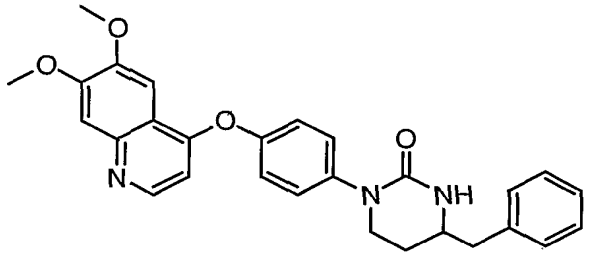
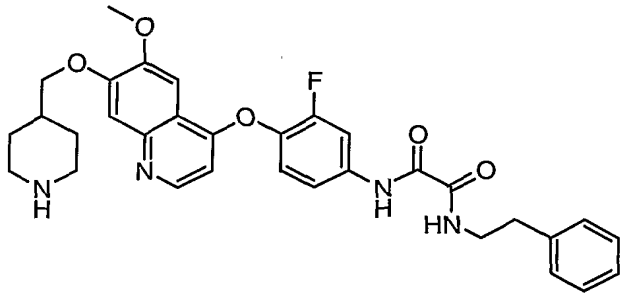
Entry	Name	Structure
120	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-methyl-N2-(phenylmethyl)leucinamide	
121	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-(phenylmethyl)valinamide	
122	4-(6,7-dimethoxy-quinolin-4-ylamino)-N-(3-phenyl-propyl)-benzamide	
123	4-benzyl-1-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-tetrahydro-pyrimidin-2-one	
124	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	

Table 1

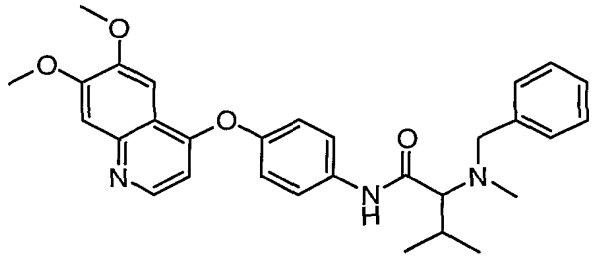
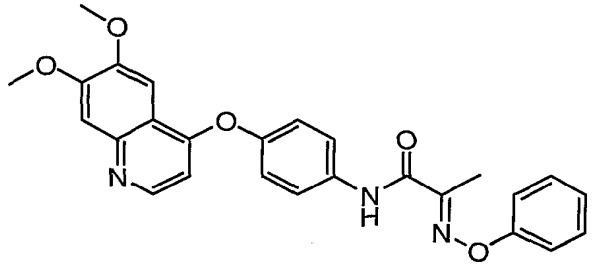
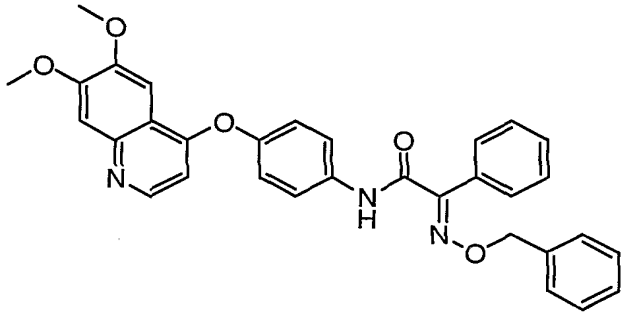
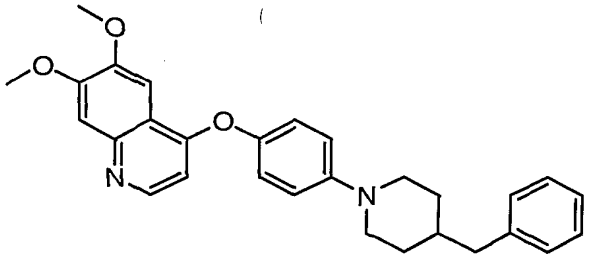
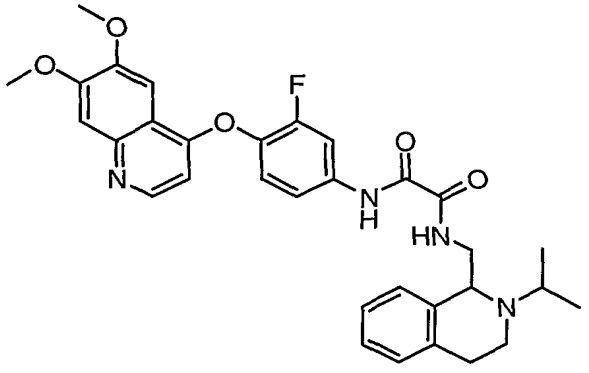
Entry	Name	Structure
125	2-(Benzyl-methyl-amino)-N-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-3-methyl-butyramide (note: Alphabetic order of prefixes ignored while selecting parent chain)	
126	N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-phenyl]-2-phenoxyimino-propionamide	
127	2-Benzyloxyimino-N-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-2-phenyl-acetamide	
128	4-[4-(4-Benzyl-piperidin-1-yl)-phenoxy]-6,7-dimethoxy-quinoline	
129	N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-N'-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-oxalamide	

Table 1

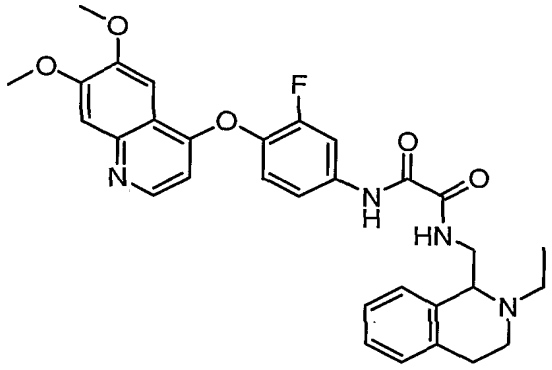
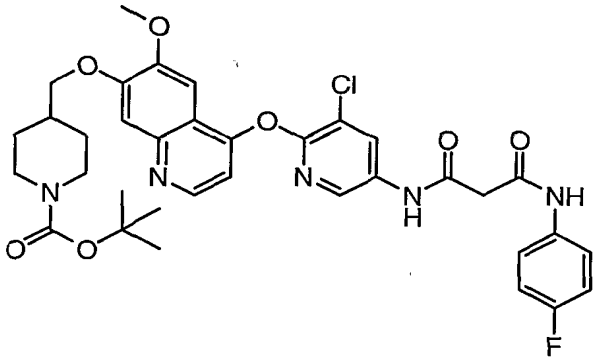
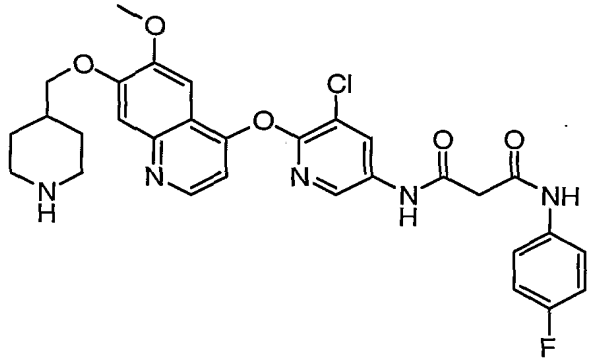
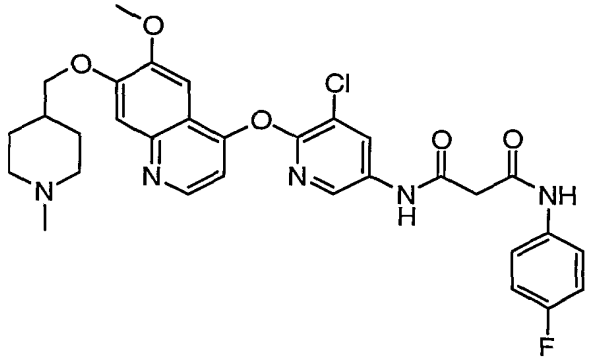
Entry	Name	Structure
130	N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-N'-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-oxalamide	
131	4-(4-{3-Chloro-5-[2-(4-fluoro-phenylcarbamoyl)-acetylamino]-pyridin-2-yloxy}-6-methoxy-quinolin-7-yloxymethyl)-piperidine-1-carboxylic acid tert-butyl ester	
132	N-{5-Chloro-6-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide	
133	N-{5-Chloro-6-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide	

Table 1

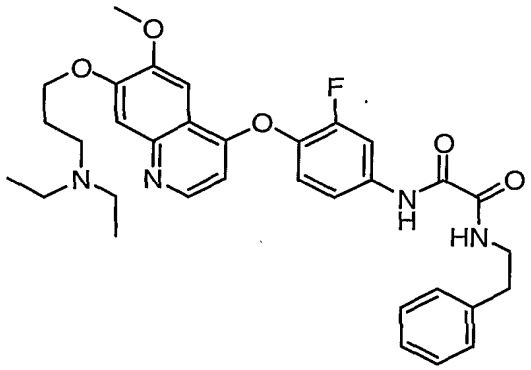
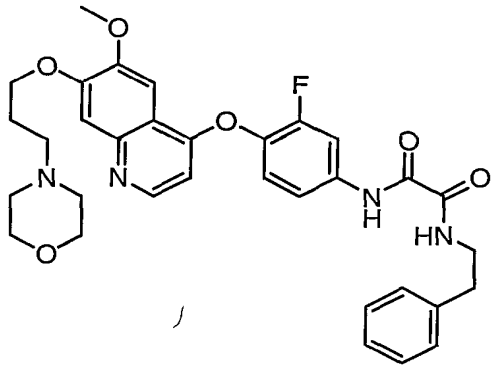
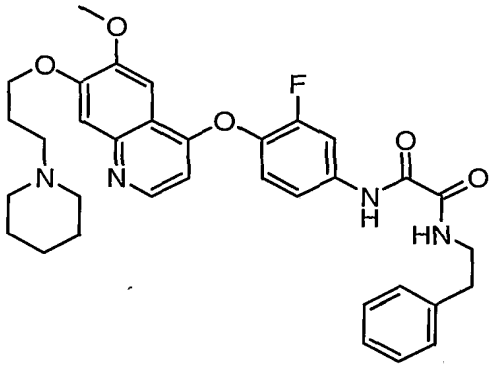
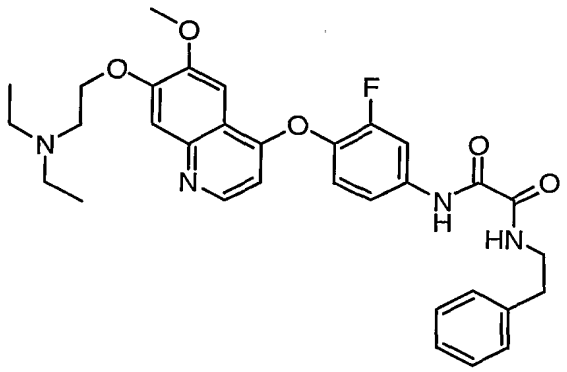
Entry	Name	Structure
134	N-{4-[7-(3-Diethylamino-propoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-N'-phenethyl-oxalamide	
135	N-{3-Fluoro-4-[6-methoxy-7-(3-morpholin-4-yl-propoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	
136	N-{3-Fluoro-4-[6-methoxy-7-(3-piperidin-1-yl-propoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	
137	N-{4-[7-(2-Diethylamino-ethoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-N'-phenethyl-oxalamide	

Table 1

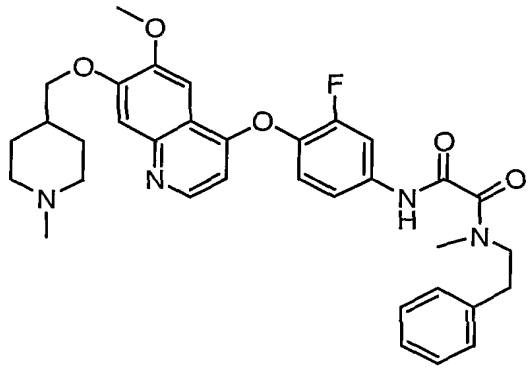
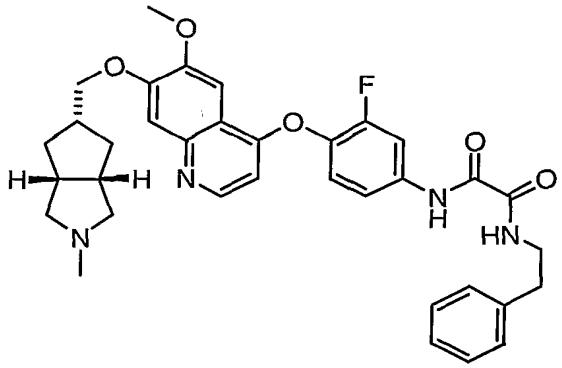
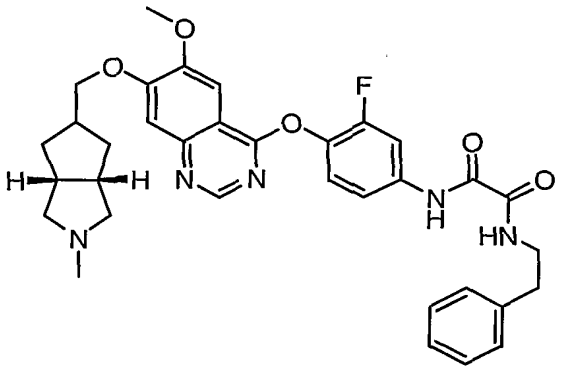
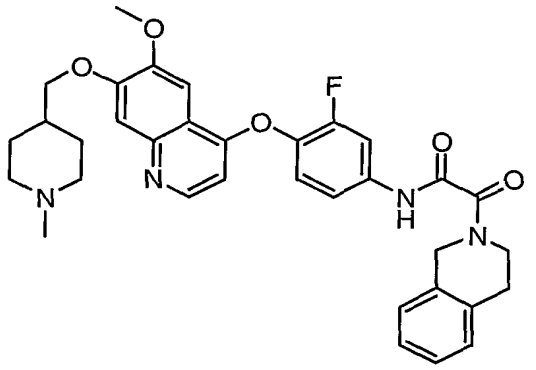
Entry	Name	Structure
138	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-methyl-N'-phenethyl-oxalamide	
139	N-{3-Fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	
140	N-{3-Fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	
141	2-(3,4-Dihydro-1H-isoquinolin-2-yl)-N-{3-fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-acetamide	

Table 1

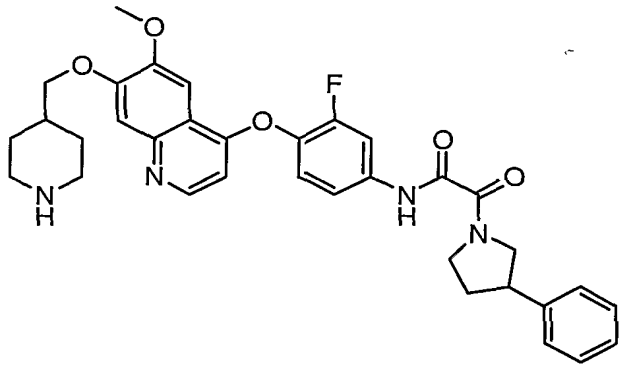
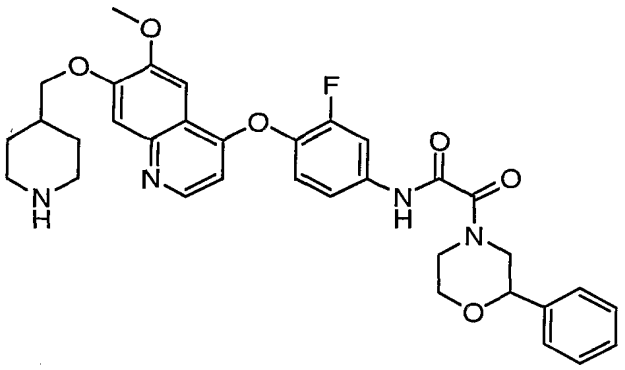
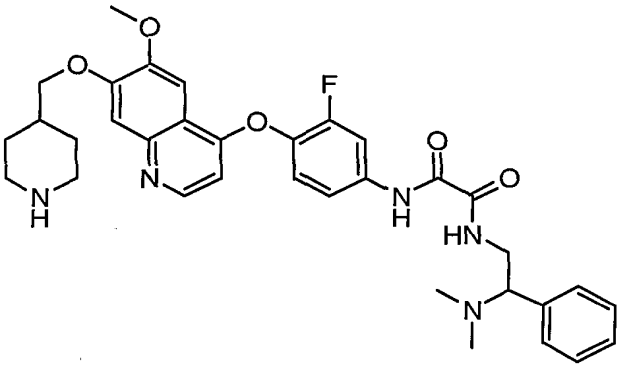
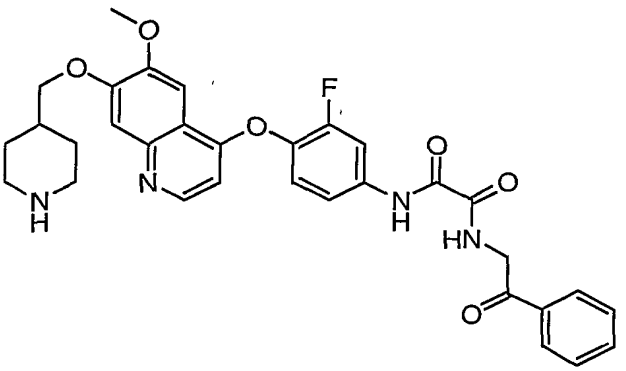
Entry	Name	Structure
142	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-2-(3-phenyl-pyrrolidin-1-yl)-acetamide	
143	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-2-(2-phenyl-morpholin-4-yl)-acetamide	
144	N-(2-Dimethylamino-2-phenyl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
145	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-oxo-2-phenyl-ethyl)-oxalamide	

Table 1

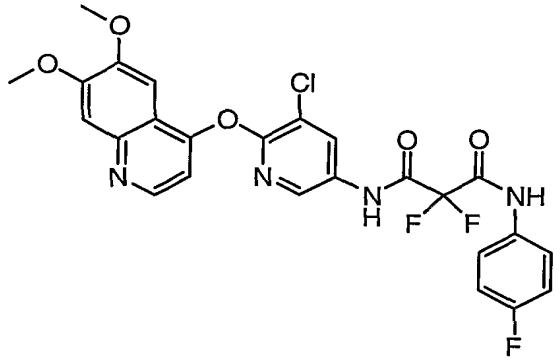
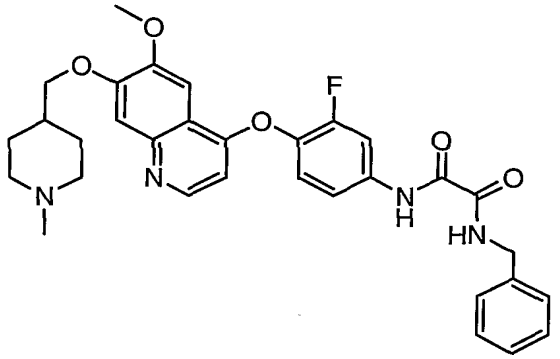
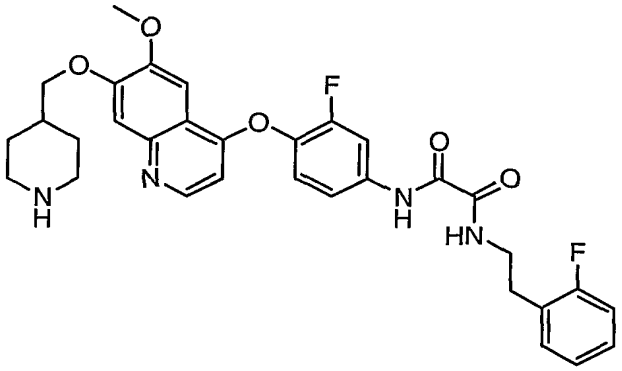
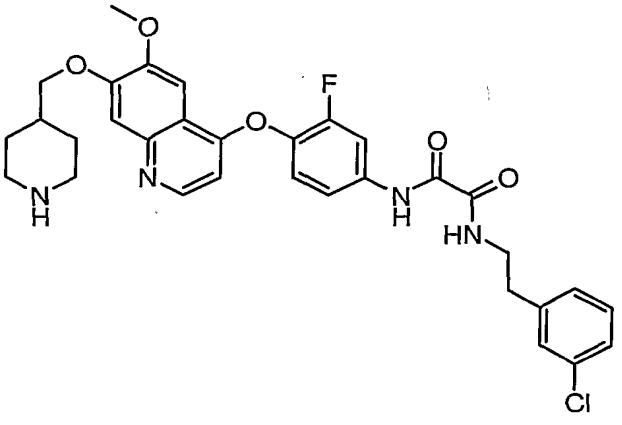
Entry	Name	Structure
146	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-2,2-difluoro-N'-(4-fluoro-phenyl)-malonamide	
147	N-Benzyl-N'-{3-fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
148	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(2-fluoro-phenyl)-ethyl]-oxalamide	
149	N-[2-(3-Chloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

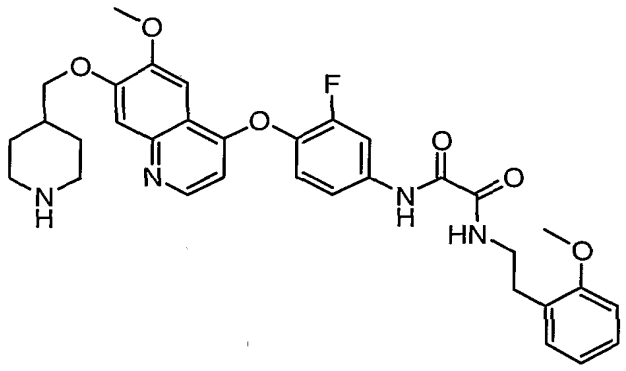
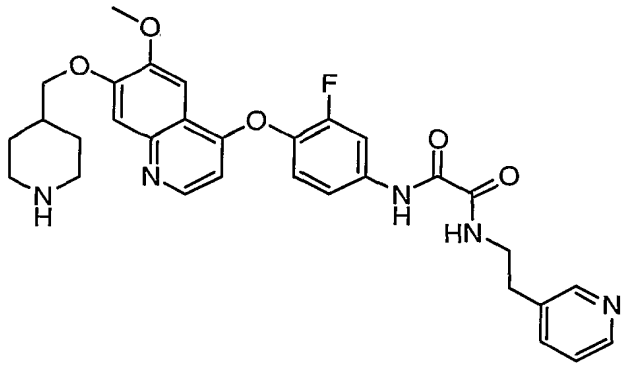
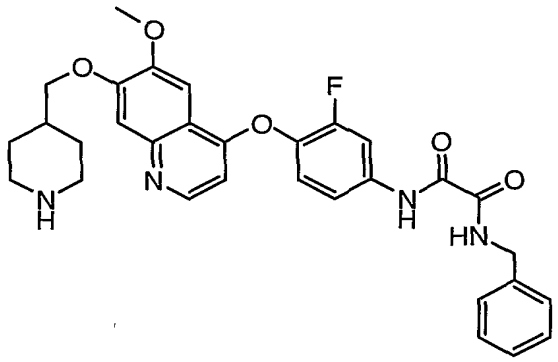
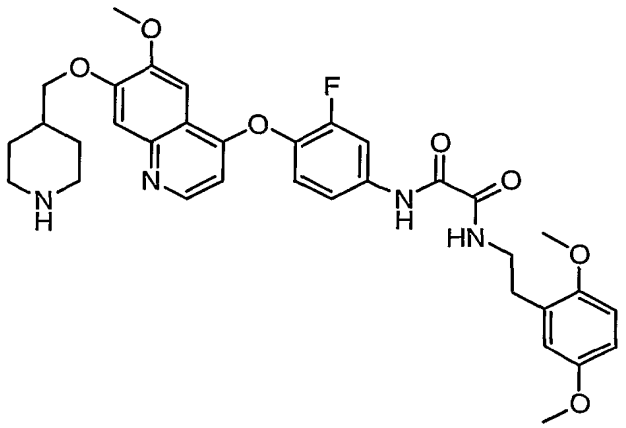
Entry	Name	Structure
150	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(2-methoxy-phenyl)-ethyl]-oxalamide	
151	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-pyridin-3-yl-ethyl)-oxalamide	
152	N-Benzyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
153	N-[2-(2,5-Dimethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

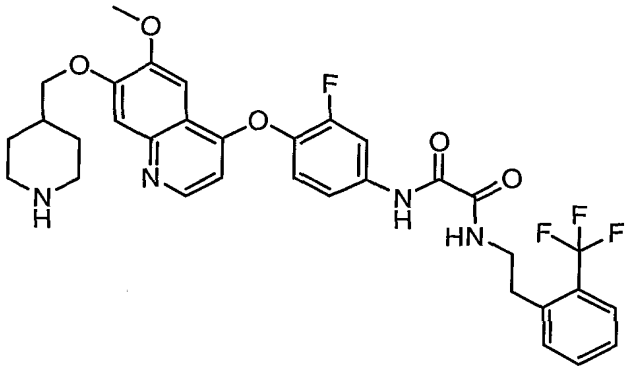
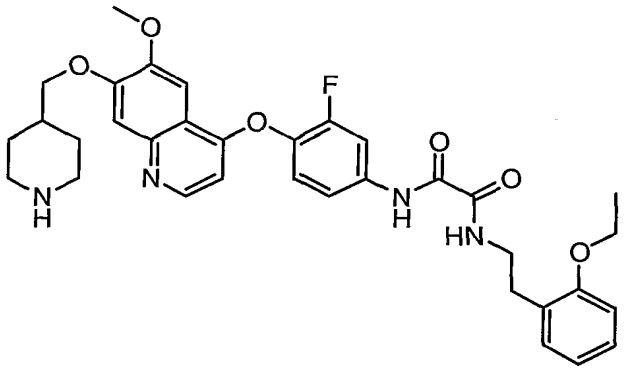
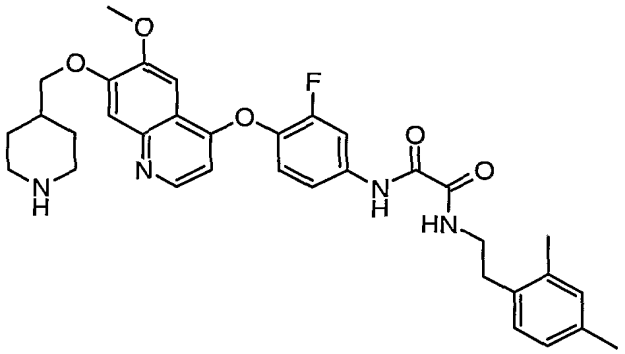
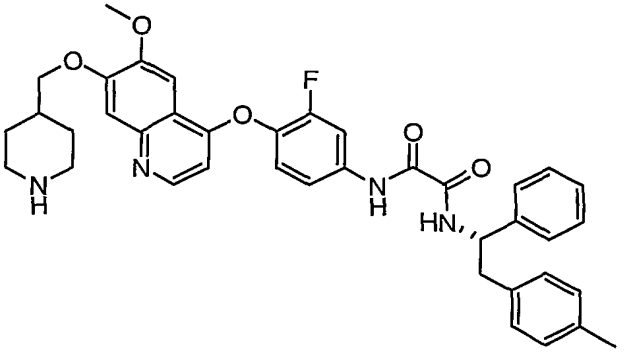
Entry	Name	Structure
154	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(2-trifluoromethyl-phenyl)-ethyl]-oxalamide	
155	N-[2-(2-Ethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
156	N-[2-(2,4-Dimethyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
157	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1*S* -phenyl-2-p-tolyl-ethyl)-oxalamide	

Table 1

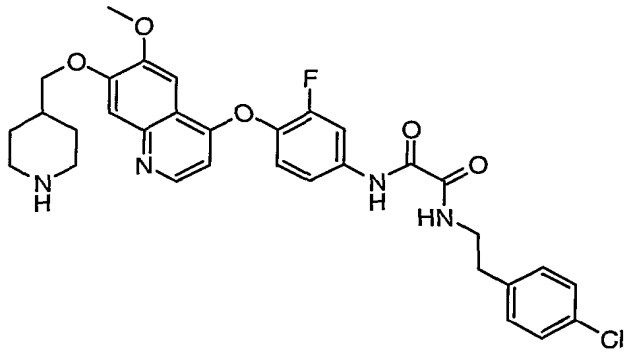
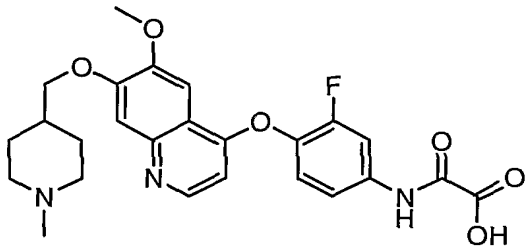
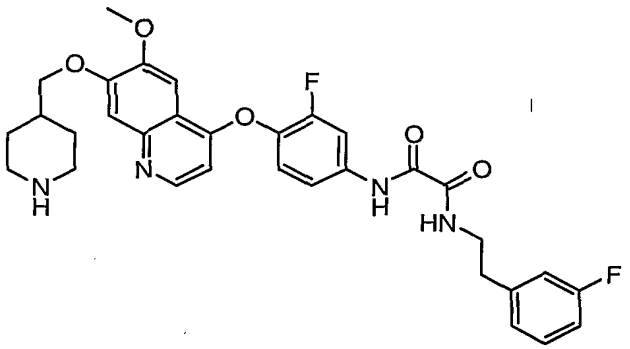
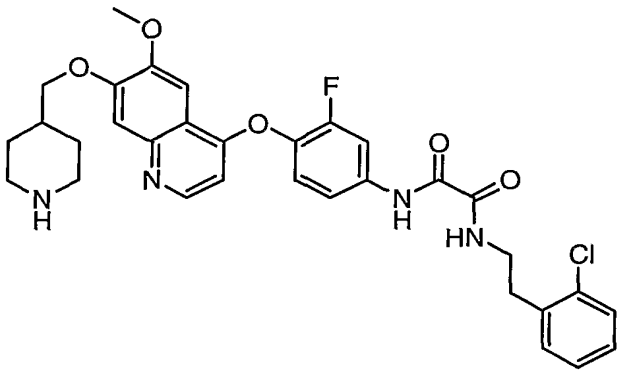
Entry	Name	Structure
158	N-[2-(4-Chloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
159	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamic acid	
160	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(3-fluoro-phenyl)-ethyl]-oxalamide	
161	N-[2-(2-Chloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

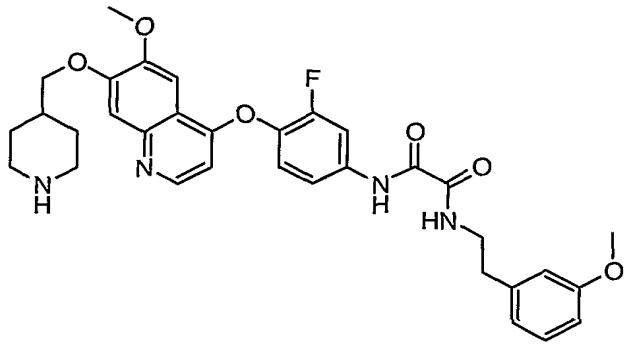
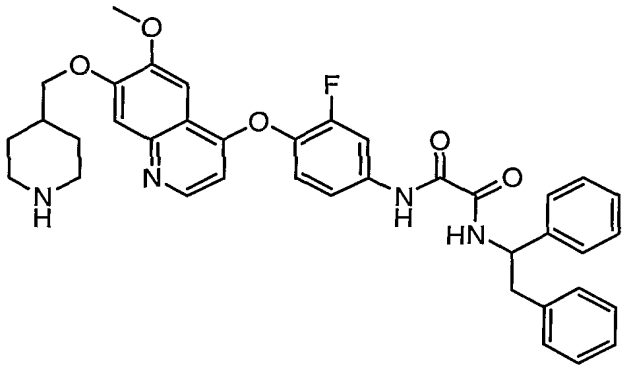
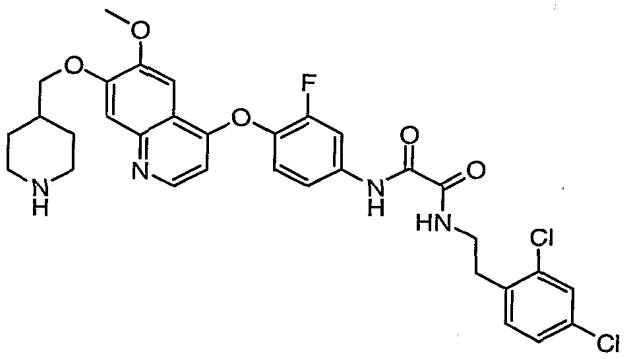
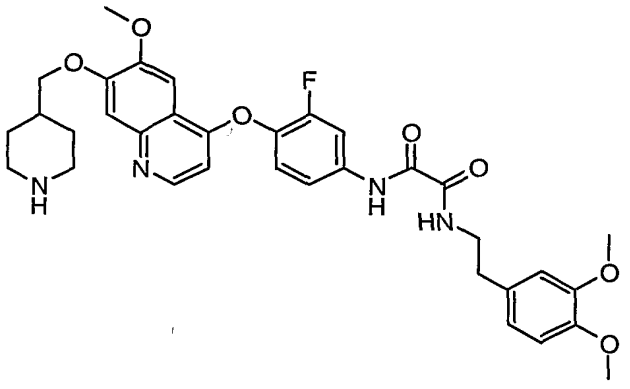
Entry	Name	Structure
162	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(3-methoxy-phenyl)-ethyl]-oxalamide	
163	N-(1,2-Diphenyl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
164	N-[2-(2,4-Dichloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
165	N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

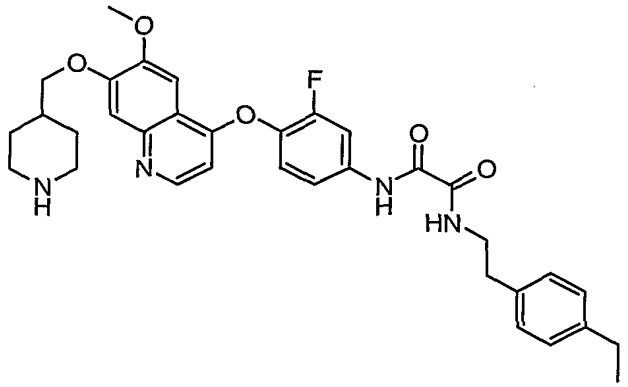
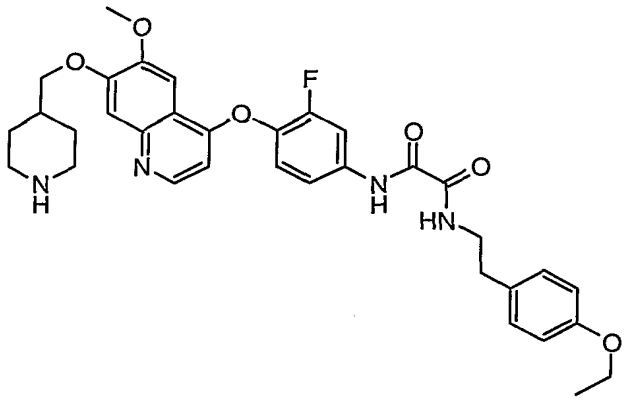
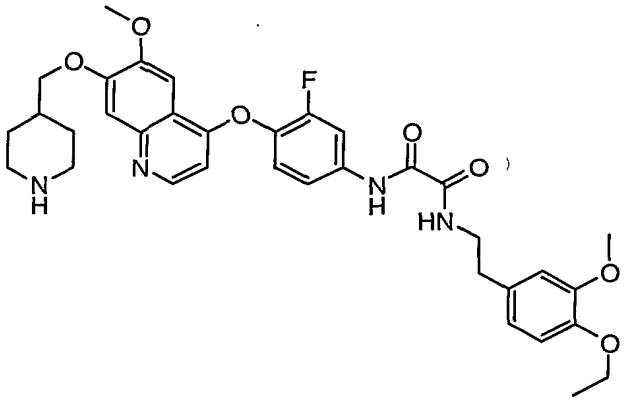
Entry	Name	Structure
166	N-[2-(4-Ethyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
167	N-[2-(4-Ethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
168	N-[2-(4-Ethoxy-3-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

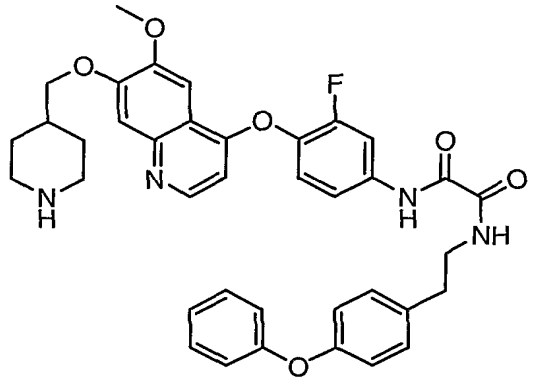
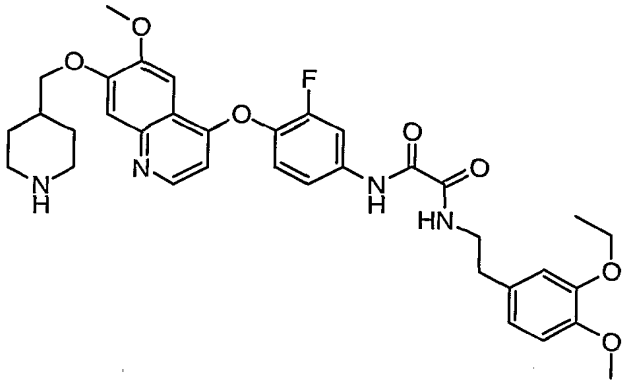
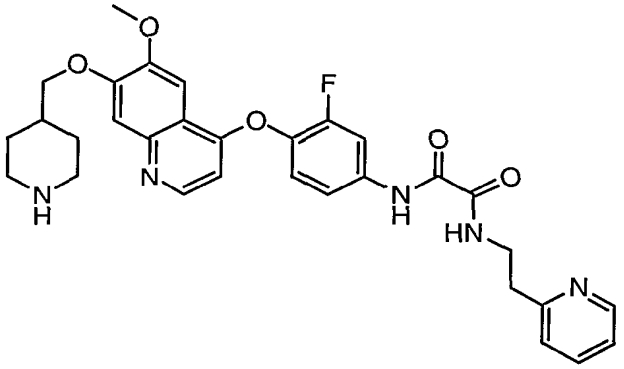
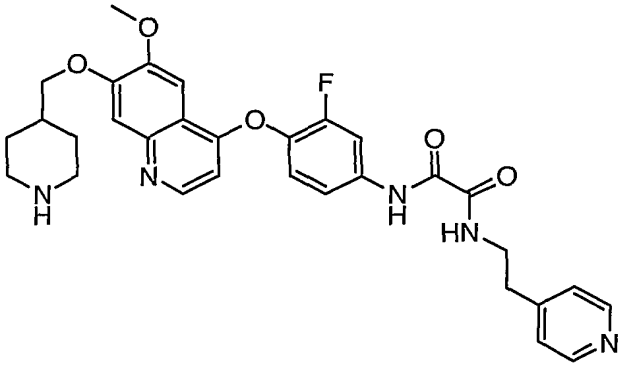
Entry	Name	Structure
169	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-phenoxy-phenyl)-ethyl]-oxalamide	
170	N-[2-(3-Ethoxy-4-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
171	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-pyridin-2-yl-ethyl)-oxalamide	
172	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-pyridin-4-yl-ethyl)-oxalamide	

Table 1

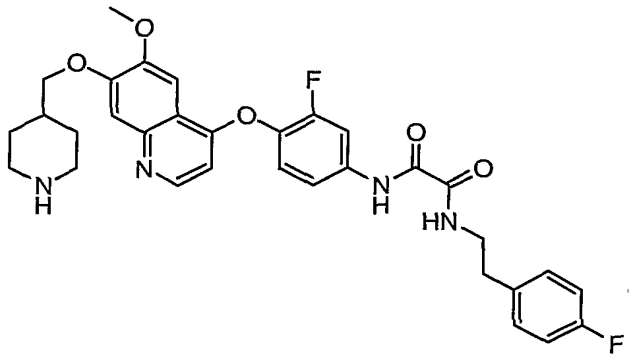
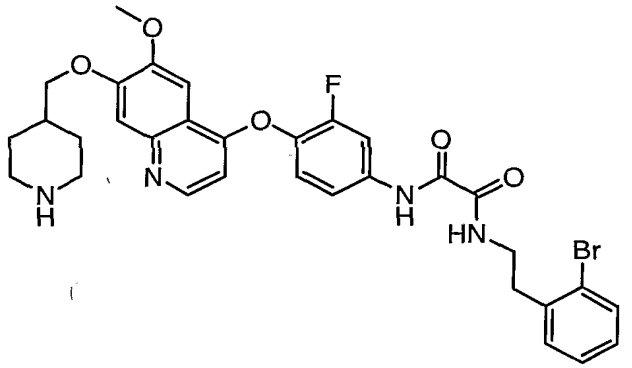
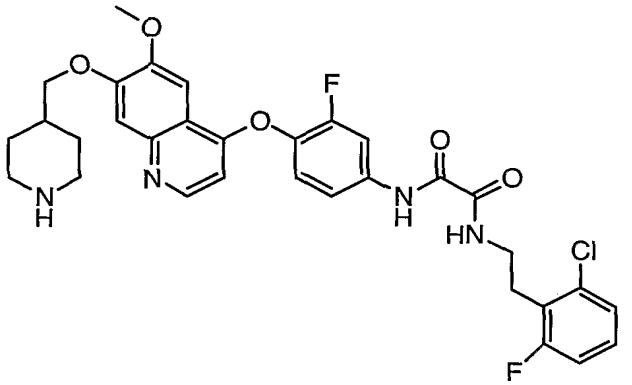
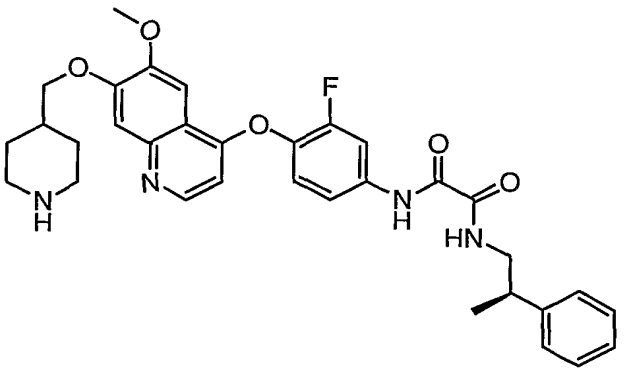
Entry	Name	Structure
173	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-fluoro-phenyl)-ethyl]-oxalamide	
174	N-[2-(2-Bromo-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
175	N-[2-(2-Chloro-6-fluoro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
176	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2*R*-phenyl-propyl)-oxalamide	

Table 1

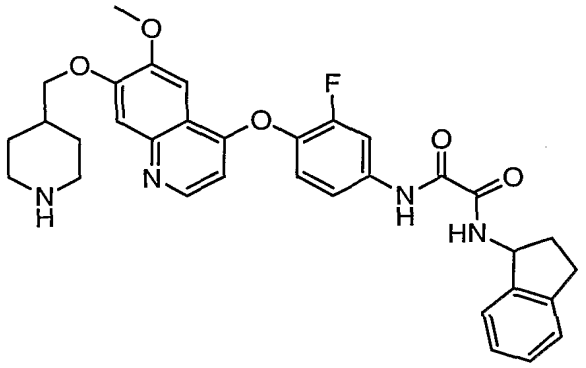
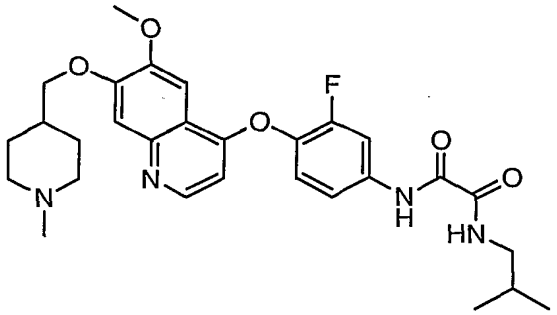
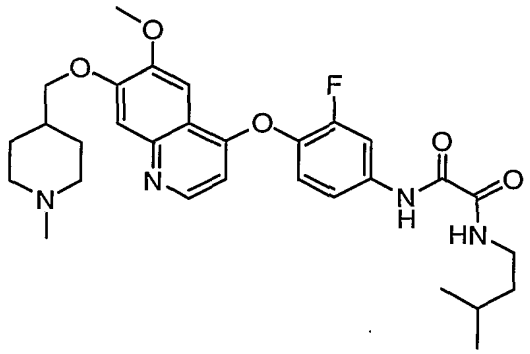
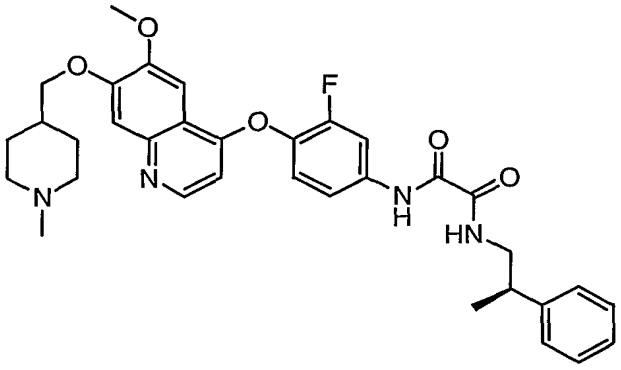
Entry	Name	Structure
177	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-indan-1-yl-oxalamide	
178	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-isobutyl-oxalamide	
179	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-methyl-butyl)-oxalamide	
180	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2*R*-phenyl-propyl)-oxalamide	

Table 1

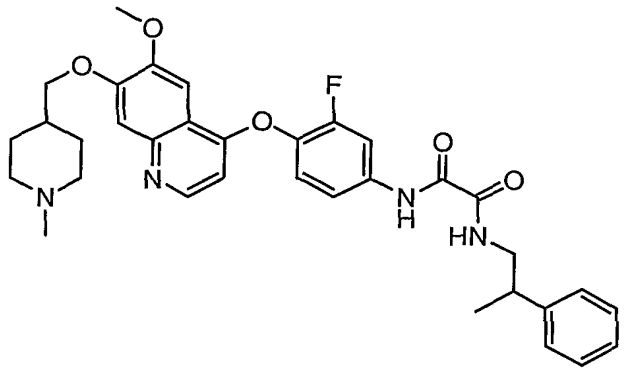
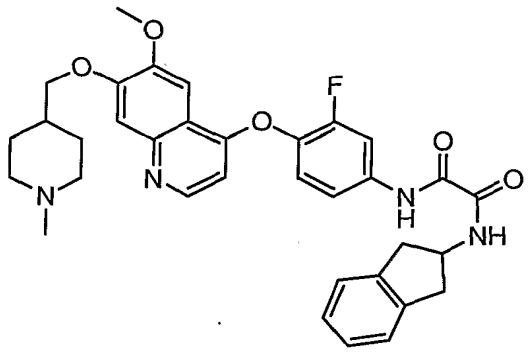
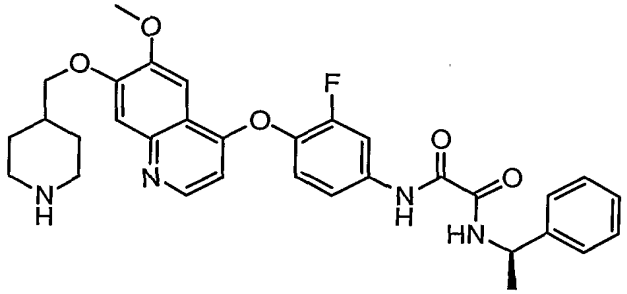
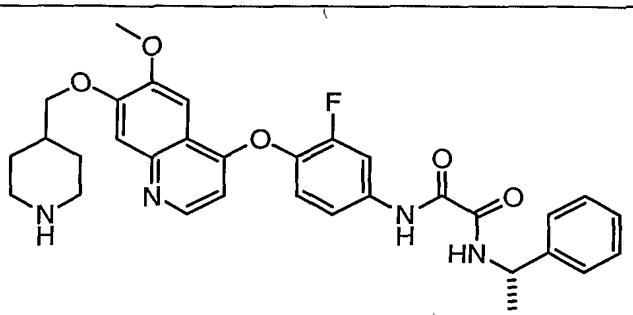
Entry	Name	Structure
181	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-phenyl-propyl)-oxalamide	
182	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-indan-2-yl-oxalamide	
183	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1*R*-phenyl-ethyl)-oxalamide	
184	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1*S*-phenyl-ethyl)-oxalamide	

Table 1

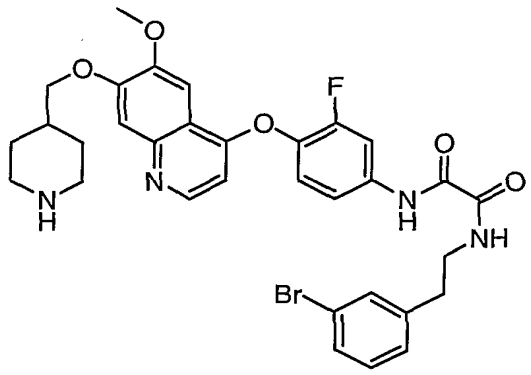
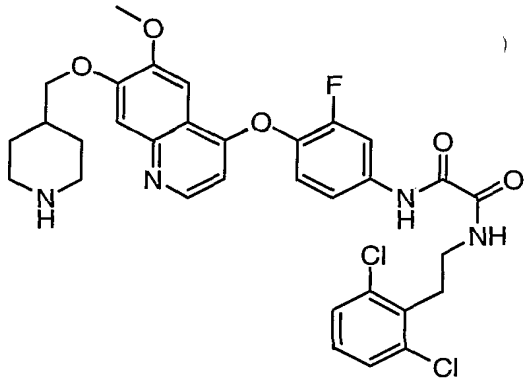
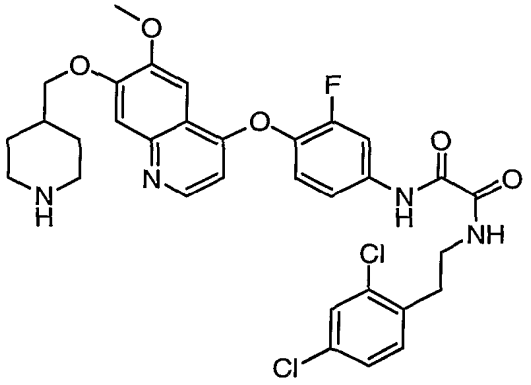
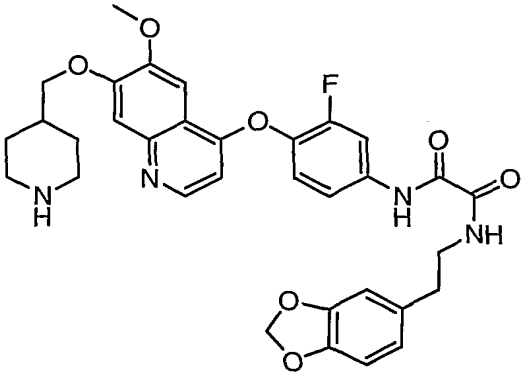
Entry	Name	Structure
185	N-[2-(3-Bromo-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
186	N-[2-(2,6-Dichloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
187	N-[2-(2,4-Dichloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
188	N-(2-Benzo[1,3]dioxol-5-yl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

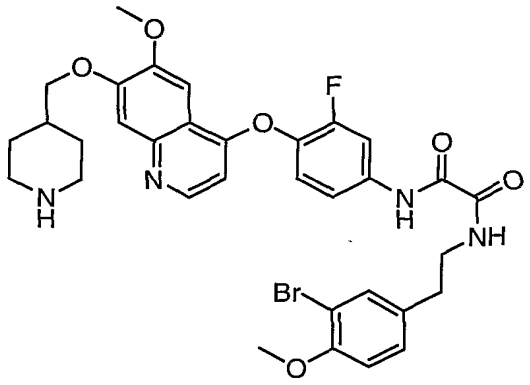
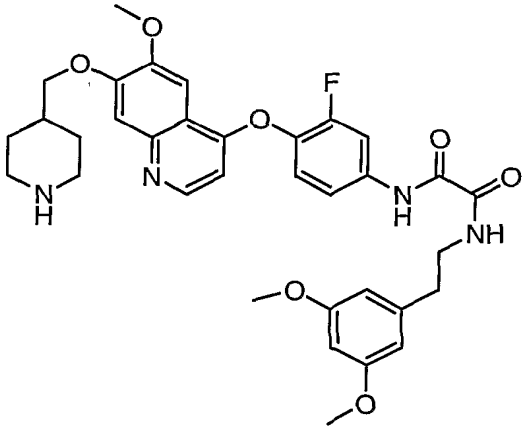
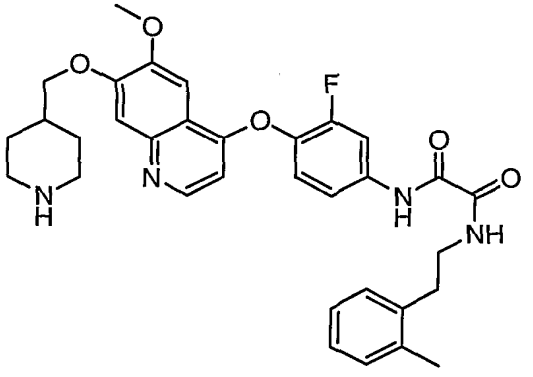
Entry	Name	Structure
189	N-[2-(3-Bromo-4-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
190	N-[2-(3,5-Dimethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
191	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-o-tolyl-ethyl)-oxalamide	

Table 1

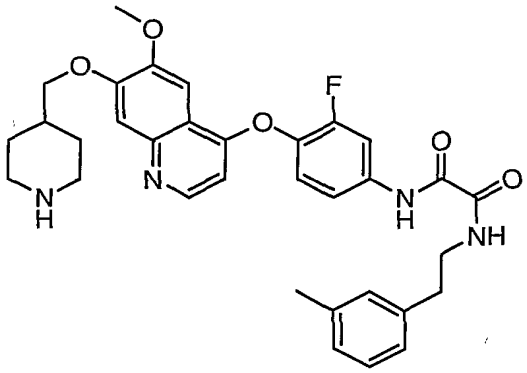
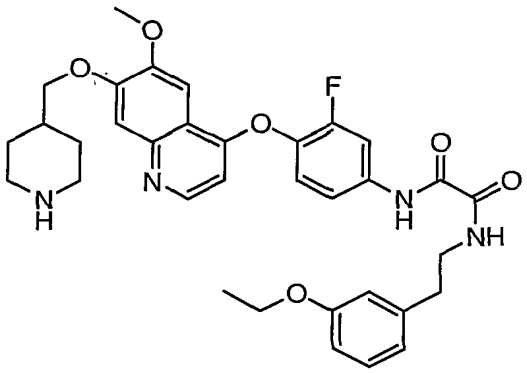
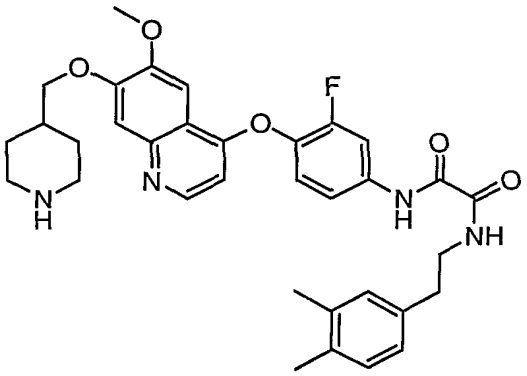
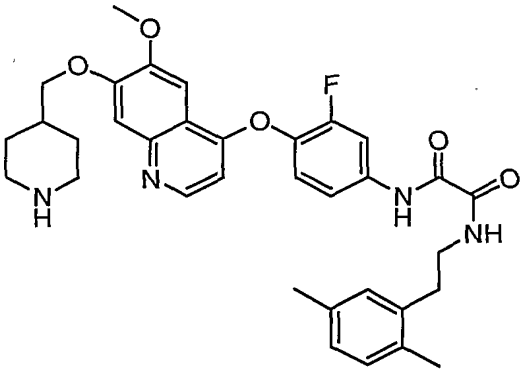
Entry	Name	Structure
192	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-m-tolyl-ethyl)-oxalamide	
193	N-[2-(3-Ethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
194	N-[2-(3,4-Dimethyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
195	N-[2-(2,5-Dimethyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

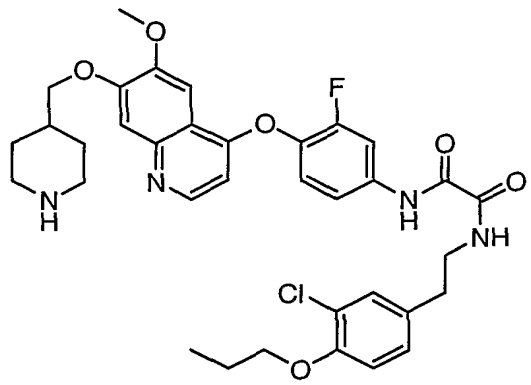
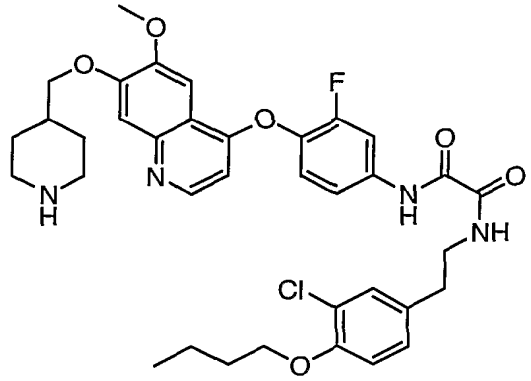
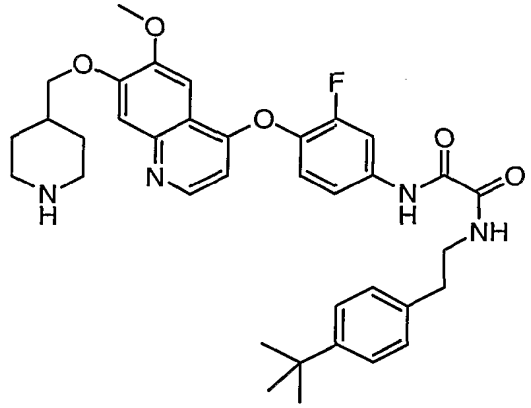
Entry	Name	Structure
196	N-[2-(3-Chloro-4-propoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
197	N-[2-(4-Butoxy-3-chloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
198	N-[2-(4-tert-Butyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

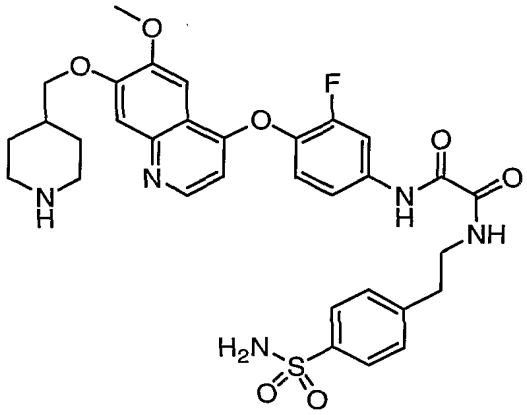
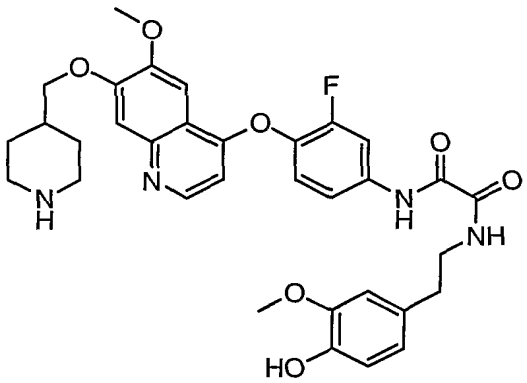
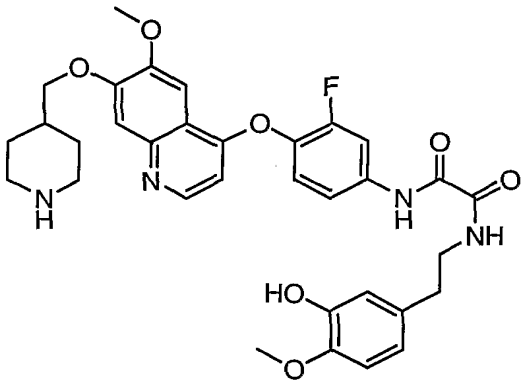
Entry	Name	Structure
199	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-sulfamoyl-phenyl)-ethyl]-oxalamide	
200	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-hydroxy-3-methoxy-phenyl)-ethyl]-oxalamide	
201	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(3-hydroxy-4-methoxy-phenyl)-ethyl]-oxalamide	

Table 1

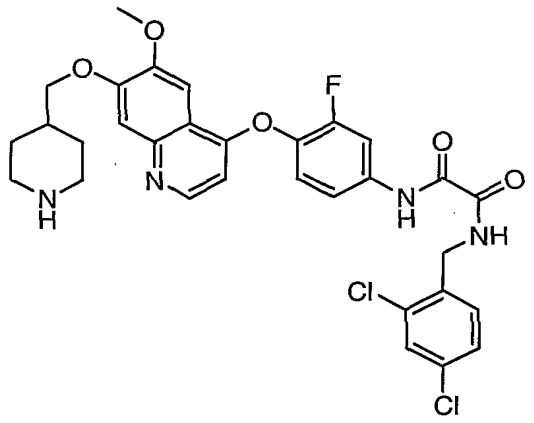
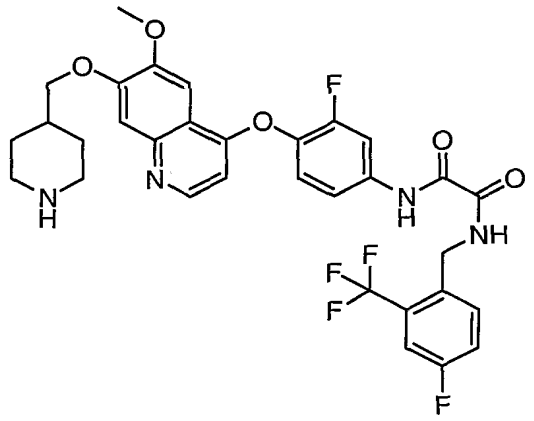
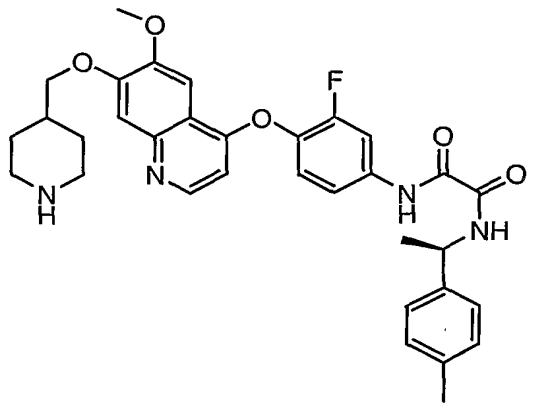
Entry	Name	Structure
202	N-(2,4-Dichloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
203	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-fluoro-2-trifluoromethyl-benzyl)-oxalamide	
204	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1-p-tolyl-ethyl)-oxalamide	

Table 1

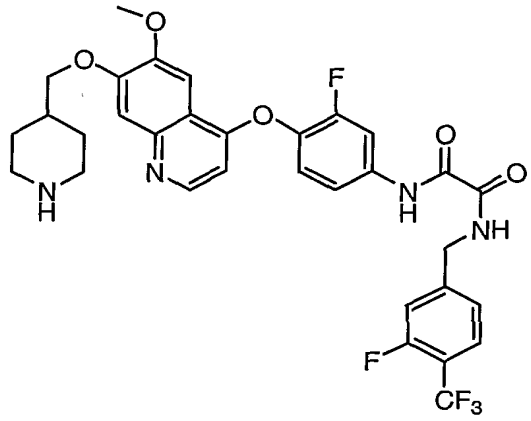
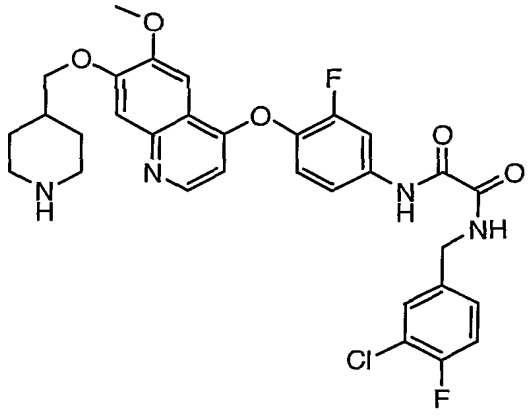
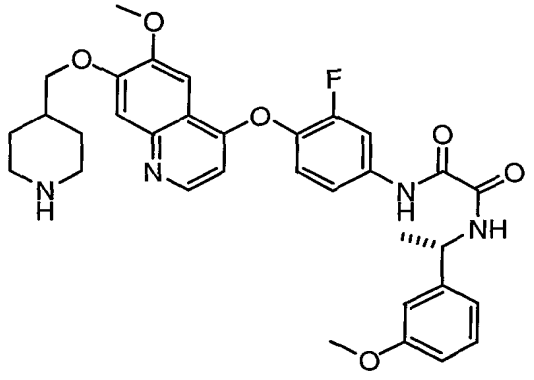
Entry	Name	Structure
205	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-fluoro-4-trifluoromethyl-benzyl)-oxalamide	
206	N-(3-Chloro-4-fluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
207	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[1-(3-methoxy-phenyl)-ethyl]-oxalamide	

Table 1

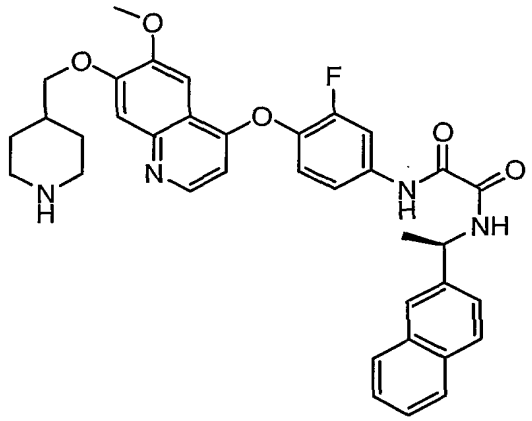
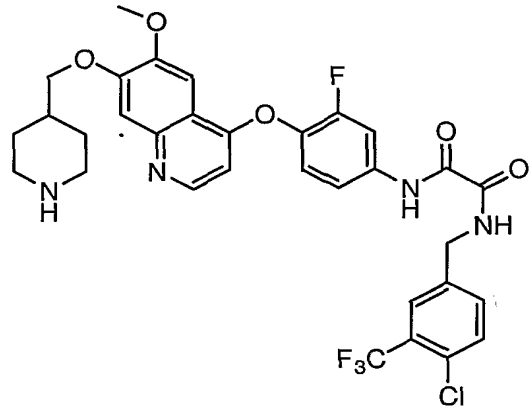
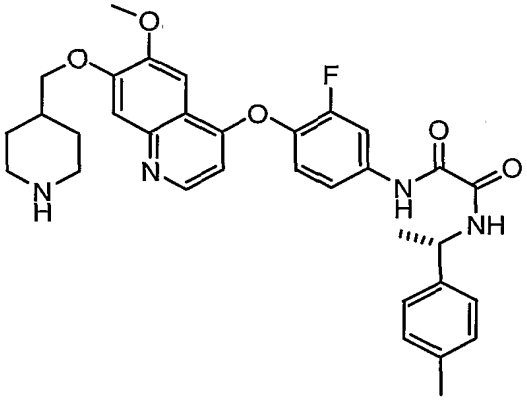
Entry	Name	Structure
208	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1-naphthalen-2-yl-ethyl)-oxalamide	
209	N-(4-Chloro-3-trifluoromethyl-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
210	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1-p-tolyl-ethyl)-oxalamide	

Table 1

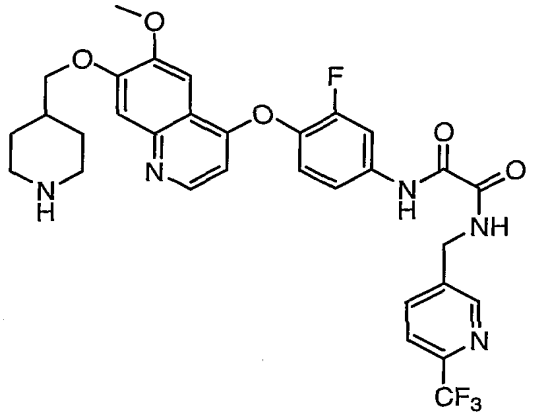
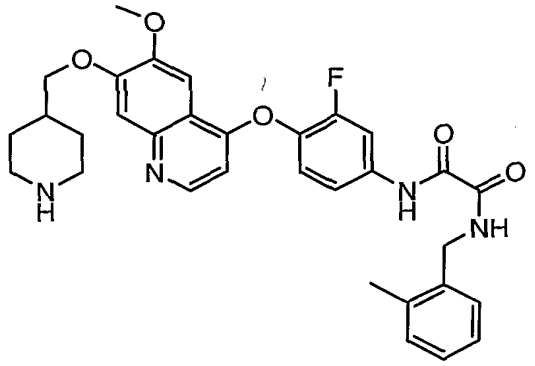
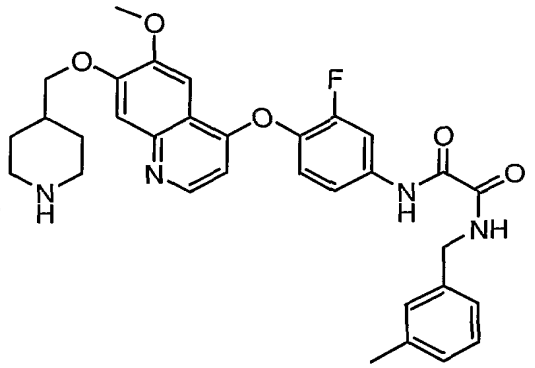
Entry	Name	Structure
211	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(6-trifluoromethyl-pyridin-3-ylmethyl)-oxalamide	
212	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-methyl-benzyl)-oxalamide	
213	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-methyl-benzyl)-oxalamide	

Table 1

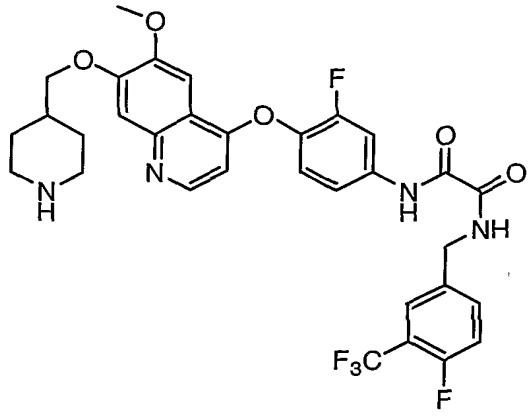
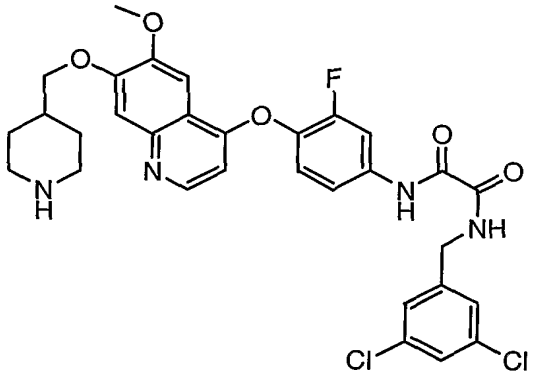
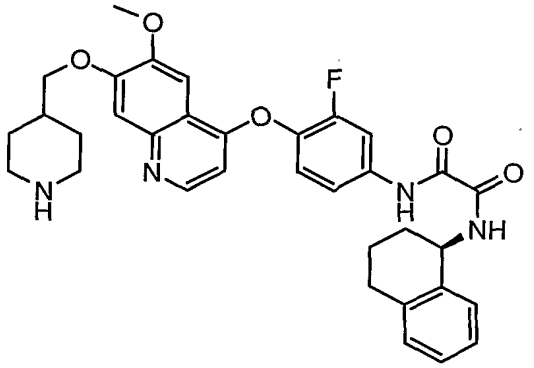
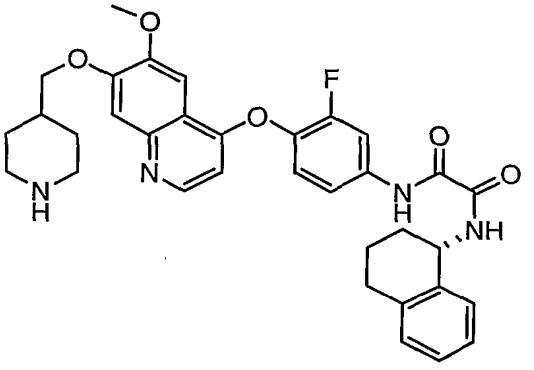
Entry	Name	Structure
214	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-fluoro-3-trifluoromethyl-benzyl)-oxalamide	
215	N-(3,5-Dichloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
216	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1R,2,3,4-tetrahydro-naphthalen-1-yl)-oxalamide	
217	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1S,2,3,4-tetrahydro-naphthalen-1-yl)-oxalamide	

Table 1

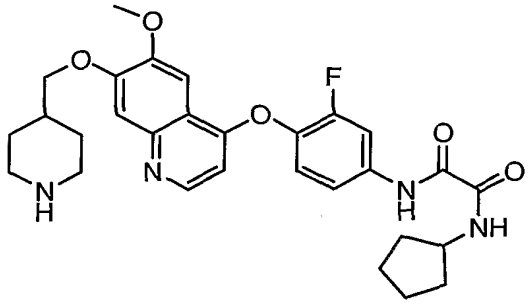
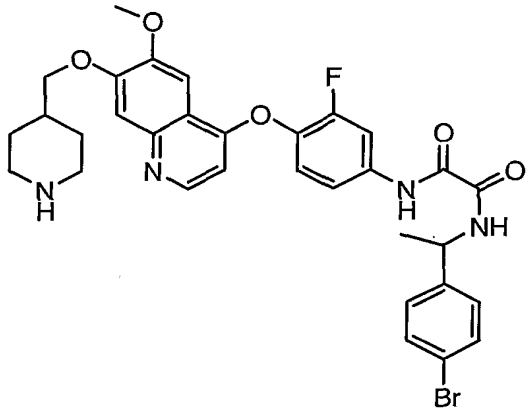
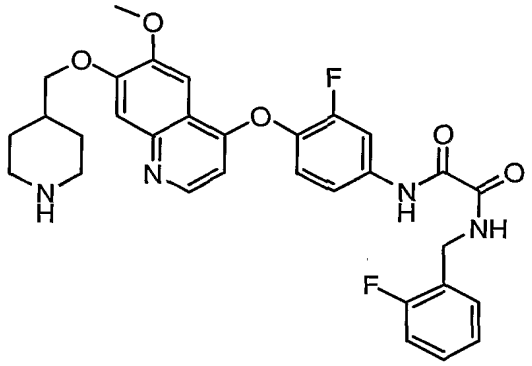
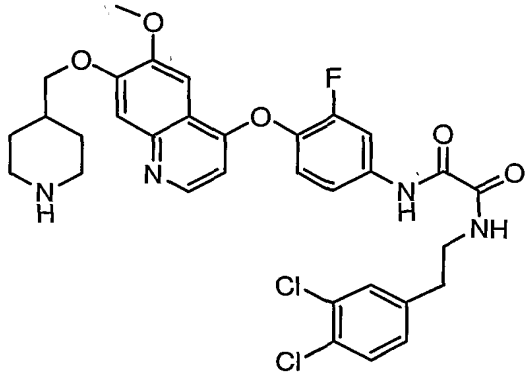
Entry	Name	Structure
218	N-Cyclopentyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
219	N-[1-(4-Bromo-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
220	N-(2-Fluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
221	N-[2-(3,4-Dichloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

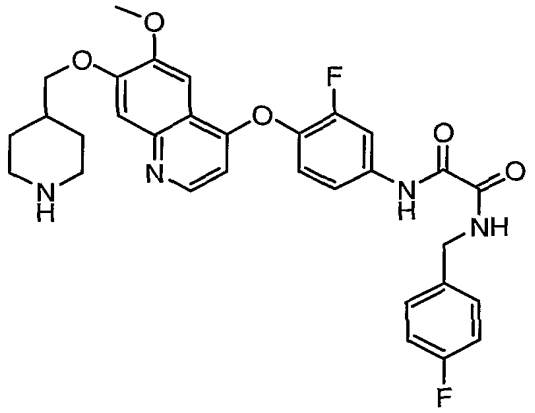
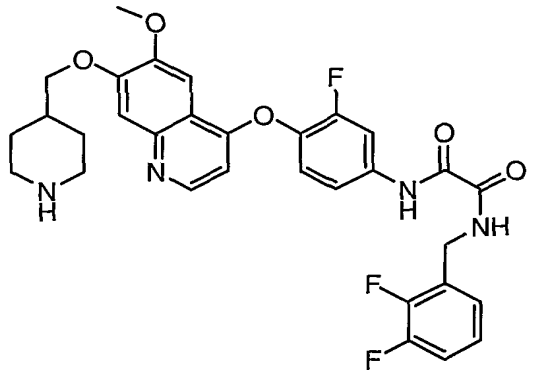
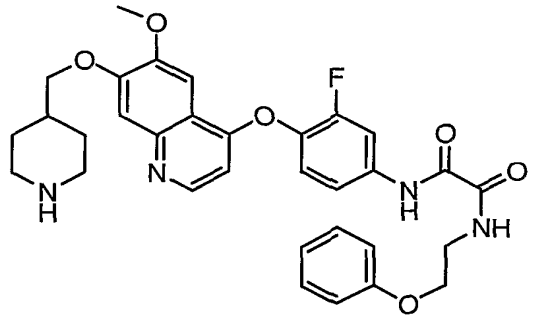
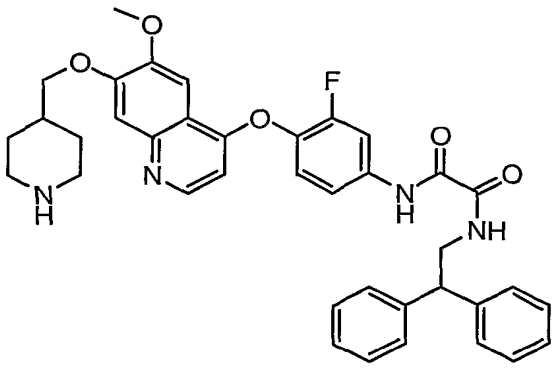
Entry	Name	Structure
222	N-(4-Fluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
223	N-(2,3-Difluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
224	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-phenoxy-ethyl)-oxalamide	
225	N-(2,2-Diphenyl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

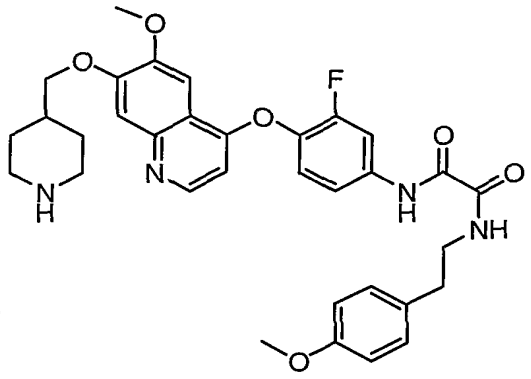
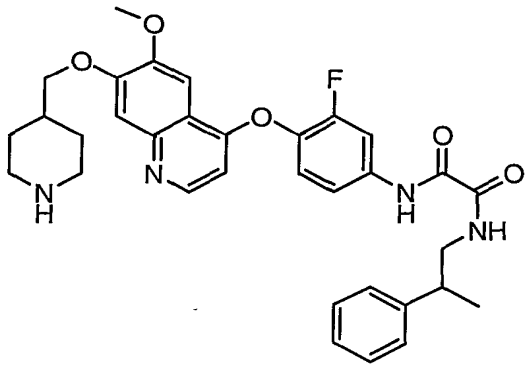
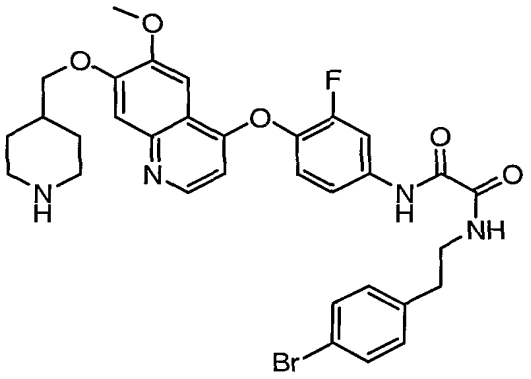
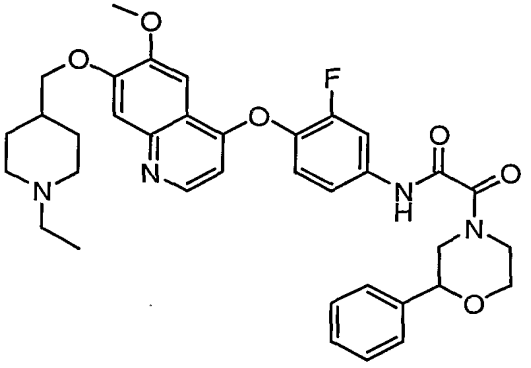
Entry	Name	Structure
226	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-methoxy-phenyl)-ethyl]-oxalamide	
227	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-phenyl-propyl)-oxalamide	
228	N-[2-(4-Bromo-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
229	N-{4-[7-(1-Ethyl-piperidin-4-ylmethoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-2-oxo-2-(2-phenyl-morpholin-4-yl)-acetamide	

Table 1

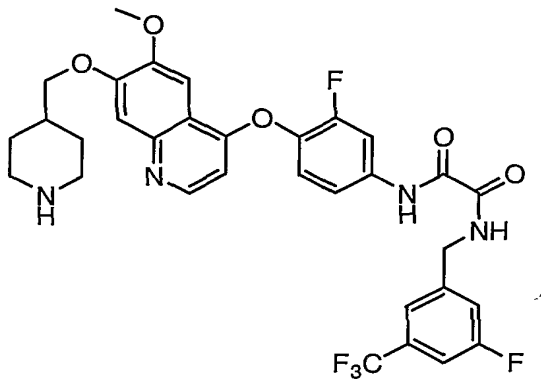
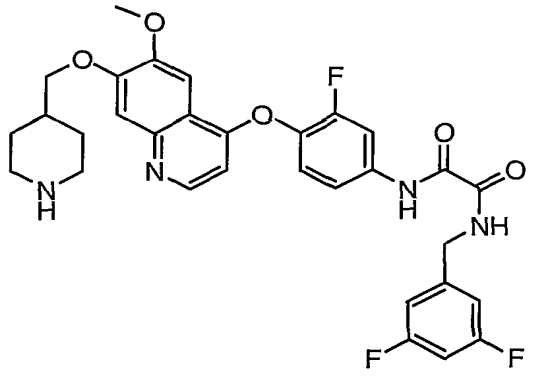
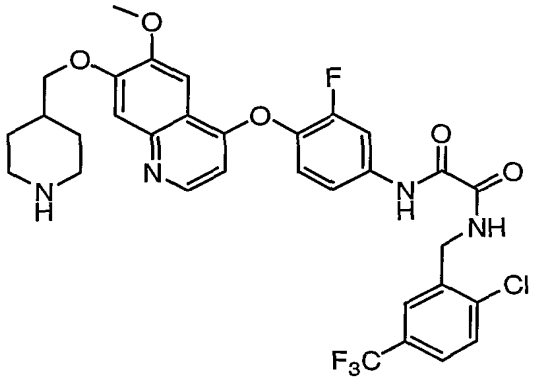
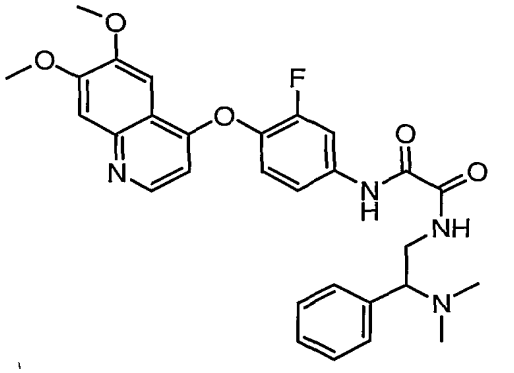
Entry	Name	Structure
230	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-fluoro-5-trifluoromethyl-benzyl)-oxalamide	
231	N-(3,5-Difluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
232	N-(2-Chloro-5-trifluoromethyl-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
233	N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-N'-(2-dimethylamino-2-phenyl-ethyl)-oxalamide	

Table 1

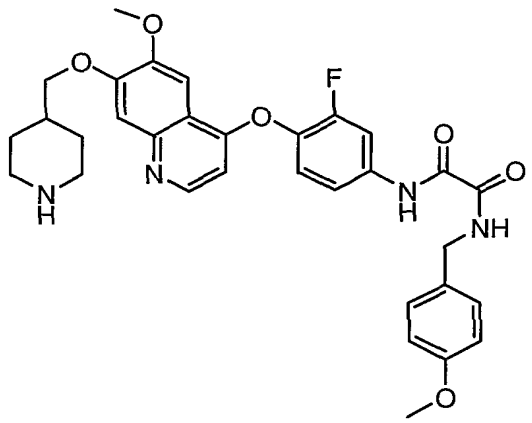
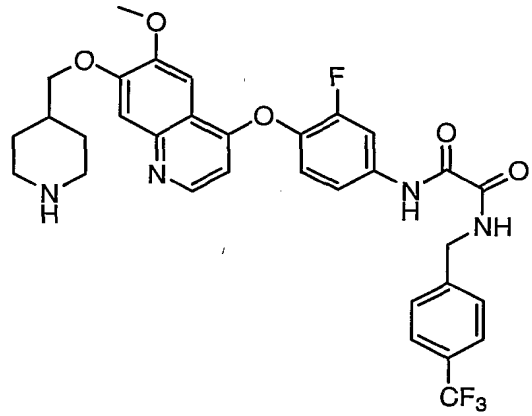
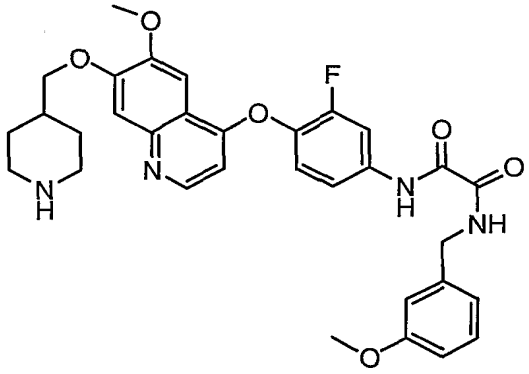
Entry	Name	Structure
234	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-methoxy-benzyl)-oxalamide	
235	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-trifluoromethyl-benzyl)-oxalamide	
236	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-methoxy-benzyl)-oxalamide	

Table 1

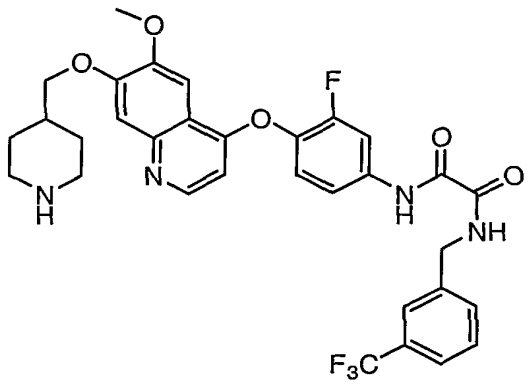
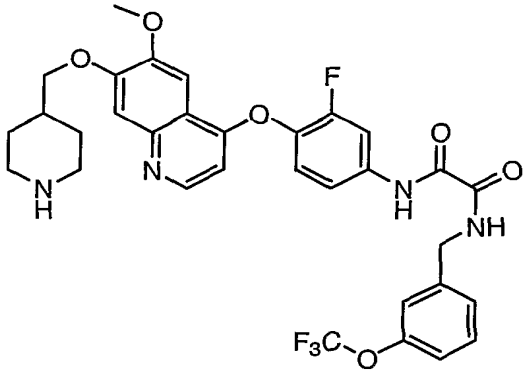
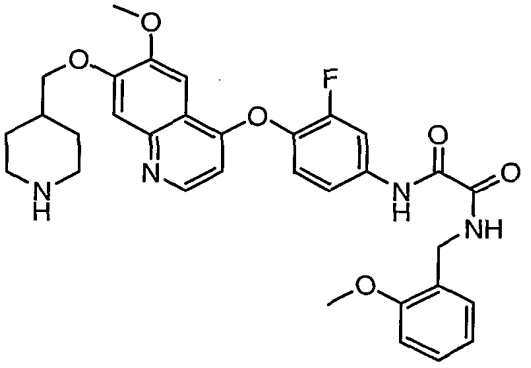
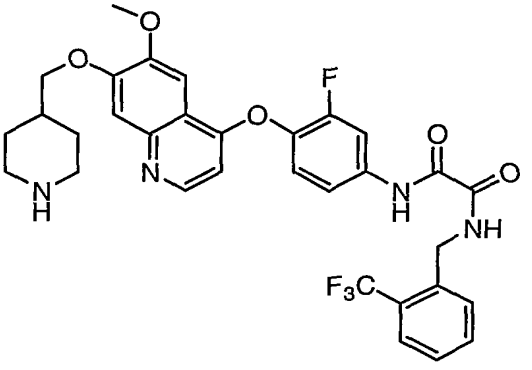
Entry	Name	Structure
237	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-trifluoromethyl-benzyl)-oxalamide	
238	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-trifluoromethoxy-benzyl)-oxalamide	
239	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-methoxy-benzyl)-oxalamide	
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Table 1

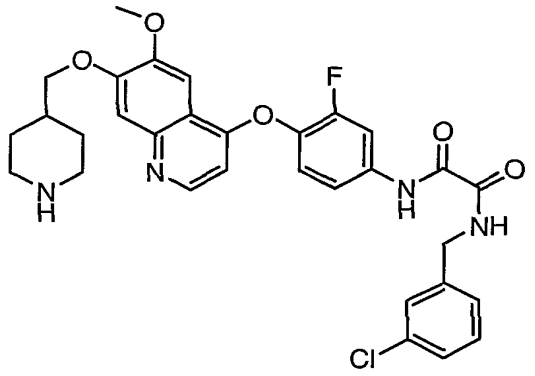
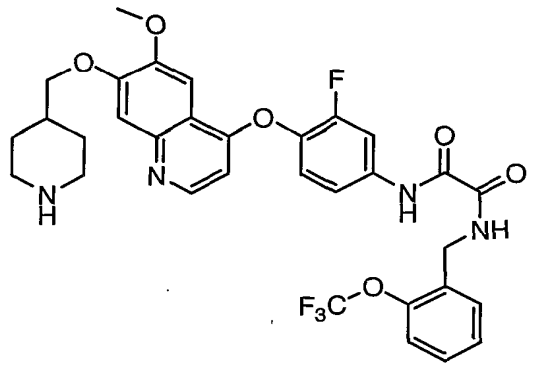
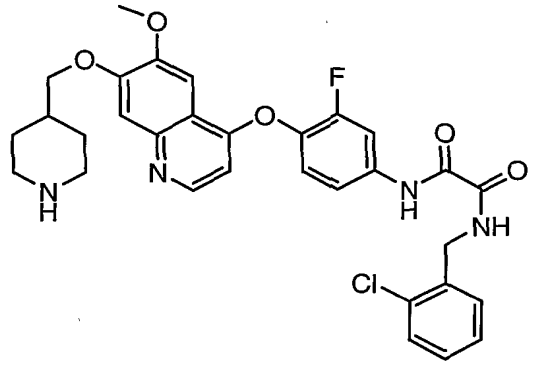
Entry	Name	Structure
241	N-(3-Chloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
242	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-trifluoromethoxy-benzyl)-oxalamide	
243	N-(2-Chloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

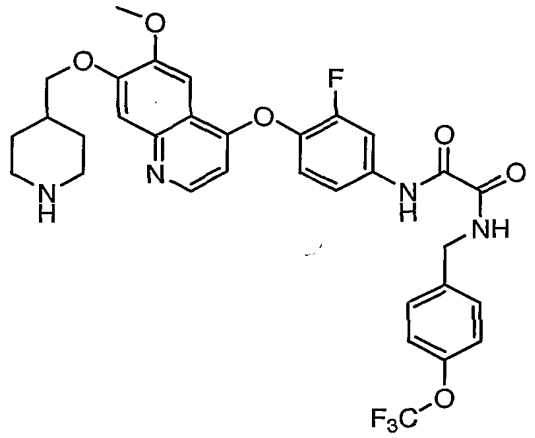
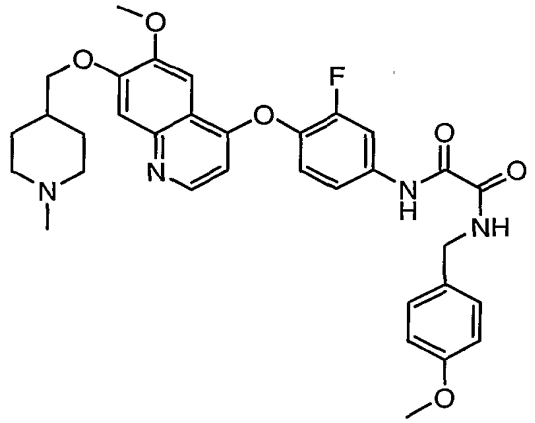
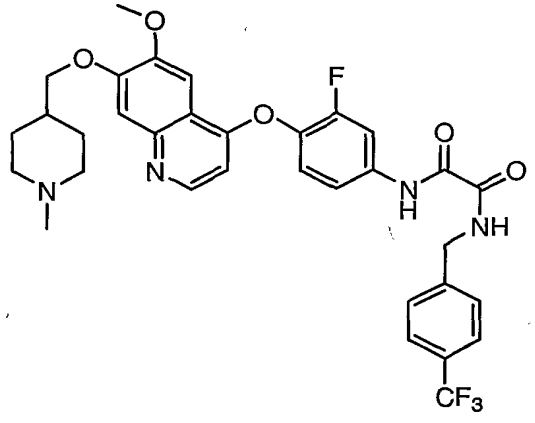
Entry	Name	Structure
244	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-trifluoromethoxy-benzyl)-oxalamide	
245	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-methoxy-benzyl)-oxalamide	
246	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-trifluoromethyl-benzyl)-oxalamide	

Table 1

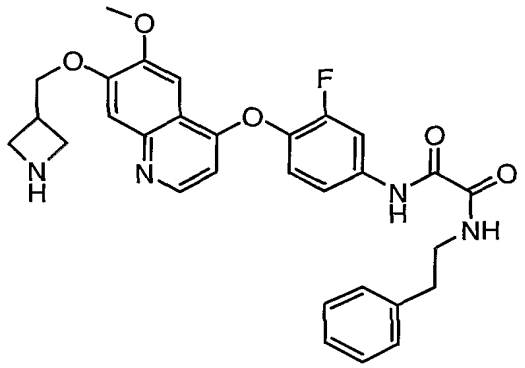
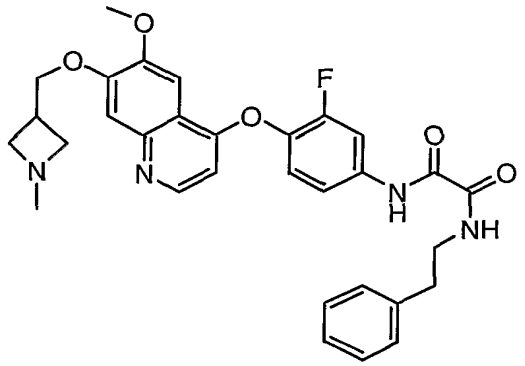
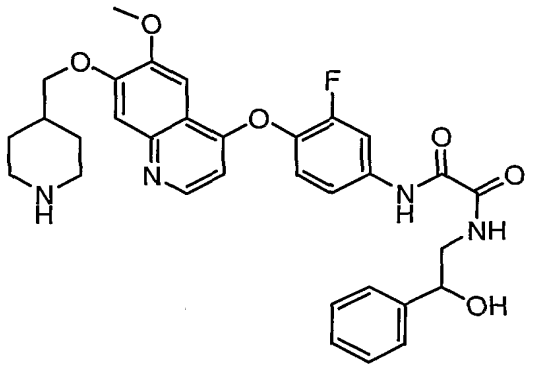
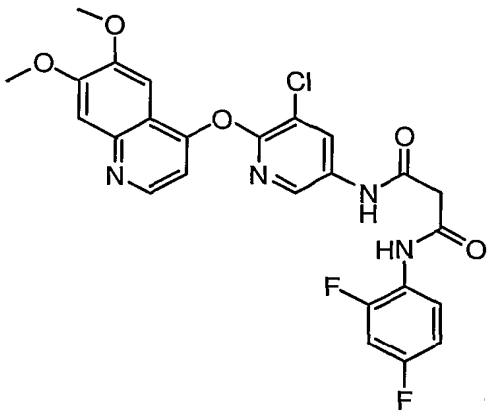
Entry	Name	Structure
247	N-{4-[7-(Azetidin-3-ylmethoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-N'-phenethyl-oxalamide	
248	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-azetidin-3-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	
249	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-hydroxy-2-phenyl-ethyl)-oxalamide	
250	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(2,4-difluoro-phenyl)-malonamide	

Table 1

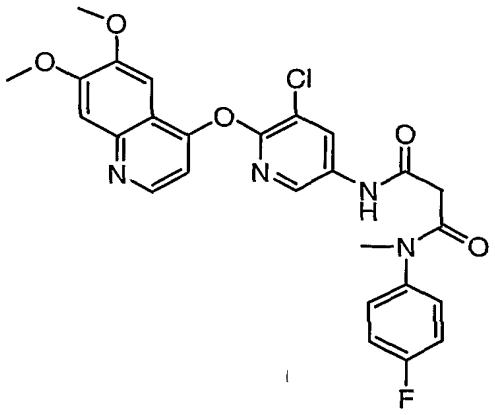
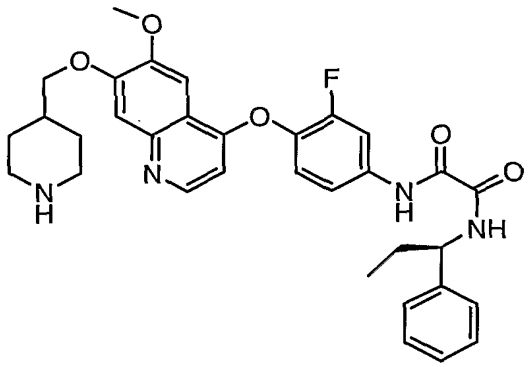
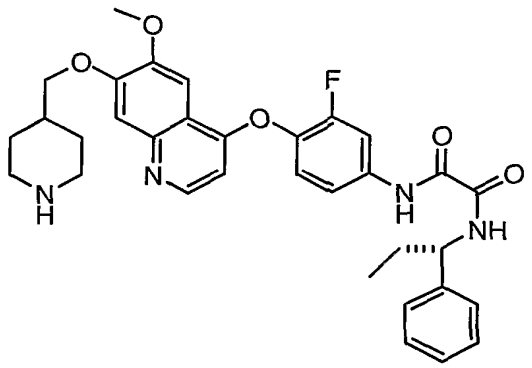
Entry	Name	Structure
251	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(4-fluoro-phenyl)-N'-methyl-malonamide	
252	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1R-phenyl-propyl)-oxalamide	
253	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1R-phenyl-propyl)-oxalamide	

Table 1

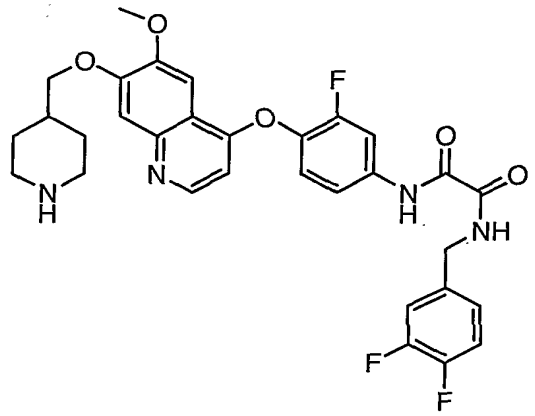
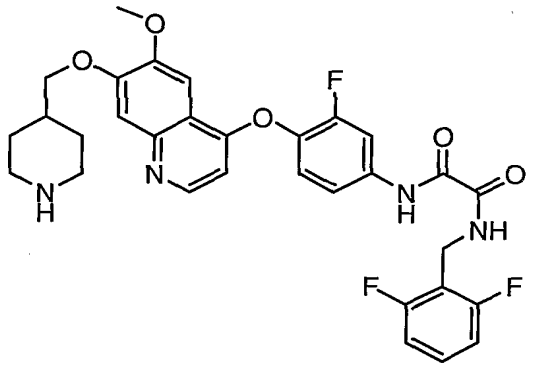
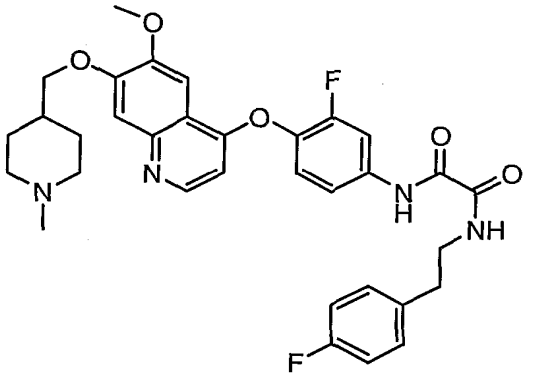
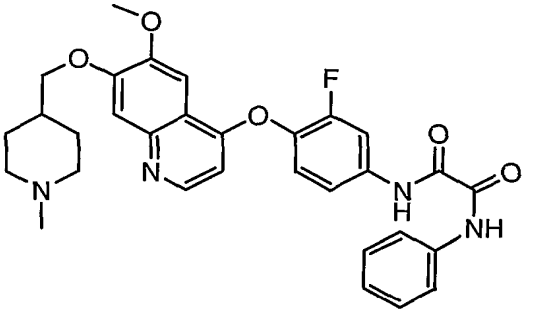
Entry	Name	Structure
254	N-(3,4-Difluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
255	N-(2,6-Difluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
256	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-fluoro-phenyl)-ethyl]-oxalamide	
257	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenyl-oxalamide	

Table 1

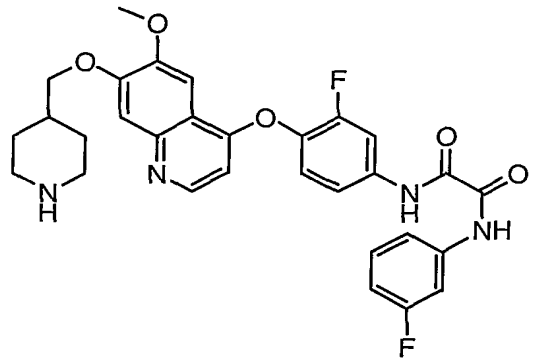
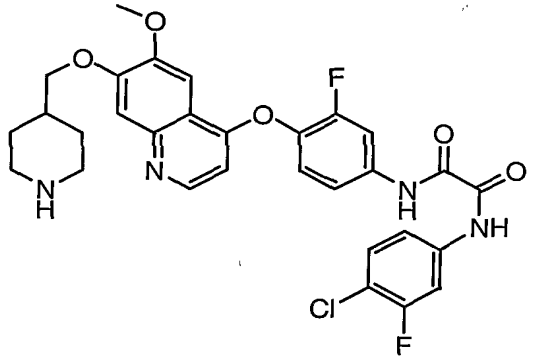
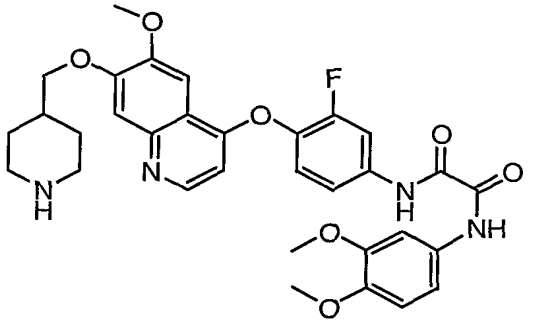
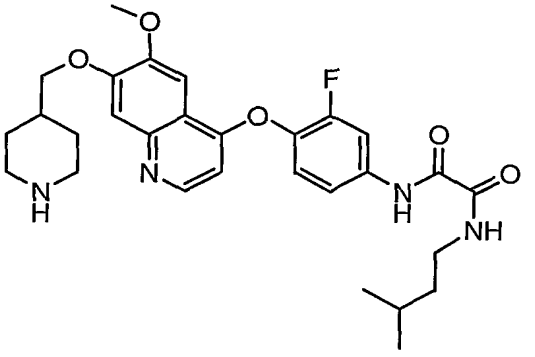
Entry	Name	Structure
258	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-fluoro-phenyl)-oxalamide	
259	N-(4-Chloro-3-fluoro-phenyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
260	N-(3,4-Dimethoxy-phenyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
261	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-methyl-butyl)-oxalamide	

Table 1

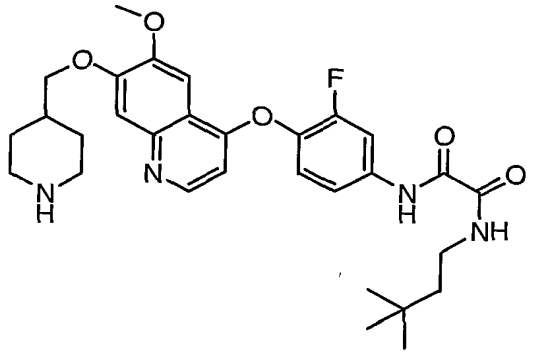
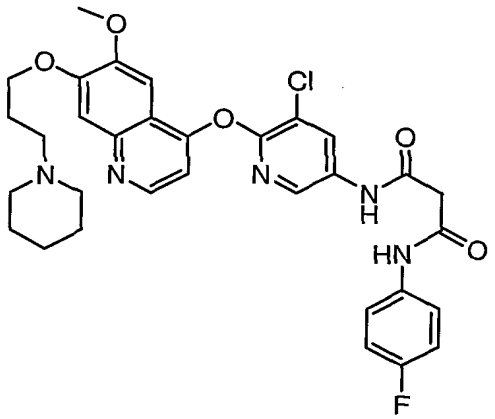
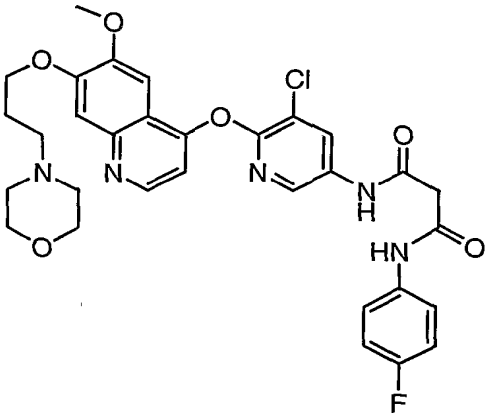
Entry	Name	Structure
262	N-(3,3-Dimethyl-butyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
263	N-{5-Chloro-6-[6-methoxy-7-(3-piperidin-1-yl-propoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide	
264	N-{5-Chloro-6-[6-methoxy-7-(3-morpholin-4-yl-propoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide	

Table 1

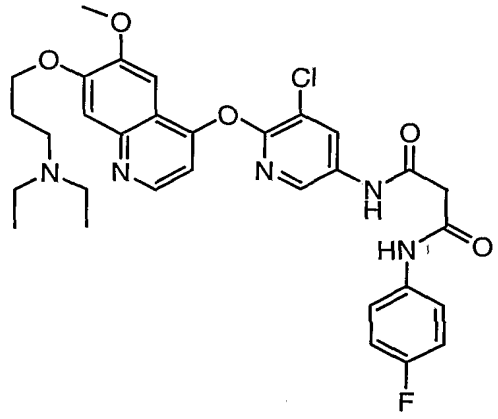
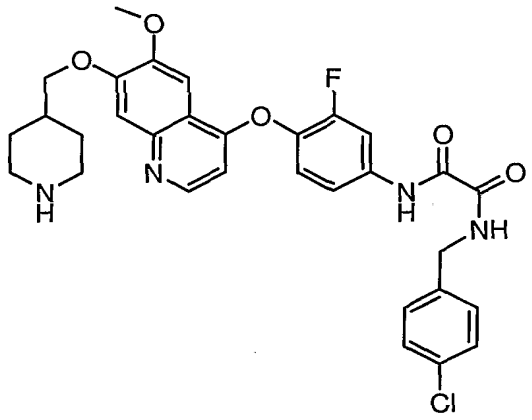
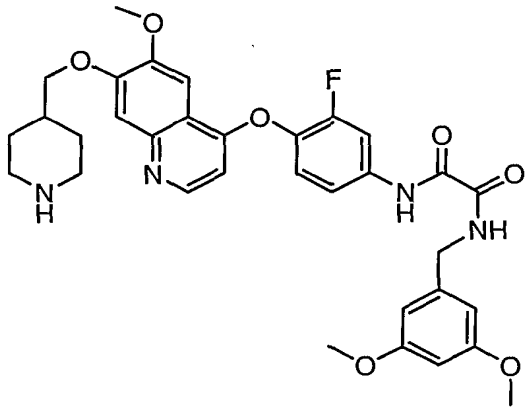
Entry	Name	Structure
265	N-{5-Chloro-6-[7-(3-diethylamino-propoxy)-6-methoxy-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide	
266	N-(4-Chloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
267	N-(3,5-Dimethoxy-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

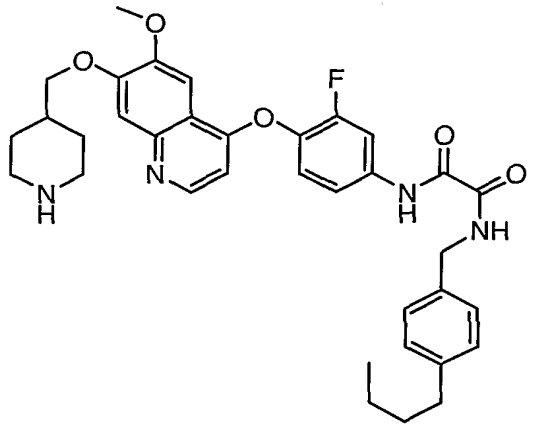
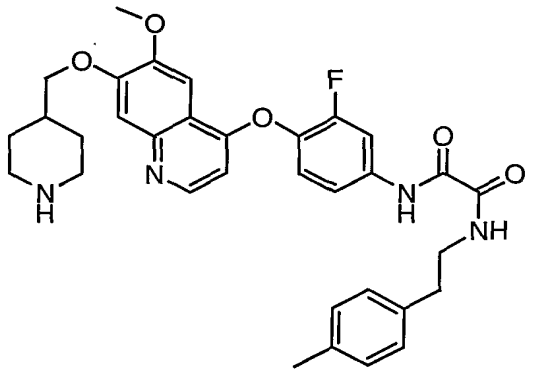
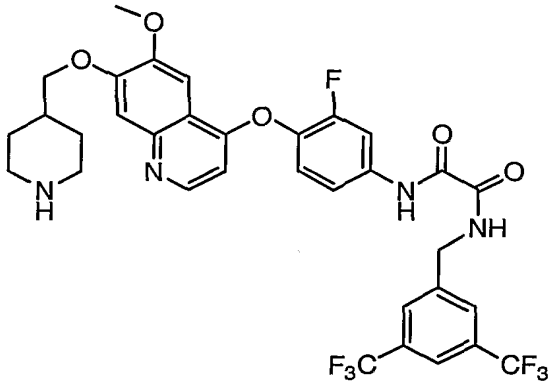
Entry	Name	Structure
268	N-(4-Butyl-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
269	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-p-tolyl-ethyl)-oxalamide	
270	N-(3,5-Bis-trifluoromethyl-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

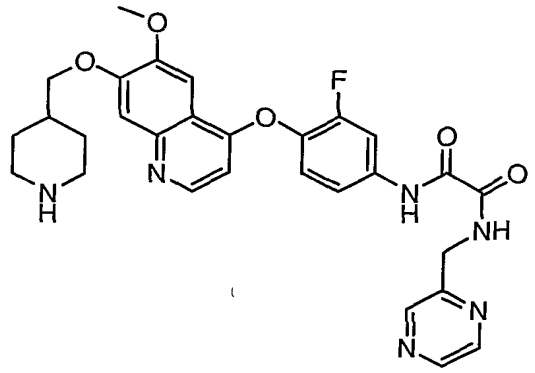
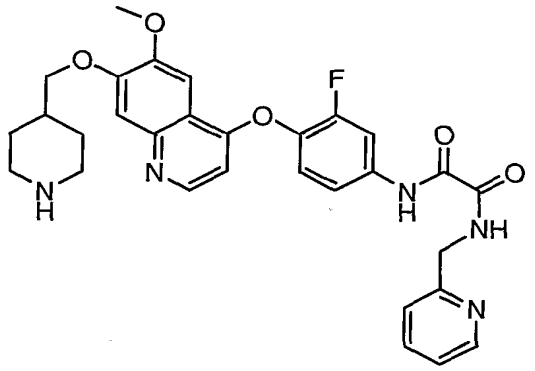
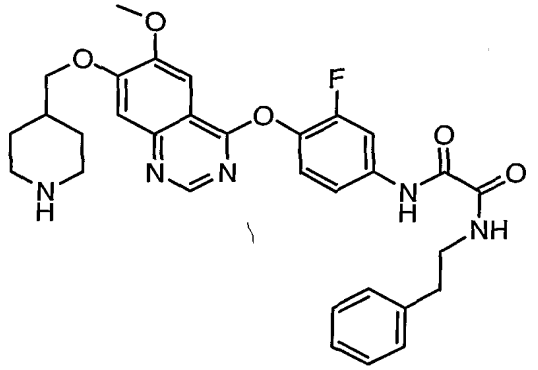
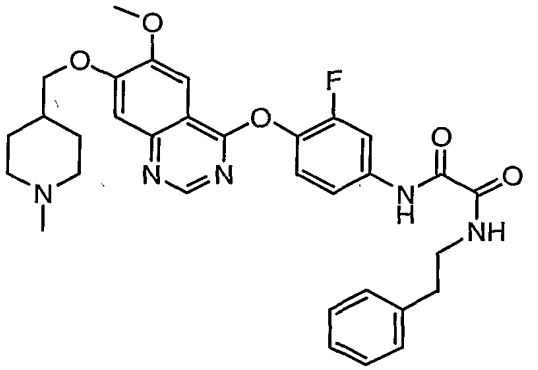
Entry	Name	Structure
271	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-pyrazin-2-ylmethyl-oxalamide	
272	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-pyridin-2-ylmethyl-oxalamide	
273	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	
274	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	

Table 1

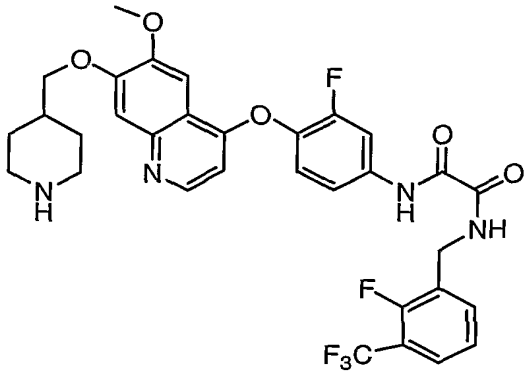
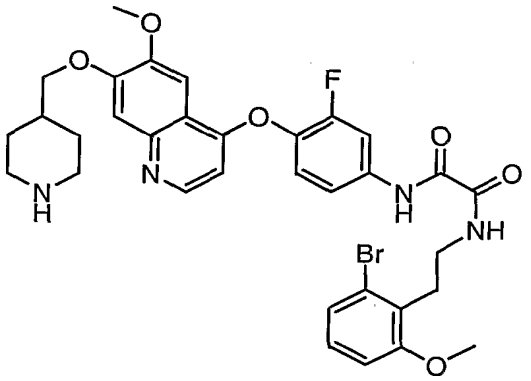
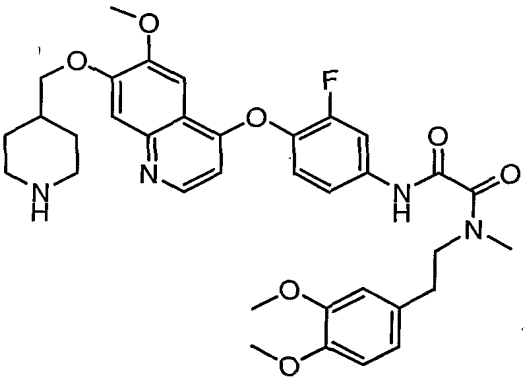
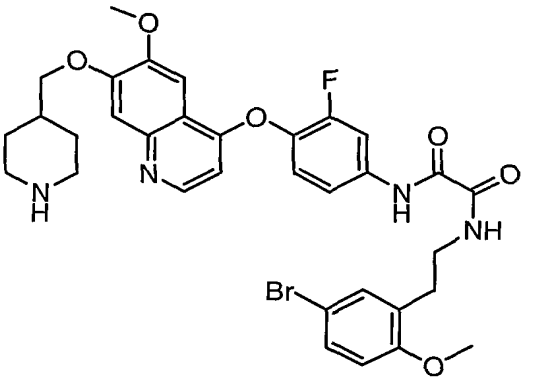
Entry	Name	Structure
275	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-fluoro-3-trifluoromethyl-benzyl)-oxalamide	
276	N-[2-(2-Bromo-6-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
277	N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N-methyl-oxalamide	
278	N-[2-(5-Bromo-2-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

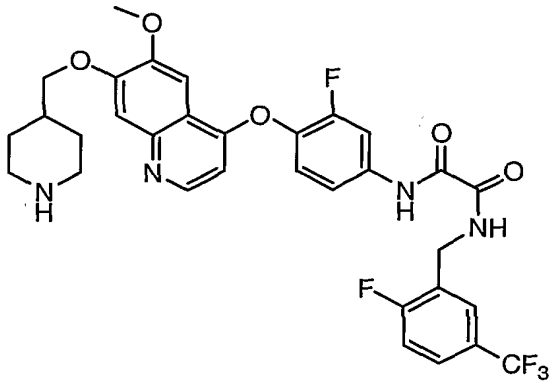
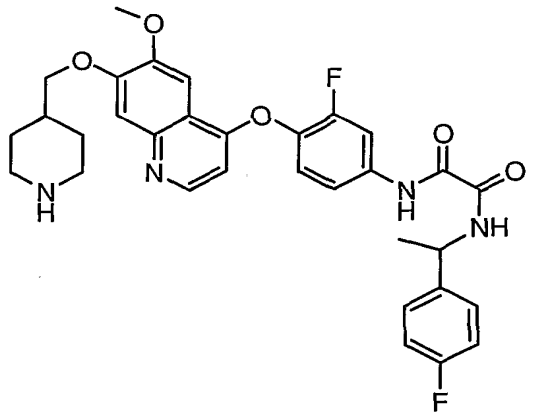
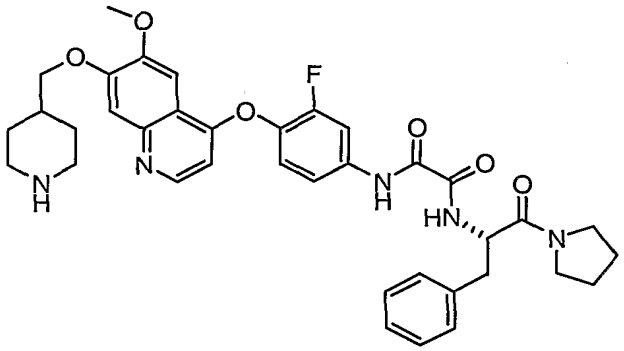
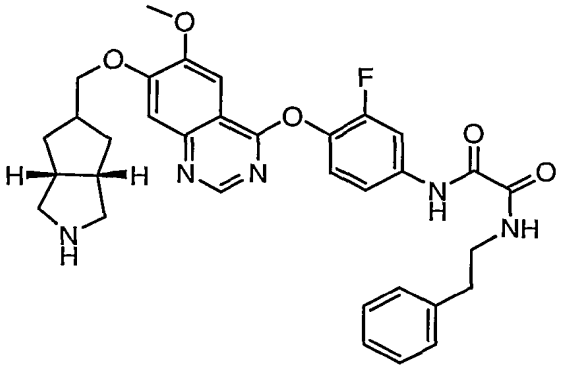
Entry	Name	Structure
279	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-fluoro-5-trifluoromethyl-benzyl)-oxalamide	
280	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[1-(4-fluoro-phenyl)-ethyl]-oxalamide	
281	N-(1S-Benzyl-2-oxo-2-pyrrolidin-1-yl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
282	N-{3-Fluoro-4-[6-methoxy-7-(octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	

Table 1

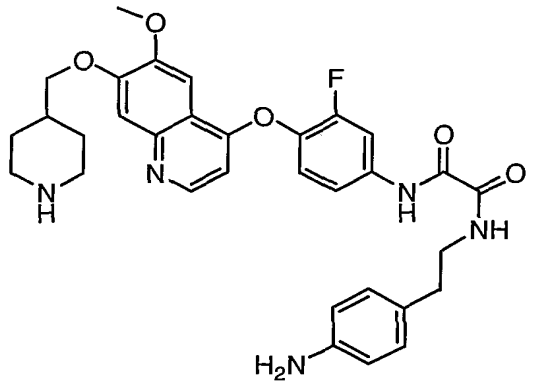
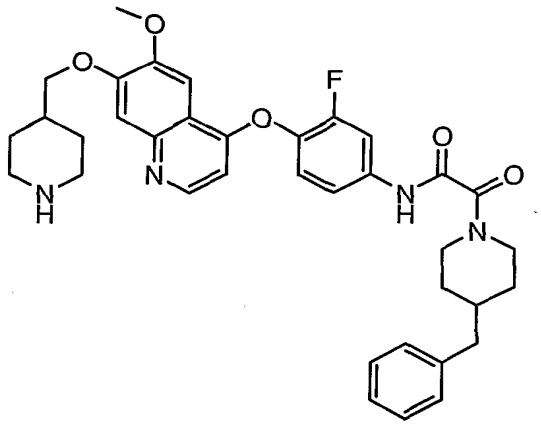
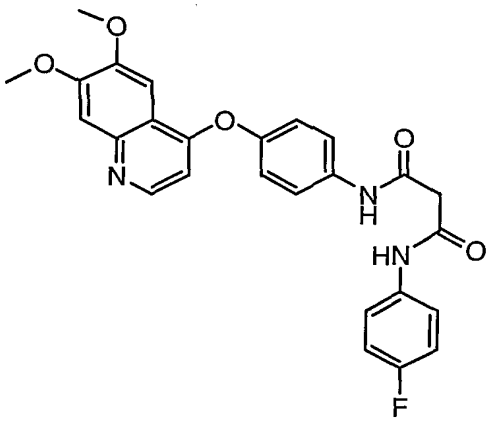
Entry	Name	Structure
283	N-[2-(4-Amino-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
284	2-(4-Benzyl-piperidin-1-yl)-N-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-acetamide	
285	N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-phenyl]-N'-(4-fluoro-phenyl)-malonamide	

Table 1

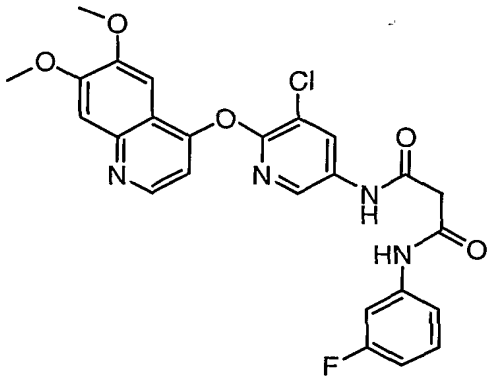
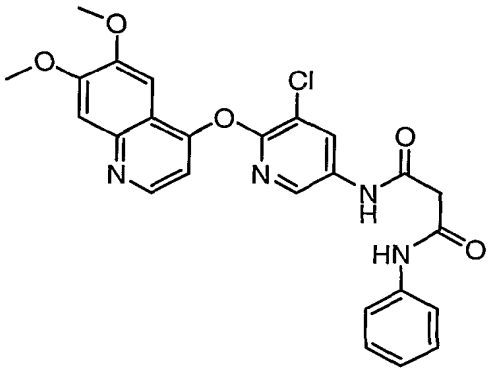
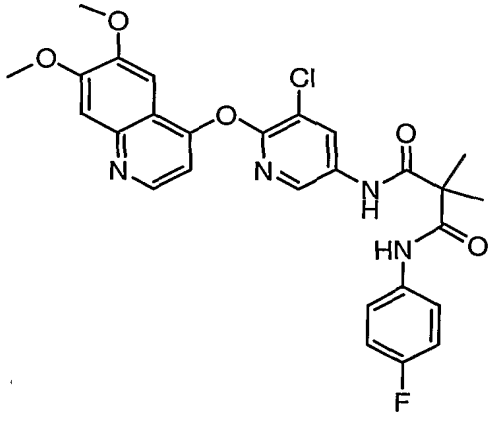
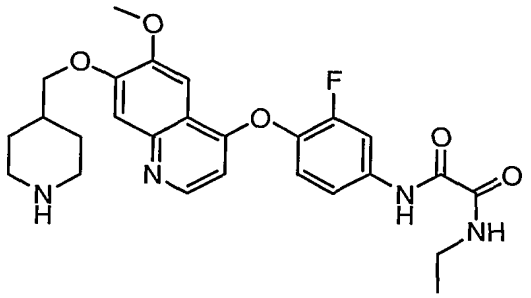
Entry	Name	Structure
286	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(3-fluoro-phenyl)-malonamide	
287	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-phenyl-malonamide	
288	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(4-fluoro-phenyl)-2,2-dimethyl-malonamide	
289	N-Ethyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

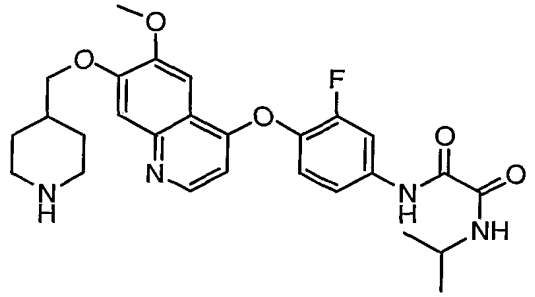
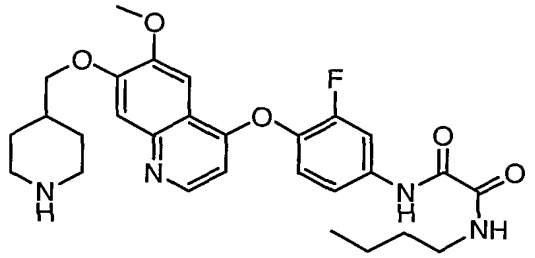
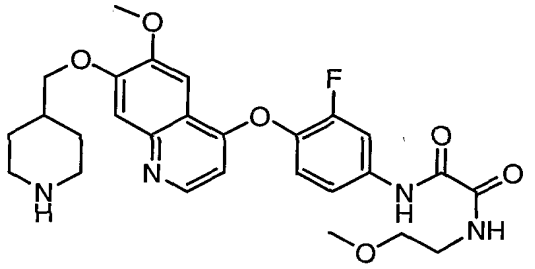
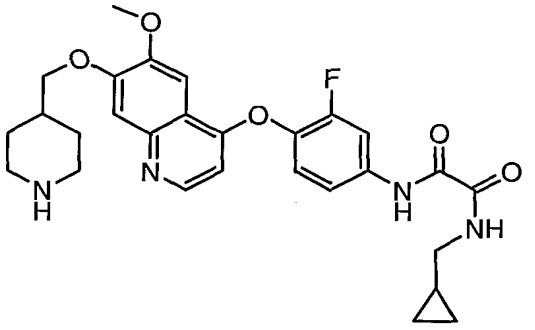
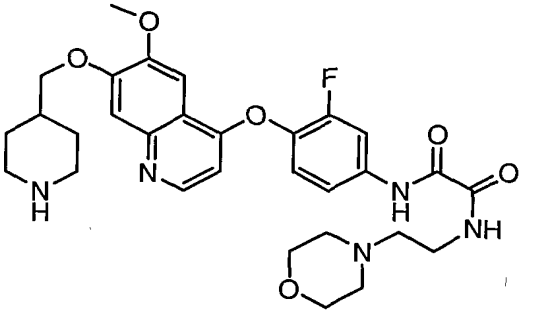
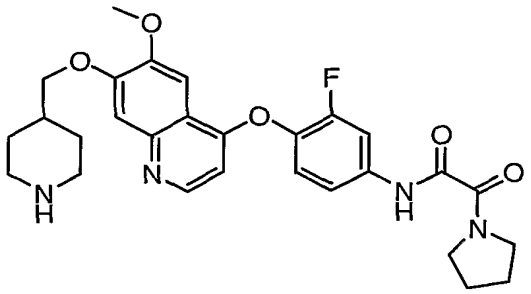
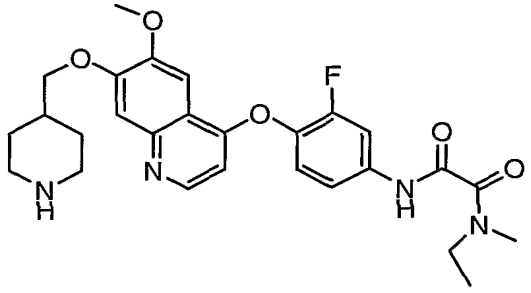
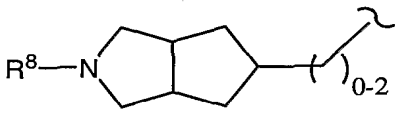
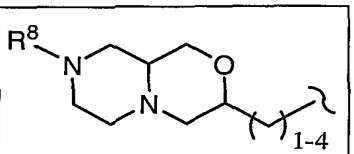
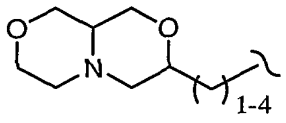
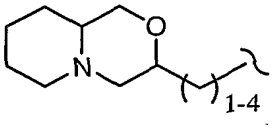
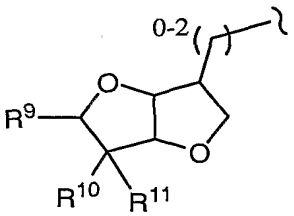
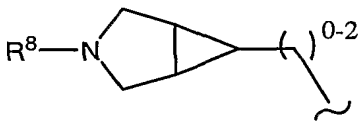
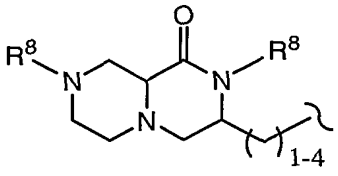
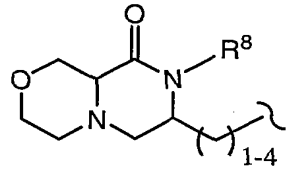
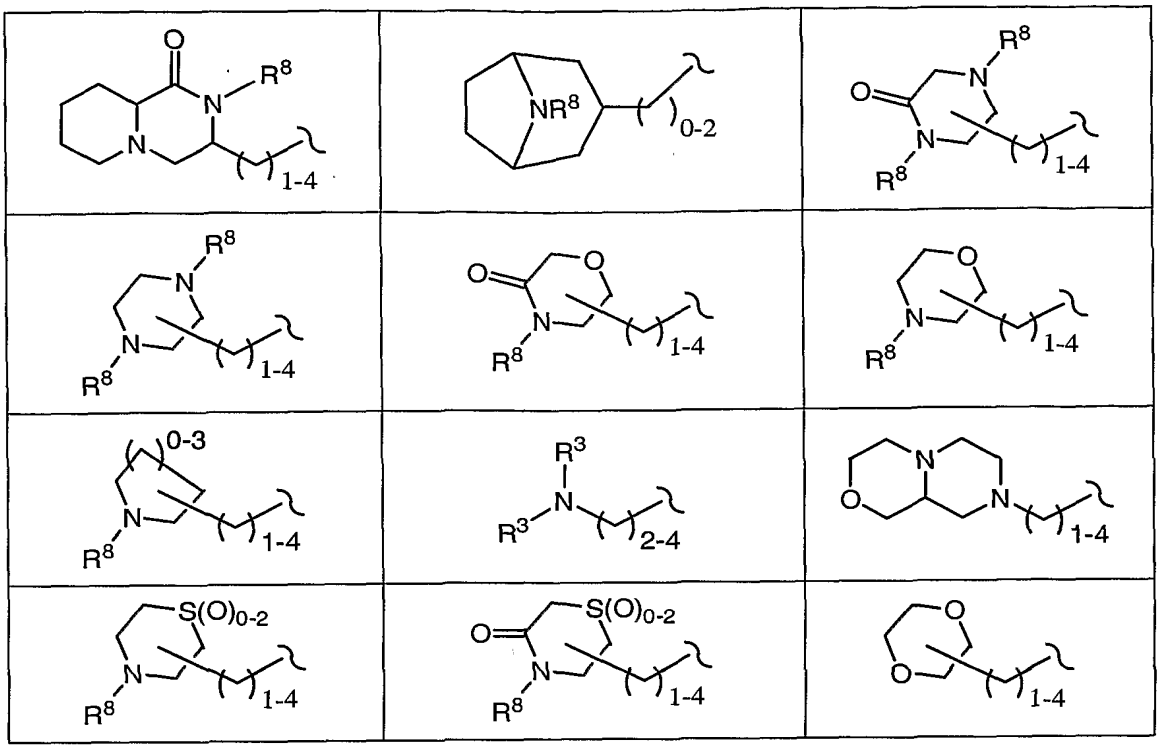
Entry	Name	Structure
290	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-isopropyl-oxalamide	
291	N-Butyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
292	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-methoxy-ethyl)-oxalamide	
293	N-Cyclopropylmethyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
294	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-morpholin-4-yl-ethyl)-oxalamide	

Table 1

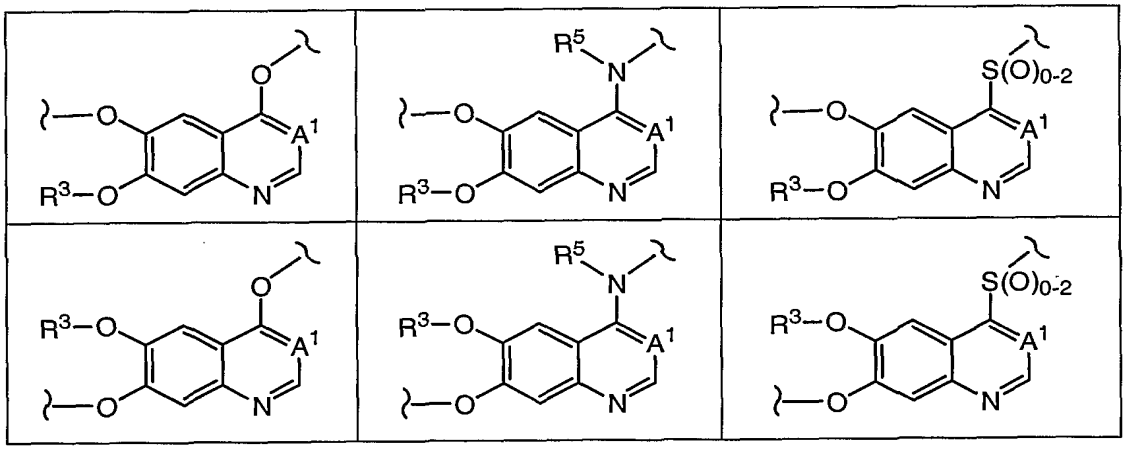
Entry	Name	Structure
295	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-2-pyrrolidin-1-yl-acetamide	
296	N-Ethyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N-methyl-oxalamide	

[0078] In another aspect, the invention comprises a compound for modulating kinase activity of formula A-B-C, or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein, A is selected from:

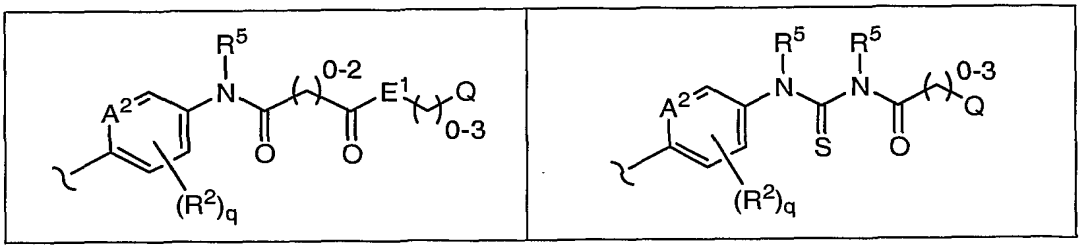
$-R^3$		
		
		

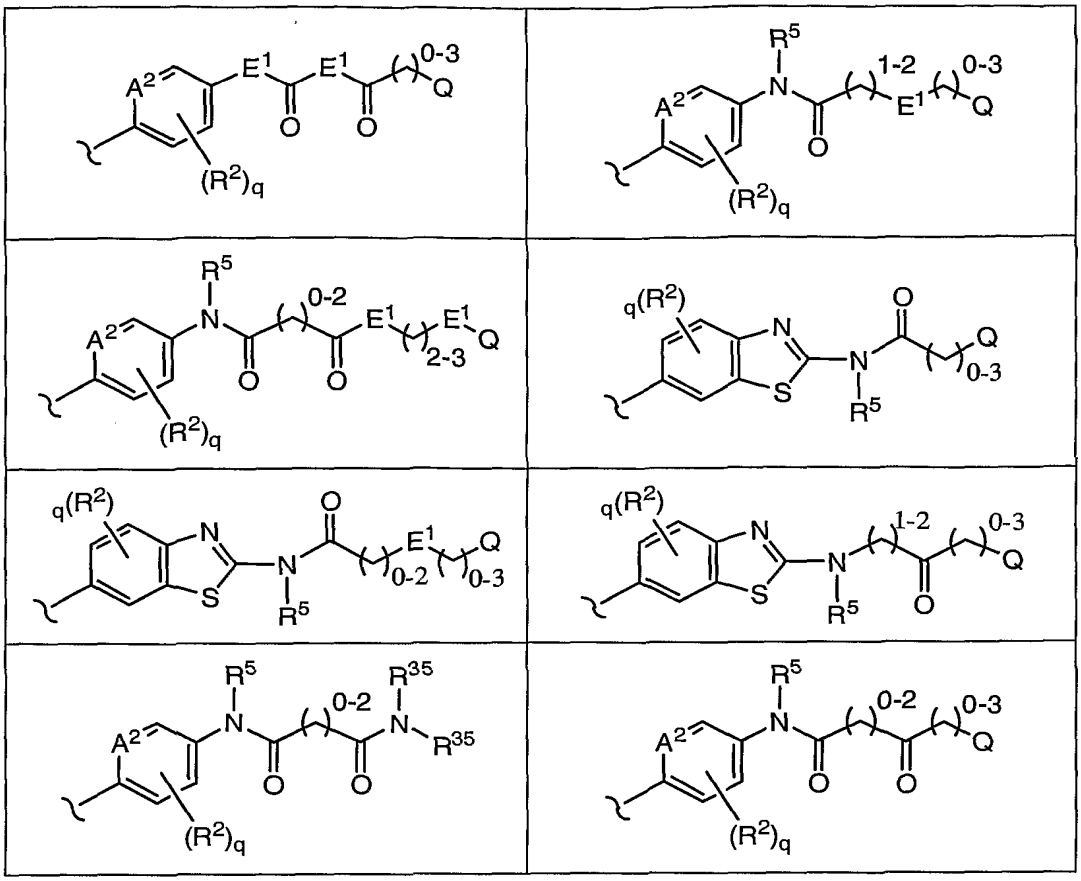


B is selected from:



and, C is selected from:





wherein R^2 is selected from -H, halogen, trihalomethyl, -CN, $-NH_2$, $-NO_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted lower alkyl;

q is 0 to 2;

each R^3 is independently selected from –H, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted arylalkyl, and optionally substituted heteroarylalkyl;

two R^3, together with the nitrogen to which they are attached, form a four- to seven-membered heteroalicyclic, said four- to seven-membered heteroalicyclic optionally containing one additional heteroatom; when one said additional heteroatom is a nitrogen, then said nitrogen is optionally substituted with a group selected from -H, trihalomethyl, $-SO_2R^5$, $-SO_2NR^5R^5$, $-CO_2R^5$, $-C(O)NR^5R^5$, $-C(O)R^5$, and optionally substituted lower alkyl;

each R^{35} is independently selected from -H, $-C(=O)R^3$, $-C(=O)OR^3$, $-C(=O)SR^3$, $-SO_2R^3$, $-C(=O)N(R^3)R^3$, and optionally substituted lower alkyl;

two R^{35}, together with the nitrogen to which they are attached, can combine to form a heteroalicyclic optionally substituted with between one and four of R^{60}, said heteroalicyclic may have an additional annular heteroatom, and said heteroalicyclic may have an aryl fused thereto, said aryl optionally substituted with an additional one to four of R^{60};

A^1 is selected from =N-, =C(H)-, and =C(CN)-;

A^2 is either =N- or =C(H)-;

R^5 is -H or optionally substituted lower alkyl;

R^8 is selected from R^3, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$;

R^9, R^{10}, and R^{11} are each independently selected from -H, and $-OR^{12}$; or

R^9 is selected from -H, and $-OR^{12}$, and R^{10} and R^{11}, when taken together, are either an optionally substituted alkylidene or an oxo; and

R^{12} is selected from -H, $-C(O)R^3$, optionally substituted lower alkylidyne, optionally substituted lower arylalkylidyne, optionally substituted lower heterocyclylalkylidyne, optionally substituted lower alkylidene, optionally substituted lower alkylidenearyl, optionally substituted lower alkylideneheterocyclyl, optionally substituted lower alkyl, optionally substituted lower alkylaryl, optionally substituted aryl, optionally substituted lower heterocyclylalkyl, and optionally substituted heterocyclyl;

or two R^{12}'s, when taken together, form 1) a corresponding spirocyclic ketal when said two R^{12}'s stem from R^{10} and R^{11}, or 2) a corresponding cyclic ketal when said two R^{12}'s stem from R^9 and one of R^{10} and R^{11};

E^1 is selected from -O-, $-CH_2-$, $-N(R^5)-$, and $-S(O)_{0-2}-$;

Q is a five- to ten-membered ring system, optionally substituted with between zero and four of R^{20};

R^{20} is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted lower alkyl;

R^{60} is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$,

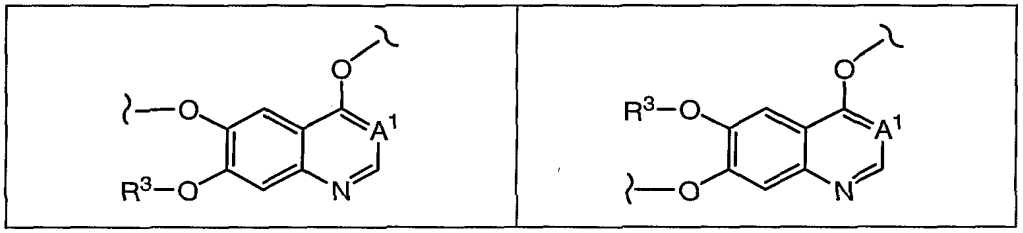
$-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted heteroarylalkyl, and optionally substituted arylalkyl;

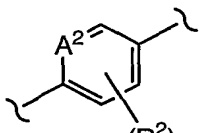
two of R^{60}, when attached to a non-aromatic carbon, can be oxo;

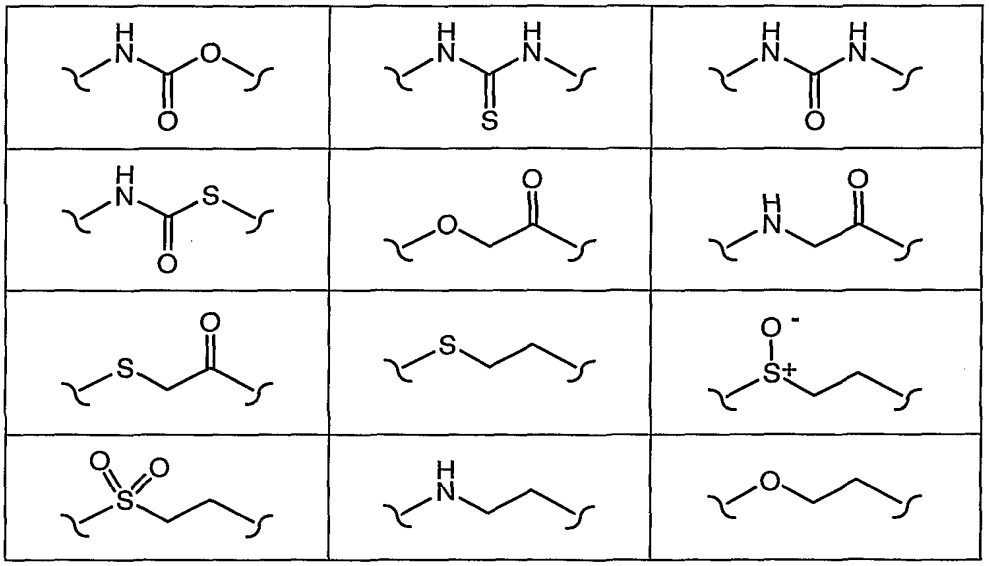
each methylene in any of the above formulae is independently optionally substituted with R^{25};

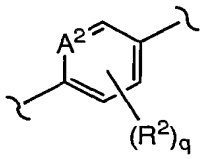
each R^{25} is independently selected from halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted arylalkyl, heteroarylalkyl, and optionally substituted lower alkyl; two of R^{25}, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered alicyclic or heteroalicyclic, two of R^{25} on a single carbon can be oxo;

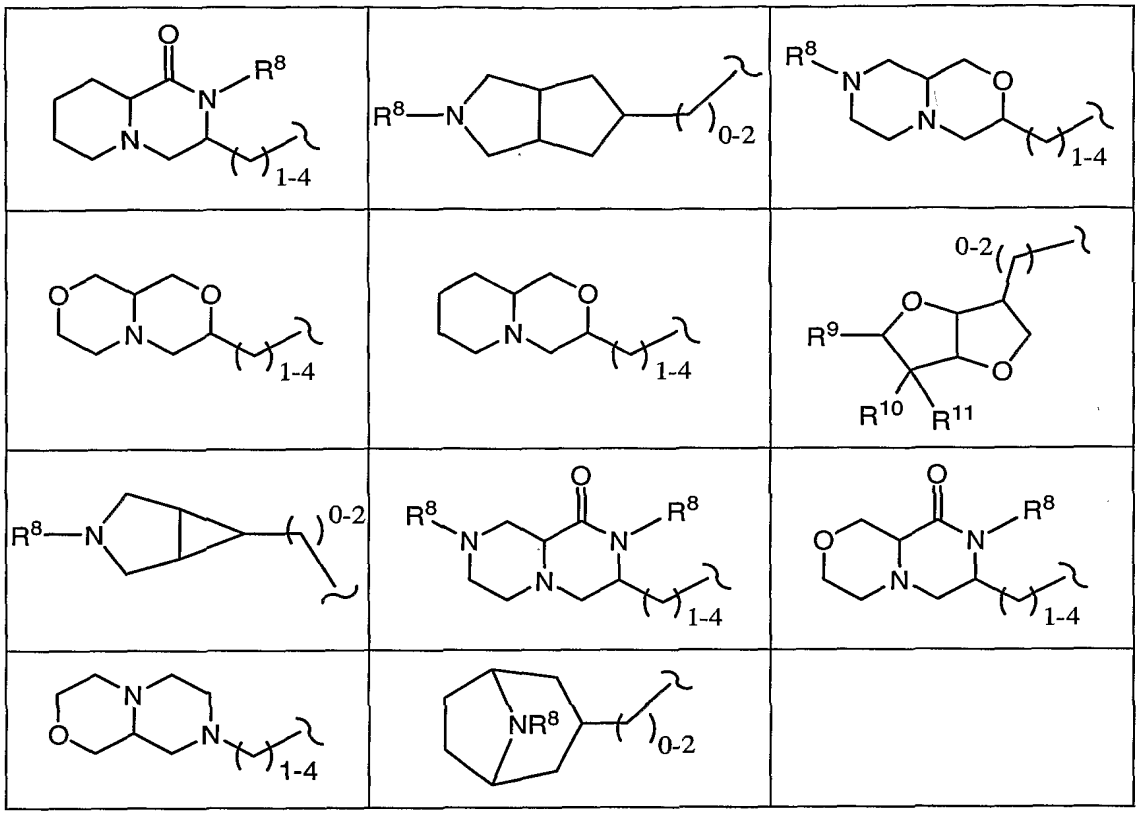
with the proviso that when B is selected from:

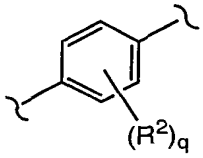


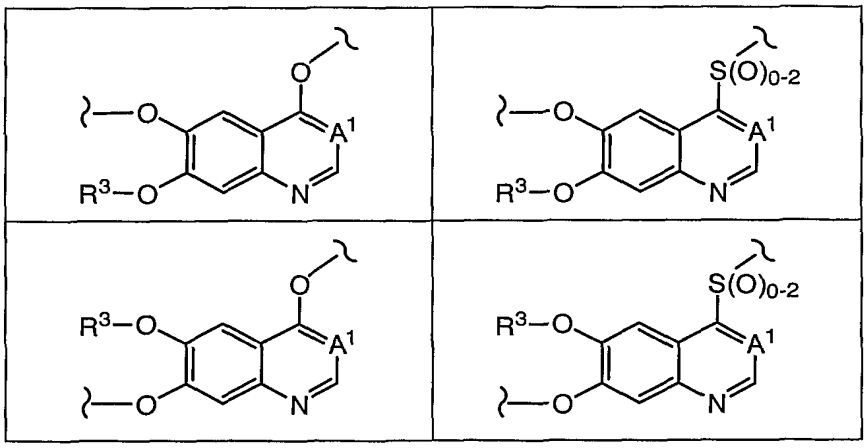
and C contains  , and the remaining portion of C contains one of:

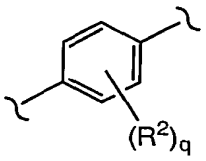
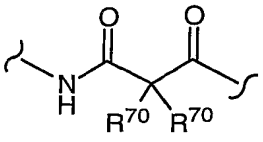


directly attached to  , then A must be one of:



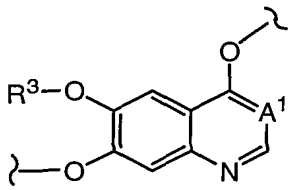
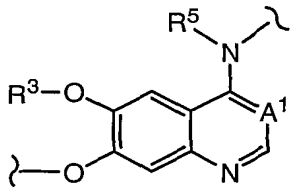
and with the proviso that when C contains  , and B is selected from:



then the portion of C directly attached to  cannot contain  , when R^{70} is selected from -H, C_{1-4}alkyl, and C_{1-4}alkoxyl.

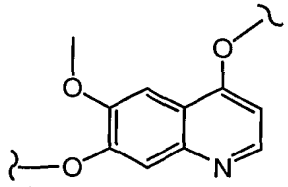
[0079] In another example the compound is according to paragraph [0078], wherein Q is selected from phenyl, napthyl, 1,2,3,4-tetrahydronaphthyl, indanyl, benzodioxanyl, benzofuranyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroisoquinolyl, pyrrolyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, tetrahydropyridinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolinyl, oxazolidinyl, triazolyl, isoxazolyl, isoxazolidinyl, thiazolyl, thiazolinyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, thienyl, benzothieliyl, and oxadiazolyl; each optionally substituted with between one and four of R^{20}; wherein each R^{20} is independently selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted lower alkyl.

[0080] In another example the compound is according to paragraph [0079], wherein B is either of the following:

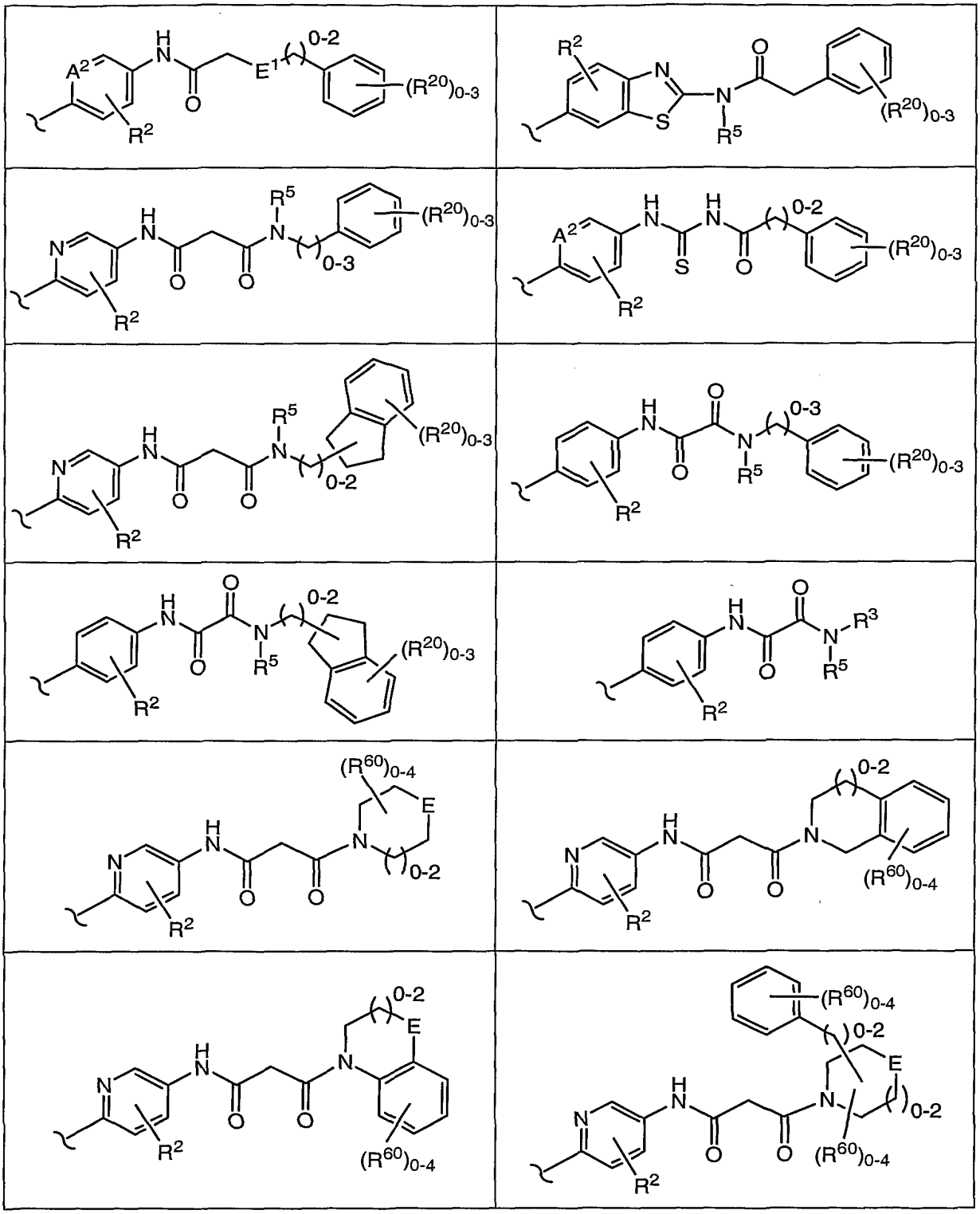



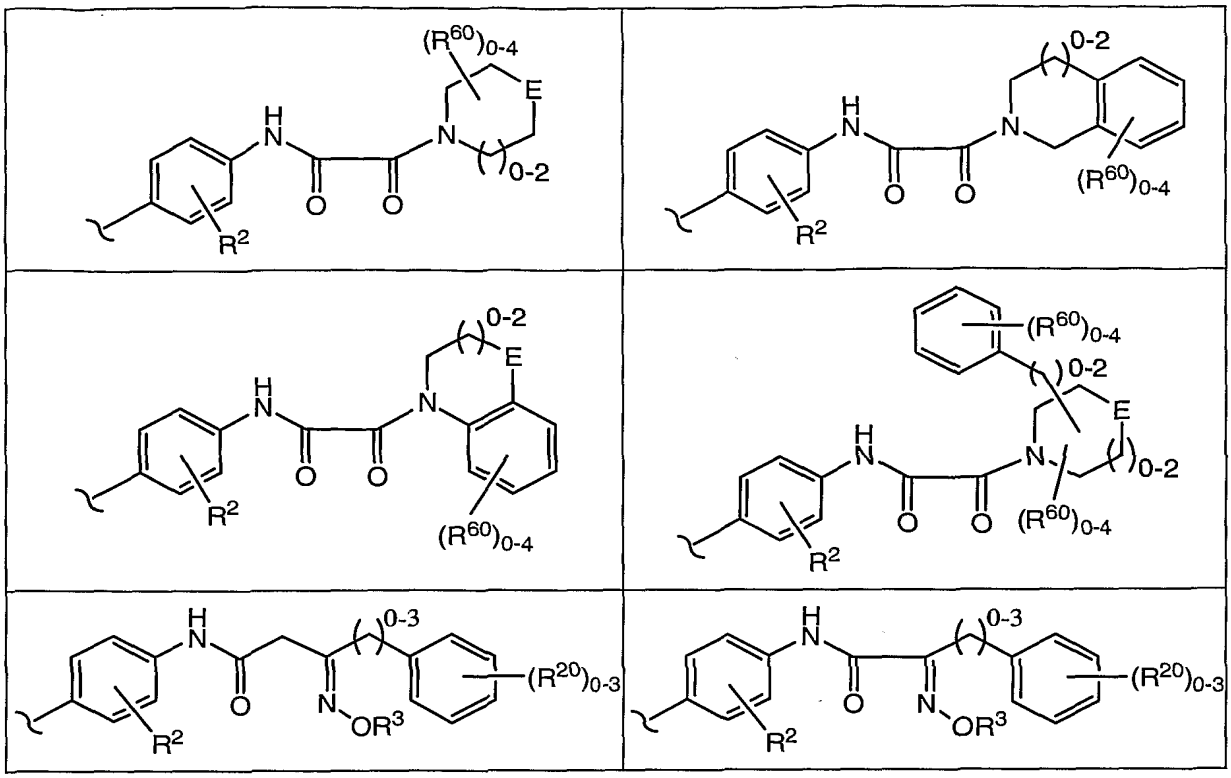
wherein A^1 is either =N- or =C(H)-.

[0081] In another example the compound is according to paragraph [0080], wherein B is



[0082] In another example the compound is according to paragraph [0081], wherein C is selected from:





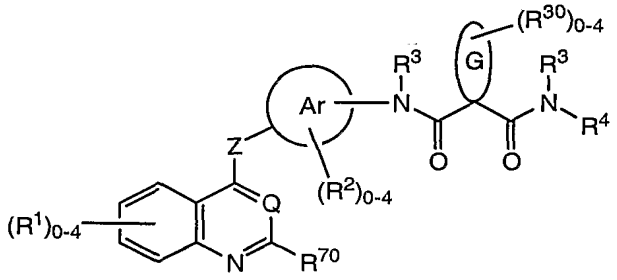
wherein R^2, R^3, R^5, R^{20}, R^{25} and R^{60} are as defined above.

[0083] In another example the compound is according to paragraph [0082], R^2 is selected from halogen, trihalomethyl, -CN, $-NO_2$, $-OR^3$, $-NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted lower alkyl

[0084] In another example the compound is according to paragraph [0083], wherein R^2 is halogen.

[0085] In another example the compound is according to paragraph [0084], wherein R^2 is either fluorine or chlorine.

[0086] In another aspect, the invention comprises a compound for modulating kinase activity according to Formula **XI**,



XI

or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein,

each R^1 is independently selected from halogen, $-OR^3$, $-NO_2$, $-NH_2$, $-NR^3R^4$, $-D-R^{50}$ and optionally substituted C_{1-6}alkyl;

R^{70} is selected from -H, halogen, $-OR^3$, $-S(O)_{0-2}R^3$, $-NO_2$, $-NH_2$, $-NR^3R^4$, and optionally substituted C_{1-6}alkyl;

Q is selected from =N-, =C(H)-, and =C(CN)-;

Z is selected from $-S(O)_{0-2}$-, -O-, and $-NR^5$-;

Ar is either a five- or six-membered arylene or a five- or six-membered heteroarylene containing between one and three heteroatoms;

G is either an optionally substituted cycloalkyl or an optionally substituted heteroalicyclic;

each R^2 is independently selected from halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted C_{1-6}alkyl;

each R^3 is independently -H or R^4;

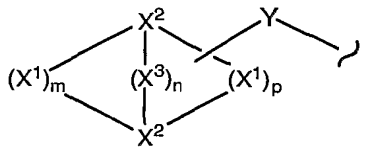
each R^4 is independently selected from optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl, optionally substituted heterocyclyl, and optionally substituted heterocyclyl C_{1-6}alkyl; or

R^3 and R^4, when taken together with a common nitrogen to which they are attached, form an optionally substituted five- to seven-membered heterocyclyl, said optionally substituted five- to seven-membered heterocyclyl optionally containing at least one additional annular heteroatom selected from N, O, S, and P;

R^5 is -H or optionally substituted C_{1-6}alkyl;

each D is independently selected from $-O-$, $-S(O)_{0-2}$-, and $-NR^5$-;

each R^{50} is independently either R^3, or according to formula **XII**;



XII

wherein X^1, X^2, and optionally X^3, represent the atoms of a saturated bridged ring system, said saturated bridged ring system comprising up to four annular heteroatoms represented by any of X^1, X^2, and X^3; wherein,

each X^1 is independently selected from $-C(R^6)R^7-$, -O-, $-S(O)_{0-2}-$, and $-NR^8-$;

each X^2 is independently an optionally substituted bridgehead methine or a bridgehead nitrogen;

each X^3 is independently selected from $-C(R^6)R^7-$, -O-, $-S(O)_{0-2}-$, and $-NR^8-$;

Y is either:

an optionally substituted lower alkylene linker, between D and either 1) any annular atom of the saturated bridged ring system, except X^2 when X^2 is a bridgehead nitrogen, or 2) any heteroatom, represented by any of R^6 or R^7; provided there are at least two carbon atoms between D and any annular heteroatom of the saturated bridged ring system or any heteroatom represented by any of R^6 or R^7;

or Y is absent, when Y is absent, said saturated bridged ring system, is directly attached to D via an annular carbon of said saturated bridged ring system, unless D is $-SO_2-$, in which case said saturated bridged ring system, is directly attached to D via an any annular atom of said saturated bridged ring system;

m and p are each independently one to four;

n is zero to two, when n equals zero, then there is a single bond between the two bridgehead X^2's;

R^6 and R^7 are each independently selected from -H, halogen, trihalomethyl, -CN, $-NH_2$, $-NO_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^4$, $-SO_2NR^3R^4$, $-CO_2R^3$, $-C(O)NR^3R^4$, $-N(R^3)SO_2R^4$, $-N(R^3)C(O)R^3$, $-NCO_2R^3$, $-C(O)R^3$, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl, optionally substituted heterocyclyl, optionally substituted heterocyclyl C_{1-6}alkyl, and a bond to either Y or D; or

R^6 and R^7, when taken together are oxo; or

R^6 and R^7, when taken together with a common carbon to which they are attached, form a optionally substituted three- to seven-membered spirocyclyl, said optionally substituted three- to seven-membered spirocyclyl optionally containing at least one additional annular heteroatom selected from N, O, S, and P;

R^8 is selected from $-R^3$, Y, $-SO_2NR^3R^4$, $-CO_2R^4$, $-C(O)NR^3R^3$, $-SO_2R^4$, and $-C(O)R^3$; and

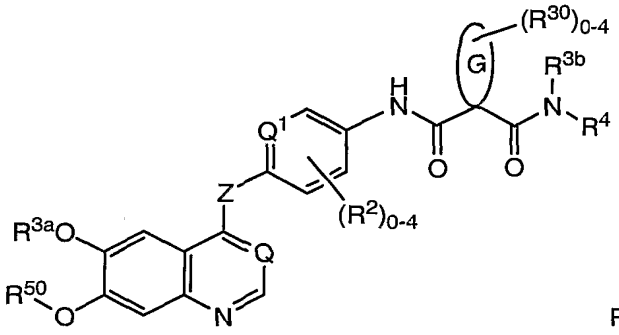
each R^{30} is independently selected from halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted C_{1-6}alkyl.

[0087] In one example, the compound is according to paragraph [0086], wherein Z is either -O- or $-NR^5-$.

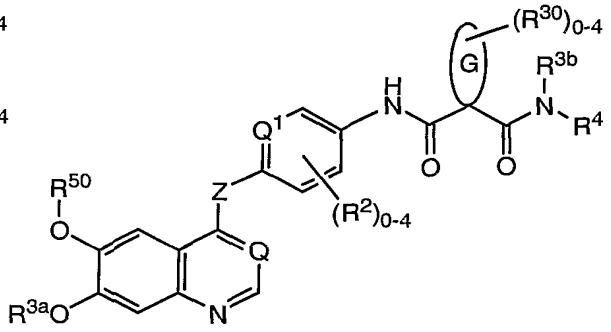
[0088] In another example, the compound is according to paragraph [0087], wherein at least one of R^1 is $-D-R^{50}$.

[0089] In another example, the compound is according to paragraph [0088], wherein D is -O- and at least one other R^1 is $-OR^3$.

[0090] In another example, the compound is according to paragraph [0089], of formula **XIIIa** or **XIIIb**:



XIIIa



XIIIb

wherein Q^1 is either =N- or =C(H)-.

[0091] In another example, the compound is according to paragraph [0090], wherein R^{50} is selected from C_{1-6}alkyl optionally substituted with at least one of optionally substituted amino, optionally substituted C_{1-6}alkyl amino, optionally substituted C_{1-6}dialkyl amino, optionally substituted heteroalicylic, and a group of formula **XII**.

[0092] In another example, the compound is according to paragraph [0091], wherein R^{3a} is C_{1-6}alkyl.

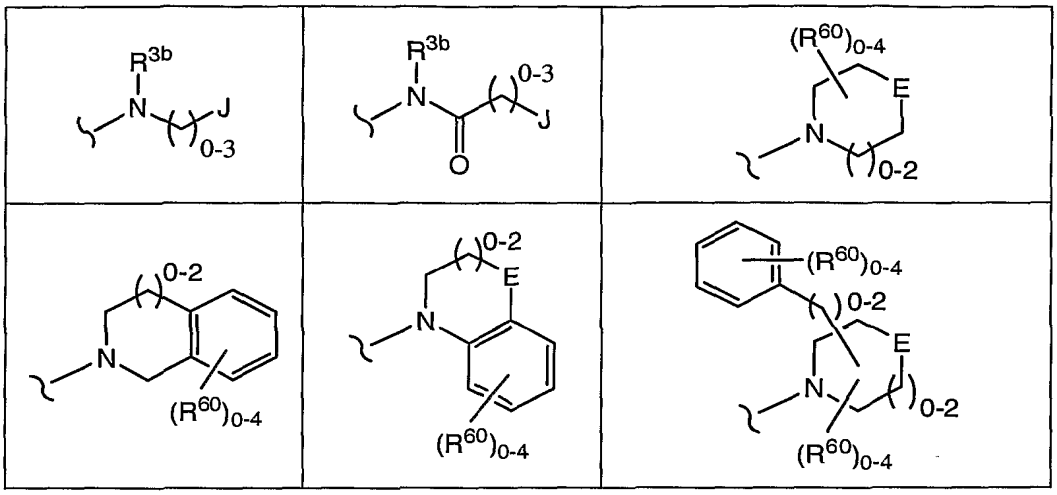
[0093] In another example, the compound is according to paragraph [0092], wherein Z is -O-.

[0094] In another example, the compound is according to paragraph [0093], wherein G is selected from cyclopropyl, aziradine, cyclobutyl, and azetidine, each optionally substituted with between zero and four of R^{30}.

[0095] In another example, the compound is according to paragraph [0094], wherein Q is either =N- or =C(H)-.

[0096] In another example, the compound is according to paragraph [0095], wherein R^2 is selected from -H, halogen, C_{1-6} alkyl and perfluoro C_{1-6} alkyl.

[0097] In another example, the compound is according to paragraph [0096], wherein $-N(R^{3b})R^4$ is selected from the following:



wherein J, is a five- to ten-membered ring, optionally substituted with between zero and five of R^{20};

each R^{20} is independently selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl, optionally substituted heterocyclyl, and optionally substituted heterocyclyl C_{1-6}alkyl;

two of R^{20}, together with the atom or atoms to which they are attached, combine to form an optionally substituted three- to seven-membered heteroalicyclic, said optionally substituted three- to seven-membered heteroalicyclic either spiro- to J or fused to J;

E is selected from -O-, $-N(R^5)$-, $-CH_2$-, and $-S(O)_{0-2}$-;

each R^{60} is independently selected from halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted heteroaryl C_{1-6}alkyl, and optionally substituted aryl C_{1-6}alkyl;

each methylene in any of the above formulae, other than those in a depicted ring, is independently optionally substituted with R^{25}; and

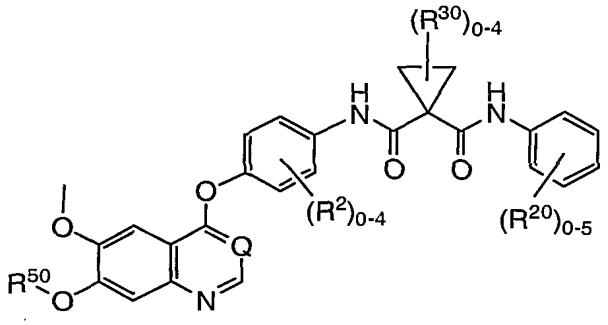
R^{25} is selected from halogen, trihalomethyl, oxo, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl, heteroaryl C_{1-6}alkyl, and optionally substituted C_{1-6}alkyl; or

two of R^{25}, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered alicyclic or heteroalicyclic;

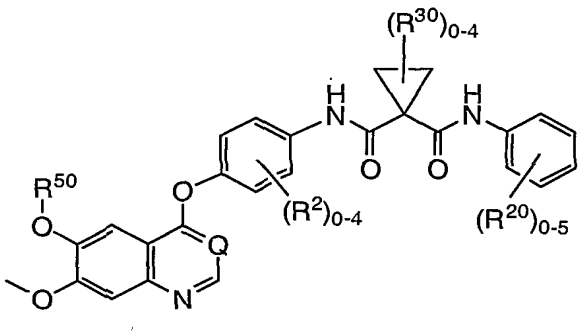
R^{3b} is equivalent to R^3 as defined above; and

R^4 and R^5 are as defined above.

[0098] In another example, the compound is according to paragraph [0097], of formula **XIVa** or **XIVb**:



XIVa



XIVb

[0099] In another example, the compound is according to paragraph [0098], wherein R^{50} is C_{1-6}alkyl optionally substituted with a group selected from optionally substituted amino, an optionally substituted alkylamino, optionally substituted dialkylamino, and optionally substituted heteroalicylic.

[0100] In another example, the compound is according to paragraph [0099], wherein the heteroalicyclic portion of said optionally substituted heteroalicyclic of R^{50} is selected from the group consisting of piperidine, piperazine, morpholine, thiomorpholine, thiomorpholine 1-oxide, thiomorpholine 1,1-dioxide, 2-oxo-morpholine, pyrrolidine, and azepine.

[0101] In another example, the compound is according to paragraph [0099], wherein R^{50} is according to formula **XII**.

[0102] In another example, the compound is according to paragraph [0101], wherein the saturated bridged ring system according to formula **XII** has a geometry selected from the group consisting of [4.4.0], [4.3.0], [4.2.0], [4.1.0], [3.3.0], [3.2.0], [3.1.0], [3.3.3], [3.3.2], [3.3.1], [3.2.2], [3.2.1], [2.2.2], and [2.2.1].

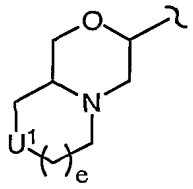
[0103] In another example, the compound is according to paragraph [0102], wherein Y is selected from $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2-$, $-CH_2-$, and absent.

[0104] In another example, the compound is according to paragraph [0103], wherein n is 0 and the saturated bridged ring system according to formula **XII** has a geometry selected from the group consisting of [4.4.0], [4.3.0], [4.2.0], [4.1.0], [3.3.0], [3.2.0], and [3.1.0].

[0105] In another example, the compound is according to paragraph [0104], wherein said saturated bridged ring system contains at least one annular nitrogen or at least one annular oxygen.

[0106] In another example, the compound is according to paragraph [0105], wherein said saturated bridged ring system contains $-NR^8-$, wherein R^8 is selected from -H, optionally substituted C_{1-6}alkyl, $-CO_2R^3$, $-C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$.

[0107] In another example, the compound is according to paragraph [0105], wherein said saturated bridged ring system is of formula **XV**,



XV

wherein U^1 is selected from $-O-$, $-S(O)_{0-2}-$, $-NR^8-$, $-CR^6R^7-$, and absent; and e is 0 or 1.

[0108] In another example, the compound is according to paragraph [0107], wherein Y is $-CH_2-$.

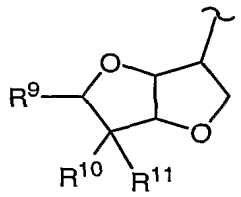
[0109] In another example, the compound is according to paragraph [0108], wherein U^1 is $-NR^8-$, wherein R^8 is selected from -H, optionally substituted lower alkyl, $-CO_2R^3$, $-C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$.

[0110] In another example, the compound is according to paragraph [0108], wherein U^1 is $-O-$.

[0111] In another example, the compound is according to paragraph [0108], wherein U^1 is absent.

[0112] In another example, the compound is according to paragraph [0103], wherein Y is selected from $-CH_2CH_2-$, $-CH_2-$, and absent.

[0113] In another example, the compound is according to paragraph [0112], wherein said saturated bridged ring system is of formula **XVI**,



XVI

wherein R^9, R^{10}, and R^{11} are each independently selected from -H, and $-OR^{12}$; or

R^9 is selected from -H, and $-OR^{12}$, and R^{10} and R^{11}, when taken together, are either an optionally substituted alkylidene or an oxo;

R^{12} is selected from -H, $-C(O)R^3$, optionally substituted lower alkylidyne, optionally substituted lower arylalkylidyne, optionally substituted lower heterocyclylalkylidyne, optionally substituted lower alkylidene, optionally substituted lower alkylidenearyl, optionally substituted lower alkylideneheterocyclyl, optionally substituted lower alkyl, optionally substituted lower alkylaryl, optionally substituted aryl, optionally substituted lower heterocyclylalkyl, and optionally substituted heterocyclyl;

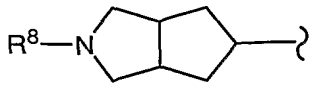
or two R^{12}'s, when taken together, form 1) a corresponding spirocyclic ketal when said two R^{12}'s stem from R^{10} and R^{11}, or 2) a corresponding cyclic ketal when said two R^{12}'s stem from R^9 and one of R^{10} and R^{11}.

[0114] In another example, the compound is according to paragraph [0113], wherein one of R^{10} and R^{11} is $-OR^{12}$, wherein R^{12} is selected from -H, $-C(O)R^3$, and optionally substituted lower alkyl; and R^9 and the other of R^{10} and R^{11} are both -H.

[0115] In another example, the compound is according to paragraph [0114], wherein Y is either $-CH_2-$ or absent.

[0116] In another example, the compound is according to paragraph [0113], wherein R^9 is an alkyl group containing at least one fluorine substitution thereon.

[0117] In another example, the compound is according to paragraph [0106], wherein said saturated bridged ring system is of formula **XVII**.



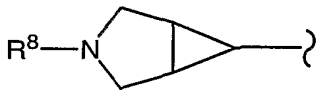
XVII

[0118] In another example, the compound is according to paragraph [0117], wherein Y is either $-CH_2-$ or absent.

[0119] In another example, the compound is according to paragraph [0118], wherein R^8 is methyl or ethyl.

[0120] In another example, the compound is according to paragraph [0119], wherein at least one of R^2 is halogen.

[0121] In another example, the compound is according to paragraph [0106], wherein said saturated bridged ring system is of formula **XVIII**.

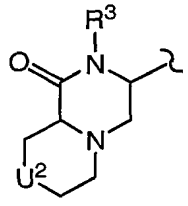


XVIII

[0122] In another example, the compound is according to paragraph [0121], wherein Y is $-CH_2-$.

[0123] In another example, the compound is according to paragraph [0122], wherein R^8 is methyl or ethyl.

[0124] In another example, the compound is according to paragraph [0105], wherein said saturated bridged ring system is of formula **XIX**



XIX

wherein U^2 is selected from -O-, $-S(O)_{0-2}-$, $-NR^8-$, $-CR^6R^7-$, and absent.

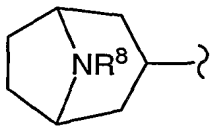
[0125] In another example, the compound is according to paragraph [0124], wherein R^3 of formula **XIX** is selected from -H and optionally substituted alkyl.

[0126] In another example, the compound is according to paragraph [0125], wherein U^2 is either $-CR^6R^7-$ or absent.

[0127] In another example, the compound is according to paragraph [0126], wherein U^2 is either $-CH_2-$ or absent.

[0128] In another example, the compound is according to paragraph [0127], wherein Y is $-CH_2-$.

[0129] In another example, the compound is according to paragraph [0106], wherein said saturated bridged ring system is according to formula **XX**.



XX

[0130] In another example, the compound is according to paragraph [0129], wherein R^8 is methyl or ethyl.

[0131] In another example, the compound is according to any of paragraphs [0099] – [0130], wherein R^2 is selected from C_{1-6} alkyl, perfluoro C_{1-6} alkyl, and halogen.

[0132] In another example, the compound is according to paragraph [0131], wherein R^2 is selected from perfluoro C_{1-3} alkyl and halogen.

[0133] In another example, the compound is according to any of paragraphs [0099] – [0130], wherein R^{20} is selected from halogen, $-CN$, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, optionally substituted heterocyclyl, and optionally substituted heterocyclyl C_{1-6}alkyl, and (two of R^{20}) together with the atom or atoms to which they are attached, an optionally substituted three- to six-membered heteroalicyclic, said optionally substituted three- to six-membered heteroalicyclic fused to the phenyl as in **XIVa** or **XIVb**.

[0134] In another example, the compound is according to paragraph [0133], wherein R^{20} is selected from halogen, $-NR^3R^4$, optionally substituted heterocyclyl, and optionally substituted heterocyclyl C_{1-6}alkyl, and (two of R^{20}) together with the atom or atoms to which they are attached, an optionally substituted five- to six-membered heteroalicyclic, said optionally substituted five- to six-membered heteroalicyclic fused to the phenyl as in **XIVa** or **XIVb**.

[0135] In another example, the compound is according to paragraph [0134], wherein R^2 is selected from C_{1-6} alkyl, perfluoro C_{1-6} alkyl, and halogen.

[0136] In another example, the compound is according to paragraph [0135], wherein R^2 is selected from perfluoro C_{1-3} alkyl and halogen.

[0137] In another example, the compound is according to paragraph [0086], selected from Table 2.

Table 2

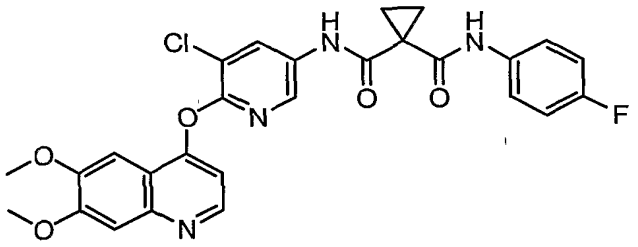
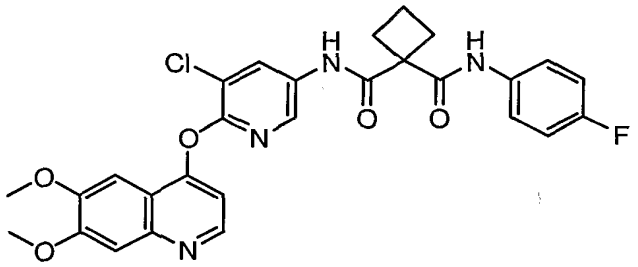
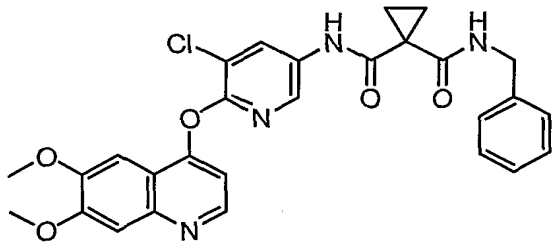
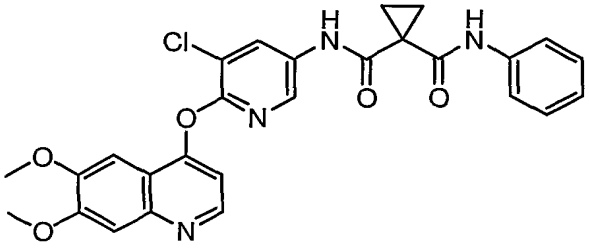
Entry	Name	Structure
1	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
2	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
3	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(phenylmethyl)cyclopropane-1,1-dicarboxamide	
4	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-phenylcyclopropane-1,1-dicarboxamide	

Table 2

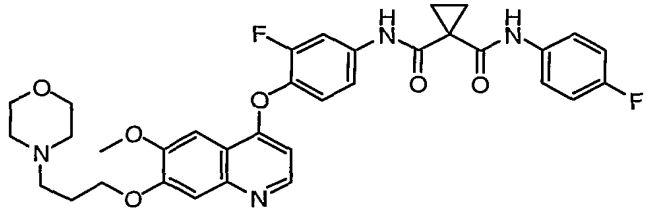
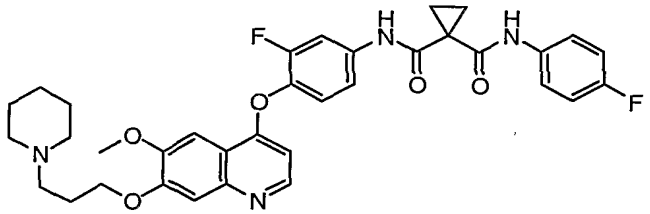
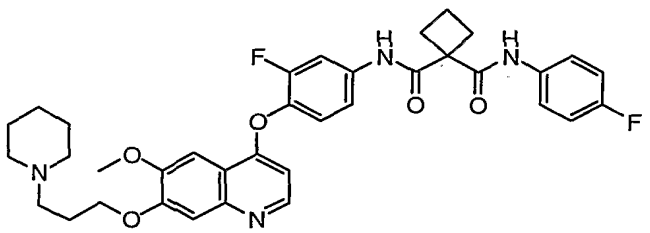
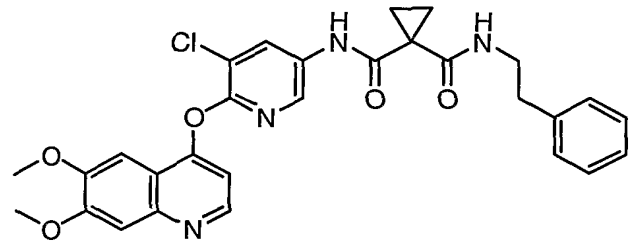
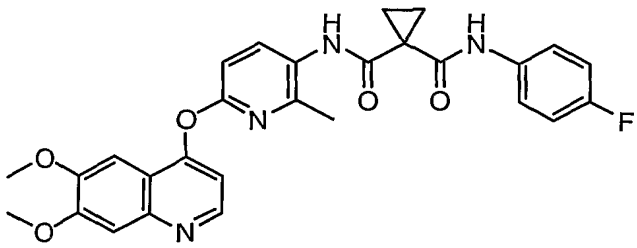
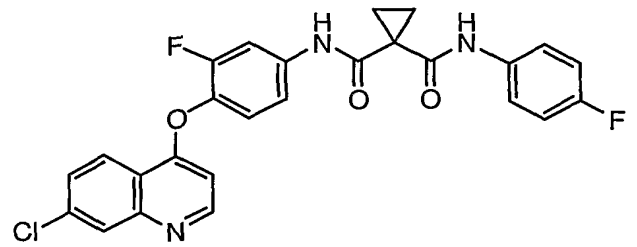
Entry	Name	Structure
5	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
6	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperidin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
7	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperidin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
8	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-phenylethyl)cyclopropane-1,1-dicarboxamide	
9	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-methylpyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
10	N-{4-[(7-chloroquinolin-4-yl)oxy]-3-fluorophenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 2

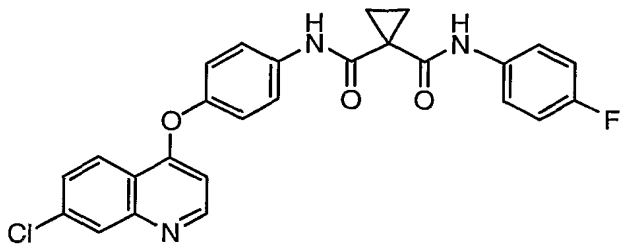
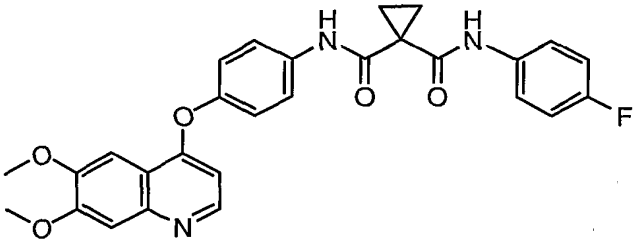
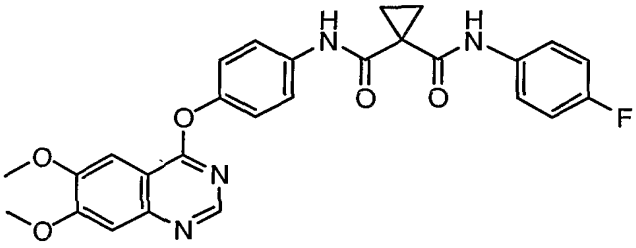
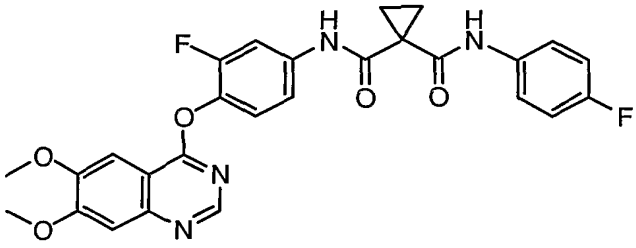
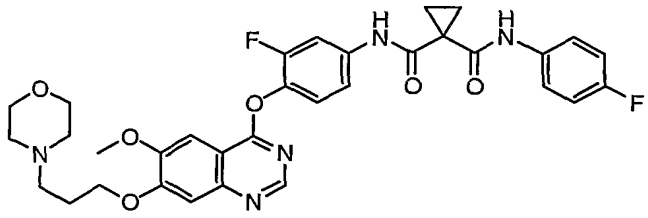
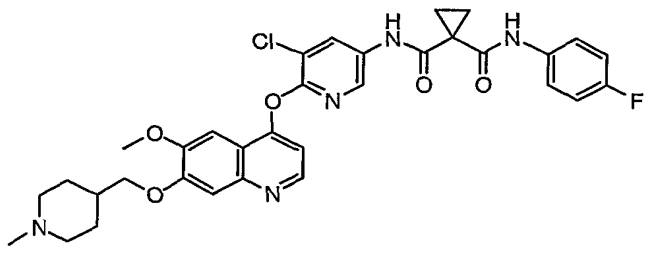
Entry	Name	Structure
11	N-{4-[(7-chloroquinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
12	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
13	N-(4-{[6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
14	N-(4-{[6,7-bis(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
15	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
16	N-{5-chloro-6-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]pyridin-3-yl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 2

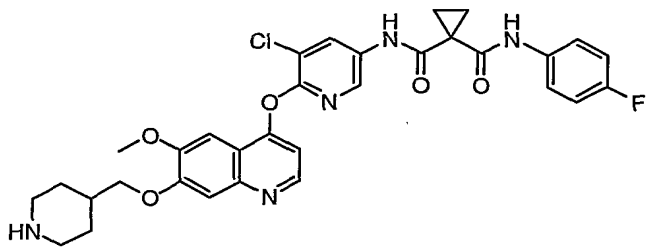
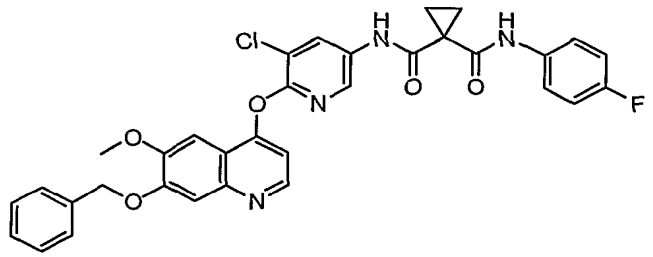
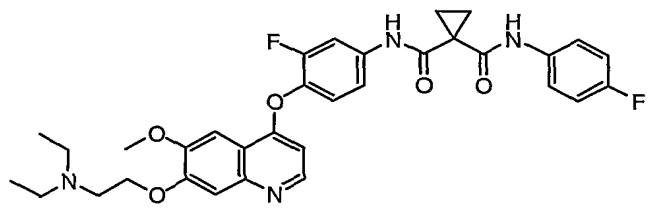
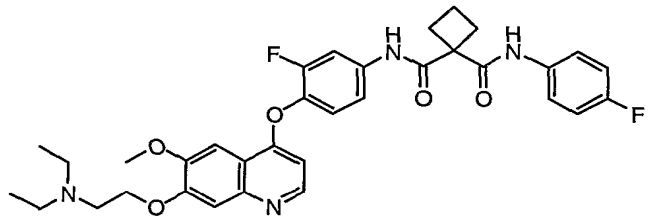
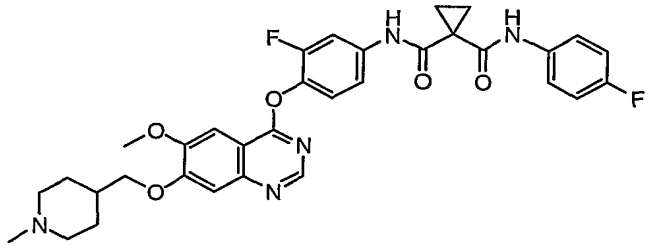
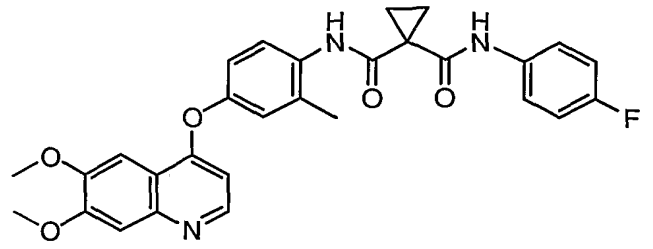
Entry	Name	Structure
17	N-[5-chloro-6-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
18	N-[5-chloro-6-({6-(methyloxy)-7-[(phenylmethyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
19	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
20	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
21	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
22	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 2

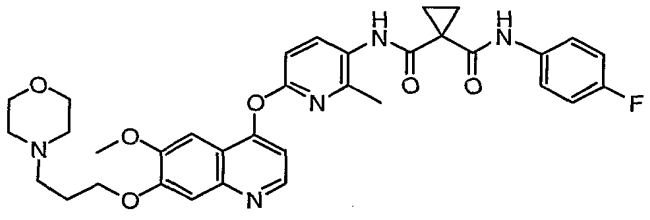
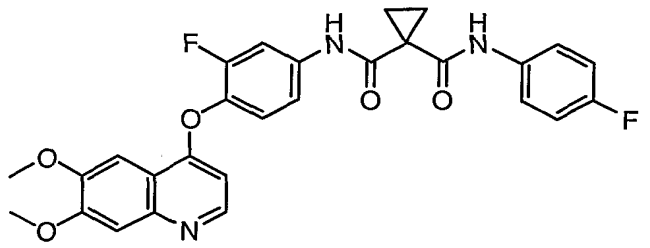
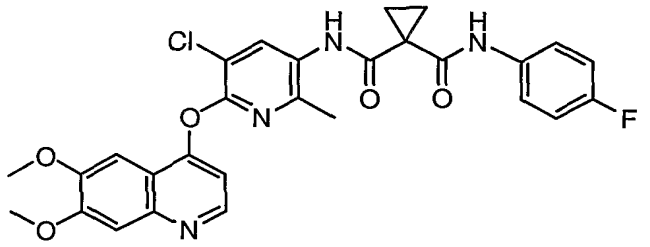
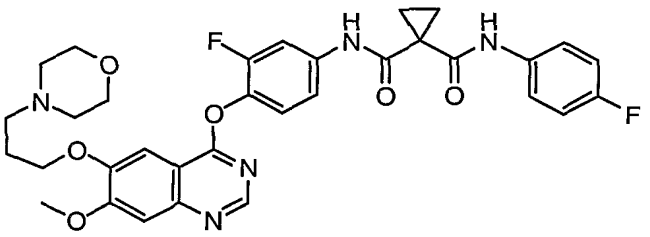
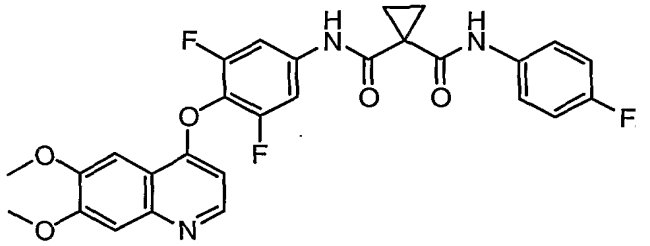
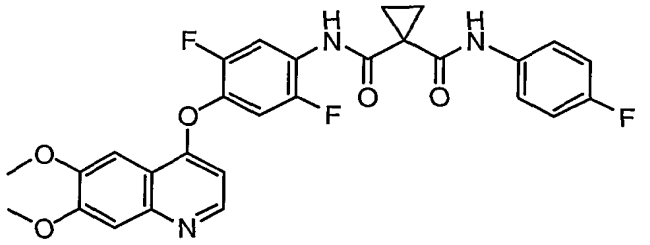
Entry	Name	Structure
23	N-(4-fluorophenyl)-N'-[2-methyl-6-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]cyclopropane-1,1-dicarboxamide	
24	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
25	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloro-2-methylpyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
26	N-[3-fluoro-4-({7-(methyloxy)-6-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
27	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3,5-difluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
28	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2,5-difluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 2

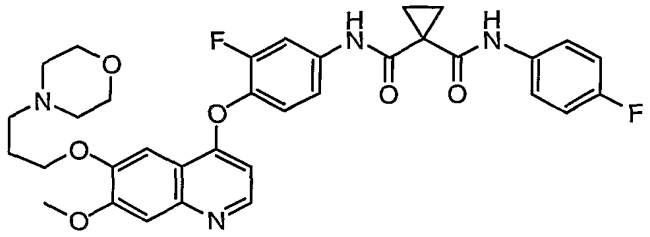
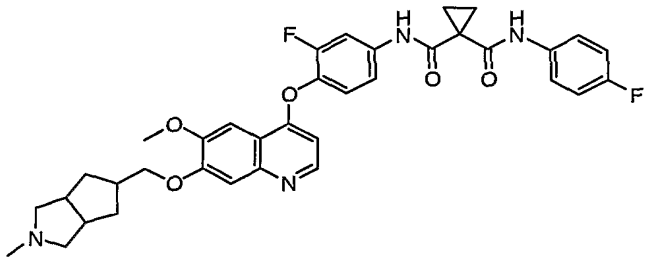
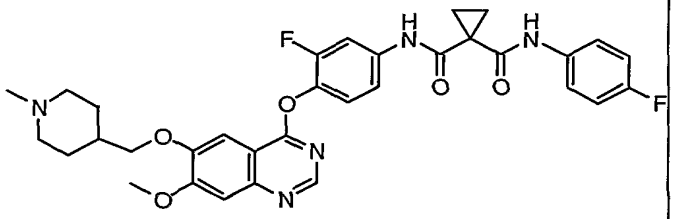
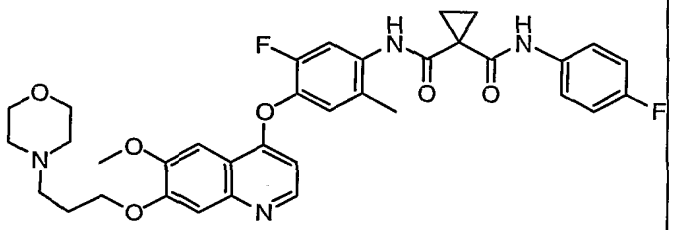
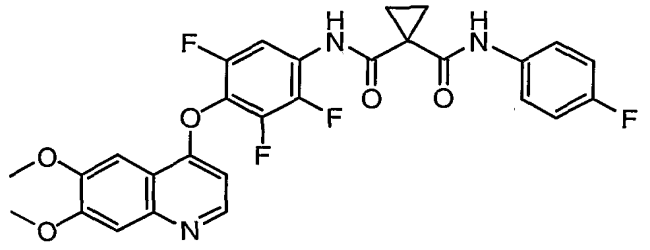
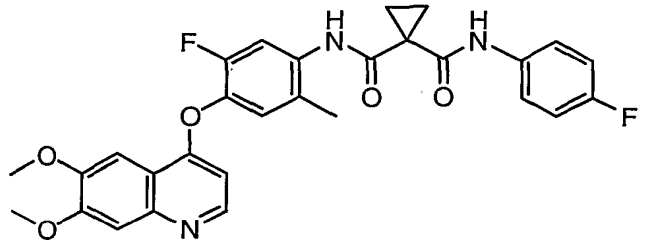
Entry	Name	Structure
29	N-[3-fluoro-4-({7-(methyloxy)-6-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
30	N-{3-fluoro-4-[(6-(methyloxy)-7-(2-methyl octahydrocyclo-penta[c]pyrrol-5-ylmethoxy)quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
31	N-{3-fluoro-4-[(7-(methyloxy)-6-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
32	N-[5-fluoro-2-methyl-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
33	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2,3,5-trifluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
34	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-2-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 2

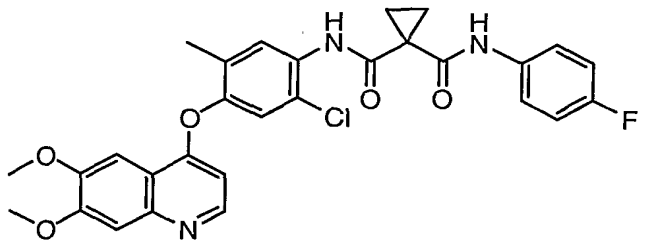
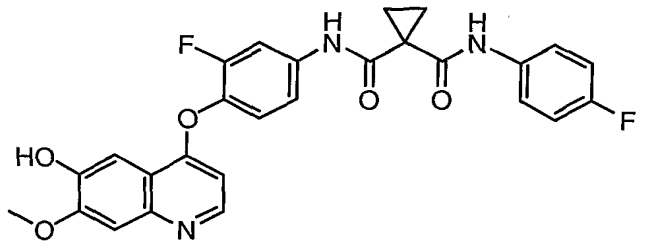
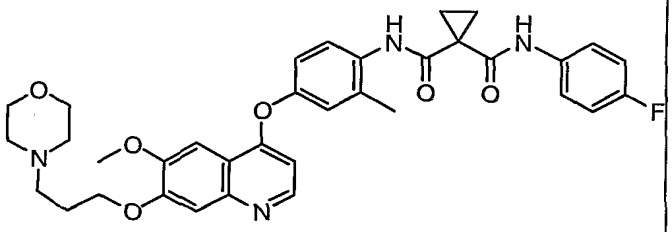
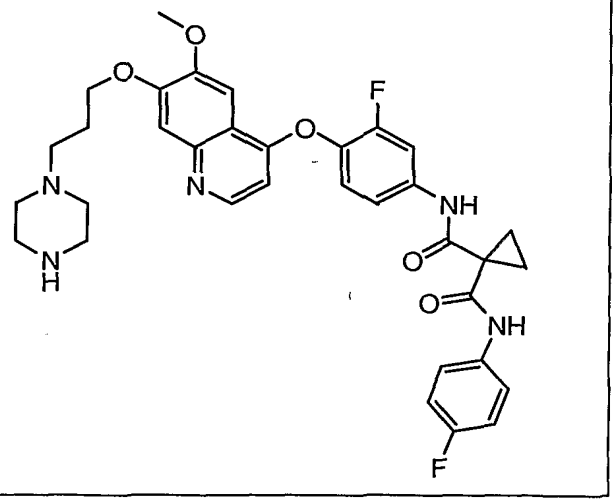
Entry	Name	Structure
35	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-chloro-5-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
36	N-(3-fluoro-4-{[6-hydroxy-7-(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
37	N-(4-fluorophenyl)-N'-[2-methyl-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]cyclopropane-1,1-dicarboxamide	
38	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 2

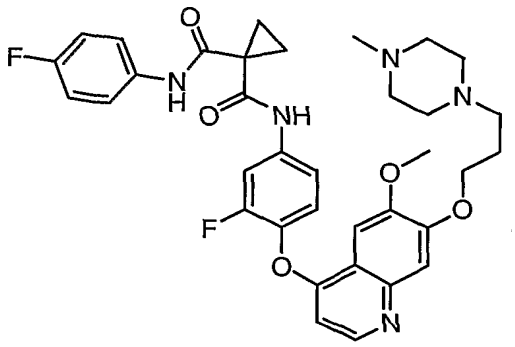
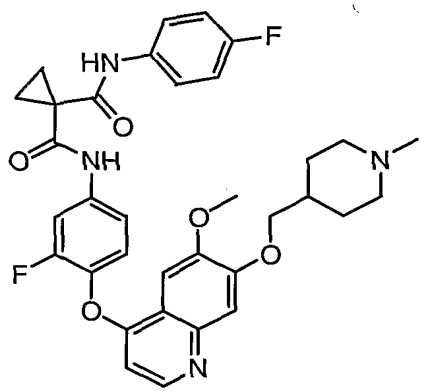
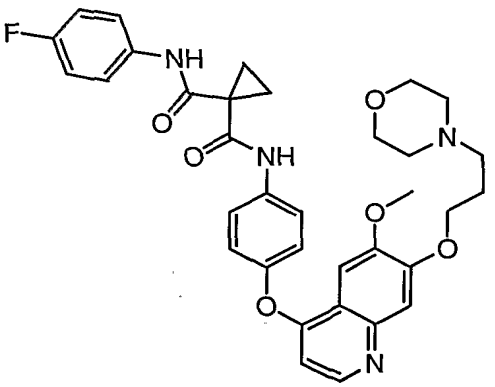
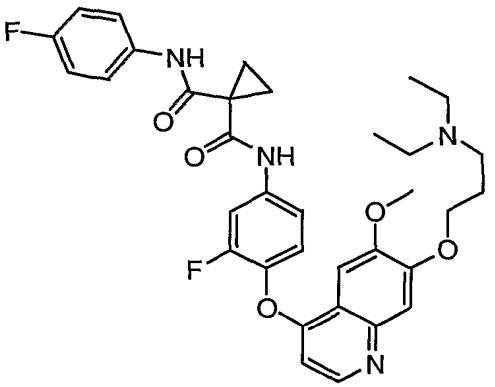
Entry	Name	Structure
39	N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
40	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
41	N-(4-fluorophenyl)-N'-[4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]cyclopropane-1,1-dicarboxamide	
42	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 2

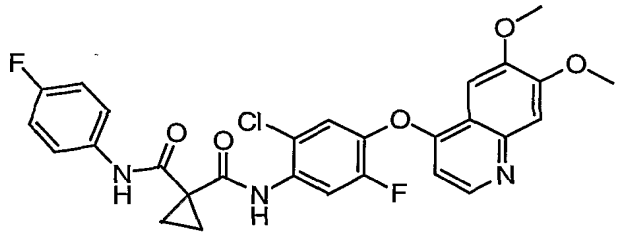
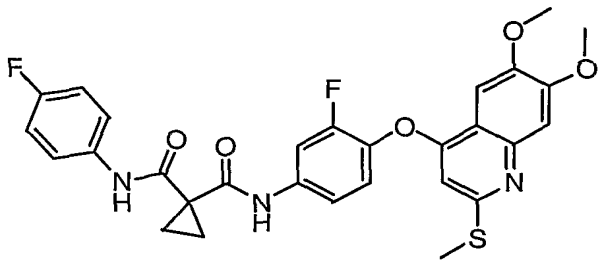
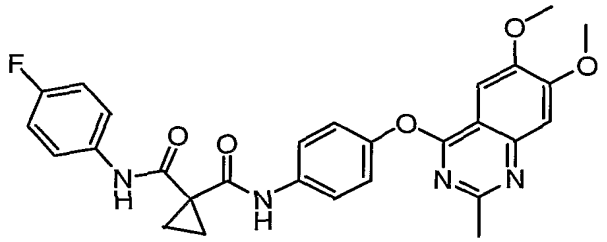
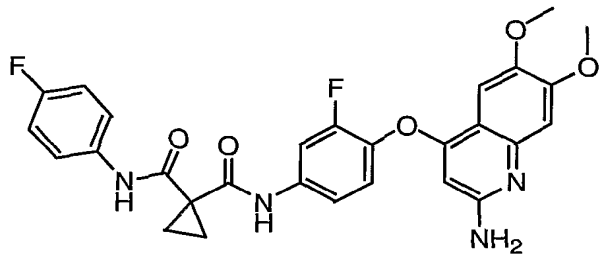
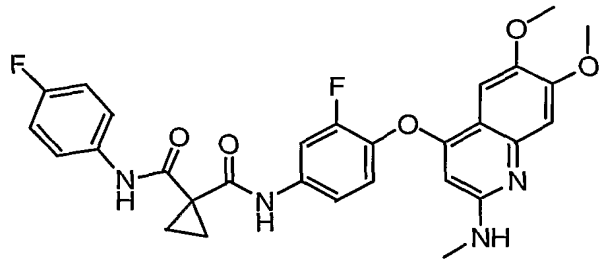
Entry	Name	Structure
43	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-chloro-5-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
44	N-(4-{[6,7-bis(methyloxy)-2-(methylthio)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
45	N-(4-fluorophenyl)-N'-(4-{[2-methyl-6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide	
46	N-(4-{[2-amino-6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
47	N-(3-fluoro-4-{[2-(methylamino)-6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 2

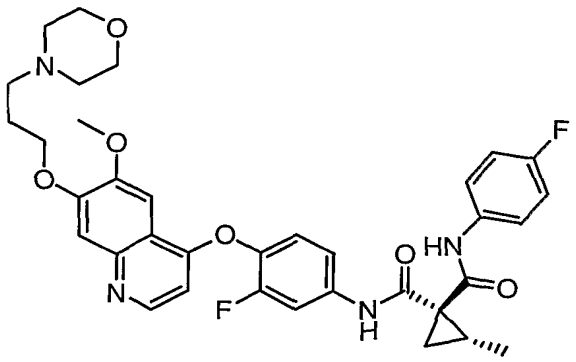
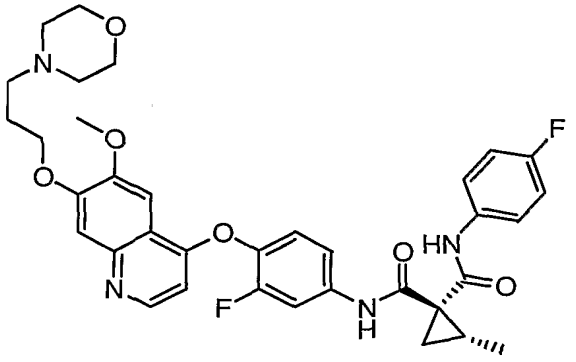
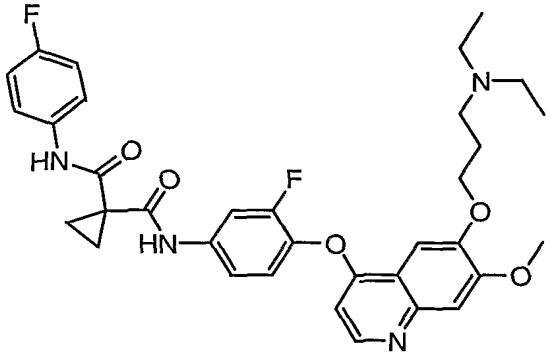
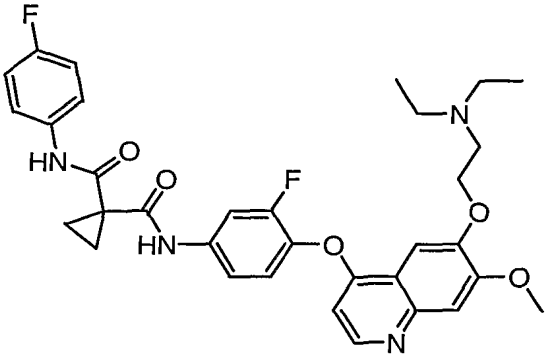
Entry	Name	Structure
48	(1S,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
49	(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
50	N-(4-{[6-{[3-(diethylamino)propyl]oxy}-7-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
51	N-(4-{[6-{[2-(diethylamino)ethyl]oxy}-7-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 2

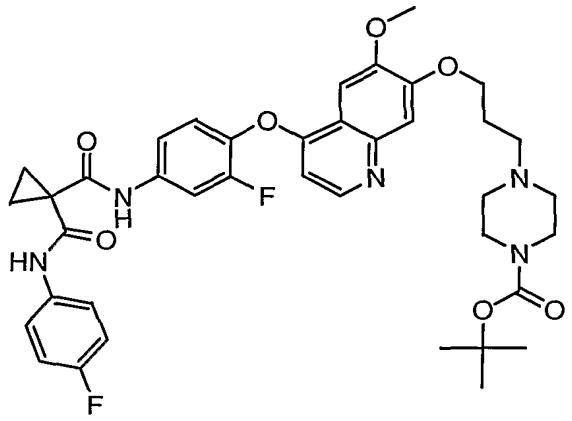
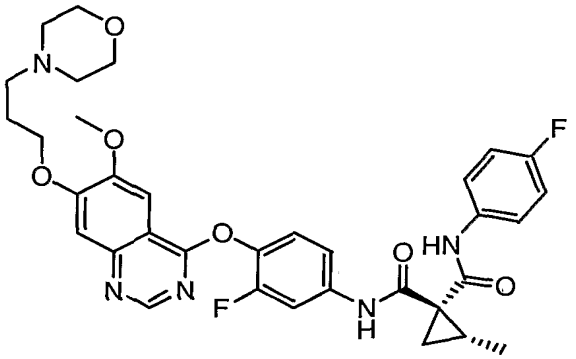
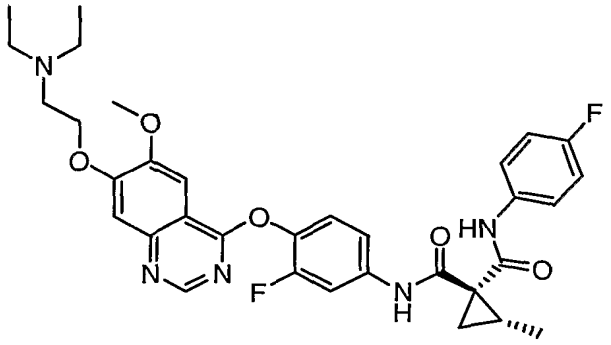
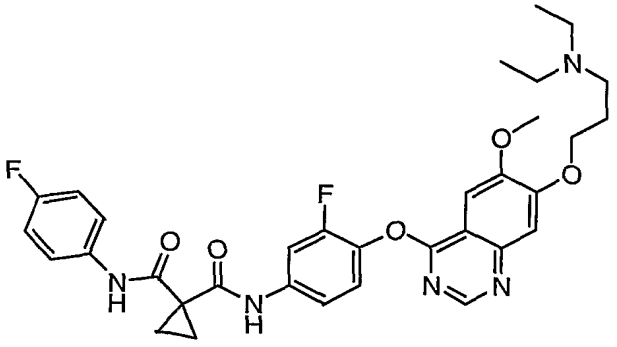
Entry	Name	Structure
52	1,1-dimethylethyl 4-(3-{[4-[(2-fluoro-4-{[(1-{[(4-fluorophenyl)amino]carbonyl}cyclopropyl)carbonyl]amino}phenyl)oxy]-6-(methyloxy)quinolin-7-yl]oxy}propyl)piperazine-1-carboxylate	
53	(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
54	(1R,2R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
55	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 2

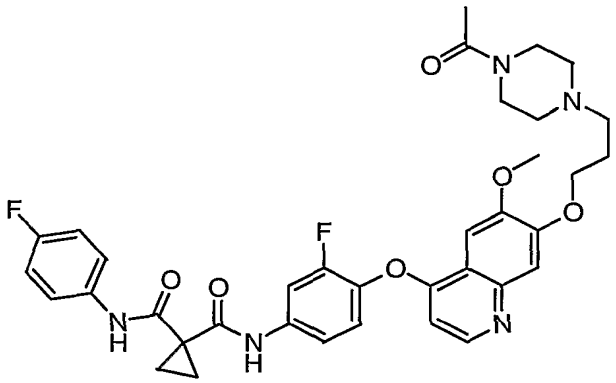
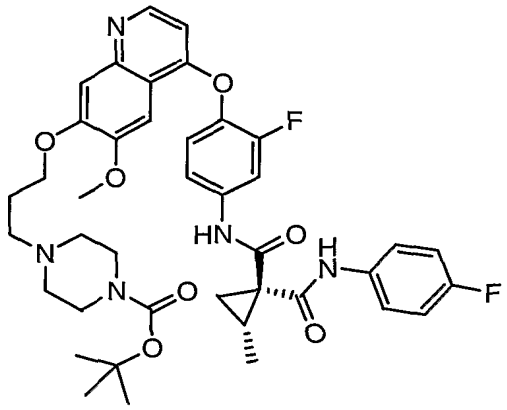
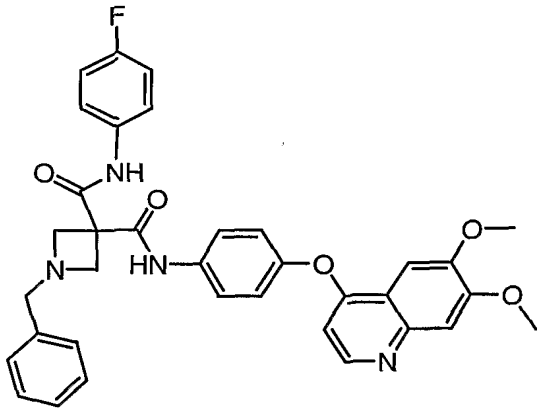
Entry	Name	Structure
56	N-(4-{[7-{[3-(4-acetylpiperazin-1-yl)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
57	1,1-dimethylethyl 4-(3-{[4-[(2-fluoro-4-{[((1R,2R)-1-{[(4-fluorophenyl)amino]carbonyl}-2-methylcyclopropyl)carbonyl]amino}phenyl)oxy]-6-(methyloxy)quinolin-7-yl]oxy}propyl)piperazine-1-carboxylate	
58	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-1-(phenylmethyl)azetidine-3,3-dicarboxamide	

Table 2

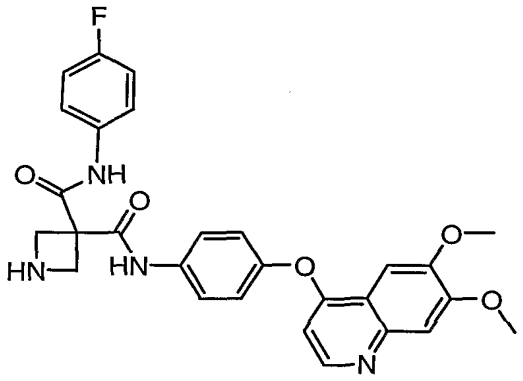
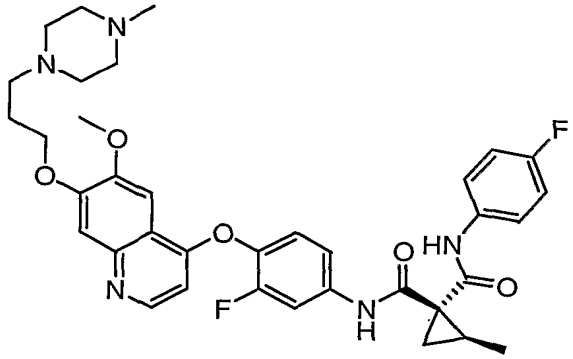
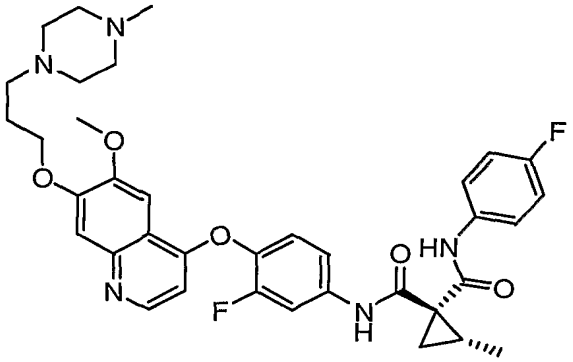
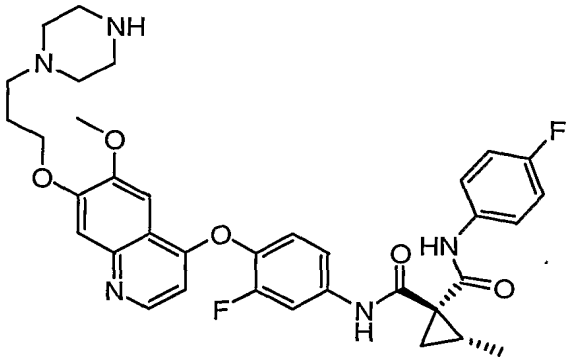
Entry	Name	Structure
59	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)azetidine-3,3-dicarboxamide	
60	(1R,2S)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
61	(1R,2R)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
62	(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	

Table 2

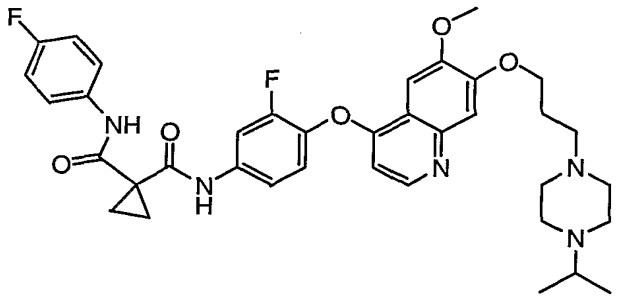
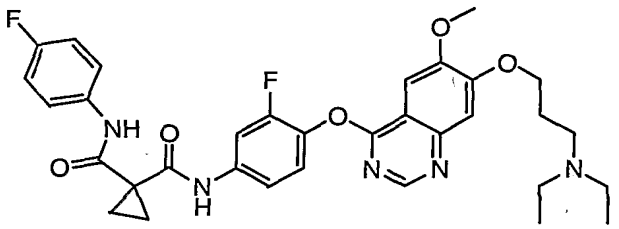
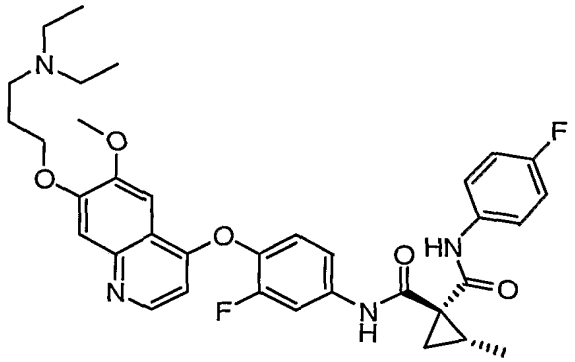
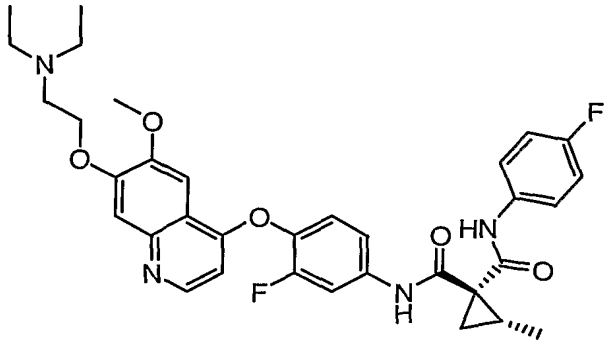
Entry	Name	Structure
63	N-(3-fluoro-4-{[7-({3-[4-(1-methylethyl)piperazin-1-yl]propyl}oxy)-6-(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
64	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
65	(1R,2R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
66	(1R,2R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	

Table 2

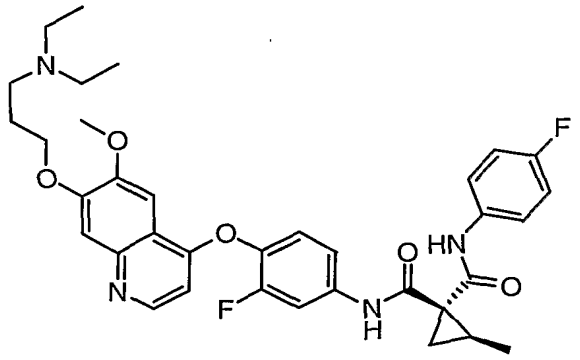
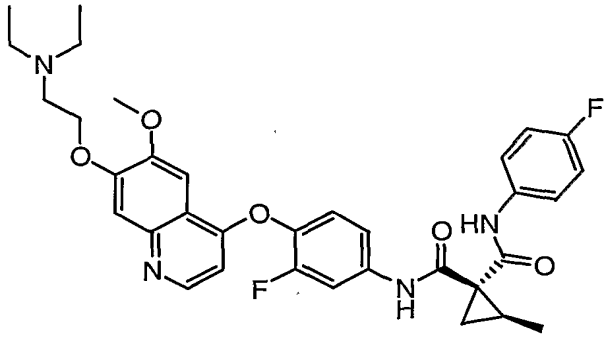
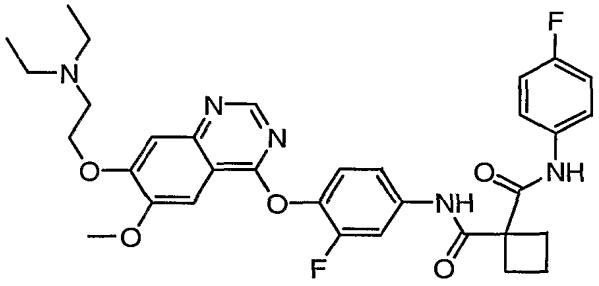
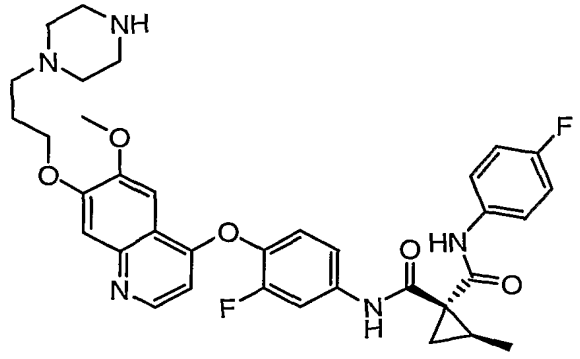
Entry	Name	Structure
67	(1R,2S)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
68	(1R,2S)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
69	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
70	(1R,2S)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	

Table 2

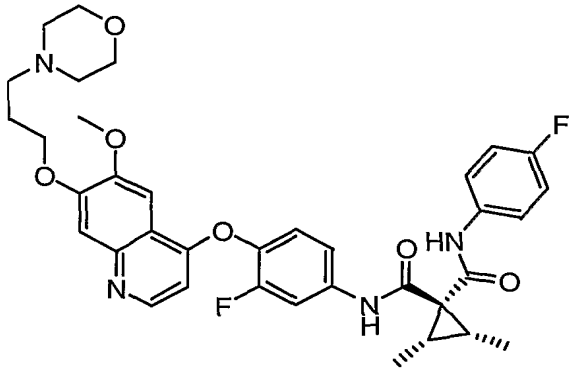
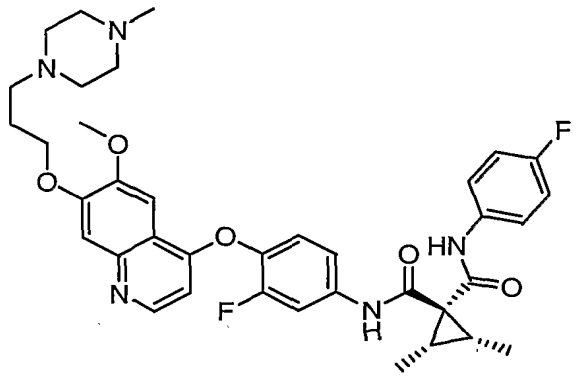
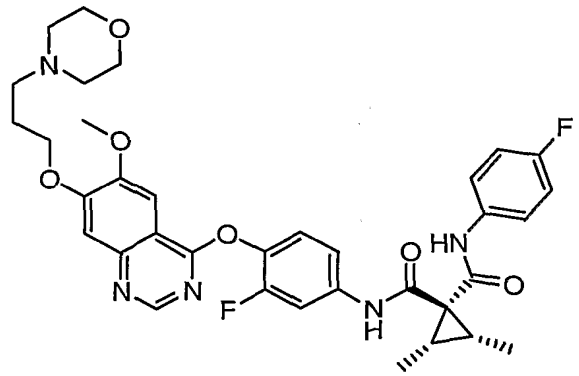
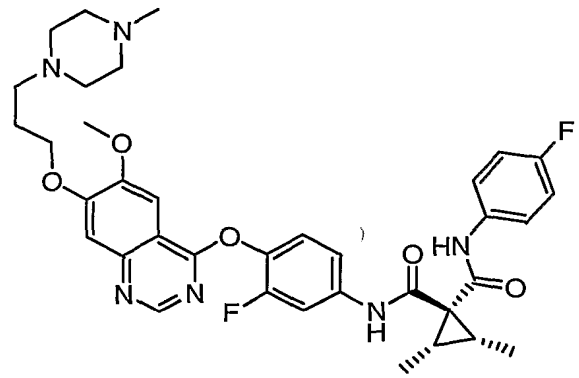
Entry	Name	Structure
71	(1R,2R,3S)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	
72	(1R,2R,3S)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	
73	(1R,2R,3S)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	
74	(1R,2R,3S)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	

Table 2

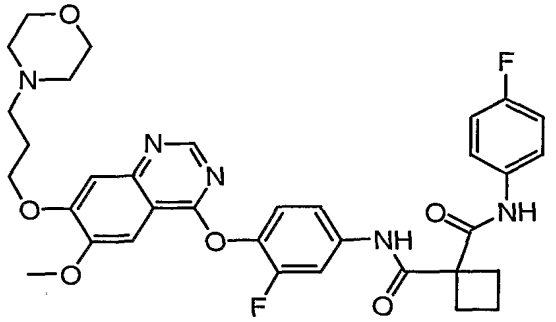
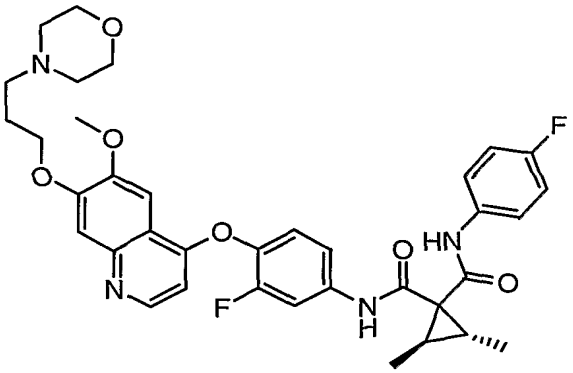
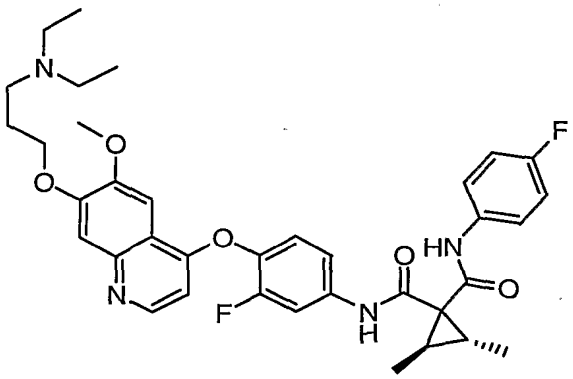
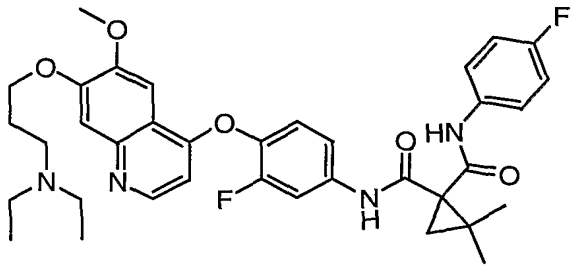
Entry	Name	Structure
75	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
76	(2R,3R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	
77	(2R,3R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	
78	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	

Table 2

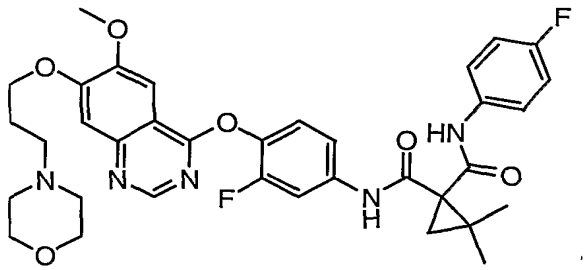
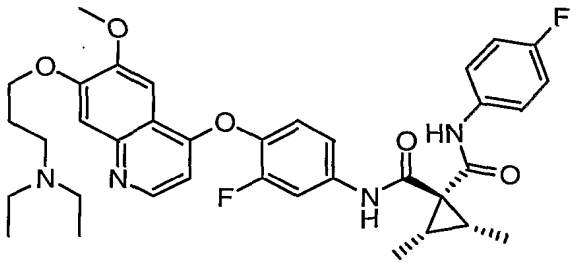
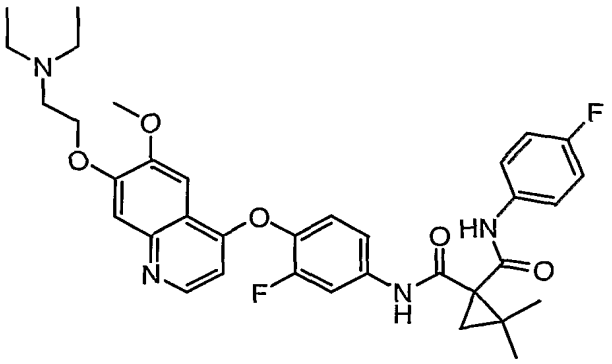
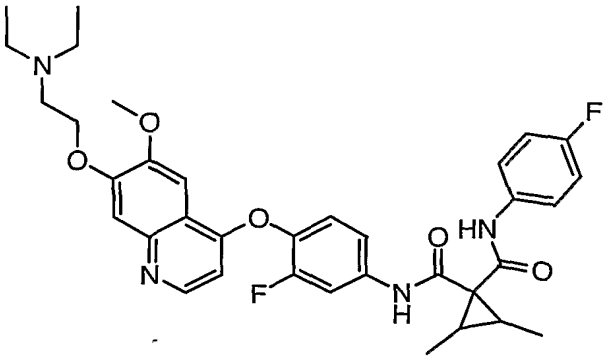
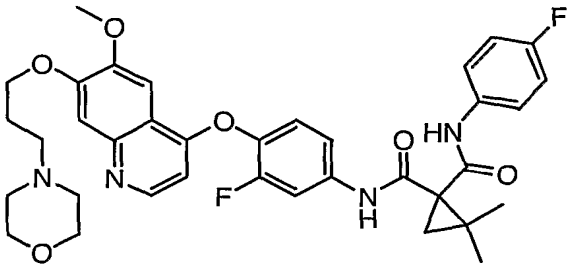
Entry	Name	Structure
79	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	
80	(1R,2R,3S)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	
81	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	
82	(1R,2R,3S)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	
83	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	

Table 2

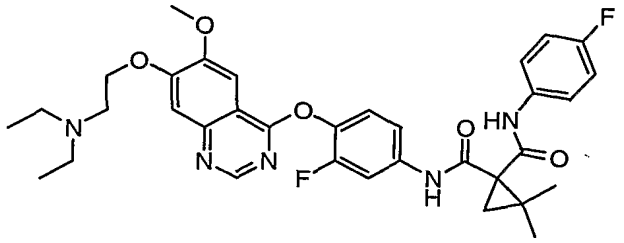
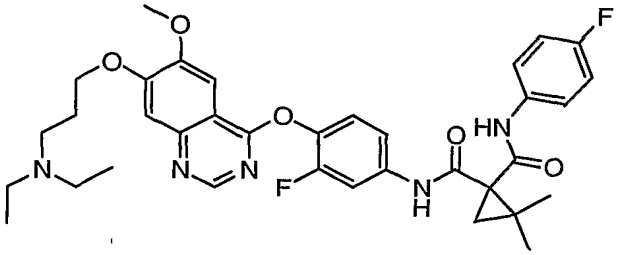
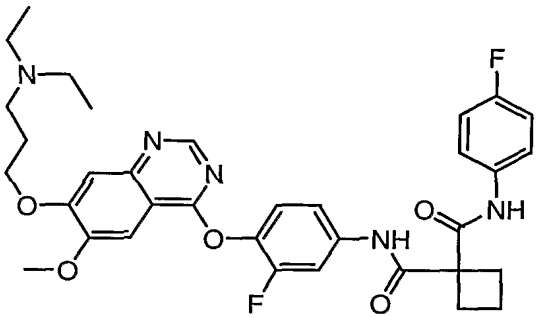
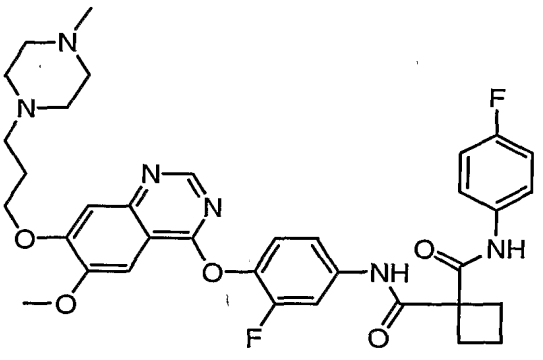
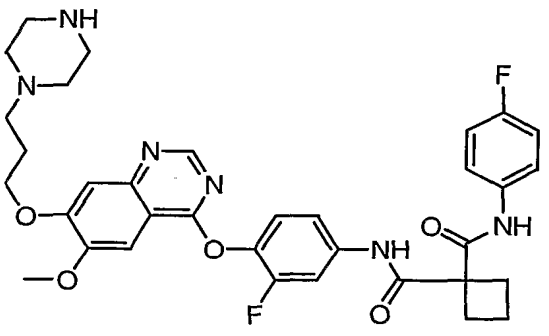
Entry	Name	Structure
84	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	
85	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	
86	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
87	N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
88	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	

Table 2

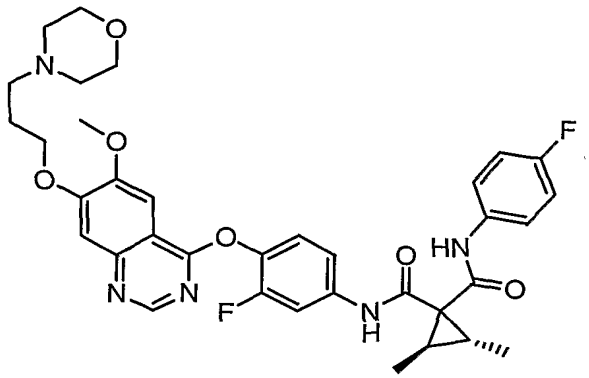
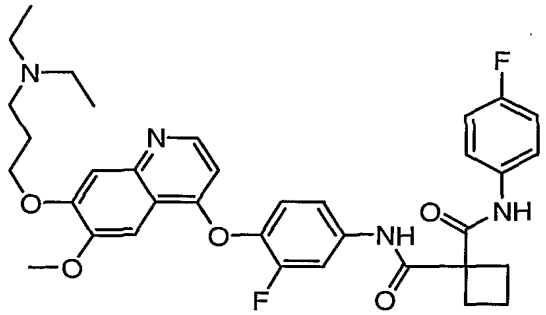
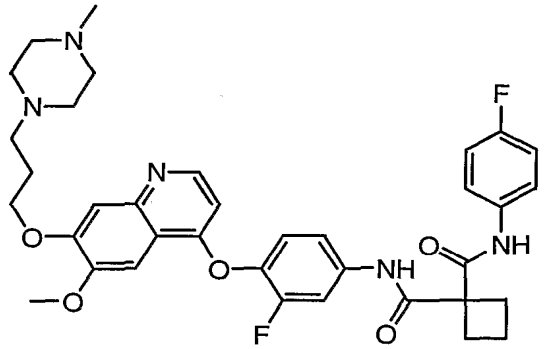
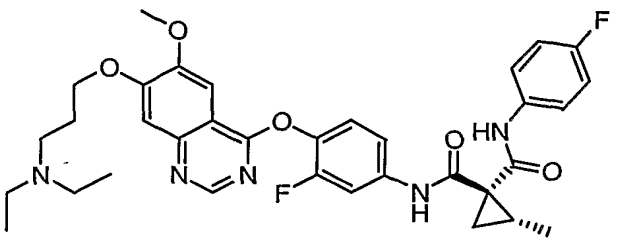
Entry	Name	Structure
89	(2R,3R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	
90	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
91	N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
92	(1R,2R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	

Table 2

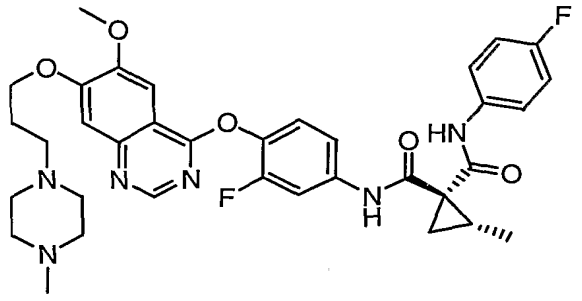
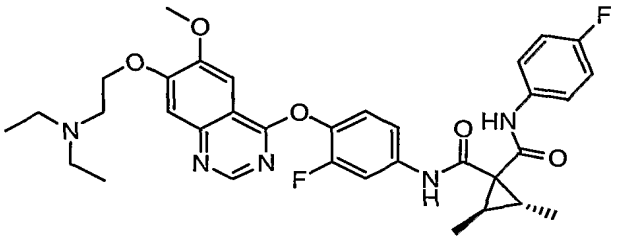
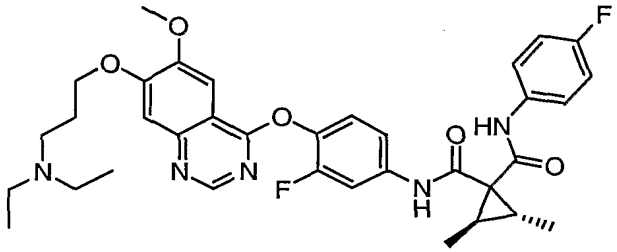
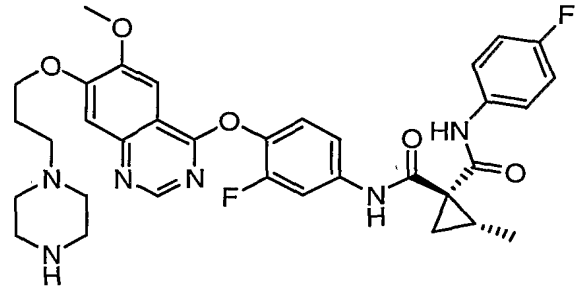
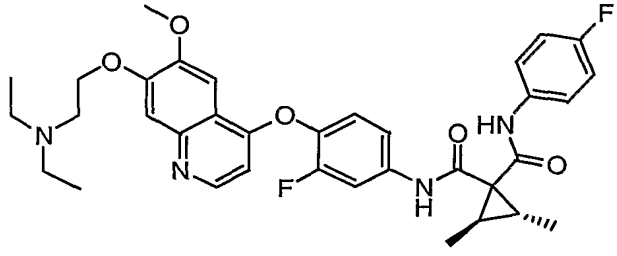
Entry	Name	Structure
93	(1R,2R)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
94	(2R,3R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	
95	(2R,3R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	
96	(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
97	(2R,3R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	

Table 2

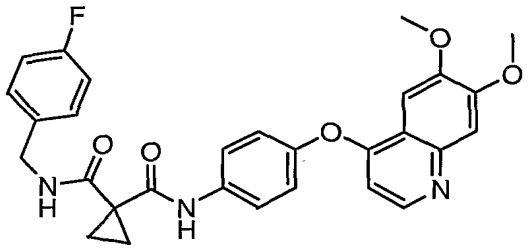
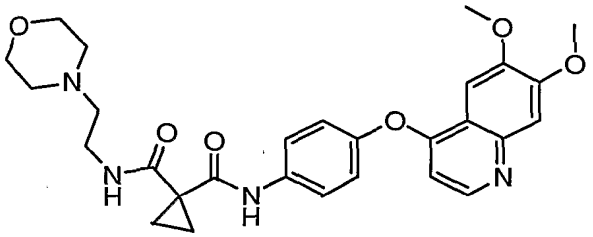
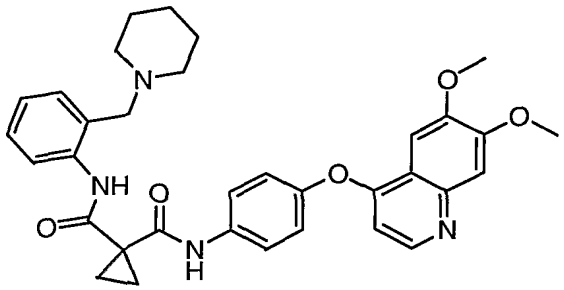
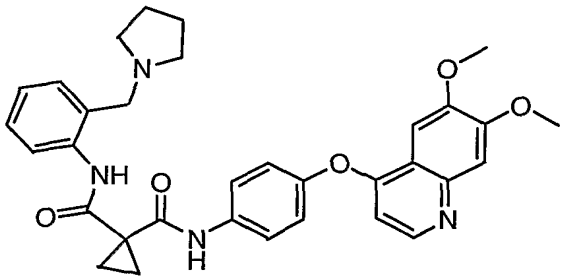
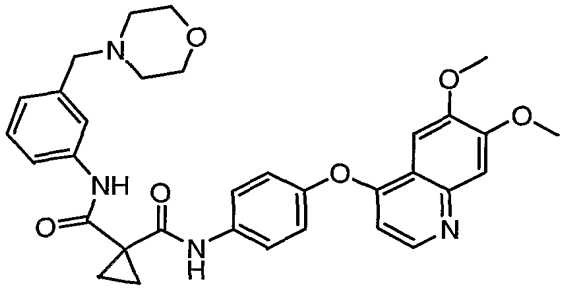
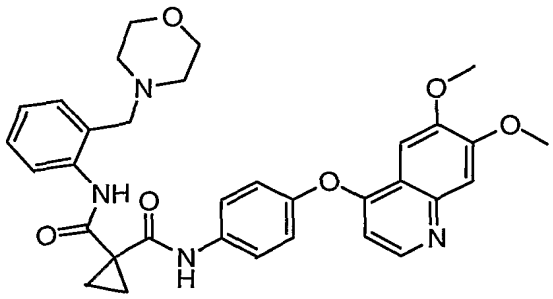
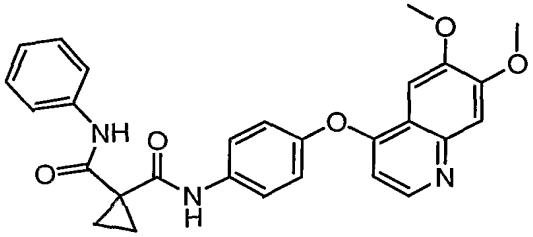
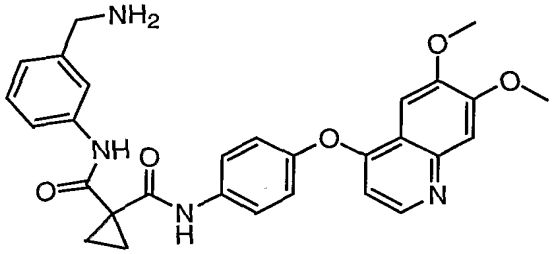
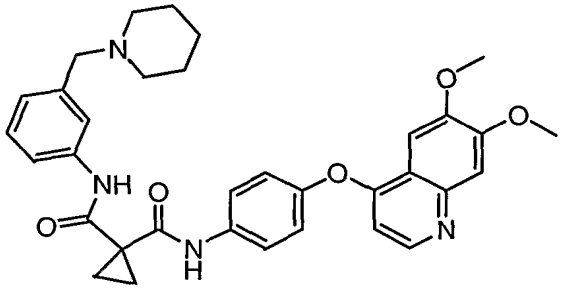
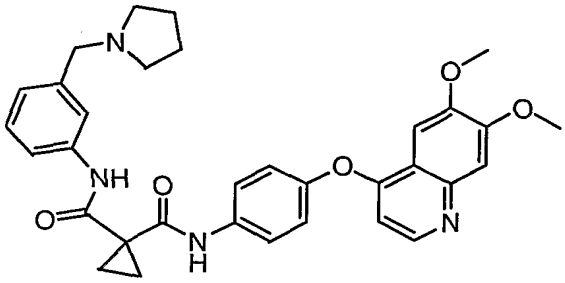
Entry	Name	Structure
98	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[(4-fluorophenyl)methyl]cyclopropane-1,1-dicarboxamide	
99	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(2-morpholin-4-ylethyl)cyclopropane-1,1-dicarboxamide	
100	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	
101	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	
102	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	

Table 2

Entry	Name	Structure
103	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	
104	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-phenylcyclopropane-1,1-dicarboxamide	
105	N-[3-(aminomethyl)phenyl]-N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide	
106	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	
107	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	

[0176] Another aspect of the invention is a pharmaceutical composition comprising a compound according to any one of paragraphs [0033]-[0120] and a pharmaceutically acceptable carrier.

[0177] Another aspect of the invention is a metabolite of the compound or the pharmaceutical composition according to any one of paragraphs [0022]-[0122].

[0178] Another aspect of the invention is a method of modulating the *in vivo* activity of a kinase, the method comprising administering to a subject an effective amount of the compound or the pharmaceutical composition according to any of paragraphs [0033]-[0121].

[0179] Another aspect of the invention is the method according to paragraph [0123], wherein modulating the *in vivo* activity of the kinase comprises inhibition of said kinase.

[0180] Another aspect of the invention is the method according to paragraph [0124], wherein the kinase is at least one of c-Met, KDR, c-Kit, flt-3, and flt-4.

[0181] Another aspect of the invention is the method according to paragraph [0125], wherein the kinase is c-Met.

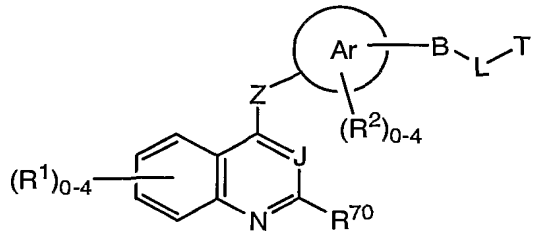
[0182] Another aspect of the invention is a method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities, the method comprising administering, to a mammal in need thereof, a therapeutically effective amount of the compound or the pharmaceutical composition as described in any one of paragraphs [0033]-[0121].

[0183] Another aspect of the invention is a method of screening for a modulator of a kinase, said kinase selected from c-Met, KDR, c-Kit, flt-3, and flt-4, the method comprising combining a compound according to any one of paragraphs [0033]-[0120], and at least one candidate agent and determining the effect of the candidate agent on the activity of said kinase.

[0184] Another aspect of the invention is a method of inhibiting proliferative activity in a cell, the method comprising administering an effective amount of a composition comprising a compound according any one of paragraphs [0033]-[0120] to a cell or a plurality of cells.

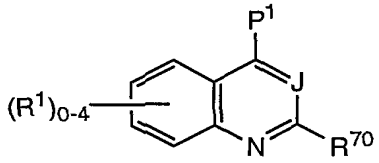
[0185] As mentioned, although improved quinolines and quinazolines of the invention can be made via conventional serial methods, due to their complex structure, more efficient

routes are desirable, particularly convergent syntheses. Thus, the present invention also comprises a process for preparing a compound of Formula **XXI**,

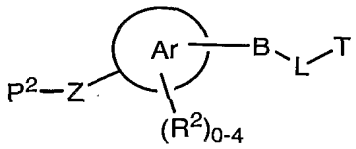


XXI

comprising reaction of a compound of Formula **XXII**, with a compound of Formula **XXIII**



XXII



XXIII

wherein,

each R^1 is independently selected from halogen, $-OR^3$, $-NO_2$, $-NH_2$, $-NR^3R^3$, $-D-R^{50}$ and optionally substituted C_{1-6}alkyl;

R^{70} is selected from -H, halogen, $-OR^3$, $-S(O)_{0-2}R^3$, $-NO_2$, $-NH_2$, $-NR^3R^3$, and optionally substituted C_{1-6}alkyl;

J is selected from =N-, =C(H)-, =C(halogen)-, and =C(CN)-;

Z is selected from $-S(O)_{0-2}-$, -O-, and $-NR^5-$;

each R^5 is independently selected from -H, optionally substituted C_{1-6}alkyl, optionally substituted aryl, and optionally substituted aryl C_{1-6}alkyl;

Ar is either a five- to ten-membered arylene or a five- to ten-membered heteroarylene containing between one and three heteroatoms;

R^2 is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted C_{1-6}alkyl;

each R^3 is independently selected from -H, $-Si(R^5)(R^5)R^5$, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted arylalkyl, and optionally substituted heteroarylalkyl;

two R^3, together with the nitrogen to which they are attached, form a four- to seven-membered heteroalicyclic, said four- to seven-membered heteroalicyclic optionally containing one additional heteroatom; when one said additional heteroatom is a nitrogen, then said nitrogen is optionally substituted with a group selected from -H, trihalomethyl, $-SO_2R^5$, $-SO_2NR^5R^5$, $-CO_2R^5$, $-C(O)NR^5R^5$, $-C(O)R^5$, and optionally substituted lower alkyl;

B is selected from absent, $-N(R^{13})-$, $-N(SO_2R^{13})-$, -O-, $-S(O)_{0-2}-$, and -C(=O)-;

L is selected from absent, $-C(=S)N(R^{13})-$, $-C(=NR^{14})N(R^{13})-$, $-SO_2N(R^{13})-$, $-SO_2-$, $-C(=O)N(R^{13})-$, $-N(R^{13})-$, $-C(=O)C_{1-2}alkylN(R^{13})-$, $-N(R^{13})C_{1-2}alkylC(=O)-$, $-C(=O)C_{0-1}alkylC(=O)N(R^{13})-$, -C(=O)-, $-C_{0-4}alkylene-$, $-C(=O)C_{0-1}alkylC(=O)OR^3-$, $-C(=NR^{14})C_{0-1}alkylC(=O)-$, $-C(=O)C_{0-1}alkylC(=O)-$, and an optionally substituted four- to six-membered heterocyclyl containing between one and three annular heteroatoms and comprising at least one nitrogen;

T is selected from -H, $-R^{13}$, $-C_{0-4}alkyl$, $-C_{0-4}alkylQ$, $-OC_{0-4}alkylQ$, $-C_{0-4}alkylOQ$, $-N(R^{13})C_{0-4}alkylQ$, $-SO_2C_{0-4}alkylQ$, $-C(=O)C_{0-4}alkylQ$, $-C_{0-4}alkylN(R^{13})Q$, and $-C(=O)N(R^{13})C_{0-4}alkylQ$, wherein each of the aforementioned $C_{0-4}alkyl$ is optionally substituted;

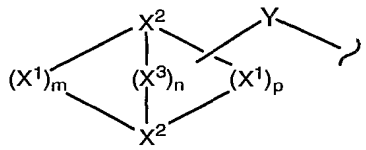
Q is a five- to ten-membered ring system, optionally substituted with between zero and four of R^{20};

each R^{20} is independently selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted $C_{1-6}alkyl$, optionally substituted aryl, optionally substituted aryl $C_{1-6}alkyl$, optionally substituted heterocyclyl, and optionally substituted heterocyclyl $C_{1-6}alkyl$;

two of R^{20}, together with the atom or atoms to which they are attached, combine to form an optionally substituted three- to seven-membered heteroalicyclic, said optionally substituted three- to seven-membered heteroalicyclic either spiro- to Q or fused to Q;

D is selected from -O-, $-S(O)_{0-2}-$, and $-NR^{15}-$;

R^{50} is either R^3, or according to formula **XXIV**;



XXIV

wherein X^1, X^2, and optionally X^3, represent the atoms of a saturated bridged ring system, said saturated bridged ring system comprising up to four annular heteroatoms represented by any of X^1, X^2, and X^3; wherein,

each X^1 is independently selected from $-C(R^6)R^7-$, -O-, $-S(O)_{0-2}-$, and $-NR^8-$;

each X^2 is independently an optionally substituted bridgehead methine or a bridgehead nitrogen;

each X^3 is independently selected from $-C(R^6)R^7-$, -O-, $-S(O)_{0-2}-$, and $-NR^8-$;

Y is either:

an optionally substituted C_{1-6}alkylene linker, between D and either 1) any annular atom of the saturated bridged ring system, except X^2 when X^2 is a bridgehead nitrogen, or 2) any heteroatom, represented by any of R^6 or R^7; provided there are at least two carbon atoms between D and any annular heteroatom of the saturated bridged ring system or any heteroatom represented by any of R^6 or R^7;

or Y is absent, when Y is absent, said saturated bridged ring system, is directly attached to D via an annular carbon of said saturated bridged ring system, unless D is $-SO_2-$, in which case said saturated bridged ring system, is directly attached to D via an any annular atom of said saturated bridged ring system;

m and p are each independently one to four;

n is zero to two, when n is zero, then there is a single bond between the two bridgehead X^2's;

R^6 and R^7 are each independently selected from -H, halogen, trihalomethyl, -CN, $-NH_2$, $-NO_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-NCO_2R^3$, $-C(O)R^3$, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl, optionally substituted heterocyclyl, optionally substituted heterocyclyl a C_{1-6}lkyl, and a bond to either Y or D; or

R^6 and R^7, when taken together are oxo; or

R^6 and R^7, when taken together with a common carbon to which they are attached, form a optionally substituted three- to seven-membered spirocyclyl, said optionally substituted three- to seven-membered spirocyclyl optionally containing at least one additional annular heteroatom selected from N, O, S, and P;

R^8 is selected from $-R^3$, Y, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$;

R^{13} is selected from -H, $-C(=O)R^3$, $-C(=O)OR^3$, $-C(=O)SR^3$, $-SO_2R^3$, $-C(=O)N(R^3)R^3$, and optionally substituted C_{1-6}alkyl;

two R^{13}, together with the atom or atoms to which they are attached, can combine to form a heteroalicyclic optionally substituted with between one and four of R^{60}, said heteroalicyclic comprising up to four annular heteroatoms, and said heteroalicyclic optionally comprising an aryl or heteroaryl fused thereto, in which case said aryl or heteroaryl is optionally substituted with an additional one to four of R^{60};

R^{14} is selected from -H, $-NO_2$, $-NH_2$, $-N(R^3)R^3$, -CN, $-OR^3$, optionally substituted C_{1-6}alkyl, optionally substituted heteroalicyclyl C_{1-6}alkyl, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl and optionally substituted heteroalicyclic;

R^{15} is a group $-M^1-M^2$, wherein M^1 is selected from absent, $-C(=S)N(R^{13})-$, $-C(=NR^{14})N(R^{13})-$, $-SO_2N(R^{13})-$, $-SO_2-$, $-C(=O)N(R^{13})-$, $-C(=O)C(=O)N(R^{13})-$, $-C_{0-4}$alkylene-, -C(=O)-, and an optionally substituted four to six-membered heterocyclyl containing between one and three heteroatoms but comprising at least one nitrogen; and M^2 is selected from -H, $-C_{0-6}$alkyl, alkoxy, $-C(=O)C_{0-4}$alkylQ, $-C_{0-4}$alkylQ, $-OC_{0-4}$alkylQ-, $-N(R^{13})C_{0-4}$alkylQ-, and $-C(=O)N(R^{13})C_{0-4}$alkylQ;

R^{60} is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted heteroaryl C_{1-6}alkyl, and optionally substituted aryl C_{1-6}alkyl;

two of R^{60}, when attached to a non-aromatic carbon, can be oxo;

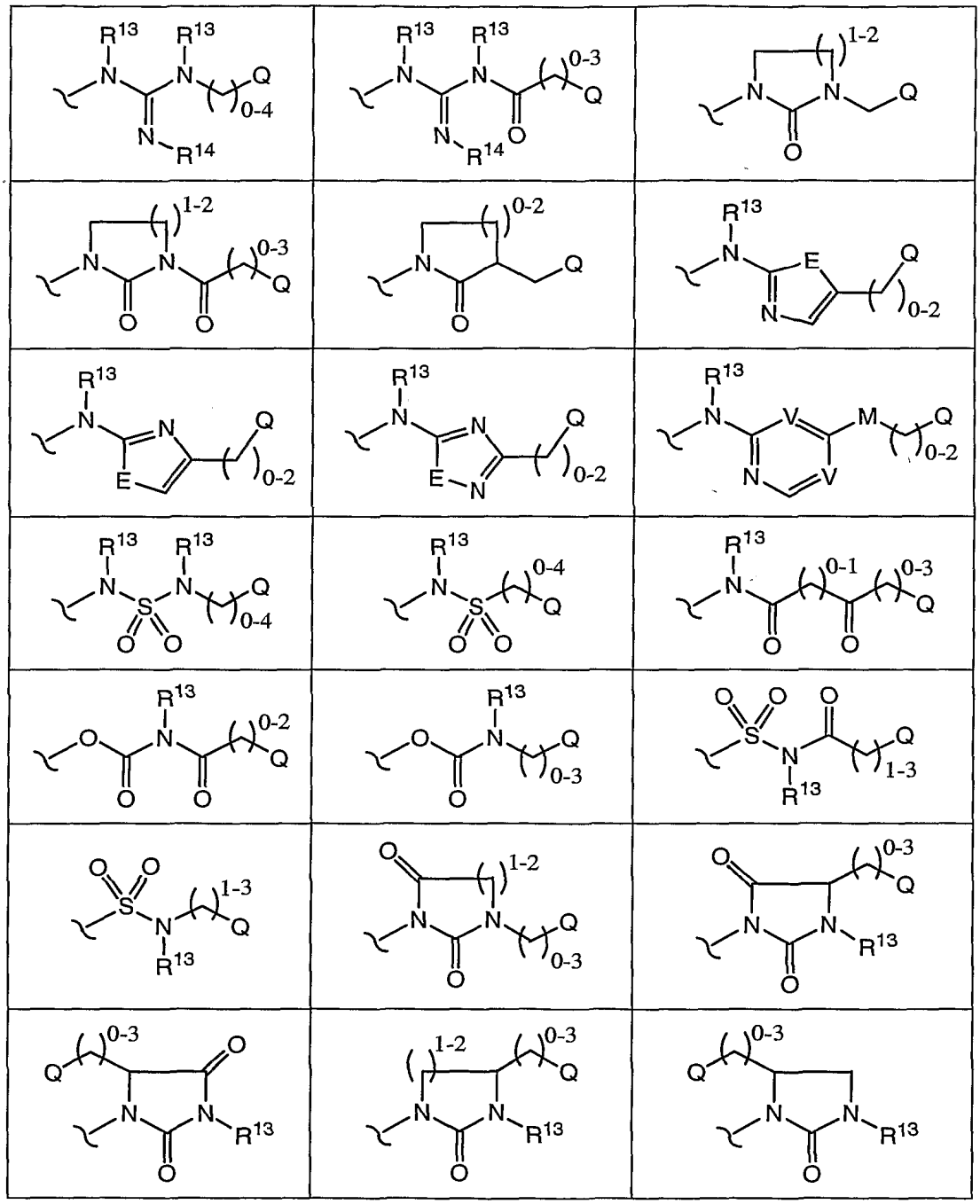
P^1 is a suitable leaving group; and

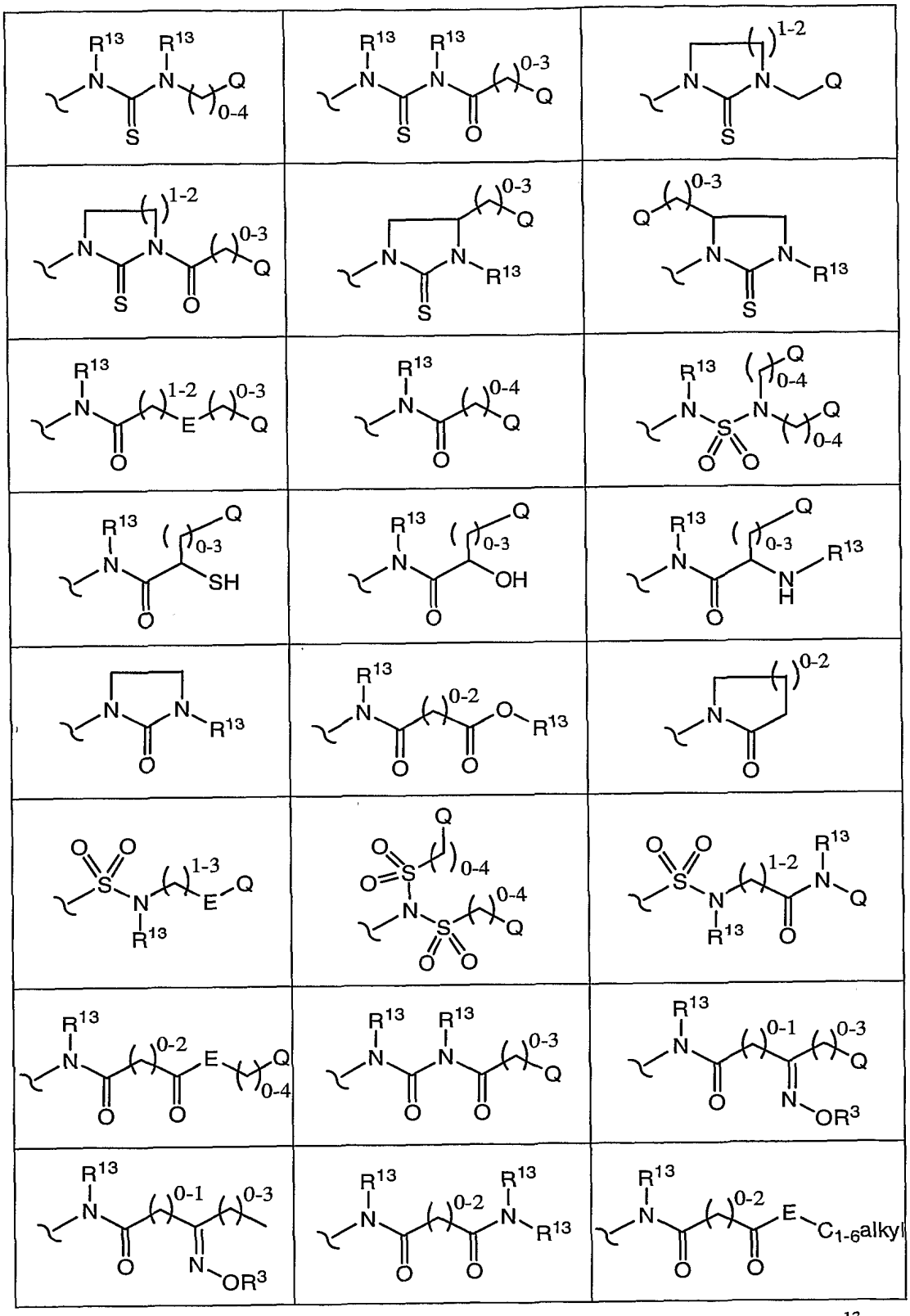
P^2 is selected from -H, a metal, and a group removed *in-situ* when combining **XXII** and **XXIII** to make **XXI**.

[0131] In one example, the process is according to paragraph [0130], wherein Ar is *para*-phenylene as defined by the substitution pattern of -Z- and -B-L-T about said phenylene.

[0132] In another example, the process is according to paragraph [0131], wherein Z is either -O- or $-NR^5-$.

[0133] In another example, the process is according to paragraph [0132], wherein -B-L-T is selected from the following:





wherein Q, R^{20}, and R^{13} are as defined above; each E is selected from -O-, -N(R^{13})-, -CH_2, and -$S(O)_{0-2}$-; M is selected from -O-, -N(R^{13})-, -CH_2-, and -C(=O)N(R^{13})-; each V is independently either =N- or =C(H)-; each methylene in any of the above formulae is

independently optionally substituted with R^{25}; and R^{25} is selected from halogen, trihalomethyl, -CN, -NO_2, -NH_2, -OR^3, -NR^3R^3, -$S(O)_{0-2}R^3$, -$SO_2NR^3R^3$, -CO_2R^3, -$C(O)NR^3R^3$, -$N(R^3)SO_2R^3$, -$N(R^3)C(O)R^3$, -$N(R^3)CO_2R^3$, -$C(O)R^3$, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl, heteroaryl C_{1-6}alkyl, and optionally substituted C_{1-6}alkyl; two of R^{25}, together with the carbon or carbons to which they are attached, can combine to form an optionally substituted three- to seven-membered alicyclic or heteroalicyclic; two of R^{25} on a single carbon can be oxo.

[0134] In another example, the process is according to paragraph [0133], wherein there is one of R^1 that is -D-R^{50} and another of R^1 that is -OR^{3a}.

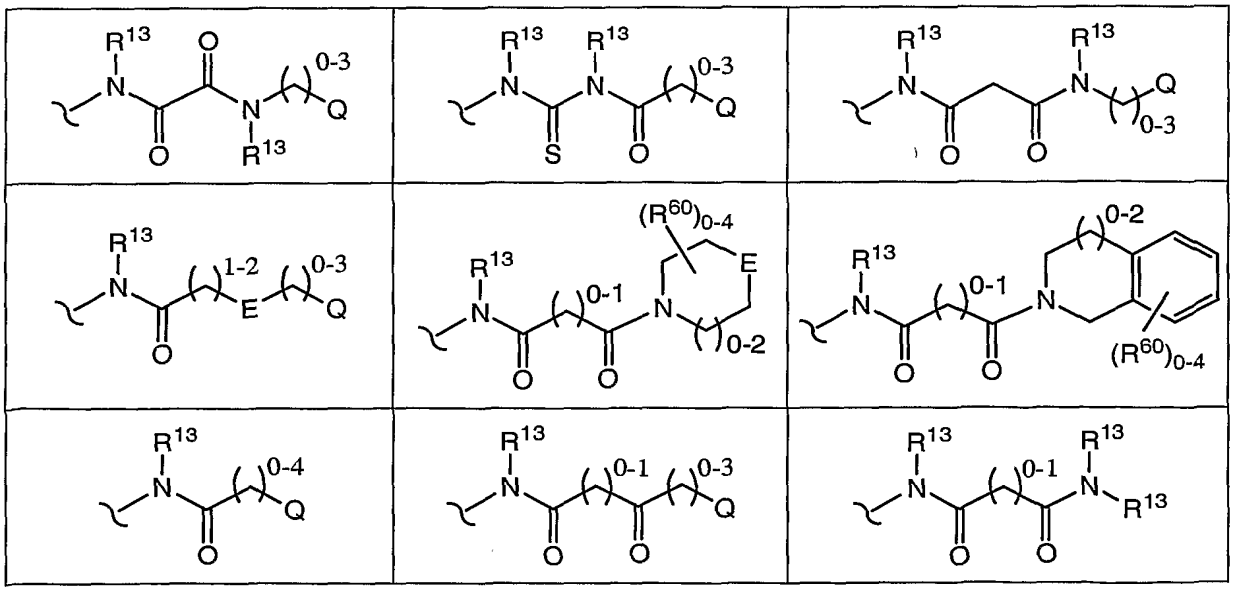
[0135] In another example, the process is according to paragraph [0134], wherein D is -O-.

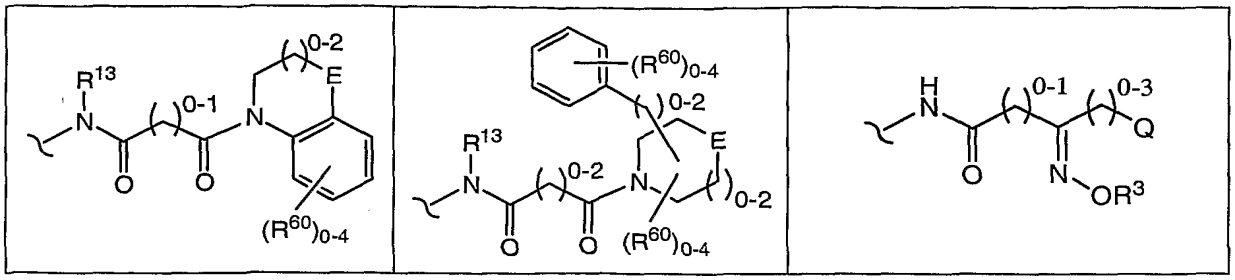
[0136] In another example, the process is according to paragraph [0135], wherein -O-R^{50} and -OR^{3a} are interchangeably located at the 6-position and 7-position of the quinazoline or quinoline according to Formula **XXI**.

[0137] In another example, the process is according to paragraph [0136], wherein -OR^{3a} is selected from -OH, -$OSi(R^5)(R^5)R^5$, and optionally substituted -OC_{1-6}alkyl.

[0138] In another example, the process is according to paragraph [0137], wherein J is =N- or =C(H)-.

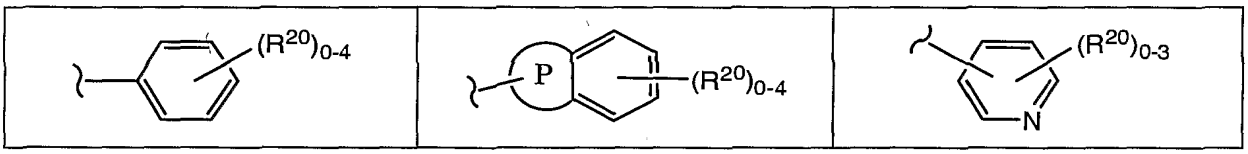
[0139] In another example, the process is according to paragraph [0138], wherein -B-L-T is selected from:





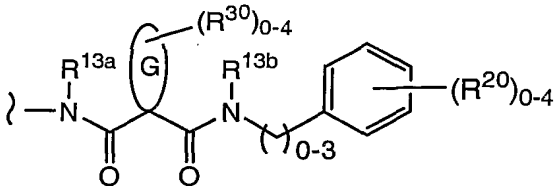
wherein Q, R^{20}, R^{13}, E, and R^{60} are as defined above; each methylene in any of the above formulae, other than those in a depicted ring, is independently optionally substituted with R^{25}; and R^{25} is selected from halogen, trihalomethyl, oxo, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl, heteroaryl C_{1-6}alkyl, and optionally substituted C_{1-6}alkyl; two of R^{25}, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered optionally substituted alicyclic or heteroalicyclic.

[0140] In another example, the process is according to paragraph [0139], wherein Q is selected from the following three formula:

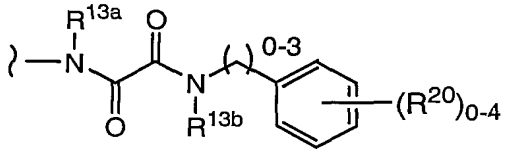


wherein R^{20} is defined as above, and P is a five- to seven-membered ring, including the two shared carbons of the aromatic ring to which P is fused, P optionally containing between one and three heteroatoms.

[0141] In another example, the process is according to paragraph [0140], wherein -B-L-T is either of formula **XXV** or formula **XXVI**,



XXV

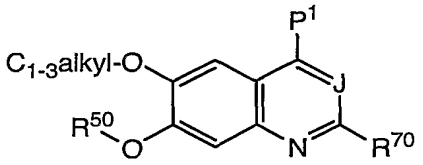


XXVI

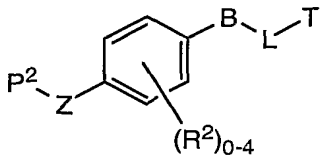
wherein R^{20} is defined as above; G is either an optionally substituted cycloalkyl or an optionally substituted heteroalicyclic; each R^{30} is independently selected from halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally

substituted C_{1-6}alkyl; and R^{3a} and R^{3b} are each independently selected from -H and optionally substituted C_{1-6}alkyl.

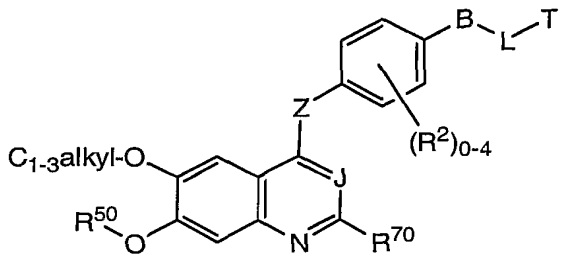
[0142] In another example, the process is according to paragraph [0141], wherein a compound of formula **XXIIa** is combined with a compound of formula **XXIIIa** to make a compound of formula **XXIa**,



XXIIa



XXIIIa



XXIa

wherein -B-L-T, Z, J, R^{50}, and R^2 are as defined above; R^{70} is selected from -H, $-NO_2$, $-NH_2$, and $-NR^3R^3$; provided when Z is $-N(R^5)-$ that R^5 is selected from -H, C_{1-3}alkyl, and aryl C_{1-3}alkyl; P^1 is selected from halogen, optionally substituted alkyl-$S(O)_{0-2}$-, optionally substituted arylsulfonate, optionally substituted alkylsulfonate, a group containing boron, an azide, a group containing phosphorus, and a metal; and P^2 is selected from -H and a metal.

[0143] In another example, the process is according to paragraph [0142], wherein P^2 is selected from -H, lithium, sodium, potassium, cesium, copper, palladium, and titanium.

[0144] In another example, the process is according to paragraph [0143], wherein Z is -O-.

[0145] In another example, the process is according to paragraph [0144], wherein P^1 is selected from chlorine, bromine, a toluene sulfonate, and trifluoromethansulfonate.

[0146] In another example, the process is according to paragraph [0145], wherein R^{70} is -H.

[0147] In another example, the process is according to paragraph [0146], wherein J is =C(H)-.

[0148] In another example, the process is according to paragraph [0147], wherein R^2 is selected from C_{1-6} alkyl, perfluoro C_{1-6} alkyl, and halogen.

[0149] In another example, the process is according to paragraph [0148], wherein **XXIIa** and **XXIIIa** are heated together, optionally with a base, optionally with microwave radiation, to form **XXIa**.

[0150] In another example, the process is according to paragraph [0149], wherein the base is selected from an organic base, an inorganic base, and a combination of an organic base and an inorganic base.

[0151] In another example, the process is according to paragraph [0150], wherein the base is selected from 2,6-lutidine, 4-N,N-dimethylaminopyridine, and a metal carbonate.

[0152] In another example, the process is according to paragraph [0151], wherein **XXIIa** and **XXIIIa** are heated together in a solvent with said base, at between about 40°C and 200°C for between about one hour and twenty-four hours to form **XXIa**.

[0153] In another example, the process is according to paragraph [0152], wherein the solvent is an organic solvent.

[0154] In another example, the process is according to paragraph [0153], wherein one molar equivalent of **XXIIa** is combined with between about one quarter and four molar equivalents of **XXIIIa**.

[0155] In another example, the process is according to paragraph [0154], wherein one molar equivalent of **XXIIa** is combined with more than one but less than two molar equivalents of **XXIIIa**.

[0156] In another example, the process is according to paragraph [0155], wherein **XXIIa** is combined with **XXIIIa** and said base in an aromatic solvent to form a mixture, and said mixture is heated to between about 100°C and 200°C for between about one and ten hours to form **Ia**.

[0157] In another example, the process is according to paragraph [0156], wherein the aromatic solvent is an optionally substituted benzene.

[0158] In another example, the process is according to paragraph [0157], wherein the aromatic solvent is bromobenzene.

[0159] In another example, the process is according to paragraph [0158], wherein the base is 4-N,N-dimethylaminopyridine.

[0160] In another example, the process is according to paragraph [0159], wherein said mixture is heated to reflux for between about three and seven hours.

[0161] In another example, the process is according to paragraph [0160], wherein said mixture is heated to reflux for between about four and six hours.

[0162] In another example, the process is according to paragraph [0155], wherein **XXIIa** is combined with **XXIIIa** and said base in a non-aromatic solvent to form a mixture, and said mixture is heated to between about 40°C and 100°C for between about one and twenty hours to form **XXIa**.

[0163] In another example, the process is according to paragraph [0162], wherein the non-aromatic solvent comprises a functional group selected from an amide, and ether, a nitrile, a halide, an ester, an amine, and a ketone.

[0164] In another example, the process is according to paragraph [0163], wherein the non-aromatic solvent is N,N-dimethylacetamide.

[0165] In another example, the process is according to paragraph [0164], wherein the base is potassium carbonate.

[0166] In another example, the process is according to paragraph [0165], wherein said mixture is heated to about 50°C between about ten and twenty hours.

[0167] In another example, the process is according to paragraph [0166], wherein the aromatic solvent is an optionally substituted pyridine.

[0168] In another example, the process is according to paragraph [0167], wherein the aromatic solvent is 2,6-lutidine.

[0169] In another example, the process is according to paragraph [0168], wherein the base is 2,6-lutidine.

[0170] In another example, the process is according to paragraph [0169], wherein said mixture is heated to reflux for between about three and seven hours.

[0171] In another example, the process is according to paragraph [0170], wherein said mixture is heated to reflux for between about four and six hours.

[0172] In another example, the process is according to paragraph [0154], wherein one molar equivalent of **XXIIIa** is combined with more than one but less than two molar equivalents of **XXIIa**.

[0173] In another example, the process is according to paragraph [0172], wherein **XXIIa** is combined with **XXIIIa** and said base in an aromatic solvent to form a mixture, and said mixture is heated to between about 100°C and 200°C for between about ten and twenty hours to form **XXIa**.

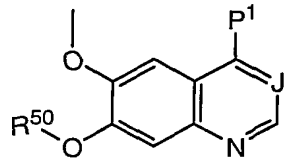
[0174] In another example, the process is according to paragraph [0173], wherein the aromatic solvent is an optionally substituted pyridine.

[0175] In another example, the process is according to paragraph [0174], wherein the aromatic solvent is 2,6-lutidine.

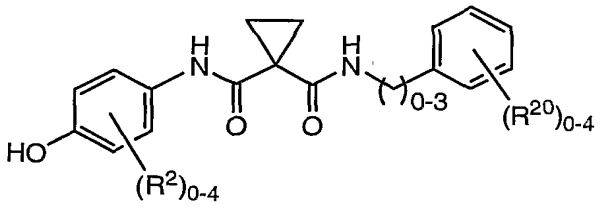
[0176] In another example, the process is according to paragraph [0175], wherein the base is 2,6-lutidine.

[0177] In another example, the process is according to paragraph [0176], wherein said mixture is heated to between about 150°C and 200°C for between about fifteen and twenty hours.

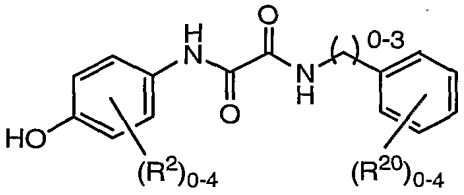
[0178] In another example, the process is according to any of paragraphs [0149] – [0177], wherein a compound of formula **XXIIb** is substituted for the compound of formula **XXIIa**, and either a compound of formula **XXIIIb** or a compound of formula **XXIIIc** is substituted for the compound of formula **XXIIIa**, in order to make a compound of formula **XXIb** or a compound of formula **XXIc**, respectively,



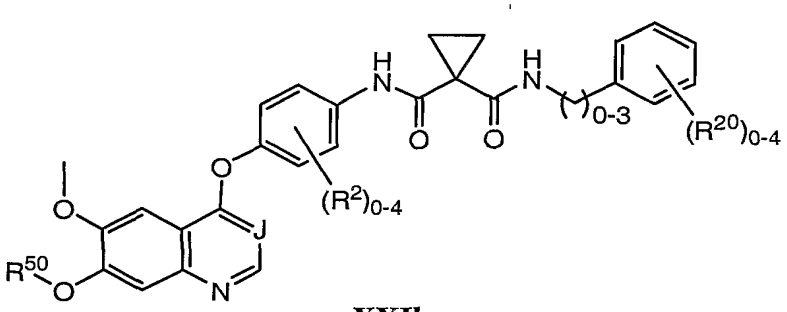
XXIIb



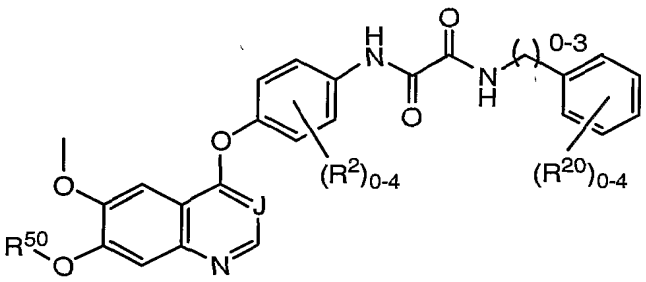
XXIIIb



XXIIIc



XXIb



XXIc

wherein J, R^{50}, R^{20} and R^2 are as defined above.

[0179] In another example, the process is according to paragraph [0178], wherein R^2, if present, is halogen.

[0180] In another example, the process is according to paragraph [0179], wherein R^2, if present, is fluorine.

[0181] In another example, the process is according to paragraph [0180], wherein R^2, if present, is up to two fluorines *ortho* to the oxygen of the phenylene to which R^2 is attached.

[0182] In another example, the process is according to paragraph [0130], used to make a compound listed in either Table 1 or Table 2.

[0183] In another example the process is according to any of paragraphs [0130] - [0182], further comprising converting said compound to a pharmaceutically acceptable salt, hydrate, or prodrug thereof.

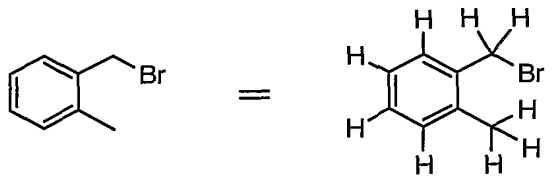
Definitions

[0184] As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in

which they are used indicates otherwise or they are expressly defined to mean something different.

[0185] The symbol "-" means a single bond, "=" means a double bond, "≡" means a triple bond. The symbol "〰" refers to a group on a double-bond as occupying either position on the terminus of a double bond to which the symbol is attached; that is, the geometry, *E*- or *Z*-, of the double bond is ambiguous. When a group is depicted removed from its parent formula, the "〜" symbol will be used at the end of the bond which was theoretically cleaved in order to separate the group from its parent structural formula.

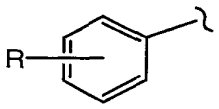
[0186] When chemical structures are depicted or described, unless explicitly stated otherwise, all carbons are assumed to have hydrogen substitution to conform to a valence of four. For example, in the structure on the left-hand side of the schematic below there are nine hydrogens implied. The nine hydrogens are depicted in the right-hand structure. Sometimes a particular atom in a structure is described in textual formula as having a hydrogen or hydrogens as substitution (expressly defined hydrogen), for example, $-CH_2CH_2-$. It is understood by one of ordinary skill in the art that the aforementioned descriptive techniques are common in the chemical arts to provide brevity and simplicity to description of otherwise complex structures.



[0187] In this application, some ring structures are depicted generically and will be described textually. For example, in the schematic below, if in the structure on the left, ring A is used to describe a "spirocyclyl," then if ring A is cyclopropyl, there are at most four hydrogens on ring A (when "R" can also be -H). In another example, as depicted on the right side of the schematic below, if ring B is used to describe a "phenylene" then there can be at most four hydrogens on ring B (assuming depicted cleaved bonds are not C-H bonds).

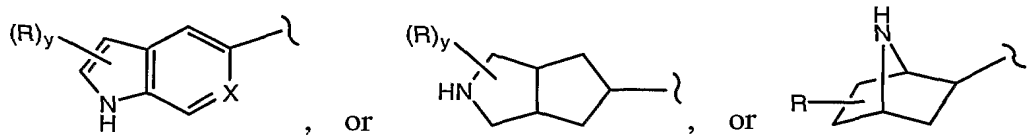


[0188] If a group "R" is depicted as "floating" on a ring system, as for example in the formula:



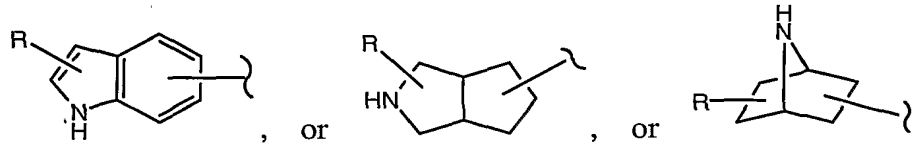
then, unless otherwise defined, a substituent "R" may reside on any atom of the ring system, assuming replacement of a depicted, implied, or expressly defined hydrogen from one of the ring atoms, so long as a stable structure is formed.

[0189] If a group "R" is depicted as floating on a fused ring system, as for example in the formulae:



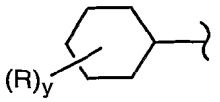
then, unless otherwise defined, a substituent "R" may reside on any atom of the fused ring system, assuming replacement of a depicted (for example the -NH- in the formula above), implied (for example as in the formula above, where the hydrogens are not shown but understood to be present), or expressly defined hydrogen (for example where in the formula above, "X" equals =CH-) from one of the ring atoms, so long as a stable structure is formed. In the example depicted, the "R" group may reside on either the 5-membered or the 6-membered ring of the fused ring system. In the formula depicted above, when y is 2 for example, then the two "R's" may reside on any two atoms of the ring system, again assuming each replaces a depicted, implied, or expressly defined hydrogen on the ring.

[0190] When there are more than one such depicted "floating" groups, as for example in the formulae:

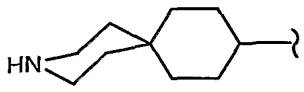


where there are two groups, namely, the "R" and the bond indicating attachment to a parent structure; then, unless otherwise defined, the "floating" groups may reside on any atoms of the ring system, again assuming each replaces a depicted, implied, or expressly defined hydrogen on the ring.

[0191] When a group "R" is depicted as existing on a ring system containing saturated carbons, as for example in the formula:



where, in this example, "y" can be more than one, assuming each replaces a currently depicted, implied, or expressly defined hydrogen on the ring; then, unless otherwise defined, where the resulting structure is stable, two "R's" may reside on the same carbon. A simple example is when R is a methyl group; there can exist a geminal dimethyl on a carbon of the depicted ring (an "annular" carbon). In another example, two R's on the same carbon, including that carbon, may form a ring, thus creating a spirocyclic ring (a "spirocyclyl" group) structure with the depicted ring as for example in the formula:



[0192] "Alkyl" is intended to include linear, branched, or cyclic hydrocarbon structures and combinations thereof, inclusively. For example, "C_8 alkyl" may refer to an *n*-octyl, *iso*-octyl, cyclohexylethyl, and the like. Lower alkyl refers to alkyl groups of from one to six carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *s*-butyl, *t*-butyl, isobutyl, pentyl, hexyl and the like. Higher alkyl refers to alkyl groups containing more that eight carbon atoms. Exemplary alkyl groups are those of C_{20} or below. Cycloalkyl is a subset of alkyl and includes cyclic hydrocarbon groups of from three to thirteen carbon atoms. Examples of cycloalkyl groups include c-propyl, c-butyl, c-pentyl, norbornyl, adamantyl and the like. In this application, alkyl refers to alkanyl, alkenyl, and alkynyl residues (and combinations thereof); it is intended to include cyclohexylmethyl, vinyl, allyl, isoprenyl, and the like. Thus when an alkyl residue having a specific number of carbons is named, all geometric isomers having that number of carbons are intended to be encompassed; thus, for example, either "butyl" or "C_4 alkyl" is meant to include *n*-butyl, *sec*-butyl, isobutyl, *t*-butyl, isobutenyl and but-2-yne radicals; and for example, "propyl" or "C_3 alkyl" each include *n*-propyl, propenyl, and isopropyl.

[0193] "Alkylene" refers to straight or branched chain divalent radical consisting solely of carbon and hydrogen atoms, containing no unsaturation and having from one to ten carbon atoms, for example, methylene, ethylene, propylene, *n*-butylene and the like. Alkylene is a subset of alkyl, referring to the same residues as alkyl, but having two points of attachment and, specifically, fully saturated. Examples of alkylene include ethylene

(-CH_2CH_2-), propylene (-$CH_2CH_2CH_2$-), dimethylpropylene (-$CH_2C(CH_3)_2CH_2$-), and cyclohexylpropylene (-$CH_2CH_2CH(C_6H_{13})$).

[0194] "Alkylidene" refers to a straight or branched chain unsaturated divalent radical consisting solely of carbon and hydrogen atoms, having from two to ten carbon atoms, for example, ethylidene, propylidene, *n*-butylidene, and the like. Alkylidene is a subset of alkyl, referring to the same residues as alkyl, but having two points of attachment and, specifically, double bond unsaturation. The unsaturation present includes at least one double bond.

[0195] "Alkylidyne" refers to a straight or branched chain unsaturated divalent radical consisting solely of carbon and hydrogen atoms having from two to ten carbon atoms, for example, propylid-2-ynyl, *n*-butylid-1-ynyl, and the like. Alkylidyne is a subset of alkyl, referring to the same residues as alkyl, but having two points of attachment and, specifically, triple bond unsaturation. The unsaturation present includes at least one triple bond.

[0196] Any of the above radicals, "alkylene," "alkylidene" and "alkylidyne," when optionally substituted, may contain alkyl substitution which itself contains unsaturation. For example, 2-(2-phenylethynyl-but-3-enyl)-naphthalene (IUPAC name) contains an *n*-butylid-3-ynyl radical with a vinyl substituent at the 2-position of said radical.

[0197] "Alkoxy" or "alkoxyl" refers to the group -O-alkyl, for example including from one to eight carbon atoms of a straight, branched, cyclic configuration, unsaturated chains, and combinations thereof attached to the parent structure through an oxygen atom. Examples include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy and the like. Lower-alkoxy refers to groups containing one to six carbons.

[0198] "Substituted alkoxy" refers to the group -O-(substituted alkyl), the substitution on the alkyl group generally containing more than only carbon (as defined by alkoxy). One exemplary substituted alkoxy group is "polyalkoxy" or -O-optionally substituted alkylene-optionally substituted alkoxy, and includes groups such as -$OCH_2CH_2OCH_3$, and glycol ethers such as polyethyleneglycol and -$O(CH_2CH_2O)_xCH_3$, where x is an integer of between about two and about twenty, in another example, between about two and about ten, and in a further example between about two and about five. Another exemplary substituted alkoxy group is hydroxyalkoxy or -$OCH_2(CH_2)_yOH$, where y is for example an

integer of between about one and about ten, in another example y is an integer of between about one and about four.

[0199] "Acyl" refers to groups of from one to ten carbon atoms of a straight, branched, cyclic configuration, saturated, unsaturated and aromatic and combinations thereof, attached to the parent structure through a carbonyl functionality. One or more carbons in the acyl residue may be replaced by nitrogen, oxygen or sulfur as long as the point of attachment to the parent remains at the carbonyl. Examples include acetyl, benzoyl, propionyl, isobutyryl, *t*-butoxycarbonyl, benzyloxycarbonyl and the like. Lower-acyl refers to groups containing one to six carbons.

[0200] "α-Amino Acids" refer to naturally occurring and commercially available amino acids and optical isomers thereof. Typical natural and commercially available α-amino acids are glycine, alanine, serine, homoserine, threonine, valine, norvaline, leucine, isoleucine, norleucine, aspartic acid, glutamic acid, lysine, omithine, histidine, arginine, cysteine, homocysteine, methionine, phenylalanine, homophenylalanine, phenylglycine, ortho-tyrosine, meta-tyrosine, para-tyrosine, tryptophan, glutamine, asparagine, proline and hydroxyproline. A "side chain of an α-amino acid" refers to the radical found on the α-carbon of an α-amino acid as defined above, for example, hydrogen (for glycine), methyl (for alanine), benzyl (for phenylalanine), and the like.

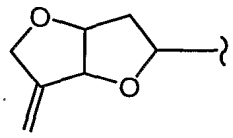
[0201] "Amino" refers to the group $-NH_2$. "Substituted amino," refers to the group -N(H)R or –N(R)R where each R is independently selected from the group: optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted heterocyclyl, acyl, carboxy, alkoxycarbonyl, sulfanyl, sulfinyl and sulfonyl, for example, diethylamino, methylsulfonylamino, furanyl-oxy-sulfonamino.

[0202] "Aryl" refers to aromatic six- to fourteen-membered carbocyclic ring, for example, benzene, naphthalene, indane, tetralin, fluorene and the like, univalent radicals. As univalent radicals, the aforementioned ring examples are named, phenyl, naphthyl, indanyl, tetralinyl, and fluorenyl.

[0203] "Arylene" generically refers to any aryl that has at least two groups attached thereto. For a more specific example, "phenylene" refers to a divalent phenyl ring radical. A phenylene, thus may have more than two groups attached, but is defined by a minimum of two non-hydrogen groups attached thereto.

[0204] "Arylalkyl" refers to a residue in which an aryl moiety is attached to a parent structure via one of an alkylene, alkylidene, or alkylidyne radical. Examples include benzyl, phenethyl, phenylvinyl, phenylallyl and the like. Both the aryl, and the corresponding alkylene, alkylidene, or alkylidyne radical portion of an arylalkyl group may be optionally substituted. "Lower arylalkyl" refers to an arylalkyl where the "alkyl" portion of the group has one to six carbons; this can also be refered to as C_{1-6} arylalkyl.

[0205] "Exo-alkenyl" refers to a double bond that emanates from an annular carbon, and is not within the ring system, for example the double bond depicted in the formula below.



[0206] In some examples, as appreciated by one of ordinary skill in the art, two adjacent groups on an aromatic system may be fused together to form a ring structure. The fused ring structure may contain heteroatoms and may be optionally substituted with one or more groups. It should additionally be noted that saturated carbons of such fused groups (i.e. saturated ring structures) can contain two substitution groups.

[0207] "Fused-polycyclic" or "fused ring system" refers to a polycyclic ring system that contains bridged or fused rings; that is, where two rings have more than one shared atom in their ring structures. In this application, fused-polycyclics and fused ring systems are not necessarily all aromatic ring systems. Typically, but not necessarily, fused-polycyclics share a vicinal set of atoms, for example naphthalene or 1,2,3,4-tetrahydro-naphthalene. A spiro ring system is not a fused-polycyclic by this definition, but fused polycyclic ring systems of the invention may themselves have spiro rings attached thereto via a single ring atom of the fused-polycyclic.

[0208] "Halogen" or "halo" refers to fluorine, chlorine, bromine or iodine. "Haloalkyl" and "haloaryl" refer generically to alkyl and aryl radicals that are substituted with one or more halogens, respectively. Thus, "dihaloaryl," "dihaloalkyl," "trihaloaryl" etc. refer to aryl and alkyl substituted with a plurality of halogens, but not necessarily a plurality of the same halogen; thus 4-chloro-3-fluorophenyl is within the scope of dihaloaryl.

[0209] "Heteroarylene" generically refers to any heteroaryl that has at least two groups attached thereto. For a more specific example, "pyridylene" refers to a divalent pyridyl

ring radical. A pyridylene, thus may have more than two groups attached, but is defined by a minimum of two non-hydrogen groups attached thereto.

[0210] "Heteroatom" refers to O, S, N, or P.

[0211] "Heterocyclyl" refers to a stable three- to fifteen-membered ring radical that consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, phosphorus, oxygen and sulfur. For purposes of this invention, the heterocyclyl radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused or bridged ring systems as well as spirocyclic systems; and the nitrogen, phosphorus, carbon or sulfur atoms in the heterocyclyl radical may be optionally oxidized to various oxidation states. In a specific example, the group $-S(O)_{0-2}-$, refers to -S- (sulfide), -S(O)- (sulfoxide), and $-SO_2-$ (sulfone). For convenience, nitrogens, particularly but not exclusively, those defined as annular aromatic nitrogens, are meant to include their corresponding *N*-oxide form, although not explicitly defined as such in a particular example. Thus, for a compound of the invention having, for example, a pyridyl ring; the corresponding pyridyl-*N*-oxide is meant to be included as another compound of the invention. In addition, annular nitrogen atoms may be optionally quaternized; and the ring radical may be partially or fully saturated or aromatic. Examples of heterocyclyl radicals include, but are not limited to, azetidinyl, acridinyl, benzodioxolyl, benzodioxanyl, benzofuranyl, carbazoyl, cinnolinyl, dioxolanyl, indolizinyl, naphthyridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrazoyl, tetrahydroisoquinolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, dihydropyridinyl, tetrahydropyridinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolinyl, oxazolidinyl, triazolyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzothieliyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, dioxaphospholanyl, and oxadiazolyl.

[0212] "Heteroalicyclic" refers specifically to a non-aromatic heterocyclyl radical. A heteroalicyclic may contain unsaturation, but is not aromatic.

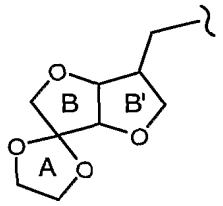
[0213] "Heteroaryl" refers specifically to an aromatic heterocyclyl radical.

[0214] "Heterocyclylalkyl" refers to a residue in which a heterocyclyl is attached to a parent structure via one of an alkylene, alkylidene, or alkylidyne radical. Examples include (4-methylpiperazin-1-yl) methyl, (morpholin-4-yl) methyl, (pyridine-4-yl) methyl, 2-(oxazolin-2-yl) ethyl, 4-(4-methylpiperazin-1-yl)-2-butenyl, and the like. Both the heterocyclyl, and the corresponding alkylene, alkylidene, or alkylidyne radical portion of a heterocyclylalkyl group may be optionally substituted. "Lower heterocyclylalkyl" refers to a heterocyclylalkyl where the "alkyl" portion of the group has one to six carbons. "Heteroalicyclylalkyl" refers specifically to a heterocyclylalkyl where the heterocyclyl portion of the group is non-aromatic; and "heteroarylalkyl" refers specifically to a heterocyclylalkyl where the heterocyclyl portion of the group is aromatic Such terms may be described in more than one way, for example, "lower heterocyclylalkyl" and "heterocyclyl C_{1-6}alkyl" are equivalent terms.

[0215] "Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. One of ordinary skill in the art would understand that, with respect to any molecule described as containing one or more optional substituents, that only sterically practical and/or synthetically feasible compounds are meant to be included. "Optionally substituted" refers to all subsequent modifiers in a term, for example in the term "optionally substituted arylC_{1-8} alkyl," optional substitution may occur on both the "C_{1-8} alkyl" portion and the "aryl" portion of the molecule; and for example, optionally substituted alkyl includes optionally substituted cycloalkyl groups, which in turn are defined as including optionally substituted alkyl groups, potentially *ad infinitum*. A list of exemplary optional substitution are listed below in the definition of "substituted."

[0216] "Saturated bridged ring system" refers to a bicyclic or polycyclic ring system that is not aromatic. Such a system may contain isolated or conjugated unsaturation, but not aromatic or heteroaromatic rings in its core structure (but may have aromatic substitution thereon). For example, hexahydro-furo[3,2-b]furan, 2,3,3a,4,7,7a-hexahydro-1H-indene, 7-aza-bicyclo[2.2.1]heptane, and 1,2,3,4,4a,5,8,8a-octahydro-naphthalene are all included in the class "saturated bridged ring system."

[0217] "Spirocyclyl" or "spirocyclic ring" refers to a ring originating from a particular annular carbon of another ring. For example, as depicted below, a ring atom of a saturated bridged ring system (rings B and B'), but not a bridgehead atom, can be a shared atom between the saturated bridged ring system and a spirocyclyl (ring A) attached thereto. A spirocyclyl can be carbocyclic or heteroalicyclic.



[0218] "Substituted" alkyl, aryl, and heterocyclyl, refer respectively to alkyl, aryl, and heterocyclyl, wherein one or more (for example up to about five, in another example, up to about three) hydrogen atoms are replaced by a substituent independently selected from: optionally substituted alkyl (for example, fluoromethyl), optionally substituted aryl (for example, 4-hydroxyphenyl), optionally substituted arylalkyl (for example, 1-phenyl-ethyl), optionally substituted heterocyclylalkyl (for example, 1-pyridin-3-yl-ethyl), optionally substituted heterocyclyl (for example, 5-chloro-pyridin-3-yl or 1-methyl-piperidin-4-yl), optionally substituted alkoxy, alkylenedioxy (for example methylenedioxy), optionally substituted amino (for example, alkylamino and dialkylamino), optionally substituted amidino, optionally substituted aryloxy (for example, phenoxy), optionally substituted arylalkyloxy (for example, benzyloxy), carboxy (-CO_2H), carboalkoxy (that is, acyloxy or -OC(=O)R), carboxyalkyl (that is, esters or -CO_2R), carboxamido, benzyloxycarbonylamino (CBZ-amino), cyano, acyl, halogen, hydroxy, nitro, sulfanyl, sulfinyl, sulfonyl, thiol, halogen, hydroxy, oxo, carbamyl, acylamino, and sulfonamido.

[0219] "Suitable leaving group" is defined as the term would be understood by one of ordinary skill in the art; that is, a carbon with such a group attached, upon reaction wherein a new bond is to be formed, loses such a group upon formation of the new bond. The invention pertains particularly with respect convergent synthesis, to reactions where such a leaving group is bonded to a reaction partner that is aromatic, undergoes a bond-forming reaction and remains aromatic. A typical example of such a reaction is a nucleophilic aromatic substitution reaction, as would be understood by one of ordinary skill in the art. However, the invention is not limited to such mechanistic restrictions; for example, reactions where there is, for example, an insertion reaction (for example by a transition metal) into the bond between the aromatic reaction partner and its leaving group

followed by reductive coupling can also be used within the scope of the invention. Examples of suitable leaving groups include halogens, optionally substituted aryl or alkyl sulfonates, phosphonates, azides, $RS(O)_{0-2}$- where R is, for example optionally substituted alkyl, optionally substituted aryl, or optionally substituted heteroaryl.

[0220] "Sulfanyl" refers to the groups: -S-(optionally substituted alkyl), -S-(optionally substituted aryl), and -S-(optionally substituted heterocyclyl).

[0221] "Sulfinyl" refers to the groups: -S(O)-H, -S(O)-(optionally substituted alkyl), -S(O)-optionally substituted aryl), and -S(O)-(optionally substituted heterocyclyl).

[0222] "Sulfonyl" refers to the groups: $-S(O_2)$-H, $-S(O_2)$-(optionally substituted alkyl), $-S(O_2)$-optionally substituted aryl), $-S(O_2)$-(optionally substituted heterocyclyl), $-S(O_2)$-(optionally substituted alkoxy), $-S(O_2)$-optionally substituted aryloxy), and $-S(O_2)$-(optionally substituted heterocyclyloxy).

[0223] "Yield" for each of the reactions described herein is expressed as a percentage of the theoretical yield.

[0224] Some of the compounds of the invention may have imino, amino, oxo or hydroxy substituents off aromatic heterocyclyl systems. For purposes of this disclosure, it is understood that such imino, amino, oxo or hydroxy substituents may exist in their corresponding tautomeric form, i.e., amino, imino, hydroxy or oxo, respectively.

[0225] Compounds of the invention are named according to systematic application of the nomenclature rules agreed upon by the International Union of Pure and Applied Chemistry (IUPAC), International Union of Biochemistry and Molecular Biology (IUBMB), and the Chemical Abstracts Service (CAS).

[0226] The compounds of the invention, or their pharmaceutically acceptable salts, may have asymmetric carbon atoms, oxidized sulfur atoms or quaternized nitrogen atoms in their structure.

[0227] The compounds of the invention and their pharmaceutically acceptable salts may exist as single stereoisomers, racemates, and as mixtures of enantiomers and diastereomers. The compounds may also exist as geometric isomers. All such single stereoisomers, racemates and mixtures thereof, and geometric isomers are intended to be within the scope of this invention.

[0228] It is assumed that when considering generic descriptions of compounds of the invention for the purpose of constructing a compound, such construction results in the creation of a stable structure. That is, one of ordinary skill in the art would recognize that there can theoretically be some constructs which would not normally be considered as stable compounds (that is, sterically practical and/or synthetically feasible, *supra*).

[0229] When a particular group with its bonding structure is denoted as being bonded to two partners; that is, a divalent radical, for example, -OCH_2-, then it is understood that either of the two partners may be bound to the particular group at one end, and the other partner is necessarily bound to the other end of the particular group, unless stated explicitly otherwise. Stated another way, divalent radicals are not to be construed as limited to the depicted orientation, for example "-OCH_2-" is meant to mean not only "-OCH_2-" as drawn, but also "-CH_2O-."

[0230] Methods for the preparation and/or separation and isolation of single stereoisomers from racemic mixtures or non-racemic mixtures of stereoisomers are well known in the art. For example, optically active (R)- and (S)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. Enantiomers (R- and S-isomers) may be resolved by methods known to one of ordinary skill in the art, for example by: formation of diastereoisomeric salts or complexes which may be separated, for example, by crystallization; via formation of diastereoisomeric derivatives which may be separated, for example, by crystallization, selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, such as silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where a desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step may be required to liberate the desired enantiomeric form. Alternatively, specific enantiomer may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting on enantiomer to the other by asymmetric transformation. For a mixture of enantiomers, enriched in a particular enantiomer, the major component enantiomer may be further enriched (with concomitant loss in yield) by recrystallization.

[0231] "Patient" for the purposes of the present invention includes humans and other animals, particularly mammals, and other organisms. Thus the methods are applicable to

both human therapy and veterinary applications. In a preferred embodiment the patient is a mammal, and in a most preferred embodiment the patient is human.

[0232] "Kinase-dependent diseases or conditions" refer to pathologic conditions that depend on the activity of one or more protein kinases. Kinases either directly or indirectly participate in the signal transduction pathways of a variety of cellular activities including proliferation, adhesion, migration, differentiation and invasion. Diseases associated with kinase activities include tumor growth, the pathologic neovascularization that supports solid tumor growth, and associated with other diseases where excessive local vascularization is involved such as ocular diseases (diabetic retinopathy, age-related macular degeneration, and the like) and inflammation (psoriasis, rheumatoid arthritis, and the like).

[0233] While not wishing to be bound to theory, phosphatases can also play a role in "kinase-dependent diseases or conditions" as cognates of kinases; that is, kinases phosphorylate and phosphatases dephosphorylate, for example protein substrates. Therefore compounds of the invention, while modulating kinase activity as described herein, may also modulate, either directly or indirectly, phosphatase activity. This additional modulation, if present, may be synergistic (or not) to activity of compounds of the invention toward a related or otherwise interdependent kinase or kinase family. In any case, as stated previously, the compounds of the invention are useful for treating diseases characterized in part by abnormal levels of cell proliferation (i.e. tumor growth), programmed cell death (apoptosis), cell migration and invasion and angiogenesis associated with tumor growth.

[0234] "Therapeutically effective amount" is an amount of a compound of the invention, that when administered to a patient, ameliorates a symptom of the disease. The amount of a compound of the invention which constitutes a "therapeutically effective amount" will vary depending on the compound, the disease state and its severity, the age of the patient to be treated, and the like. The therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to his own knowledge and to this disclosure.

[0235] "Cancer" refers to cellular-proliferative disease states, including but not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma),

alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hanlartoma, inesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinorna, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinorna, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [neplrroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis defornians), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastorna multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, SertoliLeydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma], fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma,

dermatofibroma, keloids, psoriasis; and Adrenal lands: neuroblastoma. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions.

[0236] "Pharmaceutically acceptable acid addition salt" refers to those salts that retain the biological effectiveness of the free bases and that are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, as well as organic acids such as acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

[0237] "Pharmaceutically acceptable base addition salts" include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Exemplary salts are the ammonium, potassium, sodium, calcium, and magnesium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins, and the like. Exemplary organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline, and caffeine. (See, for example, S. M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977;66:1-19 which is incorporated herein by reference.)

[0238] "Prodrug" refers to compounds that are transformed (typically rapidly) *in vivo* to yield the parent compound of the above formulae, for example, by hydrolysis in blood. Common examples include, but are not limited to, ester and amide forms of a compound having an active form bearing a carboxylic acid moiety. Examples of pharmaceutically acceptable esters of the compounds of this invention include, but are not limited to, alkyl esters (for example with between about one and about six carbons) wherein the alkyl group is a straight or branched chain. Acceptable esters also include cycloalkyl esters and

arylalkyl esters such as, but not limited to benzyl. Examples of pharmaceutically acceptable amides of the compounds of this invention include, but are not limited to, primary amides, and secondary and tertiary alkyl amides (for example with between about one and about six carbons). Amides and esters of the compounds of the present invention may be prepared according to conventional methods. A thorough discussion of prodrugs is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference for all purposes.

[0239] "Metabolite" refers to the break-down or end product of a compound or its salt produced by metabolism or biotransformation in the animal or human body; for example, biotransformation to a more polar molecule such as by oxidation, reduction, or hydrolysis, or to a conjugate (see Goodman and Gilman, "The Pharmacological Basis of Therapeutics" 8.sup.th Ed., Pergamon Press, Gilman et al. (eds), 1990 for a discussion of biotransformation). As used herein, the metabolite of a compound of the invention or its salt may be the biologically active form of the compound in the body. In one example, a prodrug may be used such that the biologically active form, a metabolite, is released *in vivo*. In another example, a biologically active metabolite is discovered serendipitously, that is, no prodrug design *per se* was undertaken. An assay for activity of a metabolite of a compound of the present invention is known to one of skill in the art in light of the present disclosure.

[0240] In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

[0241] In addition, it is intended that the present invention cover compounds made either using standard organic synthetic techniques, including combinatorial chemistry or by biological methods, such as bacterial digestion, metabolism, enzymatic conversion, and the like.

[0242] "Treating" or "treatment" as used herein covers the treatment of a disease-state in a human, which disease-state is characterized by abnormal cellular proliferation, and invasion and includes at least one of: (i) preventing the disease-state from occurring in a human, in particular, when such human is predisposed to the disease-state but has not yet

been diagnosed as having it; (ii) inhibiting the disease-state, i.e., arresting its development; and (iii) relieving the disease-state, i.e., causing regression of the disease-state. As is known in the art, adjustments for systemic versus localized delivery, age, body weight, general health, sex, diet, time of administration, drug interaction and the severity of the condition may be necessary, and will be ascertainable with routine experimentation by one of ordinary skill in the art.

[0243] One of ordinary skill in the art would understand that certain crystallized, protein-ligand complexes, in particular c-Met, c-Kit, KDR, flt-3, or flt-4-ligand complexes, and their corresponding x-ray structure coordinates can be used to reveal new structural information useful for understanding the biological activity of kinases as described herein. As well, the key structural features of the aforementioned proteins, particularly, the shape of the ligand binding site, are useful in methods for designing or identifying selective modulators of kinases and in solving the structures of other proteins with similar features. Such protein-ligand complexes, having compounds of the invention as their ligand component, are an aspect of the invention.

[0244] As well, one of ordinary skill in the art would appreciate that such suitable x-ray quality crystals can be used as part of a method of identifying a candidate agent capable of binding to and modulating the activity of kinases. Such methods may be characterized by the following aspects: a) introducing into a suitable computer program, information defining a ligand binding domain of a kinase in a conformation (e.g. as defined by x-ray structure coordinates obtained from suitable x-ray quality crystals as described above) wherein the computer program creates a model of the three dimensional structures of the ligand binding domain, b) introducing a model of the three dimensional structure of a candidate agent in the computer program, c) superimposing the model of the candidate agent on the model of the ligand binding domain, and d) assessing whether the candidate agent model fits spatially into the ligand binding domain. Aspects a-d are not necessarily carried out in the aforementioned order. Such methods may further entail: performing rational drug design with the model of the three-dimensional structure, and selecting a potential candidate agent in conjunction with computer modeling.

[0245] Additionally, one skilled in the art would appreciate that such methods may further entail: employing a candidate agent, so-determined to fit spatially into the ligand binding domain, in a biological activity assay for kinase modulation, and determining whether said candidate agent modulates kinase activity in the assay. Such methods may also include

administering the candidate agent, determined to modulate kinase activity, to a mammal suffering from a condition treatable by kinase modulation, such as those described above.

[0246] Also, one skilled in the art would appreciate that compounds of the invention can be used in a method of evaluating the ability of a test agent to associate with a molecule or molecular complex comprising a ligand binding domain of a kinase. Such a method may be characterized by the following aspects: a) creating a computer model of a kinase binding pocket using structure coordinates obtained from suitable x-ray quality crystals of the kinase, b) employing computational algorithms to perform a fitting operation between the test agent and the computer model of the binding pocket, and c) analyzing the results of the fitting operation to quantify the association between the test agent and the computer model of the binding pocket.

General Administration

[0247] Administration of the compounds of the invention, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration or agents for serving similar utilities. Thus, administration can be, for example, orally, nasally, parenterally (intravenous, intramuscular, or subcutaneous), topically, transdermally, intravaginally, intravesically, intracistemally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages.

[0248] The compositions will include a conventional pharmaceutical carrier or excipient and a compound of the invention as the/an active agent, and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, etc. Compositions of the invention may be used in combination with anticancer or other agents that are generally administered to a patient being treated for cancer. Adjuvants include preserving, wetting, suspending, sweetening, flavoring, perfuming, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form

can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

[0249] If desired, a pharmaceutical composition of the invention may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, antioxidants, and the like, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, butylalted hydroxytoluene, etc.

[0250] Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

[0251] One preferable route of administration is oral, using a convenient daily dosage regimen that can be adjusted according to the degree of severity of the disease-state to be treated.

[0252] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, cellulose derivatives, starch, alignates, gelatin, polyvinylpyrrolidone, sucrose, and gum acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, croscarmellose sodium, complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, magnesium stearate and the like (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

[0253] Solid dosage forms as described above can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain pacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedded compositions that can be used are polymeric substances and waxes. The active compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

[0254] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. Such dosage forms are prepared, for example, by dissolving, dispersing, etc., a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like; solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide; oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols and fatty acid esters of sorbitan; or mixtures of these substances, and the like, to thereby form a solution or suspension.

[0255] Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

[0256] Compositions for rectal administrations are, for example, suppositories that can be prepared by mixing the compounds of the present invention with for example suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt while in a suitable body cavity and release the active component therein.

[0257] Dosage forms for topical administration of a compound of this invention include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalmic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

[0258] Generally, depending on the intended mode of administration, the pharmaceutically acceptable compositions will contain about 1% to about 99% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and 99% to 1% by weight of a suitable pharmaceutical excipient. In one example, the composition will be between about 5% and about 75% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, with the rest being suitable pharmaceutical excipients.

[0259] Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pa., 1990). The composition to be administered will, in any event, contain a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, for treatment of a disease-state in accordance with the teachings of this invention.

[0260] The compounds of the invention, or their pharmaceutically acceptable salts, are administered in a therapeutically effective amount which will vary depending upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of the compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular disease-states, and the host undergoing therapy. The compounds of the present invention can be administered to a patient at dosage levels in the range of about 0.1 to about 1,000 mg per day. For a normal human adult having a body weight of about 70 kilograms, a dosage in the range of about 0.01 to about 100 mg per kilogram of body weight per day is an example. The specific dosage used, however, can vary. For example, the dosage can depend on a number of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well known to one of ordinary skill in the art.

Utility of compounds of the invention as screening agents

[0261] To employ the compounds of the invention in a method of screening for candidate agents that bind to, for example c-Met, KDR, c-Kit, flt-3, or flt-4, the protein is bound to a support, and a compound of the invention is added to the assay. Alternatively, the

compound of the invention is bound to the support and the protein is added. Classes of candidate agents among which novel binding agents may be sought include specific antibodies, non-natural binding agents identified in screens of chemical libraries, peptide analogs, etc. Of particular interest are screening assays for candidate agents that have a low toxicity for human cells. A wide variety of assays may be used for this purpose, including labeled in vitro protein-protein binding assays, electrophoretic mobility shift assays, immunoassays for protein binding, functional assays (phosphorylation assays, etc.) and the like.

[0262] The determination of the binding of the candidate agent to, for example, c-Met, KDR, c-Kit, flt-3, or flt-4 protein may be done in a number of ways. In one example, the candidate agent (the compound of the invention) is labeled, for example, with a fluorescent or radioactive moiety and binding determined directly. For example, thus may be done by attaching all or a portion of the c-Met, KDR, c-Kit, flt-3, or flt-4 protein to a solid support, adding a labeled agent (for example a compound of the invention in which at least one atom has been replaced by a detectable isotope), washing off excess reagent, and determining whether the amount of the label is that present on the solid support. Various blocking and washing steps may be utilized as is known in the art.

[0263] By "labeled" herein is meant that the compound is either directly or indirectly labeled with a label which provides a detectable signal, e.g., radioisotope, fluorescent tag, enzyme, antibodies, particles such as magnetic particles, chemiluminescent tag, or specific binding molecules, etc. Specific binding molecules include pairs, such as biotin and streptavidin, digoxin and antidigoxin etc. For the specific binding members, the complementary member would normally be labeled with a molecule which provides for detection, in accordance with known procedures, as outlined above. The label can directly or indirectly provide a detectable signal.

[0264] In some embodiments, only one of the components is labeled. For example, c-Met, KDR, c-Kit, flt-3, or flt-4 protein may be labeled at tyrosine positions using ^{125}I, or with fluorophores. Alternatively, more than one component may be labeled with different labels; using ^{125}I for the proteins, for example, and a fluorophor for the candidate agents.

[0265] The compounds of the invention may also be used as competitors to screen for additional drug candidates. "Candidate bioactive agent" or "drug candidate" or grammatical equivalents as used herein describe any molecule, e.g., protein, oligopeptide, small organic molecule, polysaccharide, polynucleotide, etc., to be tested for bioactivity.

They may be capable of directly or indirectly altering the cellular proliferation phenotype or the expression of a cellular proliferation sequence, including both nucleic acid sequences and protein sequences. In other cases, alteration of cellular proliferation protein binding and/or activity is screened. In the case where protein binding or activity is screened, some embodiments exclude molecules already known to bind to that particular protein. Exemplary embodiments of assays described herein include candidate agents, which do not bind the target protein in its endogenous native state, termed herein as "exogenous" agents. In one example, exogenous agents further exclude antibodies to c-Met, KDR, c-Kit, flt-3, or flt-4.

[0266] Candidate agents can encompass numerous chemical classes, though typically they are organic molecules having a molecular weight of more than about 100 daltons and less than about 2,500 daltons. Candidate agents comprise functional groups necessary for structural interaction with proteins, particularly hydrogen bonding and lipophilic binding, and typically include at least an amine, carbonyl, hydroxyl, ether, or carboxyl group, for example at least two of the functional chemical groups. The candidate agents often comprise cyclical carbon or heterocyclyl structures and/or aromatic or polyaromatic structures substituted with one or more of the above functional groups. Candidate agents are also found among biomolecules including peptides, saccharides, fatty acids, steroids, purines, pyrimidines, derivatives, structural analogs, or combinations thereof.

[0267] Candidate agents are obtained from a wide variety of sources including libraries of synthetic or natural compounds. For example, numerous means are available for random and directed synthesis of a wide variety of organic compounds and biomolecules, including expression of randomized oligonucleotides. Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available or readily produced. Additionally, natural or synthetically produced libraries and compounds are readily modified through conventional chemical, physical and biochemical means. Known pharmacological agents may be subjected to directed or random chemical modifications, such as acylation, alkylation, esterification, amidification to produce structural analogs.

[0268] In one example, the binding of the candidate agent is determined through the use of competitive binding assays. In this example, the competitor is a binding moiety known to bind to c-Met, KDR, c-Kit, flt-3, or flt-4, such as an antibody, peptide, binding partner, ligand, etc. Under certain circumstances, there may be competitive binding as between the

candidate agent and the binding moiety, with the binding moiety displacing the candidate agent.

[0269] In some embodiments, the candidate agent is labeled. Either the candidate agent, or the competitor, or both, is added first to for example c-Met, KDR, c-Kit, flt-3, or flt-4 for a time sufficient to allow binding, if present. Incubations may be performed at any temperature that facilitates optimal activity, typically between 4°C and 40°C

[0270] Incubation periods are selected for optimum activity, but may also be optimized to facilitate rapid high throughput screening. Typically between 0.1 and 1 hour will be sufficient. Excess reagent is generally removed or washed away. The second component is then added, and the presence or absence of the labeled component is followed, to indicate binding.

[0271] In one example, the competitor is added first, followed by the candidate agent. Displacement of the competitor is an indication the candidate agent is binding to c-Met, KDR, c-Kit, flt-3, or flt-4 and thus is capable of binding to, and potentially modulating, the activity of the c-Met, KDR, c-Kit, flt-3, or flt-4. In this embodiment, either component can be labeled. Thus, for example, if the competitor is labeled, the presence of label in the wash solution indicates displacement by the agent. Alternatively, if the candidate agent is labeled, the presence of the label on the support indicates displacement.

[0272] In an alternative embodiment, the candidate agent is added first, with incubation and washing, followed by the competitor. The absence of binding by the competitor may indicate the candidate agent is bound to c-Met, KDR, c-Kit, flt-3, or flt-4 with a higher affinity. Thus, if the candidate agent is labeled, the presence of the label on the support, coupled with a lack of competitor binding, may indicate the candidate agent is capable of binding to c-Met, KDR, c-Kit, flt-3, or flt-4.

[0273] It may be of value to identify the binding site of c-Met, KDR, c-Kit, flt-3, or flt-4. This can be done in a variety of ways. In one embodiment, once c-Met, KDR, c-Kit, flt-3, or flt-4 has been identified as binding to the candidate agent, the c-Met, KDR, c-Kit, flt-3, or flt-4 is fragmented or modified and the assays repeated to identify the necessary components for binding.

[0274] Modulation is tested by screening for candidate agents capable of modulating the activity of c-Met, KDR, c-Kit, flt-3, or flt-4 comprising the steps of combining a candidate agent with c-Met, KDR, c-Kit, flt-3, or flt-4, as above, and determining an alteration in the

biological activity of the c-Met, KDR, c-Kit, flt-3, or flt-4. Thus, in this embodiment, the candidate agent should both bind to (although this may not be necessary), and alter its biological or biochemical activity as defined herein. The methods include both *in vitro* screening methods and *in vivo* screening of cells for alterations in cell viability, morphology, and the like.

[0275] Alternatively, differential screening may be used to identify drug candidates that bind to native c-Met, KDR, c-Kit, flt-3, or flt-4, but cannot bind to modified c-Met, KDR, c-Kit, flt-3, or flt-4.

[0276] Positive controls and negative controls may be used in the assays. For example, all control and test samples are performed in at least triplicate to obtain statistically significant results. Incubation of samples is for a time sufficient for the binding of the agent to the protein. Following incubation, samples are washed free of non-specifically bound material and the amount of bound, generally labeled agent determined. For example, where a radiolabel is employed, the samples may be counted in a scintillation counter to determine the amount of bound compound.

[0277] A variety of other reagents may be included in the screening assays. These include reagents like salts, neutral proteins, e.g., albumin, detergents, etc which may be used to facilitate optimal protein-protein binding and/or reduce non-specific or background interactions. Also reagents that otherwise improve the efficiency of the assay, such as protease inhibitors, nuclease inhibitors, anti-microbial agents, etc., may be used. The mixture of components may be added in any order that provides for the requisite binding.

Abbreviations and their Definitions

[0278] The following abbreviations and terms have the indicated meanings throughout.

Abbreviation	Meaning
Ac	acetyl
ATP	adenosine triphosphate
BNB	4-bromomethyl-3-nitrobenzoic acid
Boc	t-butyloxy carbonyl

Abbreviation	Meaning
br	broad
Bu	butyl
°C	degrees Celsius
c-	cyclo
CBZ	CarboBenZoxy = benzyloxycarbonyl
d	doublet
dd	doublet of doublet
dt	doublet of triplet
DBU	Diazabicyclo[5.4.0]undec-7-ere
DCM	dichloromethane = methylene chloride = CH_2Cl_2
DCE	dichloroethylene
DEAD	diethyl azodicarboxylate
DIC	diisopropylcarbodiimide
DIEA	N,N-diisopropylethyl amine
DMAP	4-N,N-dimethylaminopyridine
DMF	N,N-dimethylfonnamide
DMSO	dimethyl sulfoxide
DVB	1,4-divinylbenzene
EEDQ	2-ethoxy-l-ethoxycarbonyl-1,2-dihydroquinoline
EI	Electron Impact ionization
Et	ethyl
Fmoc	9-fluorenylmethoxycarbonyl
g	gram(s)
GC	gas chromatography
h or hr	hour(s)
HATU	0-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMDS	hexamethyldisilazane
HOAc	acetic acid
HOBt	hydroxybenzotriazole
HPLC	high pressure liquid chromatography

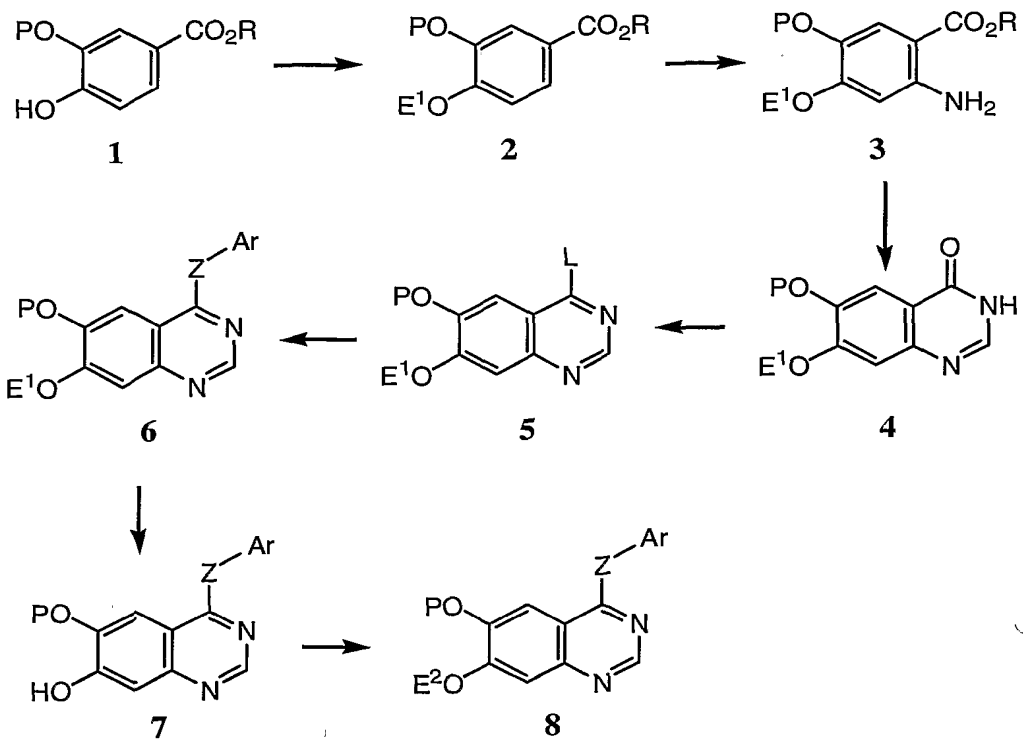
Abbreviation	Meaning
L	liter(s)
M	molar or molarity
m	multiplet
Me	methyl
mesyl	methanesulfonyl
mg	milligram(s)
MHz	megahertz (frequency)
Min	minute(s)
mL	milliliter(s)
mM	millimolar
mmol	millimole(s)
mol	mole(s)
MS	mass spectral analysis
MTBE	methyl t-butyl ether
N	normal or normality
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
nM	nanomolar
NMO	N-methylmorpholine oxide
NMR	nuclear magnetic resonance spectroscopy
PEG	polyethylene glycol
pEY	poly-glutamine, tyrosine
Ph	phenyl
PhOH	phenol
PfP	pentafluorophenol
PfPy	pentafluoropyridine
PPTS	Pyridinium p-toluenesulfonate
Py	pyridine
PyBroP	bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
q	quartet

Abbreviation	Meaning
RT	Room temperature
Sat'd	saturated
s	singlet
s-	secondary
t-	tertiary
t or tr	triplet
TBDMS	t-butyldimethylsilyl
TES	triethylsilane
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMOF	trimethyl orthoformate
TMS	trimethylsilyl
tosyl	p-toluenesulfonyl
Trt	triphenylmethyl
uL	microliter(s)
uM	Micromole(s) or micromolar

Synthesis of Compounds

[0279] Schemes 1 and 2 depict general synthetic routes for compounds of the invention and are not intended to be limiting. More specifically, Scheme 1 depicts synthesis of quinazoline compounds, and Scheme 2 depicts synthesis of quinoline compounds. Specific examples are described subsequently to these general synthetic descriptions so as to allow one skilled in the art to make and use either quinazolines or quinolines of the invention.

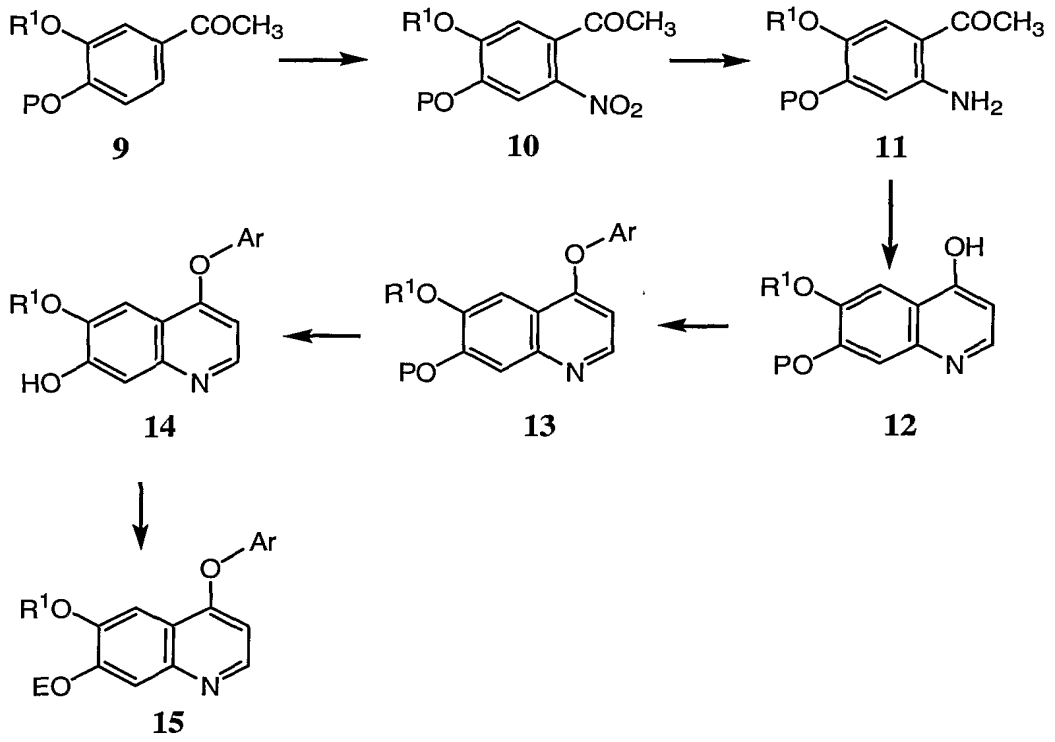
Scheme 1



[0280] Referring to Scheme 1, a benzoic ester **1**, where R is typically but not necessarily a methyl radical and P is typically but not necessarily an alkyl group, is O-alkylated at the oxygen *para* to the carboxylate group with an electrophile to afford a substituted derivative **2**. P is typically a lower alkyl group, but may be a protecting group that is removed later in a synthesis. When P is a lower alkyl group it may possess functionality initially, or be derivitized to contain such functionality at various stages of the synthesis. The group, E^1, may represent either a protecting group, e.g. benzyl, or a group that either has moieties present in compounds of the invention or possesses functionality that serve as a precursors to such groups. Aromatic ring nitration and reduction of the corresponding nitro group are carried out in a regio- and chemoselective manner by methods well known in the art to give anthranilate derivative **3**. Formation of quinazolin-4-one **4** is carried out by methods well known in the art, for example by heating **3** in formamide solution in the presence of ammonium formate or for example by heating directly with formamidine hydrochloride. Introduction of 4-position functionality groups is carried out by methods known in the art. For example, quinazolin-4-one **4** is converted to an intermediate quinazoline **5**, where "L" represents a leaving group, e.g. chlorine. Quinazoline **5** is then converted to **6** by reaction with a range of nucleophiles, e.g. amines, alcohols, and thiols. After formation of **6**, group "Z" is either left "as is" or converted at some subsequent stage to a derivative thereof. For example when Z is -NH-, then the hydrogen on the nitrogen

may optionally be replaced with an alkyl group, or when Z is sulfur, then that sulfur atom may be oxidized to, for example, a sulfone. Structure **6** may represent compounds of the invention or, for example when E^1 serves as a protecting group, E^1 may be removed to provide phenol **7**. Introduction of a group E^2 is carried out by methods well established in the art; for example alkylation with an appropriately derivatized alkyl halide (or mesylate or the like) to give **8** which also represents compounds of the invention.

Scheme 2



[0281] Scheme 2 shows a general route used to make exemplary quinolines of the invention. For example, compound **9** contains an alkyl group, R^1, a protecting group, P. The arrangement of the protected and alkylated phenolic oxygens may vary from the pattern depicted in compound **9**. Compound **9** is nitrated to provide compound **10**. The nitro group of compound **10** is reduced to give aniline **11**. Compound **11** is treated, for example, with ethyl formate under basic conditions followed by acidification and isolation to form 4-hydroxy quinoline **12**. Quinoline **12** may be converted to compounds of the invention in a number of ways. For example, the 4-oxygen is used as a nucleophile in a nucleophilic aromatic substitution reaction to form quinoline-aryl-ether **13**. In another example, compound **13** is further derivatized, via removal of protecting group P, to afford compound **14**. The 7-hydroxy of compound **14** is alkylated, for example with electrophile E, to provide a compound of the invention. As discussed in relation to Scheme 1,

variations on any of the above steps are possible, and intermediates in these schemes, for example compounds **12**, **13**, and **14** may also be compounds of the invention according to formula **I**. Also, for example, the 4-hydroxy quinoline compound **12** are converted to a corresponding 4-nitrogen or 4-sulfur quinoline using chemistry known in the art to make compounds of the invention, or alternatively the corresponding 4-nitrogen or 4-sulfur quinolines are made via routes analogous to that depicted in Schemes 1 and 2.

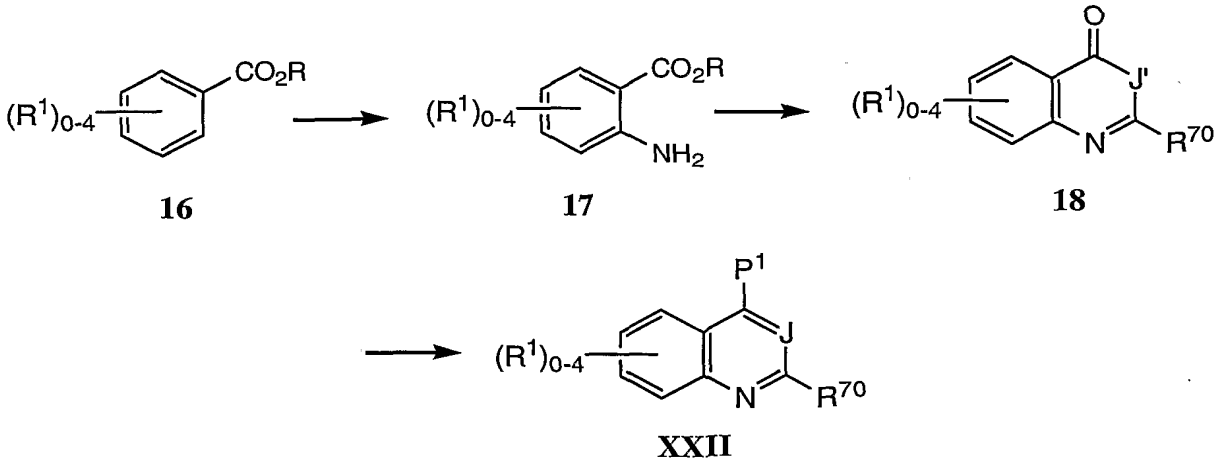
[0282] Schemes 1 and 2 are illustrative of quinolines and quinazolines having oxygen substitution at their respective 6- and 7-positions; the invention is not so limited, but rather is intended to encompass quinolines and quinazolines not necessarily having substitution, oxygen or otherwise, at their respective 6- or 7-positions.

[0283] Schemes 3 and 4 depict generalized synthetic routes to show the process of the invention to make compounds of formua **XXI** and is not intended to be limiting. More specifically, Schemes 3 and 4 depict convergent syntheses of quinoline and quinazoline compounds as described herein. Specific examples are described subsequently to this general synthetic description so as to allow one of ordinary skill in the art to practice the invention.

[0284] Referring to Scheme 3, a benzoic ester **16** for example, where R is typically but not necessarily a methyl radical and R^1 is typically but not necessarily one or more alkoxy or hydroxy groups. In a typical synthesis, at least one of R^1 within Scheme 3 is a hydroxyl which is converted (or protected)via one or more steps to a group important to the activity of the compounds as described as kinase modulators (in the case that -OH itself is desired in the final compound, then deprotection affords the -OH, *vide supra*). Preferably, but not necessarily, this group is complete once the synthesis of **XXII** is complete. By building desired complexity into **XXII** prior to combination with **XXIII**, convergent syntheses' advantages over serial syntheses are realized more fully. Regioselective aromatic ring nitration, and reduction of the corresponding nitro group, are carried out in a regio- and chemoselective manner by methods well known in the art to give anthranilate derivative **17**. Formation of quinazoline or quinoline 4-one **18** is carried out by methods well known in the art. For example by heating **17** in formamide solution in the presence of ammonium formate, or by heating **17** with formamidine hydrochloride, the quinazoline-4-one analog is made. In another example **17** is treated, for example, with ethyl formate under basic conditions followed by acidification and isolation to form the 4-hydroxy quinoline analog (a tautomer of the 4-one). In this scheme J' represents either carbon or nitrogen atom with

the appropriate number of hydrogens to fill their respective normal valence bonding schemes; J' is a precursor to J. Radicals J and R^{70} are in accord with formula **XXI**. Introduction of 4-position functionality is carried out by methods known in the art. For example, 4-one **18** is converted to **XXII**, where "P^1" represents a suitable leaving group (in accord with formula **XXI**), e.g. chlorine (via dehydration/chlorination of **18** to give **XXII**). In another example, a 4-hydroxy analog is converted to a sulfonyl ester, e.g. the trifluoromethane sulfonate.

Scheme 3

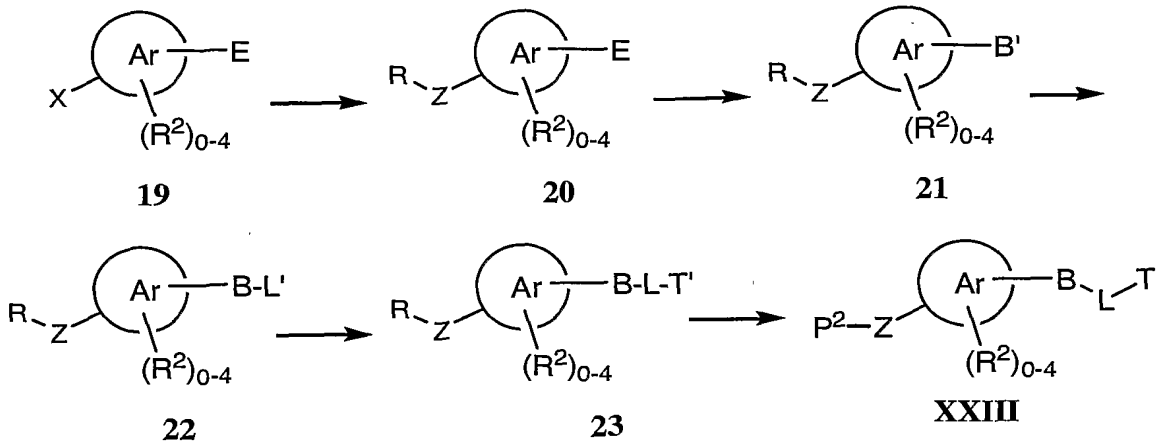


16 **17** **18**

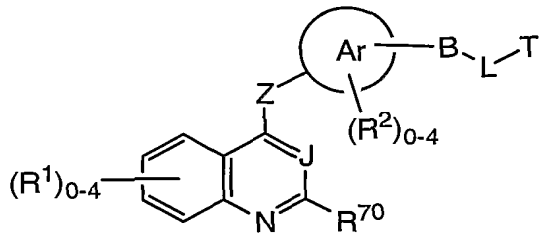
XXII

[0285] Scheme 4 shows a general route used to make compounds of formula **XXIII**. For example, aromatic compound **19**, where "X" is a leaving group, such as fluorine and "E" is an electron withdrawing group such as nitro, is converted to **20** by reaction with a range of nucleophiles, e.g. amines, alcohols, and thiols (where "Z" is oxygen, nitrogen (substituted or not), or sulfur). In this case, "R" represents a removable group, for example benzyl. In a typical synthesis, after formation of **20**, group "E" is either left "as is" or converted at some subsequent stage to a derivative thereof. In the example depicted, E is converted to B', a precursor to B in accord with formula **XXI**, to make **21**. For example if E is a nitro, then B' could might be an amino group, made via reduction of the nitro group. Structure **21** may be further derivitized by synthesis of –B-L-T in accord with formula **XXI**. In scheme 4, this is depicted as a serial process whereby L', a precursor to L, is introduced to give **22**, followed by introduction of T' (a precursor to T) to give **23**. In some cases, -L-T is preformed and appended to B. One of ordinary skill in the art would appreciate that variations on any of the above steps are possible. Compound **23** is converted to **XXIII** via conversion of T' to T and introduction of P^2 (for example, when R is benzyl, removal of the benzyl after completion of –B-L-T).

Scheme 4



[0286] As discussed above, one aspect of the invention encompasses combination of **XXII** and **XXIII** to make compounds of formula **XXI**. Because of the diversity and complexity of compounds described for kinase modulation (*vide supra*), methods of the invention provide advantages to serial synthesis.



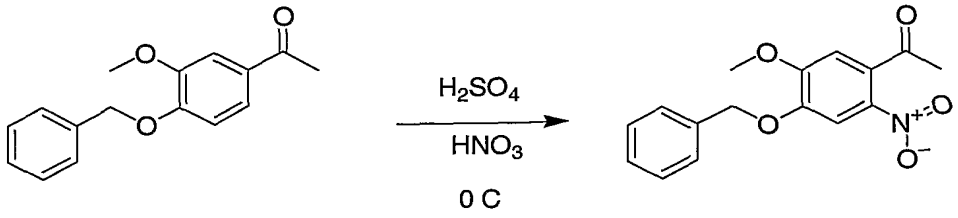
XXI

Examples

[0287] The following examples serve to more fully describe the manner of using the above-described invention, as well as to set forth the best modes contemplated for carrying out various aspects of the invention. It is understood that these examples in no way serve to limit the true scope of this invention, but rather are presented for illustrative purposes. All references cited herein are incorporated by reference in their entirety. Generally, but not necessarily, each example set out below describes a multi-step synthesis as outlined above.

Quinoline and Quinazoline Syntheses

Example 1

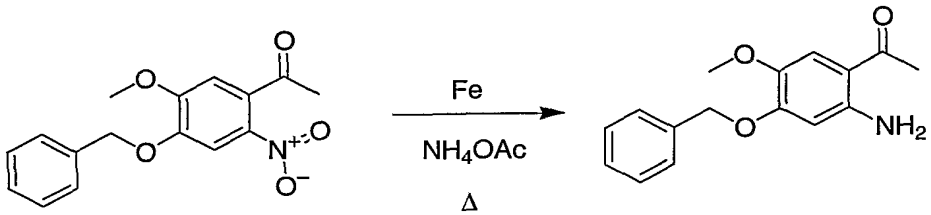


[0288] Synthesis of 1-(4-Benzyloxy-5-methoxy-2-nitro-phenyl)-ethanone. 1-(4-Benzyloxy-3-methoxy-phenyl)-ethanone (200 mmol, 51.3 g) dissolved in DCM (750ml) and the mixture cooled to 0° C. Nitric acid (90%, 300 mmol, 14 ml) was added dropwise to the cooled solution over 20 minutes. Sulfuric acid (96.2%, 300 mmol, 8.75 ml) was then added dropwise over 40 minutes at 0° C.

[0289] Additional nitric acid (200 mmol, 9.4 ml) was added dropwise over 20 minutes. The reaction mixture was diluted with water (300 ml) and wash with water (3 X 200 ml), Sat. NaHCO3 (4 X 200 ml, or until neutral). The organic layer was dried over Na2SO4 and concentrated.

[0290] The crude mixture was recrystallized with DMF to give 22.5 g of the nitro product. The DMF layer was concentrated and recrystallized with ethyl acetate to give additional 8.75g of the product. The ethyl acetate layer was concentrated and purified on silica column using 20% EtOAc/hexanes to gave another 4.75 g of the product. Total yield is 36 g, (~60%). 1H NMR (CDCl3): 7.647 (1H, s), 7.446-7.333 (5H, m), 6.745 (1H, s), 5.210 (2H, s), 3.968 (3H, s), 2.487 (3H, s).

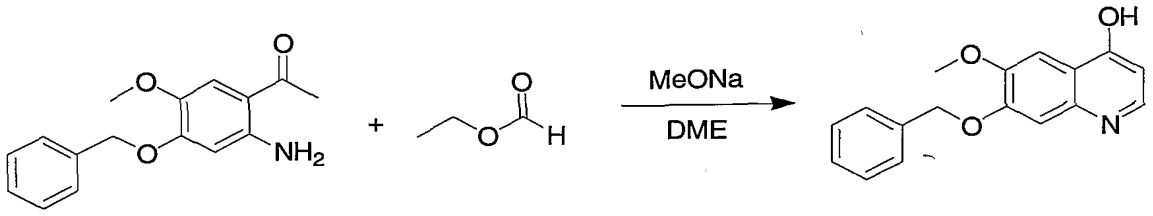
Example 2



[0291] Synthesis of 1-(2-Amino-4-benzyloxy-5-methoxy-phenyl)-ethanone. A Mixture of iron powder (477 mmol, 27 g), ammonium acetate (500 mmol, 31.g), 1-(4-Benzyloxy-5-methoxy-2-nitro-phenyl)-ethanone (120 mmol, 36 g), toluene (500 ml) and water (500 ml) was refluxed overnight, or until completion. The mixture was filtered through celite and

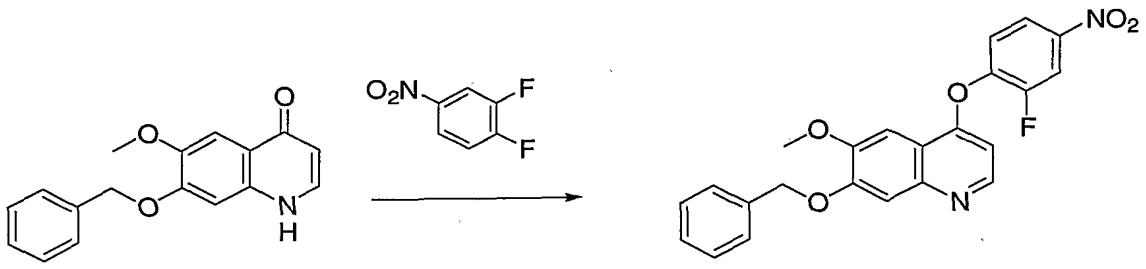
washed with EtOAc. The organic layer was washed with water and Sat. NaCl, dried over Na2SO4, and concentrated to afford the product, 90%. 1H NMR (CDCl3): 7.408-7.298 (5H, m), 7.130 (1H, s), 6.155 (2H, br), 6.104 (1H, s), 5.134 (2H, s), 3.834 (3H, s), 2.507 (3H, s). LC/MS (M+1 = 272).

Example 3



[0292] Synthesis of 7-Benzyloxy-6-methoxy-quinolin-4-ol. To a solution of 1-(2-Amino-4-benzyloxy-5-methoxy-phenyl)-ethanone (108 mmol, 29.3 g) in DME (700 ml) was added sodium methoxide (432 mmol, 23.35 g). The mixture was stirred for 30 minutes. Ethyl formate (540 mmol, 44 ml) was added and the mixture was stirred overnight. (Additional sodium methoxide may be needed if reaction is not complete as monitored by LC/MS.) After the reaction was completion, the mixture was diluted with water (40 ml) and acidified to neutral with 1M HCl. The precipitate was filtered and washed with water, dried *in vacuo* to afford 22g (72%) of 7-benzyloxy-6-methoxy-quinolin-4-ol. 1H NMR (CDCl3): 10.7 (1H, br), 7.703 (1H, s), 7.493-7.461 (1H, t), 7.431-7.413 (2H, br d), 7.372-7.333 (2H, t), 7.296-7.283 (1H, d), 6.839 (1H, s), 6.212-6.193 (1H, d), 5.212 (2H, s), 3.965 (3H, s). LC/MS (M+1 = 282).

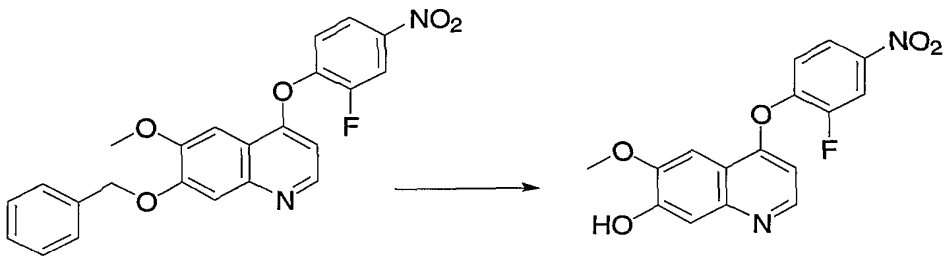
Example 4



[0293] 7-Benzyloxy-4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinoline. To a round bottom flask equipped with a magnetic stir bar was added 7-Benzyloxy-6-methoxy-1H-quinolin-4-one (12.2 g, 43.3 mmol, 1.0 eq.), acetonitrile (150ml), DMF (150ml) and

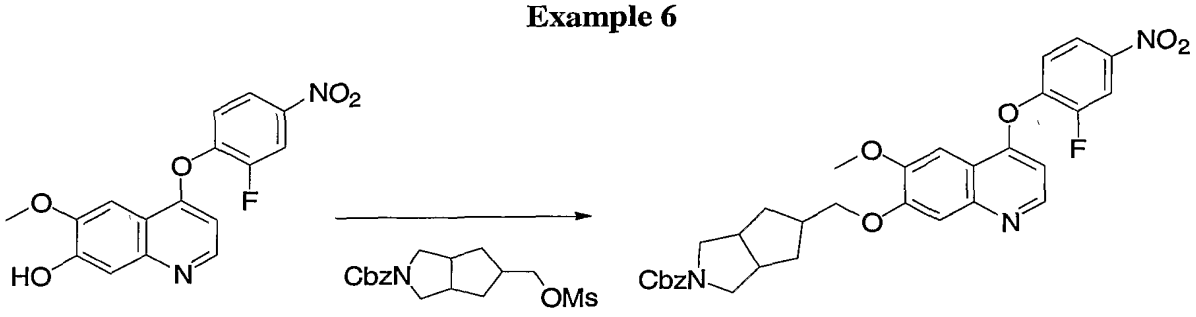
cesium carbonate (28.2 g, 86.5 mmol, 2.0 eq). The mixture was stirred at room temperature for 30 minutes at which time 1,2-difluoro-4-nitro-benzene (7.57 g, 47.6 mmol, 1.1 eq) was added over a 10 minute period. After 2 hours the reaction was complete at which time 75% of the MeCN and DMF was removed and the resulting solution was poured over into ice water. The solid was filtered and dried and further columned with a biotage system. The eluent was 1:3 ethyl acetate/hexane. Removal of the solvent afforded 7-Benzyloxy-4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinoline as a pale green solid (7.4 g, 41% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 8.53 (d, 1H), 8.42 (dd, 1H), 8.16 (m, 1H), 7.5 (m, 8H), 6.76 (d, 1H), 5.31 (s, 2H), 3.92 (s, 3H); MS (EI) for $C_{23}H_{27}FN_2O_5$: 421 (MH^+).

Example 5



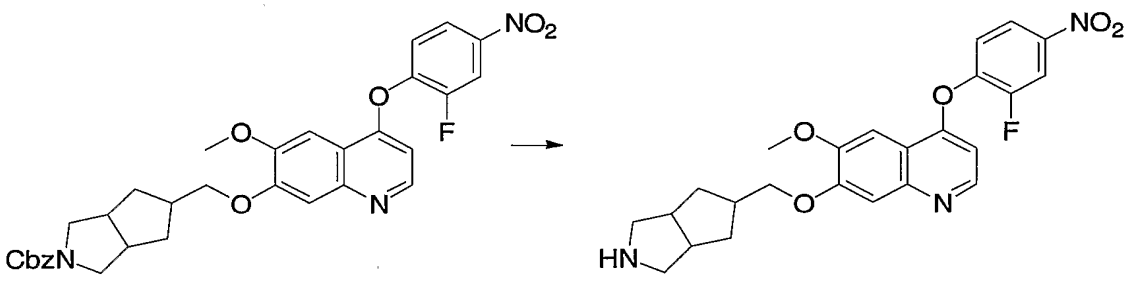
[0294] 4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-ol. To a round bottom flask equipped with a magnetic stir bar was added 7-benzyloxy-4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinoline (2.9 g, 6.9 mmol, 1.0eq) and 33% HBr in acetic acid (30 ml). The mixture was stirred at room temperature for 3 hours and diluted with ether to give a pale white solid. The solid was filtered, washed with ether and dried to yield 4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-ol as a pale white solid (2.74 g, 97.5% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 11.89 (bs, 1H), 8.87 (d, 1H), 8.57 (d, 1H), 8.30 (d, 1H), 7.89 (m, 1H), 7.73 (s, 1H), 7.55 (s, 1H), 4.03 (s, 3H); MS (EI) for $C_{16}H_{11}FN_2O_5$: 421 ($M+H^+$).

Example 6



[0295] 5-[4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-yloxymethyl]-hexahydro-cyclopenta[c]pyrrole-2-carboxylic acid benzyl ester. To a round bottom flask equipped with a magnetic stir bar was added 4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-ol (2.74 g, 6.7 mmol, 1.0 eq.), DMA (30ml) and cesium carbonate (6.6 g, 20.2 mmol, 3.0 eq). The mixture was stirred at room temperature for 30 minutes at which time 5-methanesulfonyloxymethyl-hexahydro-cyclopenta[c]pyrrole-2-carboxylic acid benzyl ester (2.6 g, 7.3 mmol, 1.1 eq) was added. The reaction was heated to 75^0 C and allowed to stir overnight. After allowing the reaction to cool to room temperature the reaction was poured into water. The solid was filtered and was then dissolved in EtOAc and washed 2X water, 1X brine and dried over $NaSO_4$. The solvent was removed to yield 5-[4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-yloxymethyl]-hexahydro-cyclopenta[c]pyrrole-2-carboxylic acid benzyl ester as a cream solid (3.7 g, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 8.55 (d, 1H), 8.15 (d, 1H), 8.09 (d, 1H), 7.32 (m, 8H), 6.52 (d, 1H), 5.11 (d, 2H), 4.13 (d, 2H), 3.95 (s, 3H), 3.57 (m, 2H), 3.43 (m, 2H), 2.93 (m, 3H), 2.16 (m, 2H), 1.39 (m, 2H); MS (EI) for $C_{32}H_{30}FN_3O_7$: 588 ($M+H^+$).

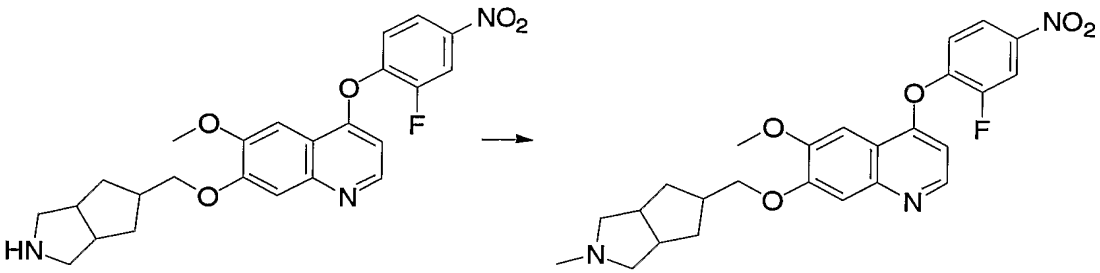
Example 7



[0296] 4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-7-(octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinoline. To a round bottom flask equipped with a magnetic stir bar was added 5-[4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-yloxymethyl]-hexahydrocyclopenta-[c]pyrrole-2-carboxylic acid benzyl ester (2.5 g, 4.1 mmol, 1.0eq), 33% HBr in acetic acid (5 ml) and acetic acid (5 ml). The mixture was stirred at room temperature for 1 hour and diluted with EtOAc to give a pale orange solid. The solid was filtered, washed with EtOAc and dried, giving 4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-7-(octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinoline (2.1 g, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 8.83 (d, 1H), 8.32 (m, 2H), 8.02 (s, 1H), 7.76 (t, 1H), 7.65 (s, 1H), 6.89 (d,

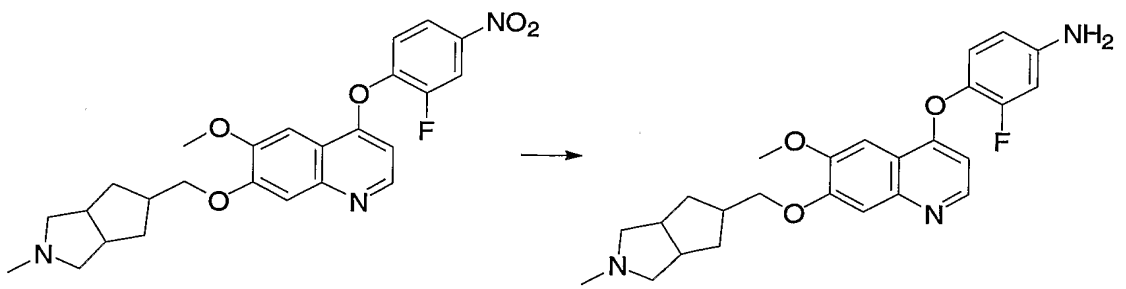
1H), 5.3 (d, 2H), 4.11 (m, 3H), 3.26 (m, 4H), 2.95 (m, 2H), 2.68 (m, 3H), 2.36 (m, 2H), 1.68 (m, 2H); MS (EI) for $C_{24}H_{24}FN_3O_5$: 454 ($M+H^+$).

Example 8



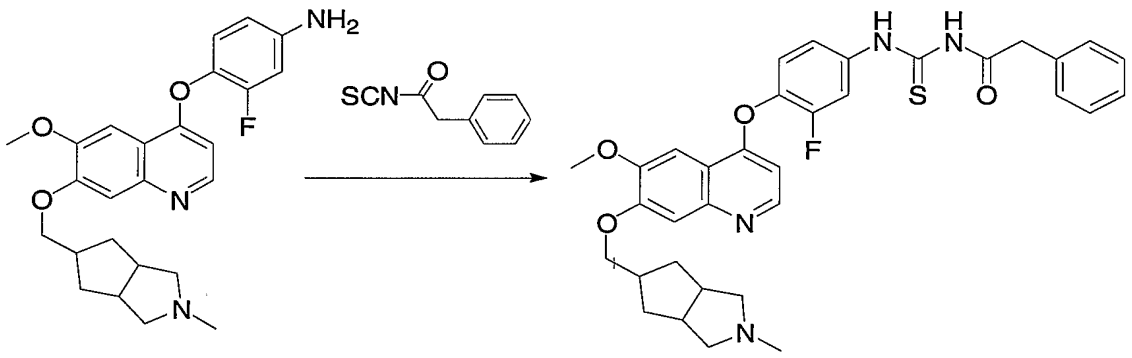
[0297] 4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinoline. To a round bottom flask equipped with a magnetic stir bar was added 4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-7-(octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinoline (2.1 g, 3.9 mmol, 1.0 eq.) and acetonitrile/water 1:1 (5ml, 5ml). The reaction mixture was then cooled to 0^0 C and 37% solution of formaldehyde in water was added (0.2 g, 7.8 mmol, 2.0 eq). While keeping the temperature at 0^0C $Na(OAc)_3BH$ was added (4.4g, 20.7 mmol, 3.0 eq). After 1 hour the pH was adjusted to 10 and the aqueous was extracted 2 x DCM (100 ml). Removal of the DCM resulted in a white solid. The compound was further purified with a biotage system using an eluent EtOAc and 5% MeOH, affording 4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-7-(2-methyl-octahydrocyclopenta-[c]pyrrol-5-ylmethoxy)-quinoline (0.9 g, 50% yield).). ^{1}H NMR (400 MHz, $CDCl_3$): 8.57 (d, 1H), 8.14 (dd, 1H), 8.12 (dd, 1H), 7.41 (s, 2H), 7.34 (t, 1H), 6.54 (d, 1H), 4.19 (d, 2H), 4.01 (s, 3H), 2.61 (m, 4H), 2.43 (m, 1H), 2.33 (s, 3H), 2.11 (m, 4H), 1.32 (m, 2H); MS (EI) for $C_{25}H_{26}FN_3O_5$: 468 ($M+H^+$).

Example 9



[0298] 3-Fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinolin-4-yloxy]-phenylamine. To a par hydrogenation reaction vessel was added 4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinoline (0.800 g, 1.6 mmol, 1.0 eq.), DMF (50 ml), EtoAc (50ml), MeOH (50ml), TEA (5ml) and 10% Pd/C (200 mg). The vessel was placed on the par hydrogenator at 35 psi overnight. The Pd was filtered and the solvent removed to give 3-fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinolin-4-yloxy]-phenylamine as an off yellow solid (0.78 g, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 8.45 (d, 1H), 7.57 (s, 1H), 7.36 (s, 1H), 7.05 (t, 1H), 6.54 (m, 2H), 6.39 (d, 1H), 4.16 (d, 2H), 4.01 (s, 3H), 3.81 (m, 3H), 2.61 (m, 3H), 2.41 (m, 1H), 2.29 (s, 3H), 2.23 (m, 2H), 1.32 (m, 2H); MS (EI) for $C_{25}H_{28}FN_3O_3$: 438 ($M+H^+$).

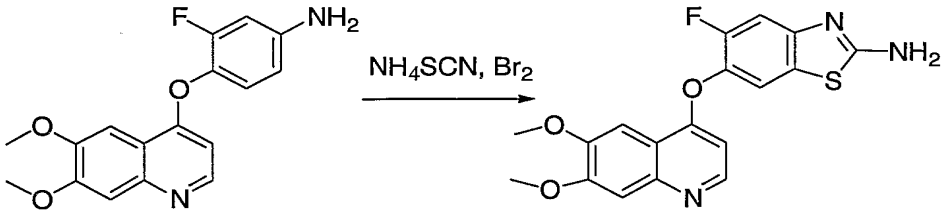
Example 10



[0299] 1-{3-Fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinolin-4-yloxy]-phenyl}-3-phenylacetyl-thiourea. To a round bottom flask equipped with a magnetic stir bar was added 3-fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinolin-4-yloxy]-phenylamine (0.78 mg, 1.7 mmol, 1.0 eq.), toluene (10ml), ethanol (10ml) and phenyl-acetyl isothiocyanate (1.64 g, 9.2 mmol, 4.5 eq). The reaction mixture was stirred at room temperature overnight. After removal of the solvent the product was purified with a biotage system using an eluent EtOAc and 4% TEA (2L) then EtOAc, 4% TEA, 1% MeOH (1L). The solvent was removed to give 1-{3-fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinolin-4-yloxy]-phenyl}-3-phenylacetyl-thiourea (0.5 g, 50% yield). ^{1}H NMR (400 MHz, DMSO): 8.48 (d, 1H), 7.92 (dd, 1H), 7.53 (s, 1H), 7.40 (m, 4H), 7.33 (d, 2H), 7.23 (m, 2H), 6.54 (d, 2H), 6.39 (d, 1H), 4.21 (d, 2H), 4.02 (s, 3H), 3.81 (m, 3H),

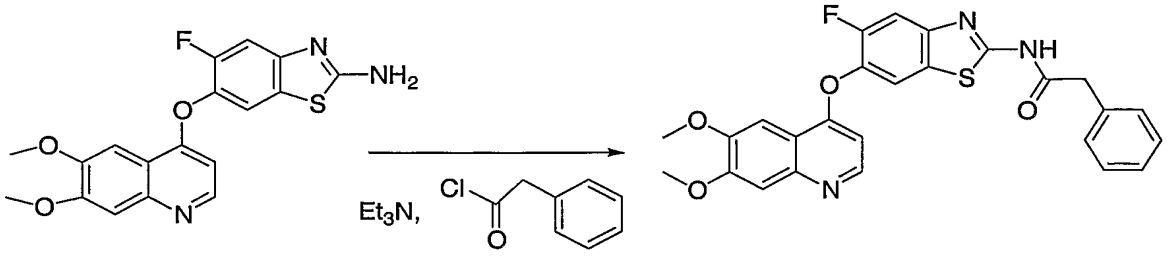
2.87 (d, 2H), 2.73 (m, 4H), 2.53 (m, 1H), 2.27 (m, 2H), 2.01 (s, 3H), 1.36 (m, 2H); MS (EI) for $C_{34}H_{35}FN_4O_4S$: 615 ($M+H^+$).

Example 11



[0300] 6-(6,7-Dimethoxy-quinolin-4-yloxy)-5-fluoro-benzothiazol-2-ylamine. 4-(6,7-dimethoxy-quinolin-4-yloxy)-3-fluoro-phenylamine (1.00g, 3.18mmol) was dissolved in AcOH (8.0ml), to which was added NH_4SCN (486mg, 6.38mmol) and the mixture cooled in an ice bath. Br_2 (0.33ml, 6.42mmol) in AcOH (0.33ml) was added dropwise with stirring. After addition was complete, the reaction mixture was stirred at room temperature. After one hour, more NH_4SCN (1.0g, 13.1mmol) was added, followed by more Br_2 (0.33ml, 6.42mmol) in AcOH (0.33ml), dropwise with stirring. The reaction mixture was then heated to reflux for several minutes. Upon cooling to room temperature, solids were filtered and washed with AcOH, followed by H_2O. The volume of the filtrate was reduced *in vacuo* and the pH adjusted to pH 9-10 with 1.0N NaOH. The resulting solids were filtered, washed with H_2O, and dried under high vacuum to give 6-(6,7-dimethoxy-quinolin-4-yloxy)-5-fluoro-benzothiazol-2-ylamine (568mg, 48%). ^{1}H-NMR (400MHz, DMSO): 8.45 (d, 1H), 7.82 (d, 1H), 7.73 (br s, 2H), 7.53 (s, 1H), 7.38 (m, 2H), 6.44 (d, 1H), 3.94 (s, 6H). LC/MS Calcd for $[M+H]^+$ 372.1, found 372.2

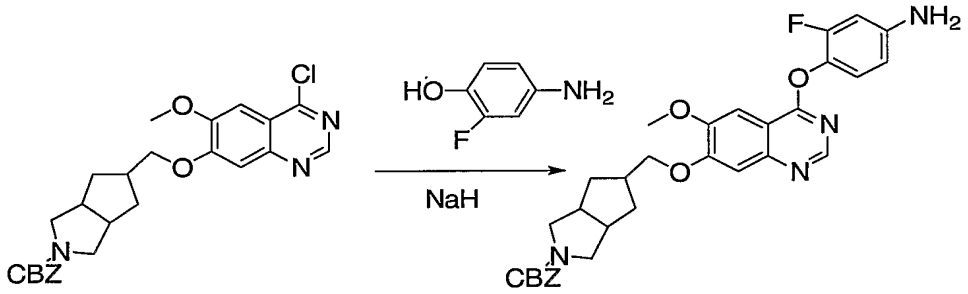
Example 12



[0301] N-[6-(6,7-Dimethoxy-quinolin-4-yloxy)-5-fluoro-benzothiazol-2-yl]-2-phenyl-acetamide. 6-(6,7-dimethoxy-quinolin-4-yloxy)-5-fluoro-benzothiazol-2-ylamine (95mg,

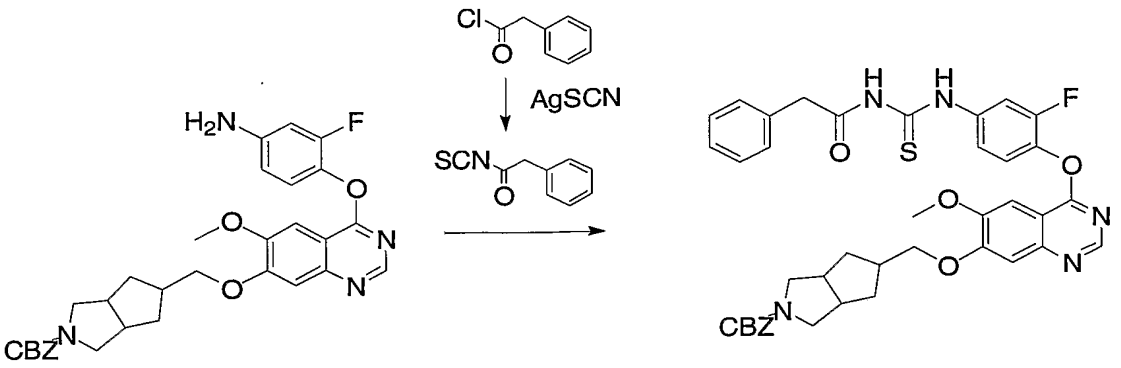
0.25mmol), Et_3N (0.10ml, 0.72mmol), phenylacetyl chloride (0.044ml, 0.33mmol), and THF (1.0ml) were combined and stirred at room temperature for 1 hr. Additional phenylacetyl chloride (0.044ml, 0.33mmol) was added and the mixture heated to reflux for 1-2 hrs. After cooling to room temperature, the reaction mixture was diluted with 1:1 AcCN:H_2O (1.0ml) and the resulting solids filtered, washed with 1:1 AcCN:H_2O and dried under high vacuum to give N-[6-(6,7-dimethoxy-quinolin-4-yloxy)-5-fluoro-benzothiazol-2-yl]-2-phenyl-acetamide (72mgs, 59%). ^{1}H-NMR (400MHz, DMSO): 12.80 (s, 1H), 8.54 (d, 1H), 8.18 (d, 1H), 7.91 (d, 1H), 7.60 (s, 1H), 7.45 (s, 1H), 7.34 (m, 4H), 7.28 (m, 1H), 6.60 (d, 1H), 3.98 (s, 3H), 3.96 (s, 3H), 3.86 (s, 2H). LC/MS Calcd for $[M+H]^+$ 490.1, found 490.0.

Example 13



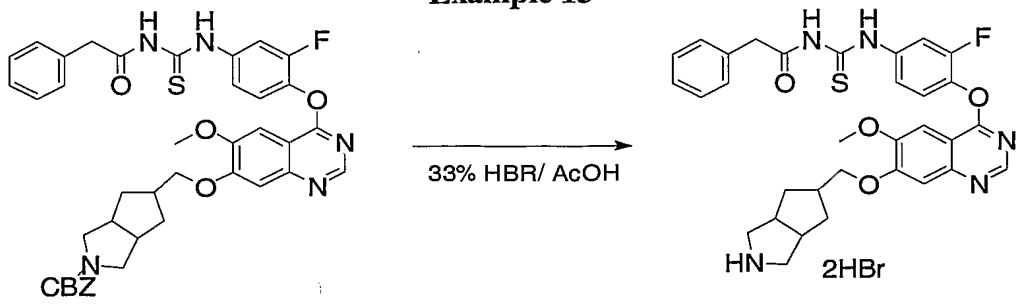
[0302] 5-[4-(4-Amino-2-fluoro-phenoxy)-6-methoxy-quinazolin-7-yloxymethyl]-hexahydro-cyclopenta[c]pyrrole-2-carboxylic acid benzyl ester. 4-Amino-2-fluoro-phenol (1.53g, 12.0mmol) was dissolved in dry DMF (30ml) to which was added 60% NaH (774mg, 19.3mmol). After the mixture was stirred at room temperature for several minutes, a suspension of 5-(4-chloro-6-methoxy-quinazolin-7-yloxymethyl)-hexahydro-cyclopenta[c]pyrrole-2-carboxylic acid benzyl ester (4.70g, 6.7mmol) in dry DMF (40ml) was added. The reaction mixture was stirred at room temperature for 1-2 hrs, then diluted with EtOAc and washed with sat'd $NaHCO_3$ (3x), H_2O (1x), sat'd NaCl (1x), dried (Na_2SO_4), and concentrated *in vacuo* to give crude 5-[4-(4-amino-2-fluoro-phenoxy)-6-methoxy-quinazolin-7-yloxymethyl]-hexahydro-cyclopenta[c]pyrrole-2-carboxylic acid benzyl ester (5.6g, ~100%) which was used in the next reaction without further purification. ^{1}H-NMR (400MHz, DMSO): 8.50 (s, 1H), 7.48 (s, 1H), 7.34 (m, 5H), 7.28 (m, 1H), 7.02 (t, 1H), 6.48 (dd, 1H), 6.40 (dd, 1H), 5.40 (br s, 2H), 5.05 (s, 2H), 4.16 (d, 2H), 3.92 (s, 3H), 3.48 (m, 2H), 3.30 (m, 2H), 2.65 (m, 2H), 2.52 (m, 1H), 2.10 (m, 2H), 1.30 (m, 2H). LC/MS Calcd for $[M+H]^+$ 559.2, found 559.4.

Example 14



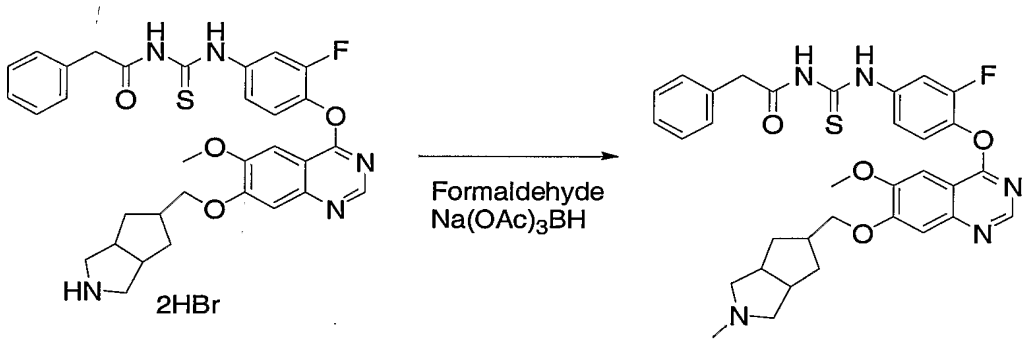
[0303] 5-{4-[2-Fluoro-4-(3-phenylacetyl-thioureido)-phenoxy]-6-methoxy-quinazolin-7-yloxymethyl}-hexahydro-cyclopenta[c]pyrrole-2-carboxylic acid benzyl ester. Phenylacetyl chloride (2.65ml, 20.0mmol) and AgSCN (4.92g, 29.6mmol) were combined in dry toluene (50ml) and heated to reflux for 2 hrs. The reaction mixture was allowed to cool to room temperature, the solids were filtered through celite and the filtrate concentrated *in vacuo*. The resulting oil was combined with 5-[4-(4-amino-2-fluoro-phenoxy)-6-methoxy-quinazolin-7-yloxymethyl]-hexahydro-cyclopenta[c]pyrrole-2-carboxylic acid benzyl ester (5.6g, 10mmol) in 1:1 EtOH:toluene (100ml) and the mixture stirred at room temperature for 1-2 hrs. The reaction mixture was diluted with EtOAc and washed with sat'd $NaHCO_3$ (3x), H_2O (1x), sat'd NaCl (1x), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (3:1 EtOAc:hexanes) to give 5-{4-[2-fluoro-4-(3-phenylacetyl-thioureido)-phenoxy]-6-methoxy-quinazolin-7-yloxymethyl}-hexahydrocyclopenta[c]pyrrole-2-carboxylic acid benzyl ester (3.61g, 49%) as a dark brown foam. ^{1}H-NMR (400MHz, DMSO): 12.44 (s, 1H), 11.80 (s, 1H), 8.54 (s, 1H), 7.90 (m, 1H), 7.53 (s, 1H), 7.48 (m, 2H), 7.38 (s, 1H), 7.34 (m, 7H), 7.28 (m, 3H), 5.05 (s, 2H), 4.16 (d, 2H), 3.94 (s, 3H), 3.72 (s, 2H), 3.48 (m, 2H), 3.30 (m, 2H), 2.65 (m, 2H), 2.52 (m, 1H), 2.10 (m, 2H), 1.30 (m, 2H). LC/MS Calcd for $[M+H]^+$ 736.2, found 736.0.

Example 15



[0304] 1-{3-Fluoro-4-[6-methoxy-7-(octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-3-phenylacetyl-thiourea, dihydrobromide salt. 5-{4-[2-Fluoro-4-(3-phenylacetyl-thioureido)-phenoxy]-6-methoxy-quinazolin-7-yloxymethyl}-hexahydro-cyclopenta[c]pyrrole-2-carboxylic acid benzyl ester (3.3g, 4.5mmol) was dissolved in AcOH (70ml) to which was added 33%HBr in AcOH (12ml). The reaction mixture was stirred at room temperature for 1 hr, diluted with Et_2O (1000ml) and the resulting solids filtered, washed with Et_2O, and dried under high vacuum to give the 1-{3-fluoro-4-[6-methoxy-7-(octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-3-phenylacetyl-thiourea, dihydrobromide salt (3.4g, 100%). ^{1}H-NMR (400MHz, DMSO): 12.42 (s, 1H), 11.80 (s, 1H), 8.84 (br s, 2H), 8.64 (s, 1H), 7.92 (m, 1H), 7.59 (s, 1H), 7.49 (m, 2H), 7.41 (s, 1H), 7.33 (m, 4H), 7.27 (m, 1H), 4.17 (d, 2H), 3.95 (s, 3H), 3.73 (s, 2H), 3.17 (m, 2H), 3.10 (m, 2H), 2.83 (m, 2H), 2.45 (m, 1H), 2.15 (m, 2H), 1.30 (m, 2H). LC/MS Calcd for $[M+H]^+$ 602.2, found 602.1.

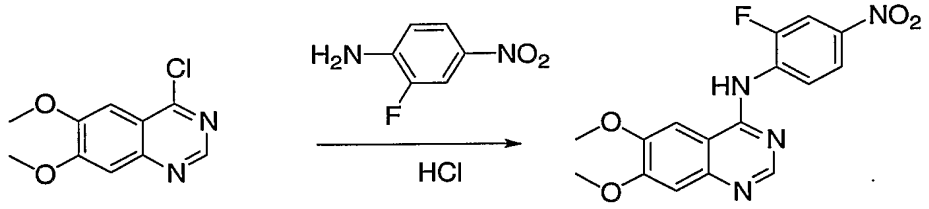
Example 16



[0305] 1-{3-Fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-3-phenylacetyl-thiourea. 1-{3-Fluoro-4-[6-methoxy-7-(octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-3-phenylacetyl-thiourea, dihydrobromide salt (3.4g, 4.5mmol) was dissolved in in a combination of AcCN (100ml), H_2O (30ml), and AcOH (2.45ml). Formaldehyde (37% in H_2O, 855ml, 10.5mmol) was added and the mixture cooled in an ice bath. $Na(OAC)_3BH$ (2.99g, 14.1mmol) was added and the reaction mixture was stirred at 0 C for 1 hr, followed by stirring at room temperature for 2 hrs. The reaction mixture was neutralized with the addition of sat'd $NaHCO_3$ and then concentrated *in vacuo*. The resulting aqueous mixture was extracted with CH_2Cl_2 (3x). The combined extractions were washed with sat'd $NaHCO_3$ (1x), sat'd NaCl (1x), dried (Na_2SO_4), and concentrated *in vacuo*. The

resulting residue was purified by flash chromatography (100% EtOAc, followed by 4% Et_3N in EtOAc) to give the free base of 1-{3-fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-3-phenylacetyl-thiourea (1.13g, 40%). The free base was converted to the HCl salt by dissolving the free base in a mixture of 1:1 AcCN:H_2O containing 2-3 equivalents of 1 N HCl and lyophilizing to give the HCl salt of 1-{3-fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-3-phenylacetyl-thiourea as a white solid. ^{1}H-NMR (400MHz, DMSO): 12.44 (s, 1H), 11.83 (s, 1H), 10.24 (br s, 1H), 8.59 (s, 1H), 7.93 (m, 1H), 7.59 (s, 1H), 7.50 (m, 2H), 7.42 (s, 1H), 7.36 (m, 4H), 7.30 (m, 1H), 4.20 (m, 2H), 3.95 (s, 3H), 3.73 (s, 2H), 3.39 (m, 2H), 3.06 (m, 2H), 2.95-2.77 (m, 5H), 2.35 (m, 1H), 2.15 (m, 2H), 1.45 (m, 2H). LC/MS Calcd for $[M+H]^+$ 616.2, found 616.2. Alternatively, the free base was converted to the acetate salt by dissolving the free base in a mixture of MeOH and CH_2Cl_2 to which was added 3 equivalents of acetic acid. The resulting mixture was concentrated *in vacuo* and the resulting residue lyophilized from 1:1 AcCN:H_2O to give the acetate salt of 1-{3-fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-3-phenylacetyl-thiourea as a white solid. ^{1}H-NMR (400MHz, $CDCl_3$): d 12.45 (s, 1H), 8.65 (s, 1H), 7.98 (dd, 1H), 7.50 (s, 1H), 7.40 (m, 4H), 7.29 (m, 4H), 4.17 (d, 2H), 4.05 (s, 3H), 3.75 (s, 2H), 2.93 (m, 2H), 2.80 (m, 2H), 2.72 (m, 2H), 2.53 (s, 3H), 2.47 (m, 1H), 2.25 (m, 2H), 2.02 (s, 3H), 1.35 (m, 2H). LC/MS Calcd for $[M+H]^+$ 616.2, found 616.2.

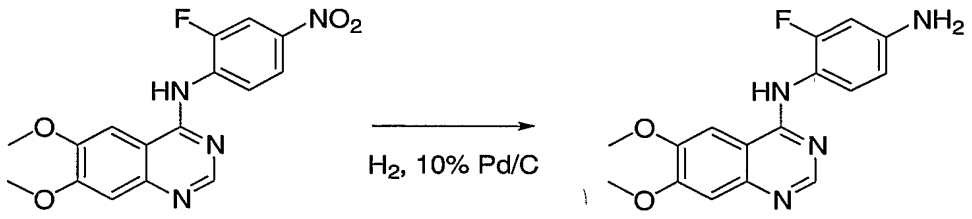
Example 17



[0306] (6,7-Dimethoxy-quinazolin-4-yl)-(2-fluoro-4-nitro-phenyl)-amine. A mixture of 4-chloro-6,7-dimethoxy-quinazoline (548mg, 2.4mmol), 2-fluoro-4-nitro-phenylamine (392mg, 2.5mmol), AcCN (10ml), and conc'd HCl (0.050ml) was heated to reflux for several hrs. After the reaction mixture was allowed to cool to room temperature, the resulting solids were filtered, washed with AcCN and air-dried to give (6,7-dimethoxy-quinazolin-4-yl)-(2-fluoro-4-nitro-phenyl)-amine (673mgs, 80%). ^{1}H-NMR (400MHz,

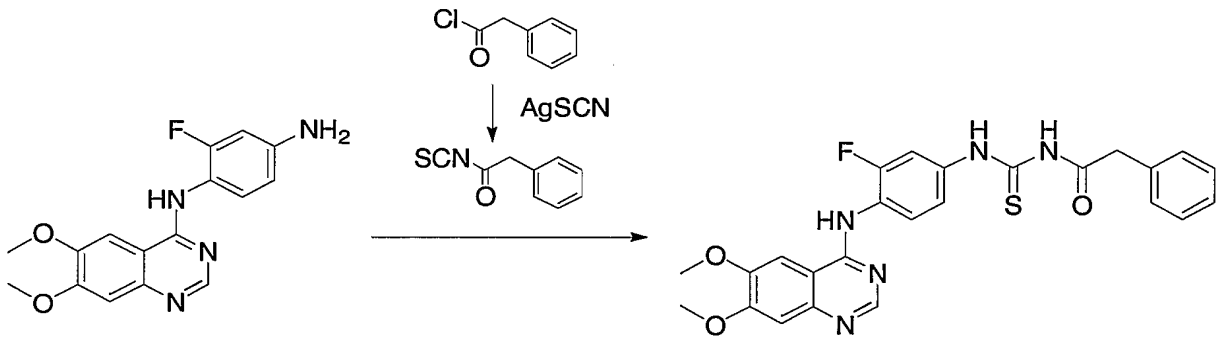
DMSO): 12.18 (br s, 1H), 8.91 (s, 1H), 8.45 (s, 1H), 8.36 (dd, 1H), 8.24 (dd, 1H), 7.91 (dd, 1H), 7.44 (s, 1H), 4.04 (s, 3H), 4.02 (s, 3H). LC/MS Calcd for $[M+H]^+$ 345.1, found 345.4.

Example 18



[0307] N[1]-(6,7-Dimethoxy-quinazolin-4-yl)-2-fluoro-benzene-1,4-diamine. (6,7-Dimethoxy-quinazolin-4-yl)-(2-fluoro-4-nitro-phenyl)-amine (673mg, 1.95mmol) was dissolved in a combination of DMF (20ml) and MeOH (20ml), to which was added 10% Pd/C (227mg). The mixture was shaken under an atmosphere of H_2 on a Parr hydrogenator at 40psi for 3hrs. The reaction mixture was filtered through celite and the filtrate concentrated *in vacuo*. The resulting residue was triturated in EtOAc/Et_2O. The resulting solids were filtered, washed with Et_2O, and dried under vacuum to give N[1]-(6,7-dimethoxy-quinazolin-4-yl)-2-fluoro-benzene-1,4-diamine (398mg, 65%) which was used in the next reaction without further purification. ^{1}H-NMR (400MHz, DMSO): 10.80 (br s, 1H), 10.30 (br s, 1H), 8.63 (s, 1H), 8.15 (s, 1H), 7.33 (s, 1H), 7.15 (m, 1H), 6.45 (m, 1H), 3.96 (s, 6H). LC/MS Calcd for $[M+H]^+$ 315.1, found 315.4.

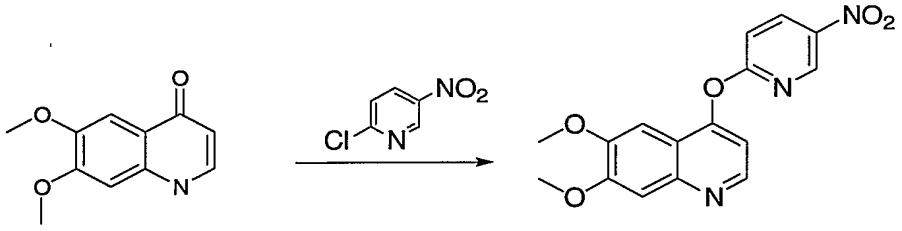
Example 19



[0308] 1-[4-(6,7-Dimethoxy-quinazolin-4-ylamino)-3-fluoro-phenyl]-3-phenylacetyl-thiourea. Phenylacetyl chloride (0.18ml, 1.4mmol) and AgSCN (338mg, 2.0mmol) were

combined in dry toluene (5ml) and heated to reflux for 2 hrs. The reaction mixture was allowed to cool to room temperature, the solids were filtered through celite and the filtrate concentrated *in vacuo*. The resulting oil was combined with N^1-(6,7-Dimethoxy-quinazolin-4-yl)-2-fluoro-benzene-1,4-diamine (398mg, 1.3mmol) in 1:1:2 EtOH:toluene:MeOH (30ml) and the mixture stirred at room temperature overnight. The resulting solids were filtered and washed with toluene, followed by hexanes. The solids were dissolved/suspended in a mixture of EtOAc/MeOH. Insoluble material was filtered and the filtrate concentrated *in vacuo*. The resulting solids were once again dissolved/suspended in a mixture of EtOAc/MeOH. In soluble material was filtered and the filtrate concentrated *in vacuo* to give 1-[4-(6,7-dimethoxy-quinazolin-4-ylamino)-3-fluoro-phenyl]-3-phenylacetyl-thiourea (105mg, 17%). ^{1}H-NMR (400MHz, DMSO): 12.53 (s, 1H), 11.86 (s, 1H), 11.44 (br s, 1H), 8.81(s, 1H), 8.25 (s, 1H), 7.94 (dd, 1H), 7.54 (m, 2H), 7.16 (m, 5H), 7.10 (m, 1H), 4.02 (s, 6H), 3.84 (s, 2H). LC/MS Calcd for $[M+H]^+$ 492.1, found 492.4.

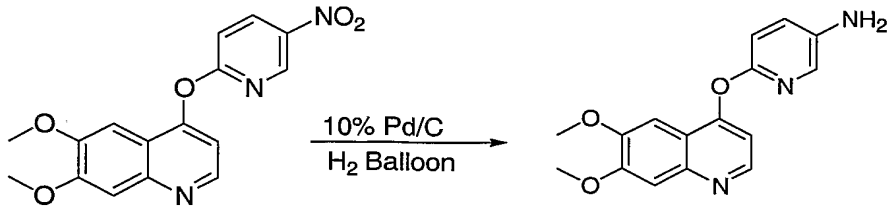
Example 20



[0309] 6,7-Dimethoxy-4-(5-nitro-pyridin-2-yloxy)-quinoline. To a round bottom flask equipped with a magnetic stir bar was added 6,7-dimethoxy-1*H*-quinolin-4-one (1.8 g, 8.77 mmol, 1.0 eq.), anhydrous acetonitrile (90 mL) and Cs_2CO_3 (3.13 g, 9.65 mmole, 1.1 eq.). The reaction mixture was stirred at room temperature for 5 minutes. Then, 2-Cl-5-nitropyridine (1.53 g, 9.65 mmol, 1.1 eq.) was added. The reaction mixture was stirred at room temperature for 16 hours. The solids were then filtered off and the filtrate was concentrated via rotary evaporation. The resulting material was taken up in EtOAc, and again the solids were filtered off. The EtOAc filtrate was concentrated. Purification was done on Biotage with solvent system EtOAc 100%. The collected pure fractions were concentrated and dried on high vacuum overnight to give 6,7-dimethoxy-4-(5-nitro-pyridin-2-yloxy)-quinoline as a yellow foam solid (0.902 g, 31.4% yield). ^{1}H NMR (400

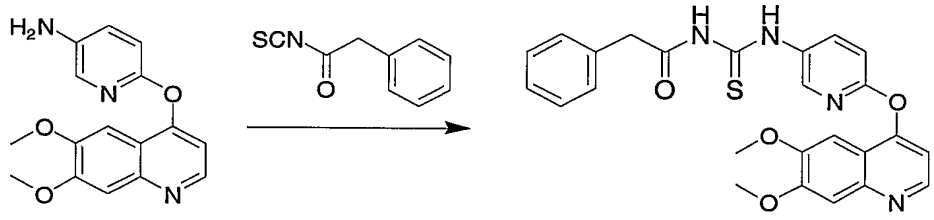
MHz, CDCl3): 9.08 (d, 1H), 8.74 (d, 1H), 8.60 (dd, 1H), 7.49 (s, 1H), 7.26 (d, 1H), 7.16 (s, 1H), 7.07 (d, 1H), 4.06 (s, 3H), 3.95 (s, 3H); MS (EI) for $C_{16}H_{13}N_3O_5$: 328 ($M+H^+$).

Example 21



[0310] 6-(6,7-Dimethoxy-quinolin-4-yloxy)-pyridin-3-ylamine. To a round bottom flask equipped with a magnetic stir bar was added 6,7-dimethoxy-4-(5-nitro-pyridin-2-yloxy)-quinoline (0.46 g, 1.41 mmol, 1.0 eq.), and THF (10 mL), MeOH (4 mL), DMF (2 mL), and TEA (2 mL). The 6,7-Dimethoxy-4-(5-nitro-pyridin-2-yloxy)-quinoline was dissolved completely in the above solution mixture, and was flushed with nitrogen for at least 5 minutes. The Pd/C (10% by weight) (0.090 g, 20% by weight) was then added. A balloon filled with H_2 was connected to the flask after the nitrogen was vacuumed out. The reaction mixture was stirred at room temperature for 4 hours. The palladium was filtered out through Celite, and the filtrated was collected and concentrated via rotary evaporation. The resulting oil-like product was taken up into 5 mL of water and 1 mL of acetonitrile and lyophilized to yield 6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-ylamine as a light brown solid (0.411 g, 98.1%). ^1H NMR (400 MHz, CDCl3): 8.54 (d, 1H), 7.85 (d, 1H), 7.53 (s, 1H), 7.41 (s, 1H), 7.18 (dd, 1H), 6.96 (d, 1H), 6.61 (d, 1H), 4.05 (s, 3H), 4.03 (s, 3H), 3.73 (s, 2H); MS (EI) for $C_{16}H_{15}N_3O_3$: 298 ($M+H^+$).

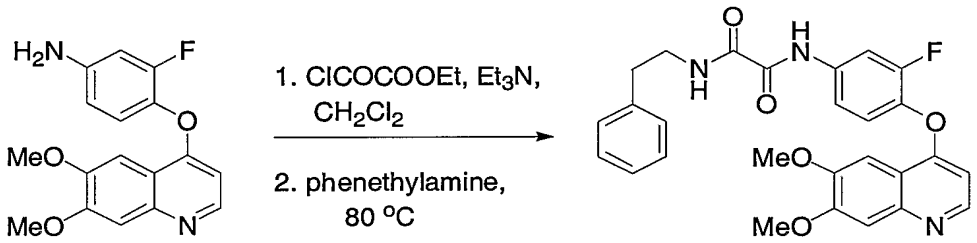
Example 22



[0311] 1-[6-(6,7-Dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-3-phenylacetyl-thiourea. To a round bottom flask equipped with a magnetic stir bar was added 6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-ylamine (85 mg, 0.0285 mmol, 1.0 eq.), and Phenyl-acetyl

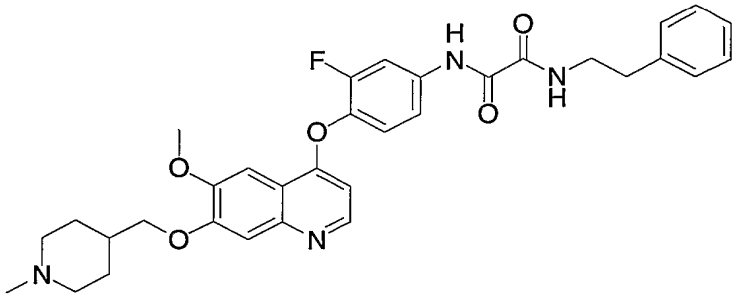
isothiocyanate (256 mg, 1.44 mmol, 5.0 eq.) dissolved in EtOAc/MeOH 50:50 (2 mL). The reaction mixture was sittred at room temperature for 12 hours, and the solvent was evaporated via rotary evaporation. Purification was done on Biotage with solvent system 95% EtOAc, 4% TEA and 1% MeOH. The combined pure fractions were concentrated and dried under vacuum overnight to yield 1-[6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-3-phenylacetyl-thiourea as a light yellow solid (40.4 mg, 29.7%). ^{1}H NMR (400 MHz, CDCl3): 8.65 (d, 1H), 8.33 (d, 1H), 8.27 (dd, 1H), 7.35 (m, 7H), 7.15 (d, 1H), 6.92 (d, 1H), 4.05 (s, 3H), 3.99 (s, 3H), 3.76 (s, 2H); MS (EI) for $C_{25}H_{22}N_4O_4S$: 475 ($M+H^+$).

Example 23



[0312] N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-N'-phenethyl-oxalamide. To a solution of 4-(6,7-dimethoxy-quinolin-4-yloxy)-3-fluoro-phenylamine (263 mg, 0.83 mmol) and Et_3N (0.223 ml, 1.67 mmol) in CH_2Cl_2 (10 mL) was added dropwise a solution of ethyl oxalyl chloride in CH_2Cl_2 (1 mL). The stirring was continued for 0.5 h at rt. The reaction mixture was then washed with aqueous saturated $NaHCO_3$ and dried over $NaSO_4$. Removal of the solvent gave the crude oxamate, which was treated with neat phenethylamine (1.0 g, 8.3 mmol) at 80 °C for 3 h. Purification by flash column chromatography (hexanes:EtOAc = 1:3) gave N-[4-(6,7-dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-N'-phenethyl-oxalamide (310 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (br s, 1 H), 8.70 (d, J = 6.3 Hz, 1 H), 7.83 (dd, J = 11.9, 2.5 Hz, 1 H), 7.60-7.54 (m, 2 H), 7.43 (s, 1 H), 7.38-7.32 (m, 3 H), 7.30-7.20 (m, 4 H), 6.41 (d, J = 5.3 Hz, 1 H), 4.07 (s, 3 H), 4.05 (s, 3 H), 3.67 (dt, J = 7.0, 7.0 Hz, 2 H), 2.92 (t, J = 7.2 Hz, 2 H). LC-MS: 490 $[M+H]^+$

Example 24



[0313] N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxyl-phenyl}-N'-phenethyl-oxalamide. To a flask containing 7-benzyloxy-4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinoline (850 mg, 2.0 mmol) was added 20 mL of 30% HBr in AcOH. The resulted solution was stirred for 4 h at rt; at this time, a large amount of precipitate formed. The crude product was filtered, washed with Et_2O and dried in air, giving 4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-7-hydroxyquinoline (609 mg, 92% yield).

[0314] To a solution of the 4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-7-hydroxyquinoline (609 mg, 1.8 mmol) in DMF (9 mL) was added K_2CO_3 (1.24 g, 9.0 mmol) and N-Boc-4-piperidinemethanol mesylate (732 mg, 2.5 mmol). The mixture was then stirred at 80 °C for 2.5 h. After it was cooled to rt, the mixture was loaded directly to a Biotage column, and eluted with solvents (hexanes:EtOAc = 1:3). The resulting product, 4-[4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-yloxymethyl]-piperidine-1-carboxylic acid tert-butyl ester, was obtained as a solid (556 mg, 56%).

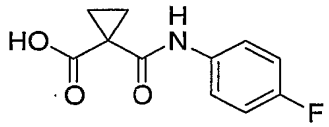
[0315] To a solution of 4-[4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-yloxymethyl]-piperidine-1-carboxylic acid tert-butyl ester (305 mg, 0.58 mmol) in CH_2Cl_2 (1 mL) was added 0.4 mL of TFA. The reaction mixture was stirred for 1.5 h and the solvents were removed under reduced pressure. The crude product was treated with $NaBH(OAc)_3$ (381 mg, 1.80 mmol) and formaldehyde (0.5 mL, 37% in H_2O). The stirring was continued for 12 h. The reaction was quenched with sat. aqueous $NaHCO_3$. 15% NaOH was added until PH = 14. The product was extracted with EtOAc. Removal of the solvent *in vacuo* gave the crude product, 4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinoline, (240 mg, 93%), which was used directly in the next reaction.

[0316] To a solution of 4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinoline (240 mg, 0.54 mmol) in EtOH (20 mL) was added 10% Pd/C (50

mg). The mixture was then hydrogenated on a Parr hydrogenator (40 psi) for 10 h. AcOH was added to dissolve the intermediate (mostly the hydroxylamine) and the hydrogenation was continued for additional 12 h. LC-MS was used to monitor the reaction progress. The solvents were removed under reduced pressure and the resulting crude product of 3-fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenylamine (about 220 mg) was used directly in the next reaction.

[0317] To a 0 °C solution of 3-fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenylamine (66 mg, 0.13 mmol) and Et_3N (0.34 mL) in CH_2Cl_2 (6 mL) was added slowly ethyl oxalyl chloride (98 mg). The reaction mixture was stirred at rt for 30 min, then diluted with CH_2Cl_2 and washed with sat. aqueous $NaHCO_3$. After dried over $MgSO_4$ and concentrated, the crude ethyl oxamate was reacted with phenethylamine (80 mg, 0.64 mmol) at 80 °C for 2 h. Purification by HPLC gave product, N-{3-fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide (52 mg, 68% yield). ^1H NMR (400 MHz) δ 9.38 (br s, 1 H), 8.48 (d, J = 5.2 Hz, 1 H), 7.83 (dd, J = 11.7, 2.6 Hz, 1 H), 7.59 (t, J = 6.2 Hz, 1 H), 7.55 (s, 1 H), 7.40-7.20 (8 H), 6.39 (d, J = 5.3 Hz, 1 H), 4.06 (d, J = 6.6 Hz, 2 H), 4.04 (s, 3 H), 3.67 (q, J = 6.8 Hz, 2 H), 2.98 (br d, J = 11.5 Hz, 2 H), 2.92 (t, J = 7.0 Hz, 2 H), 2.34 (s, 3 H), 2.10-1.80 (m, 5 H), 1.60-1.54 (m, 2 H).

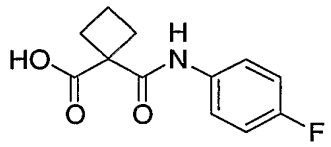
Example 25



[0318] 1-(4-Fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid. The title compound was prepared based on a modified procedure of Shih and Rankin [*Synthetic Communications*, 1996, 26(4), 833-836]: To a mixture of cyclopropane-1,1-dicarboxylic acid (21.2 g, 0.163 mol, 1.0 eq.) in anhydrous THF (200 mL) under nitrogen was added dropwise triethylamine (16.49 g, 0.163 mol, 1.0 eq.) with stirring for 30 minutes at 0°C, followed by the addition of thionyl chloride (19.39 g, 0.163 mol, 1.0 eq.) with stirring for another 30 minutes at 0°C. To the resulting mixture under nitrogen was added dropwise a solution of 4-fluoroaniline (19.92 g, 0.179 mol, 1.1 eq.) in anhydrous THF (100 mL) with stirring for 1.5 hours at 0°C. The reaction mixture was diluted with ethyl acetate and

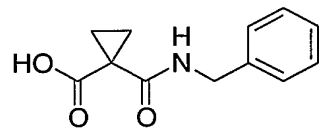
washed with 1N NaOH. The layers were separated, and the ethyl acetate layer was concentrated in vacuo to give a brownish solid. The brownish solid was washed with small amount of cold ethyl acetate, filtered and dried under vacuum to yield 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid as a white solid (23.71 g, 65.18%). ^{1}H NMR (400 MHz, CD_3OD): 7.57-7.53 (m, 2H), 7.05-7.00 (m, 2H) 1.46-1.43 (m, 2H), 1.40-1.37 (m, 2H).

Example 26



[0319] 1-(4-Fluoro-phenylcarbamoyl)-cyclobutanecarboxylic acid. To a mixture of cyclobutane-1,1-dicarboxylic acid (10.0 g, 69.4 mmol, 1.0 eq.) in anhydrous THF (100 mL) under nitrogen was added dropwise triethylamine (7.02 g, 69.4 mmol, 1.0 eq.) with stirring for 30 minutes at 0°C, followed by the addition of thionyl chloride (8.25 g, 69.4 mmol, 1.0 eq.) with stirring for another 30 minutes at 0°C. To the resulting mixture under nitrogen was added dropwise a solution of 4-fluoroaniline (8.48 g, 76.3 mmol, 1.1 eq.) in anhydrous THF (50 mL) with stirring for 1.5 hours at 0°C. The reaction mixture was diluted with ethyl acetate and extracted with 2N NaOH. The aqueous phase was titrated with 2N HCl to pH 1-2 and then extracted with ethyl acetate. The organic phase was dried with sodium sulfate and concentrated in vacuo to give 1-(4-fluoro-phenylcarbamoyl)-cyclobutanecarboxylic acid as a light pink solid (5.75 g, 34.9%). ^{1}H NMR (400 MHz, $CDCl_3$ w/1drop CD_3OD): 7.53-7.48 (m, 2H), 7.06-7.00 (m, 2H), 2.81-2.63 (m, 4H), 2.14-2.02 (m, 2H).

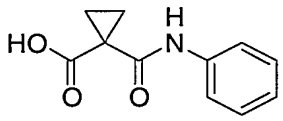
Example 27



[0320] 1-Benzylcarbamoyl-cyclopropanecarboxylic acid. The title compound was prepared based on a modified procedure of Shih and Rankin [*Synthetic Communications*, 1996, 26(4), 833-836]: To a mixture of cyclopropane-1,1-dicarboxylic acid (5.0 g, 38.4

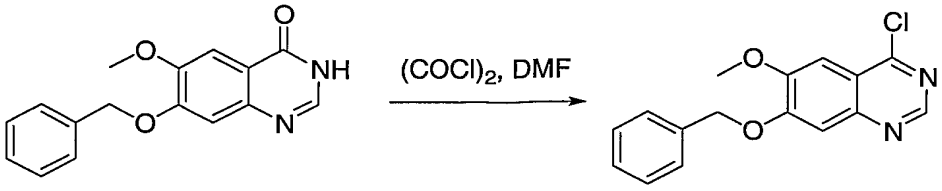
mmol, 1.0 eq.) in anhydrous THF (50 mL) under nitrogen was added dropwise triethylamine (3.89 g, 38.4 mmol, 1.0 eq.) with stirring for 30 minutes at 0°C, followed by the addition of thionyl chloride (4.57 g, 38.4 mmol, 1.0 eq.) with stirring for another 30 minutes at 0°C. To the resulting mixture under nitrogen was added dropwise a solution of benzylamine **5** (4.53 g, 42.3 mmol, 1.1 eq.) in anhydrous THF (25 mL) with stirring for 1.5 hours at 0°C. The reaction mixture was diluted with ethyl acetate and extracted with 2N NaOH (to pH 10). The aqueous phase was titrated with 2N HCl to pH 1-2 and then extracted with ethyl acetate. The organic phase was dried with sodium sulfate and concentrated in vacuo to give 1-Benzylcarbamoyl-cyclopropanecarboxylic acid as a white solid (4.39 g, 52.15%). ^{1}H NMR (400 MHz, $CDCl_3$): 8.44 (br s, 1H), 7.37-7.33 (m, 2H), 7.32-7.26 (m, 3H), 1.82-1.70 (m, 4H).

Example 28



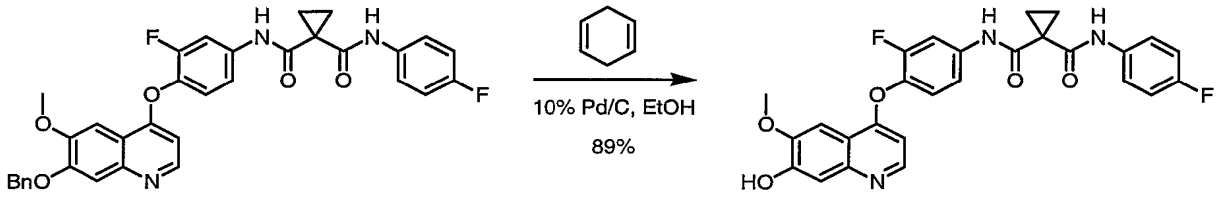
[0321] 1-Phenylcarbamoyl-cyclopropanecarboxylic acid. To a mixture of cyclopropane-1,1-dicarboxylic acid (5.29 g, 40.7 mmol, 1.0 eq.) in anhydrous THF (50 mL) under nitrogen was added dropwise triethylamine (4.12 g, 40.7 mmol, 1.0 eq.) with stirring for 30 minutes at 0°C, followed by the addition of thionyl chloride (4.84 g, 40.7 mmol, 1.0 eq.) with stirring for another 30 minutes at 0°C. To the resulting mixture under nitrogen was added dropwise a solution of phenylamine 9 (4.17 g, 44.8 mmol, 1.1 eq.) in anhydrous THF (25 mL) with stirring for 1.5 hours at 0°C. The reaction mixture was diluted with ethyl acetate and extracted with 2N NaOH (to pH >10). The aqueous phase was titrated with 2N HCl to pH 1-2 and then extracted with ethyl acetate. The organic phase was dried with sodium sulfate and concentrated in vacuo to give 1-phenylcarbamoyl-cyclopropanecarboxylic acid as a white solid (5.08 g, 60.8%). ^{1}H NMR (400 MHz, $CDCl_3$): 10.50 (br s, 1H), 7.56-7.54 (m, 2H), 7.35-7.31 (m, 2H), 7.15-7.10 (m, 1H), 1.94-1.91 (m, 2H), 1.82-1.79 (m, 2H).

Example 29



[0322] 7-Benzyloxy-4-chloro-6-methoxy-quinoline. Dry DMF (8.0ml, 103mmol) was dissolved in dry $CHCl_3$ (40ml) and cooled in an ice bath. Oxalyl chloride (9.0ml, 105mmol) in CH_2Cl_2 (10ml) was added dropwise with stirring at 0C. When the bubbling had ceased, this solution was added slowly to an ice-cold solution of 7-benzyloxy-6-methoxy-3H-quinazolin-4-one (10.0g, 35.4mmol) in dry $CHCl_3$ (60ml) and the mixture was then heated to reflux for 2-3hrs. After cooling to room temperature, H_2O (100ml) was added and the phases were separated. The aqueous phase was further extracted with $CHCl_3$ (2x). The combined $CHCl_3$ extractions were washed with sat'd NaCl (1x), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (1:1 hexanes:EtOAc, followed by 100%EtOAc) to give 7-benzyloxy-4-chloro-6-methoxy-quinoline (5.11g, 48%). LC/MS Calcd for $[M+H]^+$ 301.1, found 301.1.

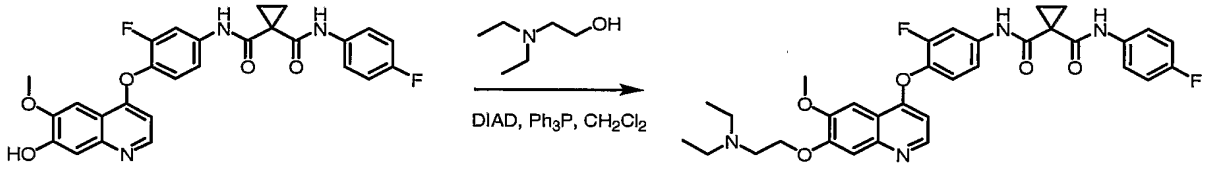
Example 30



[0323] Cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinolin-4-yloxy)-phenyl]-amide(4-fluoro-phenyl)-amide. To a solution of cyclopropane-1,1-dicarboxylic acid [4-(7-benzyloxy-6-methoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-amide (4-fluoro-phenyl)-amide (1.18g, 2.0 mmol) in EtOH (20 mL) was added 1,4-cyclohexadiene (2.0 mL, 20 mmol) and 10% Pd/C (300 mg). The reaction mixture was then heated to reflux and the stirring was continued for 2 h. It was cooled to room temperature, filtered through celite and washed with MeOH. The MeOH solution was then concentrated under reduced pressure. The residue was taken into EtOAc (200 mL).

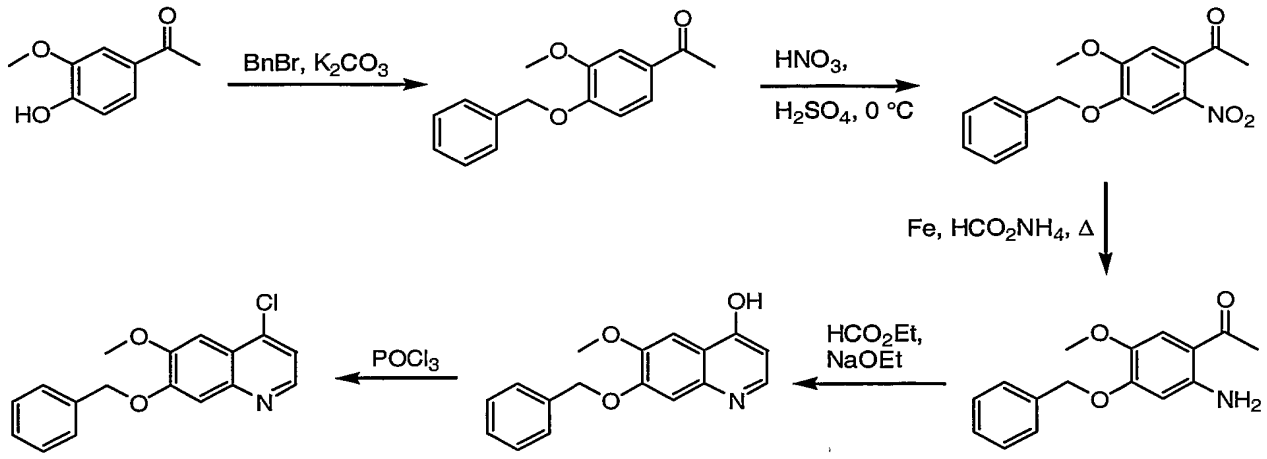
The EtOAc solution was washed with water, and dried over Na_2SO_4. Removal of the solvent under reduced pressure gave 900 mg (89%) of the crude product (90% purity by analytical HPLC), which was used in the next reaction without further purification.

Example 31



[0324] N-(4-{[7-{[2-(Diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. To a mixture of cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinolin-4-yloxy)-phenyl]-amide(4-fluoro-phenyl)-amide (186 mg, 0.36 mmol) in CH_2Cl_2 (10 mL) was added 2-(diethylamino)ethanol (63 mg, 0.54 mmol), and PPh_3 (141 mg, 0.54 mmol). DIAD (109 mg, 0.54 mmol) was then added as a CH_2Cl_2 (1 mL) solution. The resulted solution was stirred at room temperature for 2 h and the solvent was removed under reduced pressure. To the residue was added 1 N HCl (50 mL), and it was washed with EtOAc (50 mL x 2). The aqueous phase was basified by adding 15% NaOH aqueous solution until pH =11-13, and then extracted with ether (50 mL x 2). The combined organic layer was dried (MgSO4), and concentrated in vacuo. The residue was purified on preparative HPLC to give N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluoro-phenyl)cyclopropane-1,1-dicarboxamide (74 mg, 34%) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.40 (br s, 1 H), 10.02 (br s, 1 H), 8.47 (d, J = 5.2 Hz, 1 H), 7.91 (br d, J = 13.9 Hz, 1 H), 7.54-7.52 (m, 2 H), 7.55-7.50 (m, 1 H), 7.52 (s, 1 H), 7.50-7.40 (m, 1 H), 7.41 (s, 1 H), 7.16 (br t, J = 8.7 Hz, 2 H), 6.41 (br d, J = 4.7 Hz, 1 H), 4.18 (t, J = 6.0 Hz, 2 H), 3.94 (s, 3 H), 2.87 (br t, J = 6.3 Hz, 2 H), 2.59 (q, J = 7.1 Hz, 4 H), 1.47 (br s, 4 H), 1.00 (t, J = 7.0 Hz, 6 H).

Example 32



[0325] 1-(4-Benzyloxy-3-methoxyphenyl)ethanone. A solution of 4-hydroxy-3-methoxyacetophenone (40 g, 240 mmol), benzyl bromide (31.4 mL, 260 mmol) and potassium carbonate (99.6 g, 360 mmol) in DMF (800 mL) was heated to 40 °C overnight. The solution was cooled to room temperature, poured over ice and the resultant solid was filtered. This material was washed with water and dried to give 1-(4-benzyloxy-3-methoxyphenyl)ethanone (61 g, 99 %).

[0326] 1-(4-Benzyloxy-5-methoxy-2-nitrophenyl)ethanone. A stirred solution of 1-(4-benzyloxy-3-methoxyphenyl)ethanone (51.3 g, 200 mmol) in dichloromethane (750 mL) was cooled to 0 °C. Nitric acid (90 %, 14 mL, 300 mmol) was added dropwise to the cooled solution over 20 min. Sulfuric acid (96.2 %, 16.3 mL, 300 mmol) was then added dropwise over 40 min at 0 °C. Additional nitric acid (9.4 mL, 200 mmol) was added dropwise over 20 min. The reaction mixture was washed with water (3 x 200 mL), and saturated sodium bicarbonate (4 x 200 mL, or until neutral). The organic layer was dried over Na_2SO_4 and concentrated. The crude mixture was recrystallized from DMF to give 1-(4-benzyloxy-5-methoxy-2-nitrophenyl)ethanone (36 g, 60 %). ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.45-7.33 (m, 5H), 6.74 (s, 1H), 5.21 (s, 2H), 3.97 (s, 3H), 2.49 (s, 3H).

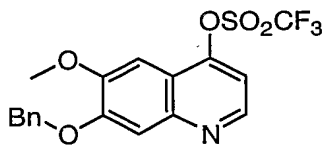
[0327] 1-(2-Amino-4-benzyloxy-5-methoxyphenyl)ethanone. A mixture of iron powder (27 g, 0.48 g atoms), ammonium formate (31 g, 500 mmol), 1-(4-benzyloxy-5-methoxy-2-nitrophenyl)ethanone (36 g, 120 mmol), toluene (500 mL) and water (500 mL) was heated to reflux overnight. The mixture was filtered through celite and washed with ethyl acetate. The combined organic layers were washed with water and brine. The organic layer was

dried over Na_2SO_4 and concentrated to afford 1-(2-amino-4-benzyloxy-5-methoxyphenyl)ethanone (29.3 g, 90 %). ^{1}H NMR ($CDCl_3$): δ 7.41-7.30 (m, 5H), 7.13 (s, 1H), 6.16 (br s, 2H), 6.10 (s, 1H), 5.13 (s, 2H), 3.83 (s, 3H), 2.51 (s, 3H). LC/MS (M+H = 272).

[0328] 7-Benzyloxy-6-methoxyquinolin-4-ol. Sodium ethoxide (74.8 g, 1.1 mol) was added to a solution of 1-(2-amino-4-benzyloxy-5-methoxyphenyl)ethanone (29.3 g, 108 mmol) in DME (700 mL) and stirred for 30 min. Ethyl formate (44 mL, 540 mmol) was added and the mixture was stirred overnight (in case of incomplete reaction, additional sodium ethoxide can be added and the reaction monitored by LC/MS). After the reaction was complete, the mixture was diluted with water (40 mL) and acidified to neutral pH with 1M HCl. The solid was filtered, washed with water and dried to afford 7-benzyloxy-6-methoxyquinolin-4-ol (22 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.7 (br s, 1H), 7.70 (s, 1H), 7.49-7.46 (t, 1H), 7.43-7.41 (br d, 2H), 7.37-7.33 (t, 2H), 7.30-7.28 (d, 1H), 6.84 (s, 1H), 6.21-6.19 (d, 1H), 5.21 (s, 2H), 3.96 (s, 3H). LC/MS (M+H = 282).

[0329] 7-Benzyloxy-4-chloro-6-methoxyquinoline. Phosphorus oxychloride (300 mL) was added to 7-benzyloxy-6-methoxyquinolin-4-ol (40 g, 140 mmol) and the mixture heated to reflux for 2 h. The mixture was carefully poured into a mixture of ice and sodium carbonate. The solution was adjusted to pH 8 with the addition of solid sodium bicarbonate and stirred at room temperature overnight. The solid was filtered and washed with water and dried to give 7-benzyloxy-4-chloro-6-methoxyquinoline as a pale brown solid (40.2 g, 95%). ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.61 (s, 1H), 7.57-7.37 (m, 8H), 5.32 (s, 2H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO): δ 152.4, 151.5, 148.5, 146.2, 139.6, 137.0, 129.2, 128.8, 121.7, 120.4, 110.1, 101.9, 70.8, 56.5; IR (cm^{-1}): 2359, 2341, 1506, 1456, 1435, 1252, 1227, 1146, 999, 845, 752, 698, 667; LC/MS (M+H = 300).

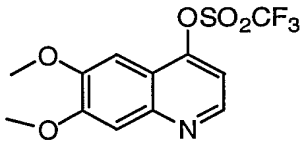
Example 33



[0330] Trifluoromethanesulfonic acid 7-benzyloxy-6-methoxy-quinolin-4-yl ester. To a dry 2L RBF containing 7-benzyloxy-6-methoxyquinolin-4-ol (75.3 g, 267 mmol) was added DCM (1 L), 4-dimethylaminopyridine (3.28 g, 26.8 mmol) and 2,6-lutidine (62 mL,

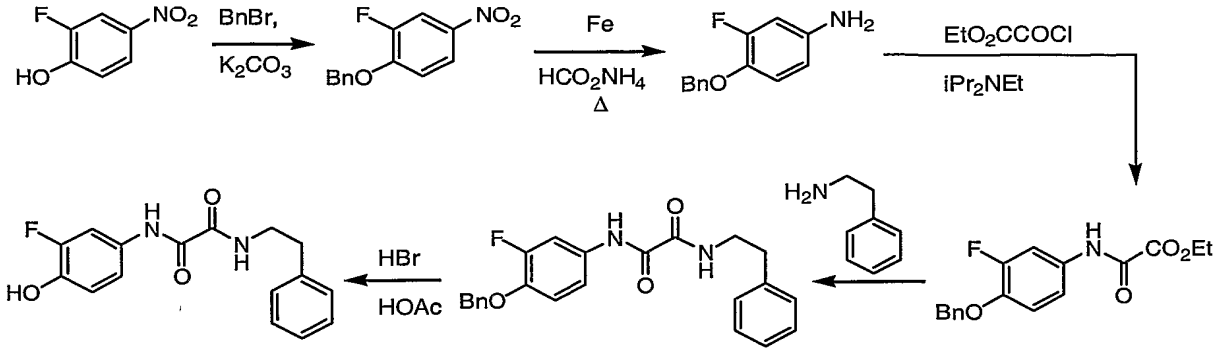
534 mmol). The mixture was cooled to –20°C by controlled addition of dry ice to an acetone bath. Trifluoromethanesulfonyl chloride (37 mL, 350 mmol) was added dropwise to the cooled solution with magnetic stirring over 25 minutes. After addition was complete, the mixture was stirred in bath for 20 minutes, then at room temperature for 3 hours. LCMS indicated reaction completion. The reaction mixture was concentrated *in vacuo* and placed under high vacuum to remove residual 2,6-lutidine. To the resulting brown solids was added methanol (3.5 L). The resulting slurry was stirred with mechanical stirrer for 30 min before adding water (1.5 L). The solids were isolated by filtration, followed by a water wash. The resulting solid was dried under high vacuum overnight yielding trifluoromethanesulfonic acid 7-benzyloxy-6-methoxy-quinolin-4-yl ester as a light brown solid (92.2 g, 83.8%). ^{1}H NMR (400MHz, DMSO, d_6): δ 8.82 (d, 1H), 7.67 (s, 1H), 7.59 (d, 1H), 7.54-7.52 (m, 2H), 7.46-7.42 (m, 2H), 7.39-7.36 (m, 1H), 7.23 (s, 1H), 5.35 (s, 2H), 3.97 (s, 3H). LC/MS: M+H = 414.

Example 34



[0331] Trifluoromethanesulfonic acid 6,7-dimethoxyquinolin-4-yl ester from 6,7-Dimethoxy-quinolin-4-ol. To a dry 1L RBF containing 6,7-dimethoxy-quinolin-4-ol (20.9 g, 102 mmol), which can be prepared according to the procedure of Riegel, B. *(J. Amer. Chem. Soc.* 1946, *68*, 1264), was added DCM (500 mL), 4-dimethylaminopyridine (1.24 g, 10 mmol) and 2,6-lutidine (24 mL, 204 mmol). The mixture was vigorously stirred at RT. Trifluoromethanesulfonyl chloride (14 mL, 132 mmol) was added dropwise to the solution. After addition was complete, the mixture was stirred ice bath for 2 to 3 hrs. On LC/MS indicating the reaction completion, the reaction mixture was concentrated *in vacuo* and placed under high vacuum to remove residual 2,6-lutidine. To the resulting brown solids was added methanol (250 mL). The resulting slurry was stirred for 30 min before adding water (1 L). The solids were isolated by filtration, followed by a water wash. The resulting solid was dried under high vacuum overnight yielding trifluoromethanesulfonic acid 6, 7-dimethoxy-quinolin-4-yl ester as a light brown solid (27 g, 80%). ^{1}H NMR (400MHz, DMSO, d_6): δ 8.82 (d, 1H), 7.59 (m, 2H), 7.20 (s, 1H), 3.97 (d, 6H). LC/MS: M+H = 338.

Example 35



[0332] 1-Benzyloxy-2-fluoro-4-nitrobenzene. A solution of 2-fluoro-4-nitrophenol (50.0 g, 318 mmol), benzyl bromide (42 mL, 350 mmol) and potassium carbonate (66.0 g, 478 mmol) in DMF (200 mL) was heated to 40 °C overnight. The solution was cooled to room temperature, poured over ice and the resultant solid was filtered. This material was washed with water and dried to give 1-benzyloxy-2-fluoro-4-nitrobenzene (75.0 g, 95 %). ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.19-8.11 (m, 2H), 7.53-7.37 (m, 6H), 5.36 (s, 2H); ^{13}C NMR (100 MHz, d_6-DMSO): δ 152.8, 152.4, 149.9, 140.9, 136.1, 129.3, 129.1, 128.7, 122.0, 115.2, 112.8, 112.6, 71.6; IR (cm^{-1}): 1499, 1346, 1279, 1211, 1142, 1072, 986, 885, 812, 789, 754, 742, 700, 648, 577.

[0333] 4-Benzyloxy-3-fluoroaniline. A mixture of iron powder (45.2 g, 0.809 g atoms), ammonium formate (53.6 g, 0.850 mol), 1-benzyloxy-2-fluoro-4-nitrobenzene (50.0 g, 0.200 mol), toluene (400 mL) and water (400 mL) was heated to reflux overnight. The mixture was filtered through Celite and washed with hot ethyl acetate. The combined organic layers were washed with water and brine, then dried over sodium sulfate and concentrated to afford 4-benzyloxy-3-fluoroaniline (44 g, 100 %). ^{1}H NMR (400 MHz, d_6-DMSO): δ 7.43-7.26 (m, 5H), 6.90 (dd, 1H), 6.49 (dd, 1H), 6.34 (m, 1H), 4.99 (br s, 2H), 4.98 (s, 2H); ^{13}C NMR (100 MHz, d_6-DMSO): δ 171.1, 155.1, 152.7, 144.9, 138.0, 137.2, 129.6, 129.0, 128.5, 118.9, 110.0, 102.9, 72.5; IR (cm^{-1}): 1510, 1454, 1277, 1215, 1126, 1007, 957, 843, 800, 789, 739, 694, 604; LC/MS (M+H = 218).

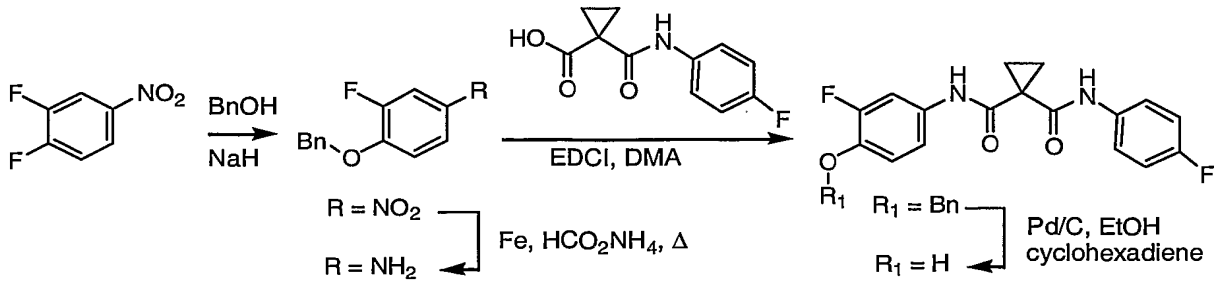
[0334] Ethyl [(4-benzyloxy-3-fluorophenyl)amino](oxo)acetate. Ethyl oxalyl chloride (44 mL, 390 mmol) was added to a solution of 4-benzyloxy-3-fluoroaniline (44 g, 180 mmol) in diisopropylethylamine (69 mL, 400 mmol) and stirred at room temperature for 15 min. The mixture was extracted with dichloromethane and washed with water and brine. The organic layer was dried over sodium sulfate and concentrated to afford ethyl [(4-

benzyloxy-3-fluorophenyl)amino](oxo)acetate (58.4 g, 100 %). ^{1}H NMR (400 MHz, d_6-DMSO): δ 10.87 (s, 1H), 7.73 (d, 1H), 7.69 (d, 1H), 7.53 (d, 1H), 7.46-7.40 (m, 4H), 5.17 (s, 2H), 4.31 (q, 2H), 1.31(t, 3H); IR (cm^{-1}): 1732, 1705, 1558, 1541, 1508, 1456, 1273, 1186, 1167, 1101, 999, 858, 741, 694; LC/MS (M+H = 318).

[0335] *N*-(4-Benzyloxy-3-flourophenyl)-*N'*-(2-phenylethyl)ethanediamide. Phenethylamine (33 mL, 520 mmol) was added to ethyl [(4-benzyloxy-3-fluorophenyl)amino](oxo)acetate (81 g, 260 mmol) and the mixture was sonicated at room temperature for 30 min. The resulting solid was filtered, washed with water and dried to give *N*-(4-benzyloxy-3-flourophenyl)-*N'*-(2-phenylethyl)ethanediamide (100 g, 99 %). ^{1}H NMR (400 MHz, d_6-DMSO): δ 10.72 (br s, 1H), 9.05 (m, 1H), 8.78 (m, 1H), 7.77 (m, 1H), 7.59 (m, 1H), 7.46-7.19 (m, 8H), 5.16 (m, 2H), 3.45 (m, 2H), 2.83 (m, 2H); IR (cm^{-1}): 2980, 2883, 1653, 1522, 1506, 1441, 1385, 1221, 1122, 951, 808, 746, 696, 584; LC/MS (M+H = 393).

[0336] *N*-(3-Fluoro-4-hydroxyphenyl)-*N'*-(2-phenylethyl)ethanediamide. A mixture of *N*-(4-benzyloxy-3-flourophenyl)-*N'*-(2-phenylethyl)ethanediamide (40 g, 100 mmol) and 38% hydrobromic acid in acetic acid (250 mL) was stirred at room temperature overnight. The resulting solid was filtered, washed with water and dried to give *N*-(3-fluoro-4-hydroxyphenyl)-*N'*-(2-phenylethyl)ethanediamide as a slightly yellow solid (30.6 g, 99 %yield). ^{1}H NMR (400 MHz, d_6-DMSO): δ 10.60 (s, 1H), 9.02 (t, 1H), 7.70 (d, 1H), 7.47 (d, 1H), 7.32-7.20 (m, 3H), 6.91 (t, 1H), 3.43 (m, 2H), 2.81 (m, 2H); ^{13}C NMR (100 MHz, d_6-DMSO): δ 160.5, 158.8, 152.0, 149.6, 142.2, 139.8, 130.3, 129.3, 129.0, 126.8, 118.1, 117.4, 109.6, 109.3 IR (cm^{-1}): 3279, 1653, 1518, 1456, 1279, 1190, 742, 696, 584; LC/MS (M+H = 303).

Example 36



[0337] 1-Benzyloxy-2-fluoro-4-nitro-benzene. To a slurry of sodium hydride (60% dispersion is oil, 693 mmol, 27.7 g) and dimethylacetamide (600 ml) was added benzyl alcohol (462 mmol, 48 ml) dropwise with stirring under N_2. The mixture was stirred for 1 hour at RT and then cooled to 0°C. 3,4-difluoronitrobenzene (508 mmol, 56.2 ml) was added to the cooled solution and stirred for 1 hour. Reaction mixture poured onto saturated ammonium chloride solution (800 ml) and stirred for 30 minutes, filtered and washed with water. The solid was stirred in ethyl acetate (500 mL), and filtered to give 54g of product. The ethyl acetate filtrate, after concentrated in vacuo, was triturated with diethyl ether (500 mL), sonicated for 2 hours, and filtered to give another 30g of product. The ether layer was concentrated and column purified using 5% EtOAc/hexanes as eluent to gave additional 15g of product. The total yield of 1-benzyloxy-2-fluoro-4-nitro-benzene was 95g (83%). (Note: the product contains ca. 5% of 3,4-Bis-benzyloxy-nitrobenzene, which is carried into the next step without further purification.) ^{1}H NMR (400MHz, $CDCl_3$): δ 8.04 –8.00 (m, 2H), 7.43-7.37 (m, 5H), 7.08 (t, 1H), 5.26 (s, 2H).

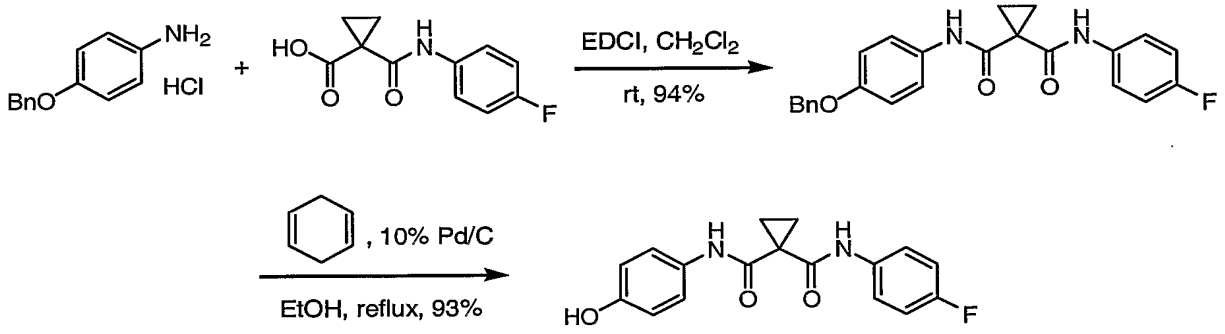
[0338] 4-Benzyloxy-3-fluoro-phenylamine. A mixture of 1-benzyloxy-2-fluoro-4-nitro-benzene (44g, 178 mmol), toluene (400 ml), ammonium formate (35 g), iron (30 g), and water (400 ml) was heated to reflux with stirring overnight. The reaction mixture was filtered through celite and washed with ethyl acetate (400ml). The organic layer was separated and washed with brine (300 ml), dried over sodium sulfate and concentrated to give 4-benzyloxy-3-fluoro-phenylamine as an oil (33.7 g, 87%). ^{1}H NMR (400MHz, $CDCl_3$): δ 7.41-7.29 (m, 5H), 6.79 (t, 1H), 6.45 (dd, 1H), 6.14 (dd, 1H), 5.02 (s, 2H), 3.50 (s, 2H). LC/MS: (M+1) 218.

[0339] Cyclopropane-1,1-dicarboxylic acid (4-benzyloxy-3-fluoro-phenyl)-amide (4-fluoro-phenyl)-amide. To a stirred mixture of 4-benzyloxy-3-fluoro-phenylamine (155.3 mmol, 33.7 g), 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (170.8 mmol, 38.13 g) and anhydrous dichloromethane (600 ml) was added EDCI (233.9 mmol, 44.7 g) in portions. After stirring at RT for 1 hr, the reaction mixture was diluted with saturated sodium bicarbonate (400 ml) and stirred for 30 minutes. The precipitate was filtered and air dried to give the 1st crop of product. The biphasic filtrate was separated, and the organic phase was washed with brine (300 ml), dried over sodium sulfate, and concentrated. The residue was taken up in DCM (100 ml), stirred for 15 minutes, and filtered to give a 2nd crop of product. The combined yield of cyclopropane-1,1-dicarboxylic acid (4-benzyloxy-3-fluoro-phenyl)-amide (4-fluoro-phenyl)-amide was 64.5

g (98%). ^{1}H NMR (400MHz, $CDCl_3$): δ 8.92 (br s, 1H), 8.88 (br s, 1H), 7.50-7.32 (m, 8H), 7.06-7.02 (m, 3H), 6.97-6.92 (t, 1H), 5.13 (s, 2H), 1.65 (s, 4H). LC/MS: (M+1) 423.

[0340] Cyclopropane-1,1-dicarboxylic acid (3-fluoro-4-hydroxy-phenyl)-amide (4-fluoro-phenyl)-amide. A mixture of cyclopropane-1,1-dicarboxylic acid (4-benzyloxy-3-fluoro-phenyl)-amide (4-fluoro-phenyl)-amide (152.8 mmol, 64.5), ethanol (800 ml), cyclohexadiene (764 mmol, 71 ml), and 10% Pd/C (2 g) was refluxed for 2 hours. Reaction mixture cooled and filtered through celite and washed with methanol. The combined filtrate was concentrated and stirred in 10% EtOAc/ether (350 ml). The resulting precipitate was filtered and washed with ether to give a 1st crop of product. The filtrate was concentrated and stirred in DCM (150 ml) to give another precipitate, which was then filtered to give a 2nd crop of product. The combined yield of cyclopropane-1,1-dicarboxylic acid (3-fluoro-4-hydroxy-phenyl)-amide (4-fluoro-phenyl)-amide was 43 g (85%) in 95% purity by HPLC (UV @ 254 nm). ^{1}H NMR (400MHz, DMSO-D6): δ 10.07 (br s, 1H), 9.92 (br s, 1H), 9.64 (br s, 1H), 7.64-7.60 (m, 2H), 7.55-7.51 (m, 1H), 7.17-7.12 (m, 3H), 6.89-6.84 (t, 1H), 1.43 (s, 4H). LC/MS: (M+1) 333.

Example 37

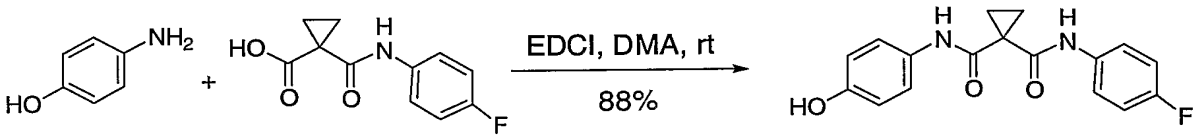


[0341] Cyclopropane-1,1-dicarboxylic acid (4-benzyloxy-phenyl)-amide (4-fluoro-phenyl)-amide. To a 0 °C suspension of 4-benzyloxyaniline hydrochloride (47.0 g, 200 mmol) and 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (49.1 g, 220 mmol) in CH_2Cl_2 (400 mL) was added EDCI (38.2 g, 200 mmol). Stirring was continued at rt for 2-4 h until the reaction was complete. CH_2Cl_2 was removed under reduced pressure. H_2O (300 mL) and MeOH (200 mL) were added, and the resulting mixture was stirred at rt for 30 min. After filtration and wash with H_2O, the solid was transferred to another flask containing 300 mL of sat. aqueous $NaHCO_3$ solution. The mixture was stirred for another 30 min. The solid was filtered, washed with water, and dried over night

on a lyophilizer, affording cyclopropane-1,1-dicarboxylic acid (4-benzyloxy-phenyl)-amide (4-fluoro-phenyl)-amide (75.8g, 95% yield) as an off-white solid.

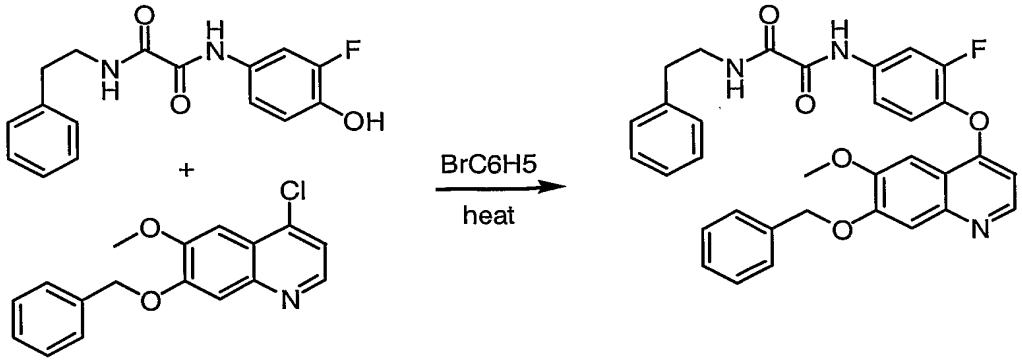
[0342] Cyclopropane-1,1-dicarboxylic acid (4-fluoro-phenyl)-amide (4-hydroxy-phenyl)-amide. To a refluxing mixture of cyclopropane-1,1-dicarboxylic acid (4-benzyloxy-phenyl)-amide (4-fluoro-phenyl)-amide (46 g, 113 mmol), 10% Pd/C (2 g) in EtOH (400 mL) was added dropwise 1,4-cyclohexadiene (62.7 mL, 678 mmol). Stirring was continued for 2-5 h until the reaction was complete. The mixture was cooled to rt, filtered through celite, and washed with EtOH. The solution was then concentrated under reduced pressure. To the flask containing the crude product was added $CHCl_3$ (200 mL). The resulting suspension was stirred for 15 min at rt. The solid was filtered, and dried in the air to give cyclopropane-1,1-dicarboxylic acid (4-fluoro-phenyl)-amide (4-hydroxy-phenyl)-amide (34.4 g, 95%, yield).

Example 38



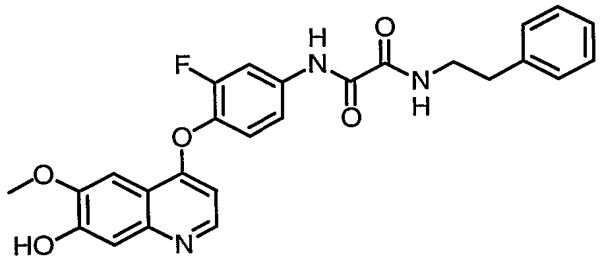
[0343] Alternate Synthesis of Cyclopropane-1,1-dicarboxylic acid (4-fluoro-phenyl)-amide (4-hydroxy-phenyl)-amide. To a solution of 4-aminophenol (2.93 g, 26.9 mmol) and 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (5.00 g, 22.4 mmol) in DMA (30 mL) was added EDCI (5.15 g, 26.9 mmol). The mixture was stirred vigorously until the reaction was complete (~ 3 h). With vigorous stirring, the reaction mixture was then poured into a flask containing sat. aqueous $NaHCO_3$ solution (200 mL). The stirring was continued for 1 h. The resulting suspension was then filtered. The solid was washed with water (50 mL), chloroform (50 mL) and dried under vacuum, affording 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (6.22g, 88% yield) as a powder (>95% purity by HPLC and ^1H NMR).

Example 39



[0344] *N*-{4-[(7-Benzyloxy-6-methoxyquinolin-4-yl)oxyl-3-fluorophenyl}-*N'*-(2-phenylethyl)ethanediamide. A mixture of 7-benzyloxy-4-chloro-6-methoxyquinoline (30 g, 100 mmol), *N*-(3-fluoro-4-hydroxyphenyl)-*N'*-(2-phenylethyl)ethanediamide (32 g, 106 mmol), DMAP (125 g, 1.02 mol) and bromobenzene (500 mL) was heated to reflux for 6 h. The mixture was cooled to room temperature and the bromobenzene was removed under reduced pressure. Methanol (500 mL) was added to the residue and the mixture was stirred at room temperature for 2 h. The resulting solid was filtered, washed with methanol and dried to give *N*-{4-[(7-benzyloxy-6-methoxyquinolin-4-yl)oxy]-3-fluorophenyl}-*N'*-(2-phenylethyl) ethanediamide (34 g, 61 %). ^{1}H NMR (400 MHz, d_6-DMSO): δ 11.05 (s, 1H), 9.15 (s, 1H), 8.47 (d, 1H), 8.05 (d, 1H), 7.84 (d, 1H), 7.56-6.36 (m, 13H), 6.46 (d, 1H), 5.32 (s, 2H), 3.97 (s, 3H), 3.47 (q, 2H), 2.86 (t, 2H); ^{13}C NMR (100 MHz, d_6-DMSO): δ 160.5, 160.2, 159.9, 159.5, 155.2, 152.7, 152.2, 150.3, 149.6, 146.9, 139.7, 137.4, 137.3, 137.2, 137.1, 129.3, 129.2, 129.1, 129.0, 128.9, 128.7, 128.6, 126.9, 124.8, 117.9, 115.3, 109.9, 102.8, 99.8, 70.6, 56.5, 41.3, 35.2; IR (cm^{-1}): 1657, 1510, 1481, 1433, 1416, 1352, 1310, 1252, 1215, 1609, 986, 891, 868, 850, 742, 696; LC/MS (M+H = 566).

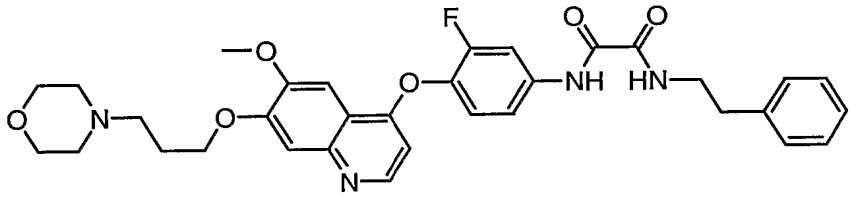
Example 40



[0345] *N*-{3-Fluoro-4-[(7-hydroxy-6-methoxyquinolin-4-yl)oxy]phenyl}-*N'*-(2-phenylethyl)ethanediamide. To a solution of *N*-{4-[(7-benzyloxy-6-methoxyquinolin-4-

yl)oxy]-3-fluorophenyl}-*N'*-(2-phenylethyl)ethanediamide (32 g, 56 mmol) in methanol (200 mL), DMF (100 mL), dichloromethane (100 mL), ethyl acetate (100 mL) and acetic acid (5 mL) was added palladium hydroxide (4.2 g) and the mixture was shaken on a Parr hydrogenator under a hydrogen pressure of 45 psi for 4 h. The resulting suspension was filtered through celite and the solid residue was washed with boiling dichloromethane (2 L) and acetone (2 L). The combined filtrates were evaporated to yield *N*-{3-fluoro-4-[(7-hydroxy-6-methoxyquinolin-4-yl)oxy]phenyl}-*N'*-(2-phenylethyl)ethanediamide as an off-white solid (25.6 g, 95 %). ^{1}H NMR (400 MHz, d_6-DMSO): δ 11.06 (s, 1H), 10.25 (br s, 1H), 9.12 (t, 1H), 8.40 (d, 1H), 8.01 (dd, 1H), 7.50-7.44 (m, 2H), 7.31-7.23 (m, 6H), 6.39 (d, 1H), 3.95 (s, 3H), 2.85 (t, 2H), 2.50 (m, 2H); IR (cm-1): 1666, 1624, 1585, 1520, 1481, 1427, 1377, 1256, 1211, 1194, 1022, 880, 850, 839, 802, 750, 700; LC/MS (M+H = 476).

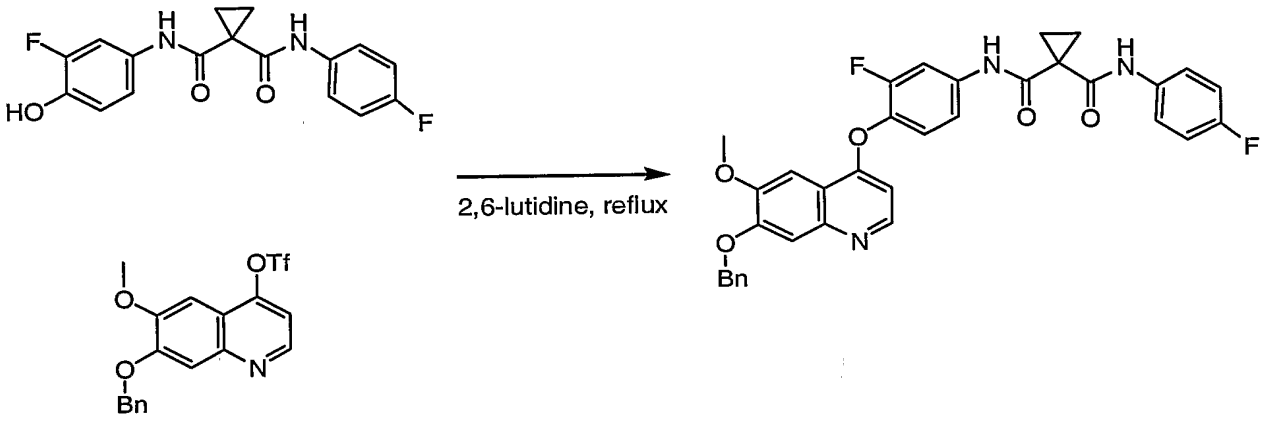
Example 41



[0346] *N*-(3-Fluoro-4-{[6-methoxy-7-(3-morpholin-4-ylpropoxy)quinolin-4-yl]oxy}phenyl)-*N'*-(2-phenylethyl)ethanediamide. A solution of *N*-{3-fluoro-4-[(7-hydroxy-6-methoxyquinolin-4-yl)oxy]phenyl}-*N'*-(2-phenylethyl)ethanediamide (25.6 g, 54 mmol), *N*-(3-chloropropyl)morpholine hydrochloride (11.7 g, 592 mmol) and potassium carbonate (16.6 g, 120 mmol) in DMF (300 mL) was heated to 80 °C overnight. Upon cooling, a majority of the DMF (250 mL) was removed on a rotary evaporator, 5% aqueous LiCl (300 mL) was added and the mixture was sonicated at room temperature. The solid was filtered, suspended in 1N HCl and washed with ethyl acetate (2 x 300 mL). The solution was adjusted to pH 14 using 2N sodium hydroxide and subsequently extracted with dichloromethane (3 x 200 mL). The organic layer was dried over sodium sulfate, filtered and evaporated to give *N*-(3-fluoro-4-{[6-methoxy-7-(3-morpholin-4-ylpropoxy)quinolin-4-yl]oxy}phenyl)-*N'*-(2-phenylethyl)ethanediamide as a yellow solid (24 g, 74 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.37 (s, 1H), 8.46 (d, 1H), 7.81 (dd, 1H), 7.57 (t, 1H), 7.53 (s, 1H), 7.42 (s, 2H), 7.34-7.20 (m, 6H), 6.39 (d, 1H), 4.27 (t, 2H), 4.03 (s, 3H), 3.71 (m, 4H), 3.65 (q, 2H), 2.91 (t, 2H), 2.56 (br s, 4H), 2.13 (m, 2H); ^{13}C NMR (100 MHz, d_6-DMSO): δ 160.1, 160.0, 159.5, 155.2, 152.7, 152.6, 150.2, 149.5, 147.1,

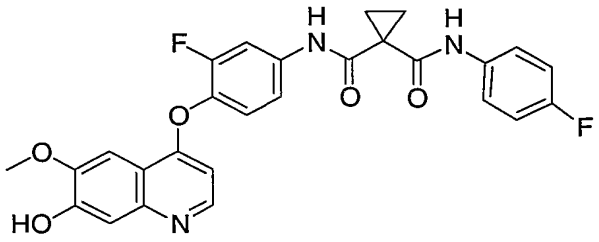
139.7, 137.3, 137.1, 129.3, 129.1, 126.9, 124.8, 117.9, 115.1, 109.2, 102.7, 99.6, 67.4, 66.9, 56.5, 55.5, 54.1, 41.3, 35.2, 26.4; IR (cm^{-1}): 1655, 1506, 1483, 1431, 1350, 1302, 1248, 1221, 1176, 1119, 864, 843, 804, 741, 700; LC/MS (M+H = 603).

Example 42



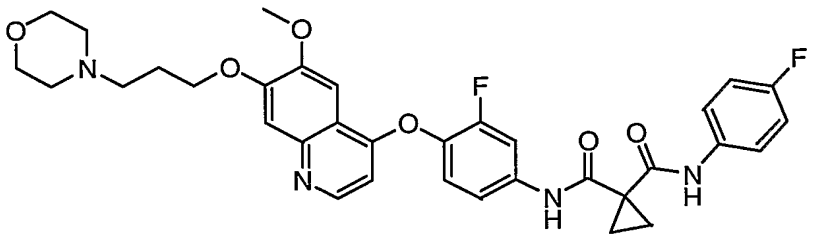
[0347] Cyclopropane-1,1-dicarboxylic acid [4-(7-benzyloxy-6-methoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-amide (4-fluoro-phenyl)-amide. To a flask containing cyclopropane-1,1-dicarboxylic acid (3-fluoro-4-hydroxy-phenyl)-amide (4-fluoro-phenyl)-amide (2.25 g, 6.7 mmol) and trifluoromethanesulfonic acid 7-benzyloxy-6-methoxy-quinolin-4-yl ester (1.87 g, 4.5 mmol) was added dry 2,6-lutidine (9 mL). The reaction mixture was heated to reflux (143°C) with vigorous stirring. The reaction progress was monitored by LC-MS. 2,6-Lutidine was removed under reduced pressure when the reaction was complete (about 6 h). The residue was treated with charcoal (1.5 g) in refluxing EtOAc (50 mL) for 15 min, and filtered through celite. The volume of the filtrate was reduced to about 20 mL and was added 20 mL of 1 N HCl. The crude product precipitated as the HCl salt, which was filtered and washed with EtOAc and H_2O (88% purity by analytical HPLC). The HCl salt was free-based with saturated aqueous $NaHCO_3$ solution. Further purification by column chromatography (hexans:EtOAc = 1:4) gave cyclopropane-1,1-dicarboxylic acid [4-(7-benzyloxy-6-methoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-amide (4-fluoro-phenyl)-amide as an off-white solid (1.3 g, 48% yield. ^1H NMR (400 MHz, DMSO, d_6): 10.41 (s, 1H), 10.02 (s, 1H), 8.48 (d, 1H), 7.92 (dd, 1H), 7.65 (m, 2H), 7.54 (m, 5H), 7.41 (m, 4H), 7.17 (m, 2H), 6.43 (d, 1H), 5.32 (s, 2H), 3.97 (s, 3H), 1.48 (m, 4H). LC/MS Calcd for $[M+H]^+$ 596.2, found 596.3.

Example 43



[0348] Cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide. To a solution of the cyclopropane-1,1-dicarboxylic acid [4-(7-benzyloxy-6-methoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-amide (4-fluoro-phenyl)-amide (22.4 g, 37.6 mmol) in EtOH (340 mL) was added 1,4-cyclohexadiene (35 mL, 376 mmol) and 10% Pd/C (2.08 g). The reaction mixture was then heated at 65°C with stirring for 3 h (Caution: H_2 gas is released from the reaction). It was then allowed to cool to room temperature, and filtered through celite follwed by a MeOH wash. The solution was then concentrated under reduced pressure. The yellow residue was taken into EtOAc (1 L). The EtOAc solution was washed with water (1X), brine (2X), dried over $MgSO_4$ and concentrated *in vacuo*. Cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide was obtained as a yellow solid (17.3 g, 91.1% yield), which were carried on to the next reaction without further purification. ^{1}H NMR (400 MHz, DMSO, d6): 10.39 (s, 1H), 10.15 (s, 1H), 10.00 (s, 1H), 8.38 (d, 1H), 7.88 (dd, 1H), 7.63 (m, 2H), 7.50 (m, 2H), 7.40 (t, 1H), 7.27 (s, 1H), 7.14 (m, 2H), 6.33 (d, 1H), 3.95 (s, 3H), 1.47 (m, 4H). LC/MS Calcd for $[M+H]^+$ 506.2, found 506.3. Anal. HPLC: 99.4% pure.

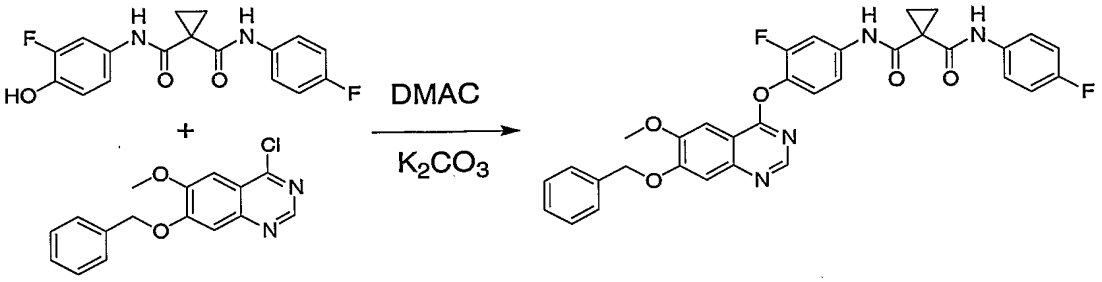
Example 44



[0349] *N*-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. To a mechanically stirred slurry of cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (16.6 g, 32.8 mmol) and

potassium carbonate (13.6 g, 98.6 mmol) in DMF (250 mL) was added 4-(3-chloropropyl)-morpholine hydrochloride (13, 7.92 g, 39.6 mmol). The resulting mixture was heated at 90°C for 5 hours (until phenol completely consumed). The reaction mixture was allowed to cool to room temperature, then dumped into water (900 mL), followed by extraction with EtOAc (3X). The combined extracts were washed with 5% LiCl (aq.) (3X) and brine (1X) followed by drying over MgSO4 and concentration in vacuo. The crude (18.8g) obtained as brown solid was further purified by flash chromatography [silica gel, 4-stage gradient system: 1) EtOAc; 2) EtOAc:MeOH:7N NH_3/MeOH (95:5:0.5); 3) DCM:MeOH:7N NH3/MeOH (95:5:0.5); 4) DCM:MeOH: 7N NH_3/MeOH (93:8:1)], affording N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide was obtained as an off white solid (15.0 g, 72% yield). 1H NMR (400 MHz, DMSO-d6): 10.41 (s, 1H), 10.02 (s, 1H), 8.47 (d, 1H), 7.91 (dd, 1H), 7.65 (m, 2H), 7.53 (m, 2H), 7.42 (t, 1H), 7.40 (s, 1H), 7.16 (m, 2H), 6.42 (d, 1H), 4.20 (t, 2H), 3.96 (s, 3H), 3.59 (t, 4H), 2.47 (t, 2H), 2.39 (br, s, 4H), 1.98 (m, 2H), 1.48 (m, 4H). LC/MS Calcd for [M+H]+ 633.3, found 633.0.

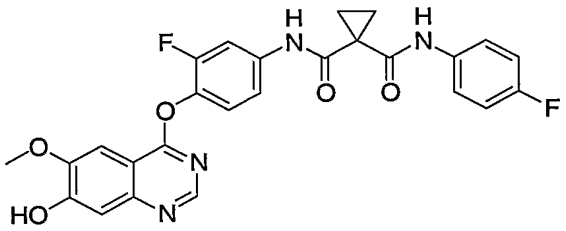
Example 45



[0350] Cyclopropane-1,1-dicarboxylic acid [4-(7-benzyloxy-6-methoxy-quinazolin-4-yloxy)-3-fluoro-phenyl]-amide (4-fluoro-phenyl)-amide: A mixture of 7-benzyloxy-4-chloro-6-methoxy-quinazoline (5 g, 16.67 mmol), cyclopropane-1,1-dicarboxylic acid (3-fluoro-4-hydroxy-phenyl)-amide (4-fluoro-phenyl)-amide (8.3 g, 25 mmol), potassium carbonate (125 mmol, 17.25 g), and dimethylacetamide (125 ml) was heated 50° C with stirring for 16h. Reaction mixture was poured onto ice/water (600 ml) and stirred for 30 minutes, and filtered. The solid was dissolved in ethyl acetate and washed with water (1x), brine, and concentrated. The crude was purified on silica get column eluting with 30% acetone in hexanes to yield cyclopropane-1,1-dicarboxylic acid [4-(7-benzyloxy-6-

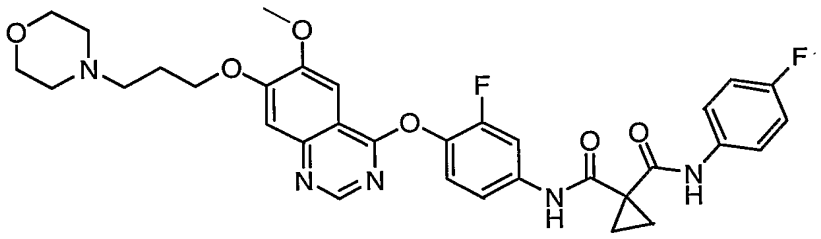
methoxy-quinazolin-4-yloxy)-3-fluoro-phenyl]-amide (4-fluoro-phenyl)-amide (7.5 g, 76%). ^{1}H NMR ($CDCl_3$): 8.64 (1H, br. s), 8.55 (1H, s), 8.33 (1H, br. s), 7.74-7.71 (1H, dd), 7.54 (1H, s), 7.48-7.33 (8H, m), 7.31-7.24 (2H, m), 7.06-7.02 (2H, m), 5.32 (2H, s), 4.06 (3H, s), 1.77-1.74 (2H, m), 1.63-1.61 (2H, m).

Example 46



[0351] Cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinazolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide. To a mixture of cyclopropane-1,1-dicarboxylic acid [4-(7-benzyloxy-6-methoxy-quinazolin-4-yloxy)-3-fluoro-phenyl]-amide (4-fluoro-phenyl)-amide (7.5 g, 12.6 mmol), acetic acid (few drops), dichloromethane (50 ml) and methanol (100 ml) was added 10% Pd/C (700 mg). The mixture was agitated in hydrogen gas (40 psi) until the reaction was complete (ca. 4 hr). The solution was filtered through celite and concentrated to give a crude product as a solid. The crude product was triturated with ether, and filtered. The filter cake was dried *in vacuo* to yield cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinazolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (6.1 g, 95% yield). ^{1}H NMR (dmso-d6): 10.86 (1H, br. s), 10.34 (1H, br. s), 10.04 (1H, br. s), 8.46 (1H, s), 7.84-7.80 (1H, dd), 7.66-7.62 (2H, m), 7.55 (1H, s), 7.47-7.45 (1H, m), 7.41-7.37 (1H, m), 7.24 (1H, s), 7.18-7.13 (2H, t), 3.98 (3H, s), 1.46 (4H, s).

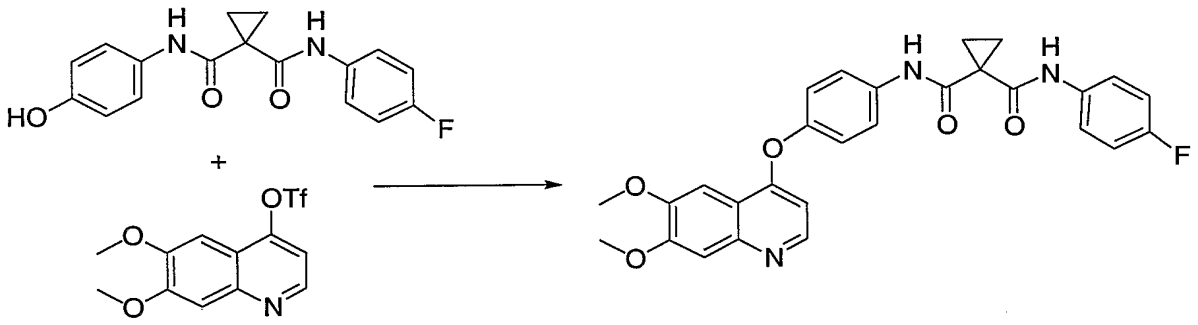
Example 47



[0352] N-[3-Fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. To a mixture of

cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinazolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (1.5 g, 2.96 mmol), 4-(3-hydroxypropyl)morpholine (0.623 mL, 4.5 mmol), triphenylphosphine (1.18 g, 4.5 mmol), and dichloromethane (50 mL) was added diisopropyl azodicarboxylate (0.886 mL, 4.5 mmol). The mixture was stirred at room temperature for 16 h, monitored by LCMS. After removal of solvent, the crude mixture was separated by flash column chromatography (silica), eluting with 5% methanol in dichloromethane to give N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarbox-amide (890 mg, 47% yield). 1HNMR (400MHz, DMSO-d6): d 10.36 (br s, 1H), 10.05 (br s, 1H), 8.55 (s, 1H), 7.83 (m, 1H), 7.64 (m, 2H), 7.57 (s, 1H), 7.44 (m, 3H), 7.18 (t, 2H), 4.27 (m, 2H), 3.99 (s, 3H), 3.61 (m, 6H), 2.40 (m, 4H), 2.01 (m, 2H), 1.47 (m, 4H). LC/MS Calcd for $[M+H]^+$ 634.2, found 634.3.

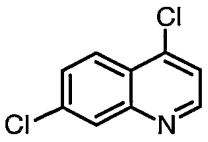
Example 48



[0353] N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. To a solution of cyclopropane-1,1-dicarboxylic acid (4-fluoro-phenyl)-amide (4-hydroxy-phenyl)-amide (6.98 g, 22.2 mmol) in anhydrous 2,6-lutidine (50 mL) was added trifluoromethanesulfonic acid 6, 7-dimethoxy-quinolin-4-yl ester (5 g, 14.8 mmol). The reaction mixture was heated at 165°C in a sealed pressure tube with stirring for 18 h. The reaction mixture was concentrated on high vacuum to completely remove lutidine. The resulting solid material was dissolved in DCM (250 mL), and washed several times with 1 N sodium hydroxide to remove the excess phenol. The crude mixture was loaded on a silica gel flash column and eluted with 75% EtOAc-hexanes, affording N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (3.2 g, 44%). ^{1}H NMR (400 MHz, d_6-DMSO): δ 10.2 (s, 1H), 10.05 (s, 1H), 8.4 (s, 1H), 7.8 (m, 2H), 7.65 (m, 2H), 7.5 (s, 1H),

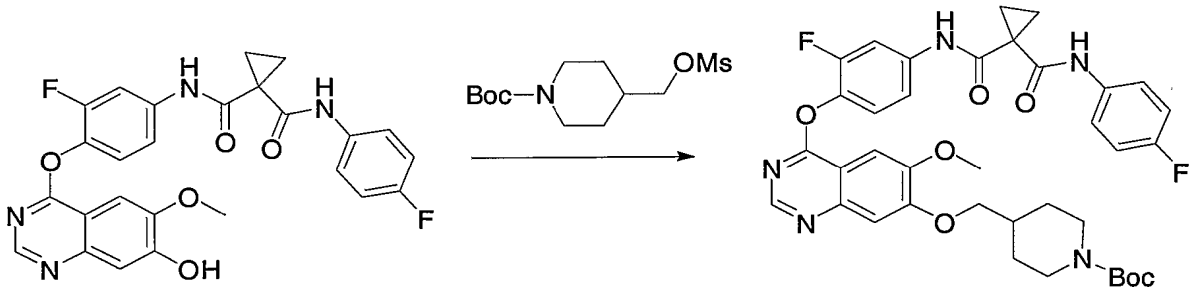
7.35 (s, 1H), 7.25 (m, 2H), 7.15(m, 2H), 6.4 (s, 1H), 4.0 (d, 6H), 1.5 (s, 4H). LC/MS: M+H= 502.

Example 49



[0354] 4,7-Dichloroquinoline. Phosphorus oxychloride (4mL, 429 mmol) was added to 7-chloro-4-hydroxyquinoline 2.86g, 15.9mmol) in a round bottom flask equipped with a reflux condenser. The mixture was heated to reflux for 2h, then allowed to cool to room temperature. The solution was concentrated *in vacuo* to a thick oil, then dumped over cracked ice. The resulting solution was neutralized with saturated $NaHCO_3$ (aq). The slurry was filtered and washed with water. The solids were dried under vacuum, afforded 4,7-dichloroquinoline as a white solid (2.79g, 88.5% yield).

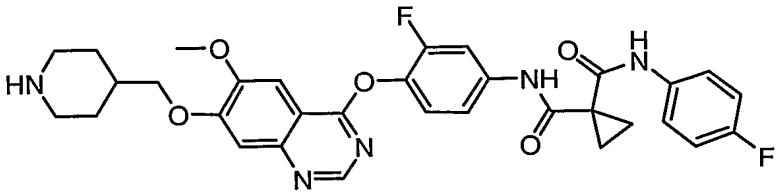
Example 50



[0355] 4-[4-(2-Fluoro-4-{[1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarbonyl]-amino}-phenoxy)-6-methoxy-quinazolin-7-yloxymethyl]-piperidine-1-carboxylic acid tert-butyl ester. Cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinazolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (325 mg, 0.64 mmol), 4-methanesulfonyloxymethyl-piperidine-1-carboxylic acid tert-butyl ester (193 mg, 0.66 mmol), K_2CO_3 (181 mg, 1.31 mmol) were combined in DMF (5 ml) and heated to 80°C overnight. The reaction was not complete and more 4-methanesulfonyloxymethyl-piperidine-1-carboxylic acid tert-butyl ester (90 mg, 0.31 mmol) and K_2CO_3 (90 mg, 0.65 mmol) were added and heating at 80°C continued for another night. The reaction mixture

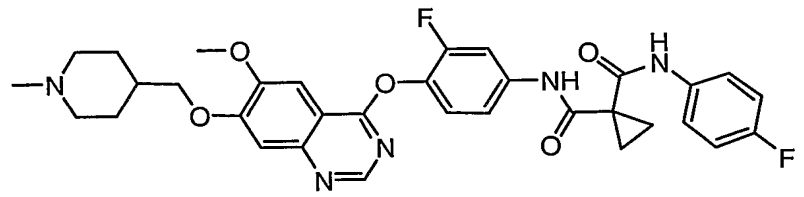
was allowed to cool to room temperature, then diluted with EtOAc and washed with H_2O (3x), sat'd NaCl (1x), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting crude material was purified by flash chromatography (1:1 hexanes:EtOAc, followed by 1:3 hexanes:EtOAc) to give 4-[4-(2-fluoro-4-{[1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarbonyl]-amino}-phenoxy)-6-methoxy-quinazolin-7-yloxymethyl]-piperidine-1-carboxylic acid tert-butyl ester (273 mg, 60%). LC/MS Calcd for $[M+H]^+$ 704.3, found 704.4.

Example 51



[0356] Cyclopropane-1,1-dicarboxylic acid {3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinazolin-4-yloxyl-phenyl}-amide (4-fluoro-phenyl)-amide, TFA salt. 4-[4-(2-Fluoro-4-{[1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarbonyl]-amino}-phenoxy)-6-methoxy-quinazolin-7-yloxymethyl]-piperidine-1-carboxylic acid tert-butyl ester (273 mg, 0.39 mmol) was dissolved in CH_2Cl_2 (8 ml) to which was added TFA (8 ml) and the mixture stirred at room temperature for 1hr. The reaction mixture was concentrated *in vacuo* and the resulting oil triturated with Et_2O. The resulting solids were filtered, washed with Et_2O and dried under high vacuum to give cyclopropane-1,1-dicarboxylic acid {3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-amide (4-fluoro-phenyl)-amide, TFA salt (222 mg, 80%). LC/MS Calcd for $[M+H]^+$ 604.2, found 604.3.

Example 52



[0357] N-{3-Fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

Cyclopropane-1,1-dicarboxylic acid {3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-amide (4-fluoro-phenyl)-amide, TFA salt (222 mg, 0.31 mmol), H_2O (3 ml), 37% formaldehyde in H_2O (0.18 ml) and acetic acid (27 drops) were combined in acetonitrile (9 ml) to which was slowly added triacetoxyborohydride (561 mg, 2.65 mmol). The mixture was stirred at room temperature for 1-2 hr, then diluted with 1N NaOH and H_2O and extracted with CH_2Cl_2 (3x). The combined CH_2Cl_2 extractions were washed with sat'd NaCl (1x), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was dissolved in a minimum of 1:1 dioxane:EtOAc to which was added 4M HCl in dioxane (1-2 ml). The resulting solids were filtered, washed with EtOAc and dried under high vacuum to give N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy] phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, HCl salt (167 mg, 83%). 1HNMR (400MHz, DMSO-d_6): δ 10.40 (s, 1H), 10.17 (br s, 1H) 10.07 (s, 1H), 8.61 (s, 1H), 7.85 (m, 1H), 7.65 (m, 2H), 7.48 (m, 2H), 7.42 (t, 1H), 7.16 (t, 2H), 4.12 (2, 2H), 4.00 (s, 3H), 3.46 (m, 2H), 2.99 (m, 2H), 2.73 (d, 3H), 2.13 (m, 1H), 2.01 (m, 2H), 1.63 (m, 2H), 1.47 (m, 4H). LC/MS Calcd for $[M+H]^+$ 618.2, found 618.3.

Synthesis of Bridged Bicyclics

[0358] The following describes synthesis of bridged bicyclics with appended leaving groups for use as, for example, alkylating agents. In the context of this invention, these alkylating agents are used, for example, to alkylate the quinazoline or quinolines on the 6- or 7-oxygens to make compounds of the invention. The invention is not limited to alkylation chemistry to append such bridged bicyclics, but rather the aforementioned description is meant only to be illustrative of an aspect of the invention.

Example 53

[0359] 1,4:3,6-dianhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-D-glucitol: To a solution of 1,4:3,6-dianhydro-2-*O*-methyl-D-glucitol (1.19g, 7.4 mmol) in dichloromethane was added pyridine (1mL, 12.36 mmol) followed by methanesulfonyl chloride (0.69mL, 8.92 mmol) and the mixture was allowed to stir at room temperature over 12 hours. The solvent was removed and the amorphous residue was partitioned with ethyl acetate and 0.1M aqueous hydrochloric acid. The aqueous phase was extracted once with additional

ethyl acetate and the combined organic layers were washed with saturated aqueous sodium chloride then dried over anhydrous magnesium sulfate. Filtration and concentration followed by drying *in vacuo* afforded 1,4:3,6-dianhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-D-glucitol (1.67g, 94% yield) as a colorless oil. GC/MS calculated for $C_8H_{14}SO_6$: 238 (M^+).

Example 54

[0360] 1,4:3,6-dianhydro-5-*O*-(phenylcarbonyl)-D-fructose ethylene glycol acetal: A solution of 1,4:3,6-dianhydro-5-*O*-(phenylcarbonyl)-D-fructose (2.00g, 8.06 mmol), ethylene glycol (5.00g, 80.6 mmol), and *p*-toluenesulfonic acid (1.53g, 8.06 mmol) in benzene (100mL) was refluxed for 90 min using a Dean-Stark Trap apparatus. The reaction mixture was diluted with ethyl acetate (100mL), washed with saturated aqueous sodium bicarbonate (2 x 50mL) then brine (50mL), and dried over anhydrous sodium sulfate. Filtration, concentration and column chromatography on silica (1:1 hexane/ethyl acetate) provided 1.44g (61% yield) of 1,4:3,6-dianhydro-5-*O*-(phenylcarbonyl)-D-fructose ethylene glycol acetal as a colorless solid. ^{1}H NMR (400 MHz; $CDCl_3$): 8.08 (m, 2H), 7.58 (m, 1H), 7.54 (m, 2H), 5.38 (dd, 1H), 4.97 (t, 1H), 4.21-4.02 (m, 7H), 3.86 (d, 1H), 3.75 (d, 1H).

Example 55

[0361] 1,4:3,6-dianhydro-D-fructose ethylene glycol acetal: To a solution of 1,4:3,6-dianhydro-5-*O*-(phenylcarbonyl)-D-fructose ethylene glycol acetal (1.44g, 4.93 mmol) in methanol (40mL) was added 50% aqueous sodium hydroxide (0.38 g, 4.75 mmol) and the mixture was stirred at room temperature for 30 minutes. Neutralization with 1M HCl, followed by concentration and column chromatography on silica (1:2 hexane/ethyl acetate) provided 0.74g (80% yield) of 1,4:3,6-dianhydro-D-fructose ethylene glycol acetal as a colorless solid. ^{1}H NMR (400 MHz; $CDCl_3$): 4.60 (t, 1H), 4.32 (m, 1H), 4.14 (d, 1H), 4.05-3.98 (m, 5H), 3.82 (s, 2H), 3.62 (dd, 1H), 2.65 (d, 1H).

[0362] 1,4:3,6-dianhydro-5-*O*-(methylsulfonyl)-D-fructose ethylene glycol acetal: To a solution of 1,4:3,6-dianhydro-D-fructose ethylene glycol acetal (0.74g, 3.93 mmol) and triethylamine (1.20g, 11.86 mmol) in dichloromethane (40mL) was added

methanesulfonyl chloride (0.90g, 7.88 mmol) at 0°C under nitrogen. The solution was warmed to room temperature and stirred for 13 h. Dichloromethane (50mL) was added, and the organic layer was washed with saturated aqueous sodium bicarbonate (30mL), water (30mL), and brine (30mL) then dried over anhydrous sodium sulfate. Filtration and concentration provided 1.02g (97%) of 1,4:3,6-dianhydro-5-*O*-(methylsulfonyl)-D-fructose ethylene glycol acetal as a yellow oil. ^{1}H NMR (400 MHz; $CDCl_3$): 5.08 (m, 1H), 4.82 (t, 1H), 4.13 (dd, 1H), 4.04 (m, 4H), 3.93 (dd, 1H), 3.87 (d, 1H), 3.81 (d, 1H), 3.13 (s, 3H).

Example 56

[0363] 1,4:3,6-dianhydro-2-deoxy-2-methylidene-D-*arabino*-hexitol: To a solution of 1,4:3,6-dianhydro-2-deoxy-2-methylidene-5-*O*-(phenylcarbonyl)-D-*arabino*-hexitol (329mg, 1.34 mmol) in methanol (10mL) was added 50% aqueous sodium hydroxide (95mg, 1.19 mmol) and the mixture was stirred at room temperature for 30 minutes. Neutralization with 4M hydrogen chloride in 1,4-dioxane followed by concentration and column chromatography on silica (1:1 hexane/ethyl acetate) provided 141mg (74%) of 1,4:3,6-dianhydro-2-deoxy-2-methylidene-D-*arabino*-hexitol as a colorless solid. ^{1}H NMR (400 MHz; $CDCl_3$): 5.37 (m, 1H), 5.20 (m, 1H), 4.80 (m, 1H), 4.54 (m, 2H), 4.43 (m, 1H), 4.26 (m, 1H), 3.95 (dd, 1H), 3.54 (dd, 1H), 2.70 (d, 1H).

[0364] 1,4:3,6-dianhydro-2-deoxy-2-methylidene-5-*O*-(methylsulfonyl)-D-*arabino*-hexitol: To a solution of 1,4:3,6-dianhydro-2-deoxy-2-methylidene-D-*arabino*-hexitol (135mg, 0.95 mmol) and triethylamine (288mg, 2.85 mmol) in dichloromethane (10mL) was added methanesulfonyl chloride (222mg, 1.94 mmol) at 0°C under nitrogen. The solution was warmed to room temperature and stirred for 18 h. Dichloromethane (50mL) was added and the organic layer was washed with saturated aqueous sodium bicarbonate (2 x 25mL), water (25mL) and brine (25mL) then dried over anhydrous sodium sulfate. Filtration and concentration provided 213mg (72%) of 1,4:3,6-dianhydro-2-deoxy-2-methylidene-5-*O*-(methylsulfonyl)-D-*arabino*-hexitol as a yellow oil. ^{1}H NMR (400 MHz; $CDCl_3$): 5.40 (m, 1H), 5.23 (m, 1H), 5.04 (m, 1H), 4.85 (m, 1H), 4.73 (t, 1H), 4.58 (m, 1H), 4.41 (m, 1H), 4.08 (dd, 1H), 3.86 (dd, 1H), 3.14 (s, 3H).

Example 57

[0365] 1,4:3,6-dianhydro-2-deoxy-5-*O*-(phenylcarbonyl)-L-*arabino*-hex-1-enitol: To a mixture of 1,4:3,6-dianhydro-5-*O*-(phenylcarbonyl)-(D)-glycitol (4.32g, 17.3 mmol), triethylamine (4.91 mL, 35.3 mmol) and 4-dimethylaminopyridine (0.63g, 5.2 mmol) in dichloromethane (50 mL) at -10 ° to -15° was added trifluromethanesulfonic anhydride (3.48mL, 20.7 mmol) dropwise over ten minutes and the resulting mixture was stirred at this temperature for 3 hours. The mixture was poured into 100 mL of ice-water and extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered then concentrated. The crude triflate was suspended in toluene (50 mL) followed by addition of 1,8-diazabicyclo[4,5,0]undec-7-ene (5.25 mL, 34.6 mmol) and the mixture was stirred at room temperature for 18 hours. The reaction mixture was poured into ice-water and partitioned then the aqueous portion was extracted with dichloromethane (3 x 50 mL). The combined organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flashed chromatography (silica gel, 5-20% ethyl acetate-hexane) to give 1,4:3,6-dianhydro-2-deoxy-5-*O*-(phenylcarbonyl)-L-*arabino*-hex-1-enitol, as a white solid, 3.10g, 77% yield. ^{1}H NMR (400MHz; $CDCl_3$): 8.08-8.06 (m, 2H), 7.61-7.57 (m, 1H), 7.56-7.43 (m, 2H), 6.62-6.61 (d, 1H), 5.48-5.46 (m,1H), 5.32-5.26 (m,1H), 5.13-5.10 (m, 2H), 4.18-4.14 (tr,1H), 3.61-3.56 (tr, 1H).

Example 58

[0366] Methyl 3,6-anhydro-5-*O*-(phenylcarbonyl)-β-L-glucofuranoside: To a solution of 1,4:3,6-dianhydro-2-deoxy-5-*O*-(phenylcarbonyl)-L-arabino-hex-1-enitol (1.00g, 4.3 mmol) in methanol (17 mL) at -4°C was added 3-chloroperoxybenzoic acid (85%, 1.35g, 8.6 mmol), and the resulting mixture was slowly warmed to room temperature and stirred for 18 hours. The reaction mixture was concentrated, diluted with dichloromethane (50 mL), washed with saturated aqueous sodium bicarbonate solution, dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (silica gel, 25-60% ethyl acetate-hexane) to give methyl 3,6-anhydro-5-*O*-(phenylcarbonyl)-β-L-glucofuranoside as a white solid, 1.03g, 83% yield. ^{1}H NMR (400MHz; $CDCl_3$): 8.11-8.08 (d, 2H), 7.61-7.56 (tr, 1H), 7.48-7.44 (m, 2H), 5.24-5.17

(m, 2H), 4.96 (s, 1H), 4.57-4.56 (d, 1H), 4.27 (s, 1H), 4.22-4.18 (dd, 1H), 4.08-4.04 (dd, 1H) 3.36 (s, 3H).

[0367] Methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(phenylcarbonyl)-β-L-glucofuranoside: A mixture of methyl 3,6-anhydro-5-*O*-(phenylcarbonyl)-β-L-glucofuranoside (1.03g, 3.7 mmol), silver (I) oxide (0.85g, 3.7 mmol) and methyl iodide (0.34 mL, 5.5 mmol) in DMF (2 mL) was heated at 60°C for 1 hour. After cooling to room temperature the reaction mixture was diluted with ethyl acetate (50 mL), filtered over celite, adsorbed on silica gel (10g) and purified by flash chromatography (silica gel, 5-30% ethyl acetate-hexane) to give methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(phenylcarbonyl)-β-L-glucofuranoside as a colorless oil, 0.82g, 76% yield. ^{1}H NMR (400MHz; $CDCl_3$): 8.11-8.09 (d, 2H), 7.60-7.56 (m, 1H), 7.46-7.44 (m, 2H), 5.24-5.20 (m, 1H), 5.18-5.09 (tr, 1H), 4.99 (s, 1H), 4.61-4.60 (d, 1H), 4.21-4.17 (tr, 1H), 4.08-4.03 (tr, 1H), 3.81 (s, 1H), 3.40 (s, 3H), 3.57 (s, 3H).

[0368] Methyl 3,6-anhydro-2-*O*-methyl-α-D-idofuranoside: A solution of methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(phenylcarbonyl)-β-L-glucofuranoside (820mg, 3.1mmol) and 50% sodium hydroxide (248 mg, 3.1 mmol) in methanol (10mL) was stirred at room temperature for 30 minutes. The material was adsorbed on silica gel (5g) and passed through a short column (15% ethyl acetate in hexanes to 5% methanol in ethyl acetate) to give methyl 3,6-anhydro-2-*O*-methyl-α-D-idofuranoside as a colorless oil, 420 mg, 85% yield. ^{1}H NMR (400MHz; $CDCl_3$): 5.04 (s, 1H), 5.84-5.81 (tr, 1H), 4.44-4.42 (tr, 1H), 4.25-4.19 (m, 1H), 3.85-3.75 (m, 1H), 3.49 (s, 3H), 3.43 (s, 3H), 2.75-2.72 (d, 1H).

[0369] Methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-β-L-glucofuranoside: Methyl 3,6-anhydro-2-*O*-methyl-α-D-idofuranoside (420 mg, 2.6 mmol) was dissolved in dichloromethane (10 mL) and pyridine (0.36 mL, 3.7 mmol) at 0°C. Methanesulfonyl chloride (0.14 mL, 3.1 mmol) was added and the resulting mixture was stirred at 0°C for 1 hour then at room temperature for 2 hours. The reaction mixture was washed with water and saturated aqueous sodium bicarbonate solution, dried over anhydrous sodium sulfate, filtered and concentrated to give methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-β-L-glucofuranoside as a colorless oil, 669mg, 95% yield, which was used without further purification.

Example 59

[0370] 3,6-anhydro-5-*O*-(phenylcarbonyl)-α-L-glucofuranose: A mixture of osmium tetroxide (4% in water, 0.25 mL, 0.03 mmol) and N-methylmorpholine (505 mg, 4.3 mmol) in 3 mL of 50% acetone in water was warmed to 60°C. A solution of 1,4:3,6-dianhydro-2-deoxy-5-*O*-(phenylcarbonyl)-L-*arabino*-hex-1-enitol (2.00g, 8.6 mmol) in 6 mL of 50% acetone in water was added over 3 hours. During this time an additional amount of N-methylmorpholine (1.01g, 8.6 mmol) was added in small portions periodically. Upon completion of the addition process the reaction was stirred for another hour and cooled to room temperature. The crude mixture was applied to a column of silica gel and flashed (0-6% methanol in 1:1 ethyl acetate:hexane) to give 3,6-anhydro-5-*O*-(phenylcarbonyl)-α-L-glucofuranose as a white solid, 1.5g, 65% yield. ^{1}H NMR (400MHz; DMSO-d_6): 8.01-7.95, (m, 2H), 7.68-7.66 (m, 1H), 7.57-7.53 (m, 2H), 5.18-5.11 (m, 2H), 4.85-4.81 (m, 1H, m), 4.37-4.35 (m, 1H), 4.05-3.96 (m, 2H), 3.85-3.83 (m, 1H).

[0371] 3,6-anhydro-2-*O*-methyl-5-*O*-(phenylcarbonyl)-α-L-glucofuranoside: 3,6-Anhydro-5-*O*-(phenylcarbonyl)-α-L-glucofuranose (576 mg, 2.2 mmol) was added to a mixture of sodium hydride (60% oil dispersion, 346 mg, 8.7 mmol) and methyl iodide (0.54mL, 8.7 mmol) in 5 mL of DMF at 0°C and the resulting mixture was stirred for 1 hour. The reaction mixture was diluted with ethyl acetate and quenched with water (5 mL). The aqueous portion was extracted with ethyl acetate (3 x 5 mL). The combined organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flashed chromatography (silica gel, 5-20% ethyl acetate in hexane) to give 3,6-anhydro-2-*O*-methyl-5-*O*-(phenylcarbonyl)-α-L-glucofuranoside as a white solid, 270 mg, 42% yield. ^{1}H NMR (400MHz; $CDCl_3$): 8.09-8.07 (m, 2H), 7.61-7.57 (m, 1H), 7.48-7.27 (m, 2H), 5.25-5.22 (m, 1H), 5.07-5.06 (d, 1H), 4.94-4.91 (m, 1H), 4.73-4.71 (m, 1H), 4.20-4.16 (m, 1H), 3.96-3.94 (m, 1H), 3.85-3.83 (tr, 1H), 3.50 (s, 3H), 3.42 (s, 3H).

[0372] Methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-α-L-glucofuranoside: A solution of methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(phenylcarbonyl)-α-L-glucofuranoside (230mg, 0.92 mmol) and 50% sodium hydroxide (74 mg, 0.92 mmol) in methanol (5 mL) was stirred at room temperature for 30 minutes. The mixture was adsorbed on silica gel (2g) and passed through a short column (15% ethyl acetate in hexanes to 5% methanol in ethyl acetate) to afford a colorless oil which was employed directly in the next step, 140

mg, 0.72 mmol, 95% yield. The alcohol was dissolved in dichloromethane (5 mL) and pyridine (121 μL, 1.03 mmol) was added at 0°C. Methanesulfonyl chloride (27μL, 0.88 mmol) was added and the resulting mixture was stirred at 0°C for 1 hour then at room temperature for 2 hours. The reaction mixture was washed with water and saturated aqueous sodium bicarbonate solution, dried over sodium sulfate, filtered and concentrated to give methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-α-L-glucofuranoside as a colorless oil, 190 mg, 96% yield.

Example 60

[0373] 3,6-Anhydro-1,2-*O*-(1-methylethylidene)-5-*O*-(phenylcarbonyl)-α-L-glucofuranose: A mixture of 3,6-anhydro-5-*O*-(phenylcarbonyl)-α-L-glucofuranose (1.00g), 2,2-dimethoxy propane (0.63 mL), p-toluenesulfonic acid (20 mg) and benzene (10 mL) was heated at reflux for 3 hours. The reaction mixture was cooled then adsorbed on silica gel (10g) and purified by flash chromatography (silica gel, 5-35% ethyl acetate in hexanes) to give 3,6-anhydro-1,2-*O*-(1-methylethylidene)-5-*O*-(phenylcarbonyl)-α-L-glucofuranose as colorless oil, 0.85g, 74% yield. ^{1}H NMR (400MHz; $CDCl_3$): 8.08-8.06 (d, 2H), 7.59-7.56 (tr, 1H), 7.46-7.42 (m, 2H), 5.99-5.98 (d, 1H), 5.35-5.31 (tr, 1H), 5.10-5.08 (d, 1H), 4.66-4.65 (d, 1H), 4.61-4.60 (d, 1H), 4.20-4.16 (dd, 1H), 3.91-3.74 (tr, 1H,), 1.50 (s, 3H), 1.34 (s, 3H).

[0374] 3,6-Anhydro-1,2-*O*-(1-methylethylidene)-5-*O*-(methylsulfonyl)-α-L-glucofuranose: A solution of 3,6-anhydro-1,2-*O*-(1-methylethylidene)-5-*O*-(phenylcarbonyl)-α-L-glucofuranose (850mg) and 50% sodium hydroxide (111 mg) in methanol (10mL) was stirred at room temperature for 30 minutes. The mixture was then adsorbed on silica gel (5g) and passed through a short column (15% ethyl acetate in hexanes to 5% methanol in ethyl acetate) and the alcohol intermediate, 390 mg, 70% yield, was used immediately in the next step. The alcohol was dissolved in dichloromethane (10 mL) and pyridine (0.32 mL) at 0°C. Methanesulfonyl chloride (0.12 mL) was added and the resulting mixture was stirred at 0°C for 1 hour then at room temperature for 2 hours. The reaction mixture was washed with water and saturated aqueous sodium bicarbonate solution, dried over anhydrous sodium sulfate, filtered and concentrated to give 3,6-anhydro-1,2-*O*-(1-methylethylidene)-5-*O*-(methylsulfonyl)-α-L-glucofuranose as a colorless oil, 485 mg, 90% yield, which was immediately employed in the next step.

Example 61

[0375] (3*S*,8a*S*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine: (*S*)-(+)-Prolinol (6.00 g, 59.3 mmol) was added to epichlorohydrin (47 mL, 600 mmol) at 0°C. The solution was stirred at 40°C for 0.5 h and then concentrated *in vacuo*. The residual oil was cooled in an ice bath and concentrated sulfuric acid (18 mL) was added dropwise with stirring. The mixture was heated at 170-180°C for 1.5 h, poured into ice (300 mL) and then basified with sodium carbonate to pH~8. The mixture was partitioned with ethyl acetate/hexanes and filtered. The filtrate was separated and the aqueous portion was extracted twice with ethyl acetate. The combined organic portion was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford oil that was purified by column chromatography (ethyl acetate for less polar product and then 30% methanol in ethyl acetate). (3*S*,8a*S*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine (less polar product) (1.87 g, 10.7 mmol, 18% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 4.06 (dd, 1H), 3.79-3.71 (m, 1H), 3.60-3.48 (m, 2H), 3.36 (dd, 1H), 3.15 (dd, 1H), 3.13-3.06 (m, 1H), 2.21-2.01 (m, 3H), 1.90-1.68 (m, 3H), 1.39-1.24 (m, 1H); MS (EI) for $C_8H_{14}NOCl$: 176 (MH^+). (3*R*,8a*S*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine (1.54 g, 8.77 mmol, 15% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 3.94-3.77 (m, 4H), 3.55 (dd, 1H), 3.02-2.93 (m, 2H), 2.45 (dd, 1H), 2.29-2.15 (m, 2H), 1.88-1.64 (m, 3H), 1.49-1.38 (m, 1H); MS (EI) for $C_8H_{14}NOCl$: 176 (MH^+).

[0376] Using the same or analogous synthetic techniques and/or substituting with alternative starting materials, the following were prepared:

[0377] (3*R*,8a*R*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine: ^{1}H NMR (400 MHz, $CDCl_3$): 4.05 (dd, 1H), 3.79-3.70 (m, 1H), 3.61-3.48 (m, 2H), 3.35 (dd, 1H), 3.15 (dd, 1H), 3.13-3.07 (m, 1H), 2.21-2.01 (m, 3H), 1.89-1.67 (m, 3H), 1.39-1.25 (m, 1H); MS (EI) for $C_8H_{14}NOCl$: 176 (MH^+).

[0378] (3*S*,8a*R*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine: ^{1}H NMR (400 MHz, $CDCl_3$): 3.93-3.77 (m, 4H), 3.55 (dd, 1H), 3.02-2.93 (m, 2H), 2.45 (dd, 1H), 2.30-2.15 (m, 2H), 1.88-1.64 (m, 3H), 1.49-1.37 (m, 1H); MS (EI) for $C_8H_{14}NOCl$: 176 (MH^+).

Example 62

[0379] (3*S*,8a*S*)-Hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl acetate: (3*S*,8a*S*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine (2.30 g, 13.1 mmol) and potassium acetate (12.8 g, 131 mmol) were stirred in dimethylformamide (25 mL) at 140°C for 20 h. The mixture was partitioned between ethyl acetate and water. The organic portion was washed twice with water, then with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford (3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl acetate as a brown oil (2.53 g, 12.7 mmol, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 4.14-4.02 (m, 3H), 3.81-3.72 (m, 1H), 3.37-3.31 (m, 1H), 3.09 (dt, 1H), 3.00 (dd, 1H), 2.21-2.00 (m, 3H), 2.10 (s, 3H), 1.90-1.67 (m, 3H), 1.39-1.24 (m, 1H); MS (EI) for $C_{10}H_{17}NO_3$: 200 (MH^+).

[0380] (3*S*,8a*S*)-Hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethanol: (3*S*,8a*S*)-Hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl acetate (2.36 g, 11.9 mmol) was treated with sodium methoxide (25 wt% solution in methanol; 2.7 mL) for 0.5 h. The mixture was cooled in an ice bath and a solution of 4M HCl in 1,4-dioxane (3 mL, 12.0 mmol) was added slowly. The mixture was stirred at room temperature for 5 minutes and then was concentrated *in vacuo* to afford a suspension which was diluted with dichloromethane, filtered and the filtrate was concentrated *in vacuo* to afford (3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethanol as a brown oil (1.93 g, >100% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 4.05 (dd, 1H), 3.73-3.65 (m, 2H), 3.62-3.56 (m, 1H), 3.39-3.34 (m, 1H), 3.10 (dt, 1H), 3.00-2.95 (m, 1H), 2.24-1.98 (m, 4H), 1.97-1.70 (m, 3H), 1.44-1.28 (m, 1H); MS (EI) for $C_8H_{15}NO_2$: 158 (MH^+).

[0381] (3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl methanesulfonate: (3*S*,8a*S*)-Hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethanol (1.00 g, 6.37 mmol) was dissolved in dichloromethane (10 mL) and triethylamine (2.4 mL, 17.3 mmol) was added at 0°C followed by dropwise addition of methanesulfonyl chloride (0.93 mL, 12.0 mmol). The solution was warmed to room temperature and stirred for 1.25 h and then was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic portion was washed with saturated sodium bicarbonate solution. The combined aqueous portion was extracted with ethyl acetate. The combined organic portion was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford (3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-

ylmethyl methanesulfonate as an orange-brown oil (1.20 g, 5.1 mmol, 80% yield). MS (EI) for $C_9H_{17}NO_4S$: 236 (MH^+).

Example 63

[0382] Octahydro-2*H*-quinolizin-3-ylmethanol: Ethyl octahydro-2*H*-quinolizine-3-carboxylate (2.35 g, 11.1 mmol) was added dropwise to a stirred suspension of lithium aluminum hydride (1 M solution in tetrahydrofuran, 33 mL, 33 mmol) in tetrahydrofuran (50 mL) at 0°C. The reaction was stirred at room temperature for 3 h. The mixture was cooled in an ice bath and ethyl acetate (6 mL) was added slowly, followed by water (1.25 mL), 15% aqueous sodium hydroxide solution (5 mL) and water (1.25 mL). The mixture was filtered through a pad of celite and washed with ether. The filtrate was concentrated *in vacuo* and dried rigorously to afford octahydro-2*H*-quinolizin-3-ylmethanol as a yellow oil (1.66 g, 9.82 mmol, 88% yield). MS (EI) for $C_{10}H_{19}NO$: 170 (MH^+).

[0383] Octahydro-2*H*-quinolizin-3-ylmethyl methanesulfonate: Octahydro-2*H*-quinolizin-3-ylmethanol (600 mg, 3.55 mmol) was dissolved in dichloromethane (8 mL) and triethylamine (1.5 mL, 10.8 mmol) was added at 0°C followed by dropwise addition of methanesulfonyl chloride (0.56 mL, 7.16 mmol). The solution was warmed to room temperature and stirred for 1.25 h and then was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The aqueous portion was extracted with ethyl acetate. The combined organic portion was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford octahydro-2*H*-quinolizin-3-ylmethyl methanesulfonate as an orange oil (796 mg, 3.22 mmol, 91% yield). MS (EI) for $C_{11}H_{21}NO_3S$: 248 (MH^+).

Example 64

[0384] (3*S*,8a*S*)-3-(Hydroxymethyl)hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one: A solution of methyl 1-[(2*S*)-3-hydroxy-2-({[(phenylmethyl)oxy]carbonyl}amino)propyl]-L-prolinate (3.50 g, 10.4 mmol) in methanol was added to 5% palladium on carbon (50 wt.% in water) in methanol and treated with hydrogen at 40 psi for 1 h. The mixture was filtered and the filtrate was brought to reflux briefly and then cooled and concentrated *in vacuo* to afford (3*S*,8a*S*)-3-(hydroxymethyl)hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one as

a colorless solid (1.50 g, 8.83 mmol, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 7.28-7.22 (m, 1H), 3.83-3.75 (m, 1H), 3.69 (dd, 1H), 3.56 (dd, 1H), 3.31 (t, 1H), 3.08 (dd, 1H), 2.92 (dt, 1H), 2.76-2.70 (m, 1H), 2.66 (dd, 1H), 2.28-2.16 (m, 1H), 2.02-1.73 (m, 3H); MS (EI) for $C_8H_{14}N_2O_2$: 171 (MH^+).

[0385] (3*S*,8a*S*)-3-({[(1,1-Dimethylethyl)(dimethyl)silyl]oxy}methyl)hexahydro-pyrrolo[1,2-*a*]pyrazin-1(2*H*)-one: To a solution of (3*S*,8a*S*)-3-(hydroxymethyl) hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (1.49 g, 8.82 mmol) in dimethylformamide (20 mL) was added triethylamine (2.45 mL, 17.6 mmol) and 4-dimethylaminopyridine (90 mg, 0.882 mmol). The solution was cooled in an ice bath and *tert*-butyldimethylsilyl chloride (2.66 g, 17.6 mmol) was added. The mixture was warmed to room temperature and stirred for 14 h. The mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate and water. The aqueous portion was extracted twice with ethyl acetate. The combined organic portion was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a pale brown solid which was triturated with ethyl acetate to afford (3*S*,8a*S*)-3-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl) hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one as an off-white solid (1.74 g, 5.84 mmol, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 6.09-5.90 (m, 1H), 3.86-3.76 (m, 1H), 3.63 (dd, 1H), 3.44 (dd, 1H), 3.25 (t, 1H), 3.10 (ddd, 1H), 2.98-2.90 (m, 1H), 2.68-2.60 (m, 1H), 2.52 (dd, 1H), 2.28-2.18 (m, 1H), 2.06-1.95 (m, 1H), 1.93-1.74 (m, 2H), 0.90 (s, 9H), 0.07 (s, 6H); MS (EI) for $C_{14}H_{28}N_2O_2Si$: 285 (MH^+).

[0386] (3*S*,8a*S*)-3-({[(1,1-Dimethylethyl)(dimethyl)silyl]oxy}methyl)-2-methylhexahydro pyrrolo[1,2-*a*]pyrazin-1(2*H*)-one: (3*S*,8a*S*)-3-({[(1,1-Dimethylethyl)(dimethyl)silyl]oxy} methyl)hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (1.51g, 5.32mmol) in dimethylformamide (8 mL) was added to an ice-cooled suspension of sodium hydride (60 wt.% dispersion in oil; 213 mg, 5.32 mmol) in dimethylformamide (8 mL). The mixture was stirred at 0°C for 0.25 h and then iodomethane (0.332 mL, 5.32 mmol) was added dropwise. The mixture was stirred at room temperature for 0.5 h and then was stirred at 70°C for 2 h. The mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate and water. The aqueous portion was extracted with ethyl acetate. The combined organic portion was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford (3*S*,8a*S*)-3-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)-2-methylhexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one as a yellow oil (1.552 g, 5.21 mmol) which was dissolved in tetrahydrofuran (20 mL) and treated with tetrabutylammonium

fluoride (1.0M solution in tetrahydrofuran; 10.4 mL, 10.4 mmol) for 2 h at room temperature. The mixture was concentrated *in vacuo* and purified by column chromatography (10% methanol in dichloromethane) to afford (3*S*,8a*S*)-3-(hydroxymethyl)-2-methylhexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one as a yellow oil (496mg, 2.70mmol, 51% yield from (3*S*,8a*S*)-3-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy} methyl)hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one). ^{1}H NMR (400 MHz, $CDCl_3$): 3.98-3.93 (m, 1H), 3.86 (dd, 1H), 3.61-3.55 (m, 1H), 3.29-3.25 (m, 1H), 3.09-3.03 (m, 1H), 3.03-2.97 (m, 1H), 3.02 (s, 3H), 2.93 (dd, 1H), 2.87-2.79 (m, 1H), 2.32-2.21 (m, 1H), 2.00-1.86 (m, 2H), 1.83-1.64 (m, 1H); MS (EI) for $C_9H_{16}N_2O_2$: 185 (MH^+).

Example 65

[0387] 1,2-Dideoxy-1-[(2*S*)-2-(methoxycarbonyl)-1-pyrrolidinyl]-2-[[(phenylmethoxy) carbonyl]amino]-D-*glycero*-hexitol: To a solution of 2-deoxy-2-{[(phenylmethyloxy) carbonyl]amino}-D-glycero-hexopyranose (5.0 g, 0.016 mol) in methanol (500 mL) was added L-proline methyl ester hydrochloride (2.8 g, 0.022 mol) and sodium cyanoborohydride (3.4 g, 0.054 mol). The solution was heated to 64 °C for 14 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* to afford 1,2-dideoxy-1-[(2*S*)-2-(methoxycarbonyl)-1-pyrrolidinyl]-2-[[(phenylmethoxy)carbonyl] amino]-D-*glycero*-hexitol (6.81 g, 100%) as a clear and colorless oil. MS (EI) for $C_{20}H_{31}N_2O_8$: 427 (MH^+).

Example 66

[0388] Methyl 1-[(2*S*)-3-hydroxy-2-({[(phenylmethyl)oxy]carbonyl}amino)propyl]-L-prolinate: 1,2-dideoxy-1-[(2*S*)-2-(methoxycarbonyl)-1-pyrrolidinyl]-2-[[(phenylmethoxy) carbonyl]amino]-D-*glycero*-hexitol (6.81 g, 0.016 mol) was taken into water (100 mL) and the resulting solution was cooled to 0°C. Sodium periodiate (14.8 g, 0.069 mol) dissolved in water was added dropwise and the resulting mixture was stirred at 0°C for 2 h. The reaction mixture was partitioned with dichloromethane (3x100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was taken up in methanol (200 mL) and the resulting solution was cooled to 0°C. Sodium borohydride

(1.98 g, 0.052 mol) was added and the reaction mixture was stirred for 1 h at 0°C. The reaction mixture was concentrated *in vacuo* and partitioned with dichloromethane and saturated aqueous ammonium chloride. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude product was purified by column chromatography (5% methanol in dichloromethane) to yield methyl 1-[(2*S*)-3-hydroxy-2-({[(phenylmethyl)oxy]carbonyl}amino)propyl]-L-prolinate (4.9 g, 92%) as a white solid. MS (EI) for $C_{17}H_{25}N_2O_5$: 337 (MH^+).

[0389] Methyl 1-[(2*S*)-3-[(methylsulfonyl)oxy]-2-({[(phenylmethyl)oxy]carbonyl}amino) propyl]-L-prolinate: Methyl 1-[(2*S*)-3-hydroxy-2-({[(phenylmethyl)oxy]carbonyl}amino) propyl]-L-prolinate (200 mg, 0.594 mmol) was dissolved in dichloromethane (5 mL) followed by the addition of 4-(dimethylamino)pyridine (3.6 mg, 0.039 mmol) and triethylamine (0.125 mL, 0.891 mmol) and the resulting mixture was cooled to 0 °C. Methanesulfonyl chloride (0.060 mL, 0.773 mmol) was added dropwise and the reaction mixture was stirred for 1 h at 0°C. The mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to afford methyl 1-[(2*S*)-3-[(methylsulfonyl)oxy]-2-({[(phenylmethyl)oxy]carbonyl}amino)propyl]-L-prolinate (246 mg, 100%) as a clear and colorless oil. MS (EI) for $C_{18}H_{27}N_2O_7S$: 415 (MH^+).

Example 67

[0390] 1,1-Dimethylethyl (3a*R*,6a*S*)-5-(hydroxymethyl)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate: Under a nitrogen atmosphere, borane tetrahydrofuran complex (1M in THF, 42 mL, 41.9 mmol) was diluted with tetrahydrofuran (42 mL) and cooled with an ice bath. Neat 2,3-dimethylbut-2-ene (5.0 mL, 41.9 mmol) was added in portions over 0.25 h and the solution was stirred at 0°C for 3 h. A solution of 1,1-dimethylethyl (3a*R*,6a*S*)-5-methylidenehexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate (1.98 g, 8.88 mmol) in tetrahydrofuran (10 mL) was added slowly, and the solution was warmed to room temperature and stirred 12 h. After cooling to 0°C, 10% aqueous sodium hydroxide (17 mL, 41.7 mmol) was added slowly, followed by 30% aqueous hydrogen peroxide (13 mL, 128 mmol) and the solution was warmed to room temperature. The solvent was removed *in vacuo* and the solution was partitioned between water and diethyl ether. The layers were separated and the aqueous layer was further extracted (3 x 50 mL diethyl ether). The

combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to provide 2.04 (95%) of 1,1-dimethylethyl (3a*R*,6a*S*)-5-(hydroxymethyl)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate, which was used without purification. ^{1}H NMR (400 MHz, $CDCl_3$): 8.50 (broad s, 1H), 3.66-3.46 (m, 3H), 3.20-3.00 (m, 2H), 2.70-2.59 (m, 2H), 2.37-2.18 (m, 1H), 2.04 (m, 1H), 1.84 (broad s, 1H), 1.70-1.55 (m, 1H), 1.46 (s, 9H), 1.17 (m, 1H), 0.93 (m, 1H).

[0391] 1,1-Dimethylethyl (3a*R*,6a*S*)-5-{[(methylsulfonyl)oxy]methyl}hexahydrocyclopenta [*c*]pyrrole-2(1*H*)-carboxylate: Methanesulfonyl chloride (0.2mL, 2.48mmol), was added dropwise to a solution of 1,1-dimethylethyl (3a*R*,6a*S*)-5-(hydroxymethyl)hexahydro cyclopenta[*c*] pyrrole-2(1*H*)-carboxylate (0.40 g, 1.65 mmol) and triethylamine (0.69 mL, 4.95 mmol) in 20 mL dichloromethane at 0°C and the reaction mixture was stirred for 1 h at room temperature. The solvent was evaporated, the resulting crude mixture was diluted with 100 mL ethyl acetate and washed with water (30 mL), 1M aqueous sodium hydroxide, brine, 1M aqueous hydrochloric acid and brine again. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting 1,1-dimethylethyl (3a*R*,6a*S*)-5-{[(methylsulfonyl)oxy]methyl}hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate was used without further purification. MS (EI) for $C_{14}H_{25}NO_5S$: 320 (MH^+), 264 (M-tBu).

Example 68

[0392] 1,1-Dimethylethyl (3a*R*,6a*S*)-5-(hydroxy)-hexahydrocyclopenta[*c*] pyrrole-2(1*H*)-carboxylate: Sodium borohydride (0.15 g, 4.00 mmol), was added to a solution of 1,1-dimethylethyl (3a*R*,6a*S*)-5-oxo-hexahydrocyclopenta[*c*] pyrrole-2(1*H*)-carboxylate (0.45 g, 2.00 mmol) in 10 mL methanol at 0°C and the reaction mixture was stirred for 1 h at this temperature. The solvent was evaporated, the crude mixture was diluted with 100 mL ethyl acetate and washed with water (30 mL), 1M aqueous hydrochloric acid and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to give 1,1-dimethylethyl (3a*R*,6a*S*)-5-(hydroxy)-hexahydrocyclopenta[*c*] pyrrole-2(1*H*)-carboxylate (0.44g, 98%). ^{1}H NMR (400 MHz, d_6-DMSO): 4.08 (m, 1H), 3.40 (m, 2H), 3.30 (m, 2H), 2.50 (m, 2H), 1.98 (m, 2H), 1.40 (s, 9H), 1.30 (m, 2H). MS (EI) for $C_{12}H_{21}NO_3$: 228 (MH^+).

[0393] 1,1-Dimethylethyl (3a*R*,6a*S*)-5-{[(methylsulfonyl)oxy]}hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate: Methanesulfonyl chloride (0.18 mL, 2.33 mmol), was added dropwise to a solution of 1,1-dimethylethyl (3a*R*,6a*S*)-5-(hydroxy)-hexahydrocyclopenta[*c*] pyrrole-2(1*H*)-carboxylate (0.44 g, 1.94 mmol) and triethylamine (0.81 mL, 5.81 mmol) in 10 mL dichloromethane at 0°C and the reaction mixture was stirred for 1 h at room temperature. The solvent was evaporated, the resulting crude mixture was diluted with 100 mL ethyl acetate and washed with water (30 mL), brine, 1M aqueous hydrochloric acid and brine again. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The resulting crude 1,1-dimethylethyl (3a*R*,6a*S*)-5-{[(methylsulfonyl)oxy]}hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate was used without further purification. MS (EI) for $C_{13}H_{23}NO_5S$: 306 (MH^+).

Example 69

[0394] 3-(Chloromethyl)hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazine: A solution of (3*R*)-morpholin-3-ylmethanol (4.21 g, 36.0 mmol) in 2-(chloromethyl)oxirane (28.2 mL, 0.360 mol) was heated to 40°C for 3 h and then the solution was concentrated *in vacuo*. The intermediate was cooled in an ice bath and treated with 30.0 mL of concentrated sulfuric acid. The mixture was heated to 170°C for 2 h and then allowed to cool to room temperature. The mixture was poured into ice-water and solid sodium bicarbonate was carefully added until the solution was basic. 10% methanol in ethyl acetate was added and the biphasic mixture was filtered. The layers were separated and the aqueous layer was extracted (3 x 100 mL 10% methanol in ethyl acetate). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (SiO_2, 2:5 hexanes:ethyl acetate) provided 3-(chloromethyl)hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazine 2.44g (35%) as two separated diastereomers. (3*R*,9a*S*)-3-(chloromethyl)hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazine: (0.886 g, 13% yield): ^1H NMR (400 MHz, $CDCl_3$): 3.91 (m, 3H), 3.82 (m, 1H), 3.68 (dt, 1H), 3.61 (dd, 1H), 3.47 (dd, 1H), 3.35 (t, 1H), 3.19 (t, 1H), 2.80 (d, 1H), 2.54 (m, 2H), 2.40 (m, 2H); MS (EI) for $C_8H_{14}NO_2Cl$: 192 (MH^+). (3*S*,9a*S*)-3-(chloromethyl)hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazine: (1.55 g, 22% yield): ^1H NMR (400 MHz, $CDCl_3$): 3.85 (m, 2H), 3.73 (m, 3H), 3.50 (m, 2H), 3.29 (t, 1H), 3.18 (t, 1H), 2.85 (dd, 1H), 2.64 (dd, 1H), 2.40 (m, 2H), 2.17 (t, 1H); MS (EI) for $C_8H_{14}NO_2Cl$: 192 (MH^+).

[0395] Hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl acetate: A suspension of (3*R*,9a*S*)-3-(chloromethyl)hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazine (1.97 g, 10.3 mmol) and potassium acetate (10.1 g, 102 mmol) in DMF (20.0 mL) was stirred at 140°C for 16 h, and then at 150°C for another 12 h. The reaction mixture was partitioned between water (250 mL) and ethyl acetate (250 mL), the organic layer was washed with 5% lithium chloride (2 x 100 mL) and brine (100 mL) then dried over anhydrous sodium sulfate and concentrated *in vacuo*. Column chromatography (SiO_2, 1:1 hexane:ethyl acetate, then 100% ethyl acetate) afforded 0.92 g (42%) of hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl acetate as a yellow oil. Distinct diastereomers as described above were converted in this step to give: (3*R*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl acetate: ^{1}H NMR (400 MHz, $CDCl_3$): 4.18 (dd, 1H), 4.00 (m, 1H), 3.80 (dd, 1H), 3.68 (dt, 1H), 3.60 (dd, 1H), 3.46 (m, 2H), 3.22 (t, 1H), 2.64 (dd, 1H), 2.53 (m, 2H), 2.43-2.35 (m, 2H), 2.10 (s, 3H), and (3*S*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl acetate: ^{1}H NMR (400 MHz, $CDCl_3$): 4.09 (d, 2H), 3.90-3.82 (m, 2H), 3.75-3.64 (m, 3H), 3.27 (t, 1H), 3.18 (t, 1H), 2.69 (dd, 1H), 2.63 (m, 1H), 2.46-2.33 (m, 2H), 2.16 (t, 1H), 2.10 (s, 3H).

[0396] (3*R*,9a*S*)-Hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl methanesulfonate: To a solution of (3*R*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl acetate (0.922 g, 4.28 mmol) in methanol (14.0 mL) was added 1.03 mL (4.50 mmol) of sodium methoxide (25% wt. in methanol) dropwise at room temperature. After 5 min., 1.6 mL (6.43 mmol) of 4.0M hydrogen chloride in dioxane was added and a pink precipitate formed. The solution was concentrated *in vacuo* and the pink solid was taken up in 30.0 mL dichloromethane. This slurry was cooled in an ice bath and triethylamine (3.0 mL, 21.5 mmol) was added, followed by methanesulfonyl chloride (0.37 mL, 4.71 mmol). The resultant yellow solution was stirred for 30 minutes at room temperature. The mixture was then partitioned between dichloromethane and saturated aqueous sodium bicarbonate then the aqueous layer was extracted (3 x 50 mL dichloromethane). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to provide crude (3*R*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl methanesulfonate which was taken on to the following reaction without purification.

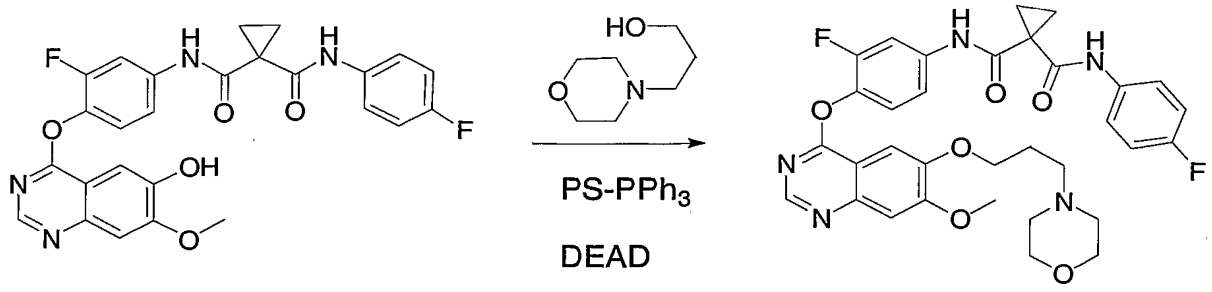
Example 70

[0397] (8a*R*)-6-(Chloromethyl)tetrahydro-1*H*-[1,3]thiazolo[4,3-*c*][1,4]oxazine: A solution of (4*R*)-1,3-thiazolidin-4-ylmethanol (0.300 g, 2.52 mmol) in 2-(chloromethyl)oxirane (2.0 mL, 25.5 mmol) was heated under nitrogen to 40°C for 12 h. The solution was then cooled to room temperature and 2-(chloromethyl)oxirane was removed *in vacuo*. The crude intermediate was cooled in ice, and was taken up in 2.0 mL of concentrated sulfuric acid. The resulting mixture was heated to 200°C for 0.5 h then poured carefully onto wet ice, which was allowed to melt. The aqueous solution was carefully made basic using solid sodium bicarbonate and the resulting mixture was filtered using water and 10% methanol in ethyl acetate as eluent. The layers were separated and the aqueous layer was extracted with 10% methanol in ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give 11.6 mg (2.4% yield) of crude (8a*R*)-6-(chloromethyl)tetrahydro-1*H*-[1,3]thiazolo[4,3-*c*][1,4]oxazine as a mixture of diastereomers which was directly taken on to the next step.

Example 71

[0398] 1,1-Dimethylethyl (3-*endo*)-3-{2-[(methylsulfonyl)oxy]ethyl}-8-azabicyclo[3.2.1]octane-8-carboxylate: To a solution of 1,1-dimethylethyl (3-*endo*)-3-(2-hydroxyethyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (30.3 mg, 1.19 mmol) in dichloromethane (4.0 mL), was added triethylamine (0.5 mL, 3.56 mmol) and the solution was cooled to 0°C under nitrogen. Methanesulfonyl chloride (0.11 mL, 1.42 mmol) was added slowly and mixture was allowed to warm to room temperature and stirred for 1h. The reaction mixture was partitioned between dichloromethane and water. The aqueous phase was extracted with dichloromethane (2 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to provide 35.1 mg (89%) of 1,1-dimethylethyl (3-*endo*)-3-{2-[(methylsulfonyl)oxy]ethyl}-8-azabicyclo[3.2.1]octane-8-carboxylate, which was carried forward for alkylation without purification.

Example 72



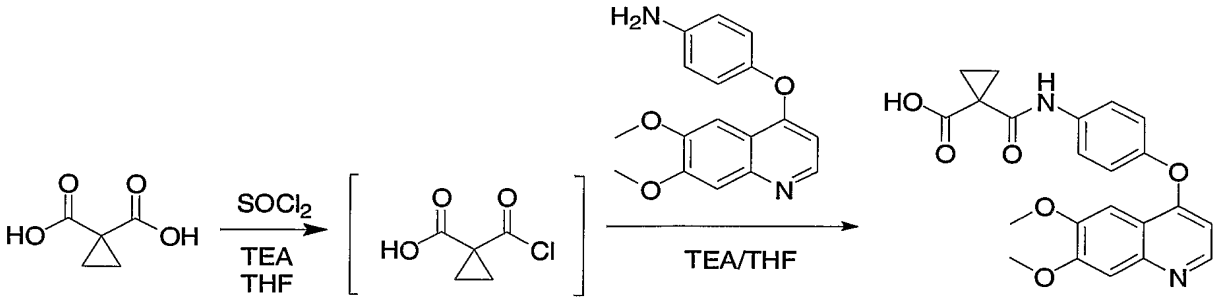
[0399] N-[3-Fluoro-4-({7-(methyloxy)-6-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. Crude cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(6-hydroxy-7-methoxy-quinazolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (333mg, 0.66mmol), PS-PPh_3 resin, (loading = 2.33mmol/g, 797mg, 1.86mmol), 3-morpholin-4-yl-propan-1-ol (0.26ml, 1.88mmol), and DEAD (0.31ml, 1.91mmol) were combined in CH_2Cl_2 (10ml) and stirred at room temperature for 1-2hrs. The reaction mixture was filtered and the resin thoroughly washed with CH_2Cl_2. The filtrate was concentrated *in vacuo* and the resulting residue was dissolved in EtOAc and washed with H_2O (4x) and sat'd NaCl (1x) and then extracted with 1N HCl (3x). The combined 1N HCl extractions were washed with EtOAc (2x). The acidic aqueous phase was then basified with 1N NaOH and extracted with EtOAc (3x). The combined EtOAc extractions were washed with H_2O (1x), sat'd NaCl (1x), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting residue was purified by preparative reverse phase HPLC (25mM NH_4OAc/acetonitrile) and the pure fractions were lyophilized to give cyclopropane-1,1-dicarboxylic acid {3-fluoro-4-[7-methoxy-6-(3-morpholin-4-yl-propoxy)-quinazolin-4-yloxy]-phenyl}-amide (4-fluoro-phenyl)-amide (42.6mg, 10%). 1HNMR (400MHz, DMSO-d6): d 10.37 (br s, 1H), 10.05 (br s, 1H), 8.55 (s, 1H), 7.84 (m, 1H), 7.65 (m, 2H), 7.58 (s, 1H), 7.43 (m, 3H), 7.16 (t, 2H), 4.27 (m, 2H), 4.00 (s, 3H), 3.60 (m, 6H), 2.39 (m, 4H), 1.99 (m, 2H), 1.47 (m, 4H). LC/MS Calcd for $[M+H]^+$ 634.2, found 634.1.

[0400] Using the same or analogous synthetic techniques and/or substituting with alternative starting materials, the following were prepared:

[0401] N-{3-fluoro-4-[(7-(methyloxy)-6-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide: ^1H NMR (400MHz, $CDCl_3$): δ 9.67 (s, 1H), 8.59 (s, 1H), 8.43 (s, 1H), 7.75 (d, 1H), 7.52 (s, 1H),

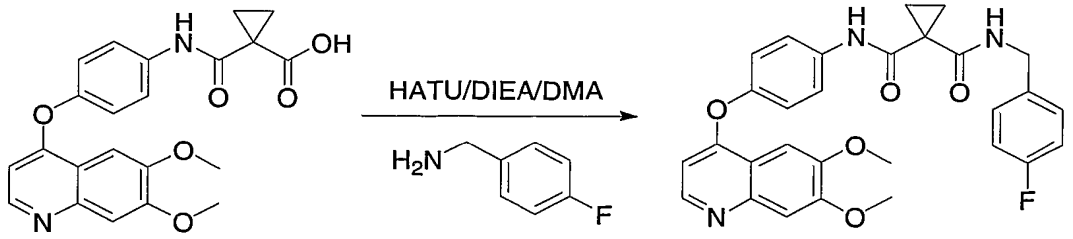
7.46 (m, 2H), 7.31 (s, 1H), 7.20 (m, 2H), 7.06 (t, 2H), 4.04 (d, 2H), 4.03 (s, 3H), 2.98 (d, 2H), 2.34 (s, 3H), 2.12-2.1.95 (m, 5H), 1.76 (m, 2H), 1.64 (m, 2H), 1.57 (m, 2H).

Example 73



[0402] Preparation of 1-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenylcarbamoyl]-cyclopropanecarboxylic acid. To the cyclopropyl di-carboxylic acid (449 mg, 3.45 mmol) in THF (3.5 mL) was added TEA (485 µL, 3.45 mmol). The resulting solution was stirred at room temperature under a nitrogen atmosphere for 40 minutes before adding thionyl chloride (250 µL, 3.44 mmol). The reaction was monitored by LCMS for the formation of mono acid chloride (quenched the sample with MeOH and looked for corresponding mono methyl ester). After 3 hours stirring at room temperature, 4-(6,7-dimethoxy-quinolin-4-yloxy)-phenylamine (1.02 g, 3.44 mmol) was added as a solid, followed by more THF (1.5 mL). Continued to stir at room temperature for 16 hours. The resulting thick slurry was diluted with EtOAc (10 mL) and extracted with 1N NaOH. The biphasic slurry was filtered and the aqueous phase was acidified with conc. HCl to pH = 6 and filtered. Both solids were combined and washed with EtOAc, then dried under vacuum. The desired product, 1-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenylcarbamoyl]-cyclopropanecarboxylic acid, was obtained (962 mg, 68.7% yield, 97% pure) as a white solid. ^{1}H NMR (D_2O/NaOH): 7.97 (d, 1H), 7.18 (d, 2H), 6.76 (m, 4H), 6.08 (d, 1H), 3.73 (s, 3H), 3.56 (s, 3H), 1.15 (d, 4H).

Example 74



[0403] 'N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[(4-fluorophenyl)methyl] cyclopropane-1,1-dicarboxamide. To a solution of 1-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenylcarbamoyl]-cyclopropanecarboxylic acid (74.3 mg, 0.182 mmol), 4-Fluoro benzylamine (25 μL, 0.219 mmol), DIEA (90.0 μL, 0.544 mmol) in DMA (1.0 mL) was added HATU (203 mg, 0.534 mmol). The resulting solution was stirred at room temperature for 1 hour before adding dropwise to water (10 mL) with stirring. The slurry was sonicated, filtered and the solids were washed with 1 N NaOH followed by water. After air drying, the solids were further purified by prep HPLC, affording 'N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[(4-fluorophenyl)methyl]cyclopropane-1,1-dicarboxamide (33 mg, 35% yield, 98% pure) as a white solid. ^{1}H NMR (DMSO, d_6): 10.82 (s, 1H), 8.80 (d, 1H), 8.50 (t, 1H), 7.83 (d, 2H), 7.74 (s, 1H), 7.56 (s, 1H), 7.30-7.38 (m, 4H), 7.15 (t, 2H), 6.80 (d, 1H), 4.32 (d, 2H), 4.04 (s, 3H), 4.03 (s, 3H), 1.42 (s, 4H).

[0404] The following compounds were prepared, in a similar manner as above, from the coupling of 1-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenylcarbamoyl]-cyclopropane carboxylic acid with a corresponding alkylamine or arylamine.

[0405] N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide. 1H NMR (DMSO-d6): 10.62 (s, 1H), 8.79 (d, 1H), 8.24 (t, 1H), 7.83 (d, 2H), 7.72 (s, 1H), 7.58 (s, 1H), 7.37 (d, 2H), 6.76 (d, 1H), 4.04 (s, 3H), 4.03 (s, 3H), 3.98 (m, 2H), 3.66 (m, 2H), 3.49 (m, 4H), 3.25 (t, 2H), 3.13 (br., 2H), 1.42 (d, 4H).

[0406] N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide. 1H NMR (DMSO-d6): 10.78 (s, 1H), 10.53 (s, 1H), 8.43 (d, 1H), 8.12 (d, 1H), 7.82 (d, 2H), 7.49 (s, 1H), 7.37 (s, 1H), 7.20-7.28 (m, 3H), 7.15 (dd, 1H), 7.01 (td, 1H), 6.35 (d, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.47 (s, 2H), 2.17 (br., 4H), 1.49 (m, 4H), 1.41 (m, 4H), 1.32 (br., 2H).

[0407] 'N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide. 1H NMR (DMSO-d6): 10.98 (s, 1H), 10.56 (s, 1H), 8.42 (d, 1H), 8.10 (dd, 1H), 7.81 (m, 2H), 7.49 (s, 1H), 7.37 (s, 1H), 7.17-7.27 (m, 4H), 7.01 (td, 1H), 6.35 (d, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.61 (s, 2H), 2.30 (br., 4H), 1.47 (br., 4H), 1.43 (m, 4H).

[0408] 'N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide. 1H NMR (DMSO-d6): 10.12 (s, 1H),

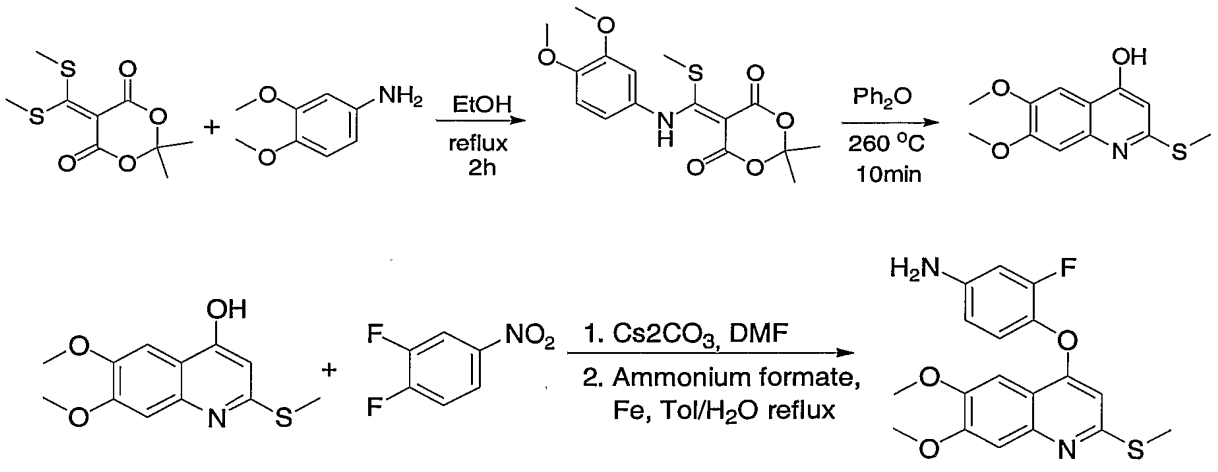
10.03 (s, 1H), 8.44 (d, 1H), 7.74 (d, 2H), 7.57 (s, 1H), 7.53 (d, 1H), 7.48 (s, 1H), 7.37 (s, 1H), 7.21 (m, 3H), 6.98 (d, 1H), 6.40 (d, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.56 (t, 4H), 3.41 (s, 2H), 2.34 (br., 4H), 1.48 (s, 4H).

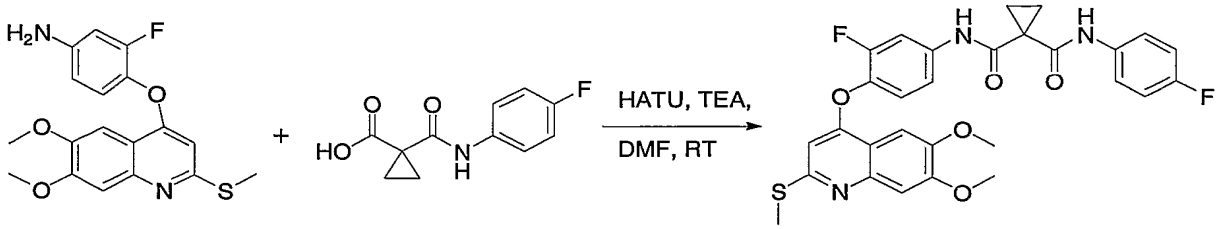
[0409] 'N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide. 1H NMR (DMSO-d6): 10.54 (s, 1H), 10.47 (s, 1H), 8.43 (d, 1H), 8.08 (d, 1H), 7.78 (d, 2H), 7.49 (s, 1H), 7.37 (d, 1H), 7.18-7.30 (m, 4H), 7.03 (t, 1H), 6.37 (d, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.50 (s, 2H), 3.44 (br., 4H), 2.20 (br., 4H), 1.48 (d, 4H).

[0410] 'N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide. 1H NMR (DMSO-d6): 10.0-10.2 (br., 2H), 8.46 (d, 1H), 7.76 (d, 2H), 7.53 (m, 3H), 7.39 (s, 1H), 7.24 (m, 3H), 6.98 (d, 1H), 6.43 (d, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.37 (s, 2H), 2.31 (br., 4H), 1.48 (m, 8H), 1.39 (br., 2H).

[0411] 'N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide. 1H NMR (DMSO-d6): 10.0-10.2 (br., 2H), 8.46 (d, 1H), 7.77 (d, 2H), 7.59 (s, 1H), 7.53 (d, 1H), 7.51 (s, 1H), 7.39 (s, 1H), 7.23 (m, 3H), 6.99 (d, 1H), 6.43 (d, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.52 (s, 2H), 2.42 (br., 4H), 1.69 (br, 4H), 1.48 (s, 4H).

Example 75





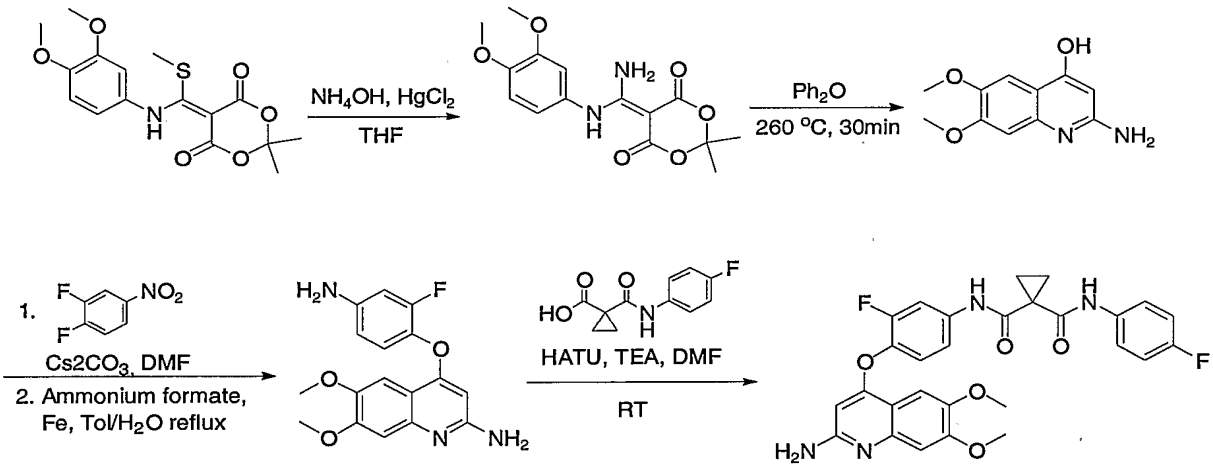
[0412] Synthesis of N-(4-{[6,7-bis(methyloxy)-2-(methylthio)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide Commercially available 5-(bis-methylsulfanyl-methylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione (3.5 g, 14 mmol) and 3,4-dimethoxyoaniline (2.2 g, 14 mmol) were reflux in EtOH (20 mL) for 2 hours. The EtOH was removed under reduced pressure and EtOAc was added to the residue. The product was filtered and washed with cold EtOAc (3X). 5-[(3,4-dimethoxy-phenylamino)-methylsulfanyl-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione was obtained as a white solid (1.7 g, 47% yield) and used without further purification. LCMS: m/z 352 $(M-H)^-$.

[0413] A mixture of 5-[(3,4-dimethoxy-phenylamino)-methylsulfanyl-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione (1.7 g, 6.6 mmol) and diphenylether (3.5 g, 21 mmol) were heated at 260 ^{0}C for 10 minutes. The mixture was cooled to room temperature and heptane was added. 6,7-Dimethoxy-2-methylsulfanyl-quinolin-4-ol was filtered and isolated as an orange solid and used without further purification (1.4 g, 83% yield). LCMS: m/z 352 $(M+H)^+$.

[0414] A mixture of 6,7-dimethoxy-2-methylsulfanyl-quinolin-4-ol (1.0 g, 4.0 mmol), 3,4-difluoronitrobenzene (0.48 mL, 4.3 mmol), cesium carbonate (2.6 g, 8.0 mmol), and DMF (15 mL) was stirred at room temperature for 12 hours, after which time, the mixture was filtered. The filtrate was extracted with DCM, washed with 10% $LiCl_{(aq.)}$, water, (1X) and brine (1X), followed by drying over Na_2SO_4 and concentration *in vacuo*. The crude solids were purified by flash chromatography (silica gel, 5% MeOH in DCM), affording the nitroquinoline (1.3 g, 85.8% yield) as an orange solid. LCMS: m/z 391 $(M+H)^+$. A mixture of nitroquinoline (0.33 g, 0.85 mmol), 5% Pt/S on carbon (0.050 g), ammonium formate (0.40 g, 6.3 mmol) in EtOH (5 mL) was heated at 80 ^{0}C for 1 hour The mixture was cooled to room temperature and the solvent removed under reduced pressure. The residue was dissolved in DCM, the mixture filtered, and the precipitate discarded. Removal of the organic solvent afforded 4-(6,7-dimethoxy-2-methylsulfanyl-quinolin-4-yloxy)-3-fluoro-phenylamine as an orange oil (220 mg, 73% yield). LCMS: m/z 361 $(M+H)^+$.

[0415] To a mixture of 4-(6,7-dimethoxy-2-methylsulfanyl-quinolin-4-yloxy)-3-fluoro-phenylamine (0.22 g, 0.61 mmol) and 1-(4-Fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (0.16 g, 0.73 mmol) in DMF (5 mL) was added TEA (0.25 mL, 1.8 mmol) followed by HATU (0.57 g, 1.5 mmol). The resulting solution was stirred overnight at room temperature. The reaction mixture was dumped into water and extracted with DCM (2X). The combined extracts were washed with 5% $LiCl_{(aq.)}$ (3X), water, (1X) and brine (1X), followed by drying over Na_2SO_4 and concentration *in vacuo*. The crude solids were purified by preparatory HPLC with ammonium acetate, affording N-(4-{[6,7-bis(methyloxy)-2-(methylthio)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (0.39 g, 11% yield) as a white solid. ^1H NMR (DMSO-d_6) δ 10.34 (s, 1H), 9.94 (s, 1H), 7.83 (d, 1H), 7.59 (m, 2H), 7.56 (m, 1H), 7.40 (m, 2H), 7.23 (s, 1H), 7.09 (t, 2H), 6.12 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 2.48 (s, 3H), 1.40 (m, 4H).

Example 76



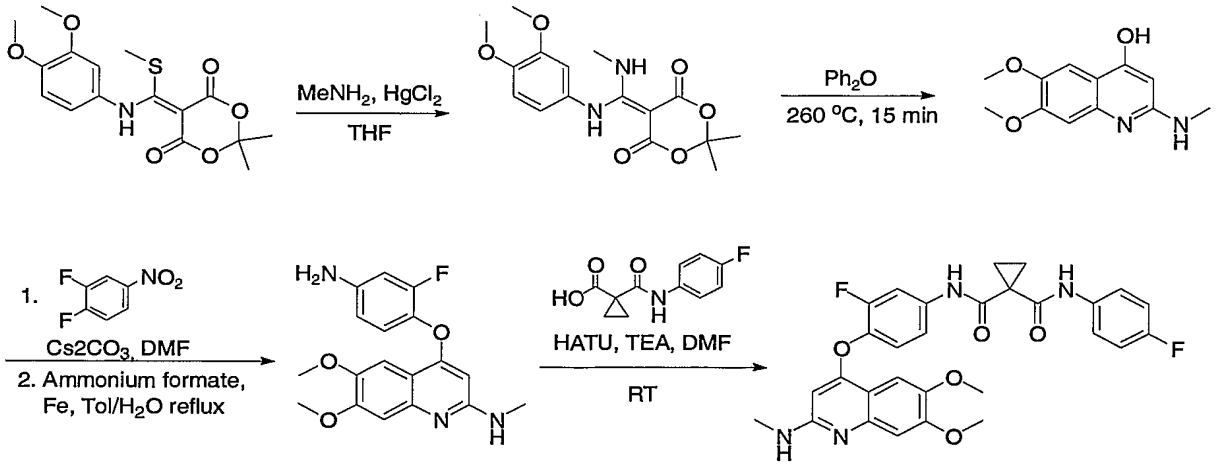
[0416] Synthesis of N-(4-{[2-amino-6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. A mixture of 5-[(3,4-dimethoxy-phenylamino)-methylsulfanyl-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione (1.0 g, 2.8 mmol), 30% ammonium hydroxide (8.5 mL), $HgCl_2$ (0.76 g, 2.8 mmol) in THF (5 mL) was stirred at room temperature for 30 minutes. The mixture was extracted with DCM and water (3X) and dried with Na_2SO_4. Concentration *in vacuo* afforded 5-[amino-(3,4-dimethoxy-phenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione as a white solid (0.90 g, 97% yield) and this compound was used without further purification. LCMS: m/z 321 $(M-H)^-$.

[0417] A mixture of 5-[amino-(3,4-dimethoxy-phenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione (0.90 g, 2.8 mmol) and diphenylether (3.0 g, 18 mmol) was heated at 260 ^{0}C for 30 minutes. The mixture was cooled to room temperature and heptane was added. Product 2-amino-6,7-dimethoxy-quinolin-4-ol was filtered and isolated as an orange solid and used without further purification (0.31 g, 33% yield). LCMS: m/z 221 $(M+H)^+$.

[0418] 4-(4-Amino-2-fluoro-phenoxy)-6,7-dimethoxy-quinolin-2-ylamine was synthesized from 2-amino-6,7-dimethoxy-quinolin-4-ol in a similar manner as 4-(6,7-dimethoxy-2-methylsulfanyl-quinolin-4-yloxy)-3-fluoro-phenylamine, and obtained as a white solid (4.0% yield). LCMS: m/z 330 $(M+H)^+$.

[0419] N-(4-{[2-amino-6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide was synthesized from 4-(4-amino-2-fluoro-phenoxy)-6,7-dimethoxy-quinolin-2-ylamine in a similar manner as N-(4-{[6,7-bis(methyloxy)-2-(methylthio)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. It was purified by preparatory HPLC using ammonium acetate and isolated as a white solid (4.0% yield). ^{1}H NMR (DMSO-d_6) δ 10.34 (s, 1H), 9.95 (s, 1H), 7.82 (d, 1H), 7.58 (m, 2H), 7.44 (d, 1H), 7.33 (t, 1H), 7.25 (s, 1H), 7.09 (t, 2H), 7.07 (s, 1H), 6.17 (br s, 2H), 5.66 (s, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 1.40 (d, 4H). LCMS: m/z 535 $(M+H)^+$.

Example 77



[0420] Synthesis of 'N-(3-fluoro-4-{[2-(methylamino)-6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. A mixture of 5-

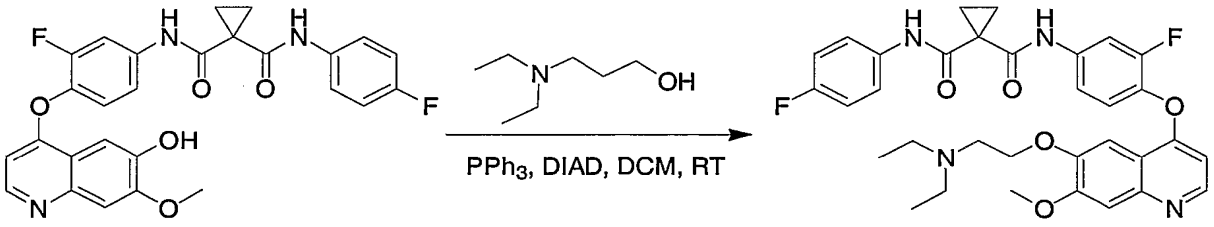
[(3,4-dimethoxy-phenylamino)-methylsulfanyl-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione (0.50 g, 1.4 mmol), methylamine (2 M in THF, 0.75 mL, 1.5 mmol), $HgCl_2$ (0.38 g, 1.4 mmol) in THF (5 mL) was stirred at room temperature for 30 minutes. The mixture was extracted with DCM and water (3X) and dried with Na_2SO_4. Concentration *in vacuo* afforded 5-[(3,4-dimethoxy-phenylamino)-methylamino-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione as a yellow solid (0.48 g, 99% yield) and this compound was used without further purification. LCMS: m/z 335 $(M-H)^-$.

[0421] A mixture of 5-[(3,4-dimethoxy-phenylamino)-methylamino-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione (0.40 g, 2.8 mmol) and diphenylether (3.0 g, 18 mmol) was heated at 260 ^{0}C for 15 minutes. The mixture was cooled to room temperature and heptane was added. Product 6,7-dimethoxy-2-methylamino-quinolin-4-ol was filtered and isolated as a tan solid and used without further purification (0.30 g, quantitative yield). LCMS: m/z 235 $(M+H)^+$.

[0422] [4-(4-Amino-2-fluoro-phenoxy)-6,7-dimethoxy-quinolin-2-yl]-methyl-amine was synthesized from 6,7-dimethoxy-2-methylamino-quinolin-4-ol in a similar manner as 4-(4-Amino-2-fluoro-phenoxy)-6,7-dimethoxy-quinolin-2-ylamine, and isolated as a yellow oil (58% yield). LCMS: m/z 330 $(M+H)^+$.

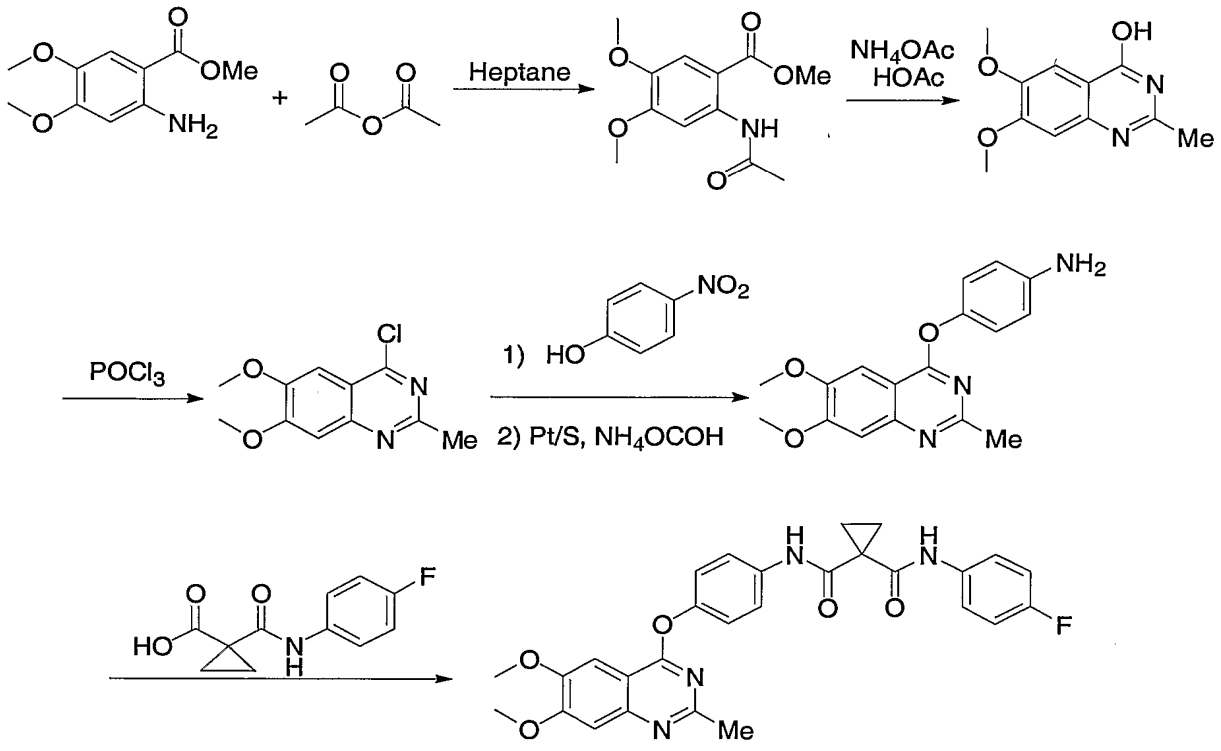
[0423] 'N-(3-fluoro-4-{[2-(methylamino)-6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide was synthesized from [4-(4-amino-2-fluoro-phenoxy)-6,7-dimethoxy-quinolin-2-yl]-methyl-amine in a similar manner as N-(4-{[6,7-bis(methyloxy)-2-(methylthio)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluoro-phenyl)cyclopropane-1,1-dicarboxamide. It was purified by preparatory HPLC using ammonium acetate and isolated as a white solid (6.0 mg, 4.0% yield). ^{1}H NMR (DMSO-d_6) δ 10.42 (s, 1H), 9.91 (s, 1H), 7.88 (dd, 1H), 7.56 (m, 2H), 7.44 (m, 4H), 7.09 (t, 2H), 5.90 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.39 (br s, 1H), 2.92 (s, 3H), 1.41 (dt, 4H). LCMS: m/z 535 $(M+H)^+$.

Example 78



[0424] 'N-(4-{[6-{[3-(diethylamino)propyl]oxy}-7-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. To a slurry of cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(6-hydroxy-7-methoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (0.12 g, 0.23 mmol), hydroxypropyldiethylamine (0.090 mL, 0.61 mmol), triphenylphosphine (0.20 g, 0.76 mmol) in DCM (10 mL) was added DIAD (0.17 mL, 0.86 mmol). The resulting mixture was stirred at room temperature for 12 hours, after which time, the solvent was removed under reduced pressure. The residue was extracted with EtOAc and 1N HCl (6X) and brine (1X) followed by drying with Na_2SO_4. Concentration of the organic fraction *in vacuo* afforded 'N-(4-{[6-{[3-(diethylamino)propyl]oxy}-7-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a yellow oil (0.18 g, wet, ca 95% purity by analytical HPLC). Further purification by preparatory HPLC using ammonium acetate afforded the product in 99% purity by analytical HPLC. LCMS: m/z 619 $(M+H)^+$. ^1H NMR (DMSO-d_6) δ 10.37 (br s, 1H), 10.00 (s, 1H), 8.44 (d, 1H), 7.87 (d, 1H), 7.62 (m, 2H), 7.49 (m, 2H), 7.41 (m, 2H), 7.13 (t, 2H), 6.40 (d, 1H), 4.17 (t, 2H), 3.93 (s, 3H), 2.59 (t, 2H), 2.49 (m, 6H), 1.91 (m, 4H), 0.94 (t, 6H).

Example 79



[0425] 'N-(4-fluorophenyl)-N'-(4-{[2-methyl-6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide. Commercially available 2-amino-4,5-dimethoxy-benzoic acid methyl ester (3g, 0.014 mol) and acetic anhydride (4.03 mL, 0.0426 mol) were heated in heptane at 100°C for 3 hours. After removal of heptane *in vaccuo*, the crude product of 2-acetylamino-4,5-dimethoxy-benzoic acid methyl ester was obtained and used without further purification. LC/MS: m/z 254 (M+H).

[0426] To the crude 2-acetylamino-4,5-dimethoxy-benzoic acid methyl ester obtained above was added ammonium acetate (7.98g, 0.104 mol) and acetic acid (10 mL). The mixture was heated at reflux in a pressure tube until the formation of the desired cyclization product, as indicated by LC/MS: m/z 221 (M+H). After cooling to RT, the reaction mixture was diluted with water, and extracted with EtOAc 3 times. The combined organic phase was basified with aq. NaOH solution, and washed 3 times with EtOAc. The aqueous layer was then acidified with aq. HCl and extracted three times with EtOAc. The combined organic extract was dired over Na_2SO_4 and concentrated in vacuo, affording 6,7-dimethoxy-2-methyl-quinazolin-4-ol (0.15g), which was used without further purification. LC/MS: m/z 221 (M+H).

[0427] A mixture of 6,7-dimethoxy-2-methyl-quinazolin-4-ol obtained from previous step (0.15g, 0.68 mmol) and POCl3 (1.59 mL, 17.04 mmol) was heated at reflux for 48 hours. The reaction mixture was poured into ice water, neutralized with $NaHCO_3$, and adjusted to basic with K_2CO_3. The mixture was cooled to 0°C with stirring. The resulting precipitate was filtered, giving 4-chloro-6,7-dimethoxy-2-methyl-quinazoline (0.094g), which was used without further purification.

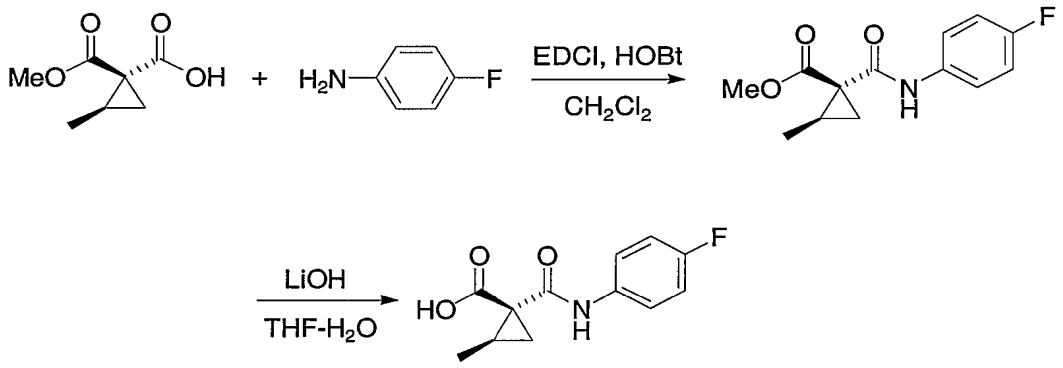
[0428] A mixture of the chloro quinazoline (0.094g, 0.397 mmol) obtained above, 4-nitrophenol (0.11g, 0.795 mmol) and bromobenzene (3mL) was heated at 160°C for 48 hours. The solvent was then removed and the reaction was taken up in MeOH. Et_2O was added and the reaction stirred 30 min and the precipitate was filtered, affording 6,7-dimethoxy-2-methyl-4-(4-nitro-phenoxy)-quinazoline (0.081g) as a very light yellow solid. LC/MS: m/z 342 (M+H).

[0429] A mixture of 6,7-dimethoxy-2-methyl-4-(4-nitro-phenoxy)-quinazoline (0.081g, 0.236 mmole), Pt/S (0.008g, 15 mol%), ammounium formate (0.098g, 1.56 mmol) and EtOH (3mL) was heated with stirring at 70°C for 3 hours. The reaction mixture was then filtered while hot and washed with hot EtOH. The crude product of 4-(6,7-dimethoxy-2-

methyl-quinazolin-4-yloxy)-phenylamine (0.924g) was obtained as a yellow solid, which was used in the next reaction without further purification. LC/MS: m/z 312 (M+H).

[0430] To a mixture of 4-(6,7-dimethoxy-2-methyl-quinazolin-4-yloxy)-phenylamine (0.100g, 0.321 mmol) and 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (0.056g, 0.386 mmol) in DMF was added DIEA (0.168 mL, 0.963 mmol), followed by HATU (0.183g, 0.482 mmol). The reaction mixture was stirred at RT for 15 hours. The mixture was diluted with EtOAc, washed with 5% LiCl aq solution three times, dried over Na2SO4, and concentrated *in vacuo*. The crude product was purified on preparative HPLC to give 'N-(4-fluorophenyl)-N'-(4-{[2-methyl-6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide (3.2 mg) as a white solid. 1H NMR (DMSO-d6) 10.15 (bs, 1H), 10.01 (bs, 1H), 7.69-7.75 (m, 2H), 7.61-7.68 (m, 2H), 7.52 (s, 1H), 7.32 (s, 1H), 7.23-7.29 (m, 2H), 7.12-7.19 (m, 2H), 3.93 (d, 6H), 2.43 (s, 3H), 1.53 (s, 4H).

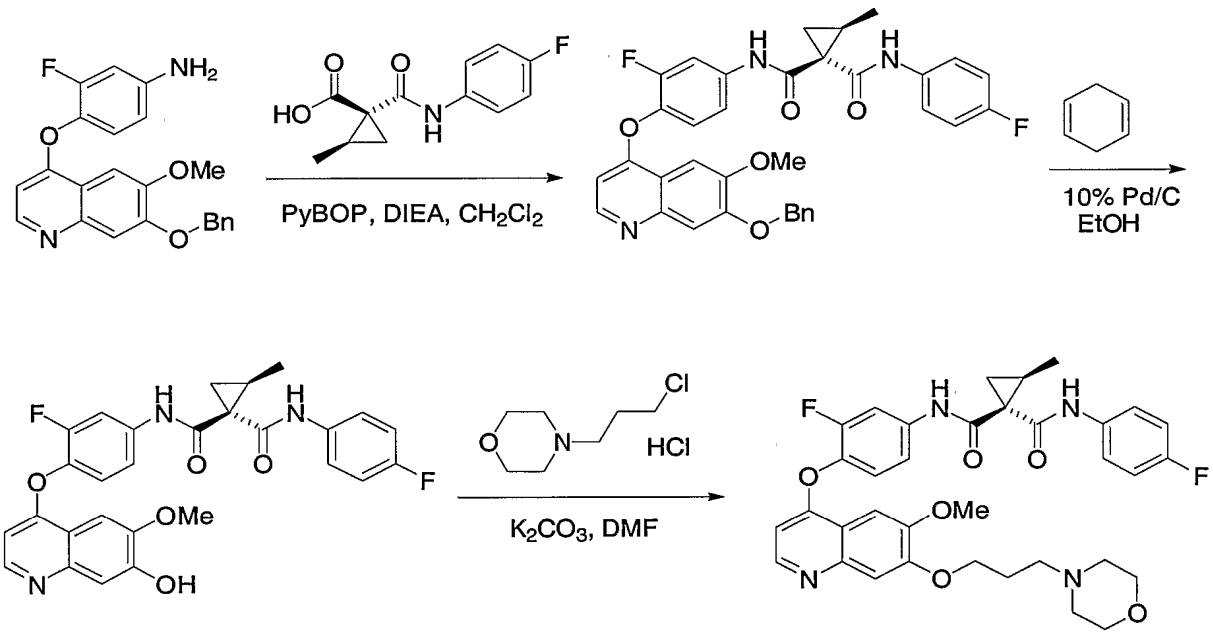
Example 80



[0431] Preparation of 1-(4-Fluoro-phenylcarbamoyl)-2-methyl-cyclopropanecarboxylic acid. 2-Methylcyclopropane-1,1-dicarboxylic acid methyl ester was prepared by following the literature procedure (Baldwin, J. E.; Adlington, R. M.; Rawlings, B. J. Tetrahedron Lett. 1985, 481.) The carboxylic acid (700 mg, 4.4 mmol) was dissolved in CH_2Cl_2 (10 mL). To the resulting solution was added 4-fluoroaniline (590 mg, 5.3 mmol), HOBt (890 mg, 6.6 mmol) and EDCI (2.5 g, 13.2 mmol). The stirring was continued for 3 h at rt. CH_2Cl_2 (30 mL) was added to the reaction mixture, and the resulting solution was washed with brine, and dried over Na_2SO_4. CH_2Cl_2 was removed under reduced pressure. Further purification by column chromatography gave 635 mg (57%) of the desired amide.

[0432] The methyl ester obtained above was then treated with $LiOH \cdot H_2O$ (116 mg, 2.78 mmol, 1.1 eqiv.) in THF (2 mL) and H_2O (1 mL) for 3h at rt. THF was removed under reduced pressure. The aqueous solution was diluted with 20 mL of H_2O, washed with ether (10 mL), and acidified with 1 N HCl. The solid was filtered, dissolved in EtOAc, and dried over Na_2SO_4. Removal of EtOAc gave the crude product of 1-(4-fluoro-phenylcarbamoyl)-2-methyl-cyclopropane-carboxylic acid, which was used in the next reaction. ^1H NMR (400 MHz, DMSO-d_6) δ 12.99 (br s, 1 H), 10.33 (br s, 1 H), 7.59 (dd, J = 9.0, 5.0 Hz, 2 H), 7.11 (dd, J = 9.0, 9.0 Hz, 2 H), 1.86-1.78 (m, 1 H), 1.43 (dd, J = 9.0, 4.2 Hz, 1 H), 1.30 (dd, J = 7.8, 4.3 Hz, 1 H), 1.19 (d, J = 6.3 Hz, 3 H).

Example 81



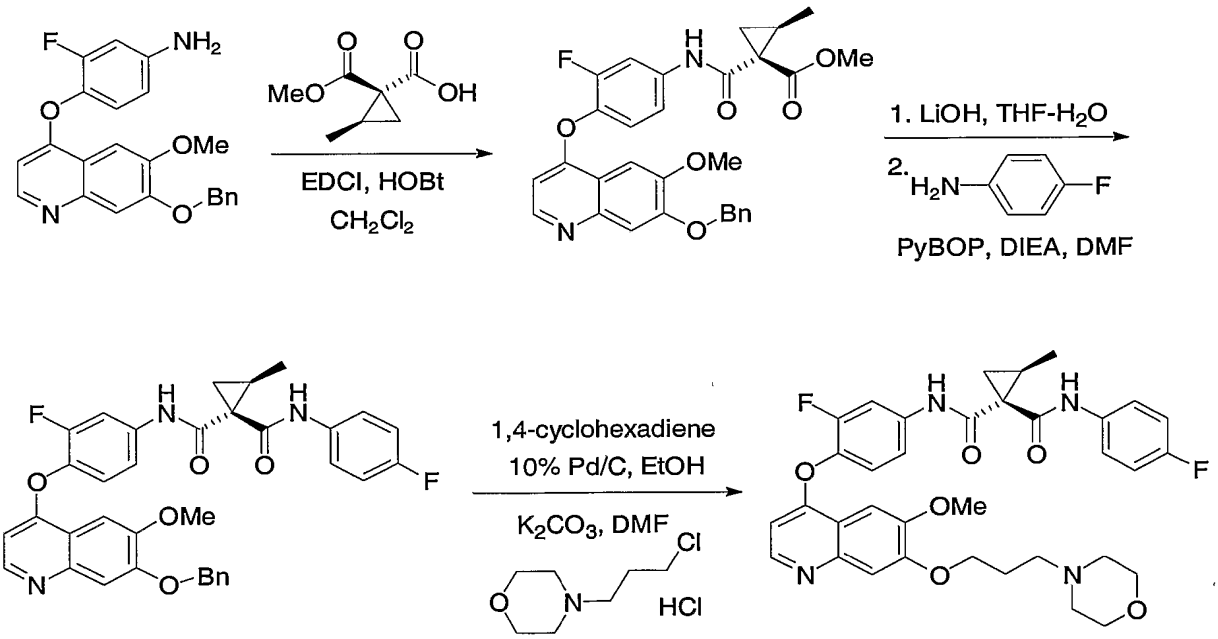
[0433] Synthesis of (1S,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl) oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide. To a solution of 4-(7-benzyloxy-6-methoxy-quinolin-4-yloxy)-3-fluoro-phenylamine (150 mg, 0.38 mmol) in CH_2Cl_2 (3 mL) was added DIEA (341 mg, 2.64 mmol), 1-(4-fluoro-phenylcarbamoyl)-2-methyl-cyclopropanecarboxylic acid (120 mg, 0.49 mmol) and PyBOP (686 mg, 1.32 mmol). The reaction mixture was stirred at rt for 6 h. After standard workup, the crude product was purified by column chromatography.

[0434] The coupling product (130 mg, 0.21 mmol) obtained above was dissolved in EtOH (2 mL). 1,4-cyclohexadiene (170 mg, 2.1 mmol) and 10% Pd/C (10 mg) were added. The

mixture was stirred for 2 h under reflux. After cooling, the mixture was filtered through Celite, and washed with MeOH. Removal of the solvents gave the crude product (136 mg), which was used in the next reaction.

[0435] To a solution of the 7-hydroxyquinoline (136 mg, 0.26 mmol) in DMF (2 mL) was added 4-(3-chloropropyl)morpholine hydrochloride (70 mg, 0.35 mmol) and K_2CO_3 (69 mg, 0.50 mmol). The reaction mixture was then stirred at 80 °C for 5 h. After cooling, EtOAc (20 mL) was added. The EtOAc solution was washed twice with brine, and dried over Na_2SO_4. Removal of EtOAc and purification by column chromatography (CH_2Cl_2 : MeOH = 10:1) gave '(1S,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide. The product was then dissolved in ethyl ether, and treated with 1.5 equiv. of 1 N HCl/ether. Filtration and lyophilization gave the HCl salt of '(1S,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (br s, 1 H), 10.26 (br s, 1 H), 10.15 (br s, 1 H), 8.74 (br s, 1 H), 7.95 (br d, J = 13.2 Hz, 1 H), 7.8-7.5 (m, 6 H), 7.16 (t, J = 8.9 Hz, 2 H), 6.82 (br s, 1 H), 4.34 (t, J = 5.9 Hz, 2 H), 4.02 (s, 3 H), 3.99 (br s, 2 H), 3.77 (br t, J = 12.0 Hz, 2 H), 3.56-3.30 (m, 4 H), 3.17-3.07 (m, 2 H), 2.40-2.30 (m, 2 H), 2.04-1.95 (m, 1 H), 1.45 (dd, J = 7.2, 4.7 Hz, 1 H), 1.36 (dd, J = 8.5, 4.5 Hz, 1 H), 1.09 (d, J = 6.2 Hz, 3 H).

Example 82



[0436] Synthesis of (1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]-quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide. To a solution of 4-(7-benzyloxy-6-methoxy-quinolin-4-yloxy)-3-fluoro-phenylamine (322 mg, 0.82 mmol) and 2-Methyl-cyclopropane-1,1-dicarboxylic acid methyl ester (195 mg, 1.23 mmol) in CH_2Cl_2 (4 mL) was added HOBt (61 mg, 0.32 mmol) and EDCI (211 mg, 1.64 mmol). The stirring was continued for 12 h at rt. The reaction mixture was then diluted with EtOAc and washed with brine. Removal of organic solvents *in vacuo* and further purification by column chromatography gave the desired coupling product (153 mg).

[0437] The product (153 mg, 0.29 mmol) obtained above was treated with $LiOH \cdot H_2O$ (15 mg, 0.35 mmol) in THF (1 mL) and H_2O (1 mL) for 2 h. THF was removed. 10 mL of H_2O was added to the mixture. The aqueous solution was washed with ether, and acidified with 1 N HCl. The solid was then filtered and dried under vacuum.

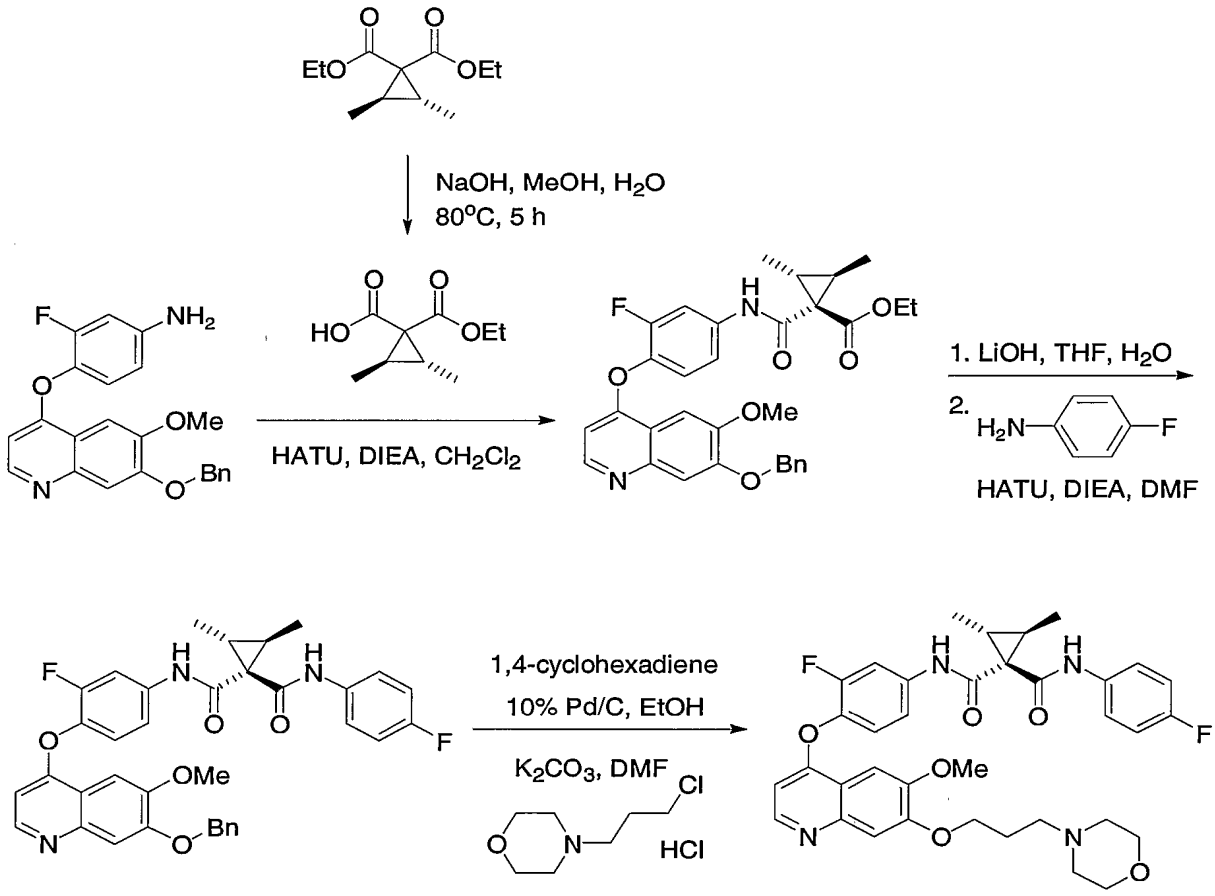
[0438] The crude carboxylic acid (118 mg, 0.23 mmol) and 4-fluoroaniline (111 mg, 0.27 mmol) were dissolved in DMF (2 mL). To this solution was added DIEA (178 mg, 1.38 mmol) and PyBOP (358 mg, 0.69 mmol). The mixture was stirred overnight at rt. It was then diluted with EtOAc, washed twice with brine. Removal of EtOAc and column chromatography gave the desired product.

[0439] The product (66 mg, 0.11 mmol) obtained above was dissolved in EtOH (2 mL). 1,4-cyclohexadiene (80 mg, 1.1 mmol) and 10% Pd/C (10 mg) were added. The mixture was stirred for 2 h under reflux. After cooling, the mixture was filtered through Celite, and washed with MeOH. Removal of the solvents gave the crude product (70 mg), which was used in the next reaction.

[0440] To a solution of the 7-hydroxyquinoline (80 mg, 0.15 mmol) in DMF (2 mL) was added 4-(3-chloropropyl)morpholine hydrochloride (62 mg, 0.31 mmol) and K_2CO_3 (64 mg, 0.46 mmol). The reaction mixture was then stirred at 80 °C for 5 h. After cooling, EtOAc (20 mL) was added. The EtOAc solution was washed twice with brine, and dried over Na_2SO_4. Removal of EtOAc and purification by column chromatography (CH_2Cl_2 : MeOH = 10:1) gave '(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide. The product was then dissolved in ethyl ether, and treated with 1.5 equiv. of 1 N HCl/ether. Filtration and lyophilization gave the HCl salt of '(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-

fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.65 (br s, 1 H), 10.54 (br s, 1 H), 9.74 (s, 1 H), 8.75 (br s, 1 H), 8.01 (br d, J = 12.9 Hz, 1 H), 7.80-7.50 (m, 6 H), 7.20-7.10 (m, 2 H), 6.84 (br s, 1 H), 4.34 (br t, J = 5 Hz, 2 H), 4.04 (s, 3 H), 4.05-3.95 (m, 2 H), 3.77 (br t, J = 11 Hz, 2 H), 3.52 (br d, J = 12.7 Hz, 4 H), 3.12 (br q, J = 9.0 Hz, 2 H), 2.40-2.30 (m, 2 H), 2.10-1.95 (m, 1 H), 1.40-1.30 (m, 2 H), 1.10 (d, J = 6.2 Hz, 3 H).

Example 83



[0441] Synthesis of '(2R,3R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]-quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide. 2,3-trans-Dimethyl-cyclopropane-1,1-dicarboxylic acid diethyl ester was prepared by following the literature procedure. (Ohishi, J. Synthesis, 1980, 690.) To a solution of 2,3-trans-dimethyl-cyclopropane-1,1-dicarboxylic acid diethyl ester (6.75 g, 31.5 mmol) in MeOH (30 mL) was added 33 mL of 1 N NaOH aqueous solution. The mixture was stirred at 85 °C for 5 h. MeOH was removed under reduced pressure; the residue was diluted with 40 mL of H_2O. The aqueous solution was washed with 20 mL of

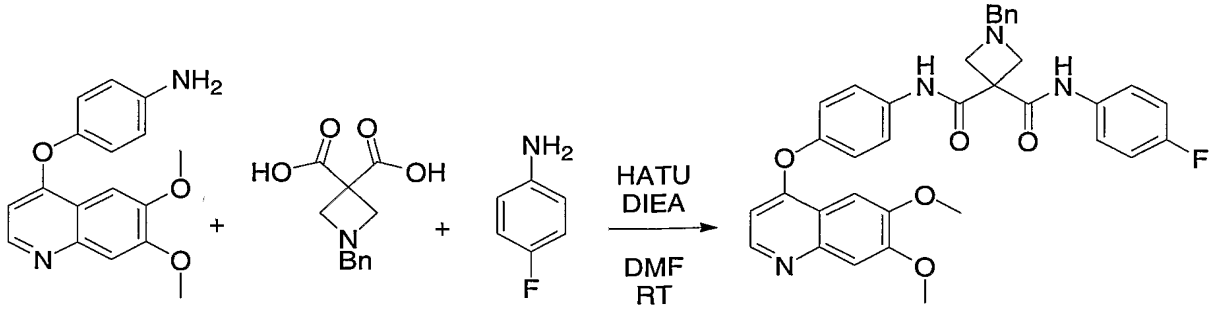
ether, and acidified with 1 N HCl. Filtration and drying under vacuum gave 4.72 g 80 %) of the desired carboxylic acid.

[0442] The aniline (1.08 g, 2.78 mmol) and the carboxylic acid (518 mg, 2.78 mmol) prepared above were dissolved in CH_2Cl_2 (15 mL). HATU (2.11 g, 5.56 mmol) and DIEA (1.8 mL, 11.1 mmol) were added. The reaction mixture was stirred at rt overnight. It was then concentrated and diluted with EtOAc. The EtOAc solution was then washed with 5% NaOH and brine. Removal of EtOAc gave the crude coupling product, which was hydrolyzed to the corresponding carboxylic acid by treatment with $LiOH•H_2O$ (175 mg, 4.17 mmol) in THF (100 mL) -H_2O (50 mL) at 60 °C for 10 h.

[0443] The carboxylic acid (850 mg, 1.60 mmol) and 4-fluoroaniline (355 mg, 3.20 mmol) were dissolved in DMF (8 mL). HATU (3.89 g, 3.2 mmol) and DIEA (1.1 ml, 6.4 mmol) were added. The reaction mixture was stirred at rt overnight. H_2O (10 mL) was added to the reaction, and a precipitate formed. The solid was filtered, washed with aqueous sat. Na_2CO_3 and ether. Further purification by column chromatography gave 596 mg (60%) of the desired product. Debenzylation was done by following the standard procedure.

[0444] To a solution of the 7-hydroxyquinoline (261 mg, 0.49 mmol) in DMF (5 mL) was added 4-(3-chloropropyl)morpholine hydrochloride (195 mg, 0.98 mmol) and K_2CO_3 (202 mg, 1.46 mmol). The reaction mixture was then stirred at 80 °C for 4 h. After cooling, EtOAc (20 mL) was added. The EtOAc solution was washed twice with brine, and dried over Na_2SO_4. Removal of EtOAc and purification by column chromatography (CH_2Cl_2 : MeOH = 10:1) gave 122 mg (37%) of '(2R,3R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethyl-cyclopropane-1,1-dicarboxamide. ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 5.1 Hz, 1 H), 8.11 (br s, 1 H), 7.77-7.70 (m, 2 H), 7.53 (s, 1 H), 7.50-7.44 (m, 2 H), 7.40 (s, 1 H), 7.22-7.16 (m, 2 H), 7.06-6.98 (m, 2 H), 6.36 (br d, J = 5.1 Hz, 1 H), 4.26 (t, J = 7.0 Hz, 2 H), 4.02 (s, 3 H), 3.72 (t, J = 4.4 Hz, 4 H), 2.57 (t, J = 7.3 Hz, 2 H), 2.50-2.42 (m, 4 H), 2.18-2.10 (m, 2 H), 1.80-1.66 (m, 2 H), 1.30-1.24 (m, 6 H).

Example 84

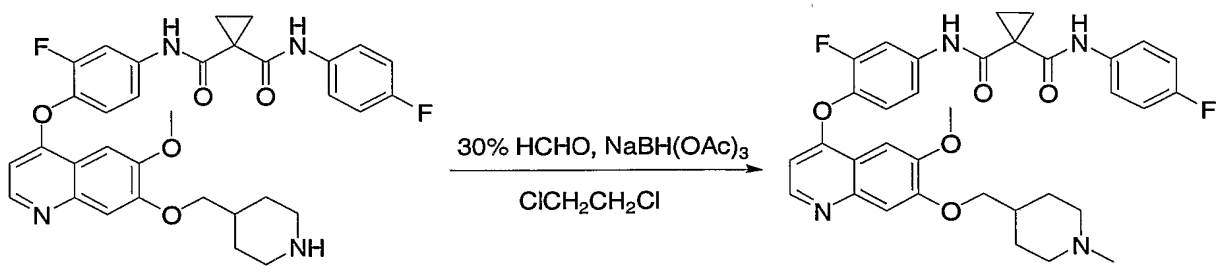


[0445] Synthesis of 'N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-1-(phenylmethyl)azetidine-3,3-dicarboxamide. 1-Benzyl-azetidine-3,3-dicarboxylic acid was prepared by following the literature procedure (Miller, R. A.; et al. Syn. Comm. 2003, 33, 3347). To a solution of 4-(6,7-dimethoxy-quinolin-4-yloxy)-phenylamine (4.2 mmol, 1 equiv.) and 4-fluoroaniline (4.2 mmol, 1 equiv.) in DMF (20 mL) was charged with DIEA (12.6 mmol, 3 equiv.) and a solution of 1-benzyl-azetidine-3,3-dicarboxylic acid (4.2 mmol, 1 equiv.) in DMF (10 mL). The reaction mixture was allowed to stir at RT and monitored by LCMS. The reaction was complete in 6 h. The reaction mixture was diluted with ethyl acetate and washed with 10% LiCl (3x), brine (3x), dried with sodium sulfate, filtered and the solvent was reduced *in vacuo*. The crude product was purified by silica gel chromatography eluting with 2% of MeOH in EtOAc. The fractions containing the desired product were further purified using preparative HPLC to give 'N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-1-(phenylmethyl)azetidine-3,3-dicarboxamide (300 mg, 12% yield) as a white solid. ^{1}HNMR (DMSO-d6): 10.0 (s, 1H), 9.90 (s, 1H), 8.45 (d, 1H), 7.80 (d, 2H), 7.70 (m, 2H), 7.50 (s, 1H), 7.40 (s, 1H), 7.48-7.15 (m, 9H), 3.95 (s, 6H), 3.70 (s, 4H), 3.60 (s, 2H). LCMS (POS): 607.2 (M+H).

[0446] N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) azetidine-3,3-dicarboxamide. To a solution of 'N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-1-(phenylmethyl)azetidine-3,3-dicarboxamide (300 mg, 0.5 mmol) in MeOH (50 mL) was charged with Pd/C (50% wet, 10% mmol, 265 mg) and acetic acid (2 mL). The reaction mixture was subjected to hydrogenolysis condition under H2 (50 psi) on a Parr Hydrogenator for 16 hr. The reaction mixture was filtered through celite and washed with MeOH. After removal of solvent in vacuo, the crude product was purified using preparative HPLC (solvent system: MeCN/H2O/NH4OAc), affording N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)

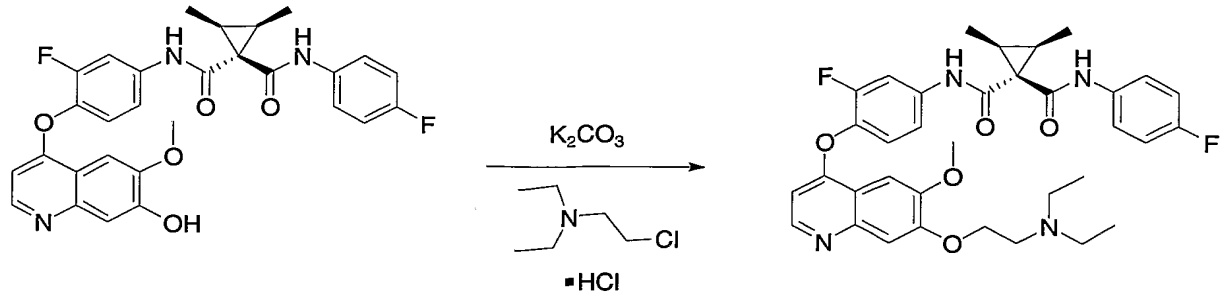
azetidine-3,3-dicarboxamide (82 mg, 32% yield) as a white solid. ^{1}HNMR (DMSO-d6): 8.46 (d, 1H), 7.84 (d, 2H), 7.70 (m, 2H), 7.50 (s, 1H), 7.40 (s, 1H), 7.24 (d, 2H), 7.20 (t, 2H), 6.44 (d, 1H), 4.03 (s, 4H), 3.95 (s, 6H), 1.90 (s, 3H, acetate salt). LCMS (POS): 517.3 (M+H).

Example 85



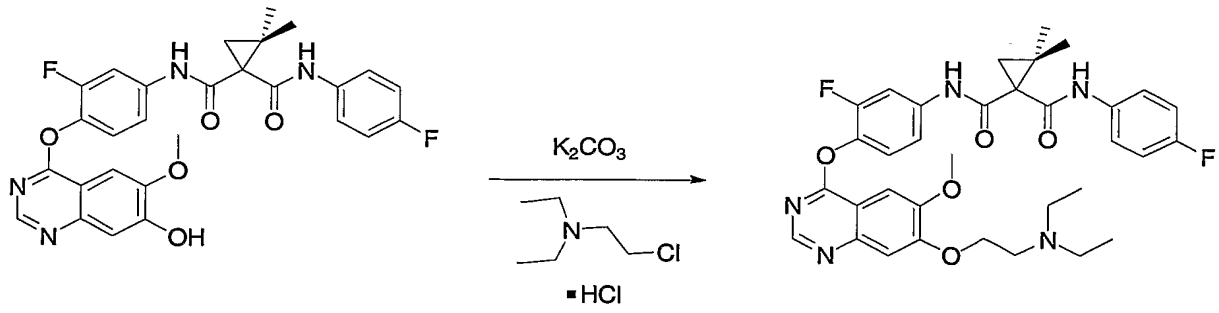
[0447] N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. To a solution of cyclopropane-1,1-dicarboxylic acid {3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-amide (4-fluoro-phenyl)-amide, TFA salt (~500 mg, 0.71 mmol) in $ClCH_2H_2Cl$ (8 mL) were added 30% formaldehyde (4 mL) and $NaBH(OAc)_3$ (752 mg, 3.55 mmol). The reaction mixture was stirred overnight. It was then quenched with aqueous sat. $NaHCO_3$, extracted with EtOAc. The organic phase was washed with brine and dried over Na_2SO_4. Drying salts were filtered, washed with EtOAc and the filtrate concentrated in vacuo to give 210mgs of crude product. The resulting residue was redissolved in EtOAc and any insoluble material filtered. To the filtrate was added 4M HCl in dioxane (200µl) and the mixture was stirred at room temperature for 1 hour. Solids were filtered, washed with EtOAc, dried under high vacuum, dissolved in 50% aqueous AcCN and lyophilized to give 'N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, HCl salt (113 mg, ~25% yield). ^{1}HNMR (400MHz, DMSO-d6): δ 10.51 (s, 1H), 10.30 (br. s, 1H), 10.04 (s, 1H), 8.80 (d, 1H), 7.99 (dd, 1H), 7.55 (m, 2H), 7.67-7.53 (m, 4H), 7.16 (t, 2H), 6.89 (d, 1H), 4.13 (d, 2H), 4.05 (s, 3H), 3.47 (m, 2H), 3.00 (m, 2H), 2.74 (d, 3H), 2.17 (m, 1H), 2.03 (m, 2H), 1.68 (m, 2H), 1.49 (m, 4H). LC/MS Calcd for $[M+H]^+$ 617.3, found 617.4. Anal. HPLC (8 min gradient): 98% pure, 3.11 min.

Example 86



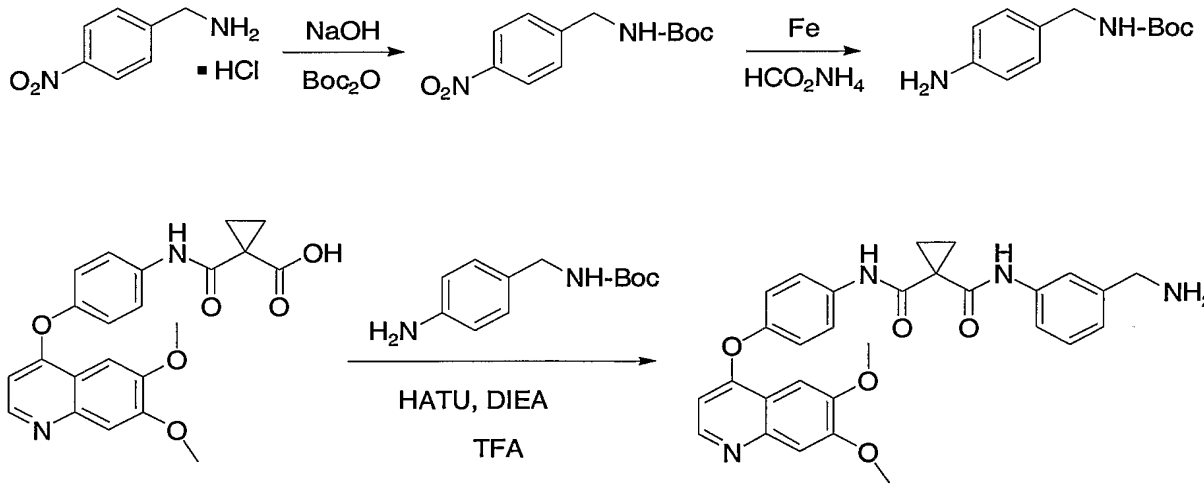
[0448] (1R,2R,3S)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide. 2,3-Dimethyl-cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (210 mg, 0.39mmol), DMA (2mls), (2-chloro-ethyl)-diethyl-amine, HCl salt (73 mg, 0.42mmol) and K_2CO_3 (136 mg, 0.98mmol) were combined and heated at 80C overnight. The reaction mixture was then diluted with H_2O and sonicated. The resulting solids were filtered, washed with H_2O and dried under high vacuum. The crude product was then purified by preparative HPLC using an ammonium acetate buffer system and lyophilized to give '(1R,2R,3S)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide (39 mg, 16% yield). ^{1}HNMR (400MHz, DMSO-d6): δ 10.14 (s, 1H), 9.61 (s, 1H), 8.46 (d, 1H), 7.87 (dd, 1H), 7.67 (m, 2H), 7.57 (m, 1H), 7.51 (s, 1H), 7.42 (s, 1H), 7.39 (m, 1H), 7.15 (t, 2H), 6.41 (d, 1H), 4.20 (m, 2H), 3.94 (s, 3H), 2.87 (m, 2H), 2.60 (m, 4H), 1.80 (m, 2H), 1.18 (s, 3H), 1.17 (s, 3H), 1.01 (m, 6H). Note: 0.5eq of AcOH is present by NMR. LC/MS Calcd for $[M+H]^+$ 633.3, found 633.4. Anal. HPLC (25 min gradient): 96% pure, 18.52 min.

Example 87



[0449] N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide. 2,2-Dimethyl-cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinazolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (203 mg, 0.38mmol), DMA (2mls), (2-chloro-ethyl)-diethyl-amine, HCl salt (73 mg, 0.42mmol) and K_2CO_3 (146 mg, 1.05mmol) were combined and heated at 80C overnight. The reaction mixture was then diluted with H_2O and extracted with CH_2Cl_2 (3x). The combined CH_2Cl_2 extractions were washed with sat'd $NaHCO_3$ (1x), sat'd NaCl (1x), dried (Na_2SO_4), and concentrated in vacuo. The resulting crude product was purified by flash chromatograghy (Silica Gel 60, 100% EtOAc, followed by 10% MeOH, 1% triethylamine in EtOAc), then dissolved in 50% aqueous AcCN and lyophilized to give 'N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethyl-cyclopropane-1,1-dicarboxamide (70 mg, 29% yield). ^{1}HNMR (400MHz, DMSO): δ 10.24 (s, 1H), 10.00 (s, 1H), 8.54 (s, 1H), 7.84 (dd, 1H), 7.66 (m, 2H), 7.56 (s, 1H), 7.51 (m, 1H), 7.43 (m, 2H), 7.18 (t, 2H), 4.26 (m, 2H), 3.98 (s, 3H), 2.88 (m, 2H), 2.59 (m, 4H), 1.58 (m, 2H), 1.18 (s, 6H), 1.00 (t, 6H). LC/MS Calcd for $[M+H]^+$ 634.3, found 634.4. Anal. HPLC (25 min gradient): 94% pure, 24.08 min.

Example 88



[0450] Synthesis of 'N-[3-(aminomethyl)phenyl]-N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide. (4-Nitro-benzyl)-carbamic acid tert-butyl ester. 4-Nitro-benzylamine, HCl salt (5.19g, 27.5mmol) was dissolved in dioxane (100mls). NaOH (3.4g, 85.0mmol) in H_2O (20mls) was added, followed by Boc

anhydride (7.6g, 34.8mmol). The mixture was stirred at room temperature. After 3hrs, the reaction mixture was diluted with EtOAc and washed with H_2O (3x), sat'd NaCl (1x), dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was triturated with hexanes, the resulting solids filtered, washed with hexanes and dried under vacuum to give (4-nitro-benzyl)-carbamic acid tert-butyl ester (6.34g, 91% yield). LC/MS Calcd for $[M+H]^+$ 253.1, found 197.0 (minus t-butyl).

[0451] (4-Amino-benzyl)-carbamic acid tert-butyl ester. (4-Nitro-benzyl)-carbamic acid tert-butyl ester (6.34g, 25.1mmol), iron powder (6.5g, 116mmol), ammonium formate (13.0g, 206mmol), H_2O (75mls), and toluene (75mls) were combined and heated to reflux. After 3hrs the reaction mixture was allowed to cool and filtered through Celite with thorough washing with EtOAc. The filtrate was transferred to a separatory funnel and the phases separated. The organic phase was further washed with H_2O (1x), sat'd NaCl (1x), dried (Na_2SO_4), and concentrated in vacuo to give (4-amino-benzyl)-carbamic acid tert-butyl ester (5.02g, 90% yield). LC/MS Calcd for $[M+H]^+$ 223.1, found 167.1 (minus t-butyl).

[0452] [3-({1-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-phenylcarbamoyl]-cyclopropane-carbonyl}-amino)-benzyl]-carbamic acid tert-butyl ester. 1-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-phenylcarbamoyl]-cyclopropanecarboxylic acid (254 mg, 0.62mmol), (4-amino-benzyl)-carbamic acid tert-butyl ester (164 mg, 0.74mmol), dry DMA (10mls), HATU (714 mg, 1.88mmol), and DIEA (325ml, 1.86mmol) were combined and stirred at room temperature. After 2hrs, the reaction mixture is diluted with H_2O and the resulting solids are filtered, washed with H_2O, followed by sat'd $NaHCO_3$, and dried under high vacuum to give crude [3-({1-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenylcarbamoyl]-cyclopropanecarbonyl}-amino)-benzyl]-carbamic acid tert-butyl ester (301 mg, 79% yield) which was used in the next reaction without further purification. LC/MS Calcd for $[M+H]^+$ 613.3, found 613.1.

[0453] N-[3-(Aminomethyl)phenyl]-N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl) cyclopropane-1,1-dicarboxamide, TFA salt. [3-({1-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-phenylcarbamoyl]-cyclopropanecarbonyl}-amino)-benzyl]-carbamic acid tert-butyl ester (50 mg, 0.081mmol) was dissolved in 50% TFA in CH_2Cl_2 (10mls) and stirred at room temperature. After 2hrs, the reaction mixture was concentrated in vacuo and the resulting residue was triturated with Et_2O. The resulting solids were filtered, washed with Et_2O and dried under high vacuum to give 'N-[3-(aminomethyl)phenyl]-N'-(4-{[6,7-

bis(methyloxy)quinolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide as the TFA salt (54 mg, 100%). ^{1}HNMR (400MHz, DMSO-d6): δ 10.28 (s, 1H), 10.19 (s, 1H), 8.77 (m, 1H), 8.21 (m, 3H), 7.84 (m, 2H), 7.76 (m, 1H), 7.71 (m, 1H), 7.58 (m, 2H), 7.38 (m, 3H), 7.19 (m, 1H), 6.76 (m, 1H), 4.03 (s, 6H), 3.39 (m, 2H), 1.53 (m, 4H). Note: all peaks are very broad and unresolved. LC/MS Calcd for $[M+H]^+$ 513.2, found 513.4. Anal. HPLC (25 min gradient): 88% pure, 12.39 min.

[0454] Table 3 contains ^{1}H-NMR data for selected compounds of the invention.

Table 3

Entry	Name	^{1}H-NMR
1	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	1H NMR (DMSO-d6): 10.52 (s, 1H), 10.02 (s, 1H), 9.38 (br., 3H), 8.79 (d, 1H), 7.98 (dd, 1H), 7.74 (s, 1H), 7.65 (m, 3H), 7.54 (m, 2H), 7.15 (t, 2H), 6.86 (d, 1H), 4.33 (t, 2H), 4.04 (s, 3H), 3.17-3.50 (m, 9H), 2.27 (br., 2H), 1.79 (m, 1H), 1.48 (m, 4H). Note: The peak at δ9.38 includes 2 TFA equivalents.
2	N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	1H NMR (DMSO-d6): 10.41 (s, 1H), 10.03 (s, 1H), 8.47 (d, 1H), 7.90 (dd, 1H), 7.64 (m, 2H), 7.52 (s, 2H), 7.42 (t, 1H), 7.39 (s, 1H), 7.16 (t, 2H), 6.41 (d, 1H), 4.18 (t, 2H), 3.95 (s, 3H), 2.47 (t, 2H), 2.6-2.8 (br., 8H), 2.17 (s, 3H), 1.97 (m, 2H), 1.48 (s, 4H).
3	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	1H NMR (400MHz, DMSO-d6): d 10.51 (s, 1H), 10.30 (br. s, 1H), 10.04 (s, 1H), 8.80 (d, 1H), 7.99 (dd, 1H), 7.55 (m, 2H), 7.67-7.53 (m, 4H), 7.16 (t, 2H), 6.89 (d, 1H), 4.13 (d, 2H), 4.05 (s, 3H), 3.47 (m, 2H), 3.00 (m, 2H), 2.74 (d, 3H), 2.17 (m, 1H), 2.03 (m, 2H), 1.68 (m, 2H), 1.49 (m, 4H).
4	N-(4-fluorophenyl)-N'-[4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]cyclopropane-1,1-dicarboxamide	^{1}H NMR (400 MHz, DMSO-d6): 8.47 (d, 1H), 8.30 (m, 1H), 8.15 (m, 1H), 7.8 (m, 2H), 7.62 (s, 1H), 7.45 (m, 2H), 7.2 (m, 3H), 7.10 (m, 2H), 6.7 (d, 1H), 4.5 (m, 2H), 4.3 (m, 2H), 4.01(s, 3H), 3.5 (br, 2H), 3.3 (m, 2H), 3.1 (m, 2H), 2.51 (m, 2H), 1.9 (m, 2H) 1.6 (m, 4H).
5	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	^{1}H NMR (400 MHz, DMSO-d6): 10.58 (s, 1H), 10.31 (bs, 1H), 10.04 (s, 1H), 8.75 (d, 1H), 7.99 (d, 1H), 7.74 (s, 1H), 7.63 (m, 4H), 7.19 (t, 2H), 6.91 (m, 1H), 4.39 (t, 2H), 4.19 (s, 3H), 3.21 (m, 7H), 2.29 (m, 2H), 1.46 (d, 4H), 1.15 (t, 6H).

Table 3

Entry	Name	^{1}H-NMR
6	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-chloro-5-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	1H NMR (DMSO-d6): 11.56 (s, 1H), 9.77 (s, 1H), 8.50 (d, 1H), 8.32 (d, 1H), 7.82 (d, 1H), 7.59 (m, 2H), 7.51 (s, 1H), 7.42 (s, 1H), 7.20 (t, 2H), 6.55 (d, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 1.73 (m, 2H), 3.65 (m, 2H).
7	N-(4-{[6,7-bis(methyloxy)-2-(methylthio)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	^{1}H NMR (DMSO-d_6) d 10.34 (s, 1H), 9.94 (s, 1H), 7.83 (d, 1H), 7.59 (m, 2H), 7.56 (m, 1H), 7.40 (m, 2H), 7.23 (s, 1H), 7.09 (t, 2H), 6.12 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 2.48 (s, 3H), 1.40 (m, 4H).
8	N-(4-fluorophenyl)-N'-(4-{[2-methyl-6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide	^{1}H NMR (DMSO-d_6) 10.15 (bs, 1H), 10.01 (bs, 1H), 7.69-7.75 (m, 2H), 7.61-7.68 (m, 2H), 7.52 (s, 1H), 7.32 (s, 1H), 7.23-7.29 (m, 2H), 7.12-7.19 (m, 2H), 3.93 (d, 6H), 2.43 (s, 3H), 1.53 (s, 4H).
9	N-(4-{[2-amino-6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	1H NMR (DMSO-d6) d 10.34 (s, 1H), 9.95 (s, 1H), 7.82 (d, 1H), 7.58 (m, 2H), 7.44 (d, 1H), 7.33 (t, 1H), 7.25 (s, 1H), 7.09 (t, 2H), 7.07 (s, 1H), 6.17 (br s, 2H), 5.66 (s, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 1.40 (d, 4H).
10	N-(3-fluoro-4-{[2-(methylamino)-6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	^{1}H NMR (DMSO-d_6) d 10.42 (s, 1H), 9.91 (s, 1H), 7.88 (dd, 1H), 7.56 (m, 2H), 7.44 (m, 4H), 7.09 (t, 2H), 5.90 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.39 (br s, 1H), 2.92 (s, 3H), 1.41 (dt, 4H).
11	(1S,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	^{1}H NMR (400 MHz, DMSO-d_6) d 10.49 (br s, 1 H), 10.26 (br s, 1 H), 10.15 (br s, 1 H), 8.74 (br s, 1 H), 7.95 (br d, J = 13.2 Hz, 1 H), 7.8-7.5 (m, 6 H), 7.16 (t, J = 8.9 Hz, 2 H), 6.82 (br s, 1 H), 4.34 (t, J = 5.9 Hz, 2 H), 4.02 (s, 3 H), 3.99 (br s, 2 H), 3.77 (br t, J = 12.0 Hz, 2 H), 3.56-3.30 (m, 4 H), 3.17-3.07 (m, 2 H), 2.40-2.30 (m, 2 H), 2.04-1.95 (m, 1 H), 1.45 (dd, J = 7.2, 4.7 Hz, 1 H), 1.36 (dd, J = 8.5, 4.5 Hz, 1 H), 1.09 (d, J = 6.2 Hz, 3 H).

Table 3

Entry	Name	^{1}H-NMR
12	(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	^{1}H NMR (400 MHz, DMSO-d_6) d 10.65 (br s, 1 H), 10.54 (br s, 1 H), 9.74 (s, 1 H), 8.75 (br s, 1 H), 8.01 (br d, J = 12.9 Hz, 1 H), 7.80-7.50 (m, 6 H), 7.20-7.10 (m, 2 H), 6.84 (br s, 1 H), 4.34 (br t, J = 5 Hz, 2 H), 4.04 (s, 3 H), 4.05-3.95 (m, 2 H), 3.77 (br t, J = 11 Hz, 2 H), 3.52 (br d, J = 12.7 Hz, 4 H), 3.12 (br q, J = 9.0 Hz, 2 H), 2.40-2.30 (m, 2 H), 2.10-1.95 (m, 1 H), 1.40-1.30 (m, 2 H), 1.10 (d, J = 6.2 Hz, 3 H).
13	N-(4-{[6-{[3-(diethylamino)propyl]oxy}-7-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	^{1}H NMR (DMSO-d_6) d 10.37 (br s, 1H), 10.00 (s, 1H), 8.44 (d, 1H), 7.87 (d, 1H), 7.62 (m, 2H), 7.49 (m, 2H), 7.41 (m, 2H), 7.13 (t, 2H), 6.40 (d, 1H), 4.17 (t, 2H), 3.93 (s, 3H), 2.59 (t, 2H), 2.49 (m, 6H), 1.91 (m, 4H), 0.94 (t, 6H).
14	N-(4-{[6-{[2-(diethylamino)ethyl]oxy}-7-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	^{1}H NMR (DMSO-d_6) d 10.36 (br s, 1H), 9.99 (s, 1H), 8.44 (d, 1H), 7.88 (dd, 1H), 7.62 (m, 2H), 7.57 (m, 2H), 7.41 (m, 2H), 7.13 (t, 2H), 6.40 (d, 1H), 4.17 (t, 2H), 3.93 (s, 3H), 2.85 (t, 2H), 2.56 (q, 4H), 2.49 (m, 4H), 0.98 (t, 6H).
15	1,1-dimethylethyl 4-(3-{[4-[(2-fluoro-4-{[(1-{[(4-fluorophenyl)amino]carbonyl}cyclopropyl)carbonyl]amino}phenyl)oxy]-6-(methyloxy)quinolin-7-yl]oxy}propyl)piperazine-1-carboxylate	^{1}H NMR (400 MHz, $CDCl_3$): 10.05 (s, 1H), 8.49-8.27 (t, 1H), 7.79-7.76 (d, 1H), 7.57 (s, 1H), 7.47-7.43 (m, 3H), 7.27-7.20 (m, 1H), 7.09-7.04 (m, 2H), 6.40-6.39 (d, 1H), 4.28-4.25 (t, 2H), 3.50 (s, 3H), 3.47-3.44, (t, 4H), 2.62-2.59 (t, 2H), 2.46-2.44 (t, 4H), 2.18-2.11 (m, 2H), 2.09 (s, 1H), 1.83-1.81 (t, 2H), 1.64-1.61 (t, 2H), 1.47 (s, 9H).
16	(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	^{1}H NMR (DMSO-d_6) d 10.40 (s, 1H), 9.65 (s, 1H), 8.45 (s, 1H), 7.79 (dd, 1H), 7.53 (m, 2H), 7.47 (s, 1H), 7.36 (m, 1H), 7.31 (m, 2H), 7.05 (t, 2H), 4.17 (t, 2H), 3.91 (s, 3H), 3.51 (t, 4H), 2.40 (t, 2H), 2.36 (m, 4H), 1.90 (m, 3H), 1.30 (m, 2H), 1.02 (d, 3H).
17	(1R,2R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	^{1}H NMR (DMSO-d_6) d 10.49 (s, 1H), 9.73 (s, 1H), 8.52 (s, 1H), 7.85 (dd, 1H), 7.61 (m, 2H), 7.54 (s, 1H), 7.41 (m, 3H), 7.12 (t, 2H), 7.23 (t, 2H), 3.96 (s, 3H), 2.86 (t, 2H), 2.56 (q, 4H), 1.98 (m, 1H), 1.34 (m, 2H), 1.07 (d, 3H), 0.97 (t, 6H).

Table 3

Entry	Name	^{1}H-NMR
18	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	1H NMR (DMSO-d6) 8.51 (s, 1H), 7.78-7.84 (m, 1H), 7.58-7.64 (m, 2H), 7.53 (s, 1H), 7.34-7.48 (m, 3H), 7.13 (t, 2H), 4.22 (t, 2H), 3.98 (s, 3H), 2.84 (t, 2H), 2.55 (q, 4H), 1.48 (s, 4H), 1.39 (t, 6H).
19	N-(4-{[7-{[3-(4-acetylpiperazin-1-yl)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	^{1}H NMR (400 MHz, $CDCl_3$): 10.04 (s, 1H), 8.48-8.47 (d, 1H), 8.21 (s, 1H), 7.79-7.76 (d, 1H), 7.57 (s, 1H), 7.52-7.44 (m, 3H), 7.28-7.20 (m, 2H), 7.09-7.05 (t, 2H), 6.40-6.39 (d, 1H), 4.30-4.26 (t, 2H), 4.04 (s, 3H), 3.64-3.62 (t, 2H), 3.49-3.47 (t, 2H), 2.62-2.58 (t, 2H), 2.50-2.44 (m, 4H), 2.17-2.12 (m, 2H), 2.10 (s, 3H), 1.84-1.81 (t, 2H), 1.64-1.61 (t, 2H).
20	1,1-dimethylethyl 4-(3-{[4-[(2-fluoro-4-{[((1R,2R)-1-{[(4-fluorophenyl)amino]carbonyl}-2-methylcyclopropyl)carbonyl]amino}phenyl)oxy]-6-(methyloxy)quinolin-7-yl]oxy}propyl)piperazine-1-carboxylate	^{1}H NMR (400 MHz, DMSO-d_6): 10.54 (s, 1H), 9.72 (s, 1H), 8.47-8.46 (d, 1H), 7.96-7.93 (dd, 1H), 7.63-7.61 (m, 2H), 7.52 (br s, 2H), 7.42-7.40 (d, 2H), 7.17-7.12 (t, 2H), 6.44-6.42 (d, 1H), 4.22-4.18 (t, 2H), 3.95 (s, 3H), 3.42-3.40 (m, 2H), 2.36-2.26 (m, 8H), 2.00-1.98 (m, 3H), 1.58-1.54 (m, 2H), 1.40 (s, 9H), 1.10-1.09 (d, 3H).
21	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-1-(phenylmethyl)azetidine-3,3-dicarboxamide	1H NMR (DMSO-d6): 10.0 (s, 1H), 9.9 (s, 1H), 8.45 (d, 1H), 7.8 (d, 2H), 7.7 (m, 2H), 7.5 (s, 1H), 7.4 (s, 1H), 7.48-7.15 (m, 9H), 3.95 (s, 6H), 3.7 (s, 4H), 3.6 (s, 2H).
22	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)azetidine-3,3-dicarboxamide	1H NMR (DMSO-d6): 8.46 (d, 1H), 7.84 (d, 2H), 7.70 (m, 2H), 7.50 (s, 1H), 7.40 (s, 1H), 7.24 (d, 2H), 7.20 (t, 2H), 6.44 (d, 1H), 4.03 (s, 4H), 3.95 (s, 6H), 1.90 (s, 3H, acetate salt).
23	(1R,2S)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	^{1}H NMR (400 MHz, DMSO-d_6): 10.26 (s, 1H), 9.75 (s, 1H), 8.47-8.46 (d, 1H), 7.91-7.87 (dd, 1H), 7.70-7.66 (m, 2H), 7.56-7.51 (m, 2H), 7.43-7.38 (m, 2H), 6.42-6.41 (d, 1H), 4.20-4.16 (t, 2H), 3.95 (s, 3H), 2.47-2.43 (m, 2H), 2.40-2.24 (m, 5H), 2.14 (s, 3H), 2.03-1.93 (m, 3H), 1.89 (s, 3H), 1.45-1.42 (m, 1H), 1.38-1.35 (m, 1H), 1.10-1.08 (d, 3H).

Table 3

Entry	Name	^{1}H-NMR
24	(1R,2R)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	^{1}H NMR (400 MHz, DMSO-d_6): 10.56 (s, 1H), 9.75 (s, 1H), 8.47-8.46 (d, 1H), 7.96-7.93 (d, 1H), 7.68-7.61 (m, 2H), 7.53-7.52 (m, 2H), 7.44-7.39 (m, 2H), 7.18-7.12 (m, 2H), 6.44-6.42 (d, 1H), 4.20-4.17 (t, 2H), 3.95 (s, 3H), 3.42-3.30 (m, 3H), 2.46-2.44 (m, 2H), 2.33 (br s, 2H), 2.15 (s, 3H), 2.05-1.94 (m, 2H), 1.89 (s, 5H), 1.40-1.35 (m, 1H), 1.10-1.09 (m, 3H).
25	(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	^{1}H NMR (400 MHz, DMSO-d_6): 10.55 (s, 1H), 9.72 (s, 1H), 8.47-8.46 (d, 1H), 7.96-7.93 (d, 1H), 7.68-7.61 (m, 2H), 7.52 (br s, 2H), 7.44-7.40 (m, 2H), 7.17-7.12 (m, 2H), 6.44-6.43 (d, 1H), 4.21-4.18 (t, 2H), 3.95 (s, 3H), 2.79 (br s, 4H), 2.47-2.44 (t, 2H), 2.38 (br s, 3H), 2.04-1.95 (m, 3H), 1.40-1.35 (m, 2H), 1.11-1.09 (m, 5H).
26	N-(3-fluoro-4-{[7-({3-[4-(1-methylethyl)piperazin-1-yl]propyl}oxy)-6-(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	^{1}H NMR (400 MHz, DMSO-d_6): 10.40 (s, 1H), 10.02 (s, 1H), 8.47-8.46 (d, 1H), 7.92-7.89 (d, 1H), 7.66-7.63 (m, 2H), 7.52-7.51 (d, 2H), 7.44-7.39 (m, 2H), 7.19-7.14 (m, 2H), 6.42-6.41 (d, 1H), 4.20-4.17 (t, 2H), 3.95 (s, 3H), 2.70-2.68 (m, 1H), 2.62-2.55 (m, 2H), 2.46-2.33 (m, 8H), 1.99-1.94 (m, 2H), 1.47 (s, 4H), 1.00-0.95 (m, 6H).
27	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	^{1}H NMR (DMSO-d_6)10.34 (s, 1H), 10.01 (s, 1H), 8.50 (s, 1H), 7.81 (dd, 1H), 7.55-7.68 (m, 2H), 7.51-7.55 (m, 2H), 7.33-7.48 (m, 3H), 7.12 (t, 2H), 4.22 (t, 2H), 3.94 (s, 3H), 2.52-2.61 (m, 2H), 2.49-2.51 (m, 4H), 1.83-1.94 (m, 2H), 1.42 (s, 4H), 0.95 (t, 6H).
28	(1R,2R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	^{1}H NMR (DMSO-d_6) d 10.52 (s, 1H), 9.70 (s, 1H), 8.44 (d, 1H), 7.92 (dd, 1H), 7.61 (m, 2H), 7.50 (m, 2H), 7.43 (m, 2H), 7.12 (t, 2H), 6.41 (d, 1H), 4.17 (t, 2H), 3.93 (s, 3H), 2.55 (m, 2H), 2.31 (m, 4H), 1.98 (m, 1H), 1.88 (m, 2H), 1.35 (m, 2H), 1.07 (d, 3H), 0.94 (t, 6H).
29	(1R,2R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	^{1}H NMR (DMSO-d_6) d 10.52 (s, 1H), 9.70 (s, 1H), 8.44 (d, 1H), 7.78 (dd, 1H), 7.61 (m, 2H), 7.51 (m, 2H), 7.41 (m, 2H), 7.12 (t, 2H), 6.41 (d, 1H), 4.17 (t, 2H), 3.93 (s, 3H), 2.85 (t, 2H), 2.57 (q, 4H), 1.98 (m, 1H), 1.34 (m, 2H), 1.07 (d, 3H), 0.98 (t, 6H).

Table 3

Entry	Name	^{1}H-NMR
30	(1R,2S)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	^{1}H NMR (DMSO-d_6) d 10.17 (s, 1H), 9.97 (s, 1H), 8.39 (d, 1H), 7.80 (dd, 1H), 7.62 (m, 2H), 7.45 (m, 2H), 7.31 (m, 2H), 7.09 (t, 2H), 6.34 (d, 1H), 4.12 (t, 2H), 3.88 (s, 3H), 2.46 (m, 2H), 2.40 (m, 4H), 1.92 (m, 1H), 1.84 (m, 2H), 1.37 (m, 1H), 1.29 (m, 1H), 1.01 (d, 3H), 0.89 (t, 6H).
31	(1R,2S)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	^{1}H NMR (DMSO-d_6) d 10.22 (s, 1H), 10.01 (s, 1H), 8.44 (d, 1H), 7.86 (dd, 1H), 7.66 (m, 2H), 7.49 (m, 2H), 7.39 (m, 2H), 7.14 (m, 2H), 6.39 (d, 1H), 4.18 (m, 2H), 3.92 (s, 3H), 2.85 (t, 2H), 2.57 (q, 4H), 1.97 (m, 1H), 1.42 (m, 1H), 1.35 (m, 1H), 1.06 (d, 3H), 0.98 (t, 6H).
32	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	^{1}H NMR ($CDCl_3$) 8.57 (s, 1H), 8.12 (s, 1H), 7.73-7.81 (m, 2H), 7.48-7.53 (m, 2H), 7.32 (s, 1H), 6.98-7.08 (m, 3H), 4.28 (t, 2H), 4.04 (s, 3H), 3.25 (t, 2H), 2.76 (q, 4H), 2.67 (q, 4H), 2.01-2.15 (m, 2H), 1.10 (t, 6H).
33	(1R,2S)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	^{1}H NMR (400 MHz, DMSO-d_6): 10.28 (s, 1H), 9.80 (s, 1H) 8.47-8.46 (d, 1H), 7.90-7.88 (d, 1H), 7.70-7.62 (m, 2H), 7.56-7.52 (m, 2H), 7.44-7.39 (m, 2H), 7.18-7.12 (m, 2H), 6.44-6.41 (t, 1H), 4.20-4.17 (t, 2H), 3.95 (s, 3H), 2.74-2.72 (t, 3H), 2.46-2.42 (m, 1H), 2.35 (br s, 3H), 2.03-1.93 (m, 3H), 1.87 (s, 4H), 1.43-1.35 (m, 2H), 1.09-1.08 (m, 3H).
34	(1r,2R,3S)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	1H NMR (DMSO-d6): 1H (10.12 ppm, s), 1H (9.6 ppm, s), 1H (8.46 ppm, d), 1H (7.88 ppm, dd), 2H (7.68 ppm, m), 1H (7.56 ppm, d), 1H (7.51 ppm, s), 2H(7.4 ppm, m), 2H (7.13 ppm, t), 1H (6.4 ppm, d), 2H (4.2 ppm, t), 3H (3.94 ppm, s), 4H (3.6 ppm, t), 2H (2.45 ppm, t), 4H (2.37 ppm, m), 2H (1.97 ppm, t), 2H (1.8 ppm, m), 6 H(1.28 ppm, d).
35	(1r,2R,3S)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	1H NMR (DMSO-d6): 1H (10.12 ppm, s), 1H (9.6 ppm, s), 1H (8.46 ppm, d), 1H (7.88 ppm, dd), 2H (7.69 ppm, m), 1H (7.58 ppm, d), 1H (7.51 ppm, s), 2H (7.4 ppm, m), 2H (7.13 ppm, t), 1H (6.4 ppm, d), 2H (4.2 ppm, t), 3H (3.95 ppm, s), 10H (2.35 ppm, m), 3H (2.14 ppm, s), 2H (1.97 ppm, t), 2H (1.8 ppm, m), 6H (1.28 ppm, d).

Table 3

Entry	Name	^{1}H-NMR
36	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	^{1}H NMR (400 MHz, DMSO-d6): 8.45 (d, 2 H), 8.15 (d, 1H), 7.8 (d, 1H), 7.45 (m, 3H), 7.25 (m, 3H), 7.0 (m, 2H), 4.20 (t, 2H), 4.0 (s, 3H), 3.7 (m, 4H), 2.67 (m, 4H), 2.45 (m, 6H), 2.0 (m, 4H).
37	(2R,3R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	^{1}H NMR (400 MHz, $CDCl_3$) d 8.44 (d, J = 5.1 Hz, 1 H), 8.11 (br s, 1 H), 7.77-7.70 (m, 2 H), 7.53 (s, 1 H), 7.50-7.44 (m, 2 H), 7.40 (s, 1 H), 7.22-7.16 (m, 2 H), 7.06-6.98 (m, 2 H), 6.36 (br d, J = 5.1 Hz, 1 H), 4.26 (t, J = 7.0 Hz, 2 H), 4.02 (s, 3 H), 3.72 (t, J = 4.4 Hz, 4 H), 2.57 (t, J = 7.3 Hz, 2 H), 2.50-2.42 (m, 4 H), 2.18-2.10 (m, 2 H), 1.80-1.66 (m, 2 H), 1.30-1.24 (m, 6 H).
38	(2R,3R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	^{1}H NMR (400 MHz, DMSO-d_6) d 10.34 (s, 1 H), 10.05 (s, 1 H), 8.46 (br s, 1 H), 7.93 (br d, J = 4.7 Hz, 1 H), 7.54-7.52 (m, 2 H), 7.52-7.50 (m, 2 H), 7.50-7.30 (m, 2 H), 7.20-7.10 (m, 2 H), 6.47 (br s, 1 H), 4.30-4.20 (m, 2 H), 3.95 (s, 3 H), 3.40-3.10 (m, 6 H), 2.60-2.40 (m, 2 H), 1.90-1.80 (m, 2 H), 1.30-1.10 (m, 12 H).
39	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	1H NMR (400MHz, DMSO-d6): d 10.47 (s, 1H), 10.16 (s, 1H), 8.43 (d, 1H), 7.92 (dd, 1H), 7.67 (m, 2H), 7.58 (m, 1H), 7.52 (s, 1H), 7.41 (m, 2H), 7.15 (t, 2H), 6.44 (d, 1H), 4.25 (t, 2H), 3.95 (s, 3H), 3.10 (m, 6H), 2.17 (m, 2H), 1.91 (s, 3H, acetate salt), 1.52 (m, 2H), 1.18 (m, 12H).
40	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	1H NMR (400MHz, DMSO-d6): d 10.21 (s, 1H), 9.97 (s, 1H), 8.51 (s, 1H), 7.81 (dd, 1H), 7.64 (m, 2H), 7.54 (s, 1H), 7.48 (m, 1H), 7.41 (m, 1H), 7.38 (s, 1H), 7.15 (t, 2H), 4.24 (t, 2H), 3.97 (s, 3H), 3.58 (m, 4H), 2.45 (t, 2H), 2.38 (m, 4H), 1.97 (m, 2H), 1.58 (m, 2H), 1.18 (s, 3H), 1.17 (s, 3H).
41	(1R,2R,3S)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	1H NMR (400MHz, DMSO-d6): d 10.14 (s, 1H), 9.61 (s, 1H), 8.46 (d, 1H), 7.87 (dd, 1H), 7.67 (m, 2H), 7.57 (m, 1H), 7.51 (s, 1H), 7.42 (s, 1H), 7.39 (m, 1H), 7.15 (t, 2H), 6.41 (d, 1H), 4.20 (m, 2H), 3.94 (s, 3H), 2.87 (m, 2H), 2.60 (m, 4H), 1.80 (m, 2H), 1.18 (s, 3H), 1.17 (s, 3H), 1.01 (m, 6H). Note: 0.5eq of AcOH is present by NMR.

Table 3

Entry	Name	^{1}H-NMR
42	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	1H NMR (400MHz, DMSO): d 10.24 (s, 1H), 10.00 (s, 1H), 8.54 (s, 1H), 7.84 (dd, 1H), 7.66 (m, 2H), 7.56 (s, 1H), 7.51 (m, 1H), 7.43 (m, 2H), 7.18 (t, 2H), 4.26 (m, 2H), 3.98 (s, 3H), 2.88 (m, 2H), 2.59 (m, 4H), 1.58 (m, 2H), 1.18 (s, 6H), 1.00 (t, 6H).
43	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	1H NMR (400MHz, DMSO-d6): d 10.21 (s, 1H), 9.97 (s, 1H), 8.51 (s, 1H), 7.82 (dd, 1H), 7.64 (m, 2H), 7.54 (s, 1H), 7.48 (m, 1H), 7.41 (m, 1H), 7.37 (s, 1H), 7.15 (t, 2H), 4.23 (t, 2H), 3.97 (s, 3H), 2.56 (m, 2H), 2.46 (m, 4H), 1.91 (m, 2H), 1.58 (m, 2H), 1.18 (s, 6H), 0.96 (t, 6H).
44	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	1H NMR (CDCl3): 8.57 (s, 1H), 8.50 (s, 1H), 8.11 (s, 1H), 7.81 (dd, 1H), 7.53 (m, 3H), 7.28 (m, 4H), 7.04 (t, 2H), 4.24 (t, 2H), 4.04 (s, 3H), 2.95 (t, 2H), 2.84 (q, 4H), 2.75 (m, 4H), 2.21 (m, 2H), 2.02 (m, 2H), 1.18 (t, 6H).
45	N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	1H NMR (CDCL3): 8.57 (s, 1H), 8.49 (s, 1H), 8.10 (s, 1H), 7.80 (d, 1H), 7.70 (br., 1H), 7.52 (m, 3H), 7.31 (m, 3H), 7.04 (t, 2H), 4.26 (t, 2H), 4.04 (s, 3H), 2.62-2.77 (m, 14H), 2.40 (s, 3H), 2.13 (m, 2H), 2.01 (m, 2H).
46	(2R,3R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	^{1}H NMR (400 MHz, $CDCl_3$) d 8.59 (s, 1 H), 8.11 (br s, 1 H), 7.80-7.76 (m, 2 H), 7.53 (s, 1 H), 7.50-7.46 (m, 2 H), 7.34 (s, 1 H), 7.26-7.24 (m, 2 H), 7.06-7.00 (m, 2 H), 4.28 (t, J = 6.6 Hz, 2 H), 4.05 (s, 3 H), 3.73 (br t, J = 4.4 Hz, 4 H), 2.57 (t, J = 7.0 Hz, 2 H), 2,52-2,45 (m, 4 H), 2.18-2.10 (m, 2 H), 1.80-1.68 (m, 2 H), 1.28-1.20 (m, 6 H).
47	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	^{1}H NMR (400 MHz, DMSO-d_6): 9.98 (s, 1H), 9.72 (s, 1H), 8.45-8.43 (d, 1H), 7.97-7.94 (dd, 1H), 7.73-7.69 (m, 2H), 7.65-7.52 (m, 3H), 7.44-7.39 (m, 1H), 7.18-7.14 (m, 2H), 6.43-6.42 (d, 1H), 4.20-4.19 (t, 2H), 3.95 (s, 3H), 2.70-2.66 (m, 6H), 2.45 (br s, 2H), 1.91-1.84 (m, 6H), 0.98 (br s, 6H).

Table 3

Entry	Name	^{1}H-NMR
48	N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	^{1}H NMR (400 MHz, DMSO-d_6): 9.99 (s, 1H), 9.73 (s, 1H), 8.45-8.43 (d, 1H), 7.97-7.93 (dd, 1H), 7.73-7.69 (m, 2H), 7.65-7.52 (m, 2H), 7.44-7.38 (m, 2H), 7.18-7.14 (m, 2H), 6.43-6.42 (d, 1H), 4.19-4.16 (t, 3H), 3.95 (s, 3H), 2.70-2.66 (m, 4H), 2.47-2.33 (m, 8H), 2.15 (s, 3H), 1.98-1.94 (m, 2H), 1.90-1.84 (m, 4H).
49	(2R,3R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	^{1}H NMR (400 MHz, $CDCl_3$) d 8.59 (br s, 1 H), 8.29 (br s, 1 H), 7.93 (s, 1 H), 7.77 (d, J = 10.8 Hz, 1 H), 7.53 (s, 1 H), 7.50-7.45 (m, 2 H), 7.32 (s, 1 H), 7.26-7.22 (m, 2 H), 7.05-6.99 (m, 2 H), 4.27 (t, J = 6.6 Hz, 2 H), 4.04 (s, 3 H), 3.03 (t, J = 6.5 Hz, 2 H), 2.67 (q, J = 7.0 Hz, 4 H), 1.80-1.70 (m, 2 H), 1.22 (br t, J = 5.3 Hz, 6 H), 1.09 (br t, J = 7.2 Hz, 6 H).
50	(2R,3R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	^{1}H NMR (400 MHz, $CDCl_3$) d 8.58 (s, 1 H), 8.40-8.36 (m, 1 H), 8.02-7.96 (m, 1 H), 7.80-7.75 (m, 1 H), 7.53 (s, 1 H), 7.52-7.50 (m, 2 H), 7.31 (s, 1 H), 7.28-7.20 (m, 2 H), 7.02 (t, J = 8.5 Hz, 2 H), 4.25 (t, J = 6.3 Hz, 2 H), 4.04 (s, 3 H), 3.00-2.90 (m, 2 H), 2.88-2.80 (m, 4 H), 2.30-2.20 (m, 2 H), 1.76-1.68 (m, 2 H), 1.25-1.15 (m, 12 H).
51	(2R,3R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	^{1}H NMR (400 MHz, $CDCl_3$) d 8.47 (d, J = 5.2 Hz, 1 H), 8.17 (br s, 1 H), 7.80-7.74 (m, 2 H), 7.55 (s, 1 H), 7.52-7.46 (m, 2 H), 7.42 (s, 1 H), 7.24-7.20 (m, 2 H), 7.05 (t, J = 8.6 Hz, 2 H), 6.38 (br d, J = 5.4 Hz, 1 H), 4.27 (t, J = 6.4 Hz, 2 H), 4.03 (s, 3 H), 3.04 (br t, J = 7.2 Hz, 2 H), 2.68 (q, J = 6.8 Hz, 4 H), 1.80-1.68 (m, 2 H), 1.26 (d, J = 6.4 Hz, 6 H), 1.09 (br t, J = 7.2 Hz, 6 H).
52	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[(4-fluorophenyl)methyl]cyclopropane-1,1-dicarboxamide	1H NMR (DMSO-d6): 10.82 (s, 1H), 8.80 (d, 1H), 8.50 (t, 1H), 7.83 (d, 2H), 7.74 (s, 1H), 7.56 (s, 1H), 7.30-7.38 (m, 4H), 7.15 (t, 2H), 6.80 (d, 1H), 4.32 (d, 2H), 4.04 (s, 3H), 4.03 (s, 3H), 1.42 (s, 4H).
53	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(2-morpholin-4-ylethyl)cyclopropane-1,1-dicarboxamide	1H NMR (DMSO-d6): 10.62 (s, 1H), 8.79 (d, 1H), 8.24 (t, 1H), 7.83 (d, 2H), 7.72 (s, 1H), 7.58 (s, 1H), 7.37 (d, 2H), 6.76 (d, 1H), 4.04 (s, 3H), 4.03 (s, 3H), 3.98 (m, 2H), 3.66 (m, 2H), 3.49 (m, 4H), 3.25 (t, 2H), 3.13 (br., 2H), 1.42 (d, 4H).

Table 3

Entry	Name	^{1}H-NMR
54	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	1H NMR (DMSO-d6): 10.78 (s, 1H), 10.53 (s, 1H), 8.43 (d, 1H), 8.12 (d, 1H), 7.82 (d, 2H), 7.49 (s, 1H), 7.37 (s, 1H), 7.20-7.28 (m, 3H), 7.15 (dd, 1H), 7.01 (td, 1H), 6.35 (d, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.47 (s, 2H), 2.17 (br., 4H), 1.49 (m, 4H), 1.41 (m, 4H), 1.32 (br., 2H).
55	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	1H NMR (DMSO-d6): 10.98 (s, 1H), 10.56 (s, 1H), 8.42 (d, 1H), 8.10 (dd, 1H), 7.81 (m, 2H), 7.49 (s, 1H), 7.37 (s, 1H), 7.17-7.27 (m, 4H), 7.01 (td, 1H), 6.35 (d, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.61 (s, 2H), 2.30 (br., 4H), 1.47 (br., 4H), 1.43 (m, 4H).
56	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	1H NMR (DMSO-d6): 10.12 (s, 1H), 10.03 (s, 1H), 8.44 (d, 1H), 7.74 (d, 2H), 7.57 (s, 1H), 7.53 (d, 1H), 7.48 (s, 1H), 7.37 (s, 1H), 7.21 (m, 3H), 6.98 (d, 1H), 6.40 (d, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.56 (t, 4H), 3.41 (s, 2H), 2.34 (br., 4H), 1.48 (s, 4H).
57	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	1H NMR (DMSO-d6): 10.54 (s, 1H), 10.47 (s, 1H), 8.43 (d, 1H), 8.08 (d, 1H), 7.78 (d, 2H), 7.49 (s, 1H), 7.37 (d, 1H), 7.18-7.30 (m, 4H), 7.03 (t, 1H), 6.37 (d, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.50 (s, 2H), 3.44 (br., 4H), 2.20 (br., 4H), 1.48 (d, 4H).
58	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-phenylcyclopropane-1,1-dicarboxamide	1H NMR (DMSO-d6): 10.14 (s, 1H), 10.03 (s, 1H), 8.44 (d, 1H), 7.74 (d, 2H), 7.62 (d, 2H), 7.48 (s, 1H), 7.37 (s, 1H), 7.27-7.31 (m, 2H), 7.19-7.23 (m, 2H), 7.05 (t, 1H), 6.41 (d, 1H), 3.93 (s, 6H), 3.92 (s, 3H), 1.48 (s, 4H).
59	N-[3-(aminomethyl)phenyl]-N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide	1H NMR (400MHz, DMSO-d6): d 10.28 (s, 1H), 10.19 (s, 1H), 8.77 (m, 1H), 8.21 (m, 3H), 7.84 (m, 2H), 7.76 (m, 1H), 7.71 (m, 1H), 7.58 (m, 2H), 7.38 (m, 3H), 7.19 (m, 1H), 6.76 (m, 1H), 4.03 (s, 6H), 3.39 (m, 2H), 1.53 (m, 4H). Note: all peaks are very broad and unresolved.
60	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	1H NMR (DMSO-d6): 10.0-10.2 (br., 2H), 8.46 (d, 1H), 7.76 (d, 2H), 7.53 (m, 3H), 7.39 (s, 1H), 7.24 (m, 3H), 6.98 (d, 1H), 6.43 (d, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.37 (s, 2H), 2.31 (br., 4H), 1.48 (m, 8H), 1.39 (br., 2H).

Table 3

Entry	Name	^{1}H-NMR
61	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	1H NMR (DMSO-d6): 10.0-10.2 (br., 2H), 8.46 (d, 1H), 7.77 (d, 2H), 7.59 (s, 1H), 7.53 (d, 1H), 7.51 (s, 1H), 7.39 (s, 1H), 7.23 (m, 3H), 6.99 (d, 1H), 6.43 (d, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.52 (s, 2H), 2.42 (br., 4H), 1.69 (br, 4H), 1.48 (s, 4H).

Assays

[0455] Kinase assays were performed by measurement of incorporation of γ-^{33}P ATP into immobilized myelin basic protein (MBP). High binding white 384 well plates (Greiner) were coated with MBP (Sigma #M-1891) by incubation of 60ul/well of 20μg/ml MBP in Tris-buffered saline (TBS; 50mM Tris pH 8.0, 138mM NaCl, 2.7mM KCl) for 24 hours at 4° C. Plates were washed 3X with 100μl TBS. Kinase reactions were carried out in a total volume of 34μl in kinase buffer (5mM Hepes pH 7.6, 15mM NaCl, 0.01% bovine gamma globulin (Sigma #I-5506), 10mM $MgCl_2$, 1mM DTT, 0.02% TritonX-100). Compound dilutions were performed in DMSO and added to assay wells to a final DMSO concentration of 1%. Each data point was measured in duplicate, and at least two duplicate assays were performed for each individual compound determination. Enzyme was added to final concentrations of 10nM or 20nM, for example. A mixture of unlabeled ATP and γ-^{33}P ATP was added to start the reaction ($2x10^6$ cpm of γ-^{33}P ATP per well (3000Ci/mmole) and either 10μM or 30μM unlabeled ATP, typically. The reactions were carried out for 1 hour at room temperature with shaking. Plates were washed 7x with TBS, followed by the addition of 50μl/well scintillation fluid (Wallac). Plates were read using a Wallac Trilux counter. This is only one format of such assays, various other formats are possible, as known to one skilled in the art.

[0456] The above assay procedure can be used to determine the IC_{50} for inhibition and/or the inhibition constant, K_i. The IC_{50} is defined as the concentration of compound required to reduce the enzyme activity by 50% under the conditions of the assay. Exemplary compositions have IC_{50}'s of, for example, less than about 100 μM, less than about 10 μM, less than about 1 μM, and further for example having IC_{50}'s of less than about 100 nM, and still further, for example, less than about 10 nM. The K_i for a compound may be

determined from the IC_{50} based on three assumptions. First, only one compound molecule binds to the enzyme and there is no cooperativity. Second, the concentrations of active enzyme and the compound tested are known (i.e., there are no significant amounts of impurities or inactive forms in the preparations). Third, the enzymatic rate of the enzyme-inhibitor complex is zero. The rate (i.e., compound concentration) data are fitted to the equation:

$$V = V_{max} E_0 \left[I - \frac{(E_0 + I_0 + K_d) - \sqrt{(E_0 + I_0 + K_d)^2 - 4E_0 I_0}}{2E_0} \right]$$

where V is the observed rate, V_{max}, is the rate of the free enzyme, I_0 is the inhibitor concentration, E_0 is the enzyme concentration, and K_d is the dissociation constant of the enzyme-inhibitor complex.

Kinase specificity assays:

[0457] Kinase activity and compound inhibition are investigated using one or more of the three assay formats described below. The ATP concentrations for each assay are selected to be close to the Michaelis-Menten constant (K_M) for each individual kinase. Dose-response experiments are performed at 10 different inhibitor concentrations in a 384-well plate format. The data are fitted to the following four-parameter equation:

$$Y = Min + (Max - Min) / (1 + (X/IC_{50})^{\wedge}H)$$

where Y is the observed signal, X is the inhibitor concentration, Min is the background signal in the absence of enzyme (0% enzyme activity), Max is the signal in the absence of inhibitor (100% enzyme activity), IC_{50} is the inhibitor concentration at 50% enzyme inhibition and H represents the empirical Hill's slope to measure the cooperativity. Typically H is close to unity.

c-Met Assay

[0458] c-Met biochemical activity was assessed using a Luciferase-Coupled Chemiluminescent Kinase assay (LCCA) format as described above. Again, kinase activity was measured as the percent ATP remaining following the kinase reaction.

Remaining ATP was detected by luciferase-luciferin-coupled chemiluminescence. Specifically, the reaction was initiated by mixing test compounds, 1μM ATP, 1μM poly-EY and 10nM c-Met (baculovirus expressed human c-Met kinase domain P948-S1343) in a 20uL assay buffer (20mM Tris-HCL pH7.5, 10mM $MgCl_2$, 0.02% Triton X-100, 100mM DTT, 2mM $MnCl_2$). The mixture is incubated at ambient temperature for 2hours after which 20uL luciferase-luciferin mix is added and the chemiluminescent signal read using a Wallac Victor^2 reader. The luciferase-luciferin mix consists of 50 mM HEPES, pH 7.8, 8.5ug/mL oxalic acid (pH 7.8), 5 (or 50) mM DTT, 0.4% Triton X-100, 0.25 mg/mL coenzyme A, 63 uM AMP, 28 ug/mL luciferin and 40,000 units of light/mL luciferase.

KDR Assay

[0459] KDR biochemical activity was assessed using a Luciferase-Coupled Chemiluminescent Kinase assay (LCCA) format. Kinase activity was measured as the percent ATP remaining following the kinase reaction. Remaining ATP was detected by luciferase-luciferin-coupled chemiluminescence. Specifically, the reaction was initiated by mixing test compounds, 3 μM ATP, 1.6 μM poly-EY and 5 nM KDR (baculovirus expressed human KDR kinase domain D807-V1356) in a 20uL assay buffer (20mM Tris-HCL pH7.5, 10mM $MgCl_2$, 0.01% Triton X-100, 1mM DTT, 3mM $MnCl_2$). The mixture is incubated at ambient temperature for 4 hours after which 20uL luciferase-luciferin mix is added and the chemiluminescent signal read using a Wallac Victor^2 reader. The luciferase-luciferin mix consists of 50 mM HEPES, pH 7.8, 8.5ug/mL oxalic acid (pH 7.8), 5 (or 50) mM DTT, 0.4% Triton X-100, 0.25 mg/mL coenzyme A, 63 uM AMP, 28 ug/mL luciferin and 40,000 units of light/mL luciferase.

flt-4 Assay

[0460] Biochemical activity for flt-4 was assessed using an Alphascreen Tyrosine Kinase protocol. AlphaScreen™ (Perkin Elmer) technology is a proximity assay employing microparticles. Singlet oxygen derived from a donor bead following laser excitation results in chemiluminescence when in proximity (100 Å) to an acceptor bead due to biomolecular interactions. For the Flt-4 assay, donor beads coated with streptavidin and acceptor beads coated with PY100 anti-phosphotyrosine antibody were used (Perkin Elmer). Biotinylated poly(Glu,Tyr) 4:1 (Perkin Elmer) was used as the substrate.

Substrate phosphorylation was measured by addition of donor/acceptor beads by chemiluminescence following donor-acceptor bead complex formation. Test compounds, 5 μM ATP, 3 nM biotinylated poly(Glu, Tyr) and 1 nM Flt-4 (baculovirus expressed human Flt-4 kinase domain D725-R1298) were combined in a volume of 20 μL in a 384-well white, medium binding microtiter plate (Greiner). Reaction mixtures were incubated for 1 hr at ambient temperature. Reactions were quenched by addition of 10 uL of 15-30 mg/mL AlphaScreen bead suspension containing 75 mM Hepes, pH 7.4, 300 mM NaCl, 120 mM EDTA, 0.3% BSA and 0.03% Tween-20. After 2-16 hr incubation at ambient temperature plates were read using an AlphaQuest reader (Perkin Elmer). IC_{50} values correlate well with those determined by radiometric assays.

flt-3 Assay

[0461] Biochemical activity for flt-3 was assessed using a Luciferase-Coupled Chemiluminescent Kinase assay (LCCA) format. Kinase activity was measured as the percent ATP remaining following the kinase reaction. Remaining ATP was detected by luciferase-luciferin-coupled chemiluminescence. Specifically, the reaction was initiated by mixing test compounds, 5 μM ATP, 3 μM poly-EY and 5 nM Flt-3 (baculovirus expressed human Flt-3 kinase domain R571-S993) in a 20uL assay buffer (20mM Tris-HCL pH7.5, 10mM $MgCl_2$, 0.01% Triton X-100, 1mM DTT, 2mM $MnCl_2$). The mixture is incubated at ambient temperature for 3 hours after which 20uL luciferase-luciferin mix is added and the chemiluminescent signal read using a Wallac Victor^2 reader. The luciferase-luciferin mix consists of 50 mM HEPES, pH 7.8, 8.5ug/mL oxalic acid (pH 7.8), 5 (or 50) mM DTT, 0.4% Triton X-100, 0.25 mg/mL coenzyme A, 63 uM AMP, 28 ug/mL luciferin and 40,000 units of light/mL luciferase.

c-Kit Assay

[0462] c-Kit biochemical activity was assessed using AlphaScreen ™ (Perkin Elmer) technology, described above. Test compounds, ATP, biotinylated poly(Glu, Tyr) and c-Kit kinase were combined in a volume of 20 μL in a 384-well white, medium binding microtiter plate (Greiner). Reaction mixtures were incubated for 1 hr at ambient temperature. Reactions were quenched by addition of 10 uL of 15-30 mg/mL AlphaScreen bead suspension containing 75 mM Hepes, pH 7.4, 300 mM NaCl, 120 mM

EDTA, 0.3% BSA and 0.03% Tween-20. After 16 hr incubation at ambient temperature plates were read using an AlphaQuest reader (Perkin Elmer).

Structure Activity Relationships

[0463] Table 4 shows structure activity relationship data for selected compounds of the invention. Inhibition is indicated as IC_{50} with the following key: A = IC_{50} less than 50 nM, B = IC_{50} greater than 50 nM, but less than 500 nM, C = IC_{50} greater than 500 nM, but less than 5000 nM, and D = IC_{50} greater than 5,000 nM. Depending upon the functionality about the quinazoline or quinoline, exemplary compounds of the invention exhibit selectivity for any of c-Met, KDR, c-Kit, flt-3, and flt-4. Abbreviations for enzymes listed in Tables 2-3 are defined as follows: c-Met refers to hepatocyte growth factor receptor kinase; KDR refers to kinase insert domain receptor tyrosine kinase; flt-4, fms-like tyrosine kinase-4, representative of the FLK family of receptor tyrosine kinases; c-Kit, also called stem cell factor receptor or steel factor receptor; and flt-3, fms-like tyrosine kinase-3. Empty cells in the tables indicate lack of data only.

Table 4

Entry	Name	c-Met	KDR	c-Kit	flt3	flt4
1	N-[({3-fluoro-4-[(6-(methyloxy)-7-{[(3aR,6aS)-octahydrocyclopenta[c]pyrrol-5-ylmethyl]oxy}quinazolin-4-yl)oxy]phenyl}amino)carbonothioyl]-2-phenylacetamide		A			A
2	N-{[(3-fluoro-4-{[7-({[(3aR,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-yl]oxy}phenyl)amino]carbonothioyl}-2-phenylacetamide	A	A	A		A
3	N-{[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)(methyl)amino]carbonothioyl}-2-phenylacetamide	C				
4	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)imidazolidin-2-one	C		C	C	
5	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylmethyl)imidazolidin-2-one	C		B	C	
6	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylacetyl)imidazolidin-2-one	B				

7	ethyl [(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)amino](oxo)acetate	B	B	C		B
8	N-{[(4-{[6,7-bis(methyloxy)quinazolin-4-yl]amino}-3-fluorophenyl)amino]carbonothioyl}-2-phenylacetamide	A	B	C		B
9	N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N-methyl-N-(2-phenylethyl)sulfamide	C				
10	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylmethyl)-1,2,4-oxadiazol-5-amine	C		B	C	
11	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)piperidin-2-one	C		C	C	
12	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(phenylmethyl)ethanediamide	B	B	B	C	B
13	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-4-phenyl-1,3-thiazol-2-amine	C		C	B	
14	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-phenylethyl)ethanediamide	A	A	A	C	A
15	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-1-phenylmethanesulfonamide	C		C	B	
16	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-2-phenylethanesulfonamide	C		C	C	
17	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-(phenylmethyl)benzenesulfonamide	C		C	C	
18	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(phenylmethyl)benzenesulfonamide	C		C	C	
19	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-(2-phenylethyl)benzenesulfonamide	C		C	C	
20	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(2-phenylethyl)benzenesulfonamide	C		C	C	
21	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-(3-phenylpropyl)benzenesulfonamide	C				
22	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)pyrrolidin-2-one	C		C	B	
23	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl (phenylmethyl)carbamate	C				
24	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl (2-phenylethyl)carbamate	C				
25	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(3-phenylpropyl)benzenesulfonamide	C				
26	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-phenylethanediamide	B	D	C		C
27	4-{[6,7-bis(methyloxy)quinolin-4-yl]amino}-N-(3-phenylpropyl)benzamide	C				

28	N-{[(3-fluoro-4-{[7-{[(2-methyloctahydrocyclopenta[c]pyrrol-5-yl)methyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}phenyl)amino]carbonothioyl}-2-phenylacetamide	A	A	A	A	A
29	N-[(Z)-[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)amino](imino)methyl]-2-phenylacetamide	C				
30	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-[2-(phenyloxy)ethyl]benzenesulfonamide	C				
31	This type of multiplicative nomenclature is not supported in current version!	C				
32	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-phenylpropane-1-sulfonamide	C				
33	N~2~-[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)sulfonyl]-N-phenylglycinamide	C				
34	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-2-phenylacetamide	C				
35	N-{[(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)amino]carbonothioyl}-2-phenylacetamide	A	C	D		C
36	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-1,3-benzothiazol-2-amine	C		C	C	
37	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-amine	C		C	C	
38	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-phenylacetamide	B	C	D		B
39	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-morpholin-4-ylethyl)ethanediamide	C		B	B	
40	1,1-dimethylethyl {2-[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)amino]-2-oxoethyl}(phenylmethyl)carbamate	C				
41	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N~2~-(phenylmethyl)glycinamide	B				
42	N~2~-acetyl-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N~2~-(phenylmethyl)glycinamide	C				
43	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-1,3-benzothiazol-2-yl)-2-phenylacetamide	B				
44	1,1-dimethylethyl {2-[(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)amino]-2-oxoethyl}(phenylmethyl)carbamate	C				
45	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N~2~-(phenylmethyl)glycinamide	C				

46	N~2~-acetyl-N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N~2~-(phenylmethyl)glycinamide	C				
47	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-3-phenylpropanamide	C				
48	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-4-phenylbutanamide	C				
49	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N~2~-methyl-N~2~-(phenylmethyl)glycinamide	C				
50	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{2-[4-(methyloxy)phenyl]ethyl}ethanediamide	C		C	C	
51	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N~2~-methyl-N~2~-(phenylmethyl)glycinamide	B	A	B	B	A
52	N-{[(4-{[6,7-bis(methyloxy)quinolin-4-yl]amino}phenyl)amino]carbonothioyl}-2-phenylacetamide	A	B	B	C	A
53	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-3-phenylpropanamide	C				
54	N-{[(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)amino]carbonothioyl}-2-phenylacetamide	A	B	C		B
55	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2,3-dihydro-1H-inden-1-yl)ethanediamide	A	B	B		B
56	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2,3-dihydro-1H-inden-2-yl)ethanediamide	C				
57	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(1,2,3,4-tetrahydronaphthalen-1-yl)ethanediamide	B	B	C		C
58	N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N-(2-phenylethyl)-N-(phenylmethyl)sulfamide	1470.06				
59	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N~2~-(trifluoroacetyl)glycinamide	B	C	B		B
60	N-{2-[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)amino]-2-oxoethyl}benzamide	B	A	A	A	A
61	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N'-(4-fluorophenyl)propanediamide	A	B	B		B
62	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[(2S)-1,2,3,4-tetrahydronaphthalen-2-yl]ethanediamide	C				

63	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(4-methylphenyl)ethyl]ethanediamide	C		C	C	
64	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-phenylpropyl)ethanediamide	B	A	B	B	B
65	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(4-chlorophenyl)ethyl]ethanediamide	A	C	B	C	C
66	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N,N'-bis(phenylmethyl)sulfamide	C				
67	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N,N'-bis(2-phenylethyl)sulfamide	C				
68	ethyl [(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)amino](oxo)acetate	C				
69	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-phenylethyl)ethanediamide	C				
70	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)propanediamide	A	B	B		C
71	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[(2R)-1,2,3,4-tetrahydronaphthalen-2-yl]ethanediamide	B	D	B		C
72	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(1-methylpyrrolidin-2-yl)ethyl]ethanediamide	C		C	C	
73	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(phenyloxy)ethyl]ethanediamide	B	B	B		C
74	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-hydroxy-1-(phenylmethyl)ethyl]urea	B				
75	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-[(4-methylphenyl)sulfonyl]-4-(phenylmethyl)imidazolidin-2-one	B	B	B	B	B
76	N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N-methyl-N-(2-phenylethyl)ethanediamide	A	B	B	B	B
77	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{[3-(trifluoromethyl)phenyl]methyl}ethanediamide	B		B	B	
78	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{2-[3-(trifluoromethyl)phenyl]ethyl}ethanediamide	C		A	B	
79	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-3-oxo-4-phenylbutanamide	C				

80	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-2-[3-(trifluoromethyl)phenyl]acetamide	C				
81	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-[2-(phenyloxy)ethyl]-1,3-benzothiazol-2-amine	B				
82	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-(2-piperidin-1-ylethyl)-1,3-benzothiazol-2-amine	C				
83	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-methyl-N-(2-phenylethyl)-1,3-benzothiazol-2-amine	C				
84	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-(2-pyrrolidin-1-ylethyl)-1,3-benzothiazol-2-amine	C				
85	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-{[3-(trifluoromethyl)phenyl]methyl}-1,3-benzothiazol-2-amine	C				
86	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-{2-[3-(trifluoromethyl)phenyl]ethyl}-1,3-benzothiazol-2-amine	C				
87	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-[3-(trifluoromethyl)phenyl]propanediamide	C				
88	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[3-(trifluoromethyl)phenyl]acetamide	C	A	B	B	B
89	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N~2~-{[3-(trifluoromethyl)phenyl]methyl}glycinamide	B	A	B	B	A
90	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N~2~-(2-phenylethyl)glycinamide	B				
91	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N~2~-{2-[3-(trifluoromethyl)phenyl]ethyl}glycinamide	B	B	B	B	A
92	1,1-dimethylethyl {2-[(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)amino]-2-oxoethyl}(phenylmethyl)carbamate	C				
93	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N~2~-(phenylmethyl)glycinamide	C				
94	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[3,5-bis(trifluoromethyl)phenyl]acetamide	C	B	B	D	C
95	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[2-chloro-5-(trifluoromethyl)phenyl]acetamide	A	A	B	B	B
96	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(2-phenylethyl)ethanediamide	A	A	A	A	A

97	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(1,2,3,4-tetrahydroisoquinolin-1-ylmethyl)ethanediamide	C				
98	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[(2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl]ethanediamide	B	B	B	A	B
99	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N~2~-methyl-N~2~-{[3-(trifluoromethyl)phenyl]methyl}glycinamide	C				
100	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N~2~-methyl-N~2~-{2-[3-(trifluoromethyl)phenyl]ethyl}glycinamide	C				
101	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N~2~-methyl-N~2~-(2-phenylethyl)glycinamide	C				
102	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-4-(phenylmethyl)imidazolidin-2-one	B	B	B	B	C
103	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridazin-3-yl)-N'-(4-fluorophenyl)propanediamide	A	C	B	A	C
104	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-chlorophenyl)propanediamide	B				
105	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(3-chlorophenyl)propanediamide	C				
106	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N~2~-methyl-N~2~-(phenylmethyl)glycinamide	C				
107	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-chlorophenyl)propanediamide	B				
108	(2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-[(methyloxy)imino]propanamide	B	B			
109	(2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-[(ethyloxy)imino]propanamide	B	A			
110	(2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-{[(phenylmethyl)oxy]imino}propanamide	B	B			
111	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-1-(phenylmethyl)prolinamide	C	C			
112	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-3-[(4-methylphenyl)sulfonyl]-4-(phenylmethyl)imidazolidin-2-one	B	C	B	C	C
113	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)imidazolidin-2-one	C	C			

114	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)-4,5-dihydro-1,3-oxazol-2-amine	C	B			
115	6,7-bis(methyloxy)-4-({4-[4-(phenylmethyl)piperazin-1-yl]phenyl}oxy)quinoline	C	C			
116	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)piperazin-2-one	C	C			
117	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N~2~-(phenylmethyl)alaninamide	C	C			
118	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N~2~-methyl-N~2~-(phenylmethyl)alaninamide	C	C			
119	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N~2~-(phenylmethyl)leucinamide	C	C			
120	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N~2~-methyl-N~2~-(phenylmethyl)leucinamide	C	C			
121	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N~2~-(phenylmethyl)valinamide	C	C			
122	N-[5-chloro-6-({6-(methyloxy)-4-[(piperidin-4-ylmethyl)oxy]quinolin-7-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)propanediamide	C	C			
123	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)tetrahydropyrimidin-2(1H)-one	C	C			
124	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(2-phenylethyl)ethanediamide	A	A	A	A	A
125	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	B	A	B
126	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	C	C			
127	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N~2~-methyl-N~2~-(phenylmethyl)valinamide	C	C			
128	(2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-[(phenyloxy)imino]propanamide	C	A			
129	(2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-phenyl-2-{[(phenylmethyl)oxy]imino}ethanamide	B	C			
130	6,7-bis(methyloxy)-4-({4-[4-(phenylmethyl)piperidin-1-yl]phenyl}oxy)quinoline	C	C			
131	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{[2-(1-methylethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]methyl}ethanediamide	B	B			
132	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[(2-ethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl]ethanediamide	B	C			

133	1,1-dimethylethyl 4-({[4-{[3-chloro-5-({3-[(4-fluorophenyl)amino]-3-oxopropanoyl}amino)pyridin-2-yl]oxy}-6-(methyloxy)quinolin-7-yl]oxy}methyl)piperidine-1-carboxylate	B	C			
134	N-[5-chloro-6-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)propanediamide	A	B	B	A	
135	N-{5-chloro-6-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]pyridin-3-yl}-N'-(4-fluorophenyl)propanediamide	A	B	B	A	
136	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-phenylethyl)ethanediamide	A	A	A	B	A
137	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(2-phenylethyl)ethanediamide	A	A	A	B	A
138	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperidin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(2-phenylethyl)ethanediamide	A	A	A	A	
139	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-phenylethyl)ethanediamide	A	A	A	A	A
140	N'-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N-methyl-N-(2-phenylethyl)ethanediamide	A	A			B
141	N-(3-fluoro-4-{[7-({[(3aR,5r,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(2-phenylethyl)ethanediamide	A	A	A	A	A
142	N-(3-fluoro-4-{[7-({[(3aR,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-yl]oxy}phenyl)-N'-(2-phenylethyl)ethanediamide	A	A	A	A	A
143	2-(3,4-dihydroisoquinolin-2(1H)-yl)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-2-oxoacetamide	A	A			
144	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-2-oxo-2-(3-phenylpyrrolidin-1-yl)acetamide	A	A	A	A	A
145	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-2-oxo-2-(2-phenylmorpholin-4-yl)acetamide	A	B	B	B	

146	N-[2-(dimethylamino)-2-phenylethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	B	A	
147	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(2-oxo-2-phenylethyl)ethanediamide	A	B	B	B	B
148	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-2,2-difluoro-N'-(4-fluorophenyl)propanediamide	C	C			
149	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(phenylmethyl)ethanediamide	A	A	A	B	A
150	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[2-(2-fluorophenyl)ethyl]ethanediamide	A	A	A	A	A
151	N-[2-(3-chlorophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	A
152	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{2-[2-(methyloxy)phenyl]ethyl}ethanediamide	A	A	A	A	A
153	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(2-pyridin-3-ylethyl)ethanediamide	A	B	B	B	
154	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(phenylmethyl)ethanediamide	A	A	A	B	A
155	N-{2-[2,5-bis(methyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	A
156	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{2-[2-(trifluoromethyl)phenyl]ethyl}ethanediamide	A	A	A	A	C
157	N-{2-[2-(ethyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	A
158	N-[2-(2,4-dimethylphenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	B	B	A	B
159	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1S)-2-(4-methylphenyl)-1-phenylethyl]ethanediamide	B	C			
160	N-[2-(4-chlorophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	B

161	({3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}amino)(oxo)acetic acid	B	C			
162	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[2-(3-fluorophenyl)ethyl]ethanediamide	A	A			A
163	N-[2-(2-chlorophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	B	A
164	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{2-[3-(methyloxy)phenyl]ethyl}ethanediamide	A	A	A	A	A
165	N-(1,2-diphenylethyl)-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	B	B	C
166	N-[2-(2,4-dichlorophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	B	B	A	B
167	N-{2-[3,4-bis(methyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	B	B	B	
168	N-[2-(4-ethylphenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	B	B	B	C
169	N-{2-[4-(ethyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	B	C	B	B	
170	N-{2-[4-(ethyloxy)-3-(methyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	B	C	B	
171	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{2-[4-(phenyloxy)phenyl]ethyl}ethanediamide	B	C	C	C	
172	N-{2-[3-(ethyloxy)-4-(methyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	C	B	B	
173	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(2-pyridin-2-ylethyl)ethanediamide	A	A	A	B	B
174	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(2-pyridin-4-ylethyl)ethanediamide	A	B	B	B	C
175	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[2-(4-fluorophenyl)ethyl]ethanediamide	A	A	A	A	A

176	N-[2-(2-bromophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	A
177	N-[2-(2-chloro-6-fluorophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	B	A
178	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(2R)-2-phenylpropyl]ethanediamide	A	A	A	B	A
179	N-(2,3-dihydro-1H-inden-1-yl)-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	A
180	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(2-methylpropyl)ethanediamide	A	B	B	B	
181	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(3-methylbutyl)ethanediamide	A	B	B	B	B
182	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-[(2R)-2-phenylpropyl]ethanediamide	A	A	A	A	A
183	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(2-phenylpropyl)ethanediamide	A	A	A	A	A
184	N-(2,3-dihydro-1H-inden-2-yl)-N'-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}ethanediamide	A	A	A	B	A
185	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1R)-1-phenylethyl]ethanediamide	A	B	B	B	
186	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1S)-1-phenylethyl]ethanediamide	A	B	A	B	C
187	N-[2-(3-bromophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	A
188	N-[2-(2,6-dichlorophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	A
189	N-[2-(1,3-benzodioxol-5-yl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	B	A	B

190	N-{5-chloro-6-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]pyridin-3-yl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	B	A	A
191	N-{2-[3-bromo-4-(methyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	B	B	B
192	N-{2-[3,5-bis(methyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	B	B
193	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[2-(2-methylphenyl)ethyl]ethanediamide	A	A	A	B	A
194	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[2-(3-methylphenyl)ethyl]ethanediamide	A	A	A	A	A
195	N-{2-[3-(ethyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	B	B	B
196	N-[2-(3,4-dimethylphenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	B	B	B
197	N-[2-(2,5-dimethylphenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	A
198	N-{2-[3-chloro-4-(propyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	B	C			
199	N-{2-[4-(butyloxy)-3-chlorophenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	B	C			
200	N-{2-[4-(1,1-dimethylethyl)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	B	C			
201	N-{2-[4-(aminosulfonyl)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	B	B	B	B
202	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{2-[4-hydroxy-3-(methyloxy)phenyl]ethyl}ethanediamide	A	B	B	A	B
203	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{2-[3-hydroxy-4-(methyloxy)phenyl]ethyl}ethanediamide	A	B	B	B	B
204	N-[(2,4-dichlorophenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	B

205	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[4-fluoro-2-(trifluoromethyl)phenyl]methyl}ethanediamide	A	A	B	A	A
206	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1R)-1-(4-methylphenyl)ethyl]ethanediamide	A	B	B	B	B
207	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[3-fluoro-4-(trifluoromethyl)phenyl]methyl}ethanediamide	A	B	B	B	B
208	N-[(3-chloro-4-fluorophenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	B
209	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{(1S)-1-[3-(methyloxy)phenyl]ethyl}ethanediamide	A	B	B	B	B
210	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1R)-1-naphthalen-2-ylethyl]ethanediamide	A	B	B	B	
211	N-{[4-chloro-3-(trifluoromethyl)phenyl]methyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	A
212	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1S)-1-(4-methylphenyl)ethyl]ethanediamide	A	B	C	B	
213	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[6-(trifluoromethyl)pyridin-3-yl]methyl}ethanediamide	A	B	C	B	B
214	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(2-methylphenyl)methyl]ethanediamide	A	A	A	A	B
215	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(3-methylphenyl)methyl]ethanediamide	A	A	A	B	A
216	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[4-fluoro-3-(trifluoromethyl)phenyl]methyl}ethanediamide	A	A	B	A	A
217	N-[(3,5-dichlorophenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	A
218	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1R)-1,2,3,4-tetrahydronaphthalen-1-yl]ethanediamide	A	B	B	B	A

219	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1S)-1,2,3,4-tetrahydronaphthalen-1-yl]ethanediamide	A	A	A	A	A
220	N-cyclopentyl-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	B	B	B	B
221	N-[1-(4-bromophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	B	B	B	B
222	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(2-fluorophenyl)methyl]ethanediamide	A	A	B	B	A
223	N-[2-(3,4-dichlorophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	
224	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(4-fluorophenyl)methyl]ethanediamide	A	A	A	A	A
225	N-[(2,3-difluorophenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	B	B	A
226	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[2-(phenyloxy)ethyl]ethanediamide	A	A	A	A	A
227	N-(2,2-diphenylethyl)-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	B	B	A	B
228	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{2-[4-(methyloxy)phenyl]ethyl}ethanediamide	A	B	B	B	B
229	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(2-phenylpropyl)ethanediamide	A	A	A	A	A
230	N-[2-(4-bromophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	B	B	B
231	N-(4-{[7-{[(1-ethylpiperidin-4-yl)methyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-2-oxo-2-(2-phenylmorpholin-4-yl)acetamide	A	B	B	B	B
232	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[3-fluoro-5-(trifluoromethyl)phenyl]methyl}ethanediamide	A	A	B	A	B
233	N-[(3,5-difluorophenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	B	A

234	N-{[2-chloro-5-(trifluoromethyl)phenyl]methyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	B	A	B
235	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(dimethylamino)-2-phenylethyl]ethanediamide	B	B	B	A	
236	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[4-(methyloxy)phenyl]methyl}ethanediamide	A	A	A	B	B
237	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[4-(trifluoromethyl)phenyl]methyl}ethanediamide	A	B	B	B	A
238	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[3-(methyloxy)phenyl]methyl}ethanediamide	A	A	A	A	B
239	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[3-(trifluoromethyl)phenyl]methyl}ethanediamide	A	A	A	A	B
240	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-({3-[(trifluoromethyl)oxy]phenyl}methyl)ethanediamide	A	A	A	A	A
241	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[2-(methyloxy)phenyl]methyl}ethanediamide	A	A	A	A	A
242	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[2-(trifluoromethyl)phenyl]methyl}ethanediamide	A	A	A	A	A
243	N-[(3-chlorophenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	B	B
244	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-({2-[(trifluoromethyl)oxy]phenyl}methyl)ethanediamide	A	A	A	A	A
245	N-[(2-chlorophenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	A
246	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-({4-[(trifluoromethyl)oxy]phenyl}methyl)ethanediamide	A	B	B	B	B
247	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-{[4-(methyloxy)phenyl]methyl}ethanediamide	A	B	A	B	
248	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-{[4-(trifluoromethyl)phenyl]methyl}ethanediamide	A	B	B	B	B

249	N-(4-{[7-[(azetidin-3-ylmethyl)oxy]-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-phenylethyl)ethanediamide	A	A			
250	N-(3-fluoro-4-{[7-{[(1-methylazetidin-3-yl)methyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(2-phenylethyl)ethanediamide	A	A	A	A	A
251	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(2-hydroxy-2-phenylethyl)ethanediamide	B	B	B	B	
252	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2,4-difluorophenyl)propanediamide	A	C			
253	N'-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N-(4-fluorophenyl)-N-methylpropanediamide	B	C			
254	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1R)-1-phenylpropyl]ethanediamide	A	B	B	B	B
255	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1S)-1-phenylpropyl]ethanediamide	A	B	C	B	
256	N-[(3,4-difluorophenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	B	A
257	N-[(2,6-difluorophenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	B	A
258	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-[2-(4-fluorophenyl)ethyl]ethanediamide	A	A	A	A	A
259	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-phenylethanediamide	A	B	C	C	B
260	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(3-fluorophenyl)ethanediamide	A	C	B	C	C
261	N-(3-chloro-4-fluorophenyl)-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	C	C	B	B
262	N-[3,4-bis(methyloxy)phenyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	C	C	B	B
263	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(3-methylbutyl)ethanediamide	A	B	A	B	B

264	N-(3,3-dimethylbutyl)-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	B
265	N-[5-chloro-6-({6-(methyloxy)-7-[(3-piperidin-1-ylpropyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)propanediamide	A	B	B	A	B
266	N-[5-chloro-6-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)propanediamide	A	B	B	A	B
267	N-(5-chloro-6-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N'-(4-fluorophenyl)propanediamide	A	B	B	A	B
268	N-[(4-chlorophenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A			
269	N-{[3,5-bis(methyloxy)phenyl]methyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A		A	
270	N-[(4-butylphenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	B	B	B	B
271	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[2-(4-methylphenyl)ethyl]ethanediamide	A	B	B	A	B
272	N-{[3,5-bis(trifluoromethyl)phenyl]methyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	C	B	
273	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(pyrazin-2-ylmethyl)ethanediamide	B	C	C	B	
274	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(pyridin-2-ylmethyl)ethanediamide	A	B	B	B	B
275	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(2-phenylethyl)ethanediamide	A	A	A	A	A
276	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(2-phenylethyl)ethanediamide	A	A	A	A	A
277	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[2-fluoro-3-(trifluoromethyl)phenyl]methyl}ethanediamide	A	A	A	A	A
278	N-{2-[2-bromo-6-(methyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	A

279	N-{2-[3,4-bis(methyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N-methylethanediamide	B	B	B	A	B
280	N-{2-[5-bromo-2-(methyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	A
281	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[2-fluoro-5-(trifluoromethyl)phenyl]methyl}ethanediamide	A	A	B	A	B
282	N-[5-chloro-6-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
283	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[1-(4-fluorophenyl)ethyl]ethanediamide	A	A	B	A	B
284	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1S)-2-oxo-1-(phenylmethyl)-2-pyrrolidin-1-ylethyl]ethanediamide	A	C	B	B	C
285	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(3aR,6aS)-octahydrocyclopenta[c]pyrrol-5-ylmethyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(2-phenylethyl)ethanediamide	A	A	A	A	A
286	N-[2-(4-aminophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	B	B	B	B
287	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-2-oxo-2-[4-(phenylmethyl)piperidin-1-yl]acetamide	A	A	B	A	B
288	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)propanediamide	A	A	A	A	A
289	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	5.581
290	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(3-fluorophenyl)propanediamide	B	C			
291	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-phenylpropanediamide	A	C	B	A	C
292	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)-2,2-dimethylpropanediamide	B	B	B	A	B
293	N-ethyl-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	B	B	B	B

294	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(1-methylethyl)ethanediamide	A	B	B	B	C
295	N-butyl-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	B	B	B	B
296	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[2-(methyloxy)ethyl]ethanediamide	B	B	B	B	C
297	N-(cyclopropylmethyl)-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	B	B	B	B
298	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(2-morpholin-4-ylethyl)ethanediamide	B	A	B	A	B
299	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-2-oxo-2-pyrrolidin-1-ylacetamide	A	B	B	B	B
300	N-ethyl-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N-methylethanediamide	A	B	C	B	B
301	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(phenylmethyl)cyclopropane-1,1-dicarboxamide	A	C	B	B	B
302	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-phenylethyl)cyclopropane-1,1-dicarboxamide	C	C			
303	N-{4-[(7-chloroquinolin-4-yl)oxy]-3-fluorophenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	C	C	B
304	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
305	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-phenylcyclopropane-1,1-dicarboxamide	A	B	B	A	
306	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-methylpyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	B	B	C	B
307	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	A	A	A	B	A
308	N-{4-[(7-chloroquinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	B	C	B
309	N-[5-chloro-6-({6-(methyloxy)-7-[(phenylmethyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	C	C	B	C

310	N-(4-{[6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
311	N-(4-{[6,7-bis(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	B	A	A
312	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
313	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperidin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
314	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperidin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	A	A	A	B	A
315	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
316	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
317	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	C	A
318	N-(4-fluorophenyl)-N'-[2-methyl-6-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]cyclopropane-1,1-dicarboxamide	A	A	B	B	B
319	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
320	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloro-2-methylpyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	C	C	B	C
321	N-[3-fluoro-4-({7-(methyloxy)-6-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	B	A	A
322	N-[3-fluoro-4-({7-(methyloxy)-6-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
323	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3,5-difluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	B	A	A
324	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2,5-difluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A

325	N-{3-fluoro-4-[(7-(methyloxy)-6-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	B	A	A
326	N-[5-fluoro-2-methyl-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	B	B	B
327	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2,3,5-trifluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	B	B	B
328	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-2-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	B	B	C	C
329	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-chloro-5-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	B	B	C	B
330	N-(3-fluoro-4-{[6-hydroxy-7-(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
331	N-(4-fluorophenyl)-N'-[2-methyl-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]cyclopropane-1,1-dicarboxamide	A	A	A	B	A
332	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
333	N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
334	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
335	N-(4-fluorophenyl)-N'-[4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]cyclopropane-1,1-dicarboxamide	A	A	A	A	A
336	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
337	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-chloro-5-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	B	B	C	C
338	N-(4-{[6,7-bis(methyloxy)-2-(methylthio)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	C	C			

339	N-(4-fluorophenyl)-N'-(4-{[2-methyl-6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide	C	C			
340	N-(4-{[2-amino-6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	C	C			
341	N-(3-fluoro-4-{[2-(methylamino)-6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	C	C			
342	(1S,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	A	A	B	A	A
343	(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	A	A	A	A	A
344	N-(4-{[6-{[3-(diethylamino)propyl]oxy}-7-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A		A	
345	N-(4-{[6-{[2-(diethylamino)ethyl]oxy}-7-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A		A	
346	1,1-dimethylethyl 4-(3-{[4-[(2-fluoro-4-{[(1-{[(4-fluorophenyl)amino]carbonyl}cyclopropyl)carbonyl]amino}phenyl)oxy]-6-(methyloxy)quinolin-7-yl]oxy}propyl)piperazine-1-carboxylate	A	A		B	
347	(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	A	A			
348	(1R,2R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	A	A		B	
349	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A		A	
350	N-(4-{[7-{[3-(4-acetylpiperazin-1-yl)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A		A	
351	1,1-dimethylethyl 4-(3-{[4-[(2-fluoro-4-{[((1R,2R)-1-{[(4-fluorophenyl)amino]carbonyl}-2-methylcyclopropyl)carbonyl]amino}phenyl)oxy]-6-(methyloxy)quinolin-7-yl]oxy}propyl)piperazine-1-carboxylate	A	A		B	

352	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-1-(phenylmethyl)azetidine-3,3-dicarboxamide	A	C		C	
353	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)azetidine-3,3-dicarboxamide	B	C		C	
354	(1R,2S)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	A	A		A	
355	(1R,2R)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	A	A		A	
356	(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	A	A		A	
357	N-(3-fluoro-4-{[7-({3-[4-(1-methylethyl)piperazin-1-yl]propyl}oxy)-6-(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A		A	
358	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A		A	
359	(1R,2R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	A	A		A	
360	(1R,2R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	A	A		A	
361	(1R,2S)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	A	A		A	
362	(1R,2S)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	A	A		A	
363	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	A	A			
364	(1R,2S)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	A	A		A	

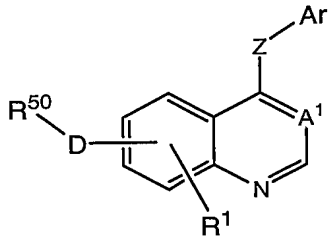
365	(1r,2R,3S)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	A	B		B	
366	(1r,2R,3S)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	A	B		B	
367	(1r,2R,3S)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	B	A		B	
368	(1r,2R,3S)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	A	A		B	
369	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	B	A		B	
370	(2R,3R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	A	A		B	
371	(2R,3R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	A	A		B	
372	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	A	A		B	
373	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	A	A		C	
374	(1r,2R,3S)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	A	B		B	
375	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	A	A		C	
376	(1r,2R,3S)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	A	B		B	

377	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	A	A		B	
378	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	A	B		C	
379	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	A	A		C	
380	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	A	A		B	
381	N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	A	A		B	
382	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	A	A		B	
383	(2R,3R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	A	A		C	
384	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	A	A		C	
385	N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	A	A		C	
386	(1R,2R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	A	A		A	
387	(1R,2R)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	A	A		A	
388	(2R,3R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	B	A		C	

389	(2R,3R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	A	A		B	
390	(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	A	A		A	
391	(2R,3R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	A	A		B	
392	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[(4-fluorophenyl)methyl]cyclopropane-1,1-dicarboxamide	B	B		A	
393	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(2-morpholin-4-ylethyl)cyclopropane-1,1-dicarboxamide	C	D		B	
394	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	B	D		B	
395	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	B	C		B	
396	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	B	A		A	
397	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	B	C		B	
398	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-phenylcyclopropane-1,1-dicarboxamide	A	A		A	
399	N-[3-(aminomethyl)phenyl]-N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide	B	A		B	
400	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	B	A			
401	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	A	A			

What is claimed is:

1. A compound for modulating kinase activity according to formula **I**,



I

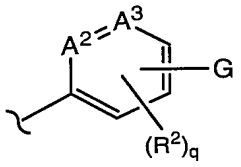
or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein,

R^1 is selected from -H, halogen, $-OR^3$, $-NO_2$, $-NH_2$, $-NR^3R^4$, and optionally substituted lower alkyl;

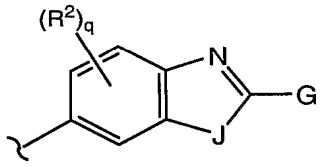
A^1 is selected from =N-, =C(H)-, and =C(CN)-;

Z is selected from $-S(O)_{0-2}$-, -O-, and $-NR^5$-;

Ar is either a group of formula **II**, or of formula **III**,



II



III

wherein,

R^2 is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted lower alkyl;

q is 0 to 4;

G is a group -B-L-T, wherein

B is selected from absent, $-N(R^{13})$-, $-N(SO_2R^{13})$-, -O-, $-S(O)_{0-2}$-, and -C(=O)-;

L is selected from absent, $-C(=S)N(R^{13})$-, $-C(=NR^{14})N(R^{13})$-, $-SO_2N(R^{13})$-, $-SO_2$-, $-C(=O)N(R^{13})$-, $-N(R^{13})$-, $-C(=O)C_{1-2}$alkyl$N(R^{13})$-, $-N(R^{13})C_{1-2}$alkylC(=O)-, $-C(=O)C_{0-1}$alkylC(=O)$N(R^{13})$-, $-C_{0-4}$alkylene-, $-C(=O)C_{0-1}$alkylC(=O)OR^3-, $-C(=NR^{14})C_{0-1}$alkylC(=O)-, -C(=O)-, $-C(=O)C_{0-1}$alkylC(=O)-, and an optionally substituted four to six-membered heterocyclyl containing

between one and three annular heteroatoms including at least one nitrogen; and

T is selected from -H, -R^{13}, -C_{0-4}alkyl, -C_{0-4}alkylQ, -OC_{0-4}alkylQ, -C_{0-4}alkylOQ, -$N(R^{13})C_{0-4}$alkylQ, -SO_2C_{0-4}alkylQ, -$C(=O)C_{0-4}$alkylQ, -C_{0-4}alkyl$N(R^{13})$Q, and -$C(=O)N(R^{13})C_{0-4}$alkylQ, wherein each of the aforementioned C_{0-4}alkyl is optionally substituted;

J is selected from -$S(O)_{0-2}$-, -O-, and -NR^{15}-;

R^3 is -H or R^4;

R^4 is selected from optionally substituted lower alkyl, optionally substituted aryl, optionally substituted lower arylalkyl, optionally substituted heterocyclyl, and optionally substituted lower heterocyclylalkyl; or

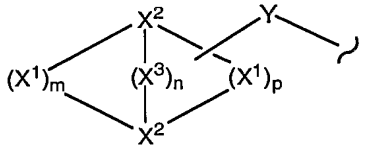
R^3 and R^4, when taken together with a common nitrogen to which they are attached, form an optionally substituted five- to seven-membered heterocyclyl, said optionally substituted five- to seven-membered heterocyclyl optionally containing at least one additional annular heteroatom selected from N, O, S, and P;

A^2 and A^3 are each independently selected from =N-, =$C(R^2)$-;

R^5 is -H or optionally substituted lower alkyl;

D is selected from -O-, -$S(O)_{0-2}$-, and -NR^{15}-;

R^{50} is either R^3, or according to formula **IV**;



IV

wherein X^1, X^2, and optionally X^3, represent the atoms of a saturated bridged ring system, said saturated bridged ring system comprising up to four annular heteroatoms represented by any of X^1, X^2, and X^3; wherein,

each X^1 is independently selected from -$C(R^6)R^7$-, -O-, -$S(O)_{0-2}$-, and -NR^8-;

each X^2 is independently an optionally substituted bridgehead methine or a bridgehead nitrogen;

each X^3 is independently selected from -$C(R^6)R^7$-, -O-, -$S(O)_{0-2}$-, and -NR^8-;

Y is either:

an optionally substituted lower alkylene linker, between D and either 1) any annular atom of the saturated bridged ring system, except X^2 when X^2 is a bridgehead nitrogen, or 2) any heteroatom, represented by any of R^6 or R^7; provided there are at least two carbon atoms between D and any annular heteroatom of the saturated bridged ring system or any heteroatom represented by any of R^6 or R^7;

or Y is absent, when Y is absent, said saturated bridged ring system, is directly attached to D via an annular carbon of said saturated bridged ring system, unless D is $-SO_2-$, in which case said saturated bridged ring system, is directly attached to D via an any annular atom of said saturated bridged ring system;

m and p are each independently 1-4;

n is 0-2, when n = 0, then there is a single bond between the two bridgehead X^2's;

R^6 and R^7 are each independently selected from -H, halogen, trihalomethyl, -CN, $-NH_2$, $-NO_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^4$, $-SO_2NR^3R^4$, $-CO_2R^3$, $-C(O)NR^3R^4$, $-N(R^3)SO_2R^4$, $-N(R^3)C(O)R^3$, $-NCO_2R^3$, $-C(O)R^3$, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted lower arylalkyl, optionally substituted heterocyclyl, optionally substituted lower heterocyclylalkyl, and a bond to either Y or D; or

R^6 and R^7, when taken together are oxo; or

R^6 and R^7, when taken together with a common carbon to which they are attached, form a optionally substituted three- to seven-membered spirocyclyl, said optionally substituted three- to seven-membered spirocyclyl optionally containing at least one additional annular heteroatom selected from N, O, S, and P;

R^8 is selected from $-R^3$, Y, $-SO_2NR^3R^4$, $-CO_2R^4$, $-C(O)NR^3R^3$, $-SO_2R^4$, and $-C(O)R^3$;

R^{13} is selected from -H, $-C(=O)R^3$, $-C(=O)OR^3$, $-C(=O)SR^3$, $-SO_2R^4$, $-C(=O)N(R^3)R^3$, and optionally substituted lower alkyl,

two R^{13}, together with the atom or atoms to which they are attached, can combine to form a heteroalicyclic optionally substituted with between one and four of R^{60}, said heteroalicyclic can have up to four annular heteroatoms, and said heteroalicyclic can have

an aryl or heteroaryl fused thereto, in which case said aryl or heteroaryl is optionally substituted with an additional one to four of R^{60};

R^{14} is selected from -H, $-NO_2$, $-NH_2$, $-N(R^3)R^4$, -CN, $-OR^3$, optionally substituted lower alkyl, optionally substituted heteroalicyclylalkyl, optionally substituted aryl, optionally substituted arylalkyl and optionally substituted heteroalicyclic;

R^{15} is a group $-M^1-M^2$, wherein M^1 is selected from absent, $-C(=S)N(R^{13})-$, $-C(=NR^{14})N(R^{13})-$, $-SO_2N(R^{13})-$, $-SO_2-$, $-C(=O)N(R^{13})-$, $-C(=O)C(=O)N(R^{13})-$, $-C_{0-4}$alkylene-, -C(=O)-, and an optionally substituted four to six-membered hetercyclyl annular containing between one and three heteratoms including at least one nitrogen; and M^2 is selected from -H, $-C_{0-6}$alkyl, alkoxy, $-C(=O)C_{0-4}$alkylQ, $-C_{0-4}$alkylQ, $-OC_{0-4}$alkylQ-, $-N(R^{13})C_{0-4}$alkylQ-, and $-C(=O)N(R^{13})C_{0-4}$alkylQ; and

Q is a five- to ten-membered ring system, optionally substituted with between zero and four of R^{20};

R^{20} is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted lower alkyl;

R^{60} is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted heteroarylalkyl, and optionally substituted arylalkyl;

two of R^{60}, when attached to a non-aromatic carbon, can be oxo;

with the proviso, only when Ar is according to formula **II**, if Y is a C_{1-6} alkylene; Z is -NH- or $-N(CH_3)-$; R^1 is a C_{1-6}alkyl optionally substituted in the 2-position by -OH or a C_{1-4}alkoxy group; R^2 is -H or halogen; n = 0; and the atoms, X^1, of one bridge of the saturated bridged ring system, when combined with both bridgehead atoms, X^2, of the saturated bridged ring system, represent:

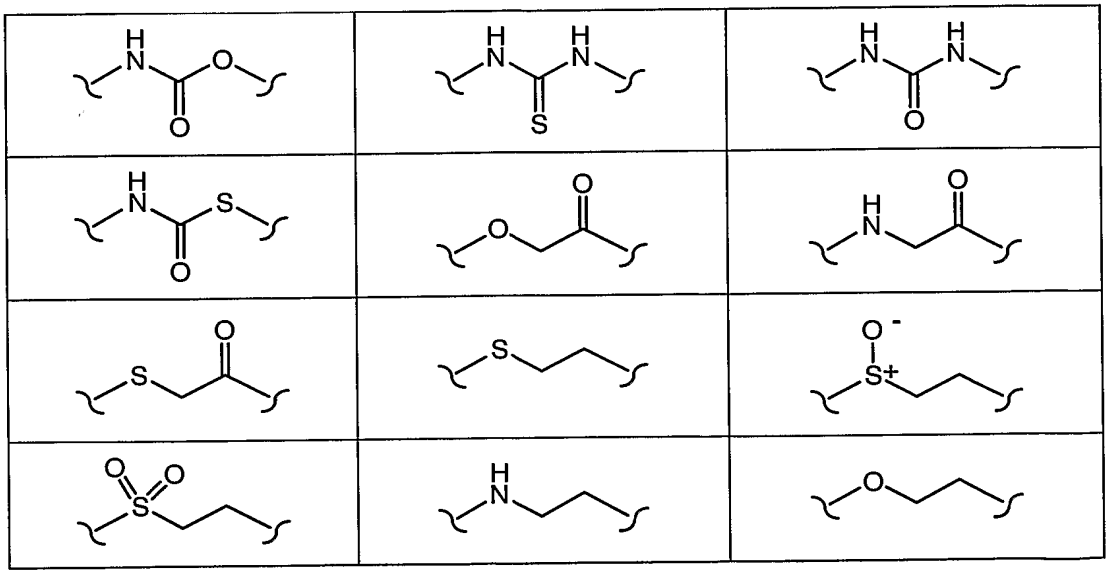
1) either a pyrrolidine or a piperidine, and any atom, X^1 or X^2, of either of said pyrrolidine or said piperidine is attached to Y, then the other bridge of said saturated bridged ring system cannot be any one of $-OC(O)CH_2-$, $-CH_2OC(O)-$, $-OC(O)CH_2CH_2-$, $-CH_2OC(O)CH_2-$, $-CH_2CH_2OC(O)-$, $-OC(O)CH_2NH-$, $-OC(O)CH_2N(C_{1-4}alkyl)-$, and $-OC(O)CH_2O-$; or

2) either a piperazine or a 4-(C_{1-4}alkyl)-piperazine, and any atom, X^1 or X^2, of either of said piperazine or said 4-(C_{1-4}alkyl)-piperazine is attached to Y, then the other bridge of said saturated bridged ring system, only when attached via the 2- and the 3-position of either of said piperazine or said 4-(C_{1-4}alkyl)-piperazine, cannot be one of $-CH_2OC(O)CH_2-$, $-CH_2CH_2OC(O)-$, and either of the two aforementioned bridges optionally substituted by one or two C_{1-2}alkyl groups; or

3) a piperazine, and any atom, X^1 or X^2, of said piperazine is attached to Y, then the other bridge of said saturated bridged ring system, only when attached via the 3- and the 4-position of said piperazine, cannot be one of $-C(O)OCH_2CH_2-$, $-CH_2OC(O)CH_2-$, and either of the two aforementioned bridges optionally substituted by one or two C_{1-2}alkyl groups, and only when either of the two aforementioned bridges are attached to the 3-position of said piperazine via their left-hand end as depicted above; or

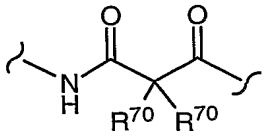
4) a 2-oxomorpholine, said 2-oxomorpholine attached to Y via its 4-position, then the other bridge of said saturated bridged ring system, only when attached via the 5- and the 6-position of said 2-oxomorpholine, cannot be one of $-(CH_2)_g-$, $-CH_2WCH_2-$, $-CH_2WCH_2CH_2-$, and $-CH_2CH_2WCH_2-$, wherein W is -O-, $-S(O)_{0-2}-$, -NH-, or $-N(C_{1-4}$alkyl)- wherein g is 2, 3, or 4;

and with the proviso that when Z is-O-, Ar is according to formula **II**, and the portion of G directly attached to Ar is selected from:



then R^{50} must be of formula **IV**;

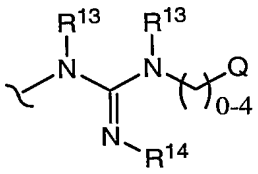
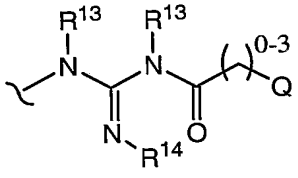
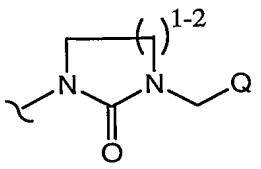
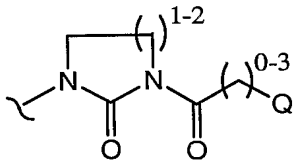
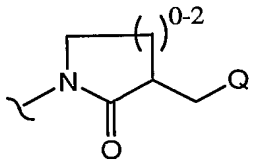
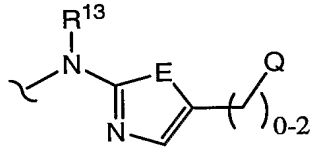
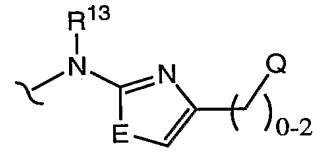
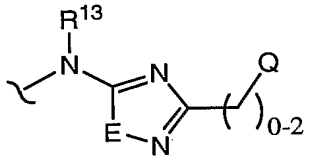
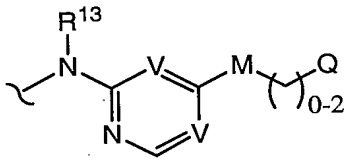
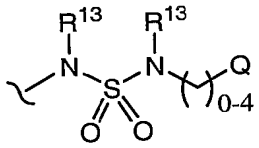
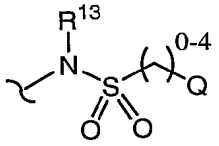
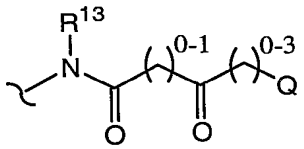
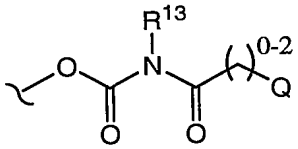
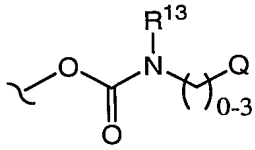
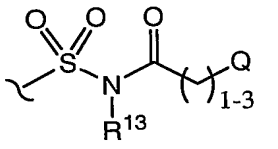
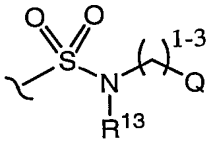
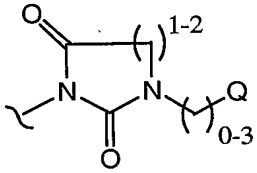
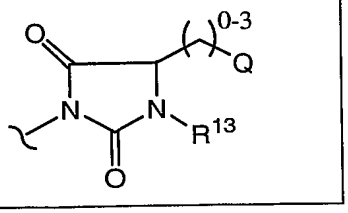
and with the proviso that when Ar is phenylene or substituted phenylene, Z is $-S(O)_{0-2}-$ or

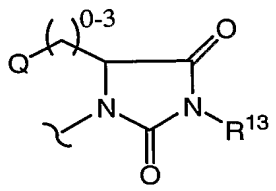
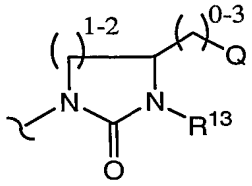
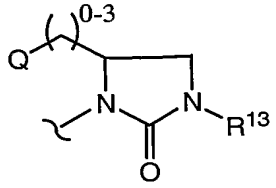
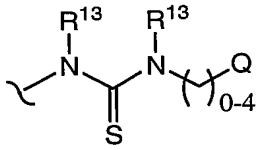
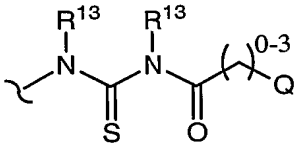
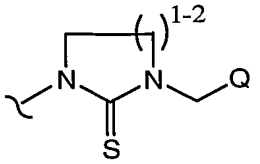
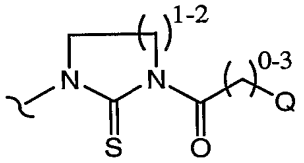
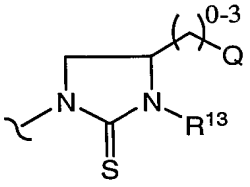
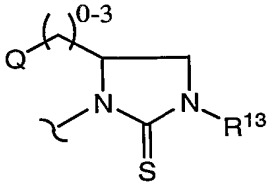
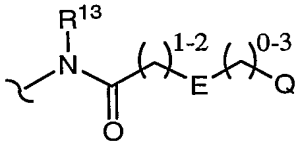
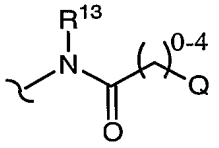
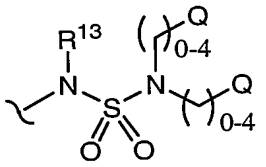
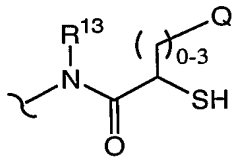
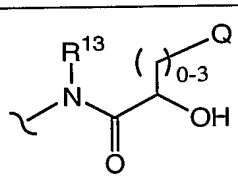
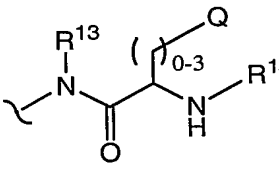
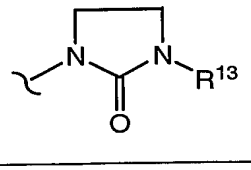
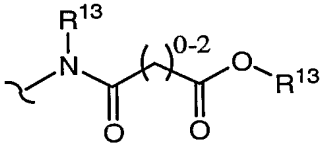
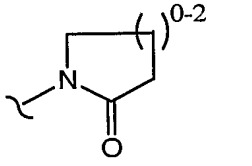
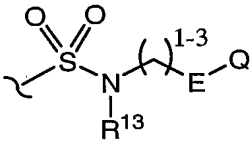
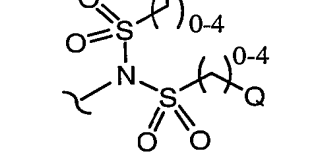
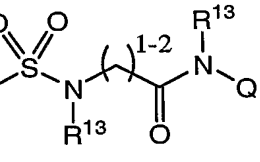
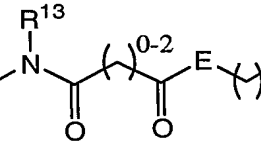
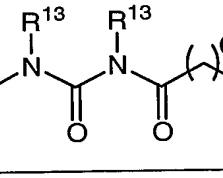
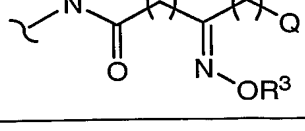
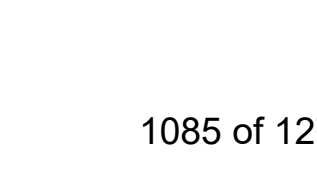


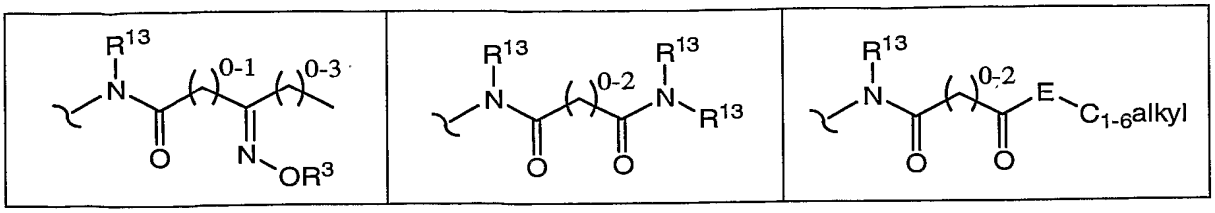
$-O-$, then the portion of G directly attached to Ar cannot contain , when R^{70} is selected from -H, C_{1-4}alkyl, and C_{1-4}alkoxyl.

2. The compound according to claim 1, wherein In one example, the compound is according to paragraph [0033], wherein Z is either -O- or $-NR^5-$.

3. The compound according to claim 2, wherein G is selected from the following:

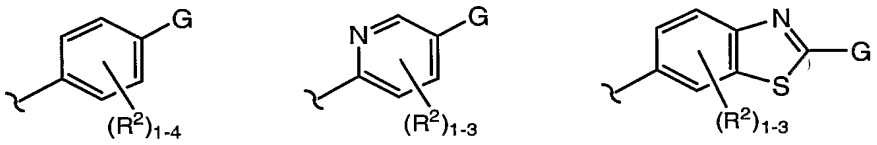
		
		
		
		
		
		



wherein wherein Q, R^{20}, and R^{13} are as defined above; each E is selected from -O-, $-N(R^{13})-$, $-CH_2-$, and $-S(O)_{0-2}-$; M is selected from -O-, $-N(R^{13})-$, $-CH_2-$, and $-C(=O)N(R^{13})-$; each V is independently either =N- or =C(H)-; each methylene in any of the above formulae is independently optionally substituted with R^{25}; and R^{25} is selected from halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted arylalkyl, heteroarylalkyl, and optionally substituted lower alkyl; two of R^{25}, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered alicyclic or heteroalicyclic, two of R^{25} on a single carbon can be oxo.

4. The compound according to claim 3, wherein Ar is according to one of formula **IIa**, **IIb**, and **IIIa**.



IIa **IIb** **IIIa**

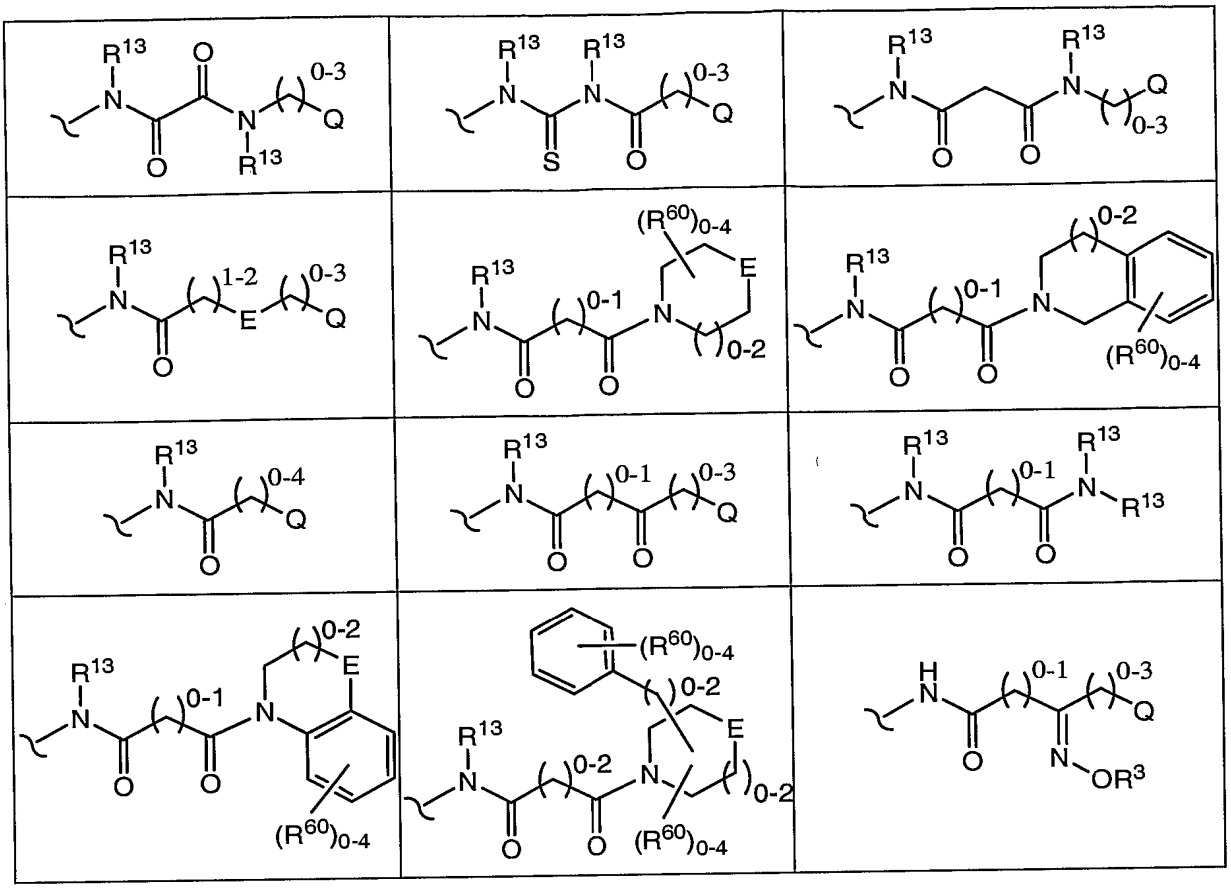
5. The compound according to claim 4, wherein D is -O- and R^1 is $-OR^3$.

6. The compound according to claim 5, wherein $-O-R^{50}$ and R^1 are interchangeably located at the 6-position and 7-position of the quinazoline or quinoline according to formula **I**.

7. The compound according to claim 6, wherein R^1 is -OH or $-OC_{1-6}$alkyl.

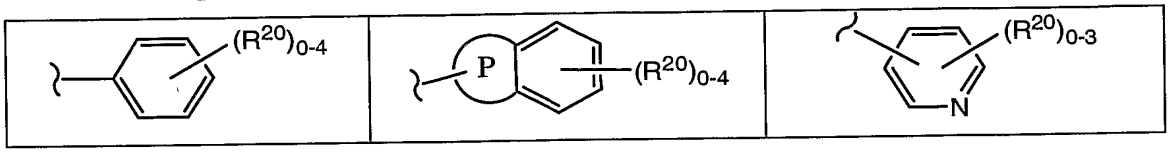
8. The compound according to claim 7, wherein A^1 is =N- or =C(H)-.

9. The compound according to claim 8, wherein G is selected from:



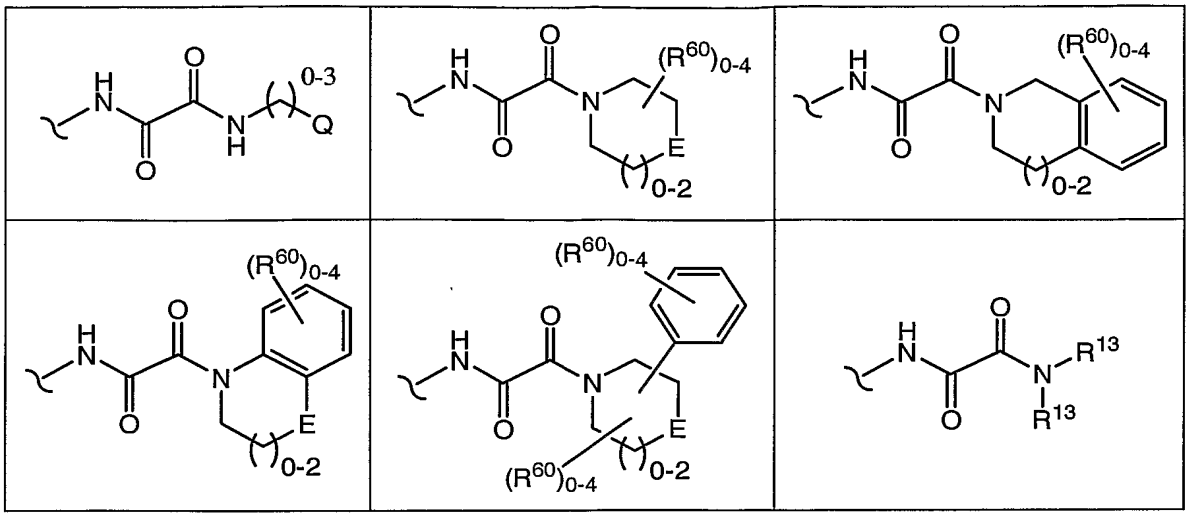
wherein Q, R^{20}, R^{13}, E, and R^{60} are as defined above; each methylene in any of the above formulae, other than those in a depicted ring, is independently optionally substituted with R^{25}; and R^{25} is selected from halogen, trihalomethyl, oxo, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted arylalkyl, heteroarylalkyl, and optionally substituted lower alkyl; two of R^{25}, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered alicyclic or heteroalicyclic.

10. The compound according to claim 9, wherein Q is selected from:



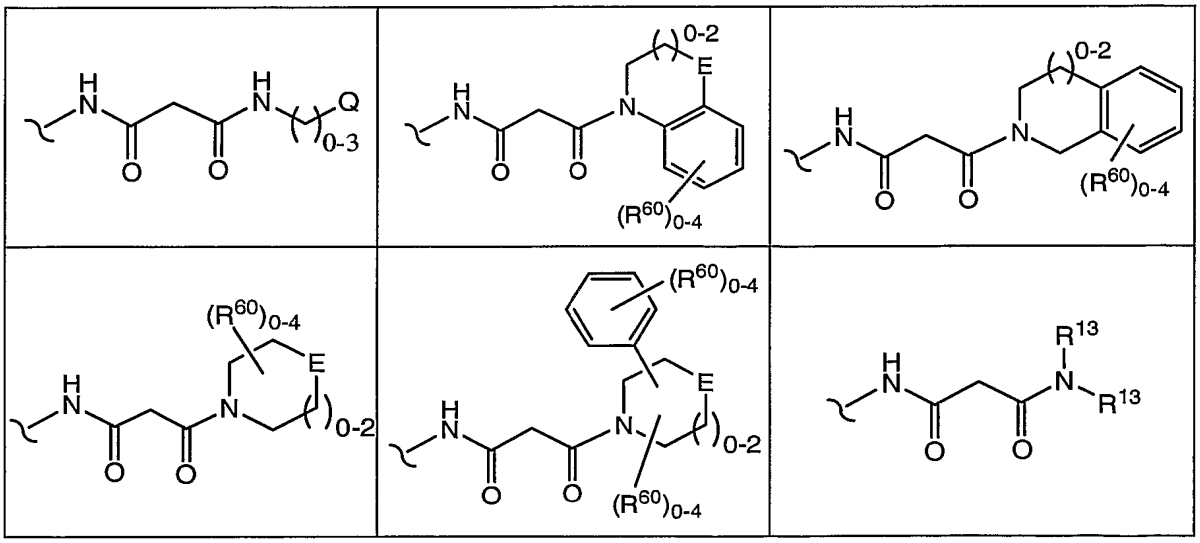
wherein R^{20} is defined as above, and P is a five- to seven-membered ring, including the two shared carbons of the aromatic ring to which P is fused, P optionally containing between one and three heteroatoms.

11. The compound according to claim 10, wherein Ar is according to formula **IIa**, and G is selected from:



wherein Q, R^{20}, R^{13}, E, and R^{60} are as defined above, and each methylene in any of the above formulae, other than those in a depicted ring, is independently optionally substituted with R^{25}; and R^{25} is selected from halogen, trihalomethyl, oxo, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted arylalkyl, heteroarylalkyl, and optionally substituted lower alkyl; two of R^{25}, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered alicyclic or heteroalicyclic.

12. The compound according to claim 10, wherein Ar is according to formula **IIb**, and G is selected from:



wherein Q, R^{20}, R^{13}, E, and R^{60} are as defined above, and each methylene in any of the above formulae, other than those depicted in a ring, is independently optionally substituted with R^{25}; and R^{25} is selected from halogen, trihalomethyl, oxo, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted arylalkyl, heteroarylalkyl, and optionally substituted lower alkyl; two of R^{25}, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered alicyclic or heteroalicyclic.

13. The compound according to claim 12, wherein the methylene between the two carbonyls of the depicted formulae is di-substituted with either optionally substituted lower alkyl, or an optionally substituted spirocycle.

14. The compound according to claim 11 or claim 12, wherein R^{50} is a heteroalicylic or a C_{1-6}alkyl-heteroalicylic.

15. The compound according to claim 14, wherein at least one of R^2 is halogen.

16. The compound according to claim 14, wherein R^{50} is according to formula **IV**.

17. The compound according to claim 16, wherein the saturated bridged ring system according to formula **IV** has a geometry selected from the group consisting of [4.4.0], [4.3.0], [4.2.0], [4.1.0], [3.3.0], [3.2.0], [3.1.0], [3.3.3], [3.3.2], [3.3.1], [3.2.2], [3.2.1], [2.2.2], and [2.2.1].

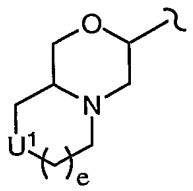
18. The compound according to claim 17, wherein Y is selected from $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2-$, $-CH_2-$, and absent.

19. The compound according to claim 18, wherein n is 0 and the saturated bridged ring system according to formula **IV** has a geometry selected from the group consisting of [4.4.0], [4.3.0], [4.2.0], [4.1.0], [3.3.0], [3.2.0], and [3.1.0].

20. The compound according to claim 19, wherein said saturated bridged ring system contains at least one annular nitrogen or at least one annular oxygen.

21. The compound according to claim 20, wherein said saturated bridged ring system contains $-NR^8-$, wherein R^8 is selected from -H, optionally substituted lower alkyl, $-CO_2R^3$, $-C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$.

22. The compound according to claim 20, wherein said saturated bridged ring system is of formula **V**,



V

wherein U^1 is selected from -O-, -$S(O)_{0-2}$-, -NR^8-, -CR^6R^7-, and absent; and e is 0 or 1.

23. The compound according to claim 22, wherein Y is -CH_2-.

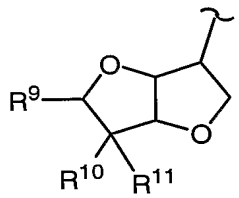
24. The compound according to claim 23, wherein U^1 is -NR^8-, wherein R^8 is selected from -H, optionally substituted lower alkyl, -CO_2R^3, -$C(O)NR^3R^3$, -SO_2R^3, and -$C(O)R^3$.

25. The compound according to claim 23, wherein U^1 is -O-.

26. The compound according to claim 23, wherein U^1 is absent.

27. The compound according to claim 20, wherein Y is selected from -CH_2CH_2-, -CH_2-, and absent.

28. The compound according to claim 27, wherein said saturated bridged ring system is of formula **VI**,



VI

wherein R^9, R^{10}, and R^{11} are each independently selected from -H, and -OR^{12}; or

R^9 is selected from -H, and -OR^{12}, and R^{10} and R^{11}, when taken together, are either an optionally substituted alkylidene or an oxo;

R^{12} is selected from -H, -$C(O)R^3$, optionally substituted lower alkylidyne, optionally substituted lower arylalkylidyne, optionally substituted lower heterocyclylalkylidyne, optionally substituted lower alkylidene, optionally

substituted lower alkylidenearyl, optionally substituted lower alkylideneheterocyclyl, optionally substituted lower alkyl, optionally substituted lower alkylaryl, optionally substituted aryl, optionally substituted lower heterocyclylalkyl, and optionally substituted heterocyclyl;

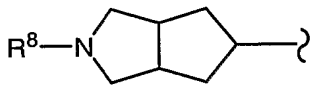
or two R^{12}'s, when taken together, form 1) a corresponding spirocyclic ketal when said two R^{12}'s stem from R^{10} and R^{11}, or 2) a corresponding cyclic ketal when said two R^{12}'s stem from R^9 and one of R^{10} and R^{11}.

29. The compound according to claim 28, wherein one of R^{10} and R^{11} is $-OR^{12}$, wherein R^{12} is selected from -H, $-C(O)R^3$, and optionally substituted lower alkyl; and R^9 and the other of R^{10} and R^{11} are both -H.

30. The compound according to claim 29, wherein Y is either $-CH_2-$ or absent.

31. The compound according to claim 30, wherein R^9 is an alkyl group containing at least one fluorine substitution thereon.

32. The compound according to claim 21, wherein said saturated bridged ring system is of formula **VII**.

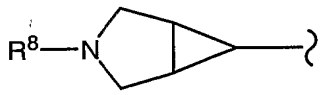


VII

33. The compound according to claim 32, wherein Y is either $-CH_2-$ or absent.

34. The compound according to claim 33, wherein R^8 is methyl or ethyl.

35. The compound according to claim 21, wherein said saturated bridged ring system is of formula **VIII**.

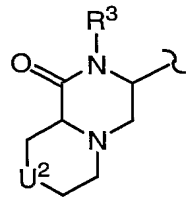


VIII

36. The compound according to claim 35, wherein Y is $-CH_2-$.

37. The compound according to claim 36, wherein R^8 is methyl or ethyl.

38. The compound according to claim 20, wherein said saturated bridged ring system is of formula **IX**



IX

wherein U^2 is selected from -O-, -S(O)$_{0-2}$-, -NR^8-, -CR^{6}R^7-, and absent.

39. The compound according to claim 38, wherein R^3 of formula **IX** is selected from -H and optionally substituted alkyl.

40. The compound according to claim 39, wherein U^2 is either -CR^{6}R^7- or absent.

41. The compound according to claim 40, wherein U^2 is either -CH_2- or absent.

42. The compound according to claim 41, wherein Y is -CH_2-.

43. The compound according to claim 21, wherein said saturated bridged ring system is according to formula **X**.



X

44. The compound according to claim 43, wherein R^8 is methyl or ethyl.

45. The compound according to claim 1, selected from Table 1.

Table 1

Entry	Name	Structure

Table 1

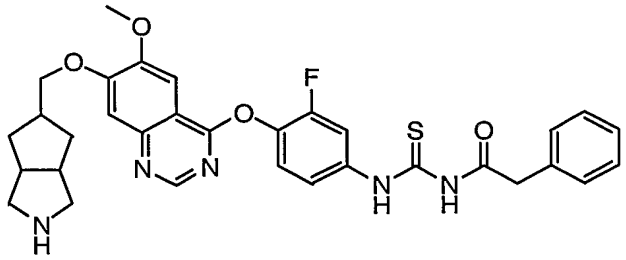
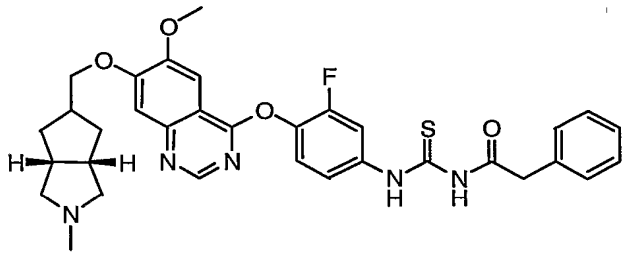
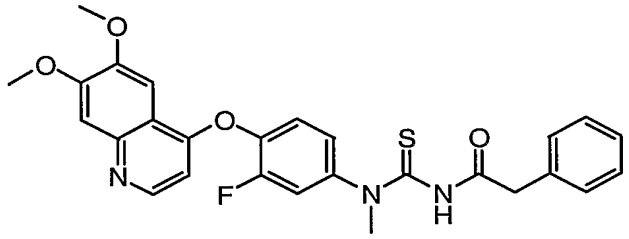
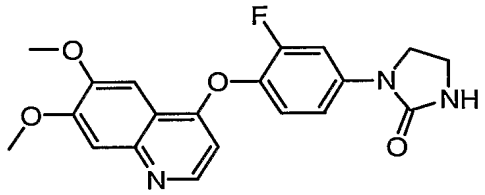
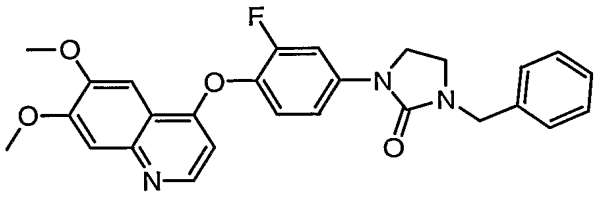
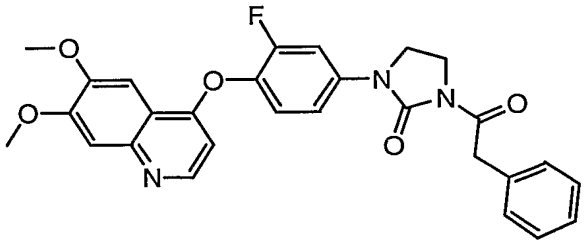
Entry	Name	Structure
1	N-[({3-fluoro-4-[(6-(methyloxy)-7-{[(3aR,6aS)-octahydrocyclopenta[c]pyrrol-5-ylmethyl]oxy}quinazolin-4-yl)oxy]phenyl}amino)carbonothioyl]-2-phenylacetamide	
2	N-{[(3-fluoro-4-{[7-({[(3aR,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-yl]oxy}phenyl)amino]carbonothioyl}-2-phenylacetamide	
3	N-{[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)(methyl)amino]carbonothioyl}-2-phenylacetamide	
4	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)imidazolidin-2-one	
5	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylmethyl)imidazolidin-2-one	
6	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylacetyl)imidazolidin-2-one	

Table 1

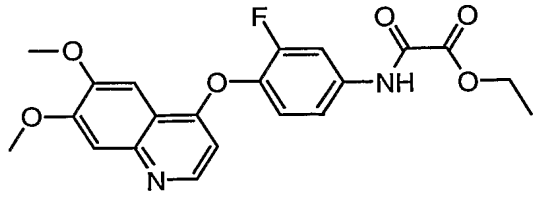
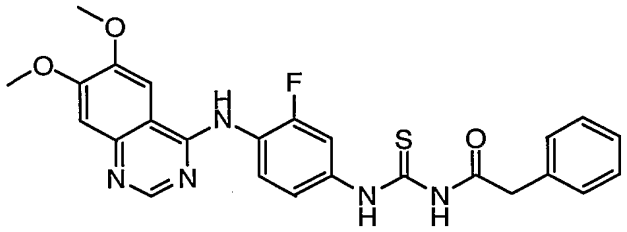
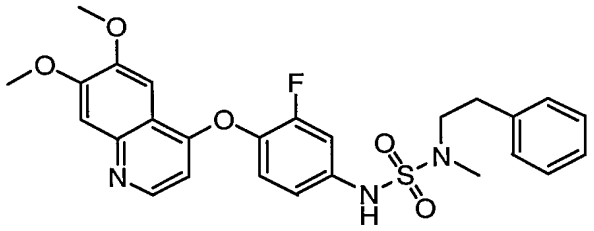
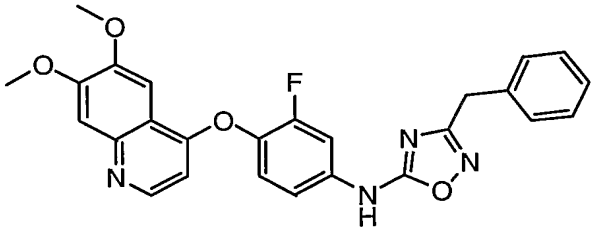
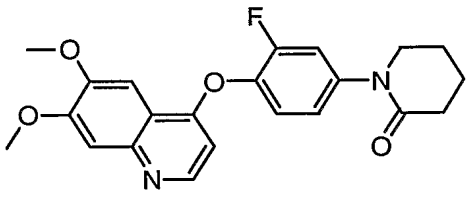
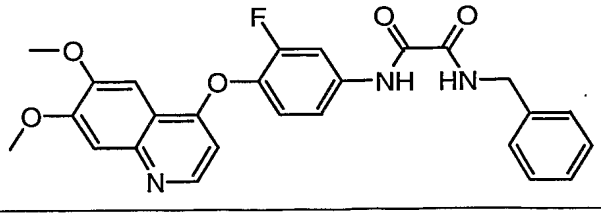
Entry	Name	Structure
7	ethyl [(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)amino](oxo)acetate	
8	N-{[(4-{[6,7-bis(methyloxy)quinazolin-4-yl]amino}-3-fluorophenyl)amino]carbonothioyl}-2-phenylacetamide	
9	N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N-methyl-N-(2-phenylethyl)sulfamide	
10	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylmethyl)-1,2,4-oxadiazol-5-amine	
11	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)piperidin-2-one	
12	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(phenylmethyl)ethanediamide	

Table 1

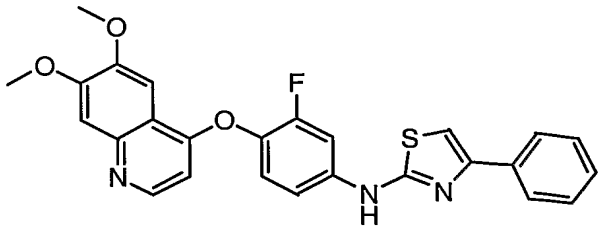
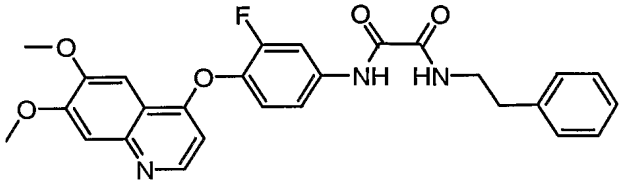
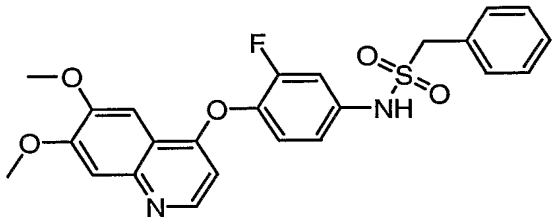
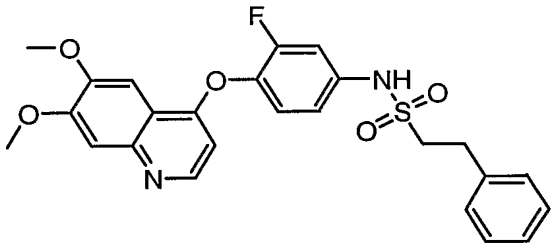
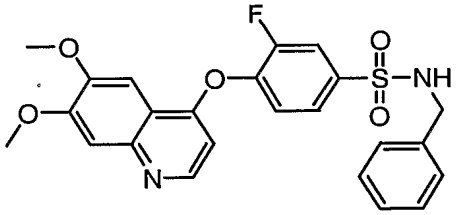
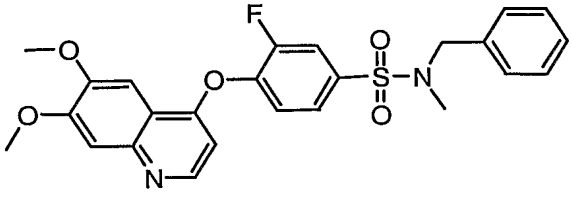
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14	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-phenylethyl)ethanediamide	
15	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-1-phenylmethanesulfonamide	
16	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-2-phenylethanesulfonamide	
17	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-(phenylmethyl)benzenesulfonamide	
18	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(phenylmethyl)benzenesulfonamide	

Table 1

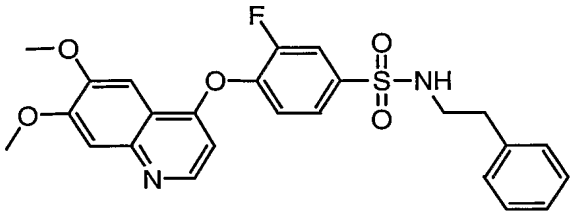
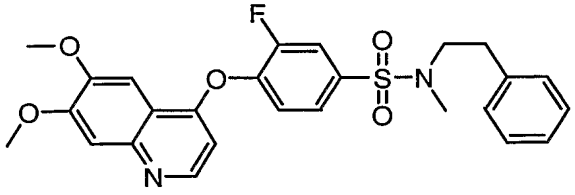
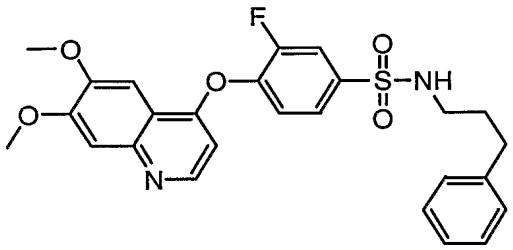
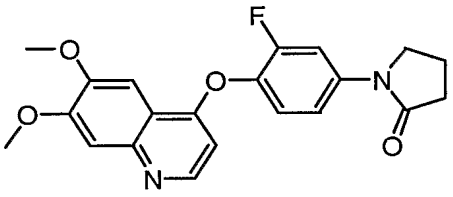
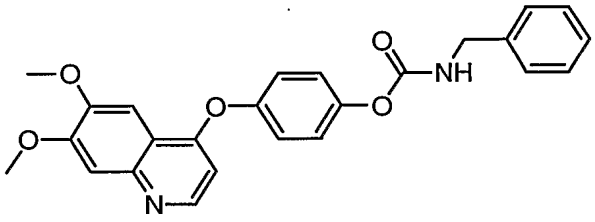
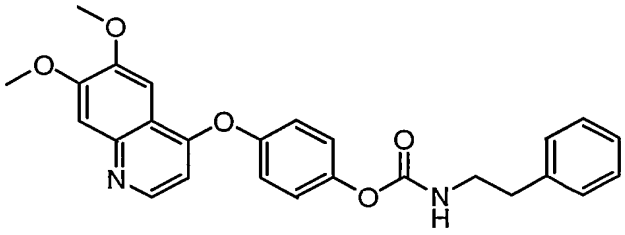
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19	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-(2-phenylethyl)benzenesulfonamide	
20	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(2-phenylethyl)benzenesulfonamide	
21	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-(3-phenylpropyl)benzenesulfonamide	
22	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)pyrrolidin-2-one	
23	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl (phenylmethyl)carbamate	
24	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl (2-phenylethyl)carbamate	

Table 1

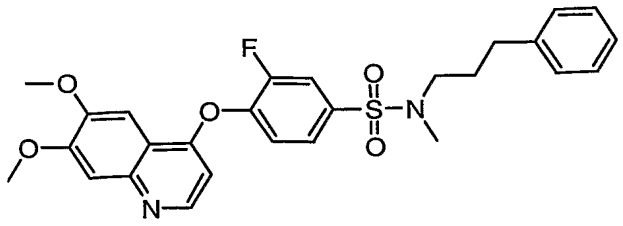
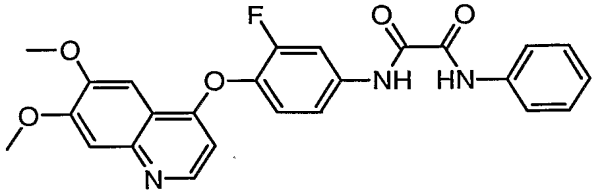
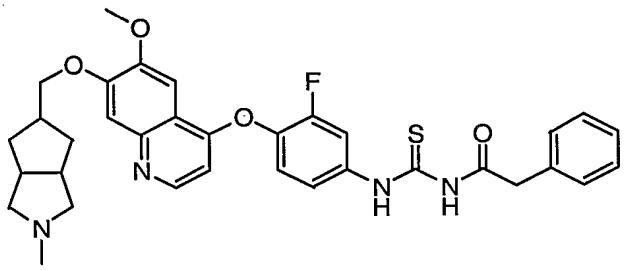
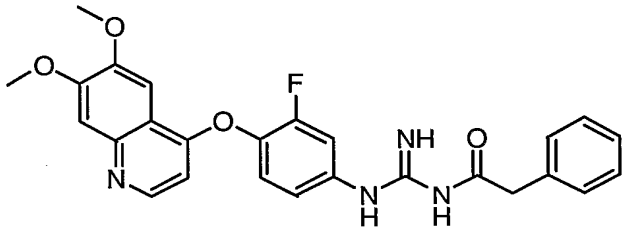
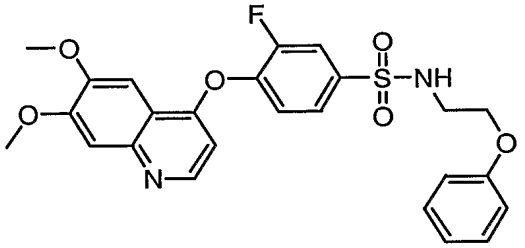
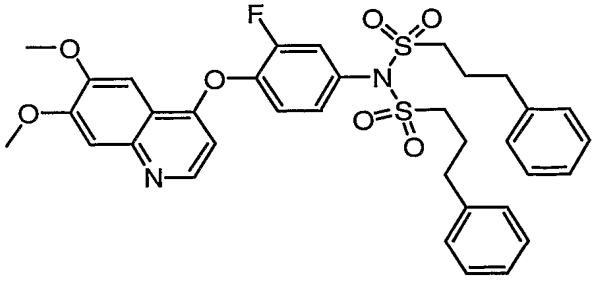
Entry	Name	Structure
25	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(3-phenylpropyl)benzenesulfonamide	
26	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-phenylethanediamide	
27	N-{[(3-fluoro-4-{[7-{[(2-methyloctahydrocyclopenta[c]pyrrol-5-yl)methyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}phenyl)amino]carbonothioyl}-2-phenylacetamide	
28	N-[(Z)-[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)amino](imino)methyl]-2-phenylacetamide	
29	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-[2-(phenyloxy)ethyl]benzenesulfonamide	
30	N,N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-bis-(3-phenylpropane-1-sulfonamide)	

Table 1

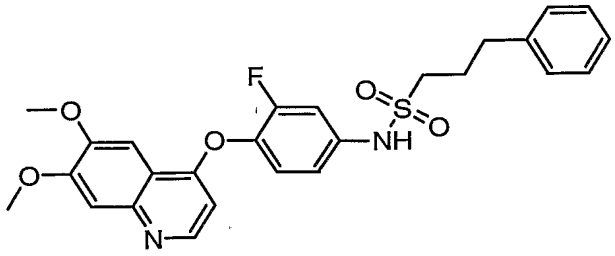
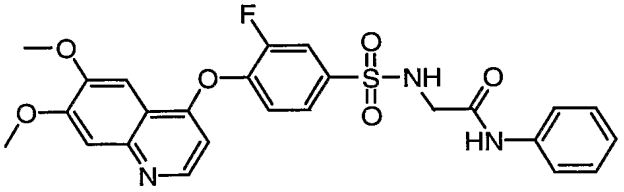
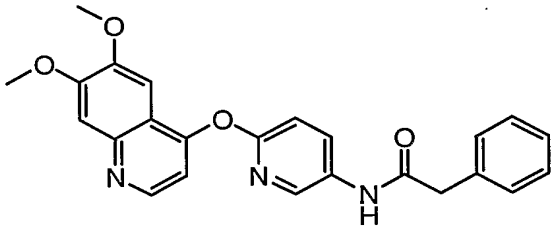
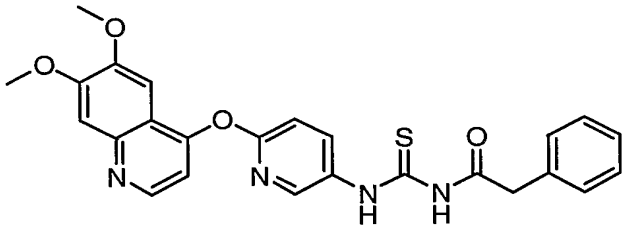
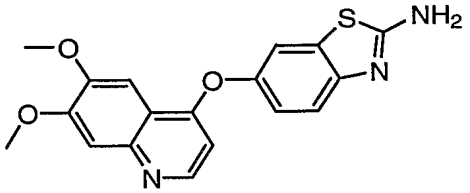
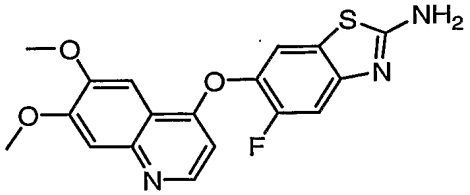
Entry	Name	Structure
31	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-phenylpropane-1-sulfonamide	
32	N2-[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)sulfonyl]-N1-phenylglycinamide	
33	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-2-phenylacetamide	
34	N-{[(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)amino]carbonothioyl}-2-phenylacetamide	
35	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-1,3-benzothiazol-2-amine	
36	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-amine	

Table 1

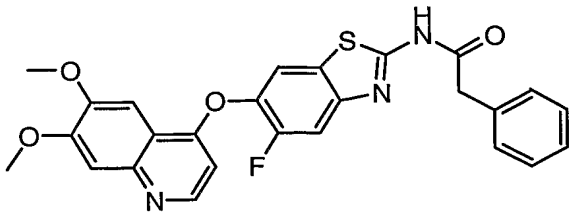
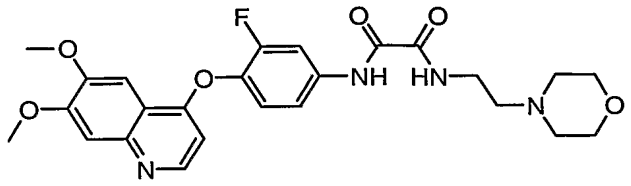
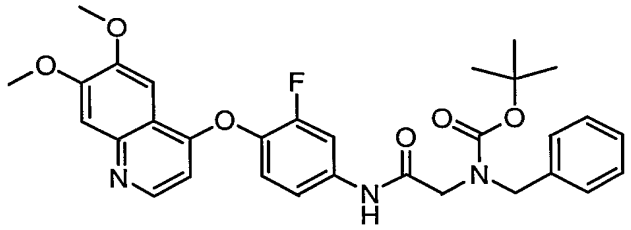
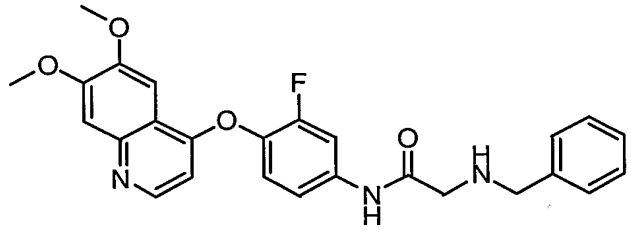
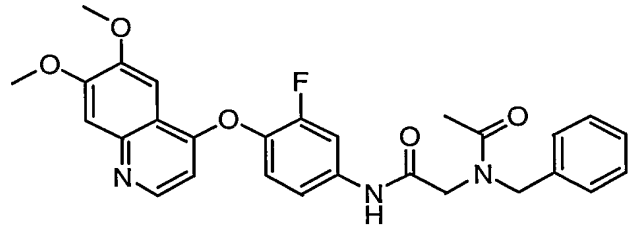
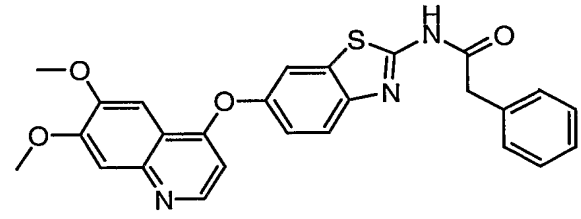
Entry	Name	Structure
37	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-phenylacetamide	
38	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-morpholin-4-ylethyl)ethanediamide	
39	benzyl-{[4-(6,7-dimethoxy-quinolin-4-yloxy)-3-fluoro-phenylcarbamoyl]-methyl}-carbamic acid tert-butyl ester	
40	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(phenylmethyl)glycinamide	
41	N2-acetyl-N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(phenylmethyl)glycinamide	
42	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-1,3-benzothiazol-2-yl)-2-phenylacetamide	

Table 1

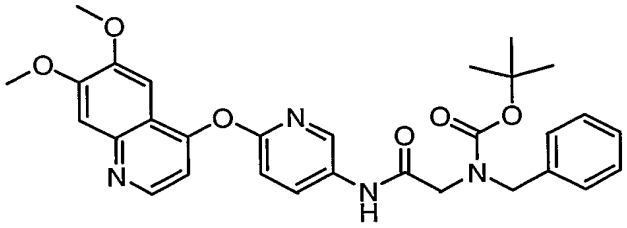
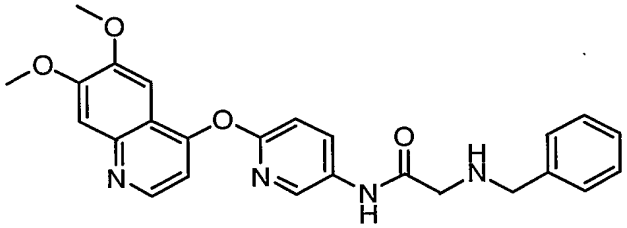
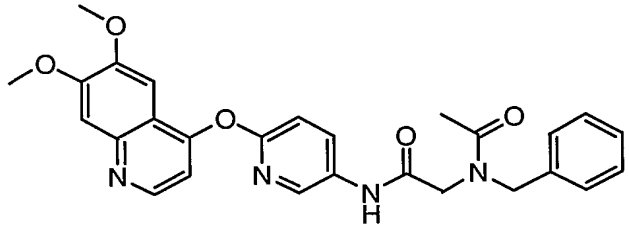
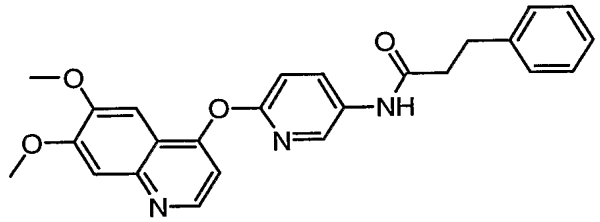
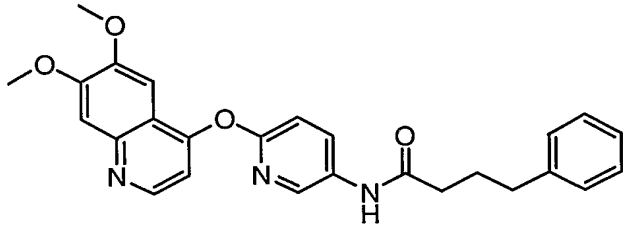
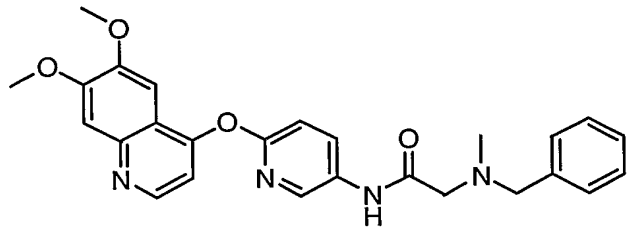
Entry	Name	Structure
43	benzyl-{[6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-ylcarbamoyl]-methyl}-carbamic acid tert-butyl ester	
44	N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N2-(phenylmethyl)glycinamide	
45	N2-acetyl-N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N2-(phenylmethyl)glycinamide	
46	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-3-phenylpropanamide	
47	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-4-phenylbutanamide	
48	N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N2-methyl-N2-(phenylmethyl)glycinamide	

Table 1

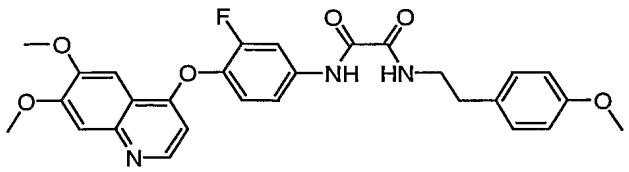
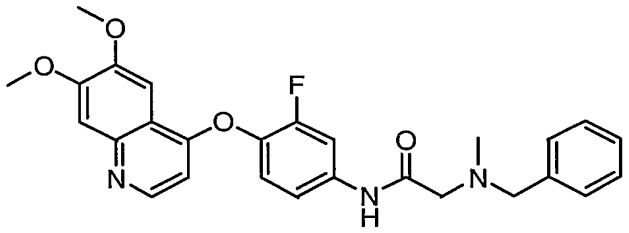
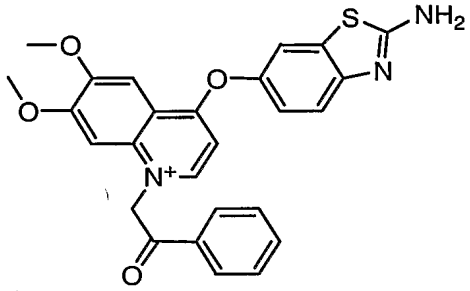
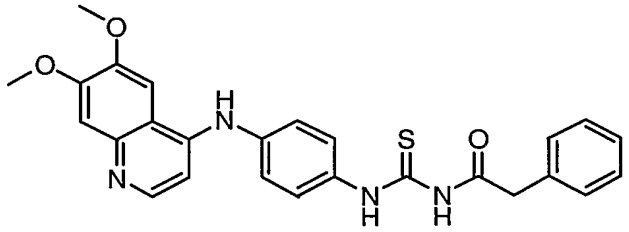
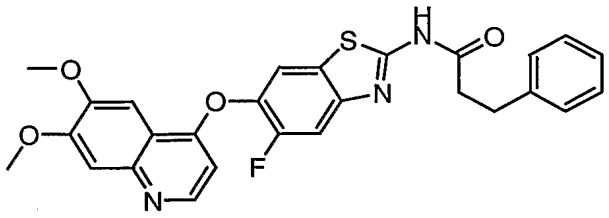
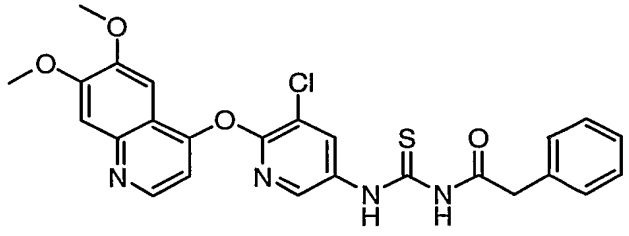
Entry	Name	Structure
49	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{2-[4-(methyloxy)phenyl]ethyl}ethanediamide	
50	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-methyl-N2-(phenylmethyl)glycinamide	
51	4-[(2-amino-1,3-benzothiazol-6-yl)oxy]-6,7-bis(methyloxy)-1-(2-oxo-2-phenylethyl)quinolinium	
52	N-{[(4-{[6,7-bis(methyloxy)quinolin-4-yl]amino}phenyl)amino]carbonothioyl}-2-phenylacetamide	
53	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-3-phenylpropanamide	
54	N-{[(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)amino]carbonothioyl}-2-phenylacetamide	

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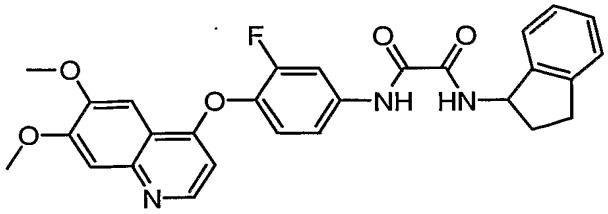
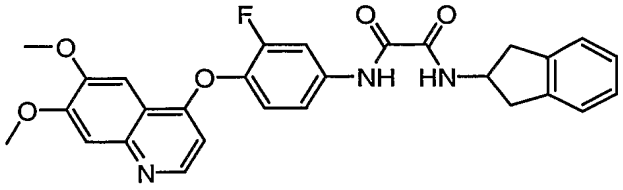
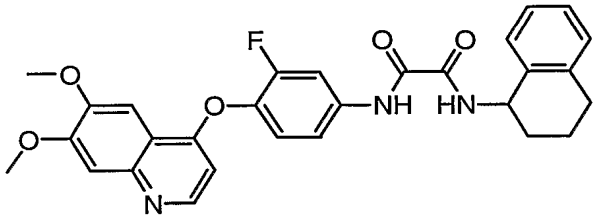
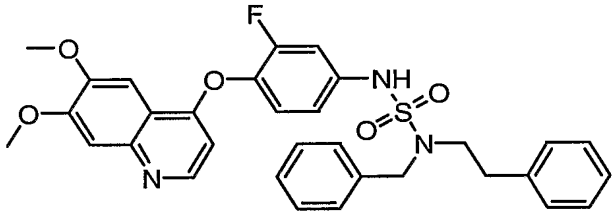
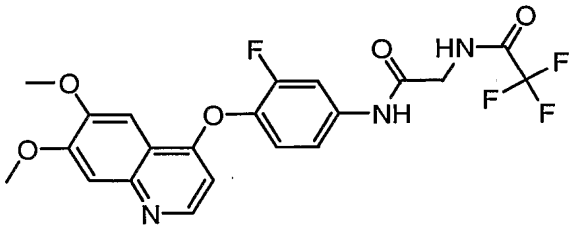
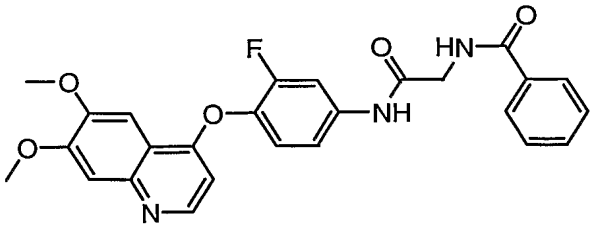
Entry	Name	Structure
55	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2,3-dihydro-1H-inden-1-yl)ethanediamide	
56	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2,3-dihydro-1H-inden-2-yl)ethanediamide	
57	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(1,2,3,4-tetrahydronaphthalen-1-yl)ethanediamide	
58	N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N-(2-phenylethyl)-N-(phenylmethyl)sulfamide	
59	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(trifluoroacetyl)glycinamide	
60	N-{[4-(6,7-dimethoxy-quinolin-4-yloxy)-3-fluoro-phenylcarbamoyl]-methyl}-benzamide	

Table 1

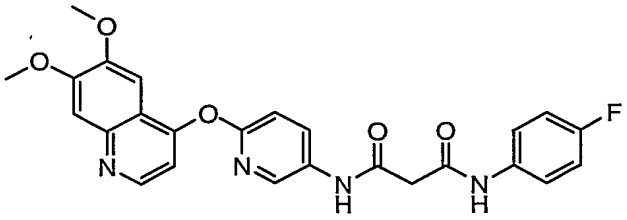
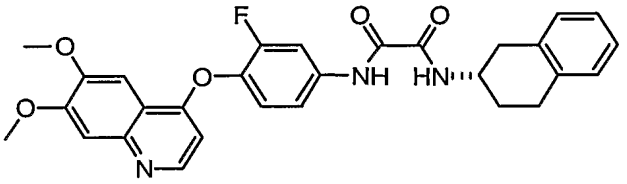
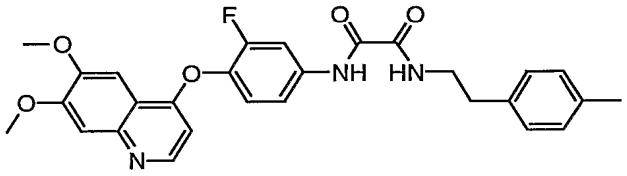
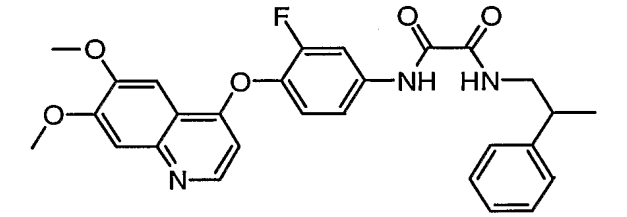
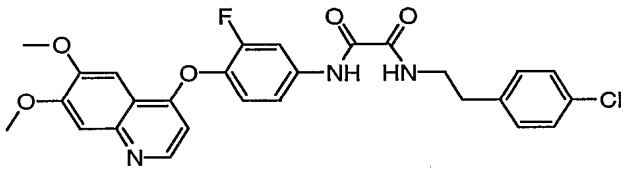
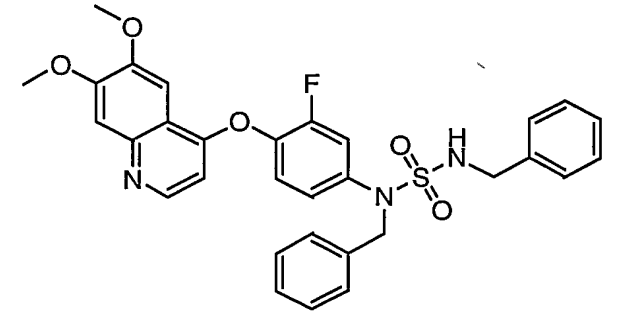
Entry	Name	Structure
61	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N'-(4-fluorophenyl)propanediamide	
62	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[(2S)-1,2,3,4-tetrahydronaphthalen-2-yl]ethanediamide	
63	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(4-methylphenyl)ethyl]ethanediamide	
64	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-phenylpropyl)ethanediamide	
65	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(4-chlorophenyl)ethyl]ethanediamide	
66	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N,N'-bis(phenylmethyl)sulfamide	

Table 1

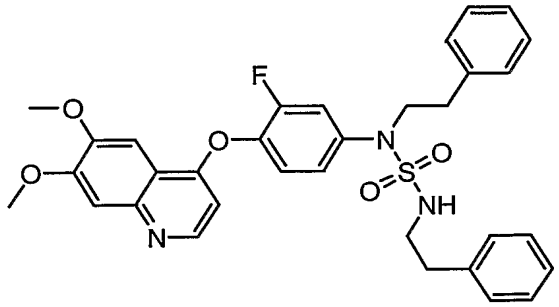
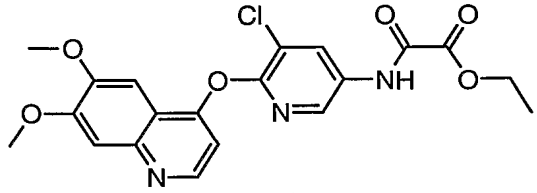
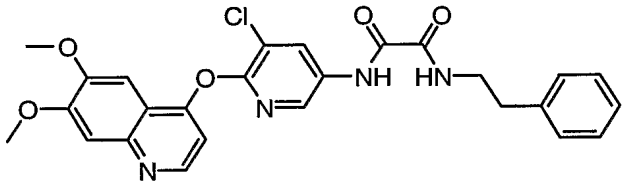
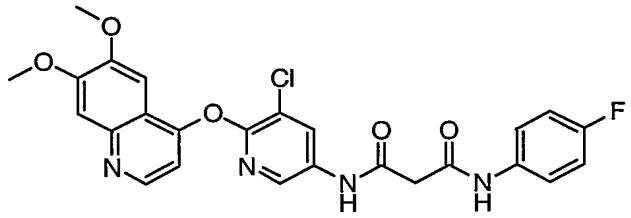
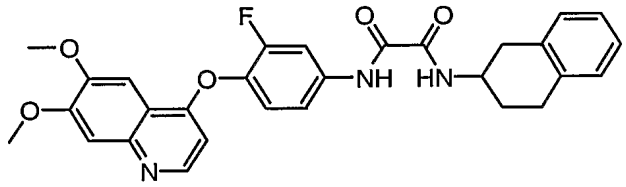
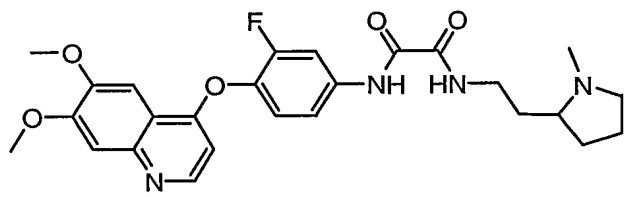
Entry	Name	Structure
67	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N,N'-bis(2-phenylethyl)sulfamide	
68	ethyl [(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)amino](oxo)acetate	
69	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-phenylethyl)ethanediamide	
70	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)propanediamide	
71	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(1,2,3,4-tetrahydronaphthalen-2-yl)ethanediamide	
72	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(1-methylpyrrolidin-2-yl)ethyl]ethanediamide	

Table 1

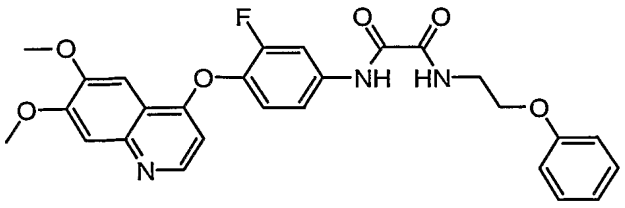
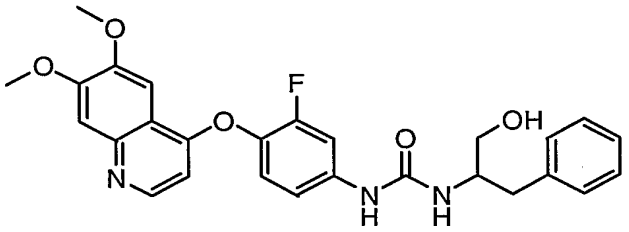
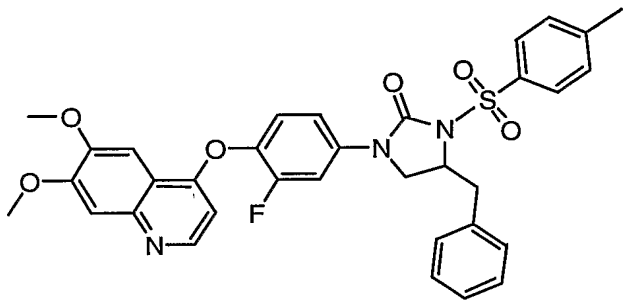
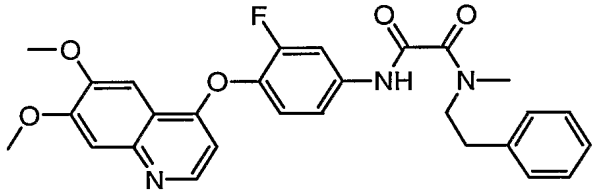
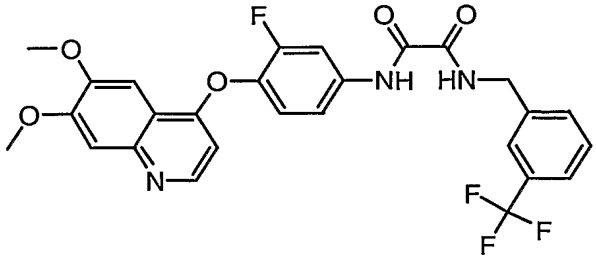
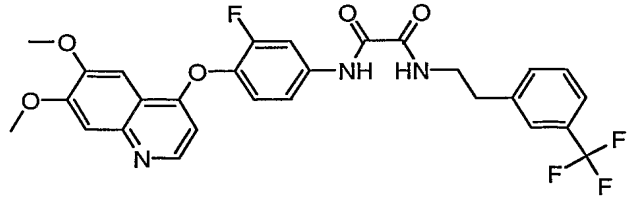
Entry	Name	Structure
73	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(phenyloxy)ethyl]ethanediamide	
74	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-hydroxy-1-(phenylmethyl)ethyl]urea	
75	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-[(4-methylphenyl)sulfonyl]-4-(phenylmethyl)imidazolidin-2-one	
76	N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N-methyl-N-(2-phenylethyl)ethanediamide	
77	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{[3-(trifluoromethyl)phenyl]methyl}ethanediamide	
78	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{2-[3-(trifluoromethyl)phenyl]ethyl}ethanediamide	

Table 1

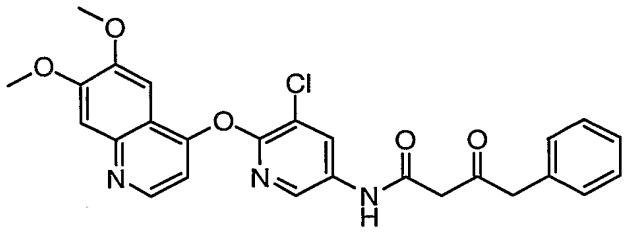
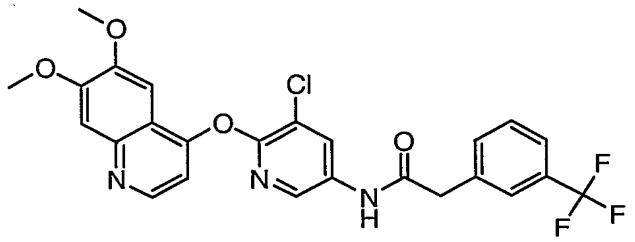
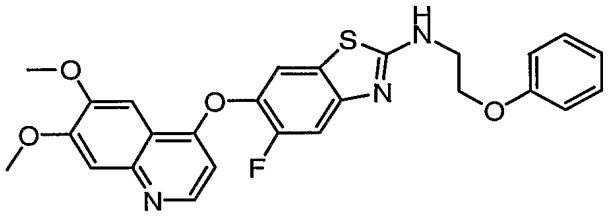
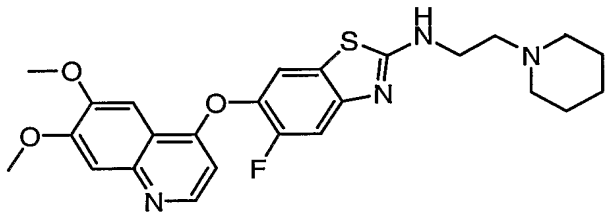
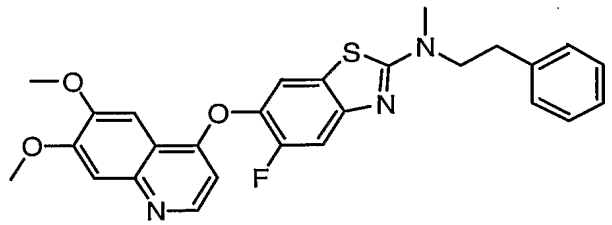
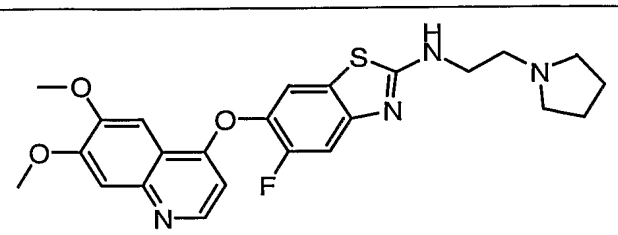
Entry	Name	Structure
79	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-3-oxo-4-phenylbutanamide	
80	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-2-[3-(trifluoromethyl)phenyl]acetamide	
81	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-[2-(phenyloxy)ethyl]-1,3-benzothiazol-2-amine	
82	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-(2-piperidin-1-ylethyl)-1,3-benzothiazol-2-amine	
83	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-methyl-N-(2-phenylethyl)-1,3-benzothiazol-2-amine	
84	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-(2-pyrrolidin-1-ylethyl)-1,3-benzothiazol-2-amine	

Table 1

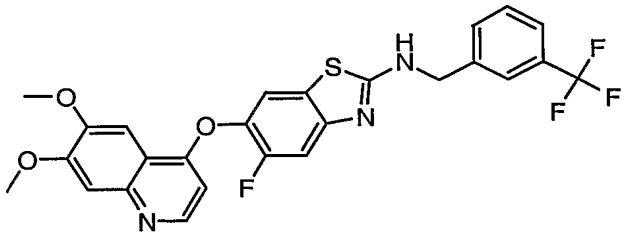
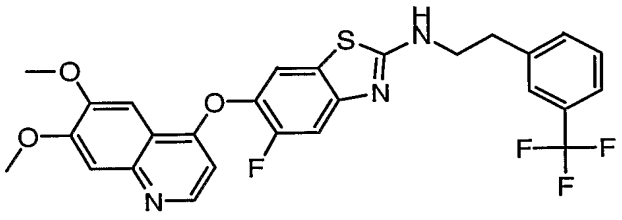
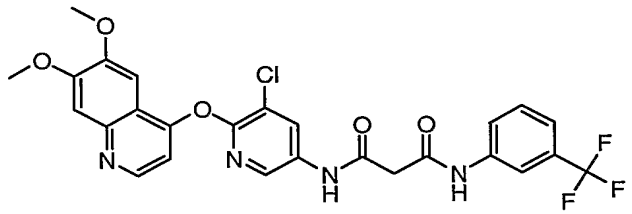
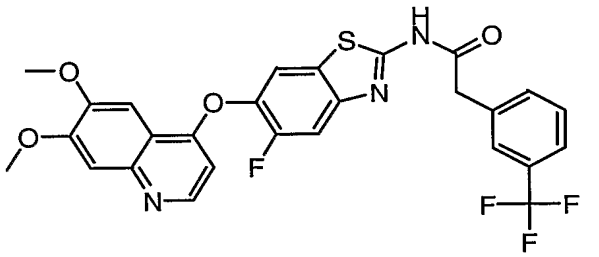
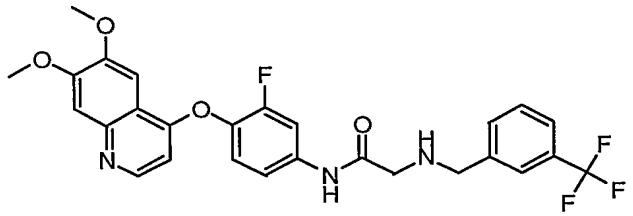
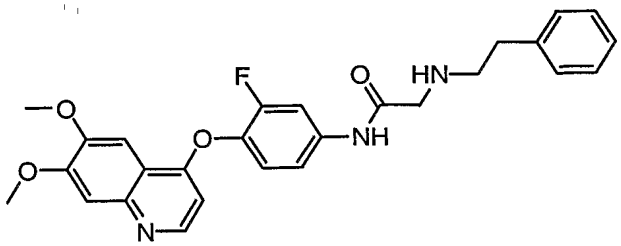
Entry	Name	Structure
85	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-{[3-(trifluoromethyl)phenyl]methyl}-1,3-benzothiazol-2-amine	
86	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-{2-[3-(trifluoromethyl)phenyl]ethyl}-1,3-benzothiazol-2-amine	
87	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-[3-(trifluoromethyl)phenyl]propanediamide	
88	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[3-(trifluoromethyl)phenyl]acetamide	
89	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-{[3-(trifluoromethyl)phenyl]methyl}glycinamide	
90	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(2-phenylethyl)glycinamide	

Table 1

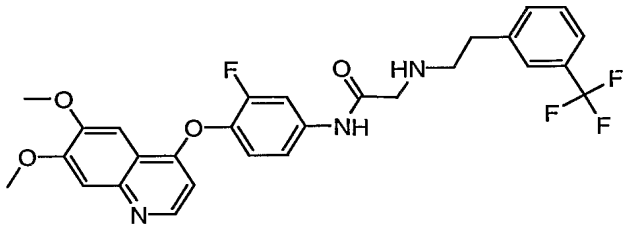
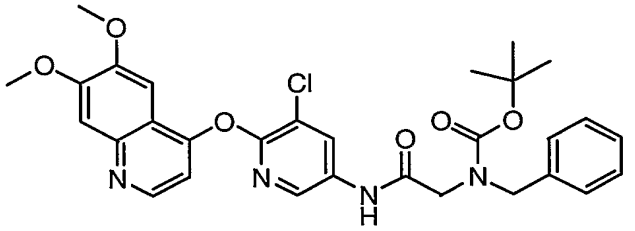
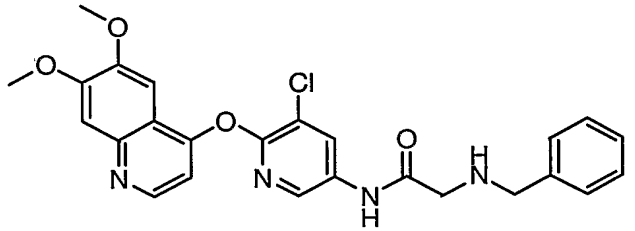
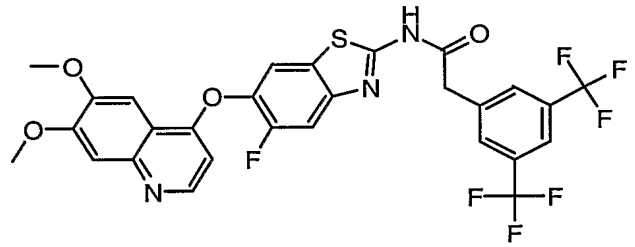
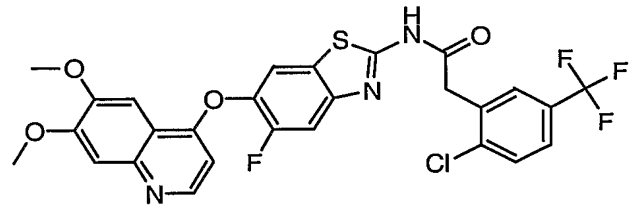
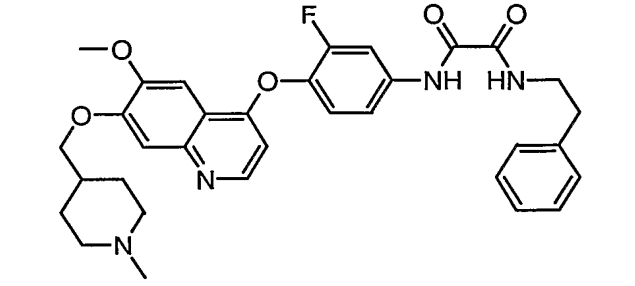
Entry	Name	Structure
91	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-{2-[3-(trifluoromethyl)phenyl]ethyl}glycinamide	
92	benzyl-{[5-chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-ylcarbamoyl]-methyl}-carbamic acid tert-butyl ester	
93	N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N2-(phenylmethyl)glycinamide	
94	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[3,5-bis(trifluoromethyl)phenyl]acetamide	
95	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[2-chloro-5-(trifluoromethyl)phenyl]acetamide	
96	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(2-phenylethyl)ethanediamide	

Table 1

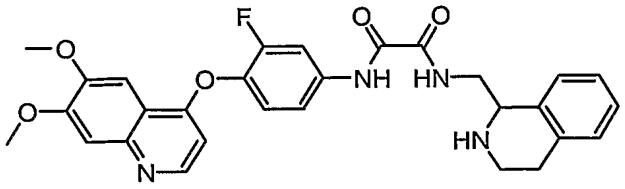
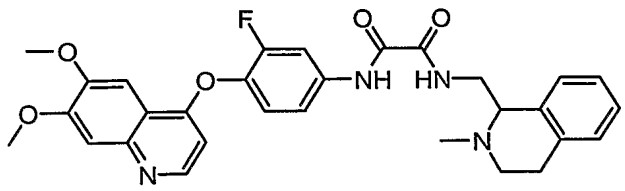
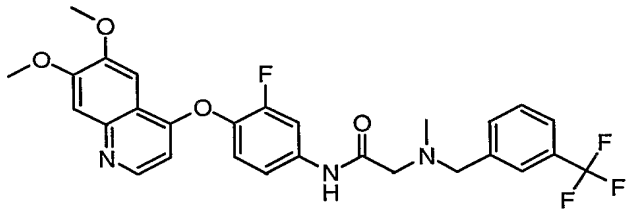
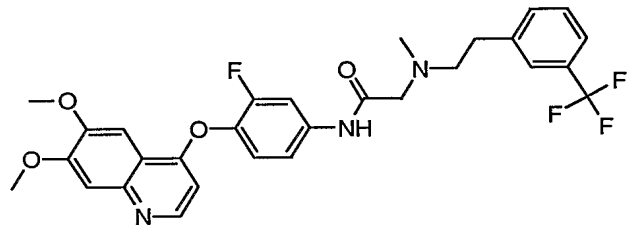
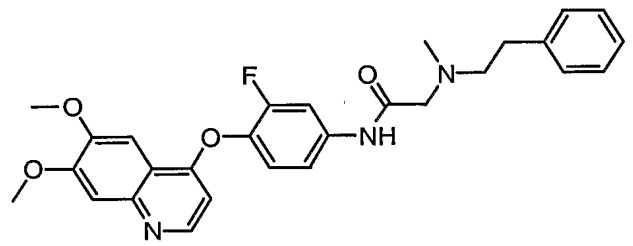
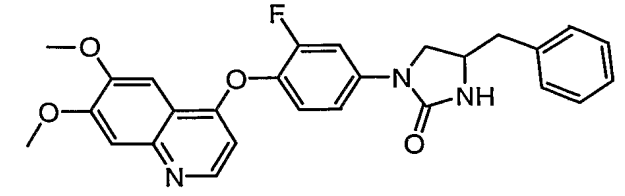
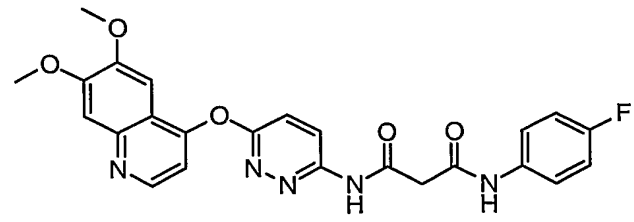
Entry	Name	Structure
97	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(1,2,3,4-tetrahydroisoquinolin-1-ylmethyl)ethanediamide	
98	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[(2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl]ethanediamide	
99	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-methyl-N2-{[3-(trifluoromethyl)phenyl]methyl}glycinamide	
100	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-methyl-N2-{2-[3-(trifluoromethyl)phenyl]ethyl}glycinamide	
101	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-methyl-N2-(2-phenylethyl)glycinamide	
102	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-4-(phenylmethyl)imidazolidin-2-one	
103	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridazin-3-yl)-N'-(4-fluorophenyl)propanediamide	

Table 1

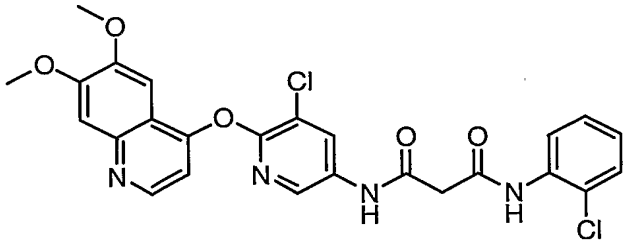
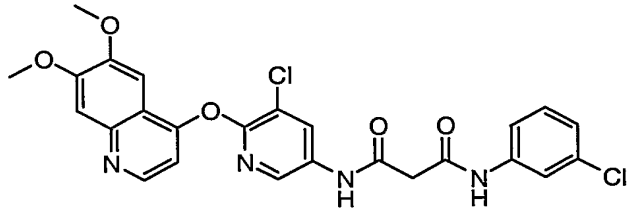
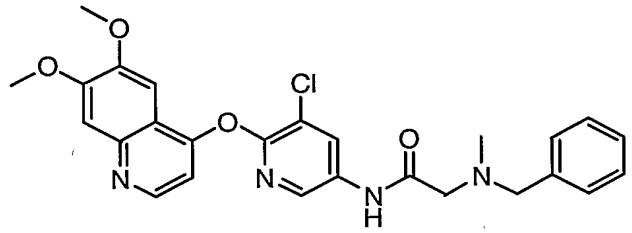
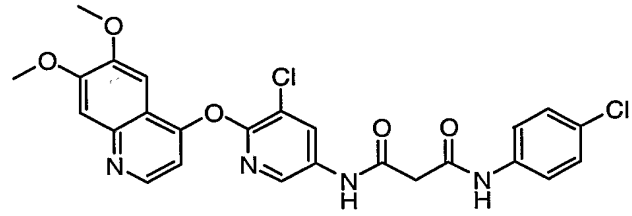
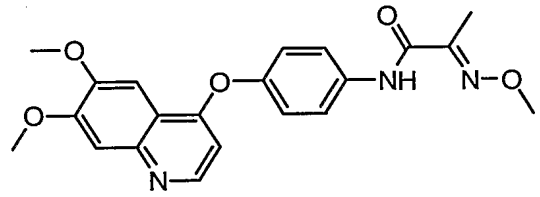
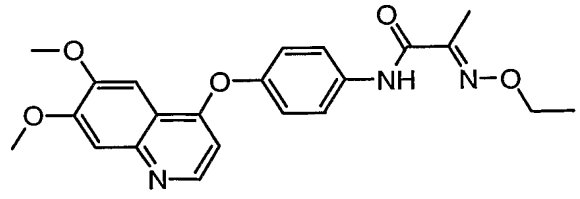
Entry	Name	Structure
104	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-chlorophenyl)propanediamide	
105	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(3-chlorophenyl)propanediamide	
106	N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N2-methyl-N2-(phenylmethyl)glycinamide	
107	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-chlorophenyl)propanediamide	
108	(2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-[(methyloxy)imino]propanamide	
109	(2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-[(ethyloxy)imino]propanamide	

Table 1

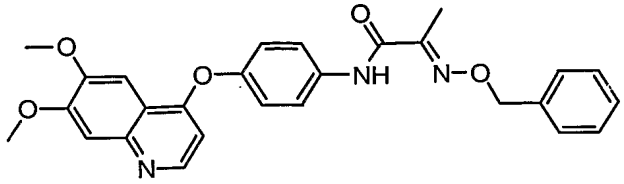
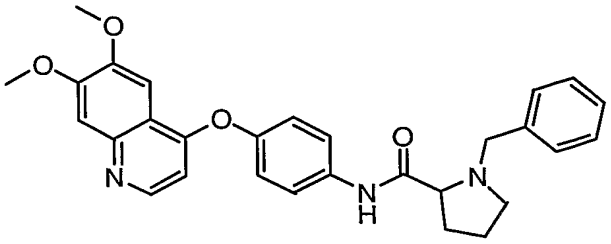
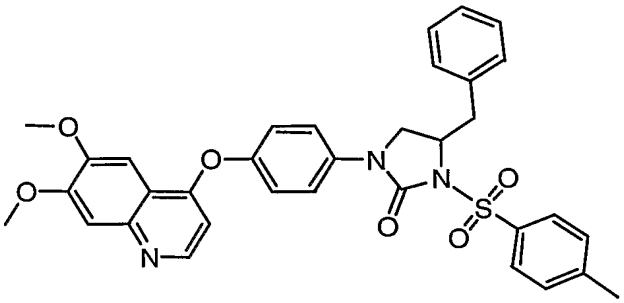
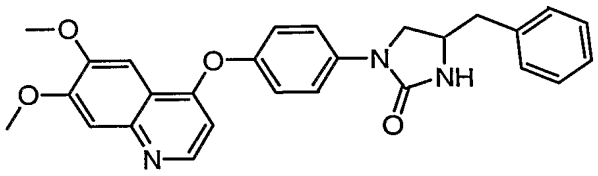
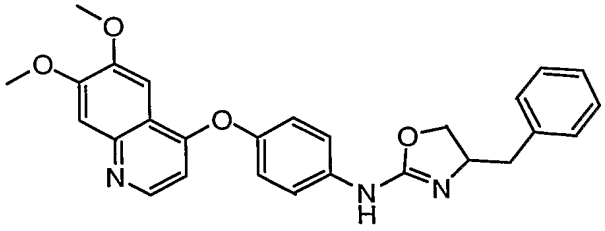
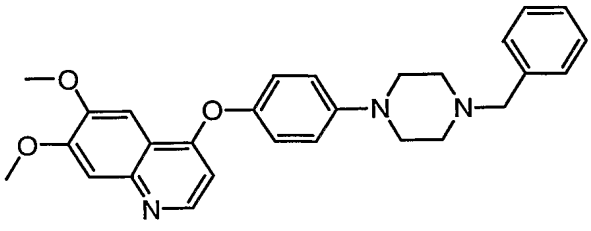
Entry	Name	Structure
110	(2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-{[(phenylmethyl)oxy]imino}propanamide	
111	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-1-(phenylmethyl)prolinamide	
112	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-3-[(4-methylphenyl)sulfonyl]-4-(phenylmethyl)imidazolidin-2-one	
113	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)imidazolidin-2-one	
114	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)-4,5-dihydro-1,3-oxazol-2-amine	
115	6,7-bis(methyloxy)-4-({4-[4-(phenylmethyl)piperazin-1-yl]phenyl}oxy)quinoline	

Table 1

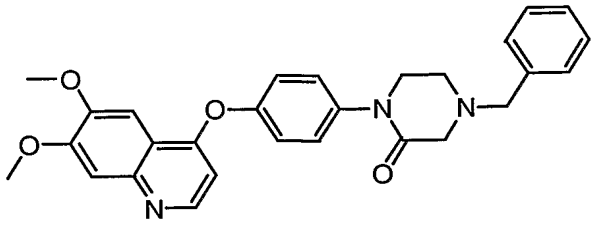
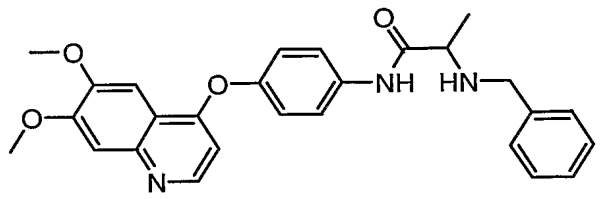
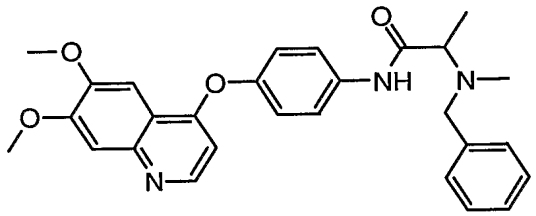
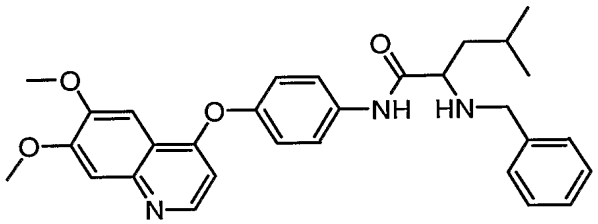
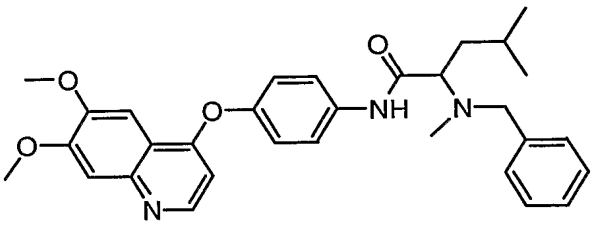
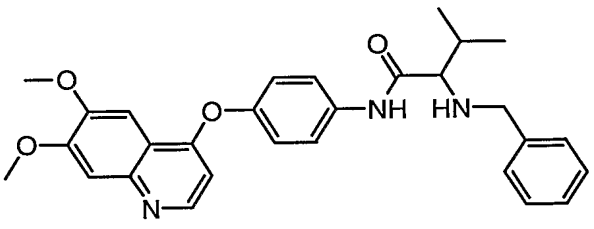
Entry	Name	Structure
116	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)piperazin-2-one	
117	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-(phenylmethyl)alaninamide	
118	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-methyl-N2-(phenylmethyl)alaninamide	
119	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-(phenylmethyl)leucinamide	
120	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-methyl-N2-(phenylmethyl)leucinamide	
121	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-(phenylmethyl)valinamide	

Table 1

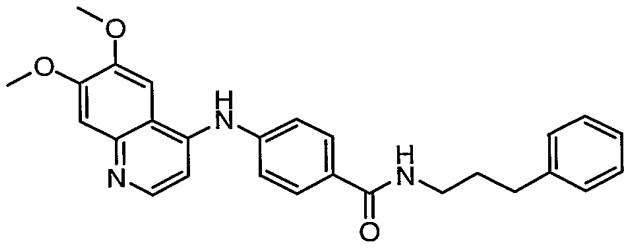
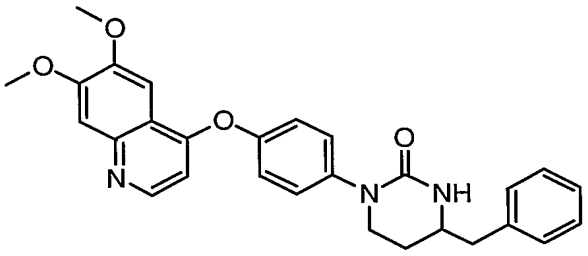
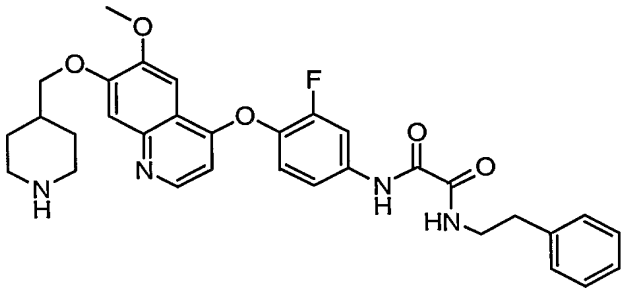
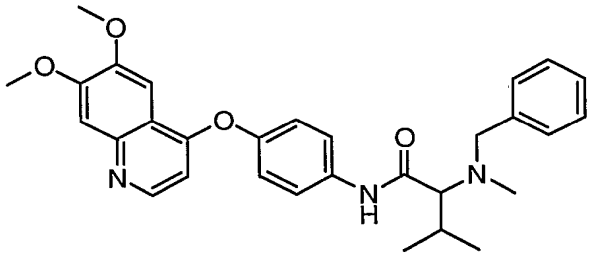
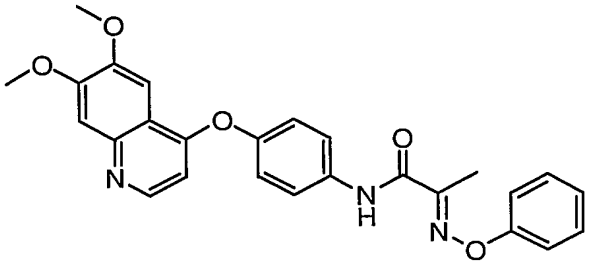
Entry	Name	Structure
122	4-(6,7-dimethoxy-quinolin-4-ylamino)-N-(3-phenyl-propyl)-benzamide	
123	4-benzyl-1-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-tetrahydro-pyrimidin-2-one	
124	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	
125	2-(Benzyl-methyl-amino)-N-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-3-methyl-butyramide (note: Alphabetic order of prefixes ignored while selecting parent chain)	
126	N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-phenyl]-2-phenoxyimino-propionamide	

Table 1

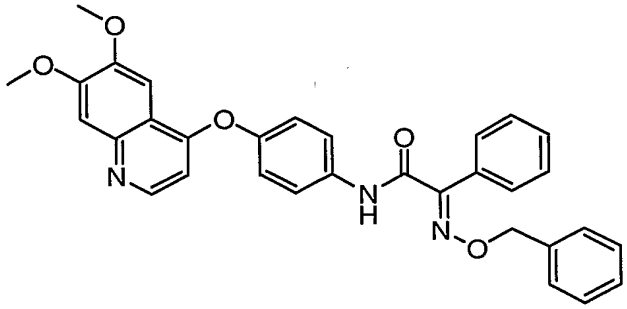
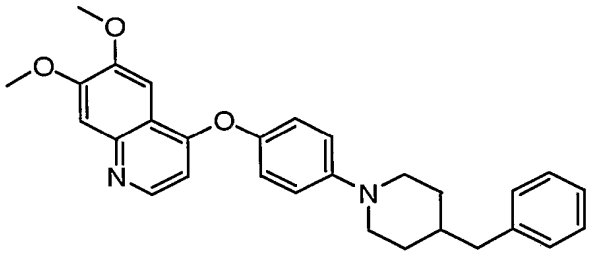
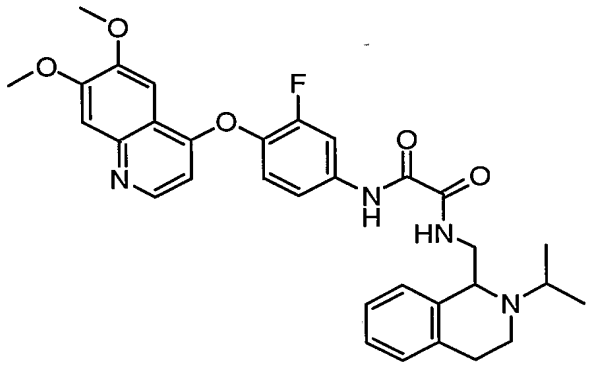
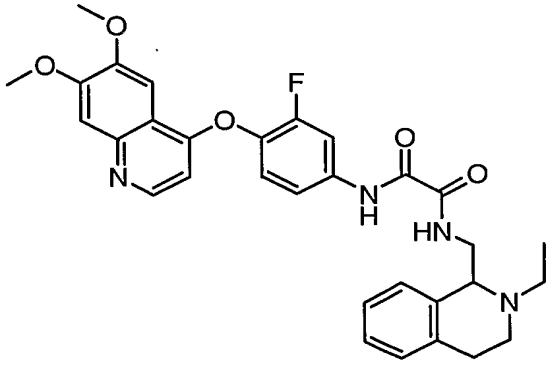
Entry	Name	Structure
127	2-Benzyloxyimino-N-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-2-phenyl-acetamide	
128	4-[4-(4-Benzyl-piperidin-1-yl)-phenoxy]-6,7-dimethoxy-quinoline	
129	N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-N'-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-oxalamide	
130	N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-N'-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-oxalamide	

Table 1

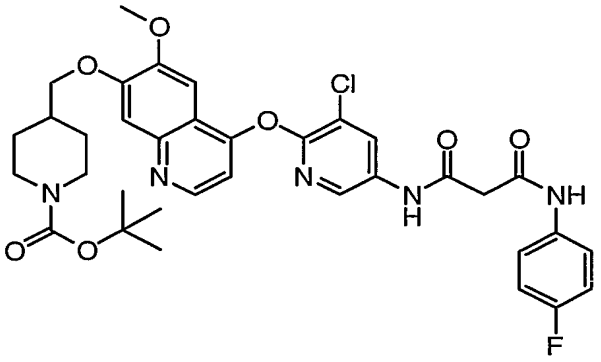
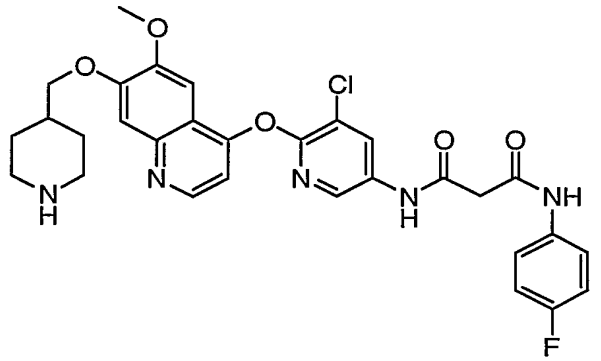
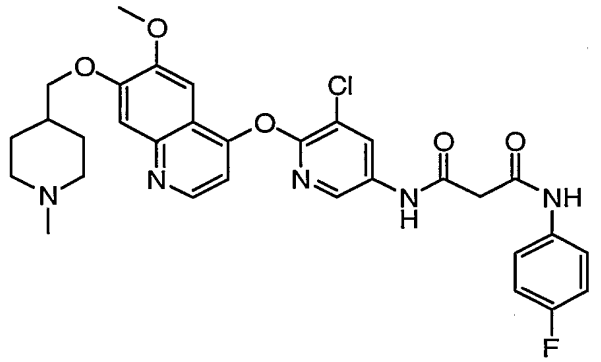
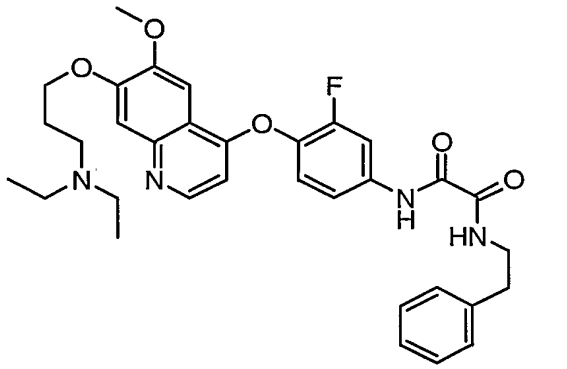
Entry	Name	Structure
131	4-(4-{3-Chloro-5-[2-(4-fluoro-phenylcarbamoyl)-acetylamino]-pyridin-2-yloxy}-6-methoxy-quinolin-7-yloxymethyl)-piperidine-1-carboxylic acid tert-butyl ester	
132	N-{5-Chloro-6-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide	
133	N-{5-Chloro-6-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide	
134	N-{4-[7-(3-Diethylamino-propoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-N'-phenethyl-oxalamide	

Table 1

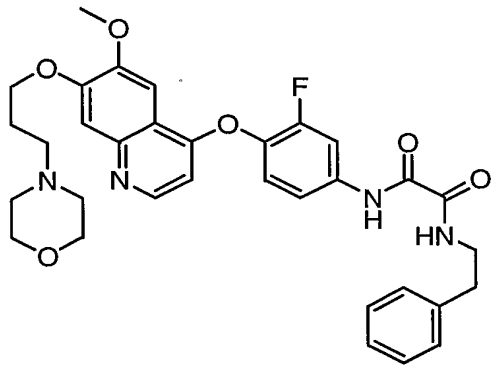
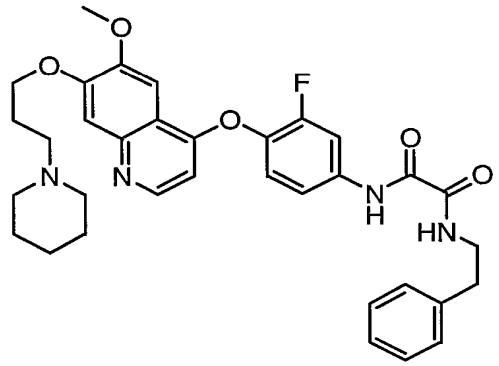
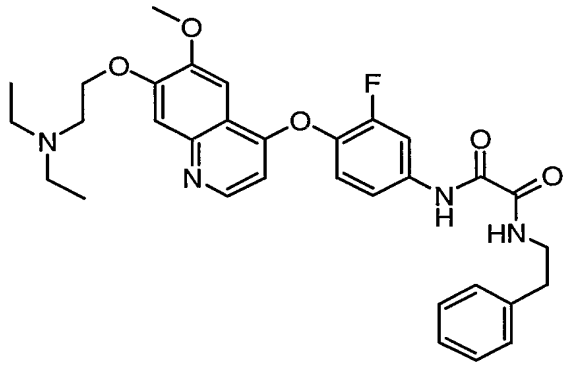
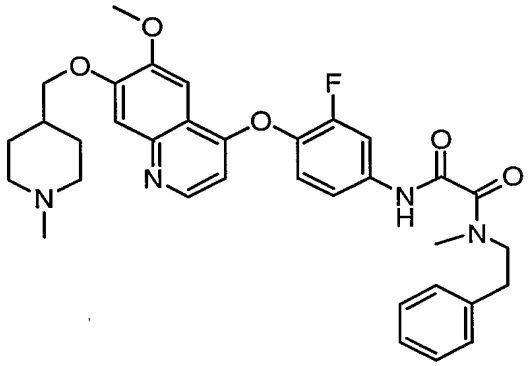
Entry	Name	Structure
135	N-{3-Fluoro-4-[6-methoxy-7-(3-morpholin-4-yl-propoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	
136	N-{3-Fluoro-4-[6-methoxy-7-(3-piperidin-1-yl-propoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	
137	N-{4-[7-(2-Diethylamino-ethoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-N'-phenethyl-oxalamide	
138	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-methyl-N'-phenethyl-oxalamide	

Table 1

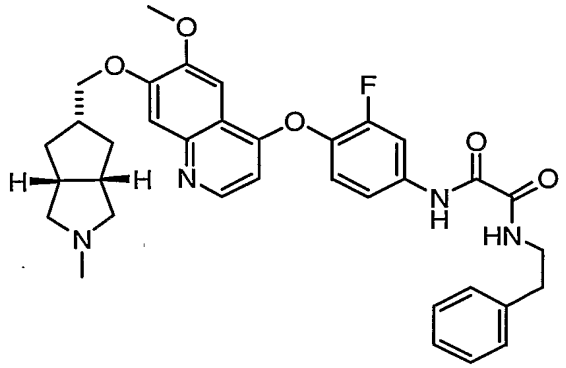
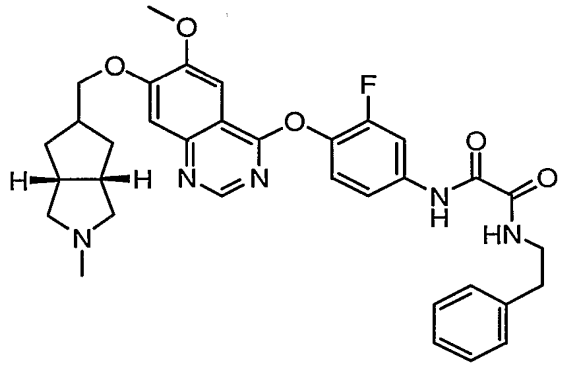
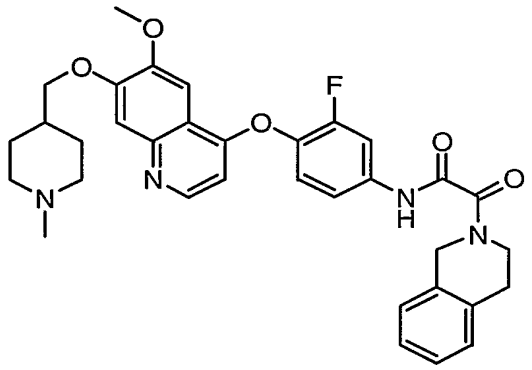
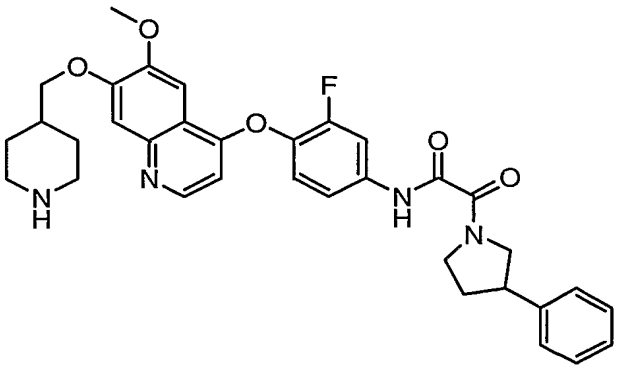
Entry	Name	Structure
139	N-{3-Fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	
140	N-{3-Fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	
141	2-(3,4-Dihydro-1H-isoquinolin-2-yl)-N-{3-fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-acetamide	
142	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-2-(3-phenyl-pyrrolidin-1-yl)-acetamide	

Table 1

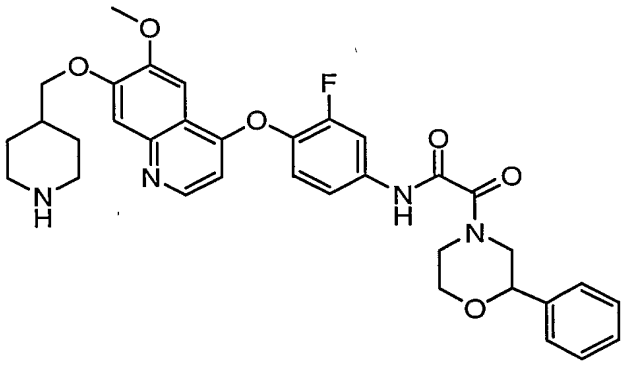
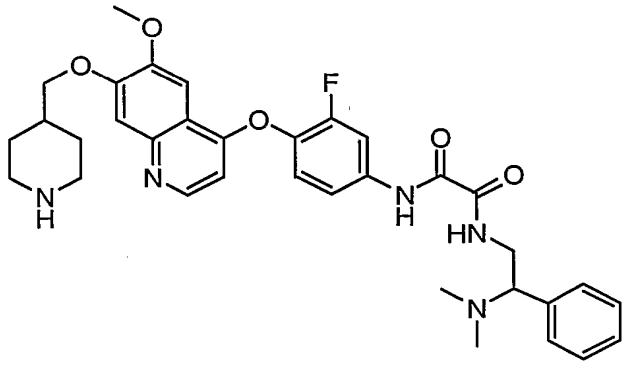
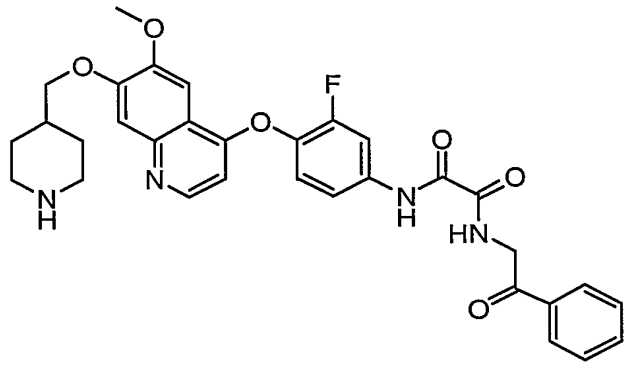
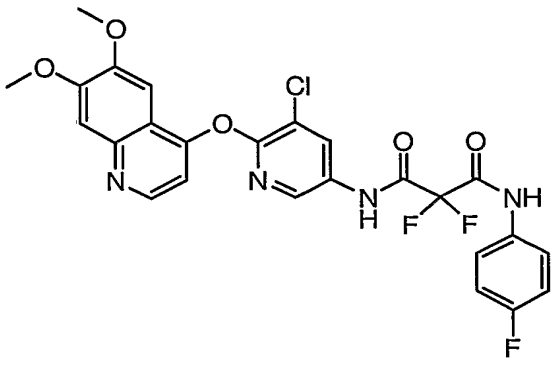
Entry	Name	Structure
143	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-2-(2-phenyl-morpholin-4-yl)-acetamide	
144	N-(2-Dimethylamino-2-phenyl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
145	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-oxo-2-phenyl-ethyl)-oxalamide	
146	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-2,2-difluoro-N'-(4-fluoro-phenyl)-malonamide	

Table 1

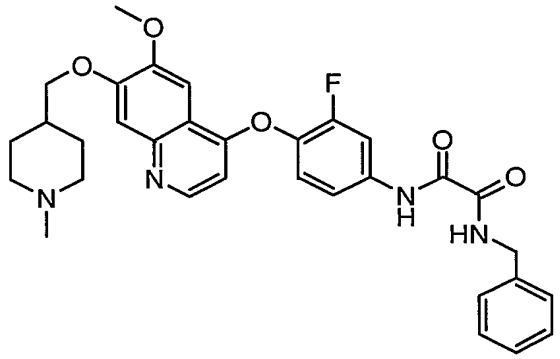
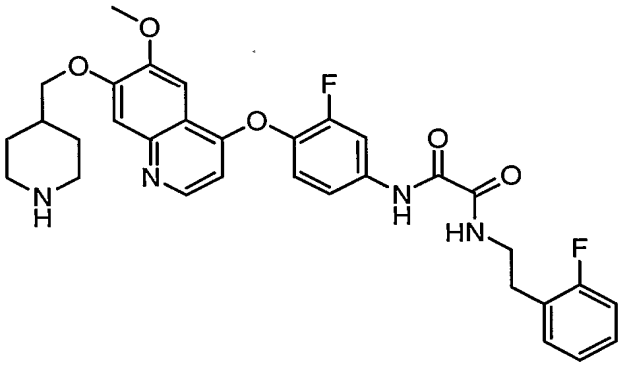
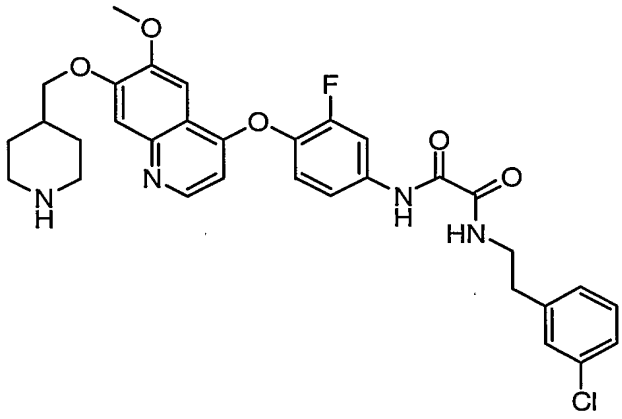
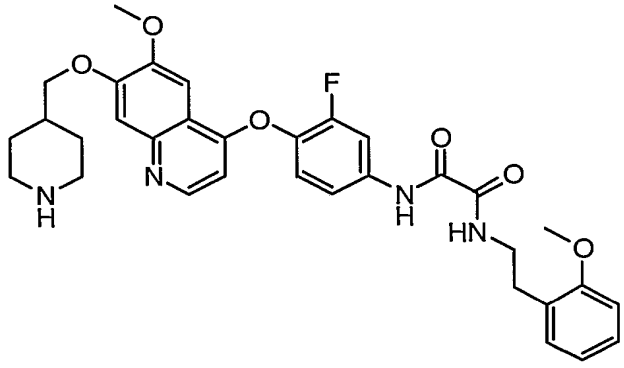
Entry	Name	Structure
147	N-Benzyl-N'-{3-fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
148	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(2-fluoro-phenyl)-ethyl]-oxalamide	
149	N-[2-(3-Chloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
150	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(2-methoxy-phenyl)-ethyl]-oxalamide	

Table 1

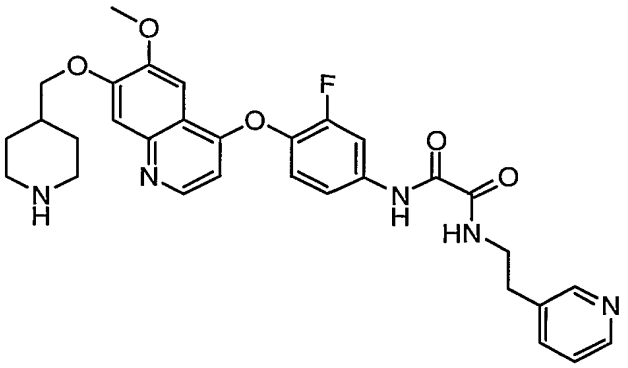
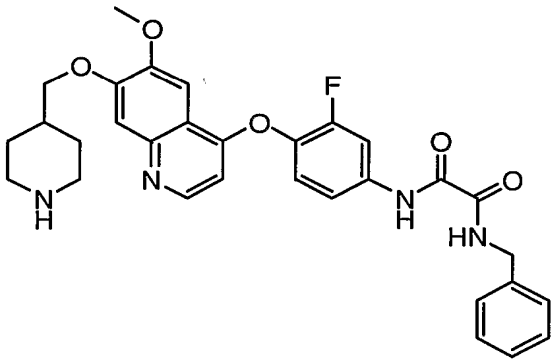
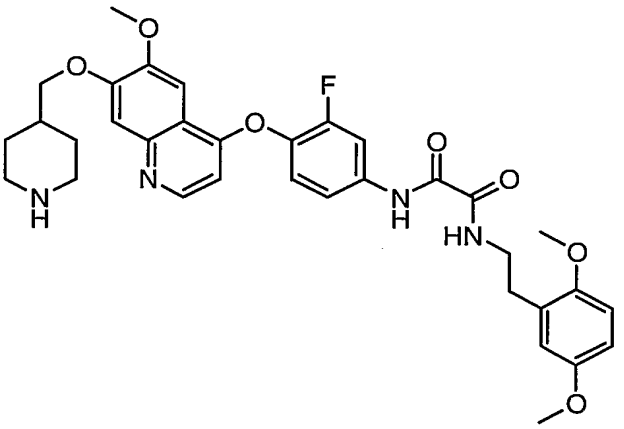
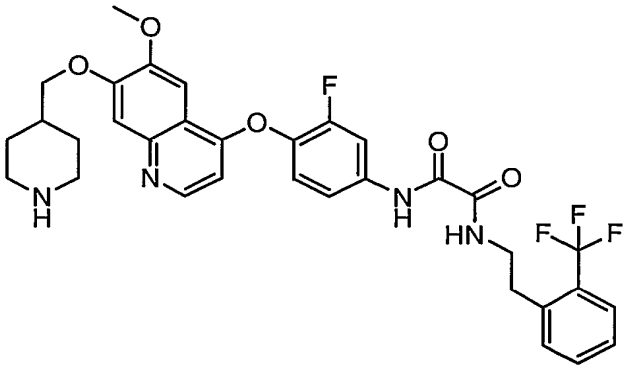
Entry	Name	Structure
151	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-pyridin-3-yl-ethyl)-oxalamide	
152	N-Benzyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
153	N-[2-(2,5-Dimethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
154	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(2-trifluoromethyl-phenyl)-ethyl]-oxalamide	

Table 1

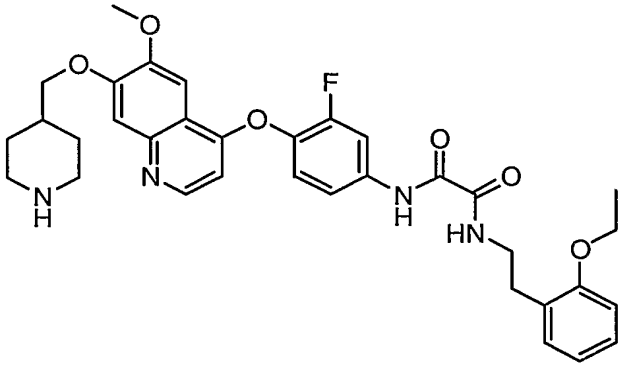
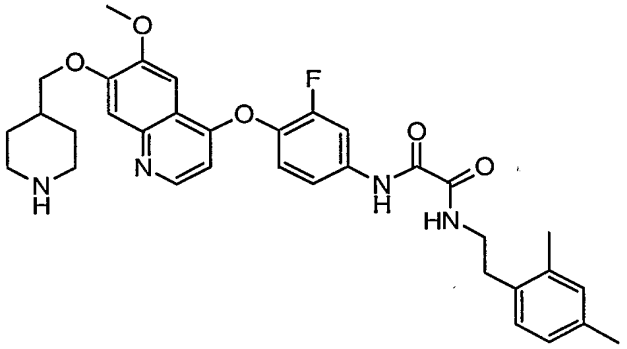
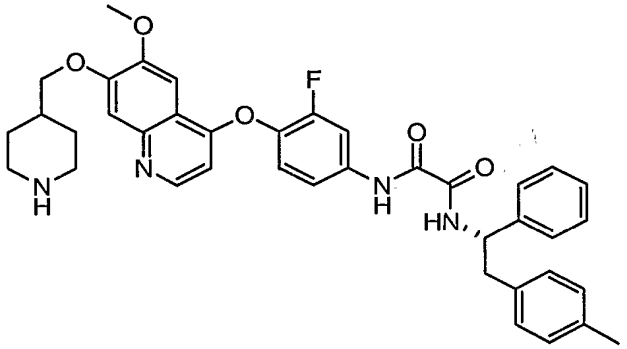
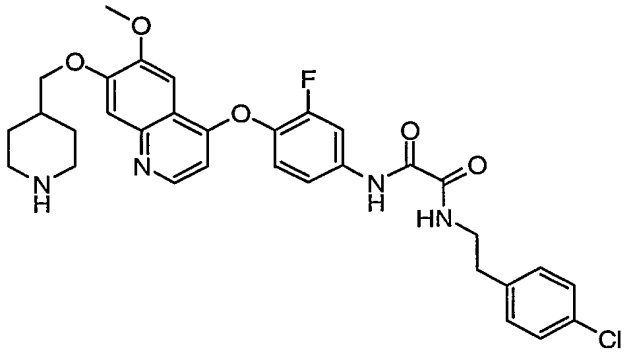
Entry	Name	Structure
155	N-[2-(2-Ethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
156	N-[2-(2,4-Dimethyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
157	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1*S* -phenyl-2-p-tolyl-ethyl)-oxalamide	
158	N-[2-(4-Chloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

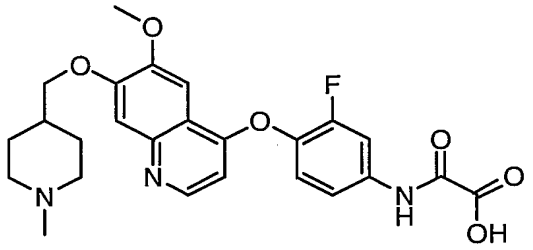
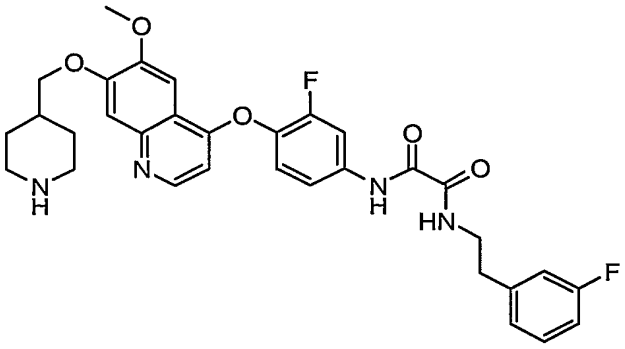
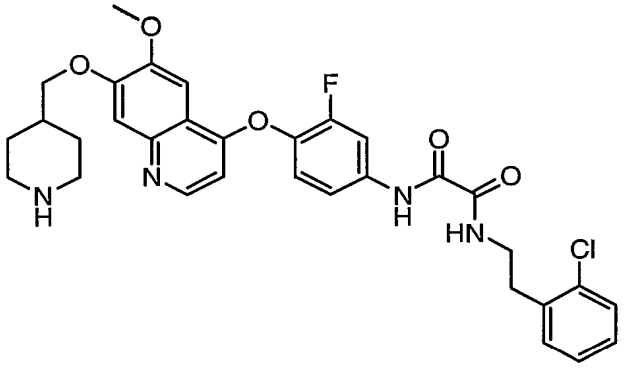
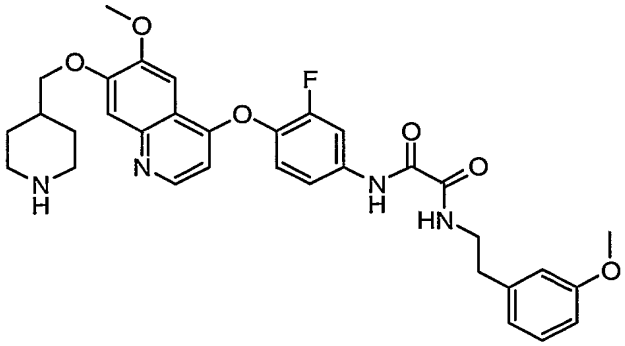
Entry	Name	Structure
159	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamic acid	
160	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(3-fluoro-phenyl)-ethyl]-oxalamide	
161	N-[2-(2-Chloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
162	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(3-methoxy-phenyl)-ethyl]-oxalamide	

Table 1

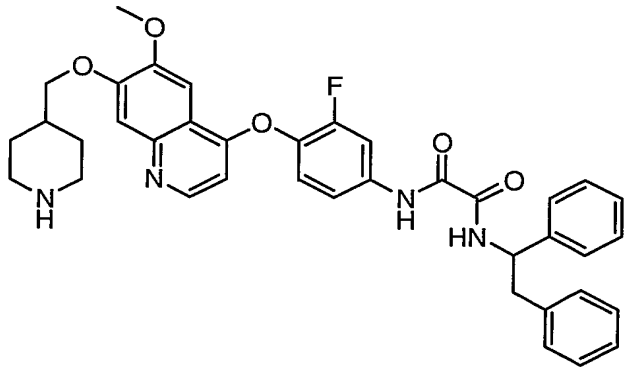
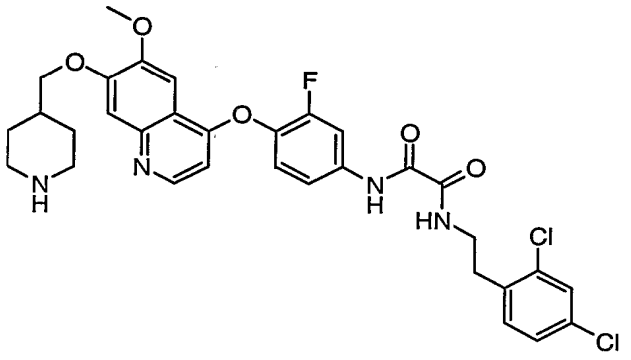
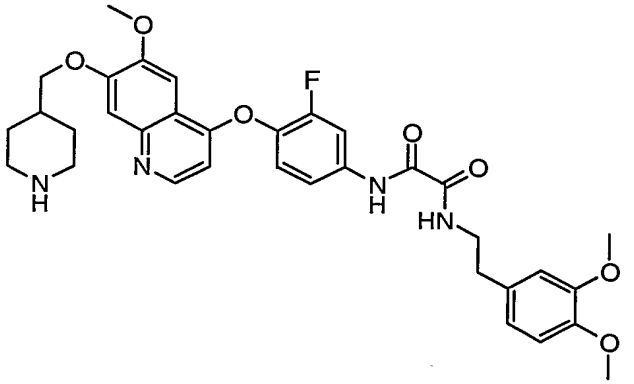
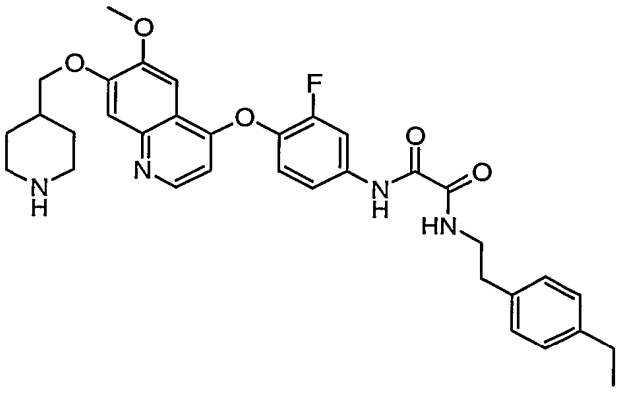
Entry	Name	Structure
163	N-(1,2-Diphenyl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
164	N-[2-(2,4-Dichloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
165	N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
166	N-[2-(4-Ethyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

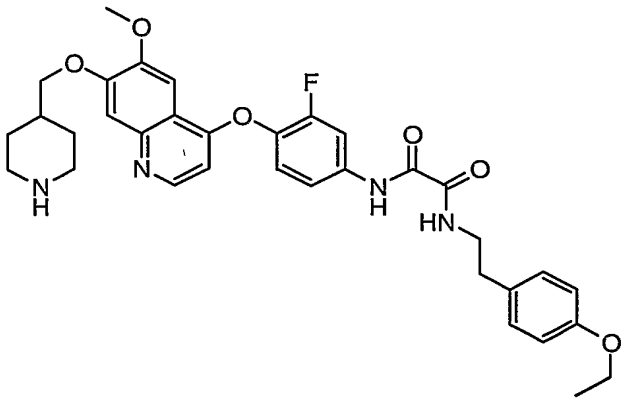
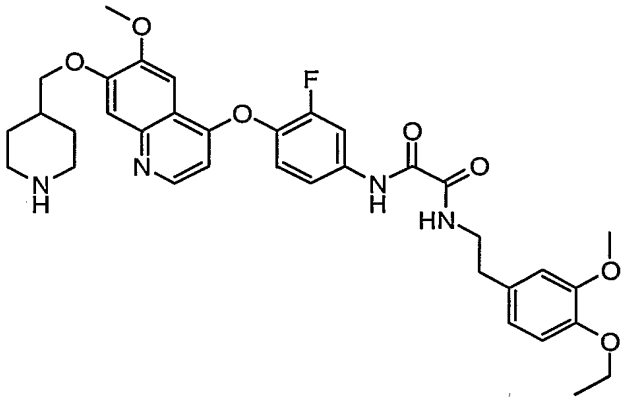
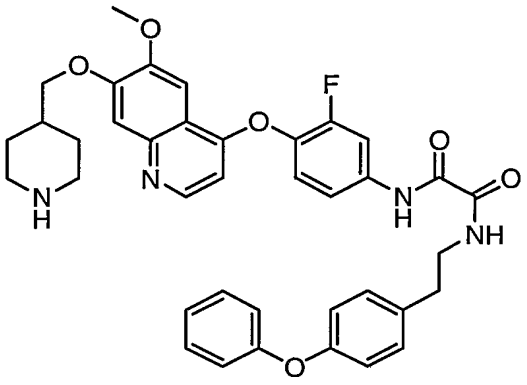
Entry	Name	Structure
167	N-[2-(4-Ethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
168	N-[2-(4-Ethoxy-3-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
169	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-phenoxy-phenyl)-ethyl]-oxalamide	

Table 1

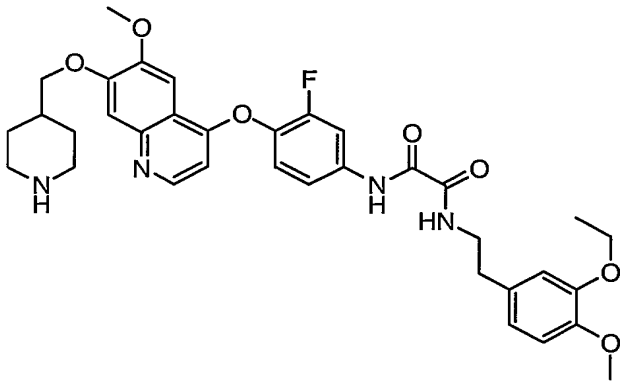
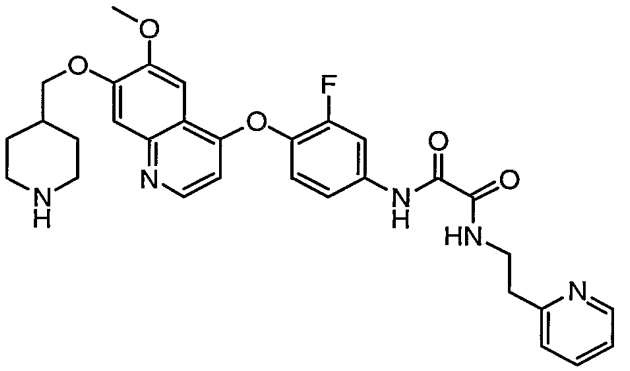
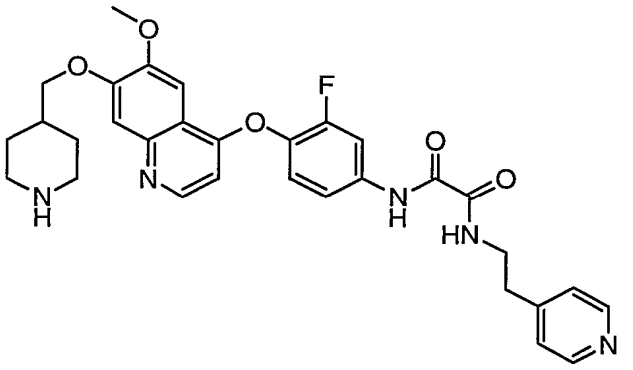
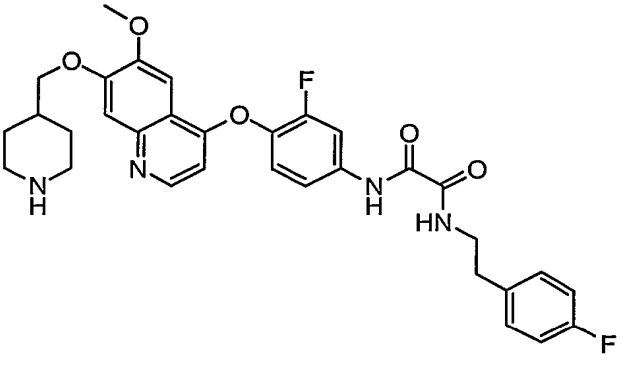
Entry	Name	Structure
170	N-[2-(3-Ethoxy-4-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
171	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-pyridin-2-yl-ethyl)-oxalamide	
172	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-pyridin-4-yl-ethyl)-oxalamide	
173	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-fluoro-phenyl)-ethyl]-oxalamide	

Table 1

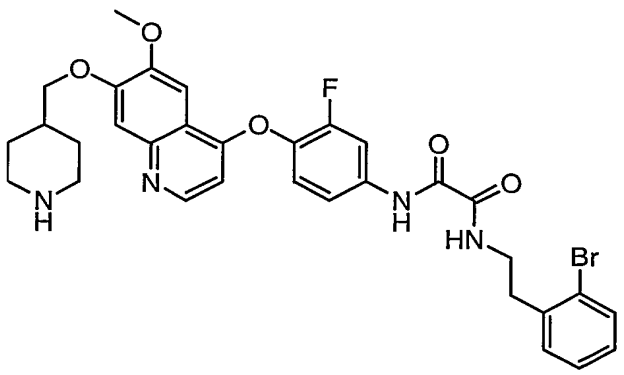
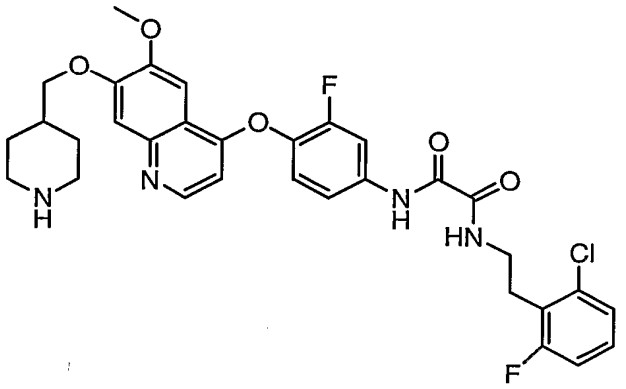
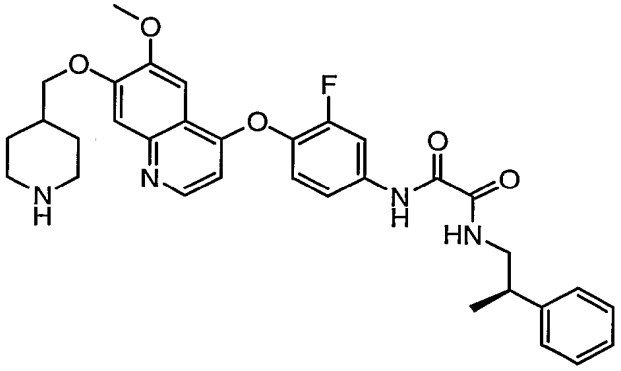
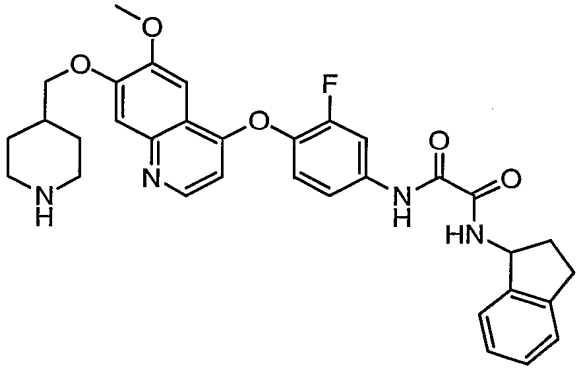
Entry	Name	Structure
174	N-[2-(2-Bromo-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
175	N-[2-(2-Chloro-6-fluoro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
176	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2*R*-phenyl-propyl)-oxalamide	
177	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-indan-1-yl-oxalamide	

Table 1

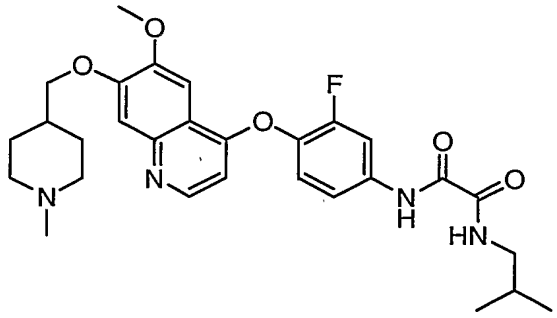
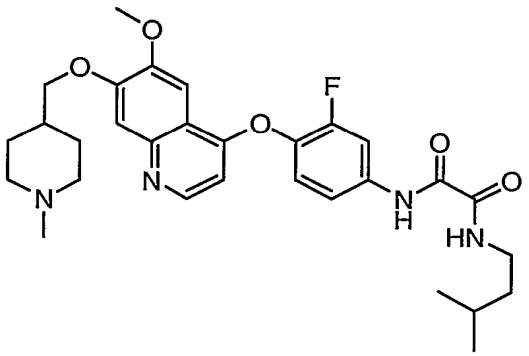
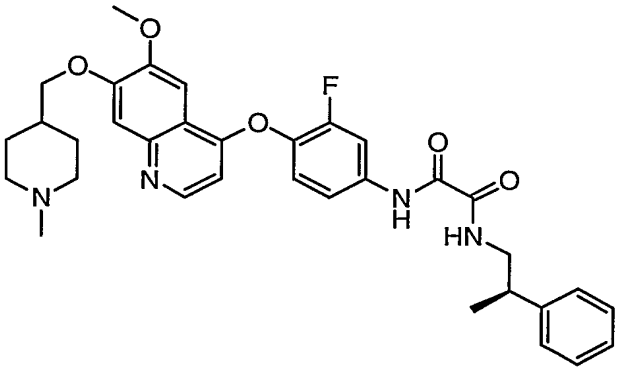
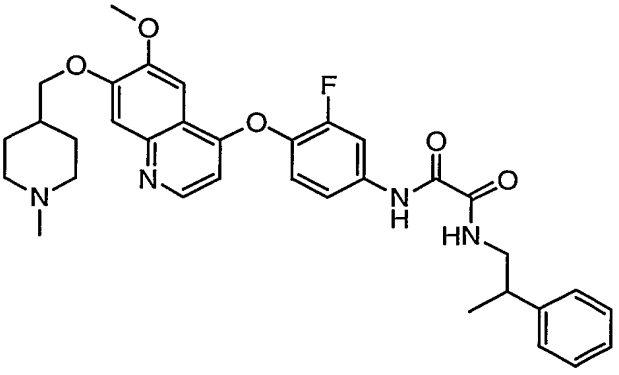
Entry	Name	Structure
178	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-isobutyl-oxalamide	
179	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-methyl-butyl)-oxalamide	
180	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2*R*-phenyl-propyl)-oxalamide	
181	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-phenyl-propyl)-oxalamide	

Table 1

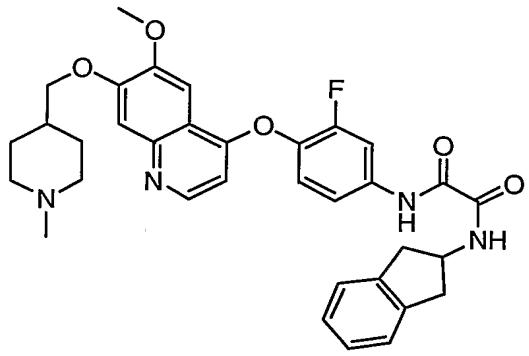
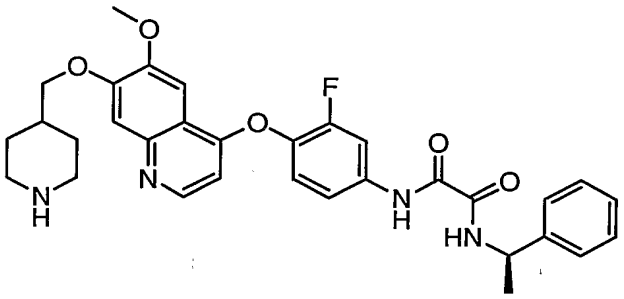
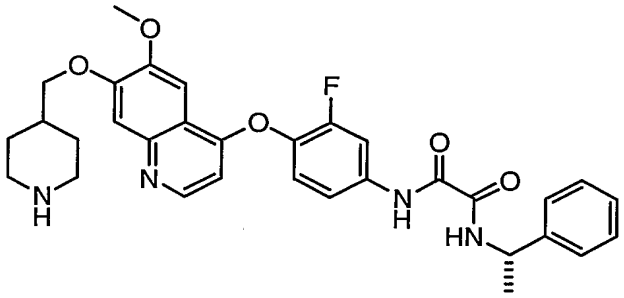
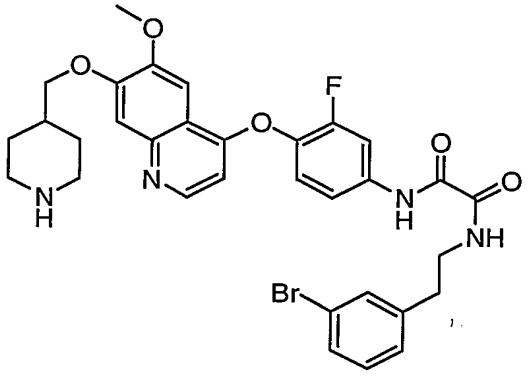
Entry	Name	Structure
182	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-indan-2-yl-oxalamide	
183	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1*R*-phenyl-ethyl)-oxalamide	
184	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1*S*-phenyl-ethyl)-oxalamide	
185	N-[2-(3-Bromo-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

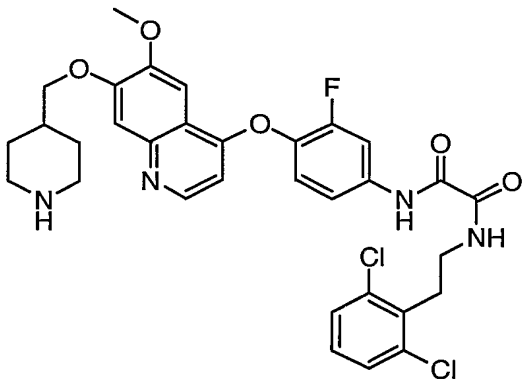
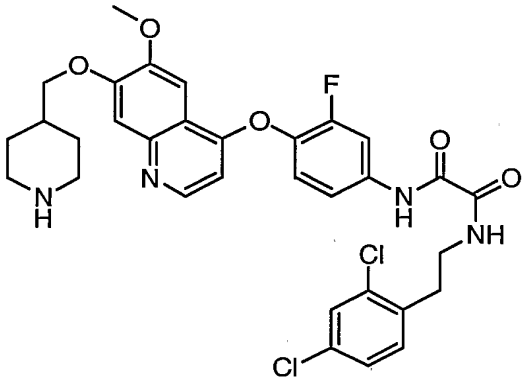
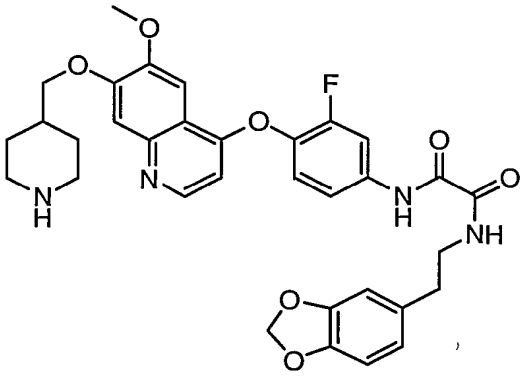
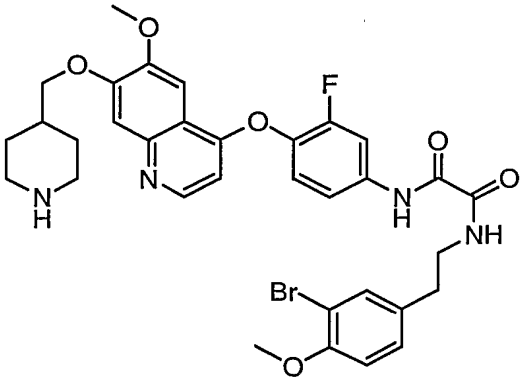
Entry	Name	Structure
186	N-[2-(2,6-Dichloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
187	N-[2-(2,4-Dichloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
188	N-(2-Benzo[1,3]dioxol-5-yl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
189	N-[2-(3-Bromo-4-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

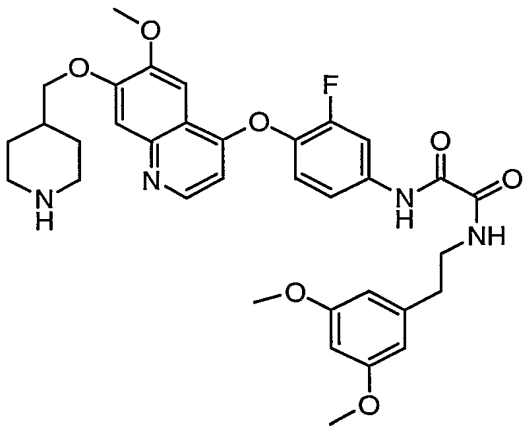
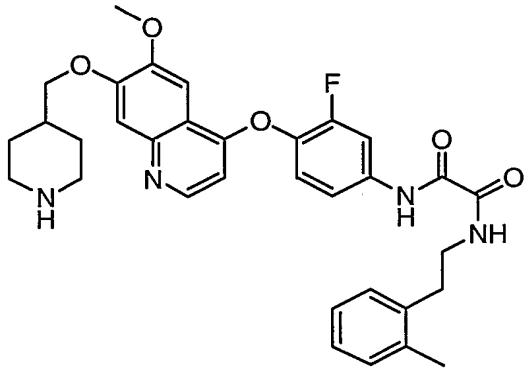
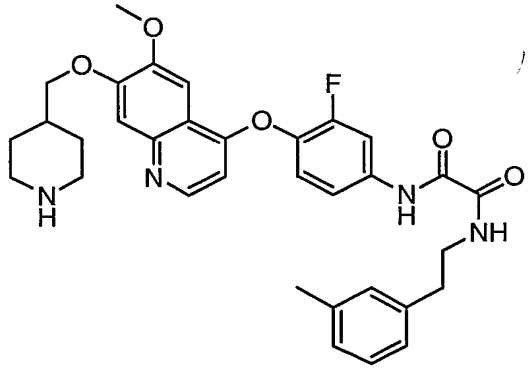
Entry	Name	Structure
190	N-[2-(3,5-Dimethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
191	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-o-tolyl-ethyl)-oxalamide	
192	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-m-tolyl-ethyl)-oxalamide	

Table 1

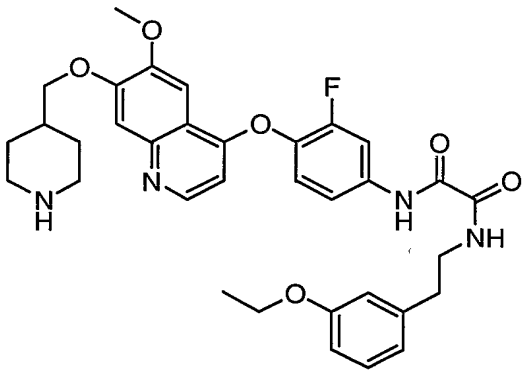
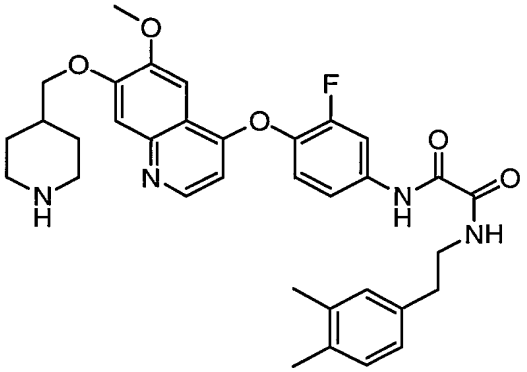
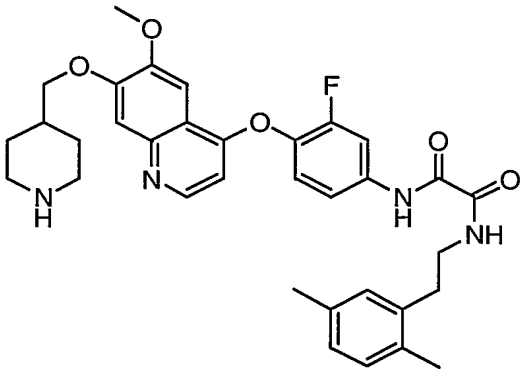
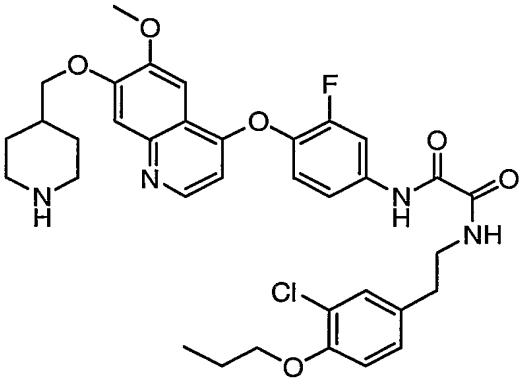
Entry	Name	Structure
193	N-[2-(3-Ethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
194	N-[2-(3,4-Dimethyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
195	N-[2-(2,5-Dimethyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
196	N-[2-(3-Chloro-4-propoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

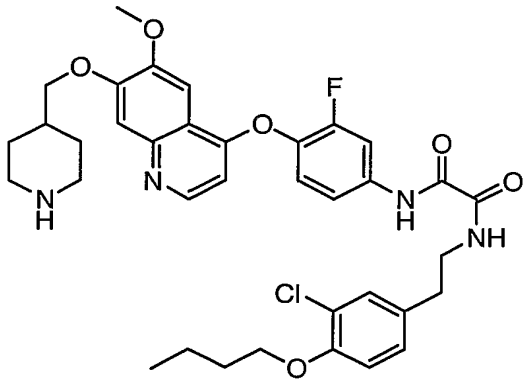
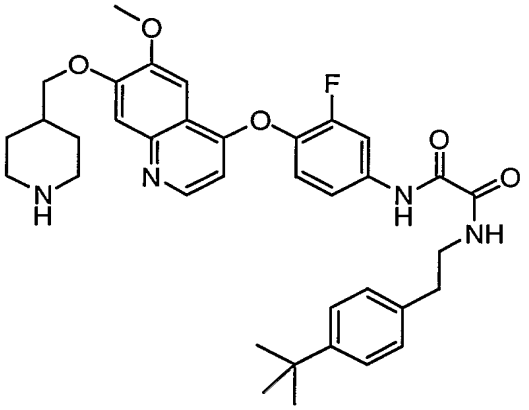
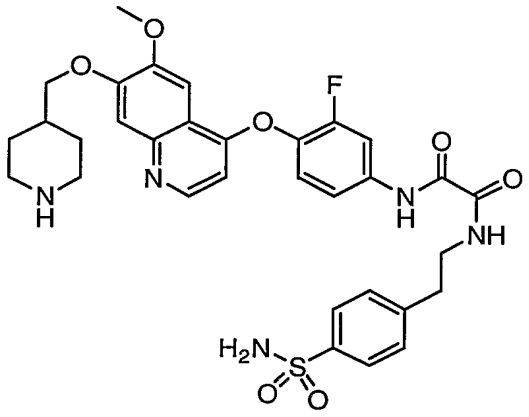
Entry	Name	Structure
197	N-[2-(4-Butoxy-3-chloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
198	N-[2-(4-tert-Butyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
199	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-sulfamoyl-phenyl)-ethyl]-oxalamide	

Table 1

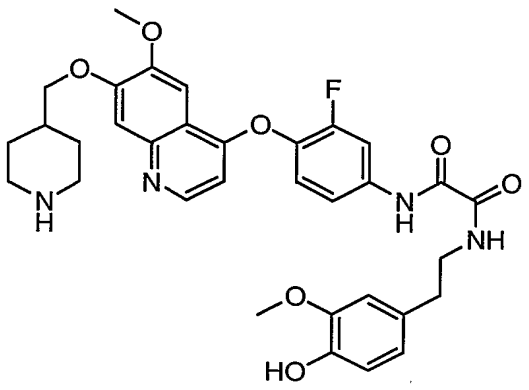
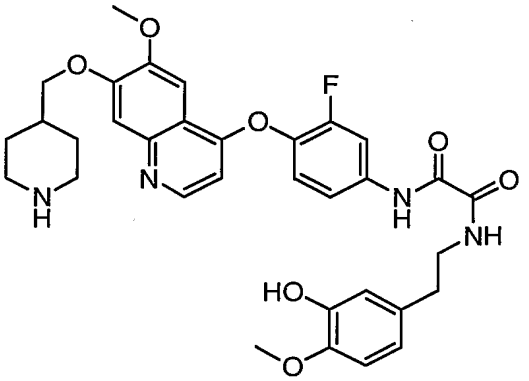
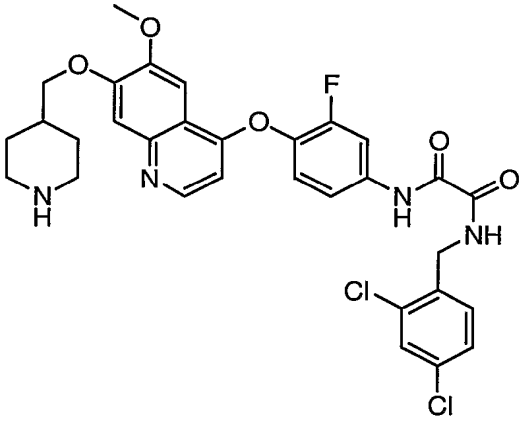
Entry	Name	Structure
200	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-hydroxy-3-methoxy-phenyl)-ethyl]-oxalamide	
201	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(3-hydroxy-4-methoxy-phenyl)-ethyl]-oxalamide	
202	N-(2,4-Dichloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

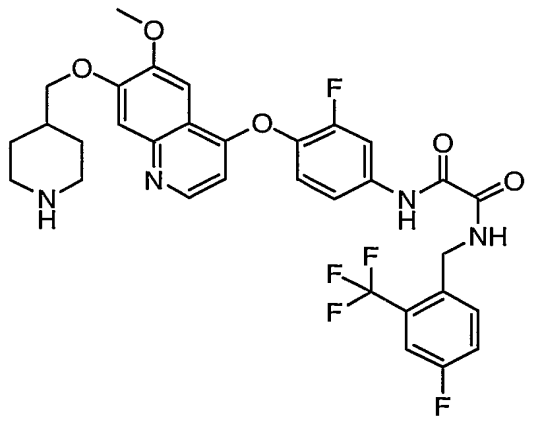
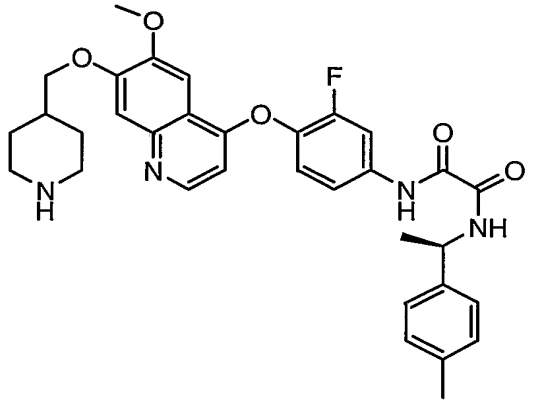
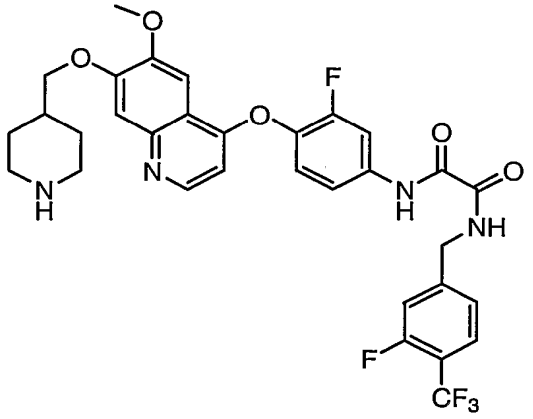
Entry	Name	Structure
203	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-fluoro-2-trifluoromethyl-benzyl)-oxalamide	
204	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1-p-tolyl-ethyl)-oxalamide	
205	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-fluoro-4-trifluoromethyl-benzyl)-oxalamide	

Table 1

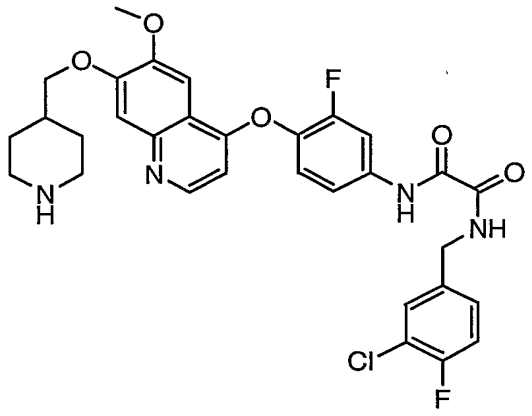
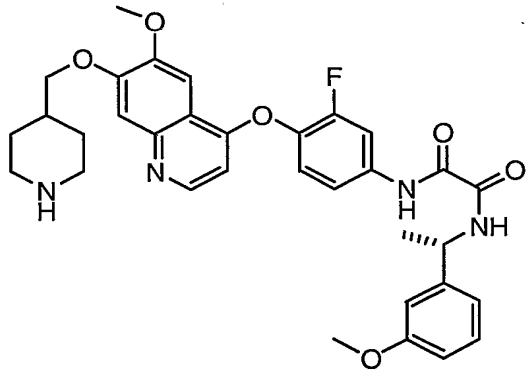
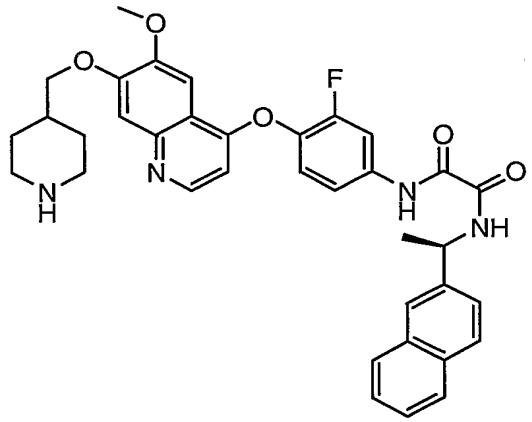
Entry	Name	Structure
206	N-(3-Chloro-4-fluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
207	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[1-(3-methoxy-phenyl)-ethyl]-oxalamide	
208	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1-naphthalen-2-yl-ethyl)-oxalamide	

Table 1

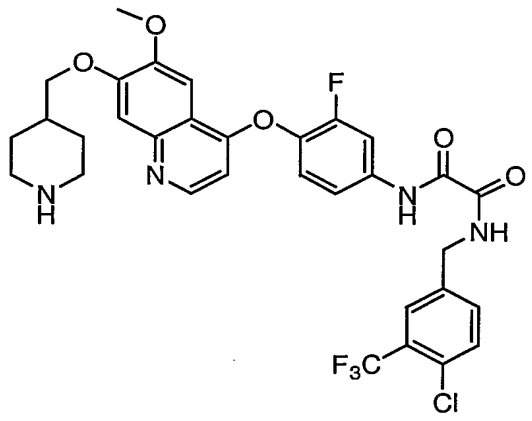
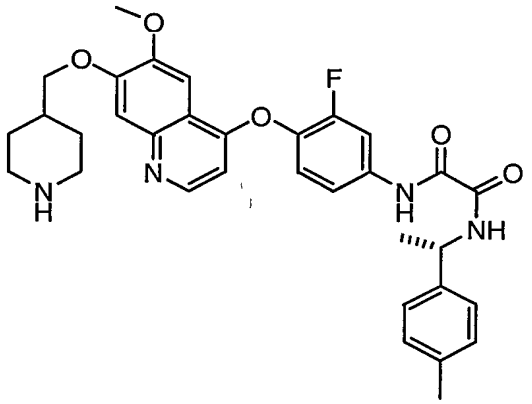
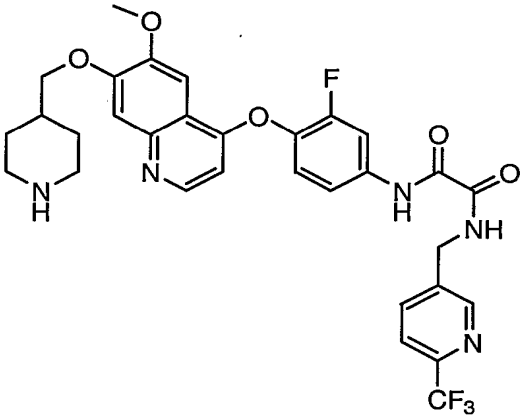
Entry	Name	Structure
209	N-(4-Chloro-3-trifluoromethyl-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
210	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1-p-tolyl-ethyl)-oxalamide	
211	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(6-trifluoromethyl-pyridin-3-ylmethyl)-oxalamide	

Table 1

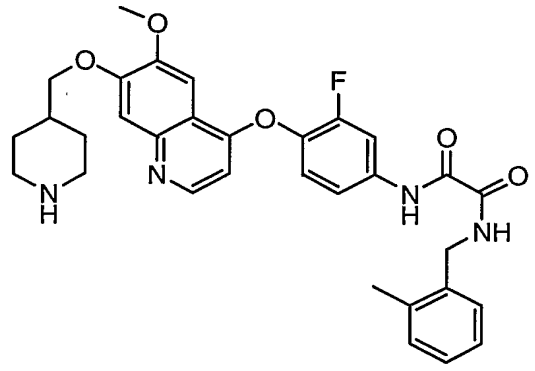
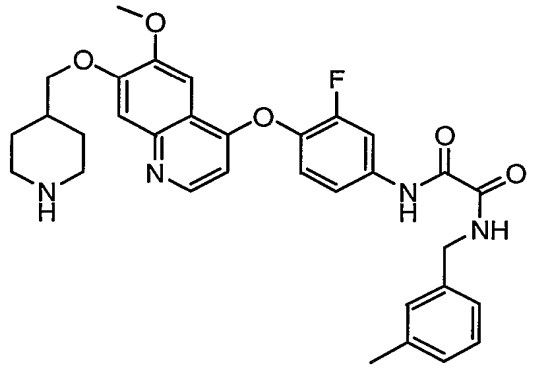
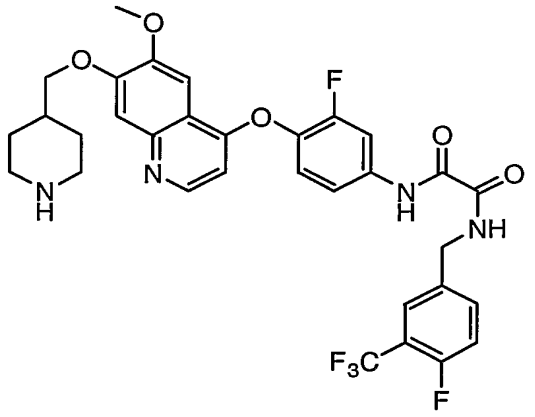
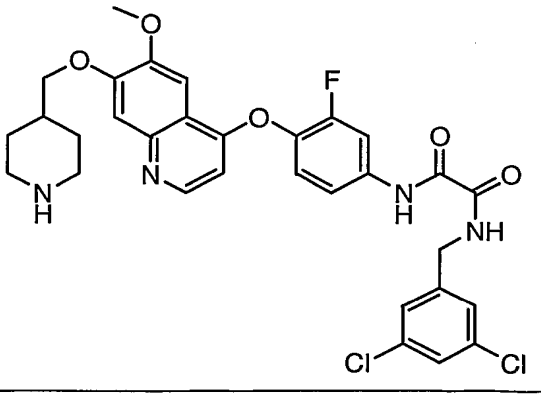
Entry	Name	Structure
212	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-methyl-benzyl)-oxalamide	
213	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-methyl-benzyl)-oxalamide	
214	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-fluoro-3-trifluoromethyl-benzyl)-oxalamide	
215	N-(3,5-Dichloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

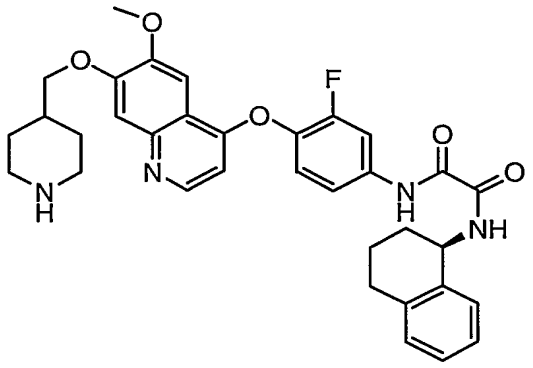
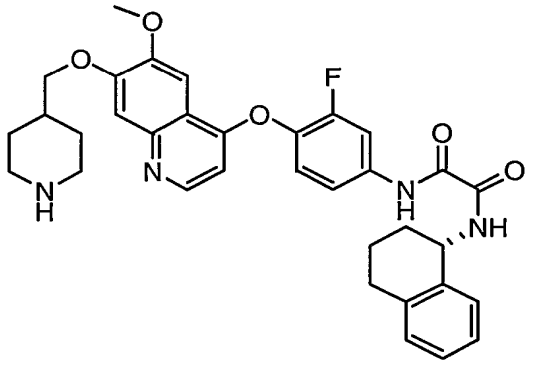
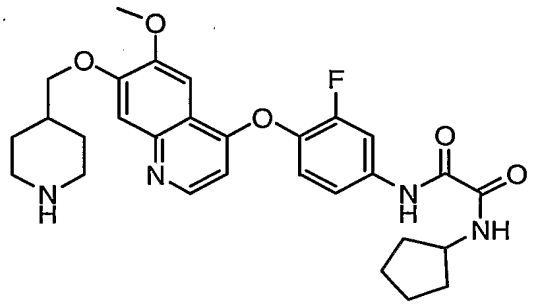
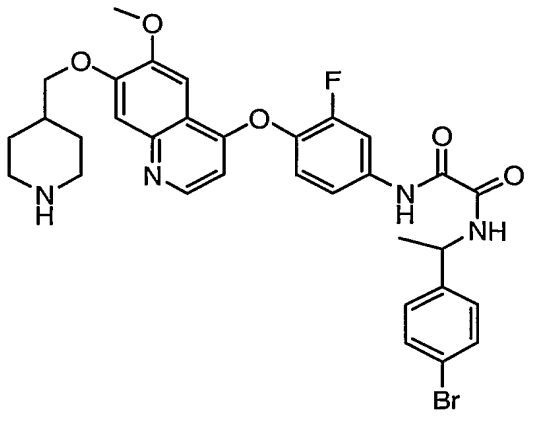
Entry	Name	Structure
216	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1R,2,3,4-tetrahydro-naphthalen-1-yl)-oxalamide	
217	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1S,2,3,4-tetrahydro-naphthalen-1-yl)-oxalamide	
218	N-Cyclopentyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
219	N-[1-(4-Bromo-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

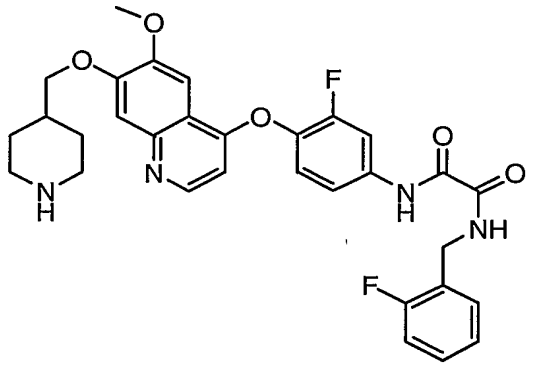
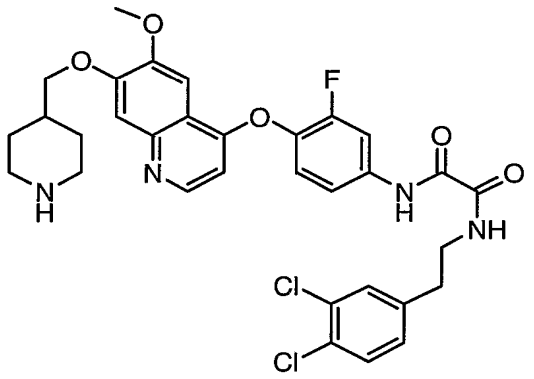
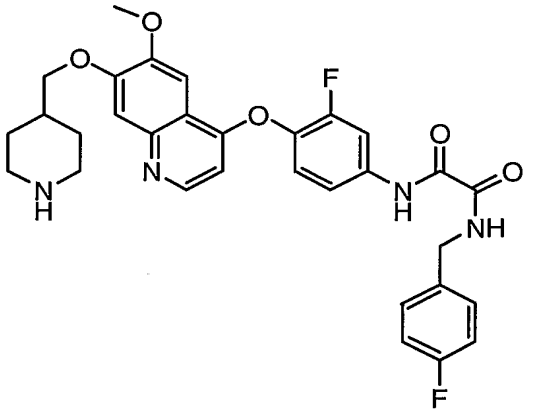
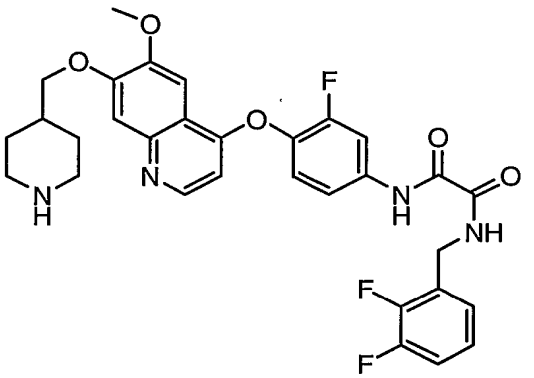
Entry	Name	Structure
220	N-(2-Fluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
221	N-[2-(3,4-Dichloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
222	N-(4-Fluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
223	N-(2,3-Difluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

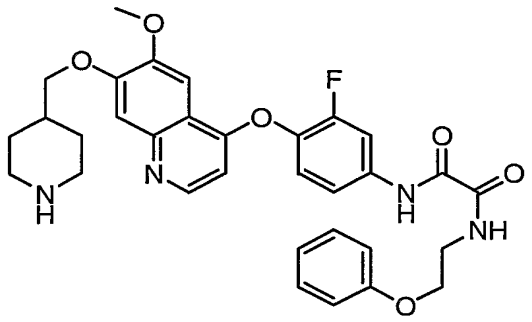
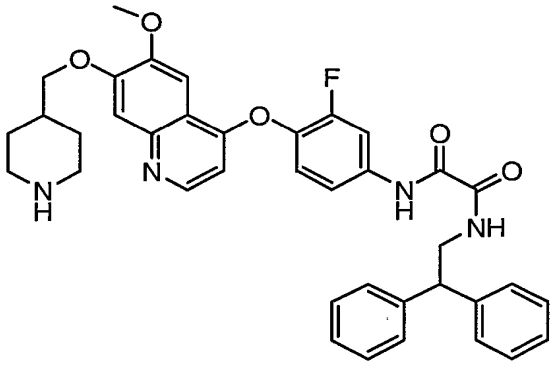
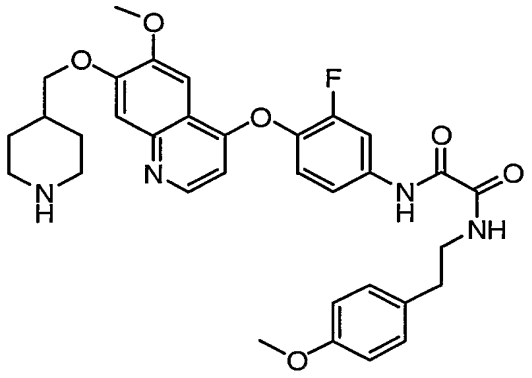
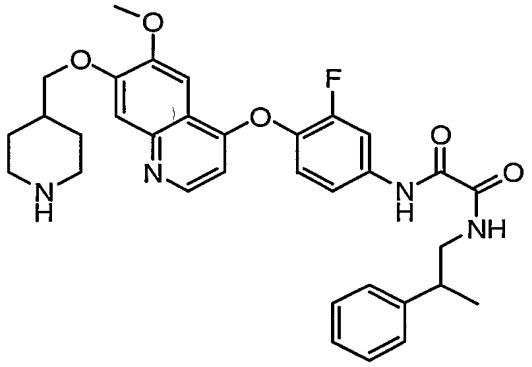
Entry	Name	Structure
224	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-phenoxy-ethyl)-oxalamide	
225	N-(2,2-Diphenyl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
226	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-methoxy-phenyl)-ethyl]-oxalamide	
227	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-phenyl-propyl)-oxalamide	

Table 1

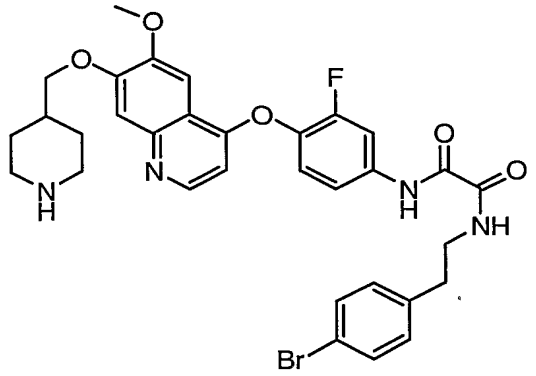
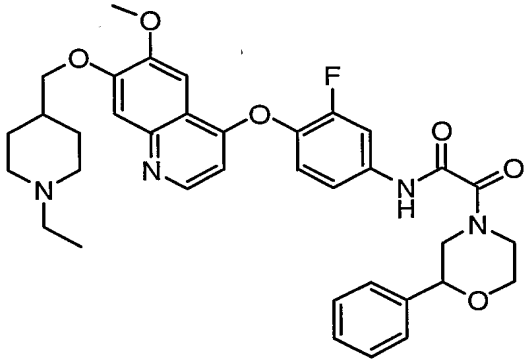
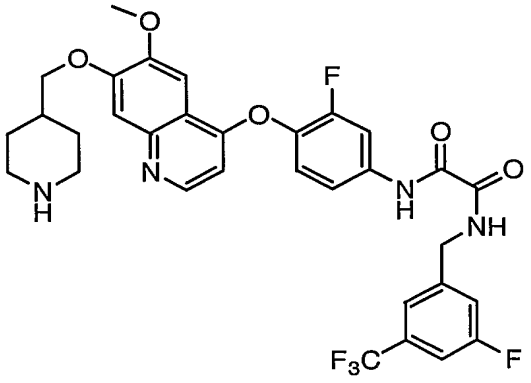
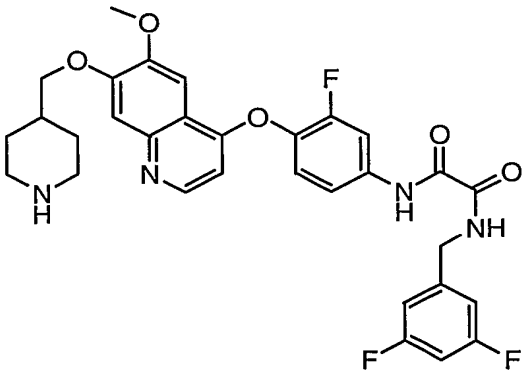
Entry	Name	Structure
228	N-[2-(4-Bromo-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
229	N-{4-[7-(1-Ethyl-piperidin-4-ylmethoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-2-oxo-2-(2-phenyl-morpholin-4-yl)-acetamide	
230	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-fluoro-5-trifluoromethyl-benzyl)-oxalamide	
231	N-(3,5-Difluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

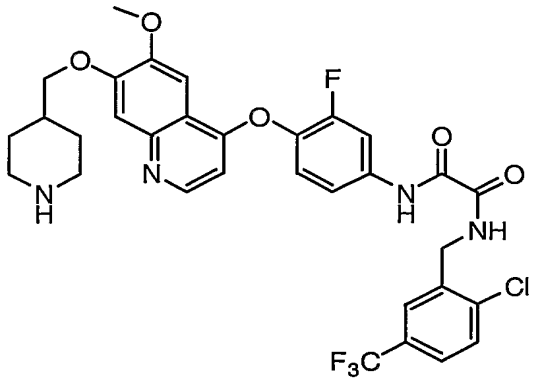
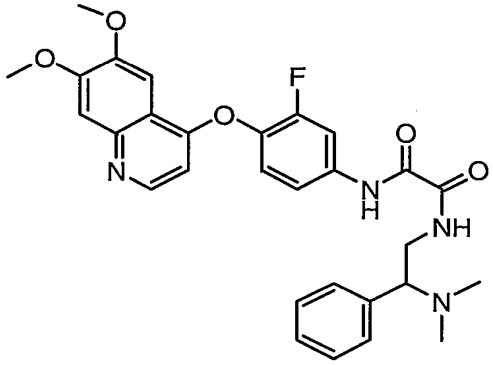
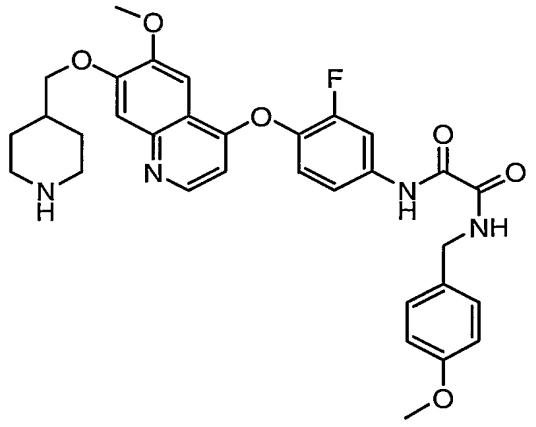
Entry	Name	Structure
232	N-(2-Chloro-5-trifluoromethyl-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
233	N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-N'-(2-dimethylamino-2-phenyl-ethyl)-oxalamide	
234	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-methoxy-benzyl)-oxalamide	

Table 1

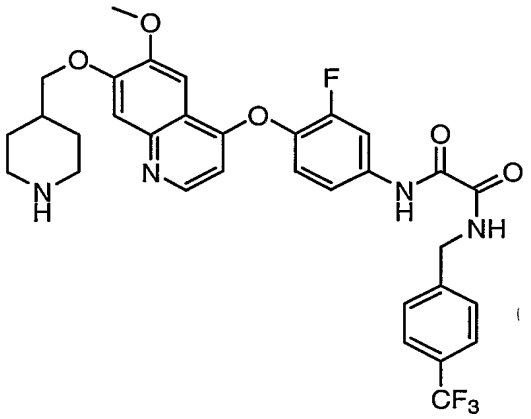
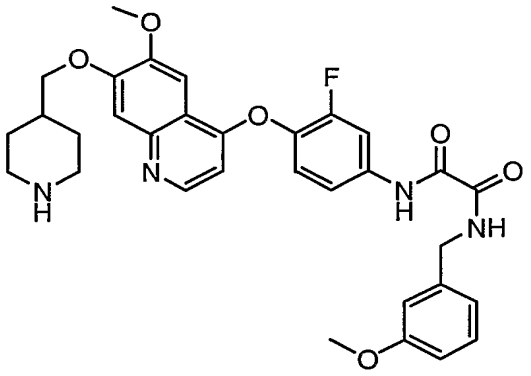
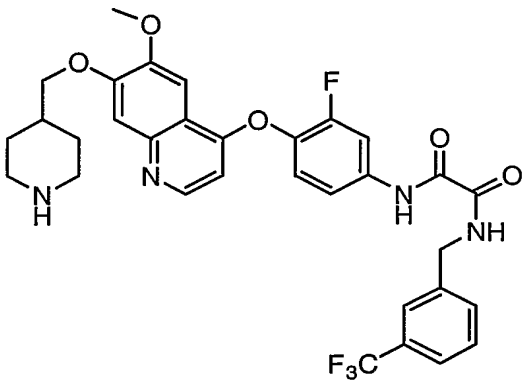
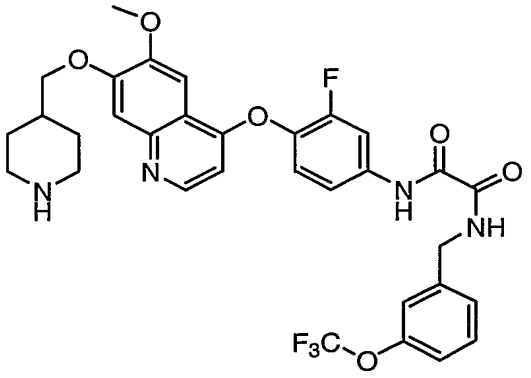
Entry	Name	Structure
235	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-trifluoromethyl-benzyl)-oxalamide	
236	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-methoxy-benzyl)-oxalamide	
237	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-trifluoromethyl-benzyl)-oxalamide	
238	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-trifluoromethoxy-benzyl)-oxalamide	

Table 1

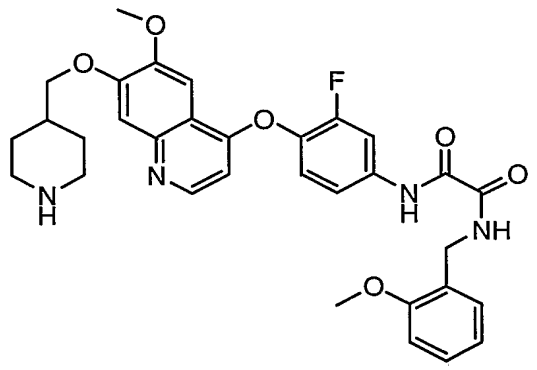
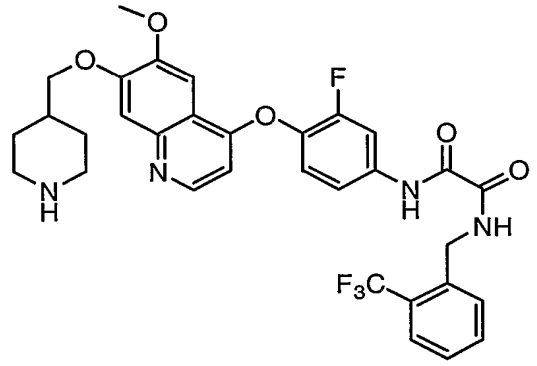
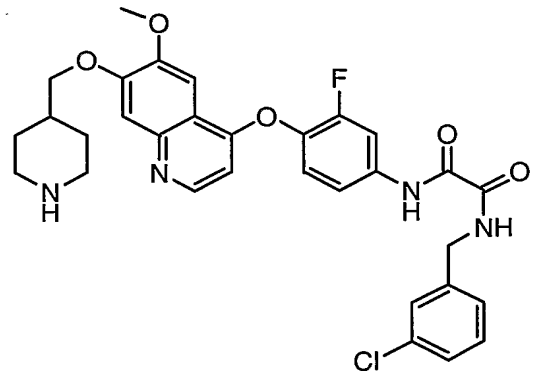
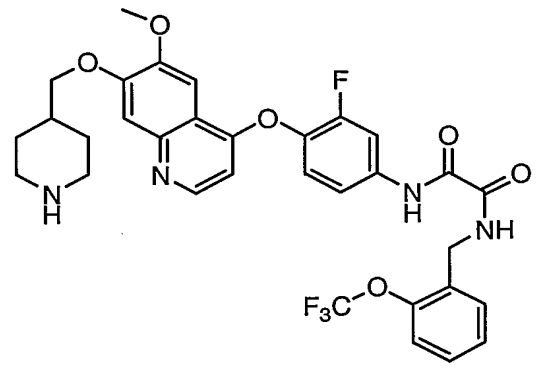
Entry	Name	Structure
239	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-methoxy-benzyl)-oxalamide	
240	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-trifluoromethyl-benzyl)-oxalamide	
241	N-(3-Chloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
242	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-trifluoromethoxy-benzyl)-oxalamide	

Table 1

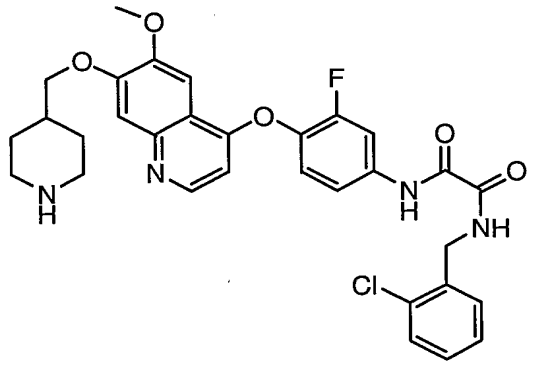
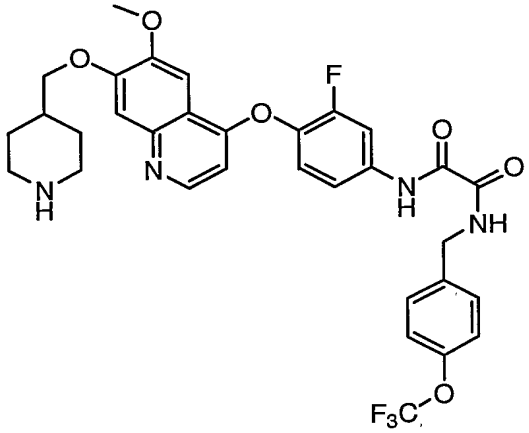
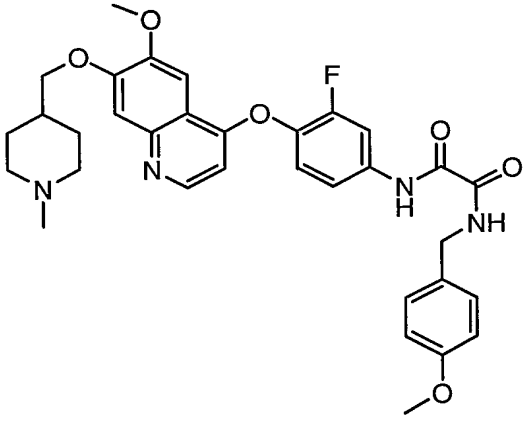
Entry	Name	Structure
243	N-(2-Chloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
244	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-trifluoromethoxy-benzyl)-oxalamide	
245	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-methoxy-benzyl)-oxalamide	

Table 1

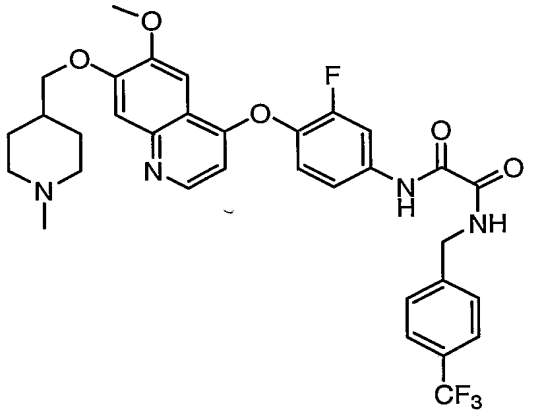
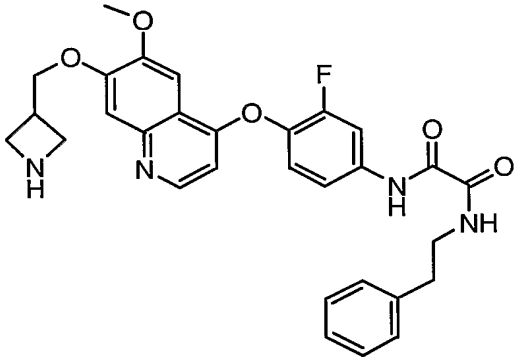
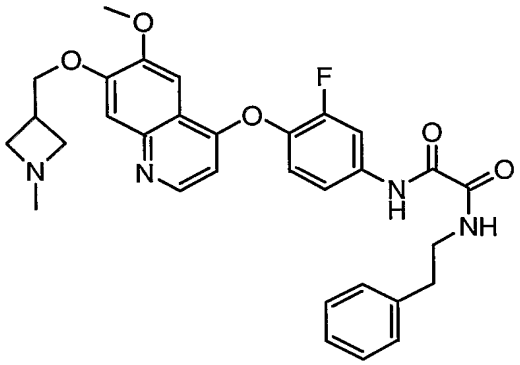
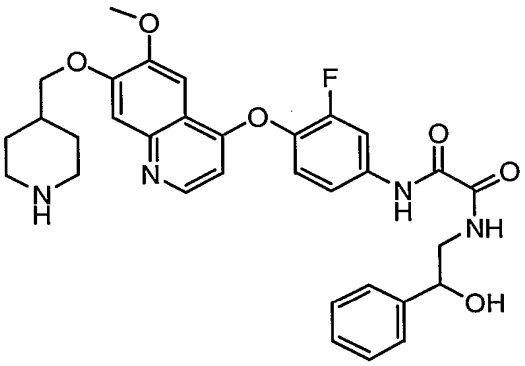
Entry	Name	Structure
246	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-trifluoromethyl-benzyl)-oxalamide	
247	N-{4-[7-(Azetidin-3-ylmethoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-N'-phenethyl-oxalamide	
248	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-azetidin-3-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	
249	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-hydroxy-2-phenyl-ethyl)-oxalamide	

Table 1

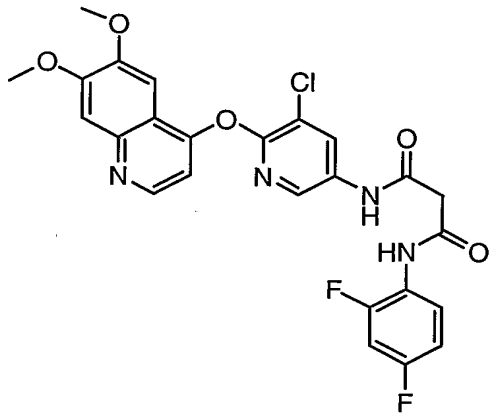
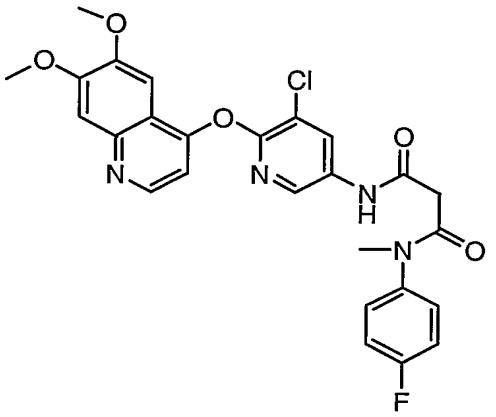
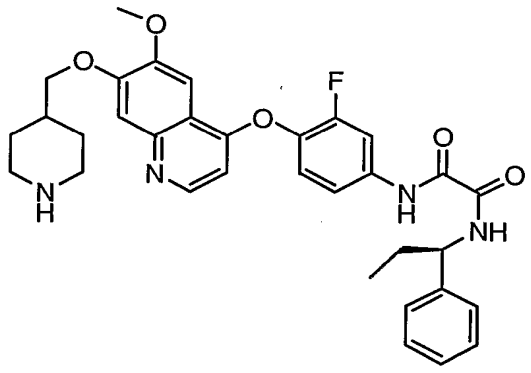
Entry	Name	Structure
250	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(2,4-difluoro-phenyl)-malonamide	
251	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(4-fluoro-phenyl)-N'-methyl-malonamide	
252	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1R-phenyl-propyl)-oxalamide	

Table 1

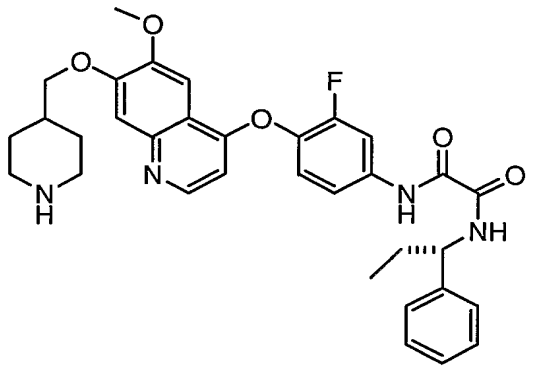
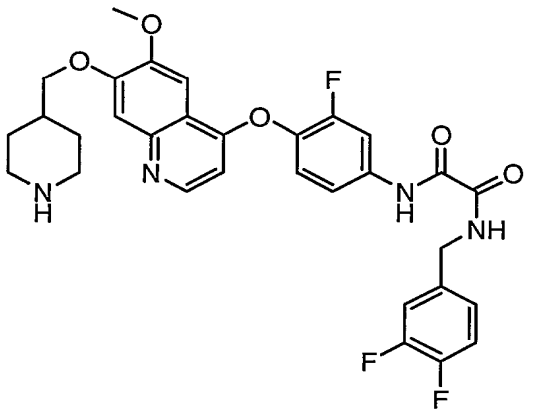
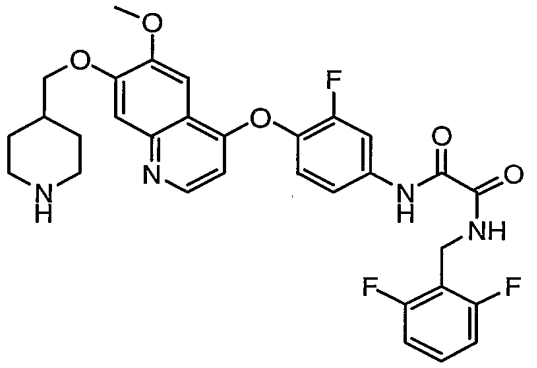
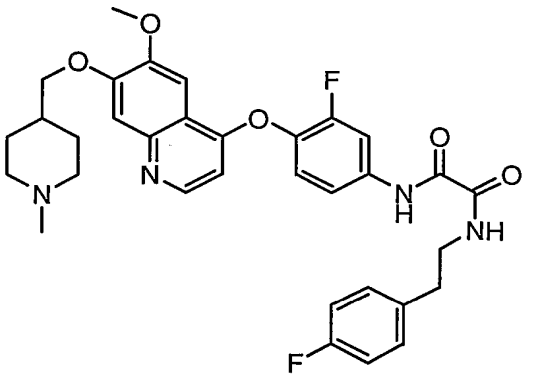
Entry	Name	Structure
253	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1R-phenyl-propyl)-oxalamide	
254	N-(3,4-Difluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
255	N-(2,6-Difluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
256	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-fluoro-phenyl)-ethyl]-oxalamide	

Table 1

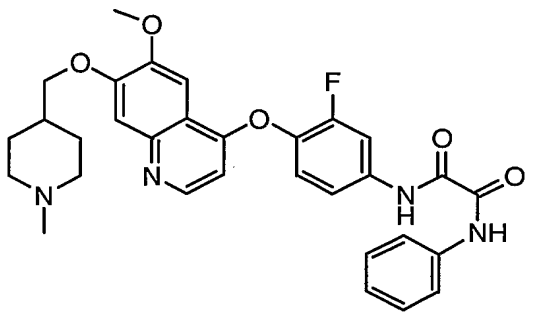
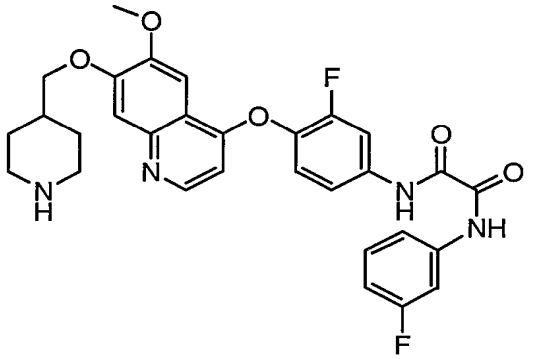
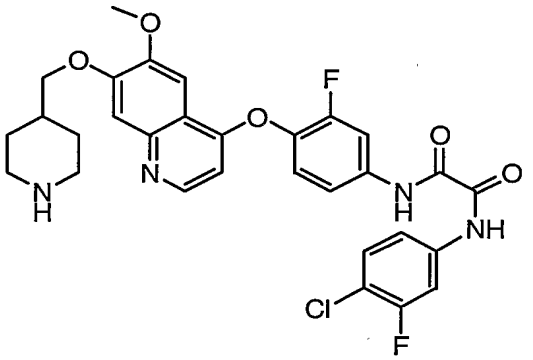
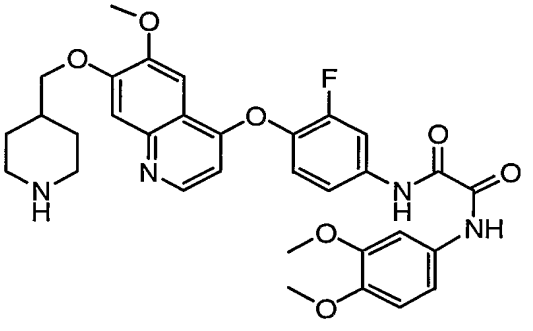
Entry	Name	Structure
257	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenyl-oxalamide	
258	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-fluoro-phenyl)-oxalamide	
259	N-(4-Chloro-3-fluoro-phenyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
260	N-(3,4-Dimethoxy-phenyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

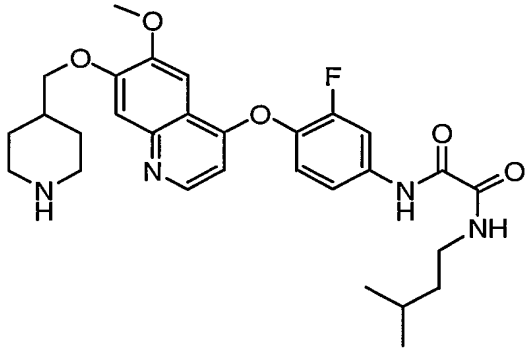
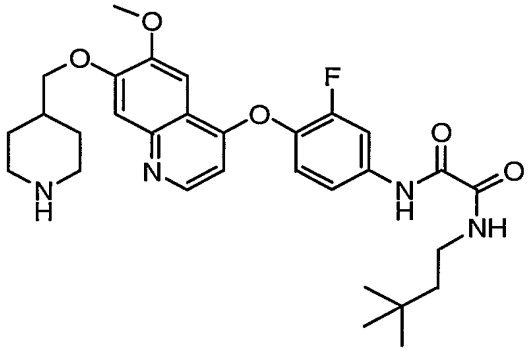
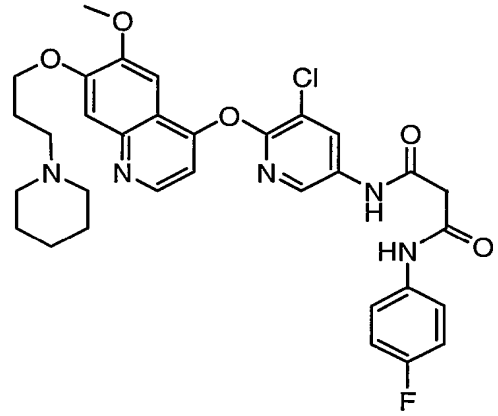
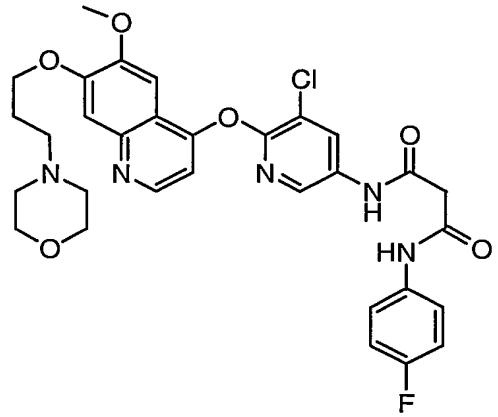
Entry	Name	Structure
261	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-methyl-butyl)-oxalamide	
262	N-(3,3-Dimethyl-butyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
263	N-{5-Chloro-6-[6-methoxy-7-(3-piperidin-1-yl-propoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide	
264	N-{5-Chloro-6-[6-methoxy-7-(3-morpholin-4-yl-propoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide	

Table 1

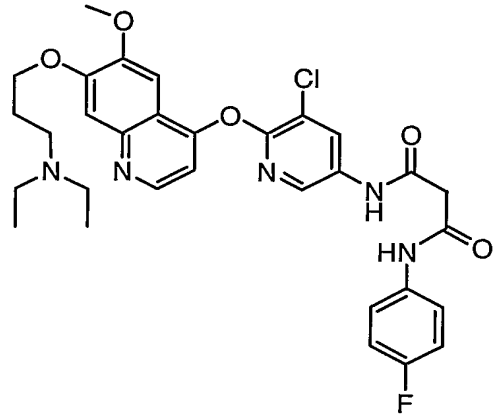
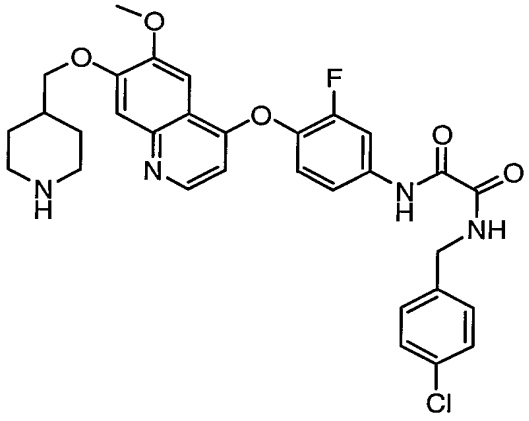
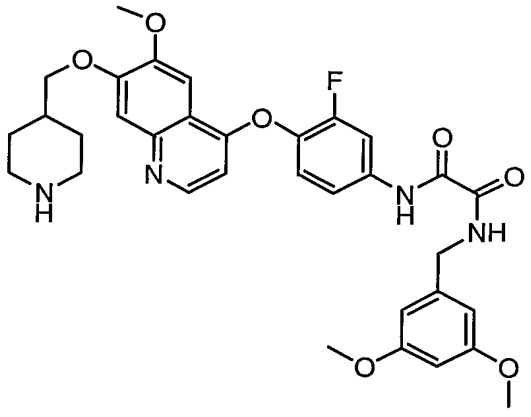
Entry	Name	Structure
265	N-{5-Chloro-6-[7-(3-diethylamino-propoxy)-6-methoxy-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide	
266	N-(4-Chloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
267	N-(3,5-Dimethoxy-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

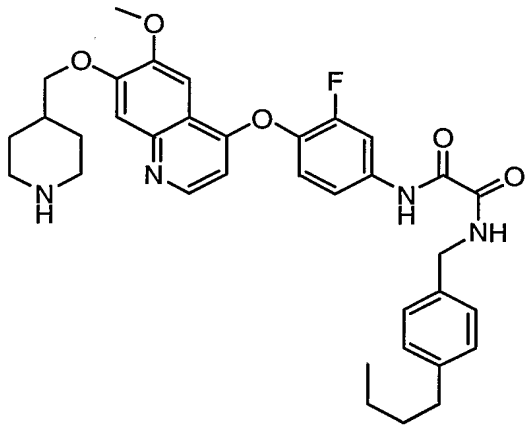
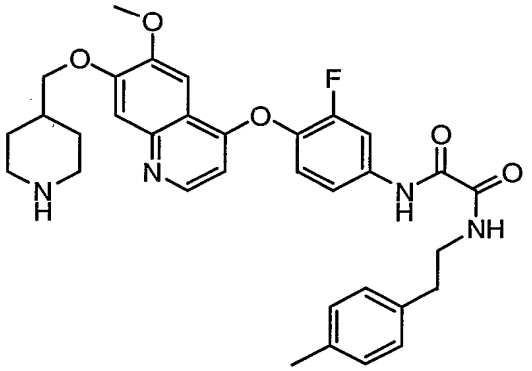
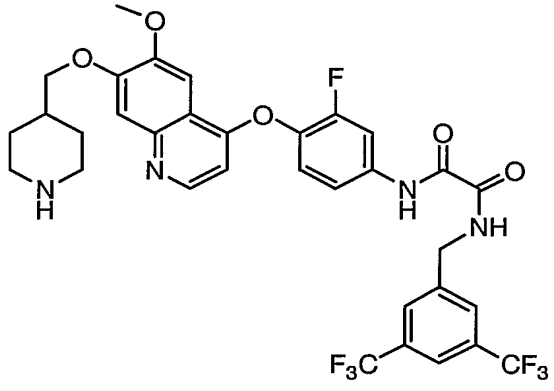
Entry	Name	Structure
268	N-(4-Butyl-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
269	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-p-tolyl-ethyl)-oxalamide	
270	N-(3,5-Bis-trifluoromethyl-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

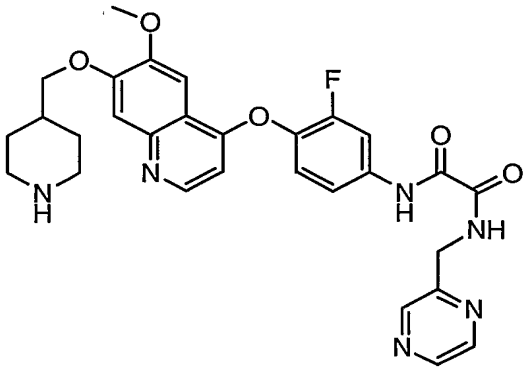
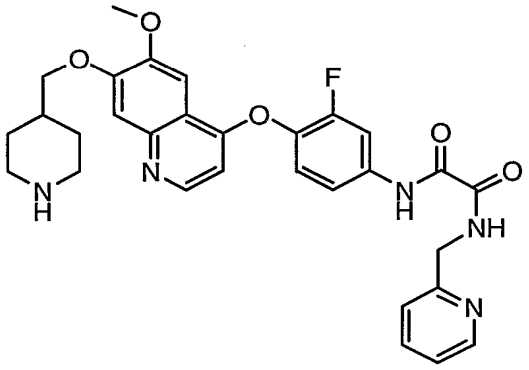
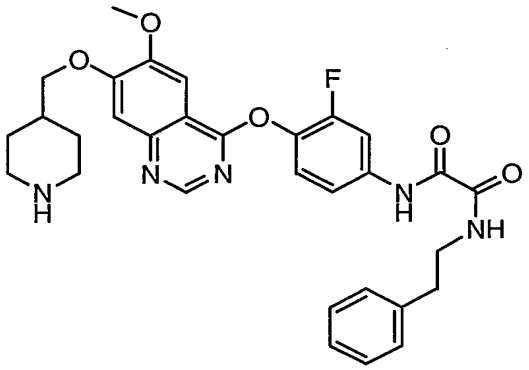
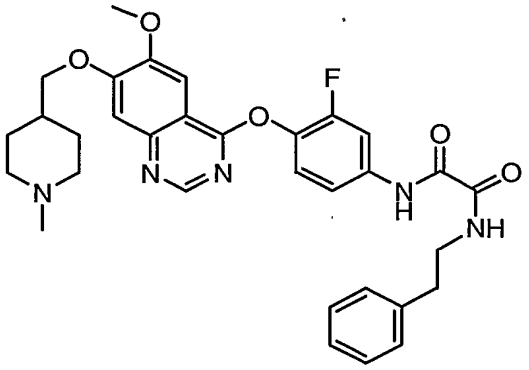
Entry	Name	Structure
271	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-pyrazin-2-ylmethyl-oxalamide	
272	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-pyridin-2-ylmethyl-oxalamide	
273	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	
274	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	

Table 1

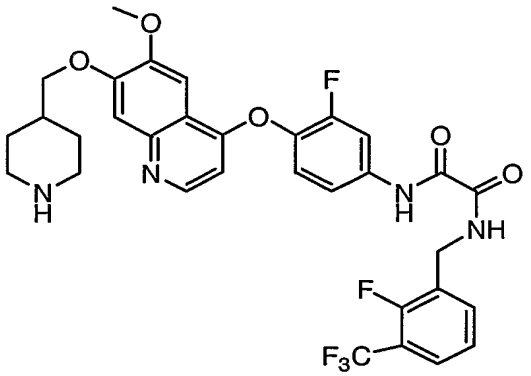
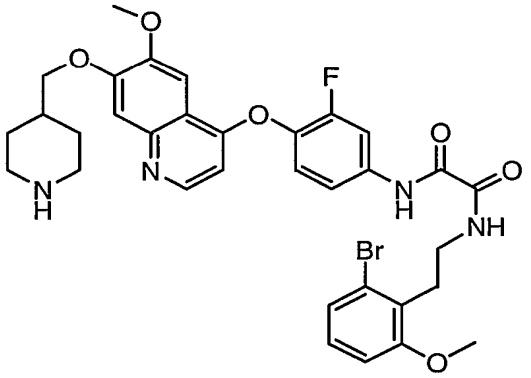
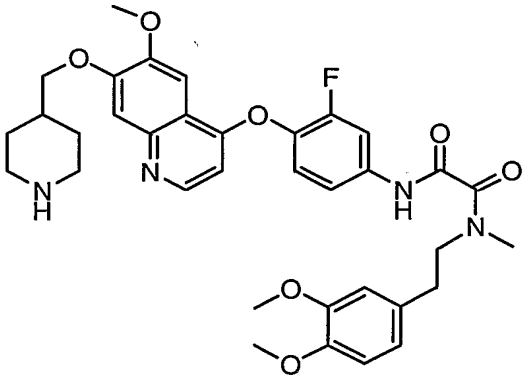
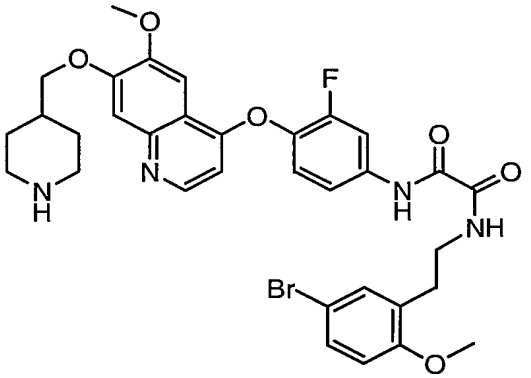
Entry	Name	Structure
275	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-fluoro-3-trifluoromethyl-benzyl)-oxalamide	
276	N-[2-(2-Bromo-6-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
277	N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N-methyl-oxalamide	
278	N-[2-(5-Bromo-2-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

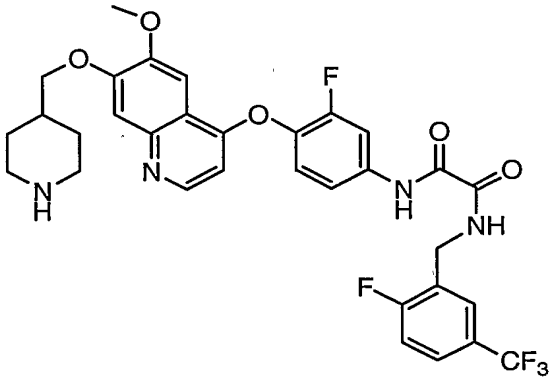
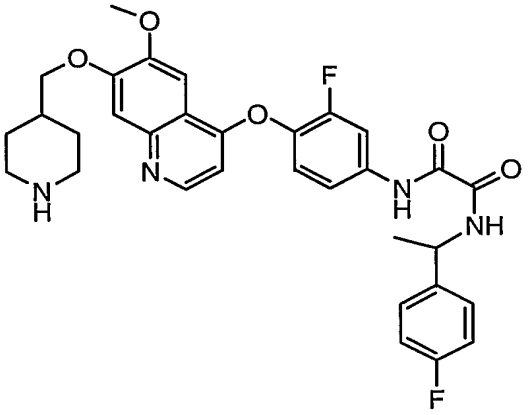
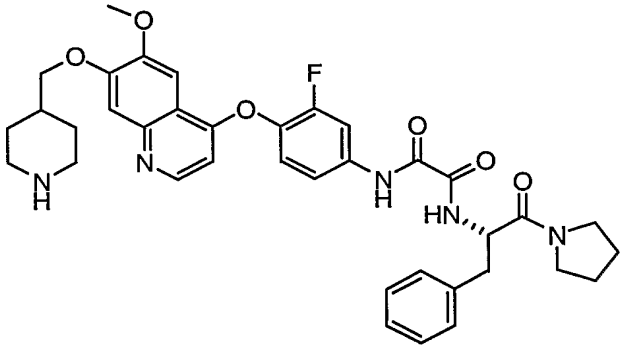
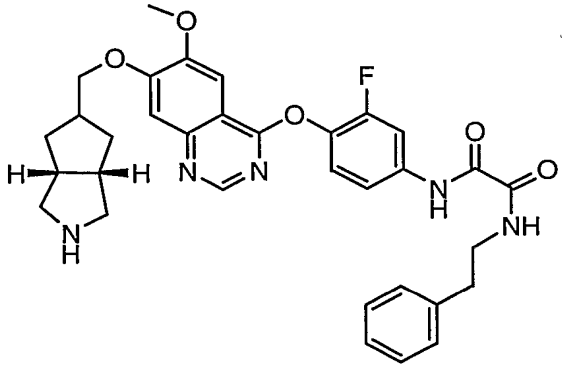
Entry	Name	Structure
279	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-fluoro-5-trifluoromethyl-benzyl)-oxalamide	
280	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[1-(4-fluoro-phenyl)-ethyl]-oxalamide	
281	N-(1S-Benzyl-2-oxo-2-pyrrolidin-1-yl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
282	N-{3-Fluoro-4-[6-methoxy-7-(octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	

Table 1

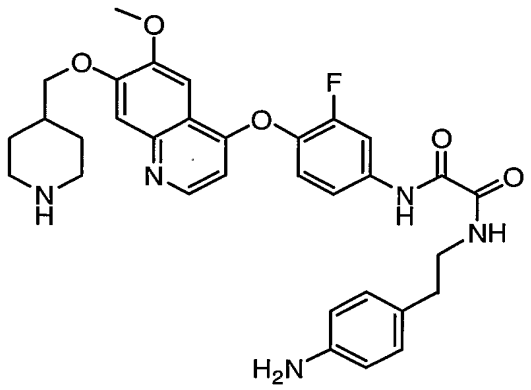
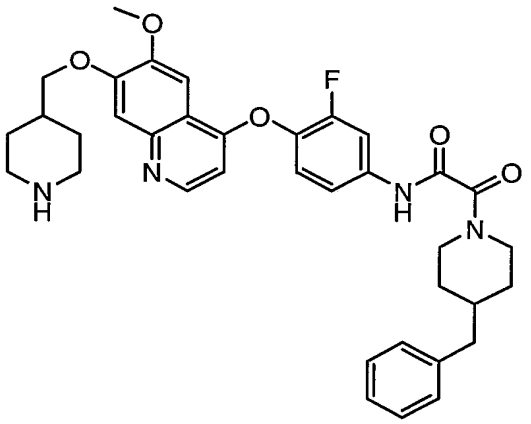
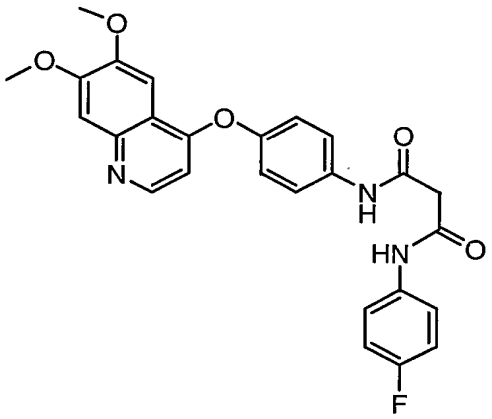
Entry	Name	Structure
283	N-[2-(4-Amino-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
284	2-(4-Benzyl-piperidin-1-yl)-N-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-acetamide	
285	N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-phenyl]-N'-(4-fluoro-phenyl)-malonamide	

Table 1

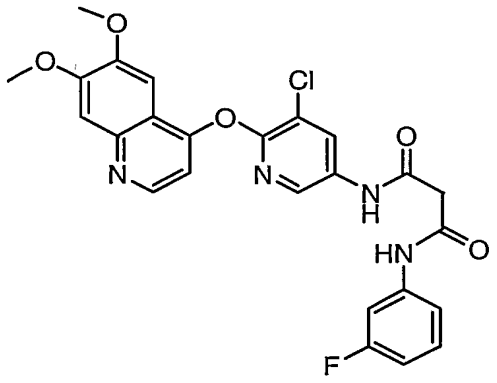
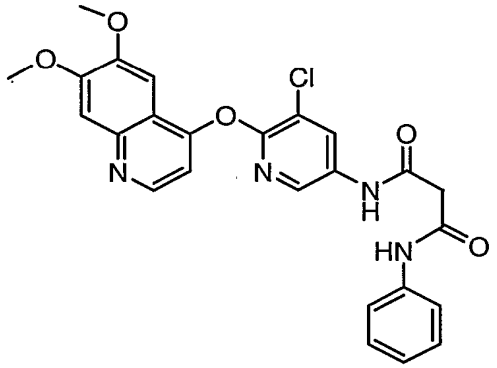
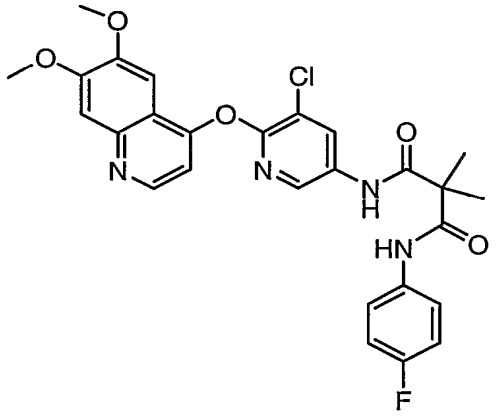
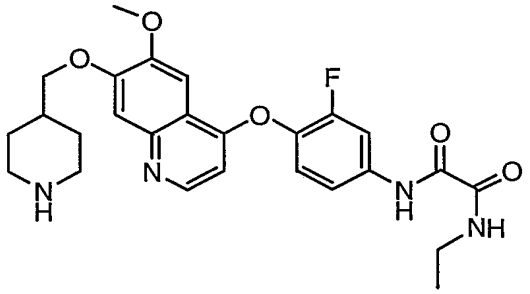
Entry	Name	Structure
286	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(3-fluoro-phenyl)-malonamide	
287	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-phenyl-malonamide	
288	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(4-fluoro-phenyl)-2,2-dimethyl-malonamide	
289	N-Ethyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

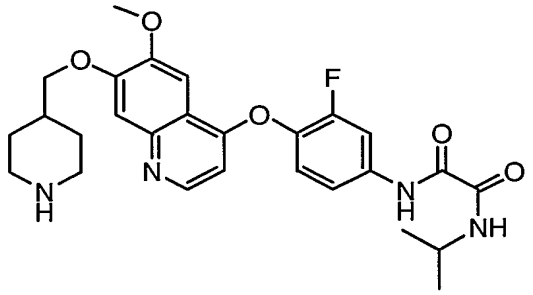
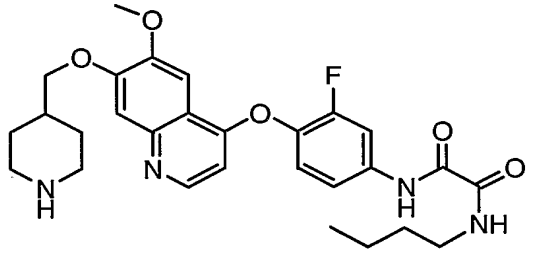
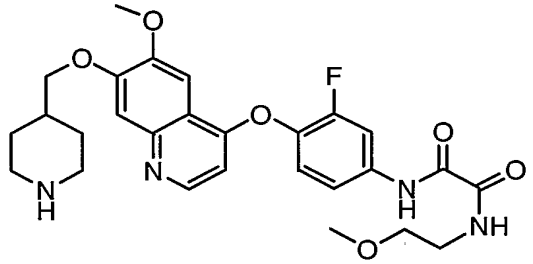
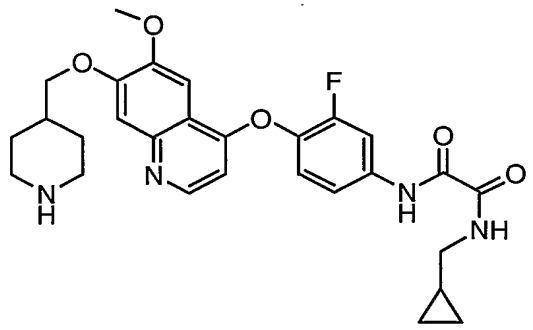
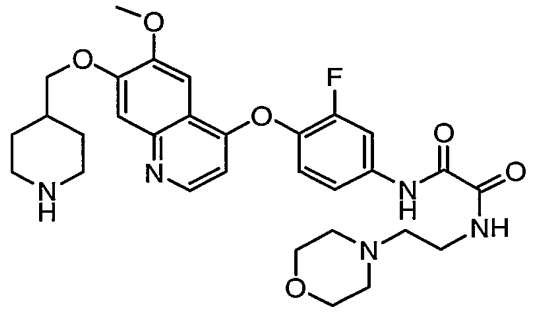
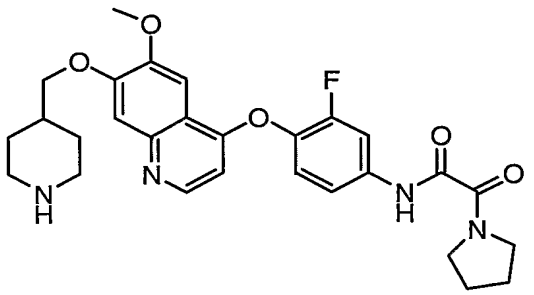
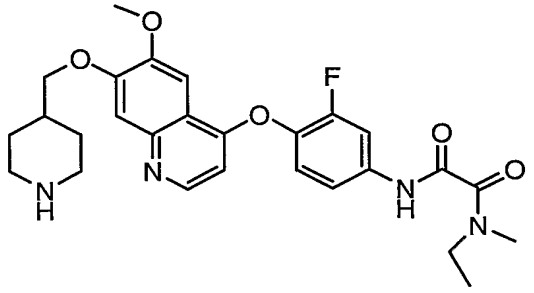
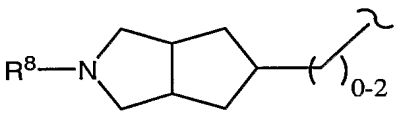
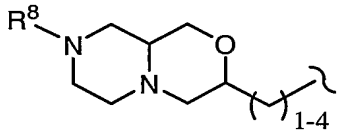
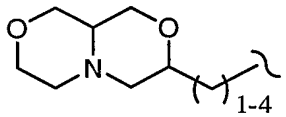
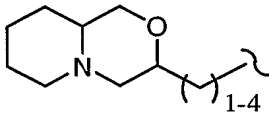
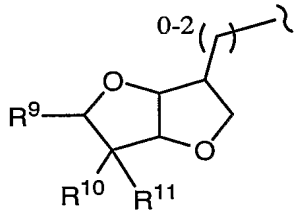
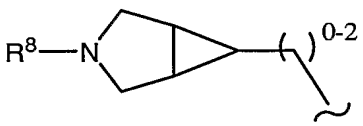
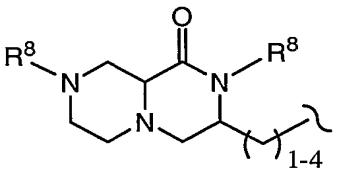
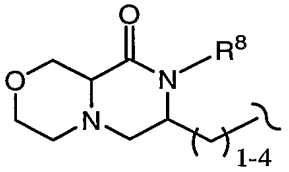
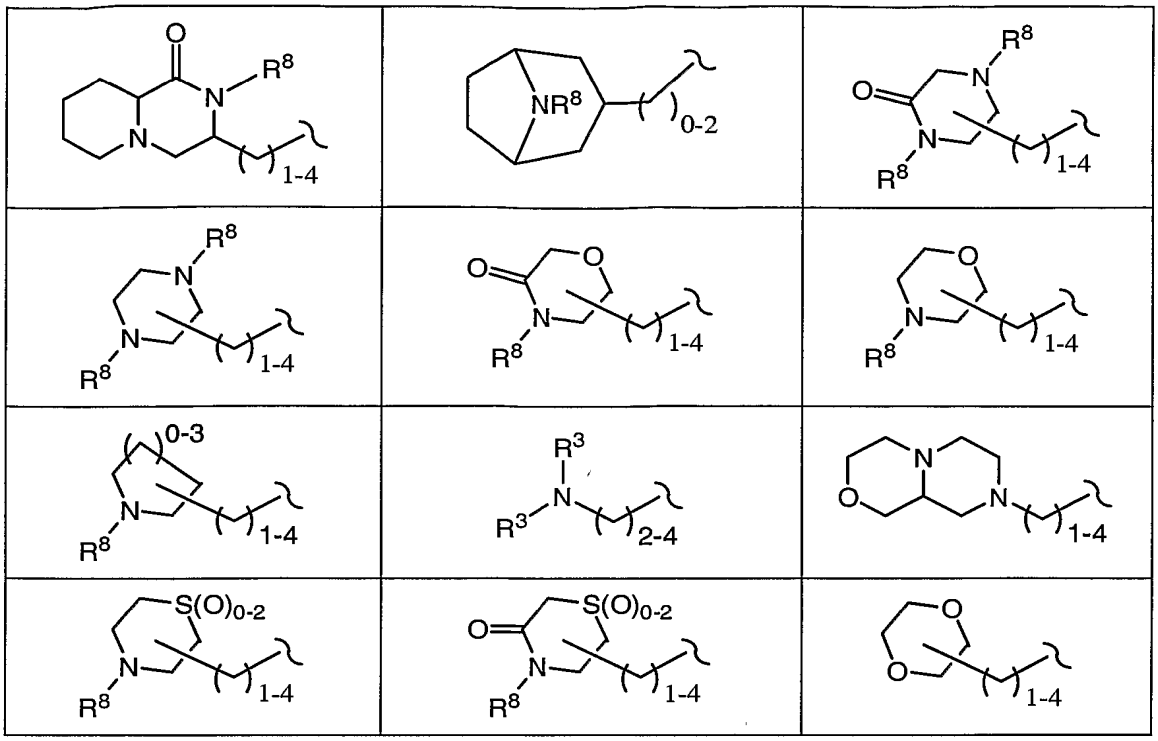
Entry	Name	Structure
290	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-isopropyl-oxalamide	
291	N-Butyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
292	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-methoxy-ethyl)-oxalamide	
293	N-Cyclopropylmethyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
294	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-morpholin-4-yl-ethyl)-oxalamide	

Table 1

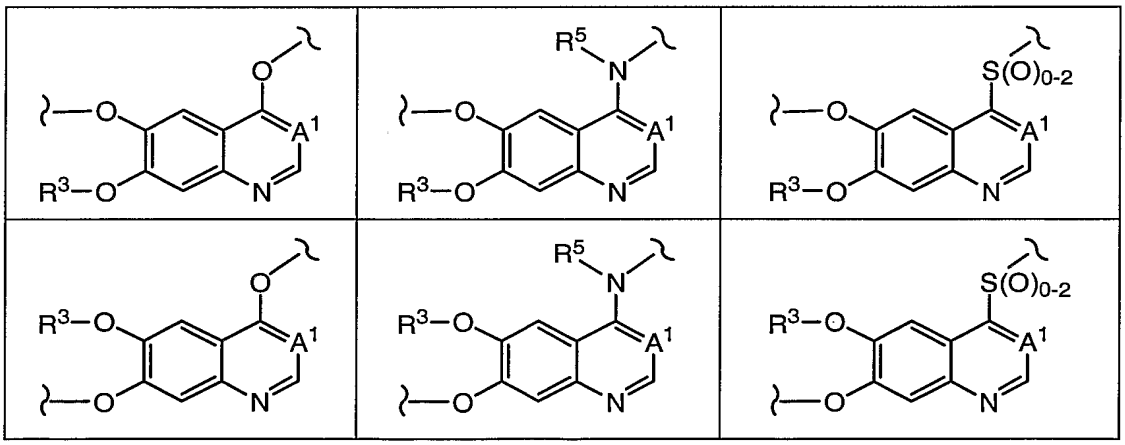
Entry	Name	Structure
295	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-2-pyrrolidin-1-yl-acetamide	
296	N-Ethyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N-methyl-oxalamide	

46. A compound for modulating kinase activity of formula A-B-C, or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein, A is selected from:

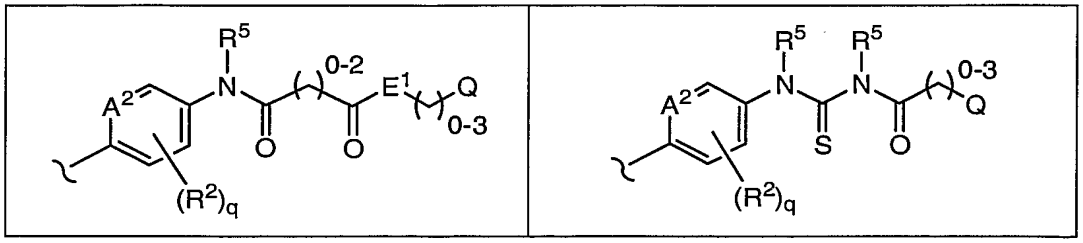
$-R^3$		
		
		

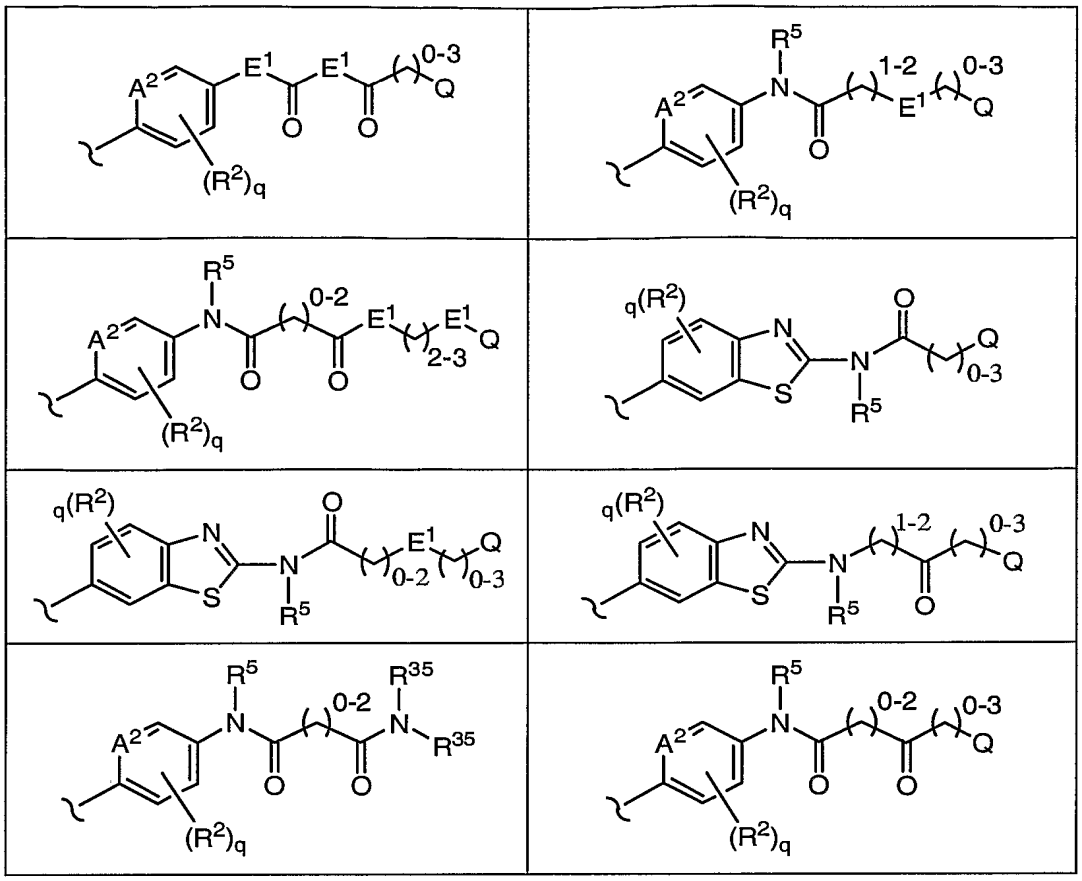


B is selected from:



and, C is selected from:





wherein R^2 is selected from -H, halogen, trihalomethyl, -CN, $-NH_2$, $-NO_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted lower alkyl;

q is 0 to 2;

each R^3 is independently selected from –H, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted arylalkyl, and optionally substituted heteroarylalkyl;

two R^3, together with the nitrogen to which they are attached, form a four- to seven-membered heteroalicyclic, said four- to seven-membered heteroalicyclic optionally containing one additional heteroatom; when one said additional heteroatom is a nitrogen, then said nitrogen is optionally substituted with a group selected from -H, trihalomethyl, $-SO_2R^5$, $-SO_2NR^5R^5$, $-CO_2R^5$, $-C(O)NR^5R^5$, $-C(O)R^5$, and optionally substituted lower alkyl;

each R^{35} is independently selected from -H, $-C(=O)R^3$, $-C(=O)OR^3$, $-C(=O)SR^3$, $-SO_2R^3$, $-C(=O)N(R^3)R^3$, and optionally substituted lower alkyl;

two R^{35}, together with the nitrogen to which they are attached, can combine to form a heteroalicyclic optionally substituted with between one and four of R^{60}, said heteroalicyclic may have an additional annular heteroatom, and said heteroalicyclic may have an aryl fused thereto, said aryl optionally substituted with an additional one to four of R^{60};

A^1 is selected from =N-, =C(H)-, and =C(CN)-;

A^2 is either =N- or =C(H)-;

R^5 is -H or optionally substituted lower alkyl;

R^8 is selected from R^3, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$;

R^9, R^{10}, and R^{11} are each independently selected from -H, and $-OR^{12}$; or

R^9 is selected from -H, and $-OR^{12}$, and R^{10} and R^{11}, when taken together, are either an optionally substituted alkylidene or an oxo; and

R^{12} is selected from -H, $-C(O)R^3$, optionally substituted lower alkylidyne, optionally substituted lower arylalkylidyne, optionally substituted lower heterocyclylalkylidyne, optionally substituted lower alkylidene, optionally substituted lower alkylidenearyl, optionally substituted lower alkylideneheterocyclyl, optionally substituted lower alkyl, optionally substituted lower alkylaryl, optionally substituted aryl, optionally substituted lower heterocyclylalkyl, and optionally substituted heterocyclyl;

or two R^{12}'s, when taken together, form 1) a corresponding spirocyclic ketal when said two R^{12}'s stem from R^{10} and R^{11}, or 2) a corresponding cyclic ketal when said two R^{12}'s stem from R^9 and one of R^{10} and R^{11};

E^1 is selected from -O-, $-CH_2-$, $-N(R^5)-$, and $-S(O)_{0-2}-$;

Q is a five- to ten-membered ring system, optionally substituted with between zero and four of R^{20};

R^{20} is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted lower alkyl;

R^{60} is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$,

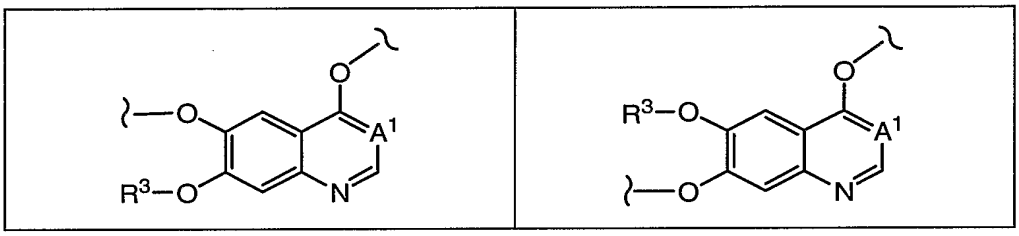
$-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted heteroarylalkyl, and optionally substituted arylalkyl;

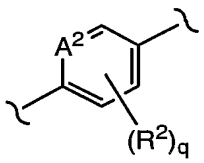
two of R^{60}, when attached to a non-aromatic carbon, can be oxo;

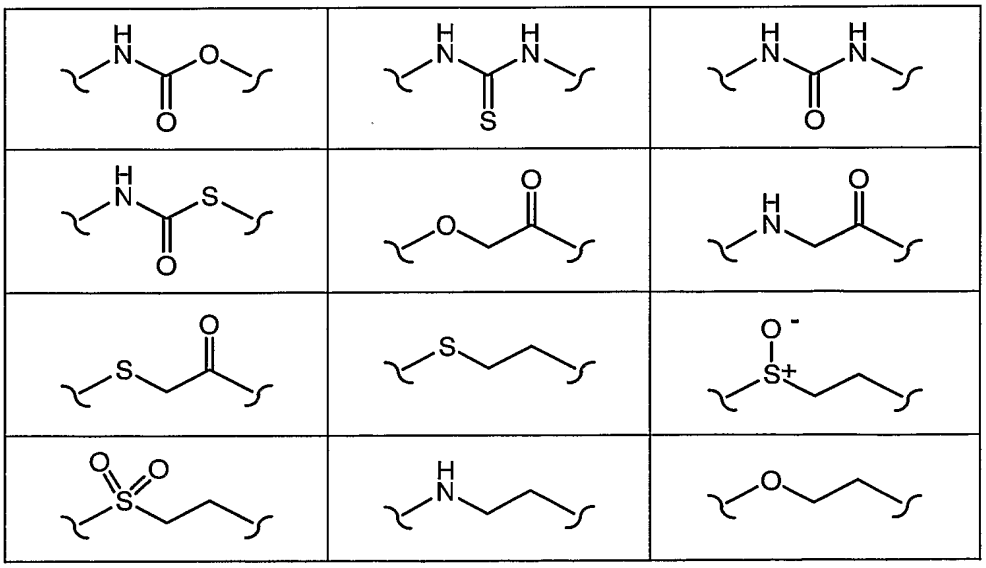
each methylene in any of the above formulae is independently optionally substituted with R^{25};

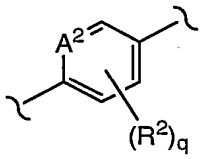
each R^{25} is independently selected from halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted arylalkyl, heteroarylalkyl, and optionally substituted lower alkyl; two of R^{25}, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered alicyclic or heteroalicyclic, two of R^{25} on a single carbon can be oxo;

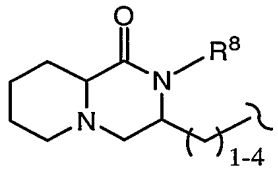
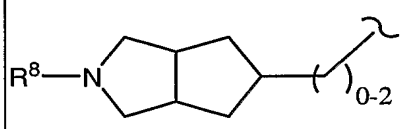
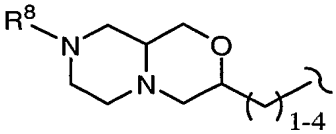
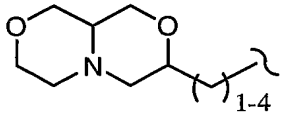
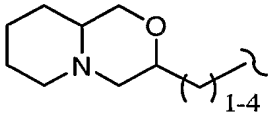
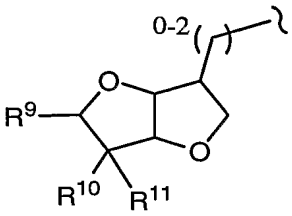
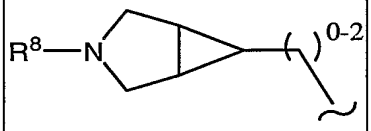
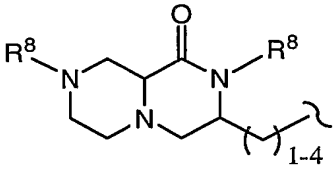
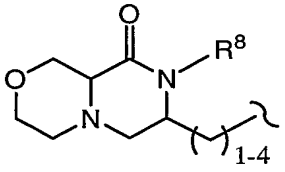
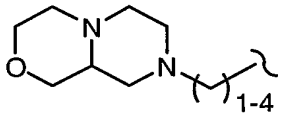
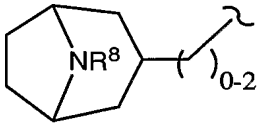
with the proviso that when B is selected from:

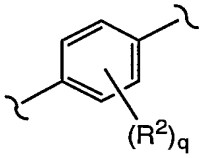


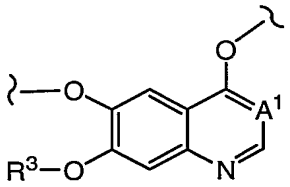
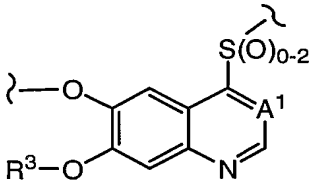
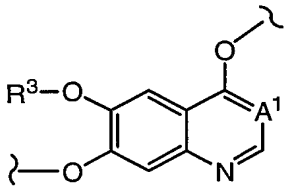
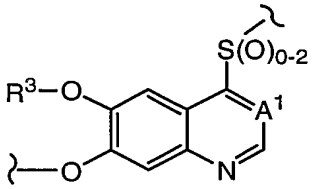
and C contains  , and the remaining portion of C contains one of:

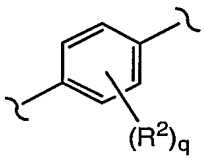
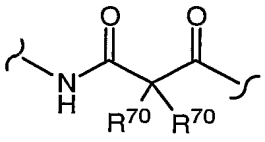


directly attached to  , then A must be one of:

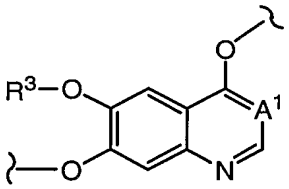
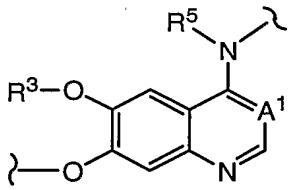
and with the proviso that when C contains  , and B is selected from:

then the portion of C directly attached to  cannot contain  , when R^{70} is selected from -H, C_{1-4}alkyl, and C_{1-4}alkoxyl.

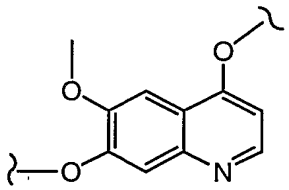
47. The compound according to claim 46, wherein Q is selected from phenyl, napthyl, 1,2,3,4-tetrahydronaphthyl, indanyl, benzodioxanyl, benzofuranyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroisoquinolyl, pyrrolyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, tetrahydropyridinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolinyl, oxazolidinyl, triazolyl, isoxazolyl, isoxazolidinyl, thiazolyl, thiazolinyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, thienyl, benzothieliyl, and oxadiazolyl; each optionally substituted with between one and four of R^{20}; wherein each R^{20} is independently selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted lower alkyl.

48. The compound according to claim 47, wherein B is either of the following:

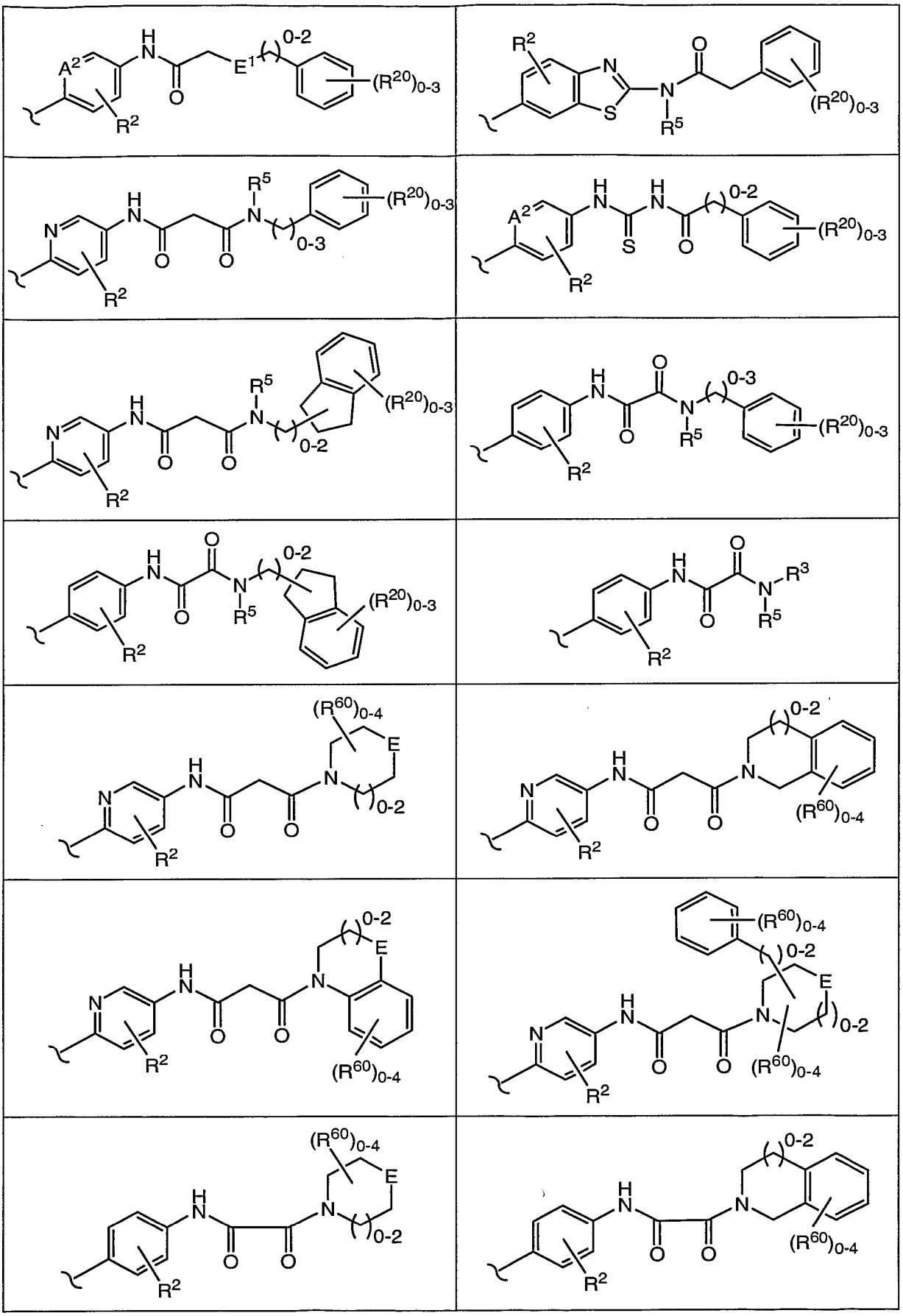



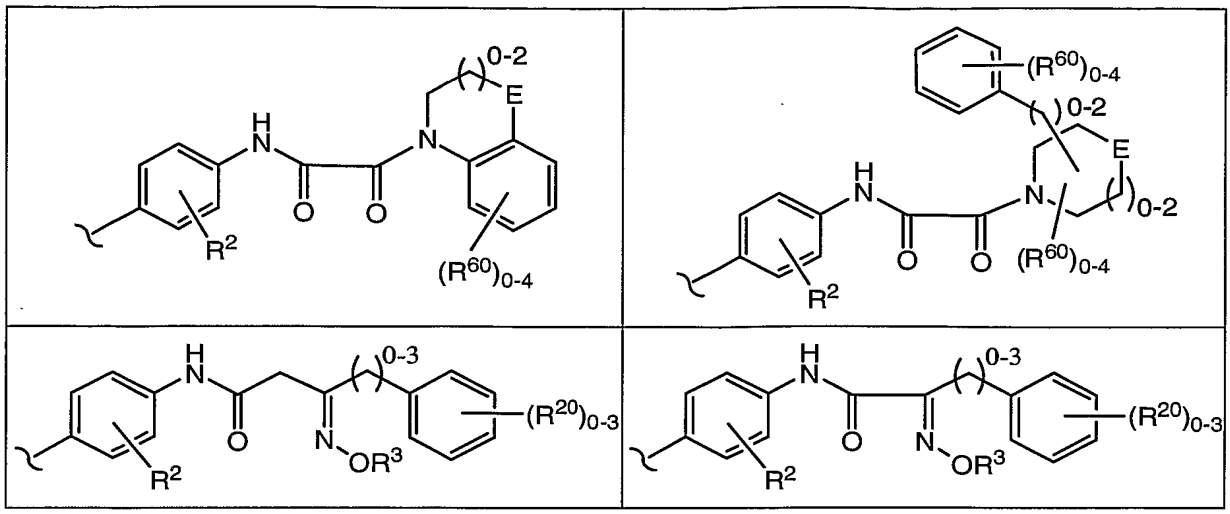
wherein A^1 is either =N- or =C(H)-.

49. The compound according to claim 48, wherein B is



50. The compound according to claim 49, wherein C is selected from:





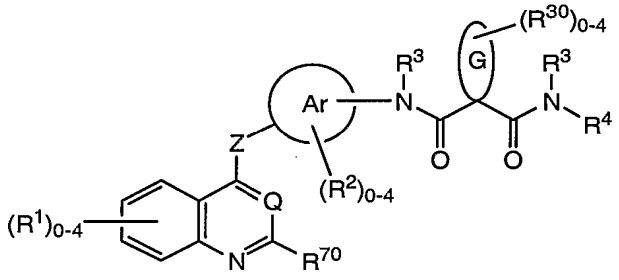
wherein R^2, R^3, R^5, R^{20}, R^{25} and R^{60} are as defined above.

51. The compound according to claim 50, R^2 is selected from halogen, trihalomethyl, -CN, -NO_2, -OR^3, -NR^3R^3, -CO_2R^3, -$C(O)NR^3R^3$, -$N(R^3)C(O)R^3$, -$N(R^3)CO_2R^3$, -$C(O)R^3$, and optionally substituted lower alkyl

52. The compound according to claim 51, wherein R^2 is halogen.

53. The compound according to claim 52, wherein R^2 is either fluorine or chlorine.

54. A compound for modulating kinase activity according to Formula **XI**,



XI

or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein,

each R^1 is independently selected from halogen, -OR^3, -NO_2, -NH_2, -NR^3R^4, -D-R^{50} and optionally substituted $C_{1\text{-}6}$alkyl;

R^{70} is selected from -H, halogen, -OR^3, -$S(O)_{0\text{-}2}R^3$, -NO_2, -NH_2, -NR^3R^4, and optionally substituted $C_{1\text{-}6}$alkyl;

Q is selected from =N-, =C(H)-, and =C(CN)-;

Z is selected from -$S(O)_{0-2}$-, -O-, and -NR^5-;

Ar is either a five- or six-membered arylene or a five- or six-membered heteroarylene containing between one and three heteroatoms;

G is either an optionally substituted cycloalkyl or an optionally substituted heteroalicyclic;

each R^2 is independently selected from halogen, trihalomethyl, -CN, -NO_2, -NH_2, -OR^3, -NR^3R^4, -$S(O)_{0-2}R^3$, -$SO_2NR^3R^3$, -CO_2R^3, -$C(O)NR^3R^3$, -$N(R^3)SO_2R^3$, -$N(R^3)C(O)R^3$, -$N(R^3)CO_2R^3$, -$C(O)R^3$, and optionally substituted C_{1-6}alkyl;

each R^3 is independently -H or R^4;

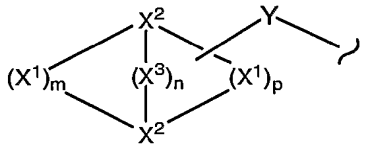
each R^4 is independently selected from optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl, optionally substituted heterocyclyl, and optionally substituted heterocyclyl C_{1-6}alkyl; or

R^3 and R^4, when taken together with a common nitrogen to which they are attached, form an optionally substituted five- to seven-membered heterocyclyl, said optionally substituted five- to seven-membered heterocyclyl optionally containing at least one additional annular heteroatom selected from N, O, S, and P;

R^5 is -H or optionally substituted C_{1-6}alkyl;

each D is independently selected from -O-, -$S(O)_{0-2}$-, and -NR^5-;

each R^{50} is independently either R^3, or according to formula **XII**;



XII

wherein X^1, X^2, and optionally X^3, represent the atoms of a saturated bridged ring system, said saturated bridged ring system comprising up to four annular heteroatoms represented by any of X^1, X^2, and X^3; wherein,

each X^1 is independently selected from -$C(R^6)R^7$-, -O-, -$S(O)_{0-2}$-, and -NR^8-;

each X^2 is independently an optionally substituted bridgehead methine or a bridgehead nitrogen;

each X^3 is independently selected from -$C(R^6)R^7$-, -O-, -$S(O)_{0-2}$-, and -NR^8-;

Y is either:

an optionally substituted lower alkylene linker, between D and either 1) any annular atom of the saturated bridged ring system, except X^2 when X^2 is a bridgehead nitrogen, or 2) any heteroatom, represented by any of R^6 or R^7; provided there are at least two carbon atoms between D and any annular heteroatom of the saturated bridged ring system or any heteroatom represented by any of R^6 or R^7;

or Y is absent, when Y is absent, said saturated bridged ring system, is directly attached to D via an annular carbon of said saturated bridged ring system, unless D is $-SO_2-$, in which case said saturated bridged ring system, is directly attached to D via an any annular atom of said saturated bridged ring system;

m and p are each independently one to four;

n is zero to two, when n equals zero, then there is a single bond between the two bridgehead X^2's;

R^6 and R^7 are each independently selected from -H, halogen, trihalomethyl, -CN, $-NH_2$, $-NO_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^4$, $-SO_2NR^3R^4$, $-CO_2R^3$, $-C(O)NR^3R^4$, $-N(R^3)SO_2R^4$, $-N(R^3)C(O)R^3$, $-NCO_2R^3$, $-C(O)R^3$, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl, optionally substituted heterocyclyl, optionally substituted heterocyclyl C_{1-6}alkyl, and a bond to either Y or D; or

R^6 and R^7, when taken together are oxo; or

R^6 and R^7, when taken together with a common carbon to which they are attached, form a optionally substituted three- to seven-membered spirocyclyl, said optionally substituted three- to seven-membered spirocyclyl optionally containing at least one additional annular heteroatom selected from N, O, S, and P;

R^8 is selected from $-R^3$, Y, $-SO_2NR^3R^4$, $-CO_2R^4$, $-C(O)NR^3R^3$, $-SO_2R^4$, and $-C(O)R^3$; and

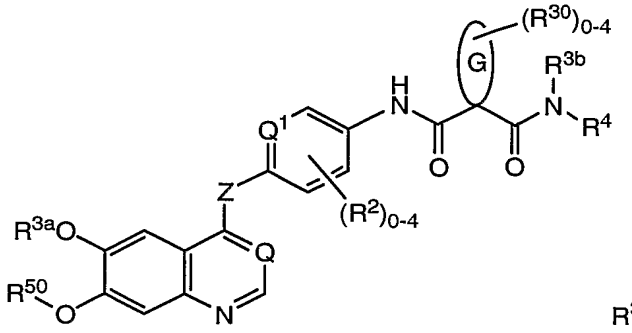
each R^{30} is independently selected from halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted C_{1-6}alkyl.

55. The compound according to claim 54, wherein Z is either -O- or $-NR^5-$.

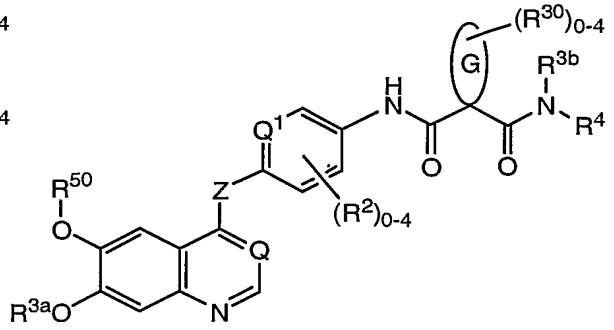
56. The compound according to claim 55, wherein at least one of R^1 is $-D-R^{50}$.

57. The compound according to claim 56, wherein D is -O- and at least one other R^1 is $-OR^3$.

58. The compound according to claim 57, of formula **XIIIa** or **XIIIb**:



XIIIa



XIIIb

wherein Q^1 is either =N- or =C(H)-.

59. The compound according to claim 58, wherein R^{50} is selected from C_{1-6}alkyl optionally substituted with at least one of optionally substituted amino, optionally substituted C_{1-6}alkyl amino, optionally substituted C_{1-6}dialkyl amino, optionally substituted heteroalicylic, and a group of formula **XII**.

60. The compound according to claim 59, wherein R^{3a} is C_{1-6}alkyl.

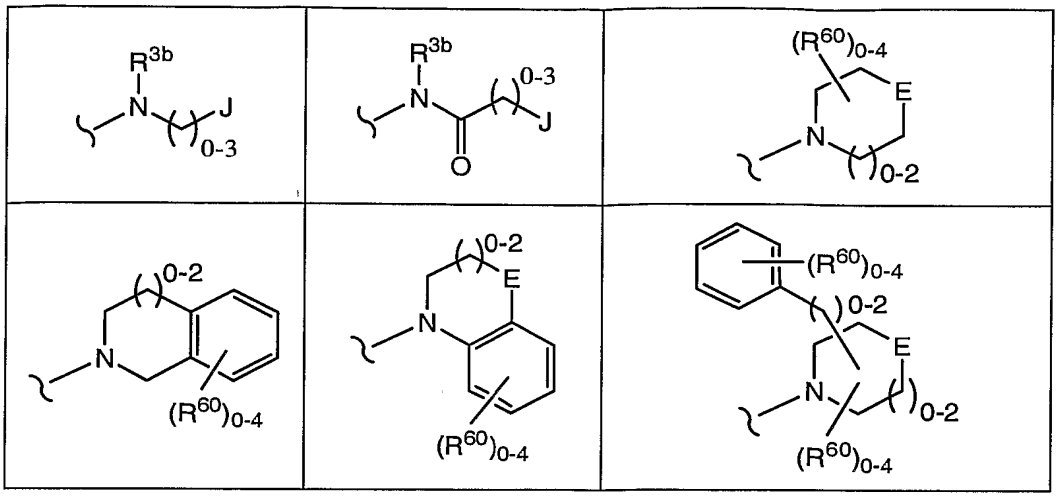
61. The compound according to claim 60, wherein Z is -O-.

62. The compound according to claim 61, wherein G is selected from cyclopropyl, aziradine, cyclobutyl, and azetidine, each optionally substituted with between zero and four of R^{30}.

63. The compound according to claim 62, wherein Q is either =N- or =C(H)-.

64. The compound according to claim 63, wherein R^2 is selected from -H, halogen, C_{1-6} alkyl and perfluoro C_{1-6} alkyl.

65. The compound according to claim 64, wherein $-N(R^{3b})R^4$ is selected from the following:



wherein J, is a five- to ten-membered ring, optionally substituted with between zero and five of R^{20};

each R^{20} is independently selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl, optionally substituted heterocyclyl, and optionally substituted heterocyclyl C_{1-6}alkyl;

two of R^{20}, together with the atom or atoms to which they are attached, combine to form an optionally substituted three- to seven-membered heteroalicyclic, said optionally substituted three- to seven-membered heteroalicyclic either spiro- to J or fused to J;

E is selected from -O-, $-N(R^5)$-, $-CH_2$-, and $-S(O)_{0-2}$-;

each R^{60} is independently selected from halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted heteroaryl C_{1-6}alkyl, and optionally substituted aryl C_{1-6}alkyl;

each methylene in any of the above formulae, other than those in a depicted ring, is independently optionally substituted with R^{25}; and

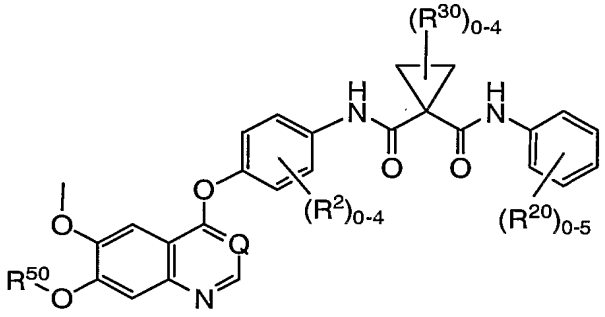
R^{25} is selected from halogen, trihalomethyl, oxo, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl, heteroaryl C_{1-6}alkyl, and optionally substituted C_{1-6}alkyl; or

two of R^{25}, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered alicyclic or heteroalicyclic;

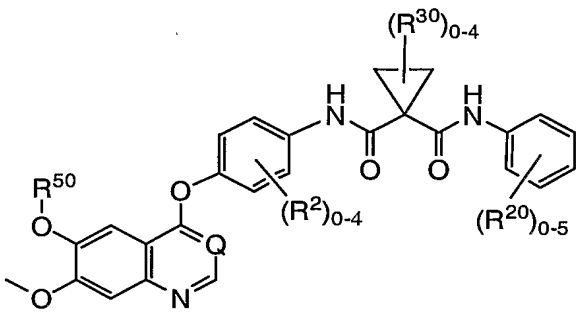
R^{3b} is equivalent to R^3 as defined above; and

R^4 and R^5 are as defined above.

66. The compound according to claim 65, of formula **XIVa** or **XIVb**:



XIVa



XIVb

67. The compound according to claim 66, wherein R^{50} is $C_{1\text{-}6}$alkyl optionally substituted with a group selected from optionally substituted amino, an optionally substituted alkylamino, optionally substituted dialkylamino, and optionally substituted heteroalicylic.

68. The compound according to claim 67, wherein the heteroalicyclic portion of said optionally substituted heteroalicyclic of R^{50} is selected from the group consisting of piperidine, piperazine, morpholine, thiomorpholine, thiomorpholine 1-oxide, thiomorpholine 1,1-dioxide, 2-oxo-morpholine, pyrrolidine, and azepine.

69. The compound according to claim 67, wherein R^{50} is according to formula **XII**.

70. The compound according to claim 69, wherein the saturated bridged ring system according to formula **XII** has a geometry selected from the group consisting of [4.4.0], [4.3.0], [4.2.0], [4.1.0], [3.3.0], [3.2.0], [3.1.0], [3.3.3], [3.3.2], [3.3.1], [3.2.2], [3.2.1], [2.2.2], and [2.2.1].

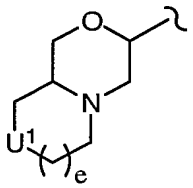
71. The compound according to claim 70, wherein Y is selected from $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2-$, $-CH_2-$, and absent.

72. The compound according to claim 71, wherein n is 0 and the saturated bridged ring system according to formula **XII** has a geometry selected from the group consisting of [4.4.0], [4.3.0], [4.2.0], [4.1.0], [3.3.0], [3.2.0], and [3.1.0].

73. The compound according to claim 72, wherein said saturated bridged ring system contains at least one annular nitrogen or at least one annular oxygen.

74. The compound according to claim 73, wherein said saturated bridged ring system contains $-NR^8-$, wherein R^8 is selected from -H, optionally substituted C_{1-6}alkyl, $-CO_2R^3$, $-C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$.

75. The compound according to claim 73, wherein said saturated bridged ring system is of formula **XV**,



XV

wherein U^1 is selected from $-O-$, $-S(O)_{0-2}-$, $-NR^8-$, $-CR^6R^7-$, and absent; and e is 0 or 1.

76. The compound according to claim 75, wherein Y is $-CH_2-$.

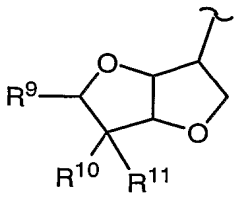
77. The compound according to claim 76, wherein U^1 is $-NR^8-$, wherein R^8 is selected from -H, optionally substituted lower alkyl, $-CO_2R^3$, $-C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$.

78. The compound according to claim 76, wherein U^1 is -O-.

79. The compound according to claim 76, wherein U^1 is absent.

80. The compound according to claim 71, wherein Y is selected from $-CH_2CH_2-$, $-CH_2-$, and absent.

81. The compound according to claim 80, wherein said saturated bridged ring system is of formula **XVI**,



XVI

wherein R^9, R^{10}, and R^{11} are each independently selected from -H, and -OR^{12}; or

R^9 is selected from -H, and -OR^{12}, and R^{10} and R^{11}, when taken together, are either an optionally substituted alkylidene or an oxo;

R^{12} is selected from -H, -$C(O)R^3$, optionally substituted lower alkylidyne, optionally substituted lower arylalkylidyne, optionally substituted lower heterocyclylalkylidyne, optionally substituted lower alkylidene, optionally substituted lower alkylidenearyl, optionally substituted lower alkylideneheterocyclyl, optionally substituted lower alkyl, optionally substituted lower alkylaryl, optionally substituted aryl, optionally substituted lower heterocyclylalkyl, and optionally substituted heterocyclyl;

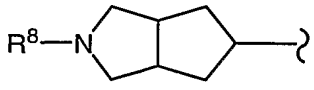
or two R^{12}'s, when taken together, form 1) a corresponding spirocyclic ketal when said two R^{12}'s stem from R^{10} and R^{11}, or 2) a corresponding cyclic ketal when said two R^{12}'s stem from R^9 and one of R^{10} and R^{11}.

82. The compound according to claim 81, wherein one of R^{10} and R^{11} is -OR^{12}, wherein R^{12} is selected from -H, -$C(O)R^3$, and optionally substituted lower alkyl; and R^9 and the other of R^{10} and R^{11} are both -H.

83. The compound according to claim 82, wherein Y is either -CH_2- or absent.

84. The compound according to claim 81, wherein R^9 is an alkyl group containing at least one fluorine substitution thereon.

85. The compound according to claim 74, wherein said saturated bridged ring system is of formula **XVII**.



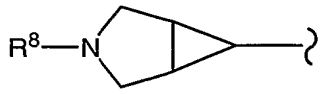
XVII

86. The compound according to claim 85, wherein Y is either -CH_2- or absent.

87. The compound according to claim 86, wherein R^8 is methyl or ethyl.

88. The compound according to claim 87, wherein at least one of R^2 is halogen.

89. The compound according to claim 74, wherein said saturated bridged ring system is of formula **XVIII**.

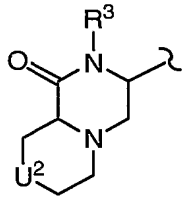


XVIII

90. The compound according to claim 89, wherein Y is $-CH_2-$.

91. The compound according to claim 90, wherein R^8 is methyl or ethyl.

92. The compound according to claim 73, wherein said saturated bridged ring system is of formula **XIX**



XIX

wherein U^2 is selected from -O-, $-S(O)_{0-2}-$, $-NR^8-$, $-CR^6R^7-$, and absent.

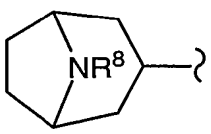
93. The compound according to claim 92, wherein R^3 of formula **XIX** is selected from -H and optionally substituted alkyl.

94. The compound according to claim 93, wherein U^2 is either $-CR^6R^7-$ or absent.

95. The compound according to claim 94, wherein U^2 is either $-CH_2-$ or absent.

96. The compound according to claim 95, wherein Y is $-CH_2-$.

97. The compound according to claim 74, wherein said saturated bridged ring system is according to formula **XX**.



98. The compound according to claim 97, wherein R^8 is methyl or ethyl.

99. The compound according to any of claims 67 through 98, wherein R^2 is selected from C_{1-6} alkyl, perfluoro C_{1-6} alkyl, and halogen.

100. The compound according to claim 99, wherein R^2 is selected from perfluoro C_{1-3} alkyl and halogen.

101. The compound according to any of claims 67 through 98, wherein R^{20} is selected from halogen, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, optionally substituted heterocyclyl, and optionally substituted heterocyclyl C_{1-6}alkyl, and (two of R^{20}) together with the atom or atoms to which they are attached, an optionally substituted three- to six-membered heteroalicyclic, said optionally substituted three- to six-membered heteroalicyclic fused to the phenyl as in **XIVa** or **XIVb**.

102. The compound according to claim 101, wherein R^{20} is selected from halogen, $-NR^3R^4$, optionally substituted heterocyclyl, and optionally substituted heterocyclyl C_{1-6}alkyl, and (two of R^{20}) together with the atom or atoms to which they are attached, an optionally substituted five- to six-membered heteroalicyclic, said optionally substituted five- to six-membered heteroalicyclic fused to the phenyl as in **XIVa** or **XIVb**.

103. The compound according to claim 102, wherein R^2 is selected from C_{1-6} alkyl, perfluoro C_{1-6} alkyl, and halogen.

104. The compound according to claim 103, wherein R^2 is selected from perfluoro C_{1-3} alkyl and halogen.

105. The compound according to claim 54, selected from Table 2.

Table 2

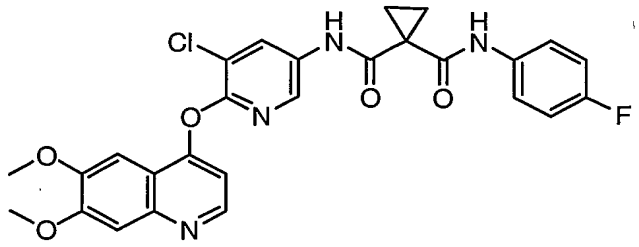
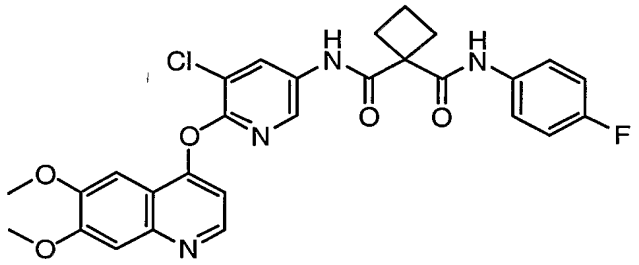
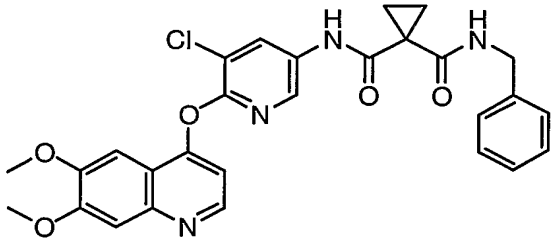
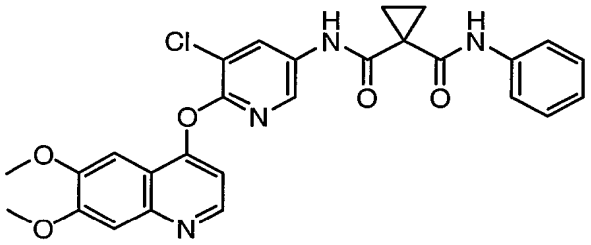
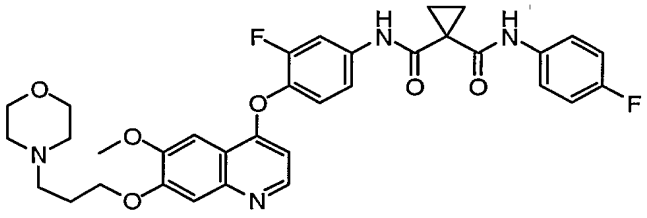
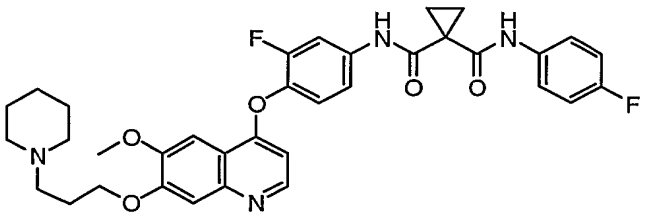
Entry	Name	Structure
1	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
2	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
3	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(phenylmethyl)cyclopropane-1,1-dicarboxamide	
4	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-phenylcyclopropane-1,1-dicarboxamide	
5	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
6	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperidin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 2

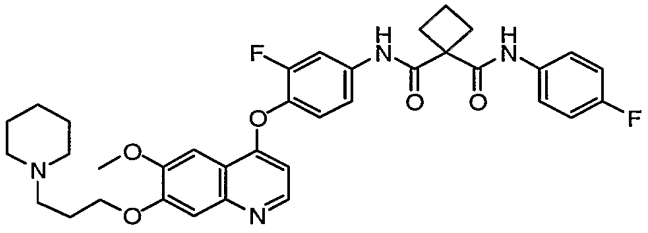
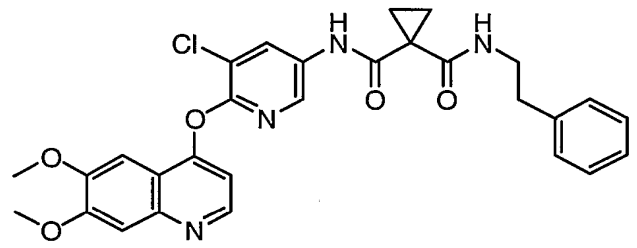
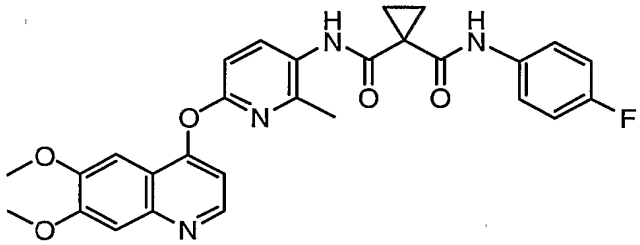
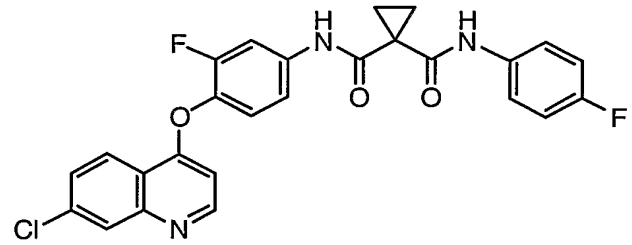
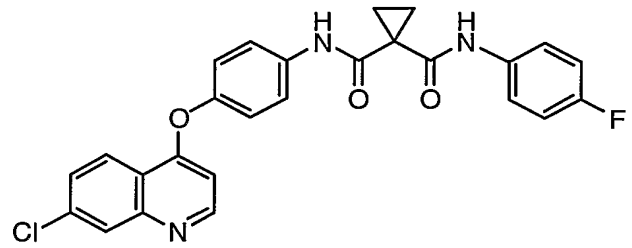
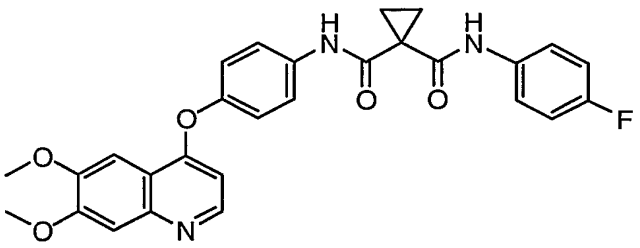
Entry	Name	Structure
7	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperidin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
8	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-phenylethyl)cyclopropane-1,1-dicarboxamide	
9	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-methylpyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
10	N-{4-[(7-chloroquinolin-4-yl)oxy]-3-fluorophenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
11	N-{4-[(7-chloroquinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
12	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 2

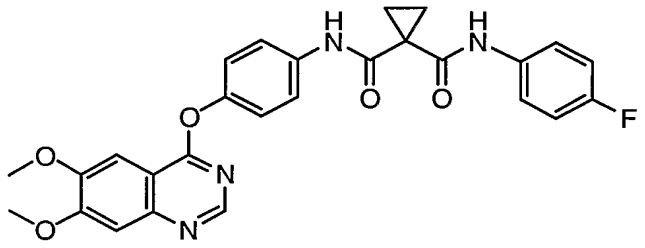
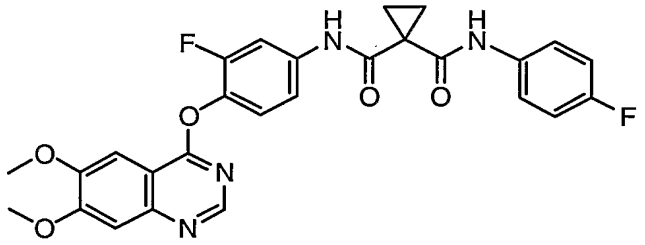
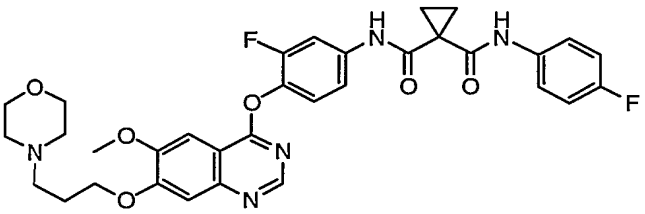
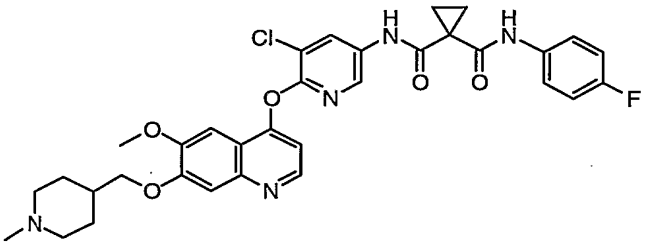
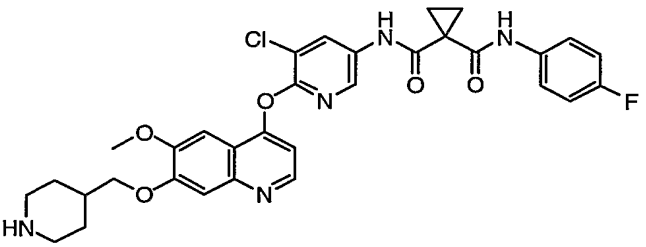
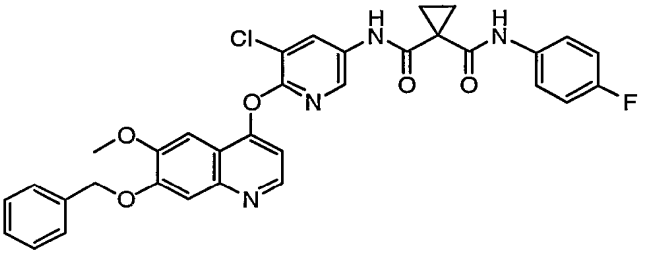
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14	N-(4-{[6,7-bis(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
15	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
16	N-{5-chloro-6-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]pyridin-3-yl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
17	N-[5-chloro-6-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
18	N-[5-chloro-6-({6-(methyloxy)-7-[(phenylmethyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 2

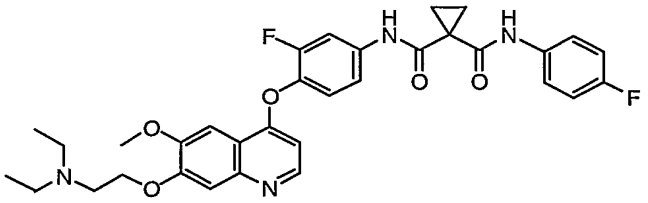
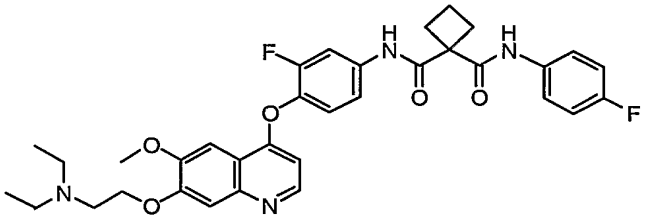
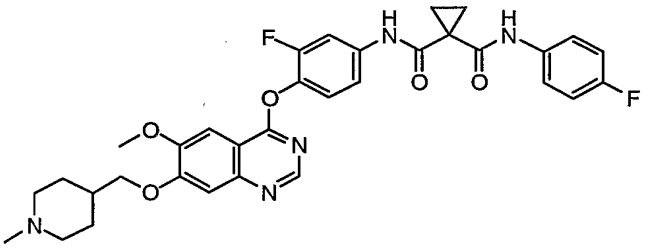
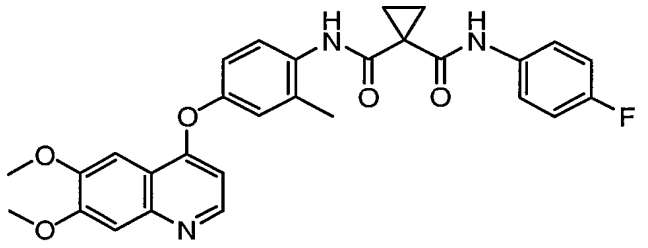
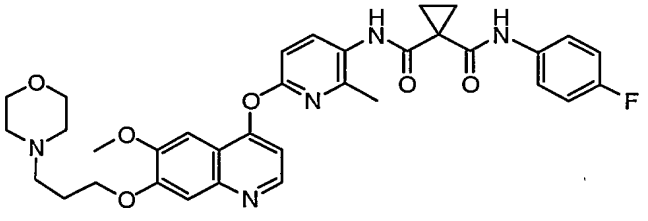
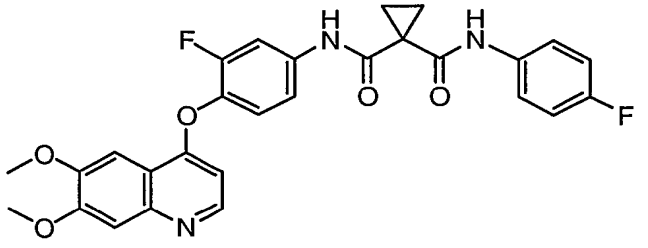
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20	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
21	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
22	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
23	N-(4-fluorophenyl)-N'-[2-methyl-6-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]cyclopropane-1,1-dicarboxamide	
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Table 2

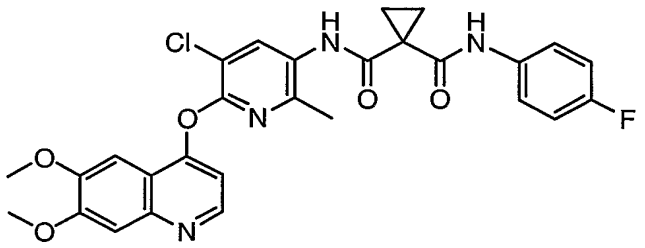
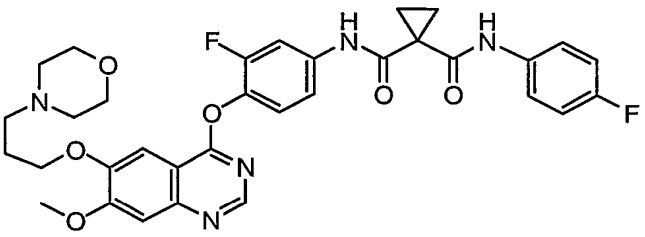
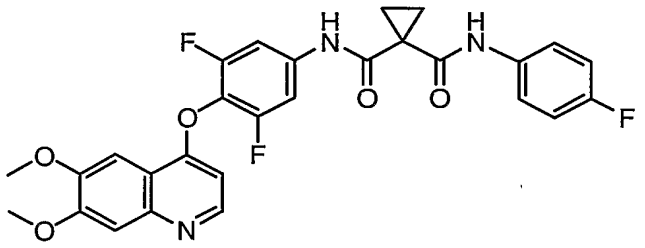
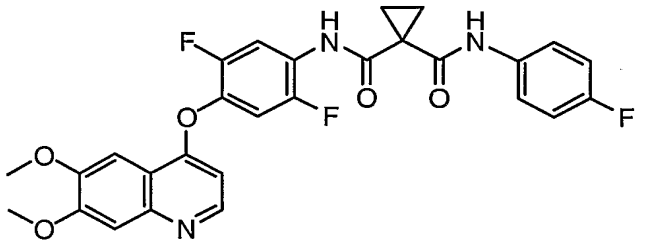
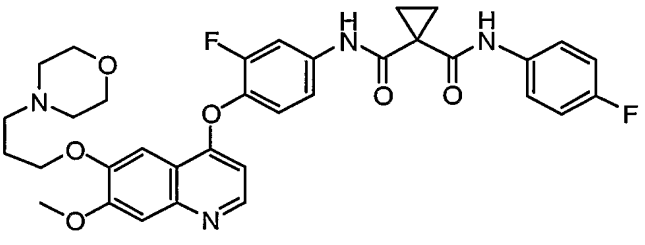
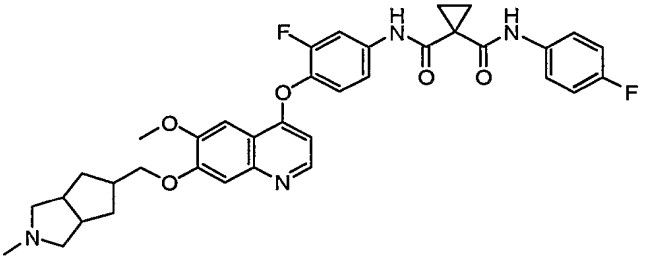
Entry	Name	Structure
25	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloro-2-methylpyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
26	N-[3-fluoro-4-({7-(methyloxy)-6-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
27	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3,5-difluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
28	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2,5-difluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
29	N-[3-fluoro-4-({7-(methyloxy)-6-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
30	N-{3-fluoro-4-[(6-(methyloxy)-7-(2-methyl octahydrocyclo-penta[c]pyrrol-5-ylmethoxy)quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 2

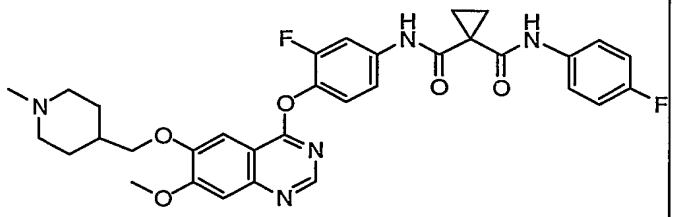
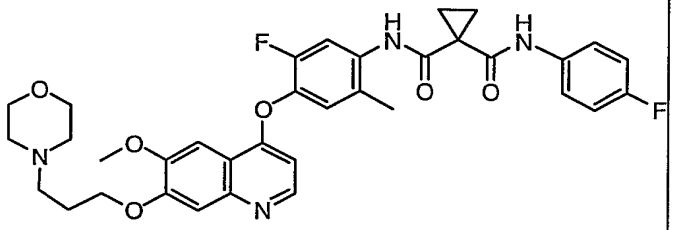
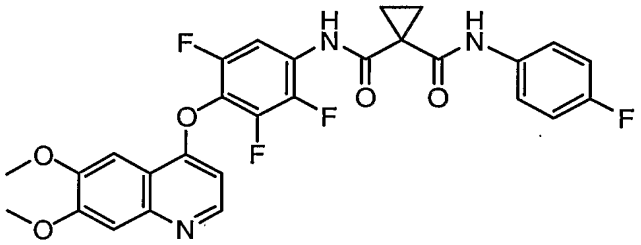
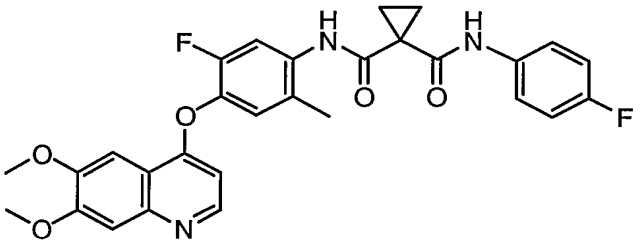
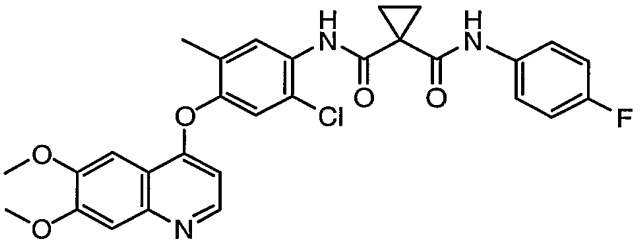
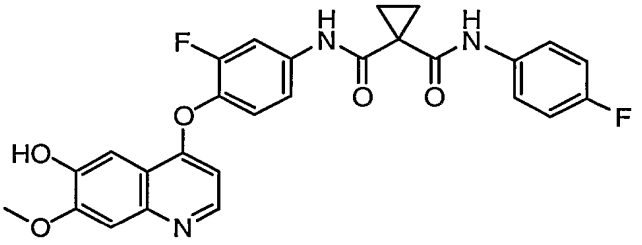
Entry	Name	Structure
31	N-{3-fluoro-4-[(7-(methyloxy)-6-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
32	N-[5-fluoro-2-methyl-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
33	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2,3,5-trifluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
34	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-2-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
35	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-chloro-5-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
36	N-(3-fluoro-4-{[6-hydroxy-7-(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 2

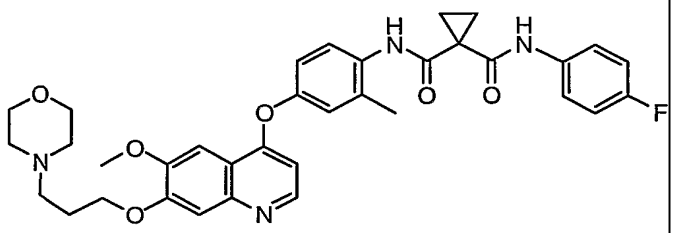
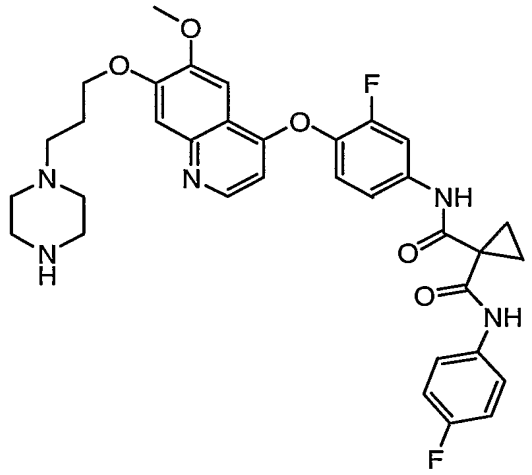
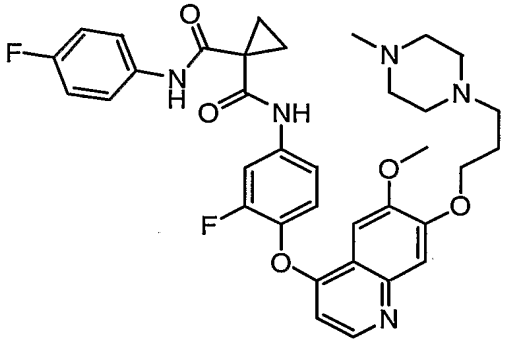
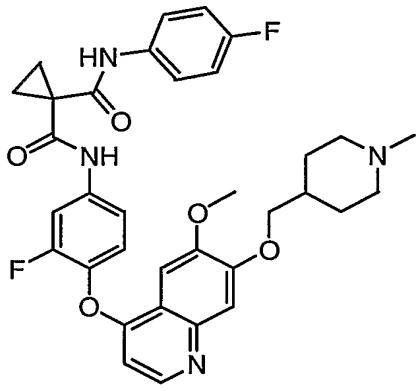
Entry	Name	Structure
37	N-(4-fluorophenyl)-N'-[2-methyl-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]cyclopropane-1,1-dicarboxamide	
38	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
39	N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
40	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 2

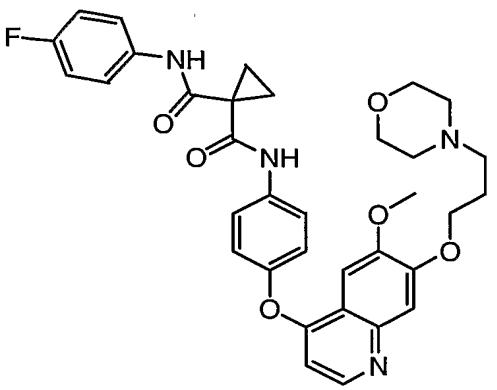
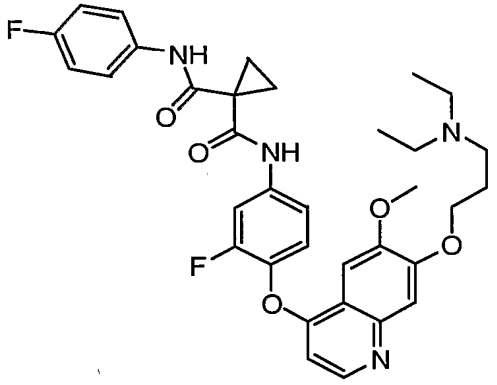
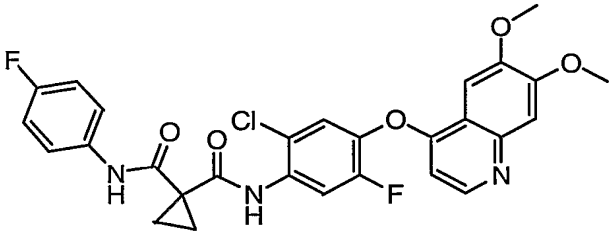
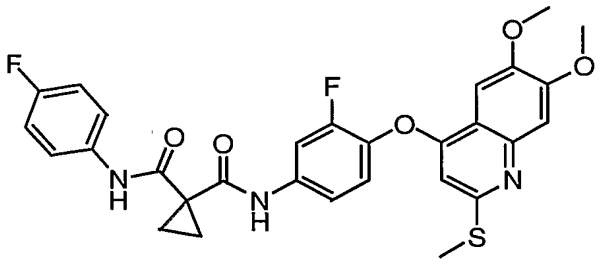
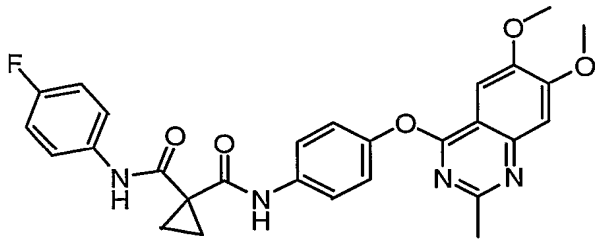
Entry	Name	Structure
41	N-(4-fluorophenyl)-N'-[4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]cyclopropane-1,1-dicarboxamide	
42	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
43	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-chloro-5-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
44	N-(4-{[6,7-bis(methyloxy)-2-(methylthio)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
45	N-(4-fluorophenyl)-N'-(4-{[2-methyl-6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide	

Table 2

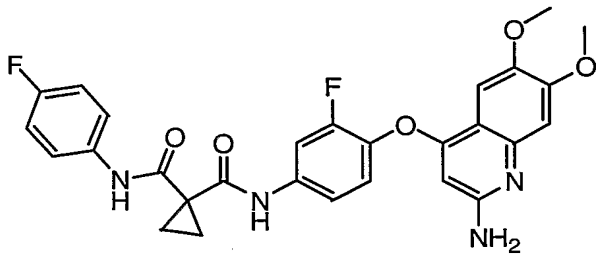
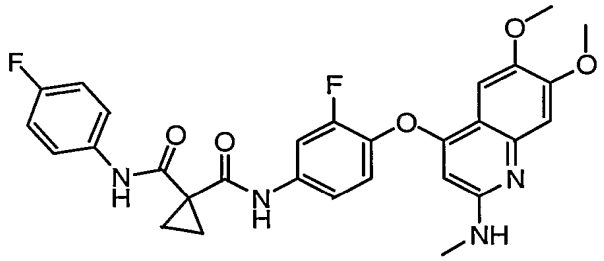
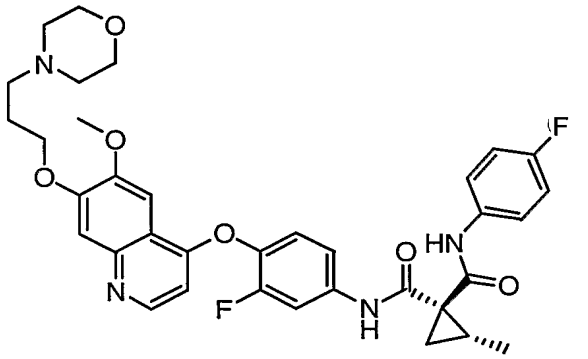
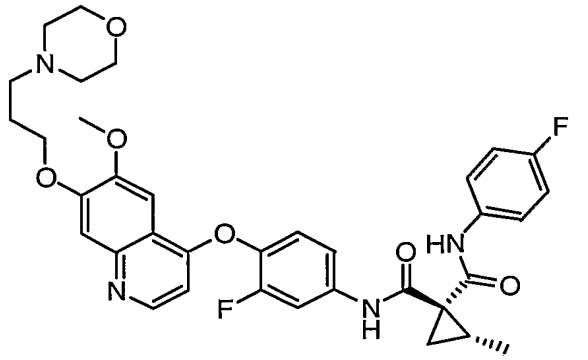
Entry	Name	Structure
46	N-(4-{[2-amino-6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
47	N-(3-fluoro-4-{[2-(methylamino)-6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
48	(1S,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
49	(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	

Table 2

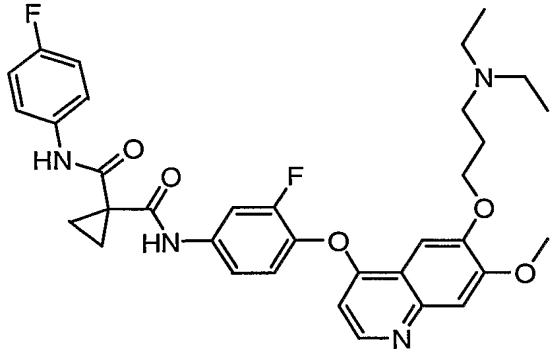
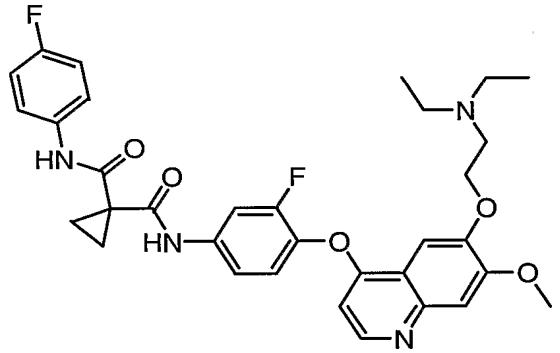
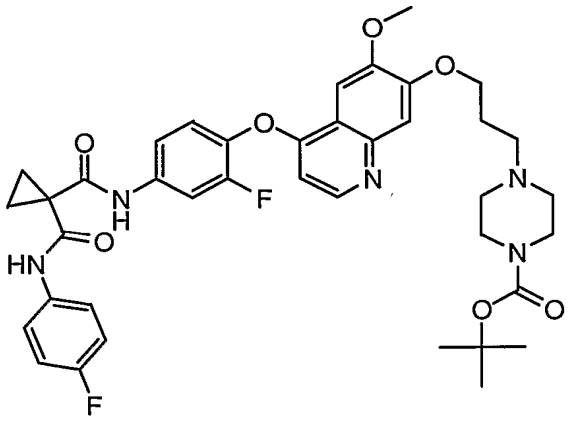
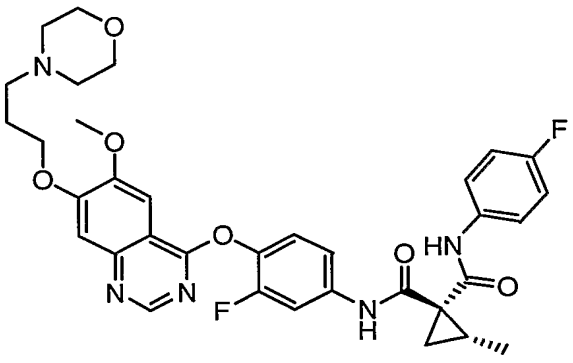
Entry	Name	Structure
50	N-(4-{[6-{[3-(diethylamino)propyl]oxy}-7-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
51	N-(4-{[6-{[2-(diethylamino)ethyl]oxy}-7-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
52	1,1-dimethylethyl 4-(3-{[4-[(2-fluoro-4-{[(1-{[(4-fluorophenyl)amino]carbonyl}cyclopropyl)carbonyl]amino}phenyl)oxy]-6-(methyloxy)quinolin-7-yl]oxy}propyl)piperazine-1-carboxylate	
53	(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	

Table 2

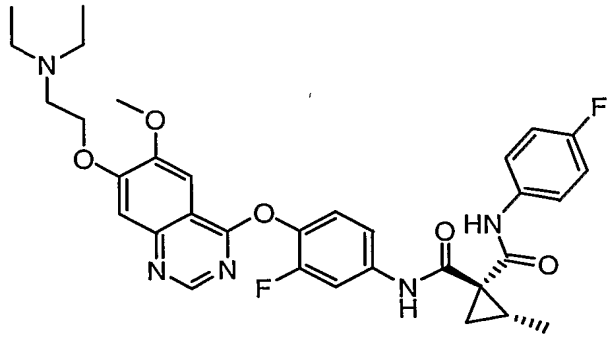
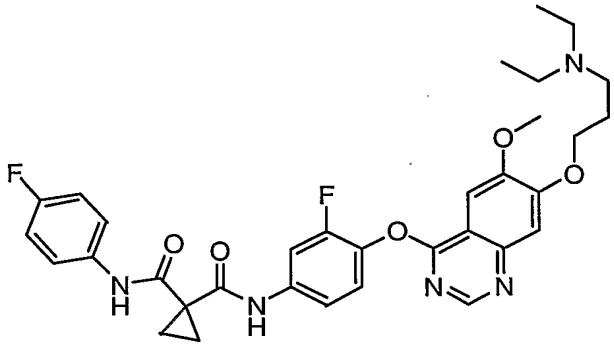
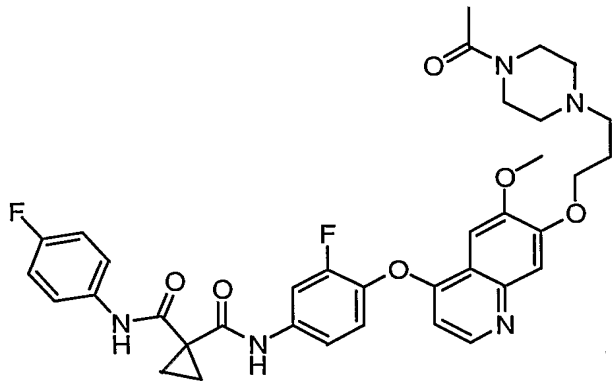
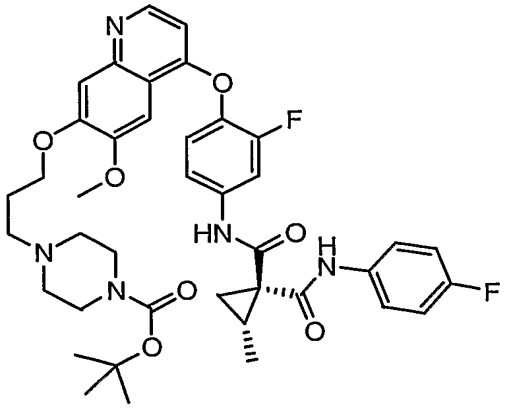
Entry	Name	Structure
54	(1R,2R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
55	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
56	N-(4-{[7-{[3-(4-acetylpiperazin-1-yl)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
57	1,1-dimethylethyl 4-(3-{[4-[(2-fluoro-4-{[((1R,2R)-1-{[(4-fluorophenyl)amino]carbonyl}-2-methylcyclopropyl)carbonyl]amino}phenyl)oxy]-6-(methyloxy)quinolin-7-yl]oxy}propyl)piperazine-1-carboxylate	

Table 2

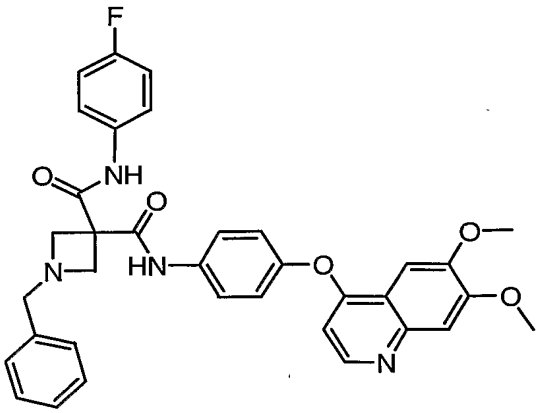
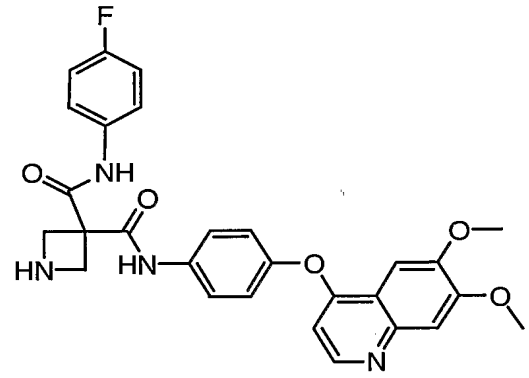
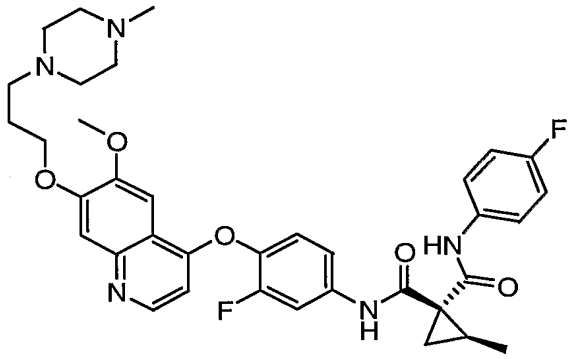
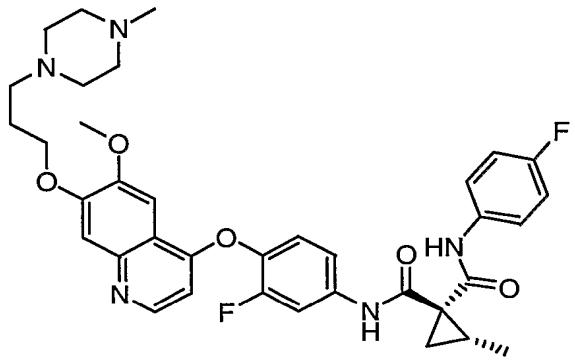
Entry	Name	Structure
58	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-1-(phenylmethyl)azetidine-3,3-dicarboxamide	
59	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)azetidine-3,3-dicarboxamide	
60	(1R,2S)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
61	(1R,2R)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	

Table 2

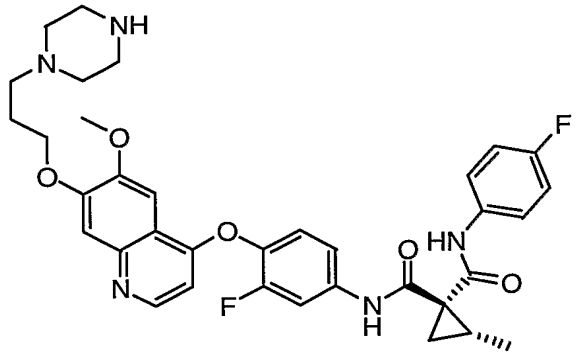
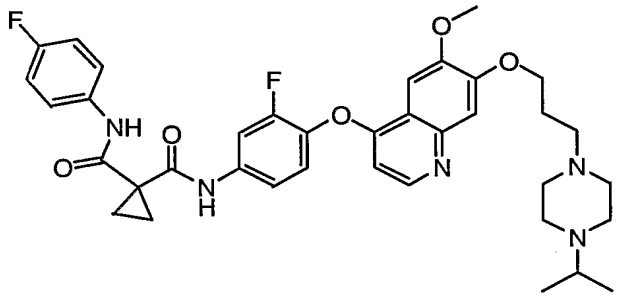
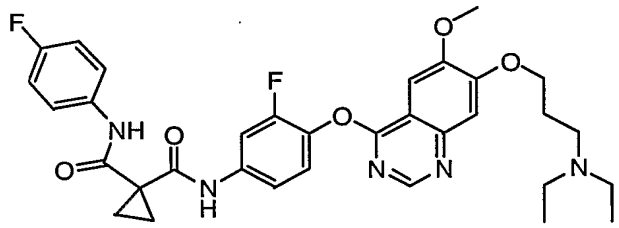
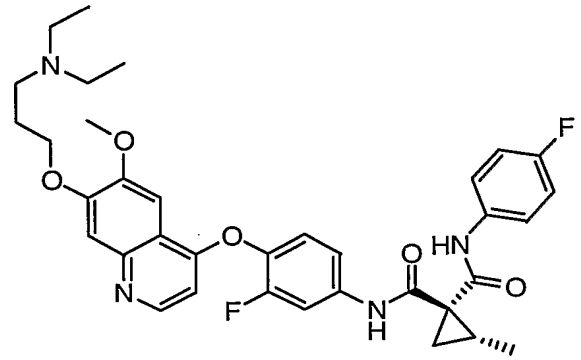
Entry	Name	Structure
62	(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
63	N-(3-fluoro-4-{[7-({3-[4-(1-methylethyl)piperazin-1-yl]propyl}oxy)-6-(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
64	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
65	(1R,2R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	

Table 2

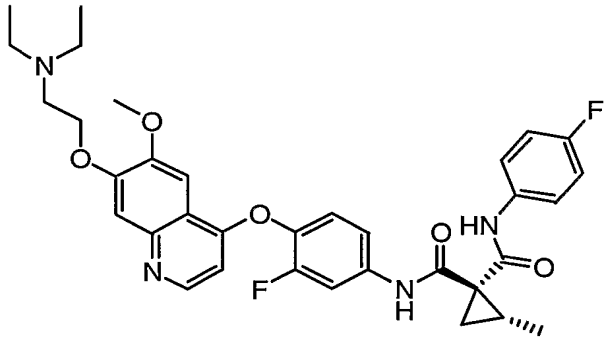
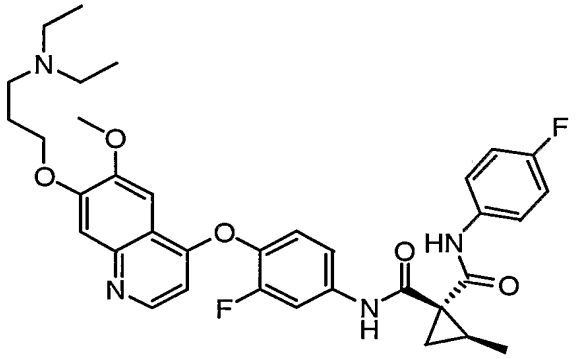
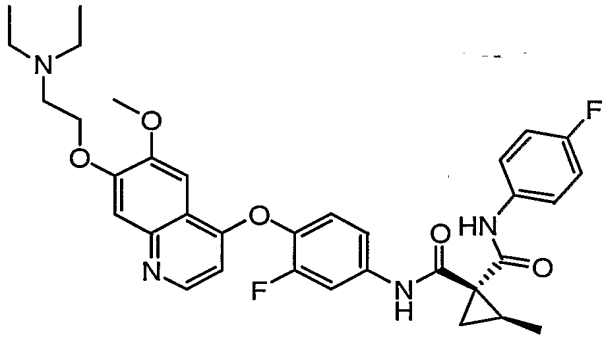
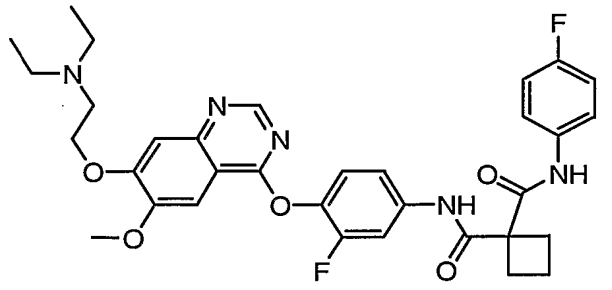
Entry	Name	Structure
66	(1R,2R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
67	(1R,2S)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
68	(1R,2S)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
69	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	

Table 2

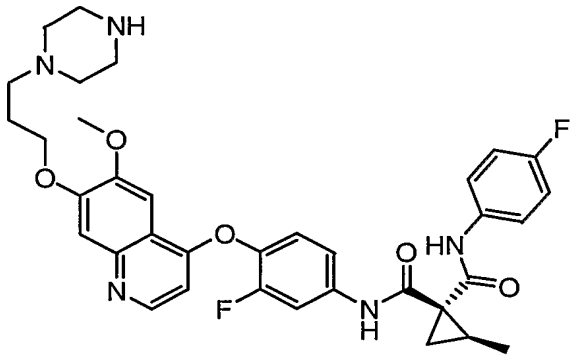
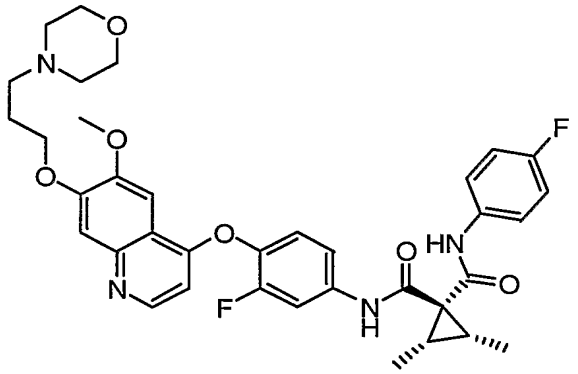
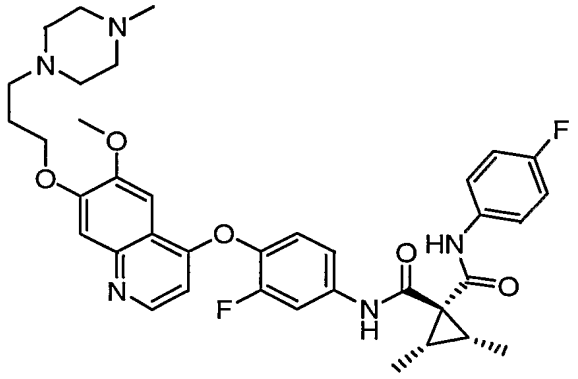
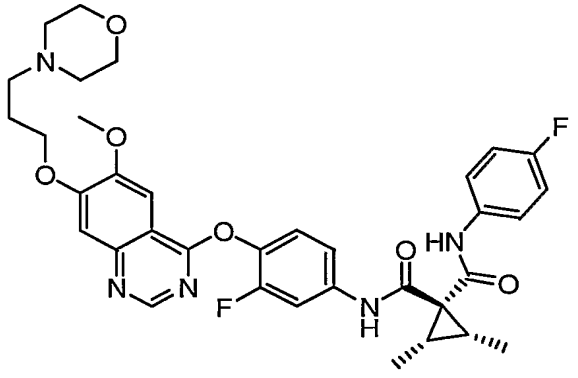
Entry	Name	Structure
70	(1R,2S)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
71	(1R,2R,3S)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	
72	(1R,2R,3S)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	
73	(1R,2R,3S)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	

Table 2

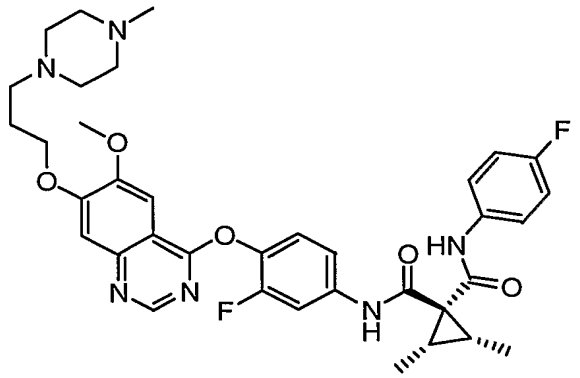
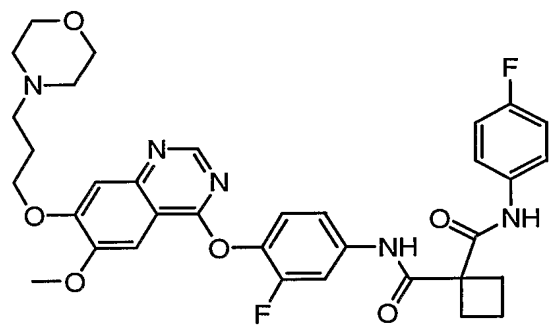
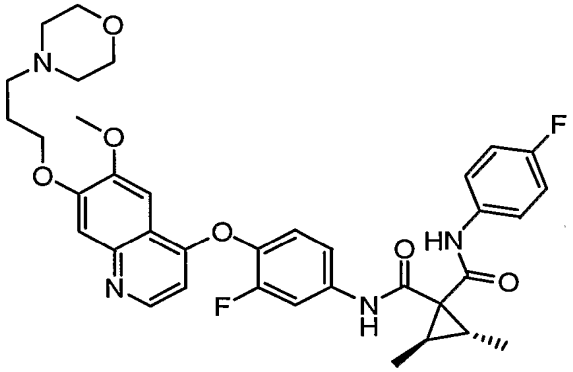
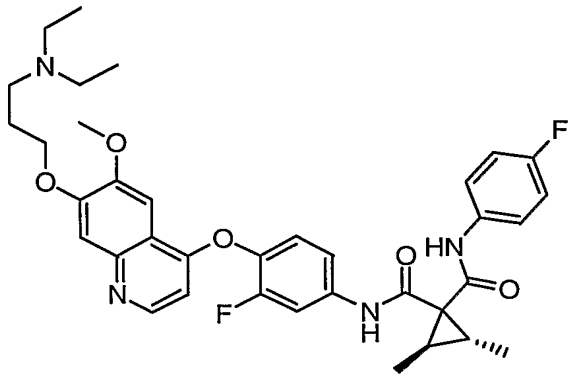
Entry	Name	Structure
74	(1R,2R,3S)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	
75	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
76	(2R,3R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	
77	(2R,3R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	

Table 2

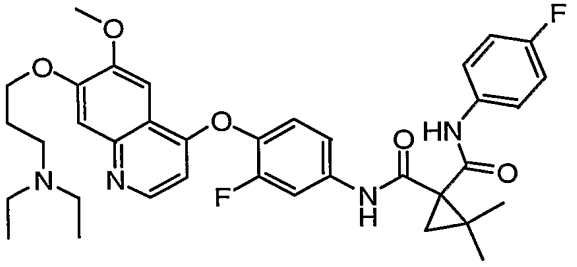
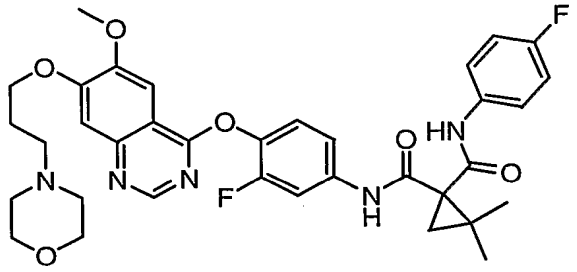
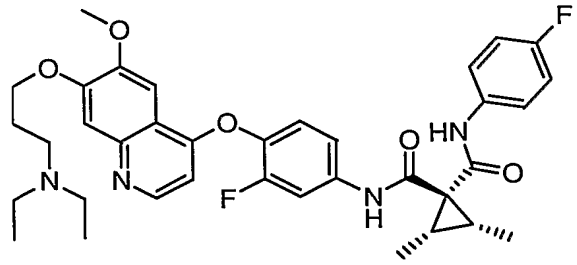
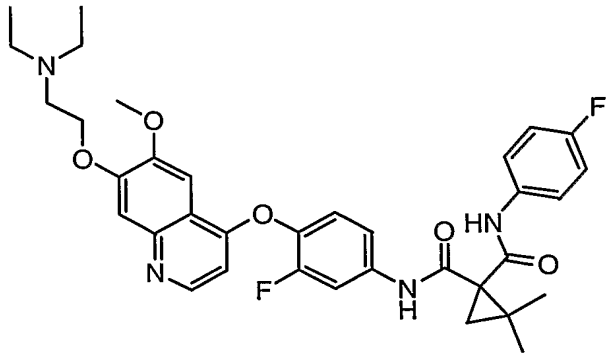
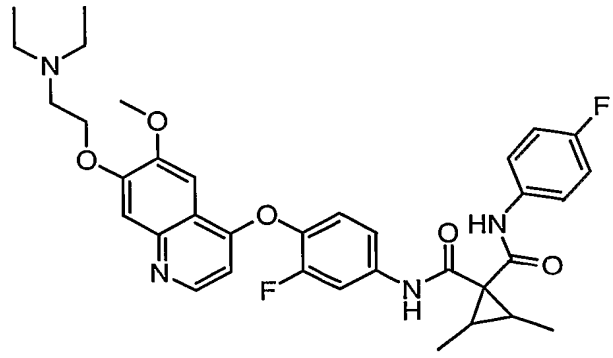
Entry	Name	Structure
78	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	
79	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	
80	(1R,2R,3S)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	
81	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	
82	(1R,2R,3S)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	

Table 2

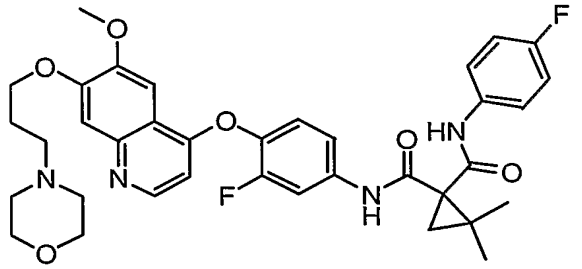
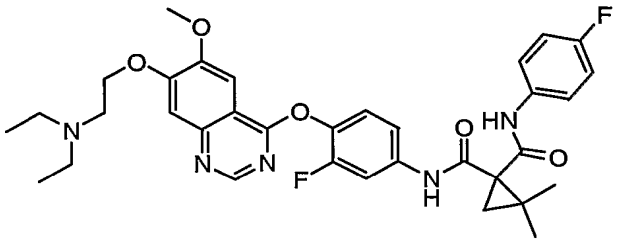
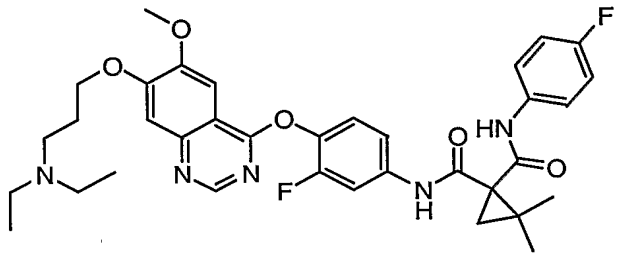
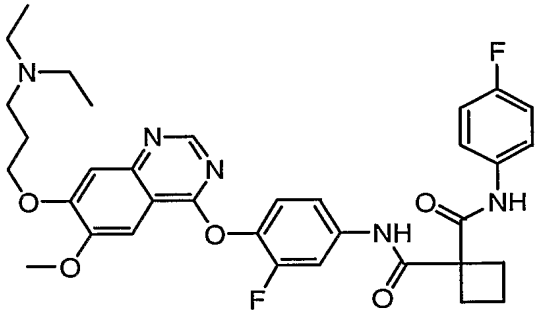
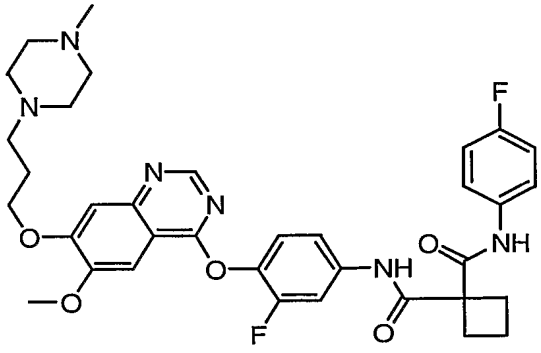
Entry	Name	Structure
83	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	
84	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	
85	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	
86	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
87	N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	

Table 2

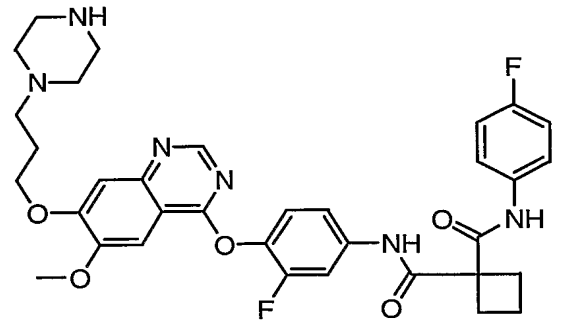
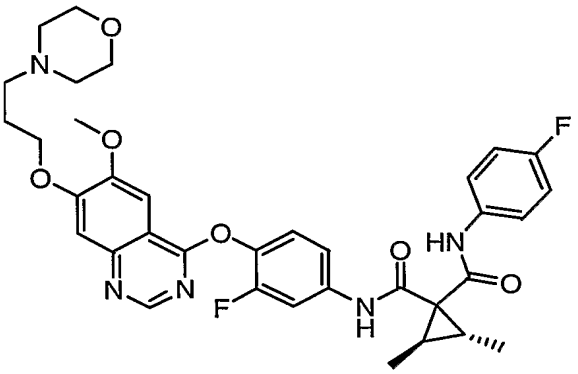
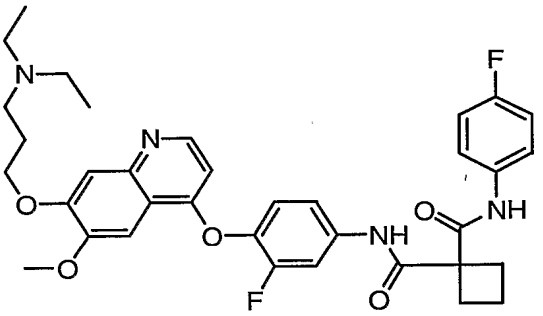
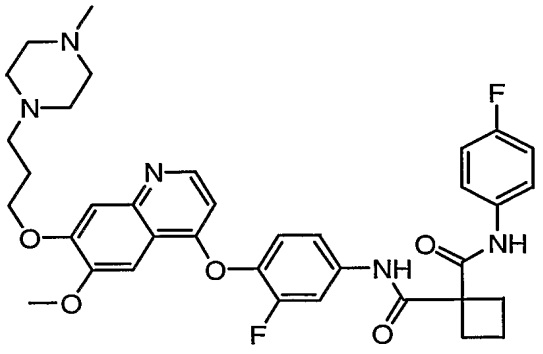
Entry	Name	Structure
88	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
89	(2R,3R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	
90	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
91	N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	

Table 2

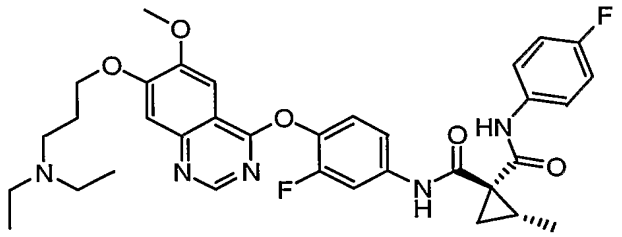
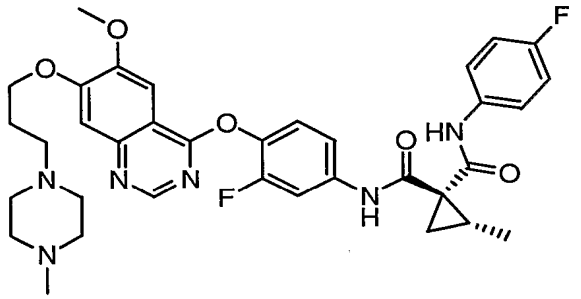
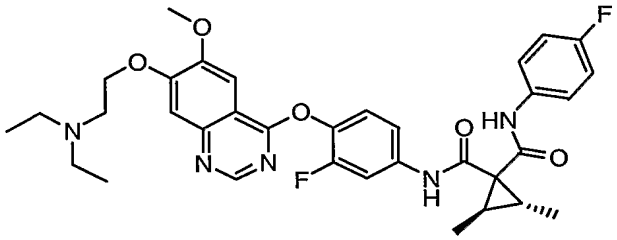
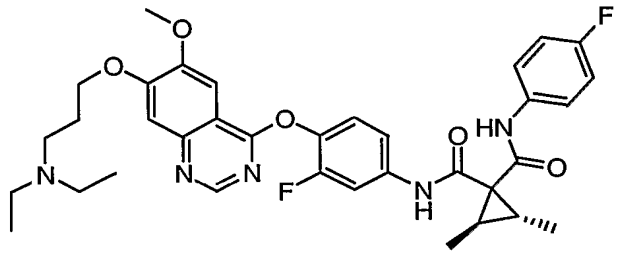
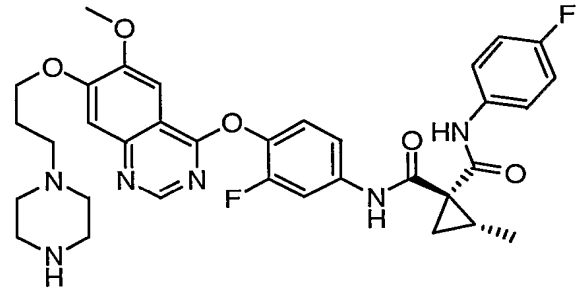
Entry	Name	Structure
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93	(1R,2R)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
94	(2R,3R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	
95	(2R,3R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	
96	(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	

Table 2

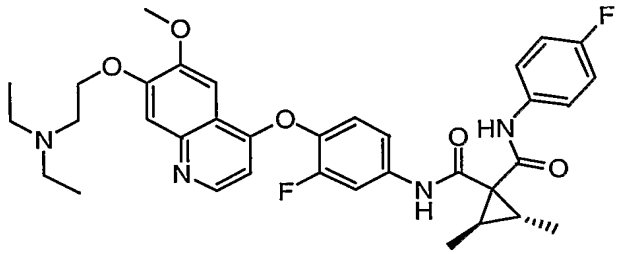
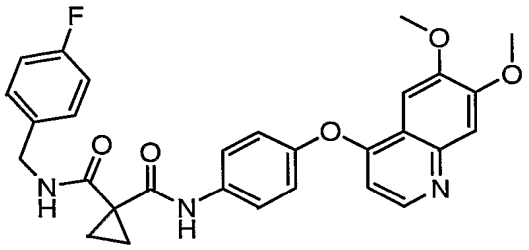
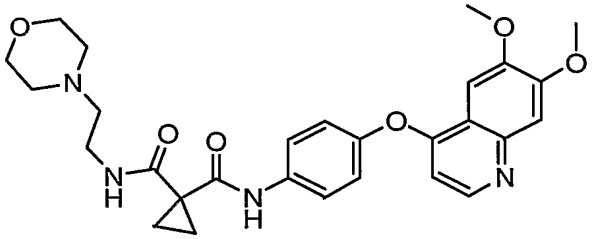
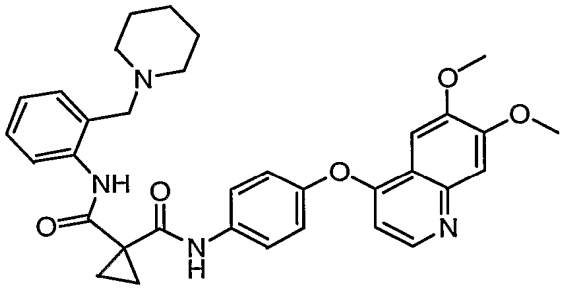
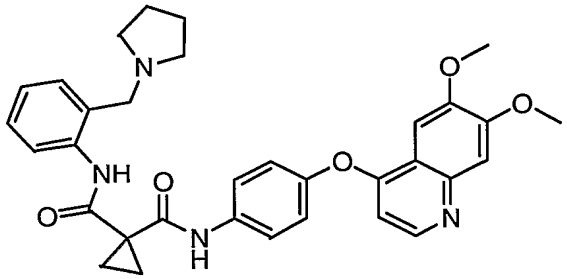
Entry	Name	Structure
97	(2R,3R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	
98	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[(4-fluorophenyl)methyl]cyclopropane-1,1-dicarboxamide	
99	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(2-morpholin-4-ylethyl)cyclopropane-1,1-dicarboxamide	
100	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	
101	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	

Table 2

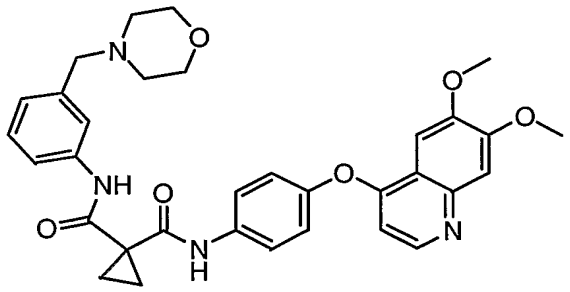
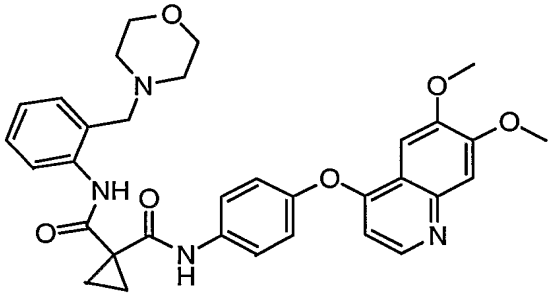
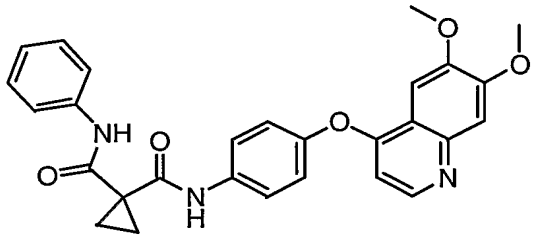
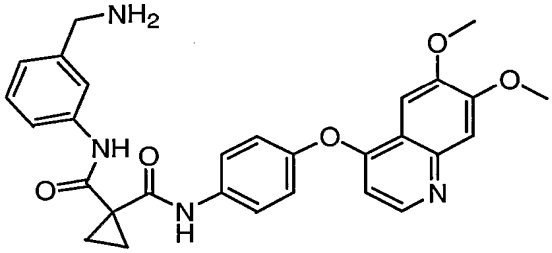
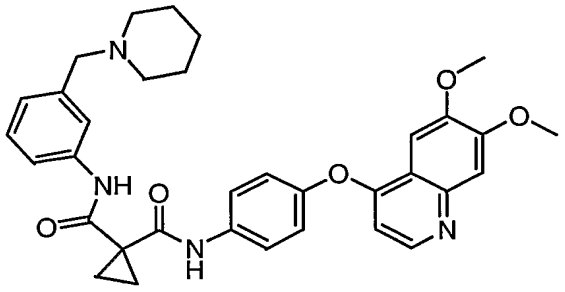
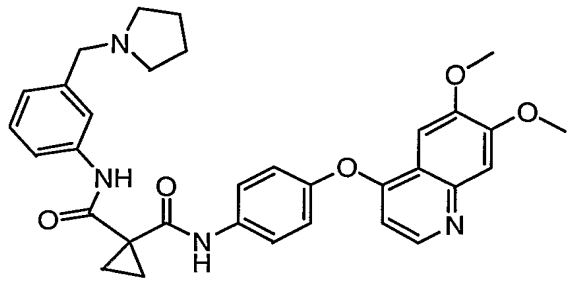
Entry	Name	Structure
102	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	
103	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	
104	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-phenylcyclopropane-1,1-dicarboxamide	
105	N-[3-(aminomethyl)phenyl]-N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide	
106	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	

Table 2

Entry	Name	Structure
107	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	

106. A pharmaceutical composition comprising a compound according to any one of claims 1 - 105 and a pharmaceutically acceptable carrier.

107. A metabolite of the compound or the pharmaceutical composition according to any one of claims 1 - 106.

108. A method of modulating the *in vivo* activity of a kinase, the method comprising administering to a subject an effective amount of the compound or the pharmaceutical composition according to any of claims 1 - 105.

109. The method according to claim 108, wherein modulating the *in vivo* activity of the kinase comprises inhibition of said kinase.

110. The method according to claim 108, wherein the kinase is at least one of c-Met, KDR, c-Kit, flt-3, and flt-4.

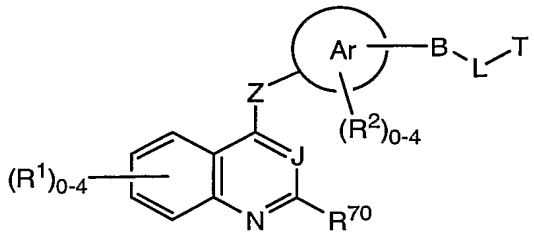
111. The method according to claim 110, wherein the kinase is c-Met.

112. A method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities, the method comprising administering, to a mammal in need thereof, a therapeutically effective amount of the compound or the pharmaceutical composition as described in any one of claims 1 - 106.

113. A method of screening for a modulator of a kinase, said kinase selected from c-Met, KDR, c-Kit, flt-3, and flt-4, the method comprising combining a compound according to any one of claims 1 - 105, and at least one candidate agent and determining the effect of the candidate agent on the activity of said kinase.

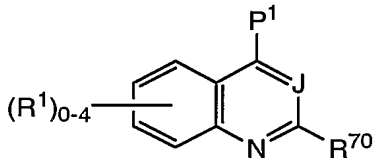
114. A method of inhibiting proliferative activity in a cell, the method comprising administering an effective amount of a composition comprising a compound according any one of claims 1 - 105 to a cell or a plurality of cells.

115. A process for preparing a compound of Formula **XXI**,

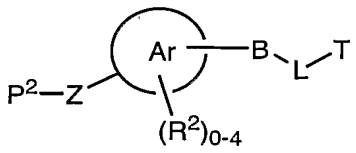


XXI

comprising reaction of a compound of Formula **XXII**, with a compound of Formula **XXIII**



XXII



XXIII

wherein,

each R^1 is independently selected from halogen, $-OR^3$, $-NO_2$, $-NH_2$, $-NR^3R^3$, $-D-R^{50}$ and optionally substituted C_{1-6}alkyl;

R^{70} is selected from -H, halogen, $-OR^3$, $-S(O)_{0-2}R^3$, $-NO_2$, $-NH_2$, $-NR^3R^3$, and optionally substituted C_{1-6}alkyl;

J is selected from =N-, =C(H)-, =C(halogen)-, and =C(CN)-;

Z is selected from $-S(O)_{0-2}$-, -O-, and $-NR^5$-;

each R^5 is independently selected from -H, optionally substituted C_{1-6}alkyl, optionally substituted aryl, and optionally substituted aryl C_{1-6}alkyl;

Ar is either a five- to ten-membered arylene or a five- to ten-membered heteroarylene containing between one and three heteroatoms;

R^2 is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted C_{1-6}alkyl;

each R^3 is independently selected from -H, $-Si(R^5)(R^5)R^5$, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted arylalkyl, and optionally substituted heteroarylalkyl;

two R^3, together with the nitrogen to which they are attached, form a four- to seven-membered heteroalicyclic, said four- to seven-membered heteroalicyclic optionally containing one additional heteroatom; when one said additional heteroatom is a nitrogen, then said nitrogen is optionally substituted with a group selected from -H, trihalomethyl, $-SO_2R^5$, $-SO_2NR^5R^5$, $-CO_2R^5$, $-C(O)NR^5R^5$, $-C(O)R^5$, and optionally substituted lower alkyl;

B is selected from absent, $-N(R^{13})-$, $-N(SO_2R^{13})-$, -O-, $-S(O)_{0-2}-$, and -C(=O)-;

L is selected from absent, $-C(=S)N(R^{13})-$, $-C(=NR^{14})N(R^{13})-$, $-SO_2N(R^{13})-$, $-SO_2-$, $-C(=O)N(R^{13})-$, $-N(R^{13})-$, $-C(=O)C_{1-2}alkylN(R^{13})-$, $-N(R^{13})C_{1-2}alkylC(=O)-$, $-C(=O)C_{0-1}alkylC(=O)N(R^{13})-$, -C(=O)-, $-C_{0-4}alkylene-$, $-C(=O)C_{0-1}alkylC(=O)OR^3-$, $-C(=NR^{14})C_{0-1}alkylC(=O)-$, $-C(=O)C_{0-1}alkylC(=O)-$, and an optionally substituted four- to six-membered heterocyclyl containing between one and three annular heteroatoms and comprising at least one nitrogen;

T is selected from -H, $-R^{13}$, $-C_{0-4}alkyl$, $-C_{0-4}alkylQ$, $-OC_{0-4}alkylQ$, $-C_{0-4}alkylOQ$, $-N(R^{13})C_{0-4}alkylQ$, $-SO_2C_{0-4}alkylQ$, $-C(=O)C_{0-4}alkylQ$, $-C_{0-4}alkylN(R^{13})Q$, and $-C(=O)N(R^{13})C_{0-4}alkylQ$, wherein each of the aforementioned $C_{0-4}alkyl$ is optionally substituted;

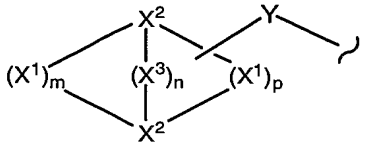
Q is a five- to ten-membered ring system, optionally substituted with between zero and four of R^{20};

each R^{20} is independently selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted $C_{1-6}alkyl$, optionally substituted aryl, optionally substituted aryl $C_{1-6}alkyl$, optionally substituted heterocyclyl, and optionally substituted heterocyclyl $C_{1-6}alkyl$;

two of R^{20}, together with the atom or atoms to which they are attached, combine to form an optionally substituted three- to seven-membered heteroalicyclic, said optionally substituted three- to seven-membered heteroalicyclic either spiro- to Q or fused to Q;

D is selected from -O-, $-S(O)_{0-2}-$, and $-NR^{15}-$;

R^{50} is either R^3, or according to formula **XXIV**;



XXIV

wherein X^1, X^2, and optionally X^3, represent the atoms of a saturated bridged ring system, said saturated bridged ring system comprising up to four annular heteroatoms represented by any of X^1, X^2, and X^3; wherein,

each X^1 is independently selected from $-C(R^6)R^7-$, -O-, $-S(O)_{0-2}-$, and $-NR^8-$;

each X^2 is independently an optionally substituted bridgehead methine or a bridgehead nitrogen;

each X^3 is independently selected from $-C(R^6)R^7-$, -O-, $-S(O)_{0-2}-$, and $-NR^8-$;

Y is either:

an optionally substituted C_{1-6}alkylene linker, between D and either 1) any annular atom of the saturated bridged ring system, except X^2 when X^2 is a bridgehead nitrogen, or 2) any heteroatom, represented by any of R^6 or R^7; provided there are at least two carbon atoms between D and any annular heteroatom of the saturated bridged ring system or any heteroatom represented by any of R^6 or R^7;

or Y is absent, when Y is absent, said saturated bridged ring system, is directly attached to D via an annular carbon of said saturated bridged ring system, unless D is $-SO_2-$, in which case said saturated bridged ring system, is directly attached to D via an any annular atom of said saturated bridged ring system;

m and p are each independently one to four;

n is zero to two, when n is zero, then there is a single bond between the two bridgehead X^2's;

R^6 and R^7 are each independently selected from -H, halogen, trihalomethyl, -CN, $-NH_2$, $-NO_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-NCO_2R^3$, $-C(O)R^3$, optionally substituted C_{1-6}alkyl, optionally substituted

aryl, optionally substituted aryl C_{1-6}alkyl, optionally substituted heterocyclyl, optionally substituted heterocyclyl a C_{1-6}lkyl, and a bond to either Y or D; or

R^6 and R^7, when taken together are oxo; or

R^6 and R^7, when taken together with a common carbon to which they are attached, form a optionally substituted three- to seven-membered spirocyclyl, said optionally substituted three- to seven-membered spirocyclyl optionally containing at least one additional annular heteroatom selected from N, O, S, and P;

R^8 is selected from $-R^3$, Y, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$;

R^{13} is selected from -H, $-C(=O)R^3$, $-C(=O)OR^3$, $-C(=O)SR^3$, $-SO_2R^3$, $-C(=O)N(R^3)R^3$, and optionally substituted C_{1-6}alkyl;

two R^{13}, together with the atom or atoms to which they are attached, can combine to form a heteroalicyclic optionally substituted with between one and four of R^{60}, said heteroalicyclic comprising up to four annular heteroatoms, and said heteroalicyclic optionally comprising an aryl or heteroaryl fused thereto, in which case said aryl or heteroaryl is optionally substituted with an additional one to four of R^{60};

R^{14} is selected from -H, $-NO_2$, $-NH_2$, $-N(R^3)R^3$, -CN, $-OR^3$, optionally substituted C_{1-6}alkyl, optionally substituted heteroalicyclyl C_{1-6}alkyl, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl and optionally substituted heteroalicyclic;

R^{15} is a group $-M^1-M^2$, wherein M^1 is selected from absent, $-C(=S)N(R^{13})-$, $-C(=NR^{14})N(R^{13})-$, $-SO_2N(R^{13})-$, $-SO_2-$, $-C(=O)N(R^{13})-$, $-C(=O)C(=O)N(R^{13})-$, $-C_{0-4}$alkylene-, -C(=O)-, and an optionally substituted four to six-membered heterocyclyl containing between one and three heteroatoms but comprising at least one nitrogen; and M^2 is selected from -H, $-C_{0-6}$alkyl, alkoxy, $-C(=O)C_{0-4}$alkylQ, $-C_{0-4}$alkylQ, $-OC_{0-4}$alkylQ-, $-N(R^{13})C_{0-4}$alkylQ-, and $-C(=O)N(R^{13})C_{0-4}$alkylQ;

R^{60} is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted heteroaryl C_{1-6}alkyl, and optionally substituted aryl C_{1-6}alkyl;

two of R^{60}, when attached to a non-aromatic carbon, can be oxo;

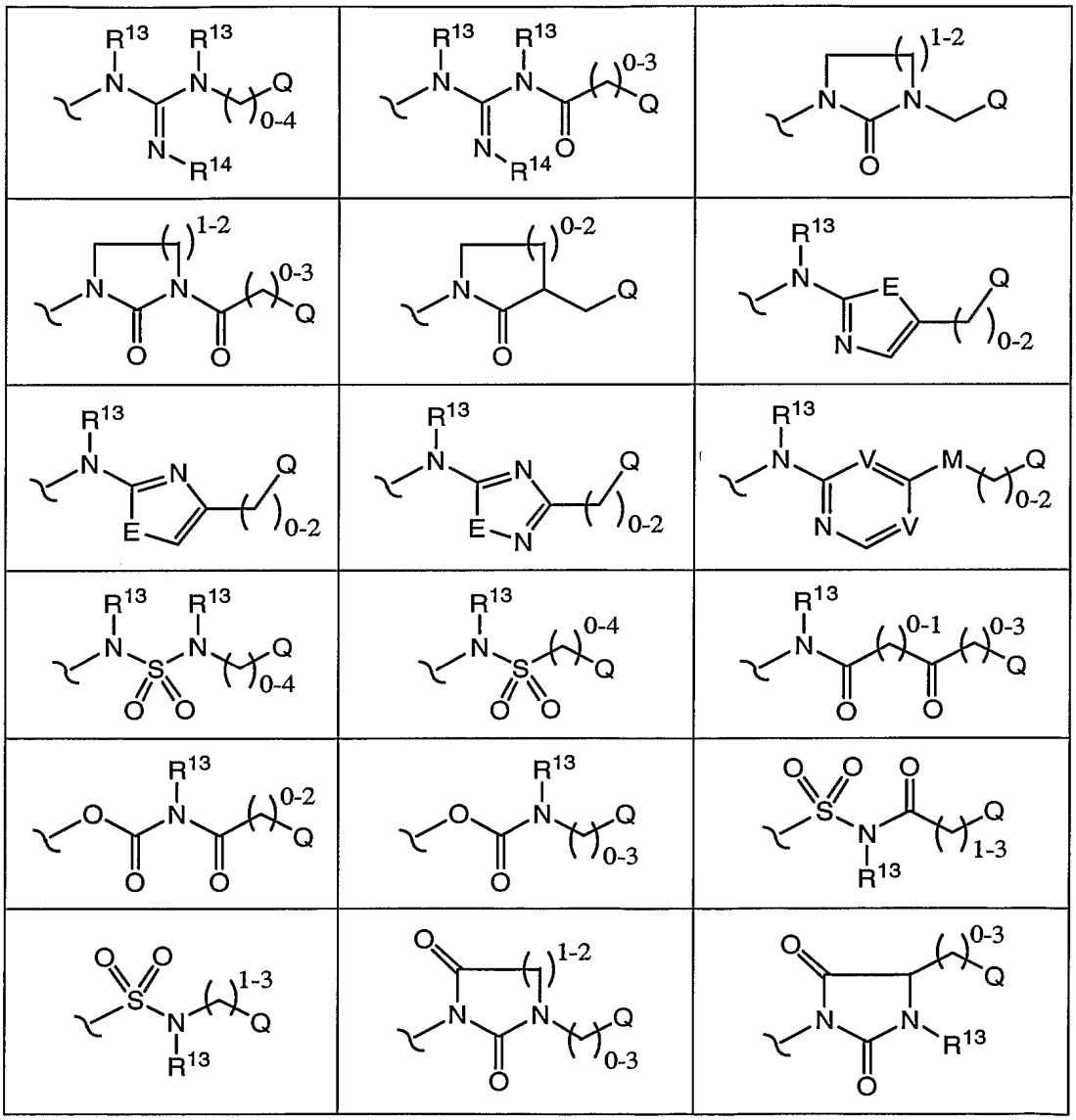
P^1 is a suitable leaving group; and

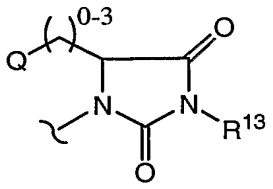
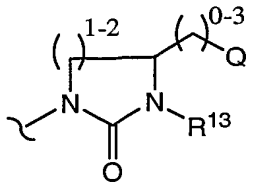
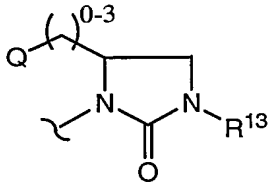
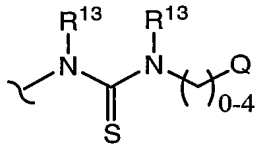
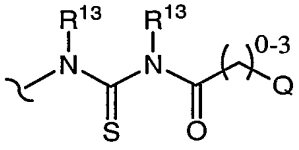
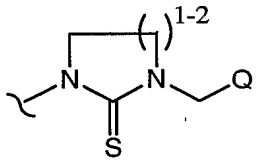
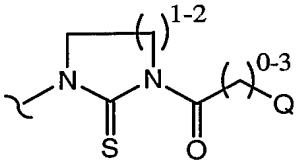
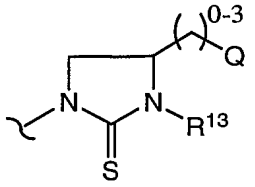
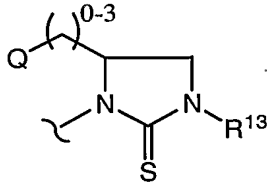
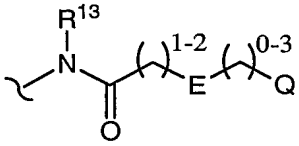
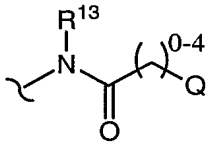
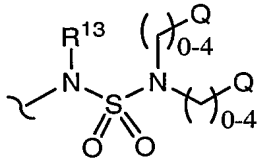
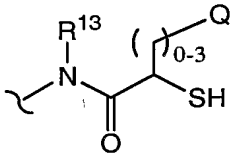
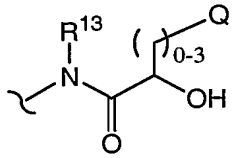
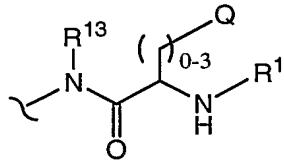
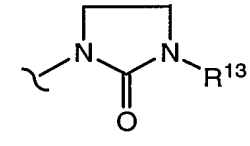
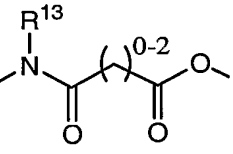
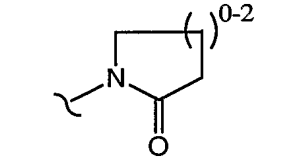
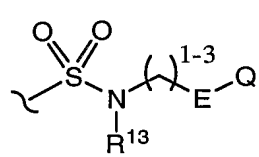
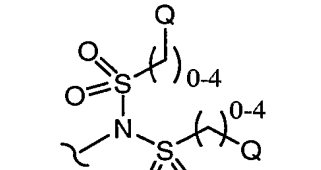
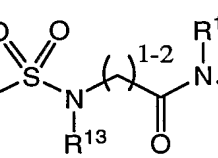
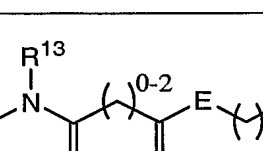
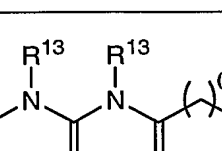
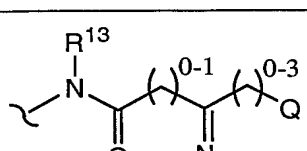
P^2 is selected from -H, a metal, and a group removed *in-situ* when combining **XXII** and **XXIII** to make **XXI**.

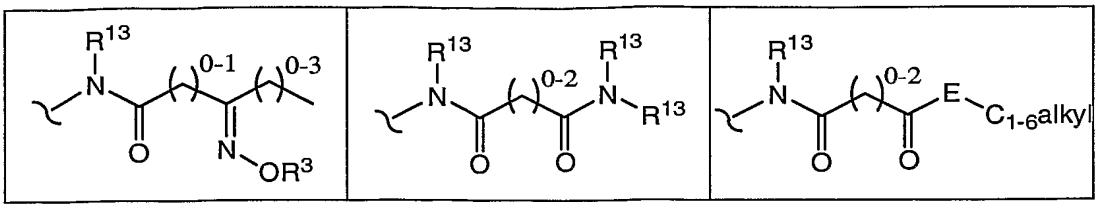
116. The process according to claim 115, wherein Ar is *para*-phenylene as defined by the substitution pattern of -Z- and -B-L-T about said phenylene.

117. The process according to claim 116, wherein Z is either -O- or $-NR^5-$.

118. The process according to claim 117, wherein -B-L-T is selected from the following:





wherein Q, R^{20}, and R^{13} are as defined above; each E is selected from -O-, -N(R^{13})-, -CH_2, and -S(O)$_{0-2}$-; M is selected from -O-, -N(R^{13})-, -CH_2-, and -C(=O)N(R^{13})-; each V is independently either =N- or =C(H)-; each methylene in any of the above formulae is independently optionally substituted with R^{25}; and R^{25} is selected from halogen, trihalomethyl, -CN, -NO_2, -NH_2, -OR^3, -NR^3R^3, -S(O)$_{0-2}R^3$, -$SO_2NR^3R^3$, -CO_2R^3, -C(O)NR^3R^3, -N(R^3)SO_2R^3, -N(R^3)C(O)R^3, -N(R^3)CO_2R^3, -C(O)R^3, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl, heteroaryl C_{1-6}alkyl, and optionally substituted C_{1-6}alkyl; two of R^{25}, together with the carbon or carbons to which they are attached, can combine to form an optionally substituted three- to seven-membered alicyclic or heteroalicyclic; two of R^{25} on a single carbon can be oxo.

119. The process according to claim 118, wherein there is one of R^1 that is -D-R^{50} and another of R^1 that is -OR^{3a}.

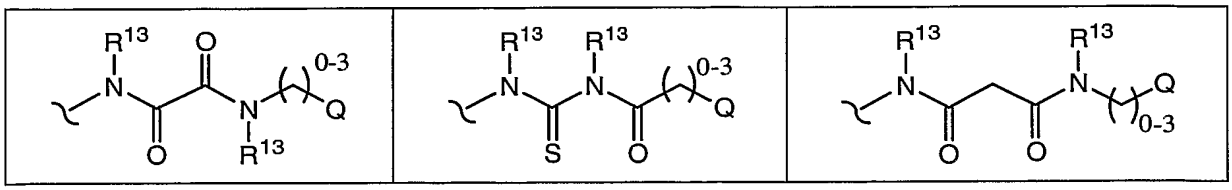
120. The process according to claim 119, wherein D is -O-.

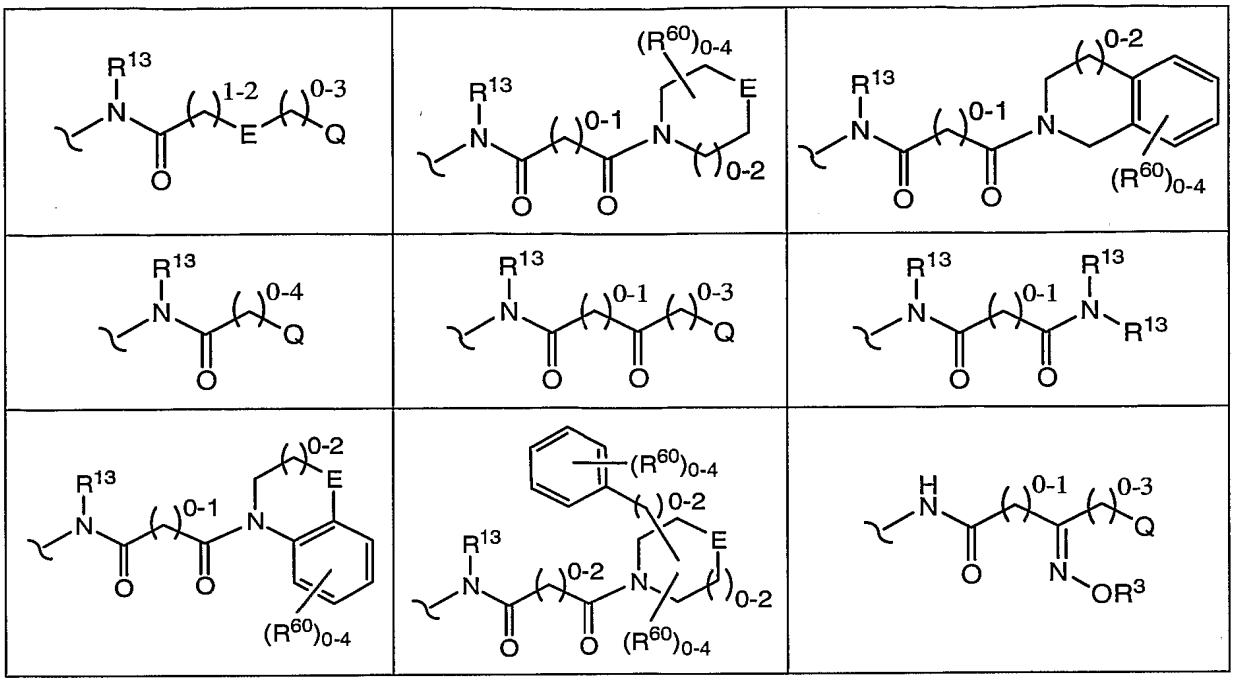
121. The process according to claim 120, wherein -O-R^{50} and -OR^{3a} are interchangeably located at the 6-position and 7-position of the quinazoline or quinoline according to Formula **XXI**.

122. The process according to claim 121, wherein -OR^{3a} is selected from -OH, -OSi(R^5)(R^5)R^5, and optionally substituted -OC_{1-6}alkyl.

123. The process according to claim 122, wherein J is =N- or =C(H)-.

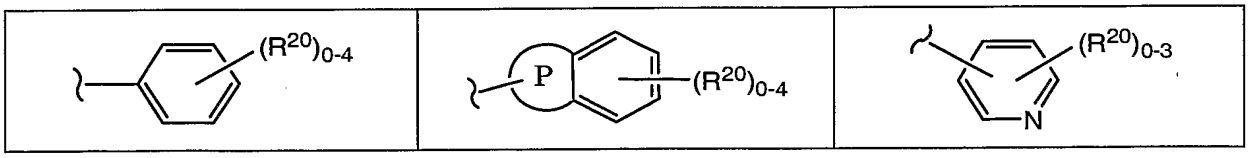
124. The process according to claim 123, wherein -B-L-T is selected from:





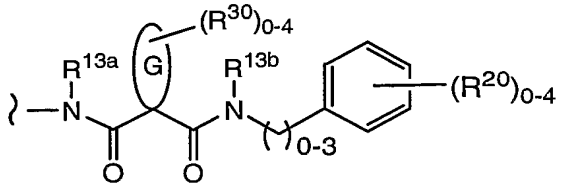
wherein Q, R^{20}, R^{13}, E, and R^{60} are as defined above; each methylene in any of the above formulae, other than those in a depicted ring, is independently optionally substituted with R^{25}; and R^{25} is selected from halogen, trihalomethyl, oxo, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl, heteroaryl C_{1-6}alkyl, and optionally substituted C_{1-6}alkyl; two of R^{25}, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered optionally substituted alicyclic or heteroalicyclic.

125. The process according to claim 124, wherein Q is selected from the following three formula:

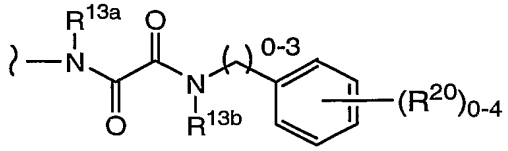


wherein R^{20} is defined as above, and P is a five- to seven-membered ring, including the two shared carbons of the aromatic ring to which P is fused, P optionally containing between one and three heteroatoms.

126. The process according to claim 125, wherein -B-L-T is either of formula **XXV** or formula **XXVI**,



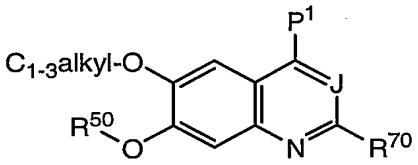
XXV



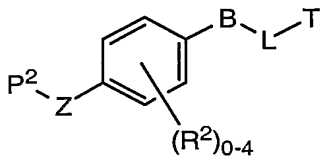
XXVI

wherein R^{20} is defined as above; G is either an optionally substituted cycloalkyl or an optionally substituted heteroalicyclic; each R^{30} is independently selected from halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted C_{1-6}alkyl; and R^{3a} and R^{3b} are each independently selected from -H and optionally substituted C_{1-6}alkyl.

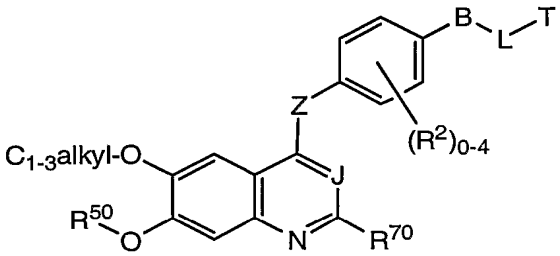
127. The process according to claim 126, wherein a compound of formula **XXIIa** is combined with a compound of formula **XXIIIa** to make a compound of formula **XXIa**,



XXIIa



XXIIIa



XXIa

wherein -B-L-T, Z, J, R^{50}, and R^2 are as defined above; R^{70} is selected from -H, $-NO_2$, $-NH_2$, and $-NR^3R^3$; provided when Z is $-N(R^5)-$ that R^5 is selected from -H, C_{1-3}alkyl, and aryl C_{1-3}alkyl; P^1 is selected from halogen, optionally substituted alkyl-$S(O)_{0-2}$-, optionally substituted arylsulfonate, optionally substituted alkylsulfonate, a group containing boron, an azide, a group containing phosphorus, and a metal; and P^2 is selected from -H and a metal.

128. The process according to claim 127, wherein P^2 is selected from -H, lithium, sodium, potassium, cesium, copper, palladium, and titanium.

129. The process according to claim 128, wherein Z is -O-.

130. The process according to claim 129, wherein P^1 is selected from chlorine, bromine, a toluene sulfonate, and trifluoromethansulfonate.

131. The process according to claim 130, wherein R^{70} is -H.

132. The process according to claim 131, wherein J is =C(H)-.

133. The process according to claim 132, wherein R^2 is selected from C_{1-6} alkyl, perfluoro C_{1-6} alkyl, and halogen.

134. The process according to claim 133, wherein **XXIIa** and **XXIIIa** are heated together, optionally with a base, optionally with microwave radiation, to form **XXIa**.

135. The process according to claim 134, wherein the base is selected from an organic base, an inorganic base, and a combination of an organic base and an inorganic base.

136. The process according to claim 135, wherein the base is selected from 2,6-lutidine, 4-N,N-dimethylaminopyridine, and a metal carbonate.

137. The process according to claim 136, wherein **XXIIa** and **XXIIIa** are heated together in a solvent with said base, at between about 40°C and 200°C for between about one hour and twenty-four hours to form **XXIa**.

138. The process according to claim 137, wherein the solvent is an organic solvent.

139. The process according to claim 138, wherein one molar equivalent of **XXIIa** is combined with between about one quarter and four molar equivalents of **XXIIIa**.

140. The process according to claim 139, wherein one molar equivalent of **XXIIa** is combined with more than one but less than two molar equivalents of **XXIIIa**.

141. The process according to claim 140, wherein **XXIIa** is combined with **XXIIIa** and said base in an aromatic solvent to form a mixture, and said mixture is heated to between about 100°C and 200°C for between about one and ten hours to form **Ia**.

142. The process according to claim 141, wherein the aromatic solvent is an optionally substituted benzene.

143. The process according to claim 142, wherein the aromatic solvent is bromobenzene.

144. The process according to claim 143, wherein the base is 4-N,N-dimethylaminopyridine.

145. The process according to claim 144, wherein said mixture is heated to reflux for between about three and seven hours.

146. The process according to claim 145, wherein said mixture is heated to reflux for between about four and six hours.

147. The process according to claim 140, wherein **XXIIa** is combined with **XXIIIa** and said base in a non-aromatic solvent to form a mixture, and said mixture is heated to between about 40°C and 100°C for between about one and twenty hours to form **XXIa**.

148. The process according to claim 147, wherein the non-aromatic solvent comprises a functional group selected from an amide, and ether, a nitrile, a halide, an ester, an amine, and a ketone.

149. The process according to claim 148, wherein the non-aromatic solvent is N,N-dimethylacetamide.

150. The process according to claim 149, wherein the base is potassium carbonate.

151. The process according to claim 150, wherein said mixture is heated to about 50°C between about ten and twenty hours.

152. The process according to claim 151, wherein the aromatic solvent is an optionally substituted pyridine.

153. The process according to claim 152, wherein the aromatic solvent is 2,6-lutidine.

154. The process according to claim 153, wherein the base is 2,6-lutidine.

155. The process according to claim 154, wherein said mixture is heated to reflux for between about three and seven hours.

156. The process according to claim 155, wherein said mixture is heated to reflux for between about four and six hours.

157. The process according to claim 139, wherein one molar equivalent of **XXIIIa** is combined with more than one but less than two molar equivalents of **XXIIa**.

158. The process according to claim 157, wherein **XXIIa** is combined with **XXIIIa** and said base in an aromatic solvent to form a mixture, and said mixture is heated to between about 100°C and 200°C for between about ten and twenty hours to form **XXIa**.

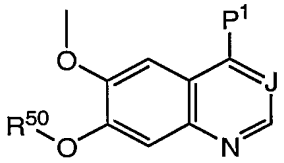
159. The process according to claim 158, wherein the aromatic solvent is an optionally substituted pyridine.

160. The process according to claim 159, wherein the aromatic solvent is 2,6-lutidine.

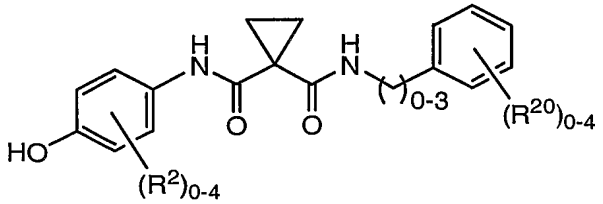
161. The process according to claim 160, wherein the base is 2,6-lutidine.

162. The process according to claim 161, wherein said mixture is heated to between about 150°C and 200°C for between about fifteen and twenty hours.

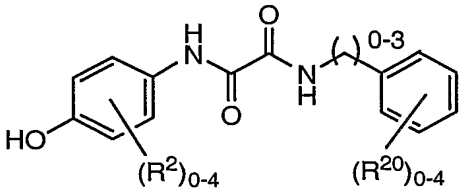
163. The process according to any of claims 134 - 162, wherein a compound of formula **XXIIb** is substituted for the compound of formula **XXIIa**, and either a compound of formula **XXIIIb** or a compound of formula **XXIIIc** is substituted for the compound of formula **XXIIIa**, in order to make a compound of formula **XXIb** or a compound of formula **XXIc**, respectively,



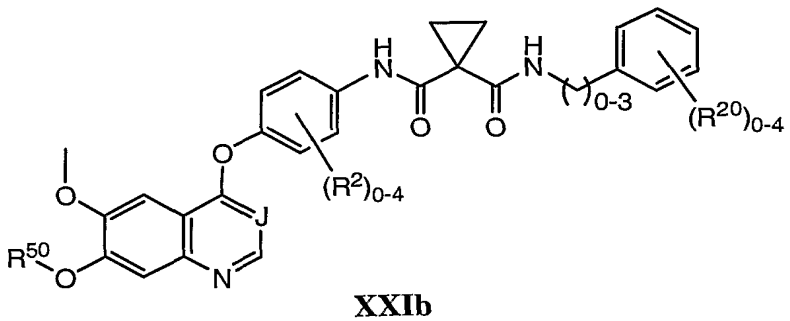
XXIIb



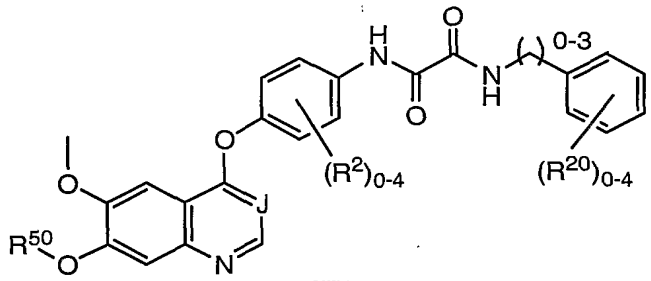
XXIIIb



XXIIIc



XXIb



XXIc

wherein J, R^{50}, R^{20} and R^2 are as defined above.

164. The process according to claim 163, wherein R^2, if present, is halogen.

165. The process according to claim 164, wherein R^2, if present, is fluorine.

166. The process according to claim 165, wherein R^2, if present, is up to two fluorines *ortho* to the oxygen of the phenylene to which R^2 is attached.

167. The process according to claim 115, used to make a compound listed in either Table 1 or Table 2.

168. The process according to any of claims 115 - 167, further comprising converting said compound to a pharmaceutically acceptable salt, hydrate, or prodrug thereof.

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/348,716	11/13/2018	10123999	224990/10-039C2-US/405045	5882

91684 7590 10/24/2018

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650 Trade Centre Way
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Kalamazoo, MI 49002-0402

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Jo Ann Wilson, San Francisco, CA;
Exelixis, Inc., Alameda, CA;

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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (03-15)
Approved for use through 07/31/2016. OMB 0651-0031
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	15348716
Filing Date	2016-11-10
First Named Inventor	Jo Ann Wilson
Art Unit	1629
Examiner Name	TBD
Attorney Docket Number	224990/10-039C2-US/405045

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	7166722		2007-01-23	MATSUNAGA, et al.	
	2	7579473		08/2009 ~~2011-07-12~~	BANNEN, et al.	
	3	7977345		2011-08-16	BANNEN, et al.	
	4	7999006		2011-08-16	LAMB, Peter	
	5	8067436		2011-11-29	BANNEN, et al.	
	6	8178532		2012-05-15	BANNEN, et al.	
	7	8314232		2012-11-20	DESCHAMPS, et al.	
	8	8476298		2013-07-02	BANNEN, et al.	

Change(s) applied to document, /P.H./ 7/19/2018

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /T.R.R/

HONIGMAN

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Via EFS Web

October 4, 2018

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313

Re: ***US Application No.: 15/348,716***
Inventor: Jo Ann Wilson
Filing Date: November 10, 2016
Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds
Confirmation No.: 5882
Attorney Docket No.: 224990/10-039C2-US/405045

Dear Sir or Madam:

Enclosed for filing please find the following documents:

1. This Cover Letter to the Commissioner for Patents;
2. Issue Fee Transmittal (PTOL-85 Part B); and
3. Certificate of Transmission under 37 C.F.R. § 1.8(a).

Submitted herewith is the $1,000.00 Issue Fee set forth in 37 C.F.R. § 1.18(a)(1) for an undiscounted entity. It is believed that no other fees are due at this time; however, if there are any additional charges, or any credits, please apply them to Deposit Account Number 503145, referencing Attorney Docket Number 224990/10-039C2-US/405045.

Very truly yours,

HONIGMAN MILLER SCHWARTZ AND COHN LLP

Heidi M. Berven, Ph.D.
Reg. No. 48,951

HMB/cwg

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax **(571)-273-2885**

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CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

91684 7590 07/05/2018
JONATHAN P. O'BRIEN, PH.D.
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650 Trade Centre Way
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UNITED STATES OF AMERICA

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(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/348,716	11/10/2016	Jo Ann Wilson	224990/10-039C2-US/405045	5882

TITLE OF INVENTION: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$500	$0.00	$0.00	$500	10/05/2018

EXAMINER	ART UNIT	CLASS-SUBCLASS
ROZOF, TIMOTHY R	1625	514-312000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Honigman Miller Schwartz and Cohn, LLP
2 Heidi M. Berven, Ph.D.
3 Jonathan P. O'Brien, Ph.D.

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Exelixis, Inc.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Alameda, CA

Please check the appropriate assignee category or categories (will not be printed on the patent): ☒ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

☒ Issue Fee

☐ Publication Fee (No small entity discount permitted)

☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

☐ A check is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☒ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 503145 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☒ Applicant changing to regular undiscounted fee status.

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NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date October 4, 2018

Typed or printed name Heidi M. Berven, Ph.D. Registration No. 48,951

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

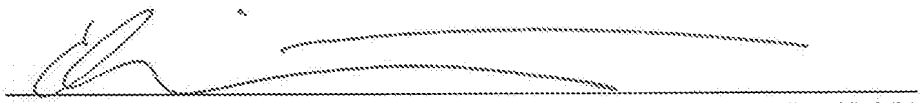
Inventor:	Jo Ann Wilson	Confirmation No.:	5882
Application No.:	15/348,716	Art Unit:	1625
Filed:	November 10, 2016	Examiner:	Timothy R. Rozof
Atty. Docket No.:	224990/10-039C2-US/405045		

Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

CERTIFICATE OF TRANSMISSION UNDER 37 C.F.R. § 1.8(a)

The undersigned hereby certifies that the following documents are being electronically filed in accordance with 37 C.F.R. § 1.6(a)(4) on this 4th day of October, 2018:

1. Cover Letter to the Commissioner for Patents;
2. Issue Fee Transmittal (PTOL-85 Part B); and
3. This Certificate of Transmission under 37 C.F.R. § 1.8(a).



Charles W. Gregg-Geist, for Heidi M. Berven, Ph.D., Reg. No. 48,951

28908461.1

Electronic Patent Application Fee Transmittal

Application Number:	15348716
Filing Date:	10-Nov-2016
Title of Invention:	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds
First Named Inventor/Applicant Name:	Jo Ann Wilson
Filer:	Heid Marie Berven/Charles Gregg-Geist
Attorney Docket Number:	224990/10-039C2-US/405045

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	1501	1	1000	1000

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1000**

Electronic Acknowledgement Receipt

EFS ID:	33919503
Application Number:	15348716
International Application Number:	
Confirmation Number:	5882
Title of Invention:	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds
First Named Inventor/Applicant Name:	Jo Ann Wilson
Customer Number:	91684
Filer:	Heid Marie Berven/Charles Gregg-Geist
Filer Authorized By:	Heid Marie Berven
Attorney Docket Number:	224990/10-039C2-US/405045
Receipt Date:	04-OCT-2018
Filing Date:	10-NOV-2016
Time Stamp:	14:45:19
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1000
RAM confirmation Number	100518INTEFSW00001056503145
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		EX10-039C2-US_IssueFee.pdf	1516273 27fcea8096b8ebf4c5d63fc8d7e813e6b2dc0f95	yes	3

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Miscellaneous Incoming Letter	1	1
	Issue Fee Payment (PTO-85B)	2	2
	Transmittal Letter	3	3

Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30621 2063b5da0f73815dcceee216c2d1b271738fdb8b	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	1546894	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/348,716	11/10/2016	1625	800	224990/10-039C2-US/405045	13	1

CONFIRMATION NO. 5882

CORRECTED FILING RECEIPT

91684
JONATHAN P. O"BRIEN, PH.D.
HONIGMAN MILLER SCHWARTZ AND COHN LLP
650 Trade Centre Way
Suite 200
Kalamazoo, MI 49002-0402

OC000000102800420

Date Mailed: 09/27/2018

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Jo Ann Wilson, San Francisco, CA;

Applicant(s)

Exelixis, Inc., Alameda, CA;

Power of Attorney: The patent practitioners associated with Customer Number 91684

Domestic Priority data as claimed by applicant

This application is a DIV of 13/984,559 03/20/2014 PAT 9717720
which is a 371 of PCT/US12/24591 02/10/2012
which claims benefit of 61/441,520 02/10/2011
and claims benefit of 61/441,527 02/10/2011

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 11/18/2016

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/348,716**

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****
Title

Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY.DOCKET NO./TITLE	REQUEST ID
15/348,716	11/10/2016	Exelixis, Inc.	224990/10-039C2-US/405045	72440

Acknowledgement of Loss of Entitlement to Entity Status Discount

The entity status change request below filed through Private PAIR on 09/26/2018 has been accepted.

CERTIFICATIONS:

Change of Entity Status:

X Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be notification of loss of entitlement to small or micro entity status, as applicable.

This portion must be completed by the signatory or signatories making the entity status change in accordance with 37 CFR 1.4(d)(4).

Signature:	/Heidi M. Berven/
Name:	Heidi M. Berven, Ph.D.
Registration Number:	48951

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	Jo Ann Wilson	Confirmation No.:	5882
Application No.:	15/348,716	Art Unit:	1625
Filed:	November 10, 2016	Examiner:	Timothy R. Rozof
Atty. Docket No.:	224990/10-039C2-US/405045		

Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

REQUEST FOR UPDATED FILING RECEIPT

The Applicant hereby requests an Updated Filing Receipt to reflect a new address for the Applicant, Exelixis, Inc. The address on record for the Applicant is: 210 East Grand Ave., South San Francisco, CA 94080, U.S.A.. The current address for the Applicant is: 1851 Harbor Bay Parkway, Alameda, CA 94502, U.S.A.. The Applicant submits herewith a marked-up Application Data Sheet (PTO/AIA/14) with the updated address information.

It is believed that no fees are due for this submission. However, if there are any charges, please apply them to Deposit Account No. 503145, with reference to Attorney Docket No. 224990/10-039C2-US/405045, and contact the Applicant's undersigned representative directly immediately.

Respectfully submitted,

Date: September 24, 2018

Heidi M. Berven, Ph.D.
Reg. No. 48,951
Honigman Miller Schwartz and Cohn LLP
650 Trade Centre Way, Suite 200
Kalamazoo, Michigan 49002
Telephone: (269) 337-7710
Facsimile: (269) 337-7711

HONIGMAN

Honigman Miller Schwartz and Cohn LLP
Attorneys and Counselors

Heidi M. Berven

(269) 337-7710
Fax: (269) 337-7711
HBerven@honigman.com

Via EFS Web

September 24, 2018

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313

Re: US Application No.: 15/348,716
Inventor: Jo Ann Wilson
Filing Date: November 10, 2016
Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds
Confirmation No.: 5882
Attorney Docket No.: 224990/10-039C2-US/405045

Dear Sir or Madam:

Enclosed for filing please find the following documents:

1. This Cover Letter to the Commissioner for Patents;
2. Request for Updated Filing Receipt;
3. Application Data Sheet (PTO/AIA/14);
4. Declaration of Inventor (PTO/AIA/01); and
5. Certificate of Transmission under 37 C.F.R. § 1.8(a).

It is believed that no fees are due for this response. However, if there are any charges for this submission, or any credits, please apply them to Deposit Account Number 503145, referencing Attorney Docket Number 224990/10-039C2-US/405045.

Very truly yours,

HONIGMAN MILLER SCHWARTZ AND COHN LLP

Heidi M. Berven, Ph.D.
Reg. No. 48,951

HMB/cwg

Electronic Acknowledgement Receipt

EFS ID:	33811213
Application Number:	15348716
International Application Number:	
Confirmation Number:	5882
Title of Invention:	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds
First Named Inventor/Applicant Name:	Jo Ann Wilson
Customer Number:	91684
Filer:	Heid Marie Berven/Charles Gregg-Geist
Filer Authorized By:	Heid Marie Berven
Attorney Docket Number:	224990/10-039C2-US/405045
Receipt Date:	24-SEP-2018
Filing Date:	10-NOV-2016
Time Stamp:	17:38:19
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		EX10-039C2-US.pdf	2554541 3f949e4ddd69a8f70023dd3e9b389efdf0bf0525	yes	11

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	11	11
	Oath or Declaration filed	10	10
	Application Data Sheet	3	9
	Request for Corrected Filing Receipt	2	2
	Miscellaneous Incoming Letter	1	1
Warnings:			
Information:			
	Total Files Size (in bytes):	2554541	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

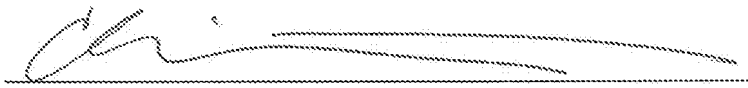
Inventor:	Jo Ann Wilson	Confirmation No.:	5882
Application No.:	15/348,716	Art Unit:	1625
Filed:	November 10, 2016	Examiner:	Timothy R. Rozof
Atty. Docket No.:	224990/10-039C2-US/405045		

Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

CERTIFICATE OF TRANSMISSION UNDER 37 C.F.R. § 1.8(a)

The undersigned hereby certifies that the following documents are being electronically filed in accordance with 37 C.F.R. § 1.6(a)(4) on this 24th day of September, 2018:

1. Cover Letter to the Commissioner for Patents;
2. Request for Updated Filing Receipt;
3. Application Data Sheet (PTO/AIA/14);
4. Declaration of Inventor (PTO/AIA/01); and
5. This Certificate of Transmission under 37 C.F.R. § 1.8(a).



Charles W. Gregg-Geist, for Heidi M. Berven, Ph.D., Reg. No. 48,951

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 15/348,716

filed on November 10, 2016.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Jo Ann Wilson Date (Optional): _____

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	224990/10-039C2-US/405045
	Application Number	15348716
Title of Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Jo Ann		Wilson	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	San Francisco	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	74 Seward Street		
Address 2			
City	San Francisco	State/Province	CA
Postal Code	94114	Country	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	91684		
Email Address	patent@honigman.com	Add Email	Remove Email

Application Information:

Title of the Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds		
Attorney Docket Number	224990/10-039C2-US/405045	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)		Suggested Figure for Publication (if any)	

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	224990/10-039C2-US/405045
	Application Number	15348716
Title of Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	91684		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Patented			Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15348716	Division of	13984559	2014-03-20	9717720	2017-08-01

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	224990/10-039C2-US/405045
	Application Number	15348716
Title of Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds	

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
13984559	a 371 of international	PCT/US12/24591	2012-02-10
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US12/24591	Claims benefit of provisional	61441520	2011-02-10
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US12/24591	Claims benefit of provisional	61441527	2011-02-10

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

			Remove
Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	224990/10-039C2-US/405045
	Application Number	15348716
Title of Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	224990/10-039C2-US/405045
	Application Number	15348716
Title of Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

(•) Assignee	( ) Legal Representative under 35 U.S.C. 117	( ) Joint Inventor
( ) Person to whom the inventor is obligated to assign.	( ) Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. [x]

Organization Name	Exelixis, Inc.		
Mailing Address Information For Applicant:			
Address 1	~~210 East Grand Ave.~~ 1851 Harbor Bay Parkway		
Address 2			
City	~~South San Francisco~~ Alameda	**State/Province**	CA
Country	US	Postal Code	~~94080~~ 94502
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button.

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	224990/10-039C2-US/405045
	Application Number	15346716
Title of Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	Given Name	Middle Name	Family Name	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		State/Province	
Country[i]		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet must be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, all joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of all joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature				Date (YYYY-MM-DD)	2018-09-24
First Name	Heidi M.	Last Name	Berven	Registration Number	48,951

Additional Signature may be generated within this form by selecting the Add button.

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	224990/10-039C2-US/405045
	Application Number	15348716
Title of Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

91684 7590 07/05/2018
JONATHAN P. O"BRIEN, PH.D.
HONIGMAN MILLER SCHWARTZ AND COHN LLP
650 Trade Centre Way
Suite 200
Kalamazoo, MICHIGAN 49002-0402
UNITED STATES OF AMERICA

EXAMINER
ROZOF, TIMOTHY R

ART UNIT	PAPER NUMBER
1625	

DATE MAILED: 07/05/2018

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/348,716	11/10/2016	Jo Ann Wilson	224990/10-039C2-US/405045	5882

TITLE OF INVENTION: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$500	$0.00	$0.00	$500	10/05/2018

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

91684 7590 07/05/2018
JONATHAN P. O"BRIEN, PH.D.
HONIGMAN MILLER SCHWARTZ AND COHN LLP
650 Trade Centre Way
Suite 200
Kalamazoo, MICHIGAN 49002-0402
UNITED STATES OF AMERICA

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/348,716	11/10/2016	Jo Ann Wilson	224990/10-039C2-US/405045	5882

TITLE OF INVENTION: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$500	$0.00	$0.00	$500	10/05/2018

EXAMINER	ART UNIT	CLASS-SUBCLASS
ROZOF, TIMOTHY R	1625	514-312000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/348,716	11/10/2016	Jo Ann Wilson	224990/10-039C2-US/405045	5882

91684 7590 07/05/2018

JONATHAN P. O"BRIEN, PH.D.
HONIGMAN MILLER SCHWARTZ AND COHN LLP
650 Trade Centre Way
Suite 200
Kalamazoo, MICHIGAN 49002-0402
UNITED STATES OF AMERICA

EXAMINER	
ROZOF, TIMOTHY R	
ART UNIT	**PAPER NUMBER**
1625	

DATE MAILED: 07/05/2018

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)

(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Notice Requiring Inventor's Oath or Declaration	Application No. 15/348,716	Applicant(s) Jo Ann Wilson	
	Examiner ROZOF, TIMOTHY R	Art Unit 1625	

This notice is an attachment to the Notice of Allowability (PTOL-37), or the Notice of Allowability For A Design Application (PTOL-37D).

An inventor's oath or declaration in compliance with 37 CFR 1.63 or 1.64 executed by or with respect to each inventor has not yet been submitted.

An oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each inventor (for any inventor for which a compliant oath, declaration, or substitute statement has not yet been submitted) MUST be filed no later than the date on which the issue fee is paid. See 35 U.S.C. 115(f). Failure to timely comply will result in ABANDONMENT of this application.

A properly executed inventor's oath to declaration has not been received for the following inventor(s):

If applicant previously filed one or more oaths, declarations, or substitute statements, applicant may have received an informational notice regarding deficiencies therein.

The following deficiencies are noted:

INFORMAL ACTION PROBLEMS

- A properly executed inventor's oath or declaration has not been received for the following inventor(s): **Jo Ann Wilson**.
  Applicant may submit the inventor's oath or declaration at any time before the Notice of Allowance and Fee(s) Due, PTOL-85, is mailed.

Questions relating to this Notice should be directed to the Application Assistance Unit at 571-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 15/348,716	Applicant(s) Wilson, Jo Ann	
	Examiner TIMOTHY R ROZOF	Art Unit 1625	AIA Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to April 17, 2018, Amendment & Remarks.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 1,3-6 and 8-13 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information , please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file areply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/TIMOTHY R ROZOF/
Primary Examiner, Art Unit 1625

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/348,716	Wilson, Jo Ann
	Examiner	Art Unit
	TIMOTHY R ROZOF	1625

CPC - Searched*		
Symbol	Date	Examiner
C07D215/233	06/18/2018	TRR
A61K31/47	06/18/2018	TRR

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
EAST search (please see the attached search report)	06/18/2018	TRR

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
C07D	215/233	06/18/2018	TRR
A61K	31/47	06/18/2018	TRR

/TIMOTHY R ROZOF/ Primary Examiner, Art Unit 1625	

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/348,716	Wilson, Jo Ann
	Examiner	**Art Unit**
	TIMOTHY R ROZOF	1625

CPC						
Symbol					**Type**	**Version**
A61K	/	31	/	47	F	2013-01-01
C07D	/	215	/	233	I	2013-01-01

CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
	/		/					

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	11	
/TIMOTHY R ROZOF/ Primary Examiner, Art Unit 1625	18 June 2018	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/348,716	Wilson, Jo Ann
	Examiner	**Art Unit**
	TIMOTHY R ROZOF	1625

INTERNATIONAL CLASSIFICATION				
CLAIMED				
C07D	/	215	/	233
A61K	/	31	/	47

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	11	
/TIMOTHY R ROZOF/ Primary Examiner, Art Unit 1625	18 June 2018	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/348,716	Wilson, Jo Ann
	Examiner	**Art Unit**
	TIMOTHY R ROZOF	1625

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	10	12												
2	3	11	13												
3	4														
4	5														
5	6														
6	8														
7	9														
8	10														
9	11														

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	11	
/TIMOTHY R ROZOF/ Primary Examiner, Art Unit 1625	18 June 2018	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office Part of Paper No.: 20180618

Bibliographic Data

Application No: 15/348,716

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☐ No ☐ Met After Allowance

Verified and Acknowledged: /TIMOTHY R ROZOF/ (Examiner's Signature) | TRR (Initials)

Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
11/10/2016	514	1625	
RULE			

APPLICANTS

Exelixis, Inc., South San Francisco, CA, UNITED STATES

INVENTORS

Jo Ann Wilson San Francisco, CA, UNITED STATES

CONTINUING DATA

This application is a DIV of 13984559 03/20/2014 PAT 9717720

13984559 is a 371 of PCT/US12/24591 02/10/2012

PCT/US12/24591 has PRO of 61441527 02/10/2011

PCT/US12/24591 has PRO of 61441520 02/10/2011

FOREIGN APPLICATIONS

IF REQUIRED, FOREIGN LICENSE GRANTED**

11/18/2016

** SMALL ENTITY **

STATE OR COUNTRY

UNITED STATES

ADDRESS

FILING FEE RECEIVED

$730

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15348716
Filing Date	2016-11-10
First Named Inventor	Jo Ann Wilson
Art Unit	1625
Examiner Name	Timothy R. Rozof
Attorney Docket Number	224990/10-039C2-US/405045

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	9724342		2017-08-08	WILSON, et al.	
	2	9809549		2017-11-07	BROWN, et al.	

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20080161305		2008-07-03	FORSYTH, et al.	
	2	20110077233		2011-03-31	BANNEN, et al.	
	3	20120252840		2012-10-04	AFTAB, et al.	
	4	20140066444		2014-03-26	SMITH, et al.	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /T.R.R/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15348716
	Filing Date	2016-11-10
	First Named Inventor	Jo Ann Wilson
	Art Unit	1625
	Examiner Name	Timothy R. Rozof
	Attorney Docket Number	224990/10-039C2-US/405045

	5	20150057310		2015-02-26	BROWN, et al.	
	6	20150202196		2015-07-23	BANNEN, et al.	
	7	20160000772		2016-01-07	AFTAB, et al.	
	8	20160051532		2016-02-25	AFTAB, et al.	
	9	20160229805		2016-08-11	WILSON, et al.	
	10	20170143689		2017-05-25	WILSON, et al.	
	11	20170266178		2017-09-21	WILSON, et al.	
	12	20170275251		2017-09-28	BROWN, et al.	
	13	20180002289		2018-01-04	BROWN, et al.	
	14	20180037552		2018-02-08	BROWN, et al.	

If you wish to add additional U.S. Published Application citation information please click the Add button.

FOREIGN PATENT DOCUMENTS

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /T.R.R/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15348716
Filing Date	2016-11-10
First Named Inventor	Jo Ann Wilson
Art Unit	1625
Examiner Name	Timothy R. Rozof
Attorney Docket Number	224990/10-039C2-US/405045

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1		☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature	/TIMOTHY R ROZOF/	Date Considered	06/18/2018

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /T.R.R/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15348716
Filing Date	2016-11-10
First Named Inventor	Jo Ann Wilson
Art Unit	1625
Examiner Name	Timothy R. Rozof
Attorney Docket Number	224990/10-039C2-US/405045

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature		Date (YYYY-MM-DD)	2018-04-17
Name/Print	Heidi M. Berven, Ph.D.	Registration Number	48,951

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /T.R.R/

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	8124	((546/153) or (514/312)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2018/06/18 18:05
L2	6268	L1 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2018/06/18 18:05
L3	508	L2 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2018/06/18 18:05
L4	96	L3 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2018/06/18 18:05
S1	1868	546/153	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2014/10/04 13:11
S2	6107	((546/153) or (514/312)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2014/10/04 13:12
S3	4920	S2 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2014/10/04 13:12
S4	476	S3 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2014/10/04 13:14
S5	88	S4 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2014/10/04 13:14
S6	2	("20070054928").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2014/10/04 13:14
S7	735	S3 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2014/10/04 15:14
S8	11	S5 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2014/10/04 15:15
S10	1907	546/153	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2015/06/03 13:56
S11	6748	((546/153) or (514/312)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2015/06/03 13:56
S12	5294	S11 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2015/06/03 13:56
S13	492	S12 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO;	OR	ON	2015/06/03 13:56

			DERWENT			
S14	96	S13 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2015/06/03 13:56
S15	2	("20070054928").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2015/06/03 13:56
S16	748	S12 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2015/06/03 13:56
S17	12	S14 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2015/06/03 13:56
S19	1924	546/153	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/01/07 13:23
S20	7064	((546/153) or (514/312)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/01/07 13:23
S21	5473	S20 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/01/07 13:23
S22	494	S21 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/01/07 13:23
S23	96	S22 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/01/07 13:23
S24	2	("20070054928").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/01/07 13:23
S25	755	S21 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/01/07 13:23
S26	12	S23 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/01/07 13:23
S27	1924	546/153	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/01/07 13:23
S28	7064	((546/153) or (514/312)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/01/07 13:23
S29	5473	S28 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/01/07 13:23
S30	494	S29 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/01/07 13:23
S31	96	S30 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/01/07 13:23
S32	2	("20070054928").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/01/07 13:23
S33	755	S29 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO;	OR	ON	2016/01/07 13:23

			DERWENT			
S34	12	S31 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/01/07 13:23
S35	0	((A61K31/47.cpc.) or (C07D215/233.cpc.)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/01/07 13:33
S36	5706	A61K31/47.cpc. C07D215/233.cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/01/07 13:33
S37	4165	S36 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/01/07 13:33
S38	546	S37 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/01/07 13:34
S39	81	S38 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/01/07 13:34
S42	1925	546/153	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S43	7164	((546/153) or (514/312)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/04/28 12:34
S44	5481	S43 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S45	494	S44 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S46	96	S45 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S47	2	("20070054928").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/04/28 12:34
S48	756	S44 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S49	12	S46 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S50	1925	546/153	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S51	7164	((546/153) or (514/312)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/04/28 12:34
S52	5481	S51 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S53	494	S52 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S54	96	S53 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO;	OR	ON	2016/04/28 12:34

			DERWENT			
S55	2	("20070054928").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/04/28 12:34
S56	756	S52 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S57	12	S54 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S58	1925	546/153	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S59	7164	((546/153) or (514/312)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/04/28 12:34
S60	5481	S59 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S61	494	S60 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S62	96	S61 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S63	2	("20070054928").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/04/28 12:34
S64	756	S60 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S65	12	S62 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S66	1925	546/153	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S67	7164	((546/153) or (514/312)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/04/28 12:34
S68	5481	S67 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S69	494	S68 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S70	96	S69 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S71	2	("20070054928").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/04/28 12:34
S72	756	S68 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S73	12	S70 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO;	OR	ON	2016/04/28 12:34

			DERWENT			
S74	0	((A61K31/47.cpc.) or (C07D215/233.cpc.)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/04/28 12:34
S75	5906	A61K31/47.cpc. C07D215/233.cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S76	4191	S75 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S77	550	S76 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S78	81	S77 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/04/28 12:34
S79	1927	546/153	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S80	7246	((546/153) or (514/312)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:36
S81	5493	S80 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S82	495	S81 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S83	96	S82 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S84	2	("20070054928").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:36
S85	757	S81 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S86	12	S83 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S87	1927	546/153	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S88	7246	((546/153) or (514/312)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:36
S89	5493	S88 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S90	495	S89 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S91	96	S90 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S92	2	("20070054928").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO;	OR	OFF	2016/08/05 11:36

			DERWENT			
S93	757	S89 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S94	12	S91 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S95	1927	546/153	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S96	7246	((546/153) or (514/312)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:36
S97	5493	S96 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S98	495	S97 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S99	96	S98 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S100	2	("20070054928").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:36
S101	757	S97 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S102	12	S99 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S103	1927	546/153	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S104	7246	((546/153) or (514/312)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:36
S105	5493	S104 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S106	495	S105 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S107	96	S106 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S108	2	("20070054928").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:36
S109	757	S105 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S110	12	S107 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:36
S111	0	((A61K31/47.cpc.) or (C07D215/233.cpc.)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO;	OR	OFF	2016/08/05 11:37

			DERWENT			
S112	6123	A61K31/47.cpc. C07D215/233.cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S113	4231	S112 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S114	566	S113 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S115	82	S114 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S116	1927	546/153	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S117	7246	((546/153) or (514/312)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:37
S118	5493	S117 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S119	495	S118 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S120	96	S119 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S121	2	("20070054928").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:37
S122	757	S118 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S123	12	S120 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S124	1927	546/153	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S125	7246	((546/153) or (514/312)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:37
S126	5493	S125 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S127	495	S126 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S128	96	S127 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S129	2	("20070054928").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:37
S130	757	S126 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO;	OR	ON	2016/08/05 11:37

			DERWENT			
S131	12	S128 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S132	1927	546/153	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S133	7246	((546/153) or (514/312)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:37
S134	5493	S133 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S135	495	S134 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S136	96	S135 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S137	2	("20070054928").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:37
S138	757	S134 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S139	12	S136 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S140	1927	546/153	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S141	7246	((546/153) or (514/312)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:37
S142	5493	S141 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S143	495	S142 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S144	96	S143 and ((c$met) or (Ret))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S145	2	("20070054928").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:37
S146	757	S142 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S147	12	S144 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S148	0	((A61K31/47.cpc.) or (C07D215/233.cpc.)).CCLS.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2016/08/05 11:37
S149	6123	A61K31/47.cpc. C07D215/233.cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO;	OR	ON	2016/08/05 11:37

			DERWENT			
S150	4231	S149 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S151	566	S150 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S152	82	S151 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2016/08/05 11:37
S153	6433	A61K31/47.cpc. C07D215/233.cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2017/01/17 13:35
S154	4302	S153 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2017/01/17 13:35
S155	573	S154 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2017/01/17 13:35
S156	83	S155 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2017/01/17 13:35
S157	7130	A61K31/47.cpc. C07D215/233.cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2017/05/23 14:41
S158	4682	S157 and @ad<="20110210"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2017/05/23 14:41
S159	580	S158 and (protein near3 kinase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2017/05/23 14:41
S160	83	S159 and (compound near3 (IA or IB))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2017/05/23 14:41
S161	1	("20120035212").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2017/06/26 14:37
S162	7223	A61K31/47.cpc. C07D215/233.cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2017/06/28 15:15
S163	1	("20120035212").PN.	US-PGPUB; USPAT	OR	OFF	2017/10/12 15:31
S164	1	("20120035212").PN.	US-PGPUB; USPAT	OR	OFF	2017/10/12 17:17
S165	1	("7169789").PN.	USPAT	OR	OFF	2017/10/12 17:35

6/18/2018 6:06:38 PM
C:\Users\trozof\Documents\EAST\Workspaces\15348716.wsp

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors:	Jo Ann Wilson, et al.	Confirmation No.:	5882
Application No.:	15/348,716	Art Unit:	1625
Filed:	November 10, 2016	Examiner:	Timothy R. Rozof
Atty. Docket No.:	224990/10-039C2-US/405045		

Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 223313-1450

RESPONSE TO THE NON-FINAL OFFICE ACTION DATED OCTOBER 17, 2017

Dear Sir or Madam:

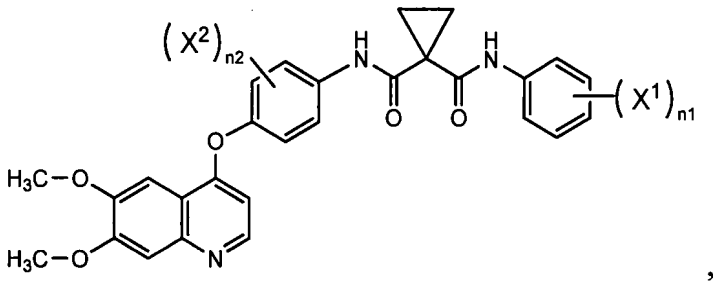
This submission is responsive to the Non-Final Office Action dated October 17, 2017.

Amendments to the claims are reflected in the listing of claims that begins on page 2.

Remarks begin on page 7.

CLAIM AMENDMENTS

1. (Currently amended) A process for preparing a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is H, Br, Cl, or F;

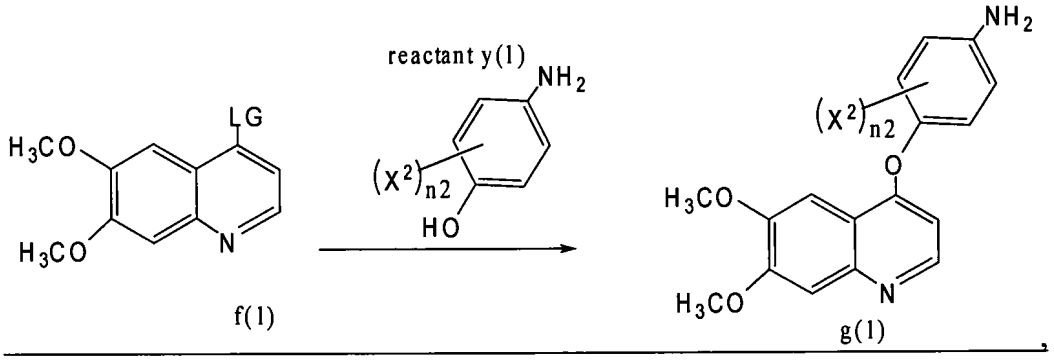
X^2 is H, Br, Cl, or F;

n1 is 1-2; and

n2 is 1-2;

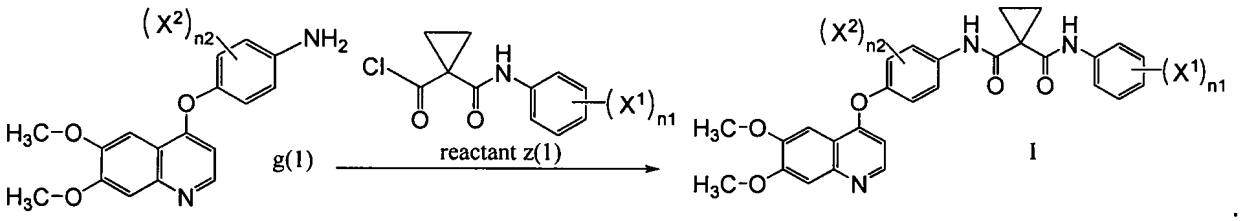
the process comprising:

reacting a compound of formula f(1) with a reactant y(1) in the presence of a non-nucleophilic base which is an alkali metal alkoxide to yield the compound of formula g(1):



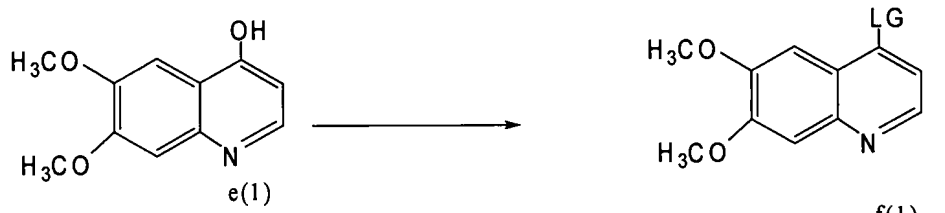
wherein LG represents a leaving group; and

contacting a compound of formula g(1) with a reactant z(1) to yield the compound of formula I:



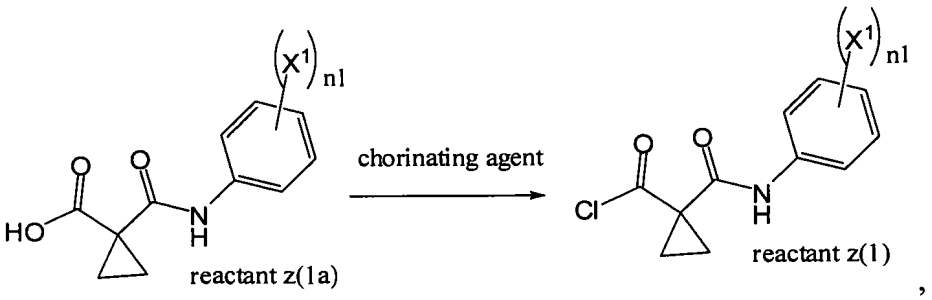
2. Cancelled.

3. (Currently amended) The process according to claim [[2]] 1, wherein the compound of formula f(1) is made by converting a compound of formula e(1) to the compound of formula f(1):



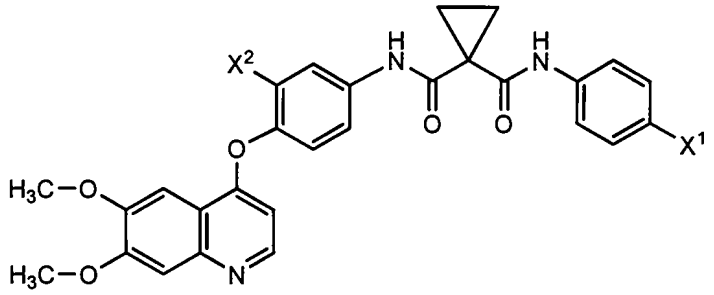
wherein LG represents a leaving group.

4. (Previously presented) The process according to claim 1, wherein reactant z(1) is made by reacting a reactant z(1a) with a chlorinating agent to yield the reactant z(1):



wherein X^1 is Br, Cl, or F; and n1 is 1-2.

5. (Previously presented) The process according to claim 1, wherein the compound of formula I is a compound of formula IA-1:



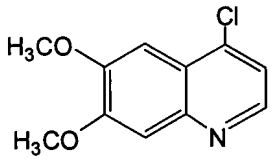
IA-1

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is H, Cl, Br, or F; and

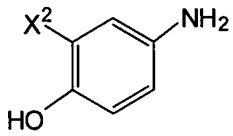
X^2 is H, Cl, Br, or F.

6. (Currently amended) The process according to claim 1 ~~claim 2~~, wherein the compound of formula f(1) is the compound f(2):



f(2) ;

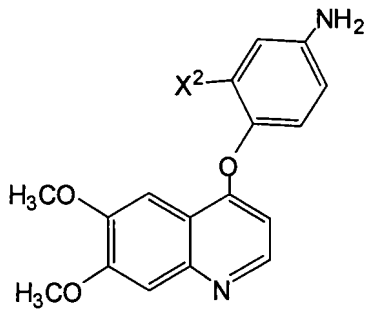
the reactant y(1) is a reactant (y)(2):



reactant (y)(2) ,

wherein X^2 is hydrogen or fluoro; and

the compound of formula g(1) is a compound of formula g(2):



g(2)

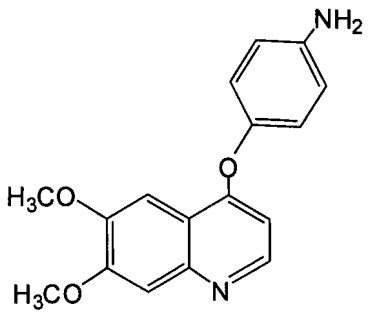
7. Cancelled.

8. (Currently amended) The process according to claim 1 ~~claim 7~~, wherein ~~the non-nucleophilic base is an alkali metal alkoxide; and~~ the reaction is carried out in a polar solvent.

9. (Original) The process according to claim 8, wherein the alkali metal alkoxide is sodium tert-butoxide, and the polar solvent is DMA.

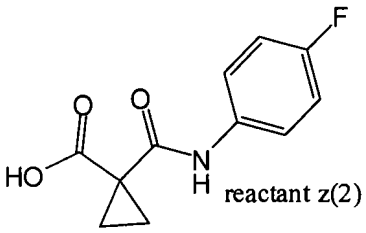
10. (Original) The process according to claim 8, wherein the alkali metal alkoxide is sodium tert-pentoxide, and the polar solvent is DMA.

11. (Previously presented) The process according to claim 4, wherein the compound of formula g(1) is the compound g(3):



g(3) ;

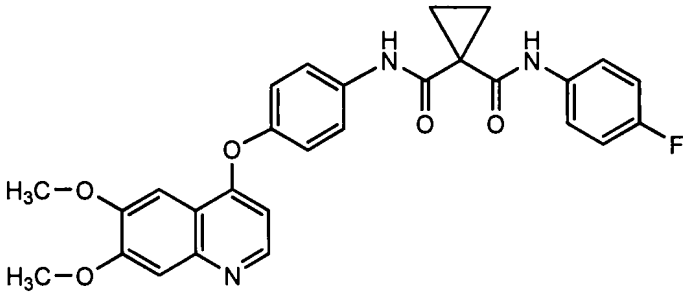
the reactant z(1a) is the reactant (z)(2):



reactant z(2)

; and

the compound of formula I is the compound of formula IA:



IA.

12. (Original) The process according to claim 11, wherein the reaction is carried out in the presence of an inorganic base.

13. (Previously presented) The process according to claim 12, wherein the inorganic base is K_2CO_3, and the reaction is carried out in a solvent comprising a combination of THF and H_2O.

14-34. Cancelled.

REMARKS

Claim Status

Claims 1, 3, 6, and 8 are currently amended. Claim 1 is currently amended to incorporate the limitations of claim 2. Claims 3 and 6 are currently amended to update the dependencies. Claim 8 is currently amended to update the dependency and to remove a limitation now incorporated into claim 1. The currently amended claims are supported by the specification and claims as originally filed and do not introduce new matter.

Claims 4, 5, 11, and 13 are previously presented.

Claims 9, 10, and 12 are original.

Claims 2, 7, and 14-34 are cancelled.

Thus, claims 1, 3-6, and 8-13 are currently pending.

Rejections under 35 U.S.C. § 102(e)

In the Office Action, the Examiner rejected claims 1, 4, 5, and 11-13 under pre-AIA 35 U.S.C. 102(e) as allegedly anticipated by US 2012/0035212 to Brown, et al. (hereinafter, "Brown"). The Applicant respectfully disagrees.

In Scheme 1 of Brown, which is reproduced on page 3 of the office action, 4-nitrophenol is coupled to 4-chloro-6,7-dimethoxy-quinoline to form 6,7-dimethyl-4-(4-nitro-phenoxy)-quinolone, which is subsequently reduced to 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine. In contrast, the captioned application claims a process that eliminates the coupling of 4-nitrophenol to 4-chloro-6,7-dimethoxy-quinoline to form 6,7-dimethyl-4-(4-nitro-phenoxy)-quinolone and the subsequent reduction, by using 4-amino phenol for the coupling reaction.

For at least this reason, the claims are not anticipated.

Rejections under 35 U.S.C. § 103

In the Office Action, the Examiner rejected claims 1-13 under pre-AIA 35 U.S.C. 103(a) as allegedly unpatentable over US 2012/0035212 to Brown, et al. (hereinafter, "Brown") in view of US 7,169,789 to Kubo, et al. (hereinafter, "Kubo"). The Applicant respectfully disagrees.

In Scheme 1 of Brown, which is reproduced on page 3 of the office action, 4-nitrophenol is coupled to 4-chloro-6,7-dimethoxy-quinoline to form 6,7-dimethyl-4-(4-nitro-phenoxy)-

quinolone, which is subsequently reduced to 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine. In contrast, the captioned application claims a process that eliminates the coupling of 4-nitrophenol to 4-chloro-6,7-dimethoxy-quinoline to form 6,7-dimethyl-4-(4-nitro-phenoxy)-quinolone and the subsequent reduction, by using 4-amino phenol for the coupling reaction. There is no disclosure or suggestion in Brown to employ an amino phenol.

Kubo discloses certain coupling reactions of a chloroquinoline with an amino phenol to form 4-aminophenoxy quinolone derivatives. In Scheme 2, sodium hydroxide was the base that was employed (See Scheme 2 and Col. 12, lines 60-67 and Production Examples 37 and 38). In Scheme 4, sodium hydride was the base that was employed (See Scheme 4 and Col. 19, lines 1-4 and Production Examples 1-4). Kubo does not disclose or suggest the use of an alkali metal alkoxide as the base, as claimed by the Applicant in currently amended claim 1.

For at least these reasons, the claims are not obviated by Brown in view of Kubo.

Information Disclosure Statement

The Applicant notes that the filing of the enclosed Information Disclosure Statement shall not be construed to be an admission that the information cited in the statement qualifies as prior art under 35 U.S.C. § § 102 or 103, or is considered to be material to patentability as defined in 37 C.F.R. § 1.56(b). The fee set forth in 37 C.F.R. § 1.17(p) is submitted in support.

Other C-Met Inhibitor Cases

The Applicant wishes to make the Examiner aware of the Applicant's other applications related to c-Met inhibitors and their use in the treatment of cancer. For the Examiner's convenience, the Applicant is providing a list of the Applicant's applications directed to the treatment of cancer using c-Met inhibitors. The Applicant understands the Examiner has electronic access to these applications and to the Office Actions that have issued in these applications, and has therefore not included copies with this Response. The Applicant will gladly provide the applications and Office Actions to the Examiner, however, upon request.

Application Number	Filing or 371 Date	Patent Number	Examiner	Status
10/573,336	09/18/2006		Koontz, Tammy J.	Abandoned
11/571,140	12/21/2006	7977345	Moore, Susanna	Expired

Application Number	Filing or 371 Date	Patent Number	Examiner	Status
11/586,751	10/26/2006	9174947	Ward, Paul V.	Issued
11/753,462	05/24/2007	8178532	Ward, Paul V.	Issued
11/753,503	05/24/2007	8476298	Ward, Paul V.	Expired
11/753,514	05/24/2007	8067436	Bernhardt, Emily A.	Issued
12/393,806	02/26/2009	7579473	Seaman, D. Margaret M.	Issued
12/911,442	10/25/2010		Ward, Paul, V.	Abandoned
13/087,094	04/14/2011		Chickos, Sarah, J.	Abandoned
13/129,183	05/13/2011		Seaman, D. Margaret M.	Abandoned
13/132,650	06/03/2011		Seaman, D. Margaret M.	Abandoned
13/145,054	10/20/2011	8877776	Carter, Kendra D	Issued
13/249,815	09/30/2011	8497284	Bernhardt, Emily A.	Issued
13/384,451	07/12/2012	8673912	Anderson, Rebecca L.	Issued
13/389,266	07/12/2012		Perreira, Melissa Jean	Abandoned
13/427,093	03/22/2012		Ward, Paul V.	Abandoned
13/438,964	04/04/2012		Brown-Pettigrew, Angela C.	Abandoned
13/634,275	09/12/2012		Anderson, Rebecca L.	Abandoned
13/753,031	01/29/2013		Pagonakis, Anna	Abandoned
13/753,146	01/29/2013		Pagonakis, Anna	Abandoned
13/810,537	08/26/2013	9724342	Pallay, Michael B.	Issued
13/810,546	08/27/2013		Branson, Daniel L.	Abandoned
13/876,290	11/05/2013		Stone, Christopher R.	Abandoned
13/876,306	11/08/2013		Lee, Andrew P.	Abandoned
13/876,318	10/25/2013		Karol, Jody Lynn	Abandoned
13/888,592	05/07/2013		Ward, Paul V.	Abandoned
13/928,977	06/27/2013		Bernhardt, Emily A.	Abandoned
13/984,559	03/20/2014	9717720	Rozof, Timothy R.	Issued
14/021,614	09/09/2013		Matos Negron, Taina Del Mar	Pending
14/115,236	02/28/2014		Anderson, James D.	Pending
14/166,545	01/28/2014		Not Yet Assigned	Abandoned
14/173,973	02/06/2014		Johannsen, Diana B.	Abandoned
14/340,871	07/25/2014	9809549	Carter, Kendra D.	Issued
14/346,570	03/21/2014		Calvillo, Y. Jeanmarie Z.	Pending
14/353,251	04/21/2014	9365516	Murray, Jeffrey H.	Issued
14/356,927	05/08/2014		Baek, Bong-Sook	Pending
14/356,938	05/08/2014		Cerioni, Daniel Lee	Abandoned
14/398,188	10/31/2014	9,861,624	Henley III, Raymond J.	Issued
14/426,580	03/06/2015		Jean-Louis, Samira J.M.	Pending
14/518,733	10/20/2014		Chickos, Sarah J.	Pending
14/668,312	03/25/2015		Brown-Pettigrew, Angela C.	Abandoned
14/699,683	04/29/2015		Perreira, Melissa Jean	Pending
14/776,337	09/14/2015		Reese, Heidi L.	Pending

Application Number	Filing or 371 Date	Patent Number	Examiner	Status
14/782,493	10/05/2015		Saeed, Kamal A.	Pending
14/782,537	10/05/2015		Alley, Genevieve S.	Pending
14/843,480	09/02/2015		Stone, Christopher R.	Pending
14/847,801	09/08/2015		Ward, Paul V.	Abandoned
14/933,801	11/05/2015		Brown-Pettigrew, Angela C.	Pending
15/066,872	03/10/2016		Ward, Paul V.	Pending
15/118,738	08/12/2016		Chandrakumar, Nizal S.	Pending
15/126,767	09/16/2016		Solola, Taofiq A.	Pending
15/133,708	04/20/2016		Murray, Jeffrey H.	Pending
15/305,854	10/21/2016		McMillian, Kara Renita	Pending
15/500,312	01/30/2017		Seaman, D. Margaret M.	Pending
15/501,582	02/03/2017		Seaman, D. Margaret M.	Pending
15/426,804	02/07/2017		Pallay, Michael B.	Pending
15/612,703	06/02/2017		Pallay, Michael B.	Pending
15/617,725	06/08/2017		Carter, Kendra D.	Pending
15/618,593	06/09/2017		Carter, Kendra D.	Pending
15/621,527	06/13/2017		Carter, Kendra D.	Pending
15/688,310	08/28/2017		Ward, Paul V.	Pending

Extension of Time

The Applicant hereby petitions for a three-month extension of time under 37 C.F.R. § 1.136(a) for responding to the Non-Final Office Action in this application dated October 17, 2017. The fee set forth in 37 C.F.R. § 1.17(a)(3) is submitted herewith.

Conclusion

The Applicant believes this submission is fully responsive to the Non-Final Office Action in this application dated October 17, 2017. The Applicant reserves the right to file divisional applications or take such other appropriate action as deemed necessary to protect the subject matter restricted, canceled, or withdrawn from this application.

It is believed that the fees due for this response are the $120.00 fee set forth in 37 C.F.R. § 1.17(p) for submission of the enclosed Information Disclosure Statement and the $700.00 fee set forth in § 1.17(a)(3) for a three-month extension of time. The Applicant hereby authorizes the Office to charge this total of $820.00 to Deposit Account Number 503145, referencing Attorney Docket Number 224990/10-039C2-US/405045. It is believed that no other fees are due at this time. However, if there are any additional charges for this submission, or any credits,

please apply them to Deposit Account Number 503145, referencing Attorney Docket Number 224990/10-039C2-US/405045.

Respectfully submitted,

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