Application Data Sheet

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Representative Customer Number:: 23460

Representative Designation::	Registration Number::	Representative Name::

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This Application	Continuation of	11/586,751	10/26/06
11/586,751	Continuation of	10/573,336	09/18/06
10/573,336	National Stage of	PCT/US04/31523	09/24/04
PCT/US04/31523	An application claiming the benefit under 35 USC 119(e) of	60/506,181	09/26/03

PCT/US04/31523	An application claiming the benefit under 35 USC 119(e) of	60/535,377	01/09/04
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FOREIGN APPLICATION INFORMATION

Country::	Application Number::	Filing Date::	Priority Claimed

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c-Met Modulators and Method of Use

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of copending U.S. Patent Application No. 11/586,751, filed on October 26, 2006, which is a continuation of U.S. Patent Application No. 10/573,336, filed on September 16, 2006, now abandoned, which is a national phase application under 35 U.S.C. § 371 of International Patent Application No. PCT/US2004/031523, filed on September 24, 2004, which claims the benefit of U.S. Provisional Patent Application 60/506,181 filed on September 26, 2003, and which also claims the benefit of U.S. Provisional Patent Application No. 60/535,377 filed on January 9, 2004, and which also claims the benefit of U.S. Provisional Patent Application No. 60/577,384 filed on June 4, 2004, 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 angiogenesis, 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] International patent application publication no. WO 01/21597 discloses substituted quinazolines linked, via a heteroatom, to an optionally substituted aromatic ring containing at least one nitrogen atom. WO 01/21597 states that the disclosed compounds inhibit aurora 2 kinase and are useful in the treatment of proliferative disease such as cancer.

[0025] U.S. patent applicaiton publication no. US 2004/0242603 discloses substituted quinolines and quinazolines linked, via a heteroatom, to a substituted phenylene. US 2004/0242603 states that the disclosed compounds have autophosphorylation inhibitory activity and antitumor activity.

[0026] International patent application publication no. WO 2005/005389 discloses bivalent malonamide derivatives, including derivatives in which substituted aryl substituents are bonded directly to the nitrogen atoms on either side of the malonamide moiety. WO 2005/005389 states that the disclosed compounds are inhibitors of raf kinase.

[0027] 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

[0028] 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.

[0029] 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.

[0030] 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.

[0031] In another aspect, the invention also provides a diagnostic agent comprising a compound of the invention and, optionally, pharmaceutically acceptable adjuvants and excipients.

[0032] 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.

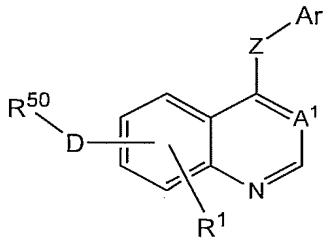
[0033] These and other features and advantages of the present invention will be described in more detail below with reference to the associated drawings.

DETAILED DESCRIPTION OF THE INVENTION

[0034] 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 artherosclerosis, myocardioinfarction, ischemia, stroke and restenosis; other inflammatory and degenerative diseases such as interbowel diseases, osteoarthritus, macular degeneration, diabetic retinopathy.

[0035] 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.

[0036] Thus, in one aspect the present invention comprises a compound for modulating kinase activity according to Formula **I**,



I

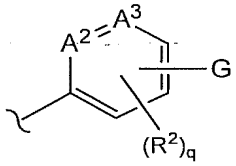
or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein,

R^1 is selected from -H, halogen, $-OR^3$, $-NO_2$, $-NH_2$, $-NR^3R^4$, and optionally substituted lower alkyl;

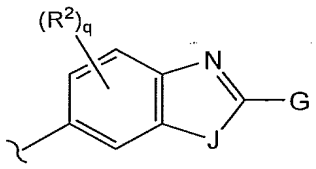
A^1 is selected from =N-, =C(H)-, and =C(CN)-;

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

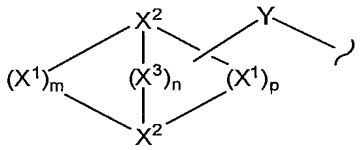
R^3 and R^4, when taken together with a common nitrogen to which they are attached, form an optionally substituted five- to seven-membered heterocyclyl, said optionally substituted five- to seven-membered heterocyclyl optionally containing at least one additional annular heteroatom selected from N, O, 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 heterocyclyl annular containing between one and three heteroatoms 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:

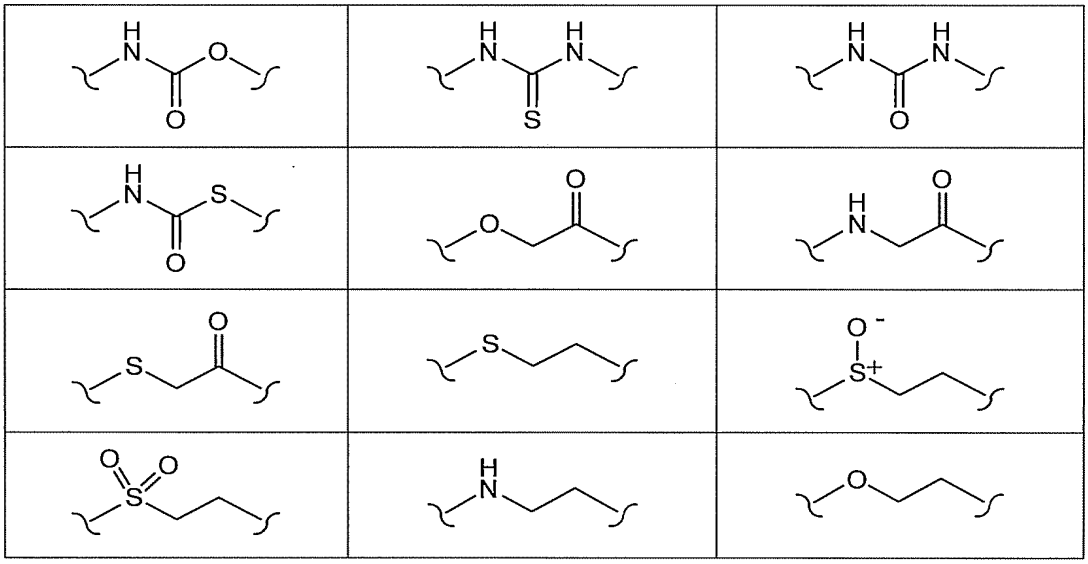
1) either a pyrrolidine or a piperidine, and any atom, X^1 or X^2, of either of said pyrrolidine or said piperidine is attached to Y, then the other bridge of said saturated bridged ring system cannot be any one of -OC(O)CH_2-, -CH_2OC(O)-, -OC(O)CH_2CH_2-, -CH_2OC(O)CH_2-, -CH_2CH_2OC(O)-, -OC(O)CH_2NH-, -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

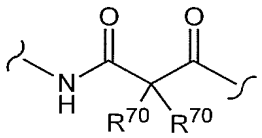
3) a piperazine, and any atom, X^1 or X^2, of said piperazine is attached to Y, then the other bridge of said saturated bridged ring system, only when attached via the 3- and the 4-position of said piperazine, cannot be one of -C(O)OCH_2CH_2-, -CH_2OC(O)CH_2-, and either of the two aforementioned bridges 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:

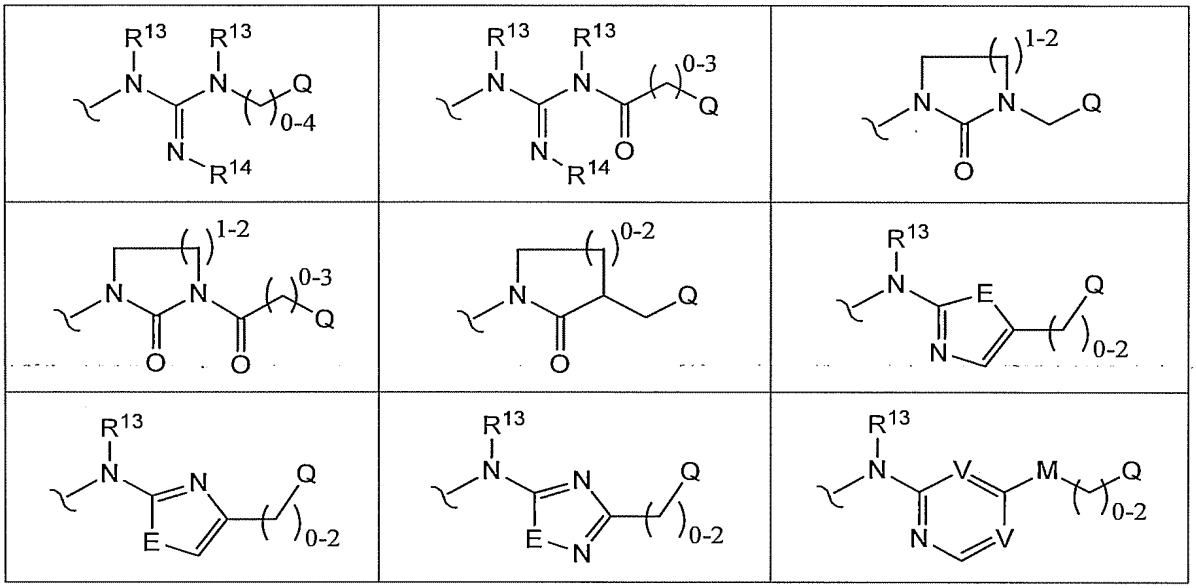


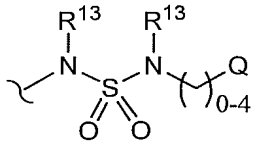
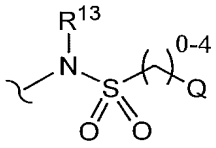
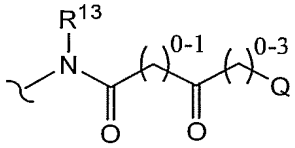
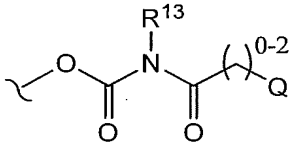
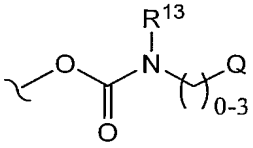
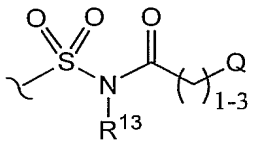
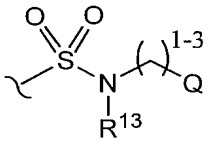
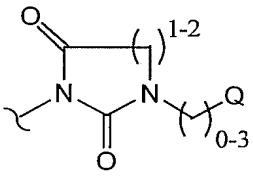
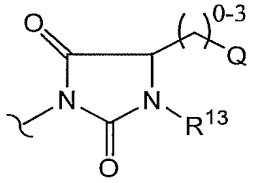
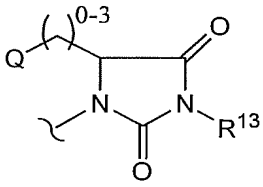
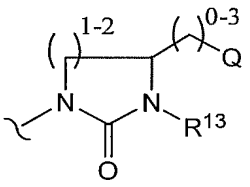
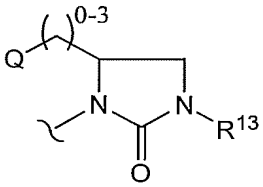
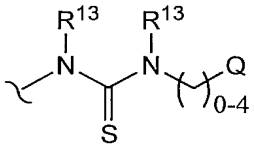
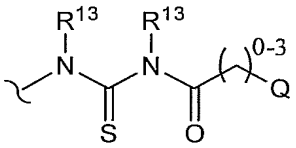
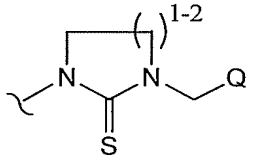
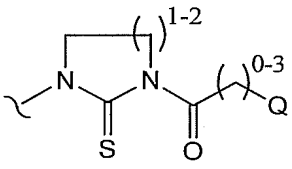
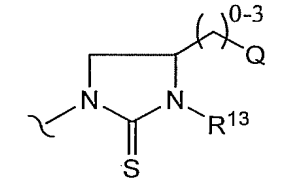
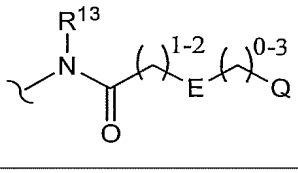
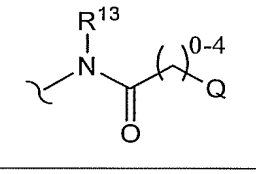
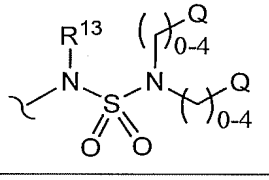
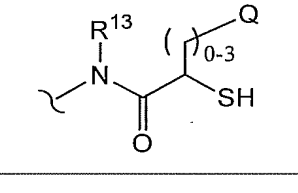
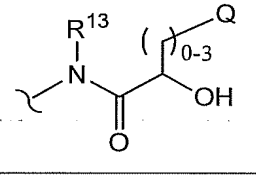
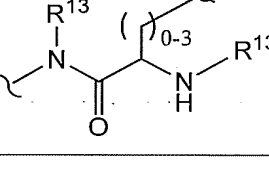
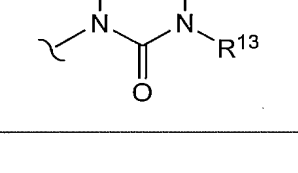
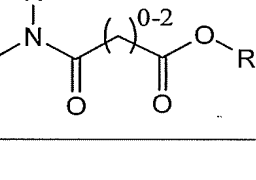
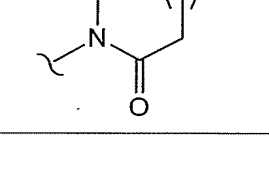
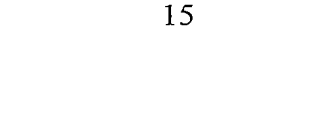
then R^{50} must be of formula **IV**;

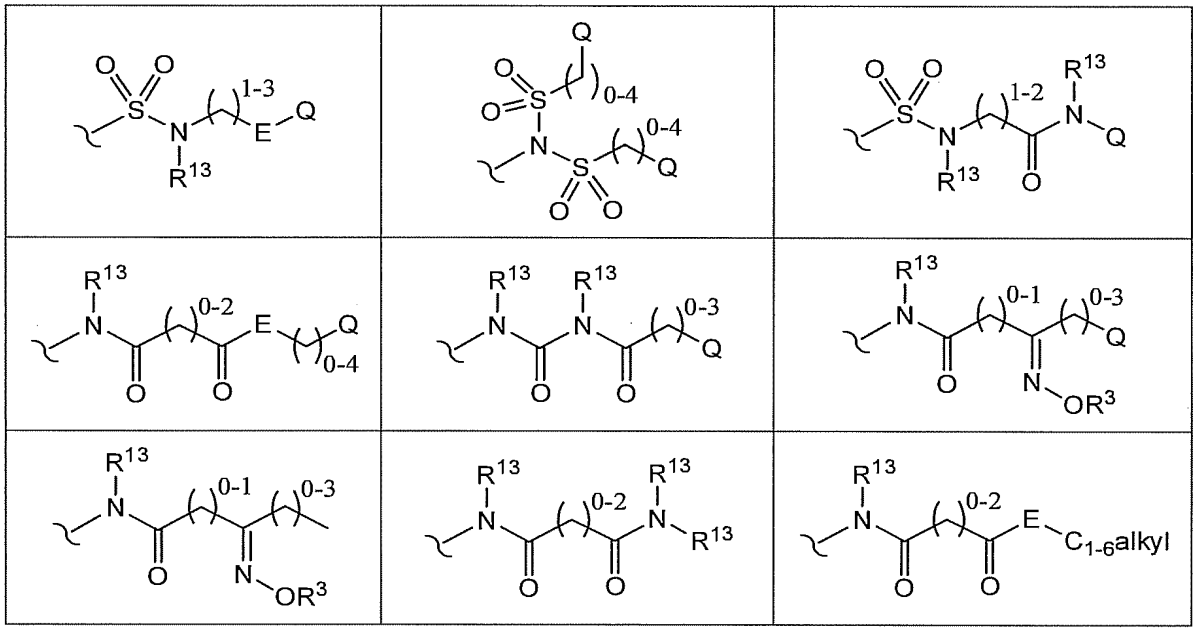
and with the proviso that when Ar is phenylene or substituted phenylene, Z is $-S(O)_{0-2}-$ or -O-, then the portion of G directly attached to Ar cannot contain , when R^{70} is selected from -H, C_{1-4}alkyl, and C_{1-4}alkoxyl.

[0037] In one example, the compound is according to Formula I, wherein Z is either -O- or $-NR^5-$.

[0038] In another example, the compound is according to Formula I, wherein Z is either -O- or $-NR^5-$ and G is selected from the following:

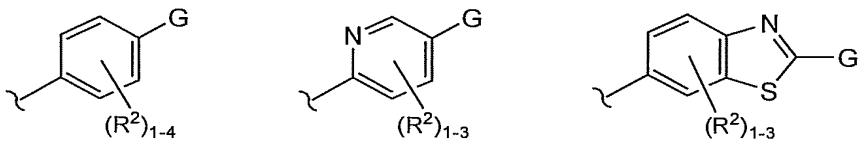




wherein Q, R^{20}, and R^{13} are as defined above; each E is selected from -O-, -N(R^{13})-, -CH_2-, and -S(O)$_{0-2}$-; M is selected from -O-, -N(R^{13})-, -CH_2-, and -C(=O)N(R^{13})-; each V is independently either =N- or =C(H)-; each methylene in any of the above formulae is independently optionally substituted with R^{25}; and R^{25} is selected from halogen, trihalomethyl, -CN, -NO_2, -NH_2, -OR^3, -NR^3R^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.

[0039] In another example, the compound is according to the preceding paragraph, wherein Ar is according to one of formula **IIa**, **IIb**, and **IIIa**.



IIa **IIb** **IIIa**

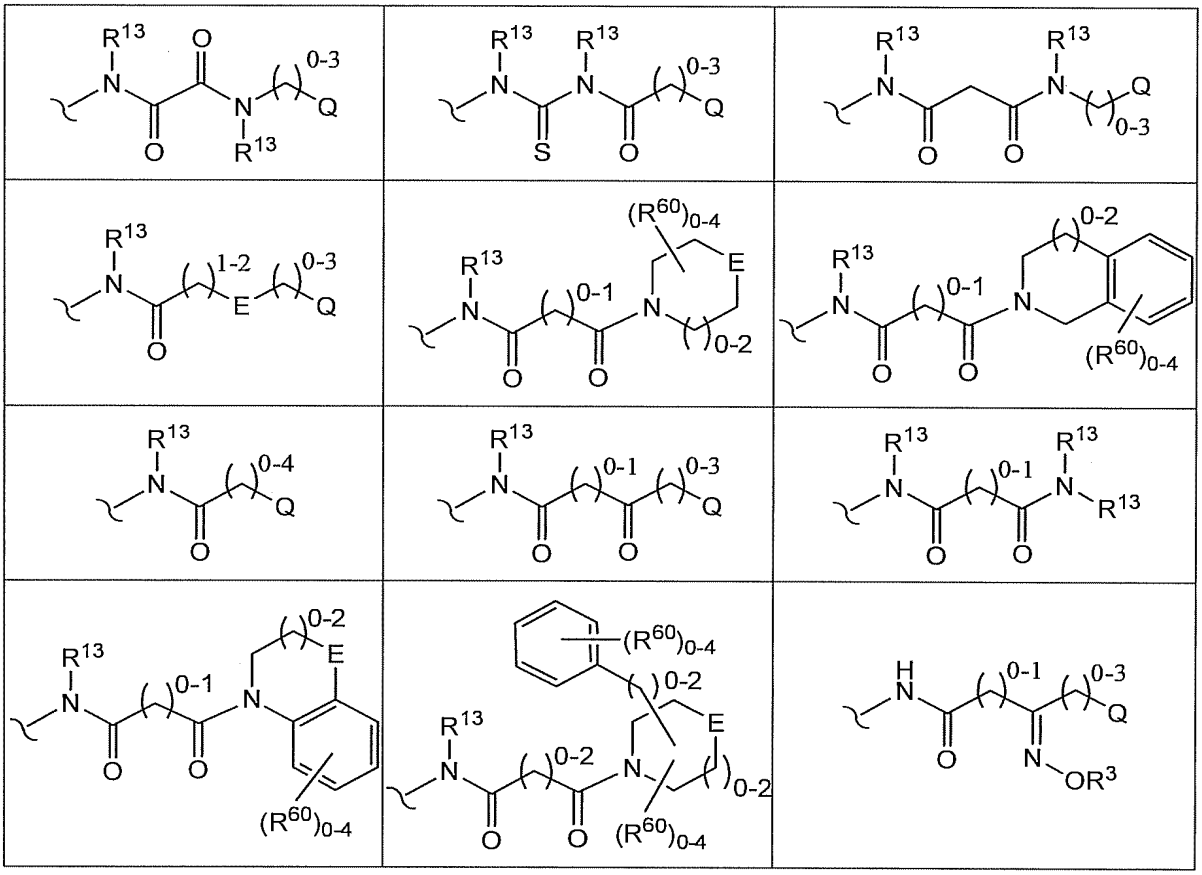
[0040] In another example, the compound is according to the preceding paragraph, wherein D is -O- and R^1 is -OR^3.

[0041] In another example, the compound is according to the preceding paragraph, 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**.

[0042] In another example, the compound is according to the preceding paragraph, wherein R^1 is -OH or -OC_{1-6} alkyl.

[0043] In another example, the compound is according to the preceding paragraph, wherein A^1 is =N- or =C(H)-.

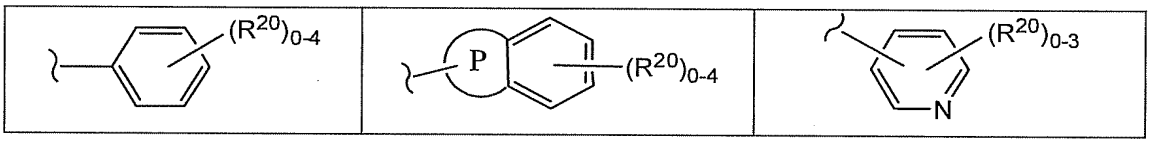
[0044] In another example, the compound is according to the preceding paragraph, wherein G is selected from:



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

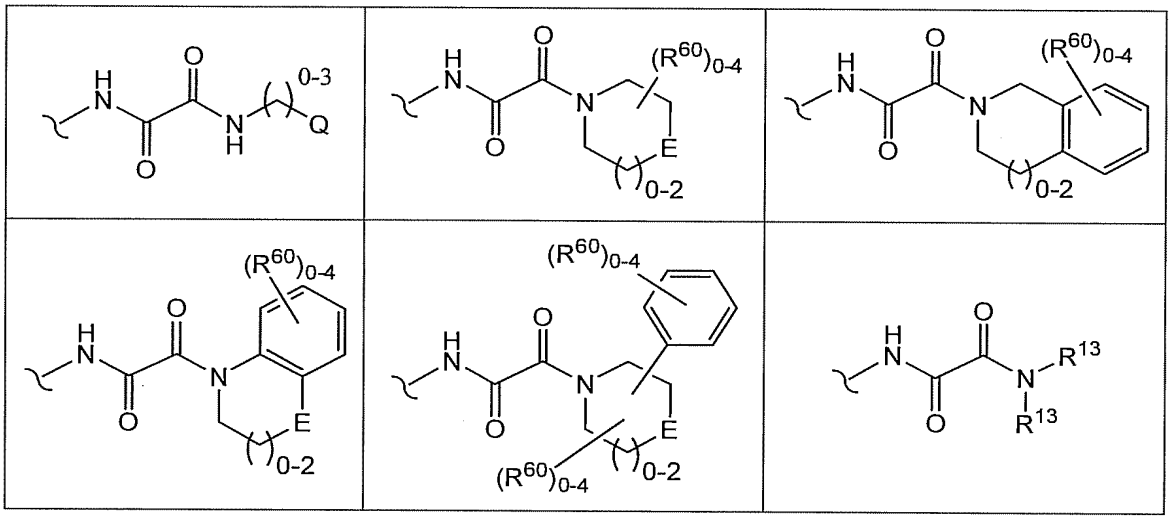
they are attached, can combine to form a three- to seven-membered alicyclic or heteroalicyclic.

[0045] In another example, the compound is according to the preceding paragraph, wherein Q is selected from:



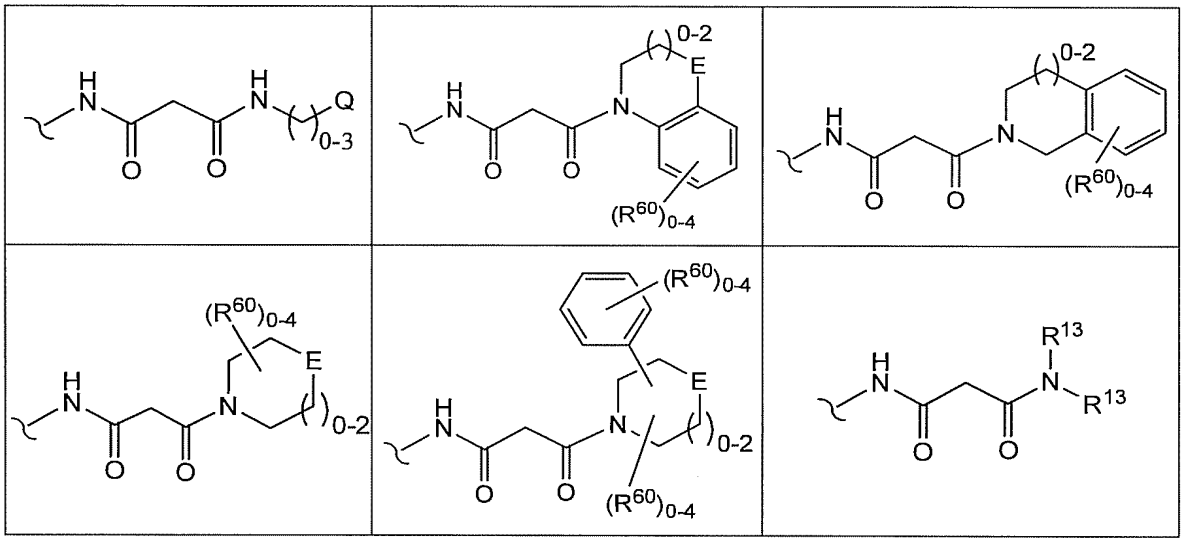
wherein R^{20} is defined as above, and P is a five- to seven-membered ring, including the two shared carbons of the aromatic ring to which P is fused, P optionally containing between one and three heteroatoms.

[0046] In another example, the compound is according to the preceding paragraph, 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.

[0047] In another example, the compound is as defined two paragraphs above, 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.

[0048] In another example, the compound is according to either of the two preceding paragraphs, 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.

[0049] In another example, the compound is as defined three paragraphs above or as defined two paragraphs above, wherein R^{50} is a heteroalicylic or a C_{1-6}alkyl-heteroalicylic.

[0050] In another example, the compound is according to the preceding paragraph, wherein at least one of R^2 is halogen.

[0051] In another example, the compound is as defined two paragraphs above, wherein R^{50} is according to formula **IV**.

[0052] In another example, the compound is according to the preceding paragraph, 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].

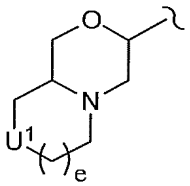
[0053] In another example, the compound is according to the preceding paragraph, wherein Y is selected from $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2-$, $-CH_2-$, and absent.

[0054] In another example, the compound is according to the preceding paragraph, 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].

[0055] In another example, the compound is according to the preceding paragraph, wherein said saturated bridged ring system contains at least one annular nitrogen or at least one annular oxygen.

[0056] In another example, the compound is according to the preceding paragraph, 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 $-C(O)R^3$.

[0057] In another example, the compound is as defined two paragraphs above, 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.

[0058] In another example, the compound is according to the preceding paragraph, wherein Y is $-CH_2-$.

[0059] In another example, the compound is according to the preceding paragraph, 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 $-C(O)R^3$.

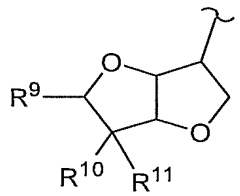
[0060] In another example, the compound is as defined two paragraphs above, wherein U^1 is -O-.

[0061] In another example, the compound is as defined three paragraphs above, wherein U^1 is absent.

[0062] In another example, the saturated bridged ring system is according to formula IV with 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] and contains at least one annular nitrogen or at least one annular oxygen, wherein n is 0 and Y is selected from $-CH_2CH_2-$, $-CH_2-$, and absent.

[0063] In another example, the compound is according to the preceding paragraph, 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;

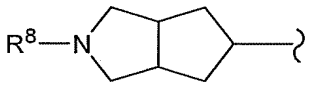
or two R^{12}'s, when taken together, form 1) a corresponding spirocyclic ketal when said two R^{12}'s stem from R^{10} and R^{11}, or 2) a corresponding cyclic ketal when said two R^{12}'s stem from R^9 and one of R^{10} and R^{11}.

[0064] In another example, the compound is according to the preceding paragraph, 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.

[0065] In another example, the compound is according to the preceding paragraph, wherein Y is either $-CH_2-$ or absent.

[0066] In another example, the compound is according to the preceding paragraph, wherein R^9 is an alkyl group containing at least one fluorine substitution thereon.

[0067] In another example, the saturated bridged ring system is of formula **VII**, wherein R^8 is selected from -H, optionally substituted lower alkyl, $-CO_2R^3$, $C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$.

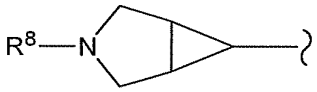


VII

[0068] In another example, the compound is according to the preceding paragraph, wherein Y is either $-CH_2-$ or absent.

[0069] In another example, the compound is according to the preceding paragraph, wherein R^8 is methyl or ethyl.

[0070] In another example, the saturated bridged ring system is of formula **VIII**.



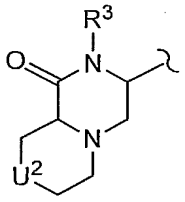
VIII

wherein R^8 is selected from -H, optionally substituted lower alkyl, $-CO_2R^3$, $-C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$.

[0071] In another example, the compound is according to the preceding paragraph, wherein Y is $-CH_2-$.

[0072] In another example, the compound is according to the preceding paragraph, wherein R^8 is methyl or ethyl.

[0073] In another example, the 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.

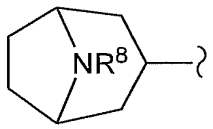
[0074] In another example, the compound is according to the preceding paragraph, wherein R^3 of formula **IX** is selected from -H and optionally substituted alkyl.

[0075] In another example, the compound is according to the preceding paragraph, wherein U^2 is either $-CR^6R^7-$ or absent.

[0076] In another example, the compound is according to the preceding paragraph, wherein U^2 is either $-CH_2-$ or absent.

[0077] In another example, the compound is according to the preceding paragraph, wherein Y is $-CH_2-$.

[0078] In another example, the saturated bridged ring system is according to formula **X**, wherein R^8 is selected from -H, optionally substituted lower alkyl, $-CO_2R^3$, $C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$.



X

[0079] In another example, the compound is according to the preceding paragraph, wherein R^8 is methyl or ethyl.

[0080] In another example, the compound is selected from Table 1.

Table 1

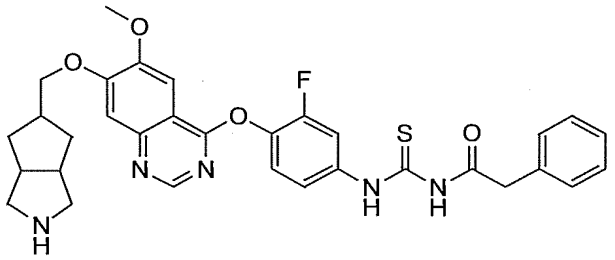
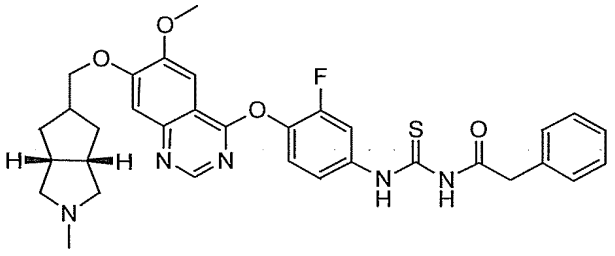
Entry	Name	Structure
1	N-[({3-fluoro-4-[(6-(methyloxy)-7-{[(3aR,6aS)-octahydrocyclopenta[c]pyrrol-5-ylmethyl]oxy}quinazolin-4-yl)oxy]phenyl}amino) carbonothioyl]-2-phenylacetamide	
2	N-{[(3-fluoro-4-{[7-({[(3aR,6aS)-2-methyloctahydrocyclopenta[c] pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-yl]oxy}phenyl)amino] carbonothioyl}-2-phenylacetamide	

Table 1

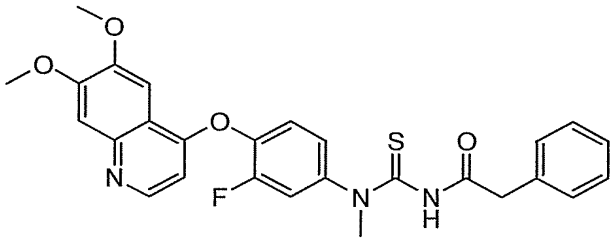
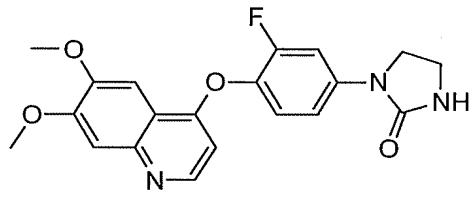
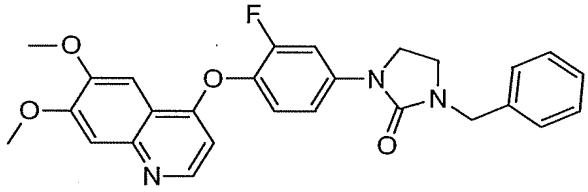
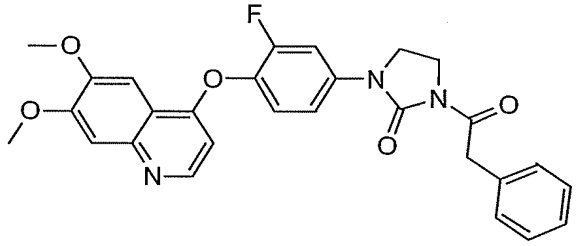
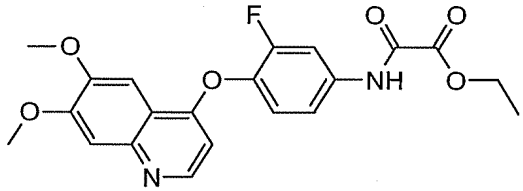
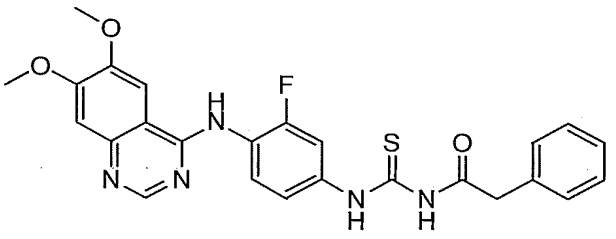
Entry	Name	Structure
3	N-{[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)(methyl)amino]carbonothioyl}-2-phenylacetamide	
4	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)imidazolidin-2-one	
5	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylmethyl)imidazolidin-2-one	
6	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylacetyl)imidazolidin-2-one	
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	

Table 1

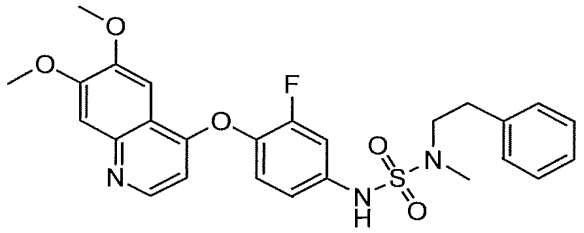
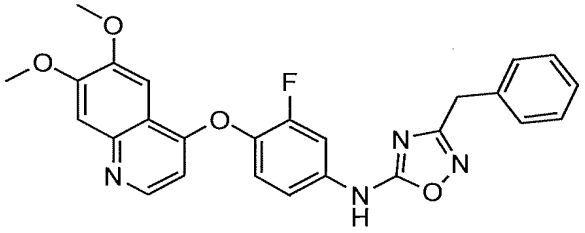
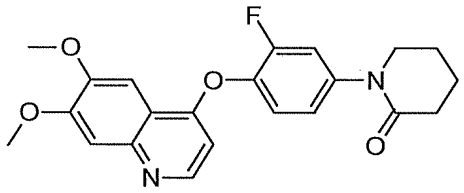
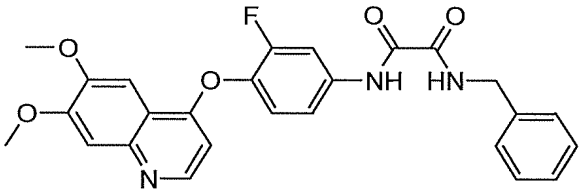
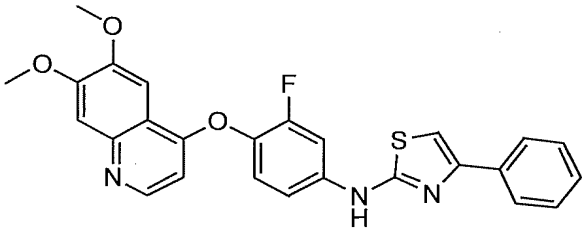
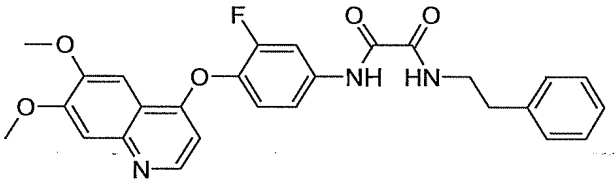
Entry	Name	Structure
9	N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N-methyl-N-(2-phenylethyl) sulfamide	
10	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylmethyl)-1,2,4-oxadiazol-5-amine	
11	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl) piperidin-2-one	
12	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(phenylmethyl)ethanediamide	
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	

Table 1

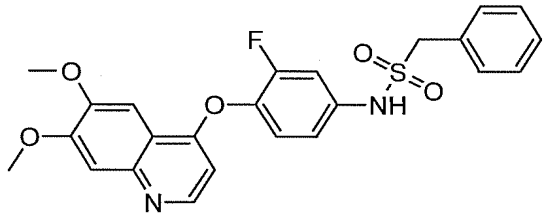
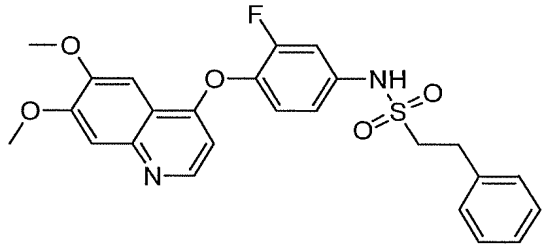
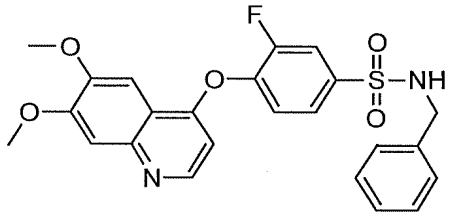
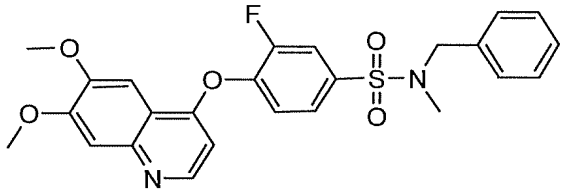
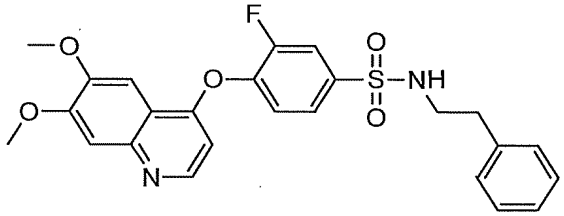
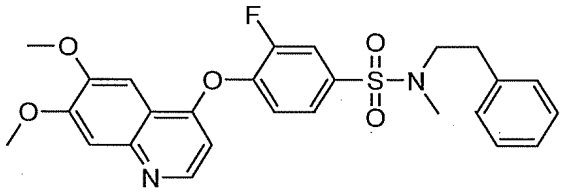
Entry	Name	Structure
15	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-1-phenylmethanesulfonamide	
16	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-2-phenylethanesulfonamide	
17	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-(phenylmethyl) benzenesulfonamide	
18	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(phenylmethyl) benzenesulfonamide	
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	

Table 1

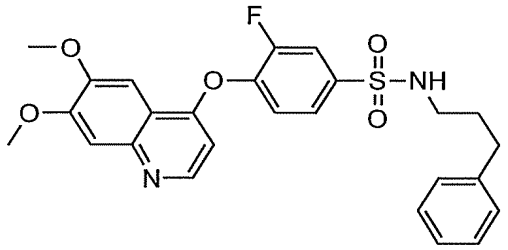
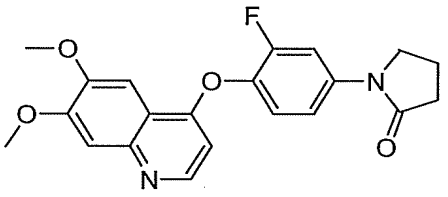
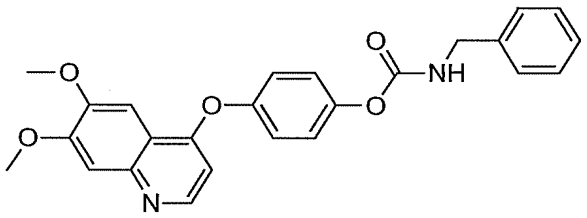
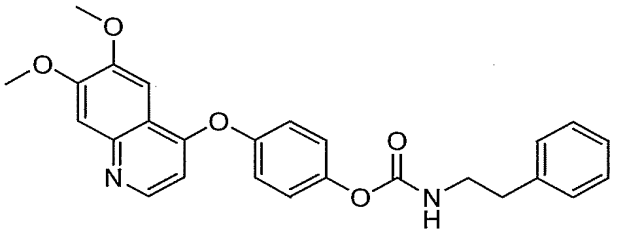
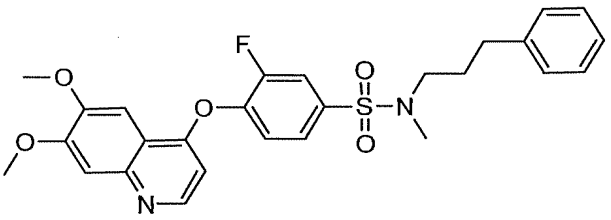
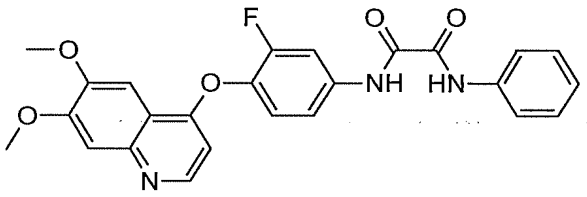
Entry	Name	Structure
21	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-(3-phenylpropyl) benzenesulfonamide	
22	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl) pyrrolidin-2-one	
23	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl (phenylmethyl)carbamate	
24	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl (2-phenylethyl)carbamate	
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	

Table 1

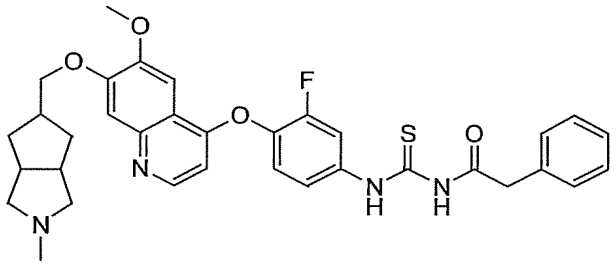
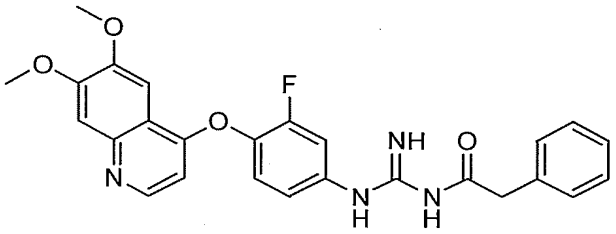
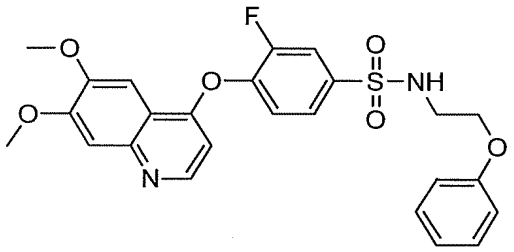
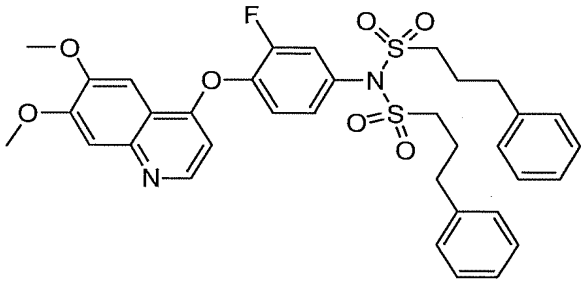
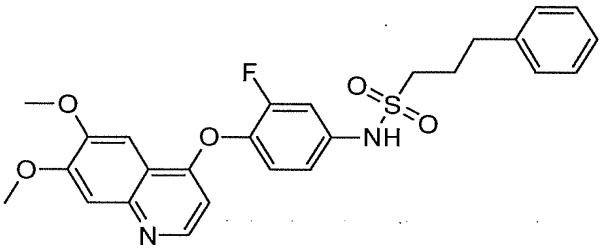
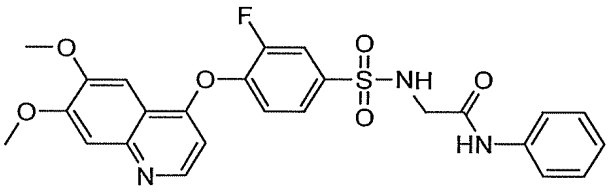
Entry	Name	Structure
27	N-{[(3-fluoro-4-{[7-{[(2-methyloctahydrocyclopenta[c]pyrrol-5-yl)methyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}phenyl)amino]carbonothioyl}-2-phenylacetamide	
28	N-[(Z)-[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)amino](imino)methyl]-2-phenylacetamide	
29	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-[2-(phenyloxy)ethyl]benzenesulfonamide	
30	N,N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-bis-(3-phenylpropane-1-sulfonamide)	
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	

Table 1

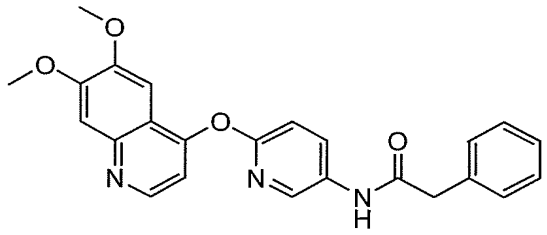
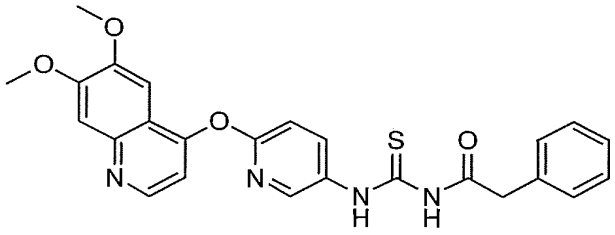
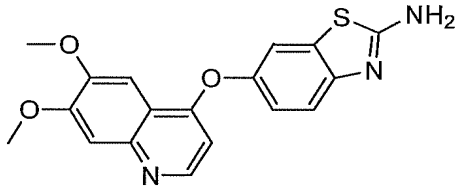
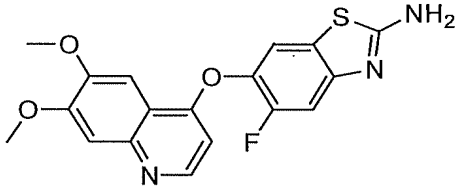
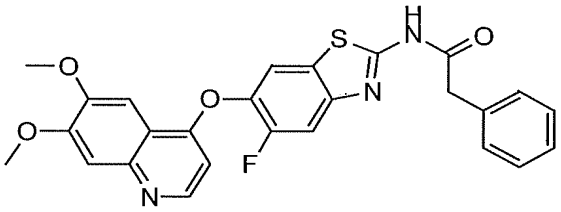
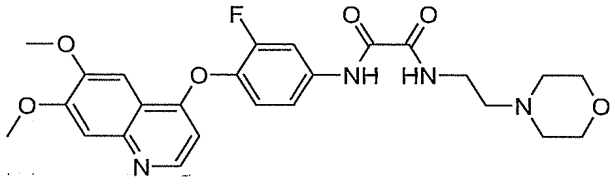
Entry	Name	Structure
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34	N-{[(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)amino]carbonothioyl}-2-phenylacetamide	
35	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-1,3-benzothiazol-2-amine	
36	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-amine	
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	

Table 1

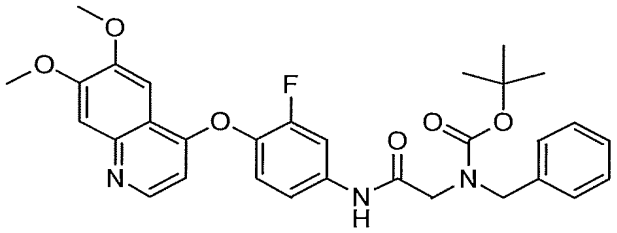
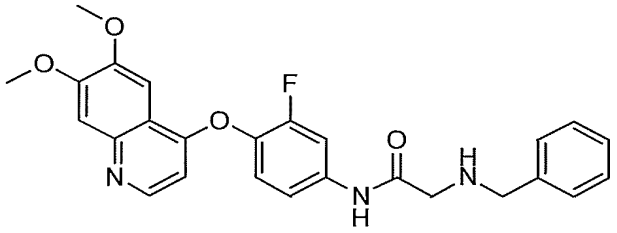
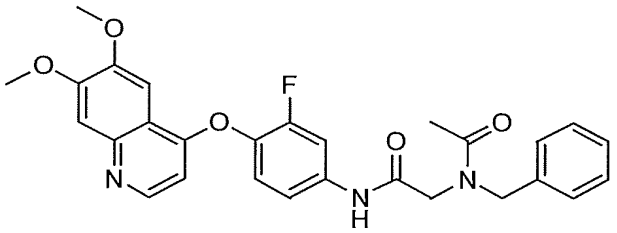
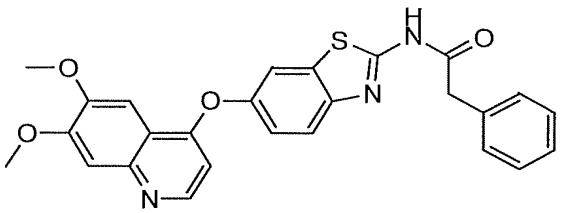
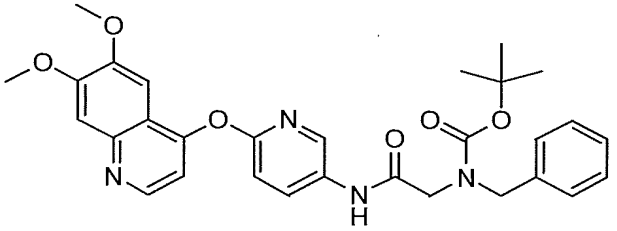
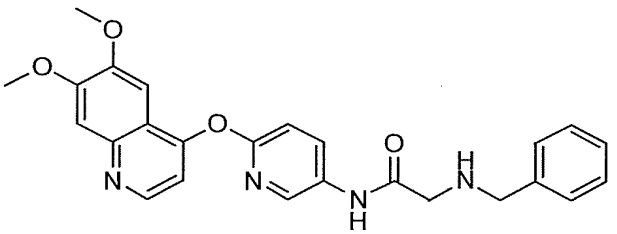
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40	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(phenylmethyl)glycinamide	
41	N2-acetyl-N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(phenylmethyl)glycinamide	
42	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-1,3-benzothiazol-2-yl)-2-phenylacetamide	
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	

Table 1

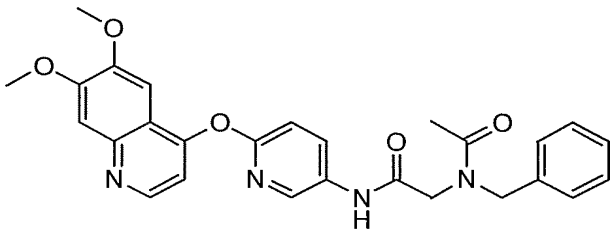
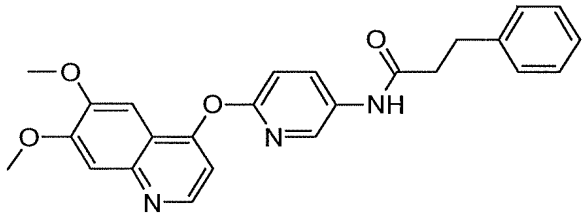
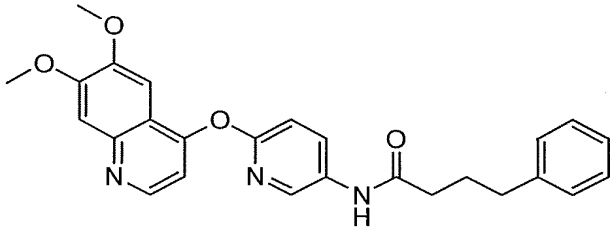
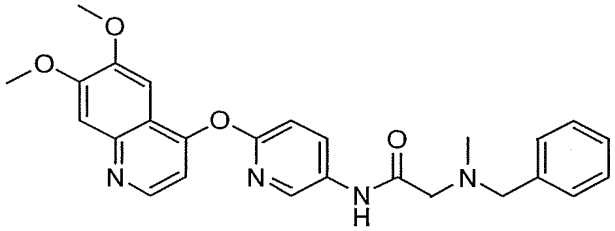
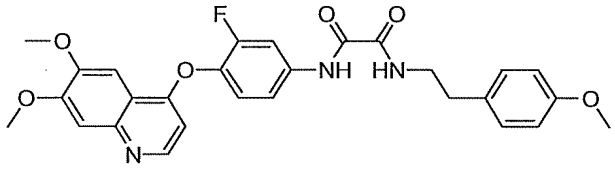
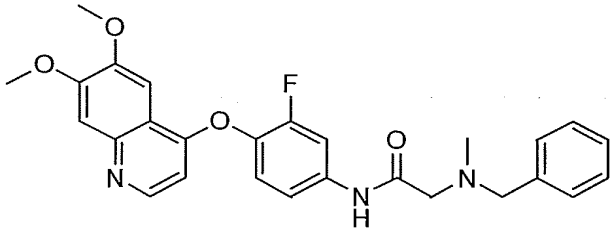
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46	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-3-phenylpropanamide	
47	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-4-phenylbutanamide	
48	N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N2-methyl-N2-(phenylmethyl)glycinamide	
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	

Table 1

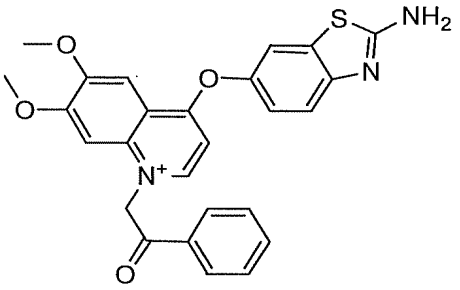
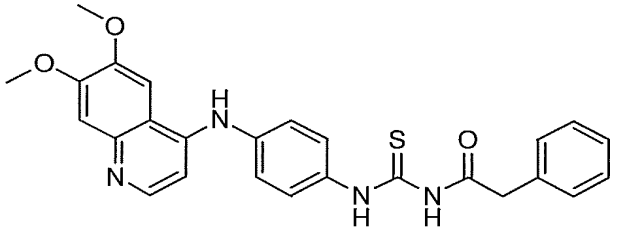
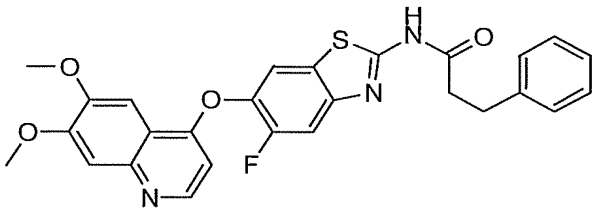
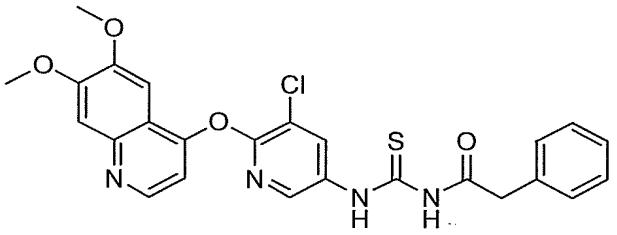
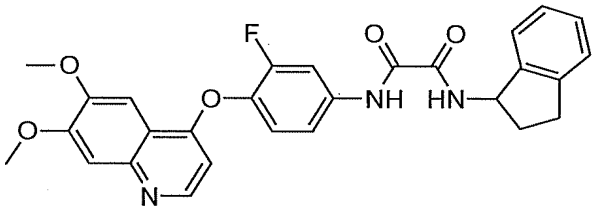
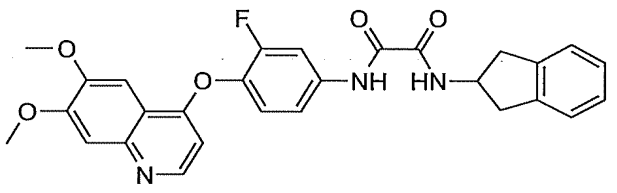
Entry	Name	Structure
51	4-[(2-amino-1,3-benzothiazol-6-yl)oxy]-6,7-bis(methyloxy)-1-(2-oxo-2-phenylethyl) quinolinium	
52	N-{[(4-{[6,7-bis(methyloxy)quinolin-4-yl]amino}phenyl)amino] carbonothioyl}-2-phenylacetamide	
53	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-3-phenylpropanamide	
54	N-{[(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)amino]carbonothioyl}-2-phenylacetamide	
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	

Table 1

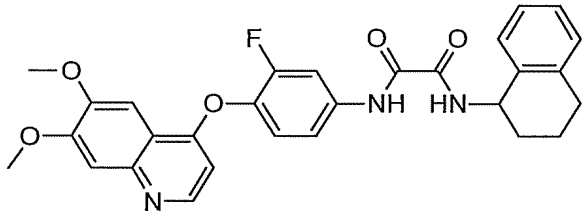
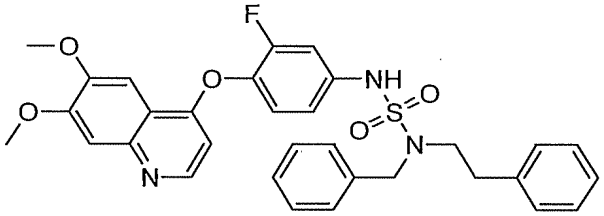
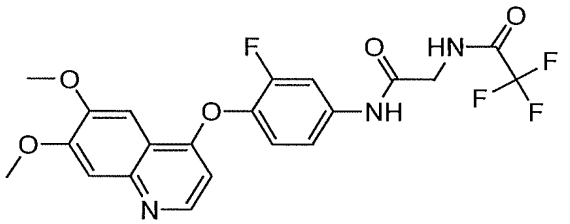
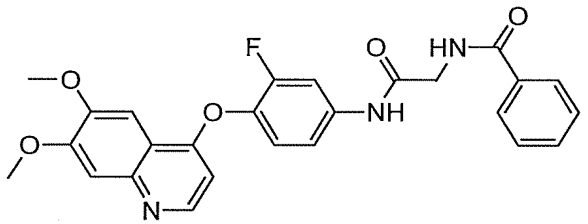
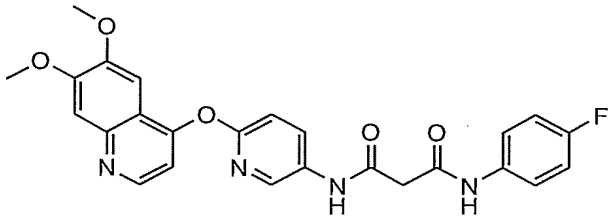
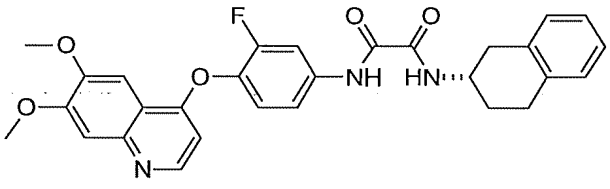
Entry	Name	Structure
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58	N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N-(2-phenylethyl)-N-(phenylmethyl)sulfamide	
59	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(trifluoroacetyl)glycinamide	
60	N-{[4-(6,7-dimethoxy-quinolin-4-yloxy)-3-fluoro-phenylcarbamoyl]-methyl}-benzamide	
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	

Table 1

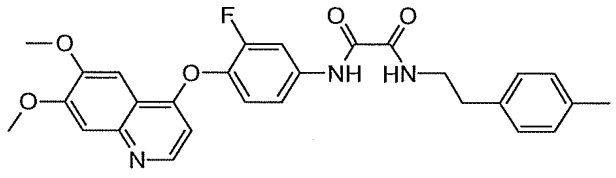
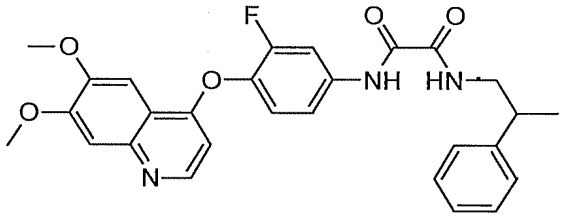
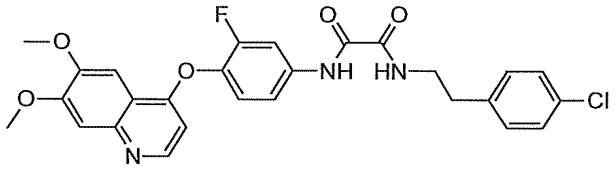
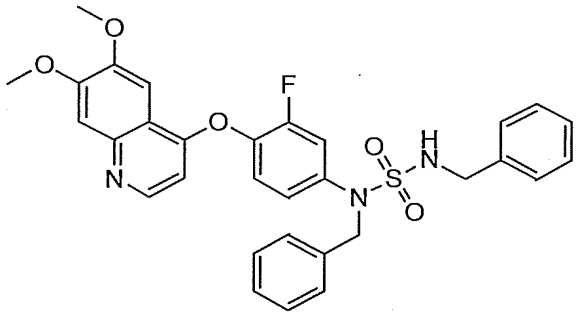
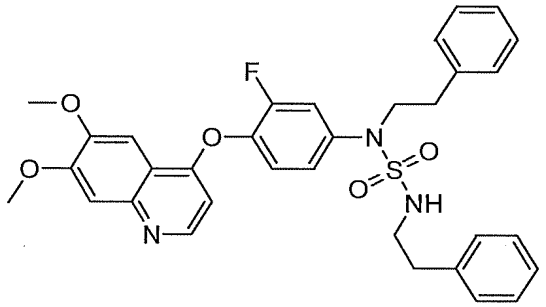
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64	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-phenylpropyl) ethanediamide	
65	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(4-chlorophenyl) ethyl]ethanediamide	
66	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N,N'-bis(phenylmethyl)sulfamide	
67	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N,N'-bis(2-phenylethyl)sulfamide	

Table 1

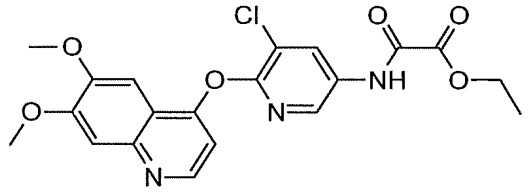
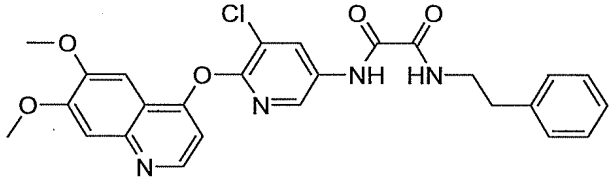
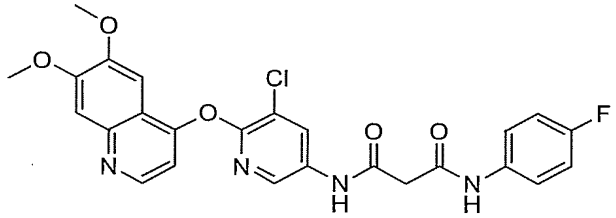
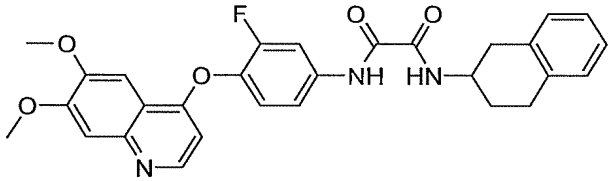
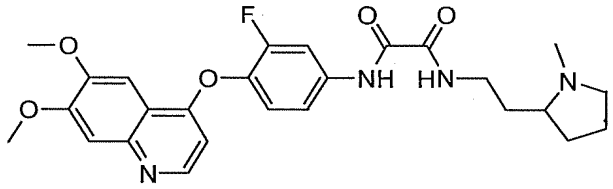
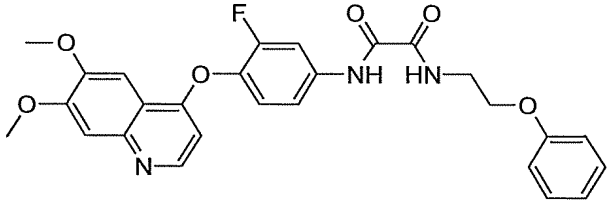
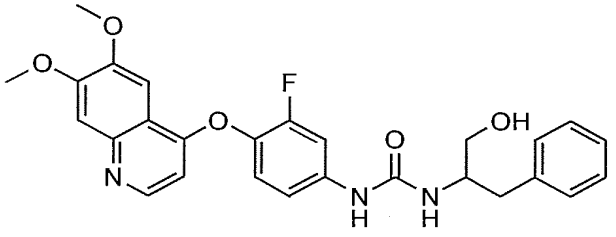
Entry	Name	Structure
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69	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-phenylethyl) ethanediamide	
70	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl) propanediamide	
71	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(1,2,3,4-tetrahydronaphthalen-2-yl)ethanediamide	
72	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(1-methylpyrrolidin-2-yl)ethyl]ethanediamide	
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	

Table 1

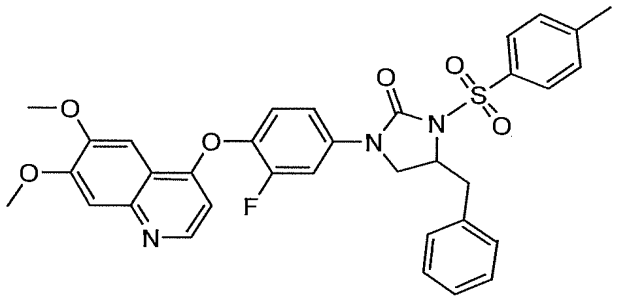
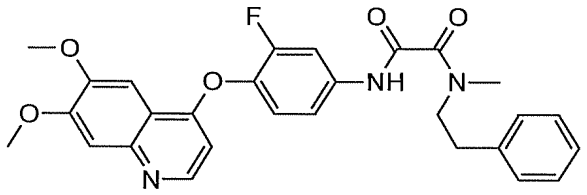
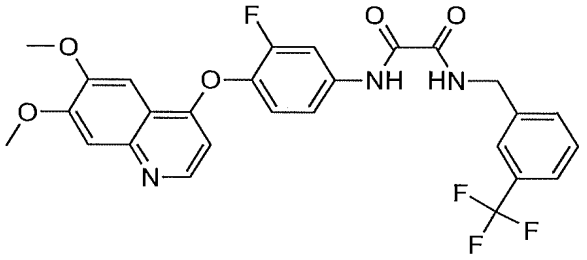
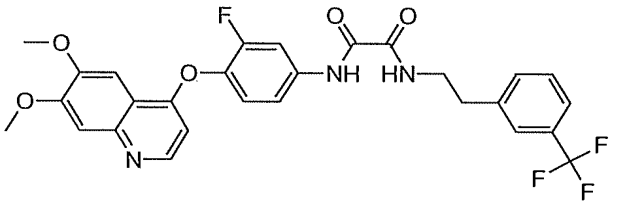
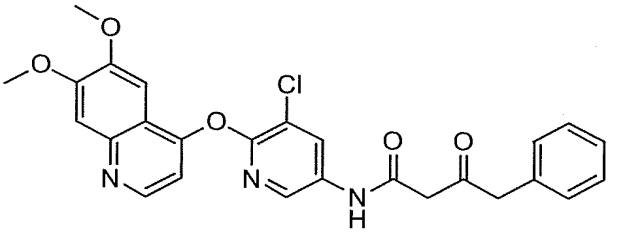
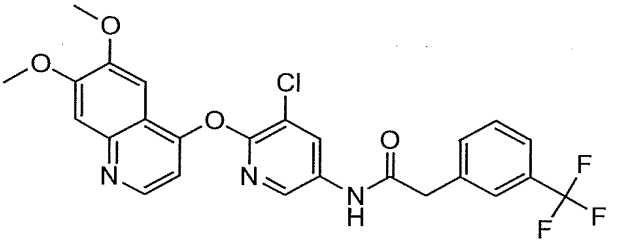
Entry	Name	Structure
75	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-[(4-methylphenyl)sulfonyl]-4-(phenylmethyl)imidazolidin-2-one	
76	N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N-methyl-N-(2-phenylethyl) ethanediamide	
77	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{[3-(trifluoromethyl) phenyl]methyl}ethanediamide	
78	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{2-[3-(trifluoromethyl) phenyl]ethyl}ethanediamide	
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	

Table 1

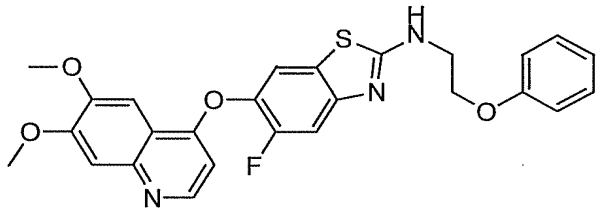
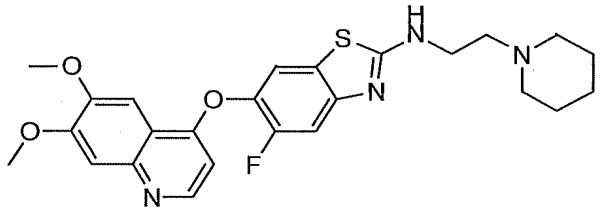
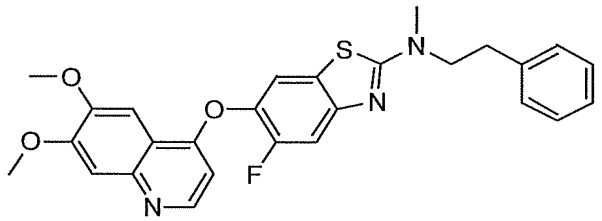
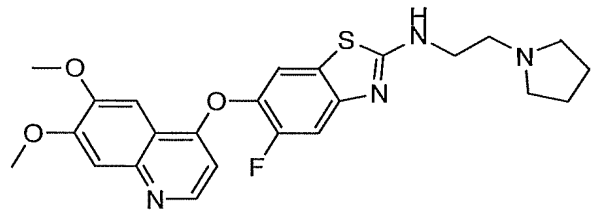
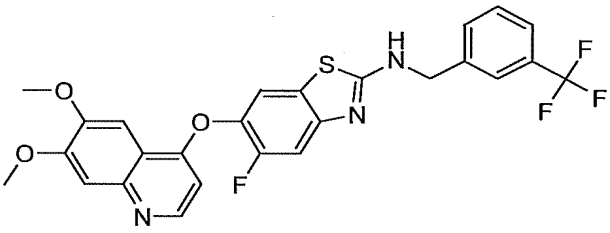
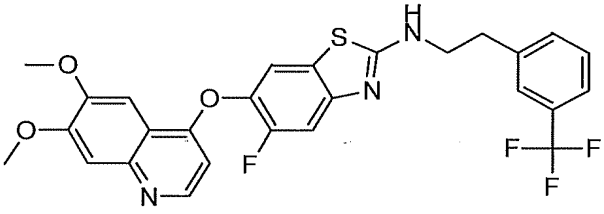
Entry	Name	Structure
81	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-[2-(phenyloxy)ethyl]-1,3-benzothiazol-2-amine	
82	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-(2-piperidin-1-ylethyl)-1,3-benzothiazol-2-amine	
83	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-methyl-N-(2-phenylethyl)-1,3-benzothiazol-2-amine	
84	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-(2-pyrrolidin-1-ylethyl)-1,3-benzothiazol-2-amine	
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	

Table 1

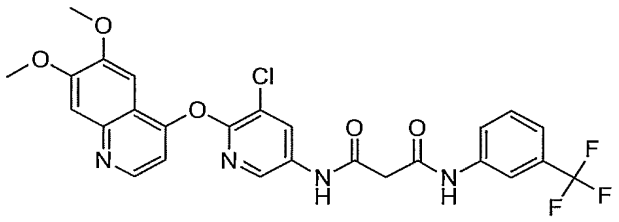
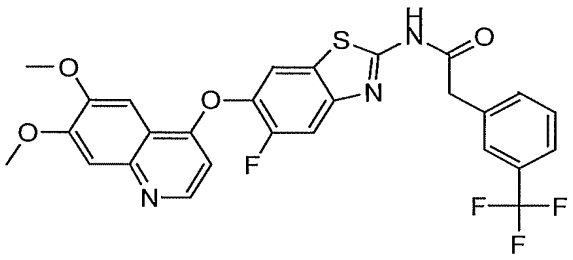
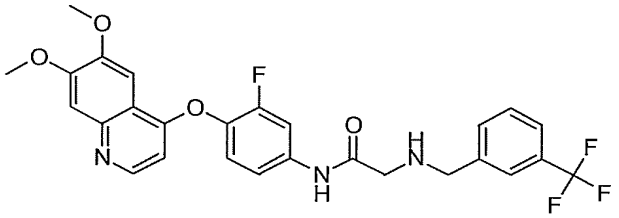
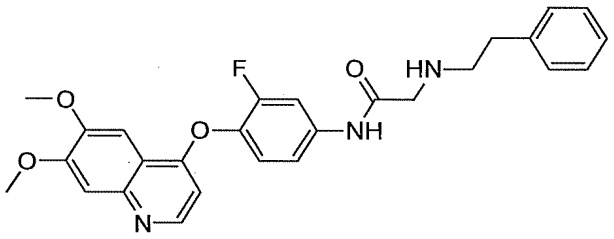
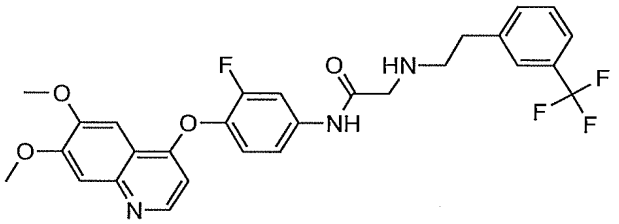
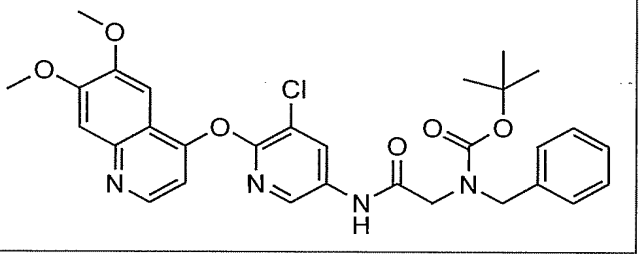
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88	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[3-(trifluoromethyl)phenyl] acetamide	
89	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-{[3-(trifluoromethyl) phenyl]methyl}glycinamide	
90	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(2-phenylethyl)glycinamide	
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	

Table 1

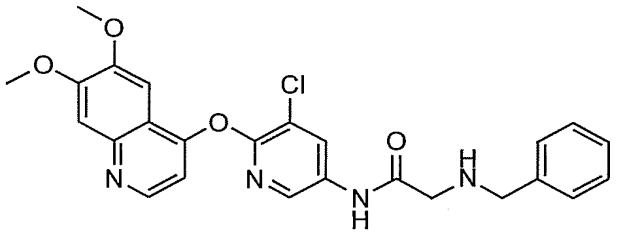
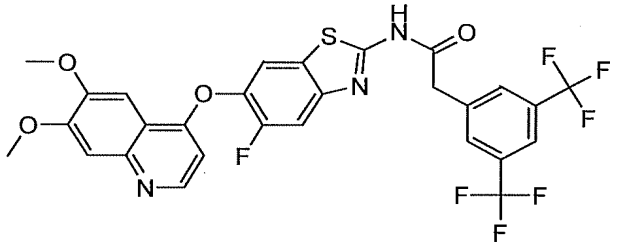
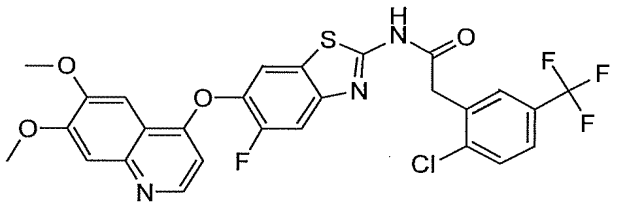
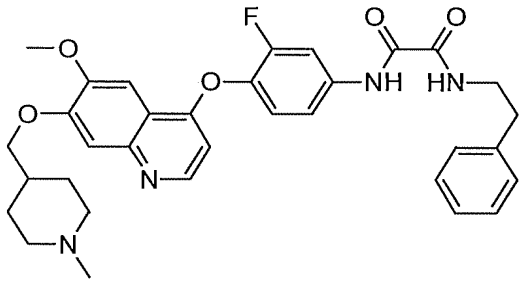
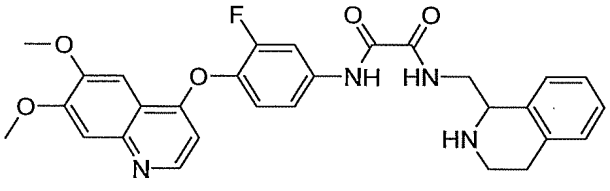
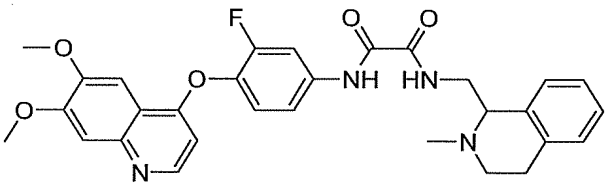
Entry	Name	Structure
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94	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[3,5-bis(trifluoromethyl) phenyl]acetamide	
95	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[2-chloro-5-(trifluoromethyl) 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	
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-	

Table 1

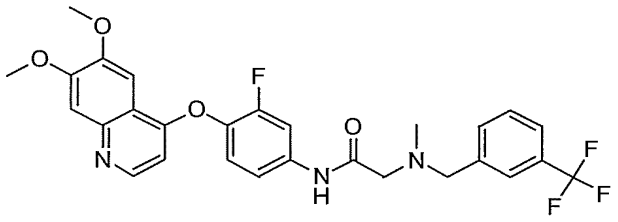
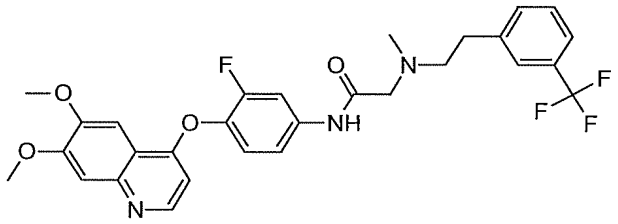
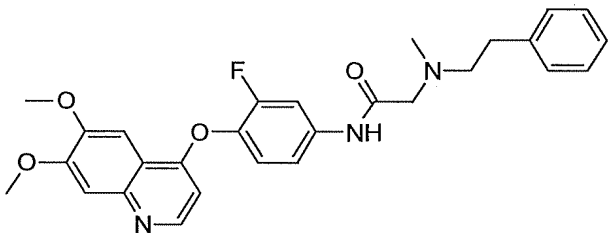
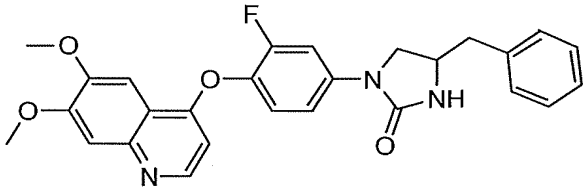
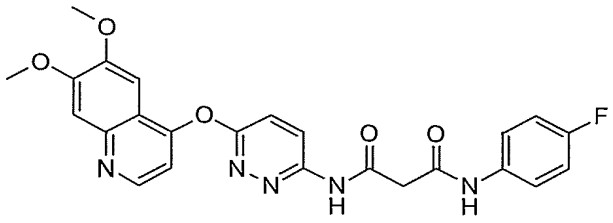
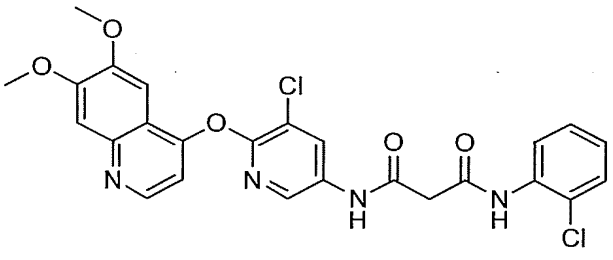
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100	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-methyl-N2-{2-[3-(trifluoromethyl)phenyl]ethyl}glycinamide	
101	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-methyl-N2-(2-phenylethyl)glycinamide	
102	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-4-(phenylmethyl)imidazolidin-2-one	
103	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridazin-3-yl)-N'-(4-fluorophenyl)propanediamide	
104	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-chlorophenyl)propanediamide	

Table 1

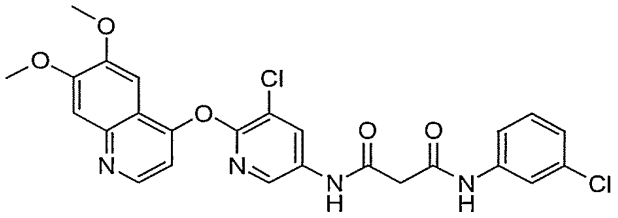
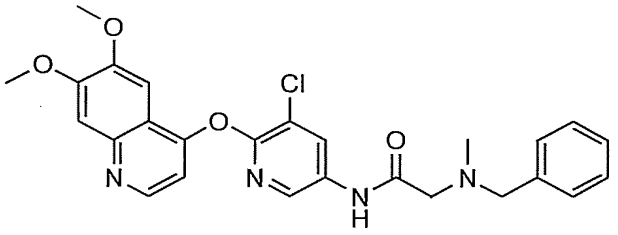
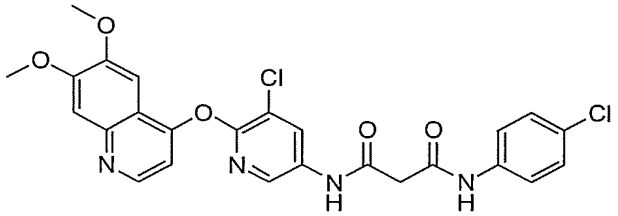
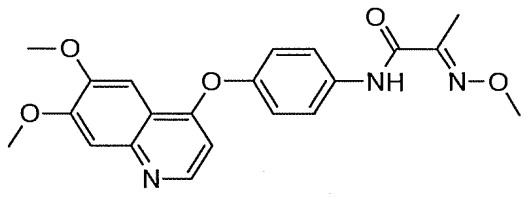
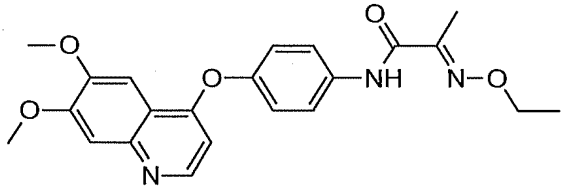
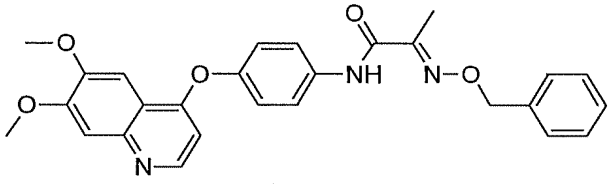
Entry	Name	Structure
105	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(3-chlorophenyl) propanediamide	
106	N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N2-methyl-N2-(phenylmethyl)glycinamide	
107	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-chlorophenyl) 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	
110	(2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-{[(phenylmethyl)oxy]imino} propanamide	

Table 1

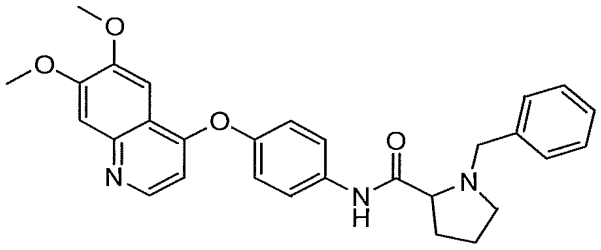
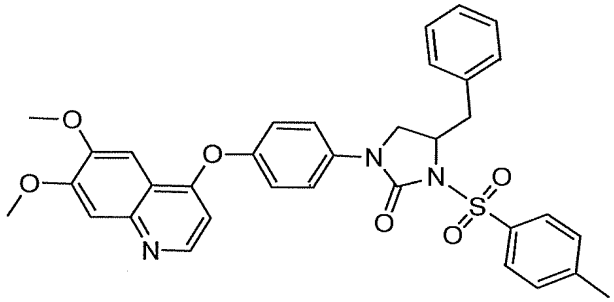
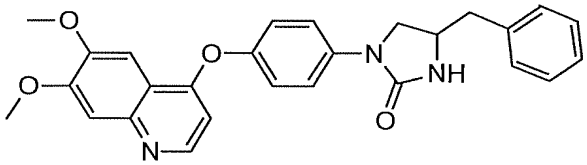
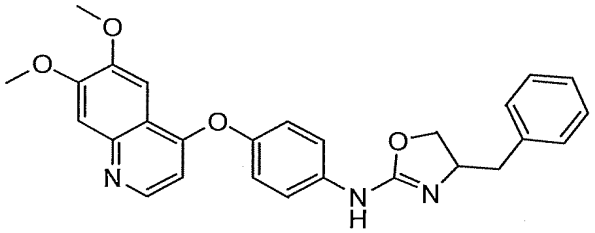
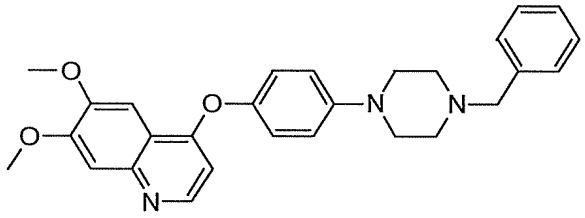
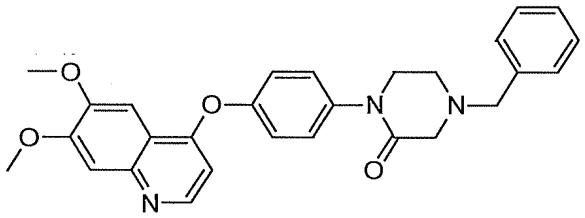
Entry	Name	Structure
111	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-1-(phenylmethyl)prolinamide	
112	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-3-[(4-methylphenyl)sulfonyl]-4-(phenylmethyl)imidazolidin-2-one	
113	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)imidazolidin-2-one	
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	
116	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)piperazin-2-one	

Table 1

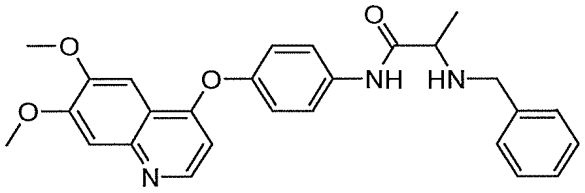
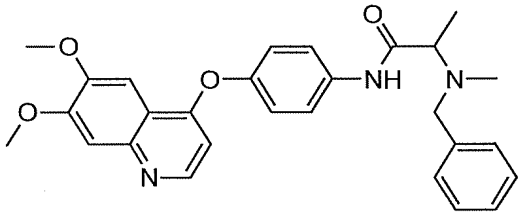
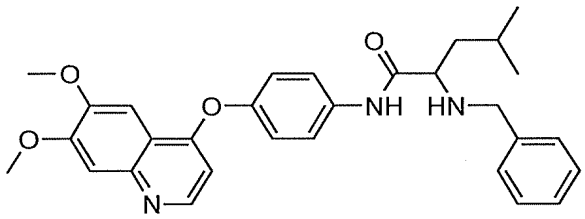
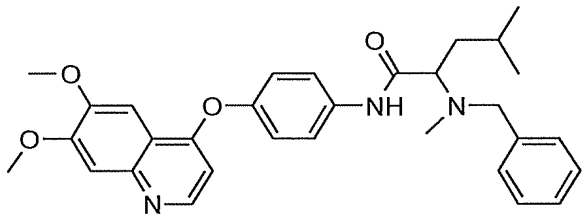
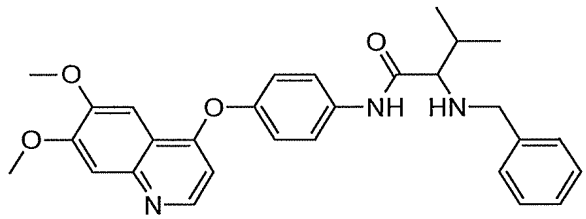
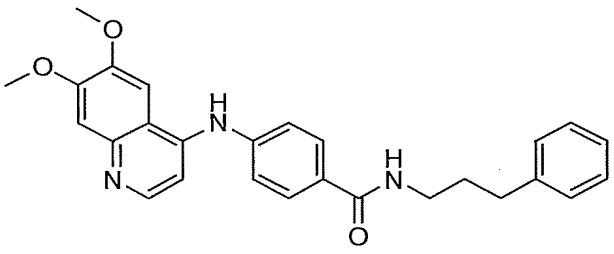
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117	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-(phenylmethyl)alaninamide	
118	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-methyl-N2-(phenylmethyl) alaninamide	
119	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-(phenylmethyl)leucinamide	
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	
122	4-(6,7-dimethoxy-quinolin-4-ylamino)-N-(3-phenyl-propyl)-benzamide	

Table 1

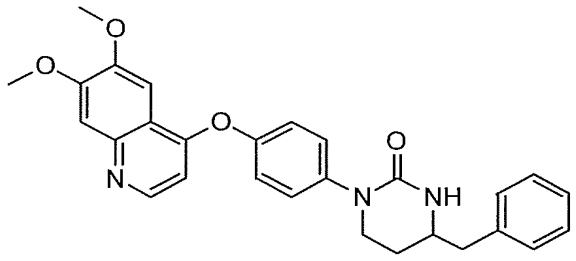
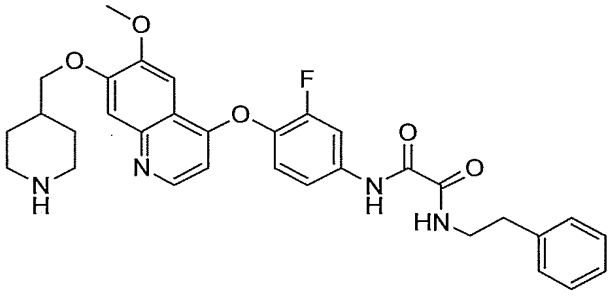
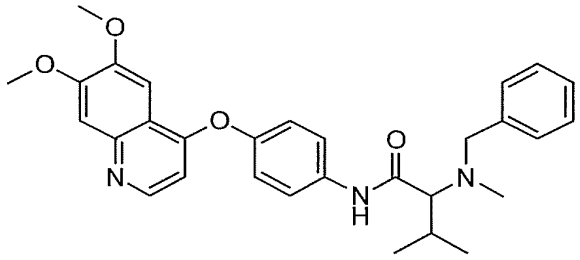
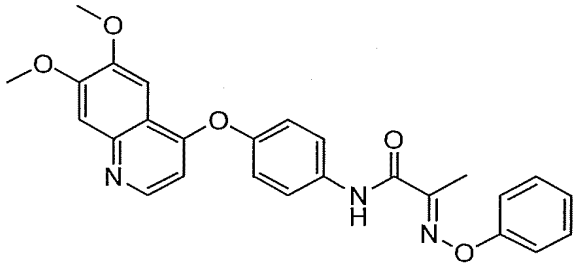
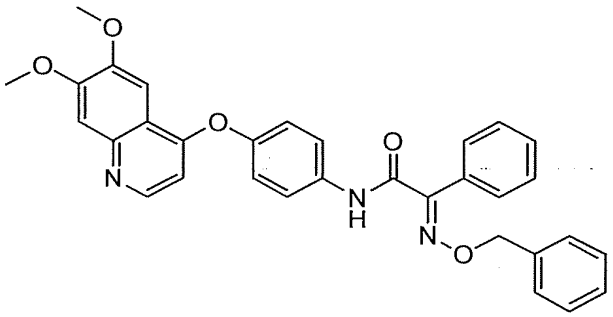
Entry	Name	Structure
123	4-benzyl-1-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-tetrahydro-pyrimidin-2-one	
124	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	
125	2-(Benzyl-methyl-amino)-N-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-3-methyl-butyramide (note: Alphabetic order of prefixes ignored while selecting parent chain)	
126	N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-phenyl]-2-phenoxyimino-propionamide	
127	2-Benzyloxyimino-N-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-2-phenyl-acetamide	

Table 1

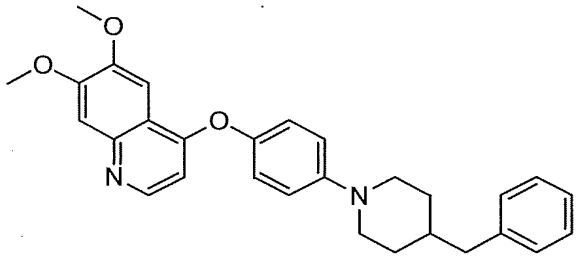
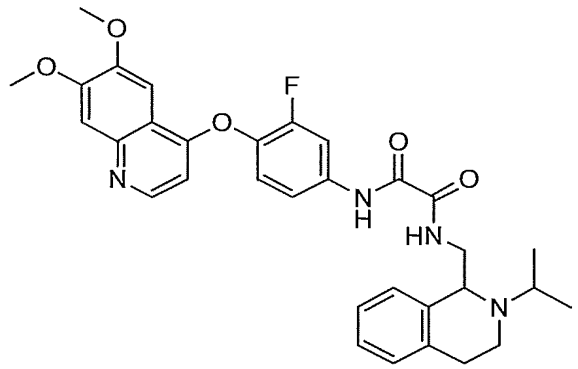
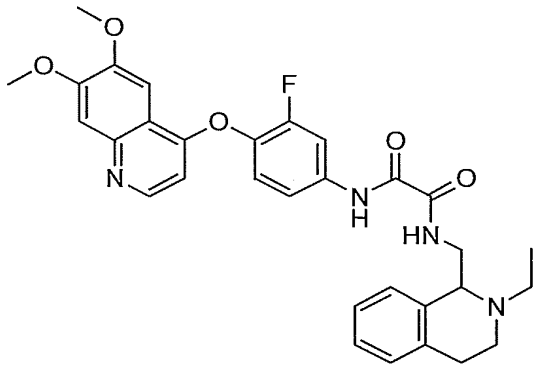
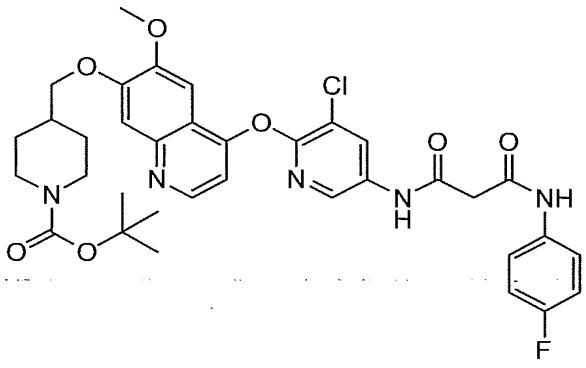
Entry	Name	Structure
128	4-[4-(4-Benzyl-piperidin-1-yl)-phenoxy]-6,7-dimethoxy-quinoline	
129	N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-N'-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-oxalamide	
130	N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-N'-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-oxalamide	
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	

Table 1

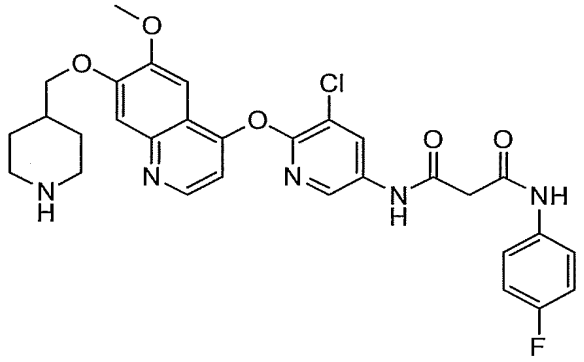
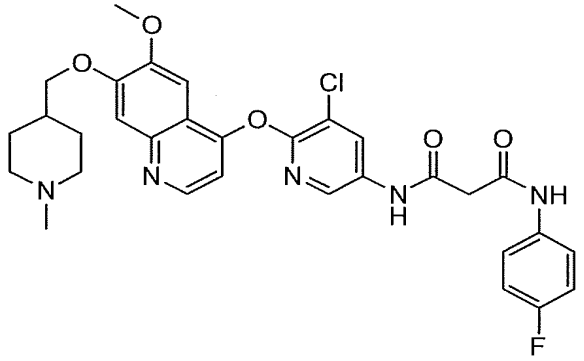
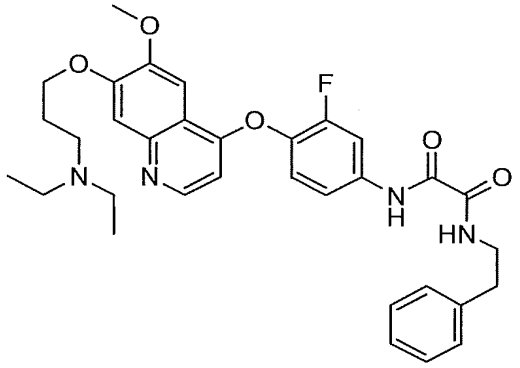
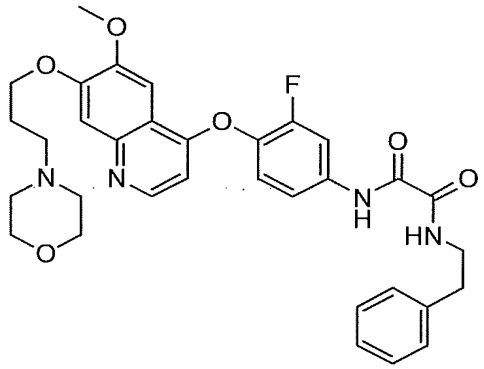
Entry	Name	Structure
132	N-{5-Chloro-6-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide	
133	N-{5-Chloro-6-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide	
134	N-{4-[7-(3-Diethylamino-propoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-N'-phenethyl-oxalamide	
135	N-{3-Fluoro-4-[6-methoxy-7-(3-morpholin-4-yl-propoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	

Table 1

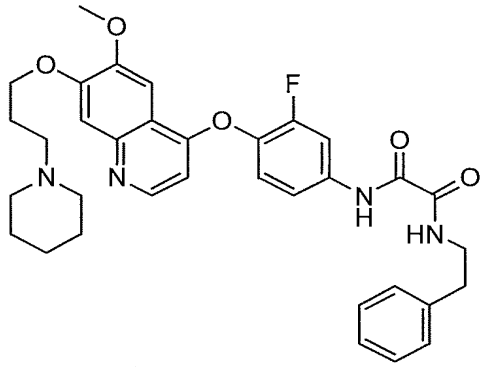
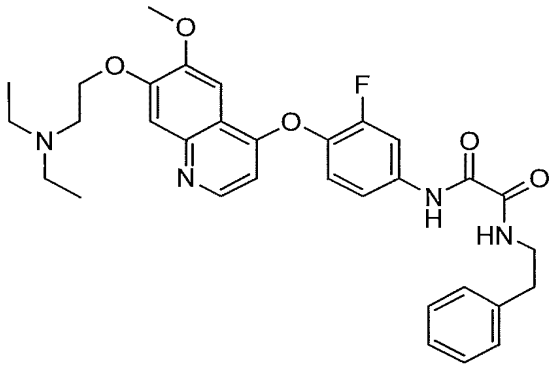
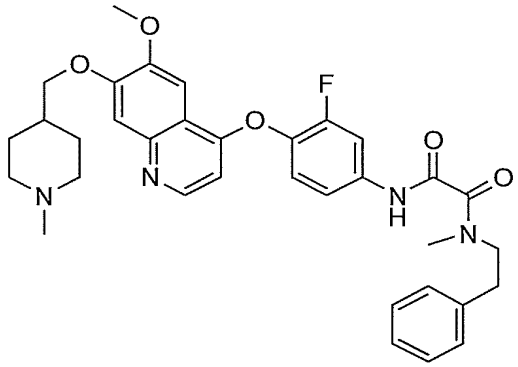
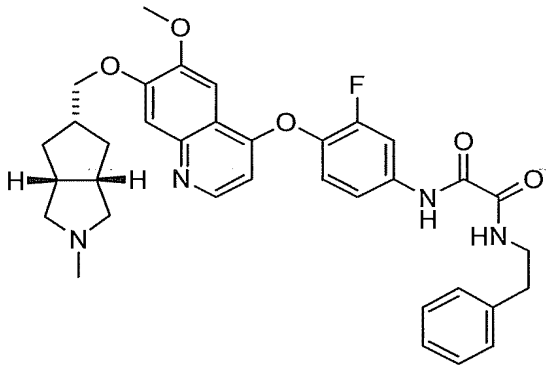
Entry	Name	Structure
136	N-{3-Fluoro-4-[6-methoxy-7-(3-piperidin-1-yl-propoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	
137	N-{4-[7-(2-Diethylamino-ethoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-N'-phenethyl-oxalamide	
138	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-methyl-N'-phenethyl-oxalamide	
139	N-{3-Fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	

Table 1

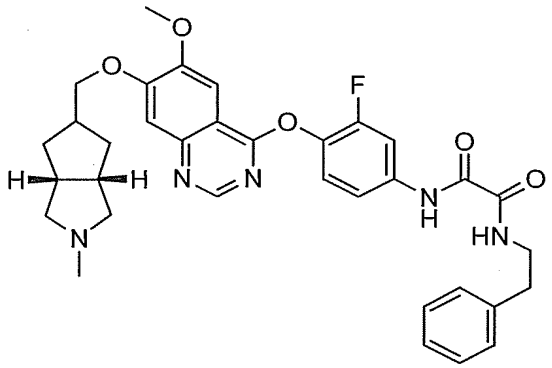
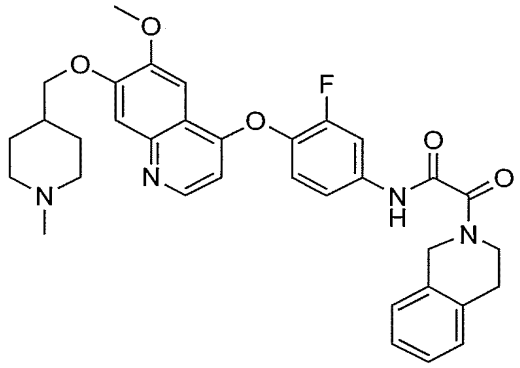
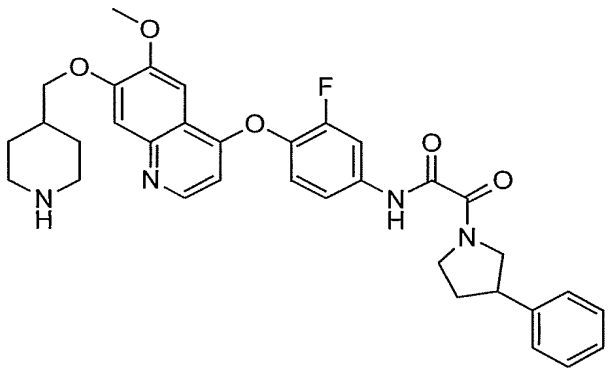
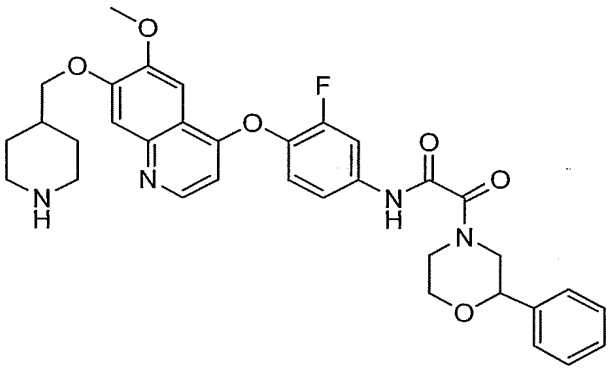
Entry	Name	Structure
140	N-{3-Fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	
141	2-(3,4-Dihydro-1H-isoquinolin-2-yl)-N-{3-fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-acetamide	
142	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-2-(3-phenyl-pyrrolidin-1-yl)-acetamide	
143	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-2-(2-phenyl-morpholin-4-yl)-acetamide	

Table 1

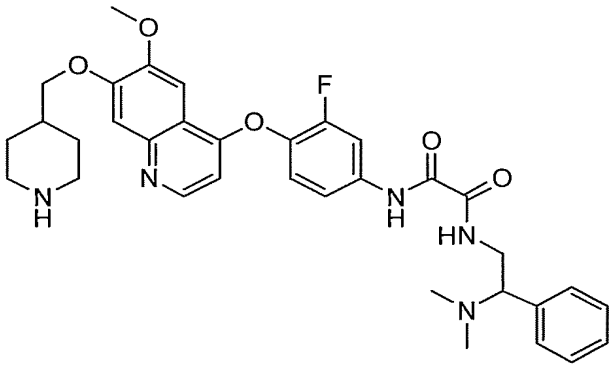
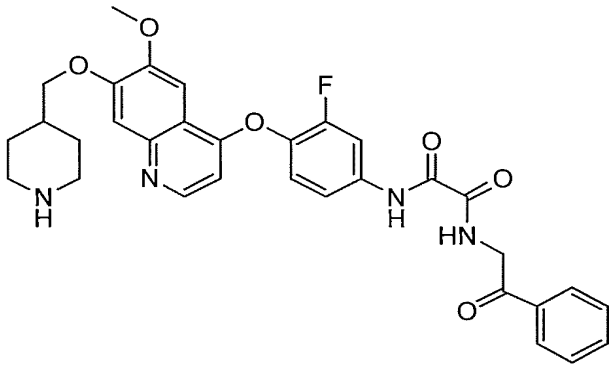
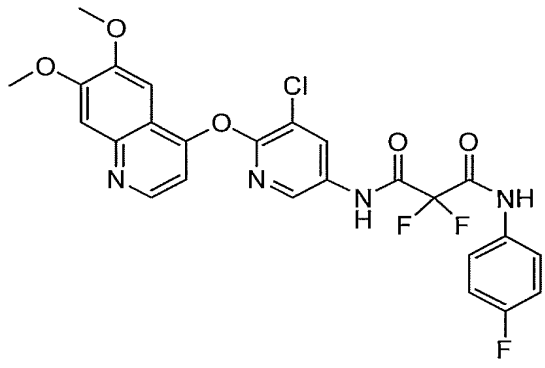
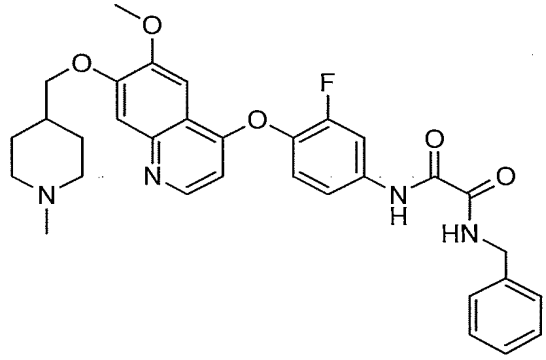
Entry	Name	Structure
144	N-(2-Dimethylamino-2-phenyl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
145	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-oxo-2-phenyl-ethyl)-oxalamide	
146	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-2,2-difluoro-N'-(4-fluoro-phenyl)-malonamide	
147	N-Benzyl-N'-{3-fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

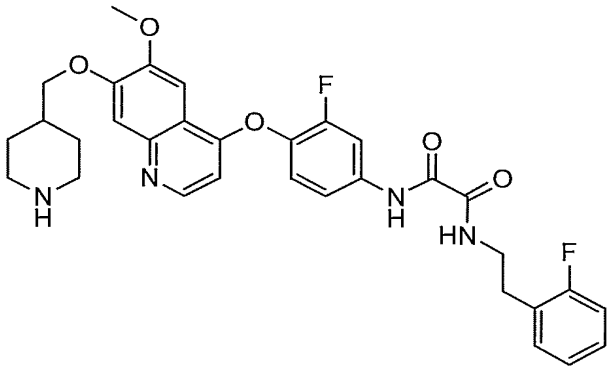
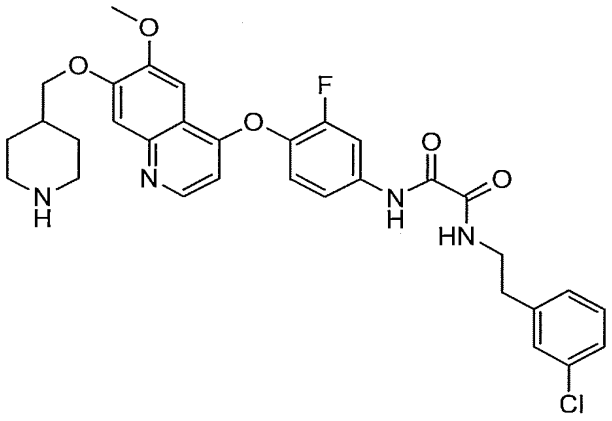
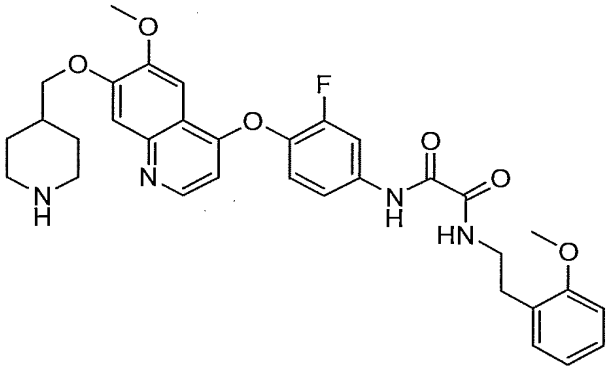
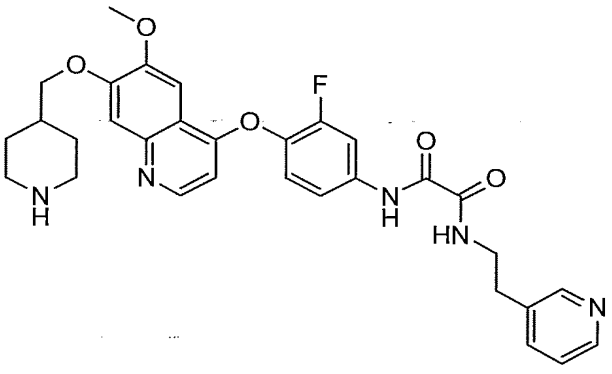
Entry	Name	Structure
148	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(2-fluoro-phenyl)-ethyl]-oxalamide	
149	N-[2-(3-Chloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
150	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(2-methoxy-phenyl)-ethyl]-oxalamide	
151	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-pyridin-3-yl-ethyl)-oxalamide	

Table 1

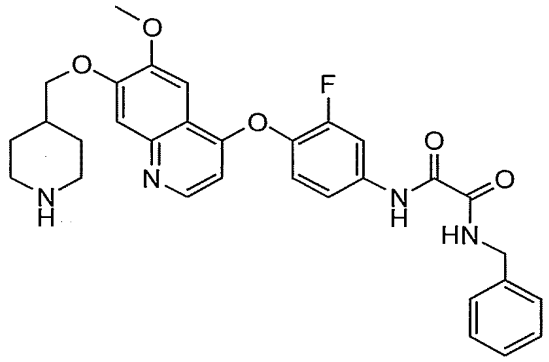
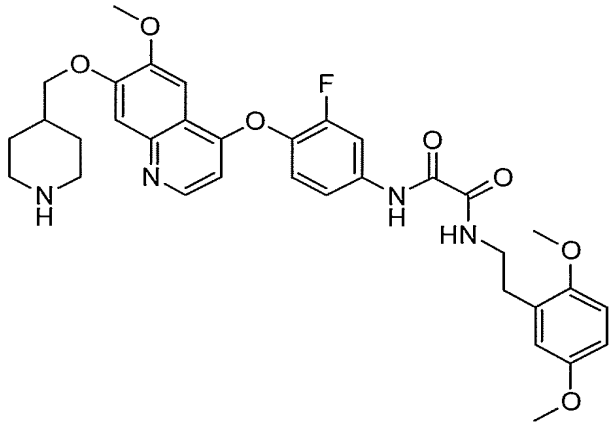
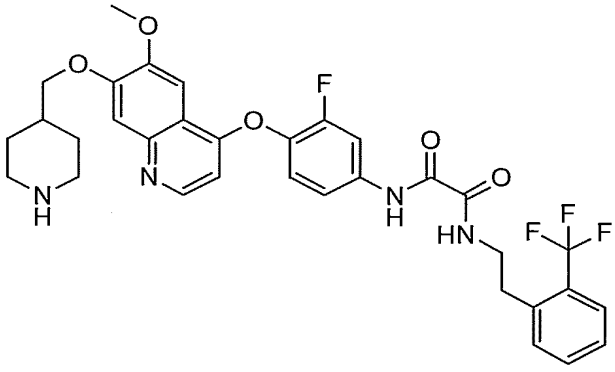
Entry	Name	Structure
152	N-Benzyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
153	N-[2-(2,5-Dimethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
154	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(2-trifluoromethyl-phenyl)-ethyl]-oxalamide	

Table 1

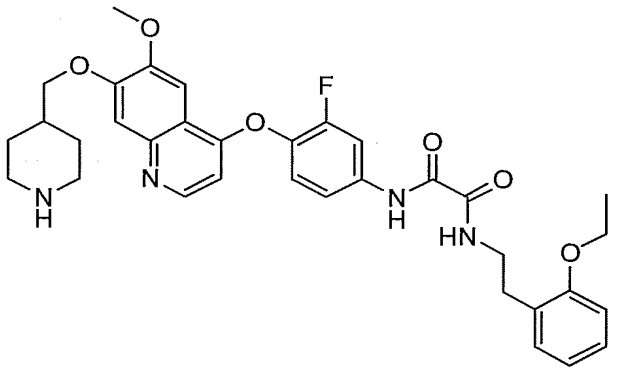
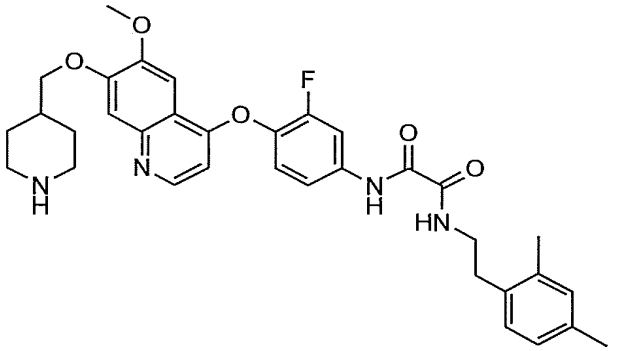
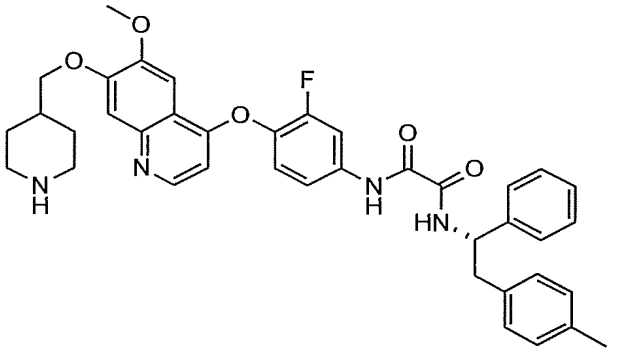
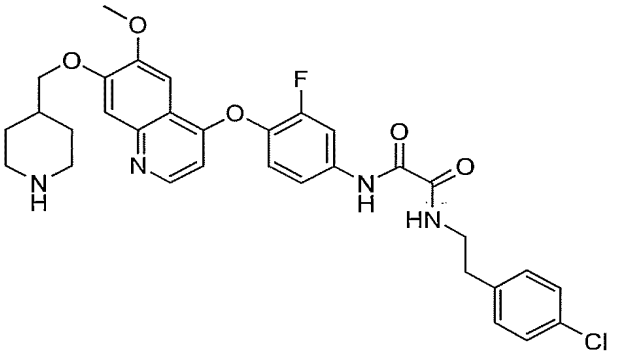
Entry	Name	Structure
155	N-[2-(2-Ethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
156	N-[2-(2,4-Dimethyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
157	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1*S*-phenyl-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

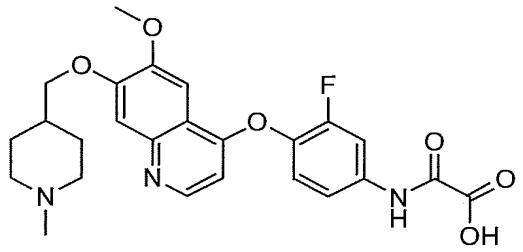
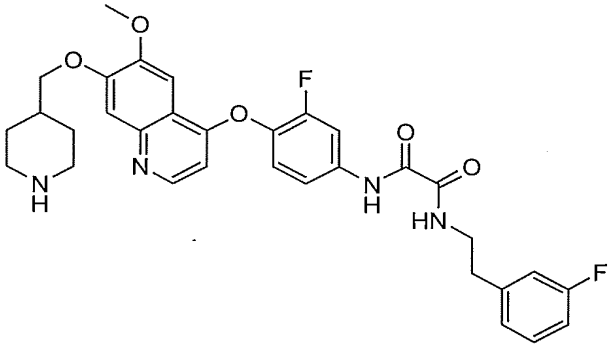
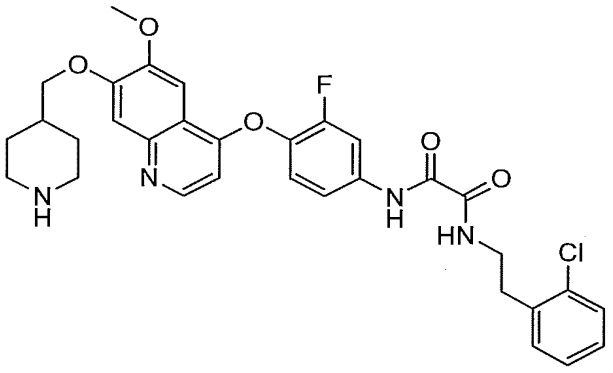
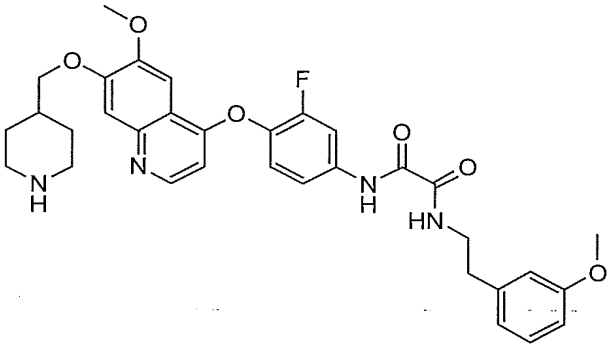
Entry	Name	Structure
159	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamic acid	
160	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(3-fluoro-phenyl)-ethyl]-oxalamide	
161	N-[2-(2-Chloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
162	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(3-methoxy-phenyl)-ethyl]-oxalamide	

Table 1

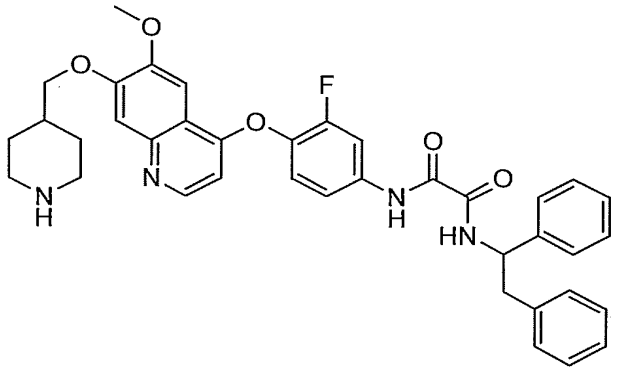
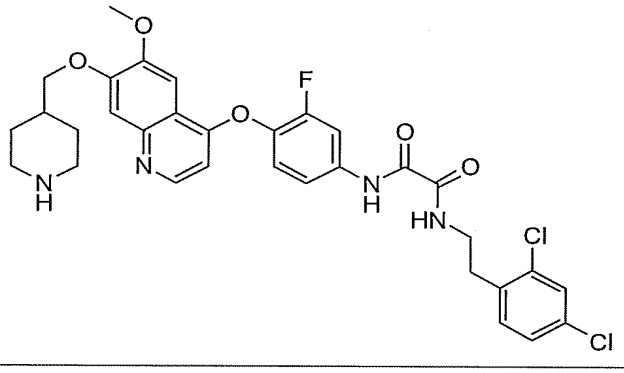
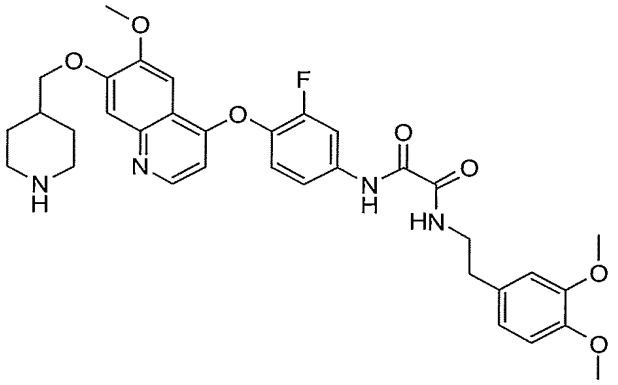
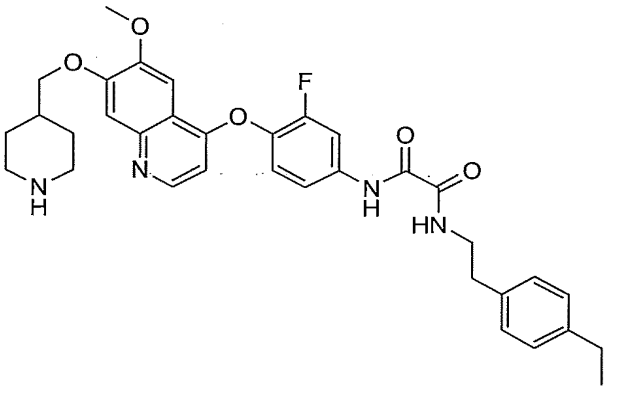
Entry	Name	Structure
163	N-(1,2-Diphenyl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
164	N-[2-(2,4-Dichloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
165	N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-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

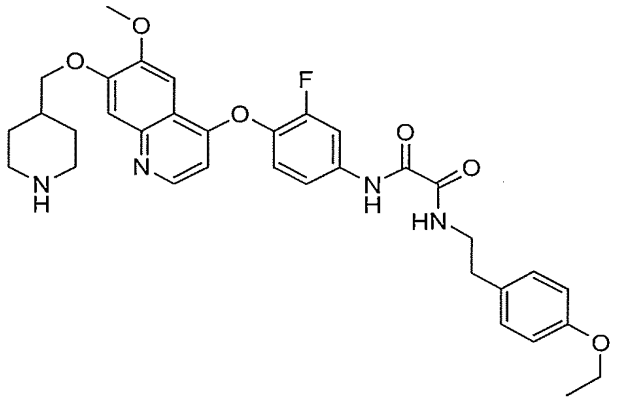
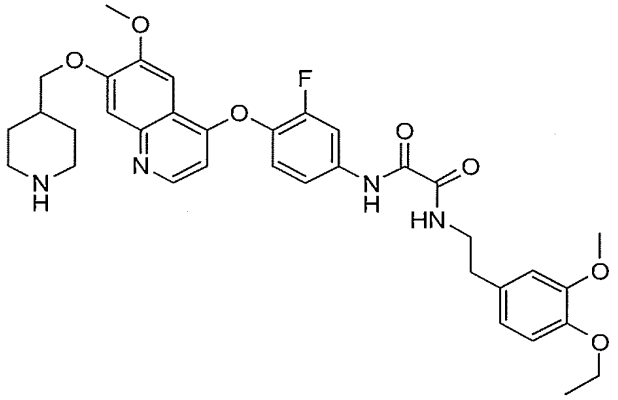
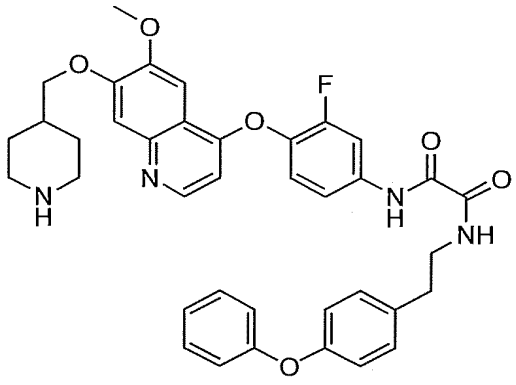
Entry	Name	Structure
167	N-[2-(4-Ethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
168	N-[2-(4-Ethoxy-3-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
169	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-phenoxy-phenyl)-ethyl]-oxalamide	

Table 1

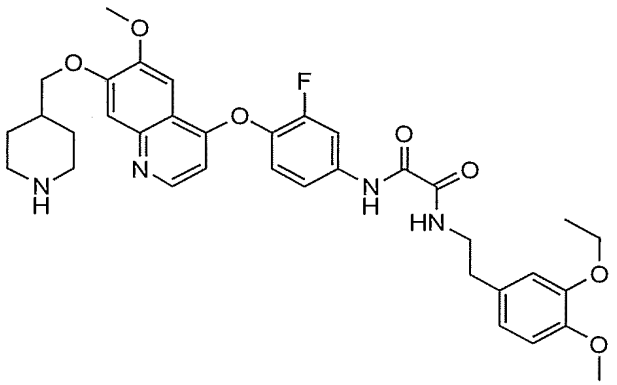
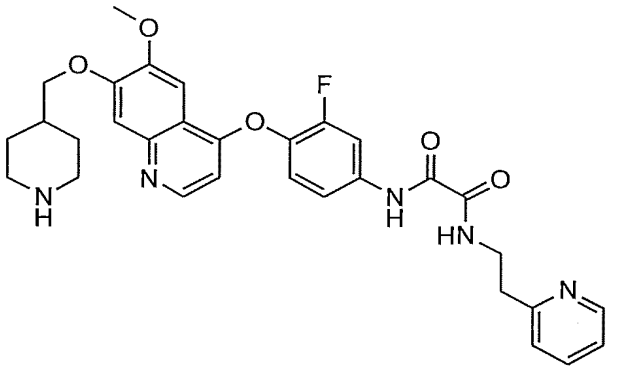
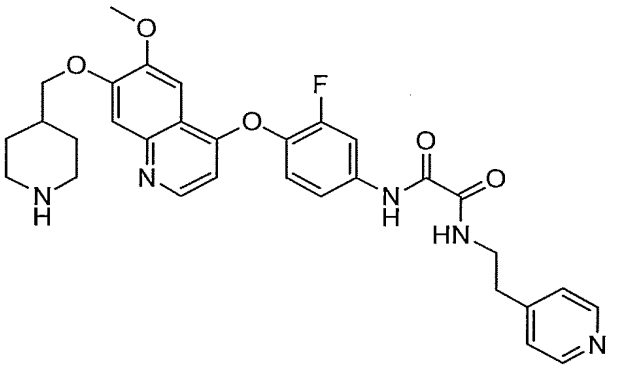
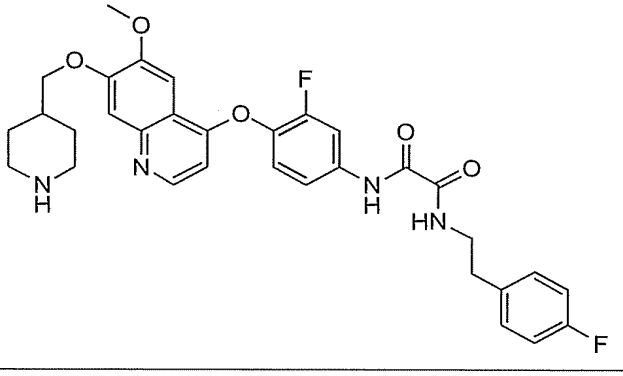
Entry	Name	Structure
170	N-[2-(3-Ethoxy-4-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
171	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-pyridin-2-yl-ethyl)-oxalamide	
172	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-pyridin-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

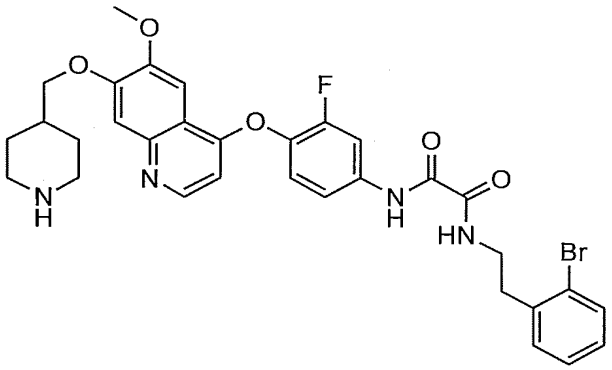
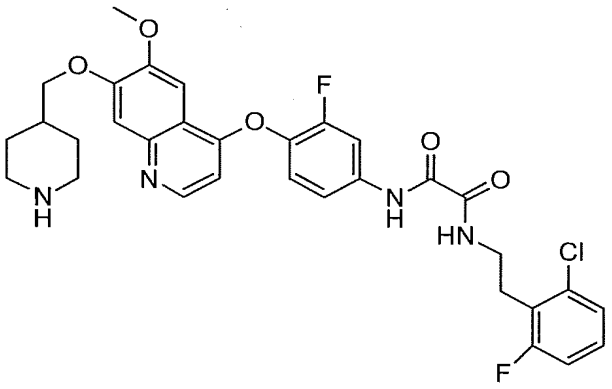
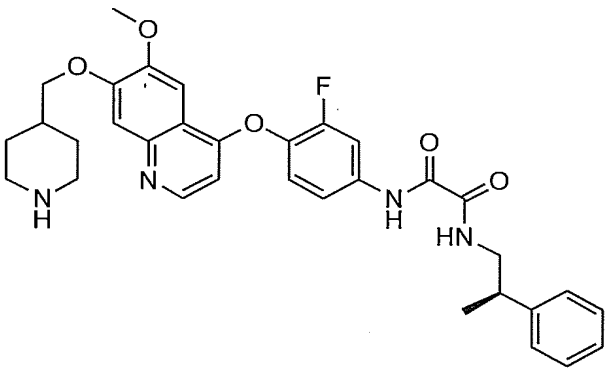
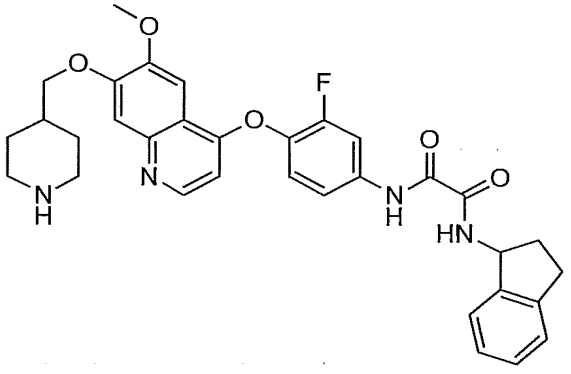
Entry	Name	Structure
174	N-[2-(2-Bromo-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
175	N-[2-(2-Chloro-6-fluoro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
176	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2*R*-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

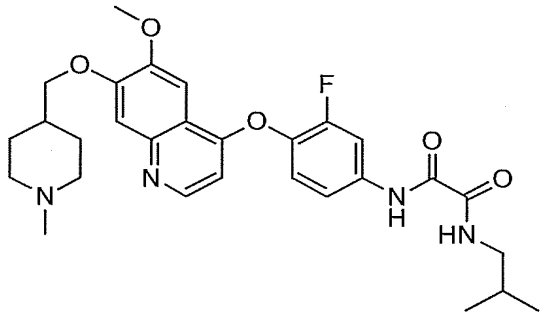
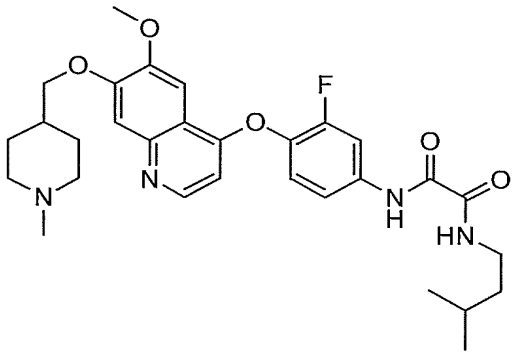
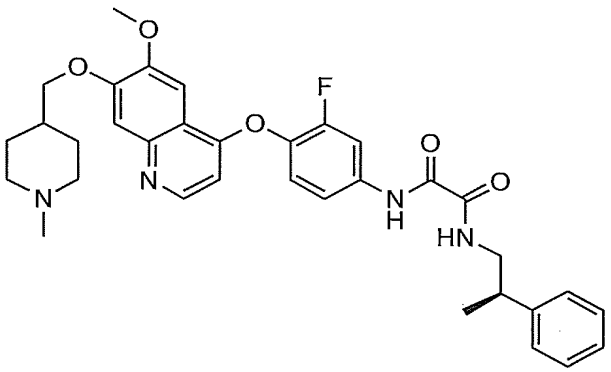
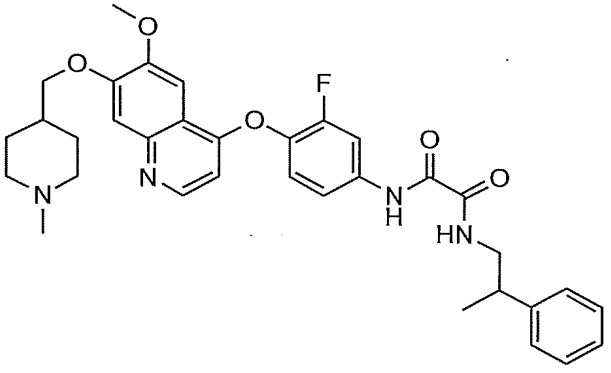
Entry	Name	Structure
178	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-isobutyl-oxalamide	
179	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-methyl-butyl)-oxalamide	
180	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2*R*-phenyl-propyl)-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

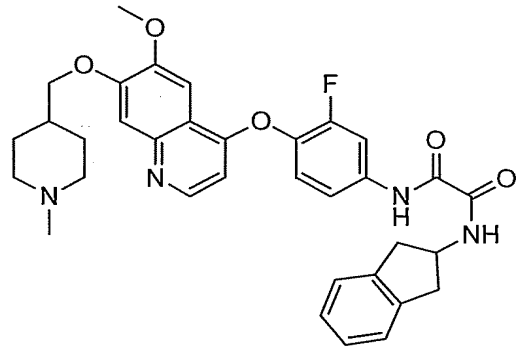
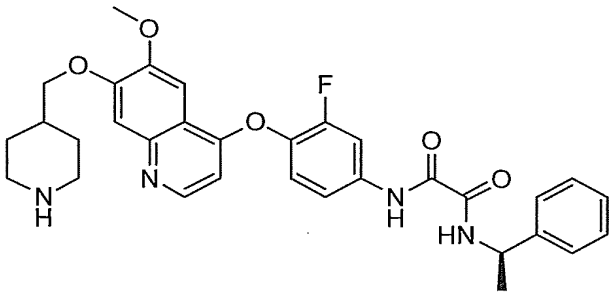
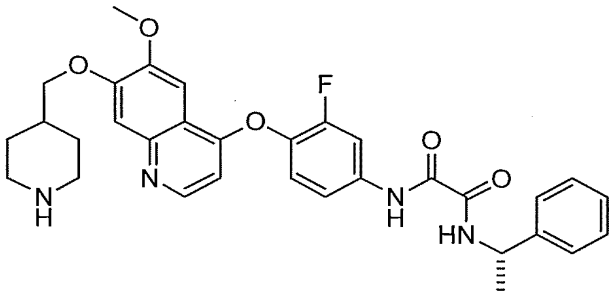
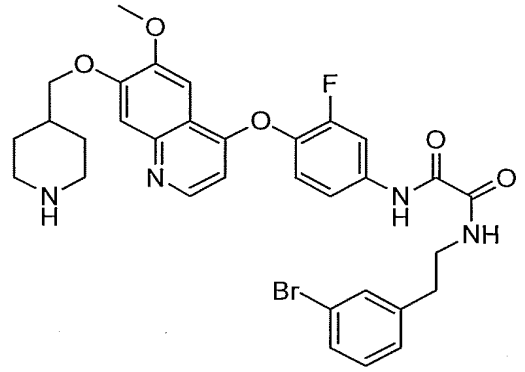
Entry	Name	Structure
182	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-indan-2-yl-oxalamide	
183	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1*R*-phenyl-ethyl)-oxalamide	
184	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1*S*-phenyl-ethyl)-oxalamide	
185	N-[2-(3-Bromo-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

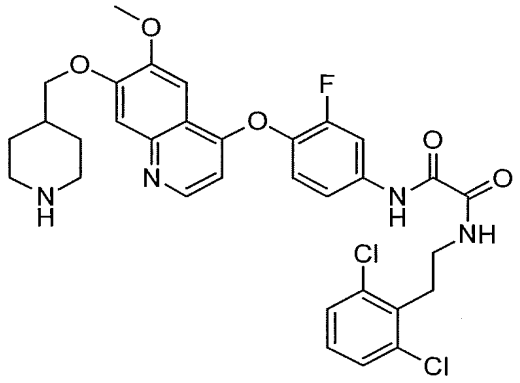
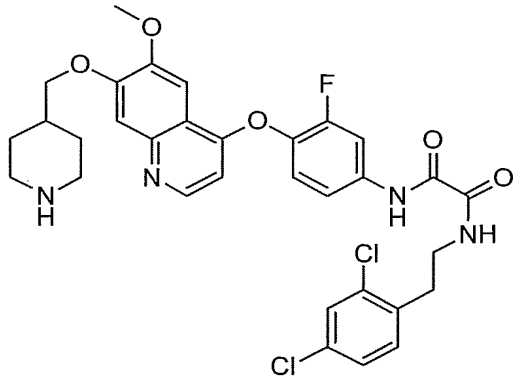
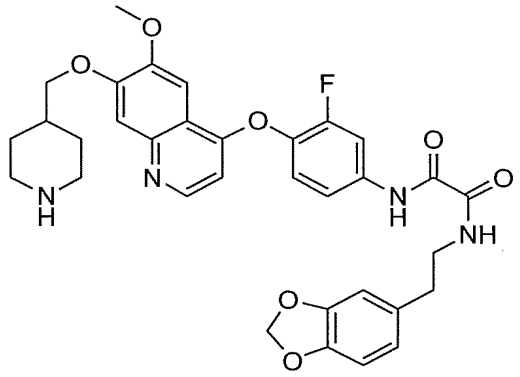
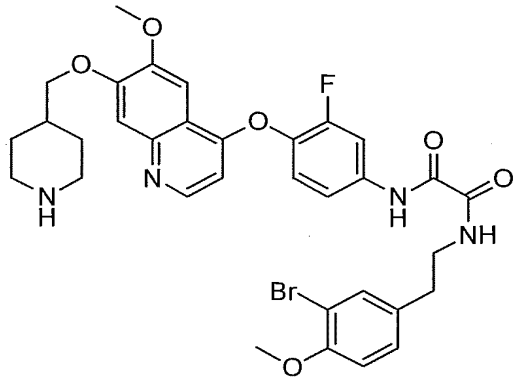
Entry	Name	Structure
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187	N-[2-(2,4-Dichloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
188	N-(2-Benzo[1,3]dioxol-5-yl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
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

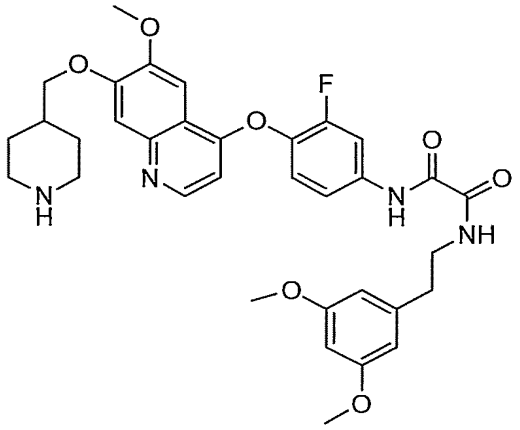
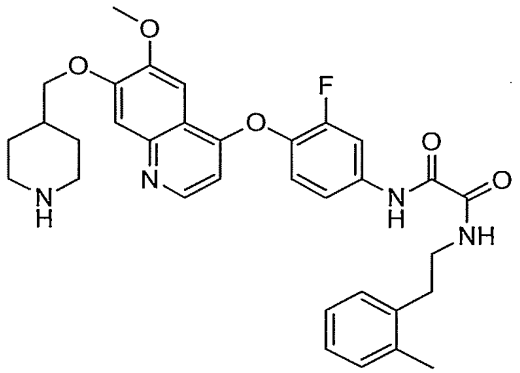
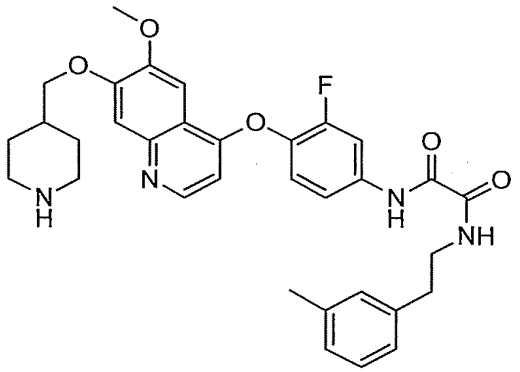
Entry	Name	Structure
190	N-[2-(3,5-Dimethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
191	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-o-tolyl-ethyl)-oxalamide	
192	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-m-tolyl-ethyl)-oxalamide	

Table 1

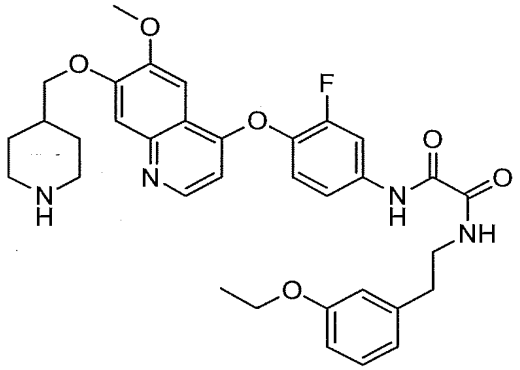
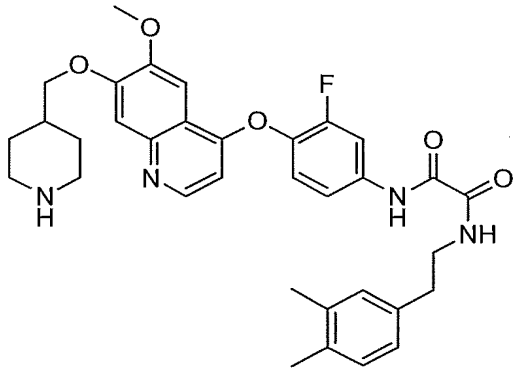
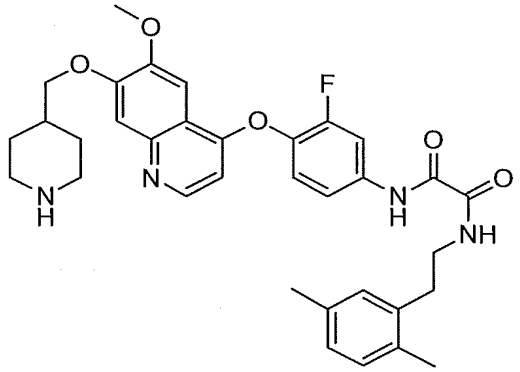
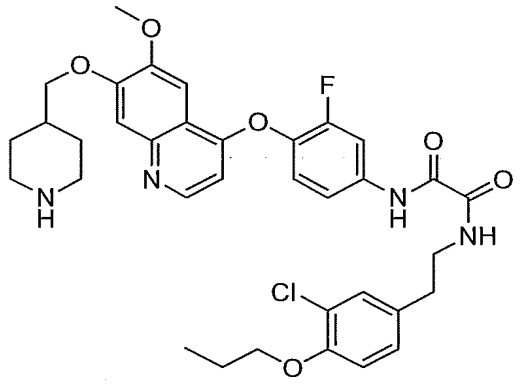
Entry	Name	Structure
193	N-[2-(3-Ethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
194	N-[2-(3,4-Dimethyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
195	N-[2-(2,5-Dimethyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-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

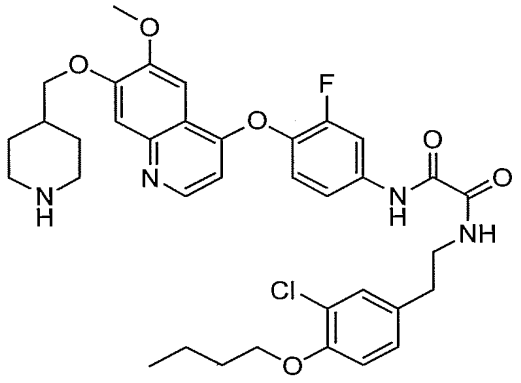
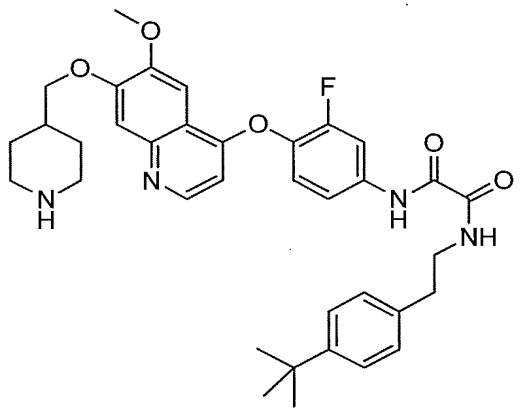
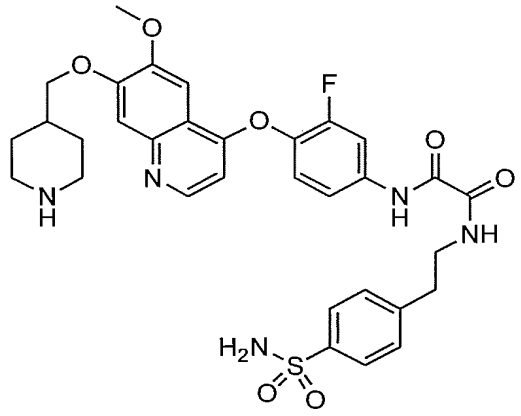
Entry	Name	Structure
197	N-[2-(4-Butoxy-3-chloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
198	N-[2-(4-tert-Butyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
199	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-sulfamoyl-phenyl)-ethyl]-oxalamide	

Table 1

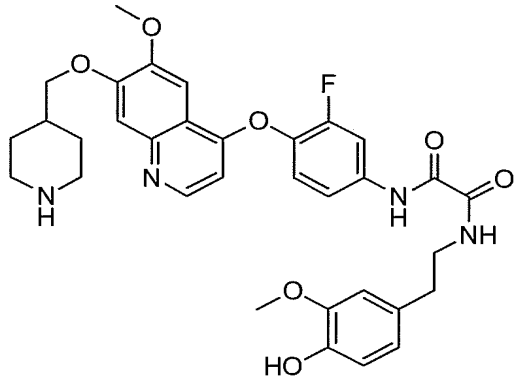
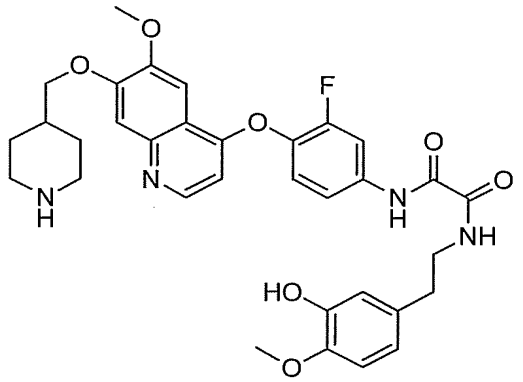
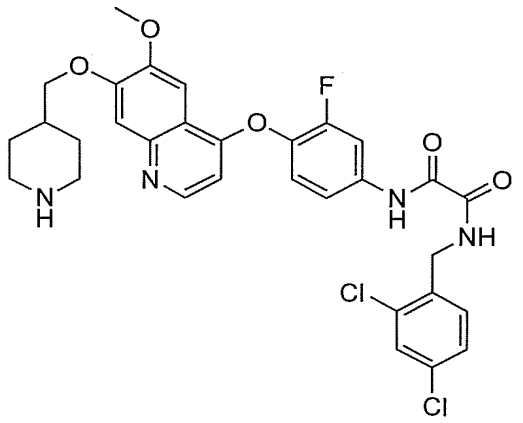
Entry	Name	Structure
200	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-hydroxy-3-methoxy-phenyl)-ethyl]-oxalamide	
201	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(3-hydroxy-4-methoxy-phenyl)-ethyl]-oxalamide	
202	N-(2,4-Dichloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

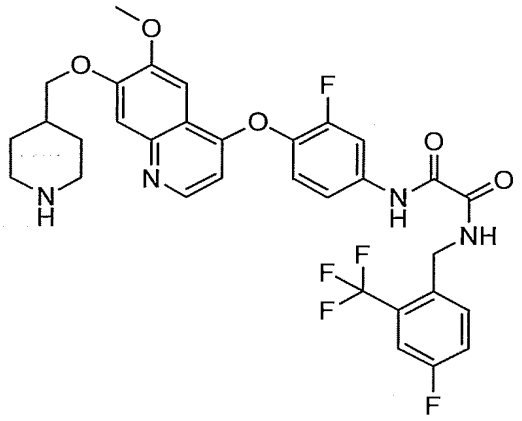
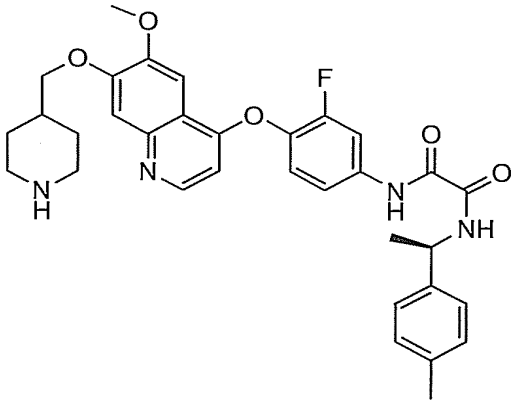
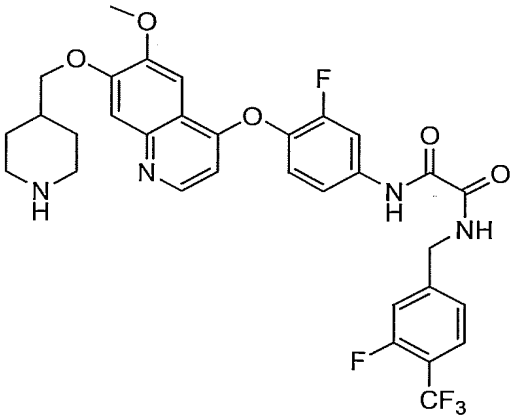
Entry	Name	Structure
203	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-fluoro-2-trifluoromethyl-benzyl)-oxalamide	
204	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1-p-tolyl-ethyl)-oxalamide	
205	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-fluoro-4-trifluoromethyl-benzyl)-oxalamide	

Table 1

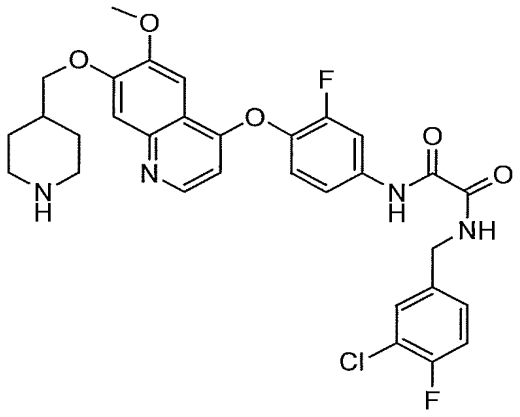
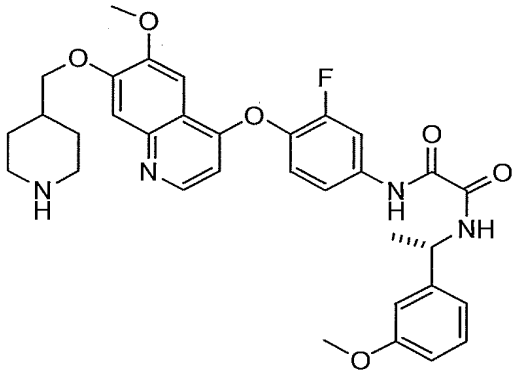
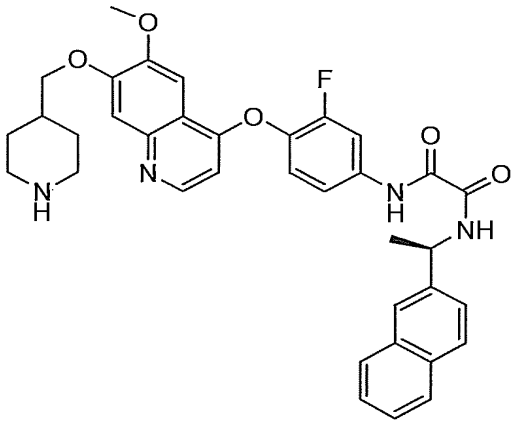
Entry	Name	Structure
206	N-(3-Chloro-4-fluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
207	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[1-(3-methoxy-phenyl)-ethyl]-oxalamide	
208	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1-naphthalen-2-yl-ethyl)-oxalamide	

Table 1

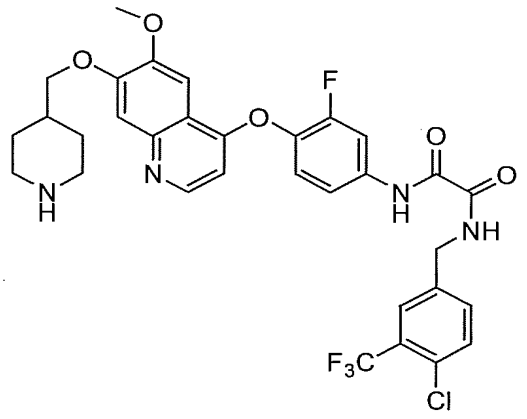
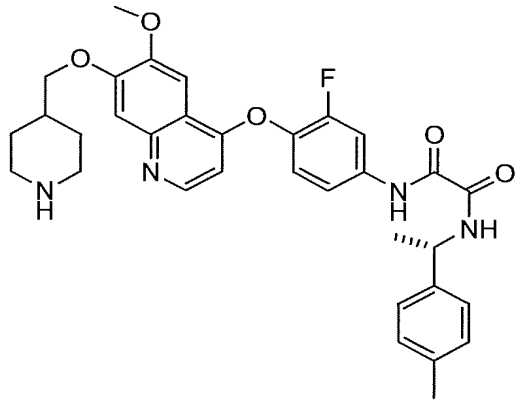
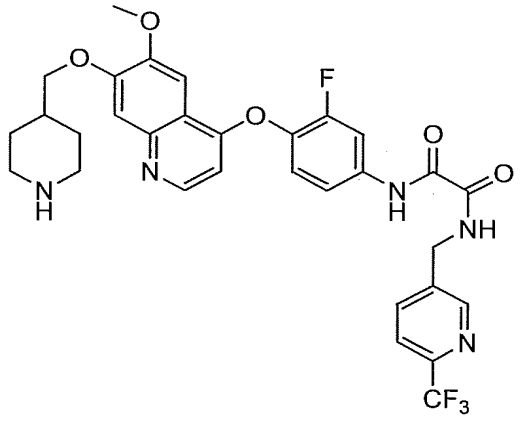
Entry	Name	Structure
209	N-(4-Chloro-3-trifluoromethyl-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
210	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1-p-tolyl-ethyl)-oxalamide	
211	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(6-trifluoromethyl-pyridin-3-ylmethyl)-oxalamide	

Table 1

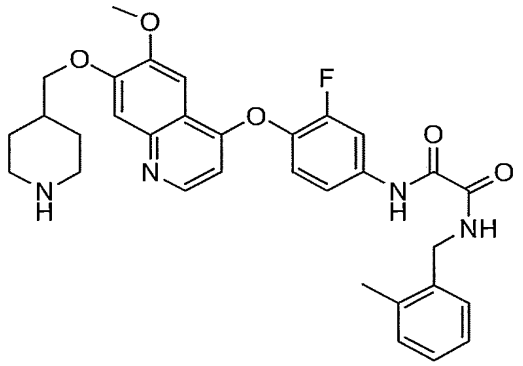
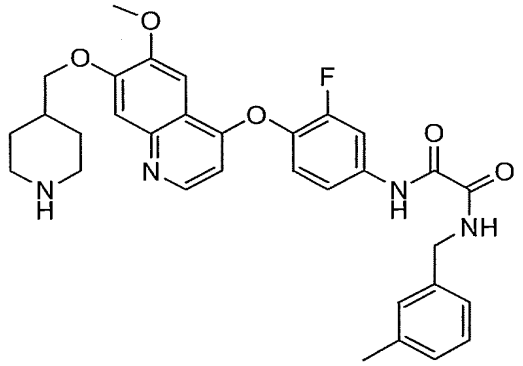
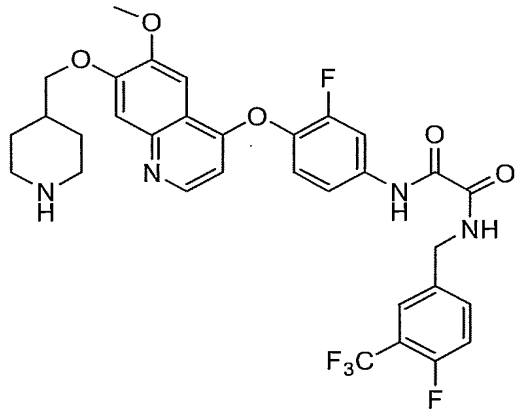
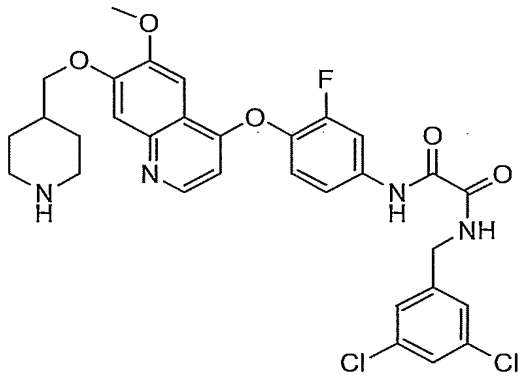
Entry	Name	Structure
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213	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-methyl-benzyl)-oxalamide	
214	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-fluoro-3-trifluoromethyl-benzyl)-oxalamide	
215	N-(3,5-Dichloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

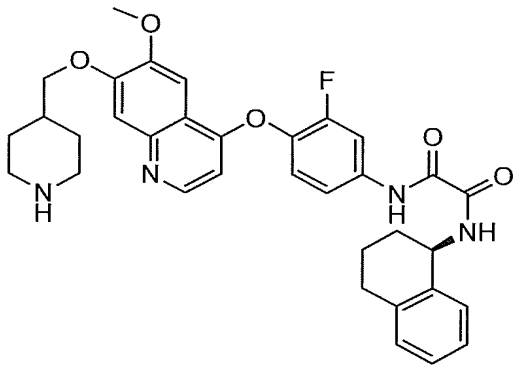
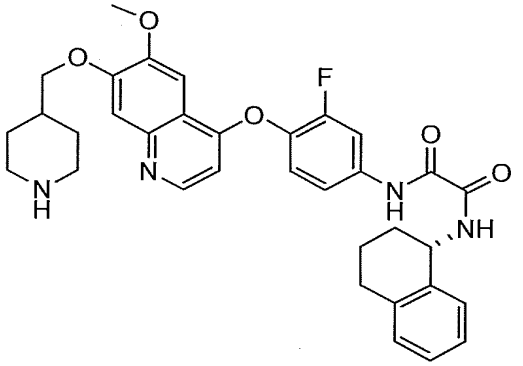
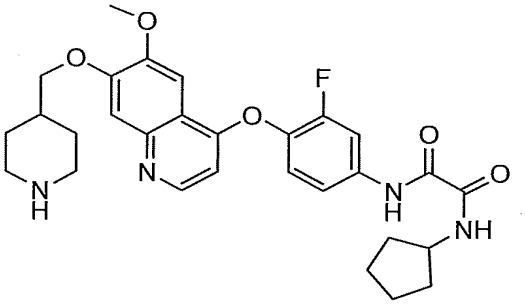
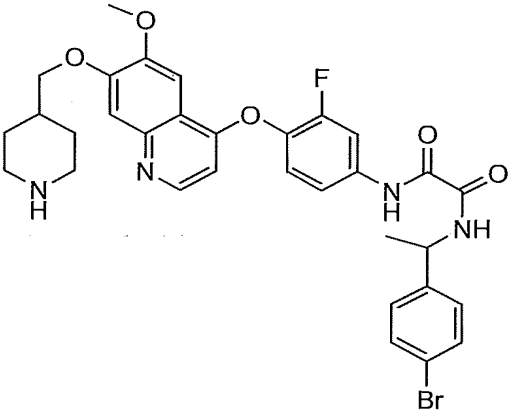
Entry	Name	Structure
216	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1R,2,3,4-tetrahydro-naphthalen-1-yl)-oxalamide	
217	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1S,2,3,4-tetrahydro-naphthalen-1-yl)-oxalamide	
218	N-Cyclopentyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-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

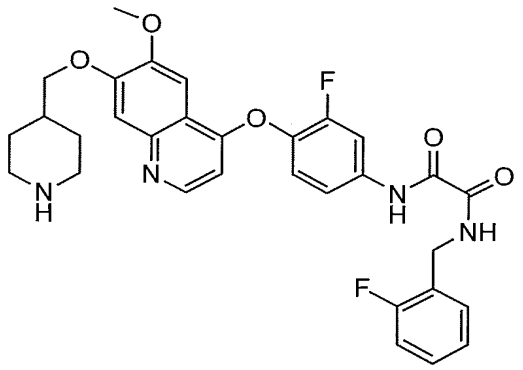
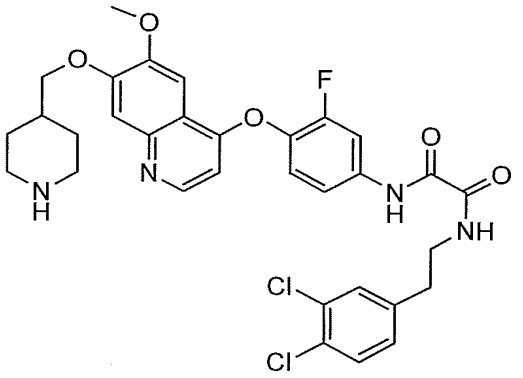
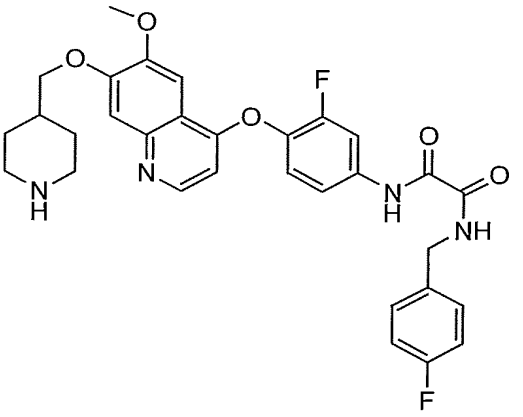
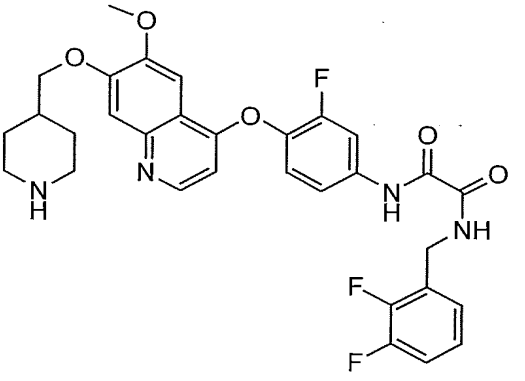
Entry	Name	Structure
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221	N-[2-(3,4-Dichloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
222	N-(4-Fluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
223	N-(2,3-Difluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

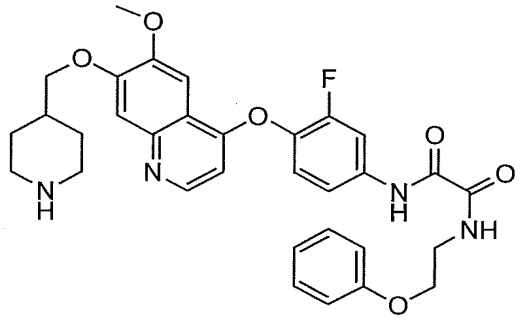
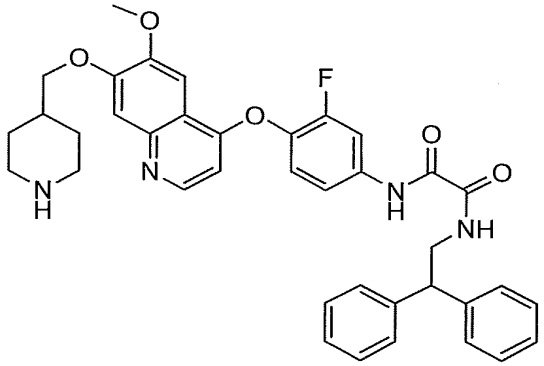
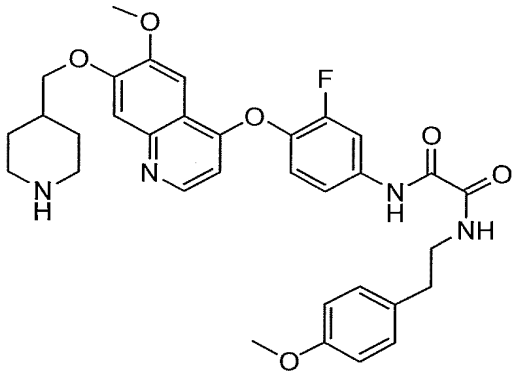
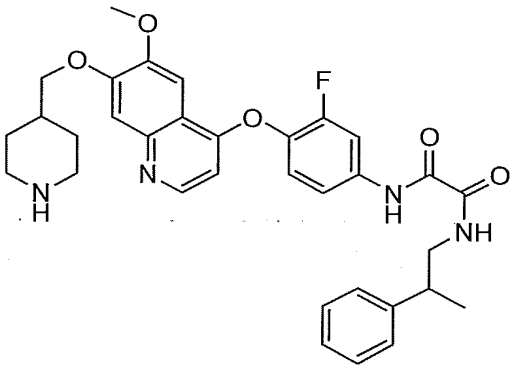
Entry	Name	Structure
224	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-phenoxy-ethyl)-oxalamide	
225	N-(2,2-Diphenyl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
226	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-methoxy-phenyl)-ethyl]-oxalamide	
227	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-phenyl-propyl)-oxalamide	

Table 1

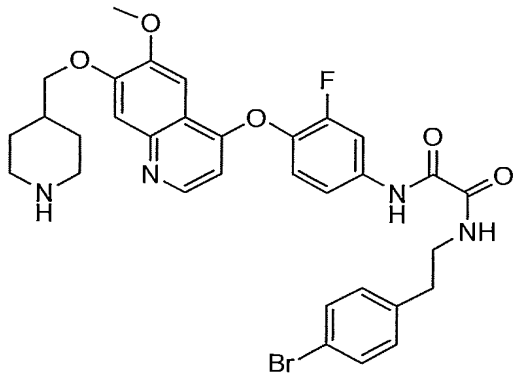
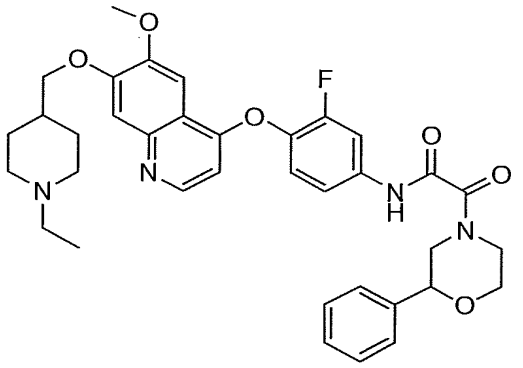
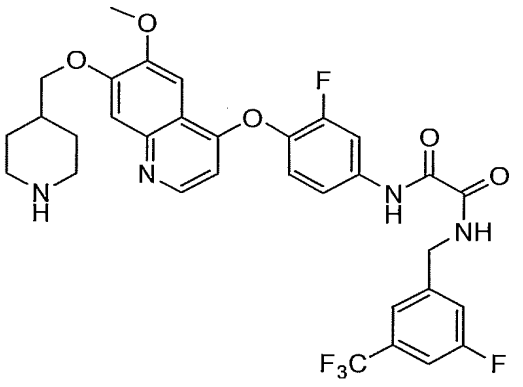
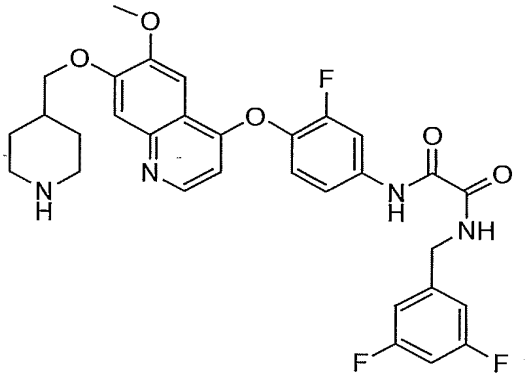
Entry	Name	Structure
228	N-[2-(4-Bromo-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
229	N-{4-[7-(1-Ethyl-piperidin-4-ylmethoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-2-oxo-2-(2-phenyl-morpholin-4-yl)-acetamide	
230	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-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

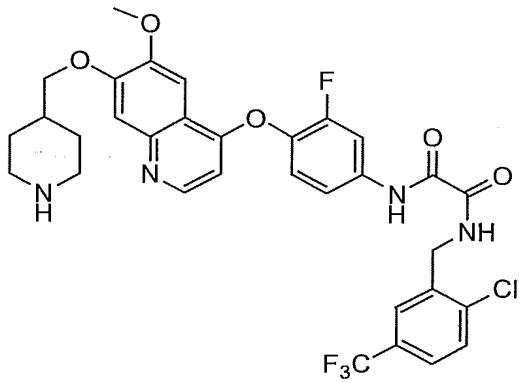
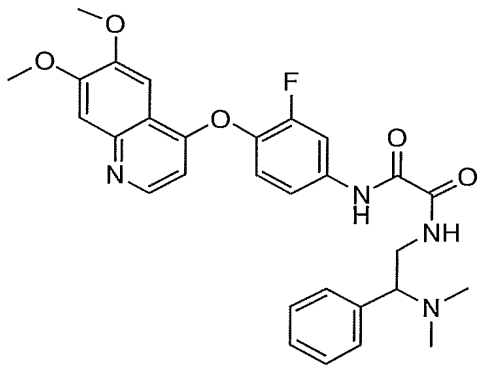
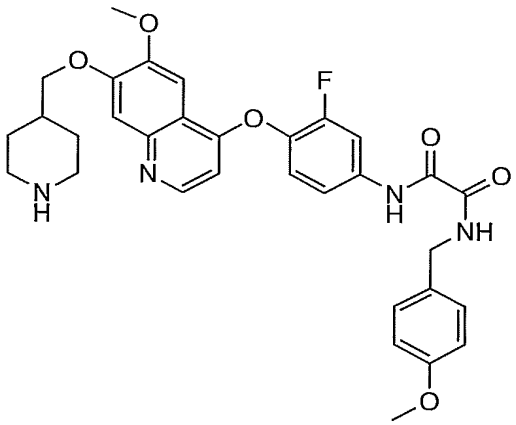
Entry	Name	Structure
232	N-(2-Chloro-5-trifluoromethyl-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
233	N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-N'-(2-dimethylamino-2-phenyl-ethyl)-oxalamide	
234	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-methoxy-benzyl)-oxalamide	

Table 1

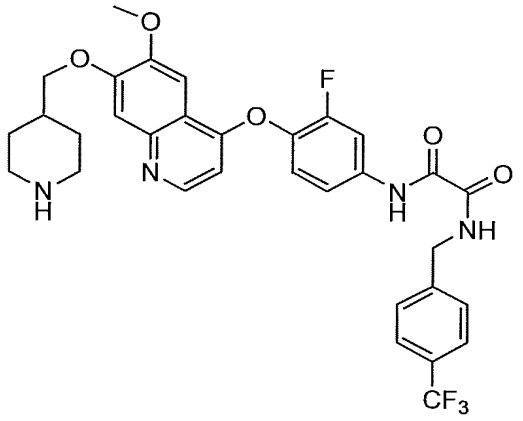
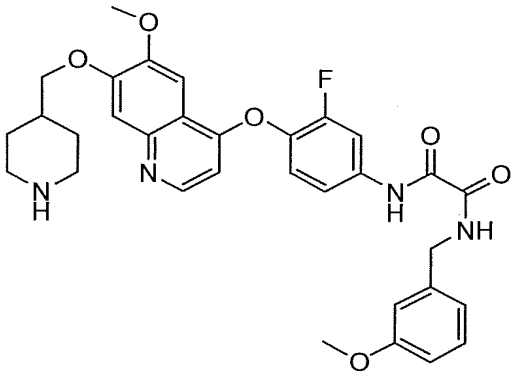
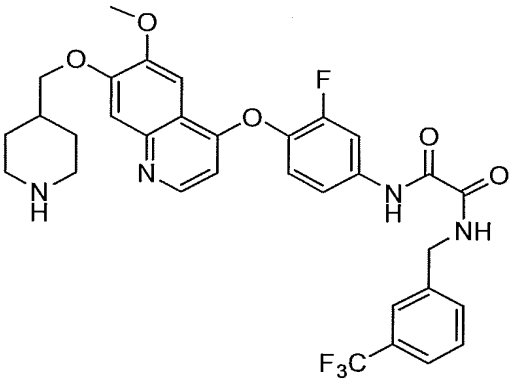
Entry	Name	Structure
235	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-trifluoromethyl-benzyl)-oxalamide	
236	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-methoxy-benzyl)-oxalamide	
237	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-trifluoromethyl-benzyl)-oxalamide	

Table 1

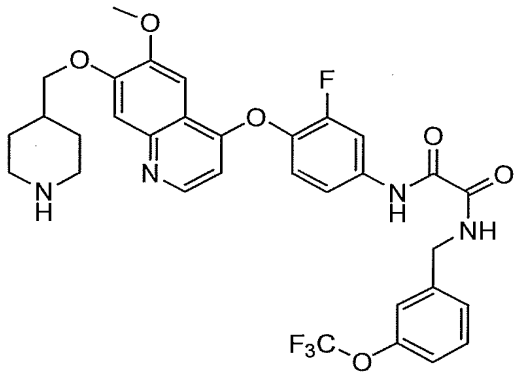
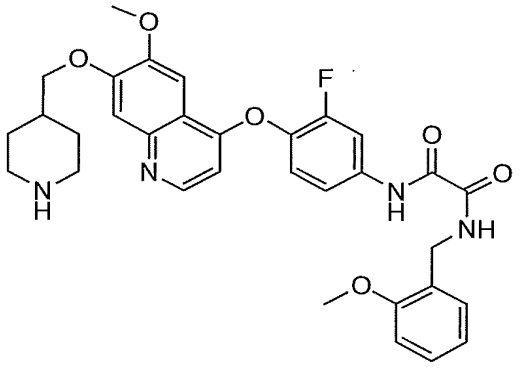
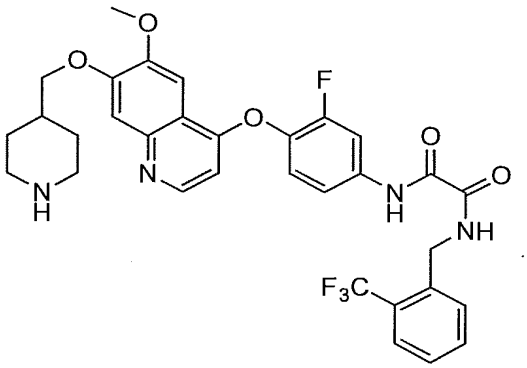
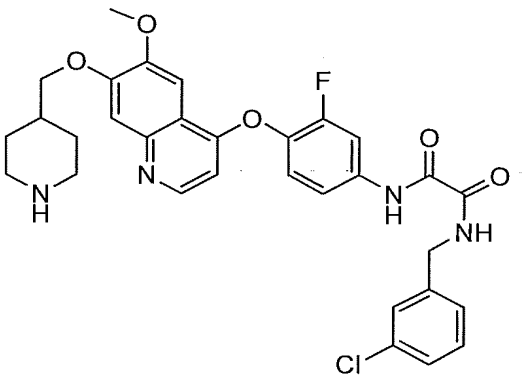
Entry	Name	Structure
238	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-trifluoromethoxy-benzyl)-oxalamide	
239	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-methoxy-benzyl)-oxalamide	
240	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-trifluoromethyl-benzyl)-oxalamide	
241	N-(3-Chloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

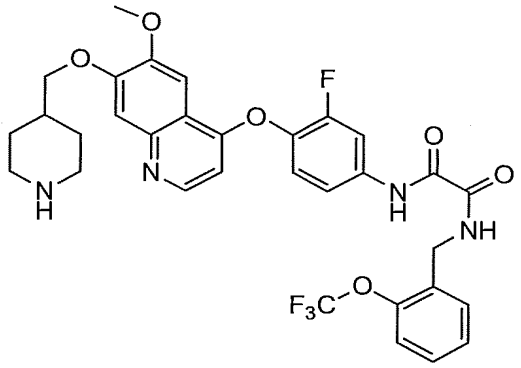
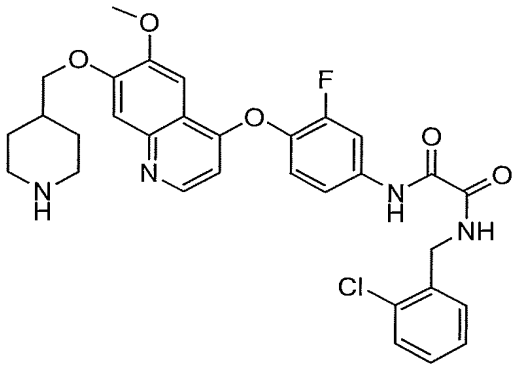
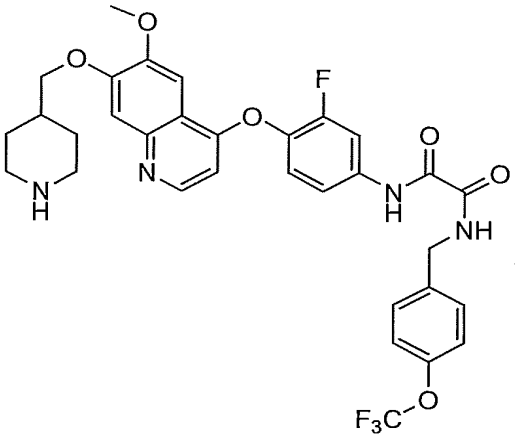
Entry	Name	Structure
242	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-trifluoromethoxy-benzyl)-oxalamide	
243	N-(2-Chloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
244	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-trifluoromethoxy-benzyl)-oxalamide	

Table 1

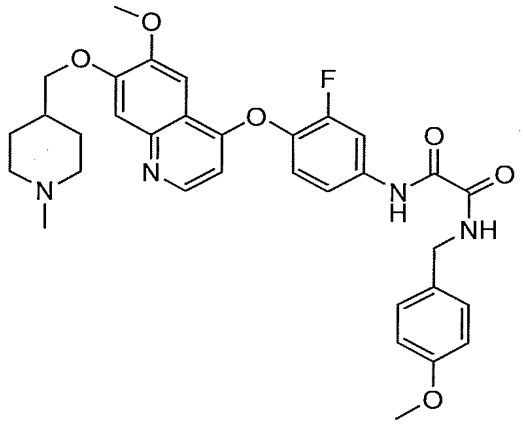
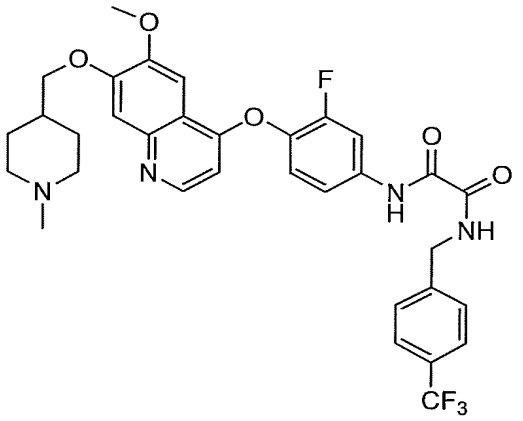
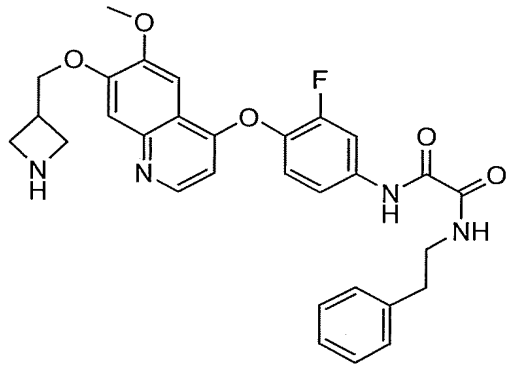
Entry	Name	Structure
245	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-methoxy-benzyl)-oxalamide	
246	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-trifluoromethyl-benzyl)-oxalamide	
247	N-{4-[7-(Azetidin-3-ylmethoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-N'-phenethyl-oxalamide	

Table 1

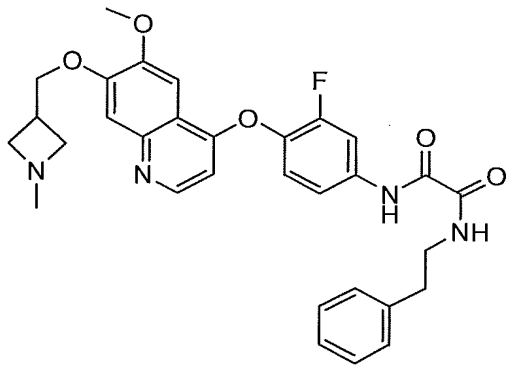
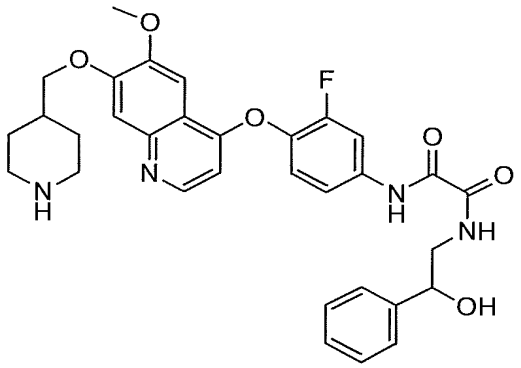
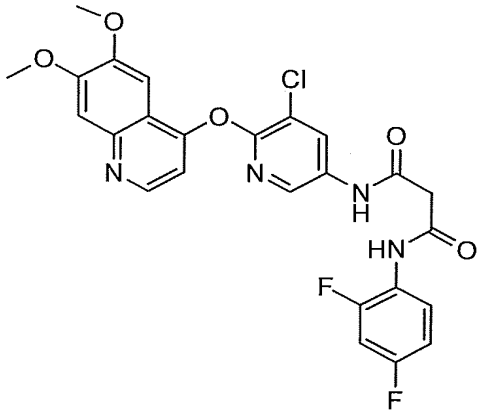
Entry	Name	Structure
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249	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-hydroxy-2-phenyl-ethyl)-oxalamide	
250	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(2,4-difluoro-phenyl)-malonamide	

Table 1

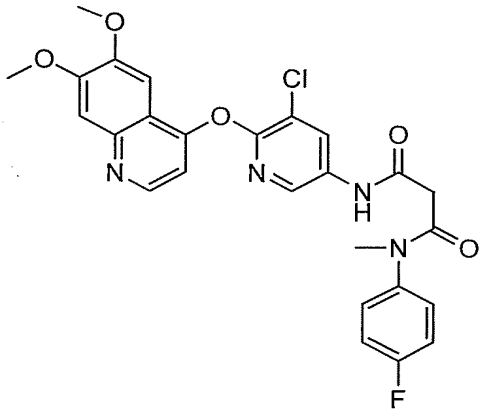
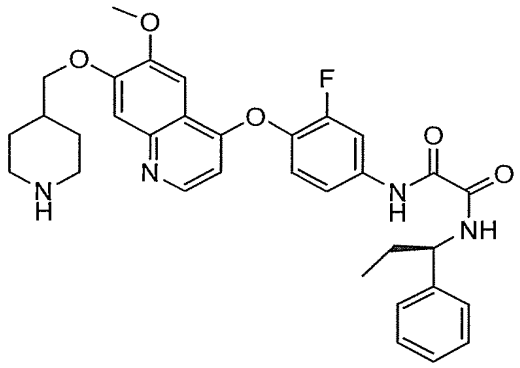
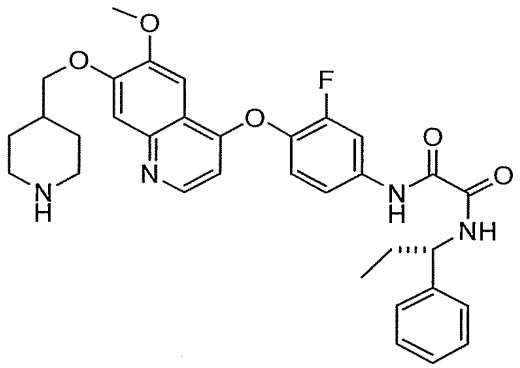
Entry	Name	Structure
251	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(4-fluoro-phenyl)-N'-methyl-malonamide	
252	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1R-phenyl-propyl)-oxalamide	
253	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1R-phenyl-propyl)-oxalamide	

Table 1

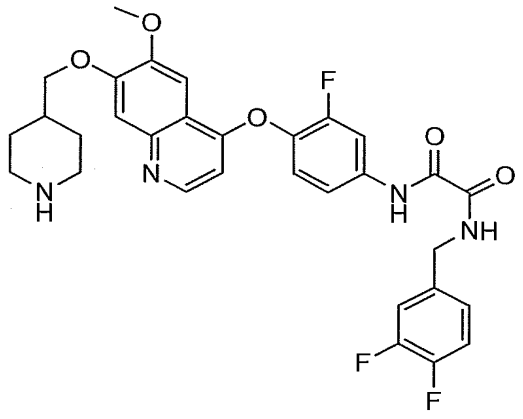
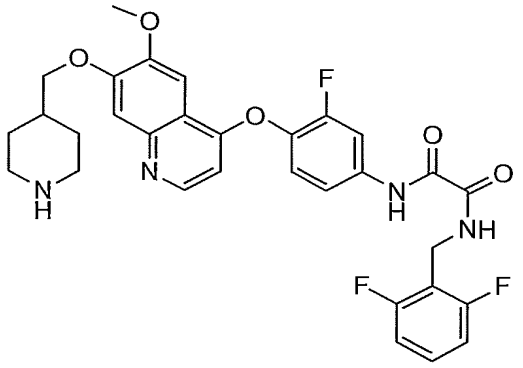
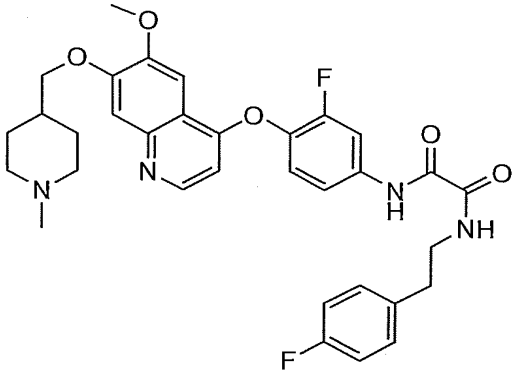
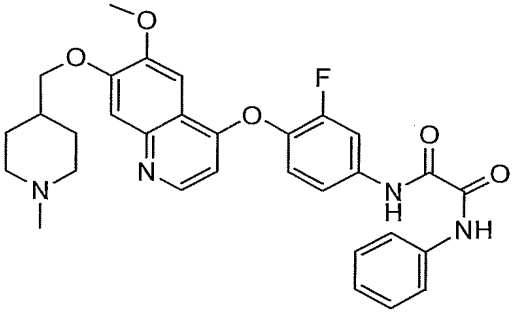
Entry	Name	Structure
254	N-(3,4-Difluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
255	N-(2,6-Difluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
256	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-fluoro-phenyl)-ethyl]-oxalamide	
257	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenyl-oxalamide	

Table 1

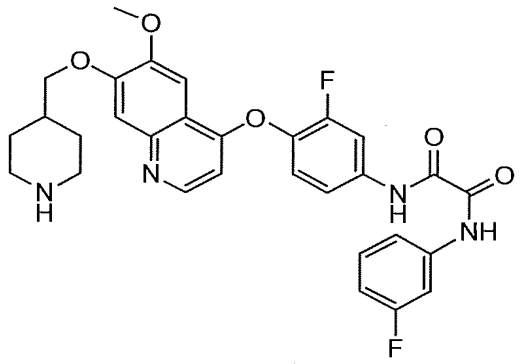
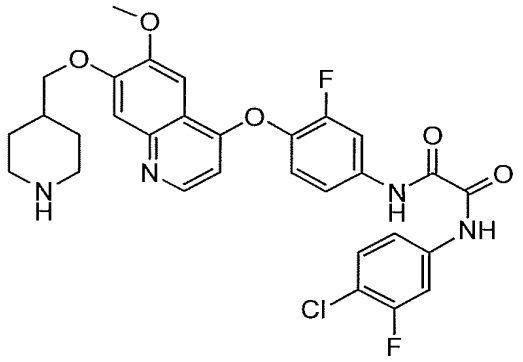
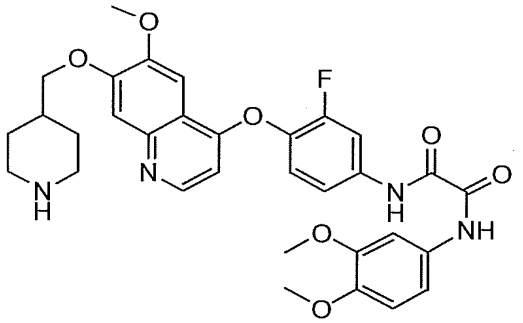
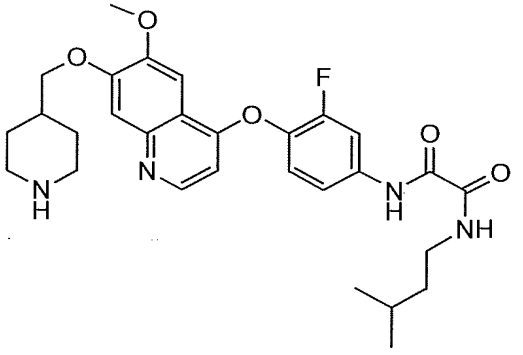
Entry	Name	Structure
258	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-fluoro-phenyl)-oxalamide	
259	N-(4-Chloro-3-fluoro-phenyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
260	N-(3,4-Dimethoxy-phenyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
261	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-methyl-butyl)-oxalamide	

Table 1

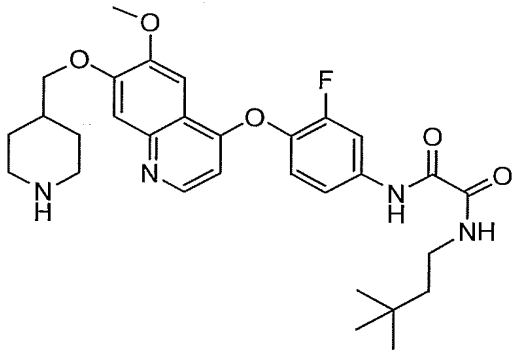
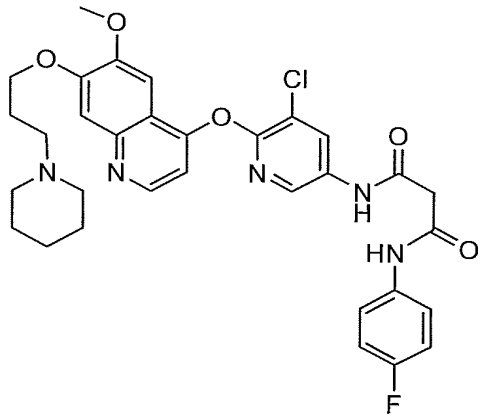
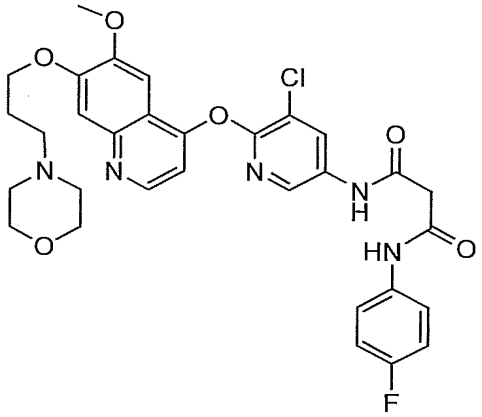
Entry	Name	Structure
262	N-(3,3-Dimethyl-butyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
263	N-{5-Chloro-6-[6-methoxy-7-(3-piperidin-1-yl-propoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide	
264	N-{5-Chloro-6-[6-methoxy-7-(3-morpholin-4-yl-propoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide	

Table 1

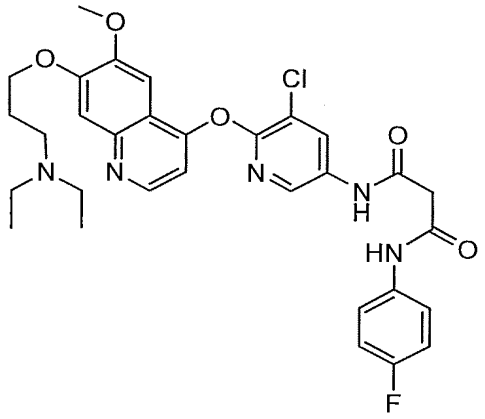
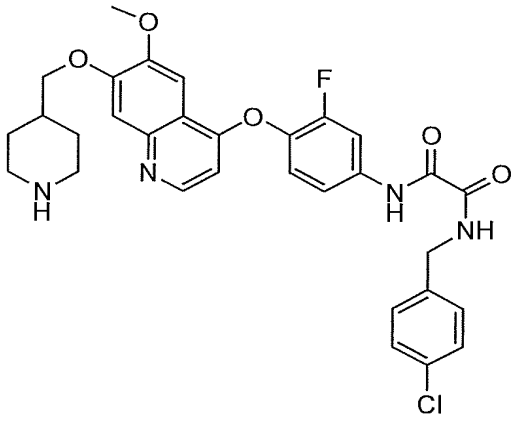
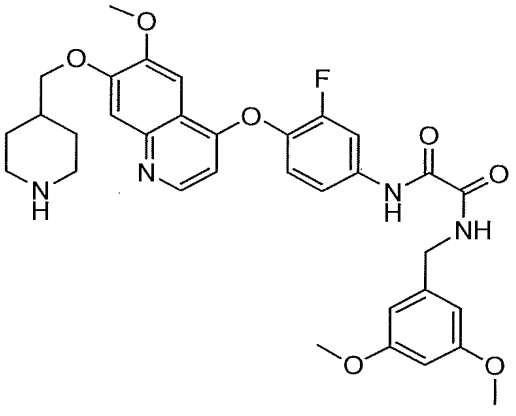
Entry	Name	Structure
265	N-{5-Chloro-6-[7-(3-diethylamino-propoxy)-6-methoxy-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide	
266	N-(4-Chloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
267	N-(3,5-Dimethoxy-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

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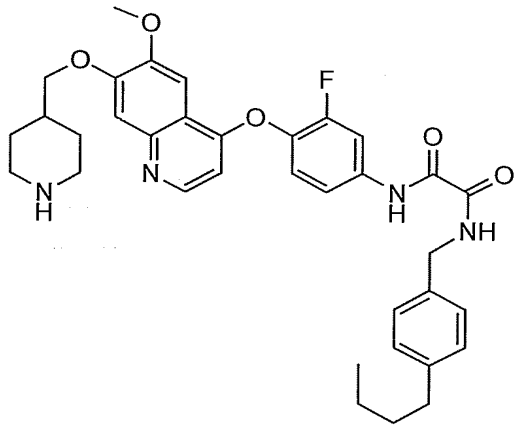
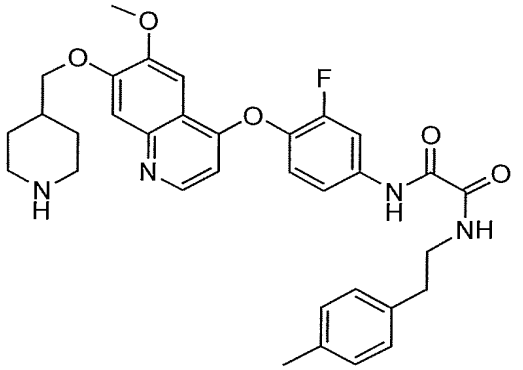
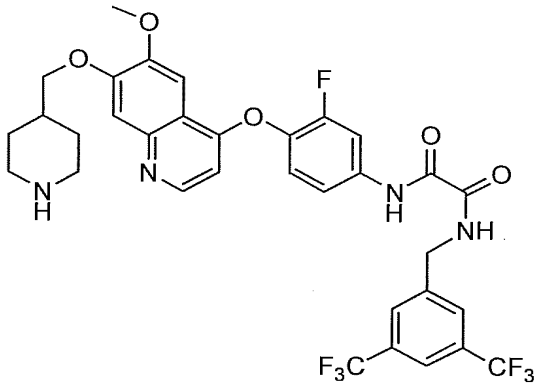
Entry	Name	Structure
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269	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-p-tolyl-ethyl)-oxalamide	
270	N-(3,5-Bis-trifluoromethyl-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

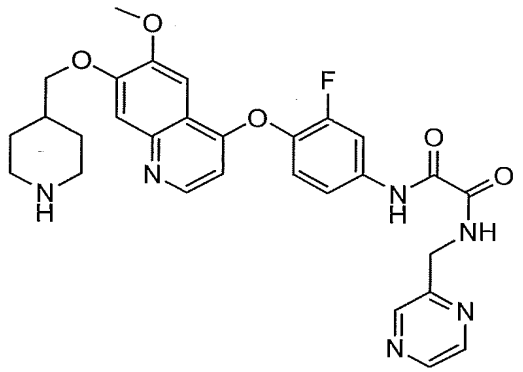
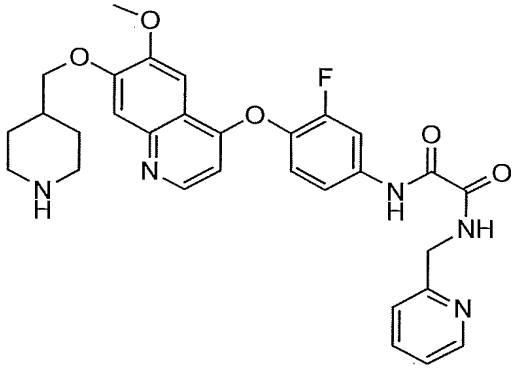
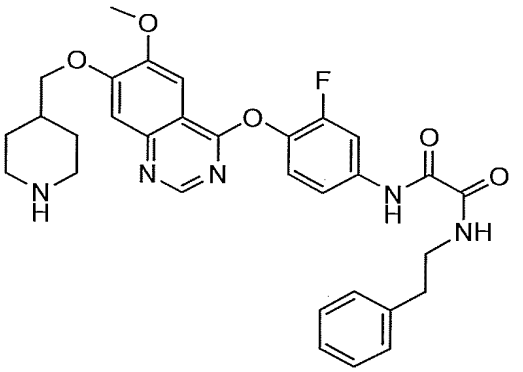
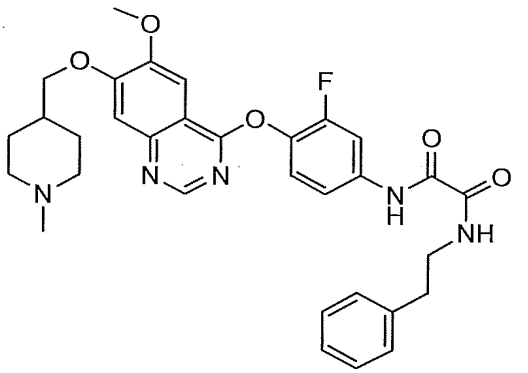
Entry	Name	Structure
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272	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-pyridin-2-ylmethyl-oxalamide	
273	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	
274	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	

Table 1

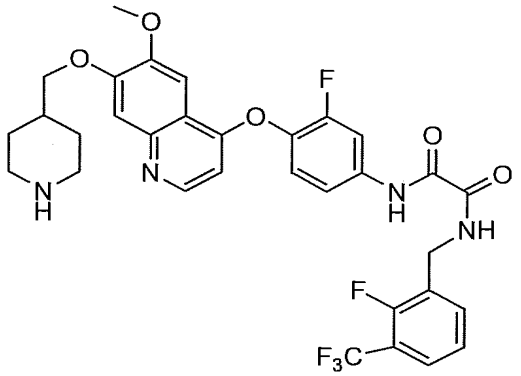
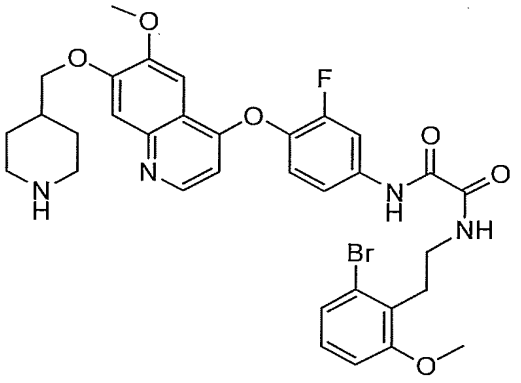
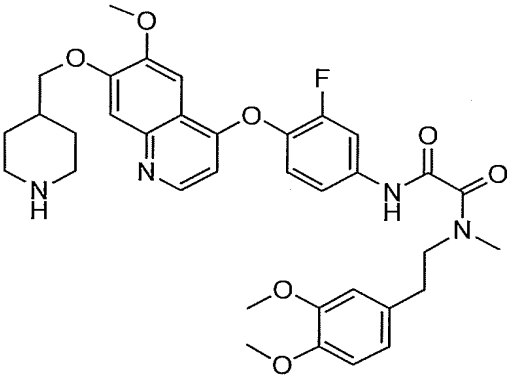
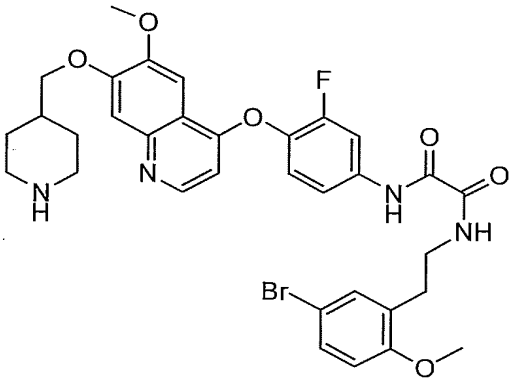
Entry	Name	Structure
275	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-fluoro-3-trifluoromethyl-benzyl)-oxalamide	
276	N-[2-(2-Bromo-6-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
277	N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-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

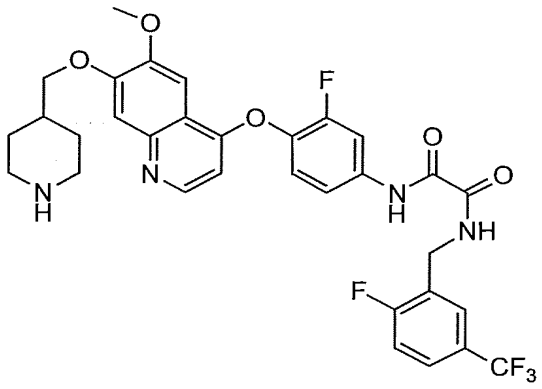
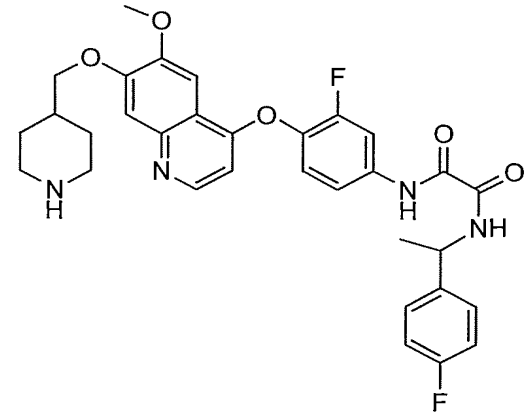
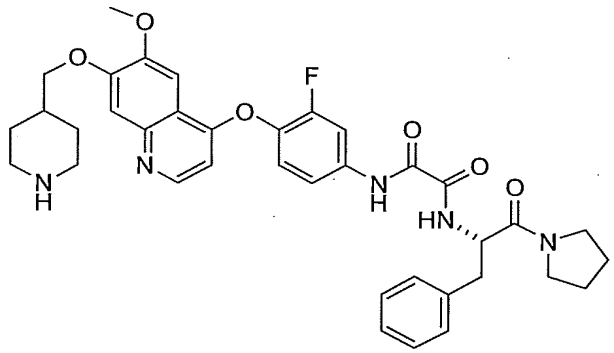
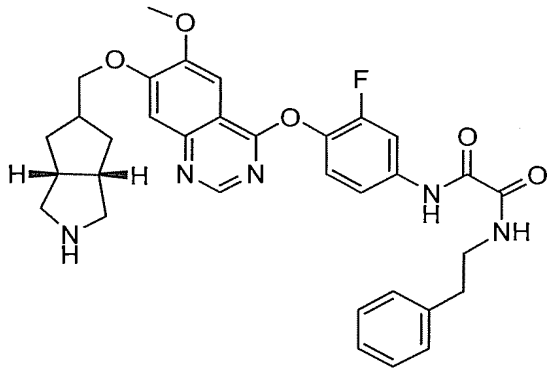
Entry	Name	Structure
279	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-fluoro-5-trifluoromethyl-benzyl)-oxalamide	
280	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[1-(4-fluoro-phenyl)-ethyl]-oxalamide	
281	N-(1S-Benzyl-2-oxo-2-pyrrolidin-1-yl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-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

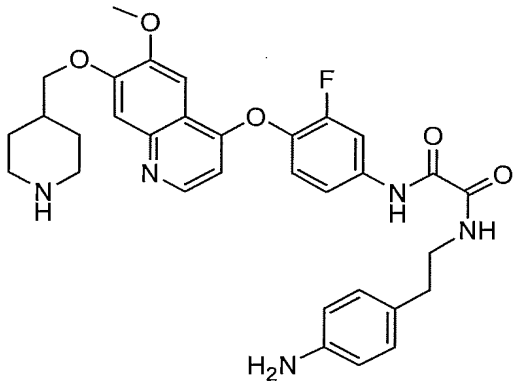
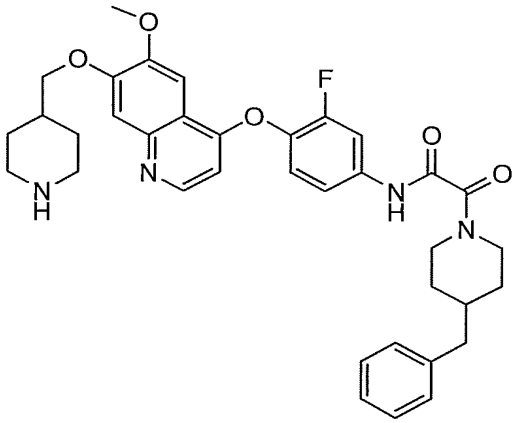
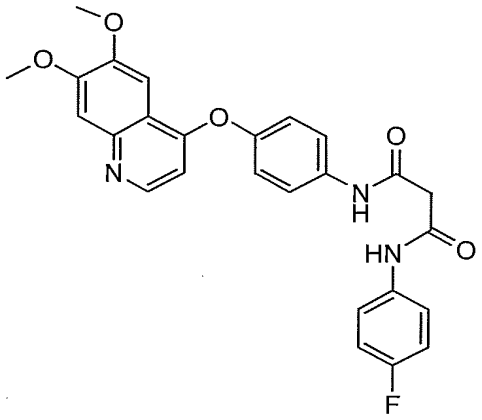
Entry	Name	Structure
283	N-[2-(4-Amino-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
284	2-(4-Benzyl-piperidin-1-yl)-N-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-acetamide	
285	N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-phenyl]-N'-(4-fluoro-phenyl)-malonamide	

Table 1

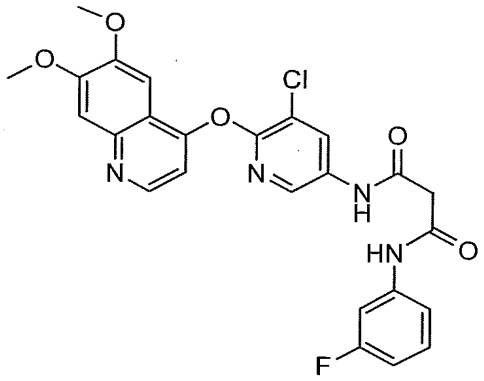
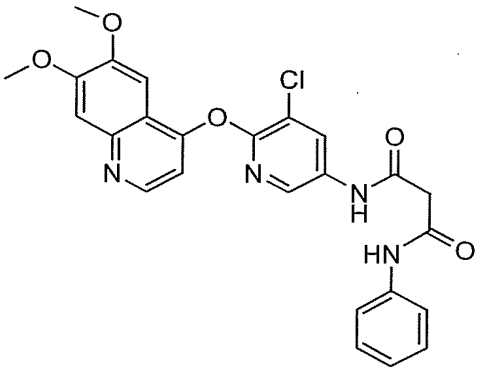
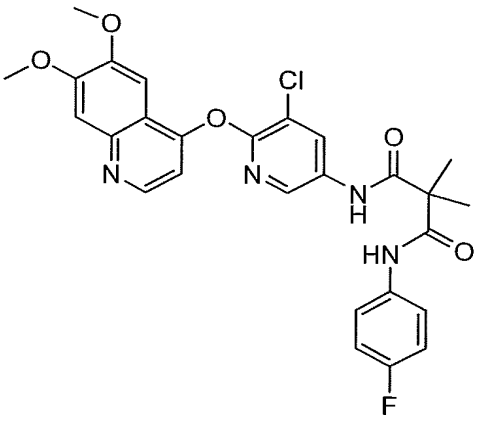
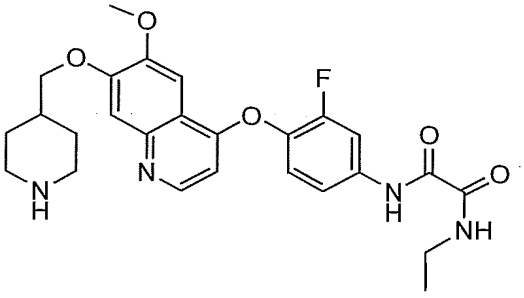
Entry	Name	Structure
286	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(3-fluoro-phenyl)-malonamide	
287	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-phenyl-malonamide	
288	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(4-fluoro-phenyl)-2,2-dimethyl-malonamide	
289	N-Ethyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

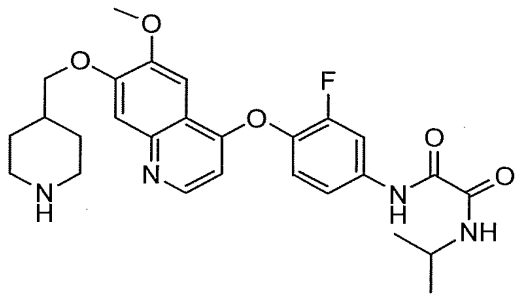
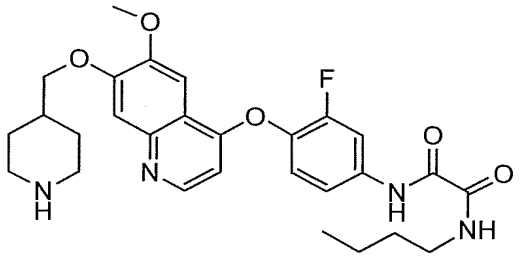
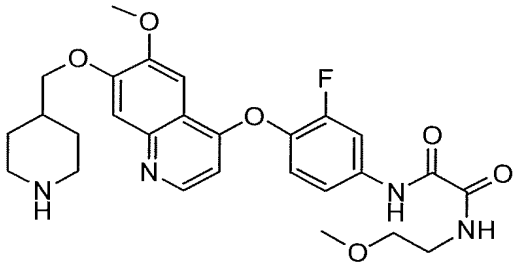
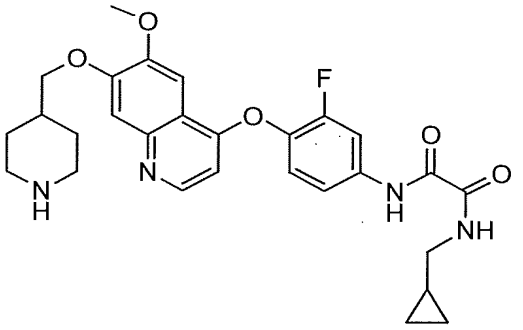
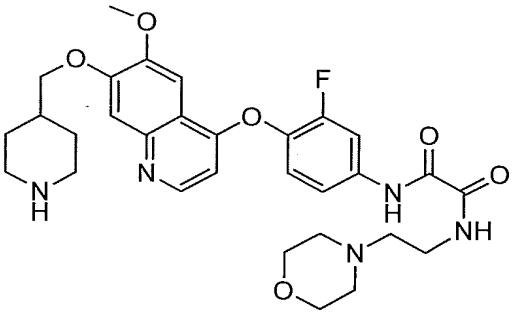
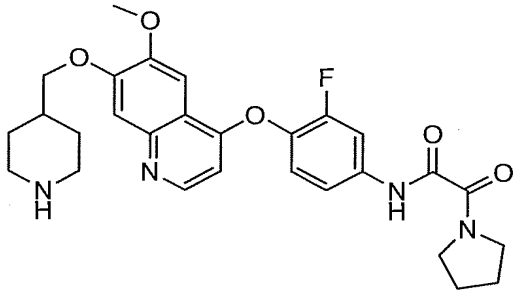
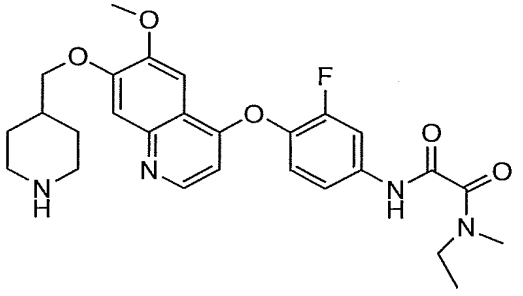
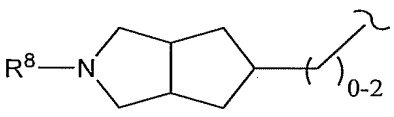
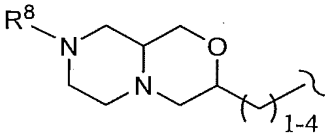
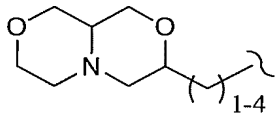
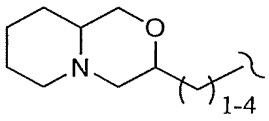
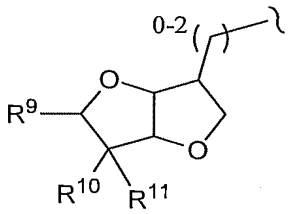
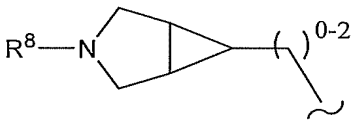
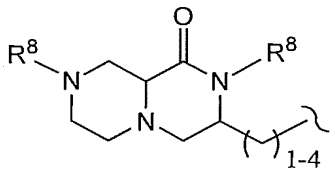
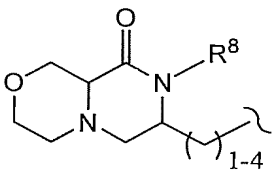
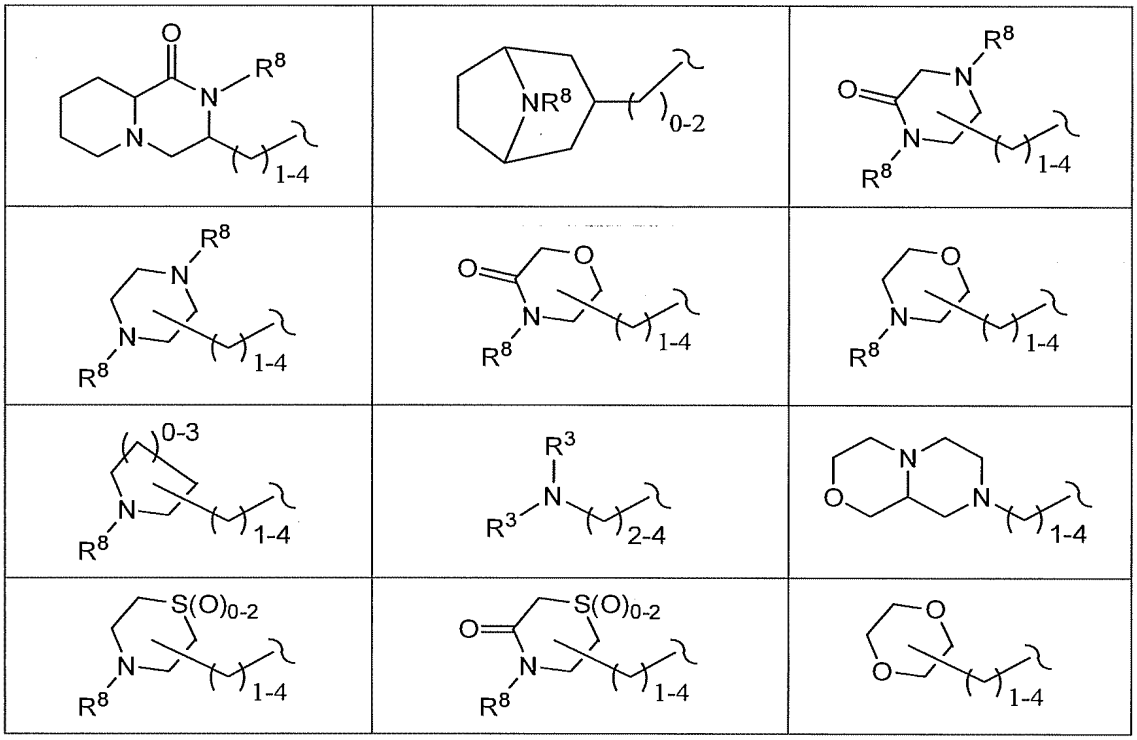
Entry	Name	Structure
290	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-isopropyl-oxalamide	
291	N-Butyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
292	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-methoxy-ethyl)-oxalamide	
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

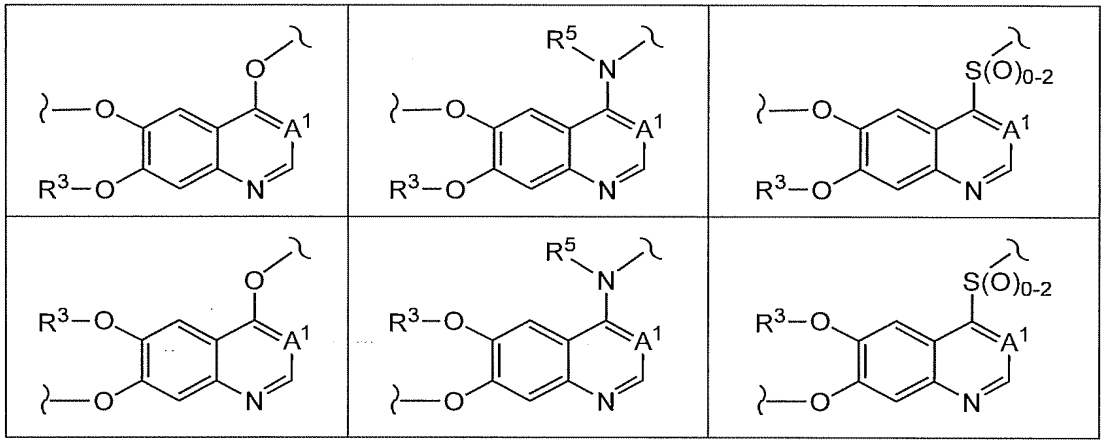
Entry	Name	Structure
295	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-2-pyrrolidin-1-yl-acetamide	
296	N-Ethyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N-methyl-oxalamide	

[0081] 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:

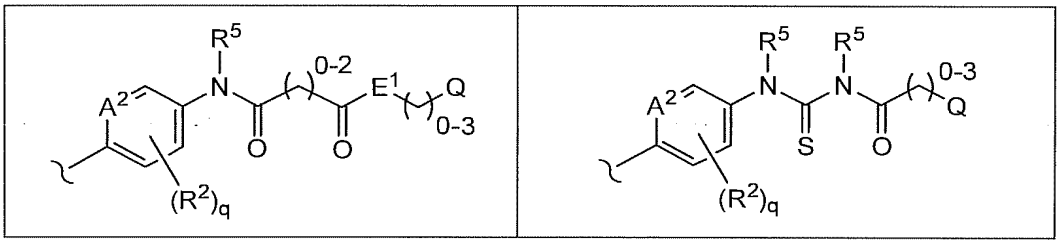
$-R^3$		
		
		

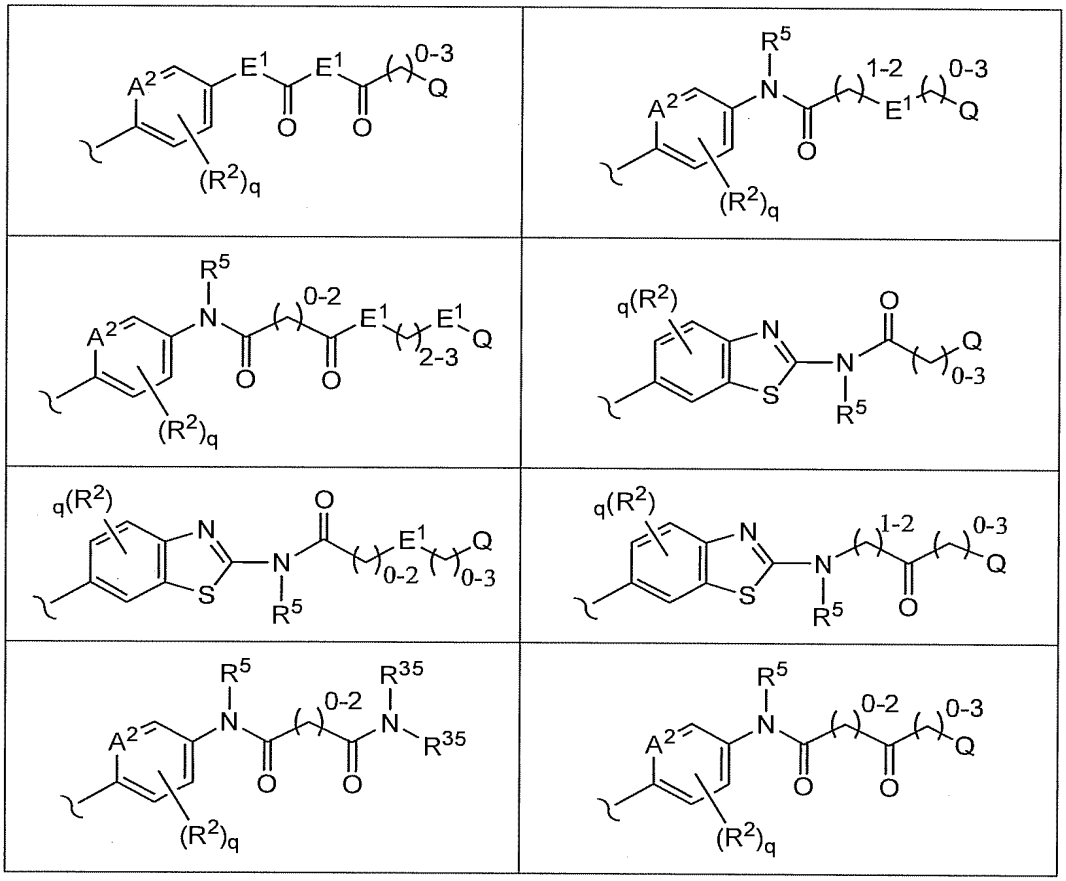


B is selected from:



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;

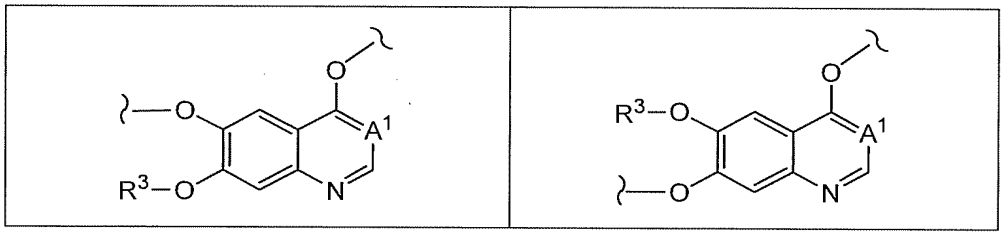
R^{60} is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted heteroarylalkyl, and optionally substituted arylalkyl;

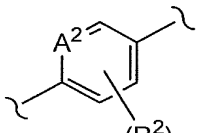
two of R^{60}, when attached to a non-aromatic carbon, can be oxo;

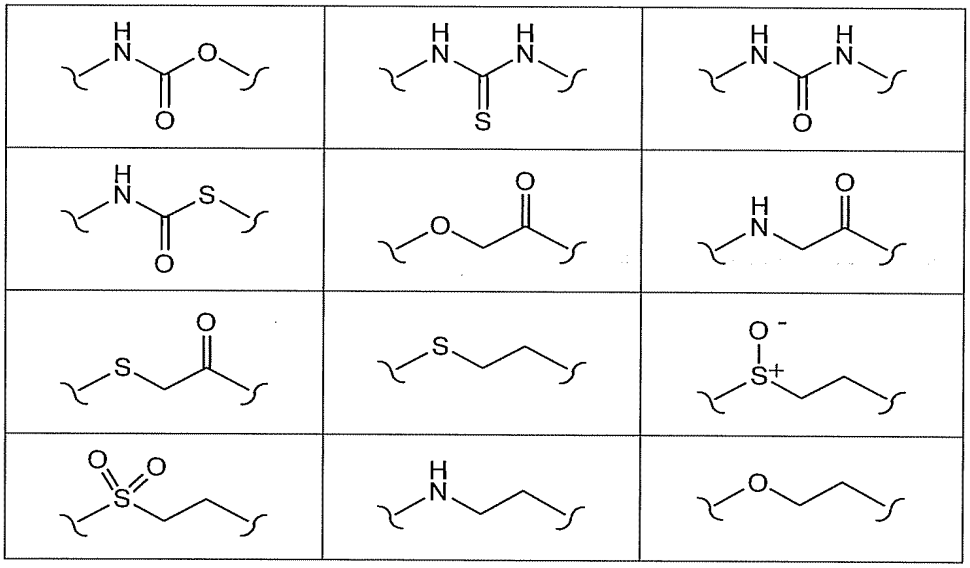
each methylene in any of the above formulae is independently optionally substituted with R^{25};

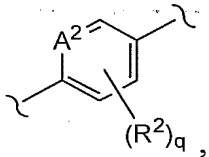
each R^{25} is independently selected from halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted arylalkyl, 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;

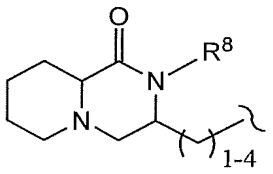
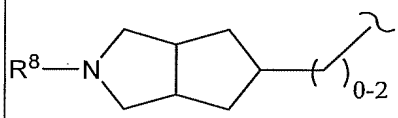
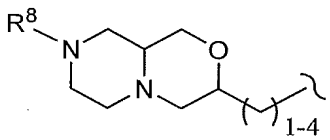
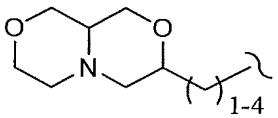
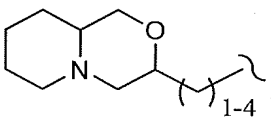
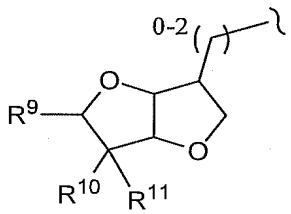
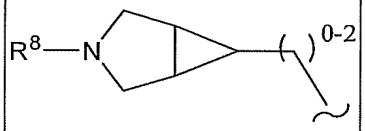
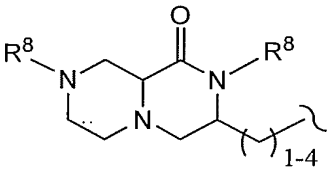
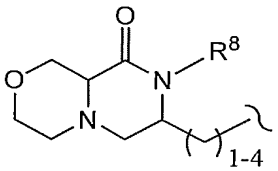
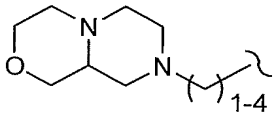
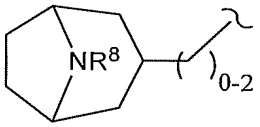
with the proviso that when B is selected from:

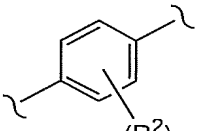


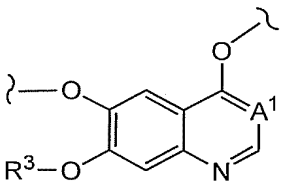
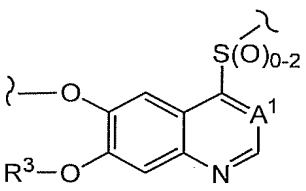
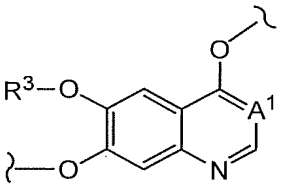
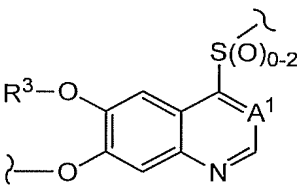
and C contains  , and the remaining portion of C contains one of:

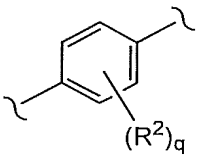
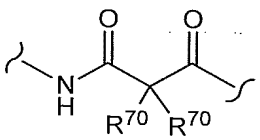


directly attached to  , then A must be one of:

and with the proviso that when C contains  , and B is selected from:

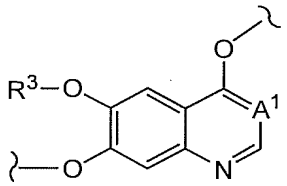
	
	

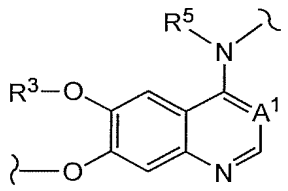
then the portion of C directly attached to  cannot contain  ,

when R^{70} is selected from -H, $C_{1\text{-}4}$alkyl, and $C_{1\text{-}4}$alkoxyl.

[0082] In another example the compound is according to the preceding paragraph, 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.

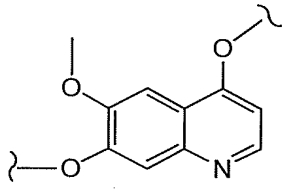
[0083] In another example the compound is according to the preceding paragraph, wherein B is either of the following:



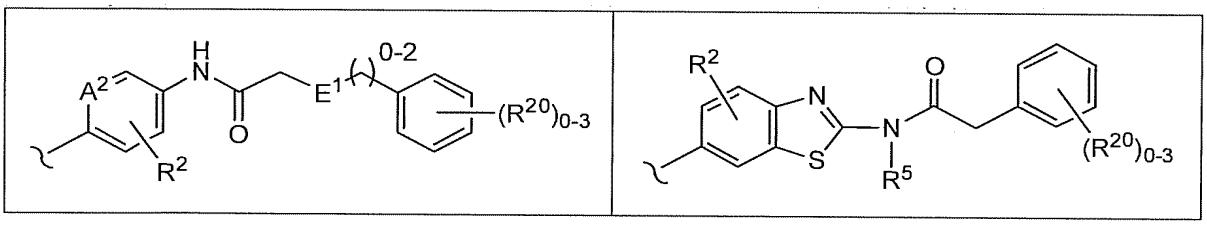


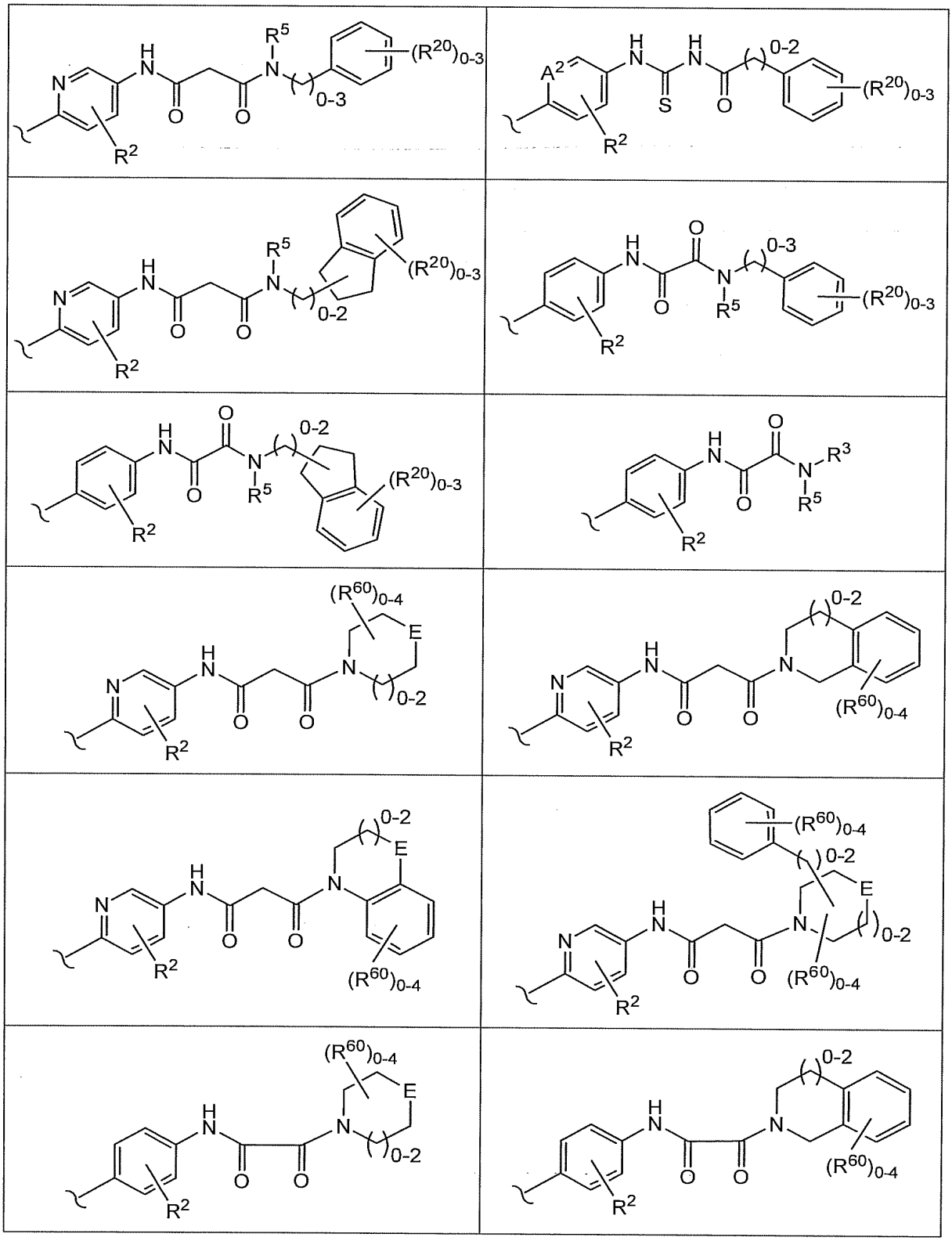
wherein A^1 is either =N- or =C(H)-.

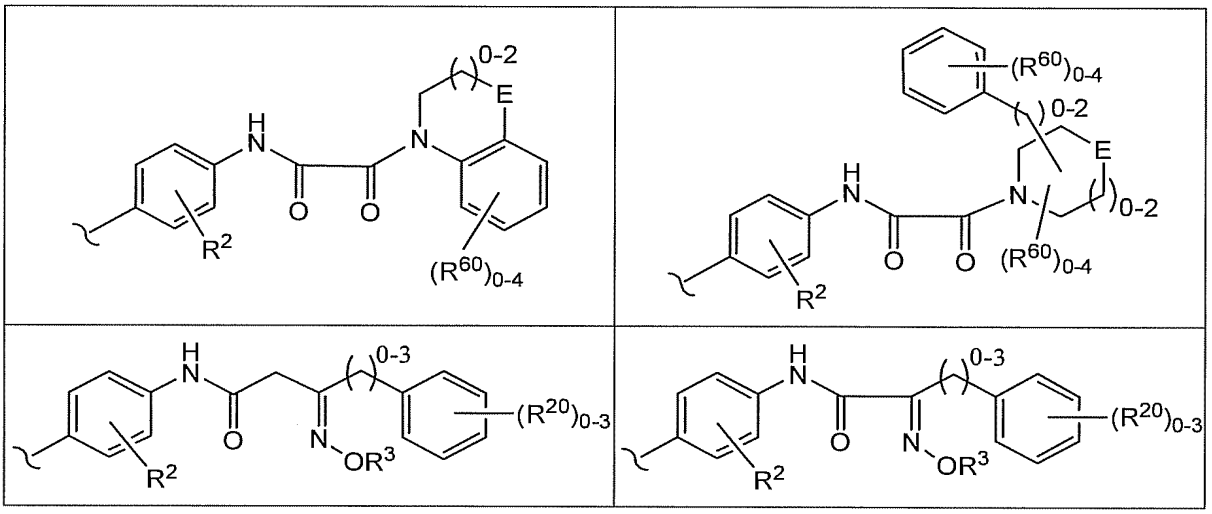
[0084] In another example the compound is according to the preceding paragraph, wherein B is



[0085] In another example the compound is according to the preceding paragraph, wherein C is selected from:







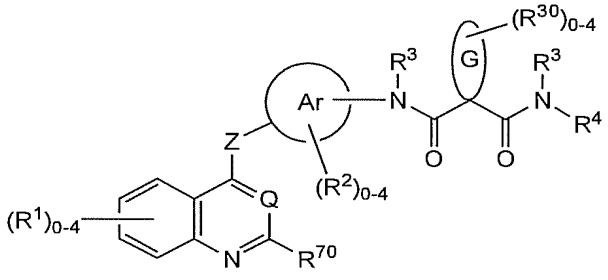
wherein R^2, R^3, R^5, R^{20}, R^{25} and R^{60} are as defined above.

[0086] In another example the compound is according to the preceding paragraph, 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

[0087] In another example the compound is according to the preceding paragraph, wherein R^2 is halogen.

[0088] In another example the compound is according to the preceding paragraph, wherein R^2 is either fluorine or chlorine.

[0089] 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 $C_{1\text{-}6}$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;

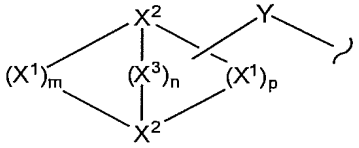
each R^4 is independently selected from optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl, optionally substituted heterocyclyl, and optionally substituted heterocyclyl C_{1-6}alkyl; or

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

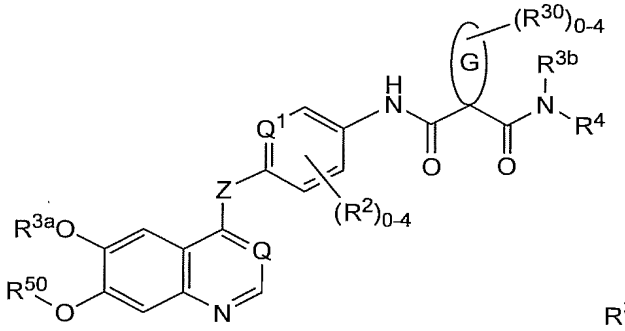
each R^{30} is independently selected from halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted C_{1-6}alkyl.

[0090] In one example, the compound is according to Formula XI, wherein Z is either -O- or -NR^5-.

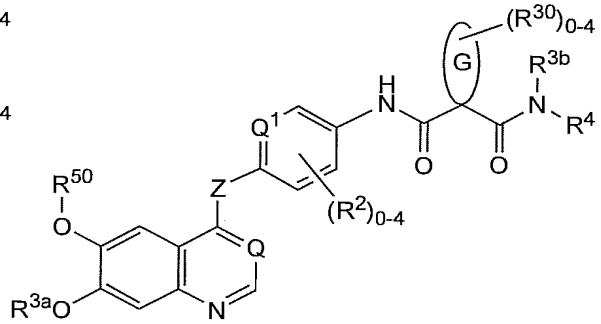
[0091] In another example, the compound is according to the preceding paragraph, wherein at least one of R^1 is -D-R^{50}.

[0092] In another example, the compound is according to the preceding paragraph, wherein D is -O- and at least one other R^1 is -OR^3.

[0093] In another example, the compound is according to the preceding paragraph, of formula **XIIIa** or **XIIIb**:



XIIIa



XIIIb

wherein Q^1 is either =N- or =C(H)-.

[0094] In another example, the compound is according to formula XIIIa or formula XIIIb, wherein R^{50} is selected from $C_{1\text{-}6}$alkyl optionally substituted with at least one of optionally substituted amino, optionally substituted $C_{1\text{-}6}$alkyl amino, optionally substituted $C_{1\text{-}6}$dialkyl amino, optionally substituted heteroalicylic, and a group of formula **XII**.

[0095] In another example, the compound is according to the preceding paragraph, wherein R^{3a} is $C_{1\text{-}6}$alkyl.

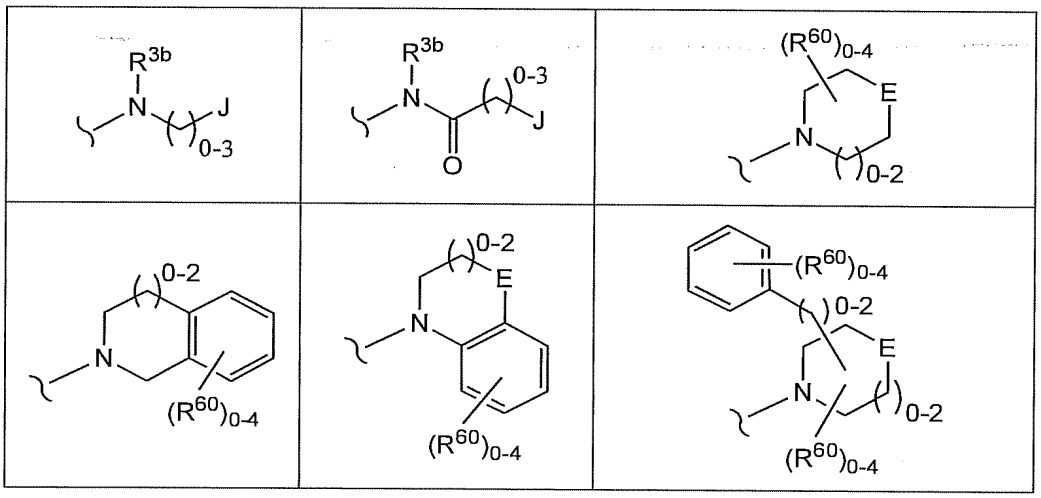
[0096] In another example, the compound is according to the preceding paragraph, wherein Z is -O-.

[0097] In another example, the compound is according to the preceding paragraph, wherein G is selected from cyclopropyl, aziradine, cyclobutyl, and azetidine, each optionally substituted with between zero and four of R^{30}.

[0098] In another example, the compound is according to the preceding paragraph, wherein Q is either =N- or =C(H)-.

[0099] In another example, the compound is according to the preceding paragraph, wherein R^2 is selected from -H, halogen, C_{1-6} alkyl and perfluoro C_{1-6} alkyl.

[00100] In another example, the compound is according to the preceding paragraph, 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

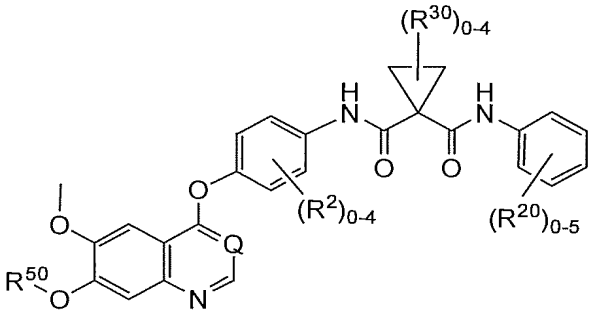
R^{25} is selected from halogen, trihalomethyl, oxo, -CN, -NO_2, -NH_2, -OR^3, -NR^3R^4, -$S(O)_{0-2}R^3$, -$SO_2NR^3R^3$, -CO_2R^3, -$C(O)NR^3R^3$, -$N(R^3)SO_2R^3$, -$N(R^3)C(O)R^3$, -$N(R^3)CO_2R^3$, -$C(O)R^3$, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl, heteroaryl C_{1-6}alkyl, 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;

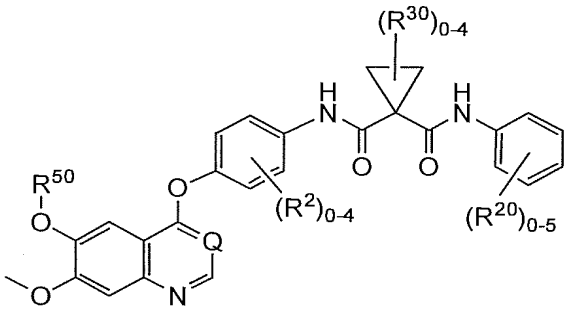
R^{3b} is equivalent to R^3 as defined above; and

R^4 and R^5 are as defined above.

[00101] In another example, the compound is according to the preceding paragraph, of formula **XIVa** or **XIVb**:



XIVa



XIVb

[00102] In another example, the compound is according to the preceding paragraph, 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.

[00103] In another example, the compound is according to the preceding paragraph, wherein the heteroalicyclic portion 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.

[00104] In another example, the compound is as defined two paragraphs above, wherein R^{50} is according to formula **XII**.

[00105] In another example, the compound is according to the preceding paragraph, 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].

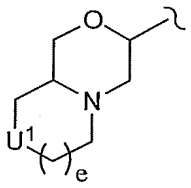
[00106] In another example, the compound is according to the preceding paragraph, wherein Y is selected from $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2-$, $-CH_2-$, and absent.

[00107] In another example, the compound is according to the preceding paragraph, 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].

[00108] In another example, the compound is according to the preceding paragraph, wherein said saturated bridged ring system contains at least one annular nitrogen or at least one annular oxygen.

[00109] In another example, the compound is according to the preceding paragraph, 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 $-C(O)R^3$.

[00110] In another example, the compound is as defined two paragraphs above, 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.

[00111] In another example, the compound is according to the preceding paragraph, wherein Y is $-CH_2-$.

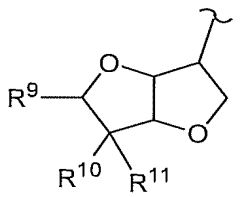
[00112] In another example, the compound is according to the preceding paragraph, wherein U^1 is $-NR^8-$, wherein R^8 is selected from -H, optionally substituted lower alkyl, $-CO_2R^3$, $-C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$.

[00113] In another example, the compound is as defined two paragraphs above, wherein U^1 is -O-.

[00114] In another example, the compound is as defined three paragraphs above, wherein U^1 is absent.

[00115] In another example, the saturated bridged ring system is according to formula **XII** and 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], and Y is selected from $-CH_2CH_2-$, $-CH_2-$, and absent.

[00116] In another example, the compound is according to the preceding paragraph, 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;

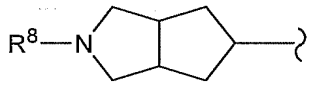
or two R^{12}'s, when taken together, form 1) a corresponding spirocyclic ketal when said two R^{12}'s stem from R^{10} and R^{11}, or 2) a corresponding cyclic ketal when said two R^{12}'s stem from R^9 and one of R^{10} and R^{11}.

[00117] In another example, the compound is according to the preceding paragraph, 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.

[00118] In another example, the compound is according to the preceding paragraph, wherein Y is either $-CH_2-$ or absent.

[00119] In another example, the compound is as defined three paragraphs above, wherein R^9 is an alkyl group containing at least one fluorine substitution thereon.

[00120] In another example, the compound is as defined eleven paragraphs above, wherein said saturated bridged ring system is of formula **XVII**, wherein R^8 is selected from -H, optionally substituted $C_{1\text{-}6}$alkyl, $-CO_2R^3$, $-C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$.



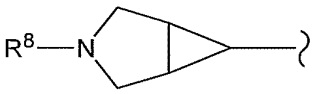
XVII

[00121] In another example, the compound is according to the preceding paragraph, wherein Y is either $-CH_2-$ or absent.

[00122] In another example, the compound is according to the preceding paragraph, wherein R^8 is methyl or ethyl.

[00123] In another example, the compound is according to the preceding paragraph, wherein at least one of R^2 is halogen.

[00124] In another example, the compound is as defined fifteen paragraphs above, wherein said saturated bridged ring system is of formula **XVIII**, wherein R^8 is selected from -H, optionally substituted $C_{1\text{-}6}$alkyl, $-CO_2R^3$, $-C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$.

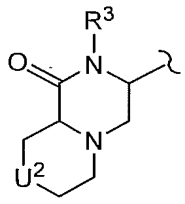


XVIII

[00125] In another example, the compound is according to the preceding paragraph, wherein Y is $-CH_2-$.

[00126] In another example, the compound is according to the preceding paragraph, wherein R^8 is methyl or ethyl.

[00127] In another example, the compound is as defined nineteen paragraphs above, 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.

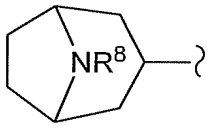
[00128] In another example, the compound is according to the preceding paragraph, wherein R^3 of formula **XIX** is selected from -H and optionally substituted alkyl.

[00129] In another example, the compound is according to the preceding paragraph, wherein U^2 is either $-CR^6R^7-$ or absent.

[00130] In another example, the compound is according to the preceding paragraph, wherein U^2 is either $-CH_2-$ or absent.

[00131] In another example, the compound is according to the preceding paragraph, wherein Y is $-CH_2-$.

[00132] In another example, the compound is as defined above, wherein said saturated bridged ring system is according to formula **XX**, 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 $-C(O)R^3$.



XX

[00133] In another example, the compound is according to the preceding paragraph, wherein R^8 is methyl or ethyl.

[00134] In another example, the compound is according to formula XIVa or XIVb, wherein R^2 is selected from C_{1-6} alkyl, perfluoro C_{1-6} alkyl, and halogen.

[00135] In another example, the compound is according to the preceding paragraph, wherein R^2 is selected from perfluoro C_{1-3} alkyl and halogen.

[00136] In another example, the compound is according to formula XIVa or XIVb, 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**.

[00137] In another example, the compound is according to the preceding paragraph, 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**.

[00138] In another example, the compound is according to the preceding paragraph, wherein R^2 is selected from C_{1-6} alkyl, perfluoro C_{1-6} alkyl, and halogen.

[00139] In another example, the compound is according to the preceding paragraph, wherein R^2 is selected from perfluoro C_{1-3} alkyl and halogen.

[00140] In another example, the compound is selected from Table 2.

Table 2

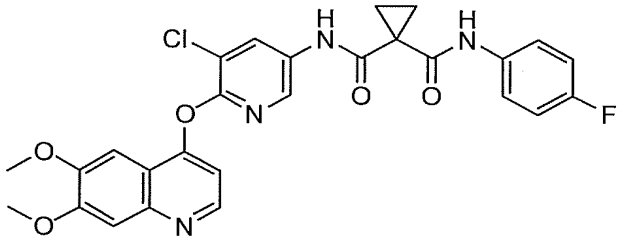
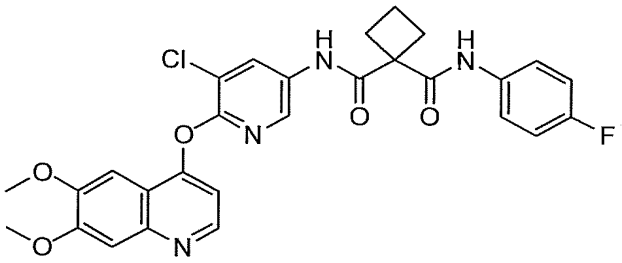
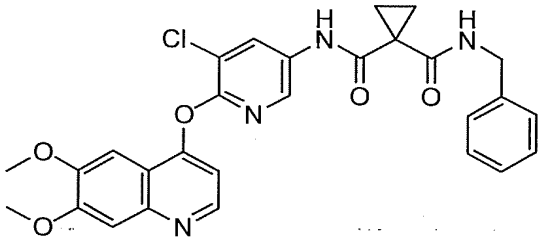
Entry	Name	Structure
1	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
2	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl) cyclobutane-1,1-dicarboxamide	
3	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(phenylmethyl) cyclopropane-1,1-dicarboxamide	

Table 2

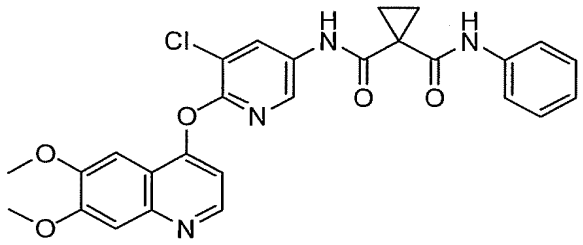
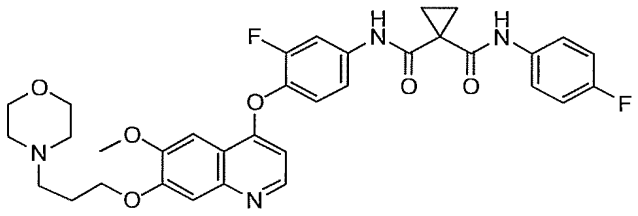
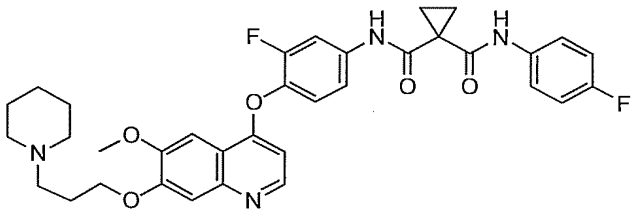
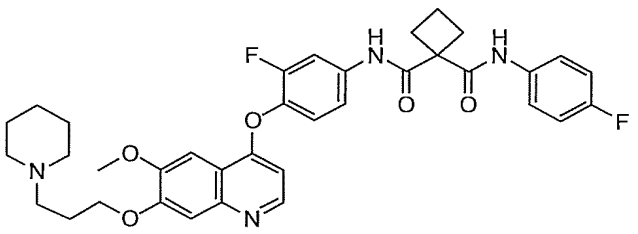
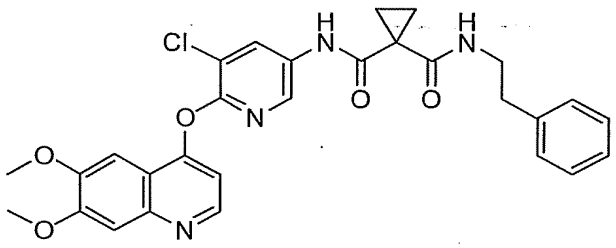
Entry	Name	Structure
4	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-phenylcyclopropane-1,1-dicarboxamide	
5	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
6	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperidin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
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	

Table 2

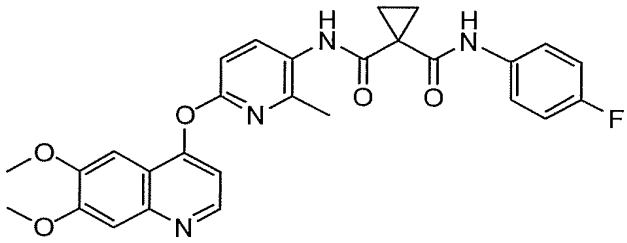
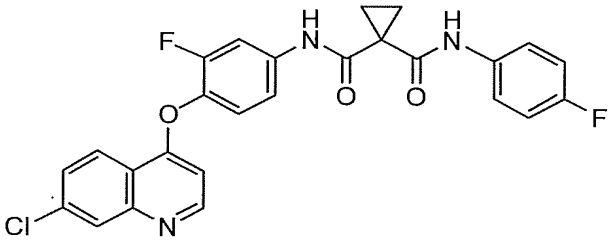
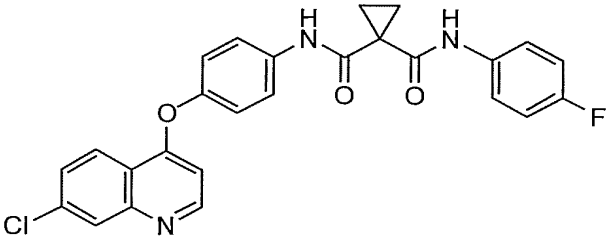
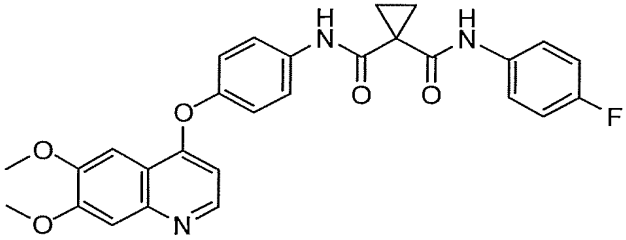
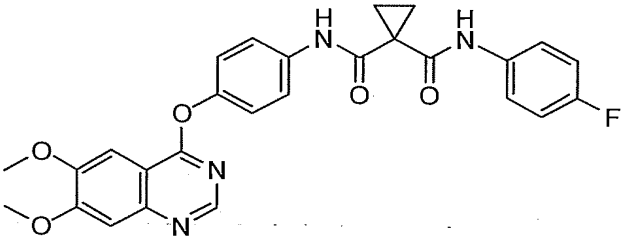
Entry	Name	Structure
9	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-methylpyridin-3-yl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
10	N-{4-[(7-chloroquinolin-4-yl)oxy]-3-fluorophenyl}-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
11	N-{4-[(7-chloroquinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
12	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
13	N-(4-{[6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	

Table 2

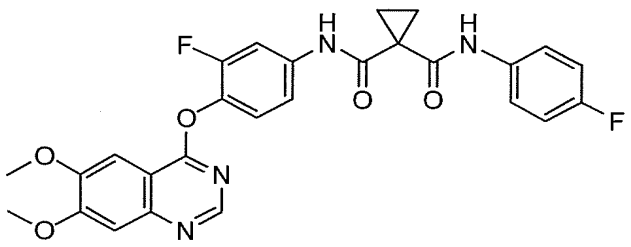
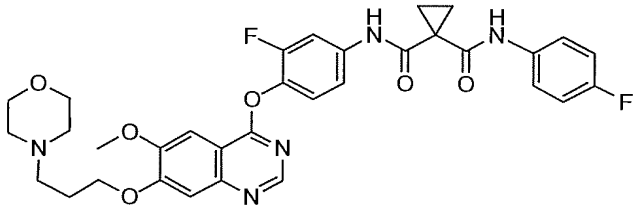
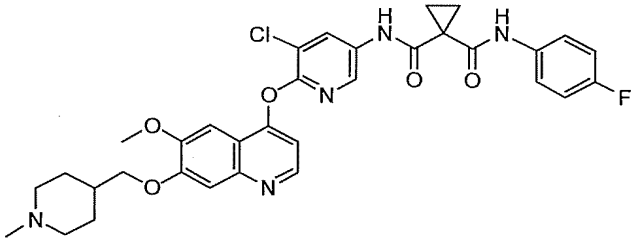
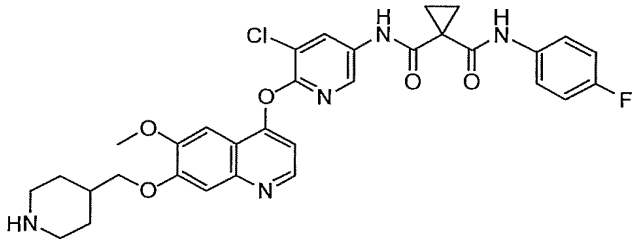
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15	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
16	N-{5-chloro-6-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]pyridin-3-yl}-N'-(4-fluorophenyl) 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	

Table 2

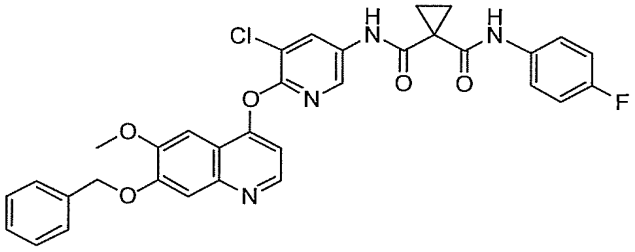
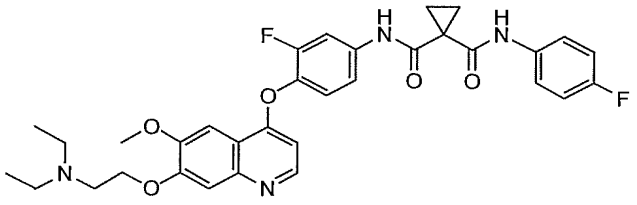
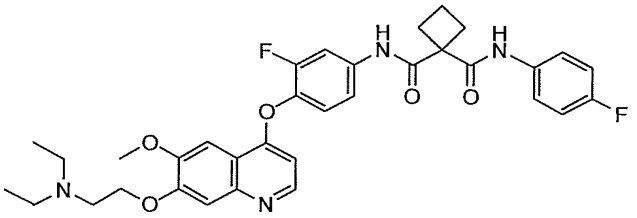
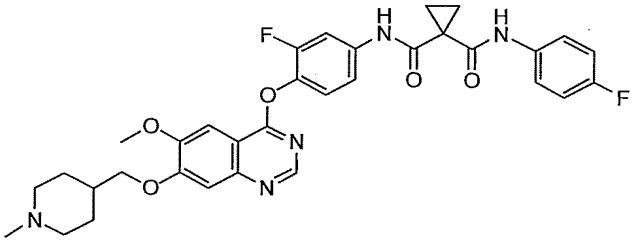
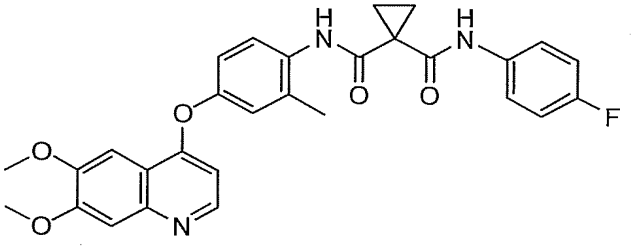
Entry	Name	Structure
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19	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
20	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl) 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

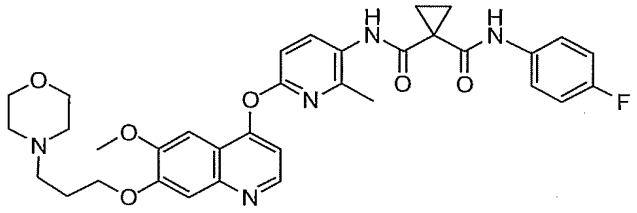
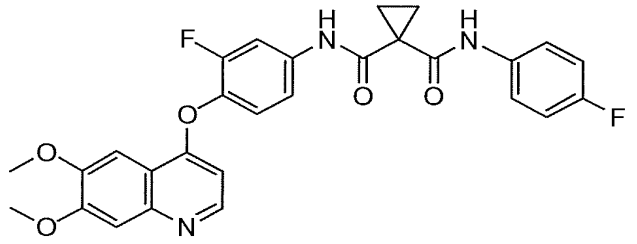
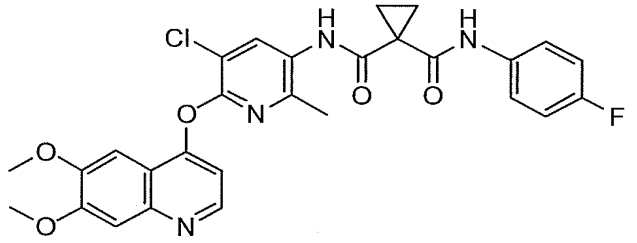
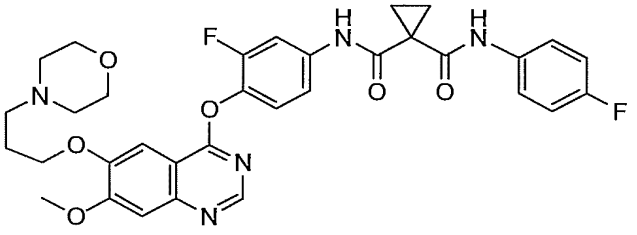
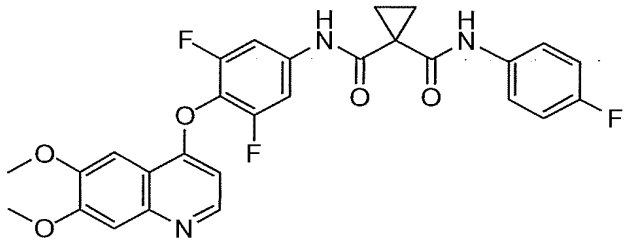
Entry	Name	Structure
23	N-(4-fluorophenyl)-N'-[2-methyl-6-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]cyclopropane-1,1-dicarboxamide	
24	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
25	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloro-2-methylpyridin-3-yl)-N'-(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	

Table 2

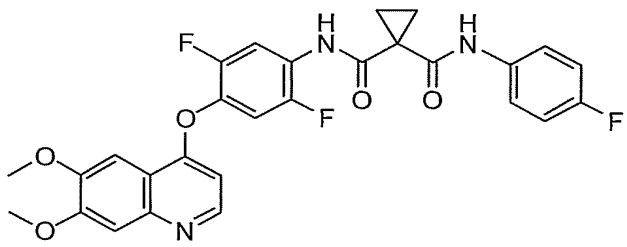
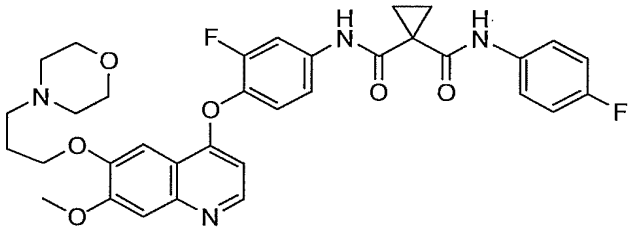
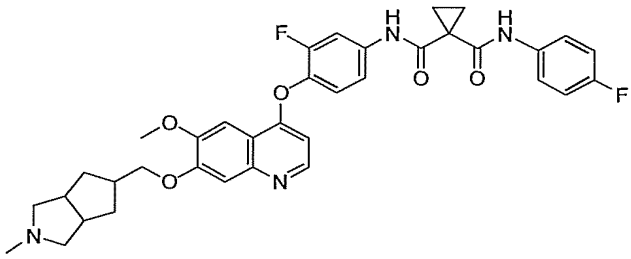
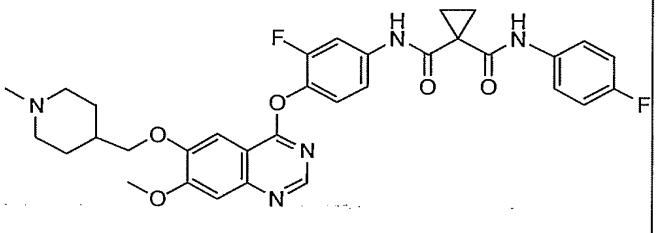
Entry	Name	Structure
28	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2,5-difluorophenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
29	N-[3-fluoro-4-({7-(methyloxy)-6-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
30	N-{3-fluoro-4-[(6-(methyloxy)-7-(2-methyl octahydrocyclo-penta[c]pyrrol-5-ylmethoxy)quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
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	

Table 2

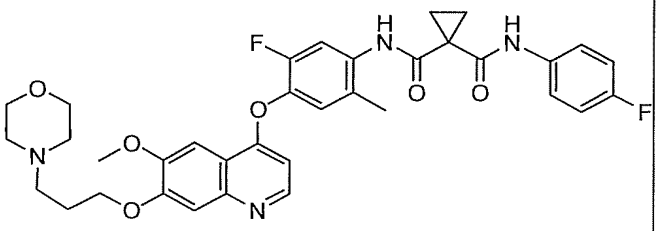
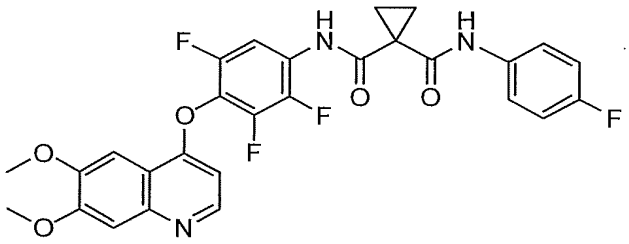
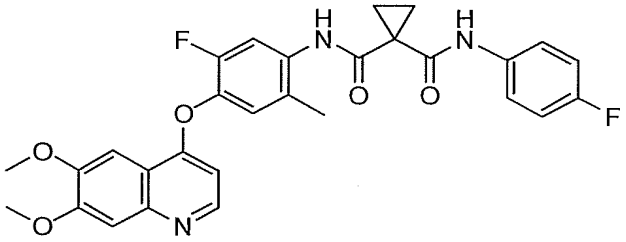
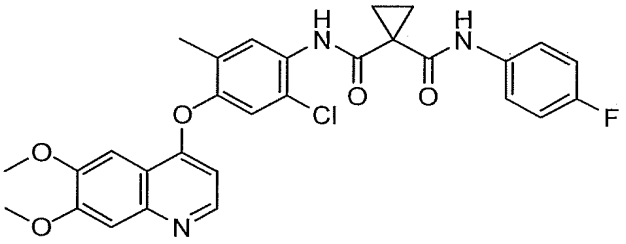
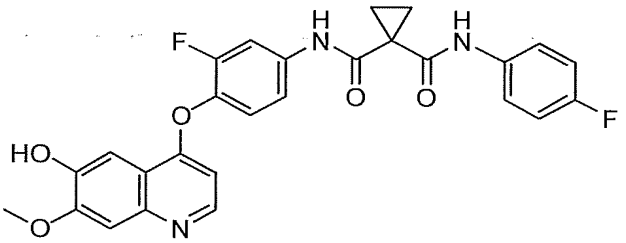
Entry	Name	Structure
32	N-[5-fluoro-2-methyl-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
33	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2,3,5-trifluorophenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
34	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-2-methylphenyl)-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

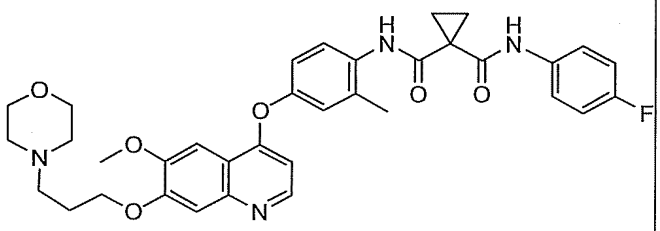
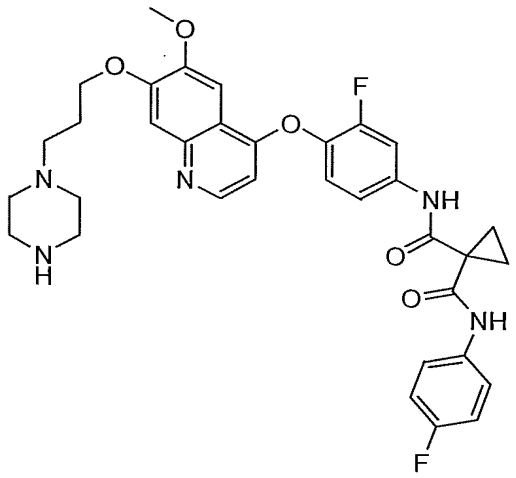
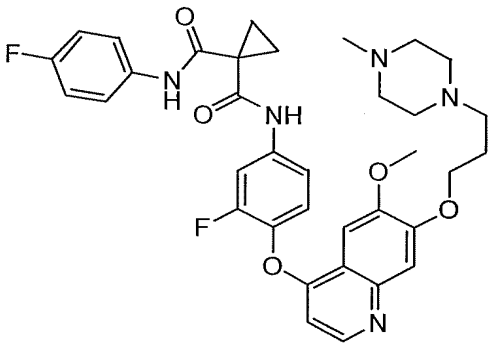
Entry	Name	Structure
37	N-(4-fluorophenyl)-N'-[2-methyl-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl] cyclopropane-1,1-dicarboxamide	
38	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
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	

Table 2

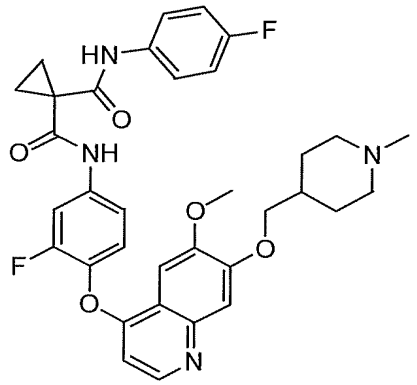
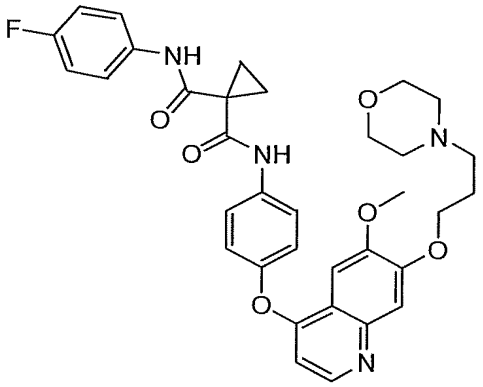
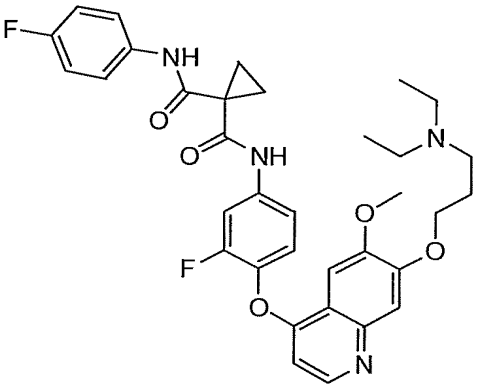
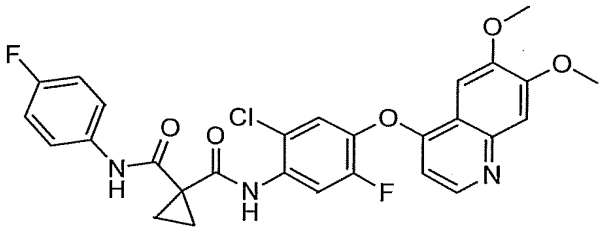
Entry	Name	Structure
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41	N-(4-fluorophenyl)-N'-[4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl] cyclopropane-1,1-dicarboxamide	
42	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl) 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	

Table 2

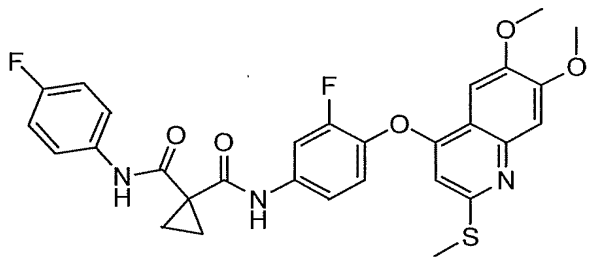
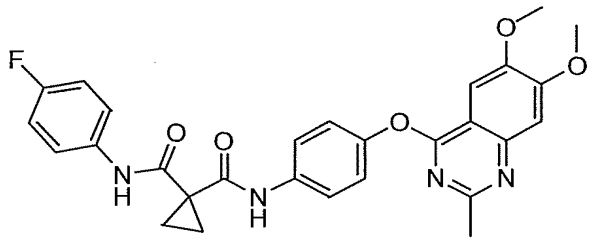
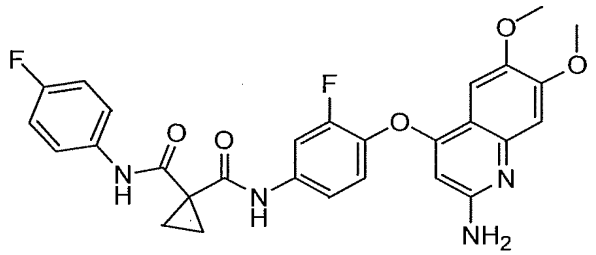
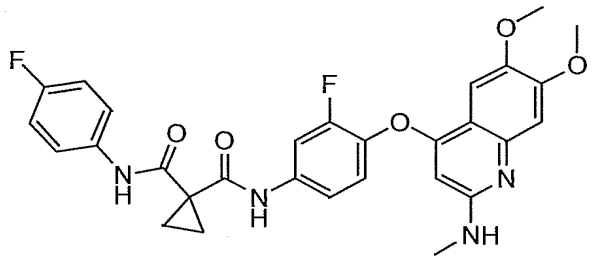
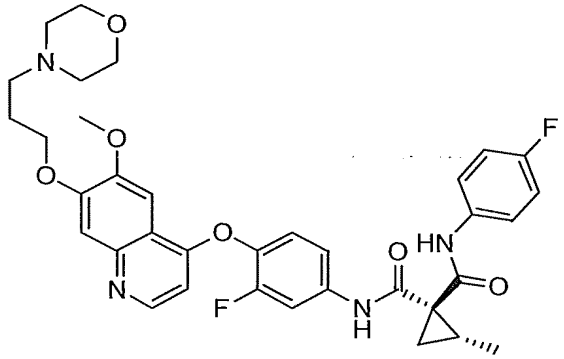
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44	N-(4-{[6,7-bis(methyloxy)-2-(methylthio)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
45	N-(4-fluorophenyl)-N'-(4-{[2-methyl-6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl) cyclopropane-1,1-dicarboxamide	
46	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	
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	

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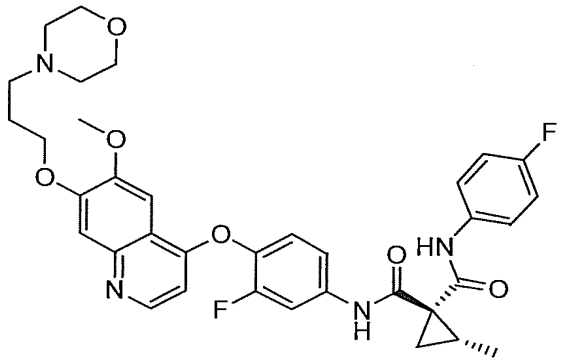
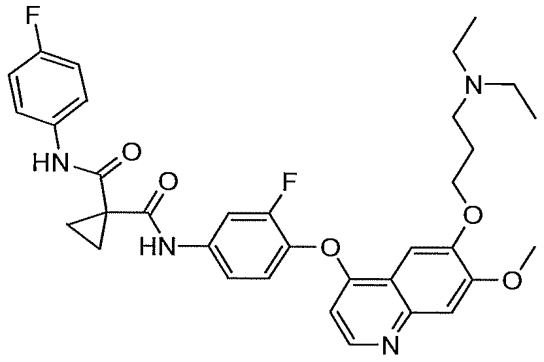
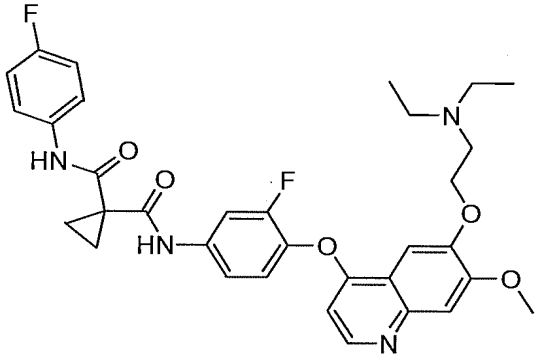
Entry	Name	Structure
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50	N-(4-{[6-{[3-(diethylamino)propyl]oxy}-7-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
51	N-(4-{[6-{[2-(diethylamino)ethyl]oxy}-7-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	

Table 2

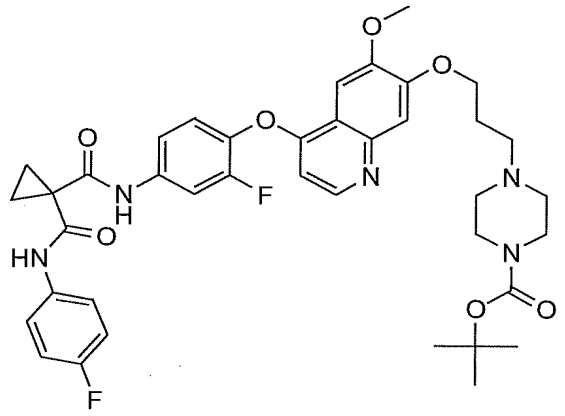
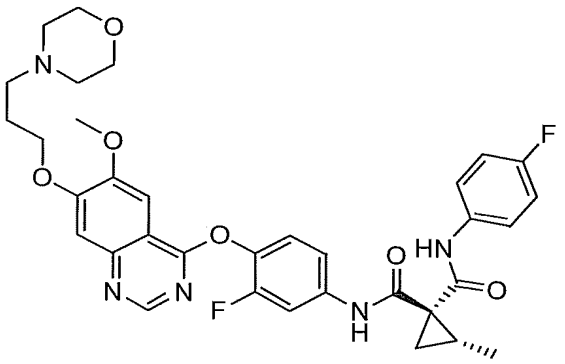
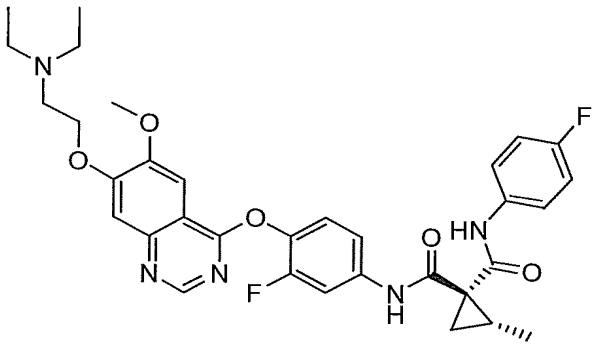
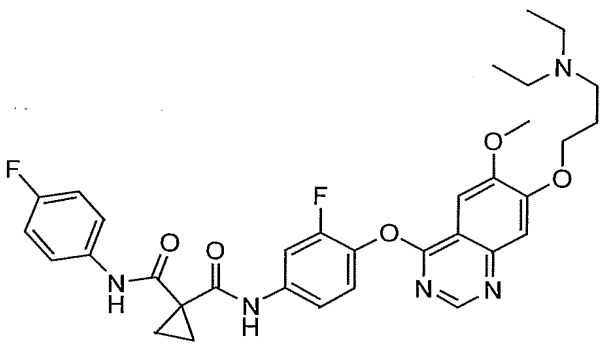
Entry	Name	Structure
52	1,1-dimethylethyl 4-(3-{[4-[(2-fluoro-4-{[(1-{[(4-fluorophenyl) amino]carbonyl}cyclopropyl)carbonyl]amino}phenyl)oxy]-6-(methyloxy) quinolin-7-yl]oxy}propyl) piperazine-1-carboxylate	
53	(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
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

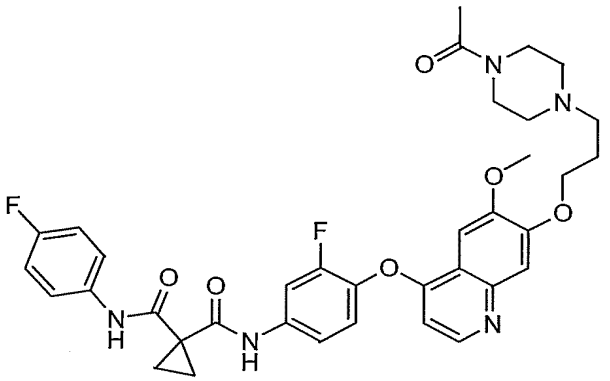
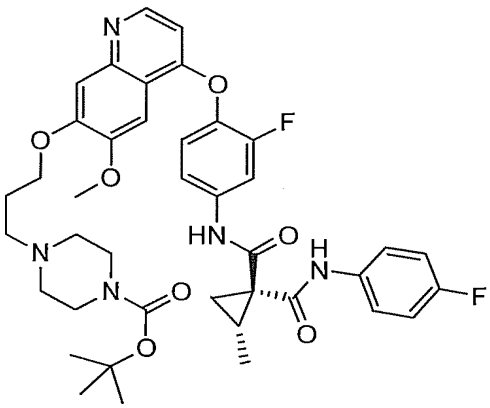
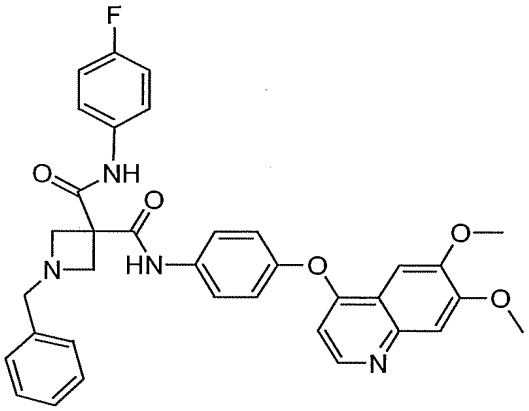
Entry	Name	Structure
56	N-(4-{[7-{[3-(4-acetylpiperazin-1-yl)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
57	1,1-dimethylethyl 4-(3-{[4-[(2-fluoro-4-{[((1R,2R)-1-{[(4-fluorophenyl)amino]carbonyl}-2-methylcyclopropyl)carbonyl]amino}phenyl)oxy]-6-(methyloxy)quinolin-7-yl]oxy}propyl)piperazine-1-carboxylate	
58	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-1-(phenylmethyl)azetidine-3,3-dicarboxamide	

Table 2

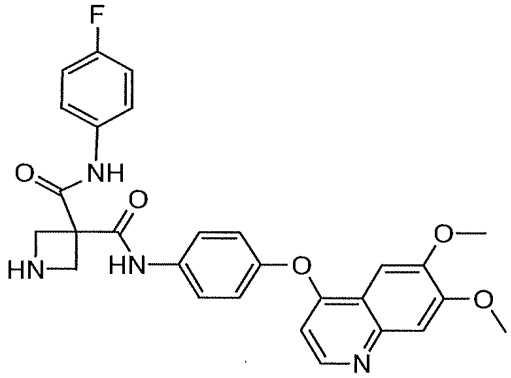
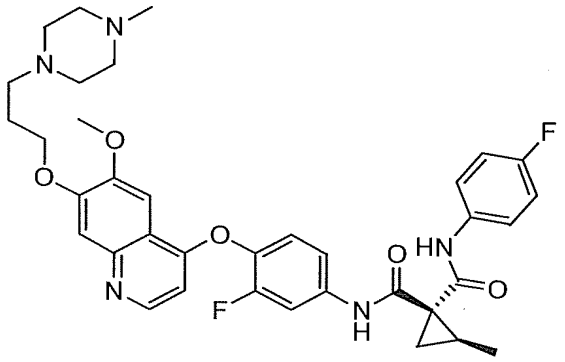
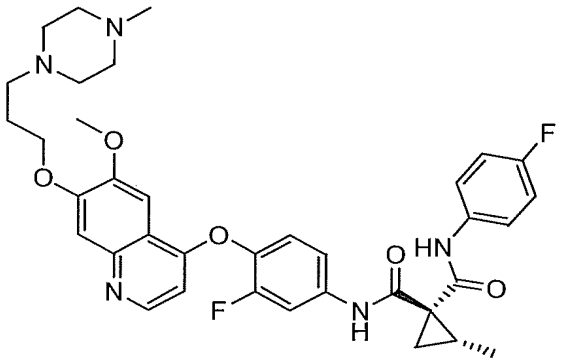
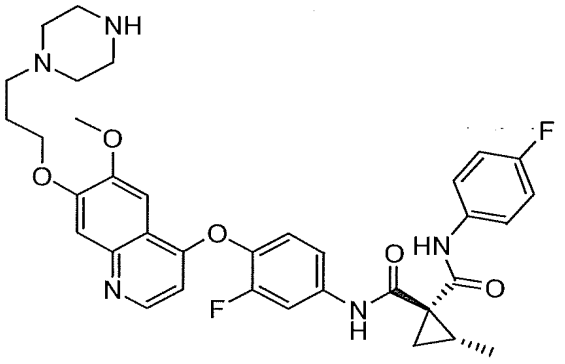
Entry	Name	Structure
59	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)azetidine-3,3-dicarboxamide	
60	(1R,2S)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
61	(1R,2R)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]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	

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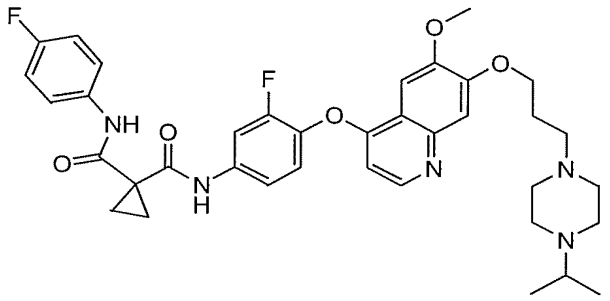
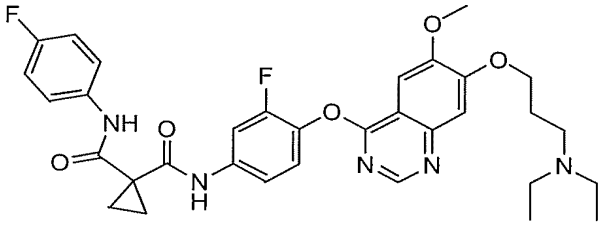
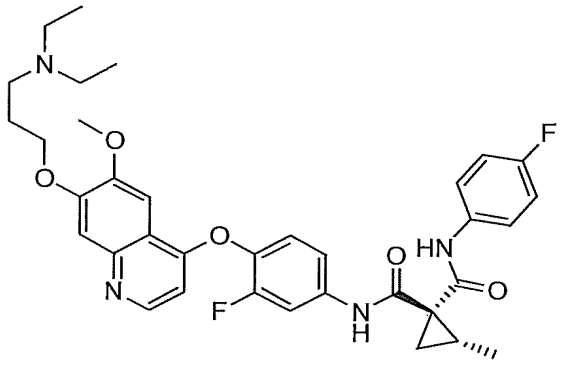
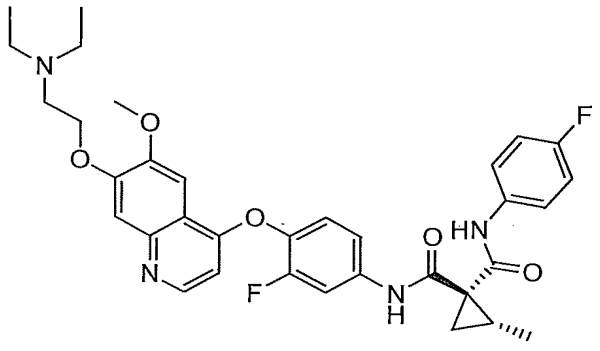
Entry	Name	Structure
63	N-(3-fluoro-4-{[7-({3-[4-(1-methylethyl)piperazin-1-yl]propyl}oxy)-6-(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
64	N-(4-{[7-{[3-(diethylamino)propyl] oxy}-6-(methyloxy) quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
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

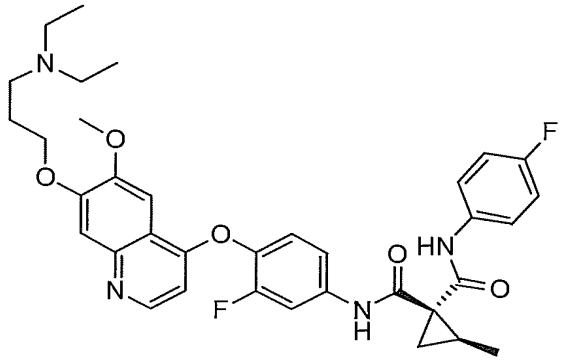
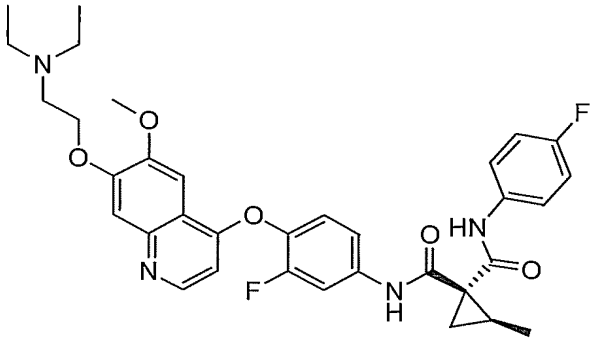
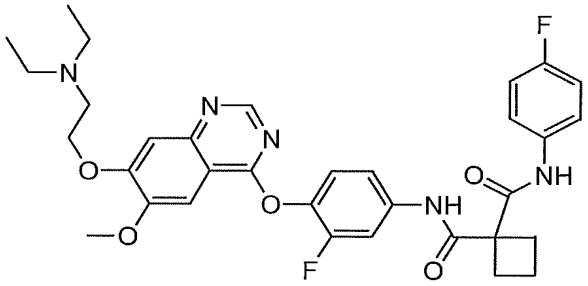
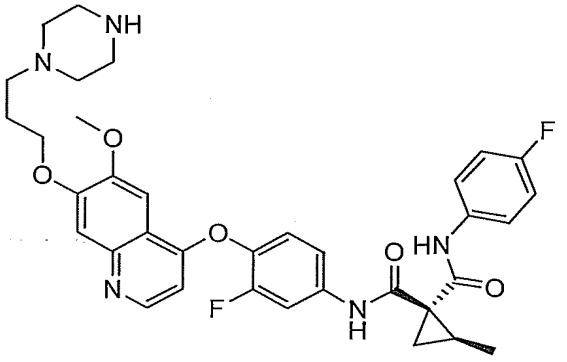
Entry	Name	Structure
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68	(1R,2S)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
69	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
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

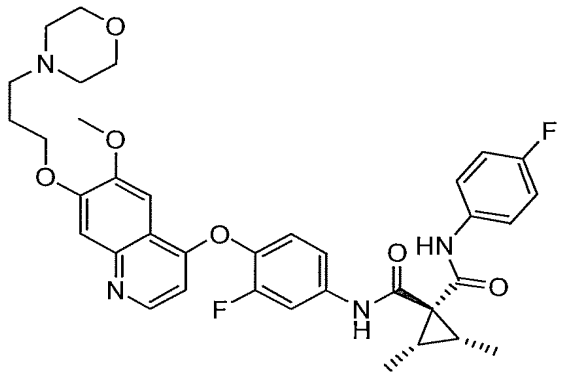
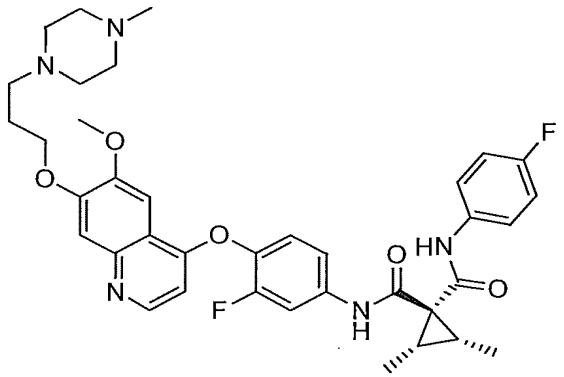
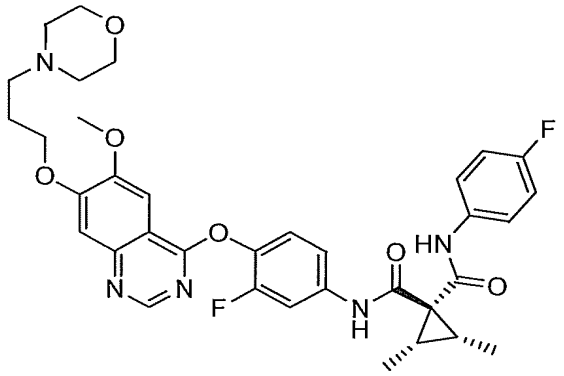
Entry	Name	Structure
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72	(1R,2R,3S)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	
73	(1R,2R,3S)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	

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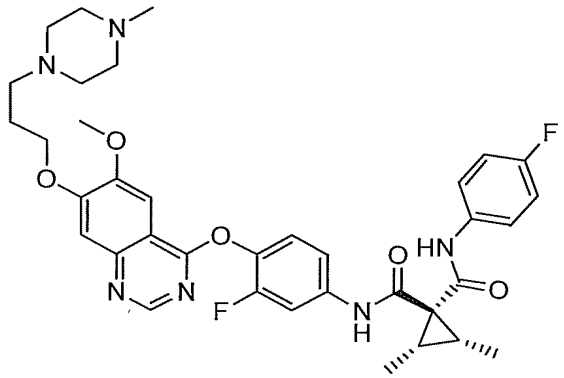
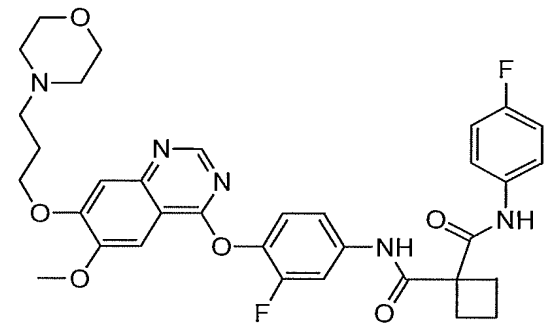
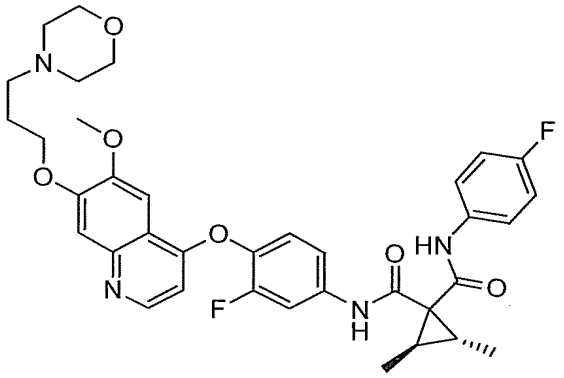
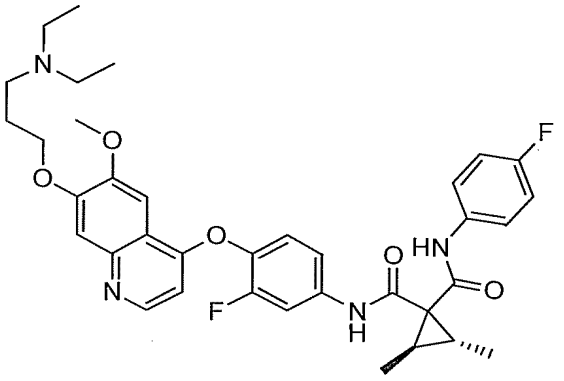
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75	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
76	(2R,3R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	
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

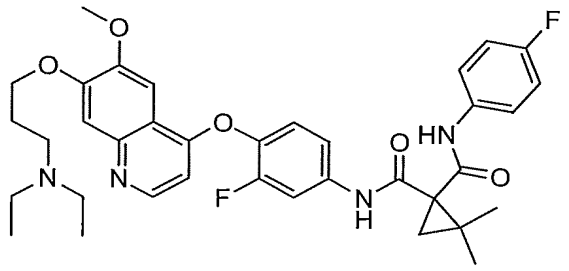
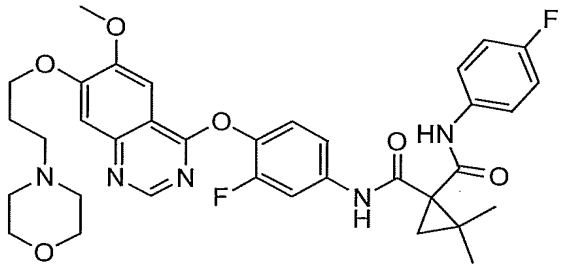
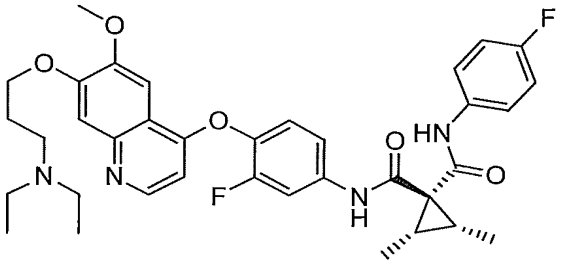
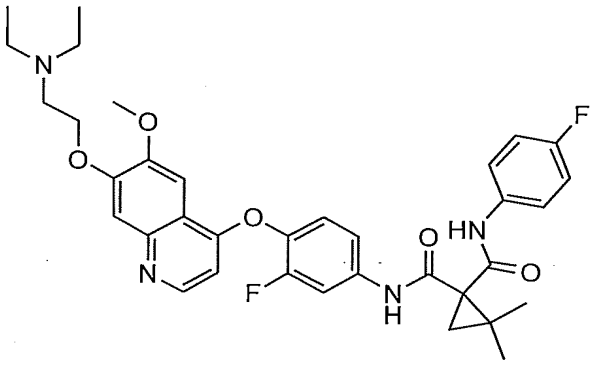
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79	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	
80	(1R,2R,3S)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2,3-dimethylcyclopropane-1,1-dicarboxamide	
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	

Table 2

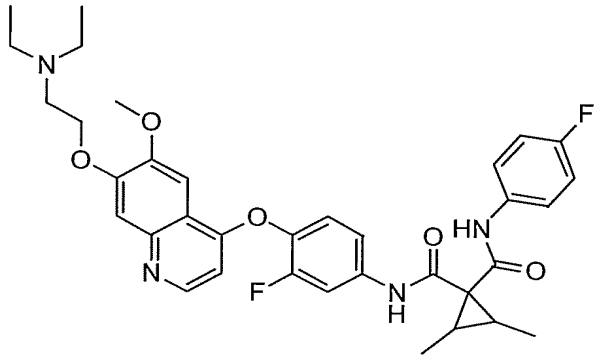
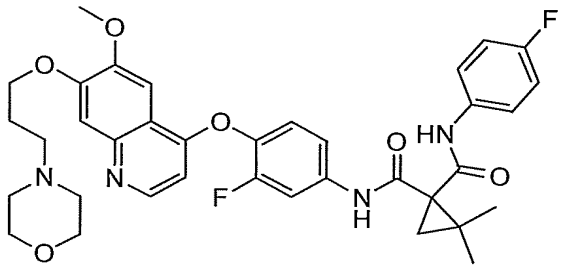
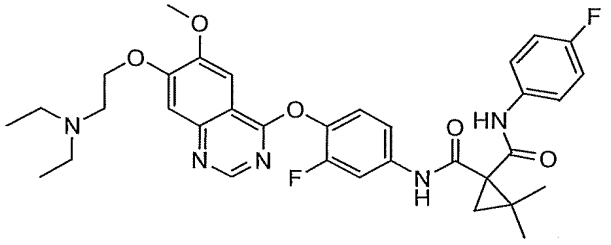
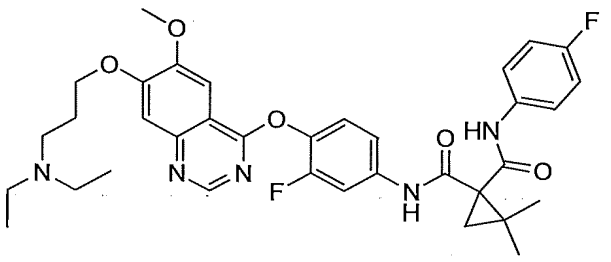
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83	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	
84	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	
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	

Table 2

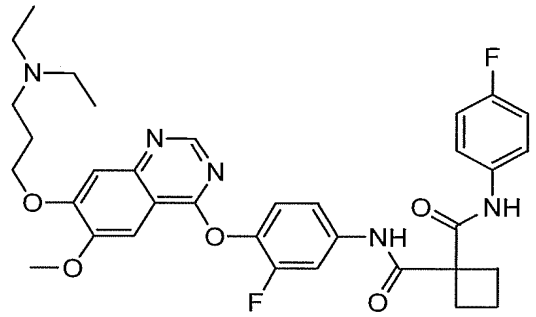
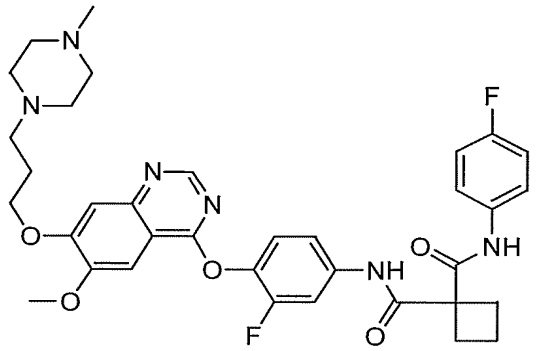
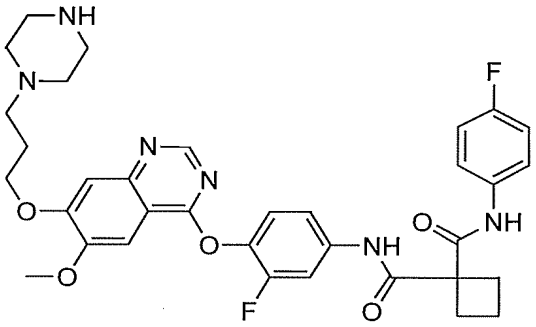
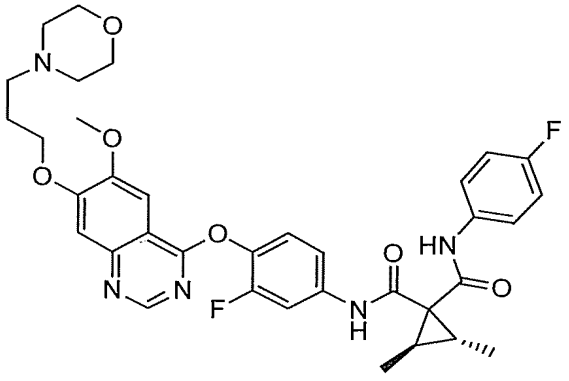
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87	N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
88	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
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	

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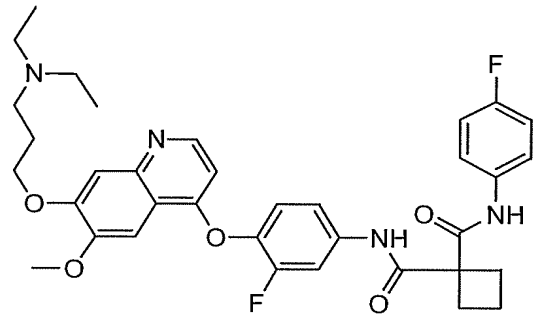
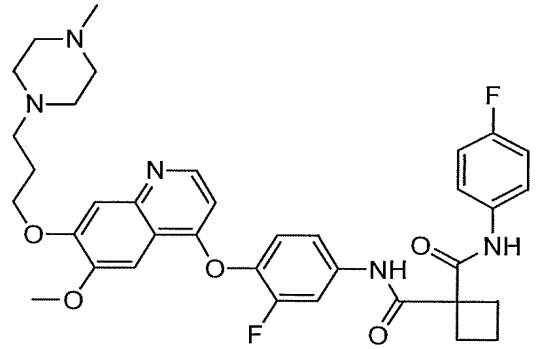
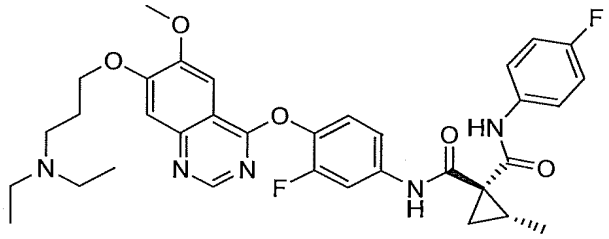
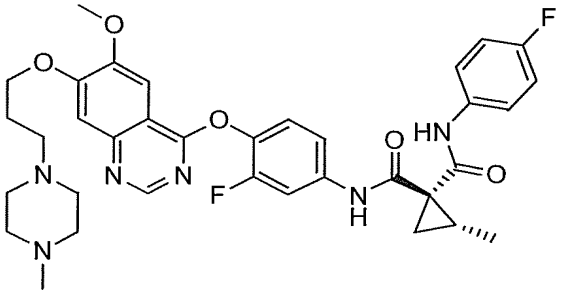
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91	N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
92	(1R,2R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
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	

Table 2

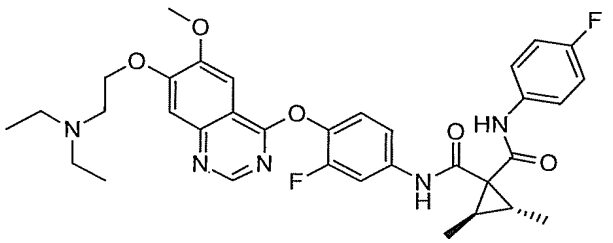
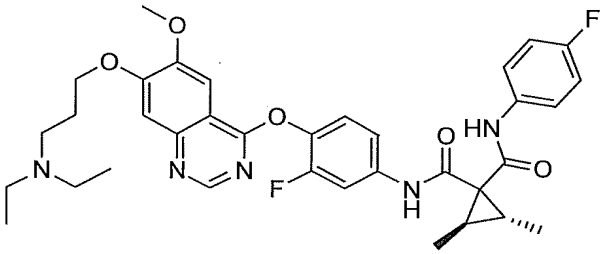
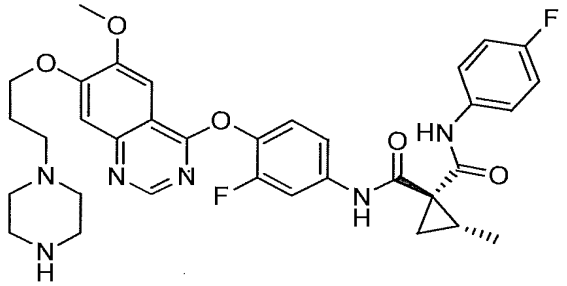
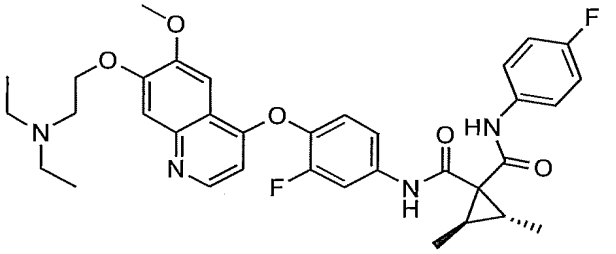
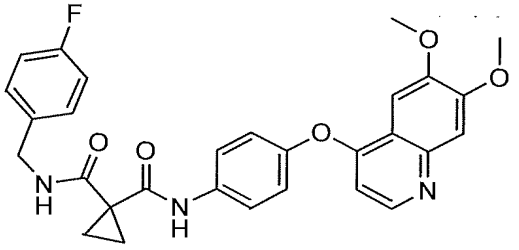
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95	(2R,3R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	
96	(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	
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	
98	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[(4-fluorophenyl)methyl]cyclopropane-1,1-dicarboxamide	

Table 2

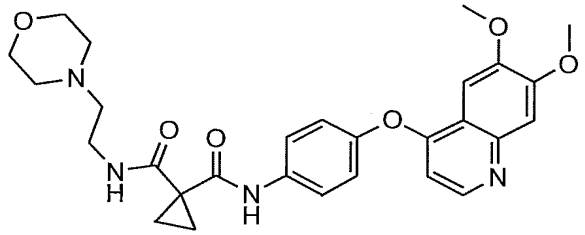
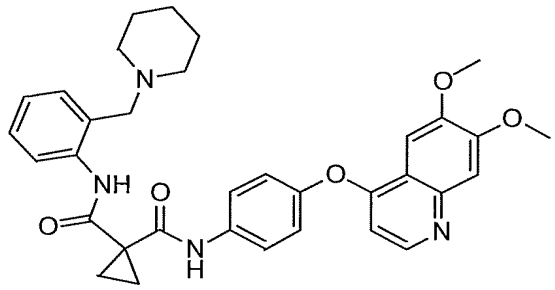
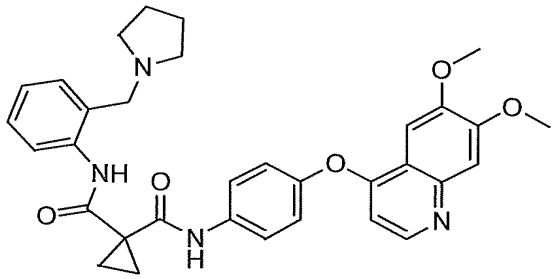
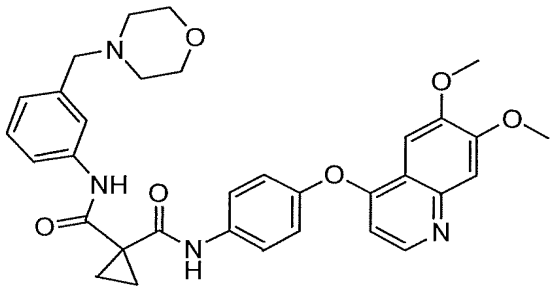
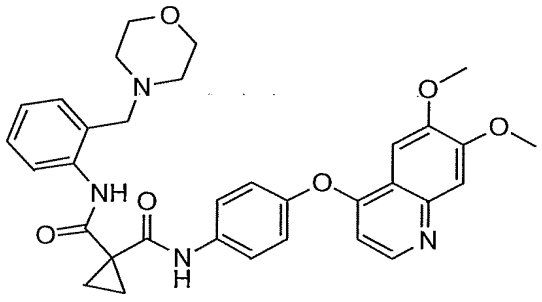
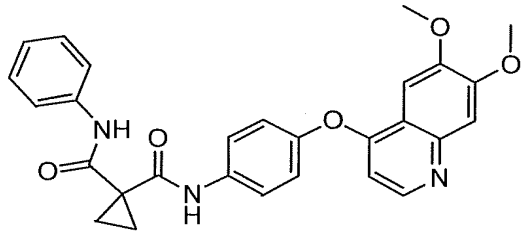
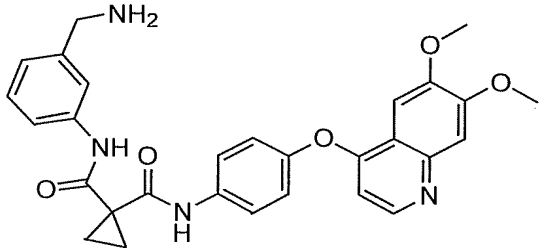
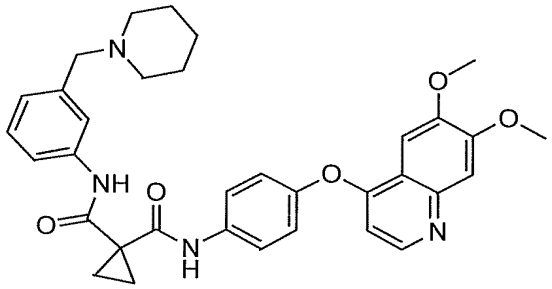
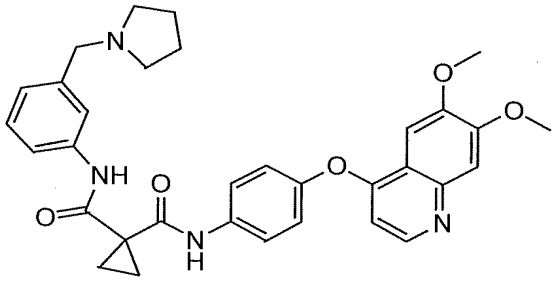
Entry	Name	Structure
99	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(2-morpholin-4-ylethyl) cyclopropane-1,1-dicarboxamide	
100	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(piperidin-1-ylmethyl) phenyl]cyclopropane-1,1-dicarboxamide	
101	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(pyrrolidin-1-ylmethyl) 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	
103	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(morpholin-4-ylmethyl) phenyl]cyclopropane-1,1-dicarboxamide	

Table 2

Entry	Name	Structure
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	

[00141] Another aspect of the invention is a pharmaceutical composition comprising a compound according to the invention and a pharmaceutically acceptable carrier.

[00142] Another aspect of the invention is a metabolite of the compound or the pharmaceutical composition according to the invention.

[00143] 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 the invention.

[00144] Another aspect of the invention is the method according to the preceding paragraph, wherein modulating the *in vivo* activity of the kinase comprises inhibition of said kinase.

[00145] Another aspect of the invention is the method according to the preceding paragraph, wherein the kinase is at least one of c-Met, KDR, c-Kit, flt-3, and flt-4.

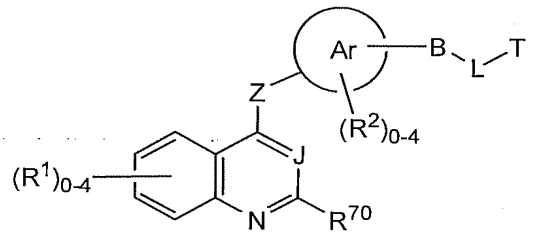
[00146] Another aspect of the invention is the method according to the preceding paragraph, wherein the kinase is c-Met.

[00147] 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 herein.

[00148] 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 the invention, and at least one candidate agent and determining the effect of the candidate agent on the activity of said kinase.

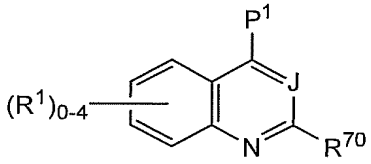
[00149] Another aspect of the invention is a method of inhibiting proliferative activity in a cell, the method comprising administering an effective amount of a composition comprising a compound according to the invention to a cell or a plurality of cells.

[00150] 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**,

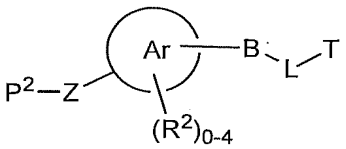


XXI

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, $-C(=S)N(R^{13})$-, $-C(=NR^{14})N(R^{13})$-, $-SO_2N(R^{13})$-, $-SO_2$-, $-C(=O)N(R^{13})$-, $-N(R^{13})$-, $-C(=O)C_{1-2}$alkyl$N(R^{13})$-, $-N(R^{13})C_{1-2}$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$_2$C$_{0-4}$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;

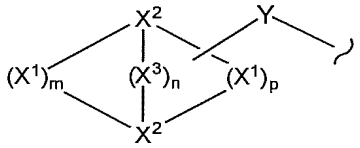
Q is a five- to ten-membered ring system, optionally substituted with between zero and four of R^{20};

each R^{20} is independently selected from -H, halogen, trihalomethyl, -CN, -NO$_2$, -NH$_2$, -OR^3, -NR^{3}R^3, -S(O)$_{0-2}$R^3, -SO$_2$NR^{3}R^3, -CO$_2$R^3, -C(O)NR^{3}R^3, -N(R^3)SO$_2$R^3, -N(R^3)C(O)R^3, -N(R^3)CO$_2$R^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;

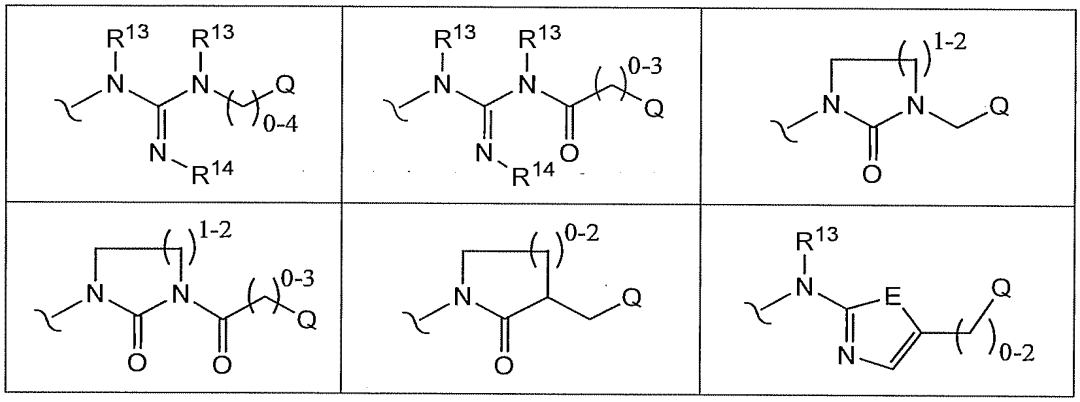
P^1 is a suitable leaving group; and

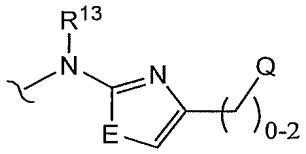
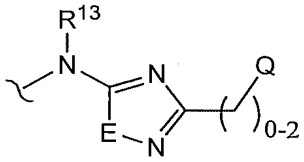
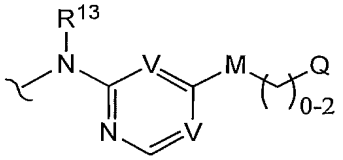
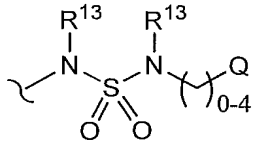
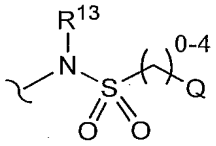
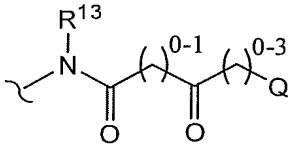
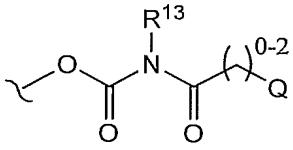
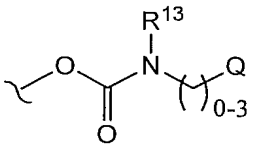
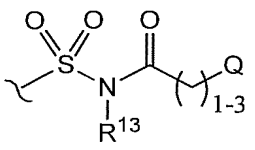
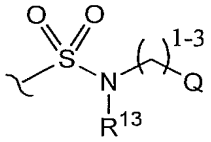
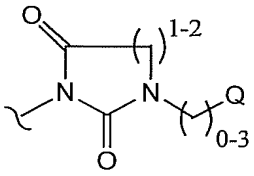
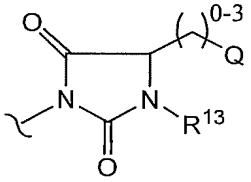
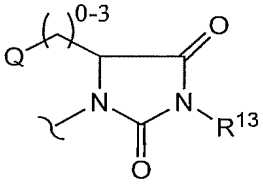
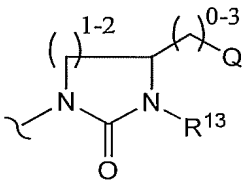
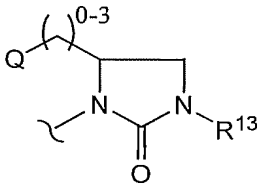
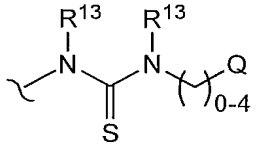
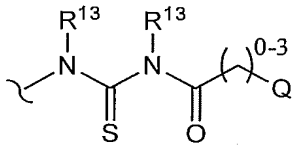
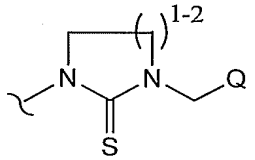
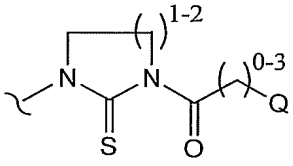
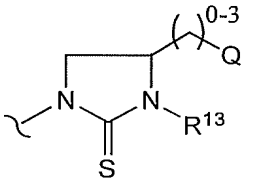
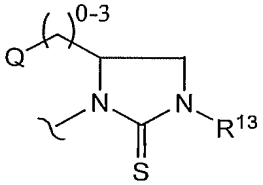
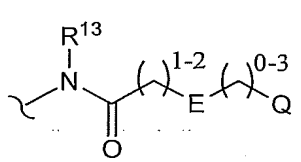
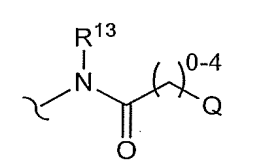
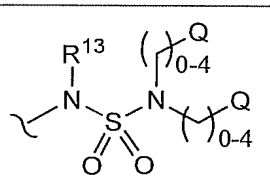
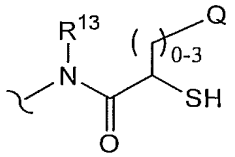
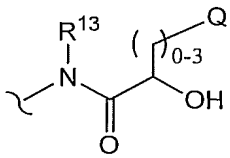
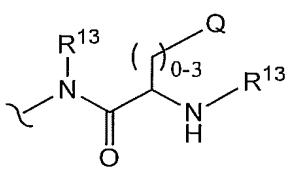
P^2 is selected from -H, a metal, and a group removed *in-situ* when combining **XXII** and **XXIII** to make **XXI**.

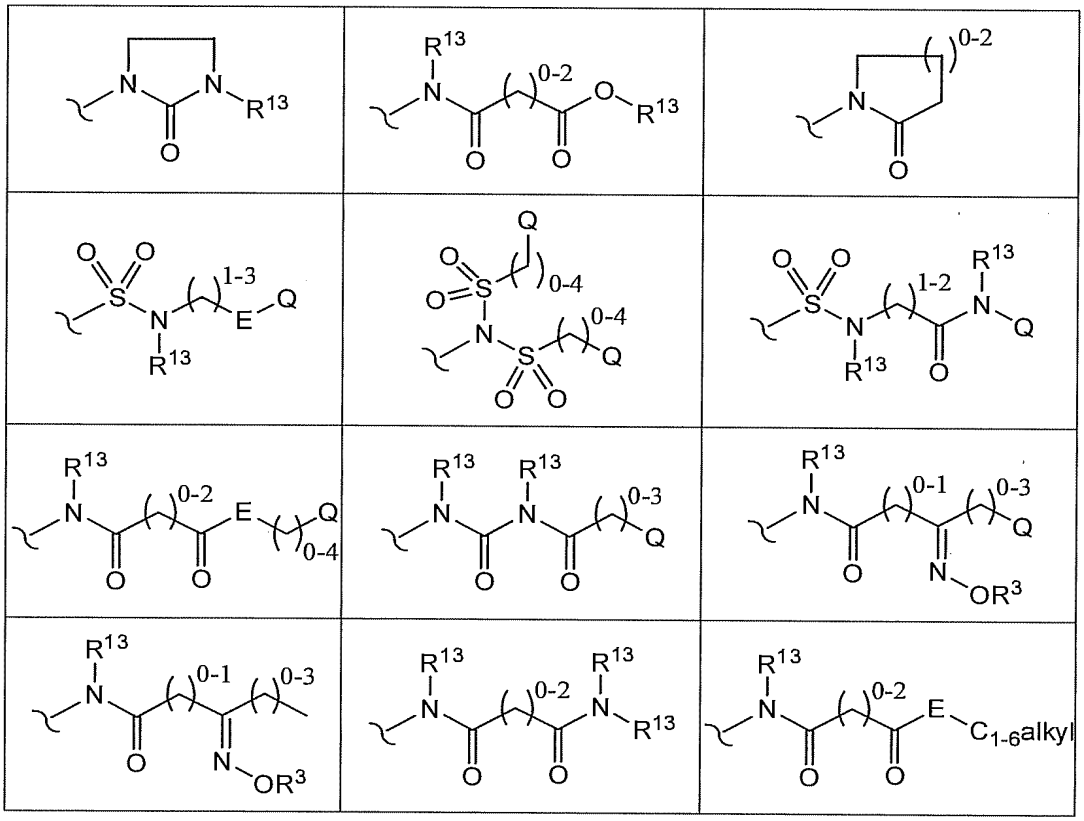
[00151] In one example, the process is according to the preceding paragraph, wherein Ar is *para*-phenylene as defined by the substitution pattern of -Z- and -B-L-T about said phenylene.

[00152] In another example, the process is according to the preceding paragraph, wherein Z is either -O- or $-NR^5-$.

[00153] In another example, the process is according to the preceding paragraph, 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.

[00154] In another example, the process is according to the preceding paragraph, wherein there is one of R^1 that is -D-R^{50} and another of R^1 that is -OR^{3a}.

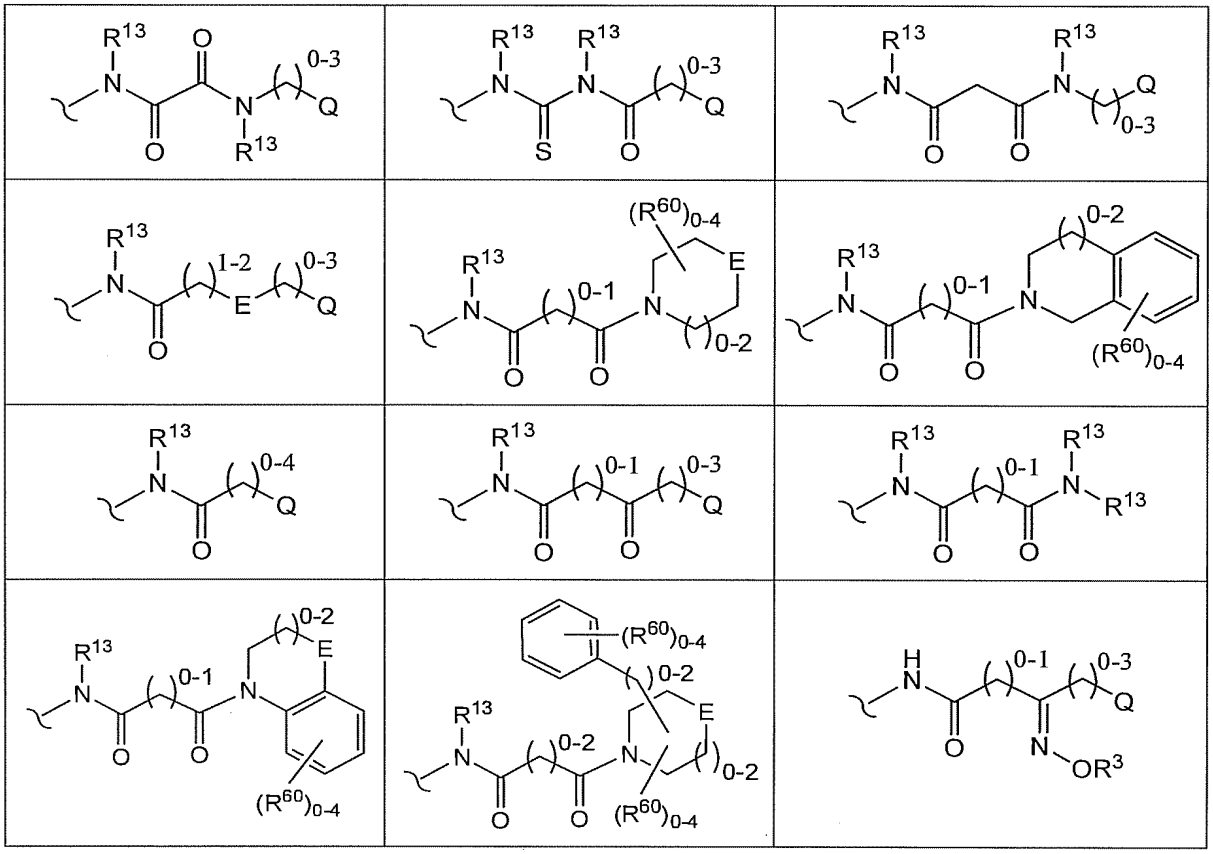
[00155] In another example, the process is according to the preceding paragraph, wherein D is -O-.

[00156] In another example, the process is according to the preceding paragraph, 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**.

[00157] In another example, the process is according to the preceding paragraph, wherein $-OR^{3a}$ is selected from -OH, $-OSi(R^5)(R^5)R^5$, and optionally substituted $-OC_{1-6}$alkyl.

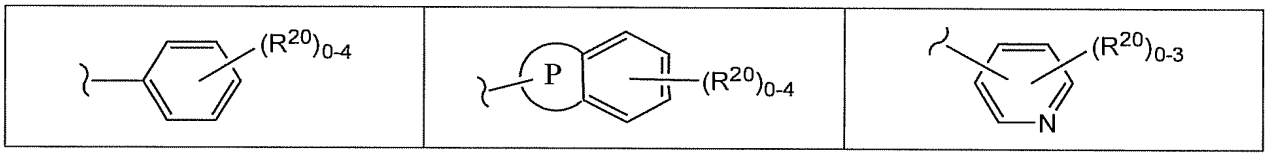
[00158] In another example, the process is according to the preceding paragraph, wherein J is =N- or =C(H)-.

[00159] In another example, the process is according to the preceding paragraph, wherein -B-L-T is selected from:



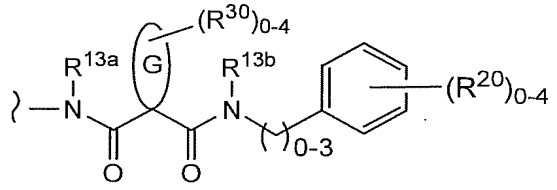
wherein Q, R^{20}, R^{13}, E, and R^{60} are as defined above; each methylene in any of the above formulae, other than those in a depicted ring, is independently optionally substituted with R^{25}; and R^{25} is selected from halogen, trihalomethyl, oxo, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, 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.

[00160] In another example, the process is according to the preceding paragraph, wherein Q is selected from the following three formulae:

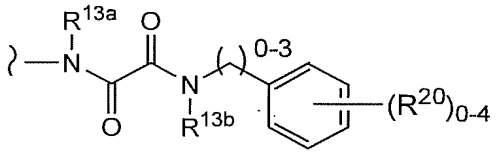


wherein R^{20} is defined as above, and P is a five- to seven-membered ring, including the two shared carbons of the aromatic ring to which P is fused, P optionally containing between one and three heteroatoms.

[00161] In another example, the process is according to the preceding paragraph, wherein -B-L-T is either of formula **XXV** or formula **XXVI**,



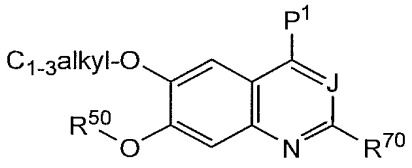
XXV



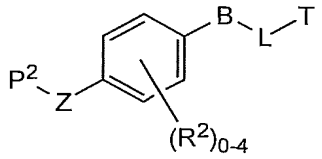
XXVI

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.

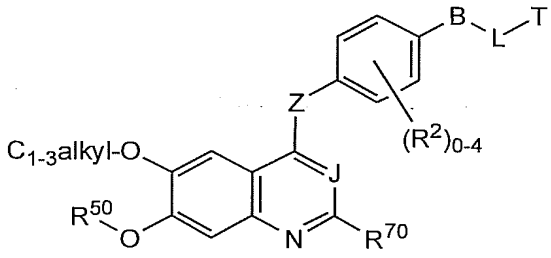
[00162] In another example, the process is according to the preceding paragraph, wherein a compound of formula **XXIIa** is combined with a compound of formula **XXIIIa** to make a compound of formula **XXIa**,



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.

[00163] In another example, the process is according to the preceding paragraph, wherein P^2 is selected from -H, lithium, sodium, potassium, cesium, copper, palladium, and titanium.

[00164] In another example, the process is according to the preceding paragraph, wherein Z is -O-.

[00165] In another example, the process is according to the preceding paragraph, wherein P^1 is selected from chlorine, bromine, a toluene sulfonate, and trifluoromethansulfonate.

[00166] In another example, the process is according to the preceding paragraph, wherein R^{70} is -H.

[00167] In another example, the process is according to the preceding paragraph, wherein J is =C(H)-.

[00168] In another example, the process is according to the preceding paragraph, wherein R^2 is selected from C_{1-6} alkyl, perfluoro C_{1-6} alkyl, and halogen.

[00169] In another example, the process is according to the preceding paragraph, wherein **XXIIa** and **XXIIIa** are heated together, optionally with a base, optionally with microwave radiation, to form **XXIa**.

[00170] In another example, the process is according to the preceding paragraph, wherein the base is selected from an organic base, an inorganic base, and a combination of an organic base and an inorganic base.

[00171] In another example, the process is according to the preceding paragraph, wherein the base is selected from 2,6-lutidine, 4-N,N-dimethylaminopyridine, and a metal carbonate.

[00172] In another example, the process is according to the preceding paragraph, 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**.

[00173] In another example, the process is according to the preceding paragraph, wherein the solvent is an organic solvent.

[00174] In another example, the process is according to the preceding paragraph, wherein one molar equivalent of **XXIIa** is combined with between about one quarter and four molar equivalents of **XXIIIa**.

[00175] In another example, the process is according to the preceding paragraph, wherein one molar equivalent of **XXIIa** is combined with more than one but less than two molar equivalents of **XXIIIa**.

[00176] In another example, the process is according to the preceding paragraph, 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**.

[00177] In another example, the process is according to the preceding paragraph, wherein the aromatic solvent is an optionally substituted benzene.

[00178] In another example, the process is according to the preceding paragraph, wherein the aromatic solvent is bromobenzene.

[00179] In another example, the process is according to the preceding paragraph, wherein the base is 4-N,N-dimethylaminopyridine.

[00180] In another example, the process is according to the preceding paragraph, wherein said mixture is heated to reflux for between about three and seven hours.

[00181] In another example, the process is according to the preceding paragraph, wherein said mixture is heated to reflux for between about four and six hours.

[00182] In another example, the process is as defined seven paragraphs above, wherein one molar equivalent of **XXIIa** is combined with more than one but less than two molar equivalents of **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**.

[00183] In another example, the process is according to the preceding paragraph, wherein the non-aromatic solvent comprises a functional group selected from an amide, an ether, a nitrile, a halide, an ester, an amine, and a ketone.

[00184] In another example, the process is according to the preceding paragraph, wherein the non-aromatic solvent is N,N-dimethylacetamide.

[00185] In another example, the process is according to the preceding paragraph, wherein the base is potassium carbonate.

[00186] In another example, the process is according to the preceding paragraph, wherein said mixture is heated to about 50°C between about ten and twenty hours.

[00187] In another example, the process is according to the preceding paragraph, wherein the aromatic solvent is an optionally substituted pyridine.

[00188] In another example, the process is according to the preceding paragraph, wherein the aromatic solvent is 2,6-lutidine.

[00189] In another example, the process is according to the preceding paragraph, wherein the base is 2,6-lutidine.

[00190] In another example, the process is according to the preceding paragraph, wherein said mixture is heated to reflux for between about three and seven hours.

[00191] In another example, the process is according to the preceding paragraph, wherein said mixture is heated to reflux for between about four and six hours.

[00192] In another example, the process is as eighteen paragraphs defined above, wherein one molar equivalent of **XXIIIa** is combined with more than one but less than two molar equivalents of **XXIIa**.

[00193] In another example, the process is according to the preceding paragraph, 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**.

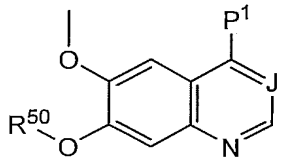
[00194] In another example, the process is according to the preceding paragraph, wherein the aromatic solvent is an optionally substituted pyridine.

[00195] In another example, the process is according to the preceding paragraph, wherein the aromatic solvent is 2,6-lutidine.

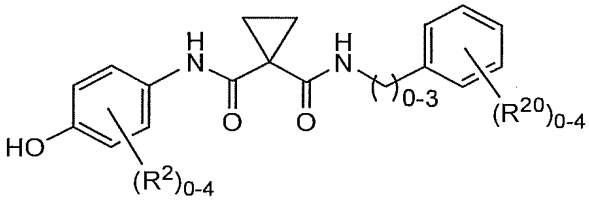
[00196] In another example, the process is according to the preceding paragraph, wherein the base is 2,6-lutidine.

[00197] In another example, the process is according to the preceding paragraph, wherein said mixture is heated to between about 150°C and 200°C for between about fifteen and twenty hours.

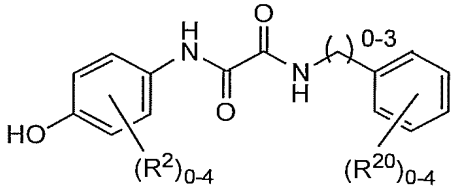
[00198] In another example, the process is as defined above in any of the twenty-nine preceding paragraphs, wherein a compound of formula **XXIIb** is substituted for the compound of formula **XXIIa**, and either a compound of formula **XXIIIb** or a compound of formula **XXIIIc** is substituted for the compound of formula **XXIIIa**, in order to make a compound of formula **XXIb** or a compound of formula **XXIc**, respectively,



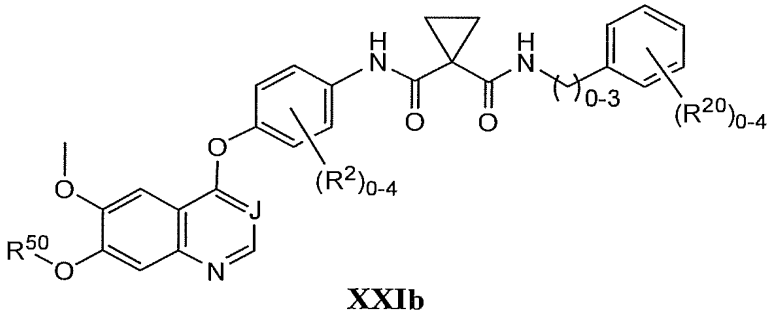
XXIIb



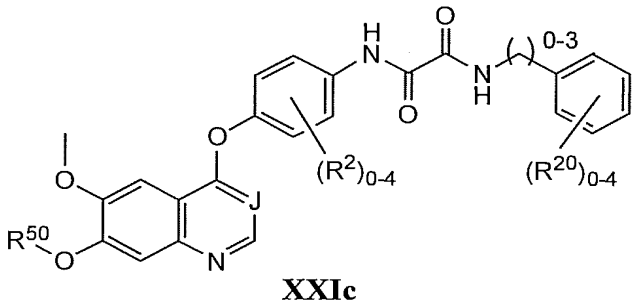
XXIIIb



XXIIIc



XXIb



XXIc

wherein J, R^{50}, R^{20} and R^2 are as defined above.

[00199] In another example, the process is according to the preceding paragraph, wherein R^2, if present, is halogen.

[00200] In another example, the process is according to the preceding paragraph, wherein R^2, if present, is fluorine.

[0201] In another example, the process is according to the preceding paragraph, wherein R^2, if present, is up to two fluorines *ortho* to the oxygen of the phenylene to which R^2 is attached.

[0202] In another example, the process is used to make a compound listed in either Table 1 or Table 2.

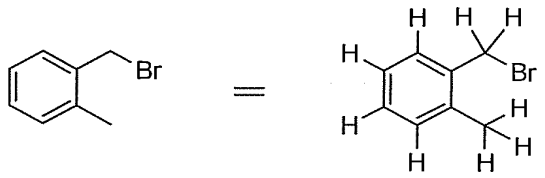
[0203] In another example the process is as defined above in any of the fifty-two preceding paragraphs, further comprising converting said compound to a pharmaceutically acceptable salt, hydrate, or prodrug thereof.

Definitions

[0204] 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.

[0205] 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.

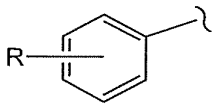
[0206] When chemical structures are depicted or described, unless explicitly stated otherwise, all carbons are assumed to have hydrogen substitution to conform to a valence of four. For example, in the structure on the left-hand side of the schematic below there are nine hydrogens implied. The nine hydrogens 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.



[0207] 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).

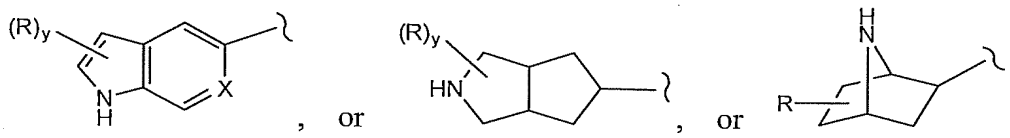


[0208] If a group "R" is depicted as "floating" on a ring system, as for example in the formula:



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.

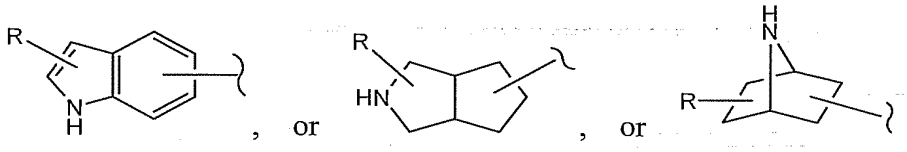
[0209] If a group "R" is depicted as floating on a fused ring system, as for example in the formulae:



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

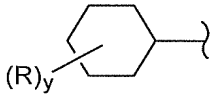
example, then the two "R's" may reside on any two atoms of the ring system, again assuming each replaces a depicted, implied, or expressly defined hydrogen on the ring.

[0210] When there are more than one such depicted "floating" groups, as for example in the formulae:

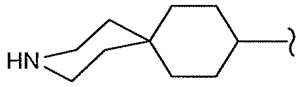


where there are two groups, namely, the "R" and the bond indicating attachment to a parent structure; then, unless otherwise defined, the "floating" groups may reside on any atoms of the ring system, again assuming each replaces a depicted, implied, or expressly defined hydrogen on the ring.

[0211] 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:



[0212] "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.

[0213] "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 ($-CH_2CH_2CH(C_6H_{13})$).

[0214] "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.

[0215] "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.

[0216] 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.

[0217] "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.

[0218] "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.

[0219] "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.

[0220] "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, ornithine, 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.

[0221] "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

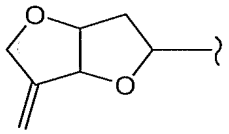
heterocyclyl, acyl, carboxy, alkoxycarbonyl, sulfanyl, sulfinyl and sulfonyl, for example, diethylamino, methylsulfonylamino, furanyl-oxy-sulfonamino.

[0222] "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.

[0223] "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.

[0224] "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 referred to as C_{1-6} arylalkyl.

[0225] "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.



[0226] 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.

[0227] "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.

[0228] "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.

[0229] "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.

[0230] "Heteroatom" refers to O, S, N, or P.

[0231] "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.

[0232] "Heteroalicyclic" refers specifically to a non-aromatic heterocyclyl radical. A heteroalicyclic may contain unsaturation, but is not aromatic.

[0233] "Heteroaryl" refers specifically to an aromatic heterocyclyl radical.

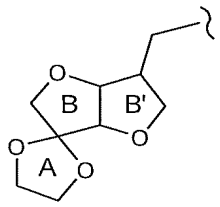
[0234] "Heterocyclylalkyl" refers to a residue in which a heterocyclyl is attached to a parent structure via one of an alkylene, alkylidene, or alkylidyne radical. Examples include (4-methylpiperazin-1-yl) methyl, (morpholin-4-yl) methyl, (pyridine-4-yl) methyl, 2-(oxazolin-2-yl) ethyl, 4-(4-methylpiperazin-1-yl)-2-butenyl, 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.

[0235] "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."

[0236] "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."

[0237] "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.



[0238] "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.

[0239] "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.

[0240] "Sulfanyl" refers to the groups: -S-(optionally substituted alkyl), -S-(optionally substituted aryl), and -S-(optionally substituted heterocyclyl).

[0241] "Sulfinyl" refers to the groups: -S(O)-H, -S(O)-(optionally substituted alkyl), -S(O)-optionally substituted aryl), and -S(O)-(optionally substituted heterocyclyl).

[0242] "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).

[0243] "Yield" for each of the reactions described herein is expressed as a percentage of the theoretical yield.

[0244] 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.

[0245] 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).

[0246] 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.

[0247] 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.

[0248] 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*).

[0249] 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-."

[0250] 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.

[0251] "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.

[0252] "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).

[0253] 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.

[0254] "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.

[0255] "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 [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, 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.

[0256] "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.

[0257] "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.)

[0258] "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.

[0259] "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.

[0260] 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.

[0261] 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.

[0262] "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.

[0263] 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.

[0264] 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.

[0265] 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.

[0266] 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

[0267] 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.

[0268] 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.

[0269] 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.

[0270] 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.

[0271] 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.

[0272] 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.

[0273] 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.

[0274] 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.

[0275] 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.

[0276] 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.

[0277] 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.

[0278] 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.

[0279] 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.

[0280] 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

[0281] 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.

[0282] 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.

[0283] 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.

[0284] 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 fluorophore for the candidate agents.

[0285] 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.

[0286] 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.

[0287] 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.

[0288] 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.

[0289] 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

[0290] 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.

[0291] 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.

[0292] 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.

[0293] 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.

[0294] 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.

[0295] 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.

[0296] 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.

[0297] 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

[0298] 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
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)

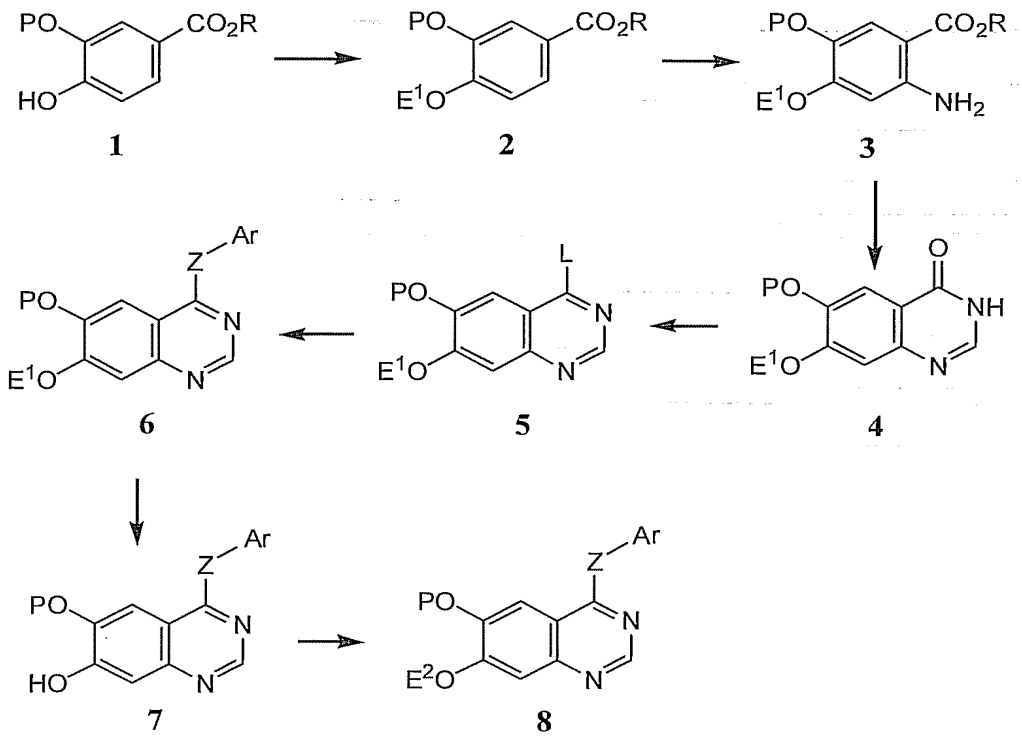
Abbreviation	Meaning
HATU	0-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMDS	hexamethyldisilazane
HOAc	acetic acid
HOBt	hydroxybenzotriazole
HPLC	high pressure liquid chromatography
L	liter(s)
M	molar or molarity
m	multiplet
Me	methyl
mesyl	methanesulfonyl
mg	milligram(s)
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

Abbreviation	Meaning
PfPy	pentafluoropyridine
PPTS	Pyridinium p-toluenesulfonate
Py	pyridine
PyBroP	bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
q	quartet
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

[0299] 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.

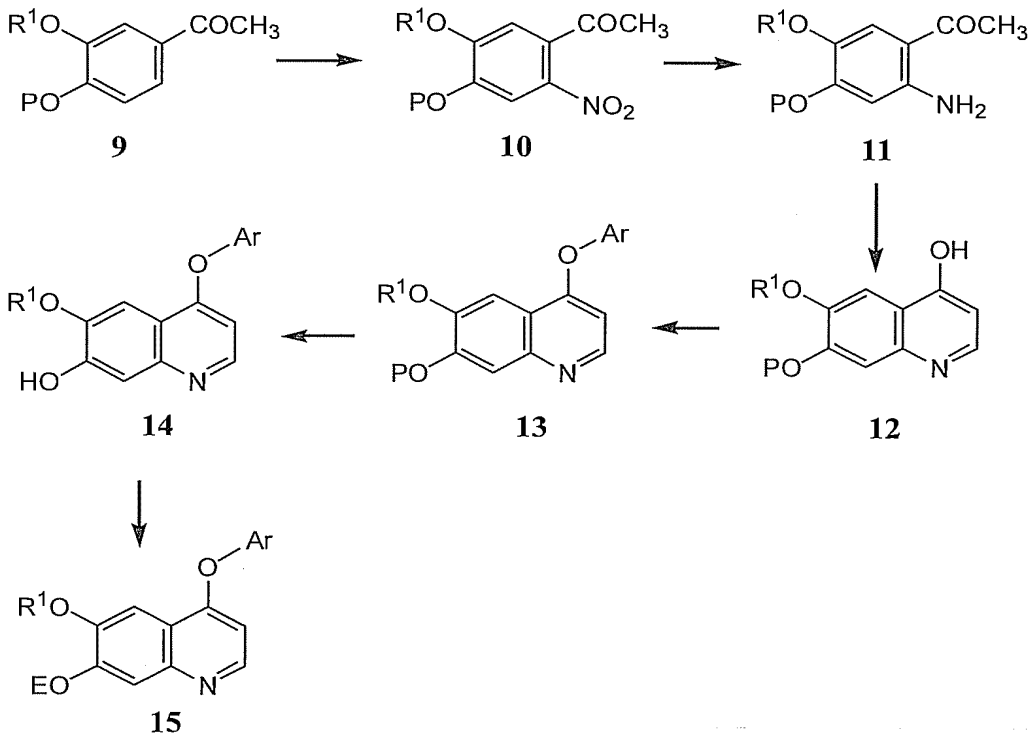
Scheme 1



[0300] 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



[0301] 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.

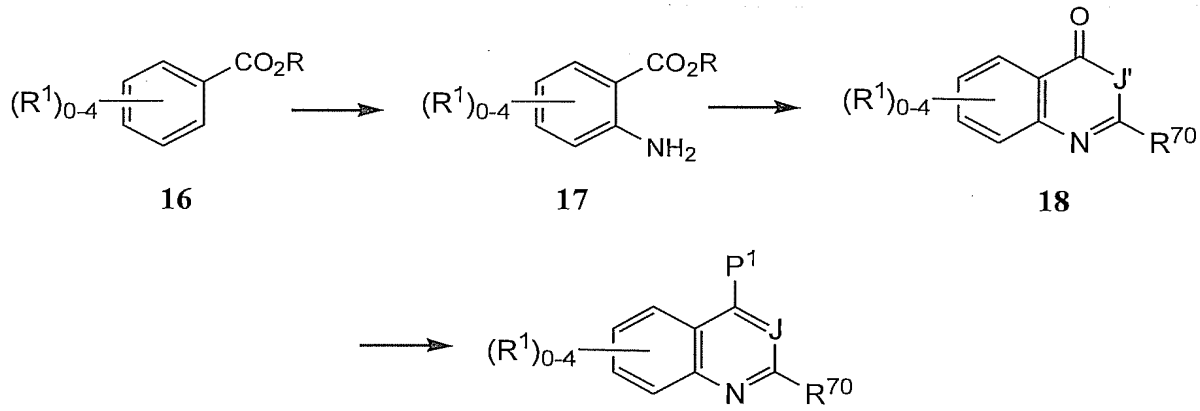
[0302] Schemes 1 and 2 are illustrative of quinolines and quinazolines having oxygen substitution at their respective 6- and 7-positions; the invention is not so limited, but rather is intended to encompass quinolines and quinazolines not necessarily having substitution, oxygen or otherwise, at their respective 6- or 7-positions.

[0303] 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.

[0304] 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



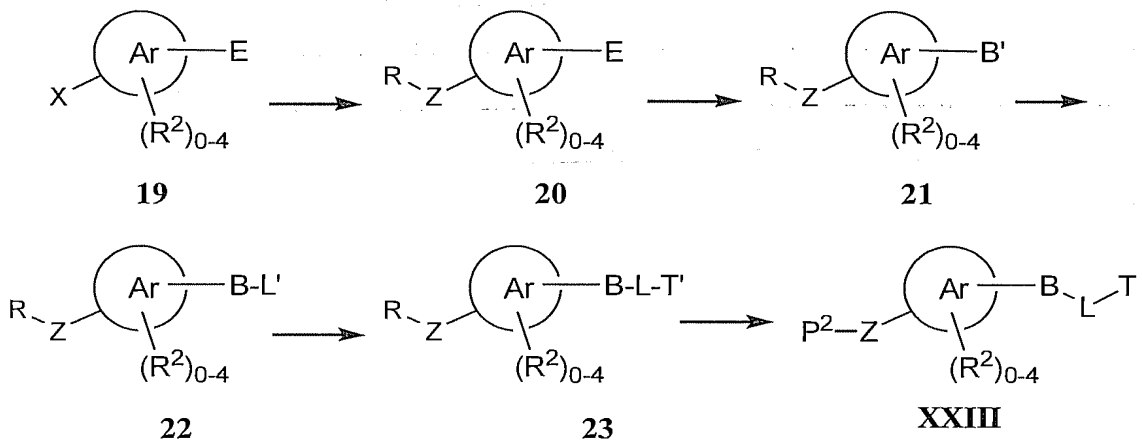
16 **17** **18**

XXII

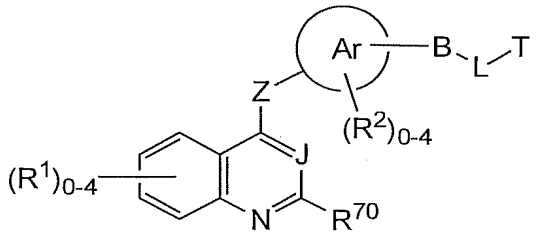
[0305] Scheme 4 shows a general route used to make compounds of formula **XXIII**. For example, aromatic compound **19**, where "X" is a leaving group, such as fluorine and "E" is an electron withdrawing group such as nitro, is converted to **20** by reaction with a range of nucleophiles, e.g. amines, 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



[0306] 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.



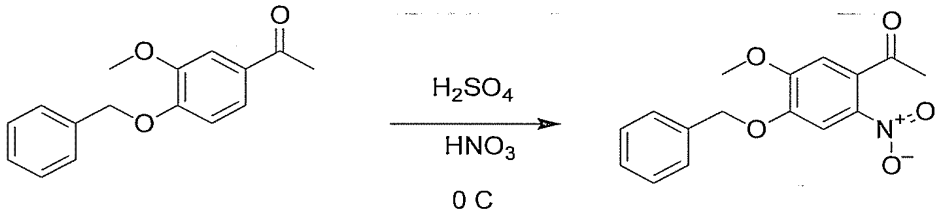
XXI

Examples

[0307] 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

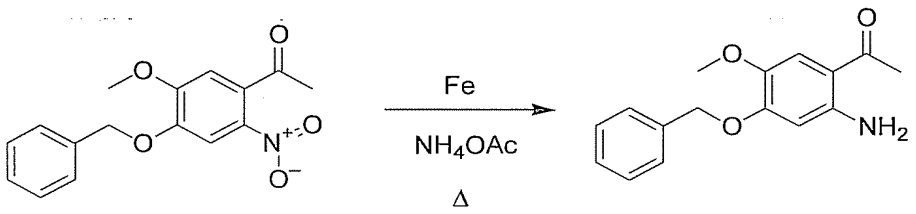


[0308] Synthesis of 1-(4-Benzyloxy-5-methoxy-2-nitro-phenyl)-ethanone. 1-(4-Benzyloxy-3-methoxy-phenyl)-ethanone (200 mmol, 51.3 g) dissolved in DCM (750ml) and the mixture cooled to 0° C. Nitric acid (90%, 300 mmol, 14 ml) was added dropwise to the cooled solution over 20 minutes. Sulfuric acid (96.2%, 300 mmol, 8.75 ml) was then added dropwise over 40 minutes at 0° C.

[0309] 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. $NaHCO_3$ (4 X 200 ml, or until neutral). The organic layer was dried over Na_2SO_4 and concentrated.

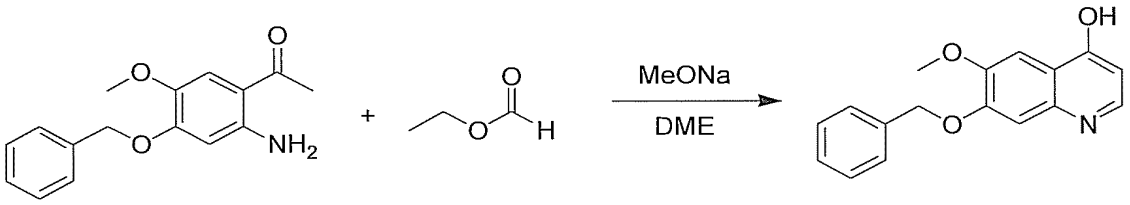
[0310] The crude mixture was recrystallized with DMF to give 22.5 g of the nitro product. The DMF layer was concentrated and recrystallized with ethyl acetate to give additional 8.75g of the product. The ethyl acetate layer was concentrated and purified on silica column using 20% EtOAc/hexanes to gave another 4.75 g of the product. Total yield is 36 g, (~60%). ^1H NMR ($CDCl_3$): 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



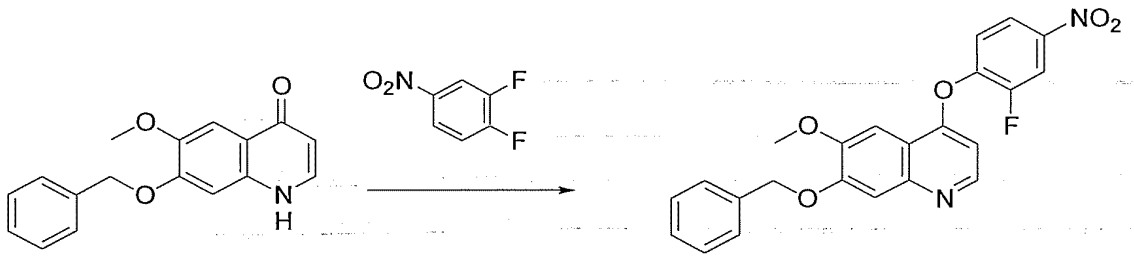
[0311] Synthesis of 1-(2-Amino-4-benzyloxy-5-methoxy-phenyl)-ethanone. A Mixture of iron powder (477 mmol, 27 g), ammonium acetate (500 mmol, 31.g), 1-(4-Benzyloxy-5-methoxy-2-nitro-phenyl)-ethanone (120 mmol, 36 g), toluene (500 ml) and water (500 ml) was refluxed overnight, or until completion. The mixture was filtered through celite and washed with EtOAc. The organic layer was washed with water and Sat. NaCl, dried over Na_2SO_4, and concentrated to afford the product, 90%. ^{1}H NMR ($CDCl_3$): 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



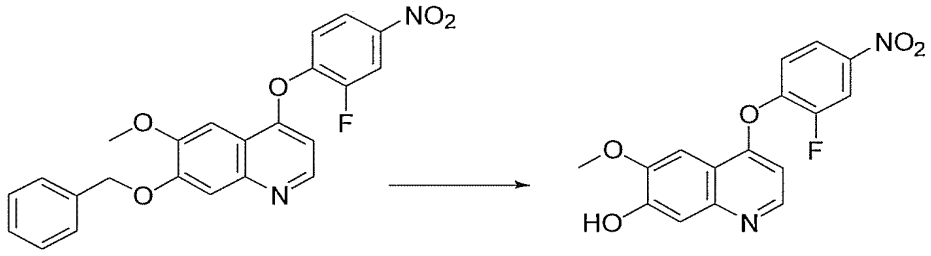
[0312] Synthesis of 7-Benzyloxy-6-methoxy-quinolin-4-ol. To a solution of 1-(2-Amino-4-benzyloxy-5-methoxy-phenyl)-ethanone (108 mmol, 29.3 g) in DME (700 ml) was added sodium methoxide (432 mmol, 23.35 g). The mixture was stirred for 30 minutes. Ethyl formate (540 mmol, 44 ml) was added and the mixture 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. ^{1}H NMR ($CDCl_3$): 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



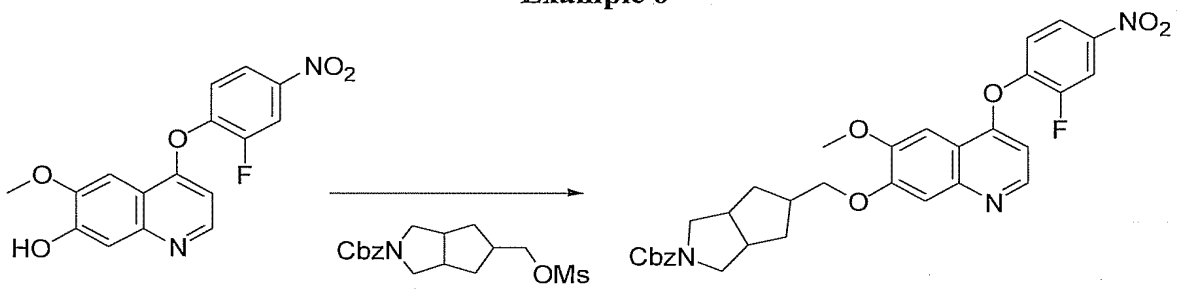
[0313] 7-Benzyloxy-4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinoline. To a round bottom flask equipped with a magnetic stir bar was added 7-Benzyloxy-6-methoxy-1H-quinolin-4-one (12.2 g, 43.3 mmol, 1.0 eq.), acetonitrile (150ml), DMF (150ml) and cesium carbonate (28.2 g, 86.5 mmol, 2.0 eq). The mixture 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



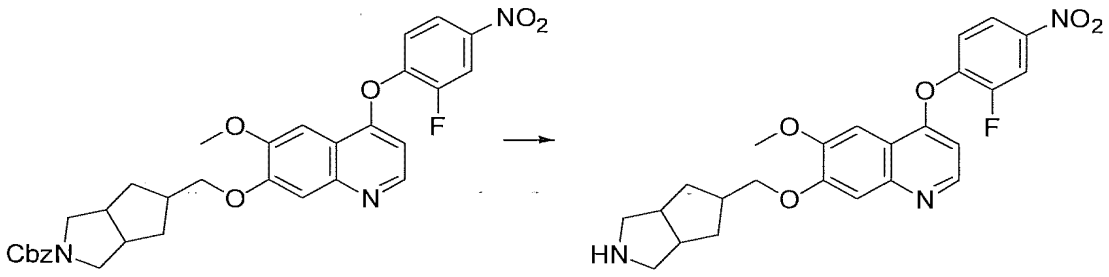
[0314] 4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-ol. To a round bottom flask equipped with a magnetic stir bar was added 7-benzyloxy-4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinoline (2.9 g, 6.9 mmol, 1.0eq) and 33% HBr in acetic acid (30 ml). The mixture was stirred at room temperature for 3 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



[0315] 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 ($M+H^+$).

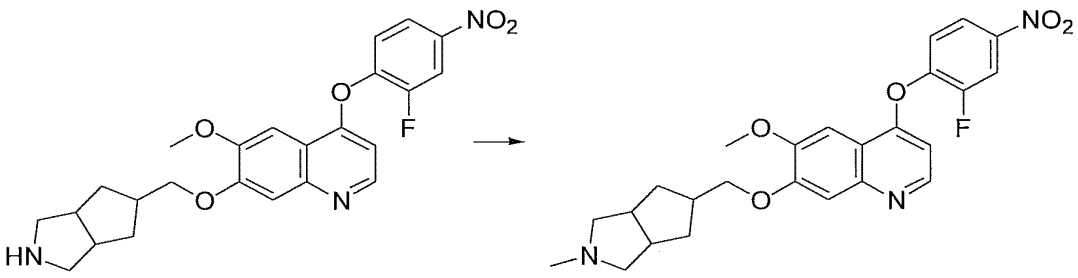
Example 7



[0316] 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-

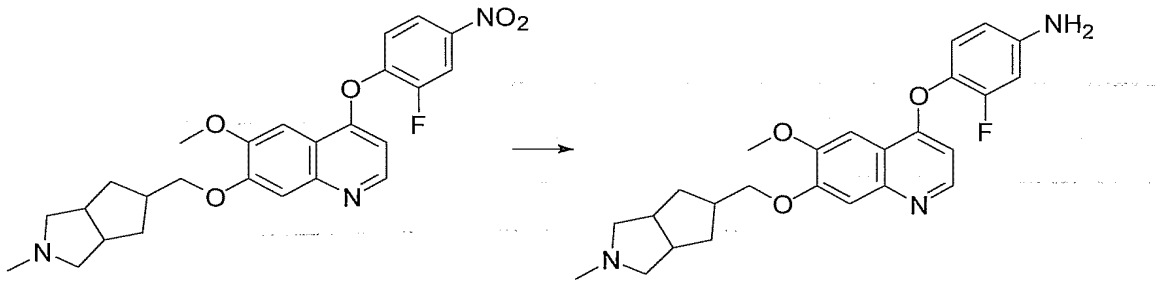
[c]pyrrole-2-carboxylic acid benzyl ester (2.5 g, 4.1 mmol, 1.0eq), 33% HBr in acetic acid (5 ml) and acetic acid (5 ml). The mixture was stirred at room temperature for 1 hour and diluted with EtOAc to give a pale orange solid. The solid was filtered, washed with EtOAc and dried, giving 4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-7-(octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-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



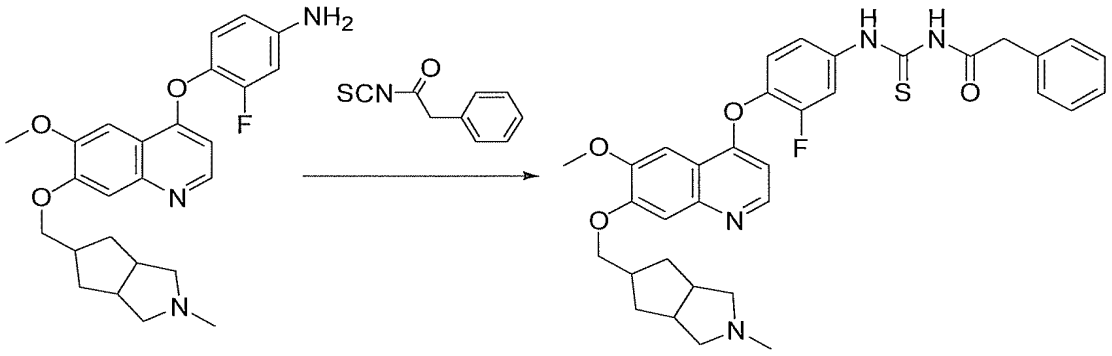
[0317] 4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinoline. To a round bottom flask equipped with a magnetic stir bar was added 4-(2-Fluoro-4-nitro-phenoxy)-6-methoxy-7-(octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinoline (2.1 g, 3.9 mmol, 1.0 eq.) 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



[0318] 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 ($M+H^+$).

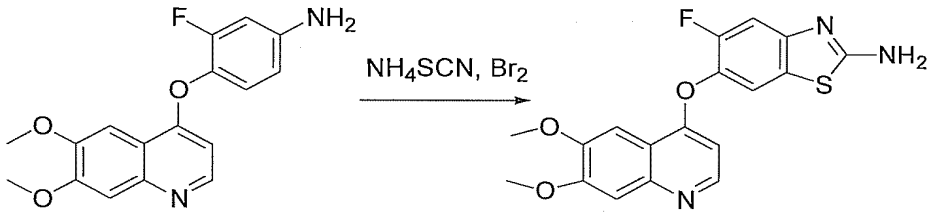
Example 10



[0319] 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

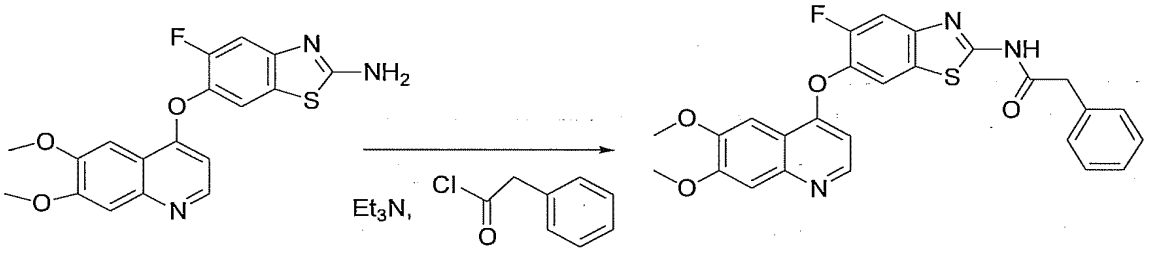
(2L) then EtOAc, 4% TEA, 1% MeOH (1L). The solvent was removed to give 1-{3-fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinolin-4-yloxy]-phenyl}-3-phenylacetyl-thiourea (0.5 g, 50% yield). ^{1}H NMR (400 MHz, DMSO): 8.48 (d, 1H), 7.92 (dd, 1H), 7.53 (s, 1H), 7.40 (m, 4H), 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



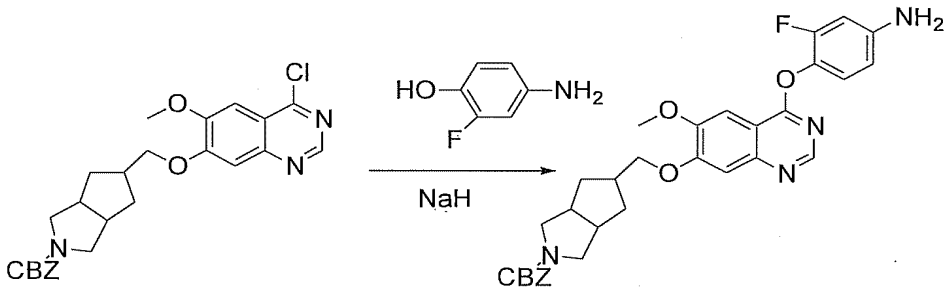
[0320] 6-(6,7-Dimethoxy-quinolin-4-yloxy)-5-fluoro-benzothiazol-2-ylamine. 4-(6,7-dimethoxy-quinolin-4-yloxy)-3-fluoro-phenylamine (1.00g, 3.18mmol) was dissolved in AcOH (8.0ml), to which was added NH_4SCN (486mg, 6.38mmol) and the mixture cooled in an ice bath. Br_2 (0.33ml, 6.42mmol) in AcOH (0.33ml) 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



[0321] 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.

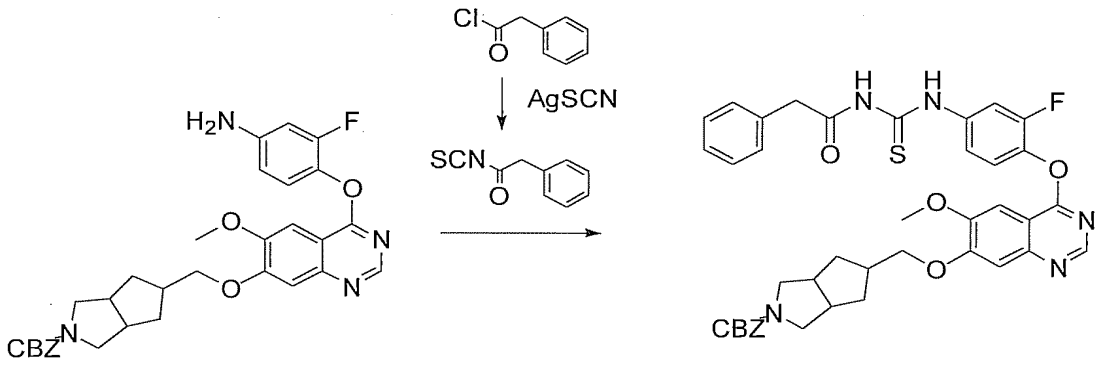
Example 13



[0322] 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

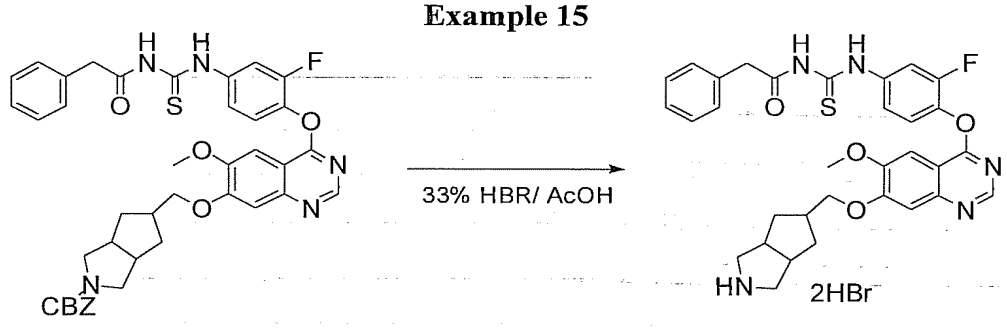
(Na_2SO_4), and concentrated *in vacuo* to give crude 5-[4-(4-amino-2-fluoro-phenoxy)-6-methoxy-quinazolin-7-yloxymethyl]-hexahydro-cyclopenta[c]pyrrole-2-carboxylic acid benzyl ester (5.6g, ~100%) which was used in the next reaction without further purification. ^{1}H-NMR (400MHz, DMSO): 8.50 (s, 1H), 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



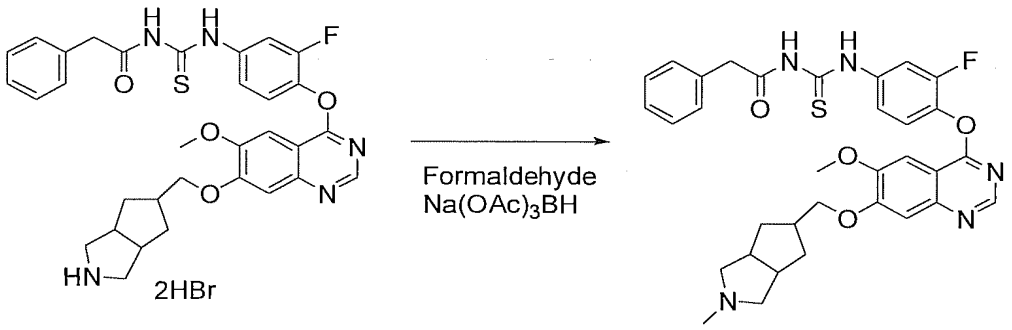
[0323] 5-{4-[2-Fluoro-4-(3-phenylacetyl-thioureido)-phenoxy]-6-methoxy-quinazolin-7-yloxymethyl}-hexahydro-cyclopenta[c]pyrrole-2-carboxylic acid benzyl ester. Phenylacetyl chloride (2.65ml, 20.0mmol) and AgSCN (4.92g, 29.6mmol) were combined in dry toluene (50ml) and heated to reflux for 2 hrs. The reaction mixture was allowed to cool to room temperature, the solids were filtered through celite and the filtrate concentrated i*n 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



[0324] 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.

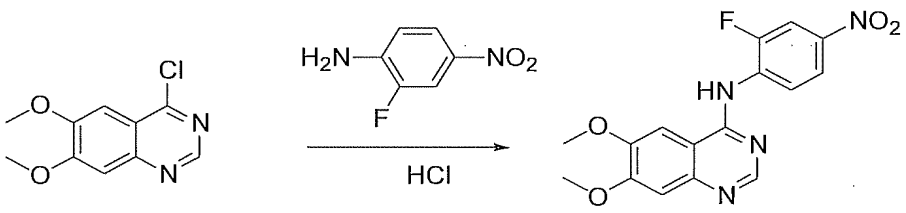
Example 16



[0325] 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)

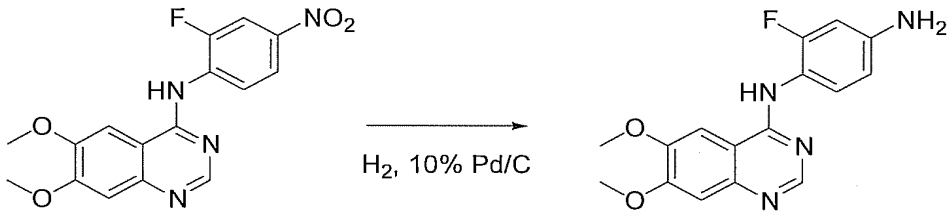
was added and the mixture cooled in an ice bath. $Na(OAC)_3BH$ (2.99g, 14.1mmol) was added and the reaction mixture was stirred at 0 C for 1 hr, followed by stirring at room temperature for 2 hrs. The reaction mixture was neutralized with the addition of sat'd $NaHCO_3$ and then concentrated *in vacuo*. 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



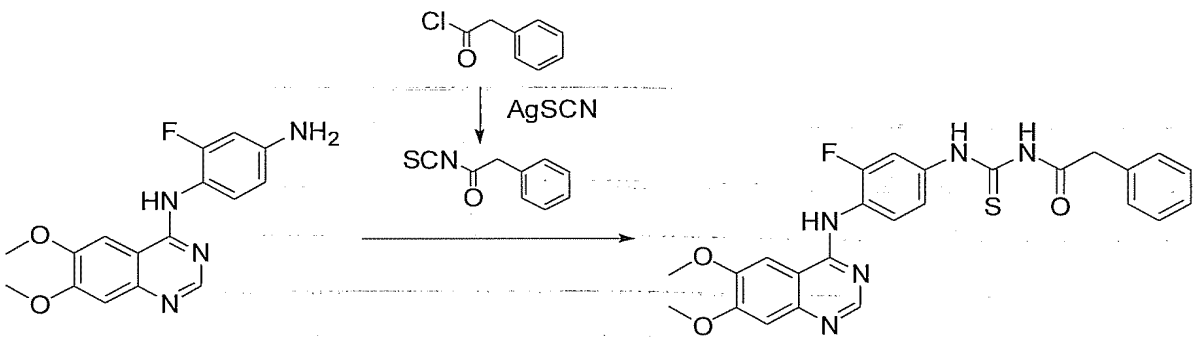
[0326] (6,7-Dimethoxy-quinazolin-4-yl)-(2-fluoro-4-nitro-phenyl)-amine. A mixture of 4-chloro-6,7-dimethoxy-quinazoline (548mg, 2.4mmol), 2-fluoro-4-nitro-phenylamine (392mg, 2.5mmol), AcCN (10ml), and conc'd HCl (0.050ml) was heated to reflux for several hrs. After the reaction mixture was allowed to 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



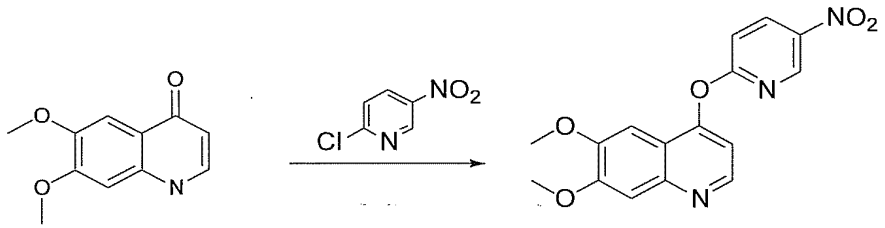
[0327] N^1-(6,7-Dimethoxy-quinazolin-4-yl)-2-fluoro-benzene-1,4-diamine. (6,7-Dimethoxy-quinazolin-4-yl)-(2-fluoro-4-nitro-phenyl)-amine (673mg, 1.95mmol) was dissolved in a combination of DMF (20ml) and MeOH (20ml), to which was added 10% Pd/C (227mg). The mixture was shaken under an atmosphere of H_2 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



[0328] 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 i*n 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.

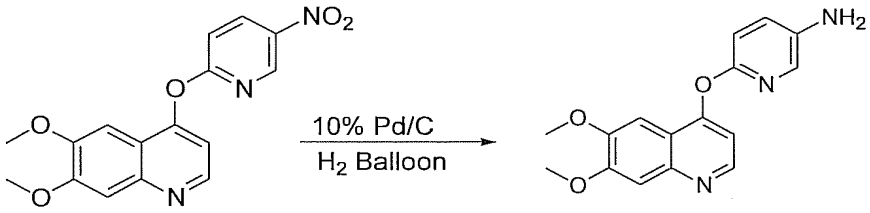
Example 20



[0329] 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-

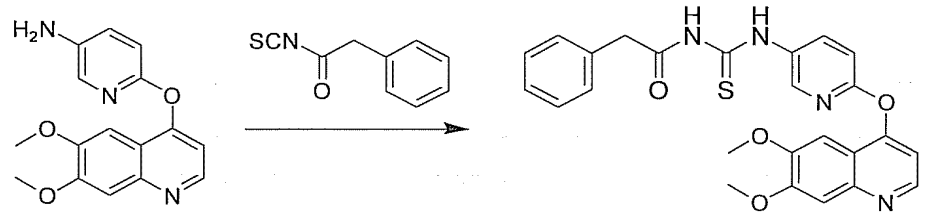
nitropyridine (1.53 g, 9.65 mmol, 1.1 eq.) was added. The reaction mixture was stirred at room temperature for 16 hours. The solids were then filtered off and the filtrate was concentrated via rotary evaporation. The resulting material was taken up in EtOAc, and again the solids were filtered off. The 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



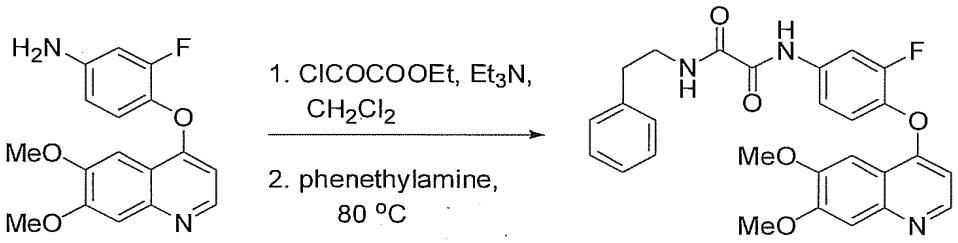
[0330] 6-(6,7-Dimethoxy-quinolin-4-yloxy)-pyridin-3-ylamine. To a round bottom flask equipped with a magnetic stir bar was added 6,7-dimethoxy-4-(5-nitro-pyridin-2-yloxy)-quinoline (0.46 g, 1.41 mmol, 1.0 eq.), and THF (10 mL), MeOH (4 mL), DMF (2 mL), and TEA (2 mL). The 6,7-Dimethoxy-4-(5-nitro-pyridin-2-yloxy)-quinoline 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%). ^{1}H 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



[0331] 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, $CDCl_3$): 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 ($M+H^+$).

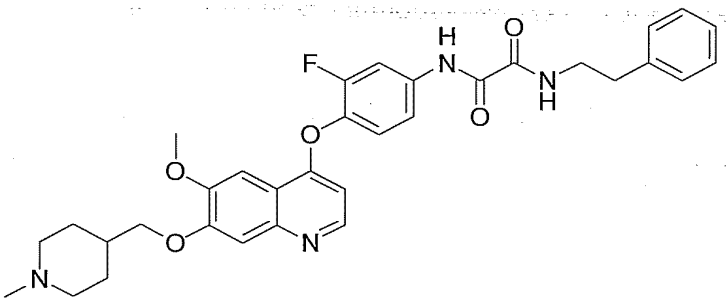
Example 23



[0332] 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



[0333] N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-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).

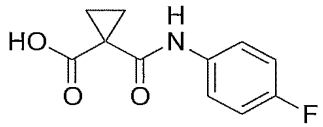
[0334] To a solution of the 4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-7-hydroxyquinoline (609 mg, 1.8 mmol) in DMF (9 mL) was added K_2CO_3 (1.24 g, 9.0 mmol) and N-Boc-4-piperidinemethanol mesylate (732 mg, 2.5 mmol). The mixture was then stirred at 80 °C for 2.5 h. After it was cooled to rt, the mixture 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%).

[0335] 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.

[0336] 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.

[0337] 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). ^{1}H 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).

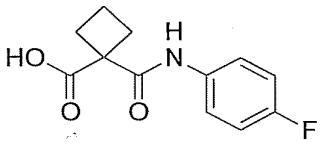
Example 25



[0338] 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

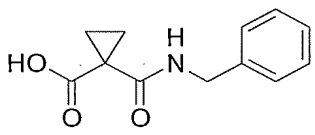
g, 0.179 mol, 1.1 eq.) in anhydrous THF (100 mL) with stirring for 1.5 hours at 0°C. The reaction mixture was diluted with ethyl acetate and washed with 1N NaOH. The layers were separated, and the ethyl acetate layer was concentrated in vacuo to give a brownish solid. The brownish solid was washed with 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



[0339] 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).

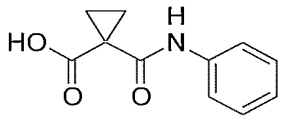
Example 27



[0340] 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

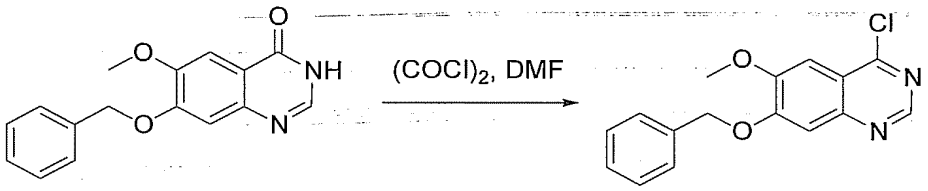
anhydrous THF (50 mL) under nitrogen was added dropwise triethylamine (3.89 g, 38.4 mmol, 1.0 eq.) with stirring for 30 minutes at 0°C, followed by the addition of thionyl chloride (4.57 g, 38.4 mmol, 1.0 eq.) with stirring for another 30 minutes at 0°C. To the resulting mixture under nitrogen was added 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



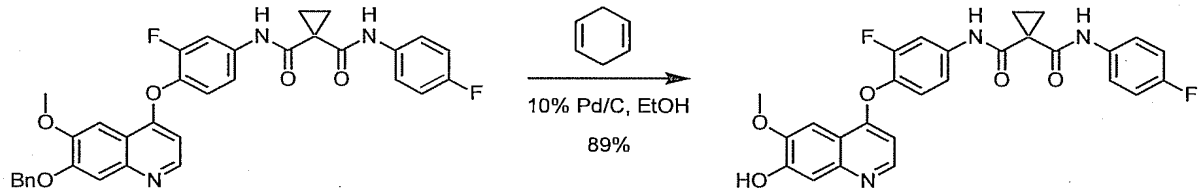
[0341] 1-Phenylcarbamoyl-cyclopropanecarboxylic acid. To a mixture of cyclopropane-1,1-dicarboxylic acid (5.29 g, 40.7 mmol, 1.0 eq.) in anhydrous THF (50 mL) under nitrogen was added dropwise triethylamine (4.12 g, 40.7 mmol, 1.0 eq.) with stirring for 30 minutes at 0°C, followed by the addition of 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



[0342] 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 0°C. 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.

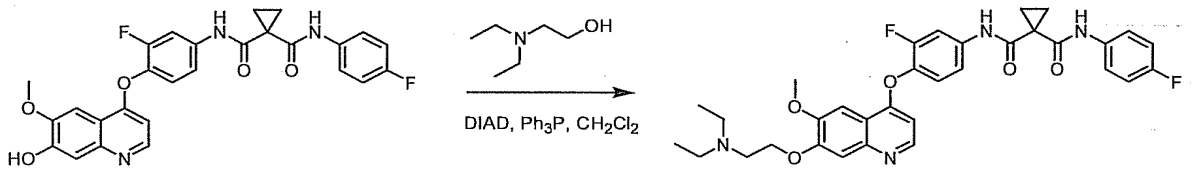
Example 30



[0343] 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

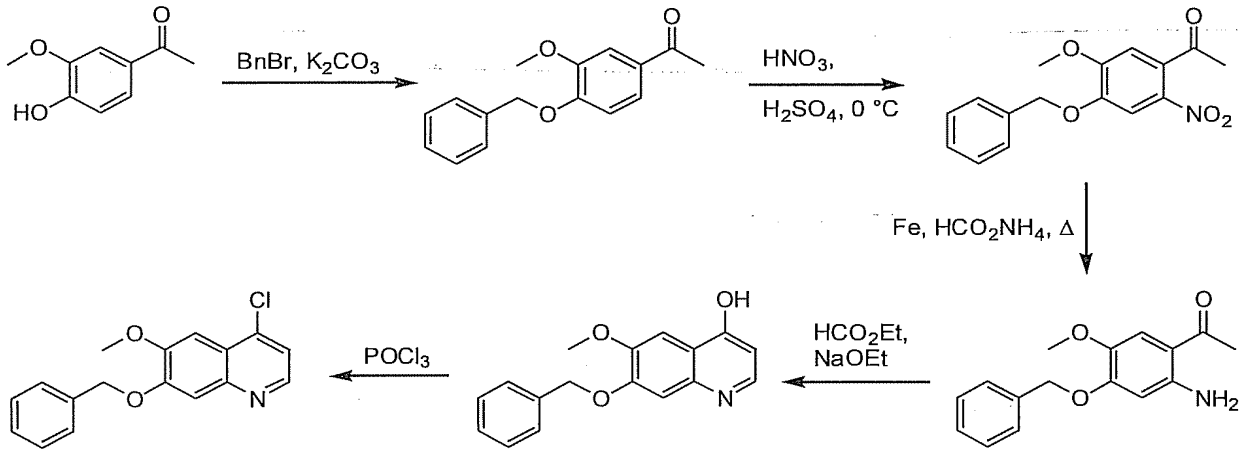
with water, and dried over Na_2SO_4. Removal of the solvent under reduced pressure gave 900 mg (89%) of the crude product (90% purity by analytical HPLC), which was used in the next reaction without further purification.

Example 31



[0344] 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 ($MgSO_4$), 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



[0345] 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 %).

[0346] 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 %). ^{1}H 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).

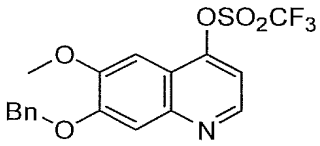
[0347] 1-(2-Amino-4-benzyloxy-5-methoxyphenyl)ethanone. A mixture of iron powder (27 g, 0.48 g atoms), ammonium formate (31 g, 500 mmol), 1-(4-benzyloxy-5-methoxy-2-nitrophenyl)ethanone (36 g, 120 mmol), toluene (500 mL) and water (500 mL) was heated to reflux overnight. The mixture was filtered through 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).

[0348] 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).

[0349] 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).

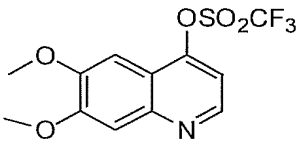
Example 33



[0350] 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

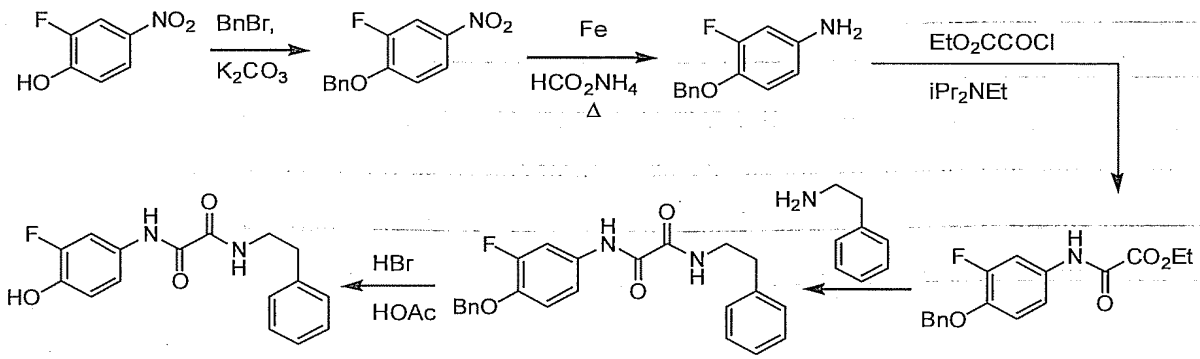
mmol). The mixture was cooled to –20°C by controlled addition of dry ice to an acetone bath. Trifluoromethanesulfonyl chloride (37 mL, 350 mmol) was added dropwise to the cooled solution with magnetic stirring over 25 minutes. After addition was complete, the mixture was stirred in bath for 20 minutes, 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



[0351] 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



[0352] 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.

[0353] 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).

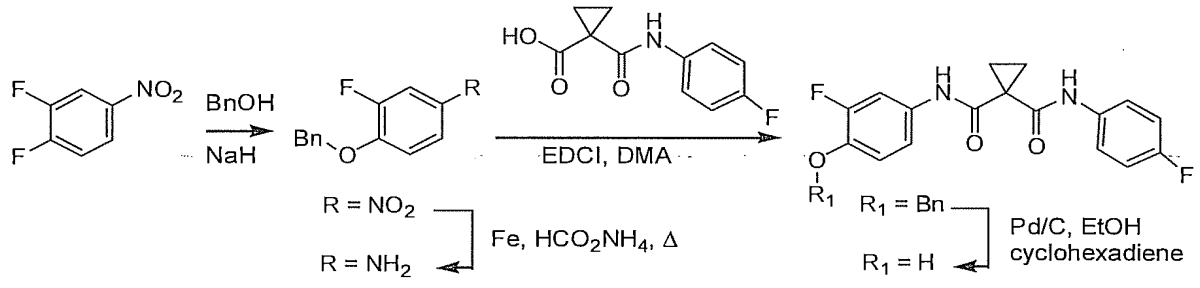
[0354] Ethyl [(4-benzyloxy-3-fluorophenyl)amino](oxo)acetate. Ethyl oxalyl chloride (44 mL, 390 mmol) was added to a solution of 4-benzyloxy-3-fluoroaniline (44 g, 180 mmol) in diisopropylethylamine (69 mL, 400 mmol) and stirred at room temperature for 15 min. The mixture was extracted with dichloromethane 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).

[0355] *N*-(4-Benzyloxy-3-flourophenyl)-*N'*-(2-phenylethyl)ethanediamide. Phenethyl-amine (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).

[0356] *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



[0357] 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

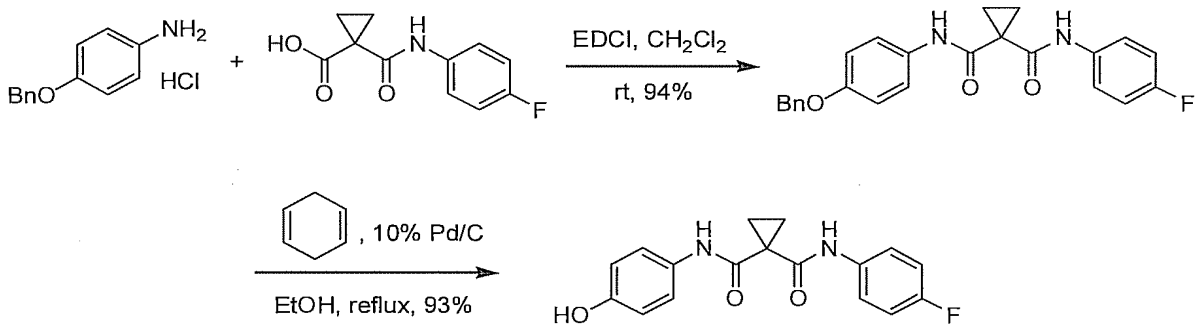
alcohol (462 mmol, 48 ml) dropwise with stirring under N_2. The mixture was stirred for 1 hour at RT and then cooled to 0°C. 3,4-Difluoronitrobenzene (508 mmol, 56.2 ml) was added to the cooled solution and stirred for 1 hour. Reaction mixture poured onto saturated ammonium chloride solution (800 ml) 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).

[0358] 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.

[0359] 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.

[0360] 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.

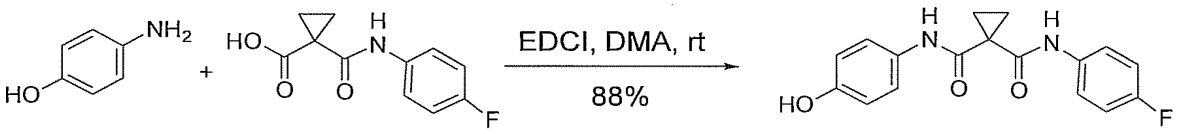
Example 37



[0361] 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.

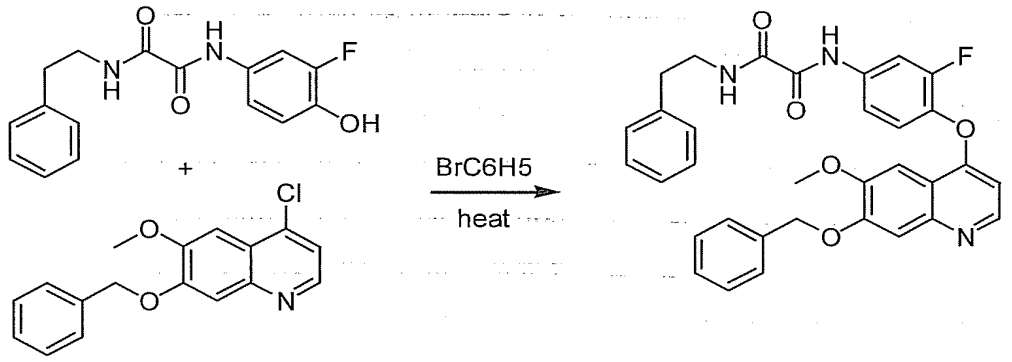
[0362] Cyclopropane-1,1-dicarboxylic acid (4-fluoro-phenyl)-amide (4-hydroxy-phenyl)-amide. To a refluxing mixture of cyclopropane-1,1-dicarboxylic acid (4-benzyloxy-phenyl)-amide (4-fluoro-phenyl)-amide (46 g, 113 mmol), 10% Pd/C (2 g) in EtOH (400 mL) was added dropwise 1,4-cyclohexadiene (62.7 mL, 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



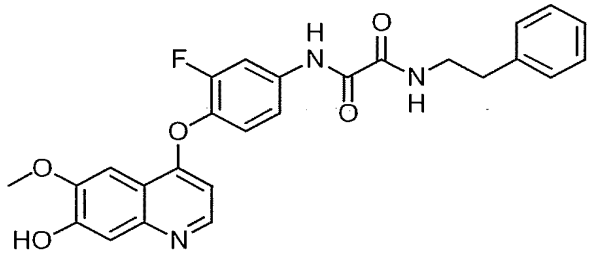
[0363] Alternate Synthesis of Cyclopropane-1,1-dicarboxylic acid (4-fluoro-phenyl)-amide (4-hydroxy-phenyl)-amide. To a solution of 4-aminophenol (2.93 g, 26.9 mmol) and 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (5.00 g, 22.4 mmol) in DMA (30 mL) was added EDCI (5.15 g, 26.9 mmol). The 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



[0364] *N*-{4-[(7-Benzyloxy-6-methoxyquinolin-4-yl)oxy]-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).

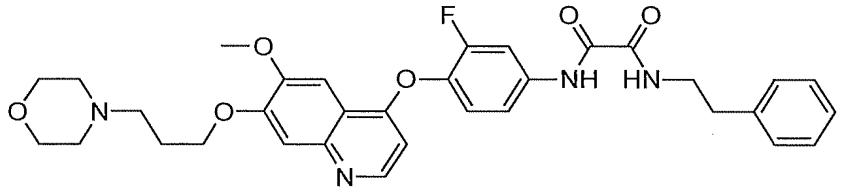
Example 40



[0365] *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).

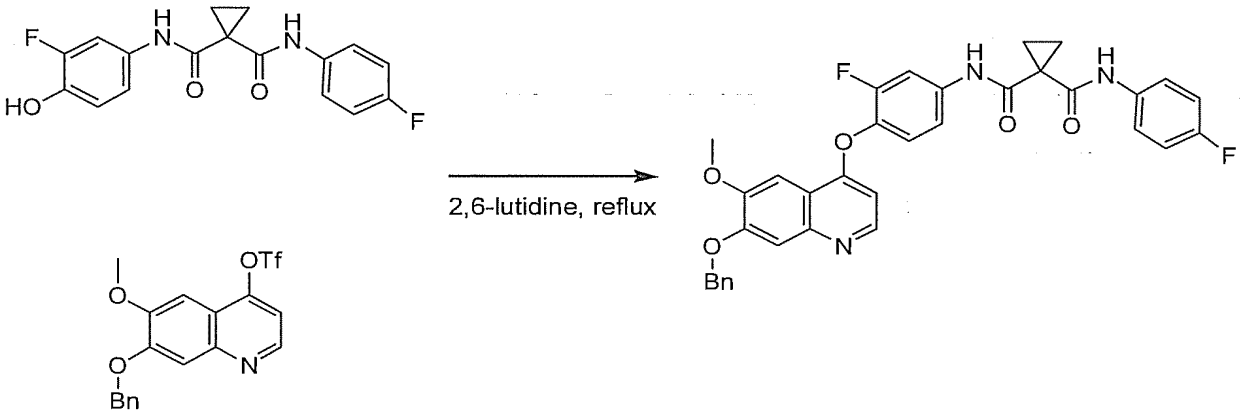
Example 41



[0366] *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):

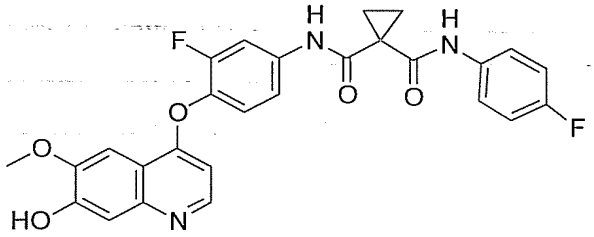
δ 160.1, 160.0, 159.5, 155.2, 152.7, 152.6, 150.2, 149.5, 147.1, 139.7, 137.3, 137.1, 129.3, 129.1, 126.9, 124.8, 117.9, 115.1, 109.2, 102.7, 99.6, 67.4, 66.9, 56.5, 55.5, 54.1, 41.3, 35.2, 26.4; IR (cm^{-1}): 1655, 1506, 1483, 1431, 1350, 1302, 1248, 1221, 1176, 1119, 864, 843, 804, 741, 700; LC/MS (M+H = 603).

Example 42



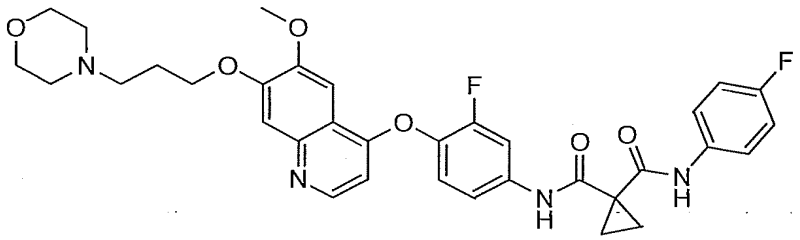
[0367] Cyclopropane-1,1-dicarboxylic acid [4-(7-benzyloxy-6-methoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-amide (4-fluoro-phenyl)-amide. To a flask containing cyclopropane-1,1-dicarboxylic acid (3-fluoro-4-hydroxy-phenyl)-amide (4-fluoro-phenyl)-amide (2.25 g, 6.7 mmol) and trifluoromethanesulfonic acid 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



[0368] 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.

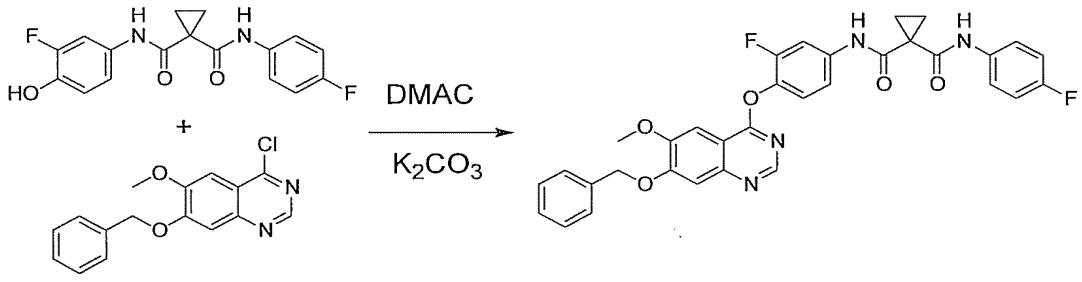
Example 44



[0369] *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 $MgSO_4$ 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 NH_3/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.

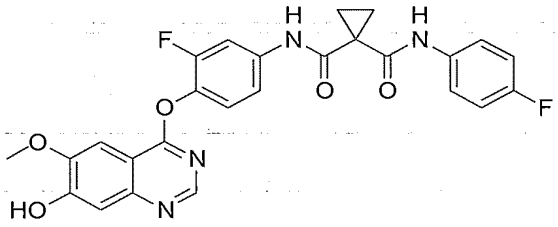
Example 45



[0370] 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%). ^1H NMR ($CDCl_3$):

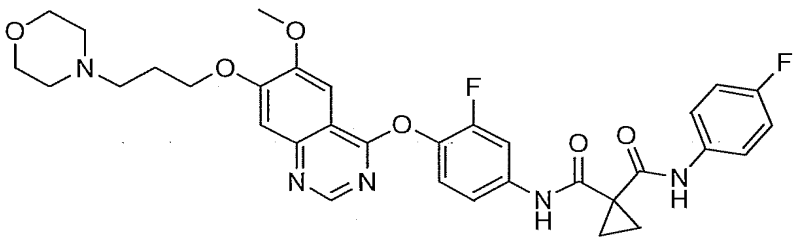
8.64 (1H, br. s), 8.55 (1H, s), 8.33 (1H, br. s), 7.74-7.71 (1H, dd), 7.54 (1H, s), 7.48-7.33 (8H, m), 7.31-7.24 (2H, m), 7.06-7.02 (2H, m), 5.32 (2H, s), 4.06 (3H, s), 1.77-1.74 (2H, m), 1.63-1.61 (2H, m).

Example 46



[0371] 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).

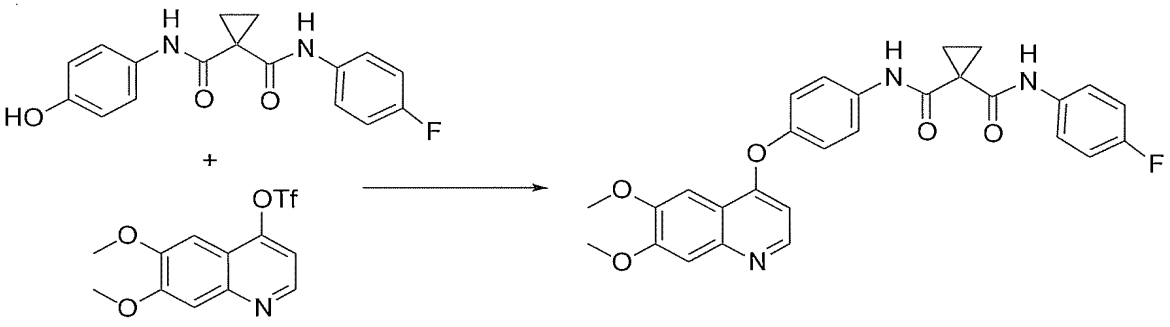
Example 47



[0372] 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)-

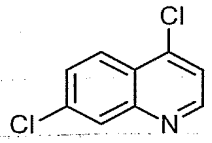
phenyl]-amide (4-fluoro-phenyl)-amide (1.5 g, 2.96 mmol), 4-(3-hydroxypropyl)morpholine (0.623 mL, 4.5 mmol), triphenylphosphine (1.18 g, 4.5 mmol), and dichloromethane (50 mL) was added diisopropyl azodicarboxylate (0.886 mL, 4.5 mmol). The mixture was stirred at room temperature for 16 h, monitored 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-dicarboxamide (890 mg, 47% yield). ^{1}H NMR (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



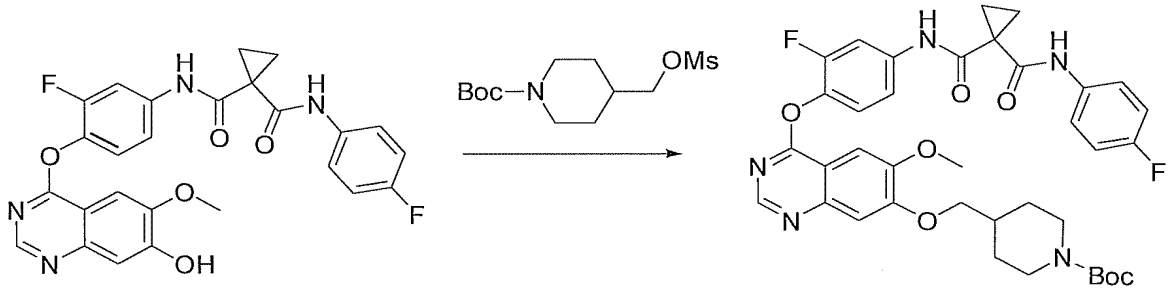
[0373] N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. To a solution of cyclopropane-1,1-dicarboxylic acid (4-fluorophenyl)-amide (4-hydroxy-phenyl)-amide (6.98 g, 22.2 mmol) in anhydrous 2,6-lutidine (50 mL) was added trifluoromethanesulfonic acid 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



[0374] 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).

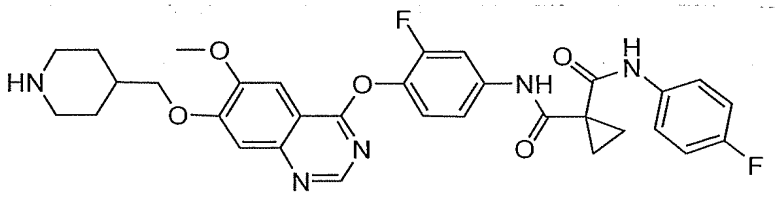
Example 50



[0375] 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

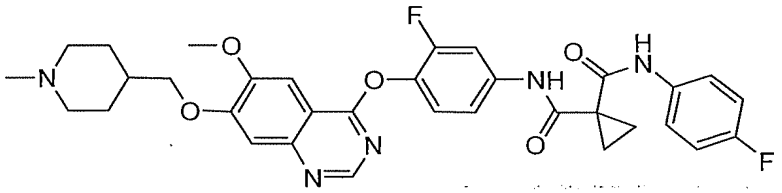
material was purified by flash chromatography (1:1 hexanes:EtOAc, followed by 1:3 hexanes:EtOAc) to give 4-[4-(2-fluoro-4-{[1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarbonyl]-amino}-phenoxy)-6-methoxy-quinazolin-7-yloxymethyl]-piperidine-1-carboxylic acid tert-butyl ester (273 mg, 60%). LC/MS Calcd for $[M+H]^+$ 704.3, found 704.4.

Example 51



[0376] 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. 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



[0377] N-{3-Fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quin-azolin-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

[0378] 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

[0379] 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

[0380] 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

[0381] 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).

[0382] 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

[0383] 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).

[0384] 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

[0385] 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

[0386] 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).

[0387] 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).

[0388] 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).

[0389] 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

[0390] 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).

[0391] 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).

[0392] 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 (27 μL, 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

[0393] 3,6-Anhydro-1,2-*O*-(1-methylethylidene)-5-*O*-(phenylcarbonyl)-α-L-gluco-furanose: 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).

[0394] 3,6-Anhydro-1,2-*O*-(1-methylethylidene)-5-*O*-(methylsulfonyl)-α-L-gluco-furanose: 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

[0395] (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): ^1H 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^+).

[0396] Using the same or analogous synthetic techniques and/or substituting with alternative starting materials, the following were prepared:

[0397] (3*R*,8a*R*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine: ^1H 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^+).

[0398] (3*S*,8a*R*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine: ^1H 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

[0399] (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). ^1H 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^+).

[0400] (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^+).

[0401] (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

[0402] 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^+).

[0403] 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

[0404] (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^+).

[0405] (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^+).

[0406] (3*S*,8a*S*)-3-({[(1,1-Dimethylethyl)(dimethyl)silyl]oxy}methyl)-2-methylhexahydropyrrolo[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). ^1H 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

[0407] 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

[0408] 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^+).

[0409] 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

[0410] 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).

[0411] 1,1-Dimethylethyl (3a*R*,6a*S*)-5-{[(methylsulfonyl)oxy]methyl}hexahydrocyclo-penta[*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}hexahydrocyclo-penta[*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

[0412] 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^+).

[0413] 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

[0414] 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): ^{1}H 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): ^{1}H 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^+).

[0415] 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).

[0416] (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

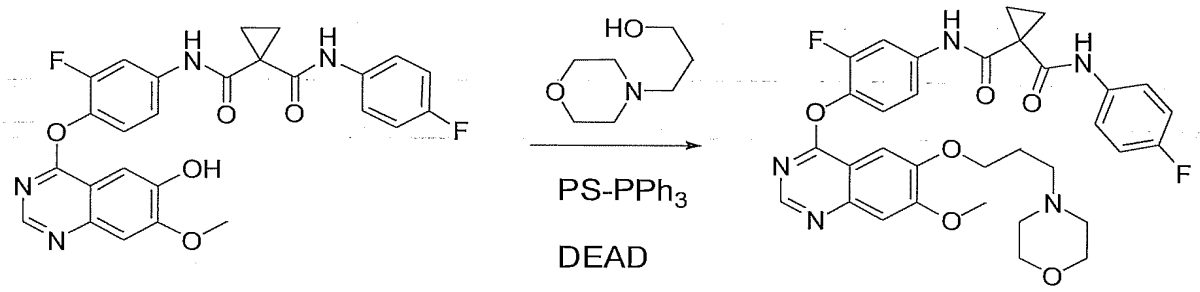
[0417] (8a*R*)-6-(Chloromethyl)tetrahydro-1*H*-[1,3]thiazolo[4,3-*c*][1,4]oxazine: A solution of (4*R*)-1,3-thiazolidin-4-ylmethanol (0.300 g, 2.52 mmol) in 2-(chloromethyl)oxirane (2.0 mL, 25.5 mmol) was heated under nitrogen to 40°C for 12 h. The solution was then cooled to room temperature and 2-(chloromethyl)oxirane 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

[0418] 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

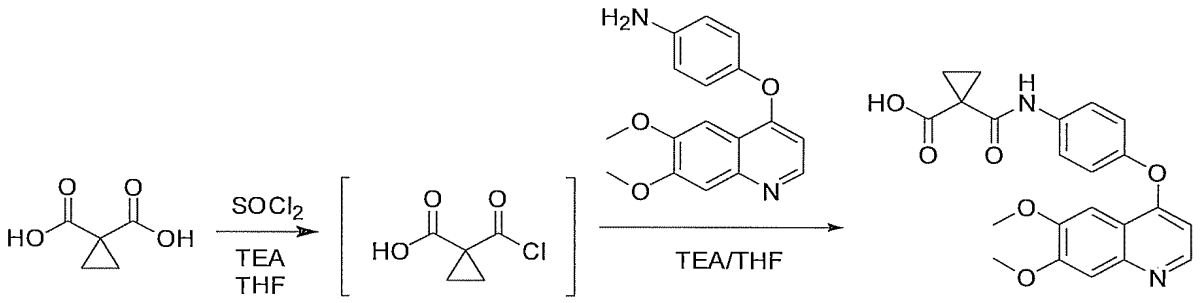


[0419] N-[3-Fluoro-4-({7-(methyloxy)-6-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. Crude cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(6-hydroxy-7-methoxy-quinazolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (333mg, 0.66mmol), PS-PPh_3 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%). ^1H NMR (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.

[0420] Using the same or analogous synthetic techniques and/or substituting with alternative starting materials, the following were prepared:

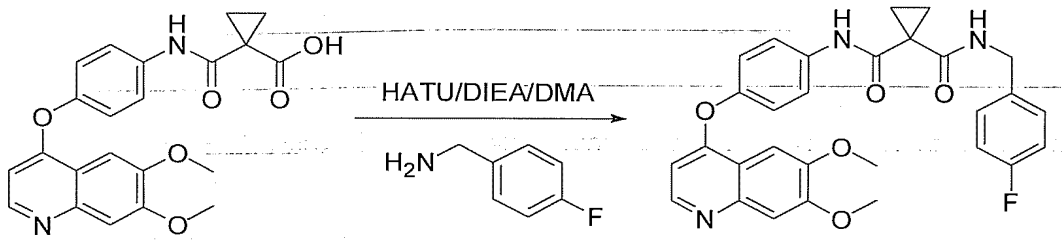
[0421] N-{3-fluoro-4-[(7-(methyloxy)-6-{[(1-methylpiperidin-4-yl)methyl]oxy}quin-azolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide: ^{1}H NMR (400MHz, $CDCl_3$): δ 9.67 (s, 1H), 8.59 (s, 1H), 8.43 (s, 1H), 7.75 (d, 1H), 7.52 (s, 1H), 7.46 (m, 2H), 7.31 (s, 1H), 7.20 (m, 2H), 7.06 (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



[0422] 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



[0423] '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).

[0424] 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.

[0425] N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide. ^{1}H 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).

[0426] N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide. ^{1}H 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).

[0427] 'N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide. ^{1}H 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).

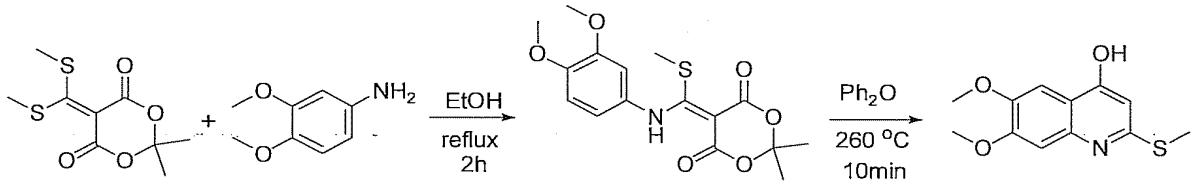
[0428] 'N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide. ^{1}H NMR (DMSO-d6): 10.12 (s, 1H), 10.03 (s, 1H), 8.44 (d, 1H), 7.74 (d, 2H), 7.57 (s, 1H), 7.53 (d, 1H), 7.48 (s, 1H), 7.37 (s, 1H), 7.21 (m, 3H), 6.98 (d, 1H), 6.40 (d, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.56 (t, 4H), 3.41 (s, 2H), 2.34 (br., 4H), 1.48 (s, 4H).

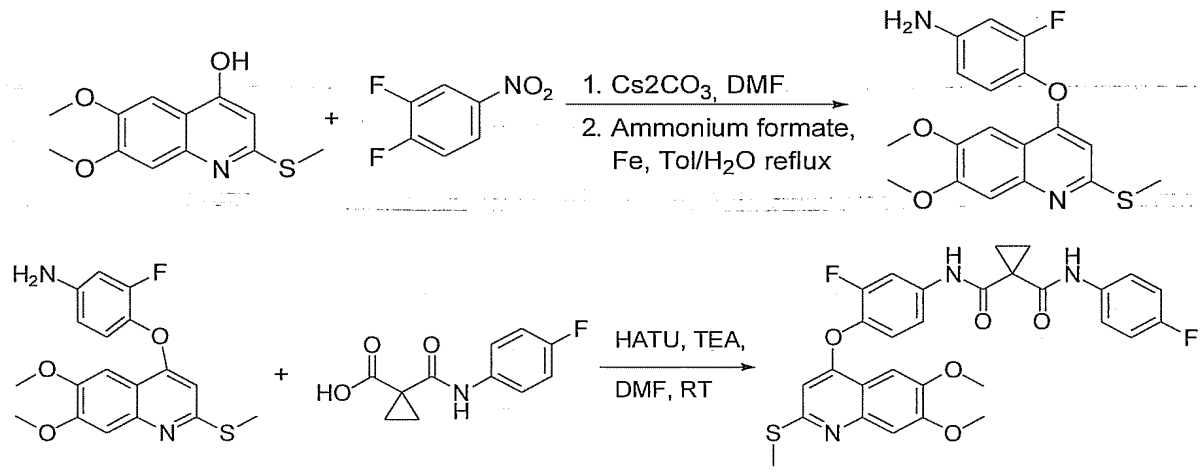
[0429] 'N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide. ^{1}H NMR (DMSO-d6): 10.54 (s, 1H), 10.47 (s, 1H), 8.43 (d, 1H), 8.08 (d, 1H), 7.78 (d, 2H), 7.49 (s, 1H), 7.37 (d, 1H), 7.18-7.30 (m, 4H), 7.03 (t, 1H), 6.37 (d, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.50 (s, 2H), 3.44 (br., 4H), 2.20 (br., 4H), 1.48 (d, 4H).

[0430] 'N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide. ^{1}H 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).

[0431] 'N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide. ^{1}H 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





[0432] 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 $(M-H)^-$.

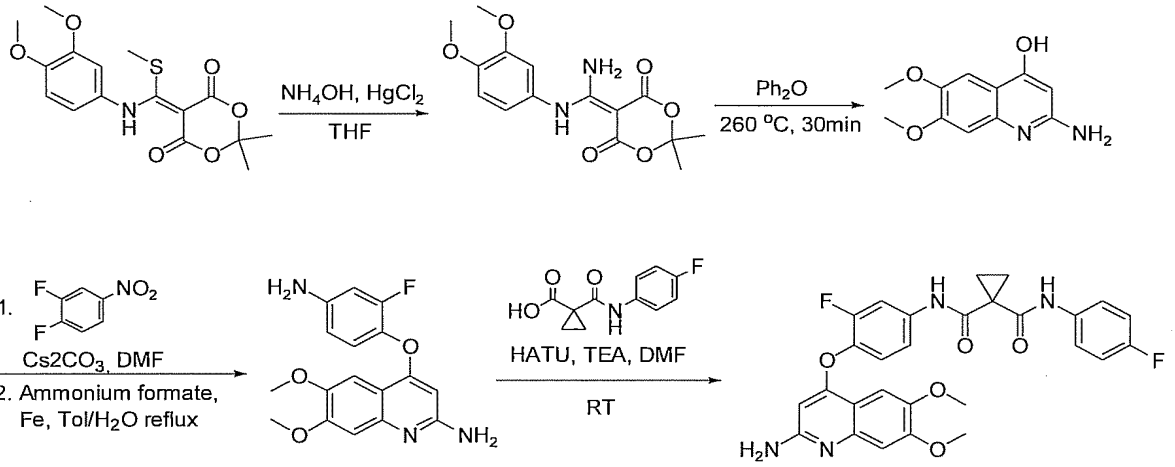
[0433] A mixture of 5-[(3,4-dimethoxy-phenylamino)-methylsulfanyl-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione (1.7 g, 6.6 mmol) and diphenylether (3.5 g, 21 mmol) were heated at 260 ^{0}C for 10 minutes. The mixture was cooled to room temperature and heptane was added. 6,7-Dimethoxy-2-methylsulfanyl-quinolin-4-ol was filtered and isolated as an orange solid and used without further purification (1.4 g, 83% yield). LCMS: m/z 352 $(M+H)^+$.

[0434] 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 $(M+H)^+$.

[0435] 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. ^{1}H 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



[0436] 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

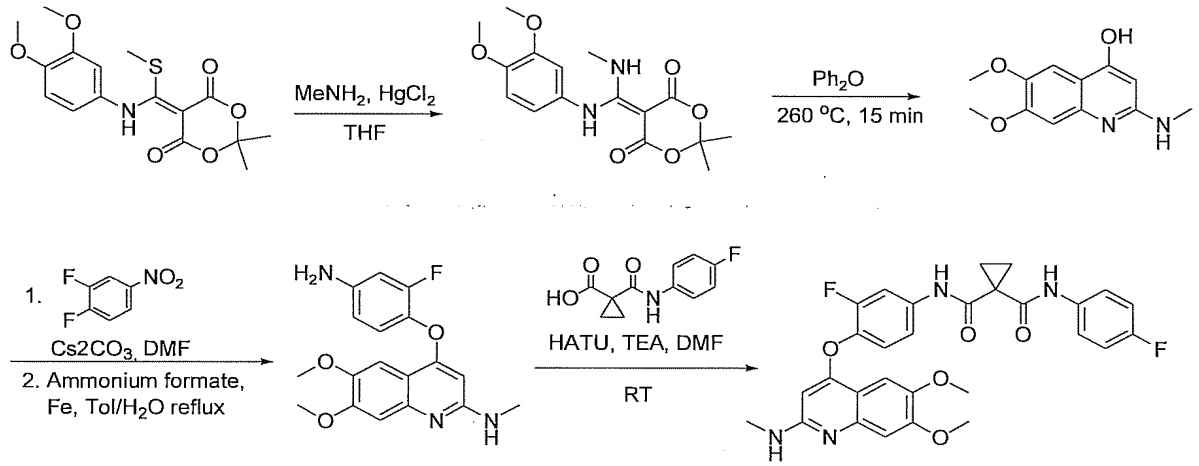
(3X) and dried with Na_2SO_4. Concentration *in vacuo* afforded 5-[amino-(3,4-dimethoxy-phenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione as a white solid (0.90 g, 97% yield) and this compound was used without further purification. LCMS: m/z 321 $(M-H)^-$.

[0437] 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 $(M+H)^+$.

[0438] 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 $(M+H)^+$.

[0439] 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



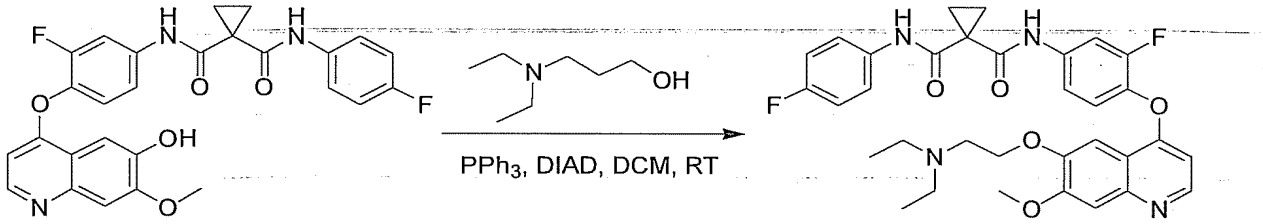
[0440] Synthesis of 'N-(3-fluoro-4-{[2-(methylamino)-6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. A mixture of 5-[(3,4-dimethoxy-phenylamino)-methylsulfanyl-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione (0.50 g, 1.4 mmol), methylamine (2 M in THF, 0.75 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 $(M-H)^-$.

[0441] 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 $(M+H)^+$.

[0442] [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 $(M+H)^+$.

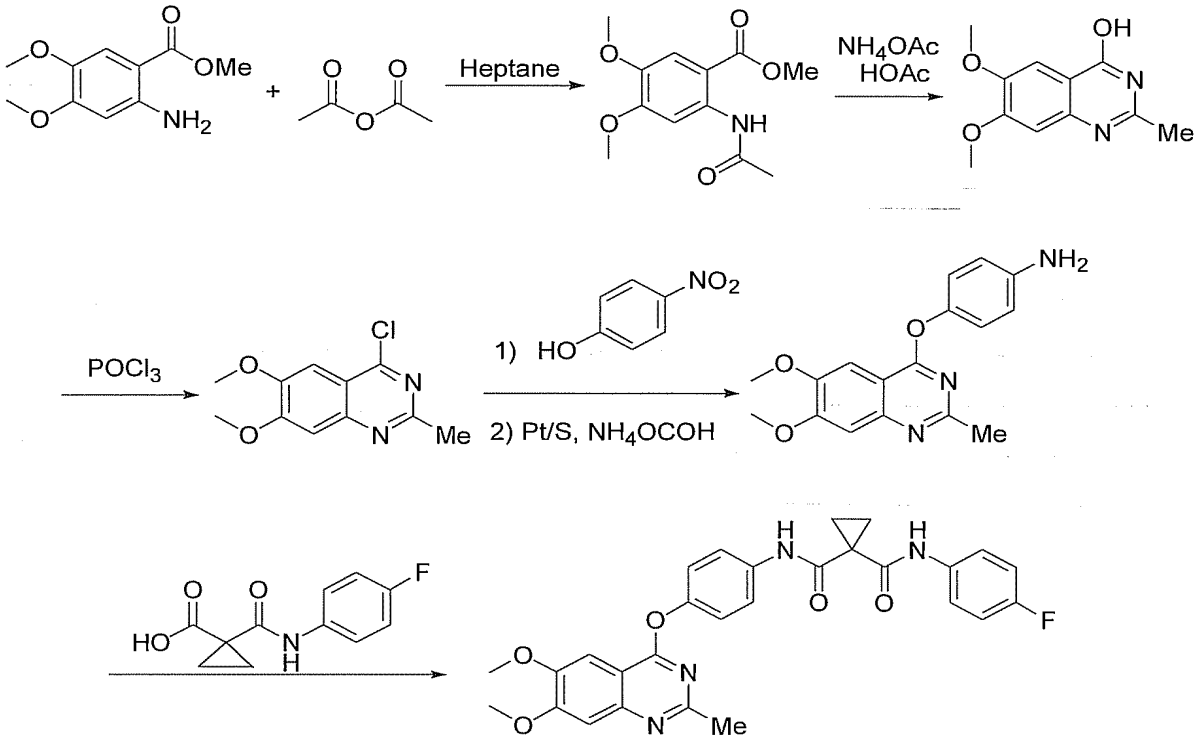
[0443] 'N-(3-fluoro-4-{[2-(methylamino)-6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide was synthesized from [4-(4-amino-2-fluoro-phenoxy)-6,7-dimethoxy-quinolin-2-yl]-methyl-amine in a similar manner as N-(4-{[6,7-bis(methyloxy)-2-(methylthio)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluoro-phenyl)cyclopropane-1,1-dicarboxamide. 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



[0444] '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



[0445] '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).

[0446] 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).

[0447] 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.

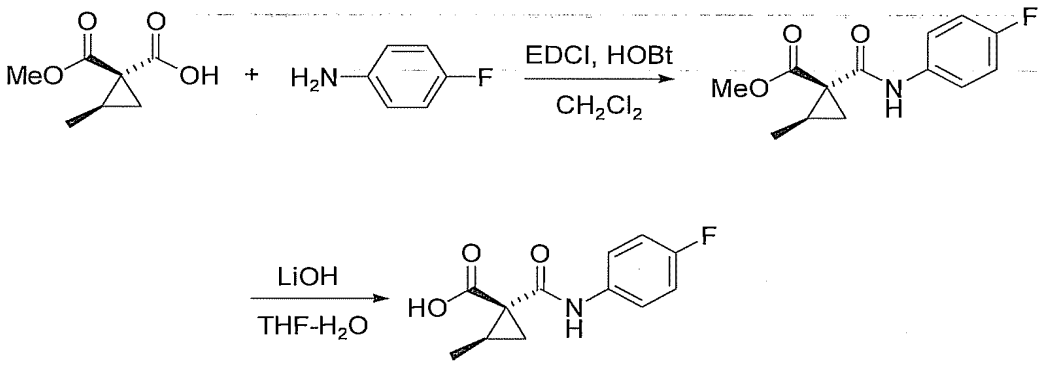
The reaction mixture was poured into ice water, neutralized with $NaHCO_3$, and adjusted to basic with K_2CO_3. The mixture was cooled to 0°C with stirring. The resulting precipitate was filtered, giving 4-chloro-6,7-dimethoxy-2-methyl-quinazoline (0.094g), which was used without further purification.

[0448] 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).

[0449] 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).

[0450] 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).

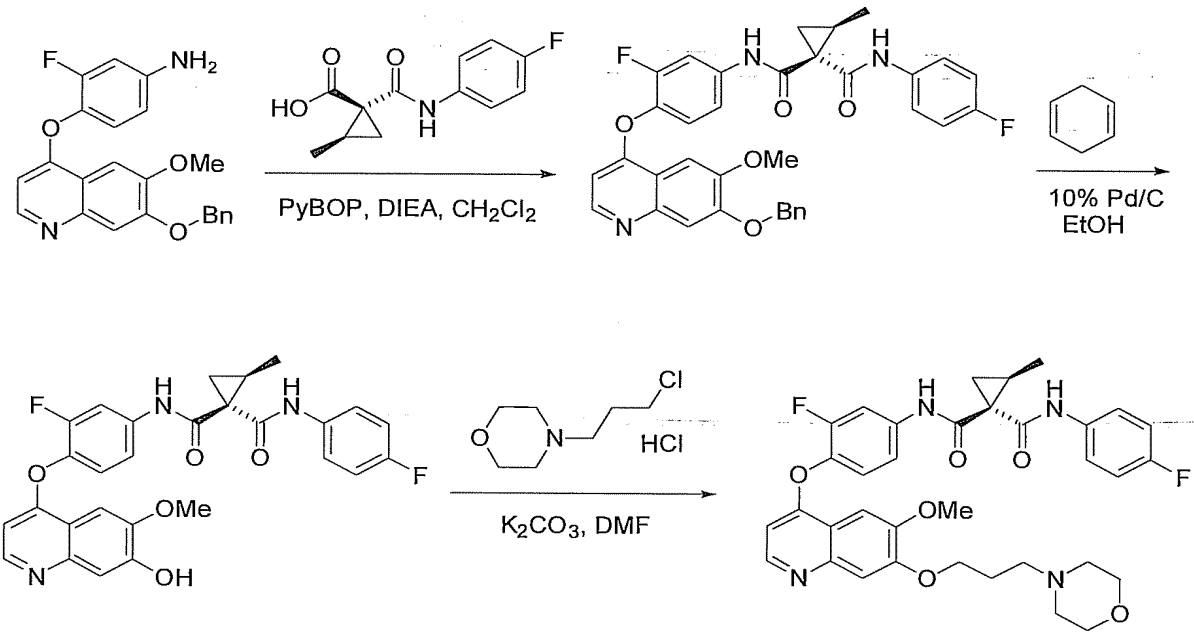
Example 80



[0451] 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.

[0452] 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



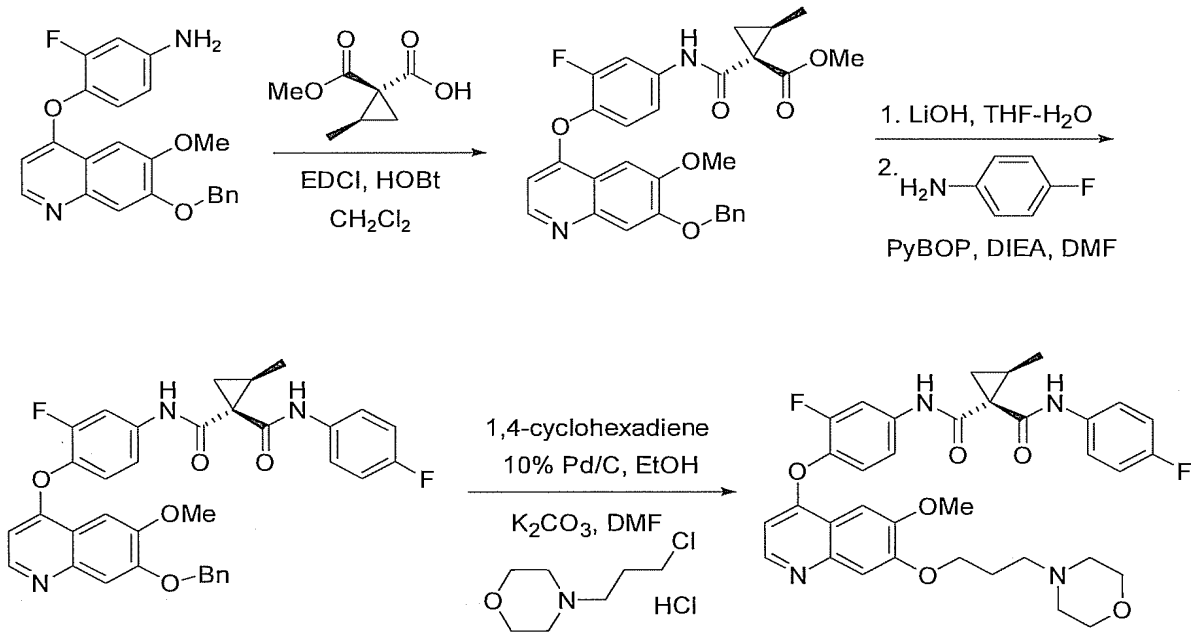
[0453] Synthesis of (1S,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl) oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide. To a solution of 4-(7-benzyloxy-6-methoxy-quinolin-4-yloxy)-3-fluoro-phenylamine (150 mg, 0.38 mmol) in CH_2Cl_2 (3 mL) was added 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.

[0454] 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.

[0455] 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



[0456] 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).

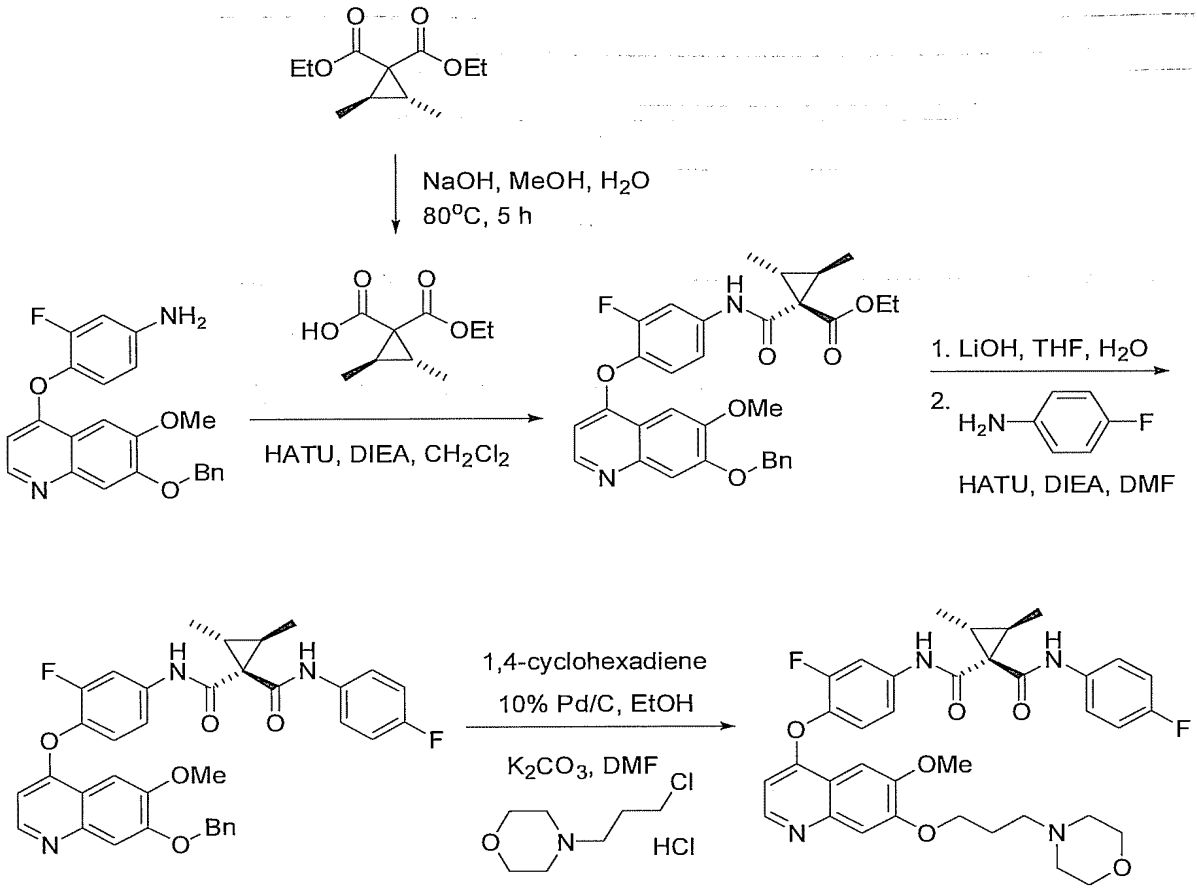
[0457] The product (153 mg, 0.29 mmol) obtained above was treated with $LiOH \cdot H_2O$ (15 mg, 0.35 mmol) in THF (1 mL) and H_2O (1 mL) for 2 h. THF was removed. 10 mL of H_2O was added to the mixture. The aqueous solution was washed with ether, and acidified with 1 N HCl. The solid was then filtered and dried under vacuum.

[0458] 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.

[0459] 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.

[0460] 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: ^1H 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



[0461] 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.

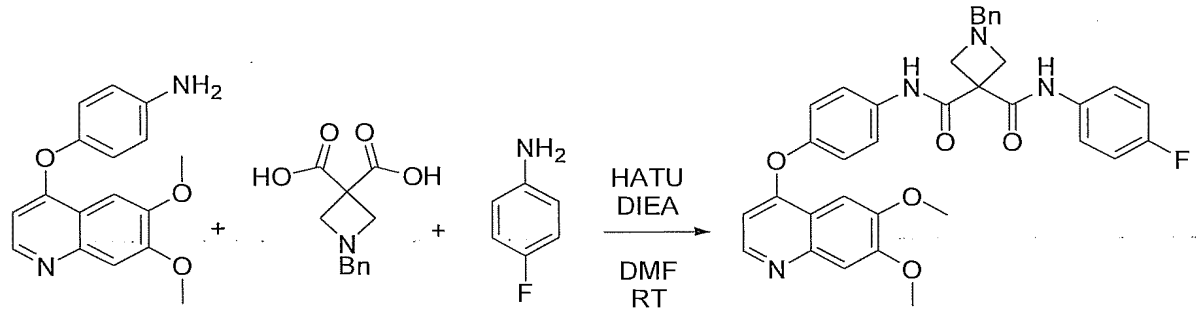
[0462] The aniline (1.08 g, 2.78 mmol) and the carboxylic acid (518 mg, 2.78 mmol) prepared above were dissolved in CH_2Cl_2 (15 mL). HATU (2.11 g, 5.56 mmol) and DIEA (1.8 mL, 11.1 mmol) were added. The reaction mixture was stirred at rt overnight. It was then concentrated and diluted with EtOAc. The 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 $LiOH \cdot H_2O$ (175 mg, 4.17 mmol) in THF (100 mL) -H_2O (50 mL) at 60 °C for 10 h.

[0463] 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.

[0464] 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

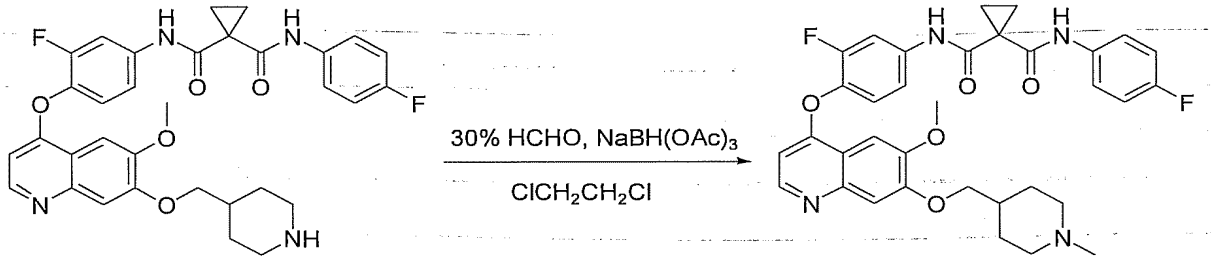


[0465] Synthesis of 'N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-1-(phenylmethyl)azetidine-3,3-dicarboxamide. 1-Benzyl-azetidine-3,3-dicarboxylic acid was prepared by following the literature procedure (Miller, R. A.; et al.

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).

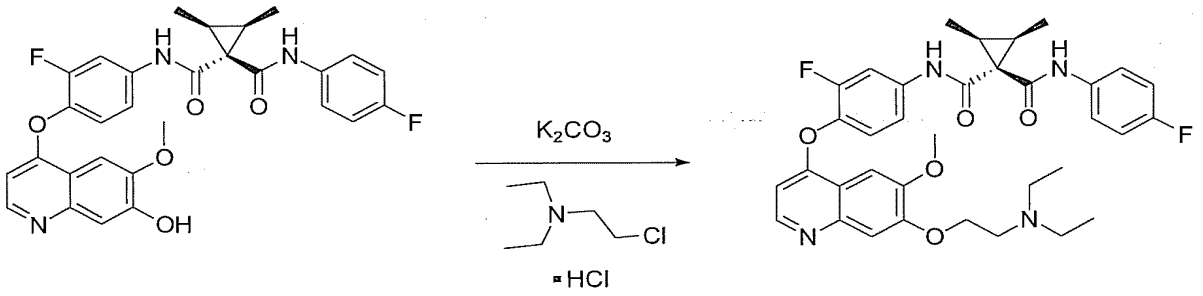
[0466] N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) azetidine-3,3-dicarboxamide. To a solution of 'N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-1-(phenylmethyl)azetidine-3,3-dicarboxamide (300 mg, 0.5 mmol) in MeOH (50 mL) was charged with Pd/C (50% 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



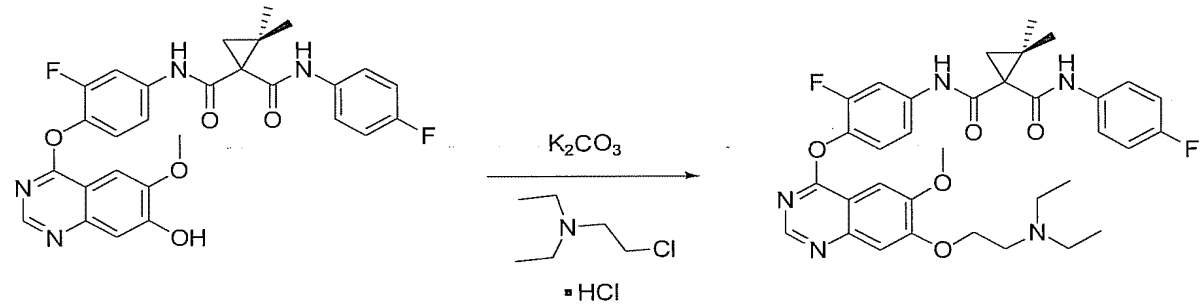
[0467] N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. To a solution of cyclopropane-1,1-dicarboxylic acid {3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-amide (4-fluoro-phenyl)-amide, 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-dicarbox-amide, 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



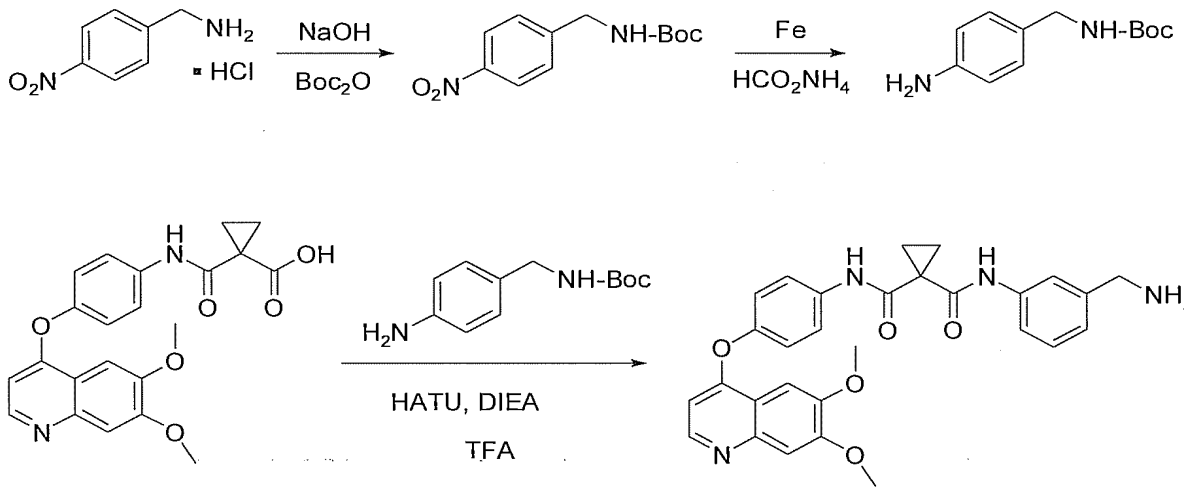
[0468] (1R,2R,3S)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide. 2,3-Dimethyl-cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (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



[0469] 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}H NMR (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



[0470] 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).

[0471] (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).

[0472] [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.

[0473] 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 2 hrs, 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.

[0474] 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

[0475] 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.

[0476] 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:

[0477] 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:

$$Y = \text{Min} + (\text{Max} - \text{Min}) / (1 + (X/IC_{50})\text{^}H)$$

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

[0478] 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

[0479] 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

[0480] 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

[0481] 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

[0482] c-Kit biochemical activity was assessed using AlphaScreen TM (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

[0483] 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	

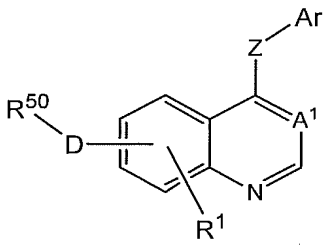
374	(1r,2R,3S)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	A	B		B	
375	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	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 of formula **I**,



I

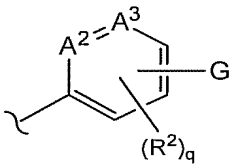
or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein,

R^1 is selected from -H, halogen, $-OR^3$, $-NO_2$, $-NH_2$, $-NR^3R^4$, and optionally substituted lower alkyl;

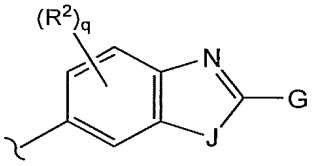
A^1 is selected from =N- and =C(H)-;

Z is -O- or $-NR^5$-;

Ar is either a group of formula **II**, or of formula **III**,



II



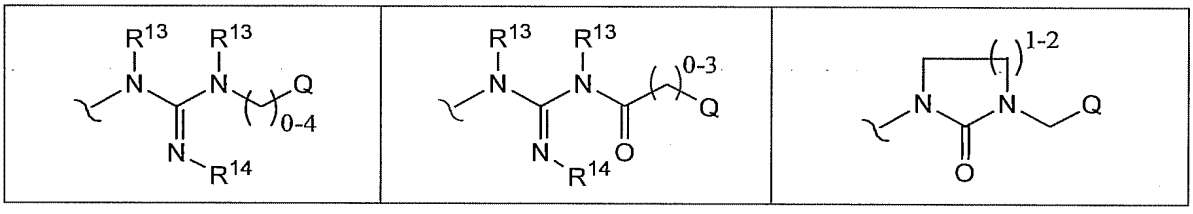
III

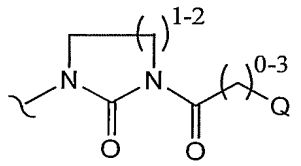
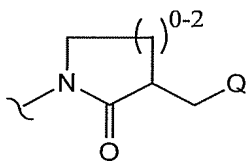
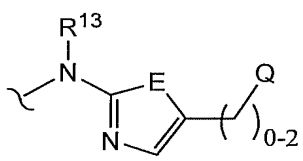
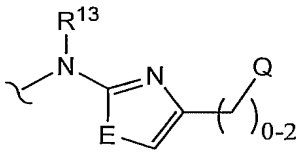
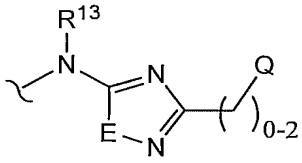
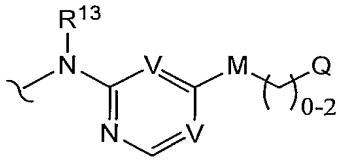
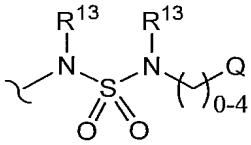
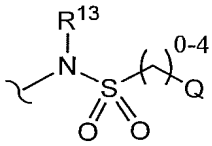
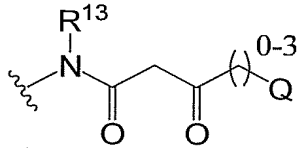
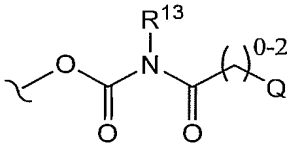
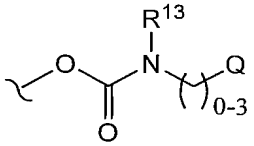
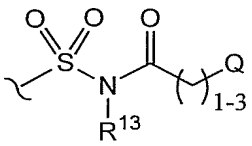
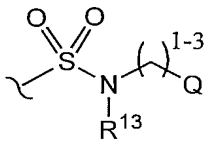
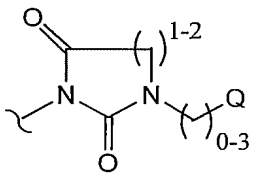
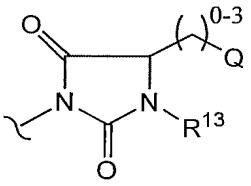
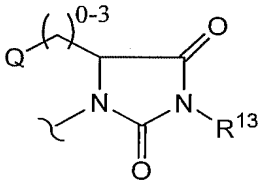
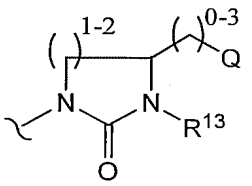
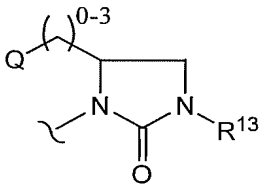
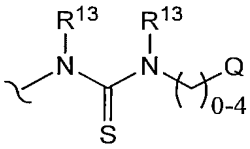
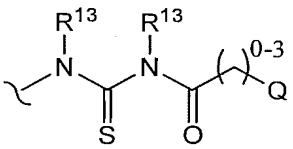
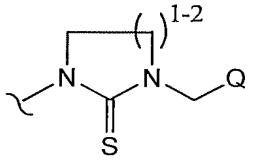
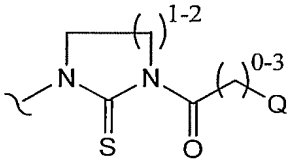
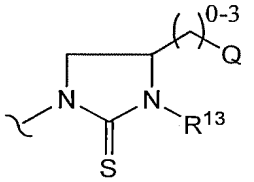
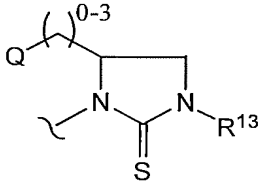
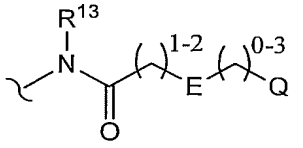
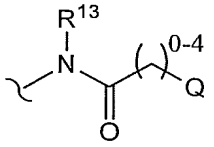
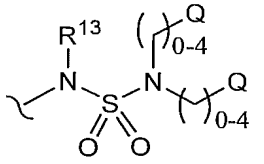
wherein,

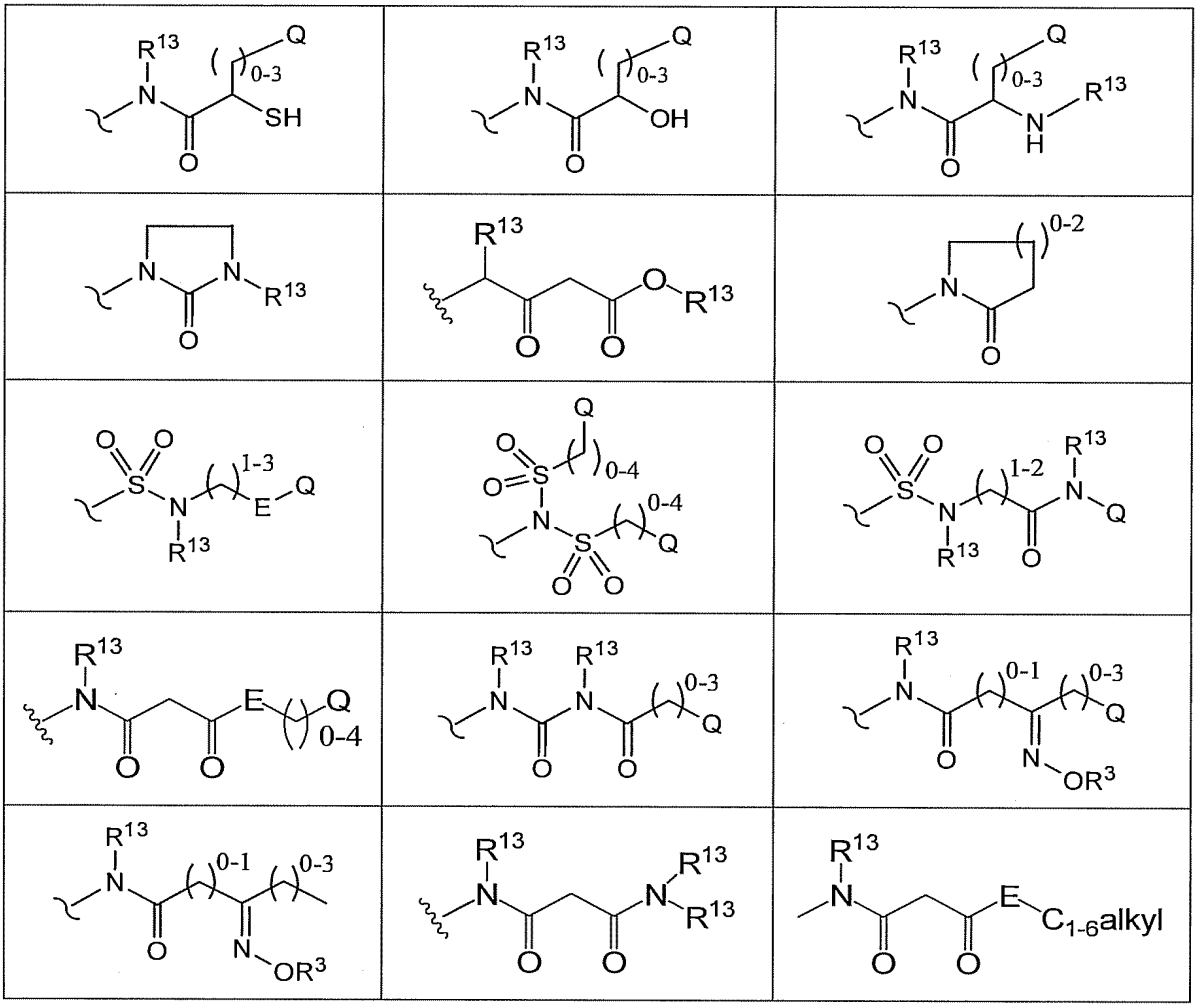
R^2 is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted lower alkyl;

q is 0 to 4;

G is selected from:





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 one or two R^{25};

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; 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; or two of R^{25} on a single carbon can be oxo;

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- and =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 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; or, 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; and

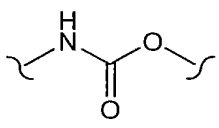
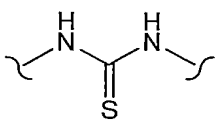
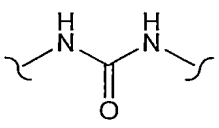
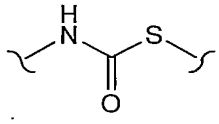
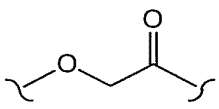
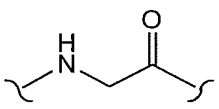
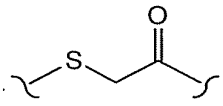
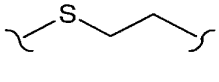
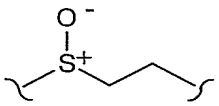
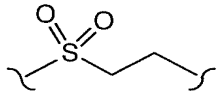
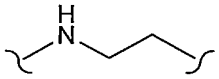
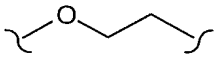
R^{60} is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted heteroarylalkyl, and optionally substituted arylalkyl; or, two of R^{60}, when attached to a non-aromatic carbon, can be oxo;

with the proviso that the conditions of:

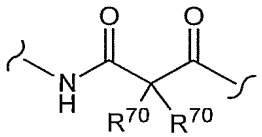
Z is-O-; and

Ar is according to formula **II**; and

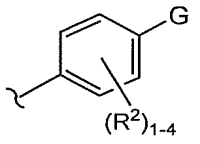
the portion of G directly attached to Ar selected from the table below:

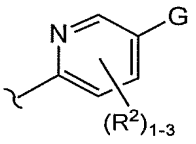
are not met at the same time; and

with the proviso that when Ar is phenylene or substituted phenylene and Z is -O-, then the portion of G directly attached to Ar cannot contain , wherein R^{70} is selected from -H, C_{1-4}alkyl, and C_{1-4}alkoxyl.

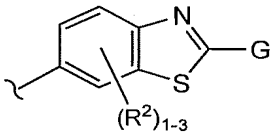
2. The compound according to claim 1, wherein Ar is according to one of formula **IIa**, **IIb**, and **IIIa**:



IIa



IIb



IIIa

3. The compound according to claim 1, wherein A^1 is =C(H)-.

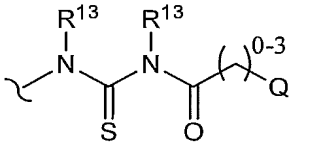
4. The compound according to claim 2, wherein Ar is of formula IIa and A^1 is =N-.

5. The compound according to claim , wherein D is -O- and R^1 is $-OR^3$.

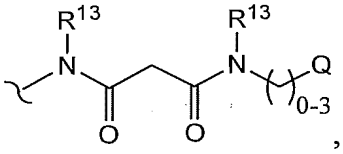
6. The compound according to claim 5, wherein $-O-R^{50}$ and R^1 are interchangeably located at the 6-position and 7-position of the quinazoline or quinoline according to formula **I**.

7. The compound according to claim 6, wherein R^1 is -OH or $-OC_{1-6}$alkyl.

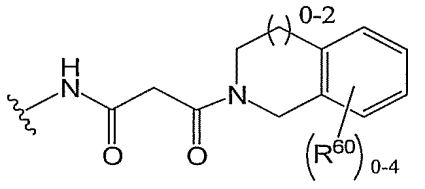
8. The compound according to claim 7, wherein G is selected from:



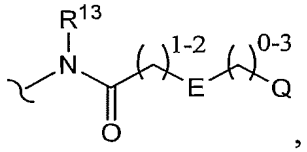
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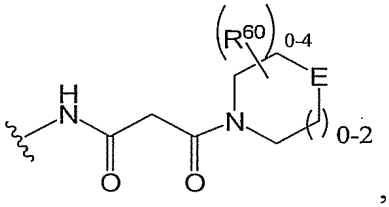
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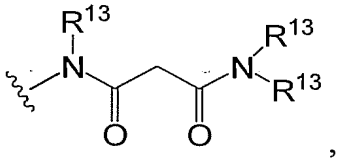
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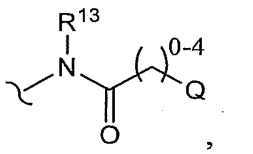
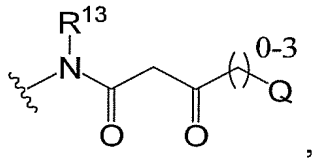
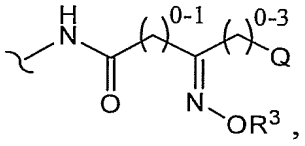
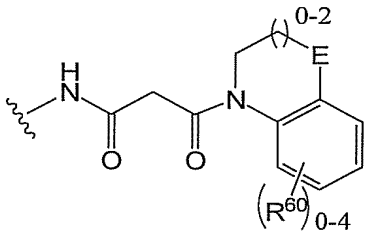
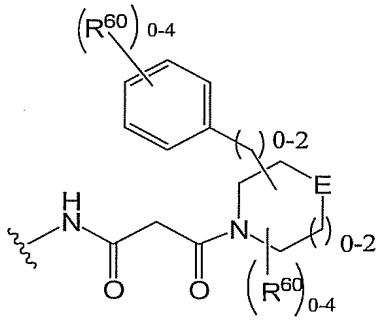
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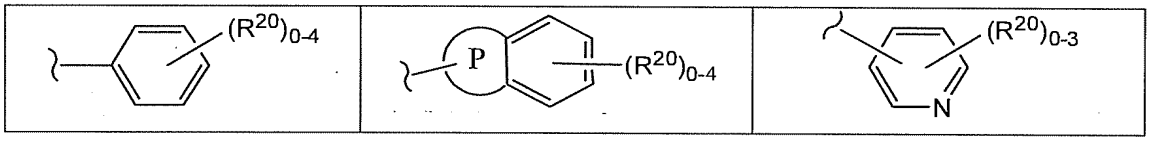


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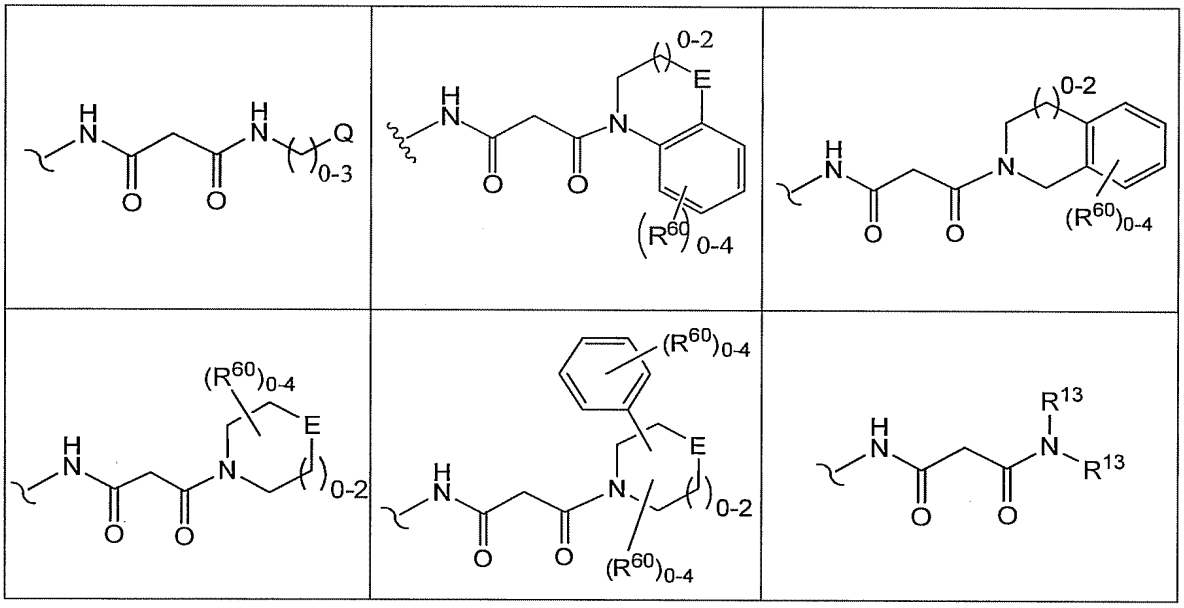
wherein Q, R^{13}, E, and R^{60} are as defined above; each methylene in any of the above formulae, other than those in a depicted ring, is independently optionally substituted with one or two R^{25}; and R^{25} is selected from halogen, trihalomethyl, oxo, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted arylalkyl, heteroarylalkyl, and optionally substituted lower alkyl; 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.

9. The compound according to claim 8, 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.

10. The compound according to claim 9, wherein Ar is according to formula **IIb**, and G is selected from:



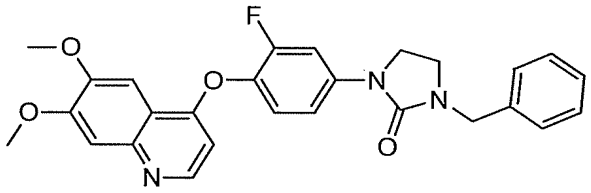
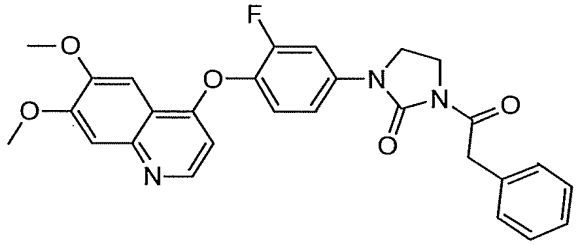
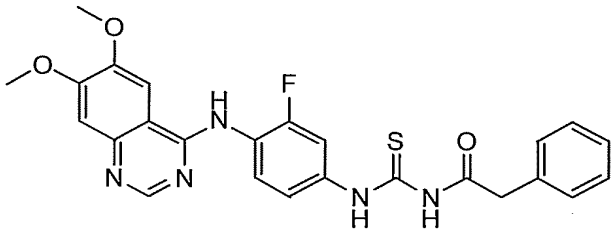
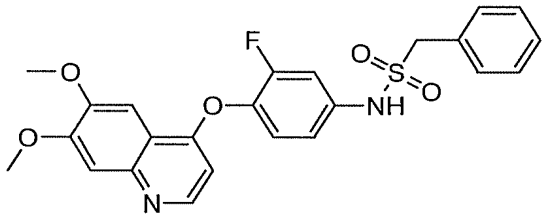
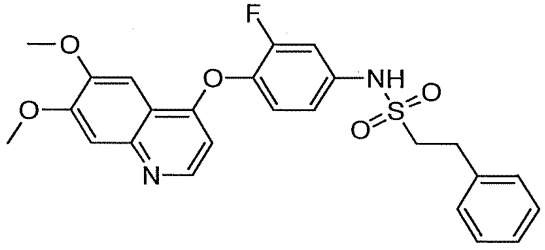
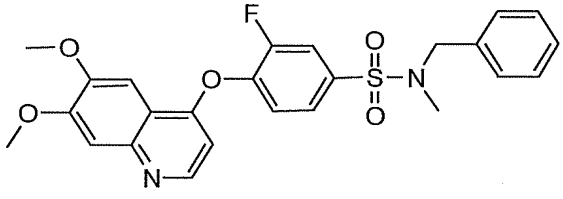
wherein Q, R^{13}, E, and R^{60} are as defined above, and each methylene in any of the above formulae, other than those depicted in a ring, is independently optionally substituted with one or two R^{25}; and R^{25} is selected from halogen, trihalomethyl, oxo, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted arylalkyl, heteroarylalkyl, and optionally substituted lower alkyl; 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.

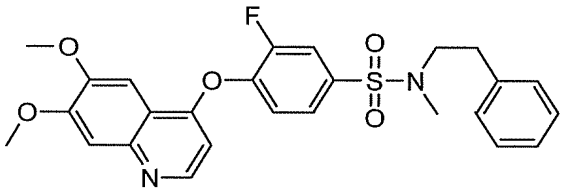
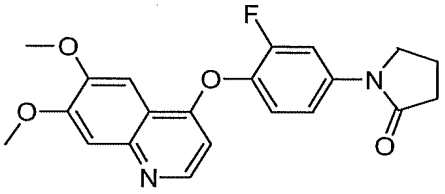
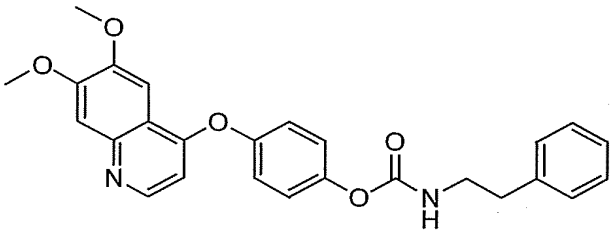
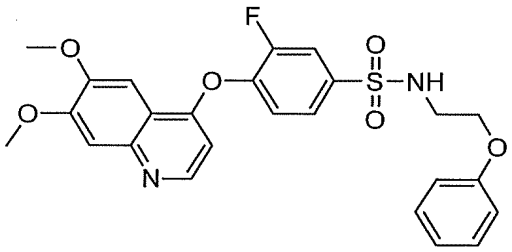
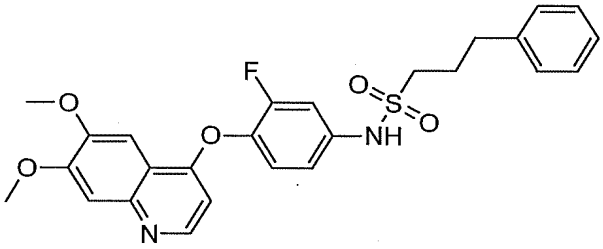
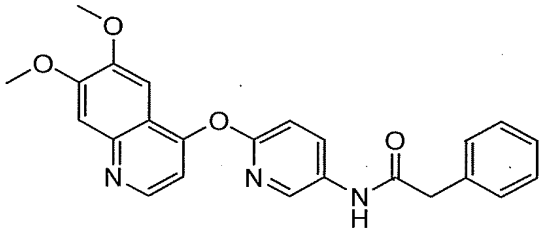
11. The compound according to claim 10, wherein the methylene between the two carbonyls of G is di-substituted with either optionally substituted lower alkyl, or an optionally substituted spirocycle.

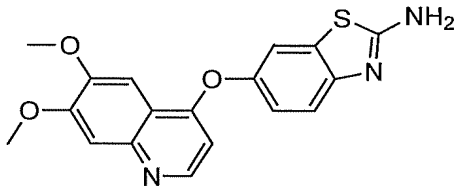
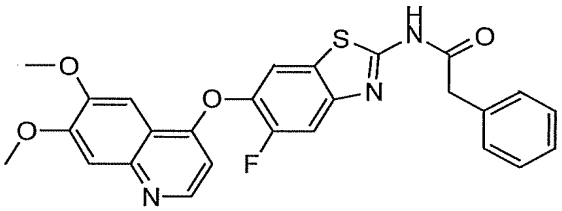
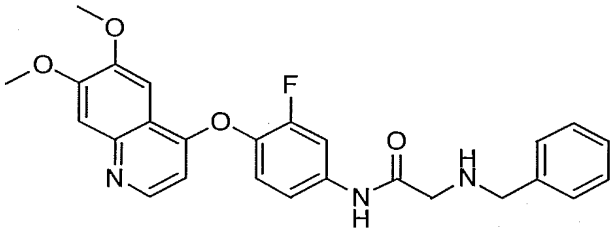
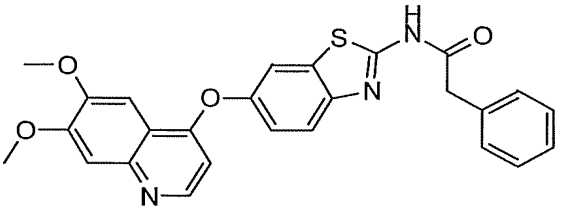
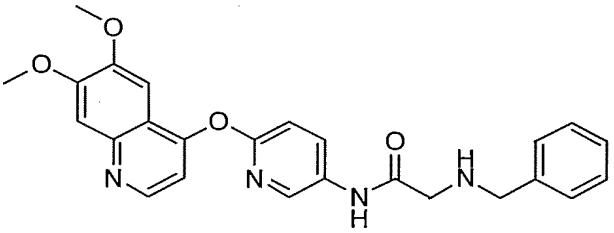
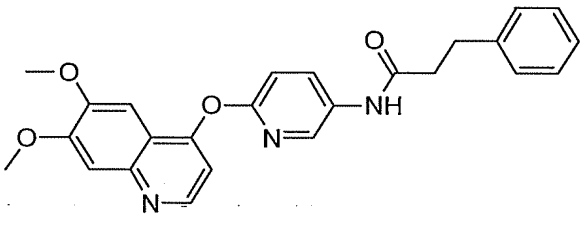
12. The compound according to claim 10, wherein R^{50} is a heteroalicylic or a C_{1-6}alkyl-heteroalicylic.

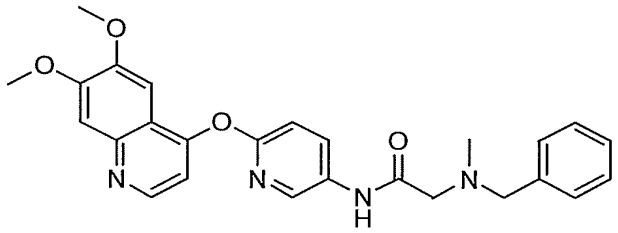
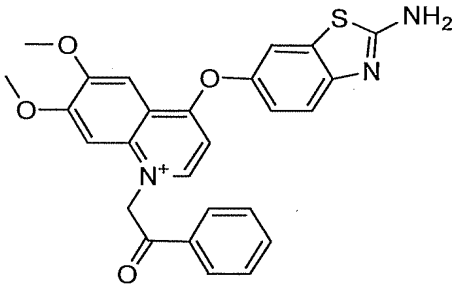
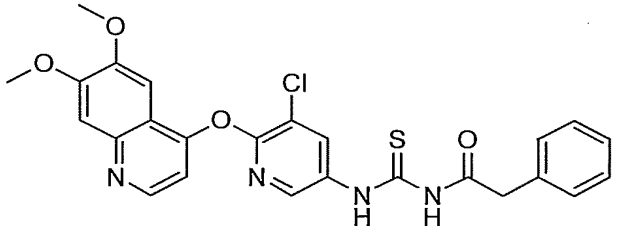
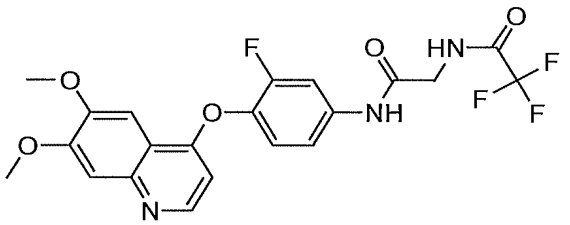
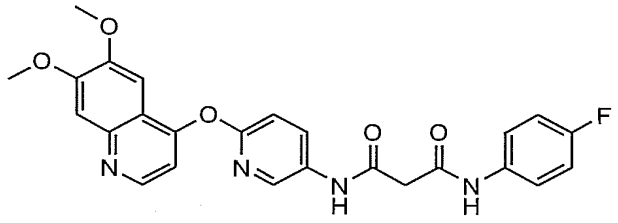
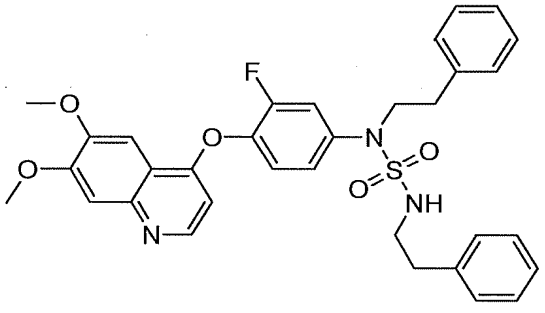
13. The compound according to claim 12, wherein at least one of R^2 is halogen.

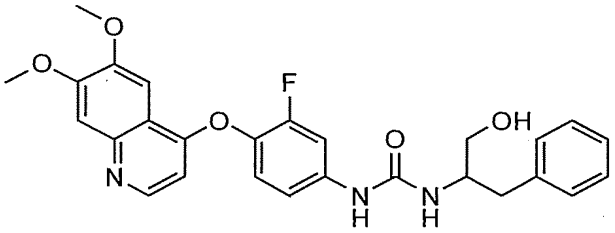
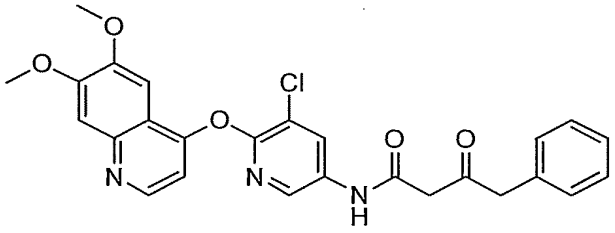
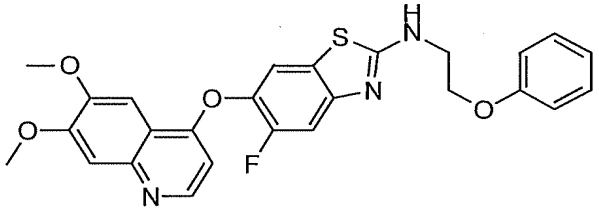
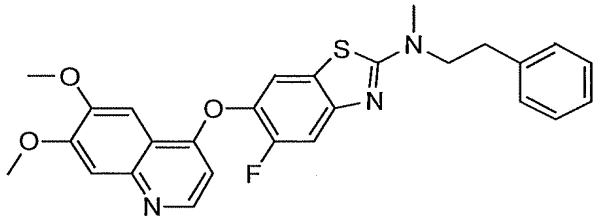
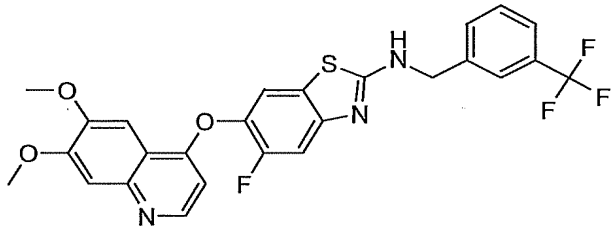
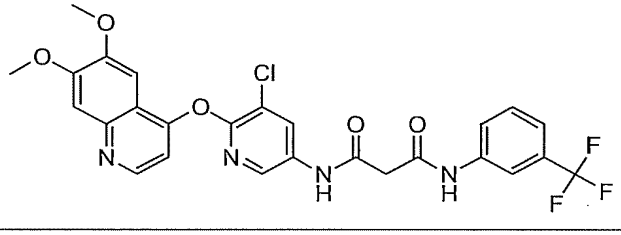
14. The compound according to claim 1, selected from one of the following compounds:

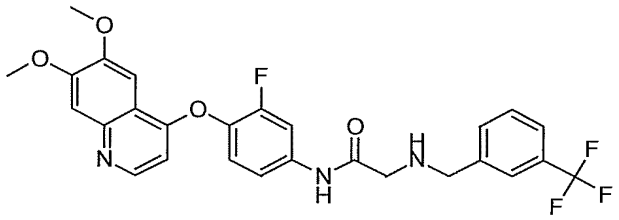
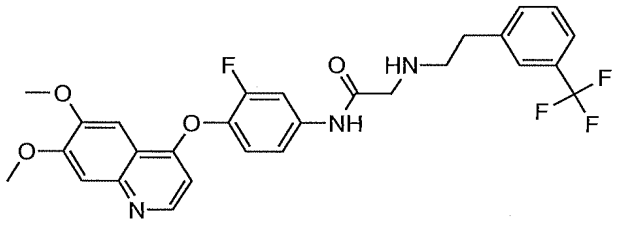
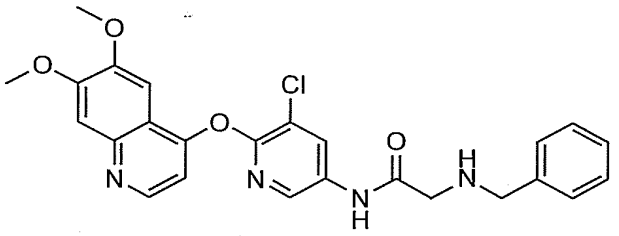
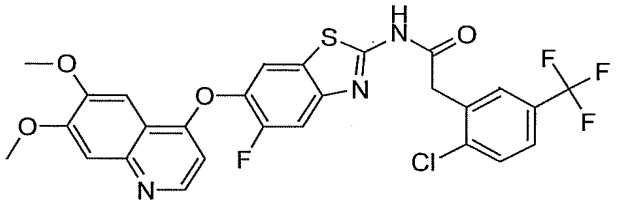
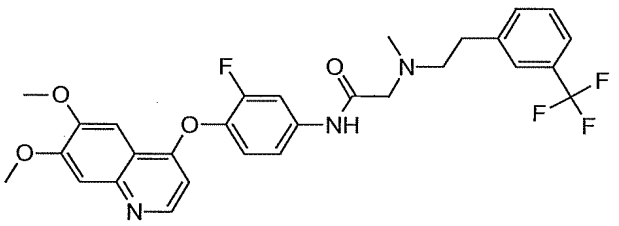
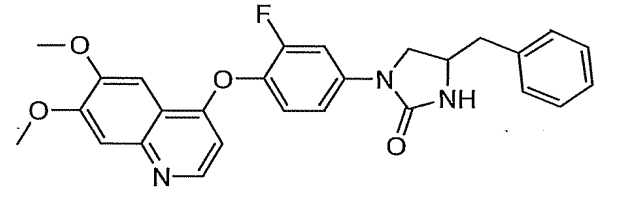
Name	Structure
1-(4-{[6,7-bis (methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylmethyl)imidazolidin-2-one	
1-(4-{[6,7-bis (methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl) 3-(phenylacetyl) imidazolidin-2-one	
N-{[(4-{[6,7-bis(methyloxy) quinazolin-4-yl]amino}-3-fluorophenyl)amino] carbonothioyl}-2-phenylacetamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-1-phenylmethanesulfonamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-2-phenylethanesulfonamide	
4-{[6,7-bis(methyloxy) quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(phenylmethyl) benzenesulfonamide	

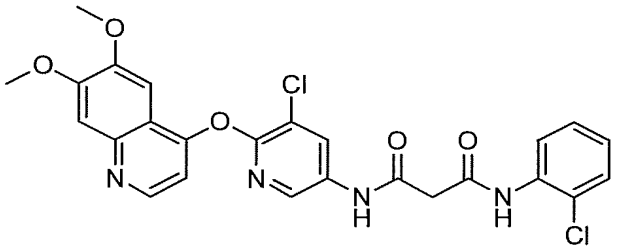
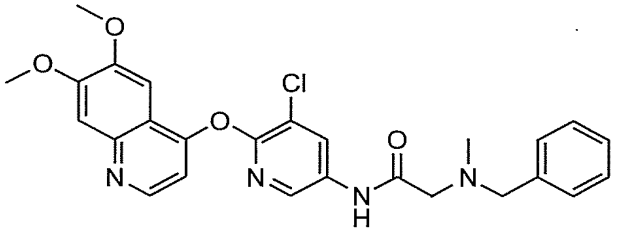
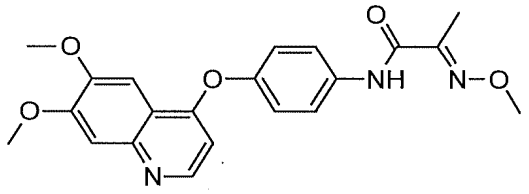
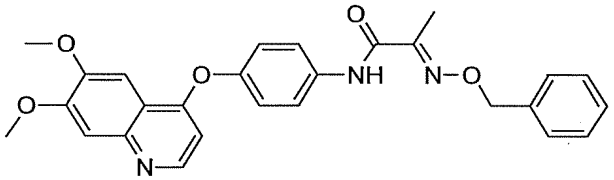
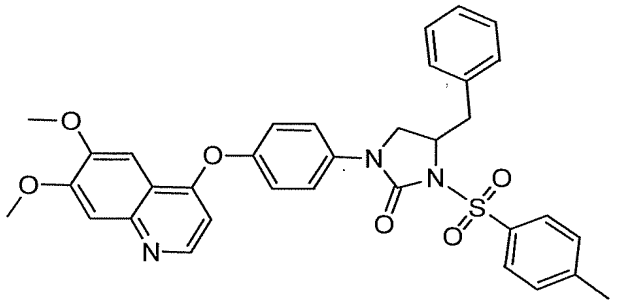
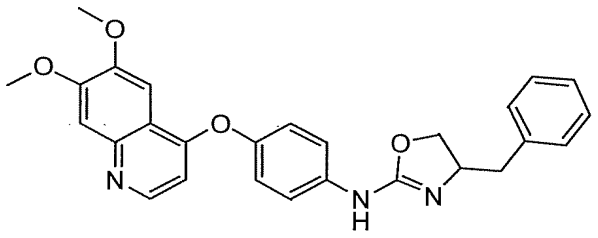
Name	Structure
4-{[6,7-bis(methyloxy) quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(2-phenylethyl) benzenesulfonamide	
1-(4-{[6,7-bis(methyloxy) quinolin-4-yl]oxy}-3-fluorophenyl)pyrrolidin-2-one	
4-{[6,7-bis(methyloxy) quinolin-4-yl]oxy}phenyl (2-phenylethyl)carbamate	
4-{[6,7-bis(methyloxy) quinolin-4-yl]oxy}-3-fluoro-N-[2-(phenyloxy)ethyl] benzenesulfonamide	
N-(4-{[6,7-bis(methyloxy) quinolin-4-yl]oxy}-3-fluorophenyl)-3-phenylpropane-1-sulfonamide	
N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-2-phenylacetamide	

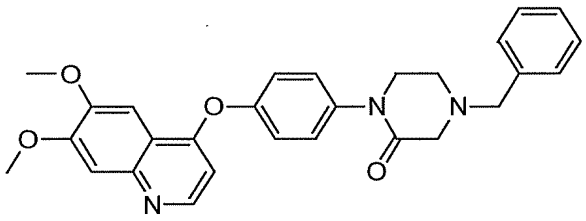
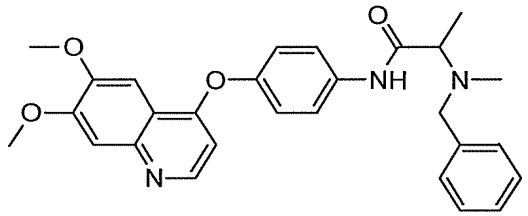
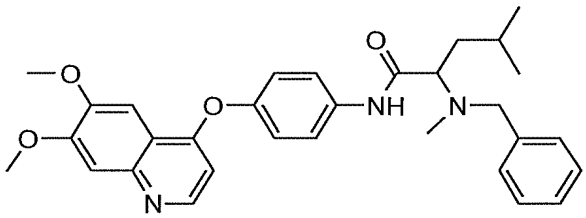
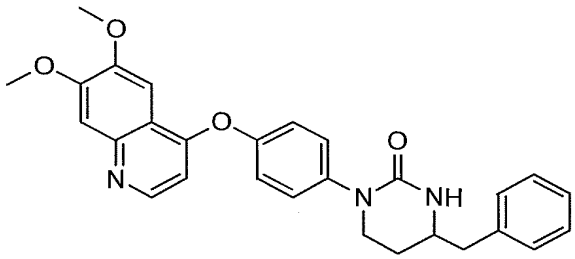
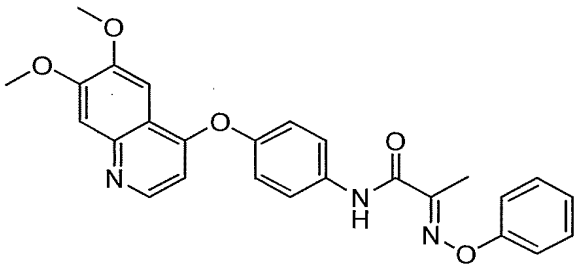
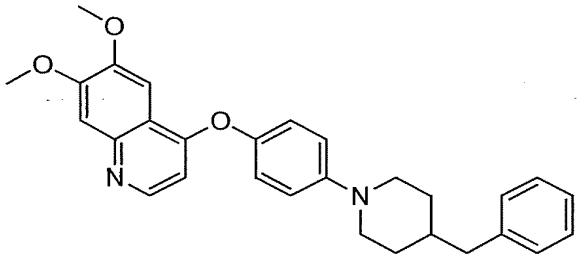
Name	Structure
6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-1,3-benzothiazol-2-amine	
N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-phenylacetamide	
N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(phenylmethyl)glycinamide	
N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-1,3-benzothiazol-2-yl)-2-phenylacetamide	
N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N2-(phenylmethyl)glycinamide	
N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-3-phenylpropanamide	

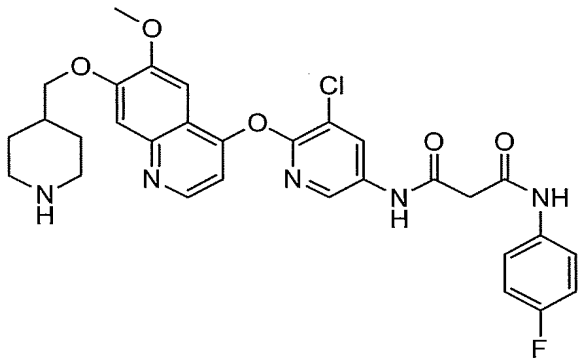
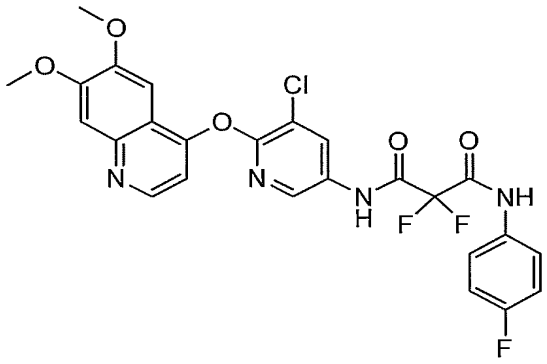
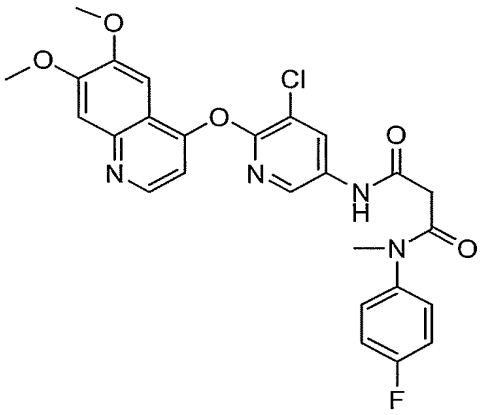
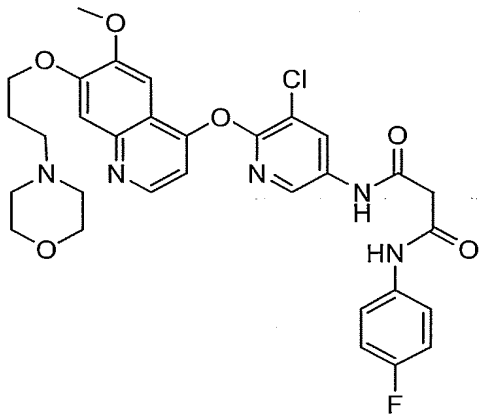
Name	Structure
N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N2-methyl-N2-(phenylmethyl)glycinamide	
4-[(2-amino-1,3-benzothiazol-6-yl)oxy]-6,7-bis(methyloxy)-1-(2-oxo-2-phenylethyl) quinolinium	
N-{[(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)amino]carbonothioyl}-2-phenylacetamide	
N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(trifluoroacetyl)glycinamide	
N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N'-(4-fluorophenyl)propanediamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N,N'-bis(2-phenylethyl)sulfamide	

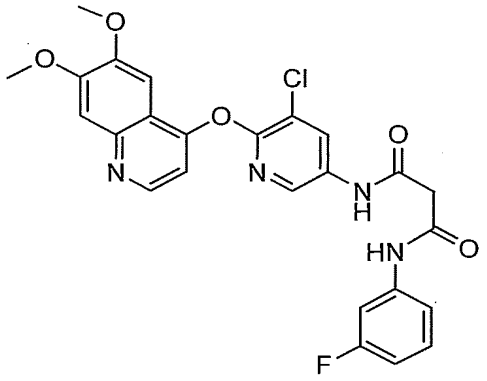
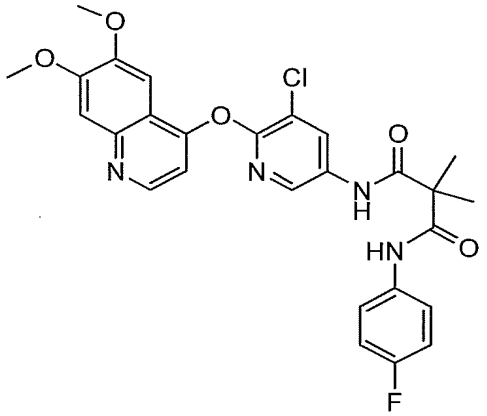
Name	Structure
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-hydroxy-1-(phenylmethyl)ethyl]urea	
N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-3-oxo-4-phenylbutanamide	
6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-[2-(phenyloxy)ethyl]-1,3-benzothiazol-2-amine	
6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-methyl-N-(2-phenylethyl)-1,3-benzothiazol-2-amine	
6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-{[3-(trifluoromethyl)phenyl]methyl}-1,3-benzothiazol-2-amine	
N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-[3-(trifluoromethyl)phenyl]propanediamide	

Name	Structure
N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-{[3-(trifluoromethyl) phenyl]methyl}glycinamide	
N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-{2-[3-(trifluoromethyl) phenyl]ethyl}glycinamide	
N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N2-(phenylmethyl) glycinamide	
N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[2-chloro-5-(trifluoromethyl) phenyl]acetamide	
N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-methyl-N2-{2-[3-(trifluoromethyl) phenyl]ethyl}glycinamide	
1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-4-(phenylmethyl)imidazolidin-2-one	

Name	Structure
N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-chlorophenyl) propanediamide	
N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N2-methyl-N2-(phenylmethyl)glycinamide	
(2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-[(methyloxy)imino] propanamide	
(2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-{[(phenylmethyl)oxy]imino} propanamide	
1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-3-[(4-methylphenyl)sulfonyl]-4-(phenylmethyl)imidazolidin-2-one	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)-4,5-dihydro-1,3-oxazol-2-amine	

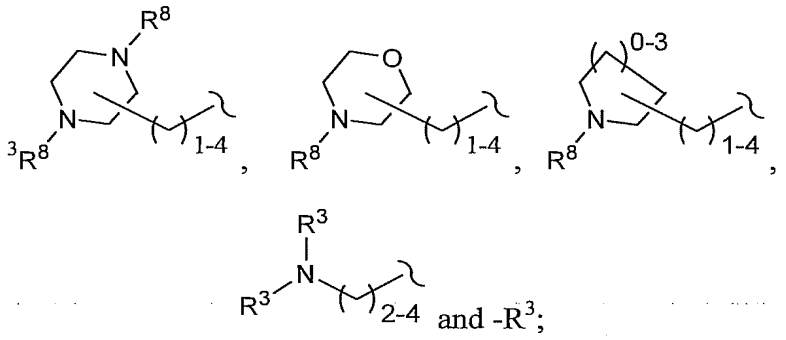
Name	Structure
1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)piperazin-2-one	
N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-methyl-N2-(phenylmethyl) alaninamide	
N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-methyl-N2-(phenylmethyl) leucinamide	
4-benzyl-1-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-tetrahydro-pyrimidin-2-one	
N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-phenyl]-2-phenoxyimino-propionamide	
4-[4-(4-Benzyl-piperidin-1-yl)-phenoxy]-6,7-dimethoxy-quinoline	

Name	Structure
N-{5-Chloro-6-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide	
N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-2,2-difluoro-N'-(4-fluoro-phenyl)-malonamide	
N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(4-fluoro-phenyl)-N'-methyl-malonamide	
N-{5-Chloro-6-[6-methoxy-7-(3-morpholin-4-yl-propoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide	

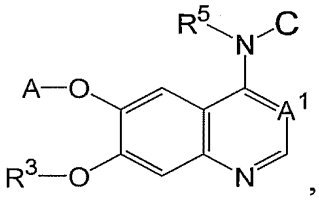
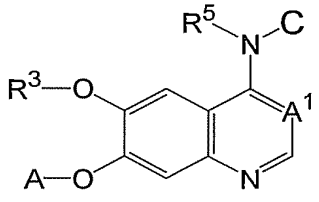
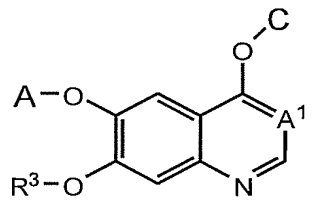
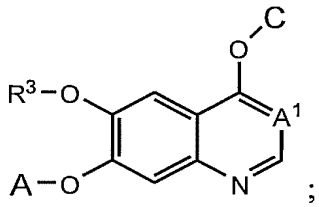
Name	Structure
N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(3-fluoro-phenyl)-malonamide	
N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(4-fluoro-phenyl)-2,2-dimethyl-malonamide	

15. A compound of formula A-B-C, or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein:

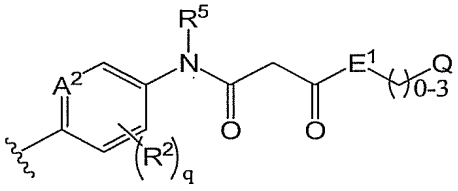
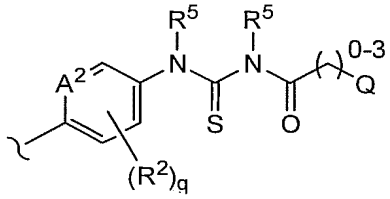
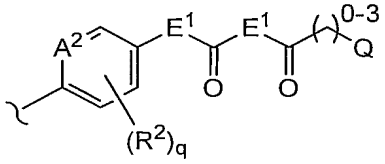
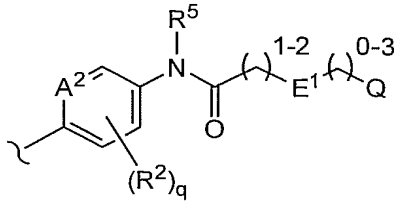
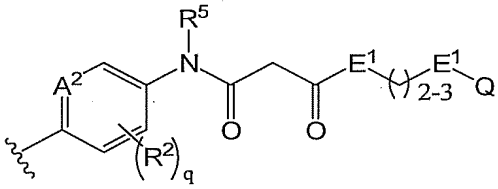
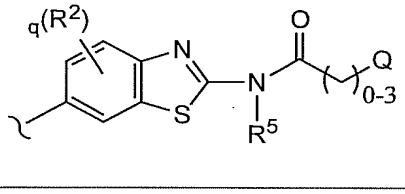
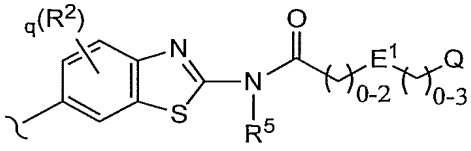
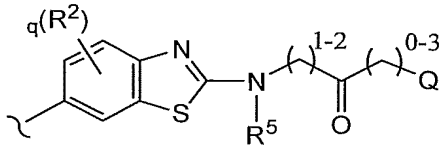
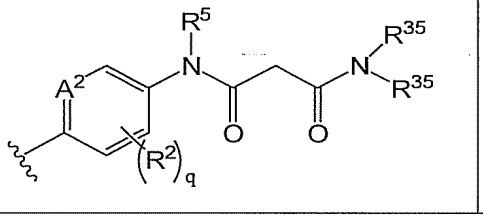
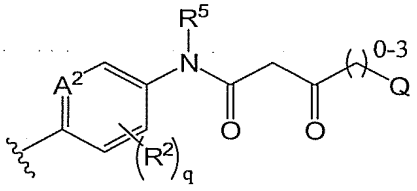
A is selected from:



B is selected from:


,


and

; 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; or, 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; or, 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- and =C(H)-;

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 $-C(O)R^3$, or an R^8 is absent and the alkylene linker of A is covalently bonded to the nitrogen atom in which R^8 is absent;

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};

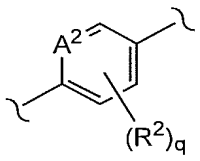
R^{20} is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted lower alkyl;

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; or, two of R^{60}, when attached to a non-aromatic carbon, can be oxo;

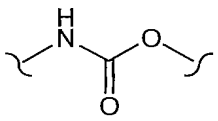
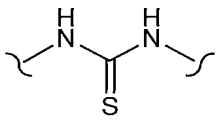
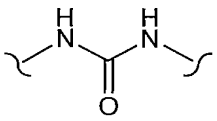
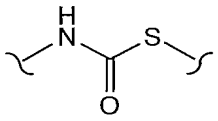
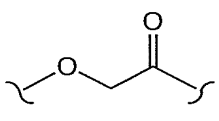
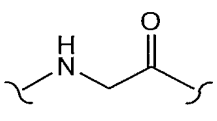
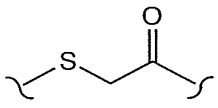
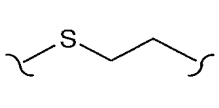
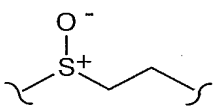
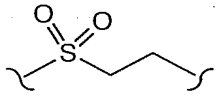
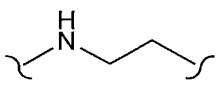
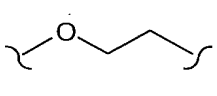
each methylene in any of the above formulae is independently optionally substituted with one or two R^{25}; and

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; 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; or two of R^{25} on a single carbon can be oxo;

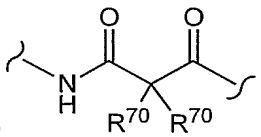
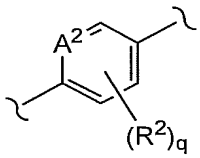
with the proviso that the conditions of:

C contains  ; and

the remaining portion of C contains one of:

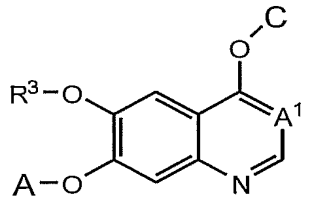
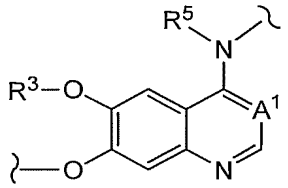
		
		
		
		

are not met at the same time; and

with the proviso that when C contains  directly attached to  and R^{70} is selected from -H, C_{1-4}alkyl, and C_{1-4}alkoxyl, then A^2 is N.

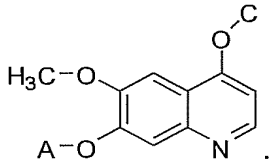
16. The compound according to claim 15, wherein Q is selected from phenyl, napthyl, 1,2,3,4-tetrahydronaphthyl, indanyl, benzodioxanyl, benzofuranyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroisoquinolyl, pyrrolyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, tetrahydropyridinyl, 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.

17. The compound according to claim 16, wherein B is:

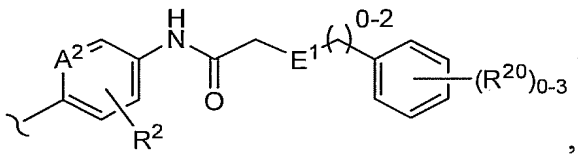
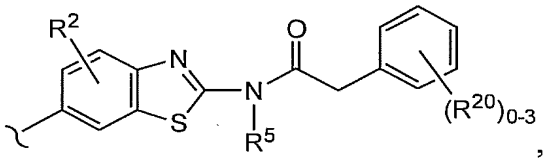
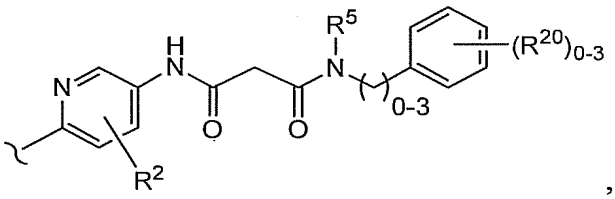
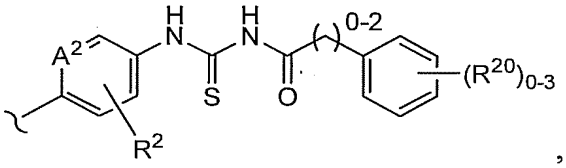
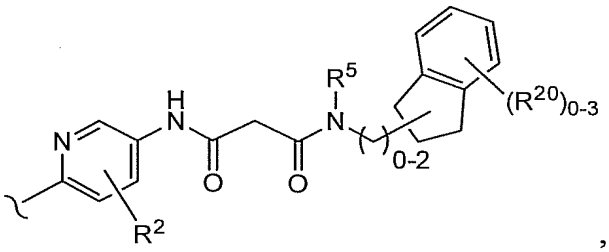
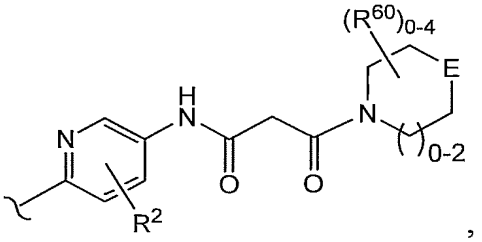
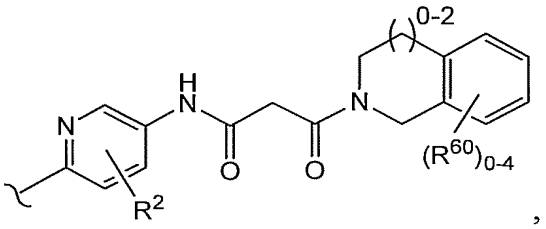
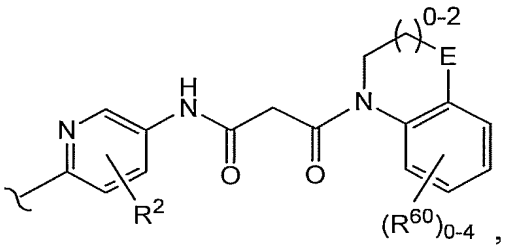
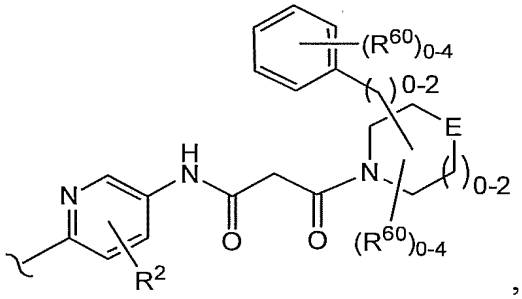
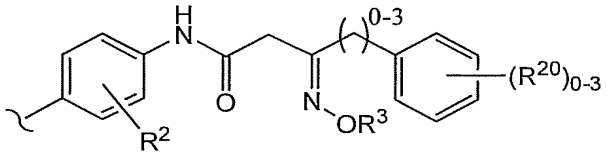
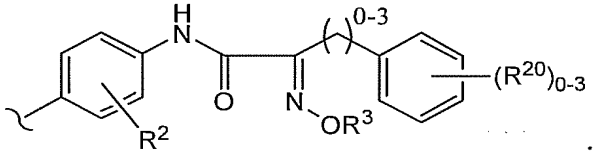
 or 

wherein A^1 is either =N- or =C(H)-.

18. The compound according to claim 17, wherein B is

.

19. The compound according to claim 18, wherein C is selected from:

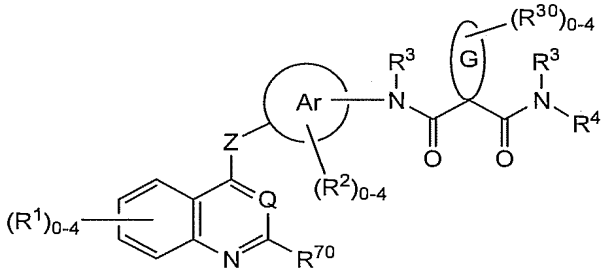

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and

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20. The compound according to claim 19, wherein 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.

21. The compound according to claim 20, wherein R^2 is halogen.

22. The compound according to claim 21, wherein R^2 is fluorine or chlorine.

23. A compound of 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;

Q is =N-, or =C(H)-;

Z is -O- or $-NR^5$-;

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^{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;

each R^{50} is R^3; and

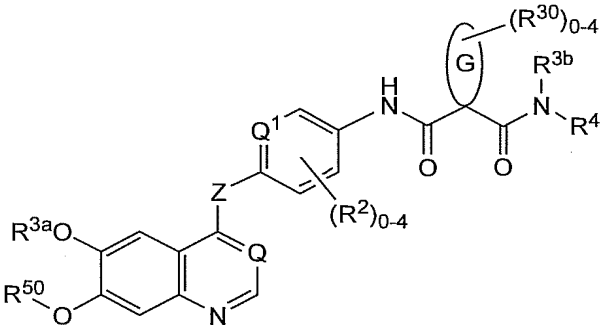
R^{70} is selected from -H, halogen, $-OR^3$, $-S(O)_{0-2}R^3$, $-NO_2$, $-NH_2$, $-NR^3R^4$, and optionally substituted C_{1-6}alkyl.

24. The compound according to claim 23, wherein R^{70} = H.

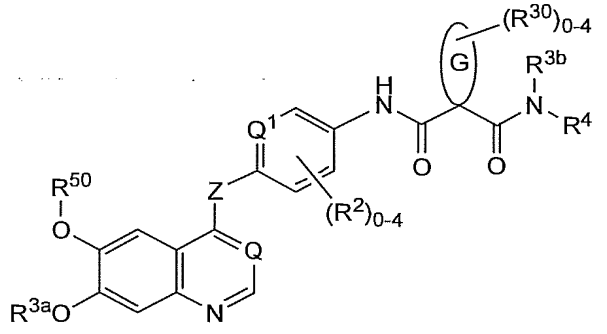
25. The compound according to claim 23, wherein at least one of R^1 is $-D-R^{50}$.

26. The compound according to claim 25, wherein D is -O- and at least one other R^1 is $-OR^3$.

27. The compound according to claim 26, of formula **XIIIa** or **XIIIb**:

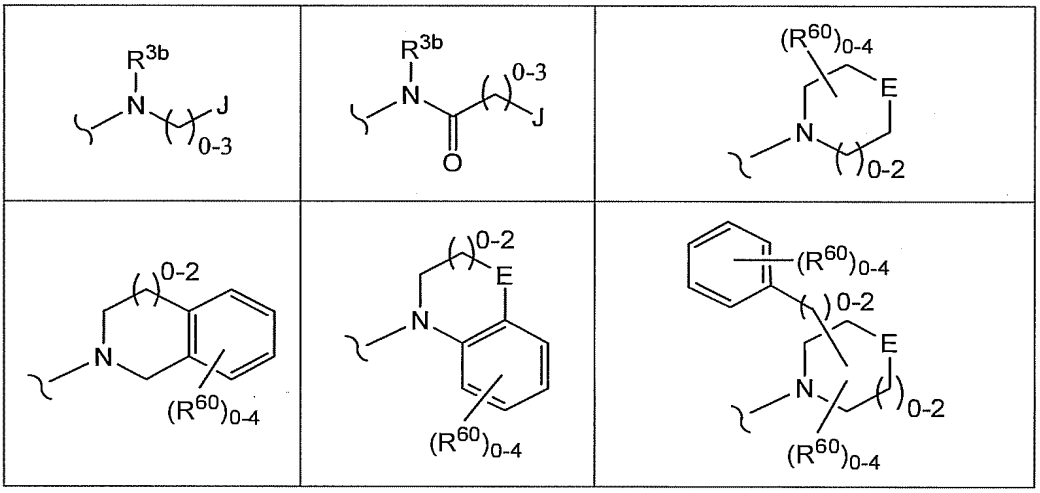


XIIIa



XIIIb

wherein Q^1 is either =N- or =C(H)-, R^{3a} is C_{1-6}alkyl, and -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}, wherein 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; or 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 one or two R^{25};

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; and

R^{3b} has the same meaning as R^3.

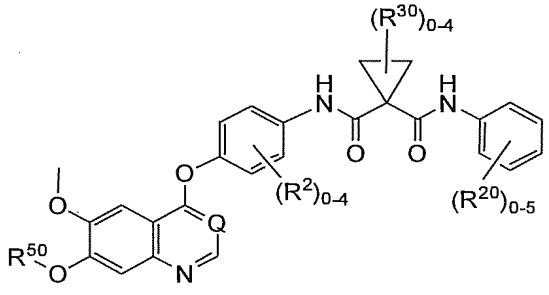
28. The compound according to claim 27, wherein R^{50} is selected from C_{1-6}alkyl optionally substituted with at least one of optionally substituted amino, optionally substituted C_{1-6}alkyl amino, optionally substituted C_{1-6}dialkyl amino, optionally substituted heteroalicylic, and a group of formula **XII**.

29. The compound according to claim 28, wherein G is selected from cyclopropyl, aziradine, cyclobutyl, and azetidine, each optionally substituted with between zero and four of R^{30}.

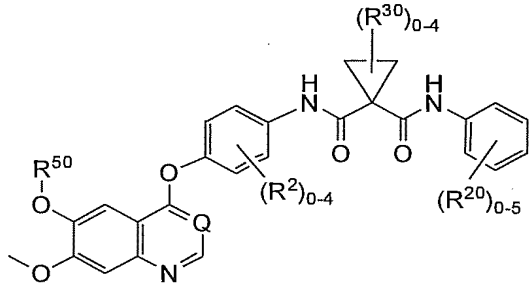
30. The compound according to claim 29, wherein R^2 is selected from -H, halogen, C_{1-6} alkyl and perfluoro C_{1-6} alkyl.

31. The compound according to claim 30, wherein $(R^{30})_{0-4}$ is $(R^{30})_0$ or methyl.

32. The compound according to claim 30, of formula **XIVa** or **XIVb**:



XIVa



XIVb

wherein R^{50} is unsubstituted C_{1-6}alkyl.

33. The compound according to claim 32, wherein Q is -CH=.

34. The compound according to claim 32, wherein $(R^{30})_{0-4} = (R^{30})_0$ or methyl.

35. The compound according to claim 32, wherein R^2 is selected from C_{1-6} alkyl, perfluoro C_{1-6} alkyl, hydrogen, and halogen.

36. The compound according to claim 32, wherein R^2 is hydrogen.

37. The compound according to claim 32, wherein R^2 is halogen.

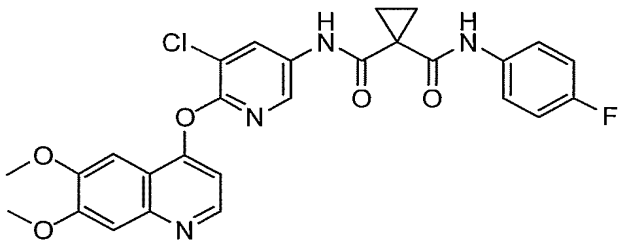
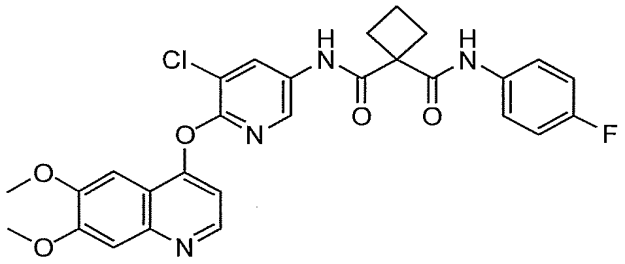
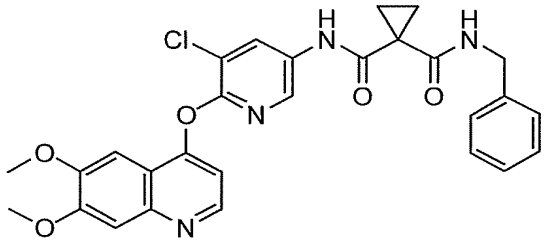
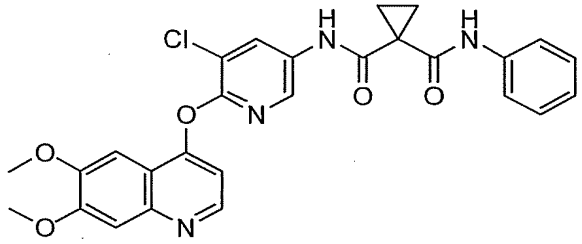
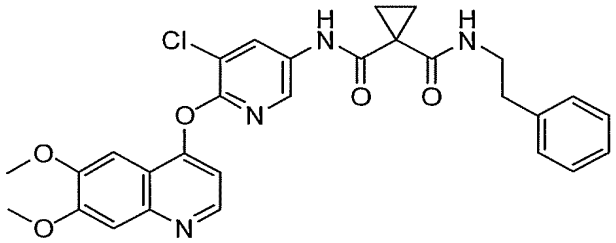
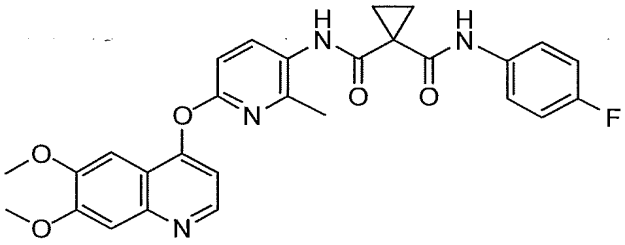
38. The compound according to claim 32, wherein R^{20} is selected from halogen, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, optionally substituted heterocyclyl, and optionally substituted heterocyclyl C_{1-6}alkyl, and (two of R^{20}) together with 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**.

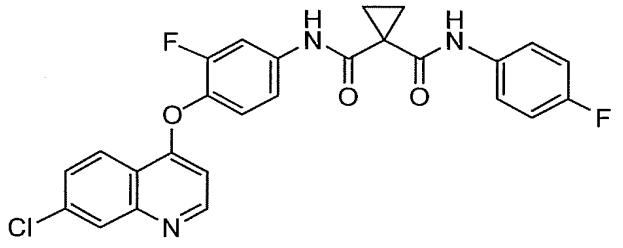
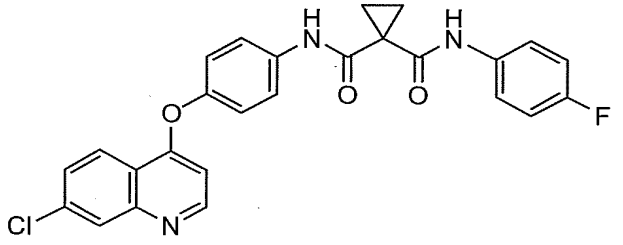
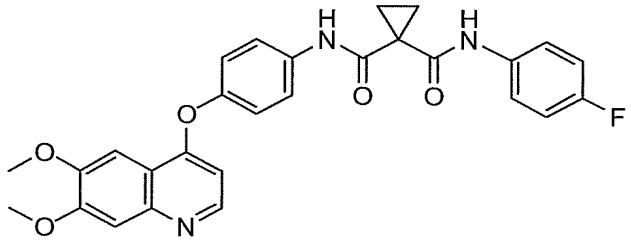
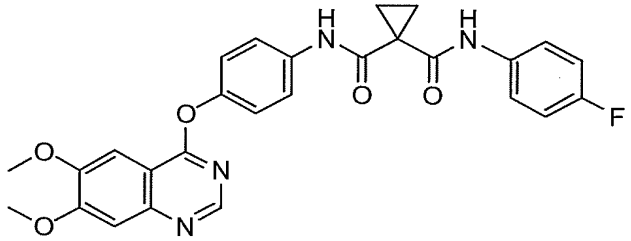
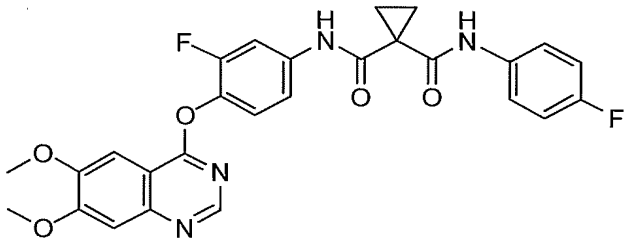
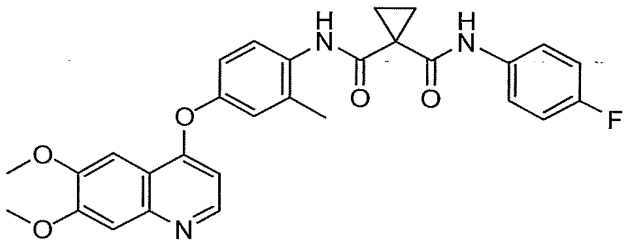
39. The compound according to claim 38, wherein R^{20} is selected from halogen, $-NR^3R^4$, optionally substituted heterocyclyl, and optionally substituted heterocyclyl C_{1-6}alkyl, and (two of R^{20}) together with the atom or atoms to which they are attached, an optionally substituted five- to six-membered heteroalicyclic, said optionally substituted five- to six-membered heteroalicyclic fused to the phenyl as in **XIVa** or **XIVb**.

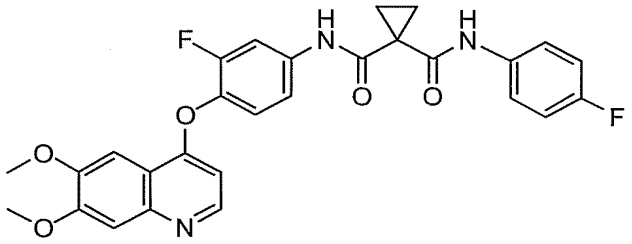
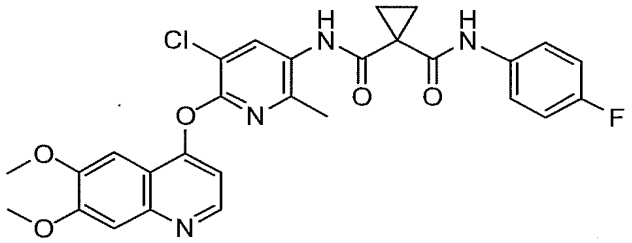
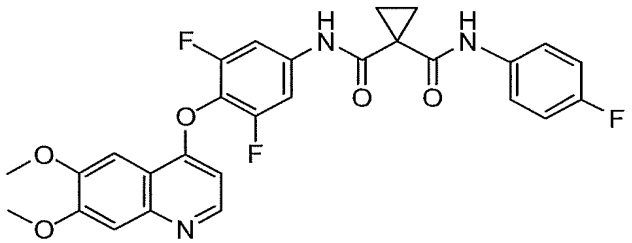
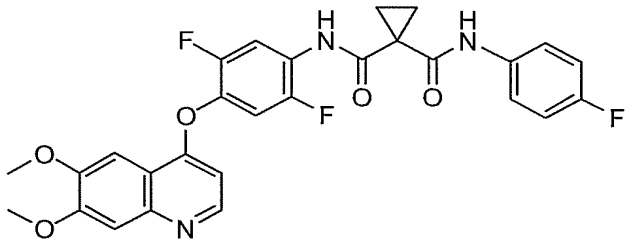
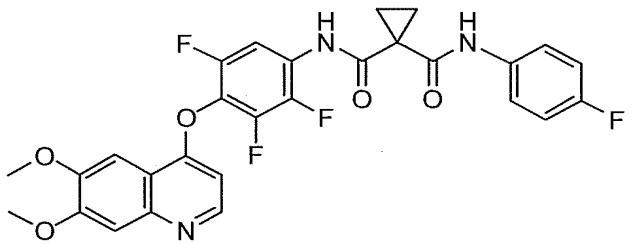
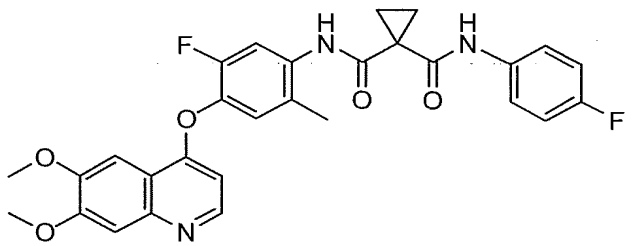
40. The compound according to claim 39, wherein R^2 is selected from C_{1-6} alkyl, perfluoro C_{1-6} alkyl, and halogen.

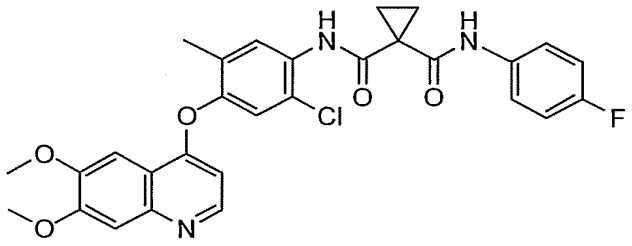
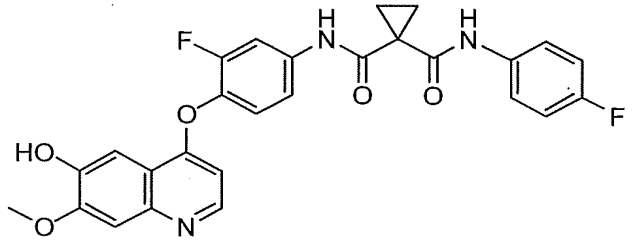
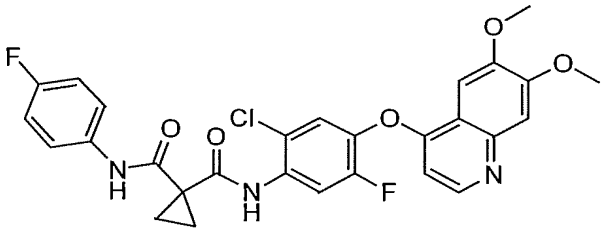
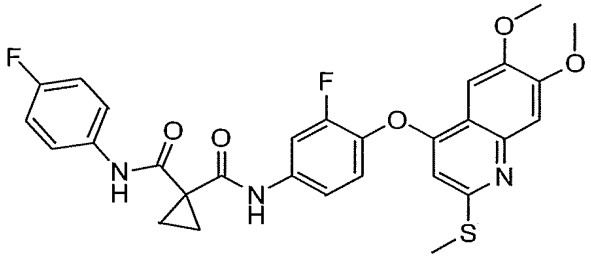
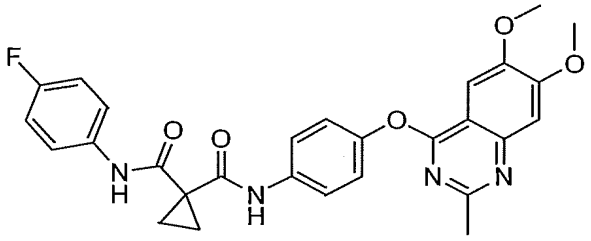
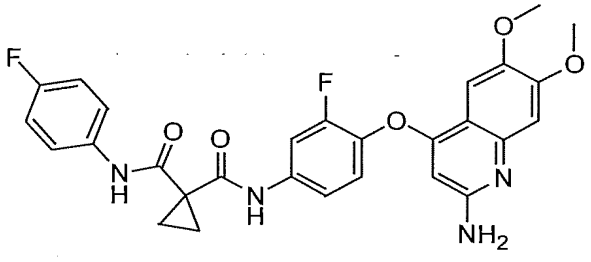
41. The compound according to claim 40, wherein R^2 is selected from perfluoro C_{1-3} alkyl and halogen.

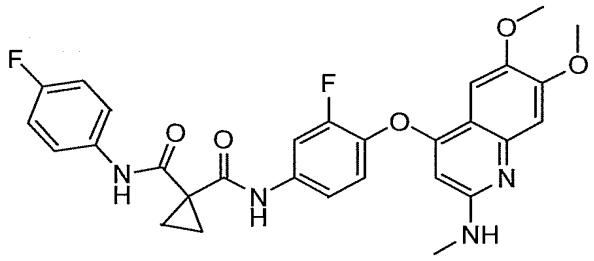
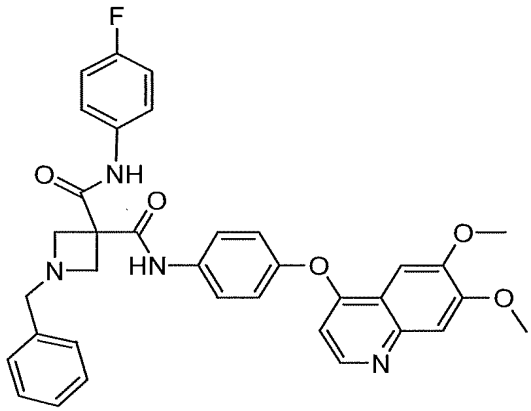
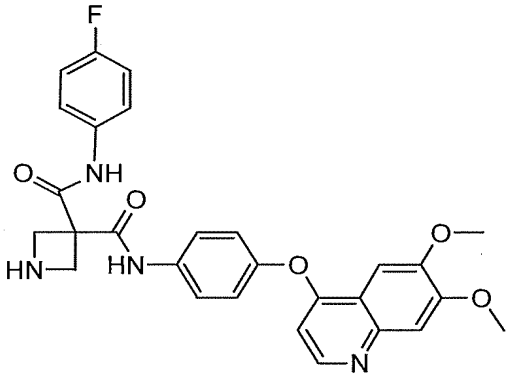
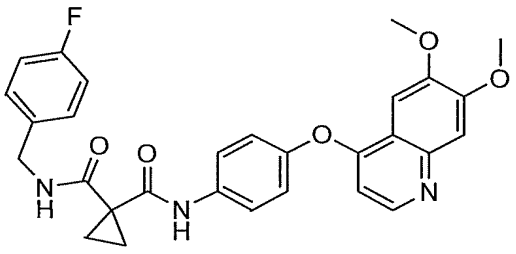
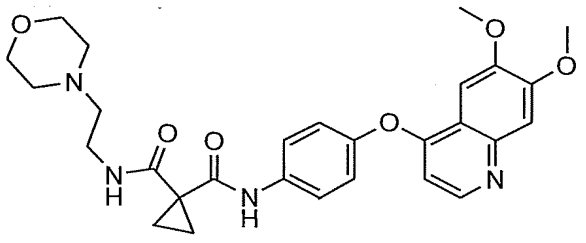
42. The compound according to claim 23 selected from the following:

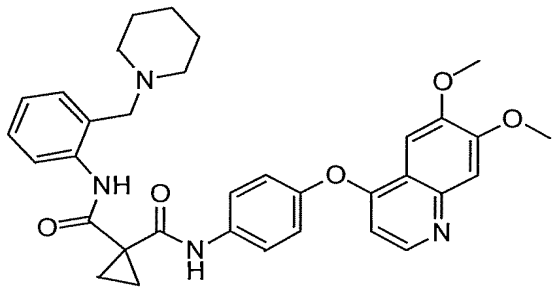
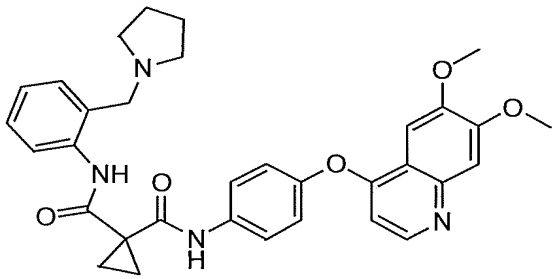
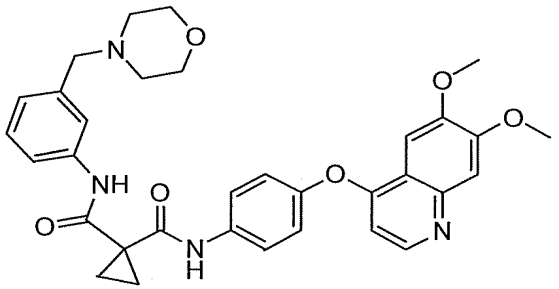
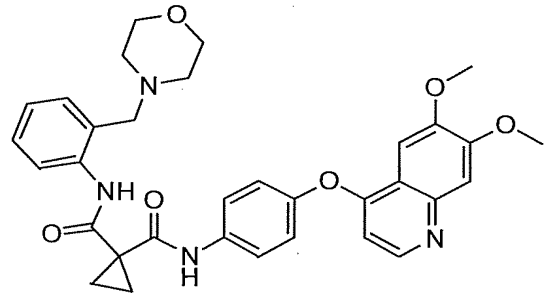
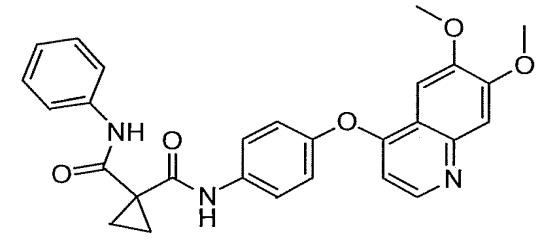
Name	Structure
N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl) cyclobutane-1,1-dicarboxamide	
N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(phenylmethyl) cyclopropane-1,1-dicarboxamide	
N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-phenylcyclopropane-1,1-dicarboxamide	
N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-phenylethyl) cyclopropane-1,1-dicarboxamide	
N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-methylpyridin-3-yl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	

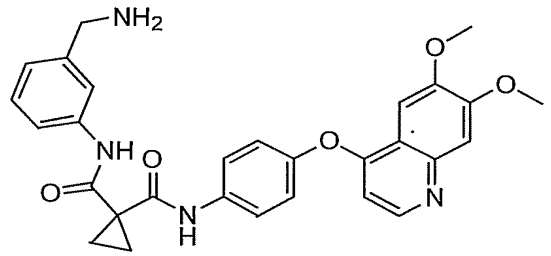
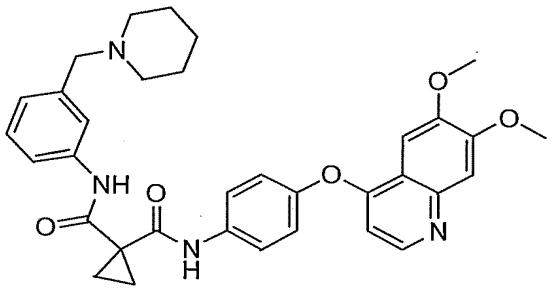
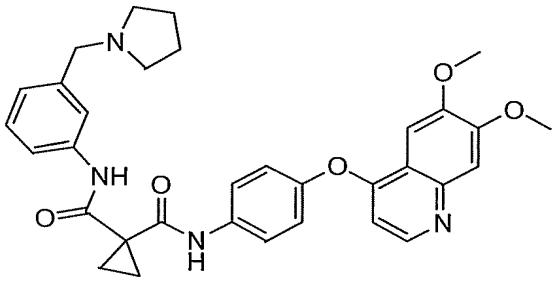
Name	Structure
N-{4-[(7-chloroquinolin-4-yl)oxy]-3-fluorophenyl}-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
N-{4-[(7-chloroquinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy) quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-methylphenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	

Name	Structure
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloro-2-methylpyridin-3-yl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3,5-difluorophenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2,5-difluorophenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2,3,5-trifluorophenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-2-methylphenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	

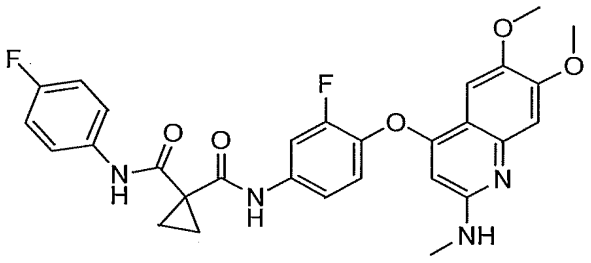
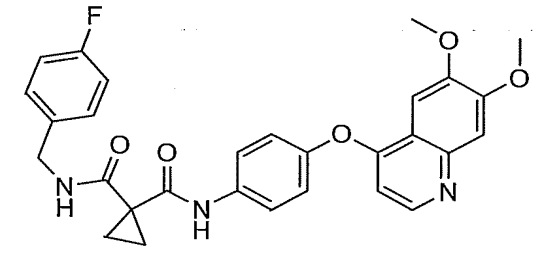
Name	Structure
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N-(3-fluoro-4-{[6-hydroxy-7-(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-chloro-5-fluorophenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)-2-(methylthio)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
N-(4-fluorophenyl)-N'-(4-{[2-methyl-6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl) cyclopropane-1,1-dicarboxamide	
N-(4-{[2-amino-6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	

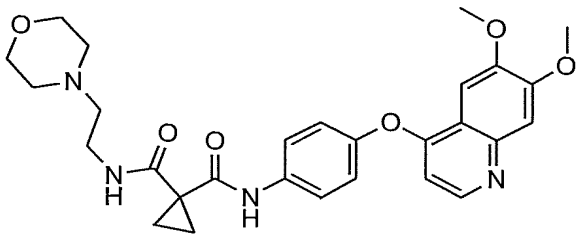
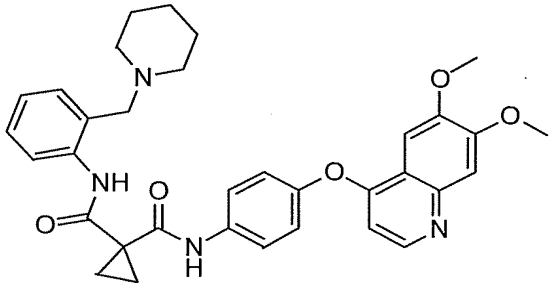
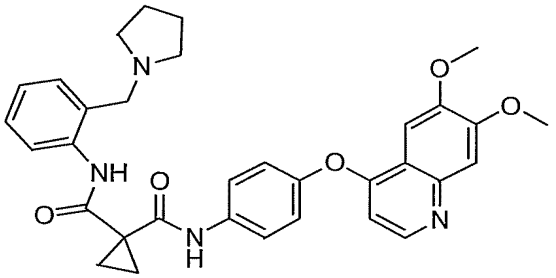
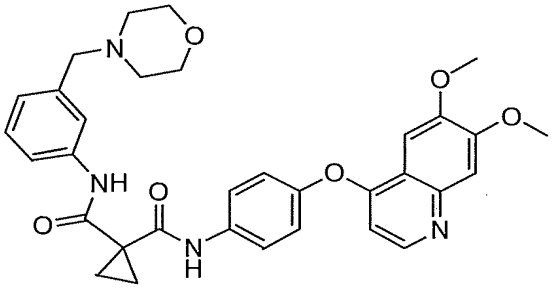
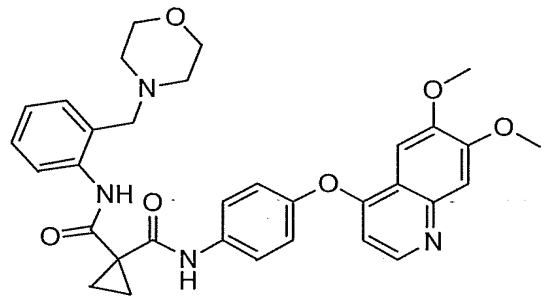
Name	Structure
N-(3-fluoro-4-{[2-(methylamino)-6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-1-(phenylmethyl)azetidine-3,3-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)azetidine-3,3-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[(4-fluorophenyl)methyl] cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(2-morpholin-4-ylethyl)cyclopropane-1,1-dicarboxamide	

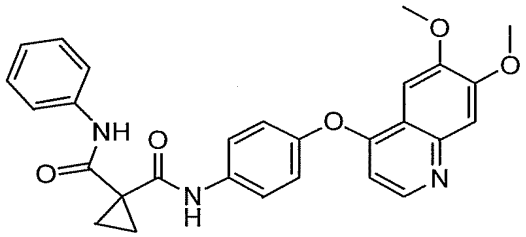
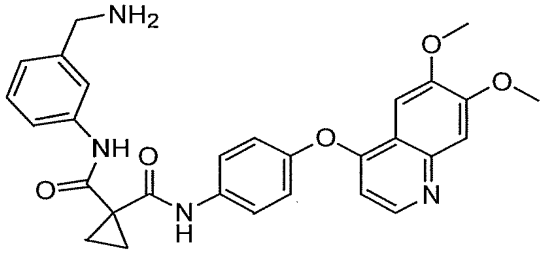
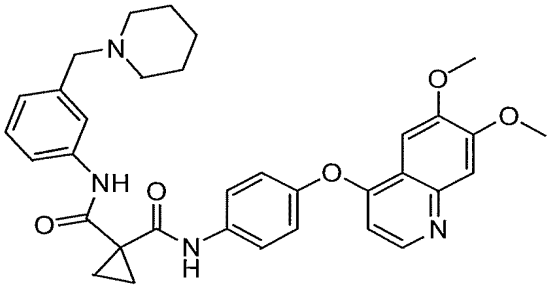
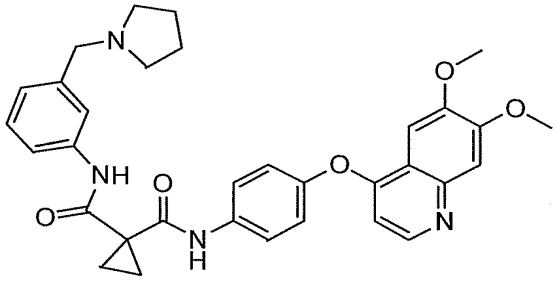
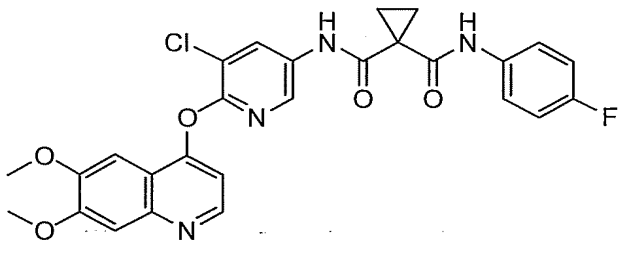
Name	Structure
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N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(pyrrolidin-1-ylmethyl) phenyl]cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(morpholin-4-ylmethyl) phenyl]cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(morpholin-4-ylmethyl) phenyl]cyclopropane-1,1-dicarboxamide	
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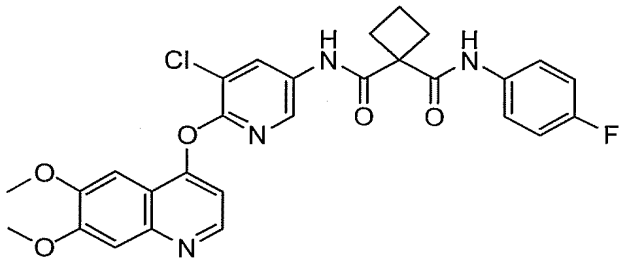
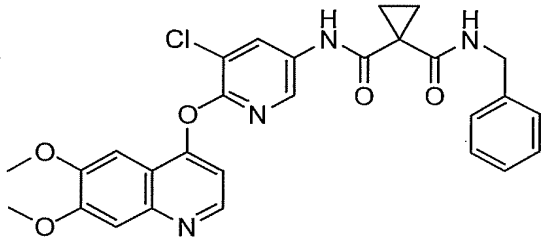
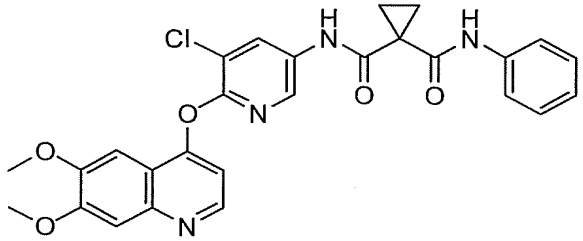
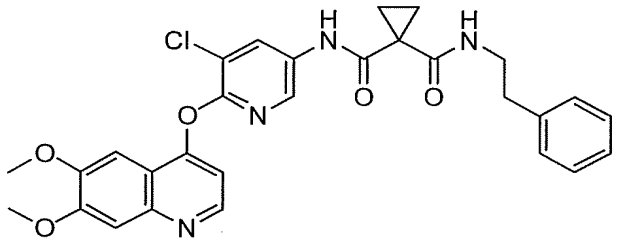
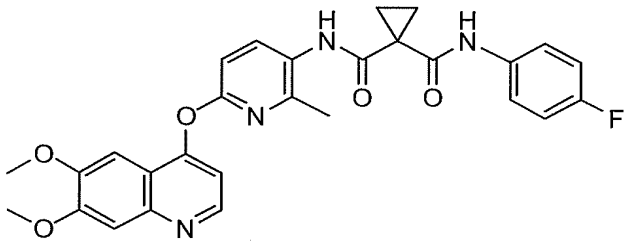
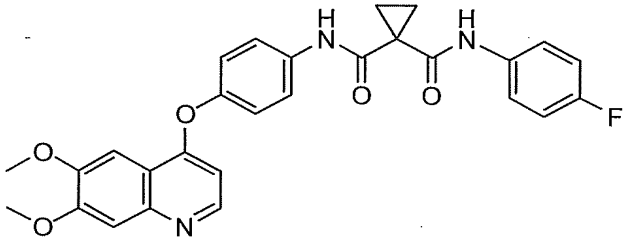
Name	Structure
N-[3-(aminomethyl) phenyl]-N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl) cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(piperidin-1-ylmethyl)phenyl] cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(pyrrolidin-1-ylmethyl)phenyl] cyclopropane-1,1-dicarboxamide	

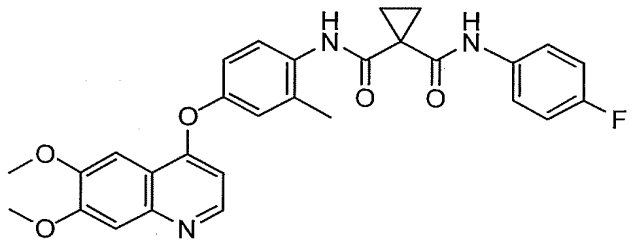
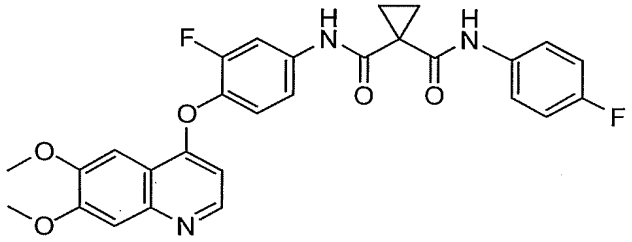
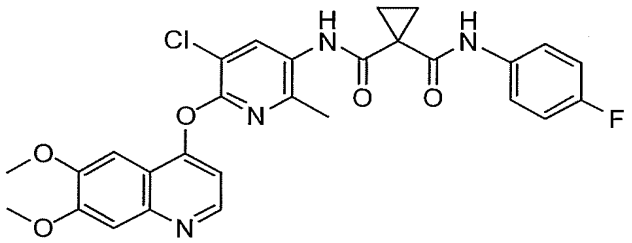
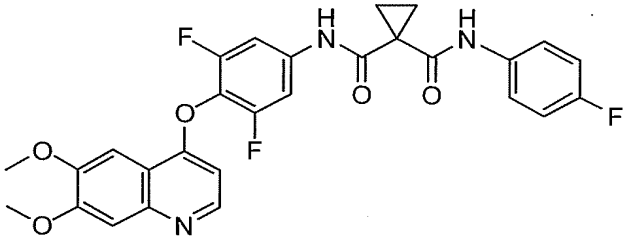
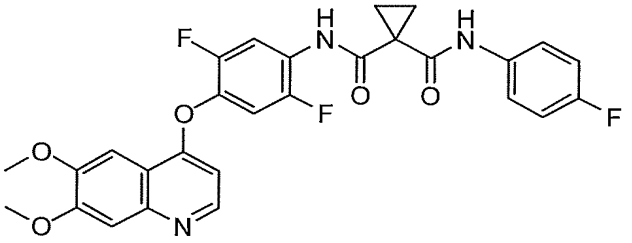
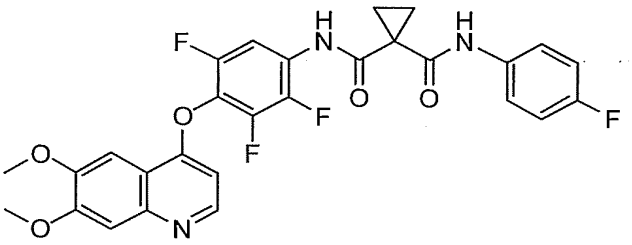
43. The compound according to claim 33 selected from the following:

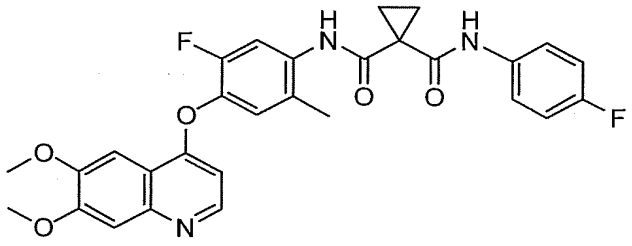
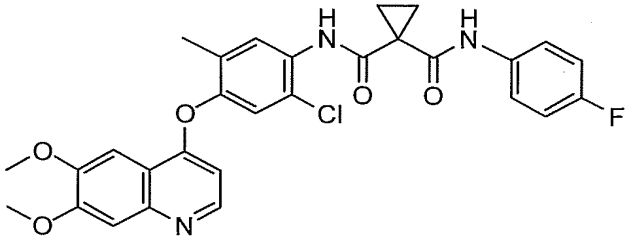
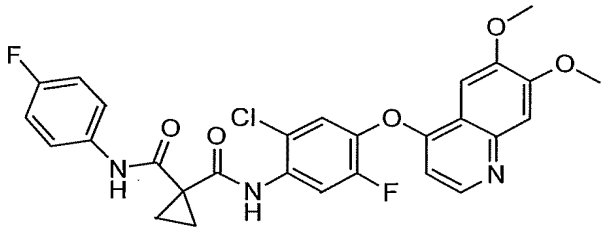
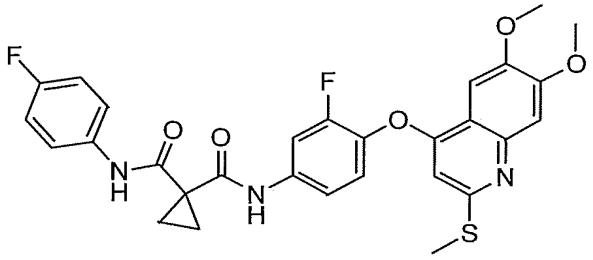
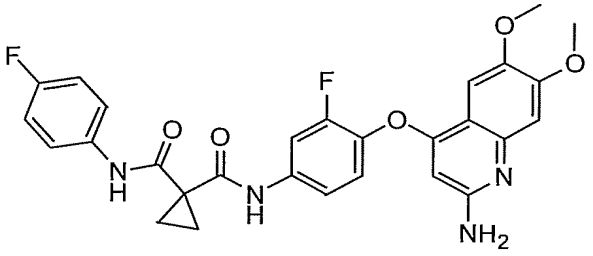
Name	Structure
N-(3-fluoro-4-{[2-(methylamino)-6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[(4-fluorophenyl)methyl] cyclopropane-1,1-dicarboxamide	

Name	Structure
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(2-morpholin-4-ylethyl)cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(piperidin-1-ylmethyl) phenyl]cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(pyrrolidin-1-ylmethyl) phenyl]cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(morpholin-4-ylmethyl) phenyl]cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(morpholin-4-ylmethyl) phenyl]cyclopropane-1,1-dicarboxamide	

Name	Structure
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-phenylcyclopropane-1,1-dicarboxamide	
N-[3-(aminomethyl)phenyl]-N'-(4-{[6,7-bis(methyloxy) quinolin-4-yl]oxy} phenyl)cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(piperidin-1-ylmethyl) phenyl]cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(pyrrolidin-1-ylmethyl) phenyl]cyclopropane-1,1-dicarboxamide	
N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	

Name	Structure
N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl) cyclobutane-1,1-dicarboxamide	
N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(phenylmethyl) cyclopropane-1,1-dicarboxamide	
N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-phenylcyclopropane-1,1-dicarboxamide	
N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-phenylethyl) cyclopropane-1,1-dicarboxamide	
N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-methylpyridin-3-yl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	

Name	Structure
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-methylphenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloro-2-methylpyridin-3-yl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3,5-difluorophenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2,5-difluorophenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2,3,5-trifluorophenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	

Name	Structure
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-2-methylphenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-chloro-5-methylphenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-chloro-5-fluorophenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)-2-(methylthio)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	
N-(4-{[2-amino-6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide	

44. A pharmaceutical composition comprising a compound according to claim 1, 15 or 23, and a pharmaceutically acceptable carrier.

45. A metabolite of the compound according to claim 1, 15 or 23.

46. A method of modulating the *in vivo* activity of a kinase, the method comprising administering to a subject a therapeutically effective amount of the compound according to claim 1, 15 or 23, or a composition containing a therapeutically effective amount of the compound.

47. The method according to claim 46, wherein modulating the *in vivo* activity of the kinase comprises inhibition of said kinase.

48. The method according to claim 46, wherein the kinase is at least one of c-Met, KDR, c-Kit, flt-3, or flt-4.

49. The method according to claim 48, wherein the kinase is c-Met.

50. 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 according to claim 1, 15 or 23, or a composition containing a therapeutically effective amount of the compound.

51. 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 comparing the kinase modulating activity of a compound according to claim 1, 15 or 23 with the modulating activity of at least one candidate agent and determining the relative effect of the candidate agent on the activity of said kinase.

52. A method of inhibiting proliferative activity in a cell, the method comprising administering an effective amount of a composition comprising a cell proliferation inhibiting-effective amount of a compound according to claim 1, 15 or 23 to a cell or a plurality of cells.



PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE THE APPLICATION OF :

Lynne Canne BANNEN et al.

USSN: 11/753,514 **FILING DATE:** August 24, 2007

GROUP ART UNIT: 1624 **CONFIRMATION NO.:** 5697

ENTITLED: C-MET MODULATORS AND METHODS OF USE

/

PRELIMINARY AMENDMENT

Commissioner for Patents
Post Office Box 1450
Washington, D.C. 22313-1450

Prior to the examination of the above-identified patent application, please enter the following amendments and consider the following remarks. No new matter is added and support for the changes can be found throughout the Specification.

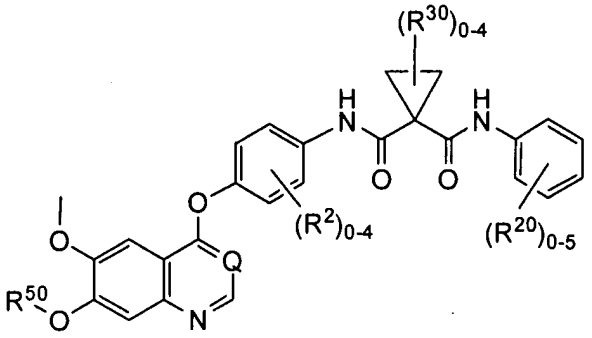
Amendments to the Claims are reflected in the listing of the claims which begin on page 2 of this paper.

Remarks/Arguments begin on page 5 of this paper.

AMENDMENTS TO THE CLAIMS

1-54. (cancelled)

55. (New) A compound according to formula **XIVa**:



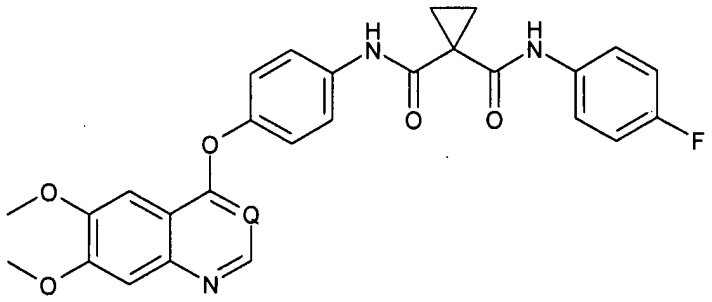
XIVa

or a pharmaceutically acceptable salt thereof, wherein:

Q is N or CH; $(R^{30})_{0-4}$ is $(R^{30})_0$; R^2 is halo; R^{20} is halo; and R^{50} is aan unsubstituted C_{1-6}alkyl group.

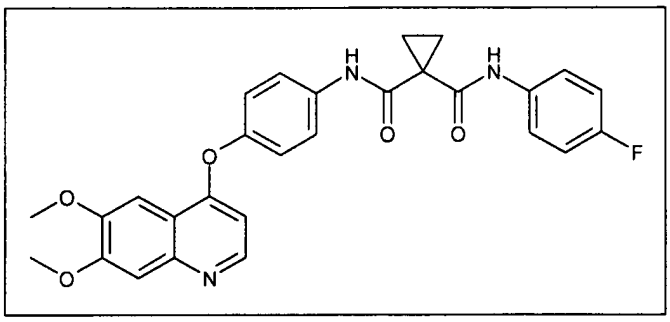
56. (New) The compound according to claim 55, or a pharmaceutically acceptable salt thereof, wherein Q is CH; $(R^2)_{0-4}$ is $(R^2)_0$; and R^{20} is chloro or fluoro.

57. (New) The compound according to claim 55 which is represented by the following structure:



or a pharmaceutically acceptable salt thereof.

58. (New) A compound which is represented by the following structure:



or a pharmaceutically acceptable salt thereof.

59. (New) A pharmaceutical composition comprising a compound according to claim 55 or a pharmaceutically acceptable salt thereof.

60. (New) A pharmaceutical composition comprising a compound according to claim 58 or a pharmaceutically acceptable salt thereof.

61. (New) The pharmaceutical composition of Claim 59 which further includes an excipient.

62. (New) The pharmaceutical composition of Claim 60 which further includes an excipient.

63. (New) A method of treating a disease or disorder, comprising administering to a mammal in need of the treatment a therapeutically effective amount of the compound according to claim 55 or a pharmaceutically acceptable salt thereof, or a composition containing a) a therapeutically effective amount of the compound or a pharmaceutically acceptable salt thereof; and optionally a b) an excipient, wherein the disease or disorder is stomach cancer, esophageal carcinoma, kidney cancer, liver cancer, ovarian carcinoma, cervical carcinoma, large bowel cancer, small bowel cancer, brain cancer, lung cancer, bone cancer, prostate carcinoma, pancreatic carcinoma, skin cancer, bone cancer, Hodgkin's disease, or non-Hodgkin's lymphoma.

64. (New) A method of treating a disease or disorder, comprising administering to a mammal in need of the treatment a therapeutically effective amount of the compound according to claim 58 or a pharmaceutically acceptable salt thereof, or a

composition containing a) a therapeutically effective amount of the compound or a pharmaceutically acceptable salt thereof; and optionally b) an excipient, wherein the disease or disorder is stomach cancer, esophageal carcinoma, kidney cancer, liver cancer, ovarian carcinoma, cervical carcinoma, large bowel cancer, small bowel cancer, brain cancer, lung cancer, bone cancer, prostate carcinoma, pancreatic carcinoma, skin cancer, bone cancer, Hodgkin's disease, or non-Hodgkin's lymphoma.

REMARKS /ARGUMENTS

The claims have been amended to expedite prosecution. All new claims in this amendment are fully supported by the specification as originally filed. Referring to published parent U.S. patent application US 2007/0054928 A1, the compound of formula XIVa in new claim 55 is described in the specification on page 100, paragraph 126; the fluoro and chloro groups within the definition of R^{20} in new claim 56 are described within the definition of the term "halogen or halo" on page 140, paragraph 258 of the specification; moreover, the fluoro and chloro groups at the R^{20} position appear numerous times in the list of compounds in Table 2 of the specification starting on page 102, paragraph 165; the term "excipient" in new claims 61-64 is described on page 144, paragraph 298 of the specification; and the list of diseases in new claims 63 and 64 are described on pages 142-143 in paragraph 285 of the specification.

No new matter has been added. The Applicants respectfully request that the amendments and new claims be entered into the record.

In view of the amendments to the claims, Applicants bring to the Examiner's attention US 2004/0242603 (the published application of U.S. Serial No. 10/480,632), which is being submitted in an IDS along with this preliminary amendment. US 2004/0242603 is the U.S. counterpart of international patent application WO 03/000660, which was previously filed in the IDS for this patent application.

It is believed that no fees are required with the submission of this preliminary

amendment, however, should a fee be necessary, the Commissioner is hereby authorized to charge any necessary fee to Deposit Account Number 50-1108.

Respectfully submitted,

January 29, 2008
Date

Robert L. Bernstein
Attorney for the Applicants
Reg. No. 46,020

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Total Number of Pages in This Submission	-8-

Application Number	11/753,514
Filing Date	05-24-2007
First Named Inventor	Lynne Canne BANNEN
Art Unit	1624
Examiner Name	TBA
Attorney Docket Number	257263/EX04-064C3

ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
  - ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☑ Other Enclosure(s) (please Identify below):
  1) Second Preliminary Amendment (7 pages);
  2) Postal Card for Acknowledgment of Receipt.

Remarks

This submission was transmitted via United States Postal Service, using Express Mail, Post Office to Addressee service and assigned tracking number EV 938 354 395 US.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	EXELIXIS, Inc.		
Signature	Robert L. Bernstein		
Printed name	Robert L. Bernstein		
Date	May 13, 2008	Reg. No.	46,020

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as ~~first class~~ express mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below:

Signature	Laura A. Huntington		
Typed or printed name	Laura A. Huntington	Date	May 13, 2008

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OIPE IAP22
MAY 13 2008
PATENT & TRADEMARK OFFICE

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE THE APPLICATION OF :

Lynne Canne BANNEN et al.

USSN: 11/753,514 **FILING DATE:** May 24, 2007

GROUP ART UNIT: 1624 **CONFIRMATION NO.:** 5697

ENTITLED: C-MET MODULATORS AND METHODS OF USE

/

PRELIMINARY AMENDMENT

Commissioner for Patents
Post Office Box 1450
Washington, D.C. 22313-1450

Prior to the examination of the above-identified patent application, please enter the following amendments and consider the following remarks. No new matter is added and support for the changes can be found throughout the Specification.

Amendments to the Specification begin at the top of page 2 of this paper.

Amendments to the Claims are reflected in the listing of the claims which begin on page 3 of this paper.

Remarks/Arguments begin on page 7 of this paper.

AMENDMENTS TO THE SPECIFICATION

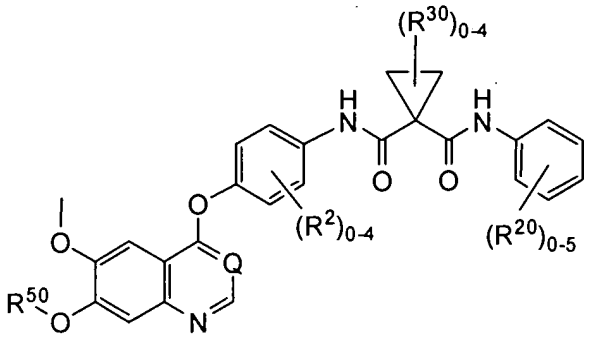
Please replace the title located at the top of page 1 of the specification with the following new title:

c-Met Modulators and Methods of Use

AMENDMENTS TO THE CLAIMS

1-64. (cancelled)

65. (New) A compound according to formula **XIVa**:



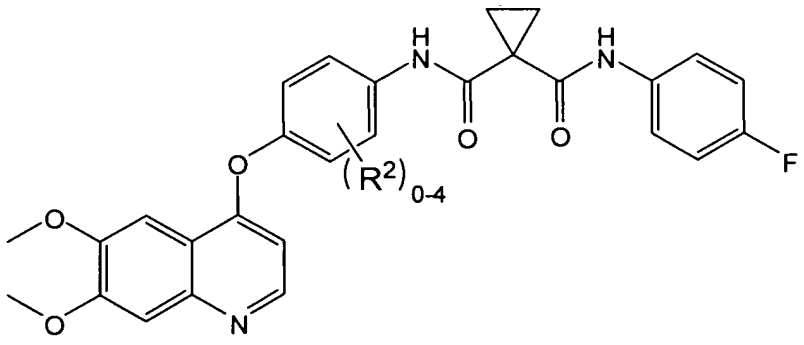
XIVa

or a pharmaceutically acceptable salt thereof, wherein:

Q is N or CH; $(R^{30})_{0-4}$ is $(R^{30})_0$; R^2 is -H or halo; R^{20} is halo; and R^{50} is an unsubstituted C_{1-6}alkyl group.

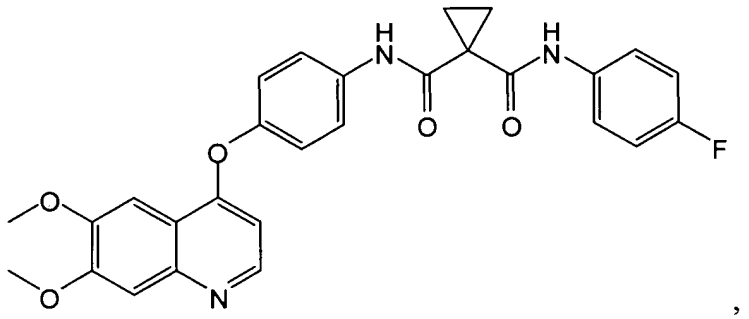
66. (New) The compound according to claim 65, or a pharmaceutically acceptable salt thereof, wherein Q is CH; R^2 is -H or fluoro; and R^{20} is chloro or fluoro.

67. (New) The compound according to claim 66 which is represented by the following structure:

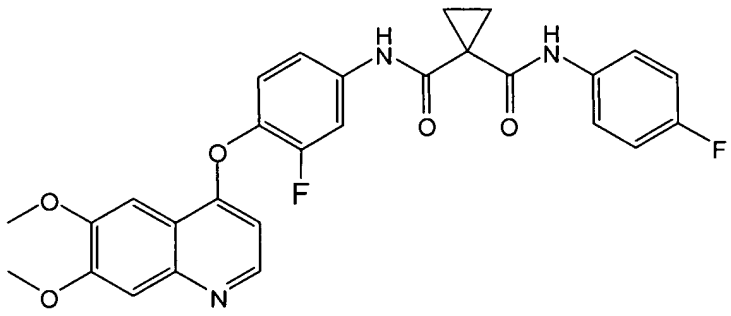


or a pharmaceutically acceptable salt thereof.

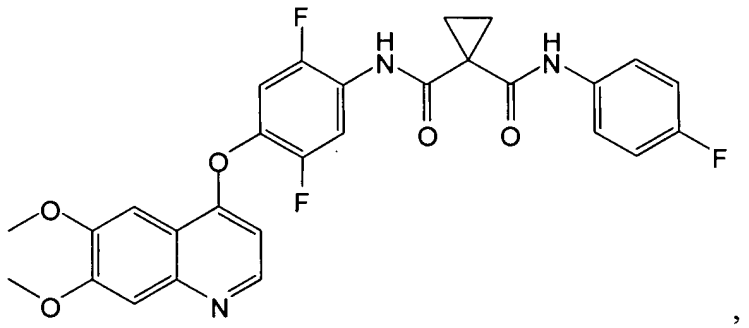
68. (New) A compound according to claim 67 which is represented by one of the following structures:



,



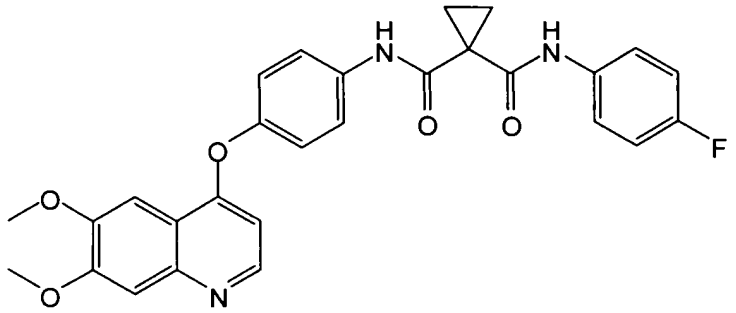
or



,

or a pharmaceutically acceptable salt of any of the above structures.

69. (New) A compound represented by the following structure:



or a pharmaceutically acceptable salt thereof.

70. (New) A pharmaceutical composition comprising a compound according to claim 65 or a pharmaceutically acceptable salt thereof.

71. (New) A pharmaceutical composition comprising a compound according to claim 69 or a pharmaceutically acceptable salt thereof.

72. (New) The pharmaceutical composition of Claim 70 which further includes an excipient.

73. (New) The pharmaceutical composition of Claim 71 which further includes an excipient.

74. (New) A method of treating a disease or disorder, comprising administering to a mammal in need of the treatment a therapeutically effective amount of the compound according to claim 65 or a pharmaceutically acceptable salt thereof, or a composition containing a) a therapeutically effective amount of the compound or a pharmaceutically acceptable salt thereof; and optionally a b) an excipient, wherein the disease or disorder is stomach cancer, esophageal carcinoma, kidney cancer, liver cancer, ovarian carcinoma, cervical carcinoma, large bowel cancer, small bowel cancer, brain cancer, lung cancer, bone cancer, prostate carcinoma, pancreatic carcinoma, skin cancer, bone cancer, Hodgkin's disease, or non-Hodgkin's lymphoma.

75. (New) A method of treating a disease or disorder, comprising administering to a mammal in need of the treatment a therapeutically effective amount of

the compound according to claim 69 or a pharmaceutically acceptable salt thereof, or a composition containing a) a therapeutically effective amount of the compound or a pharmaceutically acceptable salt thereof; and optionally b) an excipient, wherein the disease or disorder is stomach cancer, esophageal carcinoma, kidney cancer, liver cancer, ovarian carcinoma, cervical carcinoma, large bowel cancer, small bowel cancer, brain cancer, lung cancer, bone cancer, prostate carcinoma, pancreatic carcinoma, skin cancer, bone cancer, Hodgkin's disease, or non-Hodgkin's lymphoma.

REMARKS /ARGUMENTS

The claims and specification have been amended to expedite prosecution. The title in the specification has been amended to better describe the contents of the specification.

All new claims in this amendment are fully supported by the specification as originally filed. Referring to published parent U.S. patent application US 2007/0054928 A1, the compound of formula XIVa in new claim 65 is described in the specification on page 100, paragraph 126; in new claim 66, the fluoro group within the definition of R^2, and the fluoro and chloro groups within the definition of R^{20} are described within the definition of the term "halogen or halo" on page 140, paragraph 258 of the specification; moreover, the fluoro group at the R^2 position, and the fluoro and chloro groups at the R^{20} position appear numerous times in the list of compounds in Table 2 of the specification starting on page 102, paragraph 165; the term "excipient" in new claims 72-75 is described on page 144, paragraph 298 of the specification; and the list of diseases in new claims 74 and 75 are described on pages 142-143 in paragraph 285 of the specification.

No new matter has been added. The Applicants respectfully request that the amendments and new claims be entered into the record.

It is believed that no fees are required with the submission of this preliminary amendment, however, should a fee be necessary, the Commissioner is hereby authorized to charge any necessary fee to Deposit Account Number 50-1108.

Respectfully submitted,

May 13, 2008
Date

Robert L. Bernstein
Attorney for the Applicants
Reg. No. 46,020

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE THE APPLICATION OF :

Lynne Canne BANNEN et al.

USSN: 11/753,514 FILING DATE: August 24, 2007

GROUP ART UNIT: 1624 CONFIRMATION NO.: 5697

ENTITLED: C-MET MODULATORS AND METHODS OF USE

/

THIRD PRELIMINARY AMENDMENT

Commissioner for Patents
Post Office Box 1450
Washington, D.C. 22313-1450

Prior to the examination of the above-identified patent application, please enter the following amendments and consider the following remarks. No new matter is added and support for the changes can be found throughout the Specification.

Amendments to the Claims are reflected in the listing of the claims which begin on page 2 of this paper.

Remarks/Arguments begin on page 6 of this paper.

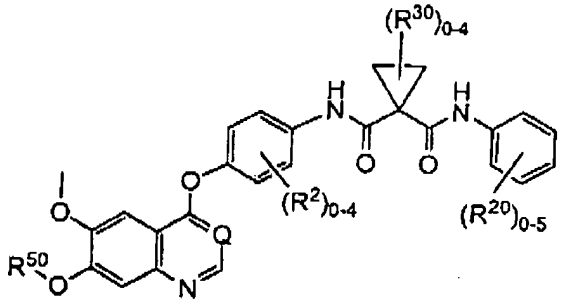
PAGE 3/8 * RCVD AT 4/22/2009 9:32:58 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-6/29 * DNIS:2738300 * CSID: * DURATION (mm-ss):03-16

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AMENDMENTS TO THE CLAIMS

1-64. (cancelled)

65. (Previously presented) A compound according to formula **XIVa**:



XIVa

or a pharmaceutically acceptable salt thereof, wherein:

Q is N or CH; $(R^{30})_{0-4}$ is $(R^{30})_0$; R^2 is H or halo; R^{20} is halo; and R^{50} is an unsubstituted C_{1-6}alkyl group.

66. (Cancelled)

67. (Cancelled)

68. (Cancelled)

69. (Cancelled)

70. (Previously presented) A pharmaceutical composition comprising a compound according to claim 65 or a pharmaceutically acceptable salt thereof.

71. (Cancelled)

72. (Previously presented) The pharmaceutical composition of Claim 70 which further includes an excipient.

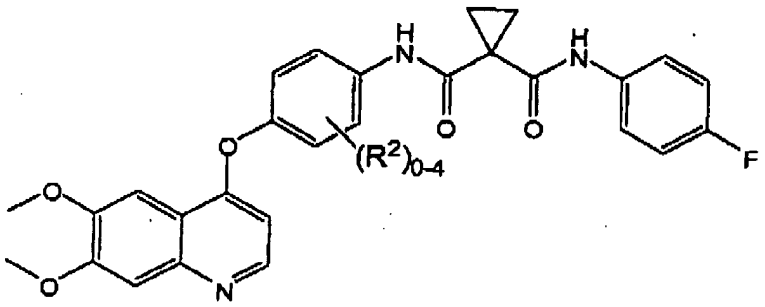
73. (Cancelled)

74. (Currently amended) A method of treating a disease or disorder, comprising administering to a mammal in need of the treatment a therapeutically effective amount of the compound according to claim 65 or a pharmaceutically acceptable salt thereof, or a composition containing a) a therapeutically effective amount of the compound or a pharmaceutically acceptable salt thereof; and optionally a b) an excipient, wherein the disease or disorder is stomach cancer, esophageal carcinoma, kidney cancer, liver cancer, ovarian carcinoma, cervical carcinoma, large bowel cancer, small bowel cancer, brain cancer, lung cancer, bone cancer, prostate carcinoma, pancreatic carcinoma, skin cancer, ~~bone cancer~~, Hodgkin's disease, or non-Hodgkin's lymphoma.

75. (Cancelled)

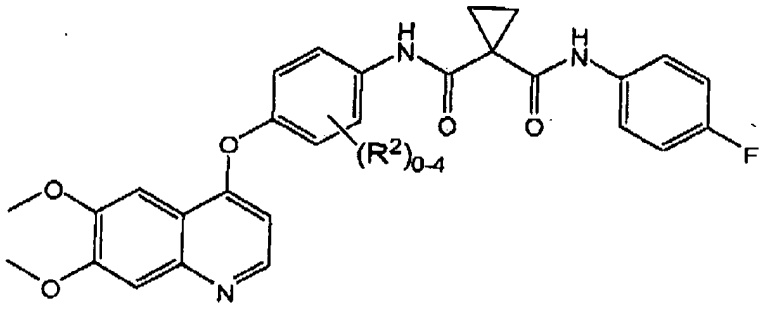
76. (New) The method according to claim 74, wherein Q is CH; (R^2) is -H or fluoro; and R^{20} is chloro or fluoro.

77. (New) The method according to claim 74, wherein the compound is represented by the following structure:



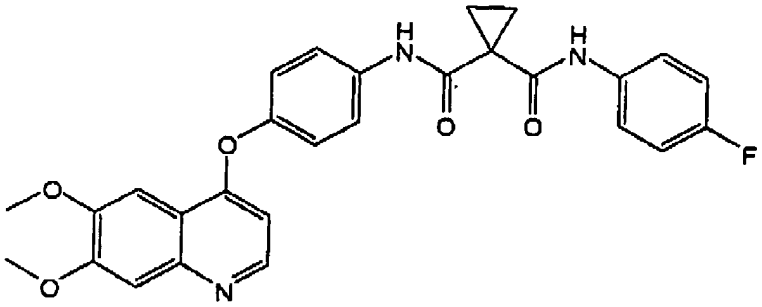
or a pharmaceutically acceptable salt thereof.

78. (New) The method according to claim 74, wherein the compound is represented by the following structure:



or a pharmaceutically acceptable salt thereof.

79. (New) A method of treating a disease or disorder, comprising administering to a mammal in need of the treatment a therapeutically effective amount of a compound according to the following structure:



or a pharmaceutically acceptable salt thereof, or a composition containing a) a therapeutically effective amount of the compound or a pharmaceutically acceptable salt thereof; and optionally b) an excipient, wherein the disease or disorder is stomach cancer, esophageal carcinoma, kidney cancer, liver cancer, ovarian carcinoma, cervical carcinoma, large bowel cancer, small bowel cancer, brain cancer, lung cancer, bone cancer, prostate carcinoma, pancreatic carcinoma, skin cancer, Hodgkin's disease, or non-Hodgkin's lymphoma.

80. (New) The method according to claim 79, wherein the disease or disorder is brain cancer.

81. (New) The method according to claim 80, wherein the brain cancer is glioma or glioblastoma.

82. (New) The method according to claim 79, wherein the disease or disorder is lung cancer.

REMARKS /ARGUMENTS

The claims have been amended to expedite prosecution. All claims in this amendment are fully supported by the specification as originally filed. Referring to published parent U.S. patent application US 2007/0054928 A1, the compound of formula XIVa in claim 65 is described in the specification on page 100, paragraph 126; the fluoro and chloro groups within the definition of R^{20} in new claim 76 are described within the definition of the term "halogen or halo" on page 140, paragraph 258 of the specification; moreover, the fluoro and chloro groups at the R^{20} position appear numerous times in the list of compounds in Table 2 of the specification starting on page 102, paragraph 165; the term "excipient" in claims 72 and 74 is described on page 144, paragraph 298 of the specification; and the list of diseases in claims 74 and 79 are described on pages 142-143 in paragraph 285 of the specification.

No new matter has been added. The Applicants respectfully request that the amendments and new claims be entered into the record.

It is believed that no fees are required with the submission of this preliminary amendment, however, should a fee be necessary, the Commissioner is hereby authorized to charge any necessary fee to Deposit Account Number 50-1108.

Respectfully submitted,

April 22, 2009
Date

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
11/753,514	05/24/2007	LYNNE CANNE BANNEN	257263/EX04-064C3

CONFIRMATION NO. 5697

23460
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TWO PRUDENTIAL PLAZA, SUITE 4900
180 NORTH STETSON AVENUE
CHICAGO, IL 60601-6731

PUBLICATION NOTICE

OC000000035630996

Title:c-MET MODULATORS AND METHODS OF USE

Publication No.US-2009-0105299-A1
Publication Date:04/23/2009

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 (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, 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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE THE APPLICATION OF :

Lynne Canne BANNEN et al.

USSN: 11/753,514 **FILING DATE:** August 24, 2007

GROUP ART UNIT: 1624 **CONFIRMATION NO.:** 5697

ENTITLED: C-MET MODULATORS AND METHODS OF USE

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FOURTH PRELIMINARY AMENDMENT

Commissioner for Patents
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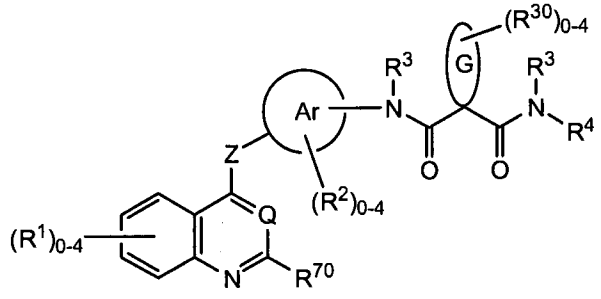
Prior to the examination of the above-identified patent application, please enter the following amendments and consider the following remarks. No new matter is added. Support for these amendments can be found throughout the Specification as originally filed.

Amendments to the Claims are reflected in the listing of the claims which begin on page 2 of this paper.

Remarks begin on page 18 of this paper.

Claims 1-82. (cancelled)

83. (New) A compound for modulating kinase activity according to Formula **XI**,



XI

or a pharmaceutically acceptable salt thereof, wherein,

each R^1 is independently selected from halo, -OH, $-NO_2$, $-NH_2$, $-NR^3R^4$, $-D-R^{50}$ and unsubstituted C_{1-6}alkyl;

R^{70} is selected from -H, halo, $-OR^3$, $-S(O)_{0-2}R^3$, $-NO_2$, $-NH_2$, $-NR^3R^4$, 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 halo, 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 unsubstituted C_{1-6}alkyl; 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,
wherein, when an alkyl, aryl or heterocyclyl group is substituted, one or more hydrogen atoms are replaced by a substituent independently selected from: alkyl, aryl, arylalkyl, heterocyclylalkyl, heterocyclyl, alkoxy, alkylenedioxy, amino, amidino, aryloxy, arylalkyloxy, carboxy, carboalkoxy, carboxyalkyl, carboxamido, benzyloxycarbonylamino, cyano, acyl, halo, nitro, sulfanyl, sulfinyl, sulfonyl, thiol, hydroxy, oxo, carbamyl, acylamino, and sulfonamido.

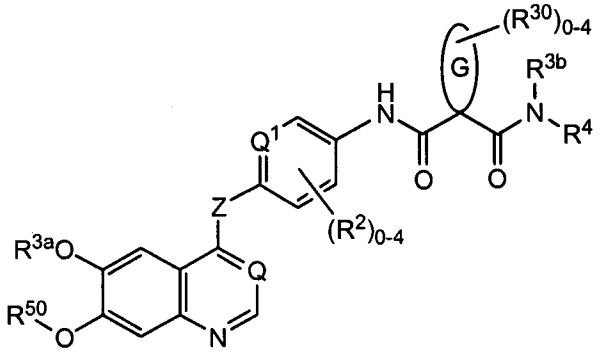
84. (New) The compound according to claim 83, wherein Z is either -O- or $-NR^5-$.

85. (New) The compound according to claim 84, wherein at least one of R^1 is

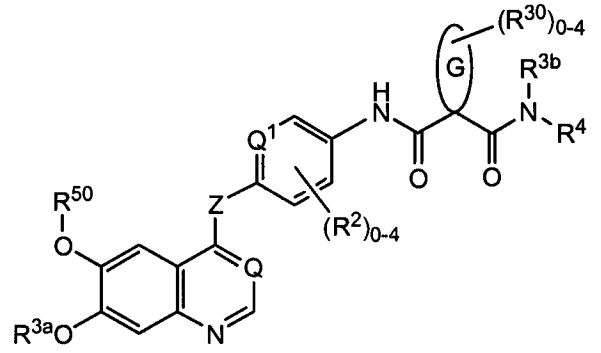
$-D-R^{50}$.

86. (New) The compound according to claim 85, wherein D is -O-.

87. (New) A compound according to formula **XIIIa** or **XIIIb**:



XIIIa



XIIIb

wherein Q^1 is either =N- or =C(H)-;

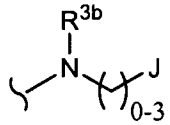
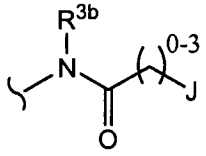
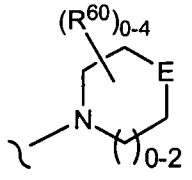
each R^2 is independently selected from halo, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted C_{1-6}alkyl;

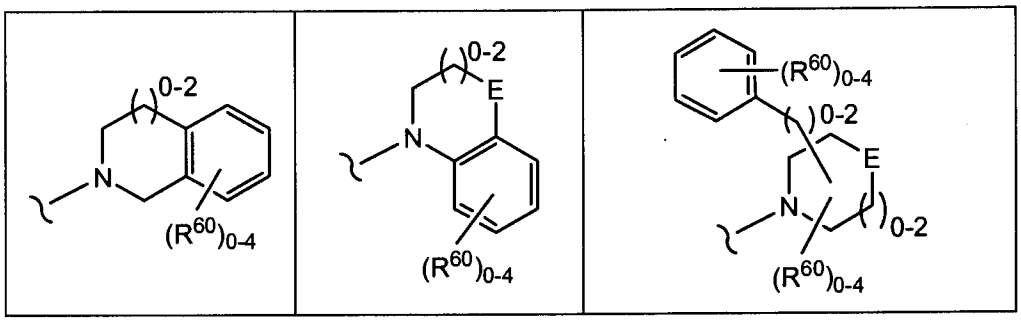
R^{3a} is C_{1-6}alkyl;

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;

$-N(R^{3b})R^4$ 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;

and R^{3b} is equivalent to R^3 as defined above;

wherein, when an alkyl, aryl or heterocyclyl group is substituted, one or more hydrogen atoms are replaced by a substituent independently selected from: alkyl, aryl, arylalkyl, heterocyclylalkyl, heterocyclyl, alkoxy, alkylenedioxy, amino, amidino, aryloxy, arylalkyloxy, carboxy, carboalkoxy, carboxyalkyl, carboxamido, benzyloxycarbonylamino, cyano, acyl, halo, nitro, sulfanyl, sulfinyl, sulfonyl, thiol, hydroxy, oxo, carbamyl, acylamino, and sulfonamido.

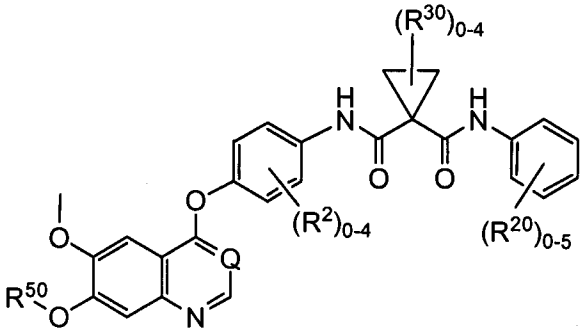
88. (New) The compound according to claim 87, wherein Z is -O-.

89. (New) The compound according to claim 88, wherein G is selec2ted from cyclopropyl, aziradine, cyclobutyl, and azetidine, each optionally substituted with between zero and four of R^{30}.

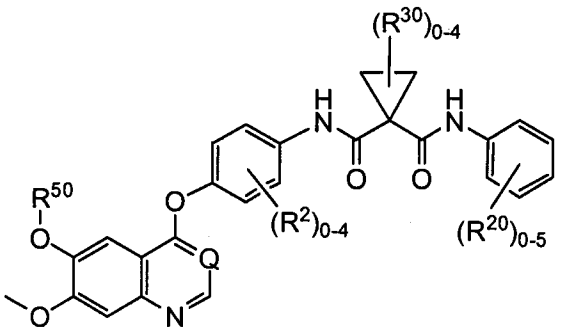
90. (New) The compound according to claim 89, wherein Q is either =N- or =C(H)-.

91. (New) The compound according to claim 90, wherein R^2 is selected from -H, halo, C_{1-6} alkyl and perfluoro C_{1-6} alkyl.

92. (New) The compound according to claim 87, of formula **XIVa** or **XIVb**:



XIVa



XIVb

93. (New) The compound according to claim 92, wherein R^2 is selected from C_{1-6} alkyl, perfluoro C_{1-6} alkyl, and halo.

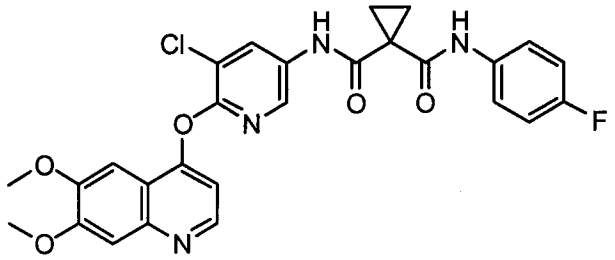
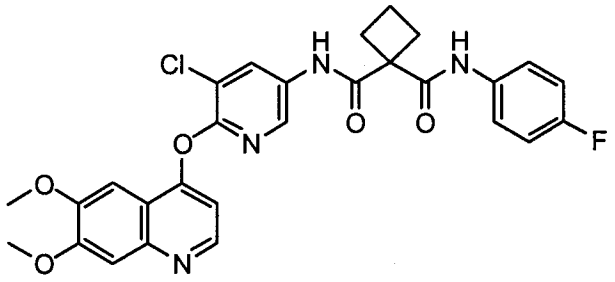
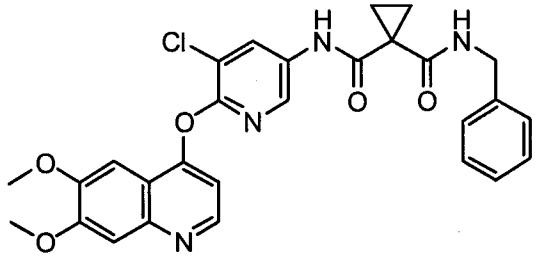
94. (New) The compound according to claim 93, wherein R^2 is selected from perfluoro C_{1-3} alkyl and halo.

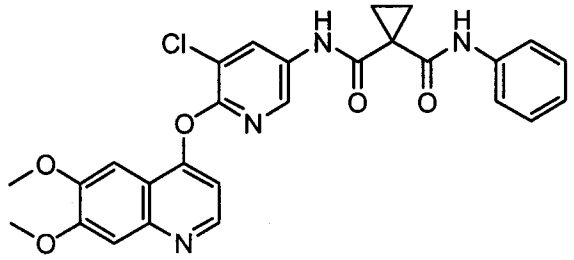
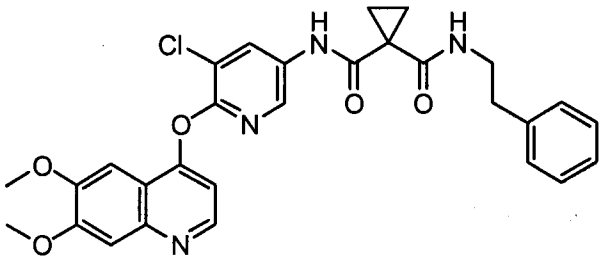
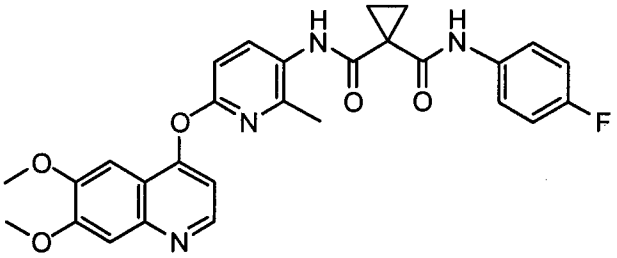
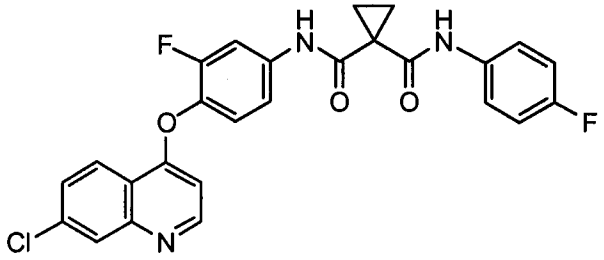
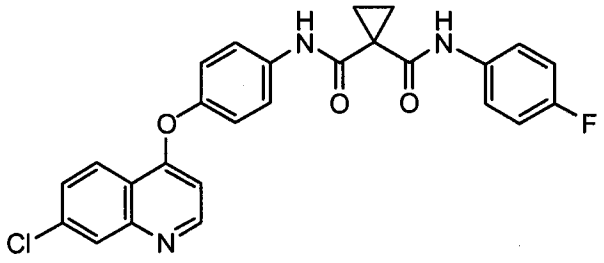
95. (New) The compound according to claim 94, wherein R^{20} is halo.

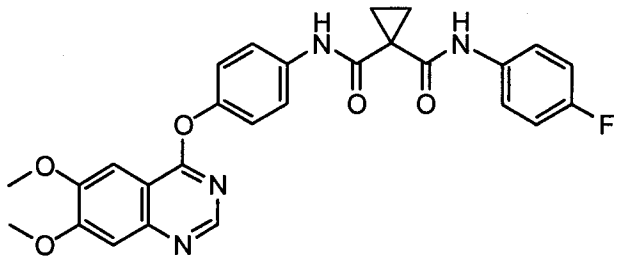
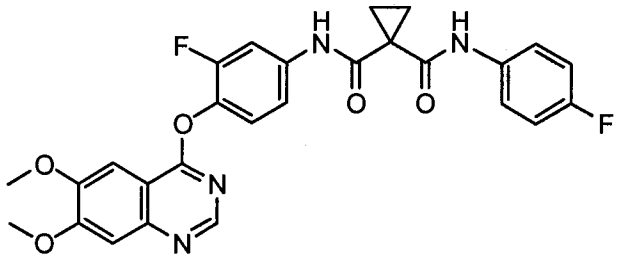
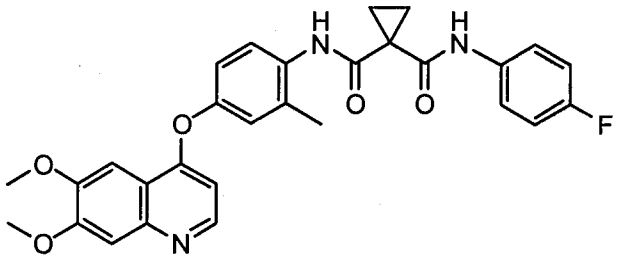
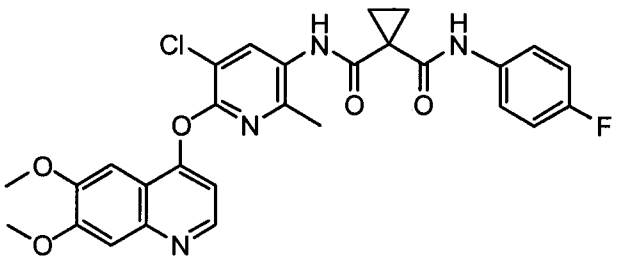
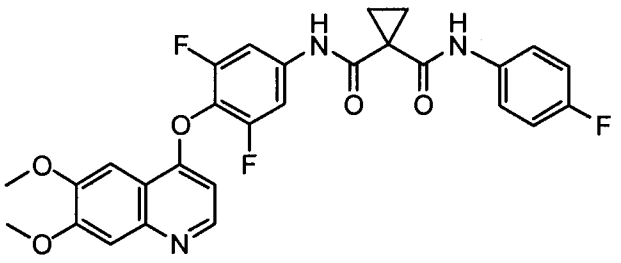
96. (New) The compound according to claim, 95, wherein R^2 is selected from C_{1-6} alkyl, perfluoro C_{1-6} alkyl and halo.

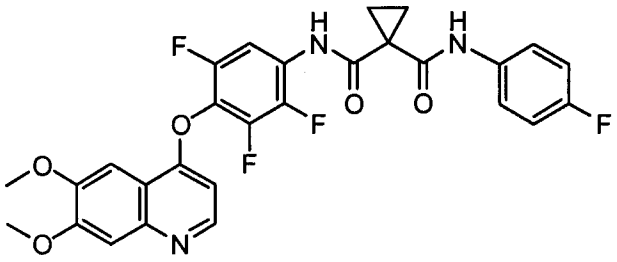
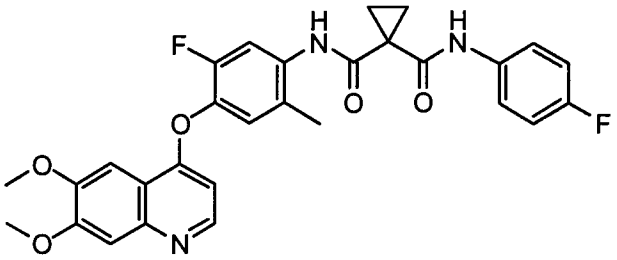
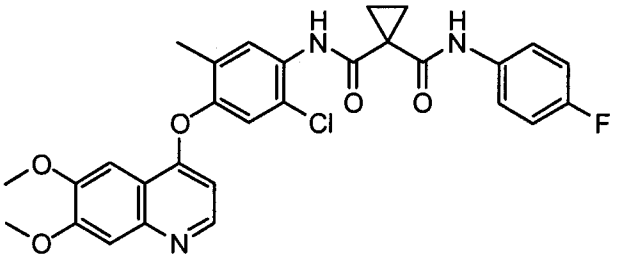
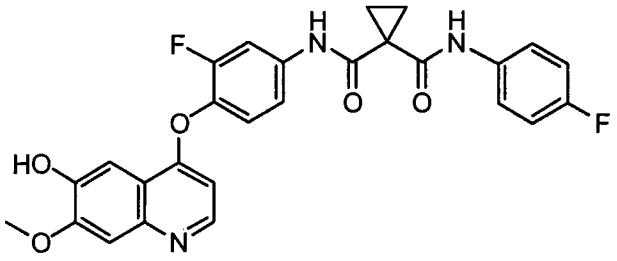
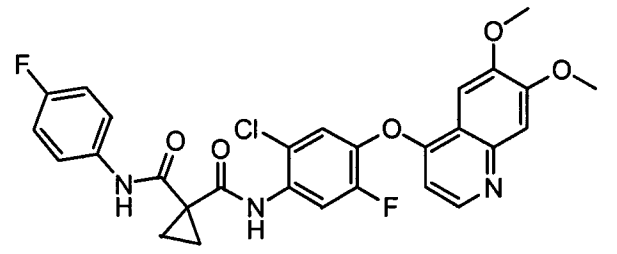
97. (New) The compound according to claim 96, wherein R^2 is halo.

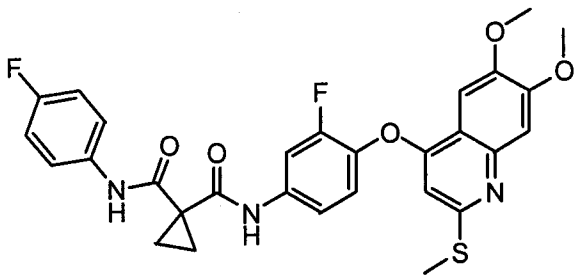
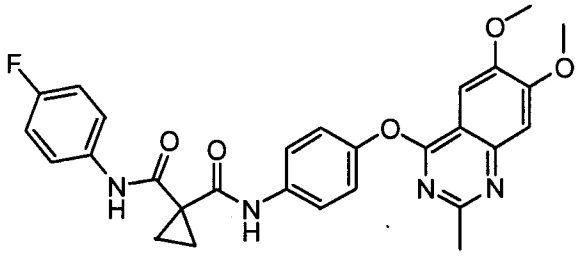
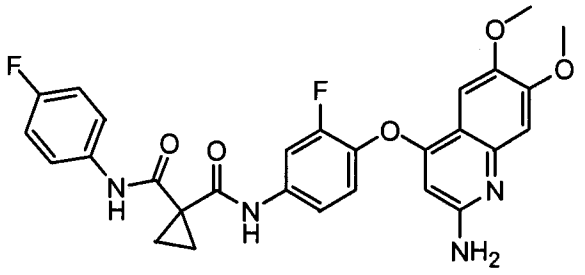
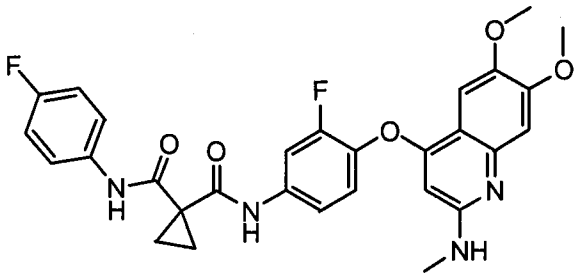
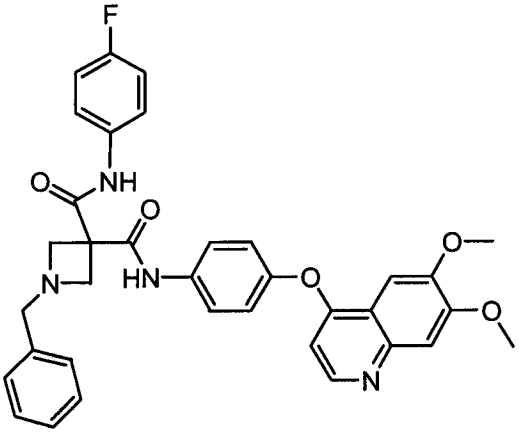
98. (New) A compound selected from the following Table:

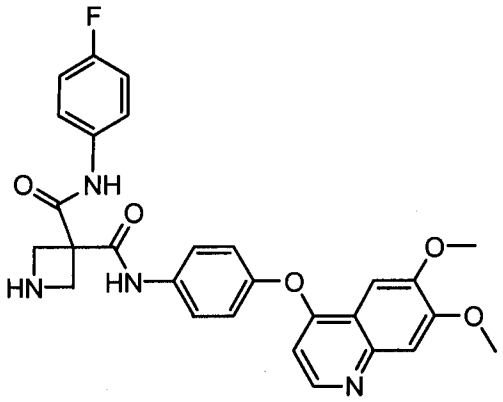
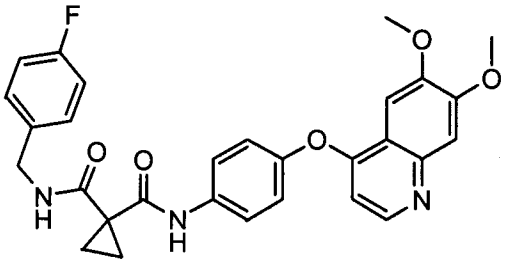
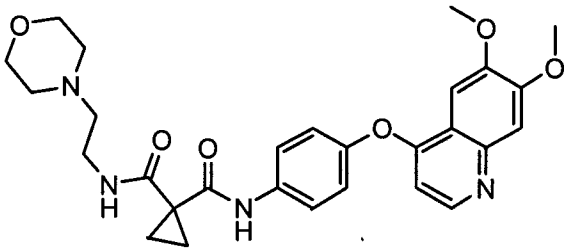
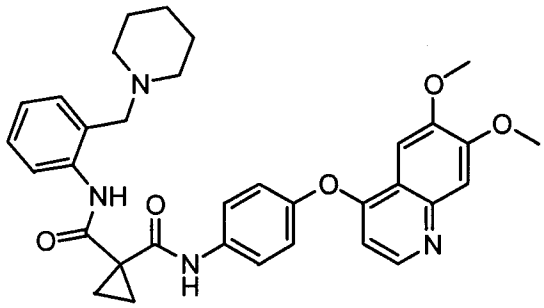
Name	Structure
N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(phenylmethyl)cyclopropane-1,1-dicarboxamide	

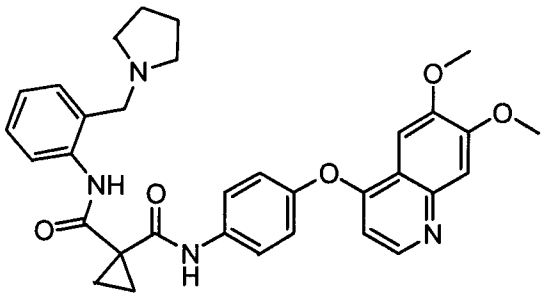
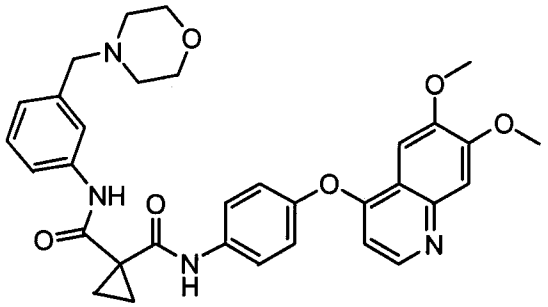
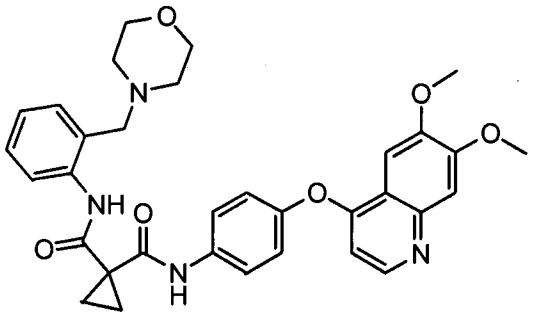
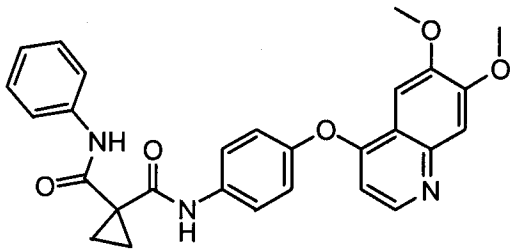
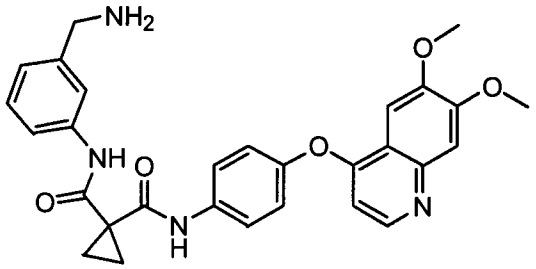
Name	Structure
N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-phenylcyclopropane-1,1-dicarboxamide	
N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-phenylethyl)cyclopropane-1,1-dicarboxamide	
N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-methylpyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
N-{4-[(7-chloroquinolin-4-yl)oxy]-3-fluorophenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
N-{4-[(7-chloroquinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

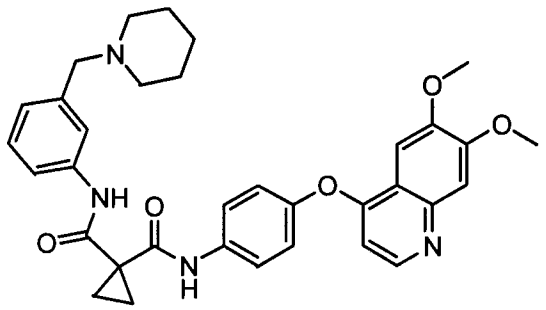
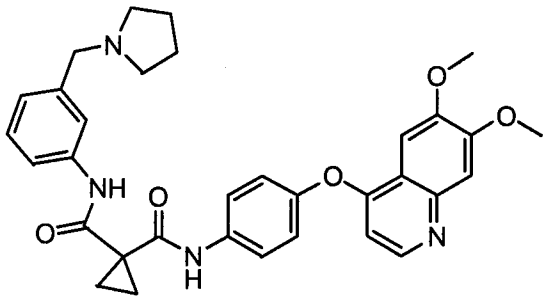
Name	Structure
N-(4-{[6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloro-2-methylpyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3,5-difluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Name	Structure
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2,3,5-trifluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-2-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-chloro-5-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
N-(3-fluoro-4-{[6-hydroxy-7-(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-chloro-5-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Name	Structure
N-(4-{[6,7-bis(methyloxy)-2-(methylthio)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
N-(4-fluorophenyl)-N'-(4-{[2-methyl-6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide	
N-(4-{[2-amino-6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
N-(3-fluoro-4-{[2-(methylamino)-6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-1-(phenylmethyl)azetidine-3,3-dicarboxamide	

Name	Structure
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)azetidine-3,3-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[(4-fluorophenyl)methyl]cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(2-morpholin-4-ylethyl)cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	

Name	Structure
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-phenylcyclopropane-1,1-dicarboxamide	
N-[3-(aminomethyl)phenyl]-N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide	

Name	Structure
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	
N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	

99. (New) A pharmaceutical composition comprising a compound according to claim 83, and a pharmaceutically acceptable carrier.

100. (New) A metabolite of the compound or the pharmaceutical composition according to claim 83.

101. (New) 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 claim 83.

102. (New) The method according to claim 101, wherein modulating the *in vivo* activity of the kinase comprises inhibition of said kinase.

103. (New) The method according to claim 102, wherein the kinase is at least one of c-Met, KDR, c-Kit, flt-3, and flt-4.

104. (New) The method according to claim 102, wherein the kinase is c-Met.

105. (New) 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 claim 83.

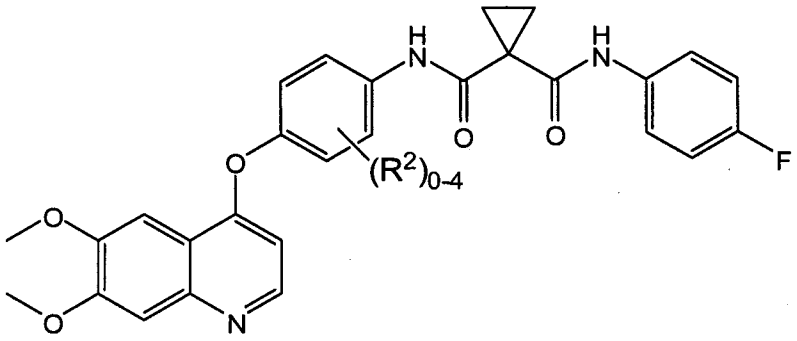
106. (New) A method of screening for a modulator of a kinase, said kinase selected from c-Met, KDR, c-Kit, flt-3, and flt-4, the method comprising combining a compound according to claim 83, and at least one candidate agent and determining the effect of the candidate agent on the activity of said kinase.

107. (New) A method of inhibiting proliferative activity in a cell, the method comprising administering an effective amount of a composition comprising a compound of claim 83, to a cell or a plurality of cells.

108. (New) A method of treating a disease or disorder, comprising administering to a mammal in need of the treatment a therapeutically effective amount of the compound according to claim 92, or a pharmaceutically acceptable salt thereof, or a composition containing a) a therapeutically effective amount of the compound or a pharmaceutically acceptable salt thereof; and optionally b) an excipient, wherein the disease or disorder is stomach cancer, esophageal carcinoma, kidney cancer, liver cancer, ovarian carcinoma, cervical carcinoma, large bowel cancer, small bowel cancer, brain cancer, lung cancer, bone cancer, prostate carcinoma, pancreatic carcinoma, skin cancer, Hodgkin's disease, or non-Hodgkin's lymphoma.

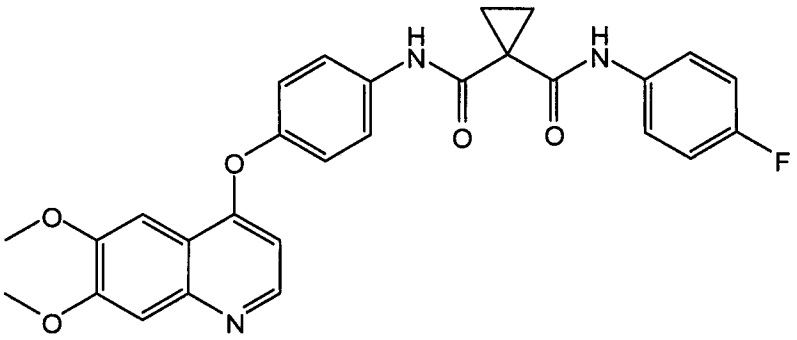
109. (New) The method according to claim 108, wherein Q is CH; (R^2) is -H or fluoro; and R^{20} is chloro or fluoro.

110. (New) The method according to claim 108, wherein the compound is represented by the following structure:



or a pharmaceutically acceptable salt thereof.

111. (New) A method of treating a disease or disorder, comprising administering to a mammal in need of the treatment a therapeutically effective amount of a compound according to the following structure:



or a pharmaceutically acceptable salt thereof, or a composition containing a) a therapeutically effective amount of the compound or a pharmaceutically acceptable salt thereof; and optionally b) an excipient, wherein the disease or disorder is stomach cancer, esophageal carcinoma, kidney cancer, liver cancer, ovarian carcinoma, cervical carcinoma, large bowel cancer, small bowel cancer, brain cancer, lung cancer, bone cancer, prostate carcinoma, pancreatic carcinoma, skin cancer, Hodgkin's disease, or non-Hodgkin's lymphoma.

112. (New) The method according to claim 111, wherein the disease or disorder is brain cancer.

113. (New) The method according to claim 111, wherein the brain cancer is glioma or glioblastoma.

114. (New) The method according to claim 111, wherein the disease or disorder is lung cancer.

REMARKS

Support for New Claim 83 can be found in original claim 54 wherein support for the definitions at the end of the claim 54 can be found in paragraph [0268], pages 141, in the specification of published parent U.S. patent application US 2007/0054928 A1.

Support for New Claim 84 can be found in original claim 55.

Support for New Claim 85 can be found in original claim 56.

Support for New Claim 86 can be found in original claim 57.

Support for New Claim 87 can be found in original claim 58, wherein the definition of $-N(R^{3b})R^4$ in original claim 65 was incorporated into claim 87. Also, the definitions of R^2, R^3 and R^4 that are in new claim 87 are from original claim 54 from which original claim 58 depends on.

Support for New Claim 88 can be found in original claim 61.

Support for New Claim 89 can be found in original claim 62.

Support for New Claim 90 can be found in original claim 63.

Support for New Claim 91 can be found in original claim 64.

Support for New Claim 92 can be found in original claim 66.

Support for New Claim 93 can be found in original claim 99.

Support for New Claim 94 can be found in original claim 100.

Support for New Claim 95 can be found in original claim 102.

Support for New Claim 96 can be found in original claim 103.

Support for New Claim 97 can be found in original claim 104.

Support for New Claim 98 can be found in original claim 105.

Support for New Claim 99 can be found in original claim 106.

Support for New Claim 100 can be found in original claim 107.

Support for New Claim 101 can be found in original claim 108.

Support for New Claim 102 can be found in original claim 109.

Support for New Claim 103 can be found in original claim 110.

Support for New Claim 104 can be found in original claim 111.

Support for New Claim 105 can be found in original claim 112.

Support for New Claim 106 can be found in original claim 113.

Support for New Claim 107 can be found in original claim 114.

Support for the list of cancers in New Claim 108 can be found on pages 142-143 in paragraph [0285] of the specification of published parent U.S. patent application US 2007/0054928 A1; and the term "excipient" is described on page 144, paragraph [0298] of the specification of published parent U.S. patent application US 2007/0054928 A1.

Support for the fluoro and chloro groups within the definition of R^{20} in New Claim 109 are described within the definition of the term "halogen or halo" on page 140, paragraph [0258] of the specification of published parent U.S. patent application US 2007/0054928 A1; moreover, the fluoro and chloro groups at the R^{20} position appear numerous times in the list of compounds in Table 2 of the specification starting on page 102, paragraph [0165]; and support for Q is CH can be found on page 99, paragraph [0123].

Support for new claims 110 and 112-113 are described above for where support can be found in new claims 108 and 109.

Support for new claim 111 can be found in original claim 105.

No new matter has been added. The Applicants respectfully request that the amendments and new claims be entered into the record.

It is believed that no fees are required with the submission of this preliminary amendment, however, should a fee be necessary, the Commissioner is hereby authorized to charge any necessary fee to Deposit Account Number 50-1108.

Respectfully submitted,

June 3, 2009
Date

/Robert L. Bernstein/
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/753,514	05/24/2007	LYNNE CANNE BANNEN	224990/04-064C3/127533	5697

91684 7590 07/20/2010

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EXAMINER	
TRUONG, TAMTHOM NGO	
ART UNIT	PAPER NUMBER
1624	
MAIL DATE	DELIVERY MODE
07/20/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/753,514	BANNEN ET AL.	
	Examiner	Art Unit	
	TAMTHOM N. TRUONG	1624	

-- 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* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, 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 *6-3-09 (Preliminary Amendment)*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ 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

4)☒ Claim(s) *83-114* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *83-114* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ 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).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

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).

a)☐ All b)☐ Some * c)☐ None of:

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) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :2/3/09, 1/29/08, 8/24/07, 5/24/07.

FIRST OFFICE ACTION

Applicant's amendment of 6-3-09 have been entered and acknowledged. Claims 1-82 have been cancelled. Claims 83-114 are pending.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 89 and 100-104 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a. Claim 89 recites the word "selec2ted" which is misspelled.

b. Claim 100 recites the word "metabolite" which does not have a definite description of what the structure of said metabolite could be. Although the specification cites example of "biotransformation to a more polar molecule such as by oxidation, reduction, or hydrolysis, or to a conjugate…", it is not clear from formula XI **where** the biotransformation occurs, and **what the final structure** of said metabolite would be.

c. Claims 101-104 are drawn to a "method of modulating the *in vivo* activity of a kinase" which is not clear whether agonizing or antagonizing is intended because the specification does not limit "modulating" to inhibition or antagonizing. Since a

compound cannot have two opposite activity, it is not clear which compounds of formula XI could agonize, and which could antagonize.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. **Missing Essential Steps:** Claims 101-104, 106 and 107 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. All the claims recite a "method of modulating...", a "method of screening...", a "method of inhibiting..." which require the steps of incubating cells, isolating unaffected kinases, and detecting affected kinases which are critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. **Scope of Enablement:** Claims 101-105 and 107-114 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating certain cancers such as breast, ovarian, colorectal, prostate, and lung cancer, does not reasonably provide enablement for a method of treating all proliferative disorders or cancers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors have been considered in the determination of an enabling disclosure:

(1) The breadth of the claims;
(2) The amount of direction or guidance presented;
(3) The state of the prior art;
(4) The relative skill of those in the art;
(5) The predictability or unpredictability of the art;
(6) The quantity of experimentation necessary;

[See ***Ex parte Forman***, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also ***In re Wands***, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims: Claims 101-104 recite a "method of modulating the *in vivo* activity of a kinase …" which covers the agonizing and antagonizing of any kinase, and there are about 500 protein kinases with countless terminal groups that could react with the claimed compounds, and thus, the scope of said claims is unduly broad.

Claim 105 recites a "method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities…" which covers diseases of unrelated underlying factors such as: cancer, rheumatoid arthritis, graft-host diseases, multiple

sclerosis, psoriasis, artherosclerosis, myocardioinfarction, ischemia, stroke, restenosis, interbowel diseases, osteoarthritis, macular degeneration and diabetic retinopathy. Note, the range of diseases affects just about all organs, particularly, the heart, the joints, the bone, the eyes, the liver, etc., and thus, the scope of said claim is also unduly broad.

Claims 107-114 are drawn to a "method of inhibiting proliferative activity...", and treating several cancers, namely, stomach cancer, esophageal carcinoma, kidney cancer, liver cancer, ovarian carcinoma, cervical carcinoma, large bowel cancer, small bowel cancer, brain cancer, lung cancer, bone cancer, prostate carcinoma, pancreatic carcinoma, skin cancer, Hodgkin's disease, or non-Hodgkin's lymphoma. Like claim 105, the scope of the recited method covers the treatment for cancers of various organs, and thus, is unduly broad.

The amount of direction or guidance presented: The claimed compounds allegedly could inhibit various kinases such as: c-Met, KDR, c-Kit, flt-3, and flt-4. The specification describes ***in-vitro*** kinase assays to determine IC_{50} of the claimed compounds on c-Met, KDR, c-Kit, flt-3, and flt-4. However, the specification does not indicate which cell line was used, except baculovirus. Also, the specification does not provide any *in-vivo* data for the reduction of tumor size or abnormal cell growth, or improving quality of the patient's life. Thus, from the *in-vitro* description alone, it does not sufficiently enable one skilled in the art to select an effective compound to treat any proliferative disorders, or cancers.

The state of the prior art: The claimed compound is commercially known as Iressa or Gefitinib which, in a preclinical studies, is shown to treat cancers such as: prostate, ovarian, breast, colon, small-cell and non-small-cell lung, and ductal carcinoma. Even for the listed

cancers, "only tumors in which inhibition of the receptor results in inhibition of down stream signaling pathways are growth arrested." (see page 861 (right column), **Grünwald V. et. al.**, REVIEW, J. Nat. Can. Inst., Vol. 95, No. 12, 6/18/03). Thus, the state of the art correlates the inhibition of EGFR to certain cancers but not all cancers that are supposedly could be treated with kinase inhibitors such as those of formula XI. Therefore, the state of the art does not support the scope of the claimed method.

The relative skill of those in the art: There has never been a compound capable of treating cancer generally, let alone inhibiting "perproliferative activity in a cell". Different types of cancers affect different organs and have different modes of growth and harm to the body as well as different vulnerabilities. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Therefore, it is beyond the skill of oncologists today to get an agent to be effective against all cancers or all hyperproliferative disorders in general.

The predictability or unpredictability of the art & The quantity of experimentation necessary: The pharmaceutical art has been known for its unpredictability due to various conflicting path ways, or biological factors that are sometimes genetically unique to individuals. In the instant case, the showing of inhibiting kinases alone does not guarantee the compound's effectiveness in treating "proliferative" disorders or cancers.

See ***Hoffman v. Klaus*** 9 USPQ 2d 1657, and ***Ex parte Powers*** 220 USPQ 925 regarding type of testing needed to support *in vivo* uses.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 83-99 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. **7,579,473**. Although the conflicting claims are not identical, they are not patentably distinct from each other because a compound of formula XIVa in US'473 **anticipates** the instant formula XI with the following substituents:

i. R^1 is –D-R^{50}; D is –O-; R^{50} is an unsubstituted C_{1-6}alkyl group;

ii. Q is =C(H)-;

iii. R^{70} is hydrogen;

iv. Z is –O-;

v. Ar is a 6-membered arylene;

vi. G is a cycloalkyl group;

vii. R^3 is hydrogen;

viii. R^4 is an aryl group.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TAMTHOM N. TRUONG whose telephone number is (571)272-0676. The examiner can normally be reached on Monday thru Friday (9:00-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on 571-272-0661. 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.

/Tamthom N. Truong/
Examiner, Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624

***
7-9-10

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/753,514	05/24/2007	LYNNE CANNE BANNEN	224990/04-064C3-US/127533	5697

91684 7590 09/10/2010

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EXAMINER	
TRUONG, TAMTHOM NGO	
ART UNIT	PAPER NUMBER
1624	
MAIL DATE	DELIVERY MODE
09/10/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Interview Summary	Application No.	Applicant(s)	
	11/753,514	BANNEN ET AL.	
	Examiner	Art Unit	
	TAMTHOM N. TRUONG	1624	

All participants (applicant, applicant's representative, PTO personnel):

(1) *TAMTHOM N. TRUONG*. (3)_____.

(2) *Robert Bernstein*. (4)_____.

Date of Interview: *31 August 2010*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☒ No.
If Yes, brief description: _____.

Claim(s) discussed: *Claims 108 and 114* .

Identification of prior art discussed: *N/A*.

Agreement with respect to the claims f)☐ was reached. g)☐ was not reached. h)☒ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *Mr. Bernstein discussed the enablement issue for method claims 108-114. Specifically, he said that the cancers recited in claim 108 had support in the overexpression of c-met as taught in many articles listed on pages 3-4. However, Mr. Bernstein woud address the "Scope of Enablement" rejection by including additional references to overcome the enablement issue* .

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

/Tamthom N. Truong/ Examiner, Art Unit 1624	/J. O. W./ Supervisory Patent Examiner, Art Unit 1624

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

———

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	: Lynne Canne Bannen, et al.	Art Unit	: 1624
Serial No.	: 11/753,514	Examiner	: Tamthom Ngo Truong
Filed	: May 24, 2007	Attorney Docket: 224990/04-064C3-US/127533	
Title	: C-MET MODULATORS AND METHOD OF USE		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO THE OFFICE ACTION DATED JULY 20, 2010

Dear Sir:

This communication is responsive to the Office Action dated July 20, 2010.

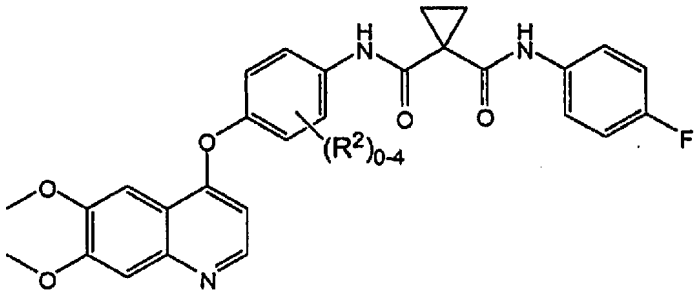
Claim Amendments begin on page 2.

Remarks begin on page 6.

Claim Amendments

1-107. Cancelled.

108. (Currently Amended) A method of treating a disease or disorder, comprising administering to a mammal in need of the treatment a therapeutically effective amount of the compound ~~according to claim 92,~~ having the following structure

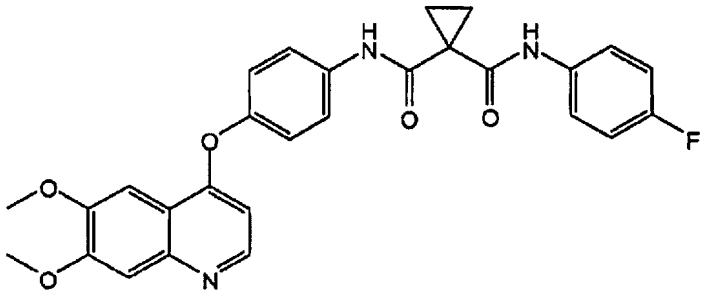


or a pharmaceutically acceptable salt thereof, wherein each R^2 is independently -H or fluoro, or a composition containing a) a therapeutically effective amount of the compound or a pharmaceutically acceptable salt thereof; and optionally b) an excipient, wherein the disease or disorder is breast cancer, stomach cancer, esophageal carcinoma, kidney cancer, liver cancer, ovarian carcinoma, cervical carcinoma, large bowel cancer, small bowel cancer, brain cancer, lung cancer, bone cancer, prostate carcinoma, pancreatic carcinoma, skin cancer, Hodgkin's disease, or non-Hodgkin's lymphoma.

109. Cancelled.

110. Cancelled.

111. (Currently Amended) The method of claim 108, ~~A method of treating a disease or disorder, comprising administering to a mammal in need of the treatment a therapeutically effective amount of a compound according to~~ wherein the compound has the following structure:



~~or a pharmaceutically acceptable salt thereof, or a composition containing a) a therapeutically effective amount of the compound or a pharmaceutically acceptable salt thereof; and optionally b) an excipient, wherein the disease or disorder is stomach cancer, esophageal carcinoma, kidney cancer, liver cancer, ovarian carcinoma, cervical carcinoma, large bowel cancer, small bowel cancer, brain cancer, lung cancer, bone cancer, prostate carcinoma, pancreatic carcinoma, skin cancer, Hodgkin's disease, or non-Hodgkin's lymphoma~~ or a pharmaceutically acceptable salt thereof.

112. (Previously Presented) The method according to claim 111, wherein the disease or disorder is brain cancer.

113. (Previously Presented) The method according to claim 111, wherein the brain cancer is glioma or glioblastoma.

114. (Previously Presented) The method according to claim 111, wherein the disease or disorder is lung cancer.

115. (New) The method according to claim 111, wherein the disease or disorder is breast cancer.

116. (New) The method according to claim 111, wherein the disease or disorder is melanoma.

117. (New) The method according to claim 111, wherein the disease or disorder is stomach cancer.

118. (New) The method according to claim 111, wherein the disease or disorder is esophageal carcinoma.

119. (New) The method according to claim 111, wherein the disease or disorder is kidney cancer.

120. (New) The method according to claim 111, wherein the disease or disorder is liver cancer.

121. (New) The method according to claim 111, wherein the disease or disorder is ovarian carcinoma.

122. (New) The method according to claim 111, wherein the disease or disorder is cervical carcinoma.

123. (New) The method according to claim 111, wherein the disease or disorder is large bowel cancer.

124. (New) The method according to claim 111, wherein the disease or disorder is small bowel cancer

125. (New) The method according to claim 111, wherein the disease or disorder is bone cancer.

126. (New) The method according to claim 111, wherein the disease or disorder is prostate carcinoma.

127. (New) The method according to claim 111, wherein the disease or disorder is pancreatic carcinoma.

128. (New) The method according to claim 111, wherein the disease or disorder is skin cancer.

129. (New) The method according to claim 111, wherein the disease or disorder is Hodgkin's disease.

130. (New) The method according to claim 111, wherein the disease or disorder is non-Hodgkin's lymphoma.

Remarks

The Applicant wishes to thank the Examiner for the Interview conducted with Attorney Robert Bernstein on August 31, 2010, as summarized by the Examiner in the Interview Summary dated September 10, 2010.

Claim Status

Claims 1-107 and 109-110 are cancelled.

Claims 108 and 111 are currently amended.

Support for the compound recited in claim 108 under 35 USC 112, first paragraph, is found in the compound of formula XIVa as recited in now-cancelled claim 92 and on page 104, paragraph 101, wherein R^2 can be 0-4 halo (Page 103, Paragraph 99); R^{20} can be halo (Page 103, Paragraph 100); Q can be CH (Page 102, paragraph 98); and R^{50} can be C_{1-6} alkyl (Page 104, Paragraph 102). The fluoro group within the definition of R^{20} is described within the definition of the term "halogen or halo" on page 154, paragraph 228; moreover, the fluoro group at the R^{20} position appears numerous times in the list of compounds in Table 2 of the specification, starting on page 109, paragraph 140.

Support for the inclusion of "breast cancer" in claim 115 is found in paragraph 13 of the specification. Thus, the inclusion of "breast cancer" does not constitute new matter.

Claims 112-114 are previously presented.

Claims 115-130 are new. Claims 115-130 depend from claim 111, which itself depends from claim 108. Each of claims 115-130 recites individually an indication that was originally recited in claim 108; therefore, claims 115-130 do not constitute new matter.

Thus, claims 108 and 111-130 are currently pending.

The claim amendments are made in the interest of expediting prosecution. The Applicant does not intend to surrender any range of equivalents to which the Applicant would otherwise be entitled in view of the prior art, nor does the Applicant agree with the Examiner's comments or arguments about the art cited in the Office Action. Further, by the present amendment, it does not follow that the amended claims have become so perfect in their description that no one could devise an equivalent. After amendment, as before, limitations in the ability to describe the present invention in language in the patent claims naturally prevent the Applicant from capturing every nuance of the invention or describing with complete precision the range of its novelty or

every possible equivalent. See, Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 62 USPQ2d 1705 (2002). Accordingly, the foregoing amendments are made specifically in the interest of expediting prosecution and there is no intention of surrendering any range of equivalents to which the Applicant would otherwise be entitled.

By amending the claims, the Applicant does not concede that patent coverage available to them would not extend as far as the original claim. The Applicant reserves the right to file divisional and/or continuation applications to pursue the breadth of the claims as filed. The Applicant seeks the timely allowance of the amended claims.

Claim Rejections

Rejection Under 35 U.S.C. § 112, Second Paragraph

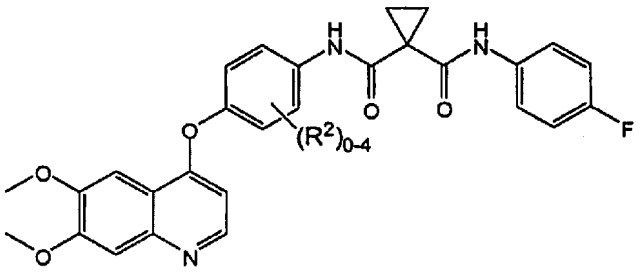
The Examiner rejected claims 89 and 100-104, under 35 U.S.C. § 112, Second Paragraph. This rejection has been rendered moot by the cancellation of these claims.

Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 101-104 and 106-107 under 35 U.S.C. § 112, First Paragraph, because the specification does not reasonably provide enablement, because the claims lack missing or essential steps. The rejection has been rendered moot by the cancellation of these claims.

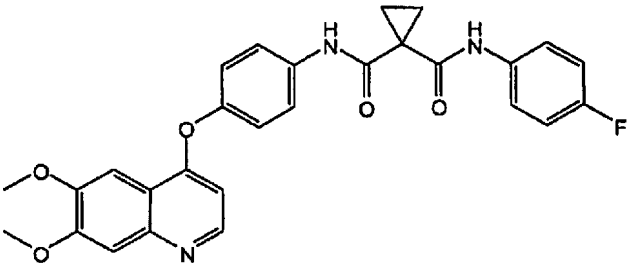
The Examiner rejected claims 101-105 and 107-114 under 35 U.S.C. § 112, First Paragraph, because the specification does not reasonably provide enablement for a method for treating all proliferative disorders or cancers. The rejection has been rendered moot by the cancellation of claims 101-105, 107, 109, and 110.

Claims 108 recites a method of treating a disease or disorder, comprising administering to a mammal in need of the treatment a therapeutically effective amount of the compound having the following structure:



Claim 108

or a pharmaceutically acceptable salt thereof, wherein each R^2 is independently -H or fluoro, or a composition containing a) a therapeutically effective amount of the compound or a pharmaceutically acceptable salt thereof; and optionally b) an excipient. Claim 111 further provides that the compound has the following structure:



Claim 111

The compounds recited in claims 108 and 111 are c-MET inhibitors (See Table 4 of the Specification, page 270).

As amended, claim 108 provides that the disease or disorder to be treated is breast cancer, stomach cancer, esophageal carcinoma, kidney cancer, liver cancer, ovarian carcinoma, cervical carcinoma, large bowel cancer, small bowel cancer, brain cancer, lung cancer, bone cancer, prostate carcinoma, pancreatic carcinoma, skin cancer, Hodgkin's disease, or non-Hodgkin's lymphoma. The Examiner indicated some of the diseases or disorders recited in claim 108 are enabled, (breast cancer, ovarian cancer, colorectal cancer, prostate cancer, and lung cancer), but that some are not (stomach cancer, esophageal cancer, kidney cancer, liver cancer, cervical carcinoma, brain cancer, bone cancer, pancreatic cancer, skin cancer, Hodgkin's disease, and non-Hodgkin's lymphoma).

The Applicant respectfully submits that the other cancers recited in claim 108 are also enabled. At the time the current application was filed, the aberrant activity of MET in human cancers and the role of MET inhibitors for treating cancer had been recognized. For example,

Trusolino (Nature Reviews Cancer 2 (2002), 289-300, a copy of which is attached herewith), correlated observed MET dysfunction (for example, MET protein overexpression) in a range of tumor types, including ones that the Examiner alleges are not enabled. Table 1 (page 293) of Trusolino, which is reproduced here for the Examiner's convenience, is instructive on this point.

Trusolino Table 1.

Table 1 | **Aberrant activity of MET and semaphorins in human cancers**

Lesion	Type of tumour	References
HGF-dependent autocrine loop	Osteosarcoma	46,48
	Rhabdomyosarcoma	47
	Breast carcinoma	55,57,66,80
MET protein overexpression	Thyroid carcinoma	49,54,60,62,71
	Ovarian carcinoma	50,67
	Pancreatic carcinoma	51
	Prostate carcinoma	52
	Renal-cell carcinoma	53
	Hepatocellular carcinoma	56,63
	Gastric carcinoma	58,68
	Oesophageal carcinoma	59
	Breast carcinoma	61
	Colorectal carcinoma	64
	Oral squamous-cell carcinoma	70
MET gene amplification	Liver metastases from colon carcinoma	81
	Hepatocellular carcinoma	69
Germ-line *MET* gene mutations	Papillary renal-cell carcinoma	72–74
	Gastric carcinoma	77
Somatic *MET* gene mutations	Papillary renal-cell carcinoma	72–74
	Childhood hepatocellular carcinoma	76
	Lymph-node metastases of head and neck squamous-cell carcinomas	82
Sema-3C protein overexpression	Metastatic lung adenocarcinoma	104
	Recurrent squamous-cell carcinomas	105

HGF, hepatocyte growth factor.

Similarly, the link between MET and other forms of cancer had also been recognized, including cervical cancer (Baykal, Gynecologic Oncology 88 (2003) 123–129), bone cancer (Borset, Leukemia and Lymphoma, 32 (1999), 249-256), skin cancer, (Elia, Journal of Cellular Biochemistry 81 (2001) 477-487), Hodgkin's Disease (Teofili, Blood, 97 (2001) 1063-1069), and Non-Hodgkins Lymphoma (Hsiao, Eur J Haematol 70 (2003) 282–9). Each of these publications is attached to this Response for the Examiner's review.

Based on Trusolino, Baykal, Borset, Elia, Teofili, and Hsiao, the state of the prior art as well as the relative skill of those in the art support the enablement of the Applicant's disclosure and the enablement of the amended claims presented herewith.

Moreover, clinical data collected by the Applicant recently presented at ASCO 2010 for the compound recited in claim 111, which is a compound of claim 108, confirms that compounds

as recited in the instantly pending claims can control cancer disease rates and reduce lesion sizes in human patients with various forms of cancer. Table 4 of Poster TPS188 (reproduced here for the Examiner's convenience) indicates that administration of a compound as claimed by the Applicant lead to positive disease control rates (DCR) in patients with a range of cancers. *See* ASCO 2010 Poster TPS188, attached herewith and available at http://www.exelixis.com/sites/default/files/pdf/ASCO_2010-XL184_203-TPS188.pdf (last visited November 9, 2010).

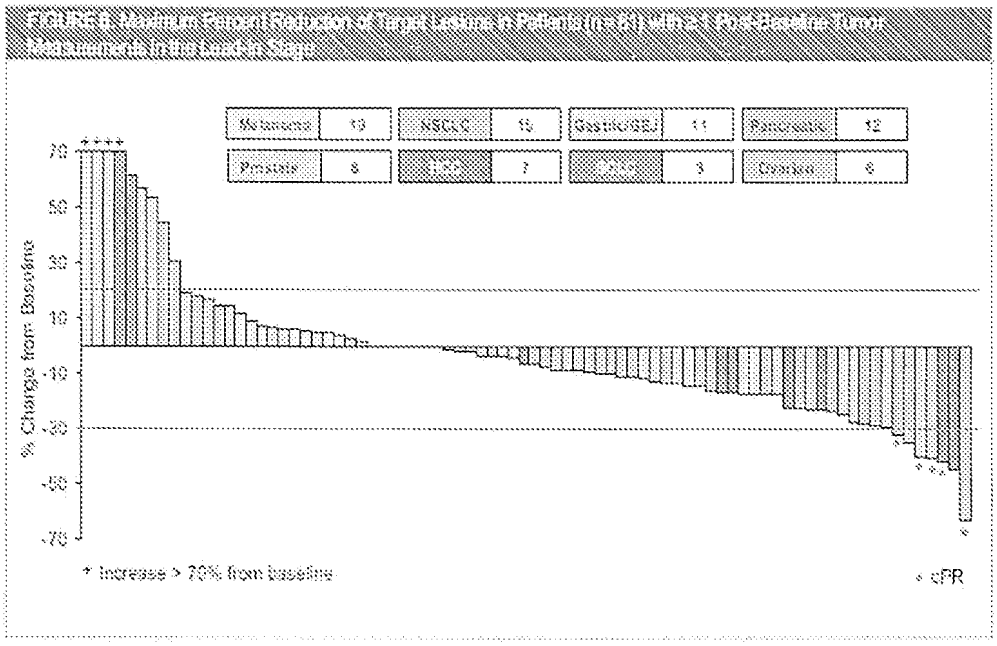
Poster TPS188 Table 4

Table 4. Tumor Data by Anatomic Category in the Evaluable Group

Type	Enrolled	Evaluable	PD	Best Response		DCR	CR	Median Duration of Response (mo)
				PR	SD			
Melanoma	41	21 (51)	6 (29)	1 (6)	12 (57)	62	79	8.2
NSCLC	25	19 (76)	4 (21)	2 (11)	9 (47)	68	67	2.0
Pancreatic	23	14 (70)	5 (36)	0	5 (36)	36	53	—
Gastric/ GEJ	18	13 (72)	4 (31)	0	5 (38)	38	55	—
Ovarian	15	4 (27)	0	1 (25)[a]	3 (75)	100	—	1.3
Prostate	15	7 (47)	1 (14)	1 (14)	3 (43)	57	56	6.7
SCLC	15	4 (27)	2 (50)	0	1 (26)	25	—	—
HCC	10	7 (70)	0	1 (14)[a]	5 (71)	85	68	6.7
Breast	10	2 (20)	0	0	1 (50)	50	—	—
Total	169							

Indeed, the use of the compound as recited by the Applicant in claim 111, which is a compound of claim 108, gave rise to target lesion reduction in clinical subjects, as shown in Figure 6 of Poster TPS188.

Poster TPS188 Figure 6



Moreover, in a 2009 ASCO disclosure, the Applicant reported the antiangiogenic effect in patients with glioblastoma of the compound recited in claim 111, which is a compound of claim 108. *See* ASCO 2009 Poster 2047, attached herewith and available at http://exelixis.com/sites/default/files/pdf/XL184-201_ASCO-2009_Clinical-Poster-2047.pdf (last visited November 9, 2009).

The Applicant therefore respectfully submits that claims 111-130 are enabled, at least for the reasons, publications, and data presented above, taken alone or collectively. Moreover, since the compound of claim 111 is embraced by and depends from claim 108, the Applicant asserts that claim 108, by extension, is also enabled. Accordingly, the Applicant respectfully requests that the rejection under 35 U.S.C. § 112, First Paragraph, be reconsidered and withdrawn, and that claims 108 and 111-130 be allowed.

Double Patenting Rejection

The Examiner raised a double patenting rejection of claims 83-99 in light of U.S. Patent No. 7,575,473. This rejection has been rendered moot by the cancellation of these claims.

Petition for Extension of Time

Applicant hereby petitions for a one month extension of time under 37 C.F.R. § 1.136 to respond to the Office Action mailed on July 20, 2010, regarding the above referenced application. Please charge Deposit Account Number 503145, referencing Attorney Docket Number 224990/04-064C3-US/127533, the amount of $65.00 to cover the extension fee for filing this Response within the one month extension period.

It is believed that no additional fees are required for this reply. However, if there are any additional charges, please apply them to the same Deposit Account No. 503145, referencing the same Attorney Docket No. 224990/04-064C3-US/127533.

Respectfully submitted,

Date: November 11, 2010

Heidi M. Berven, Ph.D.
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Reg. No. 48,951

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KALAMAZOO.74395.1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Lynne Canne Bannen, et al. Art Unit: 1624
Application No.: 11/753,514 Examiner: Tamthom Ngo Truong
Filing Date: May 24, 2007 Attorney Docket No.: 224990/04-064C3-US/127533
Title: C-Met Modulators and Methods of Use

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 §1.6(a)(4), on the 11th day of November, 2010.

1. Cover Letter to the Commissioner for Patents;
2. Petition for Extension of Time (PTO/SB/22);
3. Response to the Non-Final Office Action dated July 20, 2010; and
4. Certificate of Transmission Under 37 C.F.R. §1.8(a).

It is believed that the fee required for the filing is $65.00 to cover the extension fee for filing this Response within the one month extension period. However, if there are any additional charges or credits associated with this filing, please apply them to Deposit Account Number 503145, referencing Attorney Docket Number 224990/04-064C3-US/127533.

Lejla Duvnjak (for Heidi M. Berven, Ph.D., Reg. No. 48,951)

ACTIVE.8357625.1

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/753,514	05/24/2007	LYNNE CANNE BANNEN	224990/04-064C3-US/127533	5697

91684 7590 12/23/2010

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350 EAST MICHIGAN AVENUE, SUITE 300
Kalamazoo, MI 49007-3800

EXAMINER	
TRUONG, TAMTHOM NGO	
ART UNIT	PAPER NUMBER
1624	
MAIL DATE	DELIVERY MODE
12/23/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/753,514	BANNEN ET AL.	
	Examiner	Art Unit	
	TAMTHOM N. TRUONG	1624	

-- 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* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, 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 *11 November 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ 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

4)☒ Claim(s) *108 and 111-130* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *108 and 111-130* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ 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).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

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).

a)☐ All b)☐ Some * c)☐ None of:

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) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL ACTION

Applicant's amendment of 11-11-10 has been fully considered. The **cancellation** of claims 1-107, 109, 110 has obviated the previous rejections of 112/1st paragraph, and obviousness-type double patenting. Thus, said rejections are now withdrawn for claims 1-107. Amended remaining claims and new claims have not overcome the previous rejection of 112/1st paragraph (Scope of Enablement). Thus, said rejection is hereby maintained for claims 108 and 111-130.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement: Claims 108 and 111-130 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making a species of [(6,7-dimethoxy)-quinolin-4-yl]-[phenoxy(R^2)$_{0-4}$(4-(NH-C(O))-cyclopropyl-(C(O)NH-(para-fluorophenyl)], does not reasonably provide enablement for a method of treating various cancers that are allegedly related to c-MET. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The following factors have been considered in the determination of an enabling disclosure:

(1) The breadth of the claims;
(2) The amount of direction or guidance presented;
(3) The state of the prior art;
(4) The relative skill of those in the art;
(5) The predictability or unpredictability of the art;
(6) The quantity of experimentation necessary;

[See **Ex parte Forman**, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also **In re Wands**, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims: Claims 108 and claims dependent thereon recite a "method of treating a disease or disorder, . . ., wherein the disease or disorder is breast cancer, stomach cancer, esophageal carcinoma, kidney cancer, liver cancer, ovarian carcinoma, cervical carcinoma, large bowel cancer, small bowel cancer, brain cancer, lung cancer, bone cancer, prostate carcinoma, pancreatic carcinoma, skin cancer, Hodgkin's disease, or non-Hodgkin's disease, or non-Hodgkin's lymphoma" which covers cancers of **different organs and cell types** that are allegedly related to c-Met, thus while the scope of said claims is not unduly broad, it is not practical or rational to carry out such a treatment since different cell types may or may not have c-Met, which is a hepatocyte growth factor (HGF) receptor.

The amount of direction or guidance presented: The claimed compounds allegedly could inhibit c-Met, KDR, c-Kit, flt-3, and flt-4. The specification describes **in-vitro** kinase assays to determine IC_{50} of the claimed compounds on c-Met, KDR, c-Kit, flt-3, and flt-4. However, the specification does not indicate which cell line was used, except baculovirus. Also,

the specification does not provide any in-vivo data for the reduction of tumor size or abnormal cell growth, or improving quality of the patient's life. Thus, from the in-vitro description alone, it does not sufficiently enable one skilled in the art to select an effective compound to treat any proliferative disorders, or cancers.

Furthermore, the normal activation of c-Met (or HGF receptor) is responsible for "migration, survival (protection from apoptosis), and proliferation", and the **inappropriate** activation of c-Met is caused by mutation as disclosed by **Trusolino** (cited in applicant's remarks). Thus, to indicate an inhibitory concentration (IC_{50}) of a drug for c-Met does not mean that said drug would be effective to treat any cancer. Thus, the specification does not provide sufficient guidance for an oncologist to select the claimed compound to treat a wider range of caners.

The state of the prior art: There is a commercially known compound, Iressa or Gefitinib which, in a preclinical studies, is shown to treat cancers such as: prostate, ovarian, breast, colon, small-cell and non-small-cell lung, and ductal carcinoma. Even for the listed cancers, "only tumors in which inhibition of the receptor results in inhibition of down stream signaling pathways are growth arrested." (see **Grünwald V. et. al.** cited previously). Thus, the state of the art does not correlate the inhibition of c-Met to cancers broadly. Applicant cited several references trying to show the relationship between c-Met and cancers recited in the above claims. However, after reviewing said references, they all seem to teach the overexpresion of c-Met as a "**valuable marker**", rather than a causative factor (e.g., see Baykal (cited in the amendment), page 127, right column, line 6 beneath Table 3). Baykal indicated that it is the

tumor that causes the overexpression of c-Met, not the other way around. Thus, according to Baykal, "c-Met overexpression was found to be an independent variable for disease-free survival". Likewise, Elia found that "melanocyte-stimulating hormone (MSH), the physiological inducer of differentiation for melanocytes, was also a potent inducer of c-met expression". Thus, it is not the c-Met expression that causes the cellular differentiation. Therefore, the state of the art does **not** support the claimed method of treating various cancers by inhibiting c-Met.

The relative skill of those in the art: There has never been a compound capable of treating cancer generally, let alone treating a cancer by inhibiting a receptor that does **not** cause cellular differentiation, and whose overexpression only serves as a "marker". Various types of cancers affect organs differently as they can metastasize at a different rate. In the instant case, being that c-Met not a causative factor, inhibiting it would not treat any cancer. Therefore, it is beyond the skill of oncologists today to select the claimed compound to treat all types of cancers since the understanding in the art would not make it feasible.

The predictability or unpredictability of the art & The quantity of experimentation necessary: The pharmaceutical art has been known for its unpredictability due to various conflicting path ways, or biological factors that are sometimes genetically unique to individuals. In the instant case, the showing of IC_{50} value for c-Met alone does not guarantee the compound's effectiveness in treating the many cancers recited in the above claims.

See **Hoffman v. Klaus** 9 USPQ 2d 1657, and **Ex parte Powers** 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TAMTHOM N. TRUONG whose telephone number is (571)272-0676. The examiner can normally be reached on Monday thru Friday (9:00-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on 571-272-0661. 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.

Tamthom N. Truong
Examiner Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624

***
12-03-10

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	: Lynne Canne Bannen, et al.	Art Unit	: 1624
Serial No.	: 11/753,514	Examiner	: Tamthom Ngo Truong
Filed	: May 24, 2007	Attorney Docket:	224990/04-064C3-US/127533
Title	: C-MET MODULATORS AND METHOD OF USE		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO THE OFFICE ACTION DATED DECEMBER 23, 2010

Dear Sir:

This communication is responsive to the Office Action dated December 23, 2010.

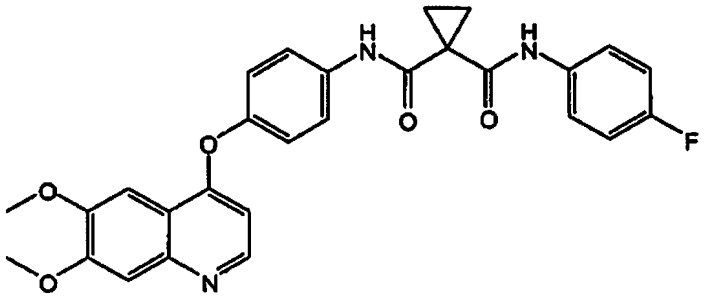
Claim Amendments begin on page 2.

Remarks begin on page 4.

Claim Amendments

1-110. Cancelled.

111. (Currently Amended) ~~The method of claim 108,~~ A method of treating a disease or disorder, comprising administering to a mammal in need of the treatment a therapeutically effective amount of a compound ~~according to wherein the compound has~~ having the following structure:



or a pharmaceutically acceptable salt thereof, or a composition containing a) a therapeutically effective amount of the compound or a pharmaceutically acceptable salt thereof; and optionally b) an excipient, wherein the disease or disorder is breast cancer, ovarian cancer, colorectal cancer, prostate cancer, or lung cancer or a pharmaceutically acceptable salt thereof.

112. Cancelled.

113. Cancelled.

114. (Previously Presented) The method according to claim 111, wherein the disease or disorder is lung cancer.

115. (Previously Presented) The method according to claim 111, wherein the disease or disorder is breast cancer.

116-120. Cancelled.

121. (Currently Amended) The method according to claim 111, wherein the disease or disorder is ovarian cancer ~~carcinoma~~.

122-125. Cancelled.

126. (Previously Presented) The method according to claim 111, wherein the disease or disorder is prostate carcinoma.

127-130. Cancelled.

131. (New) The method according to claim 111, wherein the disease or disorder is colorectal cancer.

Remarks

Claim Status

Claims 1-110, 112-113, 116-120, 122-125, and 127-130 are cancelled.

Claims 111 and 121 are currently amended.

Claims 114-115 and 126 are previously presented.

Claim 131 is new. Support for the inclusion of "breast cancer" in claim 131 is found in paragraph 13 of the specification. Thus, the inclusion of "breast cancer" does not constitute new matter.

Claims 114-115, 121, 126, and 131 depend from claim 111. Each recites individually an indication that was recited in now-cancelled 108 recited and in currently amended claim 111; therefore, these claims do not constitute new matter.

Thus, claims 111, 114-115, 121, 126, and 131 are currently pending.

By amending the claims, the Applicant does not concede that the available patent coverage would not extend as far as the original claim. Rather, the Applicant reserves the right to file continuation applications to pursue the breadth of the claims as filed. Further, by the present amendments, it does not follow that the amended claims have become so perfect in their description that no one could devise an equivalent. After amendment, as before, limitations in the ability to describe the present invention in language in the patent claims naturally prevent the Applicant from capturing every nuance of the invention or describing with complete precision the range of its novelty or every possible equivalent. See, Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 62 USPQ2d 1705 (2002). Accordingly, the foregoing amendments are made specifically in the interest of expediting prosecution and there is no intention of surrendering any range of equivalents to which the Applicant would otherwise be entitled.

The Applicant further submits that this Amendment After Final Rejection places this application in condition for allowance by amending the claims in manners that are believed to render all pending claims allowable. Accordingly, entry of the present claim amendments is an earnest attempt to advance prosecution toward allowance. Applicant respectfully requests that the Office will inform Applicants if, for any reason, the presently amended claims are not accepted.

Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner maintains the rejection of the claims under 35 U.S.C. § 112, First Paragraph. The Examiner alleges that the specification, while being enabling for making the compound recited in claim 111, is not enabled for a method of treating the list of cancers recited in the previously pending claims using the compound of claim 111.

The compound of claim 111 is in Phase II and Phase III clinical trials for the treatment of a range of cancers. The Applicant provided both references and clinical data supporting the method. Positive results included tumor shrinkage and the disappearance of bone lesions in patients with various forms of cancer.

However, in a good faith attempt at putting the claims in condition for allowance, the Applicant has amended claim 111 and cancelled claims 116-120 and 122-125. The currently pending claims recite a method for treating cancer that includes breast cancer, ovarian cancer, colorectal cancer, prostate cancer, and lung cancer. In the July 20, 2010 Office Action, the Examiner indicated that the method was enabled for these cancers (see page 4, Number 3 of the July 20, 2010 Office Action).

Accordingly, the Applicant respectfully requests that the rejection under 35 U.S.C. § 112, First Paragraph, be reconsidered and withdrawn in light of the Examiner's original determination that the method is enabled with respect to the treatment of breast cancer, ovarian cancer, colorectal cancer, prostate cancer, and lung cancer, and that currently pending claims 11, 114-115, 121, 126, and 131 are allowable for at least this reason.

Conclusion

It is believed that no additional fees are required for this reply. However, if there are any additional charges, please apply them to the same Deposit Account No. 503145, referencing the same Attorney Docket No. 224990/04-064C3-US/127533.

Respectfully submitted,

Date: March 23, 2011

Heidi M. Berven, Ph.D.
Attorney for Applicant
Reg. No. 48,951

Honigman Miller Schwartz and Cohn LLP
350West Michigan Avenue
Kalamazoo, MI 49007
Telephone: (269) 337-7710
Facsimile: (269) 337-7711

ACTIVE 8904159.1

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 NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/753,514	05/24/2007	LYNNE CANNE BANNEN	224990/04-064C3-US/127533	5697

91684 7590 06/16/2011

JONATHAN P. O'BRIEN, PH.D.
HONIGMAN MILLER SCHWARTZ AND COHN LLP
350 EAST MICHIGAN AVENUE, SUITE 300
Kalamazoo, MI 49007-3800

EXAMINER	
BERNHARDT, EMILY B	
ART UNIT	**PAPER NUMBER**
1624	

MAIL DATE	DELIVERY MODE
06/16/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

While applicants have presented evidence of actual cancer testing in a previous response (filed 11/11/10) for instant compound, descriptive support for the cancers currently (but never originally) claimed is not entirely seen in the disclosure as originally filed. Only lung cancer, ovarian carcinoma and prostate carcinoma are seen to be described in the list of cancers set forth on pp. 160-161 of applicants' specification and claimed for the first time in the amendment filed on 1/29/08.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Bernhardt whose telephone number is 571-272-0664.

If attempts to reach the examiner by telephone are unsuccessful, the acting supervisor for AU 1624, James O. Wilson can be reached at 571-272-0661. 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.

/Emily Bernhardt/
Primary Examiner, Art Unit 1624

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DO NOT ENTER: /E.B./ 06/14/2011

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Lynne Canne Bannen, et al.	Art Unit : 1624
Serial No.	:	11/753,514	Examiner : Tamthom Ngo Truong
Filed	:	May 24, 2007	Attorney Docket: 224990/04-064C3-US/127533
Title	:	C-MET MODULATORS AND METHOD OF USE	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO THE OFFICE ACTION DATED DECEMBER 23, 2010

Dear Sir:

This communication is responsive to the Office Action dated December 23, 2010.

Claim Amendments begin on page 2.

Remarks begin on page 4.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 11/753,514	**Applicant(s)** BANNEN ET AL.
	Examiner EMILY BERNHARDT	**Art Unit** 1624

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 23 March 2011 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☒ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See attached response*. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: _____.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Emily Bernhardt/
Primary Examiner, Art Unit 1624

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. 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.

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	11/753,514	Filing Date	2007-05-24	Docket Number (if applicable)	224990/04-064C3-US/127533	Art Unit	1624
First Named Inventor	LYNNE CANNE BANNEN			Examiner Name	BERNHARDT, EMILY B		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

☐ Other _____

☒ Enclosed

☒ Amendment/Reply

☐ Information Disclosure Statement (IDS)

☐ Affidavit(s)/ Declaration(s)

☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 503145

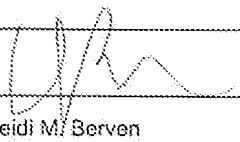
SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. 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.

Signature of Registered U.S. Patent Practitioner			
Signature		Date (YYYY-MM-DD)	2011-06-23
Name	Heidi M. Berven	Registration Number	48951

This collection of information is required by 37 CFR 1.114. 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.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Lynne Canne Bannen, et al. Art Unit : 1624
Serial No. : 11/753,514 Examiner : Emily B. Bernhardt
Filed : May 24, 2007 Attorney Docket: 224990/04-064C3-US/127533
Title : C-MET MODULATORS AND METHOD OF USE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CONTINUED EXAMINATION UNDER 37 CFR § 1.114

Dear Sir:

This Request for Continued Examination (RCE) is filed under 37 CFR § 1.114.

A submission and fee in support of Applicant's RCE is enclosed.

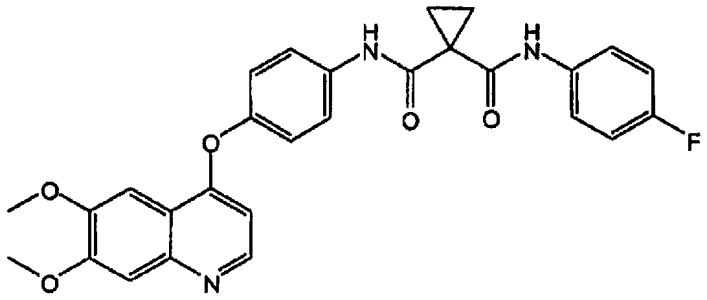
Amendments to the Claims begin on page 2.

Applicant's Remarks begin on page 4.

CLAIM AMENDMENTS

1-110. Cancelled.

111. (Currently Amended) A method of treating a disease or disorder, comprising administering to a mammal in need of the treatment a therapeutically effective amount of a compound having the following structure:



or a pharmaceutically acceptable salt thereof, or a composition containing a) a therapeutically effective amount of the compound or a pharmaceutically acceptable salt thereof; and optionally b) an excipient, wherein the disease or disorder is ~~breast cancer~~, ovarian cancer, ~~colorectal cancer~~, prostate cancer, or lung cancer or a pharmaceutically acceptable salt thereof.

112. Cancelled.

113. Cancelled.

114. (Previously Presented) The method according to claim 111, wherein the disease or disorder is lung cancer.

115-120. Cancelled.

121. (Previously Presented) The method according to claim 111, wherein the disease or disorder is ovarian cancer.

122-125. Cancelled.

126. (Currently Amended) The method according to claim 111, wherein the disease or disorder is prostate cancer ~~carcinoma~~.

127-131. Cancelled.

Summary of Interview Conducted June 23, 2011

The Applicant's representatives Heidi M. Berven and Jonathan P. O'Brien thank Examiner Bernhardt for participating in the telephone interview conducted June 23, 2011 regarding the Advisory Action mailed June 16, 2011. In the interview, the Applicant's representatives proposed to amend claim 111 to recite lung cancer, ovarian cancer, and prostate cancer and to amend the dependant claims accordingly. The Applicant's representatives cited paragraph 255, pages 160-161 as providing antecedent basis for these cancers. The Examiner indicated that she was amenable to such an amendment pending a final search. The Applicant's representatives now file the proposed claim amendments as the submission accompanying this Request for Continued Examination.

Claim Status

In this filing, claims 115 and 131 have been cancelled. Claim 111 has been amended by deleting breast cancer and colorectal cancer from the claim. Claim 126 has been amended by replacing the word "carcinoma" with the word "cancer." Support for the use of the word cancer can be found in the specification at page 9, paragraph 34, second sentence and page 160, paragraph 255, first sentence.

Thus, the claim status is as follows:

Claims 1-110, 112-113, 115-120, 122-125, and 127-131 are cancelled.

Claims 114 and 121 are previously presented.

Claims 111 and 126 are currently amended.

Thus, claims 111, 114, 121, and 126 are currently pending.

The claim amendments are made in the interest of expediting prosecution. The Applicant respectfully requests the timely allowance of the amended claims.

The Applicant does not intend to surrender any range of equivalents to which the Applicant would otherwise be entitled in view of the prior art, nor does the Applicant agree with the Examiner's comments or arguments about the art cited in the Office Action. Further, by the present amendment, it does not follow that the amended claims have become so perfect in their description that no one could devise an equivalent. After amendment, as before, limitations in the ability to describe the present invention in language in the patent claims naturally prevent the Applicant from capturing every nuance of the invention or describing with complete precision

the range of its novelty or every possible equivalent. See, Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 62 USPQ2d 1705 (2002). Accordingly, the foregoing amendments are made specifically in the interest of expediting prosecution and there is no intention of surrendering any range of equivalents to which the Applicant would otherwise be entitled.

The Applicant does not concede that patent coverage available to them would not extend as far as the original claim by amending the claims. Finally, the Applicant reserves the right to file divisional and/or continuation applications to pursue the breadth of the claims as originally filed.

Remarks Regarding Examiner's Advisory Action Dated June 16, 2011.

In the Advisory Action dated June 16, 2011, the Examiner questioned the support provided by the specification for various cancers. As the Applicant's representatives and the Examiner discussed, paragraph 255, pages 160-161 of the specification provides antecedent basis for at least lung, ovarian, and prostate cancer, amongst others. As a result, claim 111 has been amended to recite these cancers.

Conclusion

It is believed that a fee of $405 is required at this time for filing a Request for Continued Examination. However, if there are any additional charges, please apply them to the same Deposit Account No. 503145, referencing the same Attorney Docket No. 224990/04-064C3-US/127533.

Respectfully submitted,

Date: June 23, 2011

Heidi M. Berven, Ph.D.
Attorney for Applicant
Reg. No. 48,951

Honigman Miller Schwartz and Cohn LLP
350West Michigan Avenue
Kalamazoo, MI 49007
Telephone: (269) 337-7710
Facsimile: (269) 337-7711
9285961.1

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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NOTICE OF ALLOWANCE AND FEE(S) DUE

91684 7590 07/01/2011

JONATHAN P. O'BRIEN, PH.D.
HONIGMAN MILLER SCHWARTZ AND COHN LLP
350 EAST MICHIGAN AVENUE, SUITE 300
Kalamazoo, MI 49007-3800

EXAMINER
BERNHARDT, EMILY B

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 07/01/2011

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/753,514	05/24/2007	LYNNE CANNE BANNEN	224990/04-064C3-US/127533	5697

TITLE OF INVENTION: C-MET MODULATORS AND METHODS OF USE

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$0	$1810	10/03/2011

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 SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

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 07/01/2011

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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.
11/753,514	05/24/2007	LYNNE CANNE BANNEN	224990/04-064C3-US/127533	5697

TITLE OF INVENTION: C-MET MODULATORS AND METHODS OF USE

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$0	$1810	10/03/2011

EXAMINER	ART UNIT	CLASS-SUBCLASS
BERNHARDT, EMILY B	1624	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 credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information 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.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/753,514	05/24/2007	LYNNE CANNE BANNEN	224990/04-064C3-US/127533	5697

91684 7590 07/01/2011
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Kalamazoo, MI 49007-3800

EXAMINER	
BERNHARDT, EMILY B	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 07/01/2011

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 612 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 612 day(s).

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 Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

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.	Applicant(s)
	11/753,514	BANNEN ET AL.
	Examiner	Art Unit
	EMILY BERNHARDT	1624

-- 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 *6/23/11 (RCE request)*.

2. ☒ The allowed claim(s) is/are *111,114,121 and 126*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   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 a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ 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)	5. ☐ Notice of Informal Patent Application
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)	6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
3. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____	7. ☐ Examiner's Amendment/Comment
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material	8. ☐ Examiner's Statement of Reasons for Allowance
	9. ☐ Other _____.
/Emily Bernhardt/ Primary Examiner, Art Unit 1624	