

METHODS OF PREPARING QUINOLINE DERIVATIVES

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] This disclosure relates to methods of preparing compounds useful for modulating protein kinase enzymatic activity. More specifically, this disclosure relates to methods of preparing compounds useful for modulating cellular activities such as proliferation, differentiation, programmed cell death, migration and chemoinvasion.

Summary of the Related Art

[0002] 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.

[0003] 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).

[0004] Therapeutic use of kinase modulation can relate 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.

[0005] 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.

[0006] A target of interest 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.

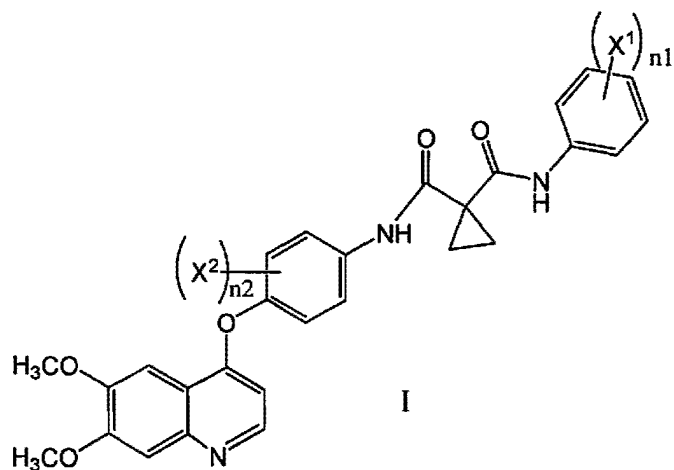
[0007] The endogenous ligand for c-Met is the hepatocyte growth factor (HGF), a potent inducer of angiogenesis, also known as "scatter factor" (SF). Binding of HGF to c-Met induces activation of the receptor via autophosphorylation resulting in an increase of receptor dependent signaling, which promotes 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).

[0008] 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.

[0009] Accordingly, there is a need for new methods of making compounds that are protein kinase modulators.

SUMMARY OF THE INVENTION

[0010] In one aspect, the disclosure relates to methods of preparing compounds of formula I:



or a pharmaceutically acceptable salt thereof, wherein:

X^1 is H, Br, Cl or F;

X^2 is H, Br, Cl or F;

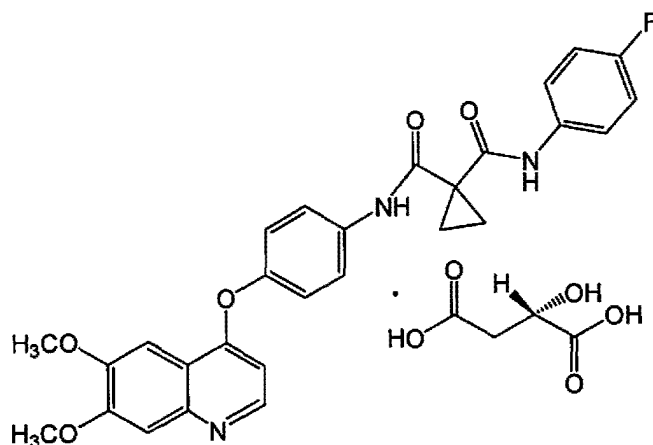
$n1$ is 1-2; and

$n2$ is 1-2,

[0011] Intermediates useful in preparing the above compounds are also disclosed.

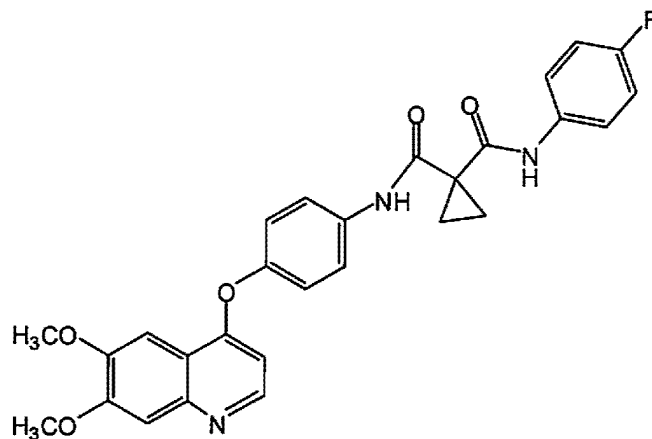
[0012] The compounds of formula I are useful as protein kinase modulators, and they inhibit various protein kinases including Ret and c-Met.

[0013] In another aspect, the invention provides a method for preparing a compound of formula IB



Formula IB

from a compound of formula IA

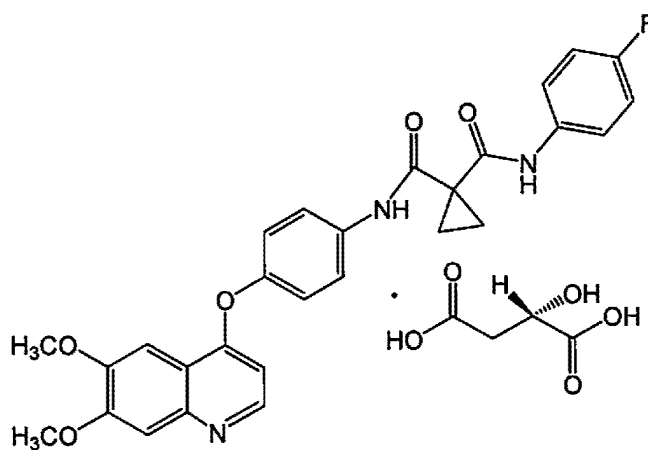


Formula IA

comprising:

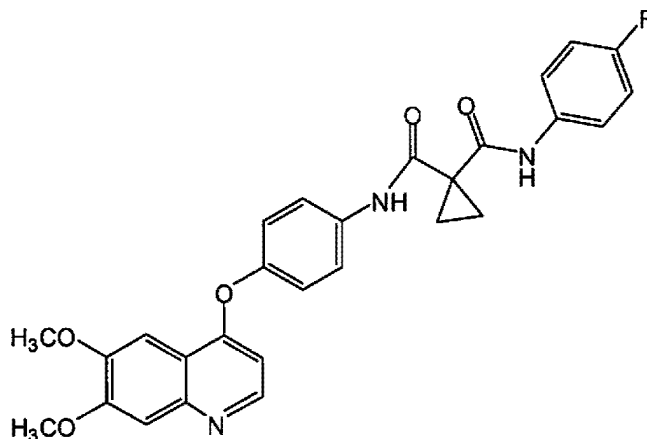
- (a) heating and agitating a mixture comprising a compound of formula IA and L-malic acid, methylethyl ketone, and water; and
- (b) cooling the mixture; and
- (c) vacuum distilling the mixture successively; and
- (d) isolating the compound of formula IB by filtration.

[0014] In another aspect, the invention provides a method for preparing a compound of formula IB



Formula IB

from a compound of formula IA



Formula IA

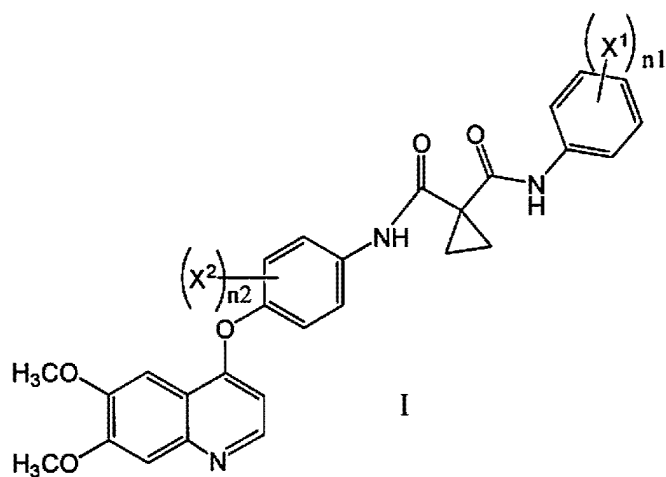
comprising:

- (a) heating and agitating a mixture comprising a compound of formula IA and L-malic acid, methylethyl ketone, and water; and
- (b) cooling the mixture;
- (c) seeding the mixture with the compound of formula IB;
- (d) vacuum distilling the mixture; and
- (d) isolating the compound of formula IB by filtration.

[0015] There are many different aspects and embodiments of the disclosure described hereinbelow, and each aspect and each embodiment is non-limiting in regard to the scope of the disclosure. The terms “aspects” and “embodiments” are meant to be non-limiting regardless of where the terms “aspect” or “embodiment” appears in this specification. The transitional term "comprising" as used herein, which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements.

DETAILED DESCRIPTION OF THE INVENTION

[0016] Aspect (1) of this disclosure relates to a method of preparing a compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein:

X^1 is H, Br, Cl or F;

X^2 is H, Br, Cl or F;

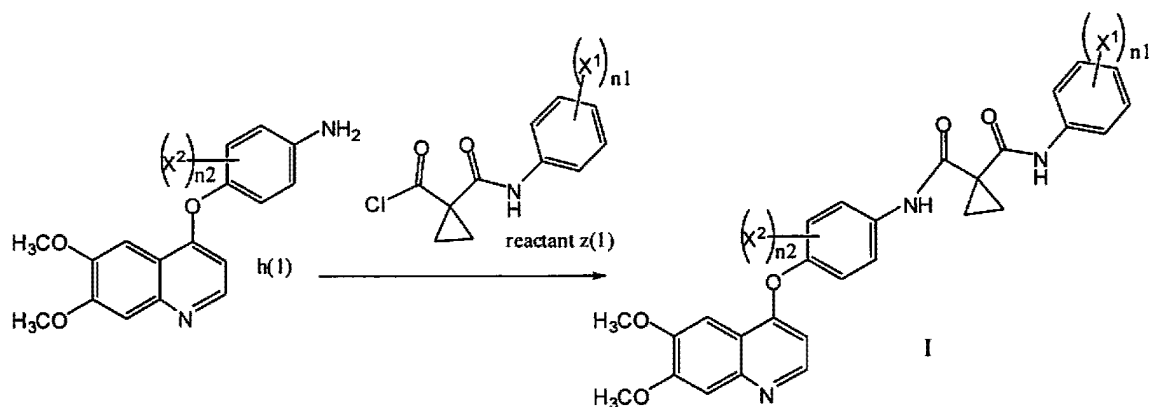
n_1 is 1-2; and

n_2 is 1-2,

the method comprising:

contacting the compound of formula g(1) with reactant z(1) to yield the compound of

Formula I:



[0017] The reaction in Aspect (1) of this disclosure is advantageously carried out under suitable reaction conditions. Non-limiting examples of suitable reaction conditions in Aspect (1) include using basic conditions. Non-limiting examples of basic conditions that can be used in Aspect (1) of this disclosure include the use of inorganic bases, such as aqueous KOH, NaOH, K_2CO_3 , Na_2CO_3 , K_3PO_4 , Na_3PO_4 , K_2HPO_4 , Na_2HPO_4 , and the like, or mixtures thereof. Other non-limiting examples of suitable reaction conditions in Aspect (1) include using suitable solvents. Non-limiting examples of suitable solvents that can be used in Aspect (1) of this disclosure include water miscible solvents, such as THF, acetone, ethanol,

and the like, or mixtures thereof. Other non-limiting examples of suitable reaction conditions in Aspect (1) include using suitable temperatures. Suitable temperatures that may be used for the reaction in Aspect (1) include a temperature at a range of from about 10°C to about 30°C, or alternatively, at a range of from about 15°C to about 28°C, or alternatively, at a range of from about 20°C to about 25°C. The product formed in Aspect (1) is in the free base form and this free base form may be converted into a pharmaceutically acceptable salt thereof, by methods known in the art. In one example, the compound of formula I can be converted to its bis-maleate salt by the addition of maleic acid and a suitable solvent. In another example, the compound of formula I can be converted to its bis-phosphate salt by the addition of phosphoric acid and a suitable solvent.

[0018] Utilities of the compound of Formula I are further described in WO 2005/030140 A2.

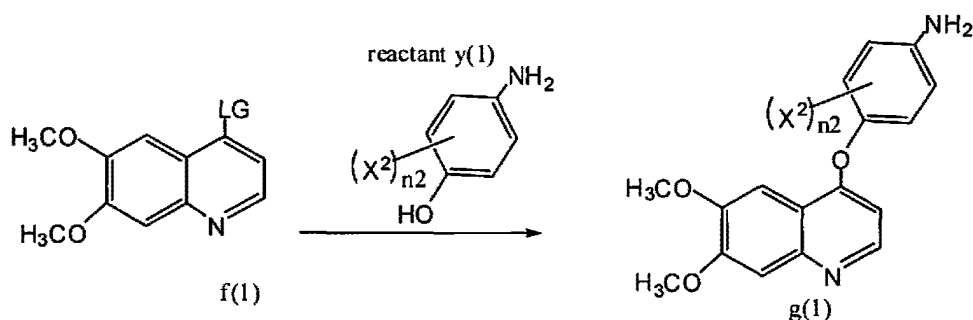
Embodiments of Aspect (1) (Part A)

- [0019] In another embodiment of Aspect (1), X^1 is Cl or F.
- [0020] In another embodiment of Aspect (1), X^2 is Cl or F.
- [0021] In another embodiment of Aspect (1), X^1 is F.
- [0022] In another embodiment of Aspect (1), X^2 is F.
- [0023] In another embodiment of Aspect (1), X^1 is H.
- [0024] In another embodiment of Aspect (1), X^2 is H.
- [0025] In another embodiment of Aspect (1), n_1 is 1.
- [0026] In another embodiment of Aspect (1), n_2 is 1.
- [0027] In another embodiment of Aspect (1), n_1 is 2.
- [0028] In another embodiment of Aspect (1), n_2 is 2.
- [0029] All compounds of formula I for Aspect (1) disclosed above include any of the disclosed alternative embodiments in Part A for each of X^1 , X^2 , n_1 or n_2 , in combination with any other of the disclosed alternative embodiments in Part A for each of X^1 , X^2 , n_1 , or n_2 , as well as a pharmaceutically acceptable salt of any such combination.

Embodiments of Aspect (1) Part B

- [0030] In another embodiment of Aspect (1), n_1 and n_2 are each 1.
- [0031] In another embodiment of Aspect (1), n_1 and n_2 are each 2.
- [0032] In another embodiment of Aspect (1), n_1 is 1; and n_2 is 2.
- [0033] In another embodiment of Aspect (1), n_1 is 2 and n_2 is 1.

- [0034] In another embodiment of Aspect (1), X^1 is H; and X^2 is F.
- [0035] In another embodiment of Aspect (1), X^1 is F; and X^2 is H.
- [0036] In another embodiment of Aspect (1), X^1 and X^2 are each H.
- [0037] In another embodiment of Aspect (1), X^1 and X^2 are each F.
- [0038] In another embodiment of Aspect (1), X^1 is Cl; and X^2 is H.
- [0039] In another embodiment of Aspect (1), X^1 is H; and X^2 is Cl.
- [0040] In another embodiment of Aspect (1), X^1 and X^2 are each Cl.
- [0041] In another embodiment of Aspect (1), X^1 is Cl; and X^2 is F.
- [0042] In another embodiment of Aspect (1), X^1 is F; and X^2 is Cl.
- [0043] In embodiment (C) of Aspect (1), the compound of formula g(1) can be made by reacting a compound of formula f(1) with reactant y(1) to yield the compound of g(1):



wherein LG represents a leaving group, and each of X^2 , and n_2 are as defined in Aspect (1), or as in any of the embodiments of Aspect (1) (Part A), of this disclosure. A non-limiting example of a leaving group includes halo groups (such as Cl, Br or F). Various compounds of reactant y(1) are commercially available, such as 2-fluoro-4-aminophenol and 4-aminophenol. Also, the skilled artisan would be able to make any variation of reactant y(1) using commercially available starting materials and by using known techniques to modify these commercially available starting materials to come up with various compounds within the scope of reactant y(1).

[0044] The reaction in embodiment (C) of Aspect (1) of this disclosure is advantageously carried out under suitable reaction conditions. Non-limiting examples of suitable reaction conditions in embodiment (C) of Aspect (1) include using suitable solvents such as polar solvents. Non-limiting examples of polar solvents that can be used include tetrahydrofuran (THF), dimethylacetamide (DMA), dimethylsulfoxide (DMSO), dimethylformamide (DMF), ethyl acetate, N-methyl pyrrolidone (NMP), propylene carbonate, and the like, or mixtures thereof. In another embodiment, the polar solvent is dimethylacetamide (DMA). In another embodiment, the polar solvent is dimethylsulfoxide (DMSO). In another embodiment, the

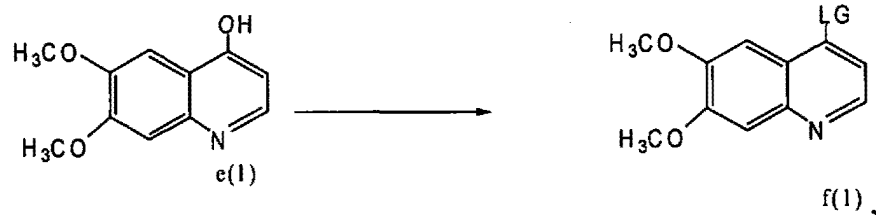
polar solvent is dimethylformamide (DMF). In another embodiment, the polar solvent is ethyl acetate. In another embodiment, the polar solvent is N-methyl pyrrolidone (NMP). In another embodiment, the polar solvent is propylene carbonate. In another embodiment, the solvent is a mixture of solvents, such as a mixture comprising THF and DMA.

[0045] In embodiment (C) of Aspect (1), the reactants f(1) and y(1) can be added together at a temperature ranging from about 10°C to about 30°C, or alternatively, from about 15°C to about 28°C, or alternatively, from about 20°C to about 25°C. The mixture is then heated to a temperature ranging from about 80°C to about 125°C, or alternatively, from about 95°C to about 110°C, or alternatively, from about 100°C to about 105°C, and the selected temperature is maintained until the reaction is complete.

[0046] Other non-limiting examples of suitable reaction conditions in this step of Aspect (1) include the use of a suitable base, such as non-nucleophilic base. Non-limiting examples of non-nucleophilic bases that can be used include lithium diisopropylamide, lithium tetramethylpiperidide and alkali metal alkoxides such as sodium tert-butoxide, potassium tert-butoxide, sodium-pentoxide, and the like, or mixtures thereof. Preferably, the base is sodium tert-butoxide or sodium tert-pentoxide or the like.

[0047] Once the reaction is substantially complete, the reaction mixture can be cooled to a temperature ranging from about 10°C to about 25°C. Precooled water can be charged at rate to maintain a temperature that ranges from about 5°C to about 35°C. Alternatively, the precooled water can be charged at rate to maintain a temperature that ranges from about 10°C to about 25°C. As a non-limiting example, the precooled water can be at a temperature ranging from about 0°C to about 10°C. As another non-limiting example, the precooled water can be at a temperature ranging from about 2°C to about 7°C. The precipitate can be collected by filtration under standard conditions and purified by standard purification techniques.

[0048] In embodiment (D) of Aspect (1), the compound of formula f(1) can be made by converting a compound of formula e(1) to the compound of formula f(1):

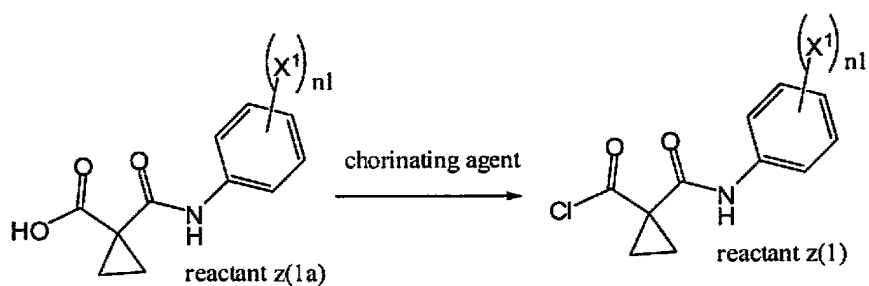


wherein LG represents a leaving group. A non-limiting example of a leaving group that could be used in embodiment (D) of Aspect (1) include halo groups (such as Cl, Br or F) that

can be added by halogenating agents. Non-limiting examples of halogenating agents that can be used in embodiment (D) of Aspect (1) include chlorinating agents, such as SOCl_2 , SO_2Cl_2 , COCl_2 , PCl_5 , POCl_3 , and the like.

[0049] The reaction in embodiment (D) of Aspect (1) of this disclosure is advantageously carried out under suitable reaction conditions. Non-limiting examples of suitable reaction conditions in embodiment (D) of Aspect (1) include the use of suitable solvents. Non-limiting example of suitable solvents that can be used in embodiment (D) of Aspect (1) during the halogenation of the compound of formula e(1) include a polar, aprotic solvent, such as CH_3CN , DMF, and the like, or mixtures thereof. In other embodiments, the chlorination can be carried out using POCl_3 in acetonitrile, COCl_2 in DMF, or SOCl_2 in DMF. The addition of the chlorination agent is advantageously carried out at a temperature ranging from about 60°C to about 90°C . In another embodiment, the addition of the chlorination agent can be carried out at a temperature ranging from about 70°C to about 85°C . In another embodiment, the addition of the chlorination agent can be carried out at a temperature ranging from about 74°C to about 80°C . The product can then be collected by filtration and purified using standard techniques.

[0050] In embodiment (E) of Aspect (1) of this disclosure, reactant z(1) can be made by reacting reactant z(1a) with a chlorinating agent to yield reactant z(1):

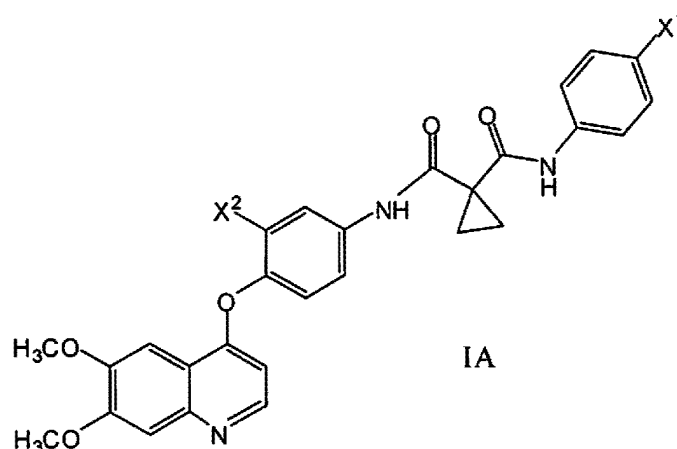


wherein X^1 is Br, Cl or F; and $n1$ is 1-2. Compounds of reactant z(1a) can be made according to the method described in Example 25 of WO 2005/030140 A2, and the skilled artisan would be able to make any necessary substitutions using commercially available starting materials to come up with various compounds within the scope of reactant z(1a). Example 25 in WO 2005/030140 A2 is incorporated herein by reference.

[0051] The reaction in embodiment (E) of Aspect (1) of this disclosure is advantageously carried out under suitable reaction conditions. Non-limiting examples of suitable reaction conditions in embodiment (E) of Aspect (1) include using a chlorinating agent such as POCl_3 , oxalyl chloride, and the like. In another embodiment of embodiment (E) of Aspect (1), oxalyl chloride is used as a chlorinating agent. Non-limiting examples of suitable reaction

conditions in embodiment (E) of Aspect (1) include carrying out the reaction at a temperature in the range from about 0°C to about 25°C, or alternatively at a temperature in the range from about 5°C to about 20°C. Other non-limiting examples of suitable reaction conditions in embodiment (E) of Aspect include carrying out the reaction in a suitable solvent. Non-limiting examples of suitable solvents that can be used in embodiment (E) of Aspect (1) include polar, aprotic solvents such as halogenated hydrocarbons, *i.e.*, dichloromethane, chloroform; or ethers, *i.e.*, Et₂O, dioxane, tetrahydrofuran (THF) containing catalytic DMF, and the like, or mixtures thereof. The resulting solution containing reactant z(1) can be used, without further processing, to make the compound of formula I in Aspect (1) of this disclosure.

[0052] In another embodiment of Aspect (1) of this disclosure, the compound of formula I is of formula I(A):

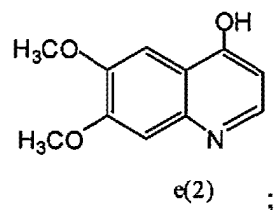


or a pharmaceutically acceptable salt thereof, wherein:

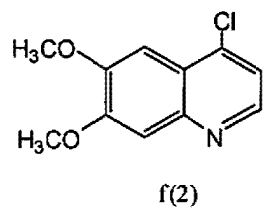
X¹ is H, Cl, Br or F; and

X² is H, Cl, Br or F. As mentioned above for the compound of formula I, the compound of formula I(A) can be in the free base form or it can be converted to a pharmaceutically acceptable salt thereof. Accordingly, the compound of formula I(A) can be converted to its bis-maleate salt by the addition of maleic acid and a suitable solvent, or the compound of formula I(A) can be converted to its bis-phosphate salt by the addition of phosphoric acid and a suitable solvent.

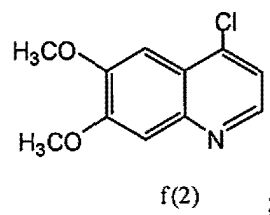
[0053] In another embodiment of Aspect (1), embodiment (D) of this disclosure, the compound of formula e(1) is of formula e(2):



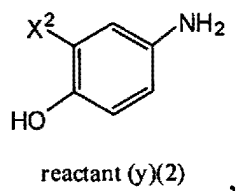
and the compound of formula f(1) is of formula f(2):



[0054] In another embodiment of Aspect (1), embodiment (C) of this disclosure, the compound of formula f(1) is of formula f(2):

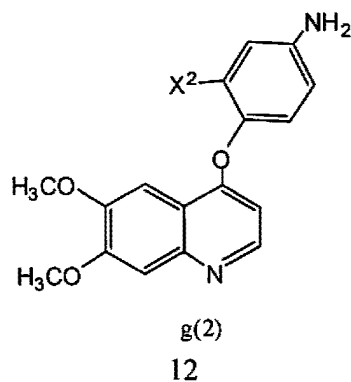


reactant y(1) is reactant (y)(2):



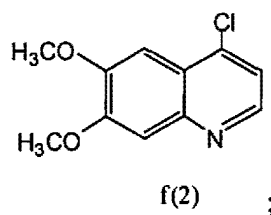
wherein X^2 is hydrogen or fluoro;

the compound of formula g(1) is of formula g(2):

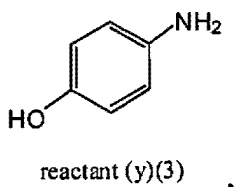


[0055] In a further embodiment of the previous embodiment, the reaction employs a non-nucleophilic base. In a further embodiment of the previous embodiment, the non-nucleophilic base is an alkali metal alkoxide; and the reaction is carried out in a polar solvent. In a further embodiment of the previous embodiment, the alkali metal alkoxide is sodium tert-butoxide, and the polar solvent is DMA.

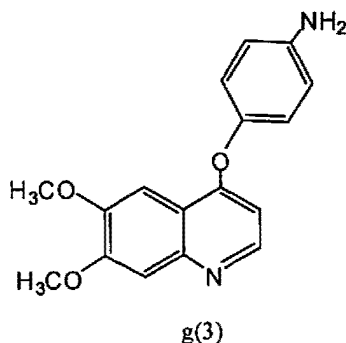
[0056] In another embodiment of Aspect (1), embodiment (C) of this disclosure, the compound of formula f(1) is of formula f(2):



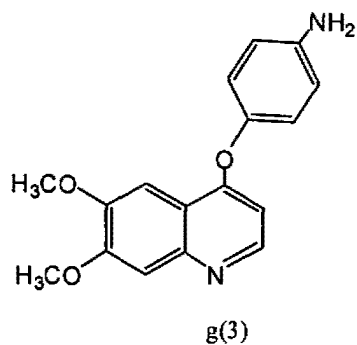
reactant y(1) is reactant (y)(3):



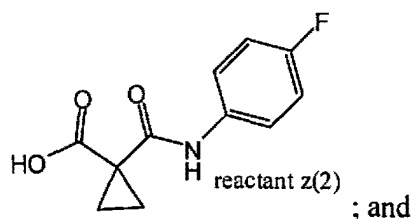
wherein X² is hydrogen or fluoro; and
the compound of formula g(1) is of formula g(3):



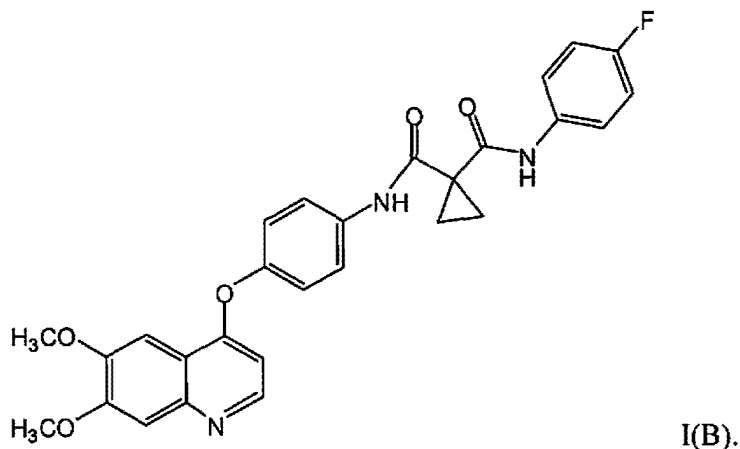
[0057] In another embodiment of Aspect (1) of this disclosure, the compound of formula g(1) is of formula g(3):



reactant z(1) is reactant (z)(2):



the compound of formula I is of formula I(B):



[0058] In a further embodiment of the previous embodiment, the reaction is carried out in the presence of an inorganic base. In a further embodiment of the previous embodiment, the inorganic base is K_2CO_3 , and the solvent employed in this reaction is a combination of THF and H_2O .

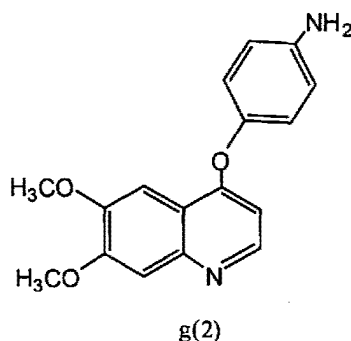
[0059] In another embodiment of Aspect (1) of this disclosure, X^1 and X^2 for each of formula g(1) and reactant z(1) are each selected from Cl or F. In another embodiment of Aspect (1) of this disclosure, X^1 and X^2 for each of formula g(2), and reactant z(1) are both F.

[0060] The compound of formula f(2), or a pharmaceutically acceptable salt thereof, can be made by converting the compound of formula e(2) to a compound of formula f(2) with a chlorinating agent in a suitable solvent:

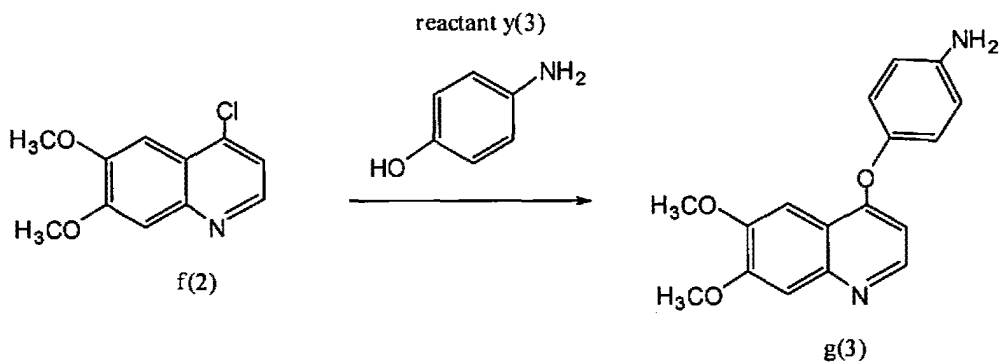


The compound of formula f(2) can be in its free base form or converted to a pharmaceutically acceptable salt thereof. The reaction conditions that can be used in this aspect include any of the reaction conditions disclosed in embodiment (E) of Aspect (1).

[0061] Aspect (2) of the disclosure relates to a method of preparing a compound of formula g(2):



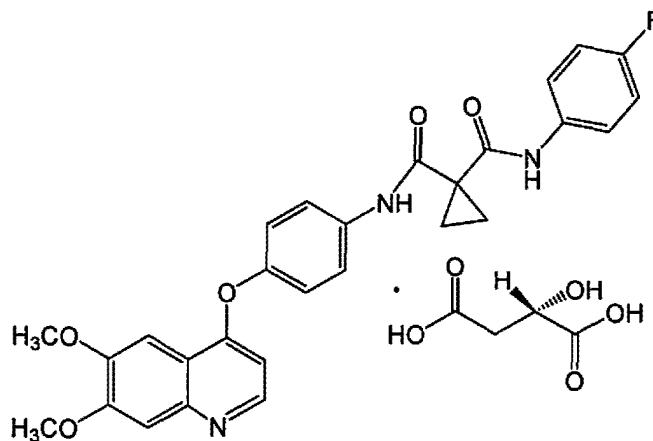
or a pharmaceutically acceptable salt thereof, the method comprising reacting the compound of formula f(2) with reactant y(3) under basic conditions in an appropriate solvent (2,6-lutidine is a sterically hindered organic mild base) to yield the compound of g(3):



The reaction conditions that can be used in this aspect include any of the reaction conditions disclosed in embodiment (C) of Aspect (1).

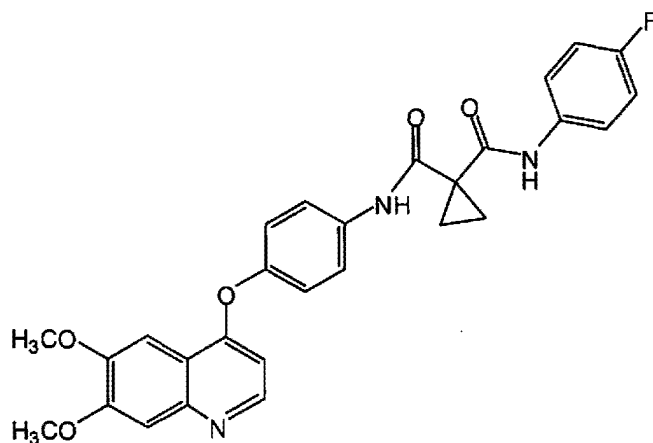
[0062] The reaction conditions that can be used in this aspect include any of the reaction conditions disclosed in alternative embodiments for embodiments (C) and (D) of Aspect (1).

[0063] As indicated above, in one aspect, the invention provides a method for preparing a compound of formula IB



Formula IB

from a compound of formula IA



Formula IA

comprising:

- (a) heating and agitating a mixture comprising a compound of formula IA and L-malic acid, methylethyl ketone, and water; and
- (b) cooling the mixture; and
- (c) vacuum distilling the mixture successively; and
- (d) isolating the compound of formula IB by filtration.

[0064] In one embodiment of this aspect, the compound of formula IA is admixed with a sufficient amount of L-malic acid in a methylethyl ketone/water (1:1) mixture. Alternatively, L-malic acid is added as a solution in water to a mixture of a compound of formula IA in methyl ethyl ketone. Generally the amount of L-malic is greater than 1 molar equivalent relative to the compound of formula IA. The mixture of the compound of formula IA and L-

malic acid in MEK/water is heated at about 40-70 °C and preferably at about 50-60 °C, and more preferably at about 55-60 °C with agitation, such as by stirring or the like, for from 1 to about 5 hours. At the end of the heating, the mixture is optionally clarified by filtering to give a clear solution. The resulting clear solution is then vacuum distilled from 1 to about 5 times at 150 to 200 mm Hg and a maximum jacket temperature of 55 °C to provide the desired crystalline compound of formula IB.

[0065] In one embodiment, L-malic acid is charged as a solution in water to the compound of formula IA. Generally the amount of L-malic is greater than 1 molar equivalent relative to the compound of formula IA. The mixture of the compound of formula IA and L-malic acid in MEK/water is heated at about 40-70 °C and preferably at about 50-60 °C, and more preferably at about 55-60 °C with agitation, such as by stirring or the like, for from 1 to about 5 hours. At the end of the heating, the mixture is optionally clarified by filtering to give a clear solution which is at a temperature of about 30-40 °C, and more preferably at a temperature of about 33-37 °C. This clear solution is optionally seeded to facilitate crystallization. After seeding, the resulting mixture is vacuum distilled as provided above.

Definitions

[0066] 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.

[0067] The word “can” is used in a non-limiting sense and in contradistinction to the word “must.” Thus, for example, in many aspects of the invention a certain element is described as “can” having a specified identity, which is meant to convey that the subject element is permitted to have that identity according to the invention but is not required to have it.

[0068] If a group “R” is depicted as “floating” on a ring system, then unless otherwise defined, the substituent(s) “R” can reside on any atom of the ring system, assuming replacement of a depicted, implied, or expressly defined hydrogen from one of the ring atoms, so long as a stable structure is formed.

[0069] 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 can

reside on any atoms of the ring system, again assuming each replaces a depicted, implied, or expressly defined hydrogen on the ring.

[0070] Pharmaceutically acceptable salts include acid addition salts.

[0071] "Pharmaceutically acceptable acid addition salt" refers to those salts that retain the biological effectiveness of the free bases and that are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, or mixtures thereof, as well as organic acids such as acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like, or mixtures thereof.

[0072] The disclosure is further illustrated by the following examples, which are not to be construed as limiting the disclosure in scope or spirit to the specific procedures described in them.

[0073] Unless specified otherwise, the starting materials and various intermediates may be obtained from commercial sources, prepared from commercially available organic compounds, or prepared using well-known synthetic methods.

Experimental Procedures

[0074] The invention is illustrated further by the following examples in Scheme 1 and the description thereof, which are not to be construed as limiting the invention in scope or spirit to the specific procedures described in them. Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the invention, as demonstrated by the following examples. Those skilled in the art will also recognize that it may be necessary to utilize different solvents or reagents to achieve some of the above transformations.

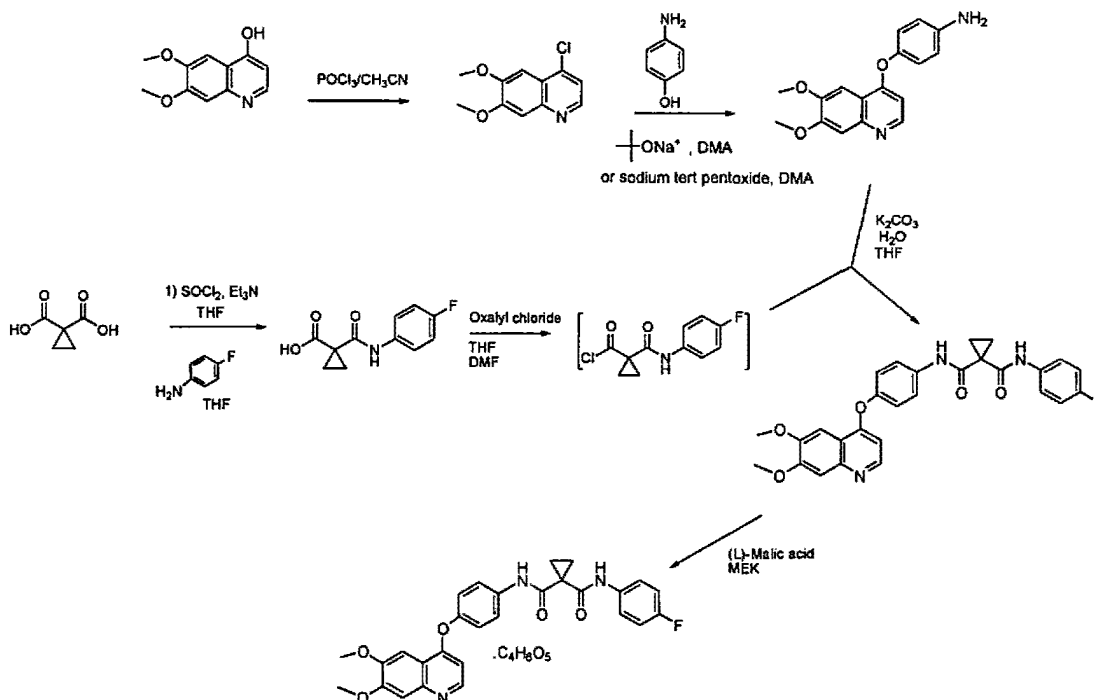
[0075] Unless otherwise specified, all reagents and solvents are of standard commercial grade and are used without further purification. The appropriate atmosphere to run the reaction under, for example, air, nitrogen, hydrogen, argon and the like, will be apparent to those skilled in the art.

Example 1

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

[0076] A synthetic route that can be used for the preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof is depicted in Figure 1:

Figure 1



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

[0077] A reactor was charged sequentially with 6,7-dimethoxy-quinoline-4-ol (47.0 kg) and acetonitrile (318.8 kg). The resulting mixture was heated to approximately 60 °C and phosphorus oxychloride (POCl₃, 130.6 kg) was added. After the addition of POCl₃, the temperature of the reaction mixture was raised to approximately 77°C. The reaction was deemed complete (approximately 13 hours) when <3% of the starting material remained (in-process high-performance liquid chromatography [HPLC] analysis). The reaction mixture was cooled to approximately 2 – 7 °C and then quenched into a chilled solution of dichloromethane (DCM, 482.8 kg), 26 % NH₄OH (251.3 kg), and water (900 L). The resulting mixture was warmed to approximately 20 – 25 °C, and phases were separated. The organic phase was filtered through a bed of AW hyflo super-cel NF (Celite; 5.4 kg) and the filter bed was washed with DCM (118.9 kg). The combined organic phase was washed with brine (282.9 kg) and mixed with water (120 L). The phases were separated and the organic phase was concentrated by vacuum distillation with the removal of solvent (approximately 95

L residual volume). DCM (686.5 kg) was charged to the reactor containing organic phase and concentrated by vacuum distillation with the removal of solvent (approximately 90 L residual volume). Methyl t-butyl ether (MTBE, 226.0 kg) was then charged and the temperature of the mixture was adjusted to – 20 to – 25 °C and held for 2.5 hours resulting in solid precipitate which was then filtered and washed with n-heptane (92.0 kg), and dried on a filter at approximately 25 °C under nitrogen to afford the title compound. (35.6 kg).

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

[0078] 4-Aminophenol (24.4 kg) dissolved in N,N-dimethylacetamide (DMA, 184.3 kg) was charged to a reactor containing 4-chloro-6,7-dimethoxyquinoline (35.3 kg), sodium t-butoxide (21.4 kg) and DMA (167.2 kg) at 20 – 25 °C. This mixture was then heated to 100 – 105°C for approximately 13 hours. After the reaction was deemed complete as determined using in-process HPLC analysis (<2% starting material remaining), the reactor contents were cooled at 15 to 20 °C and water (pre-cooled, 2 to 7 °C, 587 L) charged at a rate to maintain 15 to 30 °C temperature . The resulting solid precipitate was filtered, washed with a mixture of water (47 L) and DMA (89.1 kg) and finally with water (214 L). The filter cake was then dried at approximately 25°C on filter to yield crude 4-(6, 7 –dimethoxy–quinoline–4–yloxy)–phenylamine (59.4 kg wet, 41.6 kg dry calculated based on LOD). Crude 4-(6, 7 –dimethoxy–quinoline–4–yloxy)–phenylamine was refluxed (approximately 75 °C) in a mixture of tetrahydrofuran (THF, 211.4 kg) and DMA (108.8 kg) for approximately 1h and then cooled to 0 – 5°C and aged for approximately 1 h after which time the solid was filtered, washed with THF (147.6 kg) and dried on a filter under vacuum at approximately 25°C to yield 4-(6, 7 –dimethoxy–quinoline–4–yloxy)–phenylamine (34.0 kg).

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

[0079] 4-chloro-6,7-dimethoxyquinoline (34.8 kg) and 4-Aminophenol (30.8 kg) and sodium tert pentoxide (1.8 equivalents) 88.7 kg, 35 wt percent in THF) were charged to a reactor, followed by N,N-dimethylacetamide (DMA, 293.3 kg). This mixture was then heated to 105 – 115°C for approximately 9 hours. After the reaction was deemed complete as determined using in-process HPLC analysis (<2% starting material remaining), the reactor contents were cooled at 15 to 25 °C and water (315 kg) was added over a two hour period while maintaining the temperature between 20 and 30 °C. The reaction mixture was then agitated for an additional hour at 20 to 5°C. The crude product was collected by filtration and

washed with a mixture of 88kg water and 82.1 kg DMA, followed by 175 kg water. The product was dried on a filter drier for 53 hours. The LOD showed less than 1% w/w.

[0080] In an alternative procedure, 1.6 equivalents of sodium tert-pentoxide were used and the reaction temperature was increased from 110 – 120 °C. IN addition , the cool down temperature was increased to 35-40 °C and the starting temperature of the water addition was adjusted to 35-40 C, with an allowed exotherm to 45°C.

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

[0081] Triethylamine (19.5 kg) was added to a cooled (approximately 5 C) solution of cyclopropane-1,1-dicarboxylic acid (24.7 kg) in THF (89.6 kg) at a rate such that the batch temperature did not exceed 5°C. The solution was stirred for approximately 1.3 h, and then thionyl chloride (23.1 kg) was added, keeping the batch temperature below 10 C. When the addition was complete, the solution was stirred for approximately 4 h keeping temperature below 10 °C. A solution of 4-fluoroaniline (18.0 kg) in THF (33.1 kg) was then added at a rate such that the batch temperature did not exceed 10 C. The mixture was stirred for approximately 10 hours after which the reaction was deemed complete. The reaction mixture was then diluted with isopropyl acetate (218.1 kg). This solution was washed sequentially with aqueous sodium hydroxide (10.4 kg, 50 % dissolved in 119 L of water) further diluted with water (415 L), then with water (100 L) and finally with aqueous sodium chloride (20.0 kg dissolved in 100 L of water). The organic solution was concentrated by vacuum distillation (100 L residual volume) below 40 °C followed by the addition of n-heptane (171.4 kg), which resulted in the precipitation of solid. The solid was recovered by filtration and washed with n-Heptane (102.4 kg) resulting in wet crude, 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (29.0 kg). The crude, 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid was dissolved in methanol (139.7 kg) at approximately 25°C followed by the addition of water (320 L) resulting in slurry which was recovered by filtration, washed sequentially with water (20 L) and n-heptane (103.1 kg) and then dried on the filter at approximately 25 C under nitrogen to afford the title compound (25.4 kg).

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

[0082] Oxalyl chloride (12.6 kg) was added to a solution of 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (22.8 kg) in a mixture of THF (96.1 kg) and N, N-dimethylformamide (DMF; 0.23 kg) at a rate such that the batch temperature did not exceed 25 C. This solution was used in the next step without further processing.

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

[0083] A reactor was charged with 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (35 kg), 344 g DMF, and 175kg THF. The reaction mixture was adjusted to 12-17 °C and then to the reaction mixture was charged 19.9 kg of oxalyl chloride over a period of 1 hour. The reaction mixture was left stirring at 12-17 °C for 3 to 8 hours. This solution was used in the next step without further processing.

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

[0084] The solution from the previous step containing 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarbonyl chloride was added to a mixture of compound 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (23.5 kg) and potassium carbonate (31.9 kg) in THF (245.7 kg) and water (116 L) at a rate such that the batch temperature did not exceed 30 °C. When the reaction was complete (in approximately 20 minutes), water (653 L) was added. The mixture was stirred at 20-25 C for approximately 10 hours, which resulted in the precipitation of the product. The product was recovered by filtration, washed with a pre-made solution of THF (68.6 kg) and water (256 L), and dried first on a filter under nitrogen at approximately 25°C and then at approximately 45 C under vacuum to afford the title compound (41.0 kg, 38.1 kg, calculated based on LOD).

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

[0085] A reactor was charged with 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (35.7 kg, 1 equivalent), followed by 412.9 kg THF. To the reaction mixture was charged a solution of 48.3 K₂CO₃ in 169 kg water. The acid chloride solution described in the Alternative Preparation of 1-(4-Fluoro-phenylcarbamoyl)-cyclopropanecarbonyl chloride above was transferred to the reactor containing 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine while maintaining the temperature between 20-30 °C over a minimum of two hours. The reaction mixture was stirred at 20-25 °C for a minimum of three hours. The reaction temperature was then adjusted to 30-25 °C and the mixture was agitated. The agitation was stopped and the phases of the mixture were allowed to separate. The lower

aqueous phase was removed and discarded. To the remaining upper organic phase was added 804 kg water. The reaction was left stirring at 15-25 °C for a minimum of 16 hours.

[0086] The product precipitated. The product was filtered and washed with a mixture of 179 kg water and 157.9 THF in two portions. The crude product was dried under a vacuum for at least two hours. The dried product was then taken up in 285.1 kg THF. The resulting suspension was transferred to reaction vessel and agitated until the suspension became a clear (dissolved) solution, which required heating to 30-35 °C for approximately 30 minutes. 456 kg water were then added to the solution, as well as 20 kg SDAG-1 ethanol (ethanol denatured with methanol over two hours. The mixture was agitated at 15-25 °C for at least 16 hours. The product was filtered and washed with a mixture of 143 kg water and 126.7 THF in two portions. The product was dried at a maximum temperature set point of 40 °C.

[0087] In an alternative procedure, the reaction temperature during acid chloride formation was adjusted to 10-15 °C. The recrystallization temperature was changed from 15-25 °C to 45-50 °C for 1 hour and then cooled to 15-25 °C over 2 hours.

Preparation of cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide, XL184 (L) malate salt

[0088] Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (1-5; 13.3 kg), L-malic acid (4.96 kg), methyl ethyl ketone (MEK; 188.6 kg) and water (37.3 kg) were charged to a reactor and the mixture was heated to reflux (approximately 74°C) for approximately 2 h. The reactor temperature was reduced to 50 to 55°C and the reactor contents were filtered. These sequential steps described above were repeated two more times starting with similar amounts of 1-5 (13.3 kg), L-Malic acid (4.96 kg), MEK (198.6 kg) and water (37.2 kg). The combined filtrate was azeotropically dried at atmospheric pressure using MEK (1133.2 kg) (approximate residual volume 711 L; KF ≤ 0.5 % w/w) at approximately 74°C. The temperature of the reactor contents was reduced to 20 to 25°C and held for approximately 4 hours resulting in solid precipitate which was filtered, washed with MEK (448 kg) and dried under vacuum at 50°C to afford the title compound (45.5 kg).

Alternative Preparation of cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide, XL184 (L) malate salt

[0089] Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (47.9 kg), L-malic acid (17.2), 658.2 kg methyl

ethyl ketone, and 129.1 kg water (37.3 kg) were charged to a reactor and the mixture was heated 50-55 °C for approximately 1-3 h, and then at 55-60 °C for an additional 4-5 hours. The mixture was clarified by filtration through a 1 µm cartridge. The reactor temperature was adjusted to 20-25 °C and vacuum distilled with a vacuum at 150-200 mm Hg with a maximum jacket temperature of 55 °C to the volume range of 558-731 L.

[0090] The vacuum distillation was performed two more times with the charge of 380 kg and 380.2 kg methyl ethyl ketone, respectively. After the third distillation, the volume of the batch was adjusted to 18 v/w of Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide by charging 159.9 kg methyl ethyl ketone to give a total volume of 880L. An additional vacuum distillation was carried out by adjusting 245.7 methyl ethyl ketone. The reaction mixture was left with moderate agitation at 20-25 °C for at least 24 hours. The product was filtered and washed with 415.1 kg methyl ethyl ketone in three portions. The product was dried under a vacuum with the jacket temperature set point at 45 °C.

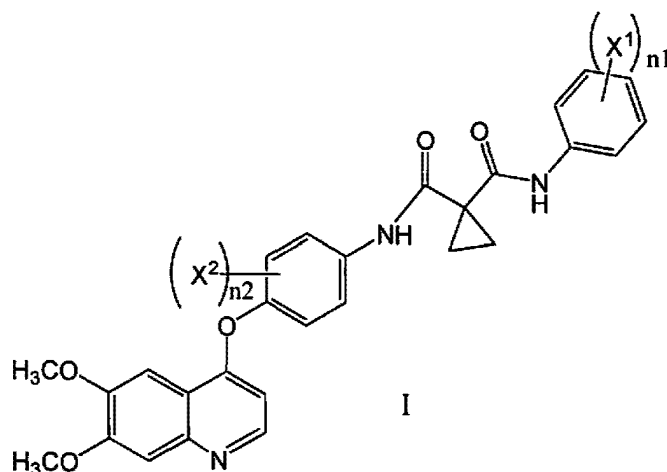
[0091] In an alternative procedure, the order of addition was changes so that a solution of 17.7 kg L-malic acid dissolved in 129.9 kg water was added to Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (48.7 kg) in methyl ethyl ketone (673.3 kg).

[0092] The foregoing disclosure has been described in some detail by way of illustration and example, for purposes of clarity and understanding. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications can be made while remaining within the spirit and scope of the invention. It will be obvious to one of skill in the art that changes and modifications can be practiced within the scope of the appended claims.

Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

We Claim:

1. A method of preparing a compound of formula I:



or a pharmaceutically acceptable salt thereof, wherein:

X^1 is H, Br, Cl or F;

X^2 is H, Br, Cl or F;

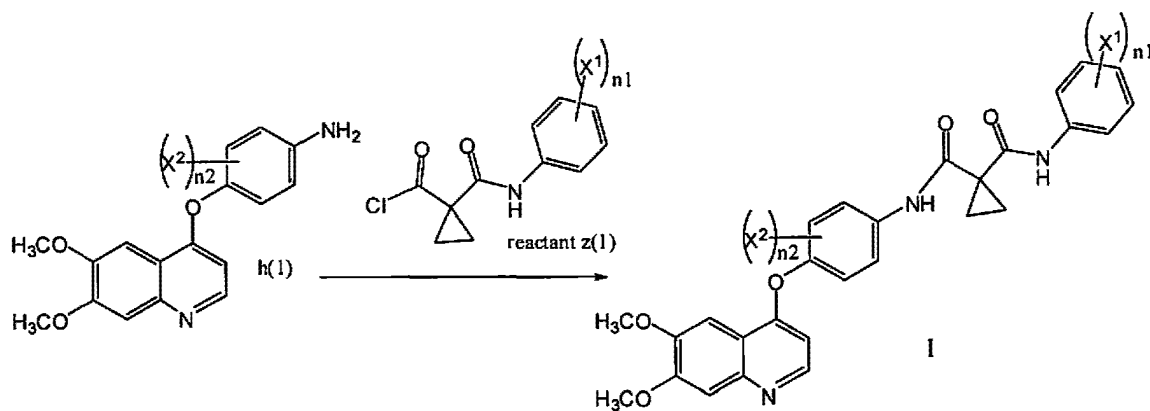
n_1 is 1-2; and

n_2 is 1-2,

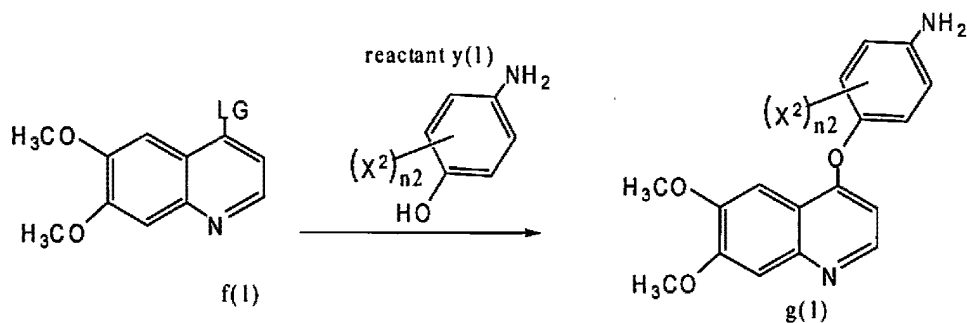
the method comprising:

contacting the compound of formula g(1) with reactant z(1) to yield the compound of formula

I:

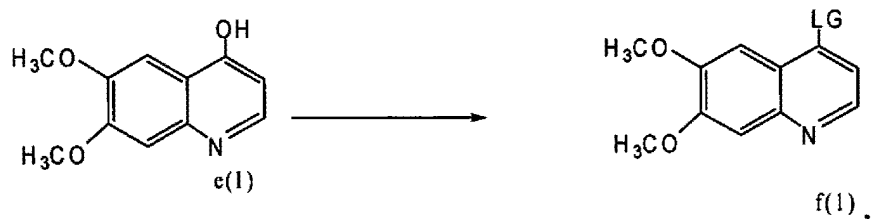


2. The method according to claim 1, wherein the compound of formula g(1) is made by reacting a compound of formula f(1) with reactant y(1) to yield the compound of formula g(1):



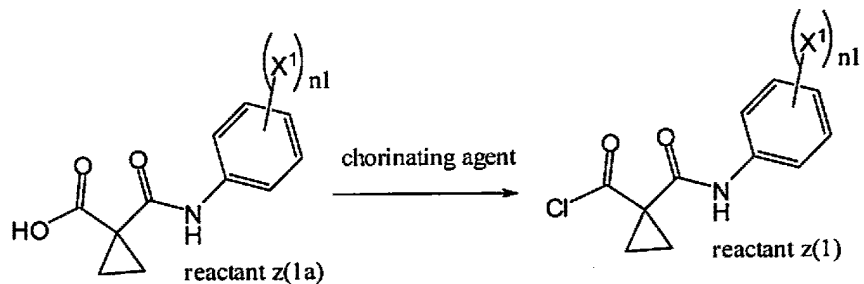
wherein LG represents a leaving group, and each X^2 and n_2 are as defined in claim 1.

3. The method according to claim 2, wherein the compound of formula f(1) is made by converting a compound of formula e(1) to the compound of formula f(1):



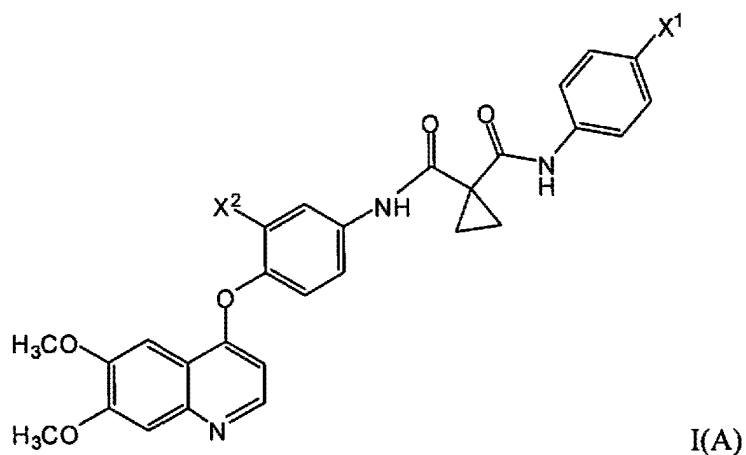
wherein LG represents a leaving group.

4. The method according to claim 1, wherein reactant z(1) is made by reacting reactant z(1a) with a chlorinating agent to yield reactant z(1):



wherein X^1 is Br, Cl or F; and n_1 is 1-2.

5. The method according to claim 1, wherein the compound of formula I is of formula IA:

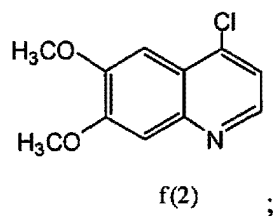


or a pharmaceutically acceptable salt thereof, wherein:

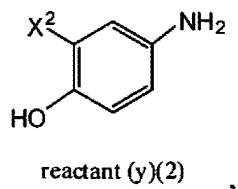
X^1 is H, Cl, Br or F; and

X^2 is H, Cl, Br or F.

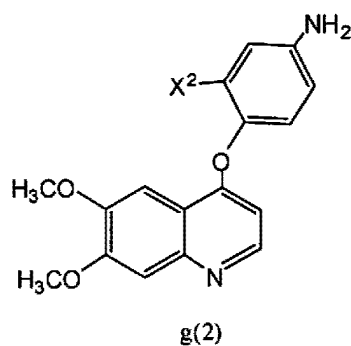
6. The method according to claim 5, wherein the compound of formula f(1) is of formula f(2):



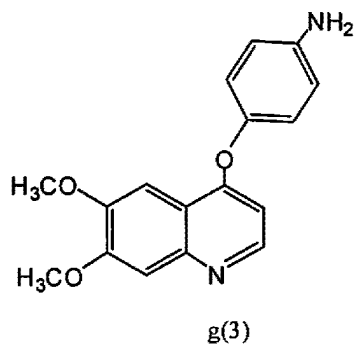
reactant y(1) is reactant (y)(2):



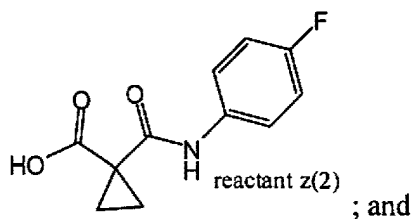
wherein X^2 is hydrogen or fluoro; and
the compound of formula g(1) is of formula g(2):



7. The method according to claim 6, wherein the reaction employs a non-nucleophilic base.
8. The method according to claim 7, wherein the non-nucleophilic base is an alkali metal alkoxide; and the reaction is carried out in a polar solvent.
9. The method according to claim 8, wherein the alkali metal alkoxide is sodium tert-butoxide, and the polar solvent is DMA.
10. The method according to claim 8, wherein the alkali metal alkoxide is sodium tert-pentoxide, and the polar solvent is DMA.
11. The method according to claim 1, wherein the compound of formula g(1) is of formula g(3):

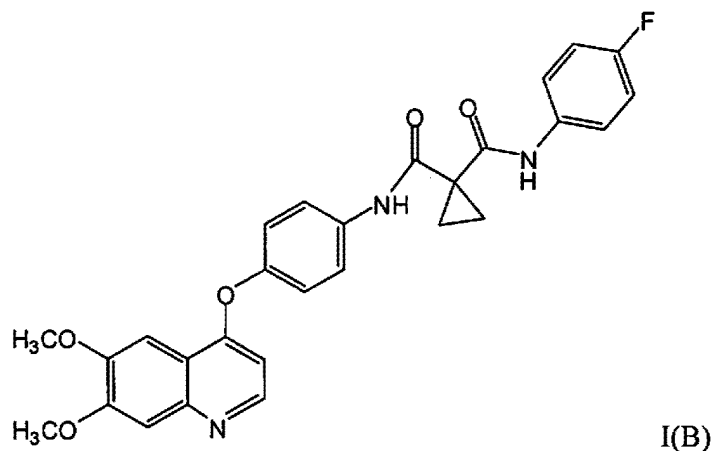


reactant z(1) is reactant (z)(2):



; and

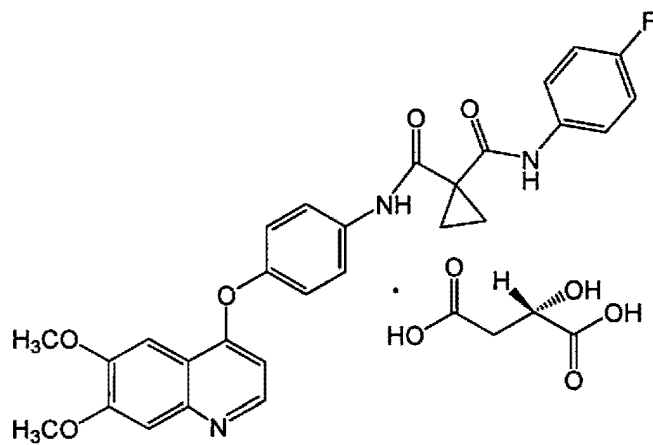
the compound of formula I is of formula I(B):



12. The method according to claim 11, wherein the reaction is carried out in the presence of an inorganic base.

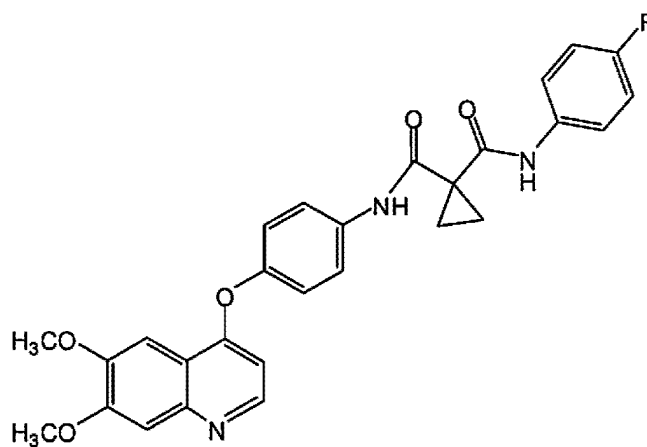
13. The method according to claim 12, wherein the inorganic base is K_2CO_3 , and the solvent employed in this reaction is a combination of THF and H_2O .

14. A method for preparing a compound of formula IB



Formula IB

from a compound of formula IA

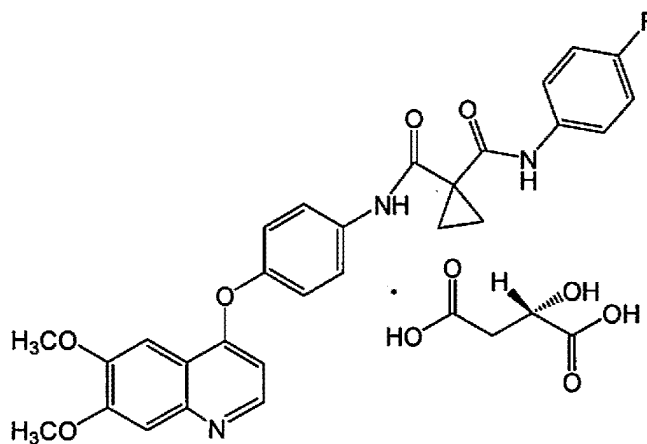


Formula IA

comprising:

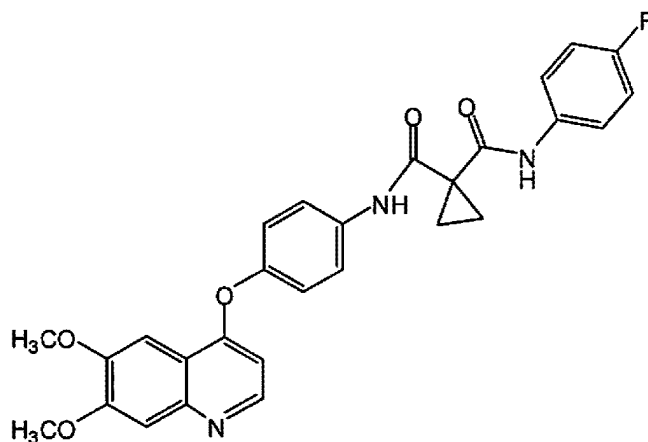
- (a) heating and agitating a mixture comprising a compound of formula IA and L-malic acid, methylethyl ketone, and water;
- (b) cooling the mixture;
- (c) vacuum distilling the mixture successively; and
- (d) isolating the compound of formula IB by filtration.

15. A method for preparing a compound of formula IB



Formula IB

from a compound of formula IA



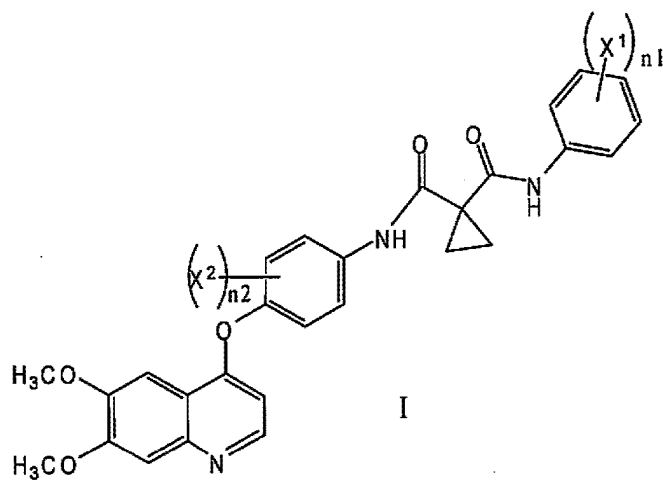
Formula IA

comprising:

- (a) heating and agitating a mixture comprising a compound of formula IA and L-malic acid, methylethyl ketone, and water;
- (b) cooling the mixture;
- (c) seeding the mixture with the compound of formula IB;
- (d) vacuum distilling the mixture; and
- (d) isolating the compound of formula IB by filtration.

ABSTRACT

Methods of preparing compounds of Formula I:



or a pharmaceutically acceptable salt thereof, wherein:

X^1 is H, Br, Cl or F;

X^2 is H, Br, Cl or F;

n_1 is 1-2; and

n_2 is 1-2.