

C-MET MODULATOR PHARMACEUTICAL COMPOSITIONS

FIELD OF THE INVENTION

[0001] Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms. One mechanism that can be exploited in cancer treatment is the modulation of protein kinase activity, because signal transduction through protein kinase activation is responsible for many of the characteristics of tumor cells. Protein kinase signal transduction is of particular relevance in, for example, renal, gastric, head and neck, lung, breast, prostate, and colorectal cancers; hepatocellular carcinoma; as well as in the growth and proliferation of brain tumor cells.

[0002] Protein kinases can be categorized as receptor type or non-receptor type. Receptor-type tyrosine kinases are comprised of a large number of transmembrane receptors with diverse biological activity. For a detailed discussion of the receptor-type tyrosine kinases see Plowman et al., DN&P 7(6): 334-339, 1994. Since protein kinases and their ligands play critical roles in various cellular activities, deregulation of protein kinase enzymatic activity can lead to altered cellular properties, such as uncontrolled cell growth associated with cancer. In addition to oncological indications, altered kinase signaling is implicated in numerous other pathological diseases, including, for example, immunological disorders, cardiovascular diseases, inflammatory diseases, and degenerative diseases. Therefore, protein kinases are attractive targets for small molecule drug discovery. Particularly attractive targets for small-molecule modulation with respect to antiangiogenic and antiproliferative activity include receptor type tyrosine kinases c-Met, KDR, c-Kit, Axl, flt-3, and flt-4.

[0003] The kinase c-Met is the prototypic member of a subfamily of heterodimeric receptor tyrosine kinases (RTKs) which include Met, Ron and Sea. The endogenous ligand for c-Met is the hepatocyte growth factor (HGF), a potent inducer of angiogenesis. Binding of HGF to c-Met induces activation of the receptor via autophosphorylation resulting in an increase of receptor dependent signaling, which promotes cell growth and invasion. Anti-HGF antibodies or HGF antagonists have been shown to inhibit tumor metastasis *in vivo* (See: Maulik et al Cytokine & Growth Factor Reviews 2002 13, 41-59). c-Met overexpression has been demonstrated on a wide variety of tumor types including breast, colon, renal, lung, squamous cell myeloid leukemia, hemangiomas, melanomas, astrocytomas, and glioblastomas. Additionally activating mutations

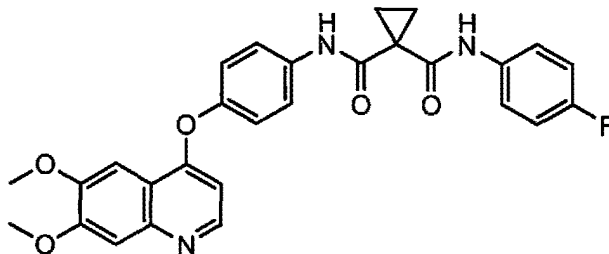
in the kinase domain of c-Met have been identified in hereditary and sporadic renal papilloma and squamous cell carcinoma. (See, e.g., Maulik et al., Cytokine & growth Factor reviews 2002 13, 41-59; Longati et al., Curr Drug Targets 2001, 2, 41-55; Funakoshi et al., Clinica Chimica Acta 2003 1-23).

[0004] Inhibition of epidermal growth factor (EGF), vascular endothelial growth factor (VEGF) and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A., Drug Disc. Technol. 2001 6, 1005-1024). Kinase KDR (refers to kinase insert domain receptor tyrosine kinase) and flt-4 (fms-like tyrosine kinase-4) are both VEGF receptors. Inhibition of EGF, VEGF and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. Drug Disc. Technol. 2001 6, 1005-1024). EGF and VEGF receptors are desirable targets for small molecule inhibition. All members of the VEGF family stimulate cellular responses by binding to tyrosine kinase receptors (the VEGFRs) on the cell surface, causing them to dimerize and become activated through transphosphorylation. The VEGF receptors have an extracellular portion having immunoglobulin-like domains, a single transmembrane spanning region and an intracellular portion containing a split tyrosine-kinase domain. VEGF binds to VEGFR-1 and VEGFR-2. VEGFR-2 is known to mediate almost all of the known cellular responses to VEGF.

[0005] Kinase c-Kit (also called stem cell factor receptor or steel factor receptor) is a type 3 receptor tyrosine kinase (RTK) belonging to the platelet-derived growth factor receptor subfamily. Overexpression of c-Kit and c-Kit ligand has been described in variety of human diseases including human gastrointestinal stromal tumors, mastocytosis, germ cell tumors, acute myeloid leukemia (AML), NK lymphoma, small-cell lung cancer, neuroblastomas, gynecological tumors and colon carcinoma. Moreover, elevated expression of c-Kit may also relate to the development of neoplasia associated with neurofibromatosis type 1 (NF-1), mesenchymal tumors GISTs and mast cell disease, as well as other disorders associated with activated c-Kit.

[0006] Kinase Flt-3 (fms-like tyrosine kinase-3) is constitutively activated via mutation, either in the juxtamembrane region or in the activation loop of the kinase domain, in a large proportion of patients with AML (Reilly, Leuk. Lymphoma, 2003, 44: 1-7).

[0007] Accordingly, small-molecule compounds that specifically inhibit, regulate, and/or modulate the signal transduction of kinases, particularly including c-Met, VEGFR2, KDR, c-Kit, Axl, flt-3, and flt-4 described above, are particularly desirable as a means to treat or prevent disease states associated with abnormal cell proliferation and angiogenesis. One such small-molecule is Compound (I), which has the chemical structure:



(I).

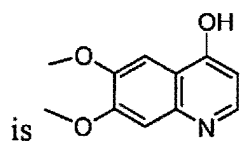
WO2005/030140 describes the synthesis of Compound (I) (Table 2, Compound 12, Example 48) and also discloses the therapeutic activity of this molecule to inhibit, regulate and/or modulate the signal transduction of kinases (Assays, Table 4, entry 289), the entire contents of which is incorporated herein by reference.

[0008] Although therapeutic efficacy is the primary concern for a therapeutic agent, the pharmaceutical composition can be equally important to its development. Generally, the drug developer endeavors to discover a pharmaceutical composition that possesses desirable properties such as satisfactory water-solubility (including rate of dissolution), storage stability, hygroscopicity, and reproducibility, all of which can impact the processability, manufacture, and/or bioavailability of the drug. Accordingly, discovery of pharmaceutical compositions that possess some or all of these desired properties is vital to drug development.

SUMMARY OF THE INVENTION

[0009] These and other needs are met by the present invention which is directed to a pharmaceutical composition comprising compound II or a pharmaceutically acceptable salt

thereof admixed with less than 100 ppm 6,7-dimethoxy-quinoline-4-ol, the structure of which



[0010] In another aspect , the invention which is directed to a pharmaceutical composition comprising compound I or a pharmaceutically acceptable salt thereof admixed with less than 50 ppm 6,7-dimethoxy-quinoline-4-ol, and a pharmaceutically acceptable carrier.

[0011] In another aspect , the invention which is directed to a pharmaceutical composition comprising compound I or a pharmaceutically acceptable salt thereof admixed with less than 25 ppm 6,7-dimethoxy-quinoline-4-ol, and a pharmaceutically acceptable carrier.

[0012] In another aspect , the invention which is directed to a pharmaceutical composition comprising compound I or a pharmaceutically acceptable salt thereof admixed with less than 15 ppm 6,7-dimethoxy-quinoline-4-ol, and a pharmaceutically acceptable carrier.

[0013] In another aspect , the invention which is directed to a pharmaceutical composition comprising compound I or a pharmaceutically acceptable salt thereof admixed with less than 10 ppm 6,7-dimethoxy-quinoline-4-ol, and a pharmaceutically acceptable carrier.

[0014] In another aspect , the invention which is directed to a pharmaceutical composition comprising compound I or a pharmaceutically acceptable salt thereof admixed with less than 5 ppm 6,7-dimethoxy-quinoline-4-ol, and a pharmaceutically acceptable carrier.

[0015] In another aspect , the invention which is directed to a pharmaceutical composition comprising compound I L-malate salt admixed with less than 5 ppm 6,7-dimethoxy-quinoline-4-ol, and a pharmaceutically acceptable carrier.

[0016] In another aspect , the invention which is directed to a pharmaceutical composition as provided in Table 1.

Table 1

Ingredient	% w/w
Compound (I)	31.68
Microcrystalline Cellulose (Avicel PH102)	38.85
Lactose anhydrous 60 M	19.42
Hydroxypropyl Cellulose, EXF	3.00
Croscarmellose Sodium	3.00
Total Intra-granular	95.95
Silicon dioxide, Colloidal PWD	0.30
Croscarmellose Sodium	3.00
Magnesium Stearate	0.75
Total	100.00

wherein the compound or its pharmaceutically acceptable salt is admixed with 100 ppm or less 6,7-dimethoxy-quinoline-4-ol.

[0017] In another embodiment, the invention is also directed to a pharmaceutical composition as provided in Table 2.

Table 2

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

wherein the compound or its pharmaceutically acceptable salt is admixed with 100 ppm or less 6,7-dimethoxy-quinoline-4-ol.

DETAILED DESCRIPTION

[0018] Various carriers used in formulating pharmaceutically acceptable compositions and known techniques for their bulk preparation and subsequent production into unit dosage forms are disclosed in Remington: The Science and Practice of Pharmacy, 21st edition, 2005, ed. D. B.

Troy, Lippincott Williams & Wilkins, Philadelphia, and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York. The amount of carriers and excipients used in a formulation can be varied according to the amount of active ingredient used (that is, Compound (I)).

Pharmaceutical Composition

[0019] Compound (I) and various pharmaceutically acceptable salts of Compound (I) are disclosed in WO2005/0030140. The malate salt of Compound (I) is disclosed in PCT/US2010/021194 (filed January 15, 2010). Both references are incorporated by reference herein in their entirety.

[0020] In one embodiment, the pharmaceutical composition is a tablet.

[0021] In another embodiment, the pharmaceutical composition is a capsule.

[0022] In another embodiment of the pharmaceutical composition is provided by Tables 1 or 2, Compound (I) is the free base.

[0023] In another embodiment of the pharmaceutical composition is provided by Tables 1 or 2, Compound (I) is the malate salt.

[0024] In another embodiment of the pharmaceutical composition is provided by Tables 1 or 2, Compound (I) is the malate salt as the N-1 polymorph.

[0025] In another embodiment of the pharmaceutical composition is provided by Tables 1 or 2, Compound (I) is the malate salt as the N-2 polymorph.

[0026] In another embodiment, the pharmaceutical composition is provided by Tables 1 or 2, is administered as a tablet unit dosage form.

[0027] In another embodiment, of the pharmaceutical composition, the compound as defined in any of the previous embodiments is admixed with 100 ppm 6,7-dimethoxy-quinoline-4-ol.

[0028] In another embodiment, of the pharmaceutical composition, the compound as defined in any of the previous embodiments is admixed with 50 ppm 6,7-dimethoxy-quinoline-4-ol.

[0029] In another embodiment, of the pharmaceutical composition, the compound as defined in any of the previous embodiments is admixed with 25 ppm 6,7-dimethoxy-quinoline-4-ol.

[0030] In another embodiment, of the pharmaceutical composition, the compound as defined in any of the previous embodiments is admixed with 15 ppm 6,7-dimethoxy-quinoline-4-ol.

[0031] In another embodiment, of the pharmaceutical composition, the compound as defined in any of the previous embodiments is admixed with 10 ppm 6,7-dimethoxy-quinoline-4-ol.

[0032] In another embodiment, of the pharmaceutical composition, the compound as defined in any of the previous embodiments is admixed with 5 ppm 6,7-dimethoxy-quinoline-4-ol.

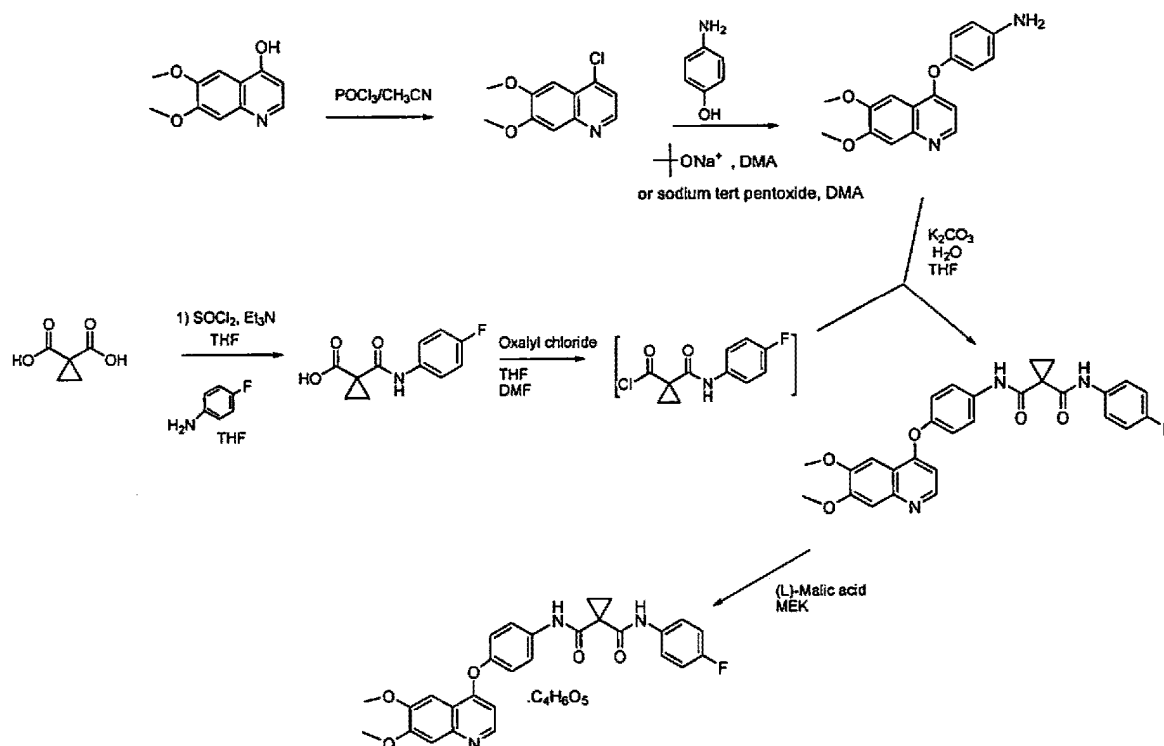
[0033] The following Examples illustrate the preparation of pharmaceutical compositions comprising Compound (I). The examples are not intended to be limiting to the scope of the invention in any respect, and should not be so construed.

EXAMPLES

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

[0034] A synthetic route that can be used for the preparation of N-(4-{[6,7-bis(methoxy)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

[0035] 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

[0036] 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

[0037] 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.

[0038] 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

[0039] 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

[0040] 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

[0041] 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

[0042] 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

[0043] 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 of described in the Alternative Preparation of 1-(4-Fluoro-phenylcarbamoyl)-cyclopropanecarbonyl chloride above was transferred to the reactor containing 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine while maintaining the temperature between 20-30 °C over a minimum of two hours. The reaction mixture was stirred at 20-25 °C for a minimum of three hours. The reaction temperature was then adjusted to 30-25 °C and the mixture was agitated. The agitation was stopped and the phases of the mixture were allowed to separate. The lower aqueous phase was removed and discarded. To the remaining upper organic phase was added 804 kg water. The reaction was left stirring at 15-25 °C for a minimum of 16 hours.

[0044] 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.

[0045] 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

[0046] 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

[0047] 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.

[0048] 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.

[0049] 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).

Pharmaceutical Compositions

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

Example 2

Ingredient	% w/w
Compound (I)	31.68
Microcrystalline Cellulose (Avicel PH102)	38.85
Lactose anhydrous 60 M	19.42
Hydroxypropyl Cellulose, EXF	3.00
Croscarmellose Sodium	3.00
Total Intra-granular	95.95
Silicon dioxide, Colloidal PWD	0.30
Croscarmellose Sodium	3.00
Magnesium Stearate	0.75
Total	100.00

[0050] The foregoing disclosure has been described in some detail by way of illustration and example, for purposes of clarity and understanding. The invention has been described with

reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications can be made while remaining within the spirit and scope of the invention. It will be obvious to one of skill in the art that changes and modifications can be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

What is claimed is:

1. A pharmaceutical composition as provided in Table 1.

Table 1

Ingredient	% w/w
Compound (I)	31.68
Microcrystalline Cellulose (Avicel PH102)	38.85
Lactose anhydrous 60 M	19.42
Hydroxypropyl Cellulose, EXF	3.00
Croscarmellose Sodium	3.00
Total Intra-granular	95.95
Silicon dioxide, Colloidal PWD	0.30
Croscarmellose Sodium	3.00
Magnesium Stearate	0.75
Total	100.00

2. A pharmaceutical composition as provided in Table 2.

Table 2

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

3. The pharmaceutical composition of claims 1 or 2m, wherein Compound I is admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.
4. The pharmaceutical composition of claims 1 or 2m, wherein Compound I is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

5. The pharmaceutical composition of claims 1 or 2m, wherein Compound I is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol.
6. The pharmaceutical composition of claims 1 or 2m, wherein Compound I is admixed with 15 ppm or less of 6,7-dimethoxy-quinoline-4-ol.
7. The pharmaceutical composition of claims 1 or 2m, wherein Compound I is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol.
8. The pharmaceutical composition of claims 1 or 2m, wherein Compound I is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

ABSTRACT

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

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