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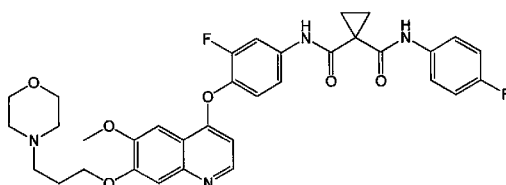
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(54) Title: METABOLITES OF N-[3-FLUORO-4-({ 6-(METHYLOXY)-7-[(3-MORPHOLIN-4-YLPROPYL)OXY]QUINOLIN-4-YL}OXY)PHENYL]-N'-(4-FLUOROPHENYL)CYCLOPROPANE-1,1-DICARBOXAMIDE



(I)

(57) Abstract: The invention relates to metabolites of foretinib (I) as well as uses thereof.

Metabolites of N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

Priority Claim

[0001] This application claims priority to United States Serial No. 61/792,562, filed March 15, 2013. The entire contents of the aforementioned application are incorporated herein.

Technical Field

[0002] This disclosure relates to metabolites of 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 c-Met inhibitor.

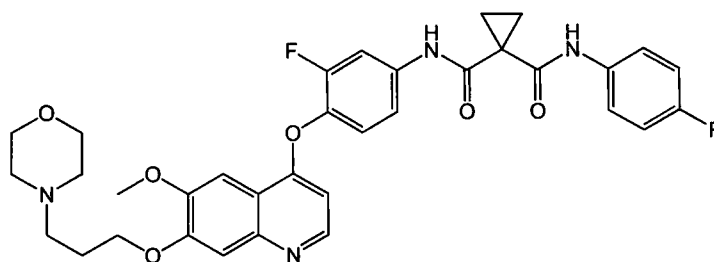
Background

[0003] Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms. One mechanism that can be exploited in cancer treatment is the modulation of protein kinase activity because signal transduction through protein kinase activation is responsible for many of the characteristics of tumor cells. Protein kinase signal transduction is of particular relevance in, for example, thyroid, gastric, head and neck, lung, breast, prostate, and colorectal cancers, as well as in the growth and proliferation of brain tumor cells.

[0004] Protein kinases can be categorized as receptor type or non-receptor type. Receptor-type tyrosine kinases are comprised of a large number of transmembrane receptors with diverse biological activity. For a detailed discussion of the receptor-type tyrosine kinases, see Plowman et al., DN&P 7(6): 334-339, 1994. Since protein kinases and their ligands play critical roles in various cellular activities, deregulation of protein kinase enzymatic activity can lead to altered cellular properties, such as uncontrolled cell growth associated with cancer. In addition to oncological indications, altered kinase signaling is implicated in numerous other pathological diseases, including, for example, immunological disorders, cardiovascular diseases, inflammatory diseases, and degenerative diseases. Therefore, protein kinases are attractive targets for small molecule drug discovery. Particularly attractive targets for small-molecule modulation with respect to antiangiogenic and antiproliferative activity include receptor type tyrosine kinases Ret, c-Met, and VEGFR2.

[0005] The kinase c-Met is the prototypic member of a subfamily of heterodimeric receptor tyrosine kinases (RTKs) which include Met, Ron, and Sea. The endogenous ligand for c-Met is the hepatocyte growth factor (HGF), a potent inducer of angiogenesis. Binding of HGF to c-Met induces activation of the receptor via autophosphorylation resulting in an increase of receptor dependent signaling, which promotes cell growth and invasion. Anti-HGF antibodies or HGF antagonists have been shown to inhibit tumor metastasis *in vivo* (See Maulik et al, Cytokine & Growth Factor Reviews, 2002, 13, 41-59). c-Met, VEGFR2, and/or Ret overexpression has been demonstrated on a wide variety of tumor types, including breast, colon, renal, lung, squamous cell myeloid leukemia, hemangiomas, melanomas, and astrocytic tumor (which includes glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components). The Ret protein is a transmembrane receptor with tyrosine kinase activity. Ret is mutated in most familial forms of medullary thyroid cancer. These mutations activate the kinase function of Ret and convert it into an oncogenic form.

[0006] Accordingly, small-molecule compounds that specifically inhibit, regulate, and/or modulate the signal transduction of kinases, particularly including Ret, c-Met, and VEGFR2 described above, are particularly desirable as a means to treat or prevent disease states associated with abnormal cell proliferation and angiogenesis. One such small-molecule is XL880, known variously as N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and alternatively as foretinib. Foretinib has the chemical structure:



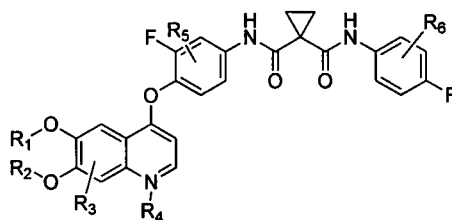
[0007] WO 2005/030140 describes the synthesis of foretinib (Example 44) and also discloses the therapeutic activity of this molecule to inhibit, regulate, and/or modulate the signal transduction of kinases (Assays, Table 4, entry 312). Example 44 begins at paragraph [0349] in WO 2005/030140.

[0008] A need remains for identifying compounds that exhibit a similar activity profile to foretinib.

Summary of the Invention

[0009] These and other needs are met by the present invention, which is directed to metabolites of foretinib.

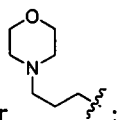
[0010] In one embodiment of this aspect, the metabolite is a compound of formula Ia



Ia

having one or more of the following attributes:

- a) R_1 is H, Me, SO_3H , or a glucuronic acid moiety;



- b) R_2 is H or

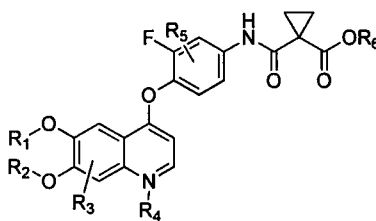
- c) R_3 is OH or OSO_3H ;

- d) R_4 is O^- , provided that when R_4 is O^- , N is N^+ ;

- e) R_5 is OH or OSO_3H ; and

- f) R_6 is OH or OSO_3H .

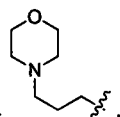
[0011] In another embodiment of this aspect, the metabolite is a compound of formula Ib



Ib

wherein:

- a) R_1 is H, Me, SO_3H , or a glucuronic acid moiety;



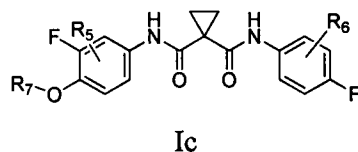
- b) R_2 is H or

- c) R_3 is H, OH, or OSO_3H ;

- d) R_4 is absent or is O^- , provided that when R_4 is O^- , N is N^+ ; and

- e) R_6 is H or Me.

[0012] In another embodiment of this aspect, the metabolite is a compound of formula Ic

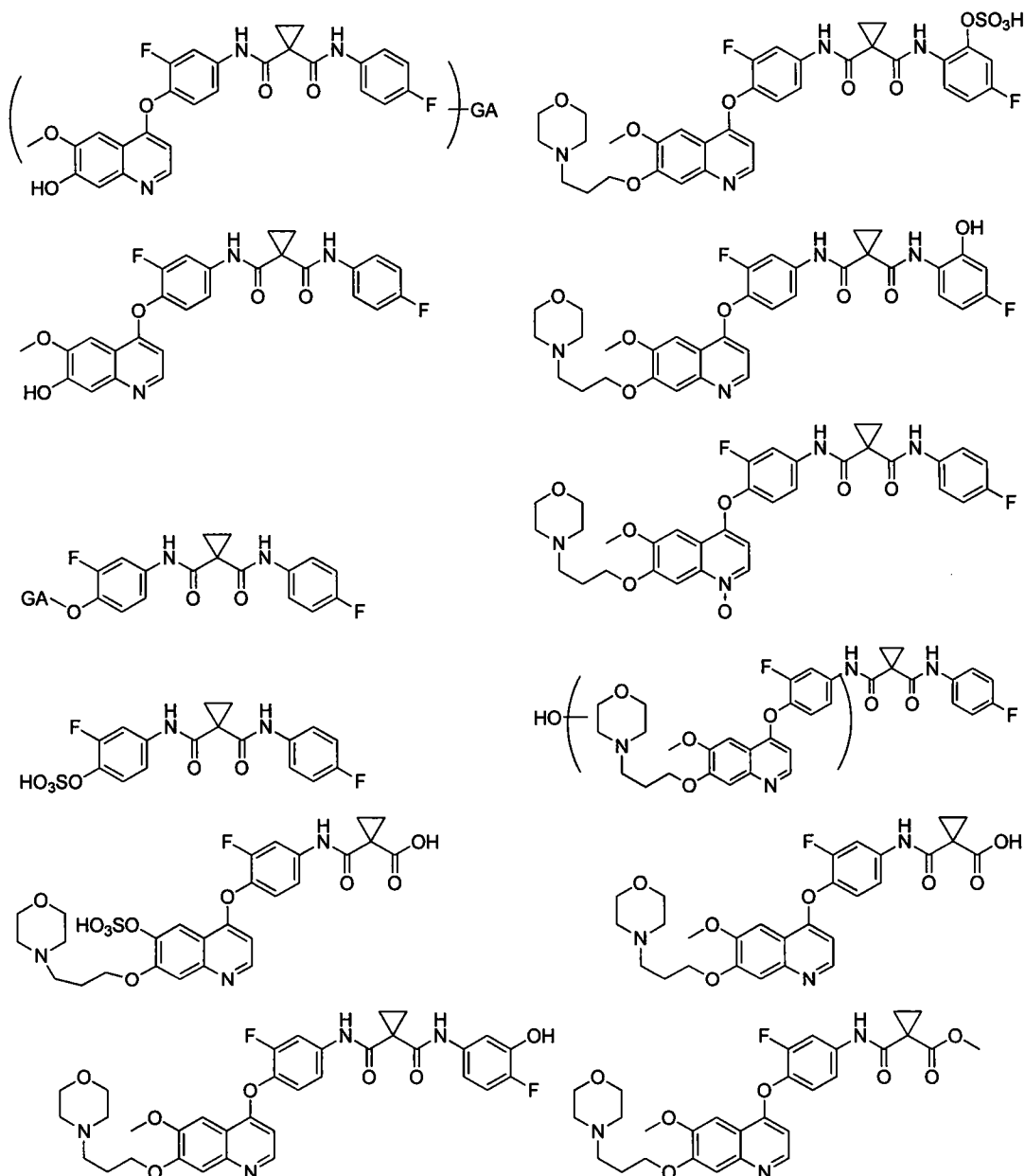


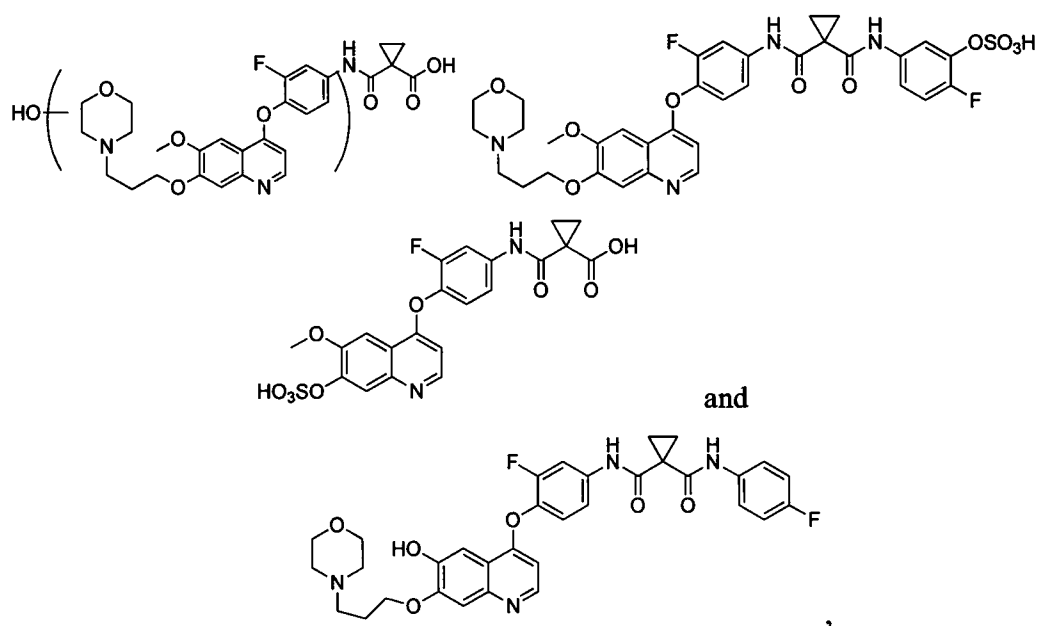
wherein:

- a) R_5 is OH or OSO_3H ;
- b) R_6 is OH or OSO_3H ; and
- c) R_7 is H, SO_3H , or a glucuronic acid moiety.

[0013] In one aspect, the invention is directed to an isolated metabolite of foretinib having formula Ia, Ib, or Ic.

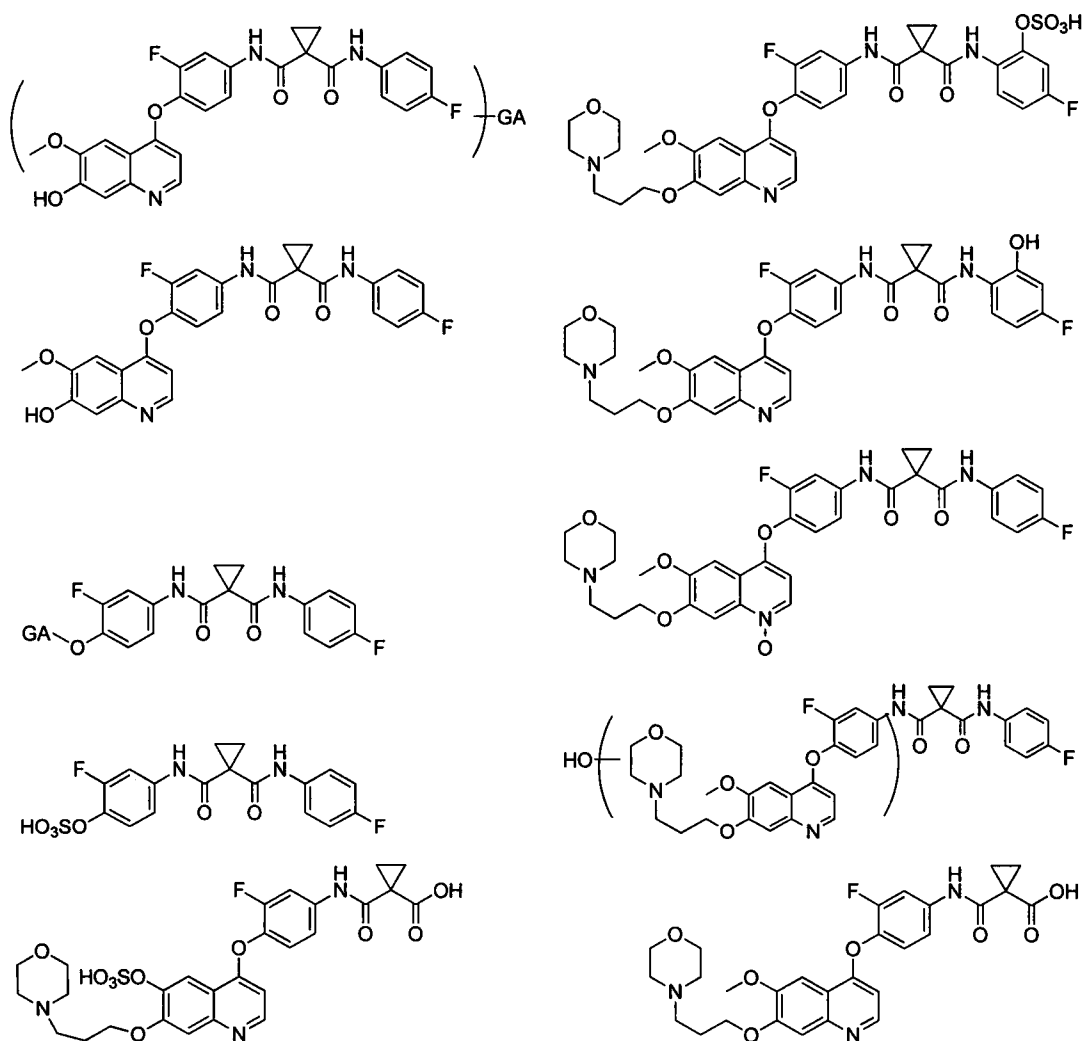
[0014] In one embodiment, the metabolite of foretinib is selected from:

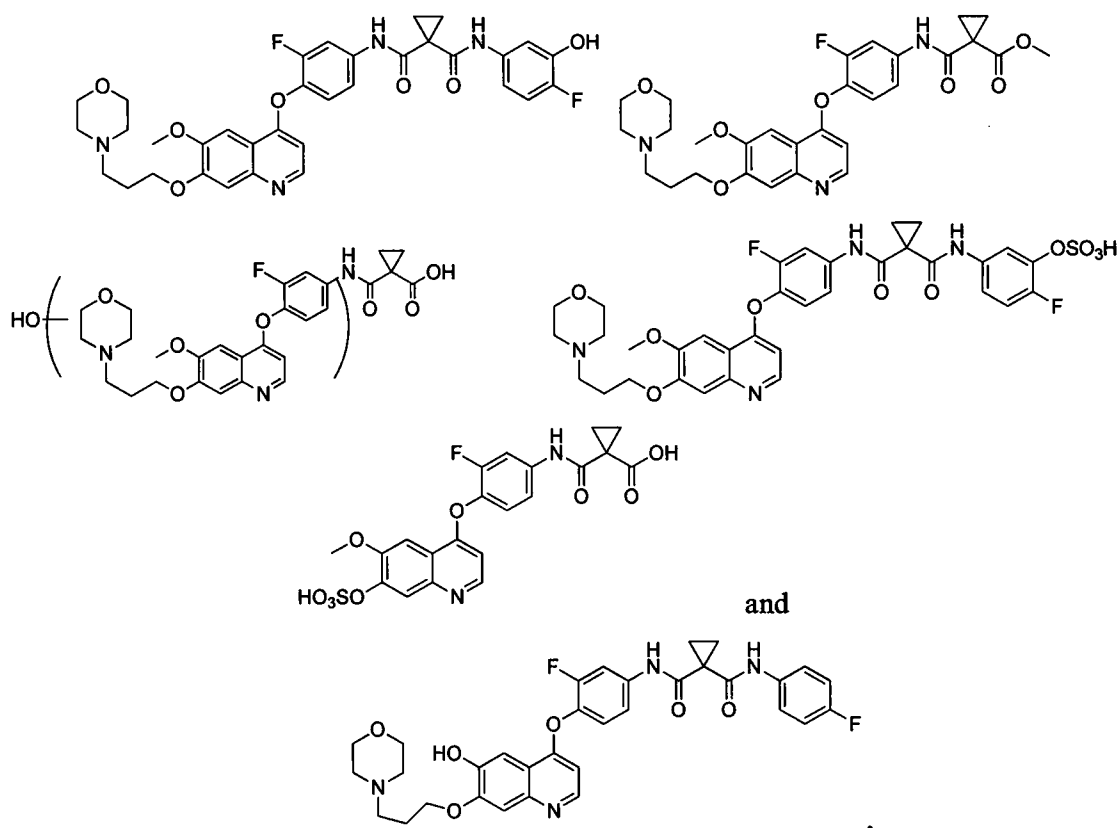




wherein GA is a glucuronic acid moiety.

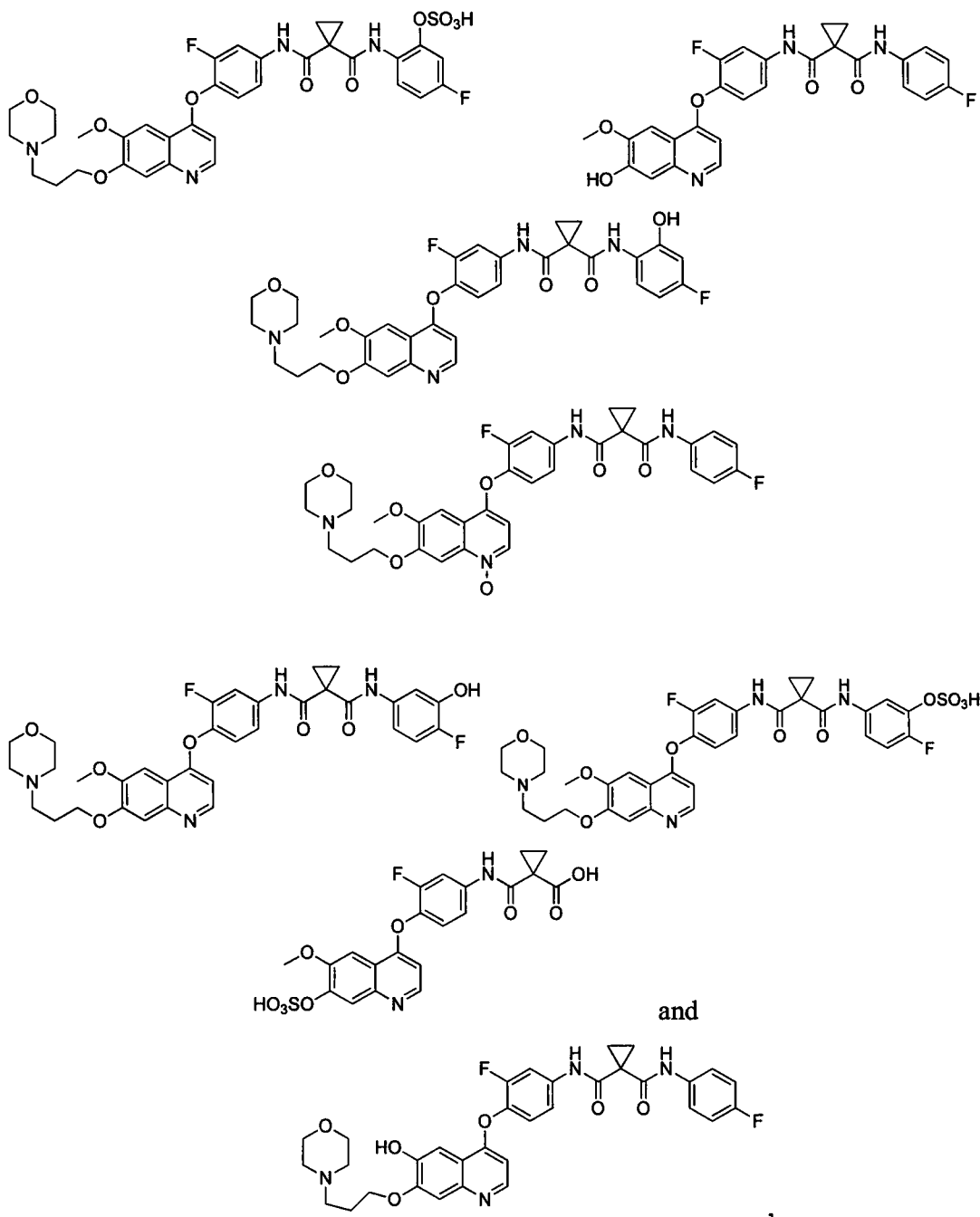
[0015] In another aspect, the invention is directed to a compound which is selected from:





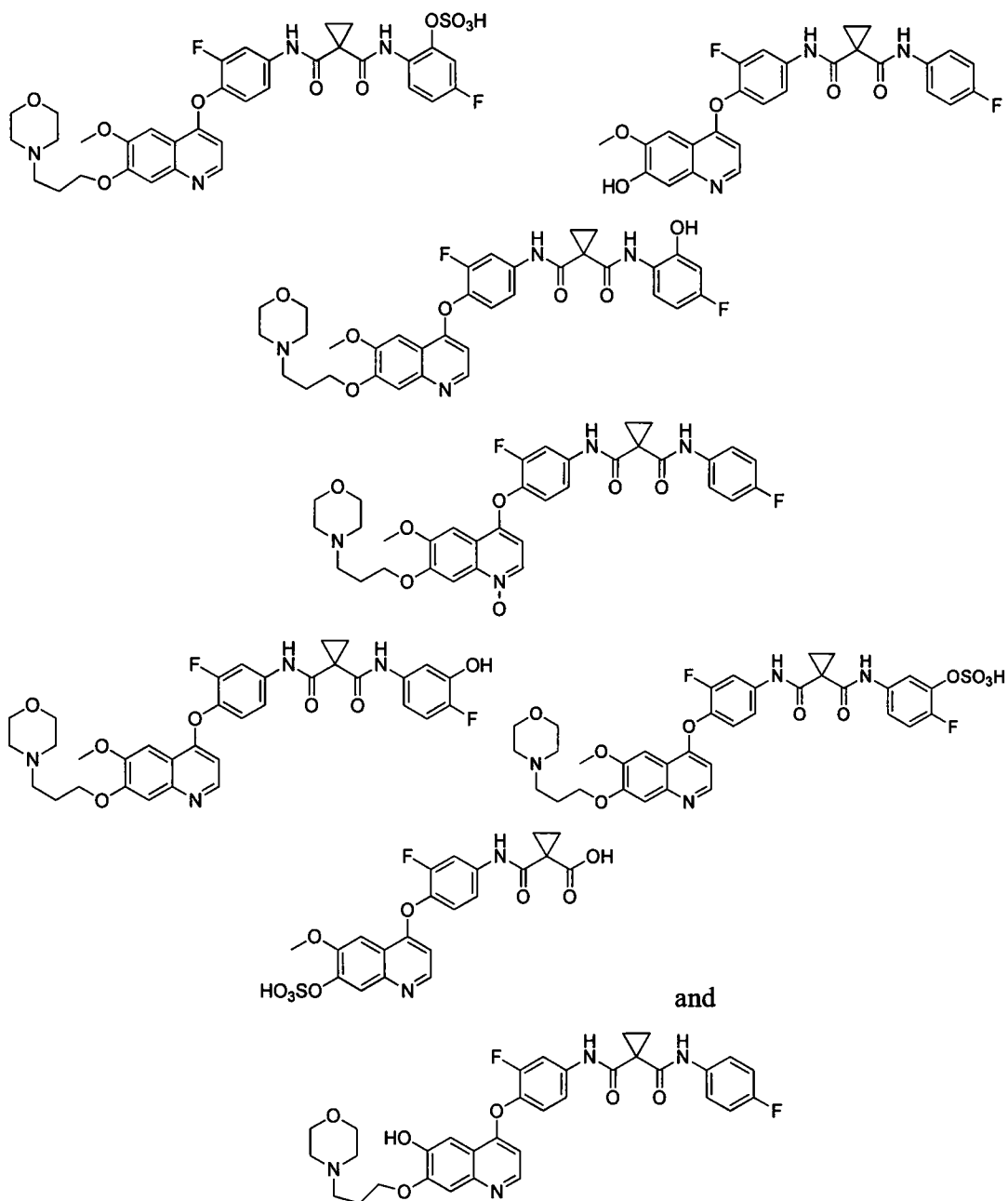
wherein GA is a glucuronic acid moiety.

[0016] In another aspect, the invention is directed to 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 a compound which is a metabolite of foretinib. In one embodiment, the metabolite is selected from:



or a pharmaceutically acceptable salt thereof.

[0017] In another aspect, the invention is directed to a pharmaceutical composition comprising a therapeutically active metabolite of foretinib and at least one pharmaceutically acceptable carrier. In one embodiment, the metabolite is selected from:



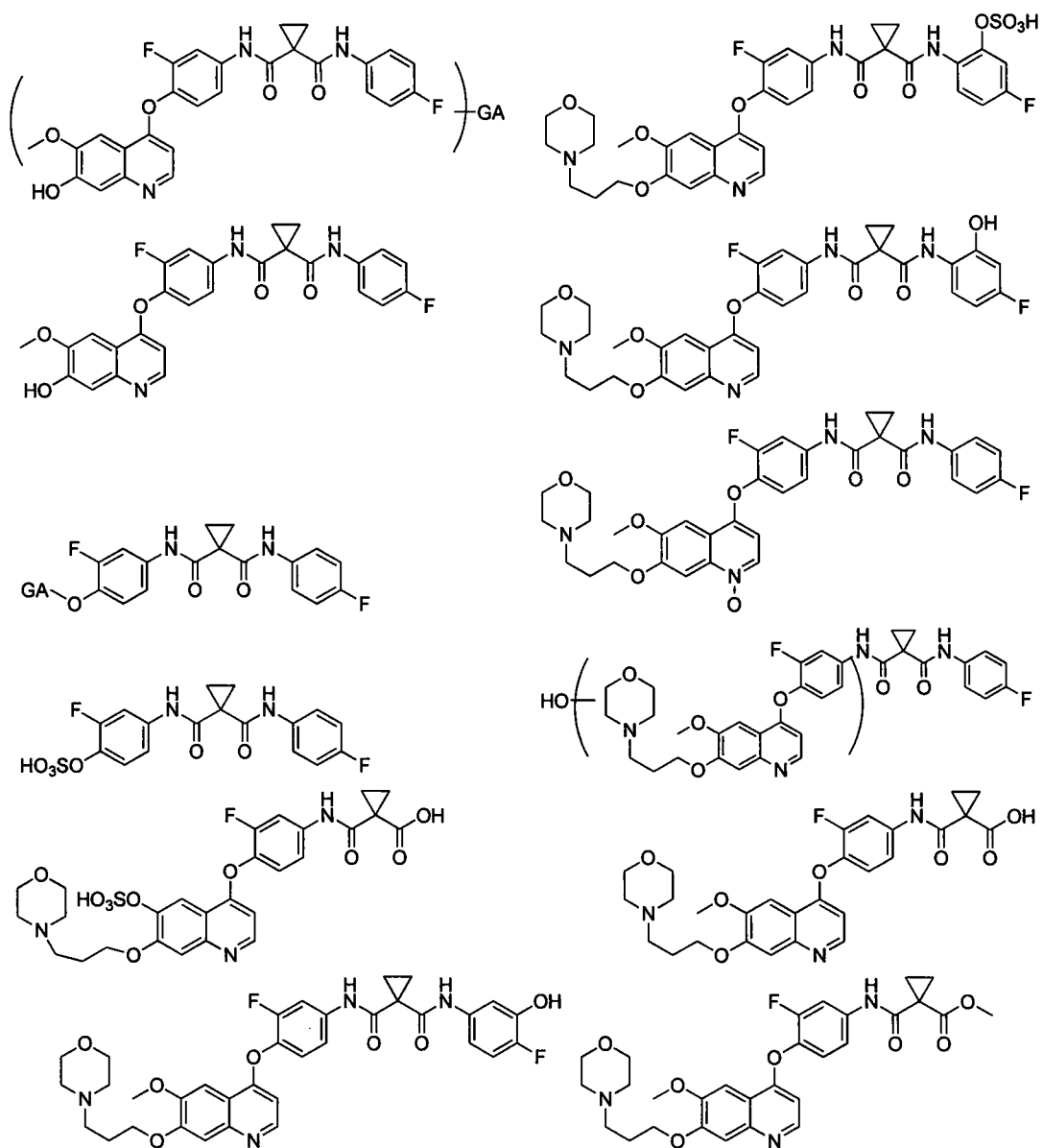
or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier.

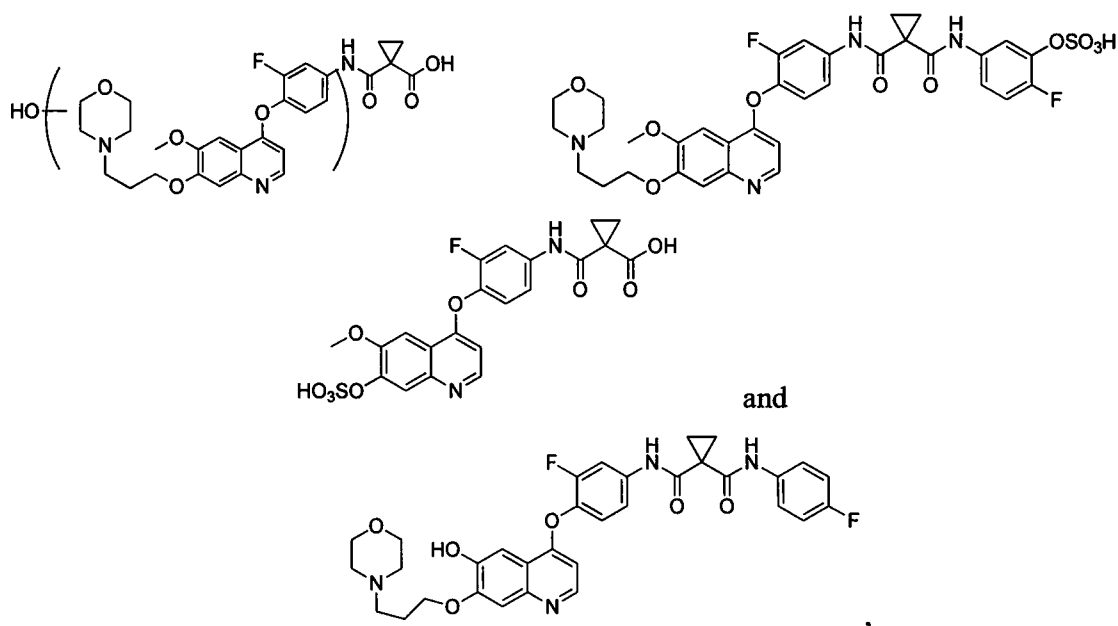
[0018] In another aspect the invention is directed to a method for identifying a metabolite of foretinib, comprising:

administering foretinib to a mammal; and

detecting or measuring a level or concentration of a metabolite of foretinib in a mammal in tissues or bodily fluids of the mammal;

wherein the metabolite is selected from the group consisting of:





wherein GA is a glucuronic acid moiety.

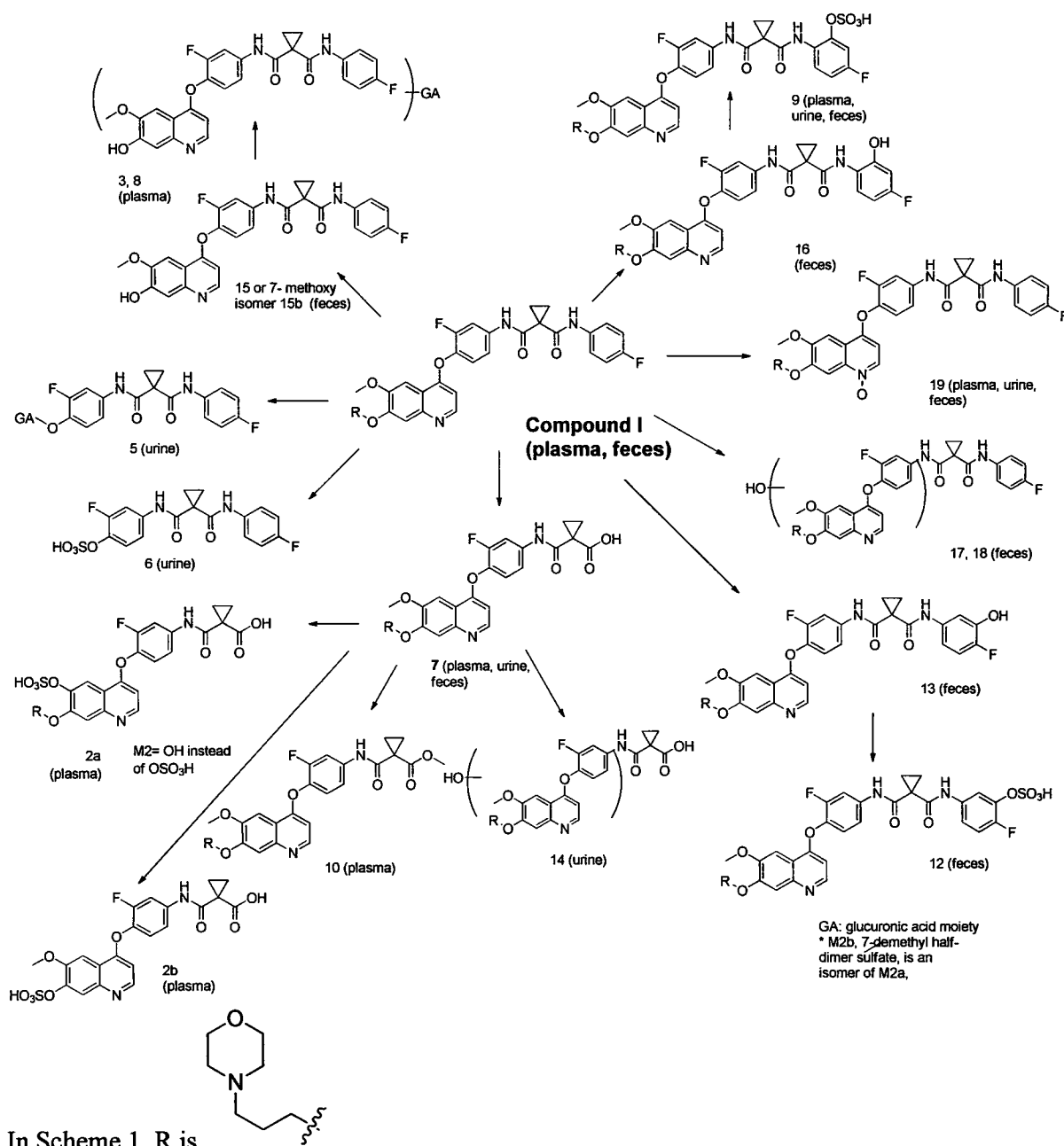
[0019] The compounds may additionally be used in other methods; for example, in bioassay methods for determining the kinase inhibitory activity of test compounds or as internal standards in related methods.

Detailed Description of the Invention

[0020] In one aspect, the invention is directed to metabolites of foretinib, particularly human metabolites. Thus, the metabolites may be referred to hereinafter as “human metabolites.” Human metabolites of foretinib include metabolites of foretinib that are formed in the bodies of human subjects after ingestion or application of foretinib according to clinical protocols regarding dosing and monitoring, including those described herein. In various embodiments, the term encompasses molecular species formed *in vivo*, whether or not the species is even detected or analyzed in a particular trial. It is also contemplated that some metabolites are unique to particular individuals, reflecting different genetic make-up and the presence and activity of various enzymes, including cytochrome P450 and UGT enzymes, which are involved in metabolism. Thus, human metabolites cover all such metabolites formed in the human body.

[0021] Some human metabolites are depicted in Scheme 1. These human metabolites are identified during clinical studies of foretinib, which appears as compound I in Scheme 1, by metabolic profiling, particularly from human plasma, urine, and feces.

Scheme 1



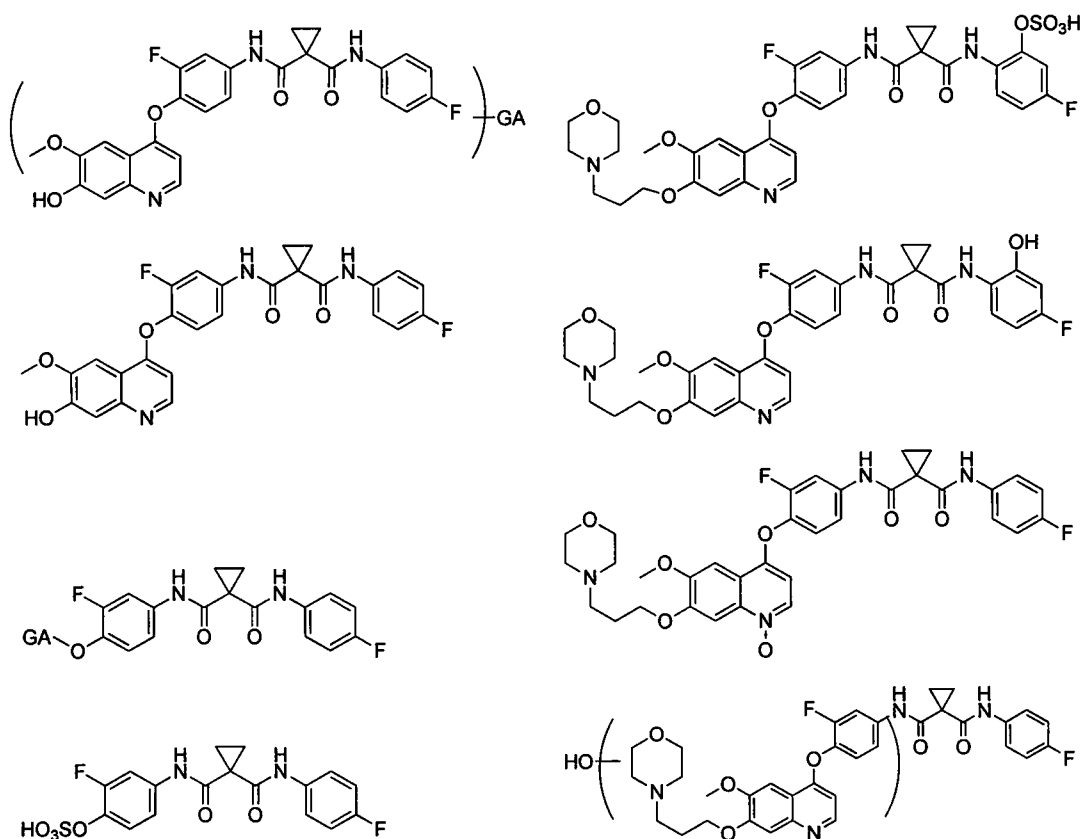
[0022] In various embodiments, the foretinib metabolites, including those depicted in Scheme 1, are isolated from body tissues and fluids, and/or are prepared synthetically according to methods available to the skilled artisan. A variety of separation processes can be carried out on tissue and fluid samples to provide samples for further analysis, such as nuclear magnetic resonance, gas chromatography (GC), liquid chromatography (LC), and mass spectrometry. In such samples, the metabolites are contained in compositions that are essentially lacking in the presence of any of the other metabolites. The presence of the metabolites can be quantified by physical methods, such as the measurement of nuclear decay

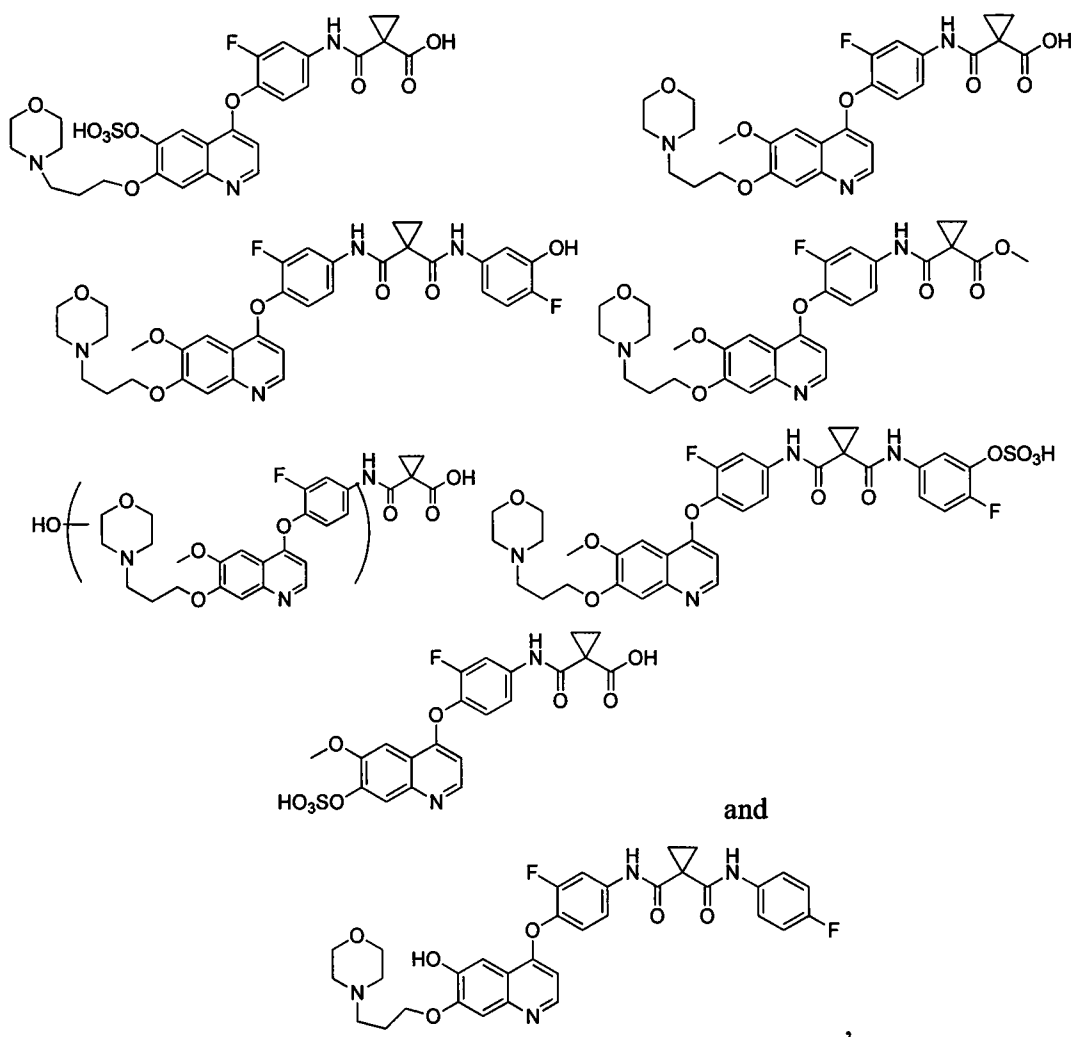
from radioactive isotopes, measurement of index of refraction, flame ionization, ionization and deflection in magnetic fields, ultraviolet (UV absorption), and the like.

[0023] In various embodiments, the human metabolites are provided in crystalline or solution forms that have considerable degrees of purity. Organic synthetic routes are available for preparing the compounds in relative pure form, for example, in purities of 80 percent or greater, 90 percent or greater, 95 percent or greater, or 99 percent or greater. Recrystallization and other purification methods can be carried out to provide compounds that are essentially 100 percent pure. Such synthetic methods and purification techniques are known in the art.

[0024] In various embodiments, the metabolites are provided in substantially pure form. “Substantially pure” means that metabolites are pure enough for FDA approval and contain essentially no contaminants or other materials. Alternatively, “substantially pure” means a level of impurity that does not adversely or unacceptably affect the properties of the compounds with respect to safety, effectiveness, stability, and other desirable properties.

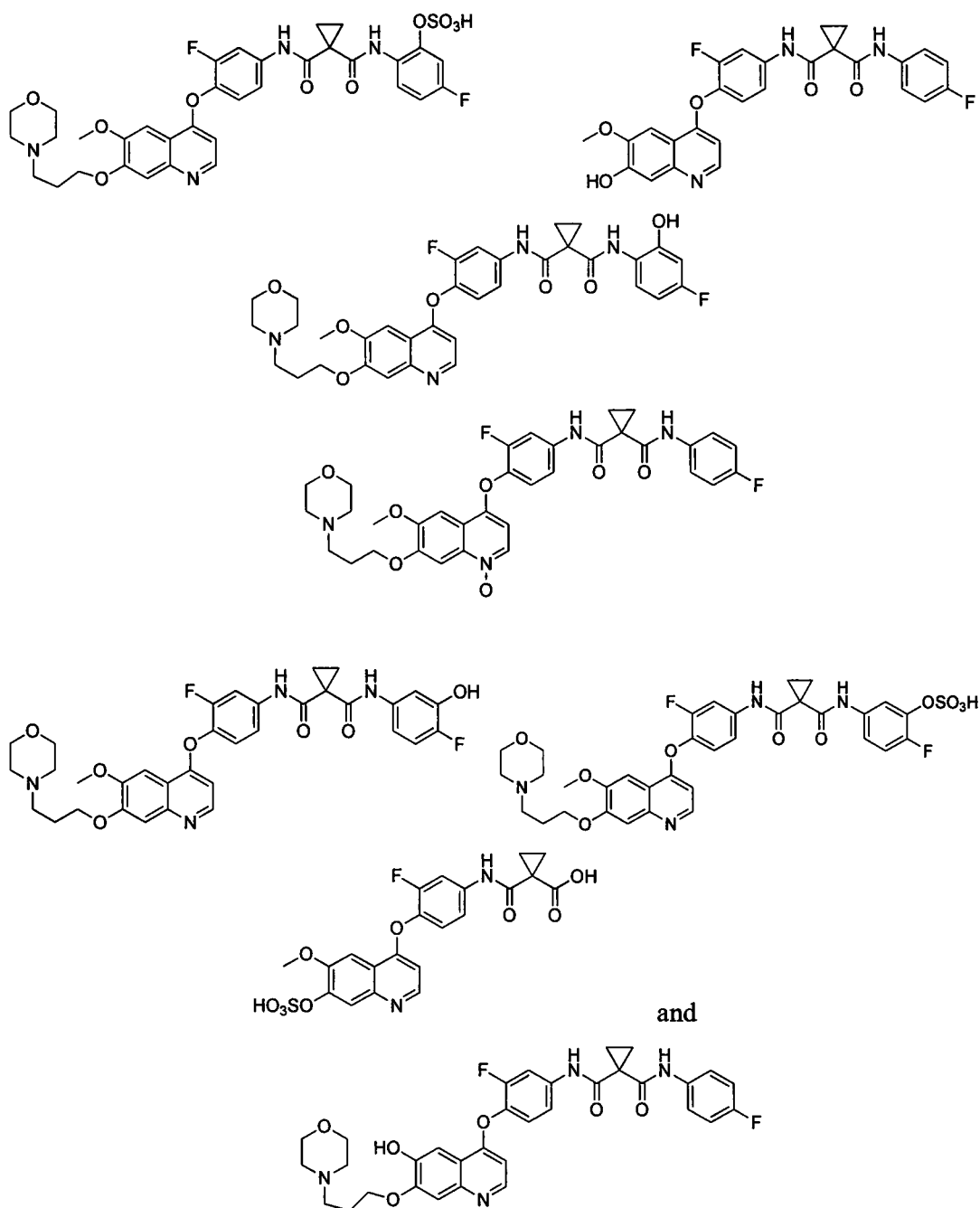
[0025] In one embodiment, the invention is directed to isolated metabolites as depicted in Scheme 1. In this and other embodiments, the metabolite is selected from:



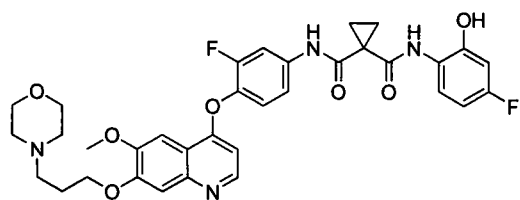


wherein GA is a glucuronic acid moiety.

[0026] More particularly, the metabolite is selected from:

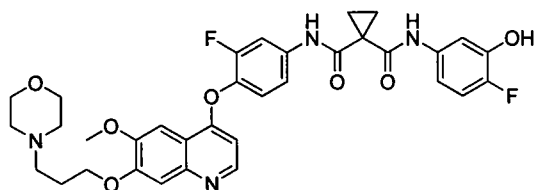


[0027] In a particular embodiment, the isolated metabolite is



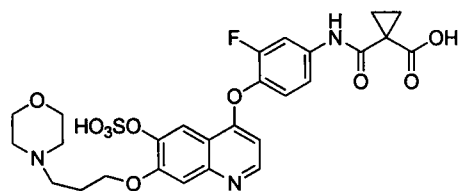
, or a pharmaceutically acceptable salt thereof.

[0028] In another particular embodiment, the isolated metabolite is



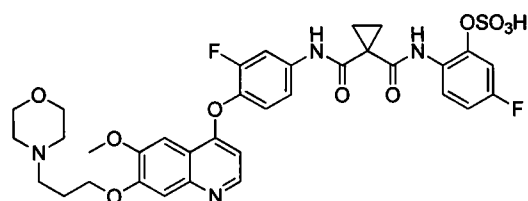
, or a pharmaceutically acceptable salt thereof.

[0029] In another particular embodiment, the isolated metabolite is



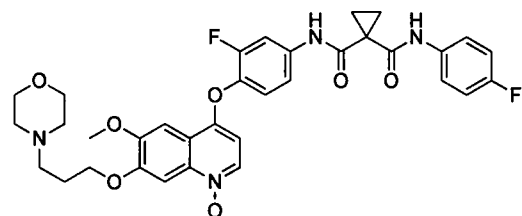
, or a pharmaceutically acceptable salt thereof.

[0030] In another particular embodiment, the isolated metabolite is



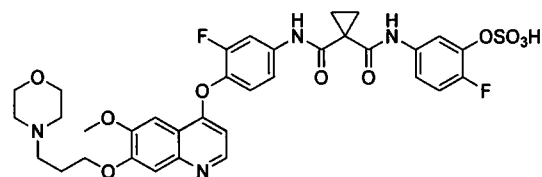
, or a pharmaceutically acceptable salt thereof.

[0031] In another particular embodiment, the isolated metabolite is



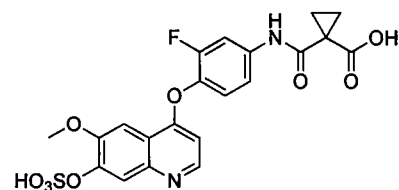
, or a pharmaceutically acceptable salt thereof.

[0032] In another particular embodiment, the isolated metabolite is



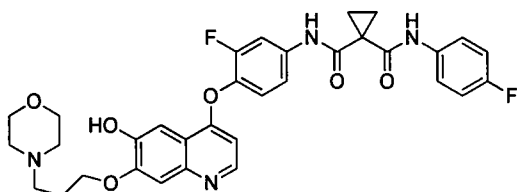
, or a pharmaceutically acceptable salt thereof.

[0033] In another particular embodiment, the isolated metabolite is



, or a pharmaceutically acceptable salt thereof.

[0034] In another particular embodiment, the isolated metabolite is



, or a pharmaceutically acceptable salt thereof.

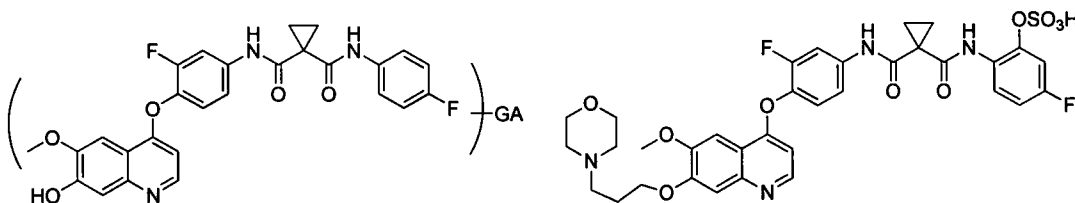
[0035] Methods of the invention include administering foretinib or a foretinib metabolite to a mammal such as a human and detecting metabolites by measuring the level of concentration of one of the metabolites in the tissues or bodily fluids of the mammal. Bodily fluids include, without limitation, blood plasma, bile, urine, and feces, while tissues include, without limitation, liver microsomes, hepatocytes, and perfused livers. In various embodiments, the metabolites are isotopically labeled with various isotopes to assist in detection or quantification of the metabolites in the tissues or bodily fluids. Thus, the metabolites include those that are labeled with ^{14}C or ^3H (tritium) for the purpose of detecting or identifying particular metabolites from their nuclear decay products. The metabolites also include metabolites labeled with ^{13}C or ^2H (deuterium) to facilitate nuclear magnetic resonance and/or mass spectrometric analysis of the compounds. As used herein, deuterated means substituted with deuterium, and tritiated means substituted with tritium. In various other embodiments, the metabolites of the invention, as depicted in Scheme 1, also include their salts, tautomers, and isotopically labeled variants (including ^{14}C , ^{13}C , ^3H , or ^2H).

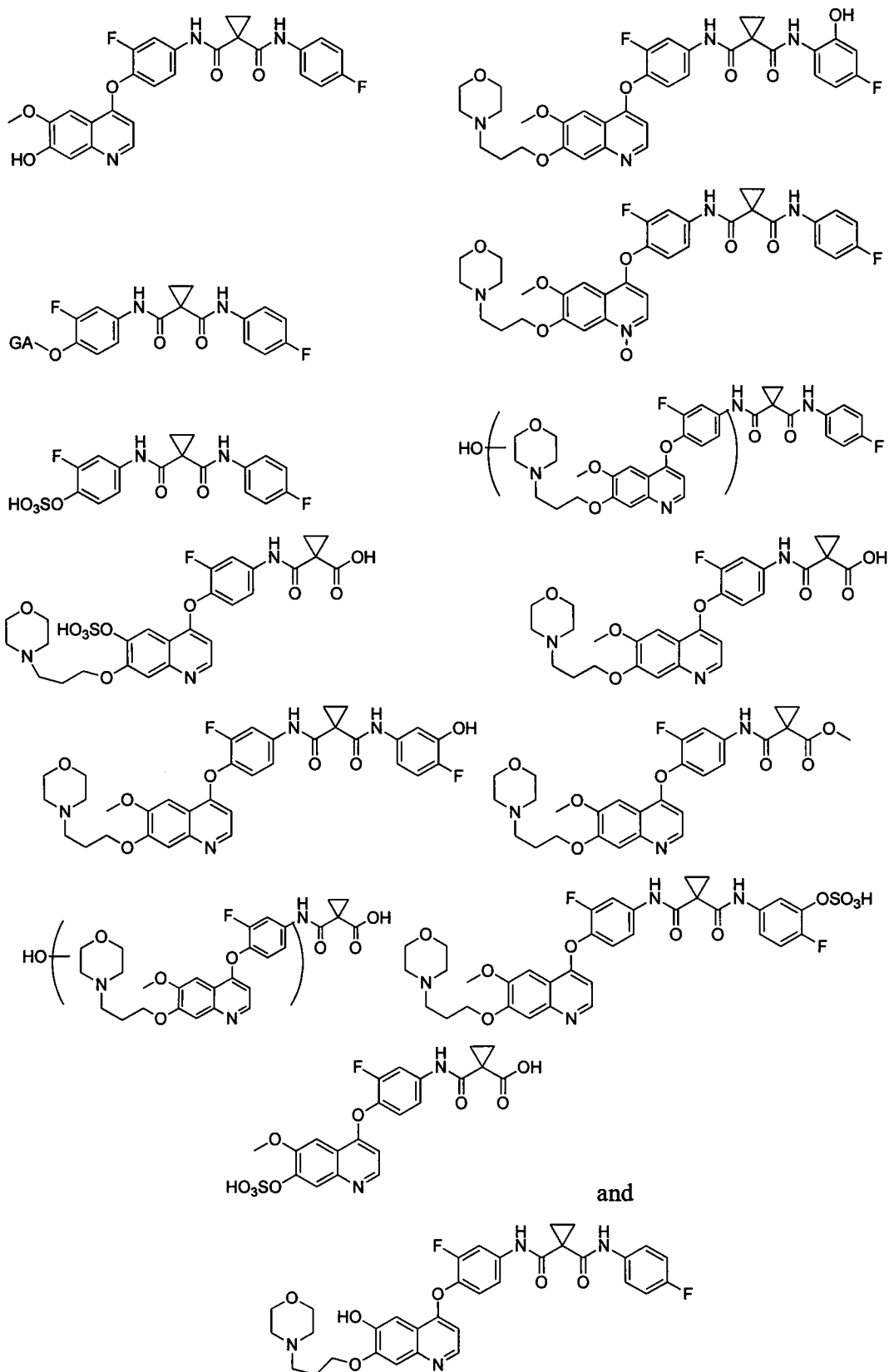
[0036] More specifically, in one embodiment, the invention provides a method for identifying a metabolite of foretinib, comprising:

administering foretinib to a mammal; and

detecting or measuring a level or concentration of a metabolite of foretinib in a mammal in tissues or bodily fluids of the mammal;

wherein the metabolite is selected from the group consisting of:

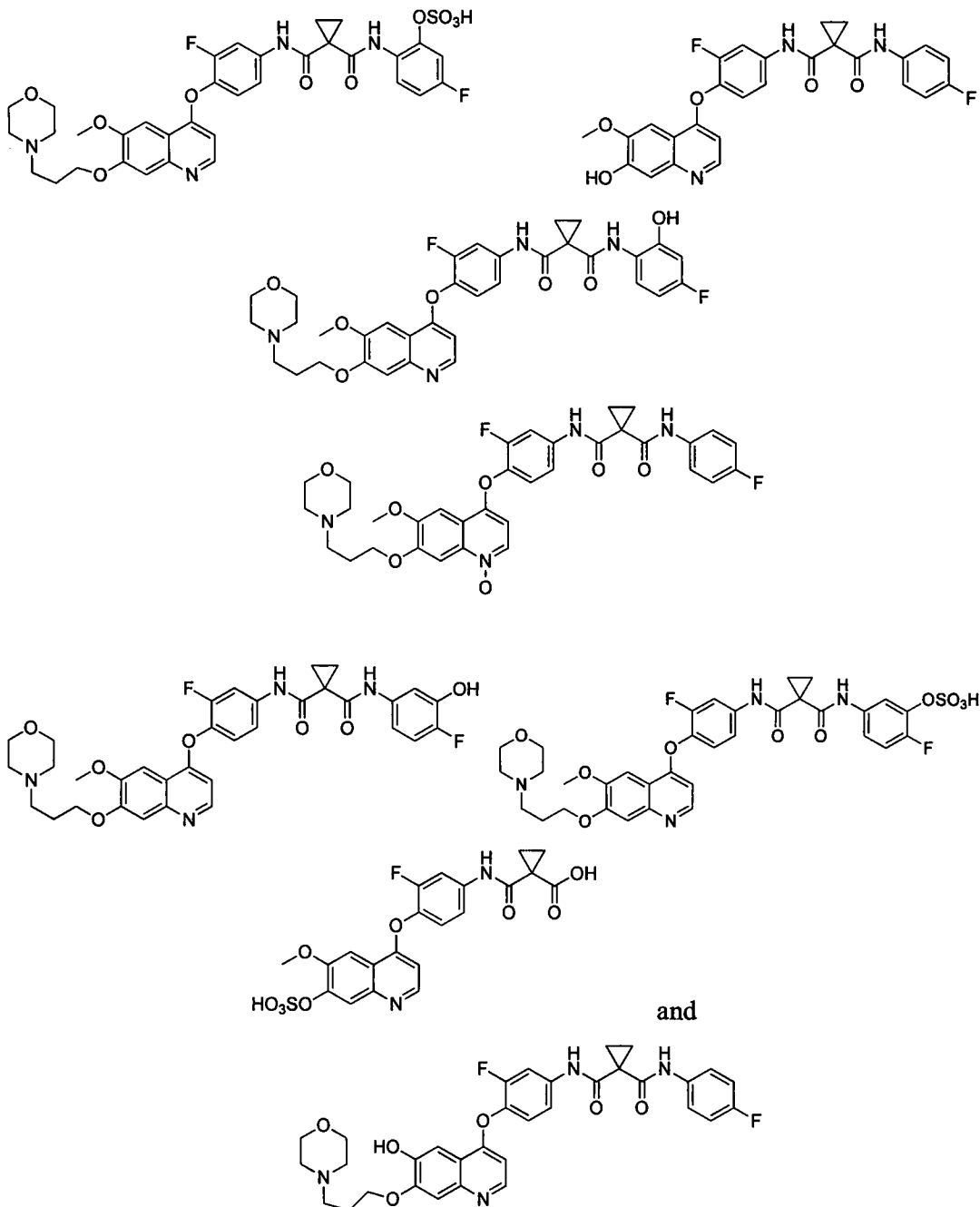




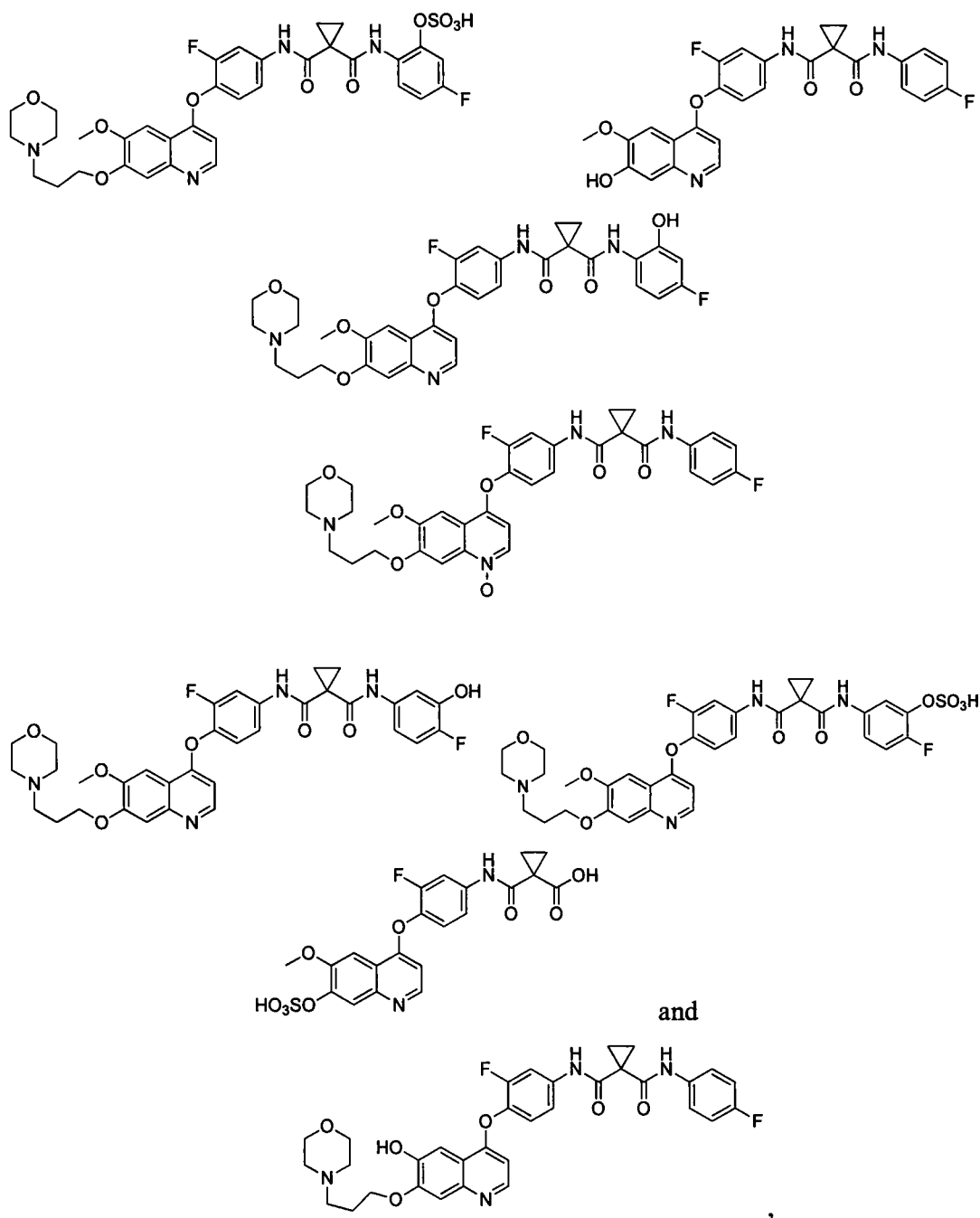
wherein GA is a glucuronic acid moiety. In the method, bodily fluids are selected from the group consisting of plasma, bile, urine, and feces. In these and other methods, the

metabolites are identified using conventional analytical techniques, including isotopic labeling and HPLC/MS.

[0037] More specifically, the metabolite is selected from:



[0038] 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 a foretinib metabolite, which is a compound selected from:



or a pharmaceutical composition comprising such a compound.

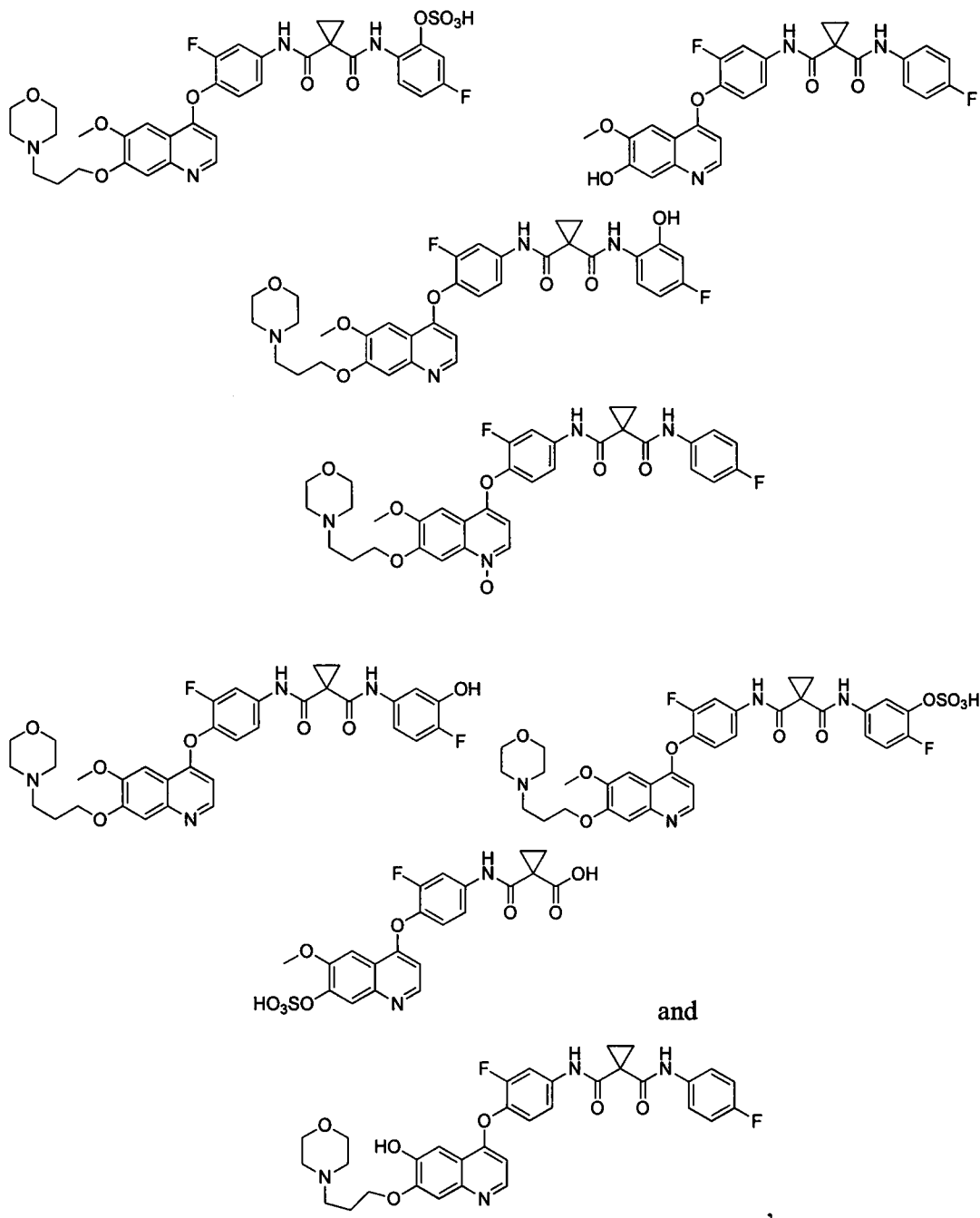
[0039] In one embodiment of this aspect, modulating the *in vivo* activity of the kinase comprises inhibition of said kinase.

[0040] In another embodiment of this aspect, the kinase is at least one of c-Met, RET, KDR, c-Kit, flt-3, and flt-4.

[0041] In another embodiment, the kinase is c-Met.

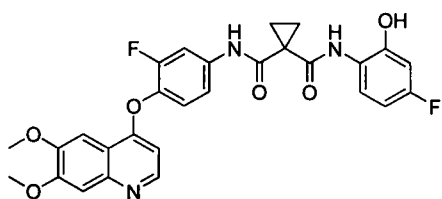
[0042] Another aspect of the invention is directed to a method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities, the

method comprising administering, to a mammal in need thereof, a therapeutically effective amount of a foretinib metabolite, which is a compound selected from:



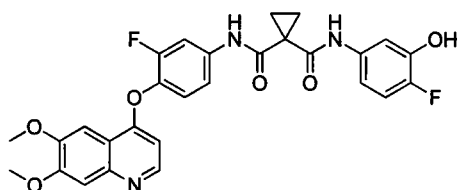
or a pharmaceutical composition comprising such a compound.

[0043] In a particular embodiment, the compound is



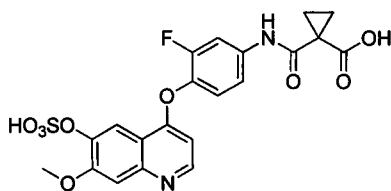
, or a pharmaceutically acceptable salt thereof.

[0044] In another particular embodiment, the compound is



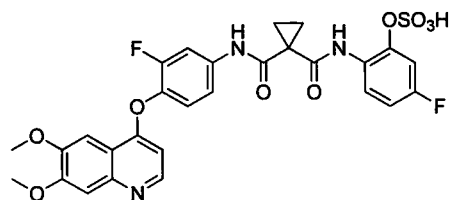
, or a pharmaceutically acceptable salt thereof.

[0045] In another particular embodiment, the compound is



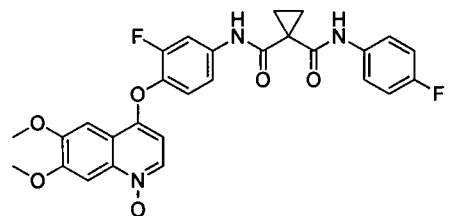
, or a pharmaceutically acceptable salt thereof.

[0046] In another particular embodiment, the compound is



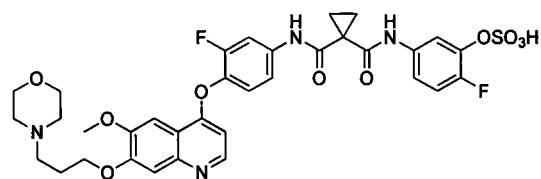
, or a pharmaceutically acceptable salt thereof.

[0047] In another particular embodiment, the compound is



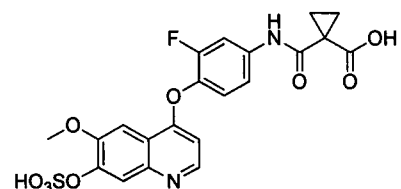
, or a pharmaceutically acceptable salt thereof.

[0048] In another particular embodiment, the compound is



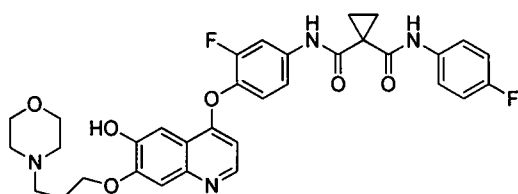
, or a pharmaceutically acceptable salt thereof.

[0049] In another particular embodiment, the compound is



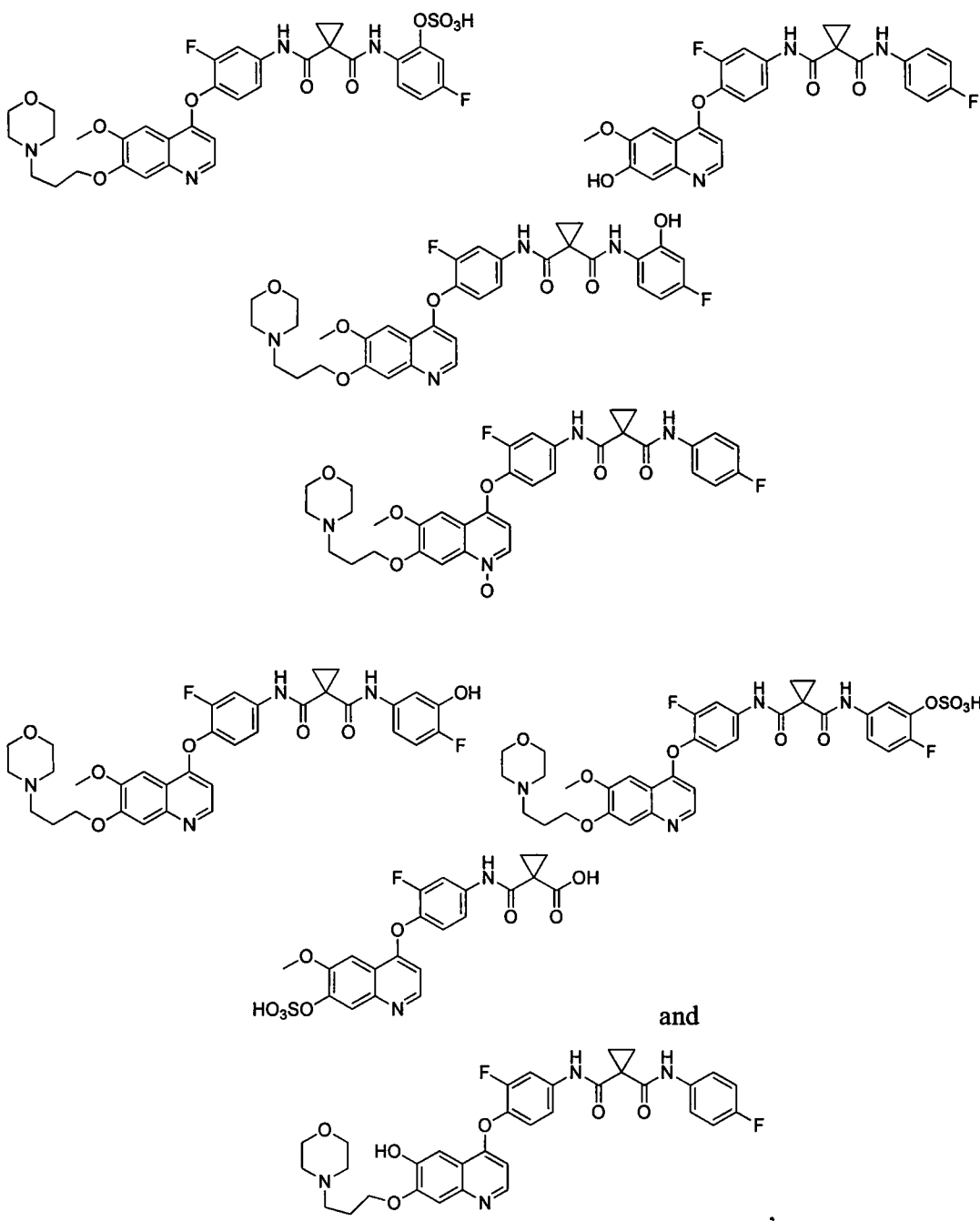
, or a pharmaceutically acceptable salt thereof.

[0050] In another particular embodiment, the compound is



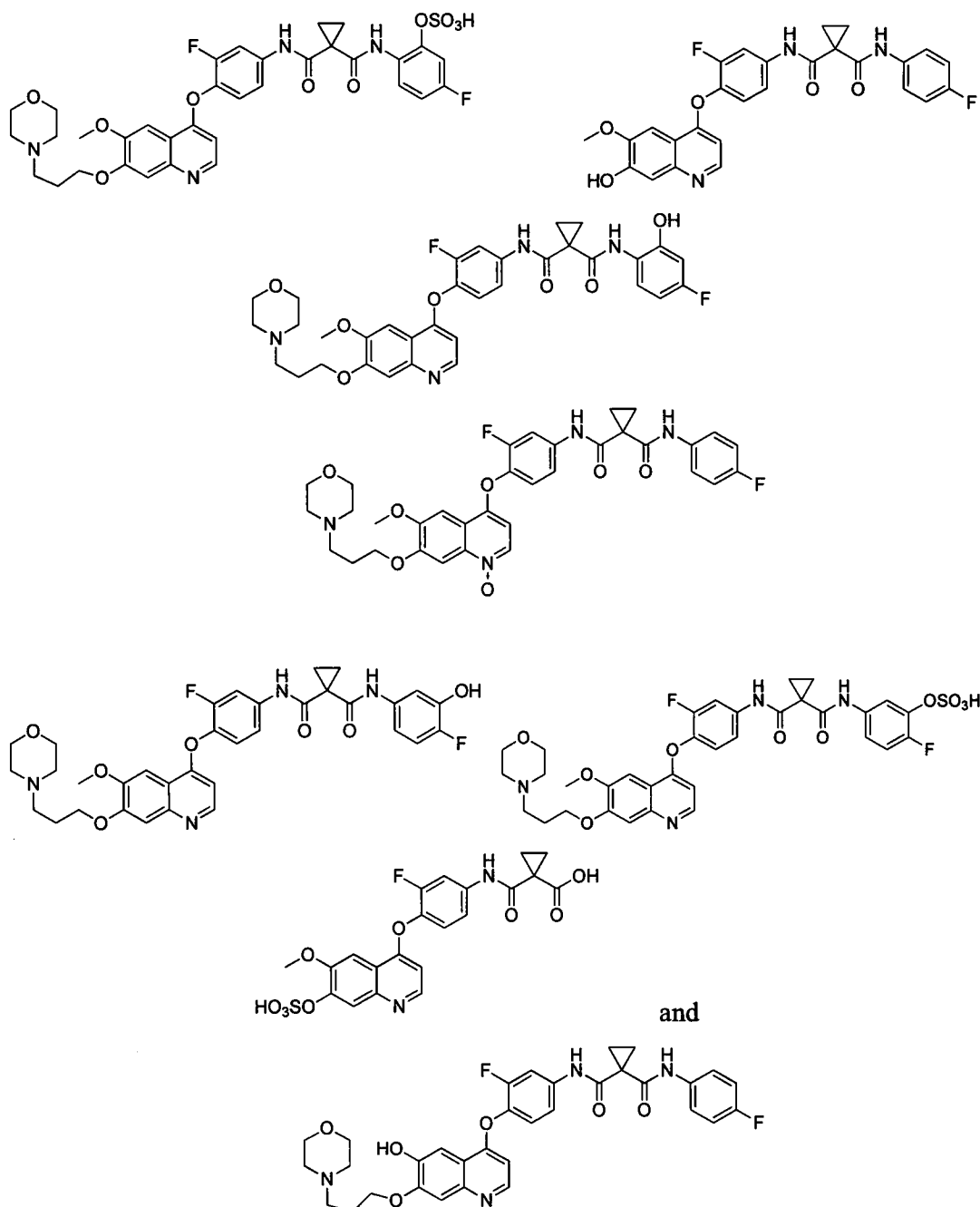
, or a pharmaceutically acceptable salt thereof.

[0051] In another aspect, the invention is directed to a method of screening for a modulator of a kinase, said kinase selected from c-Met, KDR, RET, c-Kit, flt-3, and flt-4, the method comprising combining a foretinib metabolite which is a compound selected from:



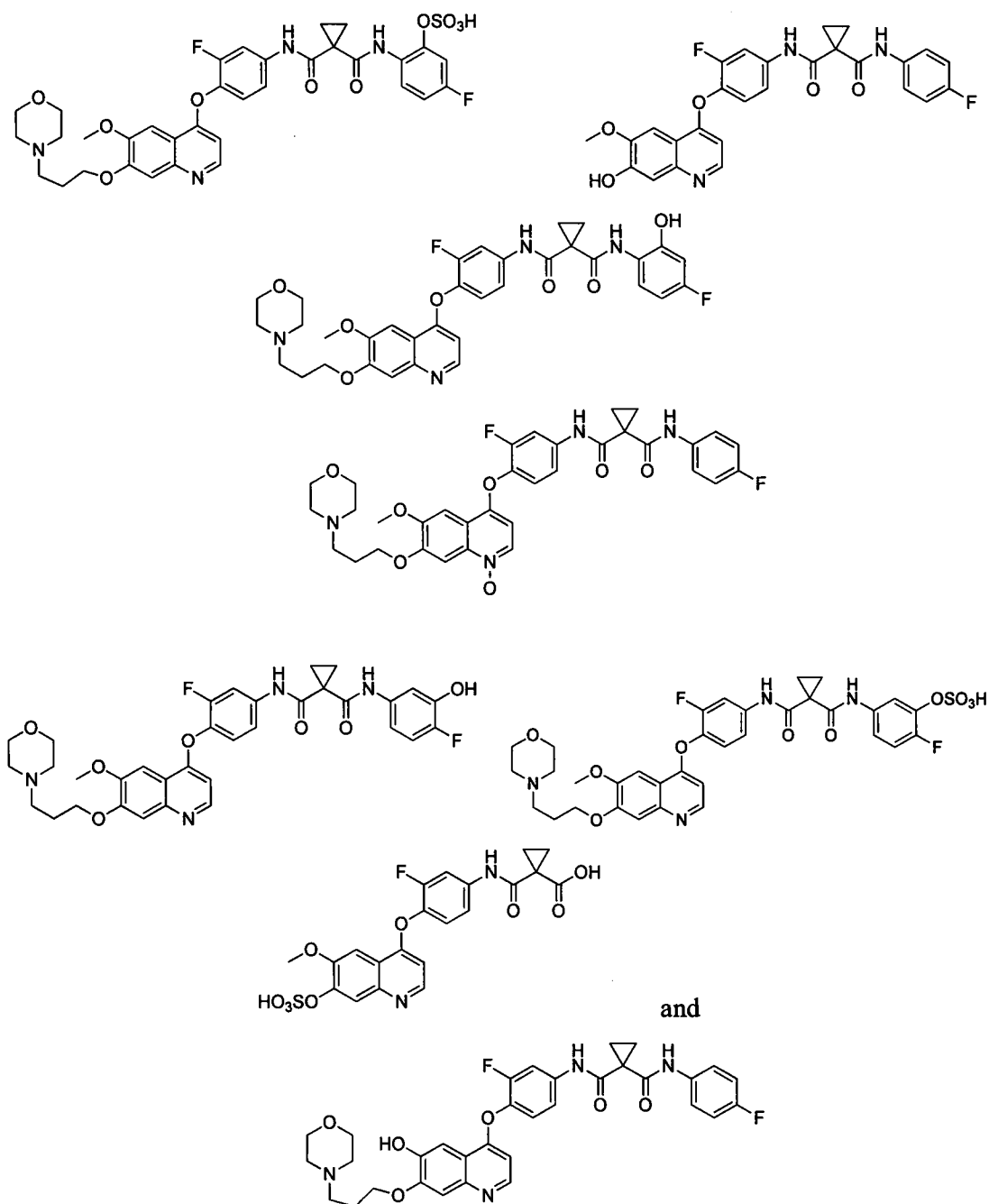
and at least one candidate agent, and determining the effect of the candidate agent on the activity of said kinase.

[0052] Another aspect of the invention is directed to a method of inhibiting proliferative activity in a cell, the method comprising administering an effective amount of a composition comprising a compound to a cell or a plurality of cells, wherein the compound is a foretinib metabolite selected from:



[0053] Another aspect of the invention is a method of screening for a modulator of a kinase, said kinase selected from c-Met, KDR, RET, c-Kit, flt-3, and flt-4, the method

comprising combining a compound and at least one candidate agent and determining the effect of the candidate agent on the activity of said kinase, wherein the compound is a foretinib metabolite selected from:



[0054] Isolated metabolites as described above that exhibit inhibitory activity against c-MET or other kinases can be formulated into suitable dosage forms for administration to humans or other mammals. In some embodiments, the metabolites may exhibit favorable toxicological profiles in comparison to conventional therapy or therapy with foretinib.

[0055] As inhibitors of c-MET, in some embodiments, the metabolites are used to treat cancer. "Cancer" includes tumor types such as tumor types including breast, colon, renal, lung, squamous cell myeloid leukemia, hemangiomas, melanomas, astrocytomas, and glioblastomas as well as other 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 hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi'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, renal cell carcinoma), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma, small cell carcinoma of the prostate), 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), malignant giant cell tumor chordoma, osteochondroma (osteochondrogenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell

carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma); Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma; as well as cancers of the thyroid including medullary thyroid cancer. Thus, the term "cancerous cell," as provided herein, includes a cell afflicted by any one of the above-identified conditions.

[0056] In one embodiment, the cancer is selected from ovarian cancer, prostate cancer, lung cancer, medullary thyroid cancer, liver cancer, gastrointestinal cancer, pancreatic cancer, bone cancer, hematologic cancer, skin cancer, kidney cancer, breast cancer, colon cancer, and fallopian tube cancer.

[0057] In another embodiment, the disease or disorder is ovarian cancer.

[0058] In another embodiment, the disease or disorder is prostate cancer.

[0059] In another embodiment, the disease or disorder is lung cancer.

[0060] In another embodiment, the disease or disorder is medullary thyroid cancer.

[0061] In another embodiment, the disease or disorder is liver cancer.

[0062] In another embodiment, the disease or disorder is gastrointestinal cancer.

[0063] In another embodiment, the disease or disorder is pancreatic cancer.

[0064] In another embodiment, the disease or disorder is bone cancer.

[0065] In another embodiment, the disease or disorder is hematologic cancer.

[0066] In another embodiment, the disease or disorder is skin cancer.

[0067] In another embodiment, the disease or disorder is kidney cancer.

[0068] In another embodiment, the disease or disorder is breast cancer.

[0069] In another embodiment, the disease or disorder is colon cancer.

[0070] In another embodiment, the disease or disorder is fallopian cancer.

[0071] In another embodiment, the disease or disorder is liver cancer, wherein the liver cancer is hepatocellular carcinoma, cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, or hemangioma.

[0072] In another embodiment, the disease or disorder is gastrointestinal cancer, wherein the gastrointestinal cancer is cancer of the esophagus which is squamous cell carcinoma, adenocarcinoma, or leiomyosarcoma; cancer of the stomach which is carcinoma, or lymphoma; cancer of the pancreas, which is ductal adenocarcinoma, insulinoma,

gucagonoma, gastrinoma, carcinoid tumors, or vipoma; cancer of the small bowel, which is adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, or cancer of the large bowel, which is adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, or leiomyoma.

[0073] In another embodiment, the disease or disorder is cancer of the pancreas, wherein the cancer of the pancreas is ductal adenocarcinoma, insulinoma, gucagonoma, gastrinoma, carcinoid tumors, or vipoma.

[0074] In another embodiment, the disease or disorder is bone cancer, wherein the bone cancer is osteosarcoma, fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant reticulum cell sarcoma, multiple myeloma, malignant giant cell tumor chordoma, osteocartiliginous exostoses, chondroblastoma, chondromyxofibroma, or osteoid osteoma.

[0075] In another embodiment, the disease or disorder is hematologic cancer, wherein the hematologic cancer is myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, or myelodysplastic syndrome.

[0076] In another embodiment, the disease or disorder is skin cancer, wherein the skin cancer is malignant melanoma, basal cell carcinoma, squamous cell carcinoma, or Kaposi's sarcoma.

[0077] In another embodiment, the disease or disorder is a renal tumor or renal cell carcinoma.

[0078] In another embodiment, the disease or disorder is breast cancer.

[0079] In another embodiment, the disease or disorder is a colon cancer tumor.

[0080] In another embodiment, the disease or disorder is fallopian tube carcinoma.

[0081] Alternatively, or additionally, the metabolites are administered to subjects or test animals not having any of the above mentioned disease states for the purpose of studying non-pharmacological effects, such as side effects, toxicity, metabolism, uptake, bioavailability, and routes of excretion.

[0082] In various embodiments, the metabolites are administered by any suitable route including oral, rectal, intranasal, intrapulmonary (e.g., by inhalation), or parenteral (e.g. intradermal, transdermal, subcutaneous, intramuscular, or intravenous) routes. Oral administration is preferred in some embodiments, and the dosage can be given with or without food, i.e. in the fasting or non-fasting state. Non-limiting examples of dosage forms include uncoated or coated tablets, capsules, powders, granules, suppositories, solutions, ointments, creams, and sprays.

[0083] Formulations of the invention suitable for oral administration are prepared as discrete units, such as capsules, cachets, or tablets, each containing a predetermined amount of the active ingredient; as a powder or granules; as solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion; or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary, or paste.

[0084] A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form, such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active, or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom. In one embodiment, acid hydrolysis of the medicament is obviated by use of an enteric coating.

[0085] An enteric coating is a means of protecting a compound of the invention in order to avoid exposing a portion of the gastrointestinal tract, typically the upper gastrointestinal tract, in particular the stomach and esophagus, to the compound of this invention. In this way, gastric mucosal tissue is protected against rates of exposure to a compound of the invention which produce adverse effects such as nausea. Alternatively, a compound of the invention is protected from conditions present in one or more portions of the gastrointestinal tract, typically the upper gastrointestinal tract.

[0086] Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

[0087] Formulations for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate.

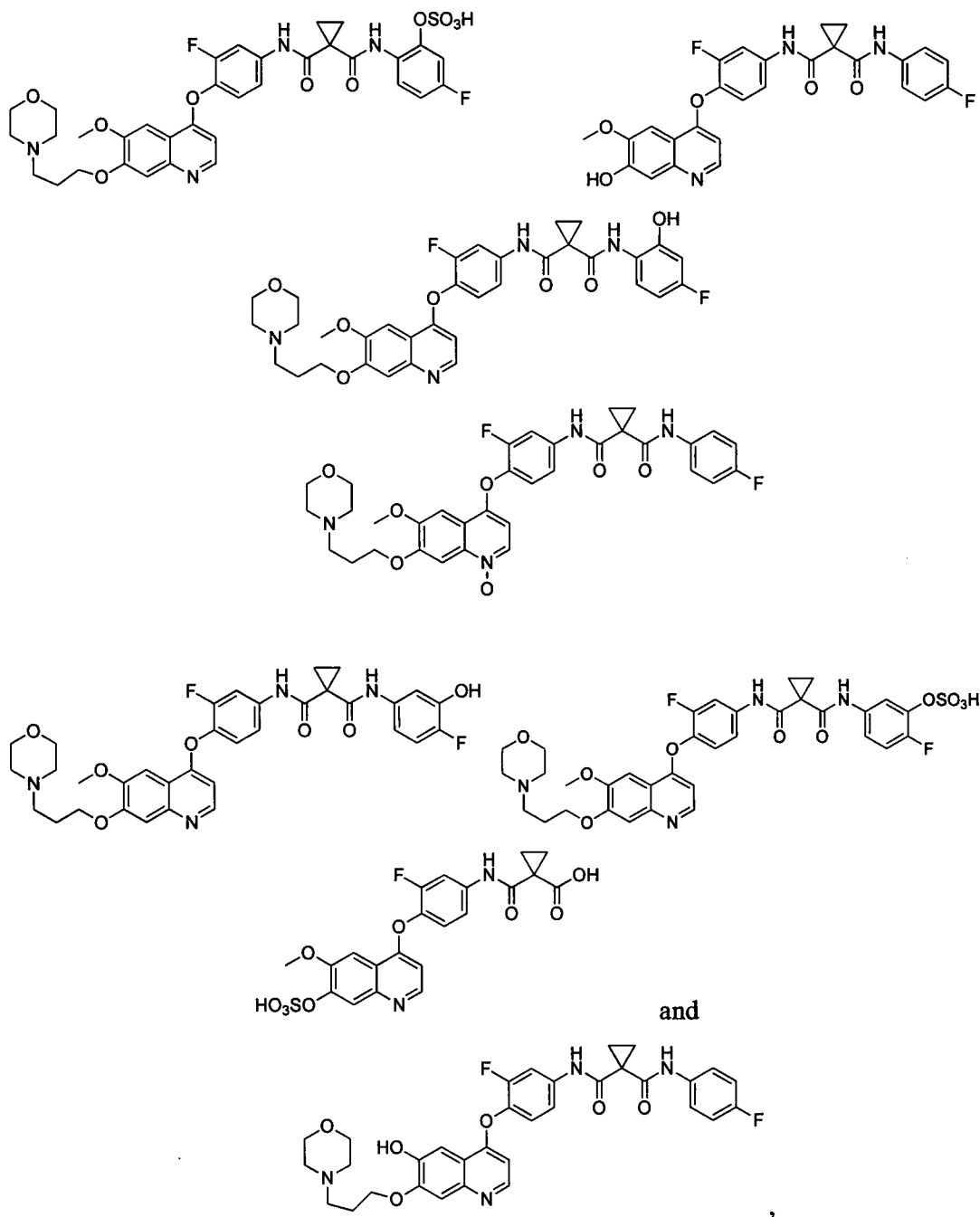
[0088] While it is possible for the active ingredients to be administered alone, it may be preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, comprise at least one active ingredient, as defined above, together with one or more acceptable carriers and optionally comprising other therapeutic ingredients. The carrier(s) must be "acceptable" in that they are compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

[0089] In various embodiments the compounds are formulated in a carrier system. Such systems are known and include binders, fillers, preservatives, disintegrants, flow regulators, plasticizers, wetting agents, emulsifiers, dispersants, lubricants, solvents, release slowing agents (including enteric coatings), antioxidants, and propellant gases. Especially when formulated for administration to humans, the active agents are preferably combined with at least one pharmaceutically acceptable carrier. Such carriers are known and include, without limitation, cellulose derivatives, polyethylene glycol, and N-vinylpyrrolidone polymers. The administration forms comprise a therapeutically effective amount of the compounds, which make up from 0.1% to about 90% by weight of the dosage form.

[0090] The compounds of this invention are formulated with conventional carriers and excipients, which are selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders, and the like. Aqueous formulations are prepared in sterile form and, when intended for delivery by other than oral administration, generally will be isotonic. All formulations will optionally contain excipients, such as those set forth in the "Handbook of Pharmaceutical Excipients" (1986). Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid, and the like.

[0091] The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, Pa.). Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

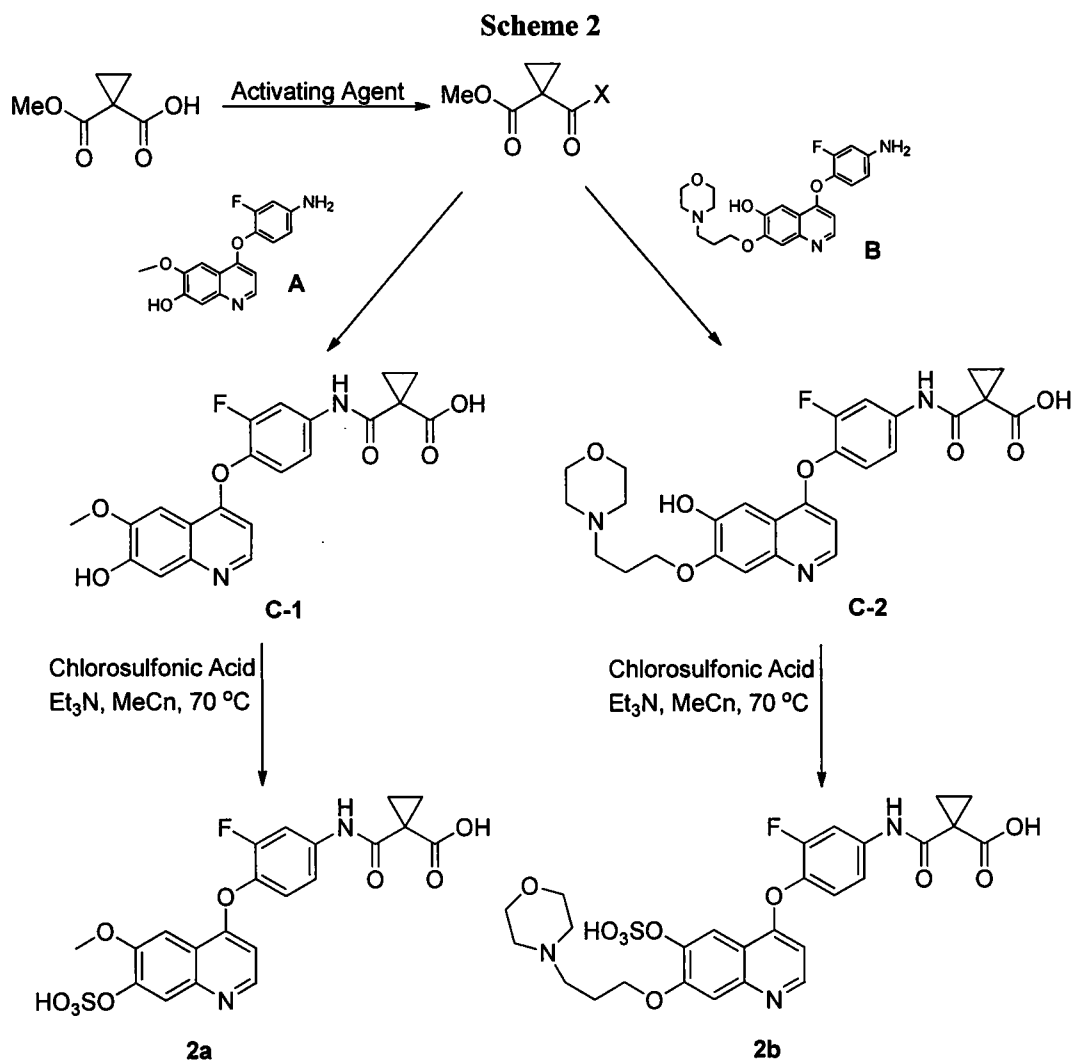
[0092] In a particular embodiment, the invention provides a pharmaceutical composition comprising a foretinib metabolite which is a compound selected from:



or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

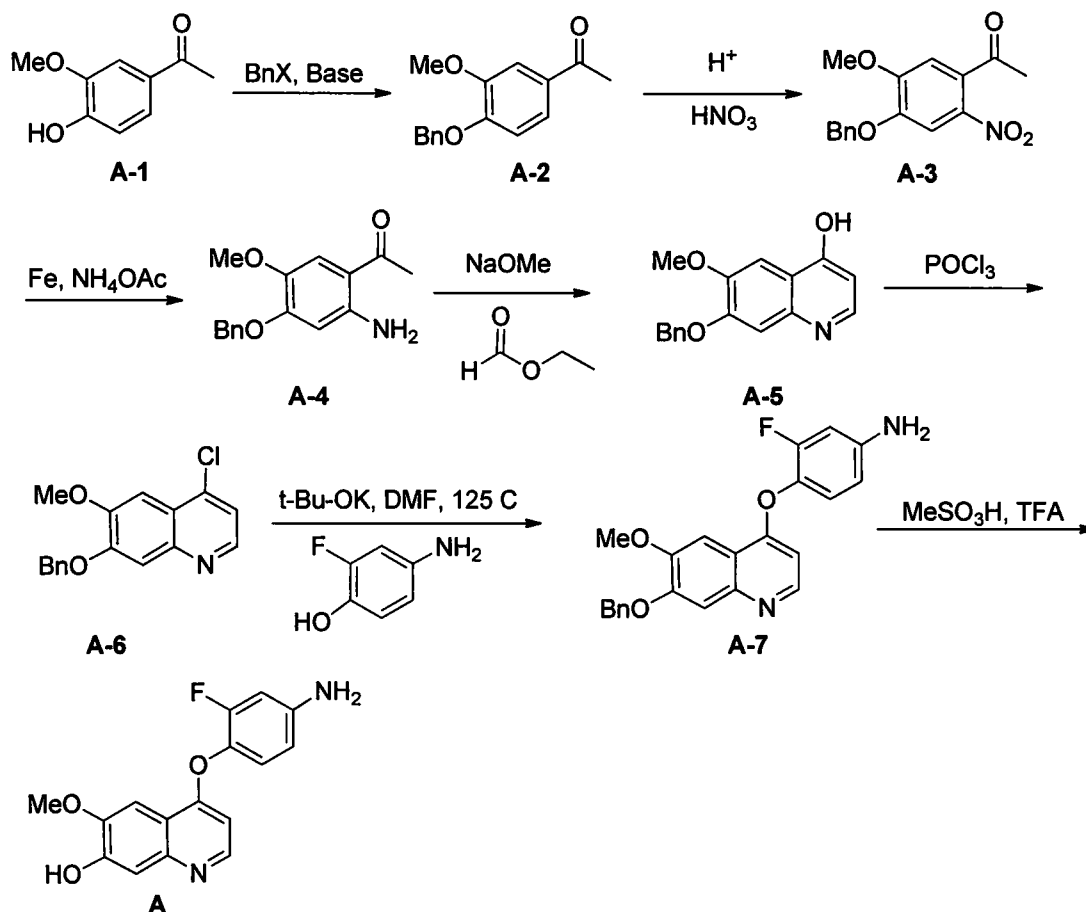
[0093] The compounds disclosed herein can be made according to methods available to the skilled practitioner. For example, as depicted in Scheme 2, peptide chemistry can be used to make the phenols **C-1** and **C-2** from the corresponding amines and carboxylic acids. A variety of processes and reagents are available for achieving such transformations and are described, for instance, in Tetrahedron 61 (2005) 10827-10852. A representative example is depicted in Scheme 2, wherein the activating agent is thionyl chloride, oxalyl chloride, or the

like. The corresponding acid chloride reacts with compound **A** or **B**, respectively, to provide phenol **C-1** or **C-2**. Subsequent reaction of phenol **C-1** or **C-2** with a sulfating agent, such as chlorosulfonic acid or sulfur trioxide-trimethylamine complex, in the presence of a base, such as triethylamine, alkali metal hydroxide or the like, can provide the corresponding hydrogen sulfate **2a** or **2b**.



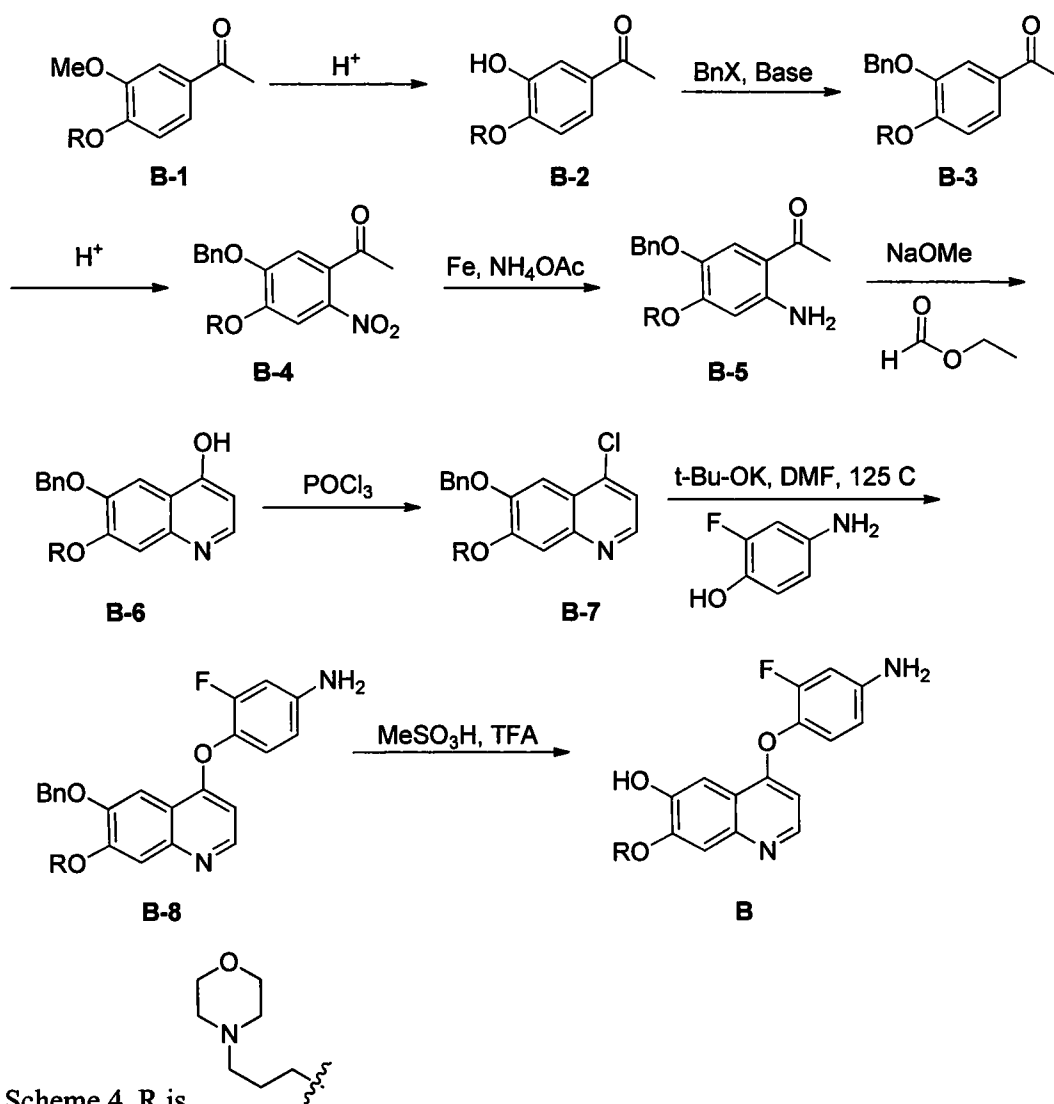
[0094] Compound **A** was prepared according to Scheme 3. Benzylation of **A-1** using a benzyl halide or the like provides benzyl-protected **A-2**. Nitration of **A-2** using a mixture of nitric acid and sulfuric acid provides **A-3**. Reduction of nitro group in **A-3** to the amine **A-4**, may be accomplished using standard nitro reduction conditions, such as iron and ammonium acetate. Cyclization of **A-4** with ethyl formate and an alkoxide such as sodium methoxide provides the **A-5**. Conversion of **A-5** to the corresponding chloride using phosphorous oxychloride provides **A-6**. Reaction of **A-6** with 4-amino phenol provides **A-7**, which is deprotected with methane sulfonic acid to provide compound **A**.

Scheme 3



[0095] Similarly, compound **B** was prepared according to Scheme 4. Demethylation of **B-1** provides **B-2**. Benzylation of **B-2** using a benzyl halide BnX , wherein X is Br , Cl , or I , or the like provides benzyl-protected **B-3**. Nitration of **B-3** using a mixture of nitric acid and sulfuric acid provides **B-4**. Reduction of nitro group in **B-4** to the amine **B-5** may be accomplished using standard nitro reduction conditions, such as iron and ammonium acetate. Cyclization of **B-5** with ethyl formate and an alkoxide such as sodium methoxide provides the **B-6**. Conversion of **B-6** to the corresponding chloride using phosphorous oxychloride provides **B-7**. Reaction of **B-7** with 4-amino phenol provides **B-8**, which was deprotected with methane sulfonic acid to provide compound **B**.

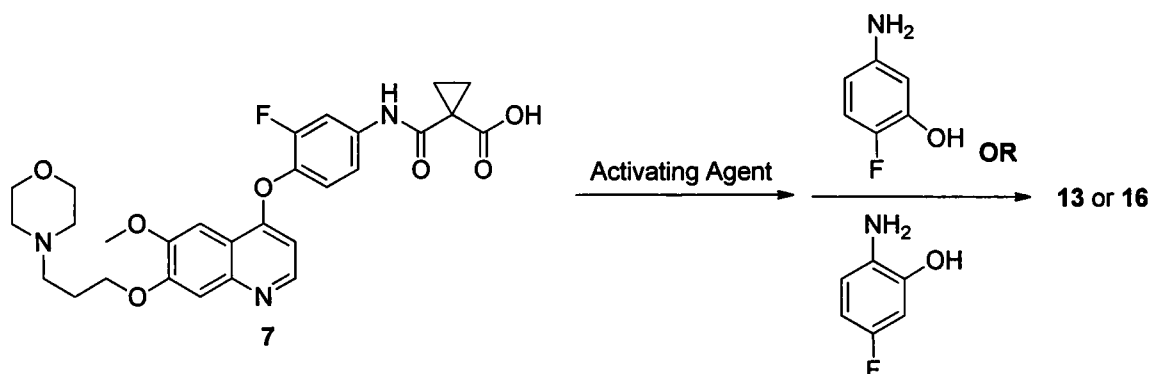
Scheme 4



In Scheme 4, R is

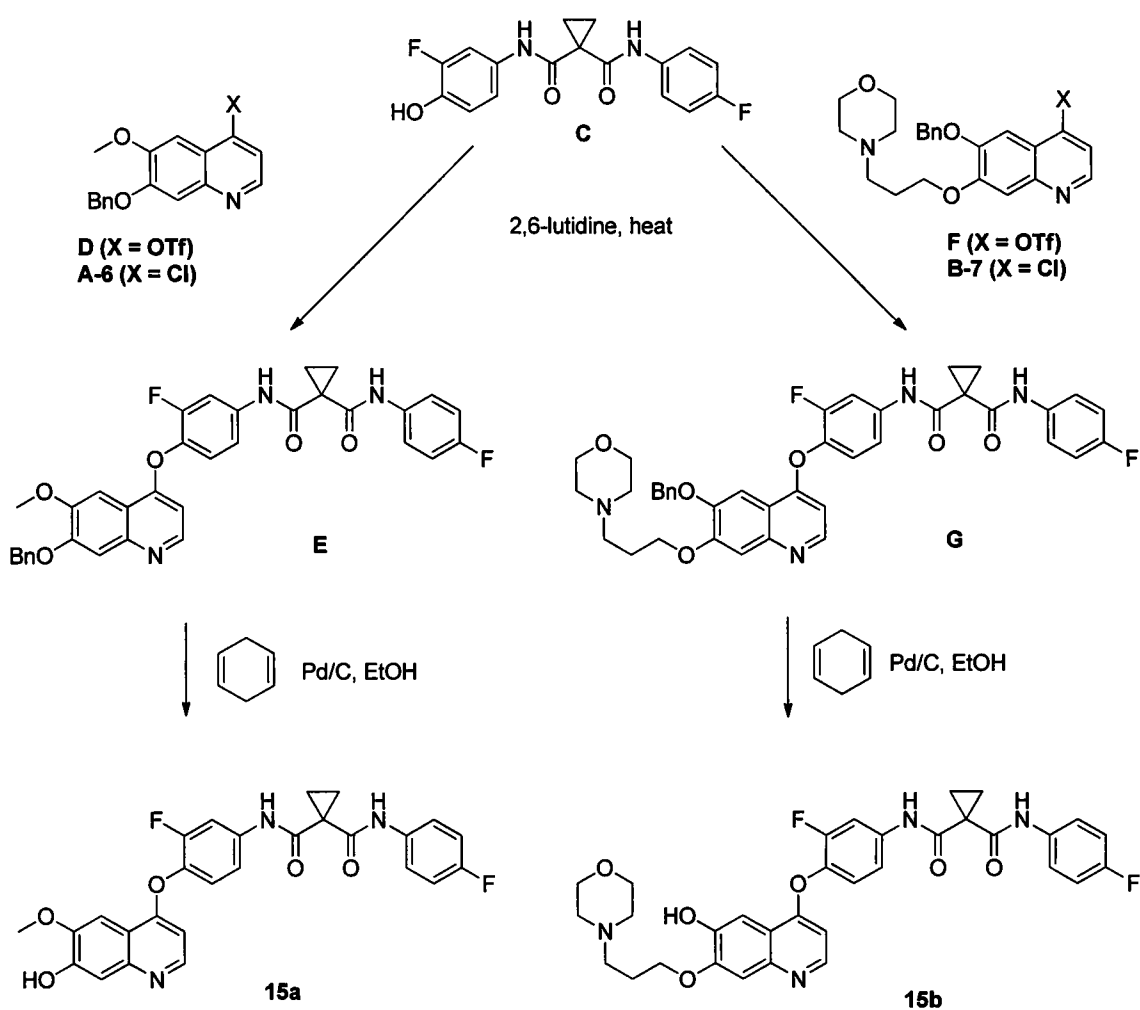
[0096] Phenols 13 and 16 can be similarly prepared from compound 7, the synthesis of which is disclosed in WO 2005/030140 as Example 73. Thus, in Scheme 5, coupling of 7 with 2-amino-5-fluorophenol (CAS Reg. No. 53981-24-1) provides 13. Coupling of 7 with 5-amino-2-fluorophenol (CAS Reg. No. 100367-48-4) provides 16.

Scheme 5



[0097] Phenols **13** and **16** can be readily converted to the corresponding sulfates **9**, and **12** depicted in Scheme 1 using, for example, a sulfating agent, such as sulfur trioxide trimethyl amine complex, in the presence of a strong hydroxide, such as potassium hydroxide, sodium hydroxide, or the like, or using chlorosulfonic acid in the presence of an amine base such as triethylamine.

[0098] The phenols **15a** and **15b** can be prepared by employing the similar method that is disclosed in WO 2005/030140 for the preparation of Example 43. Thus, in Scheme 6, coupling of phenol **C** (Example 38 in WO 2005/030140) with triflate **D** (Example 33 in WO 2005/030140), or chloride **A-6** (Example 32 in WO 2005/030140) provides **E**, which is then deprotected under Pd-catalyzed hydrogenolysis condition to yield compound **15**. Similarly, reaction of phenol **C** with triflate **F** or chloride **B-7** provides **G**, which is subjected to O-benzyl deprotection to provide compound **15b**.

Scheme 6

[0099] The N-oxide **19** can be prepared by the reaction of cabozantinib with an oxidizing agent, such as, for example a peroxide, a peracid, or the like. In one embodiment, the oxidizing agent is sodium perborate tetrahydrate.

[00100] The following non-limiting examples are meant to illustrate the invention.

Examples

Identification of Foretinib Metabolites

[00101] The objective of this study is to profile and identify metabolites of foretinib in human plasma, urine, and feces. The plasma, urine, and fecal samples are collected from a mass balance study of foretinib following a single 175 mg oral administration of foretinib (L-malate salt) containing [^{14}C] foretinib (100 μCi) in healthy male subjects.

Study Design and Plasma, Urine, and Feces Sampling

[00102] Eight male subjects participate in the study, and each subject receives a single oral dose of 175 mg of foretinib (L-malate salt) containing [^{14}C]-foretinib (100 μCi). The plasma, urine, and fecal samples are collected from the 8 subjects for the metabolite profiling.

Plasma samples are collected at pre-dose, 0.5, 1, 2, 3, 4, 5, 8, 14, 24, 72, 168, 336, 504 and 648 hours post-dose. Urine samples are collected at pre-dose, 0-8 hours, 8-24 hours, at 24-hour intervals to 480 hours post-dose, and at greater than 48-hour intervals from 504 to 1152 hours post-dose. Feces samples are collected at pre-dose, at 24-hour intervals to 480 hours post-dose, and at greater than 48-hour intervals from 504 to 1152 hours post-dose. All samples are shipped to QPS, LLC (Newark, DE) and stored at $-70\text{ }^{\circ}\text{C}$. HPLC/tandem MS coupled with a radio flow-through detector (RFD) is used for metabolite profiling and identification for samples with sufficient levels of radioactivity.

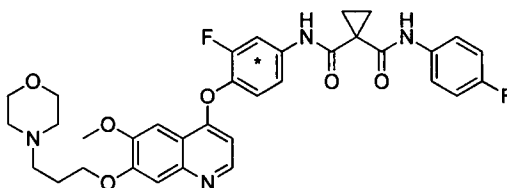
[00103] HPLC fraction collection followed by counting with TopCount NXTTM is used for radioquantitation of plasma samples with sufficient levels of radioactivity. Three (3) HPLC methods are used in this study to separate foretinib and its metabolites. HPLC Method 1 is used for the analysis of pooled urine and fecal samples and individual plasma samples from different time points. HPLC Method 2 is used for the analysis of plasma samples from a drug-drug interaction study to search for possible metabolites that may co-elute with foretinib sulfate. HPLC Method 3 is used for pooled plasma samples.

[00104] Selected samples for plasma, urine, and feces from 6 subjects are analyzed for foretinib and metabolite, and the results are reported.

[00105] Samples from 2 subjects are used for the investigation study.

Test Article

[00106] The test article for this study is a mixture of [^{14}C] foretinib and foretinib. The asterisk indicates the position of the [^{14}C] label. [^{14}C] labeled foretinib is prepared as provided in WO 2005/030140, except that [^{14}C] labeled 4-amino-2-fluorophenol is used instead of unlabeled 4-amino-2-fluorophenol.



General Chemicals and Reference Standards

[00107] Formic acid and ammonium acetate are obtained from Sigma-Aldrich Chemical Co. (St. Louis, MO). Acetonitrile (B & J brand, carbonyl free, for applications sensitive to trace aldehyde and ketone), water (B & J brand, for GC, HPLC and spectrophotometry), and methanol (HPLC grade) are purchased from Fisher Scientific (Pittsburgh, PA). Type I water is generated using an Elgastat UHQ PS water purification system. Non-radiolabeled metabolite standards (fluoroaniline cleavage product, cabozantinib sulfate, and cabozantinib N-oxide) are provided by Exelixis, Inc.

Biological Sample Collection

[00108] The plasma, urine, and fecal samples are collected from a mass balance study of foretinib following a single 175 mg oral administration of foretinib (L-malate salt) containing [^{14}C] foretinib (100 μCi) in healthy male subjects. Samples are shipped from Celerion (Lincoln, NE) to QPS, LLC (Newark, DE) on dry ice and are stored at $-70\text{ }^{\circ}\text{C}$ until analysis. Samples from 6 subjects are used for metabolite profiling, identification, and radio-quantitation. Plasma samples from two subjects are only used in a bridging study as part of investigation of co-eluting metabolites.

Sample Preparation and Radioactive Recovery for Human Plasma

[00109] For metabolite profiling, identification, and radio-quantitation, individual radiolabeled plasma samples collected at 0.5, 1, 2, 3, 4, 5, 8, 14, 24, 72, 168, and 336 hours post-dose are processed and analyzed for 6 subjects. For the investigation of co-eluting metabolites, non-radiolabeled plasma samples of six subjects are pooled, processed, and analyzed for pre-dose, 1-7, 8-96, and 120-336 hours post-dose. To bridge the metabolite data from non-radiolabeled to radiolabeled plasma samples from the human mass balance study, [^{14}C] plasma samples from 0-168 hours post-dose for each of the six subjects are also pooled using the Hamilton pooling method, processed, and analyzed by radio-quantitation. [^{14}C] Plasma samples from 1-168 hours post-dose for two subjects are pooled (equal volume), processed, and analyzed.

Initial Method for Plasma Extraction and Recovery

[00110] Two plasma samples from a subject (4 and 72 hours post-dose) are used for initial extraction and recovery determination. The total radioactivity for each plasma sample in mass balance study is provided by Exelixis, Inc. and is defined as 100%. After the samples

are thawed under a biological hood, two 0.5 mL aliquots of each plasma sample are added to 3 volumes (1.5 mL) of MeOH:ACN (20:80, v/v) and vortexed (5 min). The mixtures are centrifuged at 2000 rpm for 10 minutes, and the supernatants are transferred to clean tubes. The pellets are extracted with two additional 3 volumes of MeOH:CAN (20:80, v/v). The mixtures are centrifuged, and the supernatants are combined. Aliquots are analyzed by a 2900 TR liquid scintillation counter (LSC) (Packard Instruments, Meridian, CT). The extraction recovery is calculated as the following:

$$\text{Extraction Recovery (\%)} = (\text{DPM in supernatant} / \text{DPM in plasma sample}) \times 100$$

[00111] The supernatants from the extraction are evaporated to dryness under a stream of nitrogen in an ambient water bath. The residues are then reconstituted in 0.35 – 0.5 mL of MeOH:ACN:water (10:20:70, v/v/v). The reconstituted samples are centrifuged at 15,000 rpm for 10 minutes, and aliquots are analyzed by LSC for reconstitution recovery.

$$\text{Reconstitution Recovery (\%)} = (\text{DPM in reconstitution solution} / \text{DPM in supernatant}) \times 100$$

Plasma Sample Preparation

[00112] Radiolabeled and non-radiolabeled plasma samples are extracted employing the same method, using 1.0-2 mL plasma samples, depending on the volume available and radioactivity level of the samples. The supernatants are evaporated to dryness under a stream of nitrogen in an ambient water bath, and the residues are reconstituted in 0.35-0.5 mL of MeOH:ACN:water (10:20:70, v/v/v). The reconstituted samples are centrifuged at 15,000 rpm for 10 minutes. Aliquots of the supernatants are injected onto the HPLC system for analysis.

Sample Preparation and Radioactive Recovery for Human Urine

[00113] Pooled urine samples from a subject (0-72, 168-192, and 312-336 hours post dose) are lyophilized in triplicate (each 4 mL), and the residues are reconstituted in 1 mL of water:ACN:FA (80:20:0.1, v/v/v). The radioactivity in pooled urine and reconstituted solution is counted using LSC, and the reconstitution recovery is calculated. For metabolite profiling, identification, and radio-quantitation, pre-dose and 3 pooled urine samples (0-72 hours, 168-192 hours, and 312-336 hours post-dose) from each of the six subjects are

analyzed. Each pooled urine sample is lyophilized, the residue is reconstituted in water:ACN:FA (80:20:0.1, v/v/v), and the reconstituted sample is centrifuged at 15,000 rpm for 10 minutes before analysis.

Sample Preparation and Radioactive Recovery for Human Urine

[00114] To evaluate the extraction recovery of fecal samples, two fecal homogenate samples from a subject are thawed under a biological hood. Approximately 5.5-6 g fecal homogenate is accurately weighed out for the extraction. Fifteen mL ACN:MeOH (80:20) is added to the fecal homogenates. The mixtures are vortexed for 3 minutes and centrifuged at 3000 rpm for 10 minutes. The supernatants are transferred to clean tubes. The extraction procedure is repeated two more times. The supernatants from all three extractions are combined. The radioactivity in the combined supernatants is determined by LSC. The extraction recovery is calculated using the following formula:

$$\text{Extraction Recovery (\%)} = (\text{DPM in supernatant} / \text{DPM in fecal homogenate}) \times 100$$

[00115] The supernatant is concentrated under a nitrogen stream at ambient temperature, and the residues are reconstituted in MeOH:ACN:water (10:20:70). Aliquots of reconstitution solution are counted with LSC for reconstitution recovery.

$$\text{Reconstitution Recovery (\%)} = (\text{DPM in reconstitution solution} / \text{DPM in supernatant}) \times 100$$

$$\text{Overall Recovery (\%)} = \text{Extraction Recovery (\%)} \times \text{Reconstitution Recovery (\%)} / 100$$

[00116] For metabolite profiling, identification, and radio-quantitation, pre-dose and 3 pooled fecal samples (0-72, 168-192, and 312-336 hours post-dose) from each of the six subjects are extracted using the same procedures for extraction recovery. The supernatants are dried under a nitrogen stream, and the residues are reconstituted in water:ACN:FA (80:20:0.1, v/v/v). The reconstituted samples are centrifuged at 15,000 rpm for 10 minutes before analysis.

HPLC Column Recovery

[00117] HPLC column recovery is carried out to demonstrate that all radioactive components are effectively eluted from the column using HPLC Method 1. Aliquots of urine samples (24-48 hours post-dose) are injected onto the HPLC system with or without a column, and the eluents from 0-30 minutes are collected into clean 50 mL centrifuge tubes. The

weights of eluent from each injection are obtained after collection, and duplicate aliquots (1 mL) are counted using LSC. The average value of the counts is used to calculate the total radioactivity contained in the collected eluent with or without a column installed.

$$\text{Column Recovery (\%)} = (\text{DPM in eluent with column} / \text{DPM in eluent without column}) \times 100$$

[00118] HPLC Method 3 is used for pooled plasma only.

HPLC/MS/RFD and HPLC Radio-Analysis Systems

[00119] The system for metabolite profiling and identification (HPLC/MS/RFD) consists of a HTC PAL autosampler, a Surveyor HPLC pump, a LTQ linear ion trap mass spectrometer, and a β -RAM Model 3 RFD. The data obtained by mass spectrometry and RFD are processed by Xcalibur and Laura Lite 3 software, respectively. The HPLC eluent is split between the RFD and mass spectrometer with a ratio of 3 to 1. The following are the summary of the conditions for HPLC, mass spectrometer, and RFD.

HPLC/MS/RFD Method 1

HPLC		Surveyor HPLC pump	
• Column Type		Phenomenex Synergi Polar RP, 4.6 x 250 mm, 4 µm	
• Mobile Phases		A: H ₂ O with 0.1% FA	
		B: ACN with 0.1% FA	
• Gradient Program		Time (min)	A%
		0	80
		2	80
		22	30
		23	5
		27	5
		28	80
		34	80
			B%
			20
			20
			70
			95
			95
			20
			20
• Flow Rate		800 µL/minutes	
• Analysis Time		34 minutes	
Mass Spectrometry:		Thermo Finnigan LTQ Linear Ion Trap	
• Sheath gas flow rate		50 unit	
• Auxiliary gas flow rate		20 unit	
• Sweep gas flow rate		10 unit	
• Ion spray voltage		5 kV for ESI+; 4.3 kV for ESI-	
• Capillary temperature		300 °C	
• Capillary voltage		22 V for ESI+; -9 V for ESI-	
• Tube lens voltage		80 V for ESI+; -96 V for ESI-	
• Ionization mode		ESI+, ESI-	
Radio Flow-through Detector:		β-RAM Model 3	
• Radionuclide		¹⁴ C	
• Cell Volume		400 µL	
• Scintillation Cocktail		Ultima-Flo M, Perkin Elmer	
• Cocktail/HPLC flow ratio		3:1	

HPLC/MS Method 2

<u>HPLC</u>		Surveyor HPLC pump	
• Column Type		Phenomenex Synergi Polar RP. 4.6 x 250 mm. 4 μ m	
• Mobile Phases		A: H ₂ O with 0.1% FA	
		B: ACN with 0.1% FA	
• Gradient Program	Time (min)	A%	B%
	0	80	20
	2	80	20
	40	35	65
	42	5	95
	47	5	95
	48	80	20
	55	80	20
• Flow Rate	800 μ L/minutes		
• Analysis Time	55 minutes		

<u>Mass Spectrometry:</u>	Thermo Finnigan LTQ Linear Ion Trap
• Sheath gas flow rate	50 unit
• Auxiliary gas flow rate	20 unit
• Sweep gas flow rate	10 unit
• Ion spray voltage	5 kV
• Capillary temperature	300 °C
• Capillary voltage	22 V
• Tube lens voltage	80 V
• Ionization mode	ESI+

HPLC/MS Method 3

<u>HPLC</u>		Surveyor HPLC pump	
• Column Type		Waters Xbridge phenyl, 4.6 x 150 mm, 3.5 μm	
• Mobile Phases		A: H ₂ O with 0.1% FA	
		B: ACN with 0.15% FA	
• Gradient Program	Time (min)	A%	B%
	0	80	20
	2	80	20
	40	30	70
	42	5	95
	47	5	95
	48	80	20
	55	80	20
• Flow Rate	800 μL/minutes		
• Analysis Time	55 minutes		
<u>Mass Spectrometry:</u>		Thermo Finnigan LTQ Linear Ion Trap	
• Sheath gas flow rate	50 unit		
• Auxiliary gas flow rate	20 unit		
• Sweep gas flow rate	10 unit		
• Ion spray voltage	5 kV		
• Capillary temperature	300 °C		
• Capillary voltage	22 V		
• Tube lens voltage	80 V		
• Ionization mode	ESI+		

[00120] The HPLC-MS system for high resolution MS consists of a Michrom Bioresources Paradigm MS4B HPLC and a Thermo LTQ Orbitrap Discovery mass spectrometer. Chromatographic conditions and the ion source parameters are the same as HPLC method 1 for the LTQ system. Data are acquired with a resolution of 30000 in centroid mode.

[00121] An HPLC/TopCount NXT™ system is used for the radio-quantitation of plasma samples. The system consists of an HTC PAL autosampler, two Shimadzu HPLC pumps, and a Foxy Jr. Fraction Collector (Isco, Lincoln, NE). HPLC fractions collected in a LumaPlate™ 96-well plate are dried using an EZ-2plus Personal Evaporator (Genevac, Valley Cottage, New York), and the dried samples are counted by TopCount NXT™ Microplate Scintillation & Luminescence Counter (PerkinElmer®). The data are processed using ProFSA (PerkinElmer®) software. The HPLC methods are the same as described above.

Metabolite Identification

[00122] Metabolites that represented greater than 5% of the total radioactivity or 5% of total AUC in the matrix are identified according to the following process. Mass spectra (MS, MS/MS, and MS/MS/MS) of foretinib and its metabolite standards, provided by Exelixis, Inc., are acquired on an ion trap mass spectrometer. Major fragment patterns are proposed. Identification of these metabolites is confirmed by matching mass spectra (MS and MS/MS) and retention times with authentic reference standards. For other unknown metabolites, molecular ions are searched on LC/MS chromatograms operating in full scan positive as well as negative ionization modes at the same retention times as those found on LC-radio chromatogram. Product ion mass spectra and high resolution mass spectra are then acquired for the corresponding molecular ions. Putative metabolite structures are proposed based on the analysis of their mass fragment patterns.

Quantitation of foretinib and its Metabolites

[00123] Quantitation of foretinib and its metabolites in pooled or individual samples from each matrix at different time points or time intervals is based on integration of the corresponding peaks found on their radio-chromatograms. For plasma samples, percent of total radioactivity in the sample for each peak at each time point is calculated and converted to ng/mL.

[00124] For quantification of foretinib and its metabolites in plasma:

$$\text{ng/mL} = (\% \text{ of the total radioactivity}) \times (\text{total ng equivalent/mL for the time point})/100$$

[00125] The values of total ng equivalent/mL are obtained from the results of the human mass balance study.

[00126] For the pooled urine samples, percent of total radioactivity in the pooled sample for each peak is calculated as the % of total non-parent in the pooled samples:

$$\% \text{ of total non-parent in the pooled samples} = (\text{total radioactivity of the peak} / \text{total radioactivity of the non-parent peaks}) \times 100$$

[00127] For the pooled fecal samples, percent of total radioactivity in the pooled sample for each peak is calculated as the percent of total non-parent plus parent in the pooled samples:

% of total non-parent plus parent in the pooled samples = (total radioactivity of the peak/total radioactivity of the parent and non-parent peaks) x 100

[00128] The percent of total radioactivity in the pooled sample for each peak is converted to the percent of parent in the pooled samples:

% of parent in the pooled samples = (total radioactivity of the peak/total radioactivity of the parent peak) x 100

[00129] The limit of quantification for a radioactivity detector is defined as the ratio of signal to noise (3 to 1) on the radio-chromatogram. The low limits of quantification are 10 and 500 dpm for the TopCount and β -RAM radio flow-through detector, respectively.

Results and Discussion

Radioactive Recovery

[00130] The initial extraction recovery is determined using plasma samples from a subject at 4 hours and 72 hours post-dose with three volumes of MeOH:ACN (20:80) extracting three times. The mean extraction recoveries of radioactivity are measured. After drying down and reconstitution into MeOH:ACN solution, the reconstitution recoveries are measured again. The overall recoveries are calculated.

[00131] Urine centrifugation recoveries determined using 0-8, 24-48, 72-96, and 120-144 hour post-dose samples from the subject are measured. Urine reconstitution recovery after lyophilization is measured using pooled samples from a subject.

[00132] For pooled fecal samples from 0-48 hours post dose, the extraction, reconstitution, and overall recoveries are measured. For pooled fecal samples of 120-168 hours post dose, the extraction, reconstitution, and overall recoveries are measured.

[00133] The radioactivity recovery from HPLC column for urine sample is measured.

[00134] No correction factor is applied to the plasma, urine, and fecal radio-quantitation to account for the recovery.

Metabolite Profiling

[00135] In a subject, the major peaks on the radio-chromatograms are determined and correspond to the major metabolites. The major metabolite in plasma samples after 72 hours post-dose is identified. Minor peaks are also identified.

[00136] Representative human urine metabolite profiles, the radio-chromatograms (using HPLC Method 1) of human urine samples from 0-72 hours, 144-192 hours, and 288-336 hours post-dose are collected from a subject. The major metabolites are determined.

[00137] Representative human fecal metabolite profiles, the radio-chromatograms (using HPLC Method 1) of human fecal samples from 0-72 hours, 144-192 hours, and 288-336 hours post-dose from a. The major metabolites are observed.

Metabolite Identification Using HPLC/MS Analysis

[00138] HPLC/MS analysis of authentic standards using HPLC Method 1 show the retention times of the foretinib parent compound and metabolites.

[00139] Plasma, urine, and fecal samples are next analyzed by HPLC/MS, and the compounds are identified based on their protonated molecular ions and fragmentation patterns.

Metabolite Identification of Foretinib and its Metabolites in Human Plasma

[00140] The mass spectrum in the XIC is analyzed and compared to reference samples.

Kinase Activity of Foretinib Metabolites

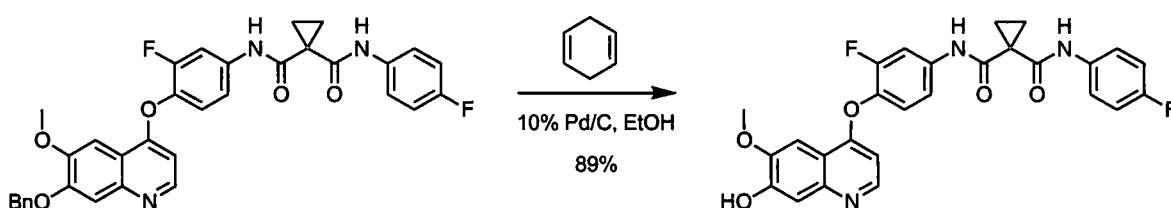
Kinase Dilution

[00141] Kinase Activity is measured and profiled by EMD Millipore according to the Kinase Profiler Service Assay Protocols Protocol Guide Volume 57.

Metabolite Synthesis and Structural Data

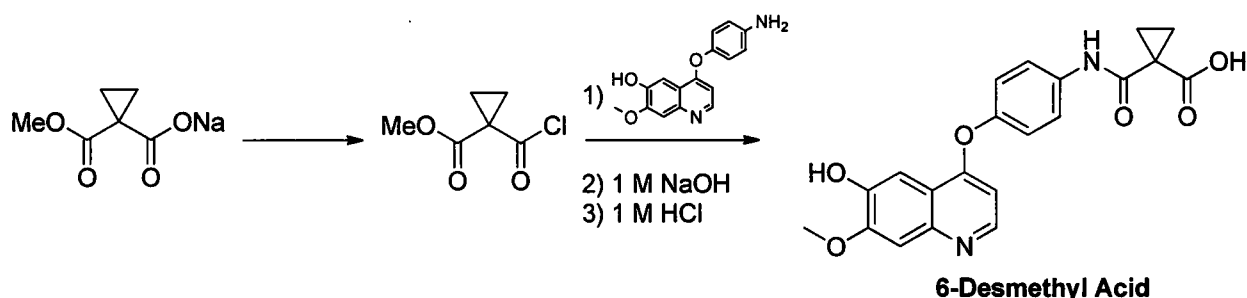
[00142] The metabolites of the invention may be prepared using methods similar to those disclosed herein.

[00143] Cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinolin-4-yloxy)-phenyl]-amide(4-fluoro-phenyl)-amide



[00144] To a solution of cyclopropane-1,1-dicarboxylic acid [4-(7-benzyloxy-6-methoxyquinolin-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 hours. 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 Na₂SO₄. 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.

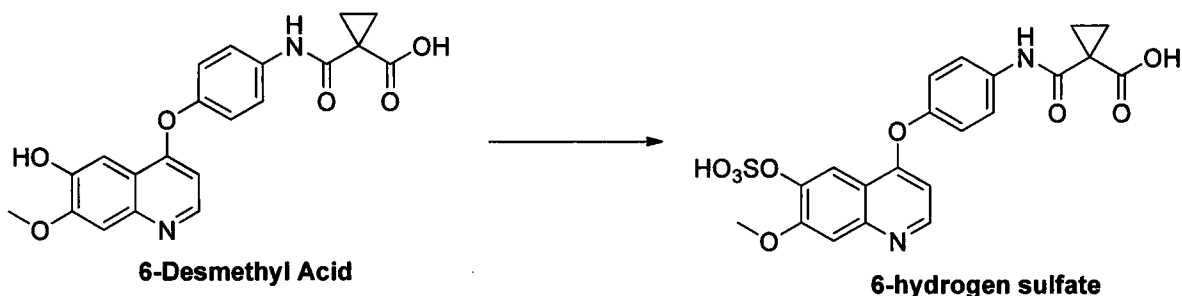
[00145] 6-Desmethyl Acid



[00146] In a vessel, 4-(4-aminophenoxy)-7-methoxyquinolin-6-ol (15.0 g; 53.3 mmol) and potassium carbonate (29.5 g; 213.3 mmol; 4 equiv) are suspended in THF (210 mL; 14 vol) and water (90 mL; 6 vol) at 20 °C. In a separate vessel, sodium 1-(methoxycarbonyl)cyclopropanecarboxylate (17.71 g; 106.6 mmol; 2 equiv.) was suspended in THF (90 mL; 6 vol). DMF (120 µL; 3 mol%) was added and cooled to less than 15 °C. Oxalyl

chloride (9.34 mL; 106.6 mmol; 2 equiv.) was added over 90 minutes, and the reaction was aged 2 hours at 10-15 °C. The acid chloride slurry was added to the suspension over 2 hours at 20-25 °C and aged at least 3 hours, whereupon HPLC analysis showed greater than 99% conversion to a mixture of the mono- and biscarbonylated material. The reaction mixture was filtered over Celite®, washed with THF (30 mL; 2 vol), and the layers are separated. 1 M NaOH (150 mL; 10 vol) was added to the upper THF layer, and the mixture was heated at 40 °C for 1 hour, whereupon HPLC analysis showed greater than 99% saponified product. The mixture was cooled to 25 °C, and the upper THF layer was removed. The aqueous layer was acidified to pH 3-4 with 1 M HCl to precipitate the product and was aged for 1 hour. The precipitate was filtered, washed with water (90 mL, 6 vol), and dried under vacuum (greater than 20 psig) with nitrogen bleed at 50 °C to give a grey to brown powder. ¹H-NMR (DMSO-d₆, 400 MHz) δ 10.8-11.0 (br s, 1H), 10.7 (s, 1H), 8.65 (d, J=6.9 Hz, 1H), 7.81 (d, J=9.3 Hz, 2H), 7.67 (s, 1H), 7.58 (s, 1H), 7.32 (d, J=9.3 Hz, 2H), 6.69 (d, J=6.9 Hz, 1H), 4.01 (s, 3H), 2.48-2.53 (m, 4H). MS (ESI-) m/z 393 [M-H]⁻.

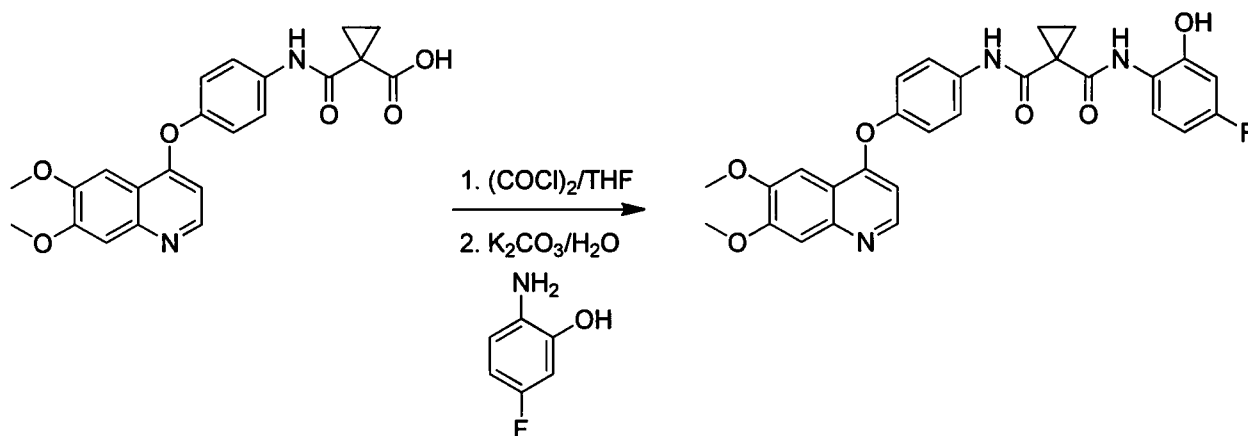
[00147] 6-Hydrogen Sulfate 6-Desmethyl Acid



[00148] 6-Desmethyl acid (120 mg; 0.30 mmol), potassium hydroxide (118 mg; 2.1 mmol; 7 equiv.), and sulfur trioxide trimethyl amine complex (292 mg; 2.1 mmol; 7 equiv.) was dissolved in water (3 mL; 25 vol) and heated to 70 °C for 2 hours, whereupon analysis by HPLC showed greater than 99% conversion. The reaction mixture was then cooled in an ice bath and acidified dropwise with 1 N aq. H₂SO₄ to approximately pH 1. The slurry was aged at 25 °C for 1 hour, filtered, washed with water (3 mL; 25 vol), and deliquored. The wet cake was then washed with acetone (3 mL; 25 vol) and dried at 35 °C under vacuum (greater than 20 psig) with nitrogen bleed for 24 hours to give a beige powder.

[00149] Alternatively, 6-desmethyl acid (120 mg; 0.30 mmol) was suspended in MeCN (50 vol, 6 mL), and triethylamine (1.27 mL, 9.12 mmol, 30 equiv.) was added and then cooled in an ice bath. Chlorosulfonic acid (101 μ L, 1.52 mmol, 5 equiv.) was added dropwise, and the reaction was then heated to 70 °C for 1 hour, whereupon analysis by HPLC showed greater than 98 percent conversion. The reaction mixture was then cooled in an ice bath for 2 hours, in which a precipitate was formed. The precipitate was removed with filtration, rinsing with cold MeCN (50 vol). The MeCN solution was then concentrated to approximately 20 vol (approximately 2 mL) and quenched with 100 vol 1N HCl and cooled in an ice bath to give a fine precipitate that was filtered, washed with 50 vol water and 50 vol acetone, and dried at 35 °C under vacuum (greater than 20 psig) with nitrogen bleed for 24 hours to give a beige powder. ¹H-NMR (DMSO-d₆, 400 MHz) δ 10.8 (s, 1H), 8.83 (d, J =5.9 Hz, 1H), 8.5 (s, 1H), 7.85 (d, J =8.5 Hz, 2H), 7.52 (s, 1H), 7.40 (d, J =8.5 Hz, 2H), 6.84 (d, J =5.9 Hz, 1H), 4.04 (s, 3H), 3.20-3.70 (br s, 1H), 1.39-1.48 (br s, 4H). MS (ESI-) m/z 473 [M-H]⁻, 236.

[00150] Ortho-Hydroxy N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

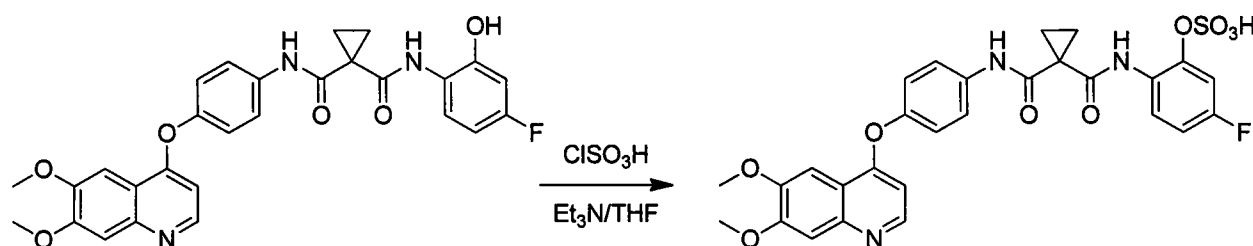


[00151] A flask was charged with the carboxylic acid (0.84 g; 2.1 mmol), THF (1.2 mL), and DMF (5 μ L), and cooled to 15 °C. To this slurry was added oxalyl chloride (0.17 mL; 2.1 mmol) dropwise over approximately 20 minutes. After 2 hours, the acid chloride slurry was added to another vessel containing a stirred suspension of the aniline (0.2 g, 1.6 mmol), potassium carbonate (0.63 g, 4.6 mmol) in THF (2.8 mL), and water (1 mL) over approximately 15 minutes. After 3 hours, HPLC analysis showed complete conversion to the product. Stirring was stopped,

the lower aqueous layer was removed, and water (30 mL) was added to precipitate the product. The product was then collected by filtration and washed with 1:1 THF-water solution (2 x 10 mL) to afford a pale grey solid. It was then further purified by flash chromatography on silica gel using methanol/dichloromethane as the mobile phase.

[00152] Alternatively, a suspension of the carboxylic acid (4.08 g; 10 mmol), aniline (1.52 g; 12 mmol), and triethylamine (2.7 mL; 20 mmol) in acetonitrile (100 mL) was treated with EDAC (2.30 g; 12 mmol) and HOBt (0.5 g; 3 mmol). The slurry was stirred overnight at room temperature, and the reaction progress was monitored by HPLC. At the end of the reaction, 150 mL of water was added, and the precipitated product was collected by filtration, washed with water, and then purified by flash chromatography. ¹H-NMR (DMSO-d₆, 400 MHz) δ 10.46 (br s, 1H), 10.29 (br s, 1H), 10.0 (br s, 1H), 8.47 (d, 1H), 7.92 (dd, 1H), 7.73 (dd, 2H), 7.51 (s, 1H), 7.40 (s, 1H), 7.28 (dd, 2H), 6.68 (dd, 1H), 6.62 (dt, 1H), 6.45 (d, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 1.60-1.55 (m, 4H). ¹³C NMR (DMSO-d₆, 100 MHz) δ 169.82, 167.67, 159.91, 157.51, 152.58, 149.97, 149.35, 149.09, 148.98, 148.86, 146.49, 135.72, 123.00, 122.97, 122.91, 122.43, 121.30, 115.17, 107.86, 105.10, 104.87, 103.16, 102.43, 102.19, 99.08, 55.74, 55.71, 55.66, 30.02, 16.51. MS (APCI+) m/z 518.3 [M+H]⁺, 500.3.

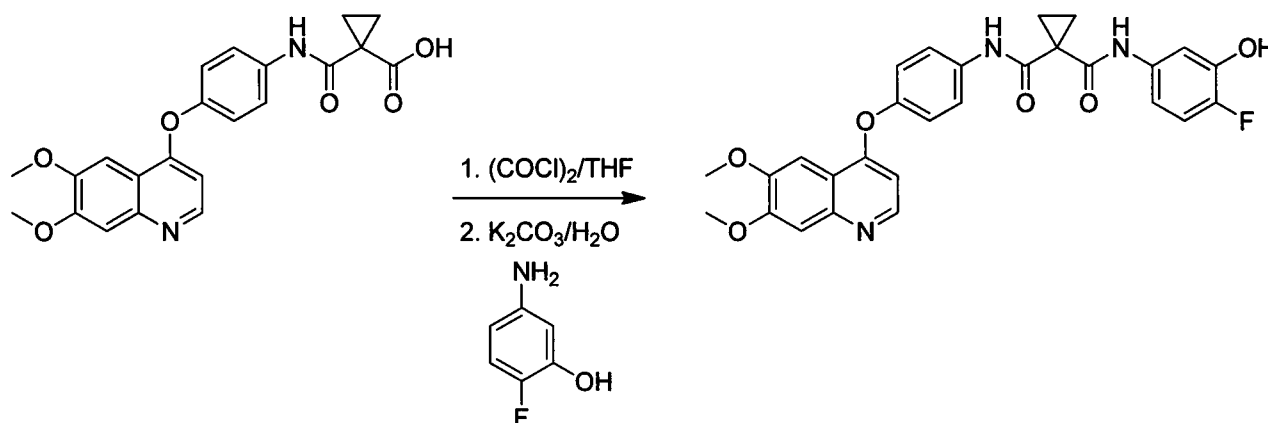
[00153] N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide Hydroxysulfate



[00154] A suspension of the hydroxy N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (0.95 g; 1.9 mmol) in THF (20 mL) was added triethylamine (5 mL; 36 mmol), and cooled to below 5 °C. Chlorosulfonic acid (1 mL; 15 mmol) was added dropwise such that the temperature remained below 10 °C, over approximately 15 minutes. After stirring overnight at room temperature, HPLC analysis showed approximately 5 percent of starting material remaining. The reaction mixture was treated with aqueous 1 N HCl (25 mL). The precipitated product was collected by filtration, washed with water (4 x 25 mL),

and dried under vacuum to yield an off-white solid (937 mg; 82 percent crude yield). Analysis by AN-HPLC showed that the product was 90.8% pure, the major impurity being the starting material. The product was purified to greater than 99 percent (AN-HPLC) by preparative HPLC on a C18 column, using aqueous ammonium acetate/acetonitrile mobile phase system. ¹H-NMR (DMSO-d₆, 400 MHz) δ 10.39 (s, 1H), 9.69 (s, 1H), 8.81 (d, 1H), 7.95 (dd, 1H), 7.85 (d, 2H), 7.77 (s, 1H), 7.51 (s, 1H), 7.11 (s, 1H), 7.08 (dd, 1H), 6.93 (dd, 1H), 6.45 (d, 1H), 4.05 (s, 3H), 4.04 (s, 3H), 1.53 (s, 4H). MS (ESI-) m/z 596.0 [M-H]⁻.

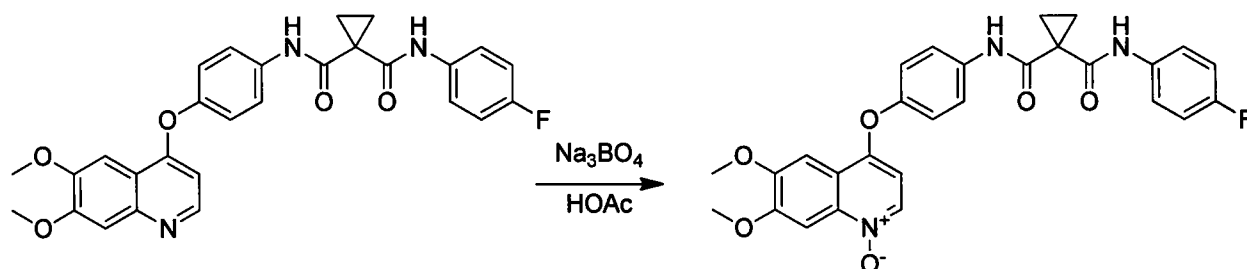
Meta-Hydroxy- N-(4-{[6,7-Bis(methoxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide



[00155] A flask was charged with the carboxylic acid (0.84 g; 2.1 mmol), THF (1.2 mL), and DMF (5 μL), and cooled to 15 °C. To this slurry was added oxalyl chloride (0.17 mL; 2.1 mmol) dropwise over approximately 20 minutes. After 2 hours, the acid chloride slurry was added to another vessel containing a stirred suspension of the aniline (0.2 g, 1.6 mmol), potassium carbonate (0.63 g, 4.6 mmol) in THF (2.8 mL), and water (1 mL) over approximately 15 minutes. After 90 minutes, HPLC analysis showed complete conversion to the product. Stirring was stopped, and the lower aqueous layer was removed and extracted with ethyl acetate (15 mL). The organic layers were combined, dried over anhydrous MgSO₄, filtered, and concentrated to yield a brown solid. The solid was then further purified by flash chromatography on silica gel using ethyl acetate/heptane as the mobile phase. ¹H-NMR (DMSO-d₆, 400 MHz) δ 10.15 (br s, 1H), 9.96 (br s, 1H), 9.89 (br s, 1H), 8.46 (d, 1H), 7.76 (d, 1H), 7.50 (s, 1H), 7.41 (d, 2H), 7.39 (s, 1H), 7.22 (d, 2H), 7.07-6.98 (m, 2H), 6.42 (d, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 1.46 (br s, 4H). ¹³C NMR (DMSO-d₆, 100 MHz) δ 168.27, 167.95, 160.02, 152.56, 149.48, 149.33, 148.86,

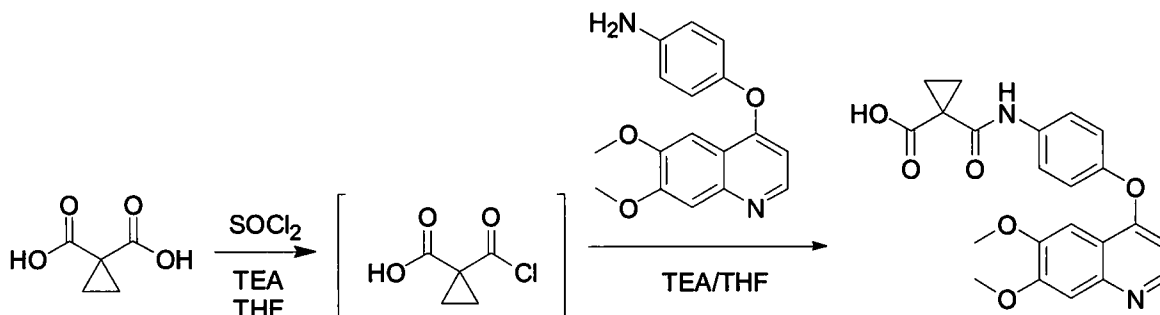
148.56, 146.46, 146.21, 144.52, 144.39, 136.45, 135.33, 135.31, 122.23, 121.22, 115.63, 115.44, 115.15, 111.29, 111.23, 110.26, 107.85, 103.04, 99.08, 55.73, 55.71, 31.66, 15.40. MS (APCI+) m/z 518.3 $[M+H]^+$, 502.3.

[00156] N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide N-Oxide



[00157] A flask was charged with N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (3.21 g; 6.4 mmol), acetic acid (32.1 mL), and sodium perborate tetrahydrate (1.98 g, 12.8 mmol) and heated to 65 °C and stirred overnight. After 24 hours, HPLC analysis showed about 38:62 starting material: product. More oxidant (1.98 g; 12.8 mmol) was added, and heating continued overnight. Solvents were removed under vacuum, and the residue was purified by flash chromatography using dichloromethane-methanol gradient (dichloromethane to 10% methanol-dichloromethane) to obtain 0.95 g of the product as a white solid. $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ 10.20 (br s, 1H), 10.08 (br s, 1H), 8.28 (d, 1H), 7.90 (s, 1H), 7.74 (d, 2H), 7.64 (dd, 2H), 7.48 (s, 1H), 7.23 (d, 2H), 7.15 (t, 2H), 6.45 (d, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 1.47 (br s, 4H). $^{13}\text{C NMR}$ (DMSO- d_6 , 100 MHz) δ 172.11, 168.18, 168.13, 159.49, 157.09, 153.34, 150.72, 150.57, 149.98, 137.41, 136.32, 135.24, 135.21, 134.06, 122.44, 122.36, 122.19, 120.65, 117.23, 11.17, 114.95, 104.37, 100.34, 99.12, 56.09, 56.03, 31.59, 15.42. MS (APCI+) m/z 518.3 $[M+H]^+$.

[00158] 1-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-phenylcarbamoyl]-cyclopropane carboxylic acid



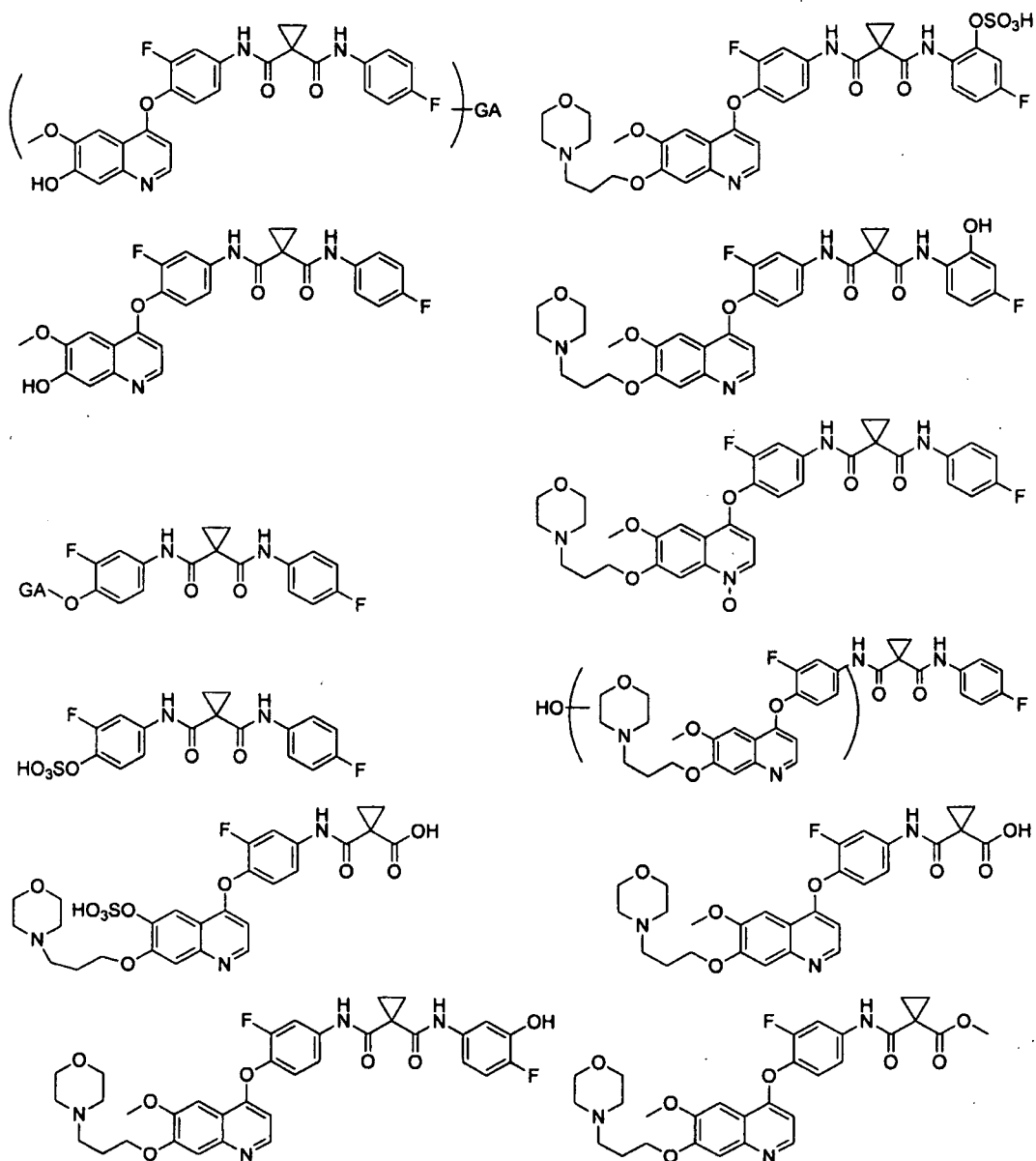
[00159] To the cyclopropyl di-carboxylic acid (449 mg, 3.45 mmol) in THF (3.5 mL) was added TEA (485 μ L, 3.45 mmol). The resulting solution was stirred at room temperature under a nitrogen atmosphere for 40 minutes before adding thionyl chloride (250 μ L, 3.44 mmol). The reaction was monitored by LCMS 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). The reaction 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 concentrated HCl to pH or approximately 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 percent yield, 97 percent pure) as a white solid. ^1H NMR ($\text{D}_2\text{O}/\text{NaOH}$): 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).

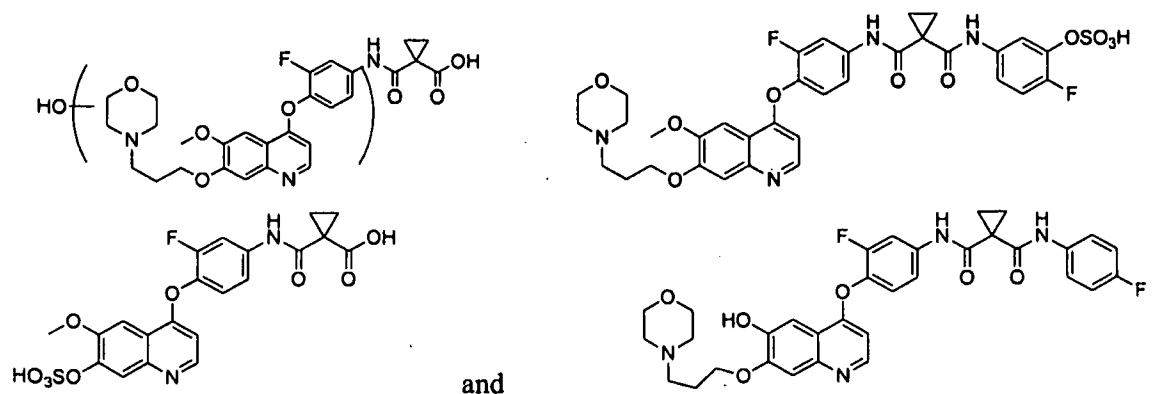
[00160] The foregoing disclosure has been described in some detail by way of illustration and example for purposes of clarity and understanding. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations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

of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

Claims

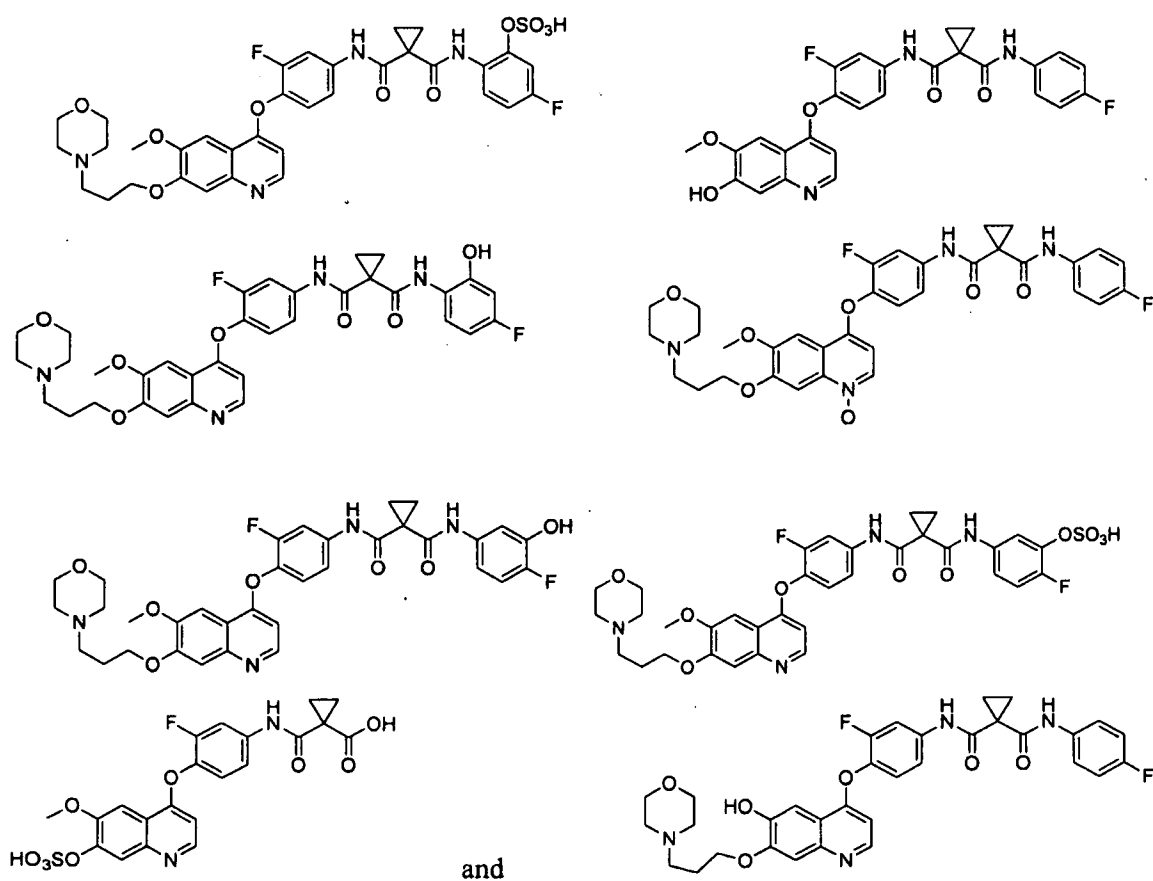
1. An isolated metabolite of foretinib or a pharmaceutically acceptable salt thereof.
2. The isolated metabolite of claim 1 which is a compound selected from:



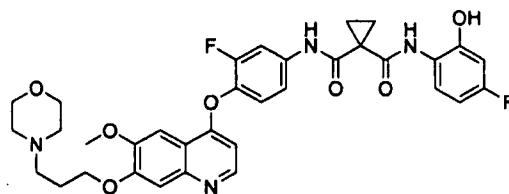


wherein GA is a glucuronic acid moiety, or a pharmaceutically acceptable salt thereof.

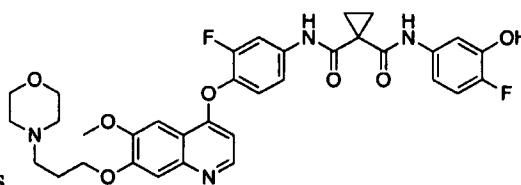
3. The isolated metabolite of claim 2, which is selected from:



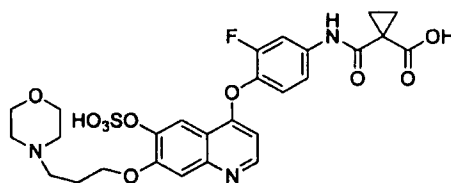
or a pharmaceutically acceptable salt thereof.



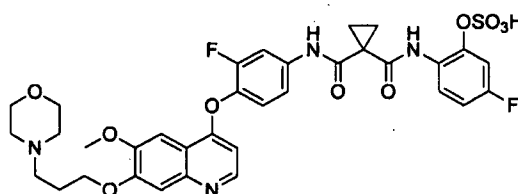
4. The isolated metabolite of claim 2 which is , or a pharmaceutically acceptable salt thereof.



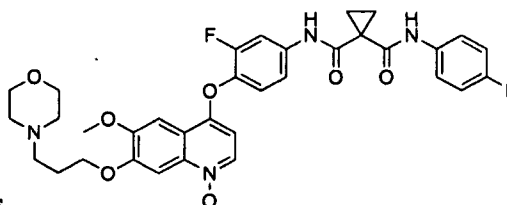
5. The isolated metabolite of claim 2 which is , or a pharmaceutically acceptable salt thereof.



6. The isolated metabolite of claim 2 which is , or a pharmaceutically acceptable salt thereof.

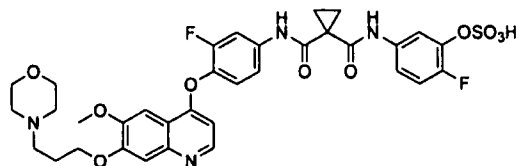


7. The isolated metabolite of claim 2 which is , or a pharmaceutically acceptable salt thereof.

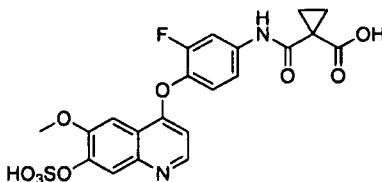


8. The isolated metabolite of claim 2 which is , or a pharmaceutically acceptable salt thereof.

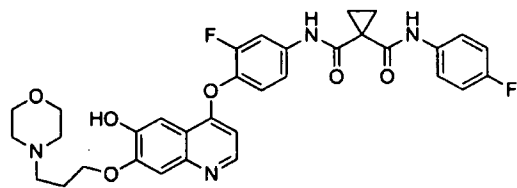
9. The isolated metabolite of claim 2 which is
or a pharmaceutically acceptable salt thereof.



10. The isolated metabolite of claim 2 which is COc1cc2c(c1)nc(CO)cc2Oc3ccc(NC(=O)C4(C)C(=O)O)cc3F, or a
pharmaceutically acceptable salt thereof.

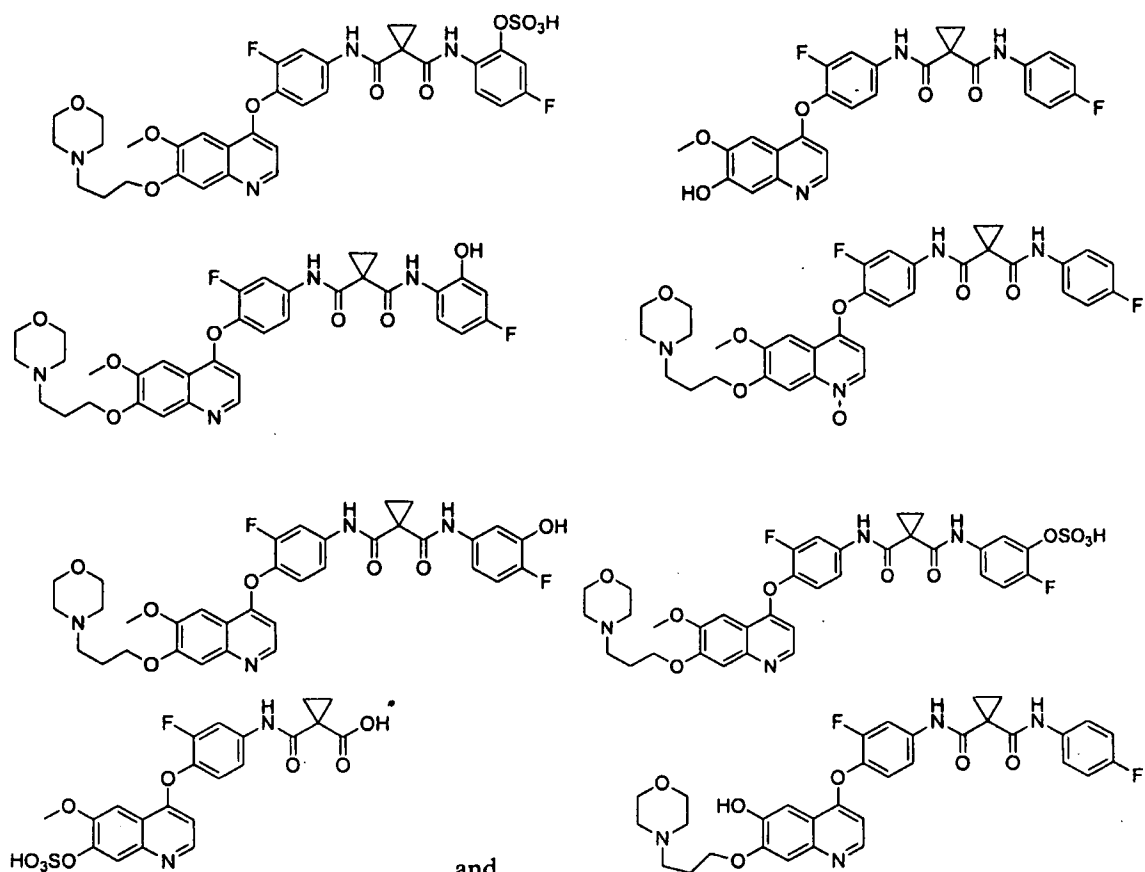


11. The isolated metabolite of claim 2 which is
or a pharmaceutically acceptable salt thereof.



12. A method of treating a disease 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 a compound of claims 1-11, or a pharmaceutically acceptable salt thereof.

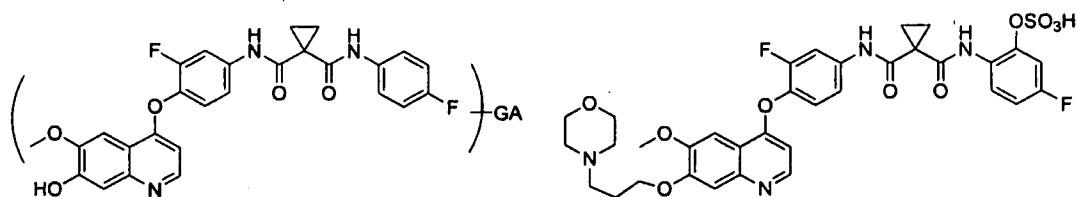
13. A pharmaceutical composition comprising:

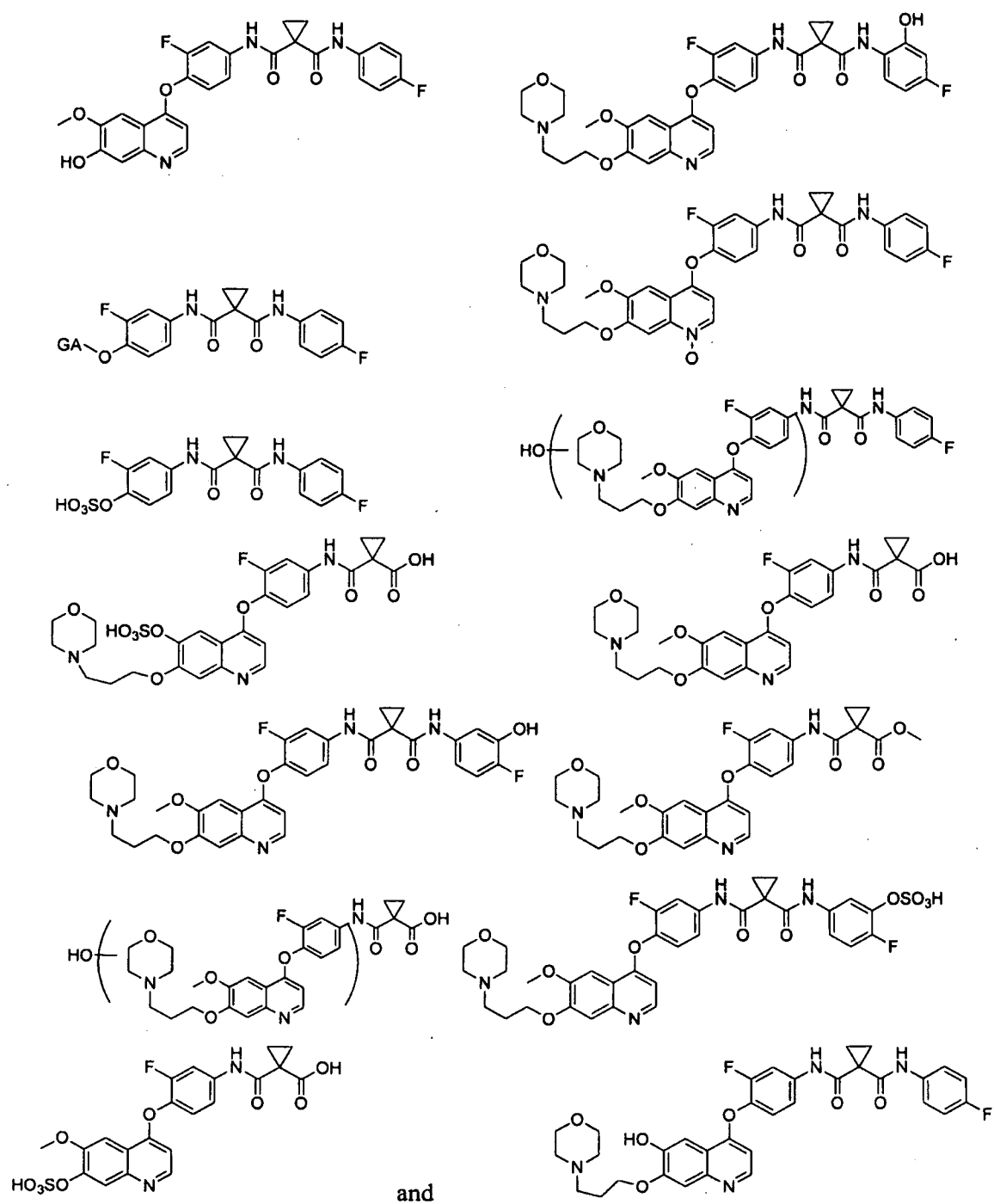


or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier.

14. The composition of claim of claim 13, which is suitable for oral administration.

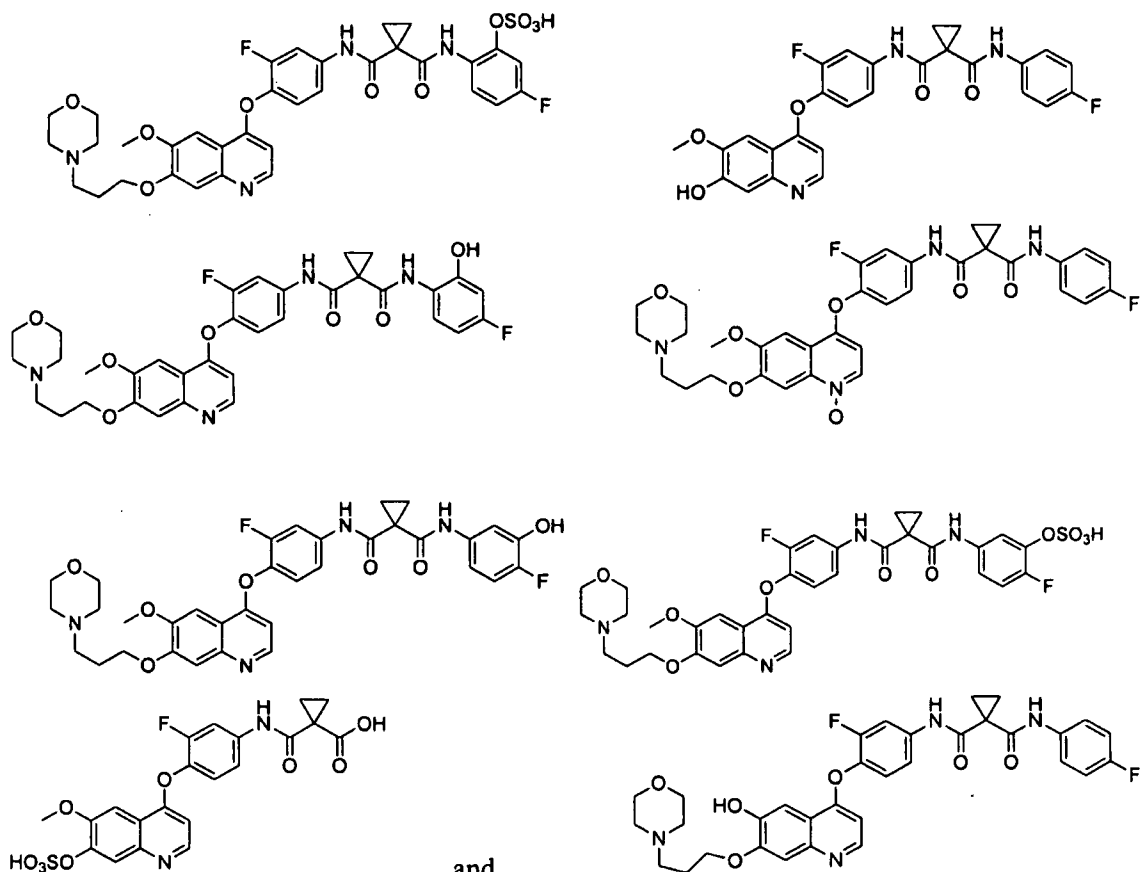
15. A compound which is selected from:





wherein GA is a glucuronic acid moiety, or a pharmaceutically acceptable salt thereof.

16. The compound of claim 15, which is selected from:



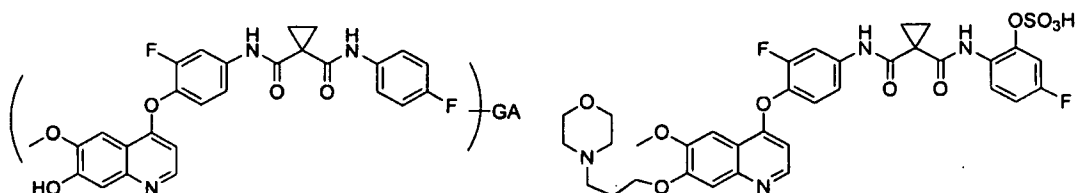
or a pharmaceutically acceptable salt thereof.

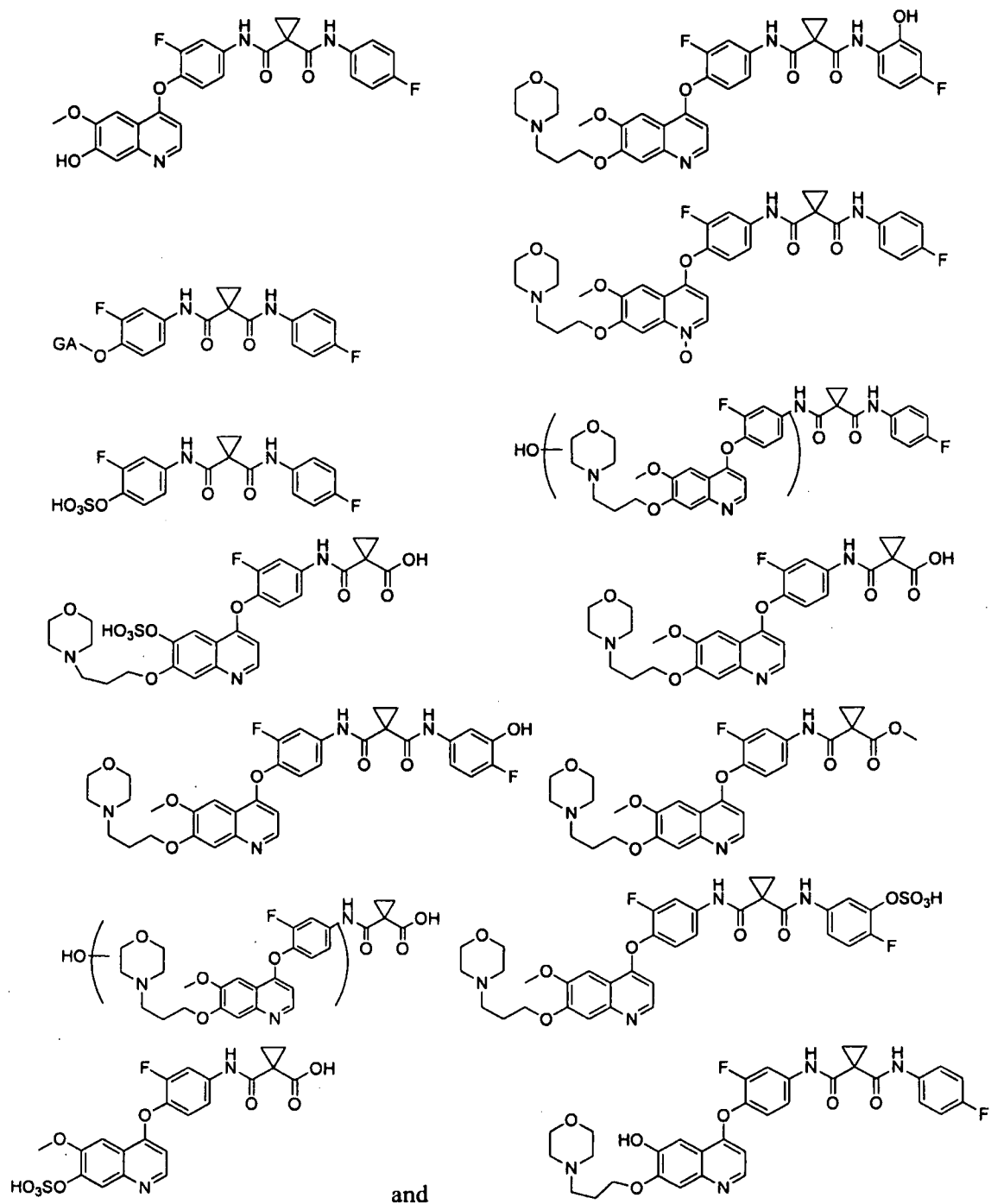
17. A method for identifying a metabolite of foretinib, comprising:

administering foretinib to a mammal; and

detecting or measuring a level or concentration of a metabolite of N-[3-fluoro-4-((6-(methoxyoxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl)oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide in a mammal in tissues or bodily fluids of the mammal;

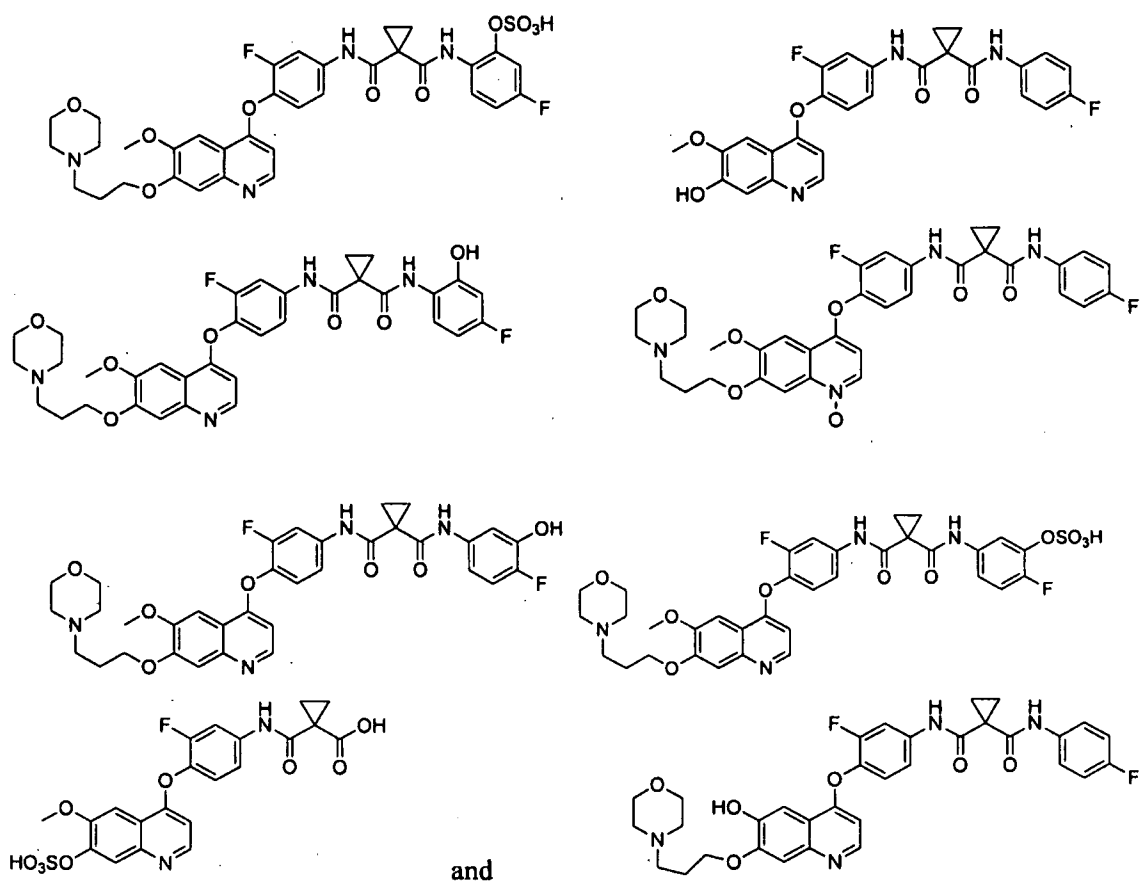
wherein the metabolite is selected from the group consisting of:





wherein GA is a glucuronic acid moiety.

18. The method of claim 17, wherein the metabolite is selected from:



19. The method according to claim 17, wherein the bodily fluids are selected from the group consisting of plasma, bile, urine, and feces.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/030498

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D215/22 C07C305/24 C07C233/60 A61K31/47 A61P35/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D C07C A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EP0-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/030140 A2 (EXELIXIS INC [US]; BANNEN LYNNE CANNE [US]; CHAN DIVA SZE-MING [US]; C) 7 April 2005 (2005-04-07) cited in the application Table 4, entry 312; paragraph [0349]; claims; examples 30,43,44 -----	1-3,12, 13,15-19

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Further documents are listed in the continuation of Box C.

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See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

9 July 2014

Date of mailing of the international search report

17/07/2014

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2014/030498

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
W0 2005030140	A2	07-04-2005	
		AT 517091 T	15-08-2011
		AT 520403 T	15-09-2011
		AT 532782 T	15-11-2011
		AU 2004275842 A1	07-04-2005
		AU 2010204459 A1	19-08-2010
		AU 2010204461 A1	19-08-2010
		CA 2537812 A1	07-04-2005
		CA 2744997 A1	07-04-2005
		DK 2210607 T3	12-12-2011
		DK 2213661 T3	19-09-2011
		DK 2392564 T3	13-01-2014
		DK 2392565 T3	05-05-2014
		EP 1673085 A2	28-06-2006
		EP 2210607 A1	28-07-2010
		EP 2213661 A1	04-08-2010
		EP 2392564 A1	07-12-2011
		EP 2392565 A1	07-12-2011
		EP 2409704 A2	25-01-2012
		EP 2609919 A2	03-07-2013
		EP 2612853 A1	10-07-2013
		ES 2369652 T3	02-12-2011
		ES 2371383 T3	30-12-2011
		ES 2436888 T3	07-01-2014
		ES 2466818 T3	11-06-2014
		HK 1141799 A1	23-03-2012
		HK 1143068 A1	18-05-2012
		HK 1164312 A1	04-07-2014
		HR P20110707 T1	31-10-2011
		HR P20110810 T1	31-12-2011
		HR P20140012 T1	14-02-2014
		JP 4638436 B2	23-02-2011
		JP 5185331 B2	17-04-2013
		JP 5185332 B2	17-04-2013
		JP 5325172 B2	23-10-2013
		JP 5325173 B2	23-10-2013
		JP 2007506777 A	22-03-2007
		JP 2010235631 A	21-10-2010
		JP 2010235632 A	21-10-2010
		JP 2010265302 A	25-11-2010
		JP 2010280674 A	16-12-2010
		JP 2011042686 A	03-03-2011
		JP 2014055190 A	27-03-2014
		JP 2014055191 A	27-03-2014
		JP 2014074059 A	24-04-2014
		PL 2210607 T3	31-01-2012
		PT 2210607 E	31-01-2012
		PT 2213661 E	15-12-2011
		SI 2210607 T1	30-11-2011
		SI 2213661 T1	30-11-2011
		SI 2392564 T1	28-02-2014
		SI 2392565 T1	30-05-2014
		US 2007054928 A1	08-03-2007
		US 2007225307 A1	27-09-2007
		US 2007244116 A1	18-10-2007
		US 2009105299 A1	23-04-2009
		US 2009170896 A1	02-07-2009
		US 2011077233 A1	31-03-2011
		US 2012022065 A1	26-01-2012

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2014/030498

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		US 2012184523 A1	19-07-2012
		US 2013252940 A1	26-09-2013
		US 2014155396 A1	05-06-2014
		W0 2005030140 A2	07-04-2005
