

COMPOSITIONS AND METHODS FOR PREPARING AND USING SAME

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 61/044,886, filed April 14, 2008, U.S. Provisional Application No. 61/159,778, filed March 12, 2009, and PCT Application No. PCT/US2008/71392 filed 28-Jul-2008; each of which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] Oncogenes -- genes that contribute to the production of cancers -- are generally mutated forms of certain normal cellular genes ("proto-oncogenes"). Oncogenes often encode abnormal versions of signal pathway components, such as receptor tyrosine kinases, serine-threonine kinases, or downstream signaling molecules. The central downstream signaling molecules are the Ras proteins, which are anchored on the inner surfaces of cytoplasmic membranes, and which hydrolyze bound guanosine triphosphate (GTP) to guanosine diphosphate (GDP). When activated by a growth factor, growth factor receptors initiate a chain of reactions that leads to the activation of guanine nucleotide exchange activity on Ras. Ras alternates between an active "on" state with a bound GTP (hereafter "Ras.GTP") and an inactive "off state" with a bound GDP. The active "on" state, Ras.GTP, binds to and activates proteins that control the growth and differentiation of cells.

[0003] For example, in the "mitogen-activated protein kinase (MAP kinase) cascade," Ras.GTP leads to the activation of a cascade of serine/threonine kinases. One of several groups of kinases known to require a Ras.GTP for their own activation is the Raf family. The Raf proteins activate "MEK1" and "MEK2," abbreviations for mitogen-activated ERK-activating kinases (where ERK is extracellular signal-regulated protein kinase, another designation for MAPK). MEK1 and MEK2 are dual-function serine/threonine and tyrosine protein kinases and are also known as MAP kinase kinases. Thus, Ras.GTP activates Raf, which activates MEK1 and MEK2, which activate MAP kinase (MAPK). Activation of MAP kinase by mitogens appears to be essential for proliferation, and constitutive activation of this kinase is sufficient to induce cellular transformation. Blockade of downstream Ras signaling, as by use of a dominant negative Raf-1 protein, can completely inhibit mitogenesis, whether induced from cell surface receptors or from oncogenic Ras mutants.

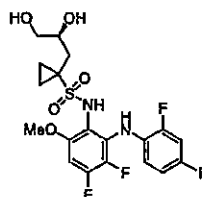
[0004] The interaction of Raf and Ras is a key regulatory step in the control of cell proliferation. To date, no substrates of MEK other than MAPK have been identified; however, recent reports indicate that MEK may also be activated by other upstream signal proteins such as MEK kinase or MEKK1 and PKC. Activated MAPK translocates and
 5 accumulates in the nucleus, where it can phosphorylate and activate transcription factors such as Elk-1 and Sap1a, leading to the enhanced expression of genes such as that for c-fos.

[0005] Once activated, Raf and other kinases phosphorylate MEK on two neighboring serine residues, S²¹⁸ and S²²² in the case of MEK1. These phosphorylations are required for activation of MEK as a kinase. In turn, MEK phosphorylates MAP kinase on two residues
 10 separated by a single amino acid: a tyrosine, Y¹⁸⁵ and a threonine, T¹⁸³. MEK appears to associate strongly with MAP kinase prior to phosphorylating it, suggesting that phosphorylation of MAP kinase by MEK may require a prior strong interaction between the two proteins. Two factors — MEK's unusual specificity and its requirement for a strong interaction with MAP kinase prior to phosphorylation -- suggest that MEK's mechanism of
 15 action may differ sufficiently from the mechanisms of other protein kinases as to allow for selective inhibitors of MEK. Possibly, such inhibitors would operate through allosteric mechanisms rather than through the more usual mechanism involving blockage of an ATP binding site.

[0006] Thus, MEK1 and MEK2 are validated and accepted targets for anti-proliferative
 20 therapies, even when the oncogenic mutation does not affect MEK structure or expression. See, e.g., U.S. Patent Publications 2003/0149015 by Barrett *et al.* and 2004/0029898 by Boyle *et al.*

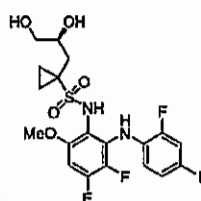
SUMMARY OF THE INVENTION

25 [0007] The invention relates to a composition comprising: about 1mg of a compound of



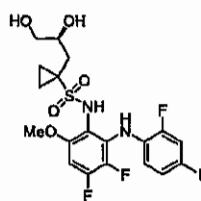
structure: ; about 222.2mg of microcrystalline cellulose; about
 12.0mg of croscarmellose sodium; about 2.4mg of sodium lauryl sulfate; and about 2.4mg
 of magnesium stearate.

[0008] The invention also relates to a composition comprising: about 10mg of a compound



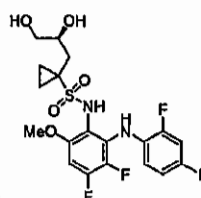
of structure: ; about 213.2mg of microcrystalline cellulose; about 12.0mg of croscarmellose sodium; about 2.4mg of sodium lauryl sulfate; and about 2.4mg of magnesium stearate.

5 [0009] The invention also relates to a composition comprising: about 20mg of a compound



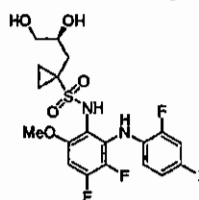
of structure: ; about 203.2mg of microcrystalline cellulose; about 12.0mg of croscarmellose sodium; about 2.4mg of sodium lauryl sulfate; and about 2.4mg of magnesium stearate.

[0010] The invention also relates to a composition comprising: about 40mg of a compound



10 of structure: ; about 183.2mg of microcrystalline cellulose; about 12.0mg of croscarmellose sodium; about 2.4mg of sodium lauryl sulfate; and about 2.4mg of magnesium stearate.

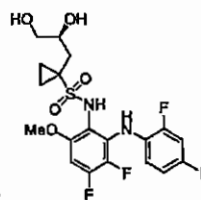
[0011] The invention also relates to a composition comprising: about 0.4% by weight of a



compound of structure: ; and about 99.6% by weight of a

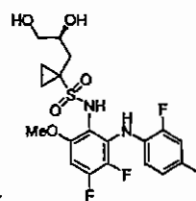
15 pharmaceutically acceptable carrier or vehicle.

[0012] The invention also relates to a composition comprising: about 4.2% by weight of a



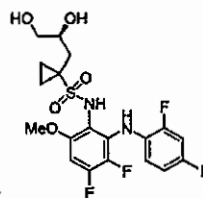
compound of structure: ; and about 95.8 % by weight of a pharmaceutically acceptable carrier or vehicle.

[0013] The invention also relates to a composition comprising: from about 2% to about



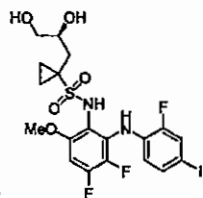
5 10% by weight of a compound of structure: ; and from about 98% to about 90% by weight of a pharmaceutically acceptable carrier or vehicle.

[0014] The invention also relates to a method for treating or preventing cancer or an inflammation disease, comprising administering to a subject in need thereof an effective amount of a pharmaceutical composition comprising: about 1mg of a compound of



10 structure: ; about 222.2mg of microcrystalline cellulose; about 12.0mg of croscarmellose sodium; about 2.4mg of sodium lauryl sulfate; and; about 2.4mg of magnesium stearate.

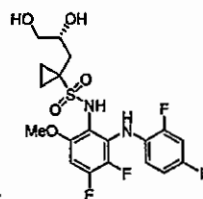
[0015] The invention also relates to a method for treating or preventing cancer or an inflammation disease, comprising administering to a subject in need thereof an effective
15 amount of a pharmaceutical composition comprising: about 10mg of a compound of



structure: ; about 213.2mg of microcrystalline cellulose; about 12.0mg of croscarmellose sodium; about 2.4mg of sodium lauryl sulfate; and about 2.4mg of magnesium stearate.

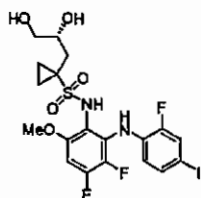
[0016] The invention also relates to a method for treating or preventing cancer or an inflammation disease, comprising administering to a subject in need thereof an effective amount of any of the pharmaceutical compositions described herein.

[0017] The invention relates to a composition comprising: about 1mg of a compound of



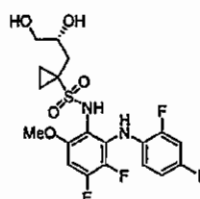
structure: ; about 222.2mg of microcrystalline cellulose; about 12.0mg of croscarmellose sodium; about 2.4mg of sodium lauryl sulfate; and about 2.4mg of magnesium stearate.

[0018] The invention also relates to a composition comprising: about 10mg of a compound



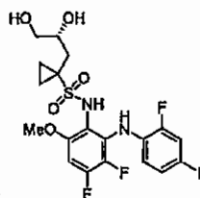
of structure: ; about 213.2mg of microcrystalline cellulose; about 12.0mg of croscarmellose sodium; about 2.4mg of sodium lauryl sulfate; and about 2.4mg of magnesium stearate.

[0019] The invention also relates to a composition comprising: about 20mg of a compound



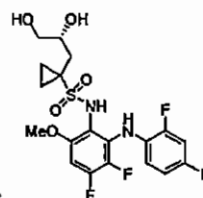
of structure: ; about 203.2mg of microcrystalline cellulose; about 12.0mg of croscarmellose sodium; about 2.4mg of sodium lauryl sulfate; and about 2.4mg of magnesium stearate.

5 [0020] The invention also relates to a composition comprising: about 40mg of a compound



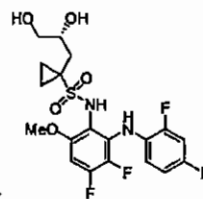
of structure: ; about 183.2mg of microcrystalline cellulose; about 12.0mg of croscarmellose sodium; about 2.4mg of sodium lauryl sulfate; and about 2.4mg of magnesium stearate.

[0021] The invention also relates to a composition comprising: about 0.4% by weight of a



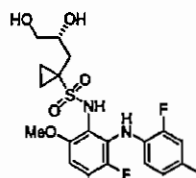
10 compound of structure: ; and about 99.6% by weight of a pharmaceutically acceptable carrier or vehicle.

[0022] The invention also relates to a composition comprising: about 4.2% by weight of a



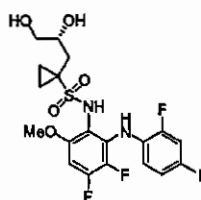
compound of structure: ; and about 95.8 % by weight of a pharmaceutically acceptable carrier or vehicle.

[0023] The invention also relates to a composition comprising: from about 2% to about



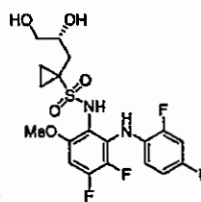
10% by weight of a compound of structure: ; and from about 98% to about 90% by weight of a pharmaceutically acceptable carrier or vehicle.

[0024] The invention also relates to a method for treating or preventing cancer or an inflammation disease, comprising administering to a subject in need thereof an effective amount of a pharmaceutical composition comprising: about 1mg of a compound of



structure: ; about 222.2mg of microcrystalline cellulose; about 12.0mg of croscarmellose sodium; about 2.4mg of sodium lauryl sulfate; and about 2.4mg of magnesium stearate.

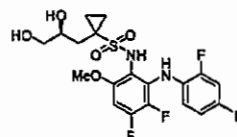
[0025] The invention also relates to a method for treating or preventing cancer or an inflammation disease, comprising administering to a subject in need thereof an effective amount of a pharmaceutical composition comprising: about 10mg of a compound of



structure: ; about 213.2mg of microcrystalline cellulose; about 12.0mg of croscarmellose sodium; about 2.4mg of sodium lauryl sulfate; and about 2.4mg of magnesium stearate.

[0026] The invention also relates to a method for treating or preventing cancer or an inflammation disease, comprising administering to a subject in need thereof an effective amount of any of the pharmaceutical compositions described herein.

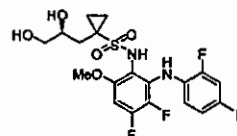
[0027] Disclosed herein, in certain instances, is a method for treating or preventing cancer or an inflammatory disease, comprising administering to a subject in need thereof from about 20mg to about 500mg per day of a compound of compound 1021:



Compound 1021

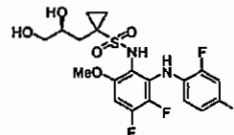
or a pharmaceutically acceptable salt thereof. In some

embodiments, compound 1021 is administered once daily. In some embodiments, compound 1021 is administered twice daily. In some embodiments, compound 1021 is administered three times per day. In some embodiments, the method is a method for treating a cancer. In some embodiments, the method is a method for treating an inflammatory disease. In some embodiments, the method comprises administering compound 1021:



Compound 1021

. In some embodiments, the method comprises administering a



Compound 1021

pharmaceutically acceptable salt of compound 1021:

. In some

embodiments, the method comprises administering from about 40mg to about 500mg per day of compound 1021. In some embodiments, the method comprises administering from about 60mg to about 500mg per day of compound 1021. In some embodiments, the method comprises administering from about 80mg to about 500mg per day of compound 1021. In some embodiments, the method comprises administering from about 50mg to about 400mg per day of a compound of compound 1021. In some embodiments, the method comprises administering from about 50mg to about 300mg per day of compound 1021. In some embodiments, the method comprises administering from about 50mg to about 200mg per day of compound 1021. In some embodiments, the method comprises administering about 50mg per day of compound 1021. In some embodiments, the method comprises administering about 60mg per day of compound 1021. In some embodiments, the method

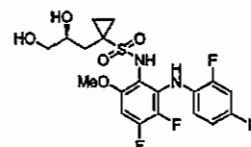
comprises administering about 70mg per day of compound 1021. In some embodiments, the method comprises administering about 80mg per day of compound 1021. In some embodiments, the method comprises administering about 90mg per day of compound 1021. In some embodiments, the method comprises administering about 100mg per day of a

5 compound 1021. In some embodiments, the method comprises administering about 110mg per day of compound 1021. In some embodiments, the method comprises administering about 120mg per day of compound 1021. In some embodiments, the method comprises administering about 130mg per day of compound 1021. In some embodiments, the method comprises administering about 140mg per day of compound 1021. In some embodiments,

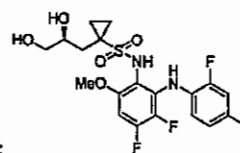
10 the method comprises administering about 150mg per day of compound 1021. In some embodiments, the method comprises administering about 175mg per day of compound 1021. In some embodiments, the method comprises administering about 200mg per day of compound 1021. In some embodiments, the method comprises administering about 250mg per day of compound 1021. In some embodiments, the method comprises administering

15 about 300mg per day of compound 1021.

[0028] Disclosed herein, in certain embodiments, is a pharmaceutical composition comprising from about 20mg to about 500mg per day of compound 1021:

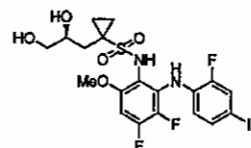


or a pharmaceutically acceptable salt thereof. In some



embodiments, the method comprises compound 1021:

20 embodiments, the composition comprises a salt of compound 1021:

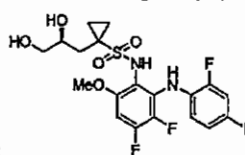


. In some embodiments, the composition further comprises a

pharmaceutically acceptable carrier. In some embodiments, the composition comprises from about 40mg to about 500mg of compound 1021. In some embodiments, the composition

comprises from about 60mg to about 500mg of compound 1021. In some embodiments, the composition comprises from about 80mg to about 500mg of compound 1021. In some embodiments, the composition comprises from about 50mg to about 400mg of compound 1021. In some embodiments, the composition comprises from about 50mg to about 300mg of compound 1021. In some embodiments, the composition comprises from about 50mg to about 200mg of compound 1021. In some embodiments, the composition comprises about 50mg of compound 1021. In some embodiments, the composition comprises about 60mg of compound 1021. In some embodiments, the composition comprises about 70mg of compound 1021. In some embodiments, the composition comprises about 80mg of compound 1021. In some embodiments, the composition comprises about 90mg of compound 1021. In some embodiments, the composition comprises about 100mg of compound 1021. In some embodiments, the composition comprises about 110mg of compound 1021. In some embodiments, the composition comprises about 120mg of compound 1021. In some embodiments, the composition comprises about 130mg of compound 1021. In some embodiments, the composition comprises about 140mg of compound 1021. In some embodiments, the composition comprises about 150mg of compound 1021. In some embodiments, the composition comprises about 175mg of compound 1021. In some embodiments, the composition comprises about 200mg of compound 1021. In some embodiments, the composition comprises about 250mg of compound 1021. In some embodiments, the composition comprises about 300mg of compound 1021.

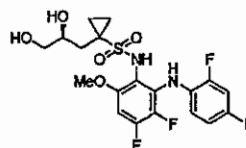
[0029] Disclosed herein, in certain embodiments, is a kit for treating a subject having cancer or an inflammatory disease, comprising: (a) from about 20mg to about 500mg per



day of compound 1021:

or a pharmaceutically acceptable salt

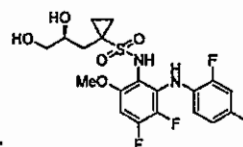
thereof; and (b) instructions for administration of the compound or a pharmaceutically acceptable salt thereof to a subject to treat cancer or an inflammatory disease. In some embodiments, the kit comprises from about 50mg to about 200mg of compound 1021:



or a pharmaceutically acceptable salt thereof. In some

embodiments, the kit is a kit for treating a subject having cancer. In some embodiments, the kit is a kit for treating a subject having an inflammatory disease.

[0030] Disclosed herein, in certain instances, is a composition for treating or preventing
 5 cancer or an inflammatory disease, comprising administering to a subject in need thereof



from about 0.5mg to about 500mg per day of compound 1021;

or a pharmaceutically acceptable salt thereof; which is administered twice daily.

INCORPORATION BY REFERENCE

10 [0031] All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

15 [0032] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

20 [0033] Figure 1 shows graphs of average tumor volume against time (days) in mice implanted with A375 Melanoma, Colo205 Colon Tumor, A431 Epidermoid Tumor or HT-29 Colon Tumor cells. Mice were dosed orally (25mg/kg, 50mg/kg or 100mg/kg), once a day, for 14 days.

[0034] Figure 2 shows a graph of % Tumor growth inhibition (%TGI) in A375 Xenograft
 25 mice dosed 50mg/kg QD, 25mg/kg BID, 50mg/kg QD and 12.5mg/kg BID.

[0035] Figure 3 shows a graph of plasma concentration (log nM) against pERK % inhibition in female nu/nu mice implanted with Colo205 tumor cells. Mice were given a single dose of 2.5, 5, 10, or 25 mg/kg.

[0036] Figure 4 shows a graph of plasma concentration (ng/mL) against time (hours) in humans after administration of a single dose 2mg (2 x 1mg capsules), 4mg (4 x 1mg capsules) or 6mg (6 x 1mg capsules).

DETAILED DESCRIPTION OF THE INVENTION

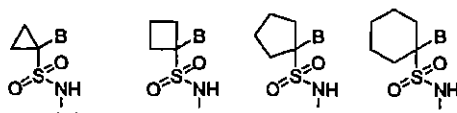
[0037] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in the application including, without limitation, patents, patent applications, articles, books, manuals, and treatises are hereby expressly incorporated by reference in their entirety for any purpose.

Certain Chemical Terminology

[0038] Unless otherwise noted, the use of general chemical terms, such as though not limited to "alkyl," "amine," "aryl," are unsubstituted.

[0039] As used herein, C₁-C_x includes C₁-C₂, C₁-C₃ . . . C₁-C_x. By way of example only, a group designated as "C₁-C₄" indicates that there are one to four carbon atoms in the moiety, i.e. groups containing 1 carbon atom, 2 carbon atoms, 3 carbon atoms or 4 carbon atoms, as well as the ranges C₁-C₂ and C₁-C₃. Thus, by way of example only, "C₁-C₄ alkyl" indicates that there are one to four carbon atoms in the alkyl group, i.e., the alkyl group is selected from among methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, and *t*-butyl. Whenever it appears herein, a numerical range such as "1 to 10" refers to each integer in the given range; e.g., "1 to 10 carbon atoms" means that the group may have 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms, 6 carbon atoms, 7 carbon atoms, 8 carbon atoms, 9 carbon atoms, or 10 carbon atoms.

[0040] The term "A and A', together with the carbon atom to which they are attached, form a 3- to 6- member saturated ring", as used herein, refers to the following structures for compounds of formula I:



Compounds of formula I

[0041] The terms "heteroatom" or "hetero" as used herein, alone or in combination, refer to an atom other than carbon or hydrogen. Heteroatoms are may be independently selected from among oxygen, nitrogen, sulfur, phosphorous, silicon, selenium and tin but are not limited to these atoms. In embodiments in which two or more heterontoms are present, the two or more heteroatoms can be the same as each another, or some or all of the two or more heteroatoms can each be different from the others.

[0042] The term "alkyl" as used herein, alone or in combination, refers to a straight-chain or branched-chain saturated hydrocarbon monoradical having from one to about ten carbon atoms, or one to six carbon atoms. Examples include, but are not limited to methyl, ethyl, n-propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-hutyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-hutyl, 2-ethyl-1-butyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, tert-amyl and hexyl, and longer alkyl groups, such as heptyl, octyl and the like. Whenever it appears herein, a numerical range such as "C₁-C₆ alkyl" or "C₁₋₆ alkyl", means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms. In one embodiment, the "alkyl" is substituted. Unless otherwise indicated, the "alkyl" is unsubstituted.

[0043] The term "alkenyl" as used herein, alone or in combination, refers to a straight-chain or branched-chain hydrocarbon monoradical having one or more carbon-carbon double-bonds and having from two to about ten carbon atoms, or two to about six carbon atoms. The group may be in either the *cis* or *trans* conformation about the double bond(s), and should be understood to include both isomers. Examples include, but are not limited to ethenyl (-CH=CH₂), 1-propenyl (-CH₂CH=CH₂), isopropenyl [-C(CH₃)=CH₂], butenyl, 1,3-butadienyl and the like. Whenever it appears herein, a numerical range such as "C₂-C₆ alkenyl" or "C₂₋₆ alkenyl", means that the alkenyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms. In one embodiment, the "alkenyl" is substituted. Unless otherwise indicated, the "alkenyl" is unsubstituted.

[0044] The term "alkynyl" as used herein, alone or in combination, refers to a straight-chain or branched-chain hydrocarbon monoradical having one or more carbon-carbon triple-bonds and having from two to about ten carbon atoms, or from two to about six carbon atoms. Examples include, but are not limited to ethynyl, 2-propynyl, 2-butylnyl, 1,3-butadiynyl and the like. Whenever it appears herein, a numerical range such as "C₂-C₆ alkynyl" or "C₂₋₆

alkynyl", means that the alkynyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms. In one embodiment, the "alkynyl" is substituted. Unless otherwise indicated, the "alkynyl" is unsubstituted.

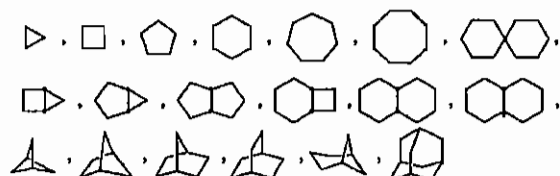
[0045] The terms "heteroalkyl", "heteroalkenyl" and "heteroalkynyl" as used herein, alone or in combination, refer to alkyl, alkenyl and alkynyl structures respectively, as described above, in which one or more of the skeletal chain carbon atoms (and any associated hydrogen atoms, as appropriate) are each independently replaced with a heteroatom (i.e. an atom other than carbon, such as though not limited to oxygen, nitrogen, sulfur, silicon, phosphorous, tin or combinations thereof), or heteroatomic group such as though not limited to -O-O-, -S-S-, -O-S-, -S-O-, =N-N=, -N=N-, -N=N-NH-, -P(O)₂-, -O-P(O)₂-, -P(O)₂-O-, -S(O)-, -S(O)₂-, -SnH₂- and the like.

[0046] The terms "haloalkyl", "haloalkenyl" and "haloalkynyl" as used herein, alone or in combination, refer to alkyl, alkenyl and alkynyl groups respectively, as defined above, in which one or more hydrogen atoms is replaced by fluorine, chlorine, bromine or iodine atoms, or combinations thereof. In some embodiments two or more hydrogen atoms may be replaced with halogen atoms that are the same as each another (e.g. difluoromethyl); in other embodiments two or more hydrogen atoms may be replaced with halogen atoms that are not all the same as each other (e.g. 1-chloro-1-fluoro-1-iodoethyl). Non-limiting examples of haloalkyl groups are fluoromethyl, chloromethyl and bromoethyl. A non-limiting example of a haloalkenyl group is bromoethenyl. A non-limiting example of a haloalkynyl group is chloroethynyl.

[0047] The term "carbon chain" as used herein, alone or in combination, refers to any alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl or heteroalkynyl group, which is linear, cyclic, or any combination thereof. If the chain is part of a linker and that linker comprises one or more rings as part of the core backbone, for purposes of calculating chain length, the "chain" only includes those carbon atoms that compose the bottom or top of a given ring and not both, and where the top and bottom of the ring(s) are not equivalent in length, the shorter distance shall be used in determining the chain length. If the chain contains heteroatoms as part of the backbone, those atoms are not calculated as part of the carbon chain length.

[0048] The term "cycloalkyl" as used herein, alone or in combination, refers to a saturated, hydrocarbon monoradical ring, containing from three to about fifteen ring carbon atoms or from three to about ten ring carbon atoms, though may include additional, non-ring carbon

atoms as substituents (e.g. methylcyclopropyl). Whenever it appears herein, a numerical range such as "C₃-C₆ cycloalkyl " or "C_{3,6} cycloalkyl ", means that the cycloalkyl group may consist of 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, i.e., is cyclopropyl, cyclobutyl, cyclopentyl or cycloheptyl, although the present definition also covers the occurrence of the term " cycloalkyl " where no numerical range is designated. The term includes fused, non-fused, bridged and spiro radicals. A fused cycloalkyl may contain from two to four fused rings where the ring of attachment is a cycloalkyl ring, and the other individual rings may be alicyclic, heterocyclic, aromatic, heteroaromatic or any combination thereof. Examples include, but are not limited to cyclopropyl, cyclopentyl, cyclohexyl, decalyl, and bicyclo [2.2.1] heptyl and adamantyl ring systems. Illustrative examples include, but are not limited to the following moieties:



 , and the like. In one embodiment, the "cycloalkyl" is substituted. Unless otherwise indicated, the "cycloalkyl" is unsubstituted.

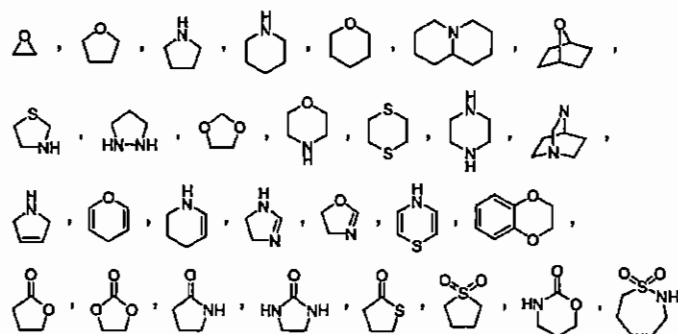
15 **[0049]** The terms "non-aromatic heterocyclyl" and "heteroalicycliclyl" as used herein, alone or in combination, refer to a saturated, partially unsaturated, or fully unsaturated nonaromatic ring monoradicals containing from three to about twenty ring atoms, where one or more of the ring atoms are an atom other than carbon, independently selected from among oxygen, nitrogen, sulfur, phosphorous, silicon, selenium and tin but are not limited to these atoms. In
20 embodiments in which two or more heteroatoms are present in the ring, the two or more heteroatoms can be the same as each another, or some or all of the two or more heteroatoms can each be different from the others. The terms include fused, non-fused, bridged and spiro radicals. A fused non-aromatic heterocyclic radical may contain from two to four fused rings where the attaching ring is a non-aromatic heterocycle, and the other individual rings
25 may be alicyclic, heterocyclic, aromatic, heteroaromatic or any combination thereof. Fused ring systems may be fused across a single bond or a double bond, as well as across bonds that are carbon-carbon, carbon-hetero atom or hetero atom-hetero atom. The terms also include radicals having from three to about twelve skeletal ring atoms, as well as those having from three to about ten skeletal ring atoms. Attachment of a non-aromatic

heterocyclic subunit to its parent molecule can be via a heteroatom or a carbon atom.

Likewise, additional substitution can be via a heteroatom or a carbon atom. As a non-

limiting example, an imidazolidine non-aromatic heterocycle may be attached to a parent

- 5 carbon atoms (imidazolidin-2-yl, imidazolidin-4-yl or imidazolidin-5-yl). In certain
embodiments, non-aromatic heterocycles contain one or more carbonyl or thiocarbonyl
groups such as, for example, oxo- and thio-containing groups. Examples include, but are not
limited to pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl,
tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino,
10 thiomorpholino, thioxanyl, piperaziny, azetidiny, oxetanyl, thietanyl, homopiperidinyl,
oxepanyl, thiepanyl, oxazepiny, diazepiny, thiazepiny, 1,2,3,6-tetrahydropyridinyl, 2-
pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl,
pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl,
pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-
15 azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinoliziny. Illustrative examples of
heterocycloalkyl groups, also referred to as non-aromatic heterocycles, include:



and the like.

[0050] The terms also include all ring forms of the carbohydrates, including but not limited
to the monosaccharides, the disaccharides and the oligosaccharides. In one embodiment,

- 20 the "non-aromatic heterocyclyl" or "heteroalicycyl" is substituted. Unless otherwise
indicated, the "non-aromatic heterocyclyl" or "heteroalicycyl" is unsubstituted.

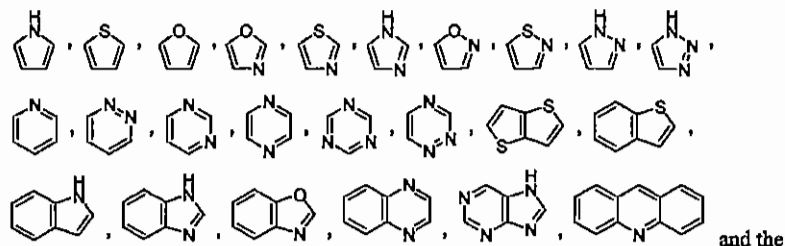
[0051] The term "aryl" as used herein, alone or in combination, refers to an aromatic
hydrocarbon radical of six to about twenty ring carbon atoms, and includes fused and non-
fused aryl rings. A fused aryl ring radical contains from two to four fused rings where the

- 25 ring of attachment is an aryl ring, and the other individual rings may be alicyclic,

heterocyclic, aromatic, heteroaromatic or any combination thereof. Further, the term aryl includes fused and non-fused rings containing from six to about twelve ring carbon atoms, as well as those containing from six to about ten ring carbon atoms. A non-limiting example of a single ring aryl group includes phenyl; a fused ring aryl group includes naphthyl, phenanthrenyl, anthracenyl, azulenyl; and a non-fused bi-aryl group includes biphenyl. In one embodiment, the "aryl" is substituted. Unless otherwise indicated, the "aryl" is unsubstituted.

[0052] The term "heteroaryl" as used herein, alone or in combination, refers to an aromatic monoradicals containing from about five to about twenty skeletal ring atoms, where one or more of the ring atoms is a heteroatom independently selected from among oxygen, nitrogen, sulfur, phosphorous, silicon, selenium and tin but not limited to these atoms and with the proviso that the ring of said group does not contain two adjacent O or S atoms. In embodiments in which two or more heteroatoms are present in the ring, the two or more heteroatoms can be the same as each another, or some or all of the two or more heteroatoms can each be different from the others. The term heteroaryl includes fused and non-fused heteroaryl radicals having at least one heteroatom. The term heteroaryl also includes fused and non-fused heteroaryls having from five to about twelve skeletal ring atoms, as well as those having from five to about ten skeletal ring atoms. Bonding to a heteroaryl group can be via a carbon atom or a heteroatom. Thus, as a non-limiting example, an imidazole group may be attached to a parent molecule via any of its carbon atoms (imidazol-2-yl, imidazol-4-yl or imidazol-5-yl), or its nitrogen atoms (imidazol-1-yl or imidazol-3-yl). Likewise, a heteroaryl group may be further substituted via any or all of its carbon atoms, and/or any or all of its heteroatoms. A fused heteroaryl radical may contain from two to four fused rings where the ring of attachment is a heteroaromatic ring and the other individual rings may be alicyclic, heterocyclic, aromatic, heteroaromatic or any combination thereof. A non-limiting example of a single ring heteroaryl group includes pyridyl; fused ring heteroaryl groups include benzimidazolyl, quinolinyl, acridinyl; and a non-fused bi-heteroaryl group includes bipyridinyl. Further examples of heteroaryls include, without limitation, furanyl, thienyl, oxazolyl, acridinyl, phenazinyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, benzothiophenyl, benzoxadiazolyl, benzotriazolyl, imidazolyl, indolyl, isoxazolyl, isoquinolinyl, indoliziny, isothiazolyl, isobenzofuroxazolyl, indazolyl, pyridyl, pyridazyl, pyrimidyl, pyrazinyl, pyrrolyl, pyrazinyl, pyrazolyl, purinyl, phthalazinyl, pteridinyl, quinolinyl, quinazolinyl,

quinoxaliny, triazolyl, tetrazolyl, thiazolyl, triazinyl, thiadiazolyl and the like, and their oxides, such as for example pyridyl-N-oxide. Illustrative examples of heteroaryl groups include the following moieties:



5 like.

In one embodiment, the "heteroaryl" is substituted. Unless otherwise indicated, the "heteroaryl" is unsubstituted.

[0053] The term "heterocyclyl" as used herein, alone or in combination, refers collectively to heteroalicycyl and heteroaryl groups. Herein, whenever the number of carbon atoms in a heterocycle is indicated (e.g., C₁-C₆ heterocycle), at least one non-carbon atom (the heteroatom) must be present in the ring. Designations such as "C₁-C₆ heterocycle" refer only to the number of carbon atoms in the ring and do not refer to the total number of atoms in the ring. Designations such as "4-6 membered heterocycle" refer to the total number of atoms that are contained in the ring (i.e., a four, five, or six membered ring, in which at least one atom is a carbon atom, at least one atom is a heteroatom and the remaining two to four atoms are either carbon atoms or heteroatoms). For heterocycles having two or more heteroatoms, those two or more heteroatoms can be the same or different from one another. Non-aromatic heterocyclic groups include groups having only three atoms in the ring, while aromatic heterocyclic groups must have at least five atoms in the ring. Bonding (i.e. attachment to a parent molecule or further substitution) to a heterocycle can be via a heteroatom or a carbon atom. In one embodiment, the "heterocyclyl" is substituted. Unless otherwise indicated, the "heterocyclyl" is unsubstituted.

[0054] The terms "halogen", "halo" or "halide" as used herein, alone or in combination refer to fluoro, chloro, bromo and/or iodo.

25

Certain Pharmaceutical Terminology

- [0055] The term "subject", "patient" or "individual" as used herein in reference to individuals suffering from a disorder, and the like, encompasses mammals and non-mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. Examples of non-mammals include, but are not limited to, birds, fish and the like. In one embodiment of the methods and compositions provided herein, the mammal is a human.
- 5
- [0056] The terms "effective amount", "therapeutically effective amount" or "pharmaceutically effective amount" as used herein, refer to an amount of at least one agent or compound being administered that is sufficient to treat or prevent the particular disease or condition. The result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an
- 10
- "effective amount" for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in a disease. An appropriate "effective" amount in any individual case may be determined using techniques, such as a dose escalation study.
- 15
- [0057] The term "pharmaceutically acceptable" as used herein, refers to a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compounds described herein, and is relatively nontoxic, i.e., the material may be administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.
- 20
- [0058] The term "pharmaceutical composition," as used herein, refers to a biologically active compound, optionally mixed with at least one pharmaceutically acceptable chemical component, such as, though not limited to carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients.
- 25
- [0059] The term "carrier" as used herein, refers to relatively nontoxic chemical compounds or agents that facilitate the incorporation of a compound into cells or tissues.
- 30
- [0060] The term "agonist," as used herein, refers to a molecule such as a compound, a drug, an enzyme activator or a hormone modulator which enhances the activity of another molecule or the activity of a receptor site.

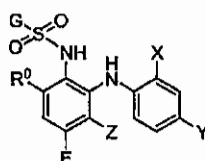
[0061] The term "antagonist," as used herein, refers to a molecule such as a compound, a drug, an enzyme inhibitor, or a hormone modulator, which diminishes, or prevents the action of another molecule or the activity of a receptor site.

[0062] The term "pharmaceutically acceptable salt" as used herein, includes salts that retain the biological effectiveness of the free acids and bases of the specified compound and that are not biologically or otherwise undesirable. Compounds described may possess acidic or basic groups and therefore may react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. Examples of pharmaceutically acceptable salts include those salts prepared by reaction of the compounds described herein with a mineral or organic acid or an inorganic base, such salts including, acetate, acrylate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, bisulfite, bromide, butyrate, butyn-1,4-dioate, camphorate, camphorsulfonate, caproate, caprylate, chlorides, chlorobenzoate, chloride, citrate, cyclopentanepropionate, decanoate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hexyne-1,6-dioate, hydroxybenzoate, γ -hydroxybutyrate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isobutyrate, lactate, maleate, malonate, methanesulfonate, mandelate, metaphosphate, methanesulfonate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, 1-naphthalenesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalates, palmoate, pectinate, persulfate, phenylacetates, phenylpropionates, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, pyrosulfate, pyrophosphate, propiolate, propionates, phthalate, , phenylbutyrate, propanesulfonate, pyrophosphates, salicylate, succinate, sulfate, sulfite, succinate, suberate, sebacate, sulfonate, tartrate, thiocyanate, tosylate undeconate and xylenesulfonate. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts. (See for example Berge *et al.*, *J. Pharm. Sci.* **1977**, *66*, 1-19.) Further, those compounds described herein which may comprise a free acid group may react with a suitable base, such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts and the like. Illustrative examples of bases include

sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate, $N^+(C_{1-4} \text{ alkyl})_4$, and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. It should be understood that the compounds described herein also include the quaternization of any basic nitrogen-containing groups they may contain. Water or oil-soluble or dispersible products may be obtained by such quaternization. See, for example, Berge *et al.*, *supra*. These salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or by separately reacting a purified compound in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed.

Compounds

[0063] Described herein are compounds of formula I, and pharmaceutically acceptable salts thereof,



formula I

wherein

Z is H or F;

X is F, Cl, CH₃, CH₂OH, CH₂F, CHF₂, or CF₃;

Y is I, Br, Cl, CF₃, C₁-C₃ alkyl, C₂-C₃ alkenyl, C₂-C₃ alkynyl, cyclopropyl, OMe, OEt, SMe, phenyl or Het, where Het is a 5- to 10- membered mono- or bicyclic heterocyclic group, which group is saturated, olefinic, or aromatic, containing 1-5 ring heteroatoms selected independently from N, O, and S; where

all said phenyl or Het groups are optionally substituted with F, Cl, Br, I, acetyl, methyl, CN, NO₂, CO₂H, C₁-C₃ alkyl, C₁-C₃ alkoxy, C₁-C₃ alkyl-C(=O)-, C₁-C₃ alkyl-C(=S)-, C₁-C₃ alkoxy-C(=S)-, C₁-C₃ alkyl-C(=O)O-, C₁-C₃ alkyl-O-(C=O)-, C₁-C₃ alkyl-C(=O)NH-, C₁-C₃ alkyl-C(=NH)NH-, C₁-C₃ alkyl-NH-(C=O)-, di-C₁-C₃ alkyl-N-(C=O)-, C₁-C₃ alkyl-C(=O)N(C₁-C₃ alkyl)-, C₁-C₃ alkyl-S(=O)₂NH- or trifluoromethyl;

all said methyl, ethyl, C₁-C₃ alkyl, and cyclopropyl groups are optionally substituted with OH;

all said methyl groups are optionally substituted with one, two, or three F atoms;

R^0 is H, F, Cl, Br, I, CH_3NH- , $(CH_3)_2N-$, C_1-C_6 alkyl, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, phenyl, monosubstituted phenyl, $O(C_1-C_4$ alkyl), $O-C(=O)(C_1-C_4$ alkyl) or $C(=O)O(C_1-C_4$ alkyl); where

5 said alkyl, alkoxy, cycloalkyl, alkenyl, alkynyl and phenyl groups are optionally substituted with 1-3 substituents selected independently from F, Cl, Br, I, OH, CN, cyanomethyl, nitro, phenyl and trifluoromethyl;

said C_1-C_6 alkyl and C_1-C_4 alkoxy groups also optionally substituted with OCH_3 or OCH_2CH_3 ;

10 G is G_1 , G_2 , R_{1a} , R_{1b} , R_{1c} , R_{1d} , R_{1e} , Ar_1 , Ar_2 or Ar_3 ; where

G_1 is C_1-C_6 alkyl optionally substituted with one amino, C_1-C_3 alkylamino, or dialkylamino group, said dialkylamino group comprising two C_1-C_4 alkyl groups which may be identical or non-identical; or

G_1 is a C_3-C_8 diamino alkyl group;

15 G_2 is a 5- or 6- membered ring, which is saturated, unsaturated, or aromatic, containing 1-3 ring heteroatoms selected independently from N, O, and S, optionally substituted with 1-3 substituents selected independently from F, Cl, OH, $O(C_1-C_3$ alkyl), OCH_3 , OCH_2CH_3 , $CH_3C(=O)NH$, $CH_3C(=O)O$, CN, CF_3 , and a 5-membered aromatic heterocyclic group containing 1-4 ring heteroatoms selected independently from N, O, and S;

20 R_{1a} is methyl, optionally substituted with 1-3 fluorine atoms or 1-3 chlorine atoms, or with OH, cyclopropoxy, or C_1-C_3 alkoxy, where said cyclopropoxy group or the C_1-C_3 alkyl moieties of said C_1-C_3 alkoxy groups are optionally substituted with one hydroxy or methoxy group, and where all C_3 -alkyl groups within said C_1-C_4 alkoxy are optionally further substituted with a second OH group;

25 R_{1b} is $CH(CH_3)-C_{1-3}$ alkyl or C_3-C_6 cycloalkyl, said alkyl and cycloalkyl groups optionally substituted with 1-3 substituents selected independently from F, Cl, Br, I, OH, OCH_3 , and CN;

R_{1c} is $(CH_2)_nO_mR'$; where

30 m is 0 or 1; and where

when m is 0, n is 1 or 2;

when m is 1, n is 2 or 3;

R' is C₁-C₆ alkyl, optionally substituted with 1-3 substituents selected independently from F, Cl, OH, OCH₃, OCH₂CH₃, and C₃-C₆ cycloalkyl;

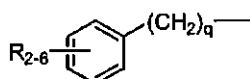
R_{1d} is C(A)(A')(B)-; where

B is H or C₁₋₄ alkyl, optionally substituted with one or two OH groups;

5 A and A' are independently H or C₁₋₄ alkyl, optionally substituted with one or two OH groups; or

A and A', together with the carbon atom to which they are attached, form a 3- to 6- member saturated ring;

R_{1e} is



R_{1e}

where

q is 1 or 2;

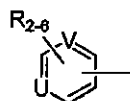
15 R₂ and R₃ are each independently, H, F, Cl, Br, CH₃, CH₂F, CHF₂, CF₃, OCH₃, OCH₂F, OCHF₂, OCF₃, ethyl, *n*-propyl, isopropyl, cyclopropyl, isobutyl, *sec*-butyl, *tert*-butyl or methylsulfonyl;

20 R₄ is H, F, Cl, Br, CH₃, CH₂F, CHF₂, CF₃, OCH₃, OCH₂F, OCHF₂, OCF₃, ethyl, *n*-propyl, isopropyl, cyclopropyl, isobutyl, *sec*-butyl, *tert*-butyl, methylsulfonyl, nitro, acetamido, amidinyl, cyano, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, 1,3,4-oxadiazol-2-yl, 5-methyl-1,3,4-oxadiazol, 1,3,4-thiadiazol, 5-methyl-1,3,4-thiadiazol 1H-tetrazolyl, N-morpholyl carbonyl amino, N-morpholysulfonyl and N-pyrrolidinylcarbonylamino;

R₅ is H, F, Cl or methyl;

R₆ is H, F, Cl or methyl;

25 Ar₁ is



Ar₁

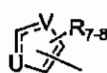
where

U and V are, independently, N, CR₂ or CR₃;

R_2 , R_3 and R_4 are, independently, H, F, Cl, Br, CH_3 , CH_2F , CHF_2 , CF_3 , OCH_3 , OCH_2F , $OCHF_2$, OCF_3 , ethyl, *n*-propyl, isopropyl, cyclopropyl, isobutyl, *sec*-butyl, *tert*-butyl, acetamido, amidinyl, cyano, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, 1,3,4-oxadiazol-2-yl, 5-methyl-1,3,4-oxadiazolyl, 1,3,4-thiadiazolyl, 5-methyl-1,3,4-thiadiazolyl, 1H-tetrazolyl, N-morpholylcarbonylamino, N-morpholylsulfonyl, N-pyrrolidinylcarbonylamino, and methylsulfonyl;

R_3 and R_4 are, independently, H, F, Cl or methyl;

Ar_2 is



Ar_2

where

the dashed line represents alternative formal locations for the second ring double bond;

U is -S-, -O- or -N=, and where

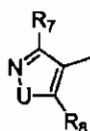
when U is -O- or -S-, V is -CH=, -CCl= or -N=;

when U is -N=, V is -CH=, -CCl=, or -N=;

R_7 is H or methyl;

R_8 is H, acetamido, methyl, F or Cl;

Ar_3 is



Ar_3

where

U is -NH-, -NCH₃- or -O-;

R_7 and R_8 are, independently, H, F, Cl, or methyl.

[0064] In addition to the definitions given herein for the groups G, R^0 , X, Y and Z, additional substitutions which could be contemplated by those of skill in the chemical and pharmaceutical arts are included.

[0065] In some embodiments, the invention provides a compound of formula 1, where G is G_1 or G_2 . In other embodiments, G is G_1 . In further or additional embodiments, G is G_2 .

- In some embodiments, the invention provides a compound of formula I, where G is R_{1a}, R_{1b}, R_{1c}, R_{1d}, R_{1e}, Ar₁, Ar₂ or Ar₃. In further or additional embodiments, G is R_{1a}, R_{1b}, R_{1c}, R_{1d} or R_{1e}. In further or additional embodiments, G is R_{1d}. In further or additional embodiments, G is R_{1b}. In further or additional embodiments, G is R_{1c}. In further or additional embodiments, G is R_{1d}. In further or additional embodiments, G is R_{1e}. In further or additional embodiments, G is Ar₁, Ar₂ or Ar₃. In further or additional embodiments, G is Ar₁. In further or additional embodiments, G is Ar₂. In further or additional embodiments, G is Ar₃.
- [0066] In some embodiments, Z is H. In some embodiments, Z is F. In some embodiments, X is F. In some embodiments, X is Cl. In some embodiments, X is CH₃. In some embodiments, X is CH₂OH. In some embodiments, X is CH₂F. In some embodiments, X is CHF₂. In some embodiments, X is CF₃. In some embodiments, X is F, Cl, or CH₃.
- [0067] In some embodiments, G is G₁ or G₂, X is F, Cl, or CH₃; Y is I, Br, Cl, CF₃, C₁-C₃ alkyl, phenyl, pyridyl, pyrrolyl, pyrazolyl, said phenyl, pyridyl, pyrrolyl, and pyrazolyl groups optionally substituted with F, Cl, Br, I, acetyl, methyl, CN, NO₂, CO₂H, C₁-C₃ alkyl, C₁-C₃ alkoxy, C₁-C₃ alkyl-C(=O)-, C₁-C₃ alkyl-C(=S)-, C₁-C₃ alkoxy-C(=S)-, C₁-C₃ alkyl-C(=O)O-, C₁-C₃ alkyl-O-(C=O)-, C₁-C₃ alkyl-C(=O)NH-, C₁-C₃ alkyl-C(=NH)NH-, C₁-C₃ alkyl-NH-(C=O)-, di-C₁-C₃ alkyl-N-(C=O)-, C₁-C₃ alkyl-C(=O)N(C₁-C₃ alkyl)-, C₁-C₃ alkyl-S(=O)₂NH- or trifluoromethyl; and Z is H or F. In further or additional embodiments, G is G₁ or G₂, and R⁰ is F, Cl, C₁-C₄ alkyl or C₁-C₄ alkoxy, said C₁-C₄ alkyl group and the C₁-C₄ alkyl moiety of said C₁-C₄ alkoxy group optionally substituted with F, Cl, OCH₃, or OCH₂CH₃. In further or additional embodiments, G is G₁ or G₂, and R⁰ is H, F, Cl, C₁-C₄ alkyl, methoxy, ethoxy, or 2-methoxy-ethoxy.
- [0068] In some embodiments, G₁ is N-methyl-2-aminoethyl. In further or additional embodiments, G₁ is (CH₃)₂N-CH₂CH₂-NH-(CH₂)_n-, where n is 1, 2, or 3. In further or additional embodiments, G₁ is (CH₃)₂N-CH₂CH₂-NH-(CH₂)_n-, where n is 1, 2, or 3, and X is F. In further or additional embodiments, G₁ is (CH₃)₂N-CH₂CH₂-NH-(CH₂)_n-, where n is 1, 2, or 3, X is F and Z is F.
- [0069] In some embodiments, G₂ is 1-piperidyl, 2-piperidyl, 3-piperidyl, or 4-piperidyl. In further or additional embodiments, G₂ is morpholyl, 1-piperazyl, or 2-piperazyl.
- [0070] In some embodiments, G is R_{1a}, R_{1b}, R_{1c}, R_{1d}, R_{1e}, Ar₁, Ar₂ or Ar₃ and X is F, Cl, or CH₃. In further or additional embodiments, G is R_{1a}, R_{1b}, R_{1c}, R_{1d}, R_{1e}, Ar₁, Ar₂ or Ar₃, X is F, Cl, or CH₃ and Y is I, Br, Cl, CF₃, or C₁-C₃ alkyl. In further or additional embodiments, G

is R_{1a} , R_{1b} , R_{1c} , R_{1d} , R_{1e} , Ar_1 , Ar_2 or Ar_3 , X is F, Cl, or CH_3 , Y is I, Br, Cl, CF_3 , or C_1 - C_3 alkyl and Z is H or F

[0071] In further or additional embodiments, G is R_{1a} , R_{1b} , R_{1c} , R_{1d} , R_{1e} , Ar_1 , Ar_2 or Ar_3 and R^0 is F, Cl, C_1 - C_4 alkyl or C_1 - C_4 alkoxy, said C_1 - C_4 alkyl group and the C_1 - C_4 alkyl moiety of said C_1 - C_4 alkoxy group optionally substituted with F, Cl, OCH_3 , or OCH_2CH_3 . In further or additional embodiments, G is R_{1a} , R_{1b} , R_{1c} , R_{1d} , R_{1e} , Ar_1 , Ar_2 or Ar_3 and R^0 is H, F, Cl, C_1 - C_4 alkyl, methoxy, ethoxy, or 2-methoxy-ethoxy.

[0072] In some embodiments, G is R_{1a} ; and Z is F. In further or additional embodiments, G is R_{1a} where R_{1a} is CH_3 , R^0 is H; and Y is Br, I, CF_3 , or CH_3 . In some embodiments, G is R_{1b} and Z is F. In further or additional embodiments, G is R_{1b} , Z is F, and R^0 is H, F, or OCH_3 . In further or additional embodiments, G is R_{1b} , Z is F, R^0 is H, F, or OCH_3 , and X is F or CH_3 . In further or additional embodiments, G is R_{1b} , Z is F, R^0 is H, F, or OCH_3 , X is F or CH_3 and Y is Br, I or CH_3 . In further or additional embodiments, G is R_{1b} where R_{1b} is C_3 - C_6 cycloalkyl. In further or additional embodiments, G is R_{1b} where R_{1b} is substituted C_3 - C_6 cycloalkyl. In further or additional embodiments, G is R_{1b} where R_{1b} is unsubstituted C_3 - C_6 cycloalkyl. In further or additional embodiments, G is R_{1b} where R_{1b} is unsubstituted C_3 - C_6 cycloalkyl and R^0 is H. In further or additional embodiments, G is R_{1b} where R_{1b} is isopropyl or cyclopropyl.

[0073] In some embodiments, G is R_{1c} , and Y is I, Br, CH_3 , or CF_3 . In further or additional embodiments, G is R_{1c} , Y is I, Br, CH_3 , or CF_3 , and Z is F. In further or additional embodiments, G is R_{1c} , Y is I, Br, CH_3 , or CF_3 , Z is F and m is zero.

[0074] In some embodiments, G is R_{1d} and R^0 is fluoro, chloro, methyl, ethyl, propyl, isopropyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, cyclopropyl, cyclobutyl, fluoromethyl, methoxy, fluoromethoxy, methylamino or dimethylamino. In further or additional embodiments, G is R_{1d} , R^0 is fluoro, chloro, methyl, ethyl, propyl, isopropyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, cyclopropyl, cyclobutyl, fluoromethyl, methoxy, fluoromethoxy, methylamino or dimethylamino and X is F, Cl, CH_3 , or mono-, di- or tri- fluoromethyl. In further or additional embodiments, G is R_{1d} , R^0 is fluoro, chloro, methyl, ethyl, propyl, isopropyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, cyclopropyl, cyclobutyl, fluoromethyl, methoxy, fluoromethoxy, methylamino or dimethylamino, X is F, Cl, CH_3 , or mono-, di- or tri- fluoromethyl and Y is I, Br, Cl, or mono-, di- or tri- fluoromethyl. In further or additional embodiments, G is R_{1d} , R^0 is fluoro, chloro, methyl, ethyl, propyl, isopropyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, cyclopropyl, cyclobutyl, fluoromethyl, methoxy, fluoromethoxy, methylamino or

dimethylamino, X is F, Cl, CH₃, or mono-, di- or tri- fluoromethyl, Y is I, Br, Cl, or mono-, di- or tri- fluoromethyl and Z is H or F. In further or additional embodiments, G is R_{1d} and R⁰ is F, Cl, methyl, ethyl, methoxy, ethoxy, or 2- methoxy-ethoxy.

- [0075] In further or additional embodiments, G is R_{1d}, R⁰ is F, Cl, methyl, ethyl, methoxy, ethoxy, or 2- methoxy-ethoxy and X is F, Cl, or CH₃. In further or additional embodiments, G is R_{1d}, R⁰ is F, Cl, methyl, ethyl, methoxy, ethoxy, or 2- methoxy-ethoxy, X is F, Cl, or CH₃ and Y is I, Br, Cl, or mono-, di- or tri- fluoromethyl. In further or additional embodiments, G is R_{1d}, R⁰ is F, Cl, methyl, ethyl, methoxy, ethoxy, or 2- methoxy-ethoxy, X is F, Cl, or CH₃, Y is I, Br, Cl, or mono-, di- or tri- fluoromethyl and Z is H or F. In further or additional embodiments, G is R_{1d} and R⁰ is H; X is F, Cl, CH₃, or mono-, di- or tri- fluoromethyl. In further or additional embodiments, G is R_{1d}, R⁰ is H; X is F, Cl, CH₃, or mono-, di- or tri- fluoromethyl and Y is I, Br, Cl, or mono-, di- or tri- fluoromethyl. In further or additional embodiments, G is R_{1d}, R⁰ is H; X is F, Cl, CH₃, or mono-, di- or tri- fluoromethyl, Y is I, Br, Cl, or mono-, di- or tri- fluoromethyl and Z is H or F.
- [0076] In further or additional embodiments, G is R_{1d} where R_{1d} is C(A)(A') is C₁-C₆ cycloalkyl. In further or additional embodiments, G is R_{1d} where R_{1d} is C(A)(A') is C₁-C₆ cycloalkyl and B is H. In further or additional embodiments, G is R_{1d} where R_{1d} is C(A)(A') is C₁-C₆ cycloalkyl and B is methyl, ethyl, 2-hydroxyethyl, *n*-propyl, 3- hydroxypropyl, 2,3-dihydroxypropyl, 3,4-dihydroxybutyl, isopropyl, 1-methyl-2-hydroxy ethyl, *n*-butyl, *sec*-butyl, isobutyl, or 2-hydroxymethyl-3-hydroxy propyl.
- [0077] In further or additional embodiments, G is R_{1d} where R_{1d} is C(A)(A') is C₁-C₆ cycloalkyl and B is 2,3-dihydroxypropyl or 3,4-dihydroxybutyl. In further or additional embodiments, G is R_{1d} where R_{1d} is C(A)(A') is C₁-C₆ cycloalkyl and B is 2,3-dihydroxypropyl or 3,4-dihydroxybutyl, in which the chiral carbon in B is in the R configuration. In further or additional embodiments, G is R_{1d} where R_{1d} is C(A)(A') is C₁-C₆ cycloalkyl and B is 2,3-dihydroxypropyl or 3,4-dihydroxybutyl, in which the chiral carbon in B is in the S configuration. In further or additional embodiments, G is R_{1d} where R_{1d} is C(A)(A') is C₁-C₆ cycloalkyl and B is methyl, optionally substituted with one OH group, or C₂-C₄ alkyl, optionally substituted with one or two OH groups. In further or additional embodiments, G is R_{1d} where R_{1d} is C(A)(A') is C₁-C₆ cycloalkyl and R⁰ is fluoro, chloro, methyl, ethyl, propyl, isopropyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, cyclopropyl, cyclobutyl, fluoromethyl, methoxy, fluoromethoxy, methylamino or dimethylamino. In further or additional embodiments, G is R_{1d} where R_{1d} is C(A)(A') is C₁-C₆ cycloalkyl and R⁰ is F, Cl,

methyl, ethyl, methoxy, ethoxy, or 2-methoxy-ethoxy. In further or additional embodiments, G is R_{1d} where R_{1d} is C(A)(A') is C₁-C₆ cycloalkyl and R⁰ is H; X is F, Cl, CH₃, or mono-, di- or tri- fluoromethyl.

[0078] In further or additional embodiments, the invention provides a composition comprising a compound of formula I, where G is R_{1d} where R_{1d} is C(A)(A') is C₁-C₆ cycloalkyl and B is 2,3-dihydroxypropyl or 3,4-dihydroxybutyl, in which the chiral carbon in B is in the R configuration, which is substantially free of the S isomer. In further or additional embodiments, the invention provides a composition comprising a compound of formula I, where G is R_{1d} where R_{1d} is C(A)(A') is C₁-C₆ cycloalkyl and B is 2,3-dihydroxypropyl, in which the chiral carbon in B is in the R configuration, which is substantially free of the S isomer. In further or additional embodiments, the invention provides a composition comprising a compound of formula I, where G is R_{1d} where R_{1d} is C(A)(A') is C₁-C₆ cycloalkyl and B is 3,4-dihydroxybutyl, in which the chiral carbon in B is in the R configuration, which is substantially free of the S isomer. In further or additional embodiments, the invention provides a composition comprising a compound of formula I, where G is R_{1d} where R_{1d} is C(A)(A') is C₁-C₆ cycloalkyl and B is 2,3-dihydroxypropyl or 3,4-dihydroxybutyl, in which the chiral carbon in B is in the S configuration, which is substantially free of the R isomer. In further or additional embodiments, the invention provides a composition comprising a compound of formula I, where G is R_{1d} where R_{1d} is C(A)(A') is C₁-C₆ cycloalkyl and B is 2,3-dihydroxypropyl, in which the chiral carbon in B is in the S configuration, which is substantially free of the R isomer. In further or additional embodiments, the invention provides a composition comprising a compound of formula I, where G is R_{1d} where R_{1d} is C(A)(A') is C₁-C₆ cycloalkyl and B is 3,4-dihydroxybutyl, in which the chiral carbon in B is in the S configuration, which is substantially free of the R isomer.

[0079] In further or additional embodiments, G is R_{1d} where R_{1d} is C(A)(A') is cyclopropyl. In further or additional embodiments, G is R_{1d} where R_{1d} is C(A)(A') is cyclopropyl and B is H. In further or additional embodiments, G is R_{1d} where R_{1d} is C(A)(A') is cyclopropyl and B is methyl, ethyl, 2-hydroxyethyl, *n*-propyl, 3-hydroxypropyl, 2,3-dihydroxypropyl, 3,4-dihydroxybutyl, isopropyl, 1-methyl-2-hydroxyethyl, *n*-butyl, *sec*-butyl, isobutyl, or 2-hydroxymethyl-3-hydroxypropyl. In further or additional embodiments, G is R_{1d} where R_{1d} is C(A)(A') is cyclopropyl and B is 2,3-dihydroxypropyl or 3,4-dihydroxybutyl. In further or additional embodiments, G is R_{1d} where R_{1d} is C(A)(A') is cyclopropyl and B is 2,3-

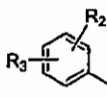
dihydroxypropyl or 3,4-dihydroxybutyl, in which the chiral carbon in B is in the R configuration. In further or additional embodiments, G is R_{1d} where R_{1d} is C(A)(A') is cyclopropyl and B is 2,3-dihydroxypropyl or 3,4-dihydroxybutyl, in which the chiral carbon in B is in the S configuration. In further or additional embodiments, G is R_{1d} where R_{1d} is C(A)(A') is cyclopropyl and B is methyl, optionally substituted with one OH group, or C₂-C₄ alkyl, optionally substituted with one or two OH groups. In further or additional embodiments, G is R_{1d} where R_{1d} is C(A)(A') is cyclopropyl and R⁰ is fluoro, chloro, methyl, ethyl, propyl, isopropyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, cyclopropyl, cyclobutyl, fluoromethyl, methoxy, fluoromethoxy, methylamino or dimethylamino. In further or additional embodiments, G is R_{1d} where R_{1d} is C(A)(A') is cyclopropyl and R⁰ is F, Cl, methyl, ethyl, methoxy, ethoxy, or 2-methoxy-ethoxy. In further or additional embodiments, G is R_{1d} where R_{1d} is C(A)(A') is cyclopropyl and R⁰ is H; X is F, Cl, CH₃, or mono-, di- or tri- fluoromethyl.

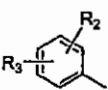
[0080] In further or additional embodiments, the invention provides a composition comprising a compound of formula I, where G is R_{1d} where R_{1d} is C(A)(A') is cyclopropyl and B is 2,3-dihydroxypropyl or 3,4-dihydroxybutyl, in which the chiral carbon in B is in the R configuration, which is substantially free of the S isomer. In further or additional embodiments, the invention provides a composition comprising a compound of formula I, where G is R_{1d} where R_{1d} is C(A)(A') is cyclopropyl and B is 2,3-dihydroxypropyl, in which the chiral carbon in B is in the R configuration, which is substantially free of the S isomer. In further or additional embodiments, the invention provides a composition comprising a compound of formula I, where G is R_{1d} where R_{1d} is C(A)(A') is cyclopropyl and B is 3,4-dihydroxybutyl, in which the chiral carbon in B is in the R configuration, which is substantially free of the S isomer. In further or additional embodiments, the invention provides a composition comprising a compound of formula I, where G is R_{1d} where R_{1d} is C(A)(A') is cyclopropyl and B is 2,3-dihydroxypropyl or 3,4-dihydroxybutyl, in which the chiral carbon in B is in the S configuration, which is substantially free of the R isomer. In further or additional embodiments, the invention provides a composition comprising a compound of formula I, where G is R_{1d} where R_{1d} is C(A)(A') is cyclopropyl and B is 2,3-dihydroxypropyl, in which the chiral carbon in B is in the S configuration, which is substantially free of the R isomer. In further or additional embodiments, the invention provides a composition comprising a compound of formula I, where G is R_{1d} where R_{1d} is

C(A)(A') is cyclopropyl and B is 3,4-dihydroxybutyl, in which the chiral carbon in B is in the S configuration, which is substantially free of the R isomer.

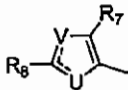
[0081] In some embodiments, G is R_{1e} and n is 1. In further or additional embodiments, G is R_{1e}, R⁰ is H, R₄₋₆ are H, R₂ and R₃ are, independently, H, F, Cl, Br, CH₃, CH₂F, CHF₂, CF₃, OCH₃, OCH₂F, OCHF₂, OCF₃, ethyl, *n*-propyl, isopropyl, cyclopropyl, isobutyl, *sec*-butyl, *tert*-butyl, and methylsulfonyl, X is F and Y is I.

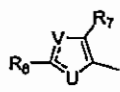
[0082] In some embodiments, G is Ar₁ where Ar₁ is phenyl optionally substituted with one group selected from acetamido, amidinyl, cyano, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, 1,3,4-oxadiazol-2-yl, 5-methyl-1,3,4-oxadiazolyl, 1,3,4-thiadiazolyl, 5-methyl-1,3,4-thiadiazolyl, 1H-tetrazolyl, N-morpholylcarbonylamino, N-morpholylsulfonyl, N-pyrrolidinylcarbonylamino, and methylsulfonyl, optionally substituted with 1-3 substituents selected independently from F, Cl, and CH₃. In further or additional embodiments, G is Ar₁ where Ar₁ is phenyl optionally substituted with one group selected from acetamido, amidinyl, cyano, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, 1,3,4-oxadiazol-2-yl, 5-methyl-1,3,4-oxadiazolyl, 1,3,4-thiadiazolyl, 5-methyl-1,3,4-thiadiazolyl, 1H-tetrazolyl, N-morpholylcarbonylamino, N-morpholylsulfonyl, N-pyrrolidinylcarbonylamino, and methylsulfonyl, optionally substituted with 1-3 substituents selected independently from F, Cl, and CH₃, R⁰ is H, X is F, Cl, or methyl and Y is Br, I, CF₃, C₁-C₃ alkyl, C₂-C₃ alkenyl, C₂-C₃ alkynyl, cyclopropyl,

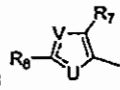
OCH₃, OCH₂CH₃ or SCH₃. In some embodiments, G is Ar₁ where Ar₁ is  and where R₂ and R₃ are, independently, H, F, Cl, CH₃, CF₃, OCH₃. In further or additional

embodiments, G is Ar₁ where Ar₁ is  and where R₂ and R₃ are, independently, H, F, Cl, CH₃, CF₃, OCH₃, X is F or CH₃, Y is I, Br, or Cl; and Z is F. In further or additional embodiments, G is Ar₁ where Ar₁ is phenyl or mono-substituted phenyl. In further or additional embodiments, G is Ar₁ where Ar₁ is phenyl or mono-substituted phenyl, X is F or CH₃, Y is I, Br, or Cl, Z is F; and R⁰ is F, methyl, ethyl, methoxy, or 2-methoxy-ethoxy. In further or additional embodiments, G is Ar₁ where U is N or CR₂ and V is N. In further or additional embodiments, G is Ar₁ where U is N or CR₂ and V is CR. In further or additional embodiments, G is Ar₁ where U is N or CR₂, V is CR, R⁰ is H, X is F, Cl, or

methyl and Y is Br, I, CF₃, C₁-C₃ alkyl, C₂-C₃ alkenyl, C₂-C₃ alkynyl, cyclopropyl, OCH₃, OCH₂CH₃ or SCH₃.

[0083] In some embodiments, G is Ar₂ where Ar₂ is  where R₇ is H or methyl and R₈ is H, acetamido, methyl, F or Cl.

5 [0084] In further or additional embodiments, G is Ar₂ where Ar₂ is  where R₇ is H or methyl, R₈ is H, acetamido, methyl, F or Cl, R⁰ is H, X is F, Cl, or methyl, Y is Br, I, CF₃, C₁-C₃ alkyl, C₂-C₃ alkenyl, C₂-C₃ alkynyl, cyclopropyl, OCH₃, OCH₂CH₃ or SCH₃, and Z is F.

[0085] In further or additional embodiments, G is Ar₂ where Ar₂ is  where U is
10 S or O, V is CH=, and R₈ is H or CH₃, R₇ is H or methyl, R₈ is H, acetamido, methyl, F or Cl, R⁰ is H, X is F, Cl, or methyl, Y is Br, I, CF₃, C₁-C₃ alkyl, C₂-C₃ alkenyl, C₂-C₃ alkynyl, cyclopropyl, OCH₃, OCH₂CH₃ or SCH₃ and Z is F. In further or additional embodiments, R⁰ is H. In further or additional embodiments, R⁰ is H, X is F or Cl and Y is Br, I, CH₂CH₃ or SCH₃.

15 [0086] In some embodiments, G is Ar₃ where U is -O-.

[0087] In further or additional embodiments, G is R_{1a}, where R_{1a} is defined as above. In further or additional embodiments, G is R_{1a}, and R⁰ is H, where R_{1a} is defined as above. In further or additional embodiments, G is R_{1a} and R⁰ is as defined above, other than H, and R_{1a} is defined as above. In further or additional embodiments, G is R_{1a}, where R_{1a} is methyl,
20 monohalomethyl, C₁-C₃ alkoxyethyl, or cyclopropoxymethyl. In further or additional embodiments, G is R_{1a}, where R_{1a} is methyl, monohalomethyl, C₁-C₃ alkoxyethyl, or cyclopropoxy methyl and where R⁰ is F, Cl, C₁-C₃ alkyl, monochloro C₁-C₃ alkyl, C₁-C₃ alkoxy, trifluoro methoxy, or 2-methoxy-ethoxy.

[0088] In further or additional embodiments, G is R_{1b}, where R_{1b} is defined as above. In
25 further or additional embodiments, G is R_{1b}, and R⁰ is H, where R_{1b} is defined as above. In further or additional embodiments, G is R_{1b}, R⁰ is H and Z is F, where R_{1b} is defined as above. In further or additional embodiments, G is R_{1b} and R⁰ is as defined above, other than H, and R_{1b} is defined as above. In further or additional embodiments, G is R_{1b}, where R_{1b} is

- isopropyl, 2-butyl, 2-pentyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, all optionally substituted with 1 or 2 substituents selected independently from F, Cl, OH, and OCH₃; Y is Br, I, methyl, or trifluoromethyl. In further or additional embodiments, G is R_{1b}, where R_{1b} is isopropyl, 2-butyl, 2-pentyl, cyclopropyl, cyclobutyl, cyclopentyl, or
- 5 cyclohexyl, optionally substituted with 1 or 2 substituents selected independently from F, Cl, OH, and OCH₃; Y is Br, I, methyl, or trifluoromethyl; and R⁰ is F, Cl, C₁-C₃ alkyl, monochloro C₁-C₃ alkyl, C₁-C₃ alkoxy, trifluoromethoxy, or 2-methoxy-ethoxy. In further or additional embodiments, G is R_{1b}, where R_{1b} is isopropyl, 2-butyl, 2-pentyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, all optionally substituted with one Cl or with 1 or 2
- 10 OH groups; and Y is Br, I, methyl, or trifluoromethyl. In further or additional embodiments, G is R_{1b}, where R_{1b} is isopropyl, 2-butyl, 2-pentyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, all optionally substituted with one Cl or with 1 or 2 OH groups; Y is Br, I, methyl, or trifluoromethyl; and R⁰ is F, Cl, C₁-C₃ alkyl, monochloro C₁-C₃ alkyl, C₁-C₃ alkoxy, trifluoromethoxy, or 2-methoxy-ethoxy.
- 15 [0089] In further or additional embodiments, G is R_{1c}, where R_{1c} is defined as above. In further or additional embodiments, G is R_{1c}, and R⁰ is H, where R_{1c} is defined as above. In further or additional embodiments, G is R_{1c} and R⁰ is as defined above, other than H, and R_{1c} is defined as above. In further or additional embodiments, G is R_{1c}, and R⁰ is H, where R_{1c} is (CH₂)_nO_mR', where m is 0 or 1, n is 2 or 3 when m is 1, and n is 1 or 2 when m is 0,
- 20 and R' is C₁-C₆ alkyl, optionally substituted with 1-3 substituents selected independently from F, Cl, OH, OCH₃, OCH₂CH₃, and C₃-C₆ cycloalkyl. In another more specific subgeneric embodiment, m is zero, n is 1 or 2, and R' is C₁-C₄ alkyl, optionally substituted as described above. In another more specific subgeneric embodiment, m is 1, n is 2 or 3, and R' is C₁-C₄ alkyl, optionally substituted as described above. In a still more specific
- 25 subgeneric embodiment, m is zero, n is 1 or 2, and R' is C₁-C₄ alkyl, optionally substituted with 1-3 groups selected from OH, OCH₃, Cl, and cyclopropyl.
- [0090] In further or additional embodiments, G is R_{1d}, where R_{1d} is defined as above. In further or additional embodiments, G is R_{1d}, and R⁰ is H, where R_{1d} is defined as above. In further or additional embodiments, G is R_{1d} and R⁰ is as defined above, other than H, and
- 30 R_{1d} is defined as above. In further or additional embodiments, G is R_{1d}, and R⁰ is H, where R_{1d} is C(A)(A')(B)- where B, A, and A' are, independently, H or C₁₋₄ alkyl, optionally substituted with one or two OH groups or halogen atoms, or A and A', together with the carbon atom to which they are attached, form a 3- to 6- member saturated ring, said ring

optionally containing one or two heteroatoms selected, independently, from O, N, and S and optionally substituted with one or two groups selected independently from methyl, ethyl, fluoro, chloro, bromo and iodo.

[0091] In further or additional embodiments, G is R_{1e} , where R_{1e} is defined as above. In

5 further or additional embodiments, G is R_{1e} , and R^0 is H, where R_{1e} is defined as above. In further or additional embodiments, G is R_{1e} and R^0 is as defined above, other than H, and R_{1e} is defined as above.

[0092] In further or additional embodiments, G is Ar_1 , where Ar_1 is defined as above. In

10 further or additional embodiments, G is Ar_1 , and R^0 is H, where Ar_1 is defined as above. In further or additional embodiments, G is Ar_1 and R^0 is as defined above, other than H, and Ar_1 is defined as above.

[0093] In further or additional embodiments, G is Ar_2 , where Ar_2 is defined as above. In

15 further or additional embodiments, G is Ar_2 , and R^0 is H, where Ar_2 is defined as above. In further or additional embodiments, G is Ar_2 and R^0 is as defined above, other than H, and Ar_2 is defined as above.

[0094] In further or additional embodiments, X is F, Cl, or CH_3 ; Y is I, Br, Cl, CF_3 or C_1-C_3

20 alkyl, and Z is H or F. In further or additional embodiments, X is F, Cl, or CH_3 ; Y is I, Br, Cl, CF_3 , or C_1-C_3 alkyl, Z is H or F, and R^0 is halogen, C_1-C_6 alkyl, monohalo C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, phenyl, monosubstituted phenyl, OR_3 , $O-C(=O)R_4$, or $C(=O)OR_5$. In further or additional embodiments, X is F, Cl, or CH_3 ; Y is I, Br, Cl, CF_3 , or C_1-C_3 alkyl, Z is H or F, and R^0 is furyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrrolyl, or pyrazolyl. In further or additional embodiments, X is F, Cl, or CH_3 ; Y is I, Br, Cl, CF_3 , or C_1-C_3 alkyl, Z is H or F, and R^0 is F, Cl, C_1-C_4 alkyl, C_1-C_3 alkoxy, trifluoromethoxy, or 2-methoxy-ethoxy.

25 [0095] In another more specific subgeneric embodiment, R_{1d} is cycloalkyl or 1-alkyl-cycloalkyl, in which the 1-alkyl group is optionally substituted with one or two OH groups or with one or two halogen atoms.

[0096] In another more specific subgeneric embodiment, R^0 is halogen, C_1-C_6 alkyl,

30 monohalo C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, phenyl, monosubstituted phenyl, OR_3 , $O-C(=O)R_4$, or $C(=O)OR_5$; and R_{1d} is cycloalkyl or 1-alkyl-cycloalkyl, in which the 1-alkyl group is optionally substituted with one or two OH groups or with one or two halogen atoms.

[0097] In another more specific subgeneric embodiment, R^0 is furyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrrolyl, or pyrazolyl; and R_{1d} is cycloalkyl or 1-alkyl-cycloalkyl, in which the 1-alkyl group is optionally substituted with one or two OH groups or one or two halogen atoms.

5 [0098] In another more specific subgeneric embodiment, R_{1d} is cycloalkyl or 1-alkyl-cycloalkyl, in which the 1-alkyl group is optionally substituted with one or two OH groups, and where Y is Br, I, methyl, or trifluoromethyl. In another more specific subgeneric embodiment, R_{1d} is cycloalkyl or 1-alkyl-cycloalkyl, in which the 1-alkyl group is optionally substituted with one or two fluorine or chlorine atoms, and where Y is Br, I,
10 methyl, or trifluoromethyl. In another more specific subgeneric embodiment, R_{1d} is cycloalkyl or (1-alkyl)-cycloalkyl, in which the 1-alkyl group is optionally substituted with one or two OH groups, and where R^0 is F, Cl, C_1 - C_3 alkyl, monochloro C_1 - C_3 alkyl, C_1 - C_3 alkoxy, trifluoromethoxy, or 2-methoxy-ethoxy. In another more specific subgeneric embodiment, R_{1d} is tetrahydrofuryl, tetrahydrothienyl, pyrrolidyl, piperidyl, piperazinyl, or morpholyl, each optionally substituted as described above, and where Y is Br, I, methyl, or trifluoromethyl. In another more specific subgeneric embodiment, R_{1d} is oxazolidinyl, thiazolidinyl, isoxazolidinyl, isothiazolidinyl, tetrahydrofuryl, tetrahydrothienyl, pyrrolidyl, piperidyl, piperazinyl, or morpholyl, each optionally substituted as described above, and where Y is Br, I, methyl, or trifluoromethyl. In another more specific subgeneric
20 embodiment, R_{1d} is cyclopropyl or 1-alkyl-cyclopropyl, in which the 1-alkyl group is optionally substituted with one or two OH groups, and where R^0 is F, Cl, methyl, ethyl, chloromethyl, C_1 - C_2 alkoxy, trifluoromethoxy, or 2-methoxy-ethoxy. In an even more specific embodiment, R_{1d} is 1-(monohydroxyalkyl) cycloalkyl. In another more specific embodiment, R_{1d} is 1-(monohydroxyalkyl) cycloalkyl, where R^0 is F, Cl, methyl, ethyl,
25 chloromethyl, C_1 - C_2 alkoxy, trifluoromethoxy, or 2-methoxy-ethoxy. In an even more specific embodiment, R_{1d} is 1-(dihydroxyalkyl) cycloalkyl. In another more specific embodiment, R_{1d} is 1-(dihydroxyalkyl) cycloalkyl, where R^0 is F, Cl, methyl, ethyl, chloromethyl, C_1 - C_2 alkoxy, trifluoromethoxy, or 2-methoxy-ethoxy.

[0099] In a more specific subgeneric embodiment U is CR_2 and V is N. In another more specific, subgeneric embodiment, U and V are both N. In a more specific, subgeneric embodiment, U is CR_2 and V is CR_3 .

[00100] In a still more specific subgeneric embodiment, this invention provides a compound of formula I, where G is Ar_1 and Ar_1 is phenyl or monosubstituted phenyl, R^0 is

F, methyl, ethyl, C₁-C₃ alkoxy, trifluoromethoxy, or 2-methoxy-ethoxy; X is F, Cl, or CH₃; Y is I; and Z is F. In another subgeneric embodiment, this invention provides a compound of formula I, where G is Ar₁, where Ar₁ is phenyl or monosubstituted phenyl, R⁰ is halogen, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, all such alkyl, cycloalkyl, alkenyl, and alkynyl groups optionally substituted with 1-3 substituents selected independently from halogen, OH, CN, cyanomethyl, nitro, phenyl, and trifluoromethyl; or R⁰ is phenyl, OR₃, furyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrrolyl, or pyrazolyl. In a more specific subgeneric embodiment, this invention provides a compound of formula I, where A is Ar₁, where Ar₁ is phenyl or monosubstituted phenyl, R⁰ is F, Cl, C₁-C₃ alkyl, C₁-C₃ alkoxy, 2-methoxyethoxy, C₂-C₃ alkenyl, C₂-C₃ alkynyl, trifluoromethyl, phenyl, furyl, or thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrrolyl, or pyrazolyl; X is F, Cl, or methyl; Y is I, Br, Cl, CF₃, or C₁-C₃ alkyl; and Z is F.

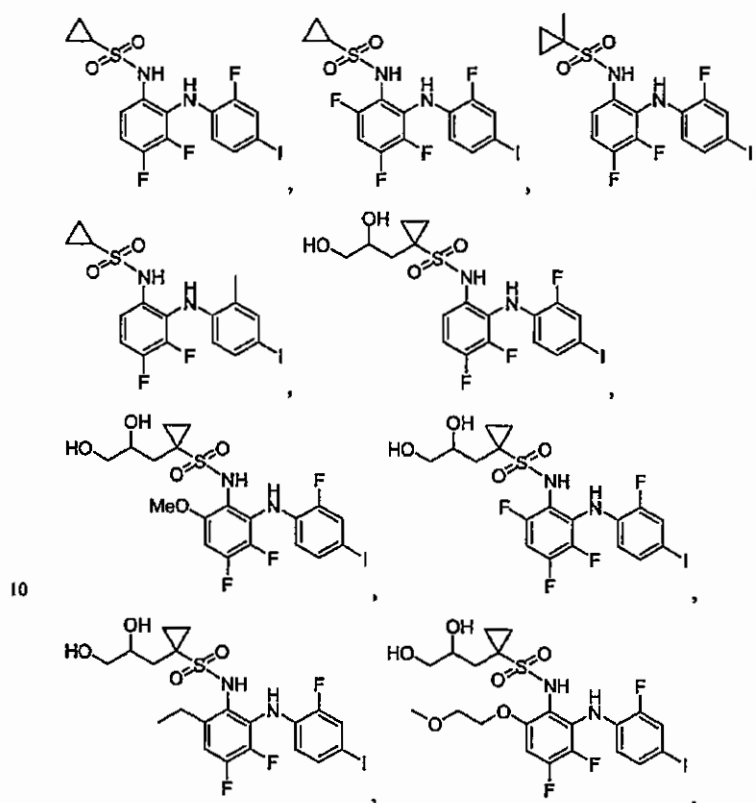
[00101] In another still more specific subgeneric embodiment, this invention provides a compound of formula I, where G is Ar₁, where Ar₁ is phenyl or monosubstituted phenyl, R⁰ is H; X is F, Cl, or CH₃; Y is Br or I; and Z is F.

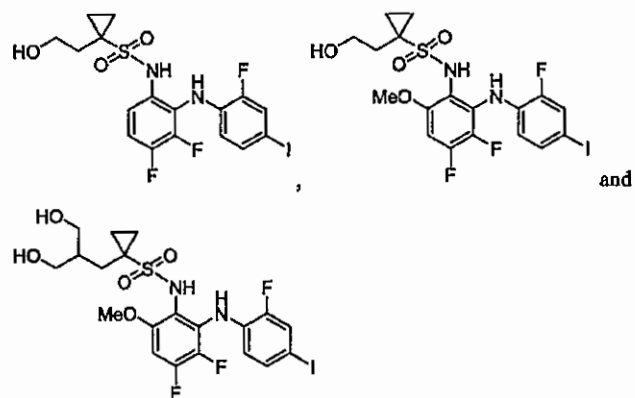
[00102] In another subgeneric embodiment his invention provides a compound of formula I, where G is Ar₂, where Ar₂ is 2-thienyl, 2-furyl, 3-thienyl, 3-furyl, 2-pyrrolyl, or 3-pyrrolyl, all optionally substituted with methoxycarbonyl, methylcarbamoyl, acetamido, acetyl, methyl, ethyl, trifluoromethyl, or halogen. In a more specific subgeneric embodiment his invention provides a compound of formula I, where G is Ar₂, where Ar₂ is 2-thienyl, 2-furyl, 3-thienyl, 3-furyl, 2-pyrrolyl, or 3-pyrrolyl, all optionally substituted with methoxycarbonyl, methylcarbamoyl, acetamido, acetyl, methyl, ethyl, trifluoromethyl, or halogen; R⁰ is other than H; X is F, Cl, or CH₃; Y is I, Br, Cl, CF₃, or C₁-C₃ alkyl, and Z is H or F. In another subgeneric embodiment this invention provides a compound of formula I, where G is Ar₂, where Ar₂ is 2-thienyl, 2-furyl, 3-thienyl, 3-furyl, 2-pyrrolyl, or 3-pyrrolyl, all optionally substituted with methoxycarbonyl, methylcarbamoyl, acetamido, acetyl, methyl, ethyl, trifluoromethyl, or halogen; R⁰ is F, Cl, C₁-C₃ alkyl, monochloro C₁-C₃ alkyl, C₁-C₃ alkoxy, trifluoromethoxy, methoxy-methoxy, or 2-methoxy-ethoxy; X is F, Cl, or CH₃; Y is I, Br, Cl, CF₃, or C₁-C₃ alkyl, and Z is H or F. In another subgeneric embodiment his invention provides a compound of formula I, where G is Ar₂, where Ar₂ is 2-thienyl, 2-furyl, 3-thienyl, 3-furyl, 2-pyrrolyl, or 3-pyrrolyl, all optionally substituted with methoxycarbonyl, methylcarbamoyl, acetamido, acetyl, methyl, ethyl, trifluoromethyl, or halogen; R⁰ is H; X is F, Cl, or CH₃; Y is I, Br, Cl, CF₃, or C₁-C₃ alkyl, and Z is H or F. In

another subgeneric embodiment his invention provides a compound of formula I, where G is Ar₂, where Ar₂ is thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrrolyl, or pyrazolyl, all optionally substituted with methoxycarbonyl, methylcarbamoyl, acetamido, acetyl, methyl, ethyl, trifluoromethyl, or halogen; R⁰ is H or methoxy; X is F, Cl, or CH₃; Y is I, Br, Cl,

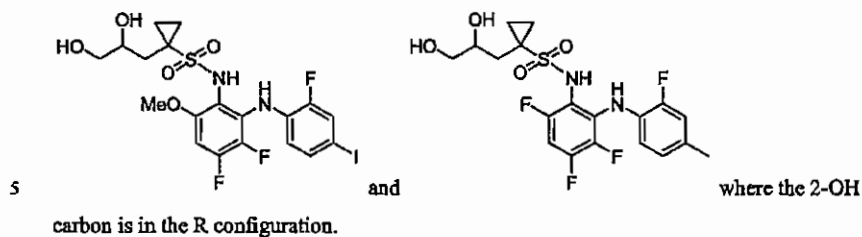
5 CF₃, or C₁-C₃ alkyl, and Z is H or F.

[00103] In some embodiments, the compound of formula (I), or a pharmaceutical salt thereof, is selected from

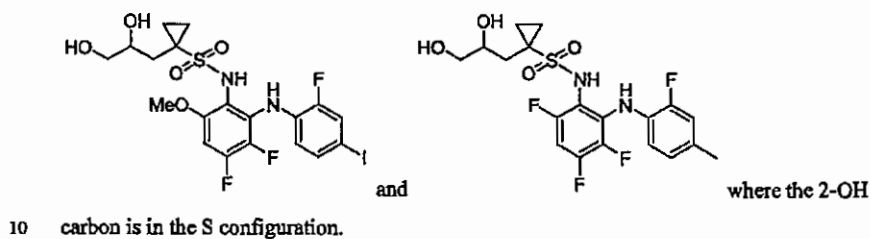




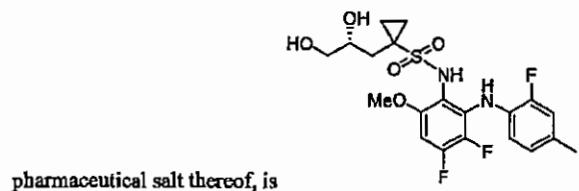
[00104] In some embodiments, the invention provides a compound of formula I, or a pharmaceutical salt thereof, selected from:



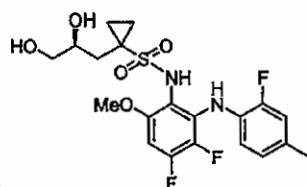
[00105] In some embodiments, the invention provides a compound of formula I, or a pharmaceutical salt thereof, selected from:



[00106] In further or additional embodiments, the compound of formula (I), or a

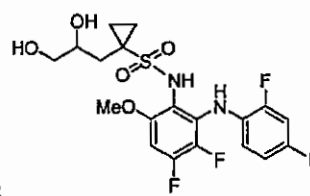


[00107] In further or additional embodiments, the compound of formula (I), or a

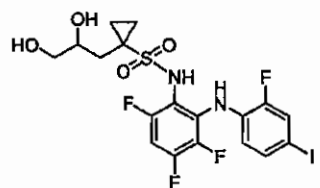


pharmaceutical salt thereof, is

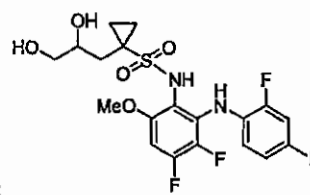
[00108] In some embodiments, the invention provides a composition comprising a compound of formula I, selected from those shown below, where the 2-OH carbon is in the



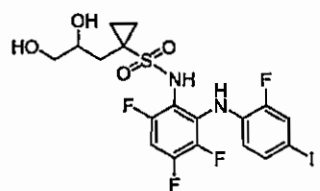
5 R configuration, substantially free of the S- isomer:



[00109] In some embodiments, the invention provides a composition comprising a compound of formula I, selected from those shown below, where the 2-OH carbon is in the



S configuration, substantially free of the R- isomer:



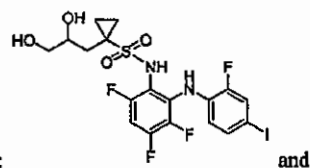
10

[00110] In some embodiments, this invention provides a compound of formula I, where Y is phenyl, pyridyl, or pyrazolyl. In another subgeneric embodiment, this invention provides a compound of formula I, where Y is substituted phenyl, pyridyl, or pyrazolyl. In yet another subgeneric embodiment, this invention provides a compound of formula I, where Y is Br or I. In one subgeneric embodiment, this invention provides a compound of formula I, where G is 1-piperidyl, 2-piperidyl, 3-piperidyl, or 4-piperidyl. In another subgeneric embodiment, this invention provides a compound of formula I, where G is 1-piperazyl or 2-piperazyl. In another subgeneric embodiment, this invention provides a compound of formula I, where G is morpholyl. In another subgeneric embodiment, this invention provides a compound of formula I, where G is N-methyl-2-aminoethyl. In one subgeneric embodiment, this invention provides a compound of formula I, where G is N-methyl-3-amino-n-propyl. In another subgeneric embodiment, this invention provides a compound of formula I, where G is $(\text{CH}_3)_2\text{N}-\text{CH}_2\text{CH}_2-\text{NH}-(\text{CH}_2)_n-$, where n is 1, 2, or 3. In another subgeneric embodiment, this invention provides a compound of formula I, where G is $(\text{CH}_3\text{CH}_2)_2\text{N}-\text{CH}_2\text{CH}_2-\text{NH}-(\text{CH}_2)_n-$, where n is 1 or 2. In a more specific subgeneric embodiment, this invention provides a compound of formula I, where G is 1-piperidyl, 2-piperidyl, 3-piperidyl, or 4-piperidyl; R° is H, halo, or methoxy; X is F; and Y is I. In another more specific subgeneric embodiment, this invention provides a compound of formula I, where G is 1-piperazyl or 2-piperazyl; R° is H, halo, or methoxy; X is F; and Y is I. In another more specific subgeneric embodiment, this invention provides a compound of formula I, where G is morpholyl; R° is H, halo, or methoxy; X is F; and Y is I. In another more specific subgeneric embodiment, this invention provides a compound of formula I, where G is N-methyl-2-aminoethyl; R° is H, halo, or methoxy; X is F; and Y is I. In another more specific subgeneric embodiment, this invention provides a compound of formula I, where G is N-methyl-3-amino-n-propyl; R° is H, halo, or methoxy; X is F; and Y is I. In another more specific subgeneric embodiment, this invention provides a compound of formula I, where G is $(\text{CH}_3)_2\text{N}-\text{CH}_2\text{CH}_2-\text{NH}-(\text{CH}_2)_n-$, where n is 1, 2, or 3; R° is H, halo, or methoxy; X is F; and Y is I. In another more specific subgeneric embodiment, this invention provides a compound of formula I, where G is $(\text{CH}_3\text{CH}_2)_2\text{N}-\text{CH}_2\text{CH}_2-\text{NH}-(\text{CH}_2)_n-$, where n is 1 or 2; R° is H, halo, or methoxy; X is F; and Y is I.

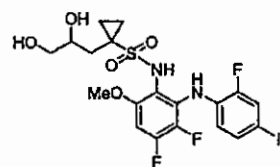
[00111] In some embodiments, the invention provides a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt thereof. In some

embodiments the pharmaceutical composition further comprises at least one pharmaceutically acceptable carrier.

[00112] In some embodiments, the invention provides a pharmaceutical composition

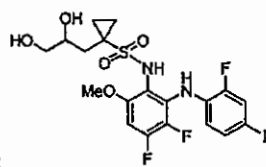
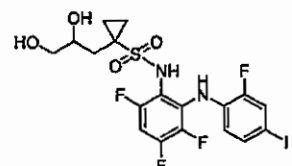


comprising a compound selected from:

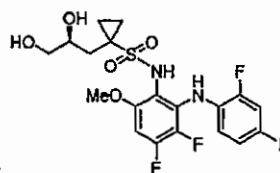


5 , or a pharmaceutically acceptable salt, thereof.

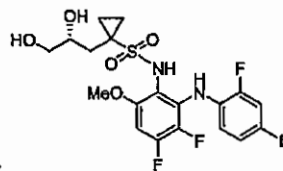
[00113] In some embodiments, the pharmaceutical composition further comprises at least one pharmaceutically acceptable carrier. In some embodiments, the compound is in the R configuration. In some embodiments, the compound is in the R configuration, substantially free of the S- isomer. In some embodiments, the compound is in the S configuration. In some embodiments, the compound is in the S configuration, substantially free of the R- isomer. In some embodiments, the compound is:



[00114] In some embodiments, the compound is:



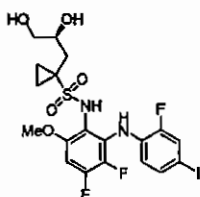
[00115] In some embodiments, the compound is:



[00116] In some embodiments, the compound is:

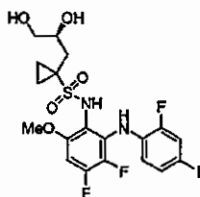
[00117] In other aspects, the present invention is directed to pharmaceutical compositions comprising effective amounts of a compound of formula I or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical compositions further comprise a pharmaceutically acceptable carrier. Such compositions may contain adjuvants, excipients, and preservatives, agents for delaying absorption, fillers, binders, adsorbents, buffers, disintegrating agents, solubilizing agents, other carriers, and other inert ingredients. Methods of formulation of such compositions are well-known in the art.

10 [00118] The invention relates to a composition comprising: about 1mg of a



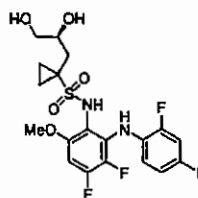
compound of structure: ; about 222.2mg of microcrystalline cellulose; about 12.0mg of croscarmellose sodium; about 2.4mg of sodium lauryl sulfate; and about 2.4mg of magnesium stearate.

[00119] The invention also relates to a composition comprising: about 10mg of a



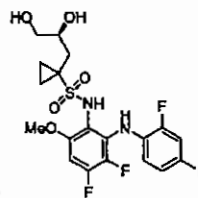
15 compound of structure: ; about 213.2mg of microcrystalline cellulose; about 12.0mg of croscarmellose sodium; about 2.4mg of sodium lauryl sulfate; and about 2.4mg of magnesium stearate.

[00120] The invention also relates to a composition comprising: about 20mg of a



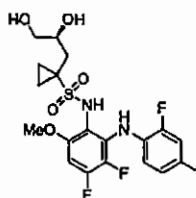
compound of structure: ; about 203.2mg of microcrystalline cellulose; about 12.0mg of croscarmellose sodium; about 2.4mg of sodium lauryl sulfate; and about 2.4mg of magnesium stearate.

5 [00121] The invention also relates to a composition comprising: about 40mg of a



compound of structure: ; about 183.2mg of microcrystalline cellulose; about 12.0mg of croscarmellose sodium; about 2.4mg of sodium lauryl sulfate; and about 2.4mg of magnesium stearate.

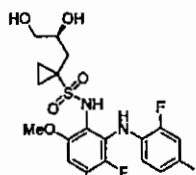
[00122] The invention also relates to a composition comprising: about 0.4% by



10 weight of a compound of structure: ; and about 99.6% by weight of a pharmaceutically acceptable carrier or vehicle.

[00123] In some embodiments, the pharmaceutically acceptable carrier or vehicle comprises microcrystalline cellulose. In further or additional embodiments, the microcrystalline cellulose is about 92.6% by weight of the composition. In further or
15 additional embodiments, the composition further comprises: about 5% by weight croscarmellose sodium; about 1% by weight sodium lauryl sulfate; and about 1% by weight magnesium stearate.

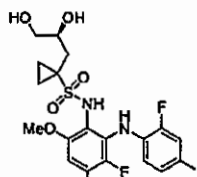
[00124] The invention also relates to a composition comprising: about 4.2% by



weight of a compound of structure: ; and about 95.8 % by weight of a pharmaceutically acceptable carrier or vehicle.

[00125] In some embodiments, the pharmaceutically acceptable carrier or vehicle comprises microcrystalline cellulose. In further or additional embodiments, the microcrystalline cellulose is about 88.8% by weight of the composition. In further or additional embodiments, the composition further comprises: about 5% by weight croscarmellose sodium; about 1% by weight sodium lauryl sulfate; and about 1% by weight magnesium stearate.

10 [00126] The invention also relates to a composition comprising: from about 2% to

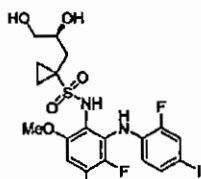


about 10% by weight of a compound of structure: ; and from about 98% to about 90% by weight of a pharmaceutically acceptable carrier or vehicle.

[00127] In some embodiments, the pharmaceutically acceptable carrier or vehicle comprises microcrystalline cellulose. In further or additional embodiments, the microcrystalline cellulose is from about 85% to about 95% by weight of the composition. In further or additional embodiments, the composition further comprises: from about 1% to about 6% by weight croscarmellose sodium; from about 0.1% to about 2% by weight sodium lauryl sulfate; and from about 0.25% to about 1.5% by weight magnesium stearate.

[00128] In some embodiments, the pharmaceutically acceptable carrier or vehicle comprises microcrystalline cellulose. In further or additional embodiments, the microcrystalline cellulose is from about 85% to about 95% by weight of the composition. In further or additional embodiments, the composition further comprises: from about 1% to about 6% by weight croscarmellose sodium; and from about 0.25% to about 1.5% by weight magnesium stearate.

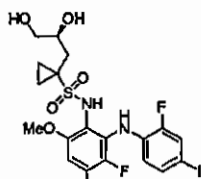
[00129] The invention also relates to a method for treating or preventing cancer or an inflammation disease, comprising administering to a subject in need thereof an effective amount of a pharmaceutical composition comprising: about 1mg of a compound of



structure: ; about 222.2mg of microcrystalline cellulose; about

5 12.0mg of croscarmellose sodium; about 2.4mg of sodium lauryl sulfate; and about 2.4mg of magnesium stearate.

[00130] The invention also relates to a method for treating or preventing cancer or an inflammation disease, comprising administering to a subject in need thereof an effective amount of a pharmaceutical composition comprising: about 10mg of a compound of

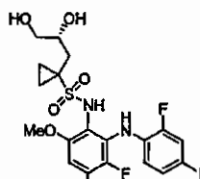


10 structure: ; about 213.2mg of microcrystalline cellulose; about

12.0mg of croscarmellose sodium; about 2.4mg of sodium lauryl sulfate; and about 2.4mg of magnesium stearate.

[00131] The invention also relates to a method for treating or preventing cancer or an inflammation disease, comprising administering to a subject in need thereof an effective
15 amount of any of the pharmaceutical compositions described herein.

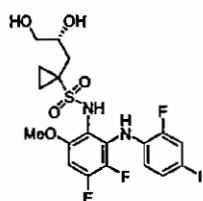
[00132] The invention relates to a composition comprising: about 1mg of a



compound of structure: ; about 222.2mg of microcrystalline

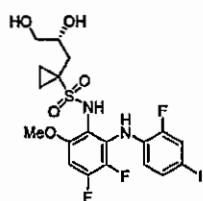
cellulose; about 12.0mg of croscarmellose sodium; about 2.4mg of sodium lauryl sulfate; and about 2.4mg of magnesium stearate.

[00133] The invention also relates to a composition comprising: about 10mg of a



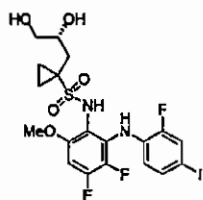
compound of structure: ; about 213.2mg of microcrystalline cellulose; about 12.0mg of croscarmellose sodium; about 2.4mg of sodium lauryl sulfate; and about 2.4mg of magnesium stearate.

5 [00134] The invention also relates to a composition comprising: about 20mg of a



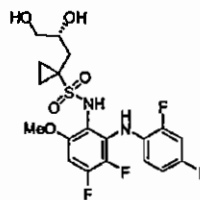
compound of structure: ; about 203.2mg of microcrystalline cellulose; about 12.0mg of croscarmellose sodium; about 2.4mg of sodium lauryl sulfate; and about 2.4mg of magnesium stearate.

[00135] The invention also relates to a composition comprising: about 40mg of a



10 compound of structure: ; about 183.2mg of microcrystalline cellulose; about 12.0mg of croscarmellose sodium; about 2.4mg of sodium lauryl sulfate; and about 2.4mg of magnesium stearate.

[00136] The invention also relates to a composition comprising: about 0.4% by

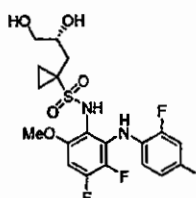


weight of a compound of structure: ; and about 99.6% by weight of a
15 pharmaceutically acceptable carrier or vehicle.

[00137] In some embodiments, the pharmaceutically acceptable carrier or vehicle comprises microcrystalline cellulose. In further or additional embodiments, the microcrystalline cellulose is about 92.6% by weight of the composition. In further or additional embodiments, the composition further comprises: about 5% by weight

5 croscarmellose sodium; about 1% by weight sodium lauryl sulfate; and about 1% by weight magnesium stearate.

[00138] The invention also relates to a composition comprising: about 4.2% by

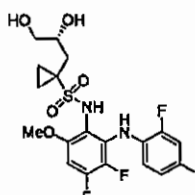


weight of a compound of structure: ; and about 95.8 % by weight of a pharmaceutically acceptable carrier or vehicle.

10 [00139] In some embodiments, the pharmaceutically acceptable carrier or vehicle comprises microcrystalline cellulose. In further or additional embodiments, the microcrystalline cellulose is about 88.8% by weight of the composition. In further or additional embodiments, the composition further comprises: about 5% by weight croscarmellose sodium; about 1% by weight sodium lauryl sulfate; and about 1% by weight

15 magnesium stearate.

[00140] The invention also relates to a composition comprising: from about 2% to



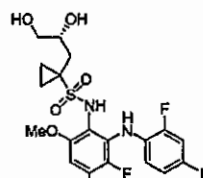
about 10% by weight of a compound of structure: ; and from about 98% to about 90% by weight of a pharmaceutically acceptable carrier or vehicle.

[00141] In some embodiments, the pharmaceutically acceptable carrier or vehicle

20 comprises microcrystalline cellulose. In further or additional embodiments, the microcrystalline cellulose is from about 85% to about 95% by weight of the composition. In further or additional embodiments, the composition further comprises: from about 1% to about 6% by weight croscarmellose sodium; from about 0.1% to about 2% by weight sodium lauryl sulfate; and from about 0.25% to about 1.5% by weight magnesium stearate.

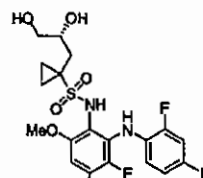
[00142] In some embodiments, the pharmaceutically acceptable carrier or vehicle comprises microcrystalline cellulose. In further or additional embodiments, the microcrystalline cellulose is from about 85% to about 95% by weight of the composition. In further or additional embodiments, the composition further comprises: from about 1% to about 6% by weight croscarmellose sodium; and from about 0.25% to about 1.5% by weight magnesium stearate.

[00143] The invention also relates to a method for treating or preventing cancer or an inflammation disease, comprising administering to a subject in need thereof an effective amount of a pharmaceutical composition comprising: about 1mg of a compound of



10 structure: ; about 222.2mg of microcrystalline cellulose; about 12.0mg of croscarmellose sodium; about 2.4mg of sodium lauryl sulfate; and about 2.4mg of magnesium stearate.

[00144] The invention also relates to a method for treating or preventing cancer or an inflammation disease, comprising administering to a subject in need thereof an effective amount of a pharmaceutical composition comprising: about 10mg of a compound of



15 structure: ; about 213.2mg of microcrystalline cellulose; about 12.0mg of croscarmellose sodium; about 2.4mg of sodium lauryl sulfate; and about 2.4mg of magnesium stearate.

[00145] The invention also relates to a method for treating or preventing cancer or an inflammation disease, comprising administering to a subject in need thereof an effective amount of any of the pharmaceutical compositions described herein.

[00146] In other aspects, the present invention is directed to a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt, thereof. In some embodiments, the pharmaceutical composition is in a form suitable for oral

administration. In further or additional embodiments, the pharmaceutical composition is in the form of a tablet, capsule, pill, powder, sustained release formulation, solution, suspension, for parenteral injection as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. In

5 further or additional embodiments, the pharmaceutical composition is in unit dosage forms suitable for single administration of precise dosages. In further or additional embodiments the amount of compound of formula I is in the range of about 0.001 to about 1000 mg/kg body weight/day. In further or additional embodiments the amount of compound of formula I is in the range of about 0.5 to about 50 mg/kg/day. In further or additional embodiments

10 the amount of compound of formula I is about 0.001 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.002 to about 6 g/day. In further or additional embodiments the amount of compound of formula I is about 0.005 to about 5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.01 to about 5 g/day. In further or additional embodiments the amount of

15 compound of formula I is about 0.02 to about 5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.05 to about 2.5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.1 to about 1 g/day. In further or additional embodiments, dosage levels below the lower limit of the aforesaid range may be more than adequate. In further or additional embodiments, dosage levels

20 above the upper limit of the aforesaid range may be required. In further or additional embodiments the compound of formula I is administered in a single dose, once daily. In further or additional embodiments the compound of formula I is administered in multiple doses, more than once per day. In further or additional embodiments the compound of formula I is administered twice daily. In further or additional embodiments the compound

25 of formula I is administered three times per day. In further or additional embodiments the compound of formula I is administered four times per day. In further or additional embodiments the compound of formula I is administered more than four times per day. In some embodiments, the pharmaceutical composition is for administration to a mammal. In further or additional embodiments, the mammal is human. In further or additional

30 embodiments, the pharmaceutical composition further comprises a pharmaceutical carrier, excipient and/or adjuvant. In further or additional embodiments, the pharmaceutical composition further comprises at least one therapeutic agent. In further or additional embodiments, the therapeutic agent is selected from the group of cytotoxic agents, anti-

angiogenesis agents and anti-neoplastic agents. In further or additional embodiments, the anti-neoplastic agent is selected from the group of consisting of alkylating agents, anti-metabolites, epidophyllotoxins; antineoplastic enzymes, topoisomerase inhibitors, procarbazines, mitoxantrones, platinum coordination complexes, biological response
5 modifiers and growth inhibitors, hormonal/anti-hormonal therapeutic agents, and haematopoietic growth factors. In further or additional embodiments, the therapeutic agent is taxol, bortezomib or both. In further or additional embodiments, the pharmaceutical composition is administered in combination with an additional therapy. In further or additional embodiments, the additional therapy is radiation therapy, chemotherapy or a
10 combination of both. In further or additional embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable salt of a compound of formula I.

[00147] In other aspects, the present invention is directed to a method for inhibiting a MEK enzyme. In some embodiments, the method comprises contacting said MEK enzyme with an amount of a composition comprising a compound of formula I or a
15 pharmaceutically acceptable salt, thereof, sufficient to inhibit said enzyme, wherein said enzyme is inhibited. In further or additional embodiments the enzyme is at least about 1% inhibited. In further or additional embodiments the enzyme is at least about 2% inhibited. In further or additional embodiments the enzyme is at least about 3% inhibited. In further or additional embodiments the enzyme is at least about 4% inhibited. In further or additional
20 embodiments the enzyme is at least about 5% inhibited. In further or additional embodiments the enzyme is at least about 10% inhibited. In further or additional embodiments the enzyme is at least about 20% inhibited. In further or additional embodiments the enzyme is at least about 25% inhibited. In further or additional embodiments the enzyme is at least about 30% inhibited. In further or additional
25 embodiments the enzyme is at least about 40% inhibited. In further or additional embodiments the enzyme is at least about 50% inhibited. In further or additional embodiments the enzyme is at least about 60% inhibited. In further or additional embodiments the enzyme is at least about 70% inhibited. In further or additional embodiments the enzyme is at least about 75% inhibited. In further or additional
30 embodiments the enzyme is at least about 80% inhibited. In further or additional embodiments the enzyme is at least about 90% inhibited. In further or additional embodiments the enzyme is essentially completely inhibited. In further or additional embodiments the MEK enzyme is MEK kinase. In further or additional embodiments the

MEK enzyme is MEK1. In further or additional embodiments the MEK enzyme is MEK2. In further or additional embodiments the contacting occurs within a cell. In further or additional embodiments the cell is a mammalian cell. In further or additional embodiments the mammalian cell is a human cell. In further or additional embodiments, the MEK enzyme is inhibited with a composition comprising a pharmaceutically acceptable salt of a compound of formula I.

[00148] In other aspects, the present invention is directed to a method of treatment of a MEK mediated disorder in an individual suffering from said disorder comprising administering to said individual an effective amount of a composition comprising a compound of formula I or a pharmaceutically acceptable salt, thereof. In some embodiments, the composition comprising a compound of formula I is administered orally, intraduodenally, parenterally (including intravenous, subcutaneous, intramuscular, intravascular or by infusion), topically or rectally. In some embodiments, the pharmaceutical composition is in a form suitable for oral administration. In further or additional embodiments, the pharmaceutical composition is in the form of a tablet, capsule, pill, powder, sustained release formulations, solution, suspension, for parenteral injection as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. In further or additional embodiments, the pharmaceutical composition is in unit dosage forms suitable for single administration of precise dosages. In further or additional embodiments, the pharmaceutical composition further comprises a pharmaceutical carrier, excipient and/or adjuvant. In further or additional embodiments the amount of compound of formula I is in the range of about 0.001 to about 1000 mg/kg body weight/day. In further or additional embodiments the amount of compound of formula I is in the range of about 0.5 to about 50 mg/kg/day. In further or additional embodiments the amount of compound of formula I is about 0.001 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.01 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.02 to about 5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.05 to about 2.5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.1 to about 1 g/day. In further or additional embodiments, dosage levels below the lower limit of the aforesaid range may be more than adequate. In further or additional embodiments, dosage levels above the upper limit of the aforesaid range may be required. In further or additional embodiments the

compound of formula I is administered in a single dose, once daily. In further or additional embodiments the compound of formula I is administered in multiple doses, more than once per day. In further or additional embodiments the compound of formula I is administered twice daily. In further or additional embodiments the compound of formula I is
5 administered three times per day. In further or additional embodiments the compound of formula I is administered four times per day. In further or additional embodiments the compound of formula I is administered more than four times per day. In some embodiments, the individual suffering from the MEK mediated disorder is a mammal. In further or additional embodiments, the individual is a human. In some embodiments, the
10 composition comprising a compound of formula I is administered in combination with an additional therapy. In further or additional embodiments, the additional therapy is radiation therapy, chemotherapy or a combination of both. In further or additional embodiments, the composition comprising a compound of formula I is administered in combination with at least one therapeutic agent. In further or additional embodiments, the therapeutic agent is
15 selected from the group of cytotoxic agents, anti-angiogenesis agents and anti-neoplastic agents. In further or additional embodiments, the anti-neoplastic agent is selected from the group of consisting of alkylating agents, anti-metabolites, epipodophyllotoxins; antineoplastic enzymes, topoisomerase inhibitors, procarbazines, mitoxantrones, platinum coordination complexes, biological response modifiers and growth inhibitors, hormonal/anti-hormonal
20 therapeutic agents, and haematopoietic growth factors. In further or additional embodiments, the therapeutic agent is selected from taxol, bortezomib or both. In some embodiments, the MEK mediated disorder is selected from the group consisting of inflammatory diseases, infections, autoimmune disorders, stroke, ischemia, cardiac disorder, neurological disorders, fibrogenetic disorders, proliferative disorders, hyperproliferative
25 disorders, non-cancer hyperproliferative disorders, tumors, leukemias, neoplasms, cancers, carcinomas, metabolic diseases, malignant disease, vascular restenosis, psoriasis, atherosclerosis, rheumatoid arthritis, osteoarthritis, heart failure, chronic pain, neuropathic pain, dry eye, closed angle glaucoma and wide angle glaucoma. In further or additional embodiments, the MEK mediated disorder is an inflammatory disease. In further or
30 additional embodiments, the MEK mediated disorder is a hyperproliferative disease. In further or additional embodiments, the MEK mediated disorder is selected from the group consisting of tumors, leukemias, neoplasms, cancers, carcinomas and malignant disease. In further or additional embodiments, the cancer is brain cancer, breast cancer, lung cancer,

ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, colorectal cancer or leukemia. In further or additional embodiments, the fibrogenetic disorder is scleroderma, polymyositis, systemic lupus, rheumatoid arthritis, liver cirrhosis, keloid formation, interstitial nephritis or pulmonary fibrosis. In further or additional embodiments, an
5 effective amount of a composition comprising a pharmaceutically acceptable salt of a compound of formula I is administered.

[00149] In other aspects, the present invention is directed to a method for degrading, inhibiting the growth of or killing a cancer cell comprising contacting said cell with an amount of a composition effective to degrade, inhibit the growth of or to kill said cell, the
10 composition comprising a compound of formula I or a pharmaceutically acceptable salt, thereof. In some embodiments, the cancer cells comprise brain, breast, lung, ovarian, pancreatic, prostate, renal, or colorectal cancer cells. In further or additional embodiments, the composition is administered with at least one therapeutic agent. In further or additional
15 embodiments, the therapeutic agent is selected from the group consisting of cytotoxic agents, anti-angiogenesis agents and anti-neoplastic agents. In further or additional embodiments, the anti-neoplastic agents selected from the group of consisting of alkylating agents, anti-metabolites, epidophyllotoxins; antineoplastic enzymes, topoisomerase inhibitors, procarbazines, mitoxantrones, platinum coordination complexes, biological
20 response modifiers and growth inhibitors, hormonal/anti-hormonal therapeutic agents, and haematopoietic growth factors. In some embodiments, the cancer cells are degraded. In further or additional embodiments, 1% of the cancer cells are degraded. In further or additional embodiments, 2% of the cancer cells are degraded. In further or additional
25 embodiments, 3% of the cancer cells are degraded. In further or additional embodiments, 4% of the cancer cells are degraded. In further or additional embodiments, 5% of the cancer cells are degraded. In further or additional embodiments, 10% of the cancer cells are degraded. In further or additional embodiments, 20% of the cancer cells are degraded. In further or additional embodiments, 25% of the cancer cells are degraded. In further or additional
30 embodiments, 30% of the cancer cells are degraded. In further or additional embodiments, 40% of the cancer cells are degraded. In further or additional embodiments, 50% of the cancer cells are degraded. In further or additional embodiments, 60% of the cancer cells are degraded. In further or additional embodiments, 70% of the cancer cells are degraded. In further or additional embodiments, 75% of the cancer cells are degraded. In

further or additional embodiments, 80% of the cancer cells are degraded. In further or additional embodiments, 90% of the cancer cells are degraded. In further or additional embodiments, 100% of the cancer cells are degraded. In further or additional embodiments, essentially all of the cancer cells are degraded. In some embodiments, the cancer cells are

5 killed. In further or additional embodiments, 1% of the cancer cells are killed. In further or additional embodiments, 2% of the cancer cells are killed. In further or additional embodiments, 3% of the cancer cells are killed. In further or additional embodiments, 4% of the cancer cells are killed. In further or additional embodiments, 5% of the cancer cells are killed. In further or additional embodiments, 10% of the cancer cells are killed. In further or additional

10 additional embodiments, 20% of the cancer cells are killed. In further or additional embodiments, 25% of the cancer cells are killed. In further or additional embodiments, 30% of the cancer cells are killed. In further or additional embodiments, 40% of the cancer cells are killed. In further or additional embodiments, 50% of the cancer cells are killed. In further or additional embodiments, 60% of the cancer cells are killed. In further or

15 additional embodiments, 70% of the cancer cells are killed. In further or additional embodiments, 75% of the cancer cells are killed. In further or additional embodiments, 80% of the cancer cells are killed. In further or additional embodiments, 90% of the cancer cells are killed. In further or additional embodiments, 100% of the cancer cells are killed. In further or additional embodiments, essentially all of the cancer cells are killed. In further or

20 additional embodiments, the growth of the cancer cells is inhibited. In further or additional embodiments, the growth of the cancer cells is about 1% inhibited. In further or additional embodiments, the growth of the cancer cells is about 2% inhibited. In further or additional embodiments, the growth of the cancer cells is about 3% inhibited. In further or additional embodiments, the growth of the cancer cells is about 4% inhibited. In further or additional

25 embodiments, the growth of the cancer cells is about 5% inhibited. In further or additional embodiments, the growth of the cancer cells is about 10% inhibited. In further or additional embodiments, the growth of the cancer cells is about 20% inhibited. In further or additional embodiments, the growth of the cancer cells is about 25% inhibited. In further or additional embodiments, the growth of the cancer cells is about 30% inhibited. In further or additional

30 embodiments, the growth of the cancer cells is about 40% inhibited. In further or additional embodiments, the growth of the cancer cells is about 50% inhibited. In further or additional embodiments, the growth of the cancer cells is about 60% inhibited. In further or additional embodiments, the growth of the cancer cells is about 70% inhibited. In further or additional

embodiments, the growth of the cancer cells is about 75% inhibited. In further or additional embodiments, the growth of the cancer cells is about 80% inhibited. In further or additional embodiments, the growth of the cancer cells is about 90% inhibited. In further or additional embodiments, the growth of the cancer cells is about 100% inhibited. In further or
5 additional embodiments, a composition comprising a pharmaceutically acceptable salt of a compound of formula I is used.

[00150] In other aspects, the present invention is directed to a method for the treatment or prevention of a proliferative disease in an individual comprising administering to said individual an effective amount of a compound of formula I or a pharmaceutically
10 acceptable salt, thereof. In some embodiments, the compound or pharmaceutically acceptable salt thereof is administered as a component of a composition that further comprises a pharmaceutically acceptable carrier or vehicle. In some embodiments, the proliferative disease is cancer, psoriasis, restenosis, autoimmune disease, or atherosclerosis. In further or additional embodiments, the proliferative disease is a hyperproliferative
15 disease. In further or additional embodiments, the proliferative disease is selected from the group consisting of tumors, leukemias, neoplasms, cancers, carcinomas and malignant disease. In further or additional embodiments, the cancer is brain cancer, breast cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, colorectal cancer or leukemia. In further or additional embodiments, the fibrogenetic disorder is scleroderma,
20 polymyositis, systemic lupus, rheumatoid arthritis, liver cirrhosis, keloid formation, interstitial nephritis or pulmonary fibrosis. In further or additional embodiments, the cancer is brain cancer, breast cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, colorectal cancer or leukemia. In further or additional embodiments, the cancer is brain cancer or adrenocortical carcinoma. In further or additional
25 embodiments, the cancer is breast cancer. In further or additional embodiments, the cancer is ovarian cancer. In further or additional embodiments, the cancer is pancreatic cancer. In further or additional embodiments, the cancer is prostate cancer. In further or additional embodiments, the cancer is renal cancer. In further or additional embodiments, the cancer is colorectal cancer. In further or additional embodiments, the cancer is myeloid leukemia. In
30 further or additional embodiments, the cancer is glioblastoma. In further or additional embodiments, the cancer is follicular lymphoma. In further or additional embodiments, the cancer is pre-B acute leukemia. In further or additional embodiments, the cancer is chronic lymphocytic B-leukemia. In further or additional embodiments, the cancer is mesothelioma.

In further or additional embodiments, the cancer is small cell line cancer. In some embodiments, the composition comprising a compound of formula I is administered in combination with an additional therapy. In further or additional embodiments, the additional therapy is radiation therapy, chemotherapy or a combination of both. In further or additional
5 embodiments, the composition comprising a compound of formula I is administered in combination with at least one therapeutic agent. In further or additional embodiments, the therapeutic agent is selected from the group of cytotoxic agents, anti-angiogenesis agents and anti-neoplastic agents. In further or additional embodiments, the anti-neoplastic agent is selected from the group of consisting of alkylating agents, anti-metabolites,
10 epidophyllotoxins; antineoplastic enzymes, topoisomerase inhibitors, procarbazines, mitoxantrones, platinum coordination complexes, biological response modifiers and growth inhibitors, hormonal/anti-hormonal therapeutic agents, and haematopoietic growth factors. In further or additional embodiments, the therapeutic agent is selected from taxol, bortezomib or both. In some embodiments, the composition is administered orally,
15 intraduodenally, parenterally (including intravenous, subcutaneous, intramuscular, intravascular or by infusion), topically or rectally. In further or additional embodiments the amount of compound of formula I is in the range of about 0.001 to about 1000 mg/kg body weight/day. In further or additional embodiments the amount of compound of formula I is in the range of about 0.5 to about 50 mg/kg/day. In further or additional embodiments the
20 amount of compound of formula I is about 0.001 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.01 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.02 to about 5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.05 to about 2.5 g/day. In further or additional embodiments the amount of
25 compound of formula I is about 0.1 to about 1 g/day. In further or additional embodiments, dosage levels below the lower limit of the aforesaid range may be more than adequate. In further or additional embodiments, dosage levels above the upper limit of the aforesaid range may be required. In further or additional embodiments the compound of formula I is administered in a single dose, once daily. In further or additional embodiments the
30 compound of formula I is administered in multiple doses, more than once per day. In further or additional embodiments the compound of formula I is administered twice daily. In further or additional embodiments the compound of formula I is administered three times per day. In further or additional embodiments the compound of formula I is administered

four times per day. In further or additional embodiments the compound of formula I is administered more than four times per day. In some embodiments, the individual suffering from the proliferative disease is a mammal. In further or additional embodiments, the individual is a human. In further or additional embodiments, an effective amount of a composition comprising a pharmaceutically acceptable salt of a compound of formula I is administered.

{00151} In other aspects, the present invention is directed to a method for the treatment or prevention of an inflammatory disease in an individual comprising administering to said individual an effective amount of compound of formula I or a pharmaceutically acceptable salt thereof. In some embodiments, the compound or pharmaceutically acceptable salt thereof is administered as a component of a composition that further comprises a pharmaceutically acceptable carrier or vehicle. In further or additional embodiments, the inflammatory disease is selected from chronic inflammatory diseases, rheumatoid arthritis, rheumatoid arthritis, spondyloarthropathies, ankylosing spondylitis, gout, tendonitis, bursitis, sciatica, gouty arthritis, osteoarthritis, juvenile arthritis, acute rheumatic arthritis, enteropathic arthritis, neuropathic arthritis, psoriatic arthritis, pyogenic arthritis, atherosclerosis, systemic lupus erythematosus, inflammatory bowel disease, irritable bowel syndrome, ulcerative colitis, reflux esophagitis, Crohn's disease, gastritis, asthma, allergies, respiratory distress syndrome, pancreatitis, chronic obstructive pulmonary disease, pulmonary fibrosis, psoriasis, eczema or scleroderma. In some embodiments, the composition comprising a compound of formula I is administered in combination with an additional therapy. In further or additional embodiments, the composition comprising a compound of formula I is administered in combination with at least one therapeutic agent. In some embodiments, the composition is administered orally, intraduodenally, parenterally (including intravenous, subcutaneous, intramuscular, intravascular or by infusion), topically or rectally. In further or additional embodiments the amount of compound of formula I is in the range of about 0.001 to about 1000 mg/kg body weight/day. In further or additional embodiments the amount of compound of formula I is in the range of about 0.5 to about 50 mg/kg/day. In further or additional embodiments the amount of compound of formula I is about 0.001 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.01 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.02 to about 5 g/day. In further or additional embodiments the amount of compound of formula I is

about 0.05 to about 2.5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.1 to about 1 g/day. In further or additional embodiments, dosage levels below the lower limit of the aforesaid range may be more than adequate. In further or additional embodiments, dosage levels above the upper limit of the aforesaid range may be required. In further or additional embodiments the compound of formula I is administered in a single dose, once daily. In further or additional embodiments the compound of formula I is administered in multiple doses, more than once per day. In further or additional embodiments the compound of formula I is administered twice daily. In further or additional embodiments the compound of formula I is administered three times per day. In further or additional embodiments the compound of formula I is administered four times per day. In further or additional embodiments the compound of formula I is administered more than four times per day. In some embodiments, the individual suffering from the inflammatory disease is a mammal. In further or additional embodiments, the individual is a human. In further or additional embodiments, an effective amount of a composition comprising a pharmaceutically acceptable salt of a compound of formula I is administered.

[00152] In other aspects, the present invention is directed to a method for the treatment or prevention of cancer in an individual comprising administering to said individual an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof. In some embodiments, the compound or pharmaceutically acceptable salt thereof is administered as a component of a composition that further comprises a pharmaceutically acceptable carrier or vehicle. In further or additional embodiments, the cancer is brain cancer, breast cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, colorectal cancer or leukemia. In further or additional embodiments, the fibrogenetic disorder is scleroderma, polymyositis, systemic lupus, rheumatoid arthritis, liver cirrhosis, keloid formation, interstitial nephritis or pulmonary fibrosis. In further or additional embodiments, the cancer is brain cancer, breast cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, colorectal cancer or leukemia. In further or additional embodiments, the cancer is brain cancer or adrenocortical carcinoma. In further or additional embodiments, the cancer is breast cancer. In further or additional embodiments, the cancer is ovarian cancer. In further or additional embodiments, the cancer is pancreatic cancer. In further or additional embodiments, the cancer is prostate cancer. In further or additional embodiments, the cancer is renal cancer. In further or

additional embodiments, the cancer is colorectal cancer. In further or additional
embodiments, the cancer is myeloid leukemia. In further or additional embodiments, the
cancer is glioblastoma. In further or additional embodiments, the cancer is follicular
lymphoma. In further or additional embodiments, the cancer is pre-B acute leukemia. In
5 further or additional embodiments, the cancer is chronic lymphocytic B-leukemia. In further
or additional embodiments, the cancer is mesothelioma. In further or additional
embodiments, the cancer is small cell line cancer. In some embodiments, the composition
comprising a compound of formula I is administered in combination with an additional
therapy. In further or additional embodiments, the additional therapy is radiation therapy,
10 chemotherapy or a combination of both. In further or additional embodiments, the
composition comprising a compound of formula I is administered in combination with at
least one therapeutic agent. In further or additional embodiments, the therapeutic agent is
selected from the group of cytotoxic agents, anti-angiogenesis agents and anti-neoplastic
agents. In further or additional embodiments, the anti-neoplastic agent is selected from the
15 group of consisting of alkylating agents, anti-metabolites, epipodophyllotoxins; antineoplastic
enzymes, topoisomerase inhibitors, procarbazines, mitoxantrones, platinum coordination
complexes, biological response modifiers and growth inhibitors, hormonal/anti-hormonal
therapeutic agents, and haematopoietic growth factors. In further or additional
embodiments, the therapeutic agent is selected from taxol, bortezomib or both. In some
20 embodiments, the composition is administered orally, intraduodenally, parenterally
(including intravenous, subcutaneous, intramuscular, intravascular or by infusion), topically
or rectally. In further or additional embodiments the amount of compound of formula I is in
the range of about 0.001 to about 1000 mg/kg body weight/day. In further or additional
embodiments the amount of compound of formula I is in the range of about 0.5 to about 50
25 mg/kg/day. In further or additional embodiments the amount of compound of formula I is
about 0.001 to about 7 g/day. In further or additional embodiments the amount of compound
of formula I is about 0.01 to about 7 g/day. In further or additional embodiments the amount
of compound of formula I is about 0.02 to about 5 g/day. In further or additional
embodiments the amount of compound of formula I is about 0.05 to about 2.5 g/day. In
30 further or additional embodiments the amount of compound of formula I is about 0.1 to
about 1 g/day. In further or additional embodiments, dosage levels below the lower limit of
the aforesaid range may be more than adequate. In further or additional embodiments,
dosage levels above the upper limit of the aforesaid range may be required. In further or

additional embodiments the compound of formula I is administered in a single dose, once daily. In further or additional embodiments the compound of formula I is administered in multiple doses, more than once per day. In further or additional embodiments the compound of formula I is administered twice daily. In further or additional embodiments the
5 compound of formula I is administered three times per day. In further or additional embodiments the compound of formula I is administered four times per day. In further or additional embodiments the compound of formula I is administered more than four times per day. In some embodiments, the individual suffering from cancer is a mammal. In further or additional embodiments, the individual is a human. In further or additional embodiments,
10 an effective amount of a composition comprising a pharmaceutically acceptable salt of a compound of formula I is administered.

[00153] In other aspects, the present invention is directed to a method of reducing the size of a tumor, inhibiting tumor size increase, reducing tumor proliferation or preventing tumor proliferation in an individual, comprising administering to said individual an
15 effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof. In some embodiments, the compound or pharmaceutically acceptable salt thereof is administered as a component of a composition that further comprises a pharmaceutically acceptable carrier or vehicle. In some embodiments, the size of a tumor is reduced. In further or additional embodiments, the size of a tumor is reduced by at least 1%. In further
20 or additional embodiments, the size of a tumor is reduced by at least 2%. In further or additional embodiments, the size of a tumor is reduced by at least 3%. In further or additional embodiments, the size of a tumor is reduced by at least 4%. In further or additional embodiments, the size of a tumor is reduced by at least 5%. In further or additional embodiments, the size of a tumor is reduced by at least 10%. In further
25 additional embodiments, the size of a tumor is reduced by at least 20%. In further or additional embodiments, the size of a tumor is reduced by at least 25%. In further or additional embodiments, the size of a tumor is reduced by at least 30%. In further or additional embodiments, the size of a tumor is reduced by at least 40%. In further or additional embodiments, the size of a tumor is reduced by at least 50%. In further
30 additional embodiments, the size of a tumor is reduced by at least 60%. In further or additional embodiments, the size of a tumor is reduced by at least 70%. In further or additional embodiments, the size of a tumor is reduced by at least 75%. In further or additional embodiments, the size of a tumor is reduced by at least 80%. In further or

additional embodiments, the size of a tumor is reduced by at least 85%. In further or additional embodiments, the size of a tumor is reduced by at least 90%. In further or additional embodiments, the size of a tumor is reduced by at least 95%. In further or additional embodiments, the tumor is eradicated. In some embodiments, the size of a tumor

5 does not increase. In some embodiments, tumor proliferation is reduced. In some embodiments, tumor proliferation is reduced by at least 1 %. In some embodiments, tumor proliferation is reduced by at least 2 %. In some embodiments, tumor proliferation is reduced by at least 3 %. In some embodiments, tumor proliferation is reduced by at least 4

10 %. In some embodiments, tumor proliferation is reduced by at least 5 %. In some embodiments, tumor proliferation is reduced by at least 10 %. In some embodiments, tumor proliferation is reduced by at least 20 %. In some embodiments, tumor proliferation is reduced by at least 25 %. In some embodiments, tumor proliferation is reduced by at least 30 %. In some embodiments, tumor proliferation is reduced by at least 40 %. In some

15 embodiments, tumor proliferation is reduced by at least 50 %. In some embodiments, tumor proliferation is reduced by at least 60 %. In some embodiments, tumor proliferation is reduced by at least 70 %. In some embodiments, tumor proliferation is reduced by at least 75 %. In some embodiments, tumor proliferation is reduced by at least 75 %. In some

20 embodiments, tumor proliferation is reduced by at least 80 %. In some embodiments, tumor proliferation is reduced by at least 90 %. In some embodiments, tumor proliferation is reduced by at least 95 %. In some embodiments, tumor proliferation is prevented. In some embodiments, the composition comprising a compound of formula I is administered in combination with an additional therapy. In further or additional embodiments, the additional

25 therapy is radiation therapy, chemotherapy or a combination of both. In further or additional embodiments, the composition comprising a compound of formula I is administered in combination with at least one therapeutic agent. In further or additional embodiments, the therapeutic agent is selected from the group of cytotoxic agents, anti-angiogenesis agents and anti-neoplastic agents. In further or additional embodiments, the anti-neoplastic agent is selected from the group of consisting of alkylating agents, anti-metabolites,

30 epidophyllotoxins; antineoplastic enzymes, topoisomerase inhibitors, procarbazines, mitoxantrones, platinum coordination complexes, biological response modifiers and growth inhibitors, hormonal/anti-hormonal therapeutic agents, and haematopoietic growth factors. In further or additional embodiments, the therapeutic agent is selected from taxol, bortezomib or both. In some embodiments, the composition is administered orally,

intraduodenally, parenterally (including intravenous, subcutaneous, intramuscular, intravascular or by infusion), topically or rectally. In further or additional embodiments the amount of compound of formula I is in the range of about 0.001 to about 1000 mg/kg body weight/day. In further or additional embodiments the amount of compound of formula I is in the range of about 0.5 to about 50 mg/kg/day. In further or additional embodiments the amount of compound of formula I is about 0.001 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.01 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.02 to about 5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.05 to about 2.5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.1 to about 1 g/day. In further or additional embodiments, dosage levels below the lower limit of the aforesaid range may be more than adequate. In further or additional embodiments, dosage levels above the upper limit of the aforesaid range may be required. In further or additional embodiments the compound of formula I is administered in a single dose, once daily. In further or additional embodiments the compound of formula I is administered in multiple doses, more than once per day. In further or additional embodiments the compound of formula I is administered twice daily. In further or additional embodiments the compound of formula I is administered three times per day. In further or additional embodiments the compound of formula I is administered four times per day. In further or additional embodiments the compound of formula I is administered more than four times per day. In some embodiments, the individual suffering from cancer is a mammal. In further or additional embodiments, the individual is a human. In further or additional embodiments, an effective amount of a composition comprising a pharmaceutically acceptable salt of a compound of formula I is administered.

[00154] In other aspects, the present invention is directed to a method for achieving an effect in a patient comprising the administration of an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof, to a patient, wherein the effect is selected from the group consisting of inhibition of various cancers, immunological diseases, and inflammatory diseases. In some embodiments, the compound or pharmaceutically acceptable salt thereof is administered as a component of a composition that further comprises a pharmaceutically acceptable carrier or vehicle. In some embodiments, the effect is inhibition of various cancers. In further or additional embodiments, the effect is inhibition of immunological diseases. In further or additional embodiments, the effect is

inhibition inflammatory diseases. In some embodiments, the composition comprising a compound of formula I is administered in combination with an additional therapy. In further or additional embodiments, the additional therapy is radiation therapy, chemotherapy or a combination of both. In further or additional embodiments, the composition comprising a compound of formula I is administered in combination with at least one therapeutic agent.

In some embodiments, the composition is administered orally, intraduodenally, parenterally (including intravenous, subcutaneous, intramuscular, intravascular or by infusion), topically or rectally. In further or additional embodiments the amount of compound of formula I is in the range of about 0.001 to about 1000 mg/kg body weight/day. In further or additional

embodiments the amount of compound of formula I is in the range of about 0.5 to about 50 mg/kg/day. In further or additional embodiments the amount of compound of formula I is about 0.001 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.01 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.02 to about 5 g/day. In further or additional

embodiments the amount of compound of formula I is about 0.05 to about 2.5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.1 to about 1 g/day. In further or additional embodiments, dosage levels below the lower limit of the aforesaid range may be more than adequate. In further or additional embodiments, dosage levels above the upper limit of the aforesaid range may be required. In further or

additional embodiments the compound of formula I is administered in a single dose, once daily. In further or additional embodiments the compound of formula I is administered in multiple doses, more than once per day. In further or additional embodiments the compound of formula I is administered twice daily. In further or additional embodiments the compound of formula I is administered three times per day. In further or additional

embodiments the compound of formula I is administered four times per day. In further or additional embodiments the compound of formula I is administered more than four times per day. In some embodiments, the individual suffering from cancer is a mammal. In further or additional embodiments, the individual is a human. In further or additional embodiments, an effective amount of a composition comprising a pharmaceutically acceptable salt of a compound of formula I is administered.

[00155] Compounds of formula I, and pharmaceutically acceptable salts, thereof, may modulate the activity of MEK enzymes; and, as such, are useful for treating diseases or

conditions in which aberrant MEK enzyme activity contributes to the pathology and/or symptoms of a disease or condition.

[00156] The tables below show examples of individual compounds provided or contemplated by this invention. These examples should in no way be construed as limiting.

5 [00157] Table 1 shows embodiments of this invention which are compounds of formula I, wherein G is R_{1a} where R_{1a} is as defined in the table and X, Y and Z are defined in the table.

Table 1

R_{1a}	X	Y	Z
CH ₃	F	I	F
CH ₃	Cl	I	F
CH ₃	F	Br	F
CH ₃	Cl	Br	F
CH ₃	F	CH ₃	F
CH ₃	Cl	CH ₃	F
CH ₃	F	CF ₃	F
CH ₃	Cl	CF ₃	F
CH ₃	F	C≡CH	F
CH ₃	Cl	C≡CH	F
CH ₃	F	SCH ₃	F
CH ₃	Cl	SCH ₃	F
CH ₃	F	(CH ₂) ₂ CH ₃	F
CH ₃	Cl	(CH ₂) ₂ CH ₃	F
CH ₃	F	CH ₂ CH ₃	F
CH ₃	Cl	CH ₂ CH ₃	F
CH ₃	F	CH ₂ OH	F
CH ₃	Cl	CH ₂ OH	F
CH ₃	F	▷	F
CH ₃	Cl	▷	F
CH ₃	CH ₃	CH=CH ₂	F
CH ₃	CH ₃	C≡CH	F
CH ₃	CH ₃	SCH ₃	F
CH ₂ F	F	I	F
CH ₂ F	Cl	I	F
CH ₂ F	F	Br	F
CH ₂ F	Cl	Br	F
CH ₂ F	F	CH ₃	F
CH ₂ F	Cl	CH ₃	F
CH ₂ F	F	CF ₃	F
CH ₂ F	Cl	CF ₃	F
CF ₃	F	I	F

R _{1a}	X	Y	Z
CF ₃	Cl	I	F
CF ₃	F	Br	F
CF ₃	Cl	Br	F
CF ₃	F	CH ₃	F
CF ₃	Cl	CH ₃	F
CF ₃	F	CF ₃	F
CF ₃	Cl	CF ₃	F
CH ₂ Cl	F	I	F
CH ₂ Cl	Cl	I	F
CH ₂ Cl	F	Br	F
CH ₂ Cl	Cl	Br	F
CH ₂ Cl	F	CH ₃	F
CH ₂ Cl	Cl	CH ₃	F
CH ₂ Cl	F	CF ₃	F
CH ₂ Cl	Cl	CF ₃	F
CHCl ₂	F	I	F
CHCl ₂	Cl	I	F
CHCl ₂	F	Br	F
CHCl ₂	Cl	Br	F
CHCl ₂	F	CH ₃	F
CHCl ₂	Cl	CH ₃	F
CHCl ₂	F	CF ₃	F
CHCl ₂	Cl	CF ₃	F
CCl ₃	F	I	F
CCl ₃	Cl	I	F
CCl ₃	F	Br	F
CCl ₃	Cl	Br	F
CCl ₃	F	CH ₃	F
CCl ₃	Cl	CH ₃	F
CCl ₃	F	CF ₃	F
CCl ₃	Cl	CF ₃	F
CH ₂ OH	F	I	F
CH ₂ OH	Cl	I	F
CH ₂ OH	F	Br	F
CH ₂ OH	Cl	Br	F
CH ₂ OH	F	CH ₃	F
CH ₂ OH	Cl	CH ₃	F
CH ₂ OH	F	CF ₃	F
CH ₂ OH	Cl	CF ₃	F
CH ₂ OMe	F	I	F
CH ₂ OMe	Cl	I	F
CH ₂ OMe	F	Br	F

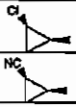
R _{1a}	X	Y	Z
CH ₂ OMe	Cl	Br	F
CH ₂ OMe	F	CH ₃	F
CH ₂ OMe	Cl	CH ₃	F
CH ₂ OMe	F	CF ₃	F
CH ₂ OMe	Cl	CF ₃	F
CH ₂ OMe	F	C≡CH	F
CH ₂ OMe	Cl	SCH ₃	F
CH ₂ OMe	CH ₃	CF ₃	F
CH ₂ OMe	CH ₃	C≡CH	F
CH ₂ OEt	F	I	F
CH ₂ OEt	Cl	I	F
CH ₂ OEt	F	Br	F
CH ₂ OEt	Cl	Br	F
CH ₂ OEt	F	CH ₃	F
CH ₂ OEt	Cl	CH ₃	F
CH ₂ OEt	F	CF ₃	F
CH ₂ OEt	Cl	CF ₃	F
CH ₂ O-◁	F	I	F
CH ₂ O-◁	Cl	I	F
CH ₂ O-◁	F	Br	F
CH ₂ O-◁	Cl	Br	F
CH ₂ O-◁	F	CH ₃	F
CH ₂ O-◁	Cl	CH ₃	F
CH ₂ O-◁	F	CF ₃	F
CH ₂ O-◁	Cl	CF ₃	F
CH ₂ O-◁	F	I	F
CH ₂ O-◁	Cl	I	F
CH ₂ O-◁	F	Br	F
CH ₂ O-◁	Cl	Br	F
CH ₂ O-◁	F	CH ₃	F
CH ₂ O-◁	Cl	CH ₃	F
CH ₂ O-◁	F	CF ₃	F
CH ₂ O-◁	Cl	CF ₃	F
CH ₂ O-◁	F	I	F
CH ₂ O-◁	Cl	I	F
CH ₂ O-◁	F	Br	F
CH ₂ O-◁	Cl	Br	F
CH ₂ O-◁	F	CH ₃	F
CH ₂ O-◁	Cl	CH ₃	F
CH ₂ O-◁	F	CF ₃	F
CH ₂ O-◁	Cl	CF ₃	F
CH ₂ O-◁	F	I	F
CH ₂ O-◁	Cl	I	F
CH ₂ O-◁	F	Br	F
CH ₂ O-◁	Cl	Br	F
CH ₂ O-◁	F	CH ₃	F
CH ₂ O-◁	Cl	CH ₃	F
CH ₂ O-◁	F	CF ₃	F
CH ₂ O-◁	Cl	CF ₃	F
CH ₂ O-◁	F	I	F

R _{1a}	X	Y	Z
	Cl	I	F
	F	Br	F
	Cl	Br	F
	F	CH ₃	F
	Cl	CH ₃	F
	F	CF ₃	F
	Cl	CF ₃	F
	F	I	F
	Cl	I	F
	F	Br	F
	Cl	Br	F
	F	CH ₃	F
	Cl	CH ₃	F
	F	CF ₃	F
	Cl	CF ₃	F
CH ₃	F	phenyl	F
CH ₃	Cl	phenyl	F
CH ₃	CH ₃	phenyl	
CH ₃	F	3-pyridyl	F
CH ₃	Cl	3-pyridyl	F
CH ₃	CH ₃	4-pyridyl	
CH ₃	F	pyrazolyl	F
CH ₃	Cl	pyrazolyl	F
CH ₃	F	4-pyridyl	F
CH ₃	Cl	4-pyridyl	F
CH ₃	CH ₃	2-(CH ₃ -SO ₂ -NH)-phenyl	F
CH ₃	CH ₃	3-(CH ₃ -SO ₂ -NH)-phenyl	F
CH ₃	Cl	3-(CH ₃ -SO ₂ -NH)-phenyl	F
CH ₃	F	3-(CH ₃ -SO ₂ -NH)-phenyl	F

[00158] Table 2 shows embodiments of this invention which are compounds of formula I, wherein G is R_{1b} where R_{1b} is as defined in the table and X, Y and Z are defined in the table.

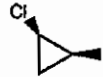
5

Table 2

R _{1b}	X	Y	Z
▷	F	I	F
▷	Cl	I	F
▷	F	Br	F
▷	Cl	Br	F
▷	F	CH ₃	F
▷	Cl	CH ₃	F
▷	F	CF ₃	F
▷	Cl	CF ₃	F
▷	F	C≡CH	F
▷	Cl	C≡CH	F
▷	F	SCH ₃	F
▷	Cl	SCH ₃	F
▷	F	CH ₂ OH	F
▷	Cl	CH ₂ OH	F
▷	F	(CH ₂) ₃ OH	F
▷	Cl	(CH ₂) ₃ OH	F
▷	F	(CH ₂) ₂ CH ₃	F
▷	Cl	(CH ₂) ₂ CH ₃	F
▷	F	CH ₂ CH ₃	F
▷	Cl	CH ₂ CH ₃	F
▷	F	(CH ₂) ₂ CH ₃	F
▷	Cl	(CH ₂) ₂ CH ₃	F
▷	CH ₃	I	F
▷	CH ₃	Br	F
▷	CH ₃	CH ₃	F
▷	CH ₃	CF ₃	F
▷	CH ₃	CH ₂ CH ₃	F
▷	CH ₃	(CH ₂) ₂ CH ₃	F
▷	CH ₃	C≡CH	F
▷	CH ₃	SCH ₃	F
▷	CH ₃	(CH ₂) ₂ CH ₃	F
	CH ₃	I	F
▷	F	CH=CH ₂	F
▷	Cl	CH=CH ₂	F

R _{1b}	X	Y	Z
	CH ₃	CH=CH ₂	F
	F		F
	F	OCH ₃	F
	Cl	(CH ₂) ₂ CH ₂ OH	F
	F	I	F
	Cl	I	F
	F	Br	F
	Cl	Br	F
	F	CH ₃	F
	Cl	CH ₃	F
	F	CF ₃	F
	Cl	CF ₃	F
	F	I	F
	Cl	I	F
	F	Br	F
	Cl	Br	F
	F	CH ₃	F
	Cl	CH ₃	F
	F	CF ₃	F
	Cl	CF ₃	F
	Cl		F
	F	(CH ₂) ₂ CH ₃	F
	Cl	C≡CH	F
	CH ₃	SCH ₃	F
	Cl	CF ₃	F
	CH ₃	CH ₃	F
	F	CH ₂ OH	F
	Cl	(CH ₂) ₃ OH	F
	F	OCH ₂ CH ₃	F
	F	I	F
	Cl	I	F
	F	Br	F

R _{1b}	X	Y	Z
	Cl	Br	F
	F	CH ₃	F
	Cl	CH ₃	F
	F	CF ₃	F
	Cl	CF ₃	F
	F	phenyl	F
	Cl	phenyl	F
	F	3-pyridyl	F
	Cl	3-pyridyl	F
	F	pyrazol-4-yl	F
	Cl	pyrazol-4-yl	F
	F	4-pyridyl	F
	Cl	4-pyridyl	F
	F	1-methyl-pyrazol-4-yl	F
	Cl	1-methyl-pyrazol-4-yl	F
	F	pyrazol-3-yl	F
	Cl	pyrazol-3-yl	F
	F	2-(CH ₃ -SO ₂ -NH)-phenyl	F
	Cl	2-(CH ₃ -SO ₂ -NH)-phenyl	F
	F	3-(CH ₃ -SO ₂ -NH)-phenyl	F
	Cl	3-(CH ₃ -SO ₂ -NH)-phenyl	F
	CH ₃	2-(CH ₃ -SO ₂ -NH)-phenyl	F
	CH ₃	3-(CH ₃ -SO ₂ -NH)-phenyl	F
	F	4-CF ₃ O-phenyl	F
	Cl	4-CF ₃ O-phenyl	F
	CH ₃	4-CF ₃ O-phenyl	F

R_{1b}	X	Y	Z
	Cl	2-(CH ₃ -SO ₂ -NH)-phenyl	F
	F	phenyl	F
		phenyl	
	Cl	3-pyridyl	F
	F	3-pyridyl	F
	Cl	pyrazol-4-yl	F
	F	pyrazol-4-yl	F
	Cl	4-pyridyl	F
	F	4-pyridyl	F
	Cl	1-methyl-pyrazol-4-yl	F
	CH ₃	1-methyl-pyrazol-4-yl	F
	F	pyrazol-3-yl	F
	Cl	pyrazol-3-yl	F
	F	2-(CH ₃ -SO ₂ -NH)-phenyl	F
	Cl	2-(CH ₃ -SO ₂ -NH)-phenyl	F
	F	phenyl	F
	Cl	phenyl	F
	F	3-pyridyl	F
	Cl	3-pyridyl	F
	Cl	pyrazol-3-yl	F

[00159] Table 3 shows embodiments of this invention which are compounds of formula I, wherein G is R_{1c} where R_{1c} is as defined in the table and X, Y and Z are defined in the table.

5

Table 3

R_{1c}	X	Y	Z
CH ₂ CH ₃	F	I	F
CH ₂ CH ₃	Cl	I	F
CH ₂ CH ₃	F	Br	F
CH ₂ CH ₃	Cl	Br	F
CH ₂ CH ₃	F	CH ₃	F

R _{1c}	X	Y	Z
CH ₂ CH ₃	Cl	CH ₃	F
CH ₂ CH ₃	F	CF ₃	F
CH ₂ CH ₃	Cl	CF ₃	F
CH ₂ CH ₃	CH ₃	CH ₃	F
CH ₂ CH ₃	CH ₃	CH ₃	F
CH ₂ CH ₃	CH ₃	C≡CH	F
CH ₂ CH ₃	CH ₃	SCH ₃	F
CH ₂ CH ₃	F	C≡CH	F
CH ₂ CH ₃	Cl	SCH ₃	F
CH ₂ CH ₃	F	▷	F
CH ₂ CH ₃	Cl	▷	F
CH ₂ CH ₃	CH ₃	▷	F
CH(CH ₃) ₂	F	OCH ₃	F
CH(CH ₃) ₂	Cl	OCH ₃	F
CH(CH ₃) ₂	F	I	F
CH(CH ₃) ₂	Cl	I	F
CH(CH ₃) ₂	F	Br	F
CH(CH ₃) ₂	Cl	Br	F
CH(CH ₃) ₂	F	CH ₃	F
CH(CH ₃) ₂	Cl	CH ₃	F
CH(CH ₃) ₂	F	CH ₂ CH ₃	F
CH(CH ₃) ₂	Cl	CH ₂ CH ₃	F
CH(CH ₃) ₂	CH ₃	CH ₂ CH ₃	F
CH(CH ₃) ₂	Cl	CH ₂ CH ₃	F
CH(CH ₃) ₂	Cl	CH(CH ₃) ₂	F
CH(CH ₃) ₂	Cl	CH(CH ₃) ₂	F
CH(CH ₃) ₂	F	CF ₃	F
CH(CH ₃) ₂	Cl	CH ₃	F
CH(CH ₃) ₂	CH ₃	Br	F
CH(CH ₃) ₂	CH ₃	C≡CH	F
CH(CH ₃) ₂	CH ₃	SCH ₃	F
CH(CH ₃) ₂	CH ₃	▷	F
CH(CH ₃) ₂	F	CH ₂ OH	F
CH(CH ₃) ₂	Cl		F
<i>n</i> -butyl	F	I	F
<i>n</i> -butyl	Cl	I	F
<i>n</i> -butyl	F	Br	F
<i>n</i> -butyl	Cl	Br	F
<i>n</i> -butyl	F	CH ₃	F
<i>n</i> -butyl	Cl	CH ₃	F
<i>n</i> -butyl	F	OCH ₃	F

R _{1c}	X	Y	Z
<i>n</i> -butyl	Cl	OCH ₃	F
<i>n</i> -butyl	CH ₃	OCH ₃	F
<i>n</i> -butyl	Cl	OCH ₂ CH ₃	F
<i>n</i> -butyl	F	OCH ₂ CH ₃	F
<i>n</i> -butyl	CH ₃	OCH ₂ CH ₃	F
<i>n</i> -butyl	F	OCH ₂ CH ₂ O H	F
<i>n</i> -butyl	F	CF ₃	F
<i>n</i> -butyl	Cl	CF ₃	F
<i>sec</i> -butyl	F	I	F
<i>sec</i> -butyl	Cl	I	F
<i>sec</i> -butyl	F	Br	F
<i>sec</i> -butyl	Cl	Br	F
<i>sec</i> -butyl	F	CH ₃	F
<i>sec</i> -butyl	Cl	CH ₃	F
<i>sec</i> -butyl	F	CF ₃	F
<i>sec</i> -butyl	Cl	CF ₃	F
CH ₂ CF ₃	F	I	F
CH ₂ CF ₃	Cl	I	F
CH ₂ CF ₃	F	Br	F
CH ₂ CF ₃	Cl	Br	F
CH ₂ CF ₃	F	CH ₃	F
CH ₂ CF ₃	Cl	CH ₃	F
CH ₂ CF ₃	F	CF ₃	F
CH ₂ CF ₃	Cl	CF ₃	F
CH ₂ CCl ₃	F	I	F
CH ₂ CCl ₃	Cl	I	F
CH ₂ CCl ₃	F	Br	F
CH ₂ CCl ₃	Cl	Br	F
CH ₂ CCl ₃	F	CH ₃	F
CH ₂ CCl ₃	Cl	CH ₃	F
CH ₂ CCl ₃	F	CF ₃	F
CH ₂ CCl ₃	Cl	CF ₃	F
CH ₂ -◻	F	I	F
CH ₂ -◻	Cl	I	F
CH ₂ -◻	F	Br	F
CH ₂ -◻	Cl	Br	F
CH ₂ -◻	F	CH ₃	F
CH ₂ -◻	Cl	CH ₃	F
CH ₂ -◻	F	CF ₃	F
CH ₂ -◻	Cl	CF ₃	F
CH ₂ CH ₂ F	F	I	F

R _{1c}	X	Y	Z
CH ₂ CH ₂ F	Cl	I	F
CH ₂ CH ₂ F	F	Br	F
CH ₂ CH ₂ F	Cl	Br	F
CH ₂ CH ₂ F	F	CH ₃	F
CH ₂ CH ₂ F	Cl	CH ₃	F
CH ₂ CH ₂ F	F	CF ₃	F
CH ₂ CH ₂ F	Cl	CF ₃	F
CH ₂ CH ₂ Cl	F	I	F
CH ₂ CH ₂ Cl	Cl	I	F
CH ₂ CH ₂ Cl	F	Br	F
CH ₂ CH ₂ Cl	Cl	Br	F
CH ₂ CH ₂ Cl	F	CH ₃	F
CH ₂ CH ₂ Cl	Cl	CH ₃	F
CH ₂ CH ₂ Cl	F	CF ₃	F
CH ₂ CH ₂ Cl	Cl	CF ₃	F
CH ₂ CH ₂ CH ₂ Cl	F	I	F
CH ₂ CH ₂ CH ₂ Cl	Cl	I	F
CH ₂ CH ₂ CH ₂ Cl	F	Br	F
CH ₂ CH ₂ CH ₂ Cl	Cl	Br	F
CH ₂ CH ₂ CH ₂ Cl	F	CH ₃	F
CH ₂ CH ₂ CH ₂ Cl	Cl	CH ₃	F
CH ₂ CH ₂ CH ₂ Cl	F	CF ₃	F
CH ₂ CH ₂ CH ₂ Cl	Cl	CF ₃	F
CH ₂ CH ₂ OH	F	I	F
CH ₂ CH ₂ OH	Cl	I	F
CH ₂ CH ₂ OH	F	Br	F
CH ₂ CH ₂ OH	Cl	Br	F
CH ₂ CH ₂ OH	F	CH ₃	F
CH ₂ CH ₂ OH	Cl	CH ₃	F
CH ₂ CH ₂ OH	F	CF ₃	F
CH ₂ CH ₂ OH	Cl	CF ₃	F
CH ₂ CH ₂ CH ₂ O H	F	I	F
CH ₂ CH ₂ CH ₂ O H	Cl	I	F
CH ₂ CH ₂ CH ₂ O H	F	Br	F
CH ₂ CH ₂ CH ₂ O H	Cl	Br	F
CH ₂ CH ₂ CH ₂ O H	F	CH ₃	F
CH ₂ CH ₂ CH ₂ O H	Cl	CH ₃	F

R_{16}	X	Y	Z
$\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$ H	F	CF_3	F
$\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$ H	Cl	CF_3	F
$(\text{CH}_2)_4\text{OH}$	F	I	F
$(\text{CH}_2)_4\text{OH}$	Cl	I	F
$(\text{CH}_2)_4\text{OH}$	F	Br	F
$(\text{CH}_2)_4\text{OH}$	Cl	Br	F
$(\text{CH}_2)_4\text{OH}$	F	CH_3	F
$(\text{CH}_2)_4\text{OH}$	Cl	CH_3	F
$(\text{CH}_2)_4\text{OH}$	F	CF_3	F
$(\text{CH}_2)_4\text{OH}$	Cl	CF_3	F
$\text{CH}_2\text{CH}_2\text{OCH}_3$	F	I	F
$\text{CH}_2\text{CH}_2\text{OCH}_3$	Cl	I	F
$\text{CH}_2\text{CH}_2\text{OCH}_3$	F	Br	F
$\text{CH}_2\text{CH}_2\text{OCH}_3$	Cl	Br	F
$\text{CH}_2\text{CH}_2\text{OCH}_3$	F	CH_3	F
$\text{CH}_2\text{CH}_2\text{OCH}_3$	Cl	CH_3	F
$\text{CH}_2\text{CH}_2\text{OCH}_3$	F	CF_3	F
$\text{CH}_2\text{CH}_2\text{OCH}_3$	Cl	CF_3	F
$(\text{CH}_2)_3\text{OCH}_3$	F	I	F
$(\text{CH}_2)_3\text{OCH}_3$	Cl	I	F
$(\text{CH}_2)_3\text{OCH}_3$	F	Br	F
$(\text{CH}_2)_3\text{OCH}_3$	Cl	Br	F
$(\text{CH}_2)_3\text{OCH}_3$	F	CH_3	F
$(\text{CH}_2)_3\text{OCH}_3$	Cl	CH_3	F
$(\text{CH}_2)_3\text{OCH}_3$	F	CF_3	F
$(\text{CH}_2)_3\text{OCH}_3$	Cl	CF_3	F
$\text{CH}_2\text{CH}_2\text{OEt}$	F	I	F
$\text{CH}_2\text{CH}_2\text{OEt}$	Cl	I	F
$\text{CH}_2\text{CH}_2\text{OEt}$	F	Br	F
$\text{CH}_2\text{CH}_2\text{OEt}$	Cl	Br	F
$\text{CH}_2\text{CH}_2\text{OEt}$	F	CH_3	F
$\text{CH}_2\text{CH}_2\text{OEt}$	Cl	CH_3	F
$\text{CH}_2\text{CH}_2\text{OEt}$	F	CF_3	F
$\text{CH}_2\text{CH}_2\text{OEt}$	Cl	CF_3	F
$\text{CH}_2\text{CH}_2\text{O}-\text{<}$	F	I	F
$\text{CH}_2\text{CH}_2\text{O}-\text{<}$	Cl	I	F
$\text{CH}_2\text{CH}_2\text{O}-\text{<}$	F	Br	F
$\text{CH}_2\text{CH}_2\text{O}-\text{<}$	Cl	Br	F
$\text{CH}_2\text{CH}_2\text{O}-\text{<}$	F	CH_3	F
$\text{CH}_2\text{CH}_2\text{O}-\text{<}$	Cl	CH_3	F

R _{1c}	X	Y	Z
CH ₂ CH ₂ O- 	F	CF ₃	F
CH ₂ CH ₂ O- 	Cl	CF ₃	F
CH ₂ CH ₂ O- 	F	I	F
CH ₂ CH ₂ O- 	Cl	I	F
CH ₂ CH ₂ O- 	F	Br	F
CH ₂ CH ₂ O- 	Cl	Br	F
CH ₂ CH ₂ O- 	F	CH ₃	F
CH ₂ CH ₂ O- 	Cl	CH ₃	F
CH ₂ CH ₂ O- 	F	CF ₃	F
CH ₂ CH ₂ O- 	Cl	CF ₃	F
CH ₂ CH ₂ CH ₂ O Et	F	I	F
CH ₂ CH ₂ CH ₂ O Et	Cl	I	F
CH ₂ CH ₂ CH ₂ O Et	F	Br	F
CH ₂ CH ₂ CH ₂ O Et	Cl	Br	F
CH ₂ CH ₂ CH ₂ O Et	F	CH ₃	F
CH ₂ CH ₂ CH ₂ O Et	Cl	CH ₃	F
CH ₂ CH ₂ CH ₂ O Et	F	CF ₃	F
CH ₂ CH ₂ CH ₂ O Et	Cl	CF ₃	F
CH ₂ CH ₂ CH ₂ O- 	F	I	F
CH ₂ CH ₂ CH ₂ O- 	Cl	I	F
CH ₂ CH ₂ CH ₂ O- 	F	Br	F
CH ₂ CH ₂ CH ₂ O- 	Cl	Br	F
CH ₂ CH ₂ CH ₂ O- 	F	CH ₃	F
CH ₂ CH ₂ CH ₂ O- 	Cl	CH ₃	F
CH ₂ CH ₂ CH ₂ O- 	F	CF ₃	F
CH ₂ CH ₂ CH ₂ O- 	Cl	CF ₃	F
CH ₂ CH ₂ CH ₂ O- 	F	I	F
CH ₂ CH ₂ CH ₂ O- 	Cl	I	F
CH ₂ CH ₂ CH ₂ O- 	F	Br	F
CH ₂ CH ₂ CH ₂ O- 	Cl	Br	F
CH ₂ CH ₂ CH ₂ O- 	F	CH ₃	F
CH ₂ CH ₂ CH ₂ O- 	Cl	CH ₃	F
CH ₂ CH ₂ CH ₂ O- 	F	CF ₃	F

R_{1c}	X	Y	Z
<chem>CH3CH2CH2O</chem> 	Cl	CF ₃	F
<chem>CH3CH2O</chem> 	F	I	F
<chem>CH3CH2O</chem> 	Cl	I	F
<chem>CH3CH2O</chem> 	F	Br	F
<chem>CH3CH2O</chem> 	Cl	Br	F
<chem>CH3CH2O</chem> 	F	CH ₃	F
<chem>CH3CH2O</chem> 	Cl	CH ₃	F
<chem>CH3CH2O</chem> 	F	CF ₃	F
<chem>CH3CH2O</chem> 	Cl	CF ₃	F
	F	I	F
	Cl	I	F
	F	Br	F
	Cl	Br	F
	F	CH ₃	F
	Cl	CH ₃	F
	F	CF ₃	F
	Cl	CF ₃	F
	F	I	F
	Cl	I	F
	CH ₃	I	F
	F	Br	F
	Cl	Br	F
	CH ₃	Br	F
	F	CH ₃	F
	Cl	CH ₃	F
	CH ₃	CH ₃	F
	F	C≡CH	F
	F	SCH ₃	F
	F	CH ₂ CH ₂ CH ₃	F
	Cl	CH ₂ CH(OH) CH ₃	F

R _{1c}	X	Y	Z
	F	CH(CH ₃) ₂	F
	Cl	CF ₃	F
CH ₂ CH ₃	F	phenyl	F
CH ₂ CH ₃	Cl	phenyl	F
CH ₂ CH ₃	F	phenyl	F
CH ₂ CH ₃	Cl	3-pyridyl	F
CH ₂ CH ₃	F	3-pyridyl	F
CH ₂ CH ₃	Cl	4-pyridyl	F
CH ₂ CH ₃	F	pyrazolyl	F
CH ₂ CH ₃	Cl	pyrazolyl	F
CH ₂ CH ₃	CH ₃	4-pyridyl	F
CH ₂ CH ₃	CH ₃	4-pyridyl	F
CH ₂ CH ₃	CH ₃	2-(CH ₃ -SO ₂ -NH)-phenyl	F
CH ₂ CH ₃	CH ₃	3-(CH ₃ -SO ₂ -NH)-phenyl	F
CH ₂ CH ₃	F	3-(CH ₃ -SO ₂ -NH)-phenyl	F
CH ₂ CH ₃	Cl	3-(CH ₃ -SO ₂ -NH)-phenyl	F
CH ₂ CH ₃	F	phenyl	F
CH ₂ CH ₃	Cl	phenyl	F
CH ₂ CH ₃	CH ₃	phenyl	F
		3-pyridyl	
CH(CH ₃) ₂	F	3-pyridyl	F
CH(CH ₃) ₂	Cl	4-pyridyl	F
CH(CH ₃) ₂	F	pyrazolyl	F
CH(CH ₃) ₂	Cl	pyrazolyl	F
CH(CH ₃) ₂	F	4-pyridyl	F
CH(CH ₃) ₂	Cl	4-pyridyl	F
CH(CH ₃) ₂	F	2-(CH ₃ -SO ₂ -NH)-phenyl	F
CH(CH ₃) ₂	Cl	3-(CH ₃ -SO ₂ -NH)-phenyl	F

R _{1c}	X	Y	Z
CH(CH ₃) ₂	F	3-(CH ₃ -SO ₂ -NH)-phenyl	F
CH(CH ₃) ₂	Cl	3-(CH ₃ -SO ₂ -NH)-phenyl	F
CH(CH ₃) ₂	CH ₃	phenyl	F
CH(CH ₃) ₂	Cl	phenyl	F
CH(CH ₃) ₂	Fl	phenyl	F
CH(CH ₃) ₂	Cl	3-pyridyl	F
		3-pyridyl	
CH(CH ₃) ₂	F	4-pyridyl	F
CH(CH ₃) ₂	Cl	pyrazolyl	F
CH(CH ₃) ₂	CH ₃	pyrazolyl	F
CH(CH ₃) ₂	CH ₃	4-pyridyl	F
CH(CH ₃) ₂	CH ₃	4-pyridyl	F
CH(CH ₃) ₂	CH ₃	2-(CH ₃ -SO ₂ -NH)-phenyl	F
CH(CH ₃) ₂	F	3-(CH ₃ -SO ₂ -NH)-phenyl	F
CH(CH ₃) ₂	Cl	3-(CH ₃ -SO ₂ -NH)-phenyl	F
		3-(CH ₃ -SO ₂ -NH)-phenyl	
<i>n</i> -butyl	F	phenyl	F
<i>n</i> -butyl	Cl	phenyl	F
<i>n</i> -butyl	F	phenyl	F
<i>n</i> -butyl	Cl	3-pyridyl	F
<i>n</i> -butyl	F	3-pyridyl	F
<i>n</i> -butyl	Cl	4-pyridyl	F
<i>n</i> -butyl	F	pyrazolyl	F
<i>n</i> -butyl	Cl	pyrazolyl	F
<i>n</i> -butyl	CH ₃	4-pyridyl	F
<i>n</i> -butyl	Cl	4-pyridyl	F
<i>n</i> -butyl	F	2-(CH ₃ -SO ₂ -NH)-phenyl	F

R _{1c}	X	Y	Z
<i>n</i> -butyl	CH ₃	3-(CH ₃ -SO ₂ -NH)-phenyl	F
<i>n</i> -butyl	F	3-(CH ₃ -SO ₂ -NH)-phenyl	F
		3-(CH ₃ -SO ₂ -NH)-phenyl	
<i>n</i> -butyl	F	phenyl	F
<i>n</i> -butyl	Cl	phenyl	F
		phenyl	
<i>sec</i> -butyl	F	3-pyridyl	F
<i>sec</i> -butyl	Cl	3-pyridyl	F
<i>sec</i> -butyl	F	4-pyridyl	F
<i>sec</i> -butyl	Cl	pyrazolyl	F
<i>sec</i> -butyl	F	pyrazolyl	F
<i>sec</i> -butyl	Cl	4-pyridyl	F
<i>sec</i> -butyl	F	4-pyridyl	F
<i>sec</i> -butyl	Cl	CF ₃	F
CH ₂ CF ₃	F	phenyl	F
CH ₂ CF ₃	Cl	phenyl	F
CH ₂ CF ₃	F	phenyl	F
CH ₂ CF ₃	Cl	3-pyridyl	F
CH ₂ CF ₃	F	3-pyridyl	F
CH ₂ CF ₃	Cl	4-pyridyl	F
CH ₂ CF ₃	F	pyrazolyl	F
CH ₂ CF ₃	Cl	pyrazolyl	F
		4-pyridyl	
CH ₂ CCl ₃	F	4-pyridyl	F
CH ₂ CCl ₃	Cl	2-(CH ₃ -SO ₂ -NH)-phenyl	F
CH ₂ CCl ₃	F	3-(CH ₃ -SO ₂ -NH)-phenyl	F
CH ₂ CCl ₃	Cl	3-(CH ₃ -SO ₂ -NH)-phenyl	F
CH ₂ CCl ₃	F	3-(CH ₃ -SO ₂ -NH)-phenyl	F
CH ₂ CCl ₃	Cl	phenyl	F
CH ₂ CCl ₃	F	phenyl	F

R _{1c}	X	Y	Z
CH ₂ CCl ₃	Cl	phenyl	F
		3-pyridyl	
CH ₂ -◁	F	3-pyridyl	F
CH ₂ -◁	Cl	4-pyridyl	F
CH ₂ -◁	F	pyrazolyl	F
CH ₂ -◁	Cl	pyrazolyl	F
CH ₂ -◁	F	4-pyridyl	F
CH ₂ -◁	Cl	4-pyridyl	F
CH ₂ -◁	F	2-(CH ₃ -SO ₂ -NH)-phenyl	F
CH ₂ -◁	Cl	3-(CH ₃ -SO ₂ -NH)-phenyl	F
		3-(CH ₃ -SO ₂ -NH)-phenyl	
CH ₂ CH ₂ F	F	3-(CH ₃ -SO ₂ -NH)-phenyl	F
CH ₂ CH ₂ F	Cl	phenyl	F
CH ₂ CH ₂ F	F	phenyl	F
CH ₂ CH ₂ F	Cl	phenyl	F
CH ₂ CH ₂ F	F	3-pyridyl	F
CH ₂ CH ₂ F	Cl	3-pyridyl	F
CH ₂ CH ₂ F	F	4-pyridyl	F
CH ₂ CH ₂ F	Cl	pyrazolyl	F
		pyrazolyl	
CH ₂ CH ₂ Cl	F	4-pyridyl	F
CH ₂ CH ₂ Cl	Cl	4-pyridyl	F
CH ₂ CH ₂ Cl	F	2-(CH ₃ -SO ₂ -NH)-phenyl	F
CH ₂ CH ₂ Cl	Cl	3-(CH ₃ -SO ₂ -NH)-phenyl	F
CH ₂ CH ₂ Cl	F	3-(CH ₃ -SO ₂ -NH)-phenyl	F
CH ₂ CH ₂ Cl	Cl	3-(CH ₃ -SO ₂ -NH)-phenyl	F
CH ₂ CH ₂ Cl	F	phenyl	F
CH ₂ CH ₂ Cl	Cl	phenyl	F

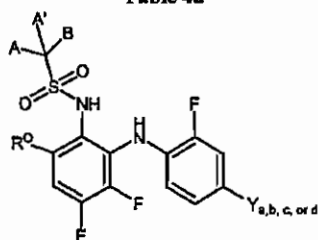
R _{1c}	X	Y	Z
		phenyl	
CH ₂ CH ₂ CH ₂ Cl	F	3-pyridyl	F
CH ₂ CH ₂ CH ₂ Cl	Cl	3-pyridyl	F
CH ₂ CH ₂ CH ₂ Cl	F	4-pyridyl	F
CH ₂ CH ₂ CH ₂ Cl	Cl	pyrazolyl	F
CH ₂ CH ₂ CH ₂ Cl	F	pyrazolyl	F
CH ₂ CH ₂ CH ₂ Cl	Cl	4-pyridyl	F
CH ₂ CH ₂ CH ₂ Cl	F	4-pyridyl	F
CH ₂ CH ₂ CH ₂ Cl	Cl	2-(CH ₃ -SO ₂ -NH)-phenyl	F
		3-(CH ₃ -SO ₂ -NH)-phenyl	
CH ₂ CH ₂ OH	F	3-(CH ₃ -SO ₂ -NH)-phenyl	F
CH ₂ CH ₂ OH	Cl	3-(CH ₃ -SO ₂ -NH)-phenyl	F
CH ₂ CH ₂ OH	F	phenyl	F
CH ₂ CH ₂ OH	Cl	phenyl	F
CH ₂ CH ₂ OH	F	phenyl	F
CH ₂ CH ₂ OH	Cl	3-pyridyl	F
CH ₂ CH ₂ OH	F	3-pyridyl	F
CH ₂ CH ₂ OH	Cl	4-pyridyl	F
		pyrazolyl	
CH ₂ CH ₂ CH ₂ O H	F	pyrazolyl	F
CH ₂ CH ₂ CH ₂ O H	Cl	4-pyridyl	F
CH ₂ CH ₂ CH ₂ O H	F	4-pyridyl	F
CH ₂ CH ₂ CH ₂ O H	Cl	2-(CH ₃ -SO ₂ -NH)-phenyl	F

R _{1c}	X	Y	Z
CH ₂ CH ₂ CH ₂ O H	F	3-(CH ₃ - SO ₂ -NH)- phenyl	F
CH ₂ CH ₂ CH ₂ O H	Cl	3-(CH ₃ - SO ₂ -NH)- phenyl	F
CH ₂ CH ₂ CH ₂ O H	F	3-(CH ₃ - SO ₂ -NH)- phenyl	F
CH ₂ CH ₂ CH ₂ O H	Cl	phenyl	F
		phenyl	
(CH ₂) ₄ OH	F	phenyl	F
(CH ₂) ₄ OH	Cl	3-pyridyl	F
(CH ₂) ₄ OH	F	3-pyridyl	F
(CH ₂) ₄ OH	Cl	4-pyridyl	F
(CH ₂) ₄ OH	F	pyrazolyl	F
(CH ₂) ₄ OH	Cl	pyrazolyl	F
(CH ₂) ₄ OH	F	4-pyridyl	F
(CH ₂) ₄ OH	Cl	4-pyridyl	F
		2-(CH ₃ - SO ₂ -NH)- phenyl	
CH ₂ CH ₂ OCH ₃	F	3-(CH ₃ - SO ₂ -NH)- phenyl	F
CH ₂ CH ₂ OCH ₃	Cl	3-(CH ₃ - SO ₂ -NH)- phenyl	F
CH ₂ CH ₂ OCH ₃	F	3-(CH ₃ - SO ₂ -NH)- phenyl	F
CH ₂ CH ₂ OCH ₃	Cl	phenyl	F
CH ₂ CH ₂ OCH ₃	F	phenyl	F
CH ₂ CH ₂ OCH ₃	Cl	phenyl	F
CH ₂ CH ₂ OCH ₃	F	3-pyridyl	F
CH ₂ CH ₂ OCH ₃	Cl	3-pyridyl	F
		4-pyridyl	
(CH ₂) ₃ OCH ₃	F	pyrazolyl	F
(CH ₂) ₃ OCH ₃	Cl	pyrazolyl	F
(CH ₂) ₃ OCH ₃	F	4-pyridyl	F
(CH ₂) ₃ OCH ₃	Cl	4-pyridyl	F

R _{1c}	X	Y	Z
(CH ₂) ₃ OCH ₃	F	2-(CH ₃ -SO ₂ -NH)-phenyl	F
(CH ₂) ₃ OCH ₃	Cl	3-(CH ₃ -SO ₂ -NH)-phenyl	F
(CH ₂) ₃ OCH ₃	F	3-(CH ₃ -SO ₂ -NH)-phenyl	F
(CH ₂) ₃ OCH ₃	Cl	3-(CH ₃ -SO ₂ -NH)-phenyl	F
		phenyl	
CH ₂ CH ₂ OEt	F	phenyl	F
CH ₂ CH ₂ OEt	Cl	phenyl	F
CH ₂ CH ₂ OEt	F	3-pyridyl	F
CH ₂ CH ₂ OEt	Cl	3-pyridyl	F
CH ₂ CH ₂ OEt	F	4-pyridyl	F
CH ₂ CH ₂ OEt	Cl	pyrazolyl	F
CH ₂ CH ₂ OEt	F	pyrazolyl	F
CH ₂ CH ₂ OEt	Cl	4-pyridyl	F

[00160] Tables 4a and 4b show embodiments of this invention which are compounds of formula I, where G = R_{1d}, Z is F, X is F and R_{1d} and R⁰ are defined in the table. Each line in the table corresponds to five species which differ only at position Y.

Table 4a



5

Y_a = CH₃; Y_b = Br; Y_c = I; Y_d = Cl;

CMPD #	A, A'	B	R ⁰
1(a-d)	H, H	H	OCH ₃
2(a-d)	H, H	H	NHCH ₃
3(a-d)	H, H	H	CH ₂ CH ₃
4(a-d)	H, H	H	CH ₂ CH=CH ₂
5(a-d)	H, H	H	CN
6(a-d)	H, H	H	CF ₃

CMPD #	A, A'	B	R ⁶
7(a-d)	H, H	H	F
8(a-d)	H, H	H	C ₆ H ₆
9(a-d)	H, H	-CH ₂ CH(OH)CH ₂ OH	OCH ₃
10(a-d)	H, H	-CH ₂ CH(OH)CH ₂ OH	NHCH ₃
11(a-d)	H, H	-CH ₂ CH(OH)CH ₂ OH	CH ₂ CH ₃
12(a-d)	-(CH ₂) ₂ -	-CH ₂ (C ₃ H ₅)	OCH ₃
13(a-d)	-(CH ₂) ₂ -	-CH ₂ (C ₃ H ₅)	NHCH ₃
14(a-d)	-(CH ₂) ₂ -	-CH ₂ (C ₃ H ₅)	CH ₂ CH ₃
15(a-d)	-(CH ₂) ₂ -	CH ₃	F
16(a-d)	-(CH ₂) ₂ -	-CH ₂ CH ₂ OH	F
17(a-d)	-(CH ₂) ₂ -	-(CH ₂) ₂ CH(OH)CH ₂ OH	F
18(a-d)	CH ₃ , H	-(CH ₂) ₂ CH(OH)CH ₂ OH	F
19(a-d)	-(CH ₂) ₂ -	CH ₃	OCH ₃
20(a-d)	-(CH ₂) ₂ -	-CH ₂ CH ₂ OH	OCH ₃
21(a-d)	-(CH ₂) ₂ -	-(CH ₂) ₂ CH(OH)CH ₂ OH	OCH ₃
22(a-d)	CH ₃ , H	-(CH ₂) ₂ CH(OH)CH ₂ OH	OCH ₃
23(a-d)	-(CH ₂) ₂ -	CH ₃	H
24(a-d)	-(CH ₂) ₂ -	-CH ₂ CH ₂ OH	H
25(a-d)	-(CH ₂) ₂ -	-(CH ₂) ₂ CH(OH)CH ₂ OH	H
26(a-d)	CH ₃ , H	-(CH ₂) ₂ CH(OH)CH ₂ OH	H
27(a-d)	H, H	H	OCH ₃
28(a-d)	H, H	H	NHCH ₃
29(a-d)	H, H	H	CH ₂ CH ₃
30(a-d)	H, H	H	CH ₂ CH=CH ₂
31(a-d)	H, H	H	CN
32(a-d)	H, H	H	CF ₃
33(a-d)	H, H	H	F
34(a-d)	H, H	H	C ₆ H ₆
35(a-d)	H, H	-CH ₂ CH(OH)CH ₂ OH	OCH ₃
36(a-d)	H, H	-CH ₂ CH(OH)CH ₂ OH	NHCH ₃
37(a-d)	H, H	-CH ₂ CH(OH)CH ₂ OH	CH ₂ CH ₃
38(a-d)	-(CH ₂) ₂ -	-CH ₂ (C ₃ H ₅)	OCH ₃
39(a-d)	-(CH ₂) ₂ -	-CH ₂ (C ₃ H ₅)	NHCH ₃
40(a-d)	-(CH ₂) ₂ -	-CH ₂ (C ₃ H ₅)	CH ₂ CH ₃
41(a-d)	-(CH ₂) ₂ -	CH ₃	F
42(a-d)	-(CH ₂) ₂ -	-CH ₂ CH ₂ OH	F
43(a-d)	-(CH ₂) ₂ -	-(CH ₂) ₂ CH(OH)CH ₂ OH	F
44(a-d)	CH ₃ , H	-(CH ₂) ₂ CH(OH)CH ₂ OH	F
45(a-d)	-(CH ₂) ₂ -	CH ₃	OCH ₃
46(a-d)	-(CH ₂) ₂ -	-CH ₂ CH ₂ OH	OCH ₃
47(a-d)	-(CH ₂) ₂ -	-(CH ₂) ₂ CH(OH)CH ₂ OH	OCH ₃
48(a-d)	CH ₃ , H	-(CH ₂) ₂ CH(OH)CH ₂ OH	OCH ₃

CMPD #	A, A'	B	R ⁰
49(a-d)	-(CH ₂) ₂ -	CH ₃	H
50(a-d)	-(CH ₂) ₂ -	-CH ₂ CH ₂ OH	H
51(a-d)	-(CH ₂) ₂ -	-(CH ₂) ₂ CH(OH)CH ₂ OH	H
52(a-d)	CH ₃ , H	-(CH ₂) ₂ CH(OH)CH ₂ OH	H

Table 4b

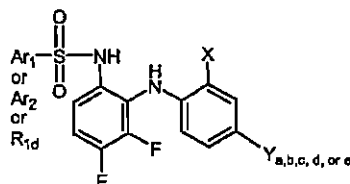
CMPD #	A, A'	B	R ⁰
1(a-d)	H, H	H	2-furanyl
2(a-d)	H, H	H	1,2,3 triazolyl-4-yl
3(a-d)	H, H	H	4-imidazolyl
4(a-d)	H, H	H	2-furanyl
5(a-d)	H, H	H	1,2,3 triazolyl-4-yl
6(a-d)	H, H	H	4-imidazolyl
7(a-d)	H, H	-(CH ₂) ₂ CH(OH)CH ₂ OH	2-furanyl
8(a-d)	H, H	-(CH ₂) ₂ CH(OH)CH ₂ OH	1,2,3 triazolyl-4-yl
9(a-d)	H, H	-(CH ₂) ₂ CH(OH)CH ₂ OH	4-imidazolyl
10(a-d)	-(CH ₂) ₂ -	-CH ₂ (C ₃ H ₅)	2-furanyl
11(a-d)	-(CH ₂) ₂ -	-CH ₂ (C ₃ H ₅)	1,2,3 triazolyl-4-yl
12(a-d)	-(CH ₂) ₂ -	-CH ₂ (C ₃ H ₅)	4-imidazolyl
13(a-d)	-(CH ₂) ₂ -	CH ₃	4-thiazolyl
14(a-d)	-(CH ₂) ₂ -	-CH ₂ CH ₂ OH	4-thiazolyl
15(a-d)	-(CH ₂) ₂ -	-(CH ₂) ₂ CH(OH)CH ₂ OH	4-thiazolyl
16(a-d)	CH ₃ , H	-(CH ₂) ₂ CH(OH)CH ₂ OH	4-thiazolyl
17(a-d)	-(CH ₂) ₂ -	CH ₃	2-oxazolyl
18(a-d)	-(CH ₂) ₂ -	-CH ₂ CH ₂ OH	2-oxazolyl
19(a-d)	-(CH ₂) ₂ -	-(CH ₂) ₂ CH(OH)CH ₂ OH	2-oxazolyl
20(a-d)	CH ₃ , H	-(CH ₂) ₂ CH(OH)CH ₂ OH	2-oxazolyl
21(a-d)	H, H	H	2-furanyl
22(a-d)	H, H	H	1,2,3 triazolyl-4-yl
23(a-d)	H, H	H	4-imidazolyl
24(a-d)	H, H	H	2-furanyl
25(a-d)	H, H	H	1,2,3 triazolyl-4-yl
26(a-d)	H, H	H	4-imidazolyl
27(a-d)	H, H	-CH ₂ CH(OH)CH ₂ OH	2-furanyl
28(a-d)	H, H	-CH ₂ CH(OH)CH ₂ OH	1,2,3 triazolyl-4-yl
29(a-d)	H, H	-CH ₂ CH(OH)CH ₂ OH	4-imidazolyl
30(a-d)	-(CH ₂) ₂ -	-CH ₂ (C ₃ H ₅)	2-furanyl
31(a-d)	-(CH ₂) ₂ -	-CH ₂ (C ₃ H ₅)	1,2,3 triazolyl-4-yl
32(a-d)	-(CH ₂) ₂ -	-CH ₂ (C ₃ H ₅)	4-imidazolyl
33(a-d)	-(CH ₂) ₂ -	CH ₃	4-thiazolyl
34(a-d)	-(CH ₂) ₂ -	-CH ₂ CH ₂ OH	4-thiazolyl
35(a-d)	-(CH ₂) ₂ -	-(CH ₂) ₂ CH(OH)CH ₂ OH	4-thiazolyl
36(a-d)	CH ₃ , H	-(CH ₂) ₂ CH(OH)CH ₂ OH	4-thiazolyl

CMPD #	A, A'	B	R ⁰
37(a-d)	-(CH ₂) ₂ -	CH ₃	2-oxazoly
38(a-d)	-(CH ₂) ₂ -	-CH ₂ CH ₂ OH	2-oxazoly
39(a-d)	-(CH ₂) ₂ -	-(CH ₂) ₂ CH(OH)CH ₂ OH	2-oxazoly
40(a-d)	CH ₃ , H	-(CH ₂) ₂ CH(OH)CH ₂ OH	2-oxazoly

[00161] Table 5a shows embodiments of this invention which are compounds of formula I, where G is Ar₁, Ar₂ or R_{1d}, and where R⁰ is H, Z is F and G and X are defined in the table. Each line in the table corresponds to five species (Y_a, Y_b, Y_c, Y_d and Y_e) which differ only at position Y, where Y_a = SCH₃; Y_b = Br; Y_c = I; Y_d = Cl; Y_e = CH₃.

5

Table 5a



Y_a = SCH₃; Y_b = Br; Y_c = I; Y_d = Cl; Y_e = CH₃

Compound #	G = R _{1d} , Ar ₁ , or Ar ₂	X
1 (a-e)	phenyl	Cl
2 (a-e)	phenyl	F
3 (a-e)	2-F-phenyl	Cl
4 (a-e)	2-F-phenyl	F
5 (a-e)	3-F-phenyl	Cl
6 (a-e)	3-F-phenyl	F
7 (a-e)	4-F-phenyl	Cl
8 (a-e)	4-F-phenyl	F
9 (a-e)	2,4-di-F-phenyl	Cl
10 (a-e)	2,4-di-F-phenyl	F
11 (a-e)	2,5-di-F-phenyl	Cl
12 (a-e)	2,5-di-F-phenyl	F
13 (a-e)	2,6-di-F-phenyl	Cl
14 (a-e)	2,6-di-F-phenyl	F
15 (a-e)	3,4-di-F-phenyl	Cl
16 (a-e)	3,4-di-F-phenyl	F
17 (a-e)	3,5-di-F-phenyl	Cl
18 (a-e)	3,5-di-F-phenyl	F
19 (a-e)	2,6-di-F-phenyl	Cl
20 (a-e)	2,6-di-F-phenyl	F
21 (a-e)	2,3,4-tri-F-phenyl	Cl

Compound #	G = R _{1d} , Ar ₁ , or Ar ₂	X
22 (a-e)	2,3,4-tri-F-phenyl	F
23 (a-e)	3,4,5-tri-F-phenyl	Cl
24 (a-e)	3,4,5-tri-F-phenyl	F
25 (a-e)	penta-F-phenyl	Cl
26 (a-e)	penta-F-phenyl	F
27 (a-e)	3-Cl-4-F-phenyl	Cl
28 (a-e)	3-Cl-4-F-phenyl	F
29 (a-e)	2-Cl-4-F-phenyl	Cl
30 (a-e)	2-Cl-4-F-phenyl	F
31 (a-e)	2-F-3-Cl-phenyl	Cl
32 (a-e)	2-F-3-Cl-phenyl	F
33 (a-e)	2-F-4-Cl-phenyl	Cl
34 (a-e)	2-F-4-Cl-phenyl	F
35 (a-e)	2-F-5-Cl-phenyl	Cl
36 (a-e)	2-F-5-Cl-phenyl	F
37 (a-e)	3-cyano-4-F-phenyl	Cl
38 (a-e)	3-cyano-4-F-phenyl	F
39 (a-e)	2-Cl-phenyl	Cl
40 (a-e)	2-Cl-phenyl	F
41 (a-e)	3-Cl-phenyl	Cl
42 (a-e)	3-Cl-phenyl	F
43 (a-e)	4-Cl-phenyl	Cl
44 (a-e)	4-Cl-phenyl	F
45 (a-e)	2,3-di-Cl-phenyl	Cl
46 (a-e)	2,3-di-Cl-phenyl	F
47 (a-e)	2,5-di-Cl-phenyl	Cl
48 (a-e)	2,5-di-Cl-phenyl	F
49 (a-e)	2,6-di-Cl-phenyl	Cl
50 (a-e)	2,6-di-Cl-phenyl	F
51 (a-e)	3,5-di-Cl-phenyl	Cl
52 (a-e)	3,5-di-Cl-phenyl	F
53 (a-e)	2,4-di-Cl-phenyl	Cl
54 (a-e)	2,4-di-Cl-phenyl	F
55 (a-e)	3,4-di-Cl-phenyl	Cl
56 (a-e)	3,4-di-Cl-phenyl	F
57 (a-e)	2,4,6-tri-Cl-phenyl	Cl
58 (a-e)	2,4,6-tri-Cl-phenyl	F
59 (a-e)	2-Cl-4-CF ₃ -phenyl	Cl
60 (a-e)	2-Cl-4-CF ₃ -phenyl	F
61 (a-e)	2-CF ₃ -phenyl	Cl
62 (a-e)	2-CF ₃ -phenyl	F

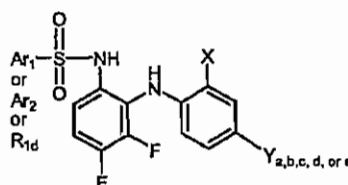
Compound #	G = R _{1d} , Ar ₁ , or Ar ₂	X
63 (a-e)	3-CF ₃ -phenyl	Cl
64 (a-e)	3-CF ₃ -phenyl	F
65 (a-e)	4-CF ₃ -phenyl	Cl
66 (a-e)	4-CF ₃ -phenyl	F
67 (a-e)	2-CF ₃ O phenyl	Cl
68 (a-e)	2-CF ₃ O phenyl	F
69 (a-e)	3-CF ₃ O phenyl	Cl
70 (a-e)	3-CF ₃ O phenyl	F
71 (a-e)	4-CF ₃ O phenyl	Cl
72 (a-e)	4-CF ₃ O phenyl	F
73 (a-e)	2-CHF ₂ O phenyl	Cl
74 (a-e)	2-CHF ₂ O phenyl	F
75 (a-e)	2-methyl-5-nitro-phenyl	Cl
76 (a-e)	2-methyl-5-nitro-phenyl	F
77 (a-e)	2-cyano-phenyl	Cl
78 (a-e)	2-cyano-phenyl	F
79 (a-e)	3-cyano-phenyl	Cl
80 (a-e)	3-cyano-phenyl	F
81 (a-e)	4-cyano-phenyl	Cl
82 (a-e)	4-cyano-phenyl	F
83 (a-e)	4-methoxy-phenyl	Cl
84 (a-e)	4-methoxy-phenyl	F
85 (a-e)	3,4-dimethoxy-phenyl	Cl
86 (a-e)	3,4-dimethoxy-phenyl	F
87 (a-e)	3-carbamyl-phenyl	Cl
88 (a-e)	3-carbamyl-phenyl	F
89 (a-e)	3-carboxyl-phenyl	Cl
90 (a-e)	3-carboxyl-phenyl	F
91 (a-e)	3-(N,N-dimethylcarbamoyl)phenyl	Cl
92 (a-e)	3-(N,N-dimethylcarbamoyl)phenyl	F
93 (a-e)	4-methylsulfonyl-phenyl	Cl
94 (a-e)	4-methylsulfonyl-phenyl	F
95 (a-e)	3-(1,3,4 oxadiazol-2-yl)phenyl	Cl
96 (a-e)	3-(1,3,4 oxadiazol-2-yl)phenyl	F
97 (a-e)	3-(1,3,4 thiadiazol-2-yl)phenyl	Cl
98 (a-e)	3-(1,3,4 thiadiazol-2-yl)phenyl	F
99 (a-e)	3-(5-methyl-1,3,4-oxadiazol)phenyl	Cl
100 (a-e)	3-(5-methyl-1,3,4-oxadiazol)phenyl	F
101 (a-e)	3-(5-methyl-1,3,4-thiadiazol)phenyl	Cl
102 (a-e)	3-(5-methyl-1,3,4-thiadiazol)phenyl	F
103 (a-e)	3-amidinyl-phenyl	Cl

Compound #	G = R _{1d} , Ar ₁ , or Ar ₂	X
104 (a-e)	3-amidinyl-phenyl	F
105 (a-e)	3-(1H-tetrazolyl)phenyl	Cl
106 (a-e)	3-(1H-tetrazolyl)phenyl	F
107 (a-e)	4-acetamido-phenyl	Cl
108 (a-e)	4-acetamido-phenyl	F
109 (a-e)	3-Cl-4-[(N-morpholinylcarbonyl)amino]phenyl	Cl
110 (a-e)	3-Cl-4-[(N-morpholinylcarbonyl)amino]phenyl	F
111 (a-e)	3-Cl-4-[(N-pyrrolidinylcarbonyl)amino]phenyl	Cl
112 (a-e)	3-Cl-4-[(N-pyrrolidinylcarbonyl)amino]phenyl	F
113 (a-e)	3,5-dimethylisoxazolyl	Cl
114 (a-e)	3,5-dimethylisoxazolyl	F
115 (a-e)	4-(N-morpholinylsulfonyl)phenyl	Cl
116 (a-e)	4-(N-morpholinylsulfonyl)phenyl	F
117 (a-e)	3-F-benzyl	Cl
118 (a-e)	3-F-benzyl	F
119 (a-e)	4-F-benzyl	Cl
120 (a-e)	4-F-benzyl	F
121 (a-e)	3-F-phenyl-ethyl	Cl
122 (a-e)	3-F-phenyl-ethyl	F
123 (a-e)	4-F-phenyl-ethyl	Cl
124 (a-e)	4-F-phenyl-ethyl	F
125 (a-e)	8-quinolinyl	Cl
126 (a-e)	8-quinolinyl	F
127 (a-e)	2-thienyl	Cl
128 (a-e)	2-thienyl	F
129 (a-e)	2,3-di-Cl-thien-5-yl	Cl
130 (a-e)	2,3-di-Cl-thien-5-yl	F
131 (a-e)	1,3,5 trimethyl-1H-pyrazolyl	Cl
132 (a-e)	1,3,5 trimethyl-1H-pyrazolyl	F
133 (a-e)	1,3-dimethyl-5-Cl-1H-pyrazolyl	Cl
134 (a-e)	1,3-dimethyl-5-Cl-1H-pyrazolyl	F
135 (a-e)	1-methyl-3CF ₃ -1H-pyrazol-4-yl	Cl
136 (a-e)	1-methyl-3CF ₃ -1H-pyrazol-4-yl	F
137 (a-e)	2-acetamido-4-methyl-thiazol-5-yl	Cl
138 (a-e)	2-acetamido-4-methyl-thiazol-5-yl	F
139 (a-e)	2,4-dimethyl-thiazol-5-yl	Cl
140 (a-e)	2,4-dimethyl-thiazol-5-yl	F
141 (a-e)	1,2-dimethyl-1H-imidazol-4-yl	Cl

Compound d #	G = R _{1d} , Ar ₁ , or Ar ₂	X
142 (a-e)	1,2-dimethyl-1H-imidazol-4-yl	F

[00162] Table 5b shows embodiments of this invention which are compounds of formula I, where G is Ar₁, Ar₂ or R_{1d}, and where R⁰ is H, Z is F and G and X are defined in the table. Each line in the table corresponds to five species (Y_a, Y_b, Y_c, Y_d and Y_e) which differ only at position Y, where Y_a = phenyl; Y_b = 3-substituted phenyl; Y_c = 3-pyridyl; Y_d = 4-pyridyl; Y_e = 3-pyrazolyl.

Table 5b



Y_a = phenyl; Y_b = 3-substituted phenyl; Y_c = 3-pyridyl; Y_d = 4-pyridyl; Y_e = 3-pyrazolyl

Compound #	G = R _{1d} , Ar ₁ , or Ar ₂	X
1 (a-e)	phenyl	Cl
2 (a-e)	phenyl	F
3 (a-e)	2-F-phenyl	Cl
4 (a-e)	2-F-phenyl	F
5 (a-e)	3-F-phenyl	Cl
6 (a-e)	3-F-phenyl	F
7 (a-e)	4-F-phenyl	Cl
8 (a-e)	4-F-phenyl	F
9 (a-e)	2,4-di-F-phenyl	Cl
10 (a-e)	2,4-di-F-phenyl	F
11 (a-e)	2,5-di-F-phenyl	Cl
12 (a-e)	2,5-di-F-phenyl	F
13 (a-e)	2,6-di-F-phenyl	Cl
14 (a-e)	2,6-di-F-phenyl	F
15 (a-e)	3,4-di-F-phenyl	Cl
16 (a-e)	3,4-di-F-phenyl	F
17 (a-e)	3,5-di-F-phenyl	Cl
18 (a-e)	3,5-di-F-phenyl	F
19 (a-e)	2,6-di-F-phenyl	Cl
20 (a-e)	2,6-di-F-phenyl	F
21 (a-e)	2,3,4-tri-F-phenyl	Cl
22 (a-e)	2,3,4-tri-F-phenyl	F
23 (a-e)	3,4,5-tri-F-phenyl	Cl
24 (a-e)	3,4,5-tri-F-phenyl	F

Compound #	G = R _{1d} , Ar ₁ , or Ar ₂	X
25 (a-e)	penta-F-phenyl	Cl
26 (a-e)	penta-F-phenyl	F
27 (a-e)	3-Cl-4-F-phenyl	Cl
28 (a-e)	3-Cl-4-F-phenyl	F
29 (a-e)	2-Cl-4-F-phenyl	Cl
30 (a-e)	2-Cl-4-F-phenyl	F
31 (a-e)	2-F-3-Cl-phenyl	Cl
32 (a-e)	2-F-3-Cl-phenyl	F
33 (a-e)	2-F-4-Cl-phenyl	Cl
34 (a-e)	2-F-4-Cl-phenyl	F
35 (a-e)	2-F-5-Cl-phenyl	Cl
36 (a-e)	2-F-5-Cl-phenyl	F
37 (a-e)	3-cyano-4-F-phenyl	Cl
38 (a-e)	3-cyano-4-F-phenyl	F
39 (a-e)	2-Cl-phenyl	Cl
40 (a-e)	2-Cl-phenyl	F
41 (a-e)	3-Cl-phenyl	Cl
42 (a-e)	3-Cl-phenyl	F
43 (a-e)	4-Cl-phenyl	Cl
44 (a-e)	4-Cl-phenyl	F
45 (a-e)	2,3-di-Cl-phenyl	Cl
46 (a-e)	2,3-di-Cl-phenyl	F
47 (a-e)	2,5-di-Cl-phenyl	Cl
48 (a-e)	2,5-di-Cl-phenyl	F
49 (a-e)	2,6-di-Cl-phenyl	Cl
50 (a-e)	2,6-di-Cl-phenyl	F
51 (a-e)	3,5-di-Cl-phenyl	Cl
52 (a-e)	3,5-di-Cl-phenyl	F
53 (a-e)	2,4-di-Cl-phenyl	Cl
54 (a-e)	2,4-di-Cl-phenyl	F
55 (a-e)	3,4-di-Cl-phenyl	Cl
56 (a-e)	3,4-di-Cl-phenyl	F
57 (a-e)	2,4,6-tri-Cl-phenyl	Cl
58 (a-e)	2,4,6-tri-Cl-phenyl	F
59 (a-e)	2-Cl-4-CF ₃ -phenyl	Cl
60 (a-e)	2-Cl-4-CF ₃ -phenyl	F
61 (a-e)	2-CF ₃ -phenyl	Cl
62 (a-e)	2-CF ₃ -phenyl	F
63 (a-e)	3-CF ₃ -phenyl	Cl
64 (a-e)	3-CF ₃ -phenyl	F
65 (a-e)	4-CF ₃ -phenyl	Cl
66 (a-e)	4-CF ₃ -phenyl	F
67 (a-e)	2-CF ₃ O phenyl	Cl
68 (a-e)	2-CF ₃ O phenyl	F
69 (a-e)	3-CF ₃ O phenyl	Cl
70 (a-e)	3-CF ₃ O phenyl	F

Compound #	G = R _{1d} , Ar ₁ , or Ar ₂	X
71 (a-e)	4-CF ₃ O phenyl	Cl
72 (a-e)	4-CF ₃ O phenyl	F
73 (a-e)	4-CHF ₂ O-phenyl	Cl
74 (a-e)	4-CHF ₂ O-phenyl	F
75 (a-e)	2-methyl-5-nitro-phenyl	Cl
76 (a-e)	2-methyl-5-nitro-phenyl	F
77 (a-e)	2-cyano-phenyl	Cl
78 (a-e)	2-cyano-phenyl	F
79 (a-e)	3-cyano-phenyl	Cl
80 (a-e)	3-cyano-phenyl	F
81 (a-e)	4-cyano-phenyl	Cl
82 (a-e)	4-cyano-phenyl	F
83 (a-e)	4-methoxy-phenyl	Cl
84 (a-e)	4-methoxy-phenyl	F
85 (a-e)	3,4-dimethoxy-phenyl	Cl
86 (a-e)	3,4-dimethoxy-phenyl	F
87 (a-e)	3-carbamyl-phenyl	Cl
88 (a-e)	3-carbamyl-phenyl	F
89 (a-e)	3-carboxyl-phenyl	Cl
90 (a-e)	3-carboxyl-phenyl	F
91 (a-e)	3-(N,N-dimethylcarbamoyl)phenyl	Cl
92 (a-e)	3-(N,N-dimethylcarbamoyl)phenyl	F
93 (a-e)	4-methylsulfonyl-phenyl	Cl
94 (a-e)	4-methylsulfonyl-phenyl	F
95 (a-e)	3-(1,3,4-oxadiazol-2-yl)phenyl	Cl
96 (a-e)	3-(1,3,4-oxadiazol-2-yl)phenyl	F
97 (a-e)	3-(1,3,4-thiadiazol-2-yl)phenyl	Cl
98 (a-e)	3-(1,3,4-thiadiazol-2-yl)phenyl	F
99 (a-e)	3-(5-methyl-1,3,4-oxadiazol)phenyl	Cl
100 (a-e)	3-(5-methyl-1,3,4-oxadiazol)phenyl	F
101 (a-e)	3-(5-methyl-1,3,4-thiadiazol)phenyl	Cl
102 (a-e)	3-(5-methyl-1,3,4-thiadiazol)phenyl	F
103 (a-e)	3-amidinyl-phenyl	Cl
104 (a-e)	3-amidinyl-phenyl	F
105 (a-e)	3-(1H-tetrazolyl)phenyl	Cl
106 (a-e)	3-(1H-tetrazolyl)phenyl	F
107 (a-e)	4-acetamido-phenyl	Cl
108 (a-e)	4-acetamido-phenyl	F
109 (a-e)	3-Cl-4-[(N-morpholinylcarbonyl)amino]phenyl	Cl
110 (a-e)	3-Cl-4-[(N-morpholinylcarbonyl)amino]phenyl	F
111 (a-e)	3-Cl-4-[(N-pyrrolidinylcarbonyl)amino]phenyl	Cl
112 (a-e)	3-Cl-4-[(N-pyrrolidinylcarbonyl)amino]phenyl	F

Compound #	G = R _{1d} , Ar ₁ , or Ar ₂	X
113 (a-e)	3,5-dimethylisoxazolyl	Cl
114 (a-e)	3,5-dimethylisoxazolyl	F
115 (a-e)	4-(N-morpholinylsulfonyl)phenyl	Cl
116 (a-e)	4-(N-morpholinylsulfonyl)phenyl	F
117 (a-e)	3-F-benzyl	Cl
118 (a-e)	3-F-benzyl	F
119 (a-e)	4-F-benzyl	Cl
120 (a-e)	4-F-benzyl	F
121 (a-e)	3-F-phenyl-ethyl	Cl
122 (a-e)	3-F-phenyl-ethyl	F
123 (a-e)	4-F-phenyl-ethyl	Cl
124 (a-e)	4-F-phenyl-ethyl	F
125 (a-e)	8-quinoliny	Cl
126 (a-e)	8-quinoliny	F
127 (a-e)	2-thienyl	Cl
128 (a-e)	2-thienyl	F
129 (a-e)	2,3-di-Cl-thien-5-yl	Cl
130 (a-e)	2,3-di-Cl-thien-5-yl	F
131 (a-e)	1,3,5 trimethyl-1H-pyrazolyl	Cl
132 (a-e)	1,3,5 trimethyl-1H-pyrazolyl	F
133 (a-e)	1,3-dimethyl-5-Cl-1H-pyrazolyl	Cl
134 (a-e)	1,3-dimethyl-5-Cl-1H-pyrazolyl	F
135 (a-e)	1-methyl-3-CF ₃ -1H-pyrazol-4-yl	Cl
136 (a-e)	1-methyl-3-CF ₃ -1H-pyrazol-4-yl	F
137 (a-e)	2-acetamido-4-methyl-thiazol-5-yl	Cl
138 (a-e)	2-acetamido-4-methyl-thiazol-5-yl	F
139 (a-e)	2,4-dimethyl-thiazol-5-yl	Cl
140 (a-e)	2,4-dimethyl-thiazol-5-yl	F
141 (a-e)	1,2-dimethyl-1H-imidazol-4-yl	Cl
142 (a-e)	1,2-dimethyl-1H-imidazol-4-yl	F
143 (a-e)	1-(2-hydroxyethyl) cyclopropyl	F
144 (a-e)	1-(3-hydroxypropyl) cyclopropyl	F
145 (a-e)	1-(2,3-dihydroxypropyl) cyclopropyl	F
146 (a-e)	1-(3,4-dihydroxybutyl) cyclopropyl	F
147 (a-e)	1-(2,3-dihydroxypropyl) cyclobutyl	F

Synthetic Procedures

[00163] In another aspect, methods for synthesizing the compounds described herein are provided. In some embodiments, the compounds described herein can be made by the methods described below. The procedures and examples below are intended to illustrate those methods. Neither the procedures nor the examples should be construed as limiting the invention in any way. Compounds described herein may also be synthesized using standard synthetic techniques known to those of skill in the art or using methods known in the art in

combination with methods described herein. In additions, solvents, temperatures and other reaction conditions presented herein may vary according to the practice and knowledge of those of skill in the art.

- [00164] Starting materials for the synthesis of the compounds as described herein may be obtained from commercial sources, such as Aldrich Chemical Co. (Milwaukee, Wis.), Sigma Chemical Co. (St. Louis, Mo.), or the starting materials can be synthesized. The compounds described herein, and other related compounds having different substituents can be synthesized using techniques and materials known to those of skill in the art, such as described, for example, in March, *ADVANCED ORGANIC CHEMISTRY* 4th Ed., (Wiley 1992); Carey and Sundberg, *ADVANCED ORGANIC CHEMISTRY* 4th Ed., Vols. A and B (Plenum 2000, 2001), and Green and Wuts, *PROTECTIVE GROUPS IN ORGANIC SYNTHESIS* 3rd Ed., (Wiley 1999) (all of which are incorporated by reference in their entirety). General methods for the preparation of compound as disclosed herein may be derived from known reactions in the field, and the reactions may be modified by the use of appropriate reagents and conditions, as would be recognized by the skilled person, for the introduction of the various moieties found in the formulae as provided herein. As a guide the following synthetic methods may be utilized.

Formation of Covalent Linkages by Reaction of an Electrophile with a Nucleophile

- [00165] The compounds described herein can be modified using various electrophiles or nucleophiles to form new functional groups or substituents. The table below entitled "Examples of Covalent Linkages and Precursors Thereof" lists selected examples of covalent linkages and precursor functional groups which yield and can be used as guidance toward the variety of electrophiles and nucleophiles combinations available. Precursor functional groups are shown as electrophilic groups and nucleophilic groups.

Covalent Linkage Product	Electrophile	Nucleophile
Carboxamides	Activated esters	Amines/anilines
Carboxamides	Acyl azides	Amines/anilines
Carboxamides	Acyl halides	Amines/anilines
Esters	Acyl halides	Alcohols/phenols
Esters	Acyl nitriles	Alcohols/phenols
Carboxamides	Acyl nitriles	Amines/anilines
Imines	Aldehydes	Amines/anilines
Hydrazones	Aldehydes or ketones	Hydrazines
Oximes	Aldehydes or ketones	Hydroxylamines

Alkyl amines	Alkyl halides	Amines/anilines
Esters	Alkyl halides	Carboxylic acids
Thioethers	Alkyl halides	Thiols
Ethers	Alkyl halides	Alcohols/phenols
Thioethers	Alkyl sulfonates	Thiols
Esters	Alkyl sulfonates	Carboxylic acids
Ethers	Alkyl sulfonates	Alcohols/phenols
Esters	Anhydrides	Alcohols/phenols
Carboxamides	Anhydrides	Amines/anilines
Thiophenols	Aryl halides	Thiols
Aryl amines	Aryl halides	Amines
Thioethers	Aziridines	Thiols
Boronate esters	Boronates	Glycols
Carboxamides	Carboxylic acids	Amines/anilines
Esters	Carboxylic acids	Alcohols
Hydrazines	Hydrazides	Carboxylic acids
N-acylureas or Anhydrides	Carbodiimides	Carboxylic acids
Esters	Diazoalkanes	Carboxylic acids
Thioethers	Epoxides	Thiols
Thioethers	Haloacetamides	Thiols
Ammotriazines	Halotriazines	Amines/anilines
Triazinyl ethers	Halotriazines	Alcohols/phenols
Amidines	Imido esters	Amines/anilines
Ureas	Isocyanates	Amines/anilines
Urethanes	Isocyanates	Alcohols/phenols
Thioureas	Isothiocyanates	Amines/anilines
Thioethers	Maleimides	Thiols
Phosphite esters	Phosphoramidites	Alcohols
Silyl ethers	Silyl halides	Alcohols
Alkyl amines	Sulfonate esters	Amines/anilines
Thioethers	Sulfonate esters	Thiols
Esters	Sulfonate esters	Carboxylic acids
Ethers	Sulfonate esters	Alcohols
Sulfonamides	Sulfonyl halides	Amines/anilines
Sulfonate esters	Sulfonyl halides	Phenols/alcohols

Examples of Covalent Linkages and Precursors Thereof

Use of Protecting Groups

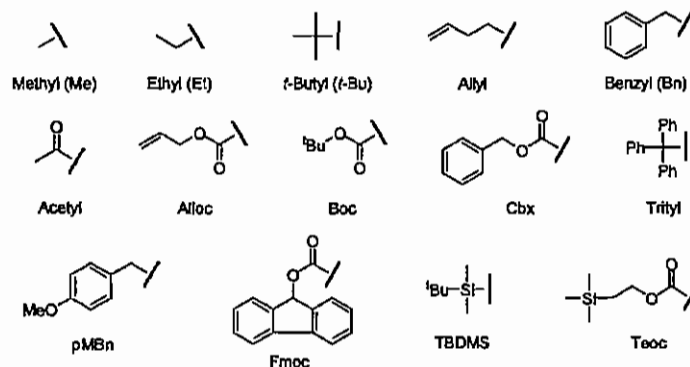
[00166] In the reactions described, it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Protecting groups can be used to block some or all reactive moieties and prevent such groups from participating in chemical reactions until the protective group is removed. In some embodiments, each protective group is removable by a different means. Protective groups

that are cleaved under totally disparate reaction conditions fulfill the requirement of differential removal. Protective groups can be removed by acid, base, and hydrogenolysis. Groups such as trityl, dimethoxytrityl, acetal and t-butyl dimethylsilyl are acid labile and may be used to protect carboxy and hydroxy reactive moieties in the presence of amino groups protected with Cbz groups, which are removable by hydrogenolysis, and Fmoc groups, which are base labile. Carboxylic acid and hydroxy reactive moieties may be blocked with base labile groups such as, but not limited to, methyl, ethyl, and acetyl in the presence of amines blocked with acid labile groups such as t-butyl carbamate or with carbamates that are both acid and base stable but hydrolytically removable.

10 [00167] Carboxylic acid and hydroxy reactive moieties may also be blocked with hydrolytically removable protective groups such as the benzyl group, while amine groups capable of hydrogen bonding with acids may be blocked with base labile groups such as Fmoc. Carboxylic acid reactive moieties may be protected by conversion to simple ester compounds as exemplified herein, or they may be blocked with oxidatively-removable
15 protective groups such as 2,4-dimethoxybenzyl, while co-existing amino groups may be blocked with fluoride labile silyl carbamates.

[00168] Allyl blocking groups are useful in the presence of acid- and base-protecting groups since the former are stable and can be subsequently removed by metal or pi-acid catalysts. For example, an allyl-blocked carboxylic acid can be deprotected with a
20 Pd-catalyzed reaction in the presence of acid labile t-butyl carbamate or base-labile acetate amine protecting groups. Yet another form of protecting group is a resin to which a compound or intermediate may be attached. As long as the residue is attached to the resin, that functional group is blocked and cannot react. Once released from the resin, the functional group is available to react.

25 [00169] Protecting or blocking groups may be selected from:

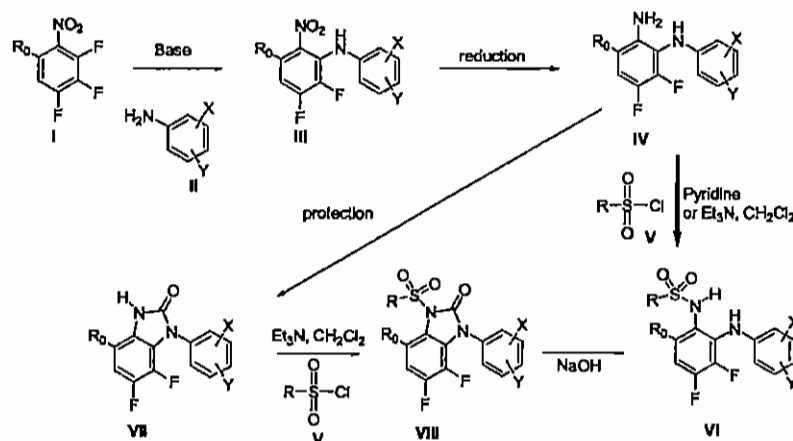


[00170] Other protecting groups, plus a detailed description of techniques applicable to the creation of protecting groups and their removal are described in Greene and Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley & Sons, New York, NY, 1999, and Kocienski, *Protective Groups*, Thieme Verlag, New York, NY, 1994, which are incorporated herein by reference in their entirety.

Making compounds of formula I

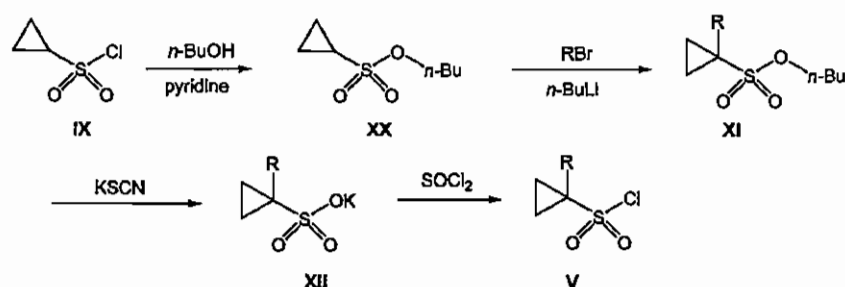
[00171] Compounds of this invention can be made by a variety of methods. The procedures below are intended to illustrate those methods, and the examples given are intended to illustrate the scope of this invention. Neither the methods nor the examples should be construed as limiting the invention in any way.

[00172] **Scheme I.** The preparation of compound of formula VI is outlined below



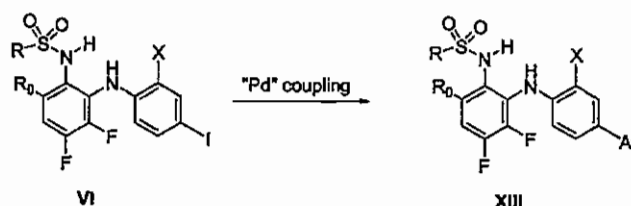
[00173] Scheme 1 above illustrates a method for making the sulfonamide derivatives of formula VI. 1,2 Diamine derivative (formula IV) can be easily prepared in two steps from the desired nitro derivatives (formula I). Compounds of formula IV can be reacted with the sulfonyl chloride derivatives (formula V, see next scheme) to form the desired sulfonamide. Alternatively, the 1,2 diamine derivatives IV can be protected to form an imidazolidone (formula VII), before being reacted with the corresponding sulfonyl chloride. Deprotection of the 1,2 diamine VIII under basic conditions provided the desired material VI.

10 [00174] **Scheme II.** The general route to synthesis compound of general formula V is outlined below



15 [00175] Scheme II above shows one example of the preparation of complex sulfonyl chloride. Compound XX can be synthesized from IX, alkylated, and converted to the potassium salt XII. Treatment of the salt with SOCl₂ or POCl₃ affords the desired compounds. Other more specific procedures to prepare unique sulfonyl chloride derivatives are reported in the experimental section.

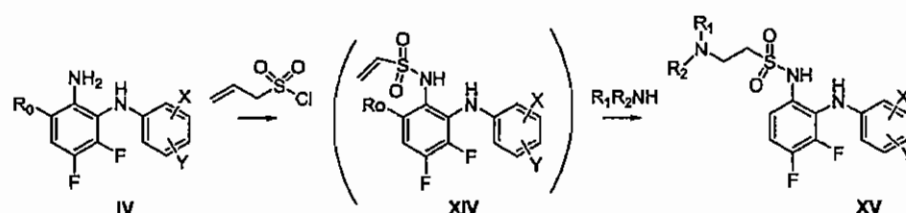
20 **Schemem III.** The general route to synthesis compound of general formula XIII is outlined in Scheme III:



[00176] Scheme III above illustrates the preparation of sulfonamide derivatives of general formula XIII. For example, these compounds can be easily obtained by reacting the compound VI with a boronic acid using a palladium catalyst under Suzuki conditions.

Scheme IV. The general route to synthesis compound of general formula XIII is outlines

5 Scheme IV:



[00177] Scheme IV above illustrates the preparation of sulfonamide derivatives of general formula XV. The vinyl sulfonamide (XIV) is reacted with amines to form derivatives of general formulas XV.

Further Forms of Compounds of formula I

Isomers of compounds of formula I

[00178] The compounds described herein may exist as geometric isomers. The compounds described herein may possess one or more double bonds. The compounds presented herein include all *cis*, *trans*, *syn*, *anti*, *entgegen* (*E*), and *zusammen* (*Z*) isomers as well as the corresponding mixtures thereof. In some situations, compounds may exist as tautomers. The compounds described herein include all possible tautomers within the formulas described herein. The compounds described herein may possess one or more chiral centers and each center may exist in the *R* or *S* configuration. The compounds described herein include all diastereomeric, enantiomeric, and epimeric forms as well as the corresponding mixtures thereof. In additional embodiments of the compounds and methods provided herein, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion may also be useful for the applications described herein. The compounds described herein can be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. Resolution of enantiomers can be carried out using covalent diastereomeric derivatives of the compounds described herein, or dissociable

complexes may be used (e.g., crystalline diastereomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chiral chromatography, or separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions," John Wiley And Sons, Inc., 1981, herein incorporated by reference in its entirety.

Labeled compounds of formula I

[00179] Also described herein are isotopically-labeled compounds of formula I and methods of treating disorders. For example, the invention provides for methods of treating diseases, by administering isotopically-labeled compounds of formula I. The isotopically-labeled compounds of formula I can be administered as pharmaceutical compositions. Thus, compounds of formula I also include isotopically-labeled compounds, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chloride, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{33}S , ^{18}F , and ^{36}Cl , respectively. Compounds described herein, pharmaceutically acceptable salts, thereof which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled compounds of formula I, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i. e., ^3H and carbon-14, i. e., ^{14}C , isotopes are often easily prepared and detectabilized. Further, substitution with heavier isotopes such as deuterium, i. e., ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be desirable in some circumstances. Isotopically labeled compounds and pharmaceutically acceptable salts thereof can generally be prepared by carrying out procedures described herein, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

[00180] The compounds described herein may be labeled by other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

Pharmaceutically acceptable salts of compounds of formula I

5 [00181] Also described herein are pharmaceutically acceptable salts of compounds of formula I and methods of treating disorders. For example, the invention provides for methods of treating diseases, by administering pharmaceutically acceptable salts of compounds of formula I. The pharmaceutically acceptable salts of compounds of formula I can be administered as pharmaceutical compositions.

10 [00182] Thus, the compounds described herein can be prepared as pharmaceutically acceptable salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, for example an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base. Base addition salts can also be prepared by reacting the free acid form of the compounds described herein with a pharmaceutically
15 acceptable inorganic or organic base, including, but not limited to organic bases such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like and inorganic bases such as aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like. In addition, the salt forms of the disclosed compounds can be prepared using salts of the starting materials or
20 intermediates.

[00183] Further, the compounds described herein can be prepared as pharmaceutically acceptable salts formed by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid, including, but not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid,
25 phosphoric acid metaphosphoric acid, and the like; and organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, Q-toluenesulfonic acid, tartaric acid, trifluoroacetic acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, arylsulfonic acid,
30 methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary

butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, and muconic acid.

Pharmaceutical compositions

5 [00184] Described herein are pharmaceutical compositions. In some embodiments, the pharmaceutical compositions comprise an effective amount of a compound formula I, or a pharmaceutically acceptable salt, thereof. In some embodiments, the pharmaceutical compositions comprise an effective amount of a compound formula I, or a pharmaceutically acceptable salt, thereof and at least one pharmaceutically acceptable carrier. In some
10 embodiments the pharmaceutical compositions are for the treatment of disorders. In some embodiments the pharmaceutical compositions are for the treatment of disorders in a mammal. In some embodiments the pharmaceutical compositions are for the treatment of disorders in a human.

15 ***MEK Modulation***

[00185] Also described herein are methods of modulating MEK activity by contacting MEK with an amount of a compound of formula I sufficient to modulate the activity of MEK. Modulate can be inhibiting or activating MEK activity. In some
20 embodiments, the invention provides methods of inhibiting MEK activity by contacting MEK with an amount of a compound of formula I sufficient to inhibit the activity of MEK. In some embodiments, the invention provides methods of inhibiting MEK activity in a solution by contacting said solution with an amount of a compound of formula I sufficient to inhibit the activity of MEK in said solution. In some embodiments, the invention provides methods of inhibiting MEK activity in a cell by contacting said cell with an
25 amount of a compound described herein sufficient to inhibit the activity of MEK in said cell. In some embodiments, the invention provides methods of inhibiting MEK activity in a tissue by contacting said tissue with an amount of a compound described herein sufficient to inhibit the activity of MEK in said tissue. In some embodiments, the invention provides methods of inhibiting MEK activity in an organism by contacting said organism with an
30 amount of a compound described herein sufficient to inhibit the activity of MEK in said organism. In some embodiments, the invention provides methods of inhibiting MEK activity in an animal by contacting said animal with an amount of a compound described herein sufficient to inhibit the activity of MEK in said animal. In some embodiments, the

invention provides methods of inhibiting MEK activity in a mammal by contacting said mammal with an amount of a compound described herein sufficient to inhibit the activity of MEK in said mammal. In some embodiments, the invention provides methods of inhibiting MEK activity in a human by contacting said human with an amount of a compound
5 described herein sufficient to inhibit the activity of MEK in said human.

Abnormal cell growth

[00186] Also described herein are compounds, pharmaceutical compositions and methods for inhibiting abnormal cell growth. In some embodiments, the abnormal cell
10 growth occurs in a mammal. Methods for inhibiting abnormal cell growth comprise administering an effective amount of a compound of formula I, or a pharmaceutically acceptable salt, thereof, wherein abnormal cell growth is inhibited. Methods for inhibiting abnormal cell growth in a mammal comprise administering to the mammal an amount of a compound of formula I, or a pharmaceutically acceptable salt, thereof, wherein the amounts
15 of the compound, or salt, is effective in inhibiting abnormal cell growth in the mammal.

[00187] In some embodiments, the methods comprise administering an effective amount of a compound of formula I, or a pharmaceutically acceptable salt, thereof, in combination with an amount of a chemotherapeutic, wherein the amounts of the compound, or its salt, and of the chemotherapeutic are together effective in inhibiting abnormal cell
20 growth. Many chemotherapeutics are presently known in the art and can be used in combination with the compounds of the invention. In some embodiments, the chemotherapeutic is selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-
25 hormones, angiogenesis inhibitors, and anti-androgens.

[00188] Also described are methods for inhibiting abnormal cell growth in a mammal comprising administering to the mammal an amount of a compound of formula I, or a pharmaceutically acceptable salt, thereof, in combination with radiation therapy, wherein the amounts of the compound, or its salt, is in combination with the radiation therapy
30 effective in inhibiting abnormal cell growth or treating the hyperproliferative disorder in the mammal. Techniques for administering radiation therapy are known in the art, and these techniques can be used in the combination therapy described herein. The administration of

the compound of formula I in this combination therapy can be determined as described herein.

[00189] The invention also relates to a method of and to a pharmaceutical composition of inhibiting abnormal cell growth in a mammal which comprises an amount of
5 a compound of formula I, or a pharmaceutically acceptable salt thereof, or an isotopically-labeled derivative thereof, and an amount of one or more substances selected from anti-angiogenesis agents, signal transduction inhibitors, and antiproliferative agents.

[00190] Anti-angiogenesis agents, such as MMP-2 (matrix-metalloproteinase 2) inhibitors, MMP-9 (matrix-metalloproteinase 9) inhibitors, and COX-11 (cyclooxygenase
10 11) inhibitors, can be used in conjunction with a compound of the present invention and pharmaceutical compositions described herein. Examples of useful COX-II inhibitors include CELEBREXTM (alecoxib), valdecoxib, and rofecoxib. Examples of useful matrix metalloproteinase inhibitors are described in WO 96/33172 (published October 24, 1996), WO 96/27583 (published March 7, 1996), European Patent Application No. 97304971.1
15 (filed July 8, 1997), European Patent Application No. 99308617.2 (filed October 29, 1999), WO 98/07697 (published February 26, 1998), WO 98/03516 (published January 29, 1998), WO 98/34918 (published August 13, 1998), WO 98/34915 (published August 13, 1998), WO 98/33768 (published August 6, 1998), WO 98/30566 (published July 16, 1998), European Patent Publication 606,046 (published July 13, 1994), European Patent Publication 931, 788
20 (published July 28, 1999), WO 90/05719 (published May 31, 1990), WO 99/52910 (published October 21, 1999), WO 99/52889 (published October 21, 1999), WO 99/29667 (published June 17, 1999), PCT International Application No. PCT/IB98/01113 (filed July 21, 1998), European Patent Application No. 99302232.1 (filed March 25, 1999), Great Britain Patent Application No. 9912961.1 (filed June 3, 1999), United States Provisional
25 Application No. 60/148,464 (filed August 12, 1999), United States Patent 5,863, 949 (issued January 26, 1999), United States Patent 5,861, 510 (issued January 19, 1999), and European Patent Publication 780,386 (published June 25, 1997), all of which are incorporated herein in their entireties by reference. Some MMP-2 and MMP-9 inhibitors have little or no activity inhibiting MMP-1, while some selectively inhibit MMP-2 and/or AMP-9 relative to
30 the other matrix-metalloproteinases (i. e., MAP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP- 7, MMP-8, MMP-10, MMP-11, MMP-12, and MMP-13). Some specific examples of MMP inhibitors useful in the present invention are AG-3340, RO 32-3555, and RS 13-0830.

Modes of Administration

[00191] Described herein are compounds of formula I or a pharmaceutically acceptable salt thereof. Also described, are pharmaceutical compositions comprising a compound of formula I or a pharmaceutically acceptable salt, thereof. The compounds and compositions described herein may be administered either alone or in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice.

[00192] Administration of the compounds and compositions described herein can be effected by any method that enables delivery of the compounds to the site of action. These methods include oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intraperitoneal, intramuscular, intravascular or infusion), topical, and rectal administration. For example, compounds described herein can be administered locally to the area in need of treatment. This may be achieved by, for example, but not limited to, local infusion during surgery, topical application, e.g., cream, ointment, injection, catheter, or implant, said implant made, e.g., out of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. The administration can also be by direct injection at the site (or former site) of a tumor or neoplastic or pre-neoplastic tissue. Those of ordinary skill in the art are familiar with formulation and administration techniques that can be employed with the compounds and methods of the invention, e.g., as discussed in Goodman and Gilman, *The Pharmacological Basis of Therapeutics*, current ed.; Pergamon; and Remington's, *Pharmaceutical Sciences* (current edition), Mack Publishing Co., Easton, Pa.

[00193] The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous, intraarticular, and intramedullary), intraperitoneal, transmucosal, transdermal, rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. 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. All methods include the step of bringing into association a compound of the subject invention or a pharmaceutically acceptable salt, thereof ("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 into the desired formulation.

[00194] Formulations suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a 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.

[00195] Pharmaceutical preparations which are useful for oral administration include tablets, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. Tablets may be 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 binders, inert diluents, or lubricating, surface active or dispersing agents. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. All formulations for oral administration should be in dosages suitable for such administration. The push-fit capsules or tablets can contain the active ingredient; in admixture with a filler such as microcrystalline cellulose, silicified microcrystalline cellulose, pregelatinized starch, lactose, dicalcium phosphate, or compressible sugar; a binder such as hypromellose, povidone or starch paste; a disintegrant such as croscarmellose sodium, crospovidone or sodium starch glycolate; a surfactant such as sodium lauryl sulfate and/or lubricants and processing aides such as talc, magnesium stearate, stearic acid or colloidal silicon dioxide and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions are useful, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or Dragee coatings for identification or to characterize different combinations of active compound doses.

[00196] Pharmaceutical preparations may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as
5 suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain
formulatory agents such as suspending, stabilizing and/or dispersing agents. The
formulations may be presented in unit-dose or multi-dose containers, for example sealed
ampoules and vials, and may be stored in powder form or in a freeze-dried (lyophilized)
condition requiring only the addition of the sterile liquid carrier, for example, saline or
10 sterile pyrogen-free water, immediately prior to use. Extemporaneous injection solutions
and suspensions may be prepared from sterile powders, granules and tablets of the kind
previously described.

[00197] Formulations for parenteral administration include aqueous and non-
aqueous (oily) sterile injection solutions of the active compounds which may contain
15 antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with
the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which
may include suspending agents and thickening agents. Suitable lipophilic solvents or
vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl
oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances
20 which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose,
sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or
agents which increase the solubility of the compounds to allow for the preparation of highly
concentrated solutions.

[00198] Pharmaceutical preparations may also be formulated as a depot
25 preparation. Such long acting formulations may be administered by implantation (for
example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for
example, the compounds may be formulated with suitable polymeric or hydrophobic
materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as
sparingly soluble derivatives, for example, as a sparingly soluble salt.

30 [00199] For buccal or sublingual administration, the compositions may take the
form of tablets, lozenges, pastilles, or gels formulated in conventional manner. Such
compositions may comprise the active ingredient in a flavored basis such as sucrose and
acacia or tragacanth.

[00200] Pharmaceutical preparations may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter, polyethylene glycol, or other glycerides.

[00201] Pharmaceutical preparations may be administered topically, that is by non-systemic administration. This includes the application of a compound of the present invention externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

[00202] Pharmaceutical preparations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as gels, liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, for instance from 1% to 2% by weight of the formulation. It may however comprise as much as 10% w/w or may comprise less than 5% w/w, or from 0.1% to 1% w/w of the formulation.

[00203] Pharmaceutical preparations for administration by inhalation are conveniently delivered from an insufflator, nebulizer pressurized packs or other convenient means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Alternatively, for administration by inhalation or insufflation, pharmaceutical preparations may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form, in for example, capsules, cartridges, gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

[00204] It should be understood that in addition to the ingredients particularly mentioned above, the compounds and compositions described herein may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

Formulations

[00205] The compounds or compositions described herein can be delivered in a vesicle, e.g., a liposome (see, for example, Langer, *Science* 1990, 249,1527-1533; Treat et al., *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Bernstein and Fidler, Ed., Liss, N.Y., pp. 353-365, 1989). The compounds and pharmaceutical compositions described herein can also be delivered in a controlled release system. In one embodiment, a pump may be used (see, Sefton, 1987, CRC Crit. Ref. Biomed. Eng. 14:201; Buchwald et al. *Surgery*, 1980 88, 507; Saudek et al. *N. Engl. J. Med.* 1989, 321, (574). Additionally, a controlled release system can be placed in proximity of the therapeutic target. (See, Goodson, *Medical Applications of Controlled Release*, 1984, Vol. 2, pp. 115-138). The pharmaceutical compositions described herein can also contain the active ingredient in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions, and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, fillers such as microcrystalline cellulose, silicified microcrystalline cellulose, pregelatinized starch, lactose, dicalcium phosphate, or compressible sugar; binders such as hypromellose, povidone or starch paste; disintegrants such as croscarmellose sodium, crospovidone or sodium starch glycolate; a surfactant such as sodium lauryl sulfate and/or lubricants and processing aides such as talc, magnesium stearate, stearic acid or colloidal silicon dioxide and, optionally,. The tablets may be un-coated or coated by known techniques to mask the taste of the drug or delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a water soluble taste masking material such as hydroxypropylmethyl-cellulose or hydroxypropylcellulose, or a time delay material such as ethyl cellulose, or cellulose acetate butyrate may be employed as appropriate. Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active

ingredient is mixed with water soluble carrier such as polyethyleneglycol or an oil medium, for example peanut oil, liquid paraffin, or olive oil. The capsule and tablet dosage forms may be prepared by various processing techniques including dry blending and wet granulation techniques. In the dry blending method of manufacture the drug substance may be incorporated into the dosage form by dry blending with the excipients followed by encapsulation into a capsule shell or compression into a tablet form. The dry blending operation may be approached in a stepwise manner and include screening steps between the blending steps to facilitate formation of a uniform blend. In the wet granulation method of manufacture the drug substance may be added to the dry excipients and mixed prior to the addition of the binder solution or the drug substance may be dissolved and added as a solution as part of granulation. In the wet granulation technique the surfactant, if used, may be added to the dry excipients or added to the binder solution and incorporated in a solution form. Capsule dosage forms may also be manufactured by dissolving the drug substance in a material that can be filled into and is compatible with hard gelatin capsule shells that can be subsequently banded and sealed. Capsule and tablet dosage forms may also be produced by dissolving the drug substance in a material such a molten form of a high molecular weight polyethylene glycol and cooling to a solid form, milling and incorporating this material into conventional capsule and tablet manufacturing processes.

[00206] Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

[00207] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as butylated hydroxyanisole or alpha-tocopherol.

[00208] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[00209] Pharmaceutical compositions may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening agents, flavoring agents, preservatives and antioxidants.

[00210] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, flavoring and coloring agents and antioxidant.

[00211] Pharmaceutical compositions may be in the form of a sterile injectable aqueous solution. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. The sterile injectable preparation may also be a sterile injectable oil-in-water microemulsion where the active ingredient is dissolved in the oily phase. For example, the active ingredient may be first dissolved in a mixture of soybean oil and lecithin. The oil solution then introduced into a water and glycerol mixture and processed to form a microemulsion. The injectable solutions or microemulsions may be introduced into a patient's blood-stream by local bolus injection.

Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulating concentration of the instant compound. In order to maintain such a constant concentration, a continuous intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS™ model 5400

5 intravenous pump. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension for intramuscular and subcutaneous administration. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or
10 suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

15 [00212] Pharmaceutical compositions may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the inhibitors with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter, glycerinated gelatin, hydrogenated
20 vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

[00213] Creams, ointments, jellies, solutions or suspensions, etc., containing a compound or composition of the invention are useful for topical administration. As used herein, topical application can include mouth washes and gargles.

25 [00214] Pharmaceutical compositions may be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art.

30 *Doses*

[00215] The amount of pharmaceutical compositions administered will firstly be dependent on the mammal being treated. In the instances where pharmaceutical compositions are administered to a human subject, the daily dosage will normally be

determined by the prescribing physician with the dosage generally varying according to the age, sex, diet, weight, general health and response of the individual patient, the severity of the patient's symptoms, the precise indication or condition being treated, the severity of the indication or condition being treated, time of administration, route of administration, the disposition of the composition, rate of excretion, drug combination, and the discretion of the prescribing physician. Also, the route of administration may vary depending on the condition and its severity. The pharmaceutical composition may be in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, *e.g.*, an effective amount to achieve the desired purpose.

Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small amounts until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired. The amount and frequency of administration of the compounds described herein, and if applicable other therapeutic agents and/or therapies, will be regulated according to the judgment of the attending clinician (physician) considering such factors as described above. Thus the amount of pharmaceutical composition to be administered may vary widely. Administration may occur in an amount of between about 0.001 mg/kg of body weight to about 100 mg/kg of body weight per day (administered in single or divided doses), or at least about 0.1 mg/kg of body weight per day. A particular therapeutic dosage can include, *e.g.*, from about 0.01 mg to about 7000 mg of compound, or, *e.g.*, from about 0.05 mg to about 2500 mg. The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, from about 1 mg to 300 mg, or 10 mg to 200 mg, according to the particular application. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, *e.g.* by dividing such larger doses into several small doses for administration throughout the day. The amount administered will vary depending on the particular IC_{50} value of the compound used. In combination applications in which the compound is not the sole therapy, it may be possible to administer lesser amounts of compound and still have therapeutic or prophylactic effect.

Dosage Forms

[00216] The pharmaceutical composition may, for example, be in a form suitable for oral administration as a tablet, capsule, pill, powder, sustained release formulations, solution, suspension, for parenteral injection as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. The pharmaceutical composition may be in unit dosage forms suitable for single administration of precise dosages. The pharmaceutical composition will include a conventional pharmaceutical carrier or excipient and a compound according to the invention as an active ingredient. In addition, it may include other medicinal or pharmaceutical agents, carriers, adjuvants, etc.

[00217] Exemplary parenteral administration forms include solutions or suspensions of active compounds in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, if desired.

[00218] Suitable pharmaceutical carriers include inert diluents or fillers, water and various organic solvents. The pharmaceutical compositions may, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus for oral administration, tablets containing various excipients, such as citric acid may be employed together with various disintegrants such as starch, alginic acid and certain complex silicates and with binding agents such as sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tableting purposes. Solid compositions of a similar type may also be employed in soft and hard filled gelatin capsules, including lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration the active compound therein may be combined with various sweetening or flavoring agents, coloring matters or dyes and, if desired, emulsifying agents or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin, or combinations thereof.

[00219] Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known, or will be apparent, to those skilled in this art. For examples, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Ester, Pa., 18th Edition (1990).

Combination Therapies

[00220] The compounds described herein or a pharmaceutically acceptable salt, thereof may be administered as a sole therapy. The compounds described herein or a pharmaceutically acceptable salt, thereof may also be administered in combination with another therapy or therapies.

5 [00221] By way of example only, if one of the side effects experienced by a patient upon receiving one of the compounds described herein is hypertension, then it may be appropriate to administer an anti-hypertensive agent in combination with the compound. Or, by way of example only, the therapeutic effectiveness of one of the compounds described
10 herein may be enhanced by administration of an adjuvant (i.e., by itself the adjuvant may only have minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced). Or, by way of example only, the benefit experienced by a patient may be increased by administering one of the compounds described herein with another therapeutic agent (which also includes a therapeutic regimen)
15 that also has therapeutic benefit. By way of example only, in a treatment for diabetes involving administration of one of the compounds described herein, increased therapeutic benefit may result by also providing the patient with another therapeutic agent for diabetes. In any case, regardless of the disease, disorder or condition being treated, the overall benefit experienced by the patient may simply be additive of the two therapeutic agents or the
20 patient may experience a synergistic benefit.

[00222] Other therapies include, but are not limited to administration of other therapeutic agents, radiation therapy or both. In the instances where the compounds described herein are administered with other therapeutic agents, the compounds described herein need not be administered in the same pharmaceutical composition as other
25 therapeutic agents, and may, because of different physical and chemical characteristics, be administered by a different route. For example, the compounds/compositions may be administered orally to generate and maintain good blood levels thereof, while the other therapeutic agent may be administered intravenously. The determination of the mode of administration and the advisability of administration, where possible, in the same
30 pharmaceutical composition, is well within the knowledge of the skilled clinician. The initial administration can be made according to established protocols known in the art, and then, based upon the observed effects, the dosage, modes of administration and times of administration can be modified by the skilled clinician. The particular choice of compound

(and where appropriate, other therapeutic agent and/or radiation) will depend upon the diagnosis of the attending physicians and their judgment of the condition of the patient and the appropriate treatment protocol. Other therapeutic agents may include chemotherapeutic agents, such as anti-tumor substances, for example those selected from, mitotic inhibitors, for example vinblastine; alkylating agents, for example cis-platin, carboplatin and cyclophosphamide; anti-metabolites, for example 5-fluorouracil, cytosine arabinoside and hydroxyurea, or, for example, an anti-metabolite disclosed in European Patent Application No. 239362 such as N- (5- [N- (3, 4-dihydro-2-methyl-4- oxoquinazolin-6-ylmethyl)-N-methylamino]-2-thenoyl)-L-glutamic acid; growth factor inhibitors; cell cycle inhibitors; intercalating antibiotics, for example adriamycin and bleomycin; enzymes, for example, interferon; and anti-hormones, for example anti- estrogens such as NolvadexTM (tamoxifen) or, for example anti-androgens such as CasodexTM (4'-cyano-3- (4-fluorophenylsulphonyl)-2-hydroxy-2-methyl-3'- (trifluoromethyl) propionanilide). Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of treatment.

[00223] The compounds and compositions described herein (and where appropriate chemotherapeutic agent and/or radiation) may be administered concurrently (*e.g.*, simultaneously, essentially simultaneously or within the same treatment protocol) or sequentially, depending upon the nature of the disease, the condition of the patient, and the actual choice of chemotherapeutic agent and/or radiation to be administered in conjunction (*i.e.*, within a single treatment protocol) with the compound/composition.

[00224] In combinational applications and uses, the compound/composition and the chemotherapeutic agent and/or radiation need not be administered simultaneously or essentially simultaneously, and the initial order of administration of the compound/composition, and the chemotherapeutic agent and/or radiation, may not be important. Thus, the compounds/compositions of the invention may be administered first followed by the administration of the chemotherapeutic agent and/or radiation; or the chemotherapeutic agent and/or radiation may be administered first followed by the administration of the compounds/compositions of the invention. This alternate administration may be repeated during a single treatment protocol. The determination of the order of administration, and the number of repetitions of administration of each therapeutic agent during a treatment protocol, is well within the knowledge of the skilled physician after evaluation of the disease being treated and the condition of the patient. For example, the

chemotherapeutic agent and/or radiation may be administered first, especially if it is a cytotoxic agent, and then the treatment continued with the administration of the compounds/compositions of the invention followed, where determined advantageous, by the administration of the chemotherapeutic agent and/or radiation, and so on until the treatment protocol is complete. Thus, in accordance with experience and knowledge, the practicing physician can modify each protocol for the administration of a compound/composition for treatment according to the individual patient's needs, as the treatment proceeds. The attending clinician, in judging whether treatment is effective at the dosage administered, will consider the general well-being of the patient as well as more definite signs such as relief of disease-related symptoms, inhibition of tumor growth, actual shrinkage of the tumor, or inhibition of metastasis. Size of the tumor can be measured by standard methods such as radiological studies, *e.g.*, CAT or MRI scan, and successive measurements can be used to judge whether or not growth of the tumor has been retarded or even reversed. Relief of disease-related symptoms such as pain, and improvement in overall condition can also be used to help judge effectiveness of treatment.

[00225] Specific, non-limiting examples of possible combination therapies include use of the compounds of the invention with agents found in the following pharmacotherapeutic classifications as indicated below. These lists should not be construed to be closed, but should instead serve as illustrative examples common to the relevant therapeutic area at present. Moreover, combination regimens may include a variety of routes of administration and should include oral, intravenous, intraocular, subcutaneous, dermal, and inhaled topical.

[00226] For the treatment of oncologic diseases, proliferative disorders, and cancers, compounds according to the present invention may be administered with an agent selected from the group comprising: aromatase inhibitors, antiestrogen, anti-androgen, corticosteroids, gonadorelin agonists, topoisomerase 1 and 2 inhibitors, microtubule active agents, alkylating agents, nitrosoureas, antineoplastic antimetabolites, platinum containing compounds, lipid or protein kinase targeting agents, IMiDs, protein or lipid phosphatase targeting agents, anti-angiogenic agents, Akt inhibitors, IGF-I inhibitors, FGF3 modulators, mTOR inhibitors, Smac mimetics, HDAC inhibitors, agents that induce cell differentiation, bradykinin 1 receptor antagonists, angiotensin II antagonists, cyclooxygenase inhibitors, heparanase inhibitors, lymphokine inhibitors, cytokine inhibitors, IKK inhibitors, P38MAPK inhibitors, ARRY-797, HSP90 inhibitors, multikinase inhibitors,

bisphosphonates, rapamycin derivatives, anti-apoptotic pathway inhibitors, apoptotic pathway agonists, PPAR agonists, RAR agonists, inhibitors of Ras isoforms, telomerase inhibitors, protease inhibitors, metalloproteinase inhibitors, aminopeptidase inhibitors, SHIP activators - AQX-MN100, Humax-CD20 (ofatumumab), CD20 antagonists, IL2-diphtheria toxin fusions.

[00227] For the treatment of oncologic diseases, proliferative disorders, and cancers, compounds according to the present invention may be administered with an agent selected from the group comprising: dacarbazine (DTIC), actinomycins C₂, C₃, D, and F₁, cyclophosphamide, melphalan, estramustine, maytansinol, rifamycin, streptovaricin, doxorubicin, daunorubicin, epirubicin, idarubicin, detorubicin, carminomycin, idarubicin, epirubicin, esorubicin, mitoxantrone, bleomycins A, A₂, and B, camptothecin, Irinotecan.RTM., Topotecan.RTM., 9-aminocamptothecin, 10,11 - methylenedioxycamptothecin, 9-nitrocamptothecin, bortezomib, temozolomide, TAS103, NPI0052, combretastatin, combretastatin A-2, combretastatin A-4, calicheamicins, neocarzinostatsins, epothilones A B, C, and semi-synthetic variants, Herceptin.RTM., Rituxan.RTM., CD40 antibodies, asparaginase, interleukins, interferons, leuprolide, and pegaspargase, 5-fluorouracil, fluorodeoxyuridine, ptorafur, 5'-deoxyfluorouridine, UFT, MITC, S-1 capecitabine, diethylstilbestrol, tamoxifen, toremefine, tolmodex, thymitaq, flutamide, fluoxymesterone, bicalutamide, finasteride, estradiol, trioxifene, dexamethasone, leuproelin acetate, estramustine, droloxifene, medroxyprogesterone, megestrol acetate, aminoglutethimide, testolactone, testosterone, diethylstilbestrol, hydroxyprogesterone, mitomycins A, B and C, porfiromycin, cisplatin, carboplatin, oxaliplatin, tetraplatin, platinum-DACH, ormaplatin, thalidomide, lenalidomide, CI-973, telomestatin, CHIR258, Rad 001, SAHA, Tubacin, 17-AAG, sorafenib, JM-216, podophyllotoxin, epipodophyllotoxin, etoposide, teniposide, Tarceva.RTM., Iressa.RTM., Imatinib.RTM., Miltefosine.RTM., Perifosine.RTM., aminopterin, methotrexate, methopterin, dichloro-methotrexate, 6-mercaptopurine, thioguanine, azattuprine, allopurinol, cladribine, fludarabine, pentostatin, 2-chloroadenosine, deoxycytidine, cytosine arabinoside, cytarabine, azacitidine, 5-azacytosine, gencitabine, 5-azacytosine-arabinoside, vincristine, vinblastine, vinorelbine, leurosine, leurosidine and vindesine, paclitaxel, taxotere and docetaxel.

[00228] For the treatment of inflammatory diseases or pain, compounds and pharmaceutically acceptable salts of the compounds according to the present invention may

be administered with an agent selected from the group comprising: corticosteroids, non-steroidal anti-inflammatories, muscle relaxants and combinations thereof with other agents, anaesthetics and combinations thereof with other agents, expectorants and combinations thereof with other agents, antidepressants, anticonvulsants and combinations thereof;

5 antihypertensives, opioids, topical cannabinoids, capsaicin, betamethasone dipropionate (augmented and nonaugmented), betamethasone valerate, clobetasol propionate, prednisone, methyl prednisolone, diflorasone diacetate, halobetasol propionate, amcinonide, dexamethasone, dexosimethasone, fluocinolone acetonide, fluocinonide, halocinonide, clocortalone pivalate, dexosimetasone, flurandrenalide, salicylates, ibuprofen, ketoprofen,

10 etodolac, diclofenac, meclofenamate sodium, naproxen, piroxicam, celecoxib, cyclobenzaprine, baclofen, cyclobenzaprine/lidocaine, baclofen/cyclobenzaprine, cyclobenzaprine/lidocaine/ketoprofen, lidocaine, lidocaine/deoxy-D-glucose, prilocaine, EMLA Cream (Eutectic Mixture of Local Anesthetics (lidocaine 2.5% and prilocaine 2.5%)), guaifenesin, guaifenesin/ketoprofen/cyclobenzaprine, amitriptyline, doxepin,

15 desipramine, imipramine, amoxapine, clomipramine, nortriptyline, protriptyline, duloxetine, mirtazepine, nisoxetine, maprotiline, reboxetine, fluoxetine, fluvoxamine, carbamazepine, felbamate, lamotrigine, topiramate, tiagabine, oxcarbazepine, carbamazepine, zonisamide, mexiletine, gabapentin/clonidine, gabapentin/carbamazepine, carbamazepine/cyclobenzaprine, antihypertensives including clonidine, codeine,

20 loperamide, tramadol, morphine, fentanyl, oxycodone, hydrocodone, levorphanol, butorphanol, menthol, oil of wintergreen, camphor, eucalyptus oil, turpentine oil; CB1/CB2 ligands, acetaminophen, infliximab, nitric oxide synthase inhibitors, particularly inhibitors of inducible nitric oxide synthase, PDE4 inhibitors -- similar mechanism to Ibuprofen (AV-411), CDC-801, JNK inhibitors - CC-401, Combination TNF/PDE4 inhibitors - CDC-

25 998, IL1 antagonists e.g. Anakinra - Kineret, AMG 108, (mAb) that targets IL-1, SHIP activators - AQX-MN100, C5 antagonists, C5a inhibitors, Pexelizumab, Pyrimidine synthesis inhibitors, lymphokine inhibitors, cytokine inhibitors, IKK inhibitors, P38MAPK inhibitors, ARRY-797, HSP90 inhibitors, multikinase inhibitors, bisphosphonates, PPAR agonists, Cox1 and Cox 2 inhibitors, Anti-CD4 therapy, B-cell inhibitors, COX/LOX dual

30 inhibitors, Immunosuppressive agents, iNOS inhibitors, NSAIDs, sPLA2 inhibitors, Colchicine, allopurinol, oxypurinol, Gold, Ridaura - Auranofin, febuxostat, Puricase, PEG-uricase formulations, Benzbromarone, Long-acting beta-2 agonists (LABAs), salmeterol (Serevent Diskus) and formoterol (Foradil), Leukotriene modifiers include montelukast

(Singulair) and zafirlukast (Accolate). Inhaled cromolyn (Intal) or nedocromil (Tilade), Theophylline. Short-acting beta-2 agonists, Ipratropium (Atrovent), Immunotherapy- (Allergy-desensitization shots), Anti-IgE monoclonal antibodies – Xolair, Common DMARDs include hydroxychloroquine (Plaquenil), the gold compound auranofin (Ridaura),

5 sulfasalazine (Azulfidine), minocycline (Dynacin, Minocin) and methotrexate (Rheumatrex), leflunomide (Arava), azathioprine (Imuran), cyclosporine (Neoral, Sandimmune) and cyclophosphamide (Cytoxan), Antibiotics, CD80 antagonists, costimulatory factor antagonists, Humax-CD20 (ofatumumab); CD20 antagonists, MEK inhibitors, NF kappa B inhibitors, anti B-cell antibodies, denosumab, mAb that specifically

10 targets the receptor activator of nuclear factor kappa B ligand (RANKL). IL17 inactivating anti-bodies, IL-17 receptor antagonists/inhibitors, CTLA inhibitors, CD20 inhibitors, soluble VEGFR-1 receptors, anti-VEGFR-1 receptor antibodies, anti-VEGF antibodies, integrin receptor antagonist, Selectin inhibitors, P-selectin and E-selectin inhibitors, Phospholipase A2 Inhibitors, Lipoxigenase Inhibitors, RANKL and RANK

15 antagonists/antibodies, Osteoprotegerin antagonists, Lymphotoxin inhibitors, B-lymphocyte stimulator, MCP-1 inhibitors, MIF inhibitors, inhibitors of : CD2, CD3, CD4, CD25, CD40 and CD40 Ligand CD152 (CTLA4), Macrolide immunosuppressants, Selective inhibitors of nucleotide metabolism, Inhibitors of chemotaxis, CXC receptor and CXC ligand inhibitors, Chemokine Antagonists, leukocyte chemotaxis inhibitors Adhesion

20 Molecule blockers, Selectins Lymphocyte Function Antigen-1 (LFA-1, CD11a) antagonists, Very Late Antigen-4 (VLA-4) antagonists, Matrix Metalloprotease Inhibitors, Elastase Inhibitors, Cathepsin Inhibitors.

[00229] For the treatment of ophthalmologic disorders and diseases of the eye, compounds and pharmaceutically acceptable salts of the compounds according to the

25 present invention may be administered with an agent selected from the group comprising: beta-blockers, carbonic anhydrase inhibitors, .alpha.- and .beta.-adrenergic antagonists including al-adrenergic antagonists, .alpha.2 agonists, miotics, prostaglandin analogs, corticosteroids, and immunosuppressant agents.

[00230] For the treatment of ophthalmologic disorders and diseases of the eye,

30 compounds pharmaceutically acceptable salts of the compounds according to the present invention may be administered with an agent selected from the group comprising: timolol, betaxolol, levobetaxolol, carteolol, levobunolol, propranolol, brinzolamide, dorzolamide, nipradilol, iopidine, brimonidine, pilocarpine, epinephrine, latanoprost, travoprost,

bimatoprost, unoprostone, dexamethasone, prednisone, methylprednisolone, azathioprine, cyclosporine, and immunoglobulins.

[00231] For the treatment of autoimmune disorders, compounds pharmaceutically acceptable salts of the compounds according to the present invention may be administered with an agent selected from the group comprising: corticosteroids, immunosuppressants, prostaglandin analogs and antimetabolites.

[00232] For the treatment of autoimmune disorders, compounds according to the present invention may be administered with an agent selected from the group comprising: dexamethasone, prednisone, methylprednisolone, azathioprine, cyclosporine, immunoglobulins, latanoprost, travoprost, bimatoprost, unoprostone, infliximab, rituximab, methotrexate, non-steroidal anti-inflammatories, muscle relaxants and combinations thereof with other agents, anaesthetics and combinations thereof with other agents, expectorants and combinations thereof with other agents, antidepressants, anticonvulsants and combinations thereof, antihypertensives, opioids, topical cannabinoids, and other agents, such as capsaicin, betamethasone dipropionate (augmented and nonaugmented), betamethasone valerate, clobetasol propionate, prednisone, methyl prednisolone, diflorasone diacetate, halobetasol propionate, amcinonide, dexamethasone, dexosimethasone, fluocinolone acetonide, fluocinonide, halocinonide, clocortalone pivalate, dexosimetasone, flurandrenalide, salicylates, ibuprofen, ketoprofen, etodolac, diclofenac, meclofenamate sodium, naproxen, piroxicam, celecoxib, cyclobenzaprine, baclofen, cyclobenzaprine/lidocaine, baclofen/cyclobenzaprine, cyclobenzaprine/lidocaine/ketoprofen, lidocaine, lidocaine/deoxy-D-glucose, prilocaine, EMLA Cream (Eutectic Mixture of Local Anesthetics (lidocaine 2.5% and prilocaine 2.5%)), guaifenesin, guaifenesin/ketoprofen/cyclobenzaprine, amitriptyline, doxepin, desipramine, imipramine, amoxapine, clomipramine, nortriptyline, protriptyline, duloxetine, mirtazepine, nisoxetine, maprotiline, reboxetine, fluoxetine, fluvoxamine, carbamazepine, felbamate, lamotrigine, topiramate, tiagabine, oxcarbazepine, carbamazepine, zonisamide, mexiletine, gabapentin/clonidine, gabapentin/carbamazepine, carbamazepine/cyclobenzaprine, antihypertensives including clonidine, codeine, loperamide, tramadol, morphine, fentanyl, oxycodone, hydrocodone, levorphanol, butorphanol, menthol, oil of wintergreen, camphor, eucalyptus oil, turpentine oil; CB1/CB2 ligands, acetaminophen, infliximab; nitric oxide synthase inhibitors, particularly inhibitors of inducible nitric oxide synthase; and other agents, such as capsaicin. PDE4 inhibitors –

- similar mechanism to Ibudilast (AV-411), CDC-801, JNK inhibitors - CC-401, Combination TNF/PDE4 inhibitors - CDC-998, IL1 antagonists e.g. Anakinra - Kineret, AMG 108, (mAb) that targets IL-1, SHIP activators - AQX-MN100, C5 antagonists, C5a inhibitors, Pexelizumab, Pyrimidine synthesis inhibitors, lymphokine inhibitors, cytokine
- 5 inhibitors, IKK inhibitors, P38MAPK inhibitors, ARRY-797, HSP90 inhibitors, multikinase inhibitors, bisphosphonates, PPAR agonists, Cox1 and cox 2 inhibitors, Anti-CD4 therapy, B-cell inhibitors, COX/LOX dual inhibitors, Immunosuppressive agents, iNOS inhibitors, NSAIDs, sPLA2 inhibitors, Colchicine, allopurinol, oxypurinol, Gold, Ridaura - Auranoftin, febuxostat, Puricase, PEG-uricase formulations, Benzbromarone,
- 10 Long-acting beta-2 agonists (LABAs), salmeterol (Serevent Diskus) and formoterol (Foradil), Leukotriene modifiers include montelukast (Singulair) and zafirlukast (Accolate). Inhaled cromolyn (Intal) or nedocromil (Tilade), Theophylline. Short-acting beta-2 agonists, Ipratropium (Atrovent), Immunotherapy-(Allergy-desensitization shots), Anti-IgE monoclonal antibodies - Xolair, Common DMARDs include hydroxychloroquine
- 15 (Plaquenil), the gold compound auranoftin (Ridaura), sulfasalazine (Azulfidine), minocycline (Dynacin, Minocin) and methotrexate (Rheumatrex), leflunomide (Arava), azathioprine (Imuran), cyclosporine (Neoral, Sandimmune) and cyclophosphamide (Cytosan), Antibiotics, CD80 antagonists, costimulatory factor antagonists, Humax-CD20 (ofatumumab); CD20 antagonists, MEK inhibitors, NF kappa B inhibitors, anti B-cell
- 20 antibodies, denosumab, mAb that specifically targets the receptor activator of nuclear factor kappa B ligand (RANKL). IL17 inactivating anti-bodies, IL-17 receptor antagonists/inhibitors, CTLA inhibitors, CD20 inhibitors, soluble VEGFR-1 receptors, anti-VEGFR-1 receptor antibodies, anti-VEGF antibodies, integrin receptor antagonist, Selectin inhibitors, P-selectin and E-selectin inhibitors, Phospholipase A2 Inhibitors ,
- 25 Lipoxigenase Inhibitors, RANKL and RANK antagonists/antibodies, Osteoprotegerin antagonists, Lymphotoxin inhibitors, B-lymphocyte stimulator, MCP-1 inhibitors, MIF inhibitors, inhibitors of : CD2, CD3, CD4 , CD25 , CD40 and CD40 Ligand CD152 (CTLA4), Macrolide immunosuppressants, Selective inhibitors of nucleotide metabolism, Inhibitors of chemotaxis, CXC receptor and CXC ligand inhibitors, Chemokine
- 30 Antagonists, leukocyte chemotaxis inhibitors Adhesion Molecule blockers, Selectins Lymphocyte Function Antigen-1 (LFA-1, CD11a) antagonists, Very Late Antigen-4 (VLA-4) antagonists, Matrix Metalloprotease Inhibitors, Elastase Inhibitors, Cathepsin Inhibitors.

[00233] For the treatment of metabolic disorders, compounds and pharmaceutically acceptable salts of the compounds according to the present invention may be administered with an agent selected from the group comprising: insulin, insulin derivatives and mimetics, insulin secretagogues, insulin sensitizers, biguanide agents, alpha-glucosidase inhibitors, 5 insulinotropic sulfonylurea receptor ligands, protein tyrosine phosphatase-1B (PTP-1B) inhibitors, GSK3 (glycogen synthase kinase-3) inhibitors, GLP-1 (glucagon like peptide-1), GLP-1 analogs, DPP-IV (dipeptidyl peptidase IV) inhibitors, RXR ligands sodium-dependent glucose co-transporter inhibitors, glycogen phosphorylase A inhibitors, an AGE breaker, PPAR modulators, LXR and FXR modulators, non-glitazone type PPARs agonist, 10 selective glucocorticoid antagonists, metformin, Glipizide, glyburide, Amaryl, meglitinides, nateglinide, repaglinide, PT-112, SB-517955, SB4195052, SB-216763, NN-57-05441, NN-57-05445, GW-0791, AGN-.sup.194.sup.204, T-1095, BAY R3401, acarbose Exendin-4, DPP728, LAF237, vildagliptin, MK-0431, saxagliptin, GSK23A, pioglitazone, rosiglitazone, (R)-1-{4-[5-methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-benzo- nesulfonyl}2,3-dihydro-1H-indole-2-carboxylic acid described in the patent 15 application WO 03/043985, as compound 19 of Example 4, and GI-262570.

Diseases

[00234] Described herein are methods of treating a disease in an individual suffering 20 from said disease comprising administering to said individual an effective amount of a compound of formula I or a pharmaceutically acceptable salt, thereof.

[00235] The invention also extends to the prophylaxis or treatment of any disease or disorder in which MEK kinase plays a role including, without limitation: oncologic, hematologic, inflammatory, ophthalmologic, neurological, immunologic, cardiovascular, 25 and dermatologic diseases as well as diseases caused by excessive or unregulated pro-inflammatory cytokine production including for example excessive or unregulated TNF, IL-1, IL-6 and IL-8 production in a human, or other mammal. The invention extends to such a use and to the use of the compounds for the manufacture of a medicament for treating such cytokine-mediated diseases or disorders. Further, the invention extends to the administration 30 to a human an effective amount of a MEK inhibitor for treating any such disease or disorder.

[00236] Diseases or disorders in which MEK kinase plays a role, either directly or via pro-inflammatory cytokines including the cytokines TNF, IL-1, IL-6 and IL-8, include,

without limitation: dry eye, glaucoma, autoimmune diseases, inflammatory diseases, destructive-bone disorders, proliferative disorders, neurodegenerative disorders, viral diseases, allergies, infectious diseases, heart attacks, angiogenic disorders, reperfusion/ischemia in stroke, vascular hyperplasia, organ hypoxia, cardiac hypertrophy, thrombin-induced platelet aggregation, and conditions associated with prostaglandin endoperoxidase synthetase-2 (COX-2).

[00237] In certain aspects of the invention, the disease is a hyperproliferative condition of the human or animal body, including, but not limited to cancer, hyperplasias, restenosis, inflammation, immune disorders, cardiac hypertrophy, atherosclerosis, pain, migraine, angiogenesis-related conditions or disorders, proliferation induced after medical conditions, including but not limited to surgery, angioplasty, or other conditions.

[00238] In further embodiments, said hyperproliferative condition is selected from the group consisting of hematologic and nonhematologic cancers. In yet further embodiments, said hematologic cancer is selected from the group consisting of multiple myeloma, leukemias, and lymphomas. In yet further embodiments, said leukemia is selected from the group consisting of acute and chronic leukemias. In yet further embodiments, said acute leukemia is selected from the group consisting of acute lymphocytic leukemia (ALL) and acute nonlymphocytic leukemia (ANLL). In yet further embodiments, said chronic leukemia is selected from the group consisting of chronic lymphocytic leukemia (CLL) and chronic myelogenous leukemia (CML). In further embodiments, said lymphoma is selected from the group consisting of Hodgkin's lymphoma and non-Hodgkin's lymphoma. In further embodiments, said hematologic cancer is multiple myeloma. In other embodiments, said hematologic cancer is of low, intermediate, or high grade. In other embodiments, said nonhematologic cancer is selected from the group consisting of: brain cancer, cancers of the head and neck, lung cancer, breast cancer, cancers of the reproductive system, cancers of the digestive system, pancreatic cancer, and cancers of the urinary system. In further embodiments, said cancer of the digestive system is a cancer of the upper digestive tract or colorectal cancer. In further embodiments, said cancer of the urinary system is bladder cancer or renal cell carcinoma. In further embodiments, said cancer of the reproductive system is prostate cancer.

[00239] Additional types of cancers which may be treated using the compounds and methods described herein include: cancers of oral cavity and pharynx, cancers of the respiratory system, cancers of bones and joints, cancers of soft tissue, skin cancers, cancers

of the genital system, cancers of the eye and orbit, cancers of the nervous system, cancers of the lymphatic system, and cancers of the endocrine system. In certain embodiments, these cancers may be selected from the group consisting of: cancer of the tongue, mouth, pharynx, or other oral cavity; esophageal cancer, stomach cancer, or cancer of the small intestine; colon cancer or rectal, anal, or anorectal cancer; cancer of the liver, intrahepatic bile duct, gallbladder, pancreas, or other biliary or digestive organs; laryngeal, bronchial, and other cancers of the respiratory organs; heart cancer, melanoma, basal cell carcinoma, squamous cell carcinoma, other non-epithelial skin cancer; uterine or cervical cancer; uterine corpus cancer; ovarian, vulvar, vaginal, or other female genital cancer; prostate, testicular, penile or other male genital cancer; urinary bladder cancer; cancer of the kidney; renal, pelvic, or urethral cancer or other cancer of the genito-urinary organs; thyroid cancer or other endocrine cancer; chronic lymphocytic leukemia; and cutaneous T-cell lymphoma, both granulocytic and monocytic.

[00240] Yet other types of cancers which may be treated using the compounds and methods described herein include: adenocarcinoma, angiosarcoma, astrocytoma, acoustic neuroma, anaplastic astrocytoma, basal cell carcinoma, blastoglioma, chondrosarcoma, choriocarcinoma, chordoma, craniopharyngioma, cutaneous melanoma, cystadenocarcinoma, endotheliosarcoma, embryonal carcinoma, ependymoma, Ewing's tumor, epithelial carcinoma, fibrosarcoma, gastric cancer, genitourinary tract cancers, glioblastoma multiforme, hemangioblastoma, hepatocellular carcinoma, hepatoma, Kaposi's sarcoma, large cell carcinoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, medullary thyroid carcinoma, medulloblastoma, meningioma mesothelioma, myelomas, myxosarcoma neuroblastoma, neurofibrosarcoma, oligodendroglioma, osteogenic sarcoma, epithelial ovarian cancer, papillary carcinoma, papillary adenocarcinomas, parathyroid tumors, pheochromocytoma, pinealoma, plasmacytomas, retinoblastoma, rhabdomyosarcoma, sebaceous gland carcinoma, seminoma, skin cancers, melanoma, small cell lung carcinoma, squamous cell carcinoma, sweat gland carcinoma, synovioma, thyroid cancer, uveal melanoma, and Wilm's tumor.

[00241] Also described are methods for the treatment of a hyperproliferative disorder in a mammal that comprise administering to said mammal a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt, thereof, in combination with an anti-tumor agent. In some embodiments, the anti-tumor agent is selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites,

intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzyme inhibitors, topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, anti-androgens, SHIP activators - AQX-MN100, Humax-CD20 (ofatumumab), CD20 antagonists, IL2-diphtheria toxin fusions.

5 [00242] The disease to be treated using the compounds, compositions and methods described herein may be a hematologic disorder. In certain embodiments, said hematologic disorder is selected from the group consisting of sickle cell anemia, myelodysplastic disorders (MDS), and myeloproliferative disorders. In further embodiments, said myeloproliferative disorder is selected from the group consisting of polycythemia vera,
10 myelofibrosis and essential thrombocythemia.

[00243] The compounds, compositions and methods described herein may be useful as anti-inflammatory agents with the additional benefit of having significantly less harmful side effects. The compounds, compositions and methods described herein are useful to treat arthritis, including but not limited to rheumatoid arthritis, spondyloarthropathies, ankylosing
15 spondylitis, gout, gouty arthritis, osteoarthritis, systemic lupus erythematosus, juvenile arthritis, acute rheumatic arthritis, enteropathic arthritis, neuropathic arthritis, psoriatic arthritis, and pyogenic arthritis. The compounds, compositions and methods described herein are also useful in treating osteoporosis and other related bone disorders. These compounds, compositions and methods described herein are also useful to treat
20 gastrointestinal conditions such as reflux esophagitis, diarrhea, inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis. The compounds, compositions and methods described herein may also be used in the treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis. In addition, the compounds, compositions and methods described herein are also useful in organ
25 transplant patients either alone or in combination with conventional immunomodulators. Yet further, the compounds, compositions and methods described herein are useful in the treatment of pruritis and vitiligo. In particular, compounds, compositions and methods described herein are useful in treating the particular inflammatory disease rheumatoid arthritis.

30 [00244] Further inflammatory diseases which may be prevented or treated include, without limitation: asthma, allergies, respiratory distress syndrome or acute or chronic pancreatitis. Furthermore, respiratory system diseases may be prevented or treated including but not limited to chronic obstructive pulmonary disease, and pulmonary fibrosis. In

addition, MEK kinase inhibitors described herein are also associated with prostaglandin endoperoxidase synthetase-2 (COX-2) production. Pro-inflammatory mediators of the cyclooxygenase pathway derived from arachidonic acid, such as prostaglandins, are produced by inducible COX-2 enzyme. Regulation of COX-2 would regulate these pro-inflammatory mediators, which affect a wide variety of cells and are important and critical inflammatory mediators of a wide variety of disease states and conditions. In particular, these inflammatory mediators have been implicated in pain, such as in the sensitization of pain receptors, and edema. Accordingly, additional MEK kinase-mediated conditions which may be prevented or treated include edema, analgesia, fever and pain such as neuromuscular pain, headache, dental pain, arthritis pain and pain caused by cancer.

[00245] Further, the disease to be treated by the compounds, compositions and methods described herein may be an ophthalmologic disorder. Ophthalmologic diseases and other diseases in which angiogenesis plays a role in pathogenesis, may be treated or prevented and include, without limitation, dry eye (including Sjogren's syndrome), macular degeneration, closed and wide angle glaucoma, retinal ganglion degeneration, ocular ischemia, retinitis, retinopathies, uveitis, ocular photophobia, and of inflammation and pain associated with acute injury to the eye tissue. The compounds, compositions and methods described herein are useful to treat glaucomatous retinopathy and/or diabetic retinopathy. The compounds, compositions and methods described herein are also useful to treat post-operative inflammation or pain as from ophthalmic surgery such as cataract surgery and refractive surgery.. In further embodiments, said ophthalmologic disorder is selected from the group consisting of dry eye, closed angle glaucoma and wide angle glaucoma.

[00246] Further, the disease to be treated by the compounds, compositions and methods described herein may be an autoimmune disease. Autoimmune diseases which may be prevented or treated include, but are not limited to: rheumatoid arthritis, inflammatory bowel disease, inflammatory pain, ulcerative colitis, Crohn's disease, periodontal disease, temporomandibular joint disease, multiple sclerosis, diabetes, glomerulonephritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Grave's disease, hemolytic anemia, autoimmune gastritis, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, atopic dermatitis, graft vs. host disease, and psoriasis. Inflammatory diseases which may be prevented or treated include, but are not limited to: asthma, allergies, respiratory distress syndrome or acute or chronic pancreatitis. In particular, compounds,

compositions and methods described herein are useful in treating the particular autoimmune diseases rheumatoid arthritis and multiple sclerosis.

[00247] Further, the disease to be treated by the compounds, compositions and methods described herein may be a dermatologic disorder. In certain embodiments, said
5 dermatologic disorder is selected from the group including, without limitation, melanoma, basal cell carcinoma, squamous cell carcinoma, and other non-epithelial skin cancer as well as psoriasis and persistent itch, and other diseases related to skin and skin structure, may be treated or prevented with MEK kinase inhibitors of this invention.

[00248] Metabolic diseases which may be treated or prevented include, without
10 limitation, metabolic syndrome, insulin resistance, and Type 1 and Type 2 diabetes. In addition, the compositions described herein may be useful to treat insulin resistance and other metabolic disorders such as atherosclerosis that are typically associated with an exaggerated inflammatory signaling.

[00249] The compounds, compositions and methods described herein are also useful
15 in treating tissue damage in such diseases as vascular diseases, migraine headaches, periarthritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, scleroderma, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephritis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, periodontitis, hypersensitivity, swelling
20 occurring after injury, ischemias including myocardial ischemia, cardiovascular ischemia, and ischemia secondary to cardiac arrest, and the like. The compounds, compositions and methods described herein may also be useful to treat allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, and atherosclerosis.

[00250] Further, the disease to be treated by the compounds, compositions and
25 methods described herein may be a cardiovascular condition. In certain embodiments, said cardiovascular condition is selected from the group consisting of atherosclerosis, cardiac hypertrophy, idiopathic cardiomyopathies, heart failure, angiogenesis-related conditions or disorders, and proliferation induced after medical conditions, including, but not limited to restenosis resulting from surgery and angioplasty.

30 [00251] Further, the disease to be treated by the compounds, compositions and methods described herein may be a neurological disorder. In certain embodiments, said neurologic disorder is selected from the group consisting of Parkinson's disease, Alzheimer's disease, Alzheimer's dementia, and central nervous system damage resulting

from stroke, ischemia and trauma. In other embodiments, said neurological disorder is selected from the group consisting of epilepsy, neuropathic pain, depression and bipolar disorders.

[00252] Further, the disease to be treated by the compounds, compositions and methods described herein may cancer such as acute myeloid leukemia, thymus, brain, lung, squamous cell, skin, eye, retinoblastoma, intraocular melanoma, oral cavity and oropharyngeal, bladder, gastric, stomach, pancreatic, bladder, breast, cervical, head, neck, renal, kidney, liver, ovarian, prostate, colorectal, esophageal, testicular, gynecological, thyroid, CNS, PNS, AIDS related AIDS-Related (e.g. Lymphoma and Kaposi's Sarcoma) or Viral-Induced cancer. In some embodiments, the compounds and compositions are for the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (e. g., psoriasis), restenosis, or prostate (e. g., benign prostatic hypertrophy (BPH)).

[00253] Further, the disease to be treated by the compounds, compositions and methods described herein may pancreatitis, kidney disease (including proliferative glomerulonephritis and diabetes- induced renal disease), pain, a disease related to vasculogenesis or angiogenesis, tumor angiogenesis, chronic inflammatory disease such as rheumatoid arthritis, inflammatory bowel disease, atherosclerosis, skin diseases such as psoriasis, eczema, and scleroderma, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, tendonitis, bursitis, sciatica, glioma, melanoma, Kaposi's sarcoma and ovarian, breast, lung, pancreatic, prostate, colon and epidermoid cancer in a mammal.

[00254] Further, the disease to be treated by the compounds, compositions and methods described herein may the prevention of blastocyte implantation in a mammal.

[00255] Patients that can be treated with the compounds described herein, or their pharmaceutically acceptable salts, according to the methods of this invention include, for example, patients that have been diagnosed as having psoriasis; restenosis; atherosclerosis; BPH; breast cancer such as a ductal carcinoma in duct tissue in a mammary gland, medullary carcinomas, colloid carcinomas, tubular carcinomas, and inflammatory breast cancer; ovarian cancer, including epithelial ovarian tumors such as adenocarcinoma in the ovary and an adenocarcinoma that has migrated from the ovary into the abdominal cavity; uterine cancer; cervical cancer such as adenocarcinoma in the cervix epithelial including squamous cell carcinoma and adenocarcinomas; prostate cancer, such as a prostate cancer

selected from the following: an adenocarcinoma or an adenocarcinoma that has migrated to the bone; pancreatic cancer such as epithelioid carcinoma in the pancreatic duct tissue and an adenocarcinoma in a pancreatic duct; bladder cancer such as a transitional cell carcinoma in urinary bladder, urothelial carcinomas (transitional cell carcinomas), tumors in the

5 urothelial cells that line the bladder, squamous cell carcinomas, adenocarcinomas, and small cell cancers; leukemia such as acute myeloid leukemia (AML), acute lymphocytic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, hairy cell leukemia, myelodysplasia, and myeloproliferative disorders; bone cancer; lung cancer such as non-small cell lung cancer (NSCLC), which is divided into squamous cell carcinomas,

10 adenocarcinomas, and large cell undifferentiated carcinomas, and small cell lung cancer; skin cancer such as basal cell carcinoma, melanoma, squamous cell carcinoma and actinic keratosis, which is a skin condition that sometimes develops into squamous cell carcinoma; eye retinoblastoma; cutaneous or intraocular (eye) melanoma; primary liver cancer (cancer that begins in the liver); kidney cancer; thyroid cancer such as papillary, follicular,

15 medullary and anaplastic; AIDS-related lymphoma such as diffuse large B-cell lymphoma, B-cell immunoblastic lymphoma and small non-cleaved cell lymphoma; Kaposi's Sarcoma; viral-induced cancers including hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatocellular carcinoma; human lymphotropic virus-type 1 (HTLV-1) and adult T-cell leukemia/lymphoma; and human papilloma virus (HPV) and cervical cancer; central

20 nervous system cancers (CNS) such as primary brain tumor, which includes gliomas (astrocytoma, anaplastic astrocytoma, or glioblastoma multiforme), Oligodendroglioma, Ependymoma, Meningioma, Lymphoma, Schwannoma, and Medulloblastoma; peripheral nervous system (PNS) cancers such as acoustic neuromas and malignant peripheral nerve sheath tumor (MPNST) including neurofibromas and schwannomas, malignant fibrous

25 cytoma, malignant fibrous histiocytoma, malignant meningioma, malignant mesothelioma, and malignant mixed Müllerian tumor; oral cavity and oropharyngeal cancer such as, hypopharyngeal cancer, laryngeal cancer, nasopharyngeal cancer, and oropharyngeal cancer; stomach cancer such as lymphomas, gastric stromal tumors, and carcinoid tumors; testicular cancer such as germ cell tumors (GCTs), which include seminomas and

30 nonseminomas, and gonadal stromal tumors, which include Leydig cell tumors and Sertoli cell tumors; thymus cancer such as thymomas, thymic carcinomas, Hodgkin disease, non-Hodgkin lymphomas carcinoids or carcinoid tumors; rectal cancer; and colon cancer.

Kits

[00256] The compounds, compositions and methods described herein provide kits for the treatment of disorders, such as the ones described herein. These kits comprise a compound, compounds or compositions described herein in a container and, optionally, instructions teaching the use of the kit according to the various methods and approaches described herein. Such kits may also include information, such as scientific literature references, package insert materials, clinical trial results, and/or summaries of these and the like, which indicate or establish the activities and/or advantages of the composition, and/or which describe dosing, administration, side effects, drug interactions, or other information useful to the health care provider.. Such information may be based on the results of various studies, for example, studies using experimental animals involving in vivo models and studies based on human clinical trials. Kits described herein can be provided, marketed and/or promoted to health providers, including physicians, nurses, pharmacists, formulary officials, and the like. Kits may also, in some embodiments, be marketed directly to the consumer.

[00257] The compounds described herein can be utilized for diagnostics and as research reagents. For example, the compounds described herein, either alone or in combination with other compounds, may be useful as tools in differential and/or combinatorial analyses to elucidate expression patterns of genes expressed within cells and tissues. As one non-limiting example, expression patterns within cells or tissues treated with one or more compounds are compared to control cells or tissues not treated with compounds and the patterns produced are analyzed for differential levels of gene expression as they pertain, for example, to disease association, signaling pathway, cellular localization, expression level, size, structure or function of the genes examined. These analyses can be performed on stimulated or unstimulated cells and in the presence or absence of other compounds which affect expression patterns.

[00258] Besides being useful for human treatment, the compounds and formulations of the present invention are also useful for veterinary treatment of companion animals (eg dogs, cats), exotic animals and farm animals (eg horses), including mammals, rodents, and the like.

[00259] The examples and preparations provided below further illustrate and exemplify the compounds of the present invention and methods of preparing such

compounds. It is to be understood that the scope of the present invention is not limited in any way by the scope of the following examples and preparations.

EXAMPLES

[00260] General procedures for the synthesis of sulfonamides

5 **Procedure A:** To a solution of the amine (1 eq) in anhydrous dichloromethane (3 mL/mmole) was added anhydrous triethylamine (5 eq). To this solution was added the sulfonyl chloride (1 eq) and the solution was stirred at room temperature for 16 h. The solvent was evaporated and the residue was purified by flash column chromatography on silica.

Procedure B: To a stirred solution of the amine (1 eq) in anhydrous pyridine (5ml/mmole) was added the sulfonyl chloride (1 - 5 eq). The reaction mixture was stirred at 40 °C for 48 hours. The reaction mixture was partitioned with water and EtOAc. The organic layer was washed with brine, dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica.

Procedure C: Substitution of the iodo-atom:

15 A suspension containing 1 eq. aryl iodide, 1.5 equiv. of the boronic acid or boronic ester, 0.25 eq. PdCl₂(dppf) x DCM and 10 eq. anhydrous K₂CO₃ powder in a deoxygenated mixture of dioxane and water (3:1) was heated in a microwave reactor for 60 min at 115 °C. It was extracted using aq. NH₄Cl / THF, and the organic fraction was dried using Na₂SO₄. The crude reaction products were purified using flash-column chromatography (Si, EtOAc / Hexanes, or CHCl₃ / MeOH). Yields: 20-40%.

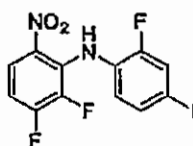
Procedure D: Synthesis of N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2-(alkylamino)ethanesulfonamide:

2-Chloro-ethanesulfonyl chloride (0.1 ml, 1 mmol) was added to a solution of 5,6-difluoro-N¹-(2-fluoro-4-iodophenyl)benzene-1,2-diamine (0.364 g, 1 mmol) and triethylamine (0.28 ml, 2 mmol) in CH₂Cl₂ (5 ml) and the reaction mixture was stirred at room temperature for 16h. Then it's treated with an excess amine (10 eq) either in solution or as a neat liquid. The reaction mixture stirred at room temperature for additional 6h. The reaction mixture diluted with CH₂Cl₂ (10 ml) and water (10 ml). The organic layer was sequentially washed with dil. HCl (2x20 ml, 2N) and saturated NaHCO₃ (2x10 ml) solution. Then the CH₂Cl₂ layer dried (MgSO₄) and evaporated to obtain the crude product. The impure product was purified under preparative HPLC conditions to obtain the pure products in 50-60 % yield.

Example 1

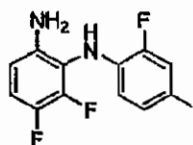
[00261] N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)methanesulfonamide:

Step A: 2,3-Difluoro-N-(2-fluoro-4-iodophenyl)-6-nitroaniline:



- 5 To a solution of 2-fluoro-4-iodoaniline (11.40 g, 47 mmol) in 100 ml anhydrous THF at 0°C, 47 ml of a 1M solution of LHMDS in THF (47 mmol) was added dropwise. The color of the solution turned dark purple. The solution was transferred *via* cannula to a dropping funnel, and the solution (containing the amine free base) was added in
- 10 small portions to a solution of 2,3,4-trifluoronitrobenzene (8.321 g, 47.0 mmol) in anhydrous THF (50 ml) at 0°C. After completion of addition the mixture was stirred under argon at room temperature for 15 hours. The volume of the solvent was reduced, followed by extraction using ethyl acetate and brine. The organic layer was dried over sodium sulfate, the solvent was removed, and the obtained dark oil was purified by flash
- 15 chromatography (EtOAc / hexane 1:5, $R_f = 0.58$) yielding the crude product, which became a brown solid upon drying *in vacuo* (yield: 6.23 g, 33.6%); $m/z = 393$ [M-1].

Step B: 5,6-Difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine:

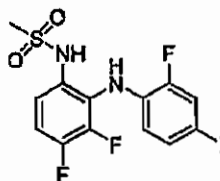


- 20 To a solution of nitro-diarylamine (6.23 g, 15.8 mmol) in 300 ml ethanol was added iron powder (13.74 g, 246 mmol) and ammonium chloride (13.59 g, 254 mmol) and the mixture was heated with stirring at 100°C oil bath temperature for 14 hours. It was filtered and the residue washed two times with ethanol. The ethanol was removed *in vacuo*, and the residue was extracted using ethyl acetate / 1M NaOH solution. During the extraction, more precipitate was formed which was filtered and discarded. The combined organic layers
- 25 were washed with brine and dried over sodium sulfate. The solvent was removed, and the crude product was recrystallized from CHCl₃ / hexane (1:50). The product was obtained as brown needles (2.094 g, 66%), $R_f = 0.44$ (EtOAc / Hex 1:3), ¹H-NMR (500 MHz, CDCl₃),

$\delta = 7.40\text{--}7.38$ (dd, 1H, $J = 11.3$ Hz, $J = 1.5$ Hz), $7.25\text{--}7.23$ (d, 1H, $J = 8.5$ Hz), $6.97\text{--}6.92$ (q, 1H, $J = 9$ Hz), $6.51\text{--}6.48$ (m, 1H), $6.24\text{--}6.21$ (t, 1H, $J = 9$ Hz), 5.3 (s, 1H, NH, br), 3.80 (s, 2H, NH₂, br), LRMS (ESI): $m/z = 365$ [M+H]⁺.

Step C: N-(3,4-difluoro-2-(2-fluoro-4-

5 **iodophenylamino)phenyl)methanesulfonamide:**

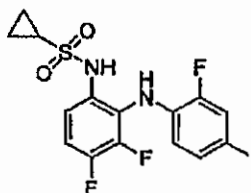


[00263] According to the general procedure A, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with methanesulfonyl chloride to obtain the desired product. ¹H NMR: (500 MHz, CDCl₃): $\delta = 7.38\text{--}7.37$ (d, 1H), $7.35\text{--}7.34$ (m, 1H),
 10 $7.27\text{--}7.26$ (m, 1H), $7.20\text{--}7.0$ (q, 1H), 6.68 (s, 1H, br), $6.15\text{--}6.12$ (q, 1H), 5.65 (s, 1H, br), 2.95 (s, 3H); $m/z = 441$ [M-1]⁺.

Example 2

[00264] **2 N-(3,4-difluoro-2-(2-fluoro-4-**

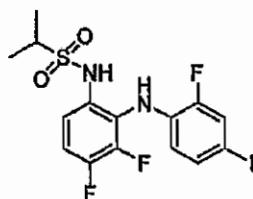
iodophenylamino)phenyl)cyclopropanesulfonamide:



15 [00265] According to the general procedure A, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with cyclopropanesulfonyl chloride to obtain the desired product. ¹H NMR: (500 MHz, CDCl₃): $\delta = 7.38\text{--}7.37$ (d, 1H), $7.35\text{--}7.34$ (m, 1H), $7.27\text{--}7.26$ (m, 1H), $7.20\text{--}7.0$ (q, 1H), 6.68 (s, 1H, br), $6.15\text{--}6.12$ (q, 1H), 5.65 (s, 1H, br),
 20 $3.25\text{--}3.20$ (m, 1H), $2.4\text{--}2.3$ (m, 2H), $2.0\text{--}1.8$ (m, 2H); $m/z = 467$ [M-1]⁺.

Example 3

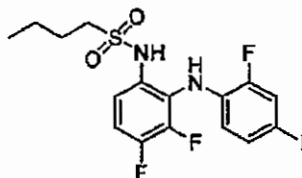
[00266] N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)propane-2-sulfonamide:



- 5 [00267] According to the general procedure A, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with isopropylsulfonyl chloride to obtain the desired product. Yield: 39%. ¹H-NMR (500 MHz, CDCl₃): δ = 7.50-7.43 (m, 1H), 7.35-7.34 (m, 1H), 7.27-7.26 (m, 1H), 7.15-7.09 (q, 1H, J = 1.6 Hz), 6.62 (s, 1H, br), 6.22-6.18 (q, 1H, J = 1.5 Hz), 5.65 (s, 1H, br), 3.30-3.28 (m, 1H), 1.38-1.37 (d, 6H, J = 1.2 Hz); m/z = 469 [M-1]⁻.

Example 4

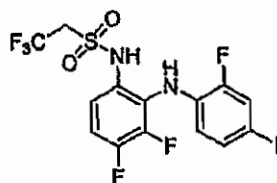
[00268] N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)butane-1-sulfonamide:



- 15 [00269] According to the general procedure A, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with n-butylsulfonyl chloride to obtain the desired product. Yield: 55%. ¹H-NMR (500 MHz, CDCl₃): δ = 7.50-7.43 (m, 1H), 7.35-7.34 (m, 1H), 7.27-7.26 (m, 1H), 7.15-7.09 (q, 1H, J = 1.6 Hz), 6.62 (s, 1H, br), 6.22-6.18 (q, 1H, J = 1.5 Hz), 5.65 (s, 1H, br), 3.06-3.031 (t, 2H, J = 1.4 Hz), 1.75-1.71 (m, 2H), 1.38-1.36 (m, 2H), 0.87-0.86 (t, 3H, J = 1.3 Hz); m/z = 483 [M-1]⁻.

Example 5

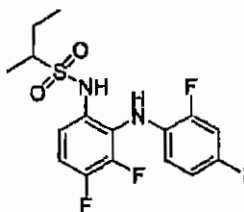
[00270] N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2,2,2-trifluoroethane sulfonamide:



[00271] According to the general procedure A, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with 1,1,1-trifluoroethylsulfonyl chloride to obtain the desired product. Yield: 28%. $m/z = 509$ $[M-1]^-$.

5 **Example 6**

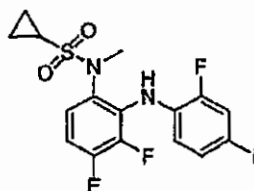
[00272] **N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)butane-2-sulfonamide:**



[00273] According to the general procedure A, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with sec-butylsulfonyl chloride to obtain the desired product. Yield: 22%. $^1\text{H-NMR}$ (500 MHz, $\text{MeOH}[d_4]$): $\delta = 7.60\text{--}7.40$ (m, 3H), 7.18–7.00 (q, 1H), 6.55–6.45 (m, 1H), 3.55–3.50 (m, 1H), 2.20–2.00 (m, 1H), 1.80–1.60 (m, 1H), 1.43–1.40 (d, 3H), 1.06–1.04 (t, 3H); $m/z = 483$ $[M-1]^-$.

Example 7

15 [00274] **N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-N-methylcyclopropane sulfonamide:**



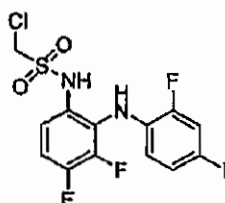
[00275] To a solution of N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)cyclopropane-sulfonamide (see Example 2) (283.9 mg, 0.61

mmol) in 3 ml anhydrous THF was added at -78°C a 1M solution of LHMDs (0.6 ml, 0.6 mol) and the solution was stirred for 10 min at this temperature. Then, methyl iodide (0.8 ml, 1.824 g, 12.9 mmol) was added and the mixture was warmed to room temperature and stirred for 7 h. The solvent was removed and the residue extracted using EtOAc and brine.

- 5 The organic fractions were dried using Na_2SO_4 and the solvent was removed. The obtained crude product was purified using flash-column chromatography (Si, EtOAc/Hexanes 1:2, $R_f = 0.45$). Yield: 205 mg, 70%. $^1\text{H-NMR}$ (500 MHz, CDCl_3): $\delta = 7.41\text{--}7.39$ (d, 1H, $J = 10$ Hz), 7.30–7.29 (d, 1H, $J = 8.0$ Hz), 7.23–7.20 (m, 1H), 6.98–6.93 (q, 1H, $J = 8.5$ Hz), 6.60 (s, 1H, br), 6.51–6.47 (m, 1H), 3.23 (s, 3H), 2.46–2.42 (m, 1H), 1.19–1.16 (m, 2H), 1.04–1.02 (m, 2H); $m/z = 481$ $[\text{M}-1]^+$.

Example 8

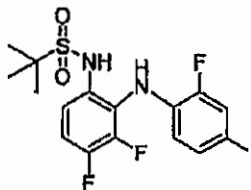
[00276] **1-Chloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl) methane sulfonamide:**



- 15 [00277] According to the general procedure A, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with chloromethanesulfonyl chloride to obtain the desired product, $m/z = 475$ $[\text{M}-1]^+$.

Example 9

- [00278] **N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2-methylpropane-2-sulfonamide:**

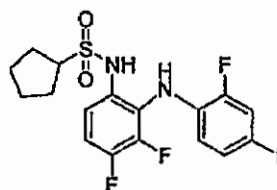


- [00279] According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with 2-methylpropane-2-sulfonyl chloride (synthesized according to the literature procedure) to obtain the desired product. $^1\text{H NMR}$

(300 MHz, CDCl_3): δ 7.50 (m, 1H), 7.43 (dd, $J = 1.8$ & 10.5 Hz, 1H), 7.28 (br s, 1H), 7.10 (dd, $J = 9.0$ & 17.7 Hz, 1H), 6.48 (br s, D_2O exchangeable, 1H), 6.19 (t, $J = 7.8$ & 9.6 Hz, 1H), 5.58 (br s, D_2O exchangeable, 1H), 1.39 (s, 9H); $m/z = 383$ $[\text{M}-1]^+$.

Example 10

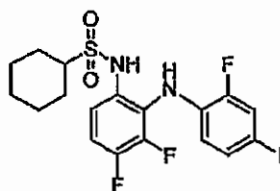
- 5 [00280] **N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)cyclopentanesulfonamide:**



- [00281] According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with cyclopentanesulfonyl chloride to obtain the desired product. ^1H NMR (300 MHz, CDCl_3): δ 7.42 (dd, $J = 2.1$ & 10.5 Hz, 1H), 7.36 (ddd, $J = 2.4$, 4.8, & 9.3 Hz, 1H), 7.25 (m, 2H), 7.10 (dd, $J = 9.6$ & 17.7 Hz, 1H), 6.67 (br s, D_2O exchangeable, 1H), 6.20 (dt, $J = 1.5$, 8.4 & 17.4 Hz, 1H), 3.53 (p, 1H), 1.80 (m, 8H); $m/z = 495$ $[\text{M}-1]^+$.

Example 11

- 15 [00282] **N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)cyclohexanesulfonamide:**

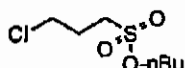


- [00283] According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with cyclohexanesulfonyl chloride to obtain the desired product. ^1H NMR (300 MHz, CDCl_3): δ 7.43 (dd, $J = 1.5$ & 10.2 Hz, 1H), 7.37 (ddd, $J = 2.4$, 4.8 & 9.6 Hz, 1H), 7.27 (m, 1H), 7.11 (dd, $J = 9.3$ & 18.0 Hz, 1H), 6.64 (br s, 1H), 6.18 (dt, $J = 1.5$, 9.0 & 17.4 Hz, 1H), 5.63 (br s, 1H), 2.95 (triplet of triplet, 2.10-1.16 (m, 10H); $m/z = 509$ $[\text{M}-1]^+$.

Example 12

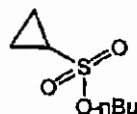
[00284] **N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-methylcyclopropane-1-sulfonamide:**

Step A: n-Butyl 3-chloro-1-propanesulfonate:



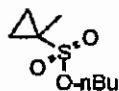
[00285] Triethylamine (28 ml, 200 mmol) in CH_2Cl_2 (50 ml) was slowly added to an ice-cooled solution of 3-chloro-1-propanesulfonyl chloride (36.6g, 200 mmol) and 1-butanol (18.4 g, 240 mmol) in CH_2Cl_2 (250 ml) and stirring was continued for 16h. The mixture was diluted with CH_2Cl_2 (200 ml), washed (aqueous HCl) and dried (MgSO_4) and the solvent was evaporated to obtain the titled product **1** (40.85 g, 95%) in crude form as slightly yellow oil which was used for the next reaction without further purification. ^1H NMR (CDCl_3) δ 0.94 (t, $J = 7.5$ Hz, 3H), 1.44 (sextet, 2H), 1.72 (quintet, 2H), 2.31 (quintet, 2H), 3.27 (t, $J = 6.9$ Hz, 2H), 3.68 (t, $J = 6.3$ Hz), 4.23 (t, $J = 6.6$ Hz, 2H).

Step B: 1-Butyl cyclopropanesulfonate:



[00286] Solutions of 1-butyl 3-chloro-1-propanesulfonate (4.6 g, 21.39 mmol in 25 ml THF) and of butyllithium (14.7 ml, 23.53 mmol, 1.6M, THF) were simultaneously added to THF (150 ml) at -78°C under nitrogen atmosphere. The solution was allowed to warm to 0°C and then quenched with water (2 ml). The volatiles evaporated under reduced pressure and the residue extracted with CH_2Cl_2 (150 ml). The extract was washed with water and dried (MgSO_4) and evaporated to give crude desired product (3.23 g, 78.22%) in almost pure form as pale yellow oil which was used for next step without further purification. ^1H NMR (300 MHz, CDCl_3) δ 0.94 (t, $J = 7.5$ Hz, 3H), 1.07 (m, 2H), 1.25 (m, 2H), 1.45 (sextet, 2H), 1.74 (quintet, 2H), 2.45 (heptet, 1H), 4.23 (t, $J = 6.6$ Hz, 2H).

Step C: Butyl 1-Methyl-cyclopropanesulfonate:



[00287] To a solution of 1-Butyl cyclopropanesulfonate (1 g, 5.58 mmol) in THF (15 ml) butyllithium solution (3.84 ml, 6.14 mmol, 1.6M, THF) was slowly added at -78°C under nitrogen atmosphere. After 15 minutes MeI (0.72 ml, 11.16 mmol) was added and the solution was allowed to warm to 0°C and quenched with water (1 ml). The volatiles
 5 evaporated under reduced pressure and the residue extracted with CH₂Cl₂ (100 ml). The extract was washed with water, dried (MgSO₄) and evaporated. The residue was purified over silica gel chromatography (eluants: hexane/ CH₂Cl₂) to obtain the titled product (0.59 g, 55.0%) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 0.84 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H), 1.43 (m, 4H), 1.53 (s, 3H), 1.74(m, 2H), 4.21 ((t, J = 6.6 Hz, 2H).

10 **Step D: 1-Potassium 1-Methyl-cyclopropanesulfonate:**



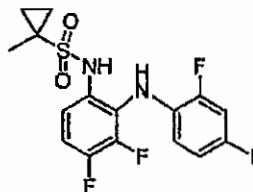
[00288] A mixture of 1-Butyl 1-Methyl-cyclopropanesulfonate (0.386 g, 2 mmol) and potassium thiocyanate (0.194 g, 2 mmol) in DME (5 ml) and water (5 ml) was refluxed for 16h. The volatiles were evaporated to obtain the crude sulfonate (0.348g, quantitative)
 15 which was dried under vacuum at 50°C for 16h. The crude product was used in the next reaction without further purification. ¹H NMR (300 MHz, D₂O) δ 0.56 (t, J = 6.3 Hz, 2H), 0.96 (t, J = 6.3 Hz, 2H), 1.26 (s, 3H).

Step E: 1-Methyl-cyclopropanesulfonylchloride:



20 [00289] A solution of 1-potassium 1-methyl-cyclopropanesulfonate (0.348 g, 2 mmol), thionyl chloride (5 ml) and DMF (5 drops) was refluxed at 60°C for 16h. The volatiles evaporated under reduced pressure and the residue extracted with CH₂Cl₂ (50 ml). The extract was washed with water, dried (MgSO₄) and evaporated to obtain the crude product as yellow gummy oil which was used in the next reaction without further
 25 purification.

Step F: N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-methylcyclopropane-1-sulfonamide:

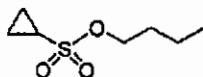


- [00290] According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with 1-methyl-cyclopropanesulfonylchloride to obtain the desired product. ^1H NMR (300 MHz, CDCl_3): δ 7.42 (dd, $J = 1.8$ & 10.5 Hz, 1H), 7.36 (ddd, $J = 2.4$, 4.5 & 9.0 Hz, 1H), 7.27 (d, $J = 6.0$ Hz, 1H), 7.07 (dd, $J = 9.3$ & 17.7 Hz, 1H), 6.24 (dt, $J = 2.1$, 8.7 & 17.4 Hz, 1H), 5.86 (br s, 1H), 1.43 (s, 3H), 1.33 (t, $J = 5.4$ Hz, 2H), 0.75 (dd, $J = 5.1$ & 6.3 Hz, 2H); $m/z = 481$ [M-1] $^-$.

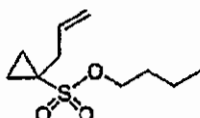
10 Example 13

[00291] N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide:

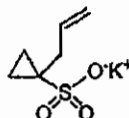
Step A: Butyl cyclopropanesulfonate:



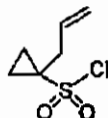
- 15 [00292] Cyclopropanesulfonyl chloride (5 g, 35 mmol, 1 eq) was dissolved in an excess BuOH (20 ml), the reaction mixture was cooled at -10°C and pyridine (5.8 mL, 70 mmol, 2 eq) was slowly added dropwise. The mixture was slowly warmed at room temperature and stirred overnight. The solvent was removed under reduced pressure and the resulting white solid was dissolved in CHCl_3 . The organic phase was washed with
- 20 water, brine and dried (MgSO_4) and concentrated to give an oil (4.8 g, 24.9 mmol, 71%). ^1H NMR (300 MHz, CDCl_3): δ 4.25 (t, 2H), 2.46 (m, 1H), 1.74 (m, 2H), 1.45 (m, 2H), 1.25 (dd, 2H), 1.09 (dd, 2H), .93 (t, 3H).

Step B: Butyl 1-allylcyclopropane-1-sulfonate:

[00293] To a solution of 1-butyl cyclopropanesulfonate (4.8 g, 24.9 mmol) in THF at -78°C was added simultaneously butyllithium solution (15.6 ml, 24.9 mmol, 1.6M, THF) and allyl iodide (24.9 mmol) under nitrogen atmosphere. The reaction mixture was stirred 2 hours at -78°C and 3 hours at room temperature. The volatiles were evaporated under reduced pressure and the residue extracted with CH₂Cl₂ (100 ml). The extract was washed with water, dried (MgSO₄) and evaporated. The residue was purified over silica gel chromatography (eluants: hexane/ CH₂Cl₂) to obtain the titled product (3.75 g, 69.0%) as a colorless oil. ¹H NMR (300 MHz, CDCl₃): δ 5.6 (m, 1H), 5.13-5.08 (t, 2H), 4.21 (t, 2H), 2.65 (d, 2H), 1.7 (m, 2H), 1.4 (m, 4H), .93 (m, 5H).

Step C: Potassium 1-allylcyclopropane-1-sulfonate:

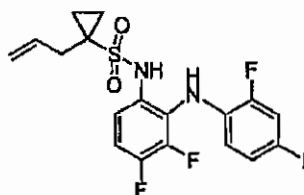
[00294] A mixture of 1-butyl 1-methyl-cyclopropanesulfonate (3.75 g, 17.2 mmol) and potassium thiocyanate (1.7 g, 17.2 mmol) in DME (20 ml) and water (20 ml) was refluxed for 16h. The volatiles were evaporated to obtain the crude sulfonate (3.44g, quantitative) which was dried under vacuum at 50°C for 16h. The crude product was used in the next reaction without further purification. ¹H NMR (CDCl₃): δ 5.6 (m, 1H), 4.91-4.85 (dd, 2H), 2.471-2.397 (d, 2H), 0.756 (m, 2H), 0.322 (m, 2H).

Step D: 1-allylcyclopropane-1-sulfonyl chloride:

[00295] A solution of potassium 1-allylcyclopropane-1-sulfonate (3.44 g, 17.2 mmol), thionyl chloride (10 ml) and DMF (5 drops) was refluxed at 60°C for 16h. The volatiles evaporated under reduced pressure and the residue extracted with CH₂Cl₂ (50 ml). The

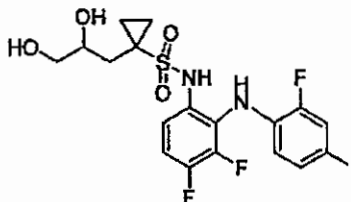
extract was washed with water, dried (MgSO_4) and evaporated to obtain the crude product as yellow gummy oil which was washed with hexane and used in the next reaction without further purification (2.7 g, 15 mmol, 87%). $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 5.728 (m, 1H), 5.191 (t, 2H), 2.9 (d, 2H), 0.756 (m, 2H), 0.322 (m, 2H).

5 **Step E: 1-allyl-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)cyclopropane-1-sulfonamide:**



[00296] According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with 1-allylcyclopropane-1-sulfonyl chloride
10 to obtain the desired product. $m/z = 507$ $[M-1]^+$.

Step F: N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide:



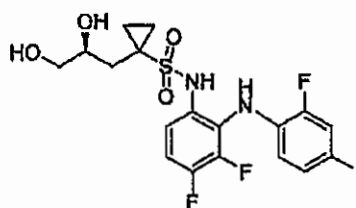
[00297] 1-Allyl-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)cyclopropane-1-sulfonamide (0.77 g, 1.52 mmol) and 4-methylmorpholine N-oxide (0.18 g, 1.52 mmol) were dissolved in THF (50 mL). Osmium tetroxide was added at room temperature (0.152 mmol, 0.965 mL, 4% in H_2O) and the reaction mixture was stirred at room temperature for 16 hours. EtOAc was added, the organic phase was washed with water, dried (MgSO_4) and concentrated under reduced
20 pressure. The residue was purified over silica gel chromatography (eluants: EtOAc/ MeOH) to obtain the titled product (0.65 g, 79%). $^1\text{H NMR}$ (300 MHz, $\text{CDCl}_3 + \text{D}_2\text{O}$): δ 7.38 (dd, $J = 1.8$ & 10.5 Hz, 1H), 7.36 (ddd, $J = 2.4$, 5.1 & 9.3 Hz, 1H), 7.25 (d, $J = 8.7$ Hz, 1H), 7.02 (dd, $J = 9.0$ & 17.7 Hz, 1H), 6.27 (dt, $J = 3.0$, 8.7 & 17.4 Hz, 1H), 3.92 (m, 1H), 3.54 (dd, J

= 3.9 & 11.1 Hz, 1H), 3.39 (dd, J = 6.6 & 11.1 Hz, 1H), 2.16 (dd, J = 9.6 & 15.9 Hz, 1H), 1.59 (d, J = 14.1 Hz, 1H), 1.41 (m, 1H), 1.26 (m, 1H), 0.83 (m, 2H); m/z = 542 $[M-1]^-$.

Example 14

[00298] (S)-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-(2,3-

5 dihydroxypropyl)cyclopropane-1-sulfonamide:

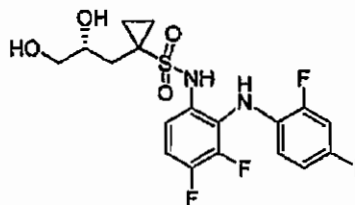


[00299] The pure S isomer was obtained by chiral HPLC separation of the racemic mixture (example 13). 1H NMR (300 MHz, $CDCl_3$ + D_2O): δ 7.38 (dd, J = 1.8 & 10.5 Hz, 1H), 7.36 (ddd, J = 2.4, 5.1 & 9.3 Hz, 1H), 7.25 (d, J = 8.7 Hz, 1H), 7.02 (dd, J = 9.0 & 17.7 Hz, 1H), 6.27 (dt, J = 3.0, 8.7 & 17.4 Hz, 1H), 3.92 (m, 1H), 3.54 (dd, J = 3.9 & 11.1 Hz, 1H), 3.39 (dd, J = 6.6 & 11.1 Hz, 1H), 2.16 (dd, J = 9.6 & 15.9 Hz, 1H), 1.59 (d, J = 14.1 Hz, 1H), 1.41 (m, 1H), 1.26 (m, 1H), 0.83 (m, 2H); m/z = 542 $[M-1]^-$.

Example 15

[00300] (R)-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-(2,3-

15 dihydroxypropyl)cyclopropane-1-sulfonamide:

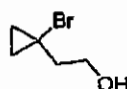


[00301] The pure R isomer was obtained by chiral HPLC separation of the racemic mixture (example 13). 1H NMR (300 MHz, $CDCl_3$ + D_2O): δ 7.38 (dd, J = 1.8 & 10.5 Hz, 1H), 7.36 (ddd, J = 2.4, 5.1 & 9.3 Hz, 1H), 7.25 (d, J = 8.7 Hz, 1H), 7.02 (dd, J = 9.0 & 17.7 Hz, 1H), 6.27 (dt, J = 3.0, 8.7 & 17.4 Hz, 1H), 3.92 (m, 1H), 3.54 (dd, J = 3.9 & 11.1 Hz, 1H), 3.39 (dd, J = 6.6 & 11.1 Hz, 1H), 2.16 (dd, J = 9.6 & 15.9 Hz, 1H), 1.59 (d, J = 14.1 Hz, 1H), 1.41 (m, 1H), 1.26 (m, 1H), 0.83 (m, 2H); m/z = 542 $[M-1]^-$.

Example 16

[00302] N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-(2-hydroxyethyl)cyclopropane-1-sulfonamide:

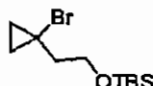
Step A: 2-(1-bromocyclopropyl)ethanol:



5

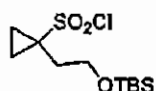
[00303] To a solution of neat diethyl zinc (3.3 ml, 3.977 g, 30 mmol) in 100 ml anhydrous DCM was added very slowly trifluoroacetic acid (2.31 ml, 3.4188 g, 30 mmol) dropwise at 0°C. (Caution: Violent gas evolution, exothermic!). After completed addition of the TFA, the suspension was stirred for 20 min at the same temperature, followed by the addition of diiodo methane (2.45 ml, 8.134 g, 30.4 mmol). It was further stirred at 0°C for 20 min, and then a solution of 3-bromobut-3-en-1-ol (1 ml, 1.523 g, 10.1 mmol) in 10 ml DCM was added at the same temperature. After complete addition, the mixture was warmed to room temperature and stirred for 4 hours. The mixture was quenched with 100 ml MeOH and 40 ml brine, and it was further stirred for 30 min. The solvents were reduced, and the residue extracted using CHCl₃ / aq. NH₄Cl. The organic layers were collected, washed with brine and water, and the solvent was removed to give 2-(1-bromocyclopropyl)-ethanol in sufficient purity (1.6564 g, 100%). ¹H-NMR (500 MHz, CDCl₃): δ = 3.90-3.83 (t, 2H), 1.91-1.87 (t, 2H), 1.71 (s, 1H, br), 1.14-1.09 (m, 2H), 0.83-0.79 (m, 2H).

20 Step B: TBS protected 2-(1-bromocyclopropyl)ethanol:



[00304] To a solution of the cyclopropyl alcohol (Step A) (1.303 g, 7.95 mmol) in 30 ml anhydrous DCM was added anhydrous pyridine (1.2 ml, 1.1736 g, 14.8 mmol) and TBSOTf (2.7 ml, 3.1077 g, 11.76 mol) and the solution was stirred at room temperature for 16h. It was extracted with CHCl₃ / brine and the organic fraction was dried with MgSO₄. The solvent was reduced and the crude product purified using flash-column chromatography (Si, CHCl₃ / hexanes 1:10, R_f = 0.4). Yield: 0.796 g, 36%. ¹H-NMR (500 MHz, CDCl₃): δ = 3.95-3.75 (t, 2H), 1.95-1.85 (t, 2H), 1.15-1.05 (m, 2H), 0.95-0.80 (m, HH), 0.15-0.05 (s, 6H).

25

Step C: TBS protected 2-(1-chlorosulfonylcyclopropyl)ethanol:

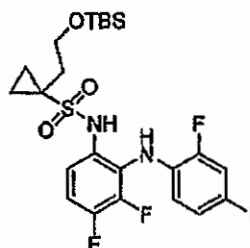
[00305] To a solution of the cyclopropyl bromide prepared in step B (1.1227 g, 4.04 mmol) in 15 ml anhydrous diethyl ether was added a 1.7 M solution of t-BuLi in pentane (4.8 ml, 8.16 mmol) at -78°C. The solution was stirred for 30 min at this temperature, and was then transferred via a transfer canola into a solution of freshly distilled sulfuryl chloride (0.65 ml, 1.029 g, 8.1 mmol) in 8 ml diethyl ether at -78°C. The yellow suspension was warmed to room temperature. The solvent was removed, and the residue was dried *in vacuo* to remove excessive sulfuryl chloride. Then, the residue was extracted two times with

5

10 hexane, and after filtration the solvent was evaporated *in vacuo* to give the sulfonyl chloride in sufficient purity as a colorless oil. Yield: 870 mg (72%). ¹H-NMR (300 MHz, CDCl₃): δ = 3.95-3.85 (t, 2H), 2.35-2.25 (t, 2H), 1.80-1.70 (m, 2H), 1.45-1.38 (m, 2H), 0.90 (s, 9H), 0.10 (s, 6H).

Step D: TBS-protected N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-(2-hydroxyethyl)cyclopropane-1-sulfonamide:

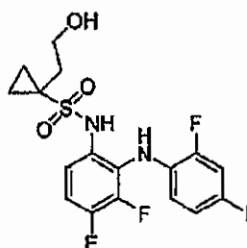
15



[00306] According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with the cyclopropylsulfonyl chloride prepared in step C to obtain the desired product. ¹H-NMR (300 MHz, CDCl₃): δ = 7.44-7.39 (dd, 1H), 7.32-7.24 (m, 2H), 7.1-6.98 (q, 1H), 6.34-6.24 (m, 1H), 6.16 (s, 1H, br), 3.85-3.75 (t, 2H), 2.15-2.00 (t, 2H), 1.35-1.20 (m, 2H), 0.95-0.75 (m, 1 1H), 0.10 (s, 6H); *m/z* = 625 [M-1].

20

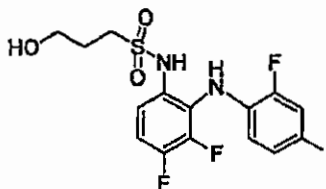
Step E: N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-(2-hydroxyethyl)cyclopropane-1-sulfonamide:



[00307] To a solution of the TBS-protected sulfonamide prepared in step D (21 mg, 0.033 mmol) in 1 ml THF was added 0.1 ml eq. 1.2N HCl solution at 0°C and the solution was stirred for 2 h. The solvents were reduced and the residue was extracted using aq. NaHCO₃ solution and EtOAc. The organic fractions were dried with MgSO₄ and the volatiles were removed. The crude product was purified using flash-column chromatography (Si, CHCl₃ / MeOH 10:1, R_f = 0.45) to give the pure product. Yield: 16.9 mg (100%). ¹H-NMR (300 MHz, CDCl₃): δ = 7.44-7.39 (dd, 1H), 7.32-7.24 (m, 2H), 7.1-6.98 (q, 1H), 6.34-6.24 (m, 1H), 6.16 (s, 1H, br), 3.85-3.75 (t, 2H), 2.15-2.00 (t, 2H), 1.35-1.20 (m, 2H), 0.95-0.85 (m, 2H); m/z = 511 [M-1]⁺.

Example 17

[00308] **N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-3-hydroxypropane-1-sulfonamide:**

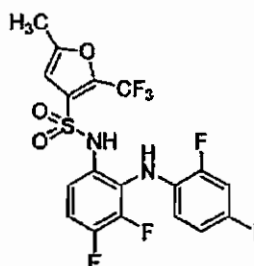


[00309] To a solution of 3-chloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-propane-1-sulfonamide (69.4 mg, 0.138 mmol) in a mixture of 8 ml 1,4-dioxane and 2 ml H₂O was added KOH powder (0.674 g, 12.0 mmol) and the mixture was heated to the reflux temperature for 3 days. It was extracted using EtOAc / brine, the organic fraction was dried with Na₂SO₄ and the volatiles were removed. The residue was purified using flash-column chromatography (Si, DCM / MeOH 5:1, R_f = 0.3). Yield: 41 mg (62%). ¹H-NMR (500 MHz, MeOH [d₄]): δ = 7.38-7.21 (d, 1H), 7.23-7.21

(d, 1H), 7.06-7.00 (q, 1H), 6.52-6.50 (m, 1H), 6.17-6.13 (t, 1H), 3.30-3.27 (t, 2H), 2.86-2.83 (t, 2H), 2.05-2.00 (m, 2H); $m/z = 485 [M-1]^+$.

Example 18

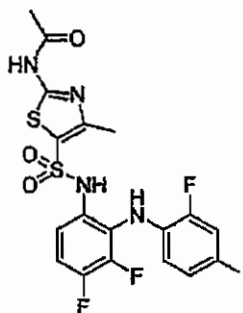
[00310] **N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2-methyl-5-(trifluoromethyl)furan-3-sulfonamide:**



[00311] According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine (0.182 mmol) was reacted with 2-methyl-5-(trifluoromethyl)furan-3-sulfonyl chloride (0.5 mmol) to form N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2-methyl-5-(trifluoromethyl)furan-3-sulfonamide. ^1H NMR (CDCl₃) δ 2.2 (s, 3H), 5.3 (s, 1H), 6.0 (dt, 1H), 6.8 (s, 1H), 6.95 (s, 1H), 7.0-7.3 (m, 3H), 7.4 (dd, 1H).

Example 19

[00312] **N-(5-(N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)sulfamoyl)-methylthiazol-2-yl)acetamide:**

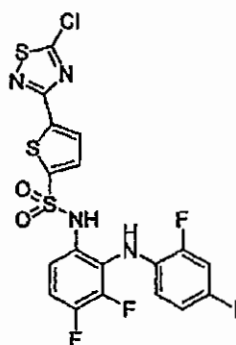


[00313] According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine (0.182 mmol) was reacted with 2-acetamido-4-methylthiazole-5-sulfonyl chloride (0.5 mmol) to obtain N-(5-(N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)sulfamoyl)-methylthiazol-2-yl)acetamide.

4-iodophenylamino)phenyl)sulfamoyl)-4-methylthiazol-2-yl)acetamide. ^1H NMR (CDCl_3) δ 2.1 (s, 3H), 2.2 (s, 3H), 5.9 (dt, 1H), 6.05 (s, 1H), 7.0-7.6 (m, 3H), 7.4 (dd, 1H), 8.0 (s, 1H).

Example 20

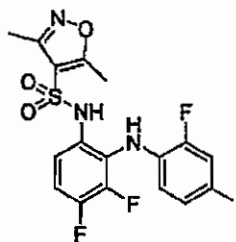
- 5 [00314] **5-(5-Chloro-1,2,4-thiadiazol-3-yl)-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl) thiophene-2-sulfonamide:**



- [00315] According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine (0.182 mmol) was reacted with 5-(5-chloro-1,2,4-thiadiazol-3-yl)thiophene-2-sulfonyl chloride (0.5 mmol) to obtain 5-(5-chloro-1,2,4-thiadiazol-3-yl)-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)thiophene-2-sulfonamide. ^1H NMR (300 MHz, CDCl_3) δ 5.8 (dt, 1H), 5.95 (s, 1H), 6.95 (d, 1H), 7.4 (m, 2H), 7.6 (d, 1H), 7.8 (s, 1H).

Example 21

- 15 [00316] **N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-3,5-dimethylisoxazole-4-sulfonamide:**

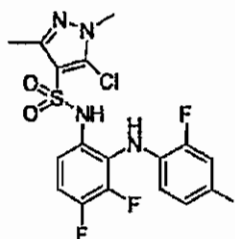


- [00317] According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl) benzene-1,2-diamine (0.182 mmol) was reacted with 3,5-dimethylisoxazole-4-

sulfonyl chloride (0.5 mmol) to obtain N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-3,5-dimethylisoxazole-4-sulfonamide. ¹H NMR (300 MHz, CDCl₃) δ 2.2 (s, 3H), 2.4 (s, 3H), 5.8 (s, 1H), 6.0 (dt, 1H), 5.95 (s, 1H), 6.9 (s, 1H), 7.0 (q, 1H), 7.2 (m, 3H), 7.4 (dd, 1H).

5 **Example 22**

[00318] **5-Chloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1,3-dimethyl-1H-pyrazole-4-sulfonamide:**

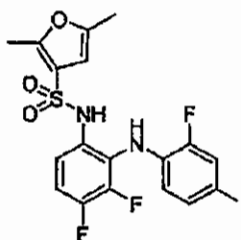


[00319] According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-

10 iodophenyl) benzene-1,2-diamine (0.182 mmol) was reacted with 5-chloro-1,3-dimethyl-1H-pyrazole-4-sulfonyl chloride (0.5 mmol) to obtain 5-chloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1,3-dimethyl-1H-pyrazole-4-sulfonamide. ¹H NMR (300 MHz, CDCl₃) δ 2.1 (s, 3H), 3.6 (s, 3H), 5.8 (s, 1H), 5.95 (dt, 1H), 7.0 (q, 1H), 7.2 (d, 1H), 7.3 (m, 2H), 7.4 (dd, 1H).

15 **Example 23**

[00320] **N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2,5-dimethylfuran-3-sulfonamide:**



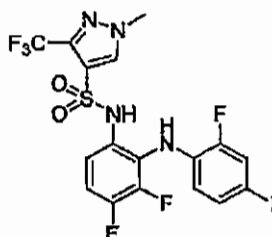
[00321] According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-

20 iodophenyl) benzene-1,2-diamine (0.182 mmol) was reacted with 2,5-dimethylfuran-3-sulfonyl chloride (0.5 mmol) to obtain N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2,5-dimethylfuran-3-sulfonamide. ¹H NMR (300 MHz, CDCl₃) δ 2.2 (s, 3H), 2.3

(s, 3H), 5.8 (s, 1H), 6.0 (dt, 1H), 6.8 (s, 1H), 7.0 (q, 1H), 7.2 (d, 1H), 7.3 (m, 2H), 7.4 (dd, 1H).

Example 24

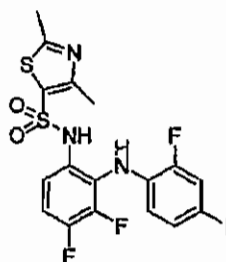
[00322] N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-sulfonamide:



[00323] According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl) benzene-1,2-diamine (0.182 mmol) was reacted with 1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-sulfonyl chloride (0.5 mmol) to obtain N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-sulfonamide. ¹H NMR (300 MHz, CDCl₃) δ 3.8 (s, 3H), 5.7 (s, 1H), 6.0 (dt, 1H), 7.0 (q, 1H), 7.2 (m, 2H), 7.4 (dd, 1H), 7.8 (s, 1H).

Example 25

[00324] N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2,4-dimethylthiazole-5-sulfonamide:

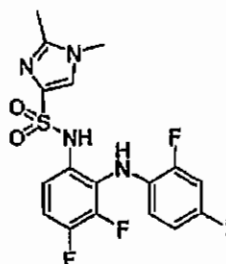


[00325] According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl) benzene-1,2-diamine (0.182 mmol) was reacted with 2,4-dimethylthiazole-5-sulfonyl chloride (0.5 mmol) to obtain N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2,4-dimethylthiazole-5-sulfonamide. ¹H NMR (300 MHz,

CDCl₃) δ 2.3 (s, 3H), 2.6 (s, 3H), 5.7 (s, 1H), 5.9 (dt, 1H), 7.1 (q, 1H), 7.2 (d, 1H), 7.3 (m, 1H), 7.4 (d, 1H), 7.4 (s, 1H).

Example 26

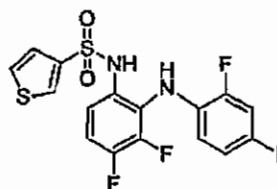
[00326] N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1,2-dimethyl-1H-imidazole-4-sulfonamide:



[00327] According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with 1,2-dimethyl-1H-imidazole-4-sulfonyl chloride to obtain the title compound. ¹H NMR (300 MHz, CDCl₃): δ 7.95 (br s, 1H), 7.37 (dd, *J* = 1.8 & 10.8 Hz, 1H), 7.32-7.14 (m, 3H), 6.98 (dd, *J* = 9.6 & 17.7 Hz, 1H), 5.87 (dt, *J* = 4.2, 9.0 & 17.4 Hz, 1H), 5.55 (br s, 1H), 3.49 (s, 3H), 2.31 (s, 3H).

Example 27

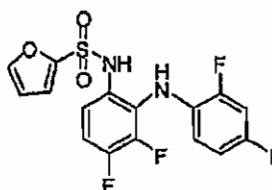
[00328] N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)thiophene-3-sulfonamide:



[00329] According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with thiophene-3-sulfonyl chloride to obtain the title compound. ¹H NMR (300 MHz, CDCl₃): δ 8.00 (dd, *J* = 1.2 & 3.3 Hz, 1H), 7.45 (dd, *J* = 0.9 & 5.1 Hz, 1H), 7.35 (m, 2H), 7.27 (m, 2H), 6.91 (dd, *J* = 9.3 & 17.1 Hz, 1H), 6.64 (ddd, *J* = 2.1, 4.8 & 8.7 Hz, 1H), 6.34 (dt, *J* = 5.4, 8.7 & 14.1 Hz, 1H), 5.98 (br d, *J* = 2.1 Hz, D₂O exchangeable, 1H).

Example 28

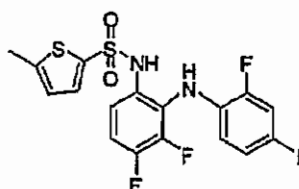
[00330] N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)furan-2-sulfonamide:



- 5 **[00331]** According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with furan-2-sulfonyl chloride to obtain the title compound. ¹H NMR (300 MHz, CDCl₃): δ 7.53 (br s, D₂O exchangeable, 1H), 7.38 (dd, *J* = 1.8 & 10.5 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.21 (d, *J* = 3.0 Hz, 1H), 6.96 (dd, *J* = 8.7 & 16.5 Hz, 1H), 6.87 (ddd, *J* = 1.8, 5.1 & 9.0 Hz, 1H), 6.53 (dd, *J* = 1.8 & 3.6 Hz, 1H),
10 6.44 (dt, *J* = 5.1, 8.7 & 13.8 Hz, 1H), 6.22 (br s, D₂O exchangeable, 1H).

Example 29

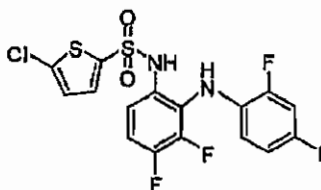
[00332] N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-5-methylthiophene-2-sulfonamide:



- 15 **[00333]** According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with 5-methylthiophene-2-sulfonyl chloride to obtain the title compound. ¹H NMR (300 MHz, CDCl₃): δ 7.34 (dd, *J* = 0.9 & 10.2 Hz, 1H), 7.30 (ddd, *J* = 2.1, 4.8 & 9.0 Hz, 1H), 7.25 (d, *J* = 3.9 Hz, 1H), 7.07 (m, 2H), 6.65 (dd, *J* = 1.2 & 3.9 Hz, 1H), 5.89 (dt, *J* = 2.4, 8.7 & 17.4 Hz, 1H), 5.54 (br s, D₂O exchangeable, 1H), 2.46 (s, 3H).
20

Example 30

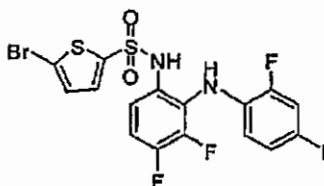
[00334] **5-Chloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)thiophene-2-sulfonamide:**



- 5 [00335] According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with 5-chlorothiophene-2-sulfonyl chloride to obtain the title compound. ¹H NMR (300 MHz, CDCl₃): δ 7.38 (dd, *J* = 1.5 & 10.2 Hz, 1H), 7.32 (ddd, *J* = 2.1, 5.1 & 9.3 Hz, 1H), 7.25 (d, *J* = 3.9 Hz, 1H), 7.10 (dd, *J* = 9.0 & 18.6 Hz, 3H), 6.84 (d, *J* = 4.2 Hz, 1H), 5.86 (dt, *J* = 1.8, 8.7 & 17.4 Hz, 1H), 5.49 (br s, D₂O exchangeable, 1H).

Example 31

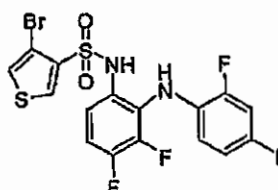
[00336] **5-Bromo-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)thiophene-2-sulfonamide:**



- 15 [00337] According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with 5-bromothiophene-2-sulfonyl chloride to obtain the title compound. ¹H NMR (300 MHz, CDCl₃): δ 7.39-7.29 (m, 2H), 7.20-7.05 (m, 3H), 6.96 (d, *J* = 3.6 Hz, 1H), 5.85 (dt, *J* = 2.1, 9.0 & 17.4 Hz, 1H), 5.54 (br s, 1H).

Example 32

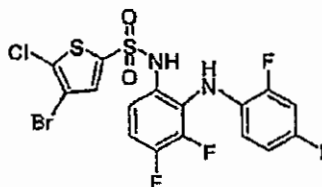
[00338] **4-Bromo-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)thiophene-3-sulfonamide:**



5 [00339] According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with 4-bromothiophene-3-sulfonyl chloride to obtain the title compound. ¹H NMR (300 MHz, CDCl₃): δ 7.48 (br m, 2H), 7.39 (dd, *J* = 1.8 & 10.5 Hz, 1H), 7.28 (ddd, *J* = 2.4, 4.8 & 9.0 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 7.02 (m, 1H), 6.02 (dt, *J* = 2.4, 8.7 & 17.4 Hz, 1H), 5.68 (br s, 1H).

10 Example 33

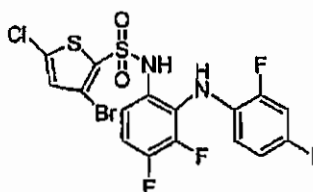
[00340] **4-Bromo-5-chloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)thiophene-2-sulfonamide:**



[00341] According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with 4-bromo-5-chlorothiophene-2-sulfonyl chloride to obtain the title compound. ¹H NMR (300 MHz, CDCl₃): δ 7.42-7.34 (m, 2H), 7.25 (br m, 3H), 7.13 (dd, *J* = 9.0 & 17.1 Hz, 1H), 6.02 (dt, *J* = 2.4, 6.6 & 17.4 Hz, 1H), 5.52 (br s, 1H).

Example 34

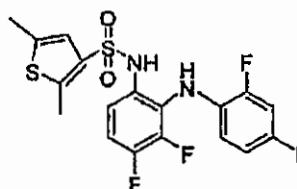
[00342] 3-Bromo-5-chloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)thiophene-2-sulfonamide:



- 5 [00343] According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with 3-bromo-5-chlorothiophene-2-sulfonyl chloride to obtain the title compound. ¹H NMR (300 MHz, CDCl₃): δ 7.41 (dd, *J* = 2.1 & 10.5 Hz, 1H), 7.35 (br m, 2H), 7.31 (dd, *J* = 2.1 & 4.2 Hz, 1H), 7.19 (d, *J* = 8.7 Hz, 1H), 7.08 (dd, *J* = 9.0 & 17.4 Hz, 1H), 6.02 (dt, *J* = 2.1, 8.4 & 17.1 Hz, 1H), 5.59 (br s, 1H).

10 Example 35

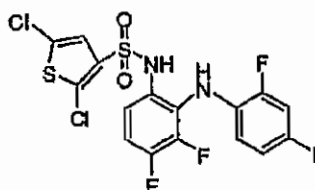
[00344] N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2,5-dimethylthiophene-3-sulfonamide:



- [00345] According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with 2,5-dimethylthiophene-3-sulfonyl chloride to obtain the title compound. ¹H NMR (300 MHz, CDCl₃): δ 7.39 (dd, *J* = 1.8 & 10.2 Hz, 1H), 7.24-7.16 (br m, 2H), 7.13 (dd, *J* = 9.0 & 17.4 Hz, 1H), 6.77 (d, *J* = 9.6 Hz, 1H), 5.98 (dt, *J* = 2.4, 8.7 & 17.4 Hz, 1H), 5.55 (br s, 1H), 2.33 (s, 6H).

Example 36

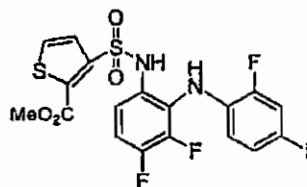
[00346] 2,5-Dichloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)thiophene-3-sulfonamide:



5 **[00347]** According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with 2,5-dichlorothiophene-3-sulfonyl chloride to obtain the title compound. ^1H NMR (300 MHz, CDCl_3): δ 7.41 (dd, $J = 1.5$ & 10.5 Hz, 1H), 7.28-7.20 (m, 2H), 7.08 (dd, $J = 9.0$ & 17.4 Hz, 2H), 6.99 (s, 1H), 6.03 (dt, $J = 2.1$, 8.7 & 17.4 Hz, 1H), 5.56 (br s, 1H).

10 **Example 37**

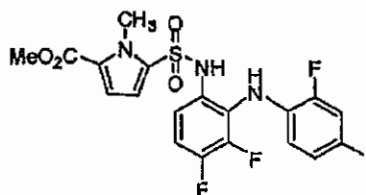
[00348] Methyl 3-(N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)sulfamoyl)thiophene-2-carboxylate:



15 **[00349]** According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl) benzene 1,2-diamine was reacted with methyl 3-(chlorosulfonyl)thiophene-2-carboxylate to obtain the title compound. ^1H NMR (300 MHz, CDCl_3): δ 8.58 (s, 1H), 7.43 (dd, $J = 5.1$ & 10.8 Hz, 2H), 7.35 (dd, $J = 1.8$ & 10.2 Hz, 1H), 7.31 (ddd, $J = 2.1$, 4.2 & 9.3 Hz, 1H), 7.04 (m, 2H), 5.88 (dt, $J = 2.7$, 8.7 & 17.4 Hz, 1H), 5.65 (br s, 1H), 3.85 (s, 3H).

Example 38

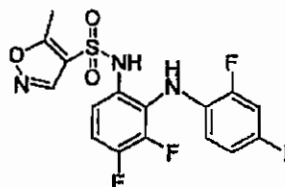
[00350] Methyl 5-(N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)sulfamoyl)-1-methyl-1H-pyrrole-2-carboxylate:



[00351] According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with methyl 5-(chlorosulfonyl)-1-methyl-1H-pyrrole-2-carboxylate to obtain the title compound. ¹H NMR (300 MHz, CDCl₃): δ 7.37 (dd, *J* = 1.8 & 10.5 Hz, 1H), 7.29 (m, 2H), 7.12-6.94 (m, 4H), 5.87 (dt, *J* = 1.8, 8.4 & 17.4 Hz, 1H), 5.56 (br s, 1H), 3.65 (s, 3H), 3.75 (s, 3H).

Example 39

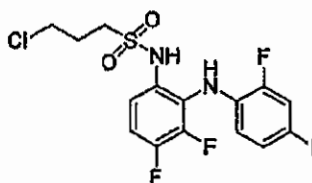
[00352] N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-5-methylisoxazole-4-sulfonamide:



[00353] According to the general procedure A, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with the corresponding sulfonyl chloride to obtain the title compound. Yield: 22%. *m/z* = 508 [M-1].

Example 40

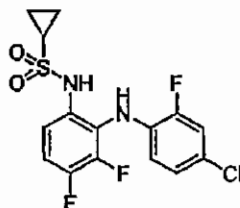
[00354] 3-Chloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)propane-1-sulfonamide:



[00355] According to the general procedure A, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with 3-chloropropane-1-sulfonyl chloride to obtain the desired product. ^1H NMR (500 MHz, CDCl_3): δ = 7.39-7.38 (d, 1H), 7.35-7.34 (m, 1H), 7.27-7.26 (m, 1H), 7.10-7.0 (q, 1H), 6.63 (s, 1H, br), 6.15-6.11 (q, 1H), 5.60 (s, 1H, br), 3.60-3.56 (t, 2H), 3.22-3.20 (m, 2H), 2.22-2.16 (m, 2H).

Example 41

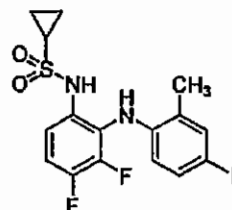
[00356] N-(2-(4-chloro-2-fluorophenylamino)-3,4-difluorophenyl)cyclopropanesulfonamide:



10 [00357] See example 1. ^1H NMR (300 MHz, CDCl_3) δ 0.85-0.95 (m, 2H), 1.05-1.15 (ra, 2H), 2.2-2.4 (m, 1H), 5.8 (s, 1H), 6.3 (t, 1H), 6.6-7.4 (m, 5H); m/z = 375 $[\text{M}-1]^+$.

Example 42

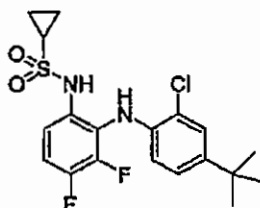
[00358] N-(3,4-difluoro-2-(4-iodo-2-methylphenylamino)phenyl)cyclopropanesulfonamide:



15 [00359] See example 1. ^1H NMR (CDCl_3) δ 0.80-1.0 (m, 2H), 1.05-1.20 (m, 2H), 1.55 (s, 3H), 2.4-2.5 (m, 1H), 5.6 (s, 1H), 6.2 (dd, 1H), 6.4 (s, 1H), 7.1 (q, 1H), 7.3-7.4 (m, 2H), 7.5 (s, 1H); m/z = 463 $[\text{M}-1]^+$.

Example 43

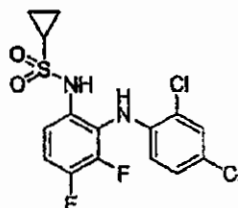
[00360] N-(2-(4-tert-butyl-2-chlorophenylamino)-3,4-difluorophenyl)
cyclopropanesulfonamide:



- 5 [00361] See example 1. ^1H NMR (300 MHz, CDCl_3) δ 0.9-1.0 (m, 2H), 1.05-1.20 (m, 2H), 1.3 (s, 9H), 2.4-2.5 (m, 1H), 5.8 (s, 1H), 6.3 (dd, 1H), 6.6 (s, 1H), 7.0-7.2 (m, 2H), 7.3-7.4 (m, 2H); $m/z = 413$ $[\text{M}-1]^-$.

Example 44

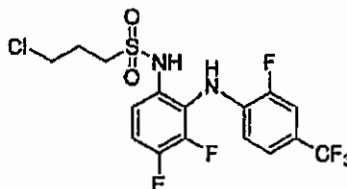
- [00362] N-(2-(2,4-dichlorophenylamino)-3,4-
10 difluorophenyl)cyclopropanesulfonamide:



- [00363] See example 1. ^1H NMR (300 MHz, CDCl_3) δ 0.9-1.0 (m, 2H), 1.05-1.20 (m, 2H), 2.4-2.5 (m, 1H), 6.0 (s, 1H), 6.3 (dd, 1H), 6.6 (s, 1H), 7.0-7.2 (m, 2H), 7.3-7.4 (m, 2H); $m/z = 392$ $[\text{M}-1]^-$.

- 15 Example 45

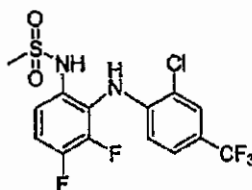
[00364] 3-Chloro-N-(3,4-difluoro-2-(2-fluoro-4-trifluoromethyl)
phenylamino)phenyl)propane-1-sulfonamide:



[00365] See example 1. ^1H NMR (300 MHz, CDCl_3): δ 7.39-7.26 (m, 2H), 7.25 (m, 1H), 7.18 (dd, $J = 9.0$ & 17.7 Hz, 1H), 6.78 (br s, D_2O exchangeable, 1H), 6.50 (t, $J = 8.1$ Hz, 1H), 6.00 (br d, D_2O exchangeable, $J = 1.5$ Hz, 1H), 3.63 (t, $J = 6.0$ & 6.3 Hz, 2H), 3.29 (t, $J = 7.2$ & 7.8 Hz, 2H), 2.26 (quintet, 2H); $m/z = 445$ $[\text{M}-1]^+$.

5 Example 46

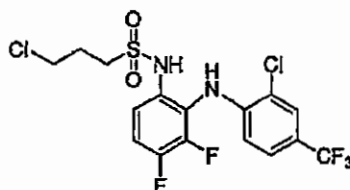
[00366] N-(3,4-difluoro-2-(2-chloro-4-trifluoromethyl)phenylamino)methanesulfonamide:



[00367] See example 1. ^1H NMR (300 MHz, CDCl_3): δ 7.65 (d, $J = 7.8$ Hz, 1H), 7.33 (m, 2H), 7.19 (dd, $J = 9.3$ & 17.4 Hz, 1H), 6.90 (br s, D_2O exchangeable, 1H), 6.45 (dd, $J = 1.5$ & 8.4 Hz, 1H), 6.39 (br s, D_2O exchangeable, 1H), 3.02 (s, 3H); $m/z = 399$ $[\text{M}-1]^+$.

Example 47

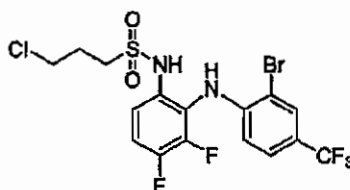
[00368] 3-Chloro-N-(3,4-difluoro-2-(2-chloro-4-trifluoromethyl)phenylamino)phenylpropane-1-sulfonamide:



15 [00369] See example 1. ^1H NMR (300 MHz, CDCl_3): δ 7.66 (d, $J = 1.5$ Hz, 1H), 7.36 (m, 2H), 7.19 (dd, $J = 9.0$ & 17.4 Hz, 1H), 6.91 (br s, D_2O exchangeable, 1H), 6.50 (dd, $J = 8.4$ & 1.5 Hz, 1H), 6.37 (s, D_2O exchangeable, 1H), 3.62 (t, $J = 6.0$ Hz, 2H), 3.29 (t, $J = 7.5$ & 7.8 Hz, 2H), 2.27 (quintet, 2H); $m/z = 462$ $[\text{M}-1]^+$.

Example 48

[00370] 3-Chloro-N-(3,4-difluoro-2-(2-bromo-4-trifluoromethyl)phenylamino)phenyl)propane-1-sulfonamide:

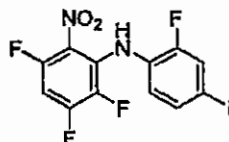


- 5 [00371] See example 1. ^1H NMR (300 MHz, CDCl_3): δ 7.82 (s, 1H), 7.38 (m, 2H), 7.20 (dd, $J = 9.0$ & 17.7 Hz, 1H), 6.62 (br s, D_2O exchangeable, 1H), 6.43 (d, $J = 8.4$ Hz, 1H), 6.23 (s, D_2O exchangeable, 1H), 3.65 (t, $J = 6.0$ Hz, 2H), 3.30 (t, $J = 7.5$ Hz, 2H), 2.28 (quintet, 2H); $m/z = 506$ [$\text{M}-1$] $^-$.

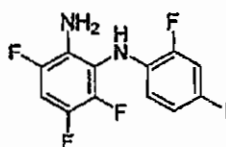
Example 49

- 10 [00372] Cyclopropanesulfonic acid (3,4,6-trifluoro-2-(2-fluoro-4-iodo-phenylamino)-phenyl)-amide:

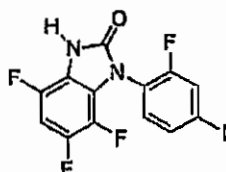
Step A: (2-Fluoro-4-iodo-phenyl)-(2,3,5-trifluoro-6-nitro-phenyl)-amine:



- [00373] A stirred solution of 2-fluoro-4-iodoaniline (3.64 gm, 15.37 mmol) in dry
 15 THF (100 ml) under nitrogen was cooled to -78°C and a solution of 1.0 M lithium hexa
 methyl disilazide ($\text{LiN}(\text{SiMe}_3)_2$) "LHMDS" (15.37 ml, 15.37 mmol) was added slowly.
 This reaction mixture was kept stirring at -78°C for another hour and then 2,3,4,6-
 tetrafluoronitrobenzene was added. The reaction mixture was allowed to warm to room
 temperature and stirring continued for another 16 hours. Ethyl acetate (200 ml) was added
 20 to the reaction mixture and was washed with water. Organic layer was dried over sodium
 sulfate and further purified by column chromatography to provide yellow solid (3.75 gm,
 yield: 59.24%). $\text{M}-\text{H}^+$: 410.9. ^1H NMR (DMSO, 300 MHz): 6.85 (t, 1H); 7.38 (d, 1H);
 7.62 (m, 2H); 8.78 (s, 1H).

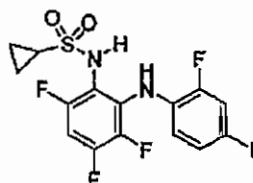
Step B: 3,4,6-Trifluoro-N²-(2-Fluoro-4-iodo-phenyl)-benzene-1,2-diamine:

- [00374] To the stirred solution of (2-fluoro-4-iodo-phenyl)-(2,3,5-trifluoro-6-nitro-phenyl)-amine 3 (5.2 gm, 12.62 mmol) in EtOH (200 ml), ammonium chloride (10.12 gm, 189.3 mmol) and iron powder (10.57 gm, 189.3 mmol) was added. This reaction mixture was kept stirring at reflux for 16 hours. Reaction mixture was allowed to cool and was filtered over celite and concentrated to dryness. The residue obtained was taken into EtOAc and was washed with water. The EtOAc layer was dried over sodium sulfate and further purified by crystallization from EtOH to provide off-white solid (3.2 gm, yield: 66.39%).
- 10 M-H⁺: 381.1. ¹H NMR (DMSO, 300 MHz): 5.0 (s, 2H); 6.2 (t, 1H); 7.2 - 7.3 (m, 2H); 7.45 (s, 1H); 7.5 (d, 1H).

Step C: 4,6,7-Trifluoro-1-(2-Fluoro-4-iodo-phenyl)-1,3,-dihydrobenzoimidazole-2-one:

- 15 [00375] To the stirred solution of 3,4,6-trifluoro-N²-(2-Fluoro-4-iodo-phenyl)-benzene-1,2- diamine 3 (0.285 gm, 0.74 mmol) in CH₂Cl₂ (2 ml), 1,1'-carbonyldiimidazole (0.125 gm, 0.75 mmol) was added. This reaction mixture was kept stirring at room temperature for 16 hours when product precipitated out. The white solid was filtered and used further without any purification. (0.2 gm, yield: 65.85%); m/z = 407 [M-1].

- 20 **Step D/E: Cyclopropanesulfonic acid (3,4,6-trifluoro-2-(2-fluoro-4-iodo-phenylamino)-phenyl)-amide:**

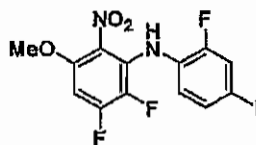


- [00376] A stirred solution of 4,6,7-trifluoro-1-(2-fluoro-4-iodo-phenyl)-1,3-dihydrobenzimidazol-2-one (0.2 gm, 0.41 mmol) in dry THF (4 ml) under nitrogen was cooled to -78°C and a solution of 1.0 M LiHMDS (0.41 ml, 0.41 mmol) was added slowly. (2 ml) followed by addition of cyclopropanesulfonyl chloride (0.050 ml, 0.49 mmol). This reaction mixture was kept stirring at room temperature for 16 hours, concentrated to dryness and was taken into EtOAc. The EtOAc was washed with water, dried over sodium sulfate and concentrated to dryness. The residue obtained 1-cyclopropanesulfonyl-4,5,7-trifluoro-3-(2-fluoro-4-iodo-phenyl)-1,3-dihydro-benzimidazol-2-one **5** was taken into dioxane (2 ml) and to this 1.0 N NaOH (0.5ml) was added and kept stirring at room 50°C for 16 hours.
- TLC indicated incomplete reaction, the product was purified by HPLC to provide off-white solid (4.4 mg) $M+H^+$: 484.7, $M-H^-$: 486.7. 1H NMR ($CDCl_3$, 300 MHz): 0.9 - 1.1 - (m, 2H); 1.1 - 1.2 (m, 2H); 2.45 - 2.55 (m, 1H); 6.05 (s, 1H); 6.44 - 6.54 (m, 1 H); 7.1 (s, 1H); 7.4 - 7.7 (d, 1H); 7.38 - 7.44 (dd, 1H); m/z = 485 $[M-1]^-$.

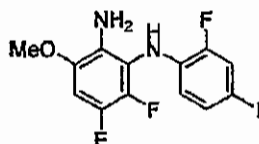
Example 50

- [00377] N-(3,4-difluoro-2-(4-fluoro-2-iodophenylamino)-6-ethoxyphenyl) cyclopropane sulfonamide:

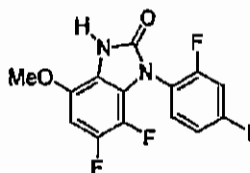
Step A: (2I-Difluoro-5-methoxy-6-nitro-phenyl)-(2-fluoro-4-iodo-phenyl)-amine:



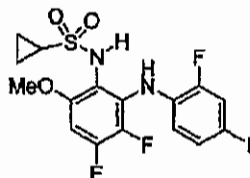
- [00378] A stirred solution of (2-fluoro-4-iodo-phenyl)-(2,3,5-trifluoro-6-nitro-phenyl)-amine (1.23 gm, 3 mmol) in dry THF (25 ml) under nitrogen was cooled to -78°C and a solution of 25% NaOMe (0.68 ml, 0.3 mmol) was added slowly. Reaction mixture was allowed to warm to room temperature and stirring continued for another 16 hours. TLC indicated incomplete reaction. Ethyl acetate (100 ml) was added to the reaction mixture and was washed with water. Organic layer was dried over sodium sulfate and further purified by column chromatography to provide yellow solid (0.6 gm, yield: 47.6%). m/z = 424 $[M=H]^+$.

Step B: 5,6-Difluoro-N1-(4-fluoro-2-iodophenyl)-3-methoxybenzene-1,2-diamine:

[00379] To the stirred solution of (2,3-difluoro-5-methoxy-6-nitro-phenyl)-(2-fluoro-4-iodo-phenyl)-amine (0.57 gm, 1.34 mmol) in EtOH (20 ml), ammonium chloride (1.18 gm, 20.16 mmol) and iron powder (1.15 gm, 21.44 mmol) was added. This reaction mixture was kept stirring at reflux for 16 hours. Reaction mixture was allowed to cool and was filtered over celite and concentrated to dryness. The residue obtained was taken into EtOAc and was washed with water. The EtOAc layer was dried over sodium sulfate and further purified by crystallization from EtOH to provide off-white solid (0.47 gm, yield: 90.3%). M-H⁺: 393.2. ¹H NMR (DMSO, 300 MHz): 3.76 (s, 3H); 6.1 (t, 1H); 6.8 - 7.0 (m, 1H); 7.2 (d, 1H); 7.35 (s, 1H); 7.42 (d, 1H).

Step C: 6,7-Difluoro-1-(4-fluoro-2-iodophenyl)-4-methoxy-1H-benzod[imidazole]-2(3H)-one:

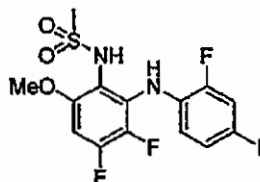
[00380] To the stirred solution of 5,6-difluoro-N1-(4-fluoro-2-iodophenyl)-3-methoxybenzene-1,2-diamine (0.17 gm, 0.43 mmol) in CH₂Cl₂ (2 ml), 1,1'-Carbonyldiimidazole (0.085 gm, 0.53 mmol) was added. This reaction mixture was kept stirring at room temperature for 16 hours when product precipitated out. The white solid was filtered and used further without any purification. (0.089 gm); m/z = 419 [M-1].

Step D/F: N-(3,4-difluoro-2-(4-fluoro-2-iodophenylamino)-6-methoxyphenyl)levcyclopropanesulfonamide:

[00381] A stirred solution of 1-(cyclopropylsulfonyl)-4,5-difluoro-3-(2-fluoro-4-iodophenyl)-7-methoxy-1H-benzo[d]imidazol-2(3H)-one (0.89 gm, 0.17 mmol) in dry THF (4 ml) under nitrogen was cooled to -78°C and a solution of 1.0 M LiHMDS (0.17 ml, 0.17 mmol) was added slowly. (2 ml) followed by addition of cyclopropanesulfonyl chloride (0.021 ml, 0.21 mmol). This reaction mixture was kept stirring at room temperature for 16 hours, concentrated to dryness and was taken into EtOAc. The EtOAc was washed with water, dried over sodium sulfate and concentrated to dryness. The resulting 1-(cyclopropylsulfonyl)-4,5-difluoro-3-(2-fluoro-4-iodophenyl)-7-methoxy-1H-benzo[d]imidazol-2(3H)-one was taken into dioxane (2 ml) and to this 1.0 N NaOH (0.5 ml) was added and kept stirring at room 50°C for 16 hours. TLC indicated incomplete reaction, the product was purified by HPLC to provide off-white solid (2.5 mg) $M+H^+$: 484.7, $M-H^-$: 497.3. 1H NMR ($CDCl_3$, 300 MHz): 0.85 - 0.95 (m, 2H); 1.05 - 1.15 (m, 2H); 2.4 - 2.5 (m, 1H); 3.9 (s, 3H); 6.1 (s, 1H); 6.4 - 6.6 (m, 2 H); 7.3 (m, 1H); 7.35 - 7.4 (dd, 1H); m/z = 497 $[M-1]^-$.

15 Example 51

[00382] Methylsulfonic acid (3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-6-methoxy-phenyl)-amide:



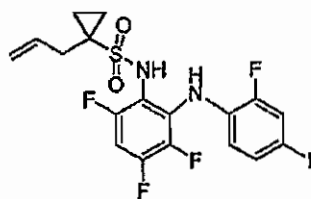
[00383] A stirred solution of 5,6-difluoro-N1-(4-fluoro-2-iodophenyl)-3-methoxybenzene-1,2-diamine (0.150 gm, 0.38 mmol) in dry CH_2Cl_2 (4 ml), TEA (.264 ml, 1.9 mmol) and methanesulfonyl chloride was added slowly. This reaction mixture was kept stirring at room temperature for 16 hours, TLC indicated incomplete reaction along with starting material two products were observed. The reaction mixture was washed with water, organic layer was dried over sodium sulfate and concentrated to dryness, the product was purified by column chromatography. The minor product was found to be the expected compound (6.4 mg). $M+H^+$: 471.5. 1H NMR ($CDCl_3$, 300 MHz): 3.9 (s, 3H); 6.05 (s, 1H); 6.4 - 6.5 (m, 1H); 6.5 - 6.6 (m, 1H); 7.2 (s, 1H); 7.28 (d, 1H); 7.35 - 7.4 (d, 1H); m/z = 471 $[M-1]^-$.

Example 52

[00384] 1-(2,3-Dihydroxy-propyl)-cyclopropanesulfonic acid [3,4,6-trifluoro-2-(4-fluoro-2-iodo-phenylamino)-phenyl]-amide:

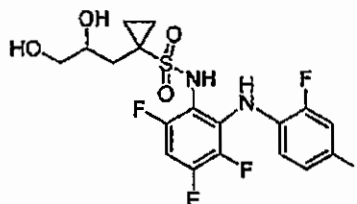
Step A: 1-Allyl-cyclopropanesulfonic acid [3,4,6-trifluoro-2-(2-fluoro-4-iodo-

5 phenylamino)phenyl]-amide:



[00385] According to the general procedure B, 1-allyl-cyclopropanesulfonyl chloride was reacted with 3,5,6-trifluoro-N¹-(2-fluoro-4-iodophenyl)benzene-1,2-diamine to obtain the title product. ¹H NMR (CDCl₃, 300 MHz): δ 7.41 (dd, 1H), 7.38 (dd, 1H), 7.09 (s, 1H),
 10 6.78 (m, 1H), 6.49 (m, 1H), 5.96 (s, 1H), 5.86 (m, 1H), 5.18 (d, 2H), 2.76 (d, 2H), 1.23 (m, 2H), 0.872 (m, 2H).

Step B: 1-(2,3-Dihydroxypropyl)-N-(3,4,6-trifluoro-2-(2-fluoro-4-iodophenylamino)phenyl)cyclopropane-1-sulfonamide:

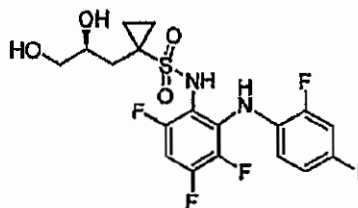


15 [00386] 1-Allyl-cyclopropanesulfonic acid [3,4,6-trifluoro-2-(2-fluoro-4-iodo-phenyl amino)- phenyl]-amide (110 mg, 0.21 mmol) and 4-methylmorpholine N-oxide (24.6 mg, 0.21 mmol) was dissolved in THF (8 mL). Osmium tetroxide was added at room temperature (0.021 mmol, 0.153 mL, 4% in H₂O) and the reaction mixture was stirred at room temperature for 16 hours. EtOAc was added, the organic phase was washed with
 20 water, dried (MgSO₄) and concentrated under reduced pressure. The residue was purified over silica gel chromatography (eluants: EtOAc/ MeOH) to obtain the titled product (0.89 g, 75 %). ¹H NMR (CDCl₃, 300 MHz): δ 7.39 (dd, J = 1.5 & 10.6 Hz, 1H), 7.29 (d, J = 8.8 Hz, 1H), 7.28 (s, 1H), 6.97 (s, 1H), 6.76 (m, 1H), 6.49 (m, 1H), 4.13 (m, 1H), 3.66 (dd, J =

3.7 & 11.4 Hz, 1H), 3.53 (dd, $J = 6.7$ & 11.2 Hz, 1H), 2.50 (dd, $J = 10.0$ & 16.1 Hz, 1H), 1.6 (m, 1H), 1.46 (m, 1H), 1.28 (m, 1H), 1.20 (m, 2H), 0.92 (m, 2H); $m/z = 559$ $[M-1]^+$.

Example 53

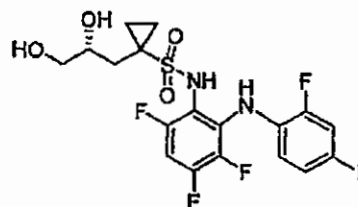
[00387] (S)-1-(2,3-dihydroxypropyl)-N-(3,4,6-trifluoro-2-(2-fluoro-4-iodophenylamino)phenyl)cyclopropane-1-sulfonamide:



[00388] The pure S isomer was obtained by chiral HPLC separation of the racemic mixture (example 52). ^1H NMR (CDCl_3 , 300 MHz): δ 7.39 (dd, $J = 1.5$ & 10.6 Hz, 1H), 7.29 (d, $J = 8.8$ Hz, 1H), 7.28 (s, 1H), 6.97 (s, 1H), 6.76 (m, 1H), 6.49 (m, 1H), 4.13 (m, 1H), 3.66 (dd, $J = 3.7$ & 11.4 Hz, 1H), 3.53 (dd, $J = 6.7$ & 11.2 Hz, 1H), 2.50 (dd, $J = 10.0$ & 16.1 Hz, 1H), 1.6 (m, 1H), 1.46 (m, 1H), 1.28 (m, 1H), 1.20 (m, 2H), 0.92 (m, 2H); $m/z = 559$ $[M-1]^+$.

Example 54

[00389] (R)-1-(2,3-dihydroxypropyl)-N-(3,4,6-trifluoro-2-(2-fluoro-4-iodophenylamino)phenyl)cyclopropane-1-sulfonamide:



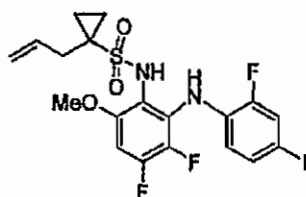
[00390] The pure R isomer was obtained by chiral HPLC separation of the racemic mixture (example 52). ^1H NMR (CDCl_3 , 300 MHz): δ 7.39 (dd, $J = 1.5$ & 10.6 Hz, 1H), 7.29 (d, $J = 8.8$ Hz, 1H), 7.28 (s, 1H), 6.97 (s, 1H), 6.76 (m, 1H), 6.49 (m, 1H), 4.13 (m, 1H), 3.66 (dd, $J = 3.7$ & 11.4 Hz, 1H), 3.53 (dd, $J = 6.7$ & 11.2 Hz, 1H), 2.50 (dd, $J = 10.0$ & 16.1 Hz, 1H), 1.6 (m, 1H), 1.46 (m, 1H), 1.28 (m, 1H), 1.20 (m, 2H), 0.92 (m, 2H); $m/z = 559$ $[M-1]^+$.

Example 55

[00391] N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide:

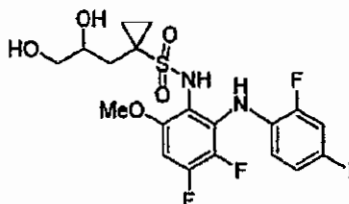
Step A: 1-Allyl-N-3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-

5 methoxyphenyl)cyclopropane-1-sulfonamide:



[00392] According to the general procedure B, 1-allyl-cyclopropanesulfonyl chloride was reacted with 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)-3-methoxybenzene-1,2-diamine to obtain the title product. ¹H NMR (CDCl₃, 300 MHz): δ 7.417 (dd, 1H), 7.309 (s, 1H), 7.25 (m, 1H), 6.89 (m, 1H), 6.52 (m, 1H), 6.427 (m, 1H), 6.03 (s, 1H), 5.668 (m, 1H), 5.11 (t, 1H), 3.9 (s, 3H), 2.75 (d, 2H), 1.21 (m, 2H), 0.767 (m, 2H).

Step B: N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide:

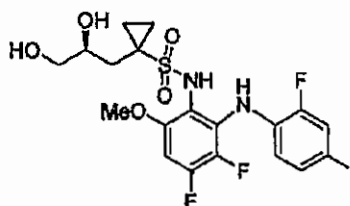


15 [00393] 1-Allyl-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)cyclopropane-1-sulfonamide (97 mg, 0.18 mmol) and 4-methylmorpholine N-oxide (21 mg, 0.18 mmol) were dissolved in THF (8 mL). Osmium tetroxide was added at room temperature (0.018 mmol, 0.13 mL, 4% in H₂O) and the reaction mixture was stirred at room temperature for 16 hours. EtOAc was added, the organic phase was washed with water, dried (MgSO₄) and concentrated under reduced pressure. The residue was purified over silica gel chromatography (eluants: EtOAc/ MeOH) to obtain the titled product (0.80 g, 78 %). ¹H NMR (CDCl₃, 300 MHz): δ 7.38 (dd, J = 1.7 & 10.3 Hz, 1H), 7.26 (m, 1H), 7.14 (s, 1H), 6.87 (s, 1H), 6.53 (dd, J = 6.8 & 11.4 Hz, 1H), 6.43 (m, 1H), 4.06 (m, 1H), 3.89 (s, 3H), 3.63 (dd, J = 3.7 & 11.1 Hz, 1H), 3.49 (dd, J = 6.4 & 11.1 Hz, 1H), 2.3 (dd, J = 9.7 &

16.1 Hz, 1H), 1.77 (dd, $J = 1.9$ & 16.0 Hz, 1H), 1.37 (m, 1H), 1.25 (m, 1H), 1.21 (m, 2H), 0.86 (m, 2H); $m/z = 571$ [M-1]⁻.

Example 56

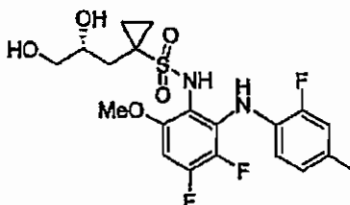
[00394] (S)-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide:



[00395] The pure S isomer was obtained by chiral HPLC separation of the racemic mixture (example 55). ¹H NMR (CDCl₃, 300 MHz): δ 7.38 (dd, $J = 1.7$ & 10.3 Hz, 1H), 7.26 (m, 1H), 7.14 (s, 1H), 6.87 (s, 1H), 6.53 (dd, $J = 6.8$ & 11.4 Hz, 1H), 6.43 (m, 1H), 4.06 (m, 1H), 3.89 (s, 3H), 3.63 (dd, $J = 3.7$ & 11.1 Hz, 1H), 3.49 (dd, $J = 6.4$ & 11.1 Hz, 1H), 2.3 (dd, $J = 9.7$ & 16.1 Hz, 1H), 1.77 (dd, $J = 1.9$ & 16.0 Hz, 1H), 1.37 (m, 1H), 1.25 (m, 1H), 1.21 (m, 2H), 0.86 (m, 2H); $m/z = 571$ [M-1]⁻.

Example 57

[00396] (R)-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide:

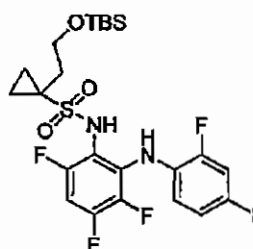


[00397] The pure R isomer was obtained by chiral HPLC separation of the racemic mixture (example 55). ¹H NMR (CDCl₃, 300 MHz): δ 7.38 (dd, $J = 1.7$ & 10.3 Hz, 1H), 7.26 (m, 1H), 7.14 (s, 1H), 6.87 (s, 1H), 6.53 (dd, $J = 6.8$ & 11.4 Hz, 1H), 6.43 (m, 1H), 4.06 (m, 1H), 3.89 (s, 3H), 3.63 (dd, $J = 3.7$ & 11.1 Hz, 1H), 3.49 (dd, $J = 6.4$ & 11.1 Hz, 1H), 2.3 (dd, $J = 9.7$ & 16.1 Hz, 1H), 1.77 (dd, $J = 1.9$ & 16.0 Hz, 1H), 1.37 (m, 1H), 1.25 (m, 1H), 1.21 (m, 2H), 0.86 (m, 2H); $m/z = 571$ [M-1]⁻.

Example 58

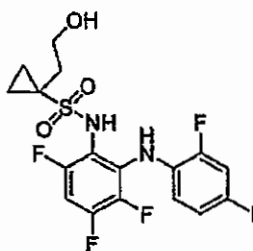
[00398] **1-(2-hydroxyethyl)-N-(3,4,6-trifluoro-2-(2-fluoro-4-iodophenylamino)phenyl) cyclopropane-1-sulfonamide:**

Step A: TBS-protected 1-(2-hydroxyethyl)-N-(3,4,6-trifluoro-2-(2-fluoro-4-iodophenylamino) phenyl) cyclopropane-1-sulfonamide:



[00399] According to the general procedure B, the sulfonyl chloride prepared in step C of example 16 was reacted with 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)-3-fluorobenzene-1,2- diamine to obtain the title product. Yield: 13%. ¹H-NMR (300 MHz, CDCl₃): δ = 7.51 (s, 1H, br), 7.37-7.35 (d, 1H), 7.27-7.25 (d, 1H), 6.94 (s, 1H, br), 6.78-6.68 (m, 1H), 6.46-6.44 (m, 1H), 3.90-3.88 (t, 2H), 2.12-2.10 (t, 2H), 1.31-1.28 (m, 2H), 0.91-0.89 (m, 2H), 0.86 (s, 9H), 0.05 (s, 6H); *m/z* = 643 [M-1]⁺

Step B: 1-(2-hydroxyethyl)-N-(3,4,6-trifluoro-2-(2-fluoro-4-iodophenylamino)-phenyl) cyclopropane-1-sulfonamide:

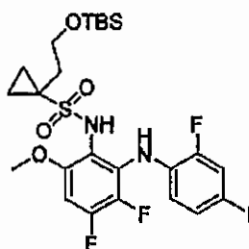


[00400] Same procedure as in step E, example 16. Yield: 100%. ¹H-NMR (300 MHz, CDCl₃): δ = 7.51 (s, 1H, br), 7.37-7.35 (d, 1H), 7.27-7.25 (d, 1H), 6.94 (s, 1H, br), 6.78-6.68 (m, 1H), 6.46-6.44 (m, 1H), 3.90-3.88 (t, 2H), 2.12-2.10 (t, 2H), 1.31-1.28 (m, 2H), 0.91-0.89 (m, 2H); *m/z* = 529 [M-1]⁺.

Example 59

[00401] **N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2-hydroxyethyl)cyclopropane-1-sulfonamide:**

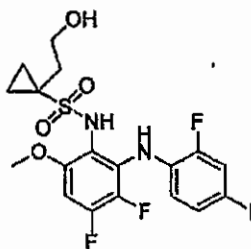
Step A: TBS-protected N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2-hydroxyethyl)cyclopropane-1-sulfonamide:



[00402] According to the general procedure B, the sulfonyl chloride prepared in step C of example 16 was reacted with 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)-3-methoxybenzene-1,2-diamine to obtain the title product. Yield: 37%. ¹H-NMR (300 MHz, CDCl₃):

10 δ = 7.40-7.34 (dd, 1H), 7.23-7.21 (m, 1H), 6.61 (s, 1H, br), 6.57-6.49 (dd, 1H), 6.48-6.39 (m, 1H), 3.9-3.7 (m, 5H), 2.15-2.05 (t, 2H), 1.30-1.20 (m, 2H), 0.95-0.80 (m, 11H), 0.05 (s, 6H); m/z = 655 [M-1]⁻.

Step B: N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2-hydroxyethyl)cyclopropane-1-sulfonamide:

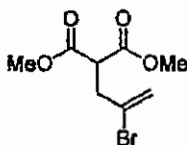


15 [00403] Same procedure as in step E, example 16. Yield: 100%. ¹H-NMR (300 MHz, CDCl₃): δ = 7.40-7.34 (dd, 1H), 7.23-7.21 (m, 1H), 6.61 (s, 1H, br), 6.57-6.49 (dd, 1H), 6.48-6.39 (m, 1H), 3.9-3.7 (m, 5H), 2.15-2.05 (t, 2H), 1.30-1.20 (m, 2H), 0.95-0.80 (m, 2H); m/z = 541 [M-1]⁻.

Example 60

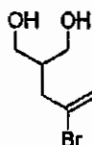
[00404] N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(3-hydroxy-2-(hydroxymethyl)propyl)cyclopropane-1-sulfonamide:

Step A: Dimethyl 2-(2-bromoallyl)malonate:



5 To a suspension of sodium hydride (5.0 g, 125 mmol) in HMPA (50 ml, distilled from calcium hydride) was added a solution of dimethyl malonate (11.7 ml, 100 mmol) in HMPA (5 ml) at 0°C under argon. The mixture was heated to 50°C and stirred 1 hour. Following this the solution was again cooled to 0°C, and a solution of 2,3-
10 dibromopropene (12.2 ml, 100 mmol) in HMPA (5 ml) was added to the reaction mixture. Next, the solution was warmed to 40°C and stirred for 1 hour. The reaction mixture was quenched with aq. HCl (10%, 88 ml) and extracted with ether (3 x 45 ml). The organic fractions were collected, dried over MgSO₄, and the solvent was removed *in vacuo*. The crude oil was purified via silica gel chromatography (eluants: chloroform/hexane) to obtain
15 the titled product as a colorless oil (16.3 g, 65%). ¹H-NMR (300 MHz, CDCl₃) δ 5.70 (d, J = 1.8 Hz, 1 H), 5.48 (d, J = 1.8 Hz, 1H), 3.63 (t, J = 7.5 Hz, 1 H), 3.76 (s, 6 H), 3.04 (d, J = 7.5 Hz, 2 H).

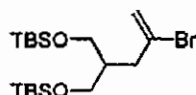
Step B: 2-(2-Bromoallyl)propane-1,3-diol:



20 [00406] Lithium aluminum hydride (1.9 g, 7.65 mmol) was slurried in anhydrous diethyl ether (50 ml) and cooled to -78°C in a dry ice/acetone bath. A solution of the product from step A (0.639 g, 16.84 mmol) in dry ether (26 ml) was then added dropwise. After the malonate was added, the solution was allowed warm to room temperature and stirring was continued for 3 hours. The reaction was quenched with brine (50 ml), extracted
25 with ethyl acetate (3 x 25 ml) and dried over MgSO₄. The solvent was removed *in vacuo* to give the desired product (1.3 g, 86%) which was used for the next step without further

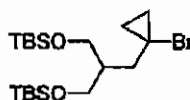
purification. $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 5.66 (d, $J = 1.2$ Hz, 1 H), 5.48 (d, $J = 1.5$ Hz, 1 H), 3.86 (m, 2 H), 3.73 (m, 2 H), 2.51 (d, $J = 7.5$ Hz, 2 H), 2.40 (br s, 2 H), 2.15 (m, 1 H).

Step C: Di-tert-butyltrimethylsilyl protected 2-(2-bromoallyl)propane-1,3-diol:



5 [00407] The product from step B (2.8 g, 14.20 mmol) was dissolved in anhydrous THF (140 ml). Anhydrous pyridine (2.5 ml, 31.24 mmol) was added, and the solution was cooled to 0°C . tert-Butyldimethylsilyltriflate (7.2 ml, 31.24 mmol) was added dropwise, and upon completion, the reaction solution was heated to 35°C . After stirring for 6 days, the reaction was quenched with 100 ml brine, extracted with ethyl acetate (3 x 50 ml) and
10 dried over MgSO_4 . The combined organic phases were evaporated to obtain the crude product (5.5 g, 91%) as a yellow oil which was used in the next step without further purification. $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 5.54 (d, $J = 0.9$ Hz, 1 H), 5.40 (d, $J = 1.2$ Hz, 1 H), 3.55 (d, $J = 5.4$, 4 H), 2.40 (d, $J = 6.9$ Hz, 2 H), 1.97 (m, 1 H), 0.85 (s, 18 H), 0.02 (s, 9 H).

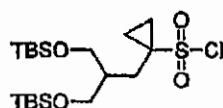
15 **Step D: Di-tert-butyltrimethylsilyl protected 2-((1-bromocyclopropyl)methyl)propane-1,3-diol:**



[00408] A reaction flask was charged with anhydrous CH_2Cl_2 (10 ml) and diethyl zinc (1.0 M in hexanes, 4.65 ml, 4.65 mmol) at 0°C . Trifluoroacetic acid (0.358 ml, 4.65
20 mmol) was added dropwise and the solution was allowed to stir for 20 minutes. Diiodomethane (0.375 ml, 4.65 mmol) was then added and the solution was stirred for another 20 minutes. Finally, the product from step C (0.492 g, 1.16 mmol) was added and the solution was allowed to warm to ambient temperature, stirring for 16 hours. The reaction was quenched with saturated aqueous NH_4Cl . The layers were partitioned and the
25 aqueous phase was extracted with chloroform (3 x 5 ml). The combined organic phases were washed with brine (10 ml), dried over MgSO_4 , and the volatiles were removed *in vacuo*. The resulting crude was purified via silica gel chromatography (eluants: chloroform/hexanes) to provide the product as a clear oil (0.280 g, 64%). $^1\text{H-NMR}$ (300

MHz, CDCl₃) δ 3.66 (d, J = 5.4, 4 H), 2.08 (m, 1 H), 1.64 (d, J = 6.9, 2 H), 1.13 (m, 2 H), 0.88 (s, 18 H), 0.81 (m, 2 H), 0.04 (s, 9 H).

Step E: Di-tert-butyl dimethylsilyl protected 1-(3-hydroxy-2-(hydroxymethyl)propyl)cyclopropane-1-sulfonyl chloride:



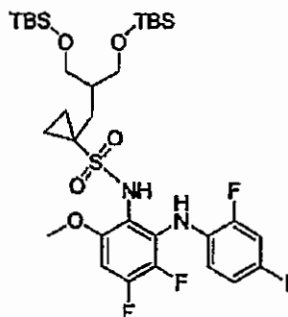
5

[00409] The product from step D (0.507 g, 1.16 mmol) was dissolved in anhydrous ether (6 ml) and the reaction solution was cooled to -78°C. Following this, tert-butyllithium (1.7 M in pentane, 1.50 ml, 2.55 mmol) was added dropwise over 5 minutes. After stirring for 0.5 hours, the lithiated product was transferred via cannula to a stirred solution of sulfur

10 sulfonyl chloride (0.206 ml, 2.55 mmol) in dry ether (6 ml) at -78°C. Once the transfer is complete, the solution was allowed to warm to room temperature, the solvent was evaporated and the resulting white solid was slurried in dry hexanes. This slurry was immediately filtered through celite, and all volatiles were removed *in vacuo*. The resulting crude product (0.376 g, 71%) was isolated as a yellow oil and was used in the following

15 step without further purification. ¹H-NMR (300 MHz, CDCl₃) δ 3.60 (m, 4 H), 2.16 (m, 1 H), 2.03 (d, 2 H), 0.88 (s, 18 H), 0.04 (s, 9 H).

Step F: Di-tert-butyl dimethylsilyl protected N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(3-hydroxy-2-(hydroxymethyl)propyl)cyclopropane-1-sulfonamide:

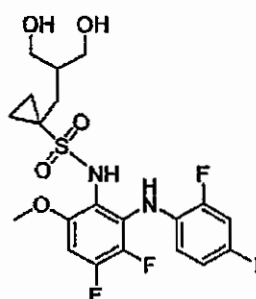


20

[00410] 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)-3-methoxybenzene-1,2-diamine (8.8 mg, 0.022 mmol) was dissolved in anhydrous pyridine (0.5 ml) under an argon atmosphere. The product from step E (20.5 mg, 0.045 mmol), dissolved in dry pyridine (0.5

ml), was added to the reaction flask and the mixture was heated at 80°C for 21 hours. The solvent was removed *in vacuo* and the resulting crude was purified via silica gel chromatography (eluent: ethyl acetate/hexanes) to provide the title compound (2.75 mg, 15%). *m/z* 813.5 (M-1).

5 **Step G: N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(3-hydroxy-2-(hydroxymethyl)propyl)cyclopropane-1-sulfonamide:**

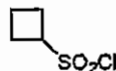


[00411] The product from step F (27.9 mg, 0.0342 mmol) was dissolved in THF (1 ml) and treated with aqueous HCl (1.2 N, 0.2 ml) at 0°C. The resulting solution was stirred
10 for 4 hours. Following this, the reaction was quenched with saturated aqueous NaHCO₃,
extracted with ethyl acetate, dried over MgSO₄ and the volatiles were removed *in vacuo*.
The resulting crude was purified via silica gel chromatography (eluent:
methanol/chloroform) followed by LC-MS purification to provide the title compound (11.8
mg, 59%). ¹H-NMR (300 MHz, CD₃OD) δ 7.32 (dd, 1 H), 7.21 (d, 1 H), 6.76 (dd, 1 H),
15 6.33 (m, 1 H), 3.82 (s, 3 H), 3.52 (d, 4 H), 2.01 (m, 1 H), 1.88 (d, 2 H), 1.07 (m, 2 H), 0.75
(m, 2 H), *m/z* 585.3 (M-1).

Example 61

[00412] **N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)
cyclobutane sulfonamide:**

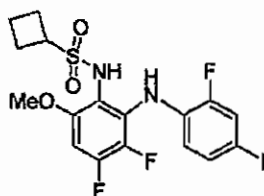
20 **Step A: Cyclobutanesulfonyl chloride:**



[00413] To a suspension of Mg turnings (0.790 g, 32.5 mmol) in 20 ml anhydrous diethyl ether was added a solution of cyclobutylbromide (1.8 ml, 2.5722 g, 19.1 mmol) in 20 ml diethyl ether in small portions with strong stirring. After the initial exothermic

reaction had ceased, the mixture was further heated to the reflux temperature for 30 min. The suspension was cooled down to room temperature and the supernatant was added in small portions to an ice-cold solution of sulfonyl chloride (4.6 ml, 7.728 g, 57.2 mmol) in 30 ml anhydrous DCM. After complete addition, the suspension was warmed to room temperature and the volatiles were removed *in vacuo*. The residue was dried in oil-pump vacuo for 15 min, then it was extracted with hexane (150 ml). The hexane suspension was filtered and the hexane was removed in vacuo to give the crude product as dark purple oil which was used for the next step without further purification. There is still some unreacted cyclopropylbromide present. Crude yield: 1.1 g (38%).

Step B: N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)cyclobutanesulfonamide:

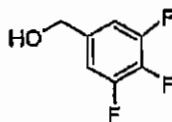


[00414] According to the general procedure B, the cyclobutylsulfonyl chloride prepared in the step above was reacted with 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)-3-methoxy-benzene-1,2-diamine to obtain the title product. Yield: 75%. ¹H-NMR (300 MHz, CDCl₃): δ = 7.44 (s, 1H, br), 7.41-7.36 (dd, 1H), 7.24-7.23 (m, 1H), 6.54-6.38 (m, 2H), 5.90 (s, 1H, br), 3.85-3.75 (m, 5H), 2.60-2.40 (m, 2H), 2.25-2.15 (m, 1H), 2.15-1.95 (m, 2H); *m/z* = 511 [M-1]⁻.

Example 62

[00415] N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methylphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide:

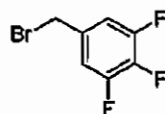
Step A: (3,4,5-Trifluorophenyl)methanol:



[00416] To a cooled (-5° C) solution of 3,4,5-trifluorobenzaldehyde (7.0 g, 43.75 mmol) in a mixture (50 ml, 9:1) of THF and water NaBH₄ (1.662 g, 43.75 mmol) was slowly added in portions over a period of 30 min. The reaction mixture was allowed to

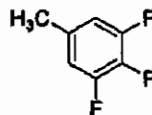
attain room temperature over a period of 2h and carefully poured into ice-cold dil HCl (200 ml, 1N). The oily layer was extracted into CH₂Cl₂ (250 ml) and the organic layer washed with water (200 ml), dried (MgSO₄) and evaporated. The crude product (7.08 g, quantitative) obtained was taken forward without further purification.

5 **Step B: 5-(Bromomethyl)-1,2,3-trifluorobenzene:**



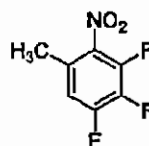
[00417] To a solution of the (3,4,5-Trifluorophenyl)methanol (40 mmol) in CH₂Cl₂ (150 ml), a solution of thionyl bromide (6.16 ml, 80 mmol) in CH₂Cl₂ (50 ml) was added slowly. The reaction mixture stirred at room temperature for 16h and poured into ice-water (200 ml). The organic layer was separated and washed with saturated NaHCO₃ (2x200 ml), water (200 ml), dried (MgSO₄) and evaporated to obtain the corresponding bromo compound as a pale yellow oil in quantitative yield. The crude product was carried forward for the next reaction without further purification.

10 **Step C: 1,2,3-Trifluoro-5-methylbenzene:**



15 [00418] The above bromo compound (40 mmol) was mixed with triethylsilane (48 mmol) and the reaction mixture was treated with solid PdCl₂ (4 mmol) in small portions. After a few minutes a vigorous exothermic reaction was ensued and care was taken to reflux the contents of the flask by placing a reflux condenser. The reaction mixture was stirred at room temperature for additional 6h and the contents were allowed to settle over 16h. Then the crude liquid product was decanted carefully and carried forward for the next reaction without further purification. It was assumed that the reaction proceeds in quantitative yield.

20 **Step D: 1,2,3-Trifluoro-5-methyl-4-nitrobenzene:**



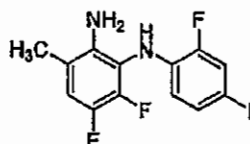
[00419] 1,2,3-Trifluoro-5-methylbenzene (40 mmol) was added to conc. H_2SO_4 (50 ml) at 0-5° C. Then the reaction mixture was slowly treated with conc. HNO_3 (3.39 ml, 48.44 mmol, 90%) while maintaining the internal temperature below 20° C. The reaction mixture was stirred at room temperature for 16h and poured onto ice (300 g) and the oily layer was extracted with CH_2Cl_2 (2x125 ml). The organic layer was washed with water (2x200 ml), brine (200 ml) and dried (MgSO_4) and evaporated to obtain the crude product which was purified over flash silica gel chromatography to obtain the title product (6.5 g, 85%). $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 6.96 (septet, 1H), 2.39 (s, 3H). $^{19}\text{F-NMR}$ (CDCl_3): δ -128.18, -141.50, -159.05.

10 **Step E: 2,3-Difluoro-N-(2-fluoro-4-iodophenyl)-5-methyl-6-nitroaniline:**



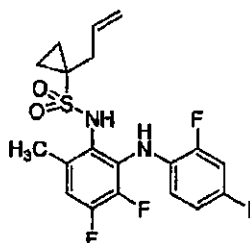
[00420] 2-Fluoro-4-iodoaniline and 1,2,3-trifluoro-5-methyl-4-nitrobenzene were reacted using the condition described in Example 1 (Step A) to form the title compound. M-H^+ : 407.9

15 **Step F: 5,6-Difluoro-N1-(2-fluoro-4-iodophenyl)-3-methylbenzene-1,2-diamine:**



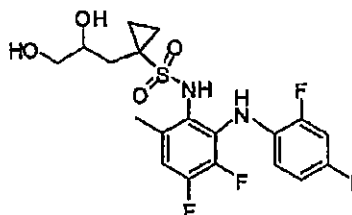
[00421] 2,3-Difluoro-N-(2-fluoro-4-iodophenyl)-5-methyl-6-nitroaniline was reduced using the condition described in Example 1 (step B) to form the title compound. M-H^+ : 377.4

Step G: 1-Allyl-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methylphenyl)cyclopropane-1-sulfonamide:



[00422] According to the general procedure B, 1-allyl-cyclopropanesulfonyl chloride (142 mg, 0.4 mmol) was reacted with 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)-3-methylbenzene-1,2-diamine (150 mg, 0.4 mmol) to obtain the title product (100 mg, 47%); $m/z = 521$ $[M-1]^+$.

Step H: N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methylphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide:

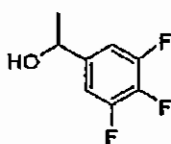


[00423] 1-Allyl-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methylphenyl)cyclopropane-1-sulfonamide (150 mg, 0.29 mmol) and 4-methylmorpholine N-oxide (33 mg, 0.29 mmol) was dissolved in THF (5 mL). Osmium tetroxide was added at room temperature (0.029 mmol, 0.18 mL, 4% in H_2O) and the reaction mixture was stirred at room temperature for 16 hours. EtOAc was added, the organic phase was washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified over silica gel chromatography (eluants: EtOAc/ MeOH) to obtain the titled product (0.110 g, 68 %). 1H -NMR (300 MHz, $CDCl_3$): δ 7.07 (m, 1H), 6.97 (br m, 2H), 6.84 (m, 2H), 6.60 (br m, 2H), 3.98 (br m, 1H), 3.58 (m, 1H), 3.43 (m, 1H), 3.20 (d, $J = 3.9$ Hz, 1H), 2.42 (s, 3H), 2.31 (dd, $J = 9.9$ & 15.6 Hz, 1H), 2.01 (br t, 1H), 2.31 (dd, $J = 9.9$ & 15.6 Hz, 1H), 1.66 (dd, $J = 2.1$ & 15.9 Hz, 1H), 1.52 (m, 1H), 1.40 (m, 1H), 0.91 (m, 2H).

Example 63

[00424] **1-(2,3-Dihydroxypropyl)-N-(6-ethyl-3,4-difluoro-2-(2-fluoro-4-iodophenylamino) phenyl) cyclopropane-1-sulfonamide:**

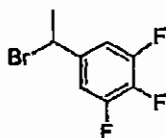
Step A: 1-(3,4,5-Trifluorophenyl)ethanol:



[00425] An ethereal solution (17.41 ml, 52.24 mmol, 3M) of MeMgBr was slowly added at - 78° C to a solution of 3,4,5-trifluorobenzaldehyde (6.96 g, 43.53 mmol) in THF (125 ml). The reaction mixture was stirred at room temperature for 16h and was cooled (0° C) and was quenched, sequentially, with excess ethyl acetate (10 ml) and water (5 ml).

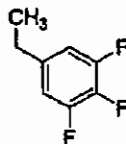
Excess anhydrous MgSO₄ (5 g) was added and stirred for 30 minutes at room temperature. The suspension was filtered over celite and the solids were washed with ethyl acetate (2x25 ml). The combined filtrate was evaporated to obtain the product in quantitative yield (7.65 g).

Step B: 5-(1-Bromoethyl)-1,2,3-trifluorobenzene:



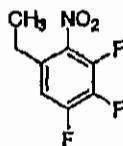
To a solution of the 1-(3,4,5-Trifluorophenyl)ethanol: (7.65 g, 43.5 mmol) in CH₂Cl₂ (250 ml), a solution of thionyl bromide (18.1 g, 87 mmol) in CH₂Cl₂ (50 ml) was added slowly. The reaction mixture stirred at room temperature for 16h and poured into ice-water (200 ml). The organic layer was separated and washed with saturated NaHCO₃ (2x200 ml), water (200 ml), dried (MgSO₄) and evaporated to obtain the corresponding bromo compound as a pale yellow oil in quantitative yield (10.4 g). The crude product was carried forward for the next reaction without further purification.

Step C: 5-Ethyl-1,2,3-trifluorobenzene:



[00427] The above bromo compound (9.65 g, 40.4 mmol) was mixed with triethylsilane (41 mmol) and the reaction mixture was treated with solid PdCl_2 (177 mg, 4 mmol) in small portions. After a few minutes a vigorous exothermic reaction was ensued and care was taken to reflux the contents of the flask by placing a reflux condenser. The reaction mixture was stirred at room temperature for additional 6h and the contents were allowed to settle over 16h. Then the crude liquid product was decanted carefully and carried forward for the next reaction without further purification. It was assumed that the reaction proceeds in quantitative yield.

Step D: 1-Ethyl-3,4,5-trifluoro-2-nitrobenzene:



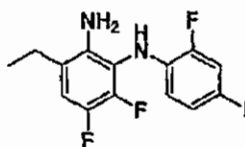
[00428] 1,2,3-Trifluoro-5-methylbenzene (6.46 g, 40.4 mmol) was added to conc. H_2SO_4 (50 ml) at 0-5° C. Then the reaction mixture was slowly treated with conc. HNO_3 (3.39 ml, 48.44 mmol, 90%) while maintaining the internal temperature below 20° C. The reaction mixture was stirred at room temperature for 16h and poured onto ice (300 g) and the oily layer was extracted with CH_2Cl_2 (2x125 ml). The organic layer was washed with water (2x200 ml), brine (200 ml) and dried (MgSO_4) and evaporated to obtain the crude product which was purified over flash silica gel chromatography to obtain the title product (6.6 g, 79%). ^1H NMR (CDCl_3): δ 6.98 (septet, 1H), 2.68 (q, 2H), 1.26 (t, $J = 7.8$ & 7.2 Hz, 3H).

Step E: 3-Ethyl-5,6-difluoro-N-(2-fluoro-4-iodophenyl)-2-nitroaniline:



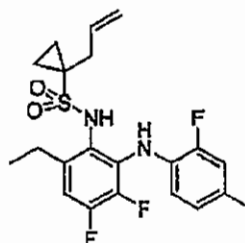
[00429] 2-Fluoro-4-iodoaniline (2.05 g, 10 mmol) and 1-ethyl-3,4,5-trifluoro-2-nitrobenzene (2.37 g, 10 mmol) were reacted using the condition described in example 1 (Step A) to form the title compound (2.47 g, 60%); $m/z = 407$ [$\text{M}-1$] $^-$.

Step F: 3-Ethyl-5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine:



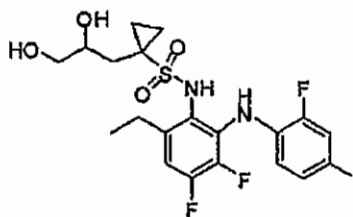
[00430] 1,2,3-Trifluoro-5-methyl-4-nitrobenzene (2.47 g, 5.85 mmol) was reduced using the condition described in example 1 (Step B) to form the title compound. M-H⁺: 393

5 Step G: 1-Allyl-N-(6-ethyl-3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)cyclopropane-1-sulfonamide:



[00431] According to the general procedure B, 1-allyl-cyclopropanesulfonyl chloride (230 mg, 1.27 mmol) was reacted with 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)-3-methylbenzene-1,2-diamine (100 mg, 0.255 mmol) to obtain the title product (72 mg, 53%); m/z = 535 [M-1].

Step H: 1-(2,3-Dihydroxypropyl)-N-(6-ethyl-3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)cyclopropane-1-sulfonamide:



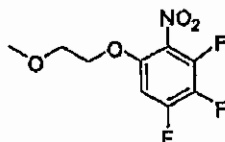
15 [00432] 1-Allyl-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methylphenyl)cyclopropane-1-sulfonamide (70 mg, 0.13 mmol) and 4-methylmorpholine N-oxide (15 mg, 0.13 mmol) was dissolved in THF (2 mL). Osmium tetroxide was added at room temperature (0.013 mmol) 0.075 mL, 4% in H₂O and the reaction mixture was stirred at room temperature for 16 hours. EtOAc was added, the organic phase was washed with

water, dried (MgSO₄) and concentrated under reduced pressure. The residue was purified over silica gel chromatography (eluants: EtOAc/MeOH) to obtain the titled product. ¹H NMR (300 MHz, CDCl₃): δ 7.38 (dd, *J* = 2.1 & 10.8 Hz, 1H), 7.27 (m, 2H), 7.12 (br s, 1H), 6.91 (dd, *J* = 8.1 & 10.8 Hz, 1H), 6.69 (br s, 1H), 6.36 (dt, *J* = 4.8, 8.7 & 13.5 Hz, 1H), 4.00 (m, 1H), 3.62 (dd, *J* = 3.6 & 10.5 Hz, 1H), 3.47 (br m, 2H), 2.81 (q, 2H), 2.40 (dd, *J* = 10.2 & 15.9 Hz, 1H), 1.73 (br m, 2H), 1.58 (m, 1H), 1.43 (m, 1H), 0.94 (m, 2H).

Example 64

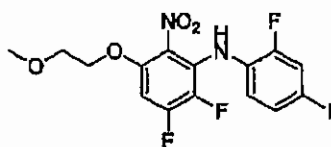
[00433] N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-(2-methoxyethoxy)phenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide:

10 Step A: 1,2,3-Trifluoro-5-(2-methoxyethoxy)-4-nitrobenzene:



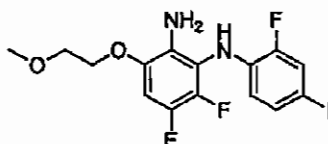
[00434] To a mixture of 3,4,5-trifluoro-2-nitrophenol (1.93, 10 mmol), Ph₃P (3.93 g, 15 mmol), and 2-methoxy-ethanol (1.18 ml, 15 mmol) in anhydrous THF (25 ml) a solution of diisopropyl azodicarboxylate (2.91 ml, 15 mmol) in THF (5 ml) was added at 0° C and the reaction mixture was stirred at room temperature for 16h. The volatiles were evaporated and the residue was dissolved in CH₂Cl₂ (100 ml) and the organic layer was washed with water (100 ml), brine (100 ml) dried (MgSO₄) and evaporated. The residue obtained was purified over flash silica gel chromatography to obtain the titled product in 68% (1.70 g) yield. ¹H NMR (300 MHz, CDCl₃): δ 6.78 (ddd, *J* = 2.4, 6.0, 11.7 Hz, 1H), 4.19 (t, *J* = 4.5 Hz, 2H), 3.72 (t, *J* = 4.5 Hz, 2H), 3.39 (s, 3H).

20 Step B: 2,3-Difluoro-N-(2-fluoro-4-iodophenyl)-5-(2-methoxyethoxy)-6-nitroaniline:



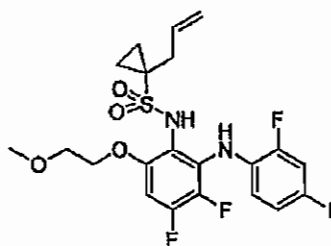
[00435] 2-Fluoro-4-iodoaniline (1.6 g, 6.8 mmol) and 1,2,3-trifluoro-5-(2-methoxyethoxy)-4-nitrobenzene (1.7 g, 6.8 mmol) were reacted using the condition described in Example 1 (Step A) to form the title compound (1.02 g, 32%); *m/z* = 467 [M-1].

Step C: 5,6-Difluoro-N1-(2-fluoro-4-iodophenyl)-3-(2-methoxyethoxy)benzene-1,2-diamine:



[00436] 2,3-Difluoro-N-(2-fluoro-4-iodophenyl)-5-(2-methoxyethoxy)-6-nitroaniline
 5 (1.017 g, 2.17 mmol) was reduced using the condition described in Example 1 (Step B) to form the title compound; $m/z = 337$ [M-1].

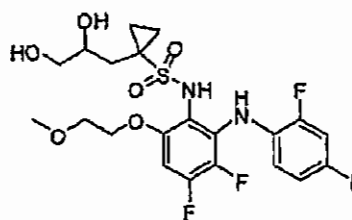
Step D: 1-Allyl-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-(2-methoxyethoxy)phenyl)cyclopropane-1-sulfonamide:



10 [00437] According to the general procedure B, 1-allyl-cyclopropanesulfonyl chloride (450 mg, 2.5 mmol) was reacted with 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)-3-(2-methoxyethoxy)benzene-1,2-diamine (219 mg, 2.5 mmol) to obtain the title product (230 mg, 78%); $m/z = 581$ [M-1].

Step E: N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-(2-methoxyethoxy)phenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide:

15

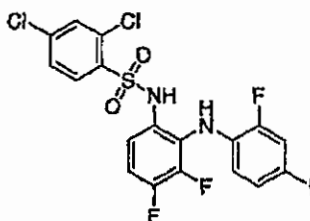


[00438] 1-allyl-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-(2-methoxyethoxy)phenyl)cyclopropane-1-sulfonamide (230 mg, 0.395 mmol) and 4-methylmorpholine N-oxide (46 mg, 0.395 mmol) was dissolved in THF (2 mL). Osmium

tetroxide was added at room temperature (0.039 mmol, 0.25 mL, 4% in H₂O) and the reaction mixture was stirred at room temperature for 16 hours. EtOAc was added, the organic phase was washed with water, dried (MgSO₄) and concentrated under reduced pressure. The residue was purified over silica gel chromatography (eluant: EtOAc/MeOH) to obtain the titled product. ¹H NMR (300 MHz, CDCl₃): δ 7.36 (dd, *J* = 1.8 & 10.5 Hz, 1H), 7.27 (m, 2H), 6.56 (dd, *J* = 6.9 & 11.4 Hz, 1H), 6.40 (dt, *J* = 5.7, 7.5 & 12.9 Hz, 1H), 4.17 (m, 2H), 4.01 (m, 1H), 3.78 (m, 2H), 3.60 (dd, *J* = 3.6 & 11.1 Hz, 1H), 3.47 (m, 1H), 3.45 (s, 3H), 2.36 (dd, *J* = 9.6 & 15.9 Hz, 1H), 1.78 (dd, *J* = 2.4 & 15.6 Hz, 1H), 1.45-1.25 (m, 2H), 0.89 (m, 2H).

Example 65

[00439] 2,4-dichloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)benzene sulfonamide:

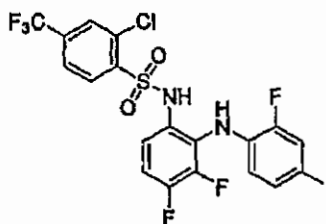


[00440] Synthesized by method A using the appropriate sulfonyl chloride, *m/z* = 571

[M-1].

Example 66

[00441] 2-chloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-4-(trifluoromethyl)benzenesulfonamide:

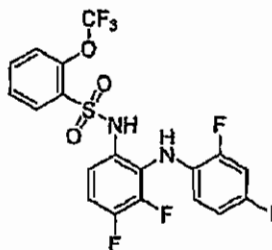


[00442] Synthesized by method A using the appropriate sulfonyl chloride, *m/z* = 605

[M-1].

Example 67

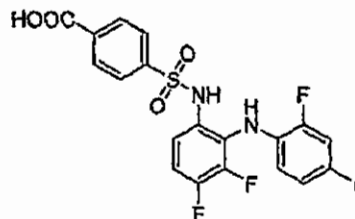
[00443] N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2-(trifluoromethoxy) benzene sulfonamide:



5 [00444] Synthesized by method A using the appropriate sulfonyl chloride, $m/z = 587$ [M-1].

Example 68

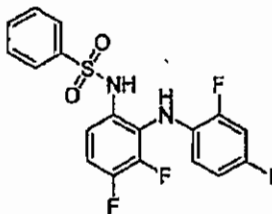
[00445] 4-(N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)sulfamoyl)benzoic acid:



10 [00446] Synthesized by method A using the appropriate sulfonyl chloride, $m/z = 584$ [M-1].

Example 69

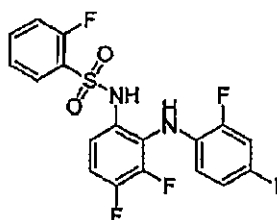
[00447] N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)benzenesulfonamide:



[00448] Synthesized by method A using the appropriate sulfonyl chloride, $m/z = 503$
[M-1].

Example 70

[00449] N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2-fluorobenzene
5 sulfonamide:



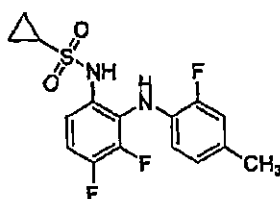
[00450] Synthesized by method A using the appropriate sulfonyl chloride, $m/z = 521$
[M-1].

[00451] General procedure D: substitution of the iodine atom:

10 [00452] A suspension containing 1 eq. aryl iodide, 1.5 equiv. of the boronic acid or boronic ester, 0.25 eq. $\text{PdCl}_2(\text{dppf}) \times \text{DCM}$ and 10 eq. anhydrous K_2CO_3 powder in a deoxygenated mixture of dioxane and water (3:1) was heated in a microwave reactor for 60 min at 115°C . It was extracted using aq. $\text{NH}_4\text{Cl}/\text{THF}$, and the organic fraction was dried using Na_2SO_4 . The crude reaction products were purified using flash-column
15 chromatography (Si, EtOAc/Hexanes, or $\text{CHCl}_3/\text{MeOH}$). Yields: 20-40%.

Example 71

[00453] N-(3,4-difluoro-2-(2-fluoro-4-methylphenylamino)phenyl)cyclopropanesulfonamide;



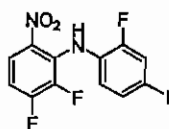
20 [00454] Synthesized by General procedure D: $^1\text{H-NMR}$ (500 MHz, CDCl_3): $\delta = 7.38$ - 7.36 (m, 1H), 7.06 - 7.03 (q, 1H), 6.92 - 6.90 (1H), 6.73 - 6.72 (d, 1H), 6.63 (s, 1H, br), 6.37 - 6.33 (t, 1H), 5.54 (s, 1H, br), 2.42 - 2.39 (m, 1H), 2.25 (s, 3H), 1.14 - 1.11 (m, 2H), 0.94 - 0.90 (m, 2H); $m/z = 355$ [M-1].

[00455] Where racemic mixtures of chiral compounds have been resolved into separate enantiomers, the phrase "substantially free" of the epimer, as used herein, means an enantiomeric excess of at least 90%.

Example 72

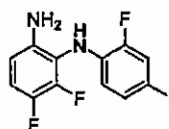
- 5 [00456] N-(3,4-difluoro-2-(2-fluoro-4-(1H-pyrazol-4-yl)phenylamino)phenyl)cyclopropane sulfonamide

Step A: 2,3-Difluoro-N-(2-fluoro-4-iodophenyl)-6-nitroaniline:



- To a solution of 2-fluoro-4-iodoaniline (11.40 g, 47 mmol) in 100 ml anhydrous THF at 0 °C, 47 ml of a 1M solution of LHMDS in THF (47 mmol) was added dropwise. The color of the solution turned dark purple. The solution was transferred via cannula to a dropping funnel, and the solution (containing the amine free base) was added in small portions to a solution of 2,3,4-trifluoronitrobenzene (8.321 g, 47.0 mmol) in anhydrous THF (50 ml) at 0 °C. After completion of addition the mixture was stirred under argon at room temperature for 15 hours. The volume of the solvent was reduced, followed by extraction using ethyl acetate and brine. The organic layer was dried over sodium sulfate, the solvent was removed, and the obtained dark oil was purified by flash chromatography (EtOAc / hexane 1:5, R_f = 0.58) yielding the crude product, which became a brown solid upon drying *in vacuo* (yield: 6.23 g, 33.6%). m/z = 393 [M-1].

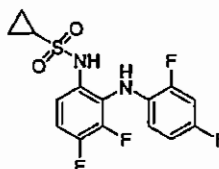
- 20 Step B: 5,6-Difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine



- To a solution of nitro-diarylamine (6.23 g, 15.8 mmol) in 300 ml ethanol was added iron powder (13.74 g, 246 mmol) and ammonium chloride (13.59 g, 254 mmol) and the mixture was heated with stirring at 100 °C oil bath temperature for 14 hours. It was filtered and the residue washed two times with ethanol. The ethanol was removed *in vacuo*, and the residue was extracted using ethyl acetate / 1M NaOH solution. During the extraction, more precipitate was formed which was filtered and discarded. The combined organic layers were washed with brine and dried over sodium sulfate. The solvent was removed, and the crude

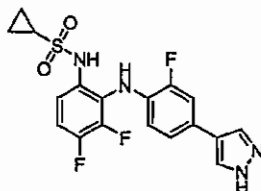
- product was recrystallized from CHCl_3 / hexane (1:50). The product was obtained as brown needles (2.094 g, 66%). $R_f = 0.44$ (EtOAc / Hex 1:3). $^1\text{H-NMR}$ (500 MHz, CDCl_3): $\delta =$ 7.40-7.38 (dd, 1H, $J = 11.3$ Hz, $J = 1.5$ Hz), 7.25-7.23 (d, 1H, $J = 8.5$ Hz), 6.97-6.92 (q, 1H, $J = 9$ Hz), 6.51-6.48 (m, 1H), 6.24-6.21 (t, 1H, $J = 9$ Hz), 5.3 (s, 1H, NH, br), 3.80 (s, 2H, NH_2 , br); LRMS (ESI): $m/z = 365$ $[\text{M}+\text{H}]^+$.

Step C: N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)cyclopropane sulfonamide:



- According to the general procedure A, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with cyclopropanesulfonyl chloride to obtain the desired product. (500 MHz, CDCl_3): $\delta =$ 7.38-7.37 (d, 1H), 7.35-7.34 (m, 1H), 7.27-7.26 (m, 1H), 7.20-7.0 (q, 1H), 6.68 (s, 1H, br), 6.15-6.12 (q, 1H), 5.65 (s, 1H, br), 3.25-3.20 (m, 1H), 2.4-2.3 (m, 2H), 2.0-1.8 (m, 2H); $m/z = 467$ $[\text{M}-1]^-$.

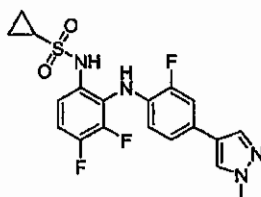
- Step D: N-(3,4-difluoro-2-(2-fluoro-4-(1H-pyrazol-4-yl)phenylamino)phenyl)cyclopropanesulfonamide:**



General procedure C : $^1\text{H-NMR}$ (500 MHz, CDCl_3): $\delta =$ 8.00-7.90 (m, 2H), 7.30-7.20 (m, 2H), 7.15-7.10 (m, 1H), 7.05-7.00 (m, 1H), 6.70-6.60 (m, 1H), 2.40-2.35 (m, 1H), 1.05-1.0 (m, 2H), 0.95-0.85 (m, 2H); $m/z = 407$ $[\text{M}-1]^-$.

Example 73

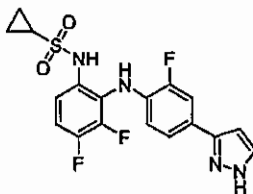
[00457] N-(3,4-difluoro-2-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)phenylamino)phenyl) cyclopropanesulfonamide



- 5 Synthesized by General procedure C : $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ = 7.95 (s, 1H), 7.75 (s, 1H), 7.30-7.20 (m, 2H), 7.15-7.10 (m, 1H), 7.05-7.00 (m, 1H), 6.70-6.60 (m, 1H), 3.95 (s, 3H), 2.40-2.35 (m, 1H), 1.05-1.0 (m, 2H), 0.95-0.85 (m, 2H); m/z = 421 $[\text{M}-1]^+$

Example 74

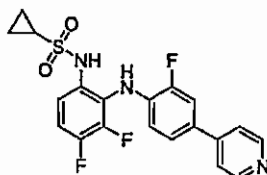
- [00458] N-(3,4-difluoro-2-(2-fluoro-4-(1H-pyrazol-3-yl)phenylamino)phenyl) cyclopropanesulfonamide
- 10



Synthesized by General procedure C : $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ = 7.90 (s, 1H), 7.80 (s, 1H), 7.30-7.20 (m, 2H), 7.15-7.10 (m, 1H), 7.05-7.00 (m, 1H), 6.70-6.60 (m, 1H), 3.95 (s, 3H), 2.40-2.35 (m, 1H), 1.05-1.0 (m, 2H), 0.95-0.85 (m, 2H); m/z = 407 $[\text{M}-1]^+$

- 15 Example 75

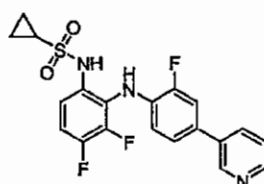
[00459] N-(3,4-difluoro-2-(2-fluoro-4-(pyridin-4-yl)phenylamino)phenyl) cyclopropanesulfonamide



Synthesized by General procedure C : $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ = 8.62-8.61 (d, 2H), 7.43-7.41 (m, 4H), 7.23-7.22 (m, 1H), 7.16-7.11 (q, 1H), 6.61-6.58 (t, 1H), 6.11 (s, 1H, br), 2.53-2.50 (m, 1H), 1.21-1.10 (m, 2H), 1.02-0.99 (m, 2H); m/z = 418 $[\text{M}-1]^+$.

Example 76

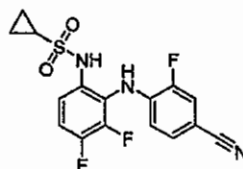
- 5 [00460] **N-(3,4-difluoro-2-(2-fluoro-4-(pyridin-3-yl)phenylamino)phenyl)cyclopropanesulfonamide**



- Synthesized by General procedure C : $^1\text{H-NMR}$ (500 MHz, $[\text{D}_6]-\text{DMSO}$): δ = 9.45 (s, 1H), 8.91 (s, 1H), 8.54 (s, 1H), 8.07-8.06 (d, 1H), 7.76-7.70 (m, 2H), 7.46-7.34 (m, 2H), 7.34-7.33 (d, 2H), 6.80-6.78 (m, 1H), 0.86-0.79 (m, 4H); m/z = 418 $[\text{M}-1]^+$.

Example 77

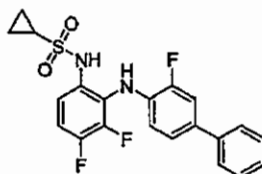
- [00461] **N-(2-(4-cyano-2-fluorophenylamino)-3,4-difluorophenyl)cyclopropanesulfonamide**



- 15 A suspension containing the aryl iodide (75.5 mg, 0.161 mmol), CuCN (46.6 mg, 0.520 mmol) and $\text{Pd}(\text{OAc})_2$ (0.47 mg) in 1 ml anhydrous DMF was heated to 130 $^\circ\text{C}$ for 60 min. in a microwave reactor. The mixture was extracted using brine / THF, and the organic fractions were dried using Na_2SO_4 . Subsequent flash-column chromatography gave the product as a dark red semi-solid (R_f = 0.42 (EtOAc/Hexanes 1:1). Yield: 15 %.
- 20 m/z = 366 $[\text{M}-1]^+$.

Example 78

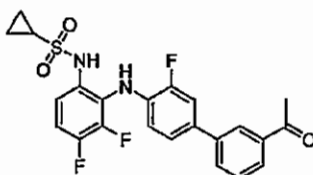
[00462] **N-(3,4-difluoro-2-(3-fluorobiphenyl-4-ylamino)phenyl)cyclopropanesulfonamide**



- 5 Synthesized by General procedure C : $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ = 7.55-7.53 (m, 2H), 7.45-7.3 (m, 5H), 7.20-7.15 (d, 1H), 7.13-7.10 (q, 1H), 6.70 (s, 1H, br), 6.60-6.55 (t, 1H), 5.75 (s, 1H, br), 2.53-2.50 (m, 1H), 1.21-1.10 (m, 2H), 1.02-0.99 (m, 2H); m/z = 417 $[\text{M}-1]^+$.

Example 79

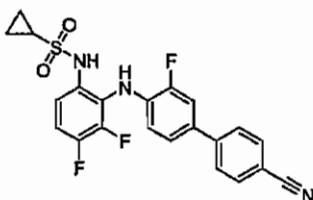
[00463] **N-(2-(3'-acetyl-3-fluorobiphenyl-4-ylamino)-3,4-difluorophenyl)cyclopropanesulfonamide**



- 10 Synthesized by General procedure C : $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ = 8.6 (s, 1H), 7.86-7.85 (d, 1H), 7.68-7.66 (d, 1H), 7.49-7.46 (t, 1H), 7.38-7.33 (m, 2H), 7.20-7.18 (d, 1H), 7.09-7.03 (q, 1H), 6.90 (s, 1H, br), 6.57-6.54 (t, 1H), 5.90 (s, 1H, br), 2.61 (s, 3H), 2.46-2.43 (m, 1H), 1.15-1.13 (m, 2H), 0.94-0.91 (m, 2H); m/z = 459 $[\text{M}-1]^+$.

Example 80

[00464] **N-(2-(4'-cyano-3-fluorobiphenyl-4-ylamino)-3,4-difluorophenyl)cyclopropanesulfonamide**



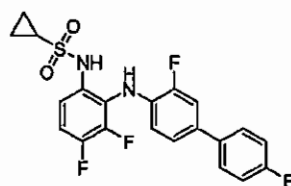
- 20 Synthesized by General procedure C : $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ = 7.68-7.66 (m, 2H), 7.58-7.57 (m, 2H), 7.38-7.35 (m, 2H), 7.20-7.18 (d, 1H), 7.18-7.02 (q, 1H), 6.67 (s, 1H, br),

6.58-6.54 (t, 1H), 5.99 (s, 1H, br), 2.47-2.44 (m, 1H), 1.15-1.13 (m, 2H), 0.94-0.91 (m, 2H);
 $m/z = 442 [M-1]^+$.

Example 81

[00465] **N-(2-(3,4'-difluorobiphenyl-4-ylamino)-3,4-**

5 **difluorophenyl)cyclopropanesulfonamide**

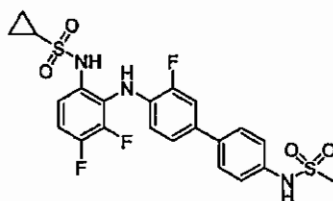


Synthesized by General procedure C: $^1\text{H-NMR}$ (500 MHz, CDCl_3): $\delta = 7.44-7.37$ (m, 3H),
 7.29-7.27 (d, 1H), 7.11-7.05 (m, 4H), 6.70 (s, 1H, br), 6.53-6.50 (t, 1H), 5.81 (s, 1H, br),
 2.47-2.44 (m, 1H), 1.15-1.13 (m, 2H), 0.94-0.91 (m, 2H); $m/z = 435 [M-1]^+$.

10 **Example 82**

[00466] **N-(3,4-difluoro-2-(3-fluoro-4'-(methylsulfonamido)biphenyl-4-**

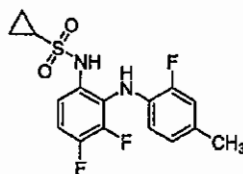
ylamino)phenyl) cyclopropanesulfonamide



15 Synthesized by General procedure C: $^1\text{H-NMR}$ (500 MHz, $[\text{D}_6]-\text{DMSO}$): $\delta = 9.39$ (s, 1H,
 br), 7.63-7.60 (m, 3H), 7.53-7.50 (d, 1H), 7.30-7.23 (m, 4H), 7.74-7.65 (m, 1H), 2.99 (s,
 3H), 0.80-0.73 (m, 4H); $m/z = 510 [M-1]^+$.

Example 83

[00467] **N-(3,4-difluoro-2-(2-fluoro-4-**
methylphenylamino)phenyl)cyclopropanesulfonamide

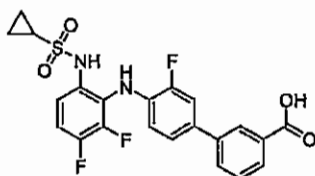


20

Synthesized by General procedure C : $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ = 7.38-7.36 (m, 1H), 7.06-7.03 (q, 1H), 6.92-6.90 (1H), 6.73-6.72 (d, 1H), 6.63 (s, 1H, br), 6.37-6.33 (t, 1H), 5.54 (s, 1H, br), 2.42-2.39 (m, 1H), 2.25 (s, 3H), 1.14-1.11 (m, 2H), 0.94-0.90 (m, 2H); m/z = 355 $[\text{M}-1]^-$.

5 **Example 84**

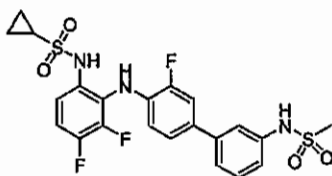
[00468] **4'-(6-(cyclopropanesulfonamido)-2,3-difluorophenylamino)-3'-fluorobiphenyl-3-carboxylic acid**



10 Synthesized by General procedure C : $^1\text{H-NMR}$ (500 MHz, $[\text{D}_4]\text{-MeOH}$): δ = 8.21 (s, 1H), 7.93-7.91 (d, 1H), 7.73-7.72 (d, 1H), 7.47-7.43 (m, 2H), 7.33-7.31 (d, 2H), 7.15-7.12 (q, 1H), 6.71-6.68 (m, 1H), 2.51-2.46 (m, 1H), 0.94-0.93 (m, 2H), 0.88-0.87 (m, 2H); m/z = 499 $[\text{M}-1]^-$.

Example 85

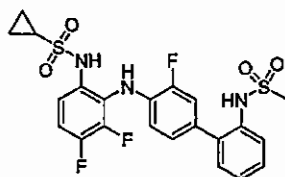
15 [00469] **N-(3,4-difluoro-2-(3-fluoro-3'-(methylsulfonamido)biphenyl-4-ylamino)phenyl) cyclopropanesulfonamide**



20 Synthesized by General procedure C : $^1\text{H-NMR}$ (500 MHz, $[\text{D}_4]\text{-MeOH}$): δ = 7.92 (s, 1H), 7.46-7.34 (m, 5H), 7.34-7.31 (d, 1H), 7.29-7.22 (m, 1H), 7.16-7.15 (q, 1H), 6.74-6.71 (m, 1H), 2.80 (s, 3H), 2.54-2.51 (m, 1H), 0.94-0.92 (m, 2H), 0.91-0.90 (m, 2H); m/z = 510 $[\text{M}-1]^-$.

Example 86

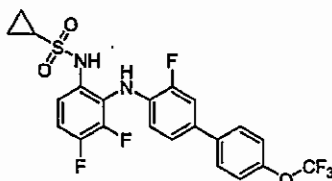
[00470] **N-(3,4-difluoro-2-(3-fluoro-2'-(methylsulfonylamido)biphenyl-4-ylamino)phenyl) cyclopropanesulfonamide**



- 5 Synthesized by General procedure C : $^1\text{H-NMR}$ (500 MHz, $[\text{D}_4]\text{-MeOH}$): δ = 7.50-7.49 (d, 1H), 7.40-7.32 (m, 4H), 7.29-7.28 (d, 1H), 7.26-7.10 (m, 2H), 6.73-6.71 (m, 1H), 2.80 (s, 3H), 2.51-2.49 (m, 1H), 0.94-0.92 (m, 2H), 0.91-0.90 (m, 2H); m/z = 510 $[\text{M}-1]^+$.

Example 87

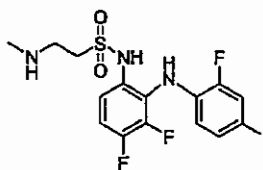
- 10 [00471] **N-(3,4-difluoro-2-(3-fluoro-4'-(trifluoromethoxy)biphenyl-4-ylamino)phenyl) cyclopropanesulfonamide**



Synthesized by General procedure C : $^1\text{H-NMR}$ (500 MHz, $[\text{D}_4]\text{-MeOH}$): δ = 7.69-7.67 (d, 2H), 7.46-7.43 (d, 1H), 7.36-7.33 (m, 4H), 7.30-7.29 (q, 1H), 6.73-6.72 (m, 1H), 2.51-2.49 (m, 1H), 0.94-0.92 (m, 2H), 0.91-0.90 (m, 2H); m/z = 501 $[\text{M}-1]^+$.

- 15 **Example 88**

[00472] **N-(3,4-Difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2-(methylamino) ethanesulfonamide**

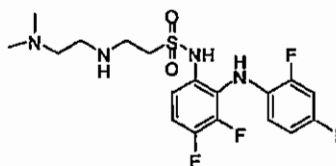


- 20 Synthesized by General procedure D. $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 9.01 (br s, D_2O exchangeable, 1H), 7.36 (dd, J = 2.1 & 10.5 Hz, 1H), 7.27 (m, 1H), 7.17 (m, 1H), 7.03 (dd,

$J = 9.0$ & 16.8 Hz, 1H), 6.48 (s, D₂O exchangeable, 1H), 6.31 (dt, $J = 3.0, 8.7$ & 17.4 Hz, 1H), 3.45 (br t, 2H), 3.31 (br s, 2H), 2.65 (s, 3H), 1.80 (br s, D₂O exchangeable, 1H).

Example 89

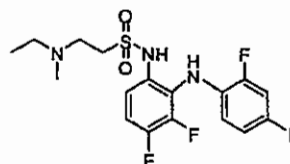
- [00473] N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2-(2-(dimethylamino)ethylamino) ethanesulfonamide



- Synthesized by General procedure D. ¹H NMR (300 MHz, CDCl₃): δ 7.35 (m, 1H), 7.25 (m, 1H), 7.18 (d, $J = 8.7$ Hz, 1H), 7.02 (dd, $J = 8.7$ & 18.0 Hz, 1H), 6.38 (m, 1H), 6.18 (dd, $J = 8.7$ & 17.1 Hz, 1H), 3.62 (t, $J = 5.7$ & 6.3 Hz, 2H), 3.35 (m, 2H), 3.26 (m, 2H), 3.26 (t, $J = 5.7$ & 6.6 Hz, 2H), 3.11 (t, $J = 5.1$ & 6.0 Hz, 2H), 2.85 (s, 6H).

Example 90

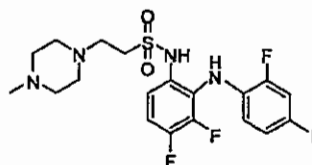
- [00474] N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2-(ethyl(methyl)amino) ethanesulfonamide



- Synthesized by General procedure D. ¹H NMR (300 MHz, (CDCl₃ + D₂O)): δ 7.39 (dd, $J = 1.5$ & 10.5 Hz, 1H), 7.31 (m, 2H), 7.07 (dd, $J = 9.0$ & 17.4 Hz, 1H), 6.30 (dt, $J = 2.4, 9.0$ & 17.4 Hz, 1H), 3.55 (t, $J = 6.9$ & 7.8 Hz, 2H), 3.38 (br t, $J = 6.0$ & 8.7 Hz, 2H), 3.05 (q, 2H), 2.69 (s, 3H), 1.31 (t, $J = 7.2$ Hz, 3H).

Example 91

- [00475] N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2-(4-methylpiperazin-1-yl) ethanesulfonamide



Synthesized by General procedure D. ¹H NMR (300 MHz, CD₃OD): δ 7.45 (dd, *J* = 2.1 & 10.8 Hz, 1H), 7.30 (m, 2H), 7.16 (dd, *J* = 9.6 & 17.7 Hz, 1H), 6.39 (dt, *J* = 3.3, 9.3 & 17.7 Hz, 1H), 3.26 (m, *J* = 7.5 Hz, 2H), 3.10 (br m, 6H), 2.87 (s, 3H), 2.82 (t, *J* = 7.5 Hz, 2H), 2.48 (br m, 4H).

5

In vitro Biological Activity

Example 92

[00476] Generation of IC₅₀ Data

Materials and preparation of reagents: Human GST-MEK1 and the constitutively active
 10 allele GST-MEK1^{CA} (harboring the mutations Ser218Asp and Ser222Asp) were subcloned
 into the yeast expression vector pGEM4Z (Promega, Madison, WI) from the wild type
 human MEK1 cDNA. GST-MEK1^{CA} was expressed in *Escherichia coli* and partially
 purified using Glutathione Sepharose 4B affinity resin (Amersham Pharmacia Biotech,
 Piscataway, NJ). The ERK2 allele was subcloned from MAPK2/Erk2 cDNA (wild type) in
 15 pUSEamp (Upstate Biotechnology, Inc., Waltham, MA) into the vector pET21a (Novagen,
 Madison, WI) resulting in an N-terminal histidine-tagged mouse ERK2 allele. ERK2 was
 expressed and purified to homogeneity [Zhang, 1993 #33]. Myelin basic protein (MBP)
 was purchased from Gibco BRL (Rockville, MD). EasyTides adenosine 5'-triphosphate
 (ATP) ([γ-³³P]) (NEN Perkin Elmer, Wellesley, MA) was the source of radiolabel for all
 20 kinase reactions. Activated Raf-1 (truncated) and activated MAPKinase 2/ERK2 were
 purchased from Upstate, Inc. (Lake Placid, NY). 4-20% Criterion Precast gels were
 purchased from Bio-Rad (Hercules, CA).

[00477] Determination of enzymatic activity: Compounds were diluted from
 dimethylsulfoxide (DMSO) stocks into 1xHMNDE (20 mM HEPES pH 7.2, 1 mM MgCl₂,
 25 100 mM NaCl, 1.25 mM DTT, 0.2 mM EDTA). A typical 25-microliter assay contained
 0.002 nanomoles MEK1^{CA}, 0.02 nanomoles ERK2, 0.25 nanomoles MBP, 0.25 nanomoles
 unlabeled ATP, and 0.1 μCi [γ-³³P] ATP. The screening assay essentially comprised four
 additions. Five μl of diluted compound were dispensed to 96-well assay plates. Ten μl of
 2.5x enzyme cocktail (MEK1^{CA} and ERK2 only) were then added to each well followed by
 30 a pre-incubation for 30 minutes at ambient temperature. Ten μl of 2.5x substrate cocktail
 (labeled and unlabeled ATP plus MBP) were then added, followed by incubation for 60
 minutes at ambient temperature. Finally, 100 μl of 10% trichloroacetic acid (TCA) were
 added and incubated for 30 minutes at room temperature to halt the reaction and precipitate

radiolabeled protein products. Reaction products were harvested on glass fiber 96 well filter plates prewetted with water and 1% pyrophosphate. The filter plate was then washed 5 times with water. Water was displaced by absolute ethanol and the plate was allowed to air dry for 30 minutes at room temperature. A back seal was applied manually and 40 μ l of scintillation cocktail were dispensed to each well. A top seal was applied and the plate was counted in the TopCount for two seconds per well.

[00478] For certain experiments a truncated version of MEK that requires activation by Raf kinase were used.

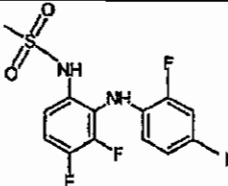
Example 93

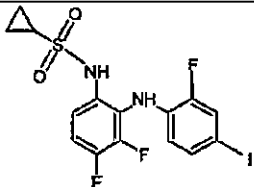
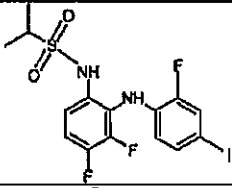
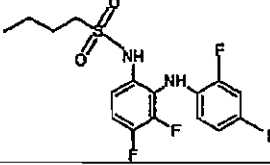
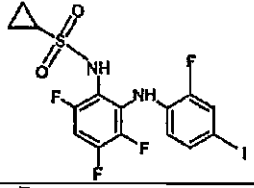
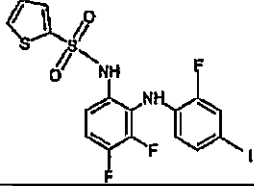
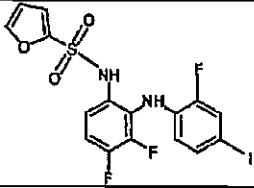
10 [00479] Generation of EC50 Data

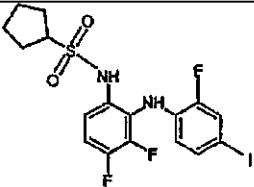
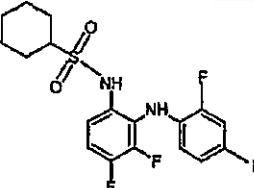
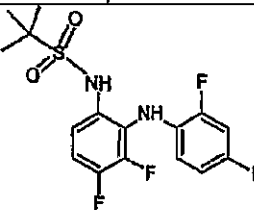
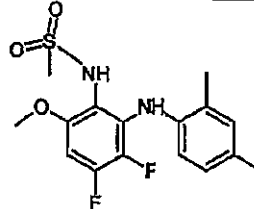
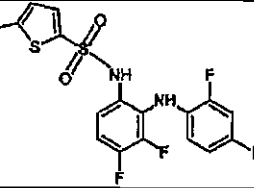
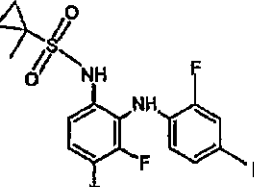
Effects of compounds in the cell were determined by Western blotting for phosphorylated ERK. MDA-MB-231 breast cancer cells were plated in a 48 well plate at 20,000 cells per well and grown in a 37° humidified CO₂ incubator. The following day, the growth media (DMEM + 10% fetal bovine serum) was removed and replaced with starve media (DMEM + 0.1% fetal bovine serum). Cells were incubated in the starve media for sixteen hours and then treated with a range of compound concentrations for thirty minutes. After incubation with compound, cells were stimulated with 100ng/ml EGF for five minutes. The cells were then lysed and analyzed by Western blot using a monoclonal antibody raised to phosphorylated ERK. The signal was amplified using a secondary antibody conjugated to a near -IR dye and detected on a Licor Odyssey scanner. The intensity of signal was quantitated and this data was used to generate dose response curves and EC50 calculations.

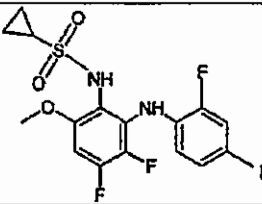
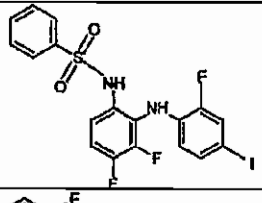
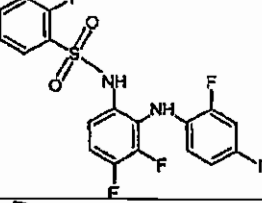
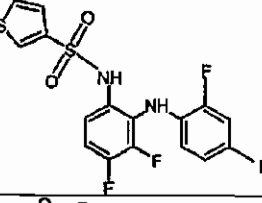
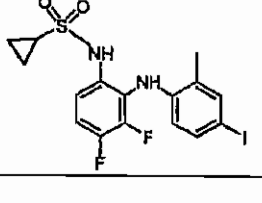
Legend: A, EC₅₀ = < 2.0nM; B, EC₅₀ = 2.0-15nM; C, EC₅₀ = 15nM-100nM;

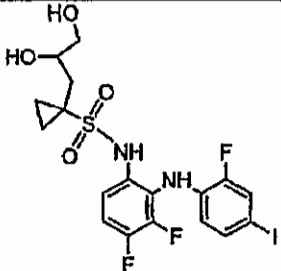
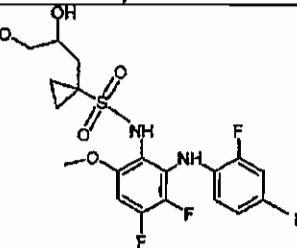
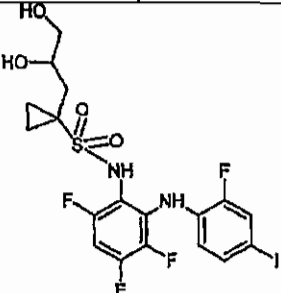
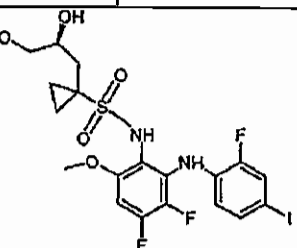
D, EC₅₀ > 100nM, IC₅₀ < 20 μ M; F, EC₅₀ > 100nM, IC₅₀ > 20 μ M

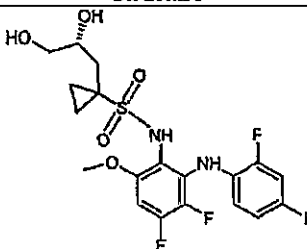
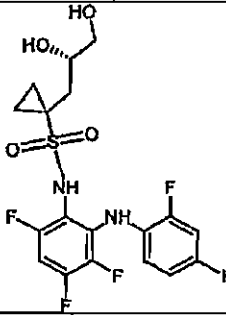
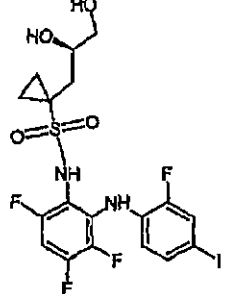
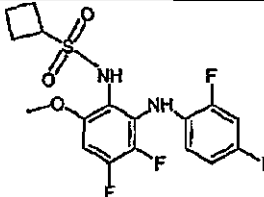
Compound Number	Structure	Activity μ M
1000		A

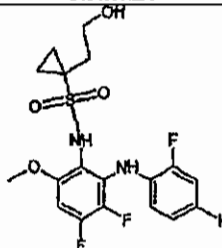
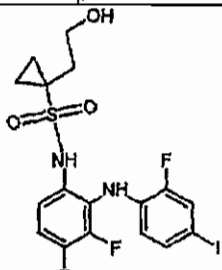
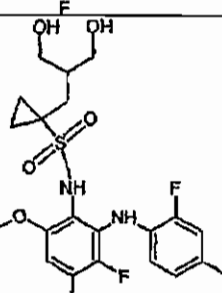
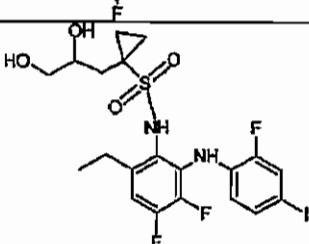
Compound Number	Structure	Activity μ M
1001		A
1002		B
1003		C
1004		C
1005		C
1006		C

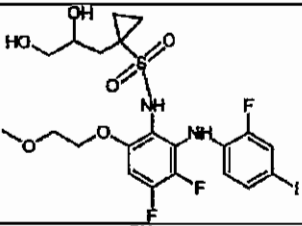
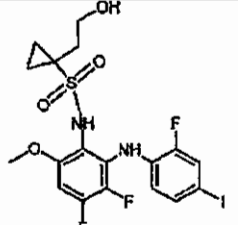
Compound Number	Structure	Activity μM
1007		C
1008		C
1009		C
1010		A
1011		C
1012		B

Compound Number	Structure	Activity μM
1013		B
1014		C
1015		D
1016		C
1017		B

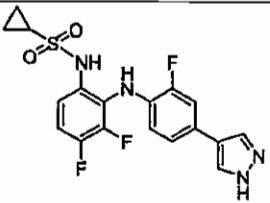
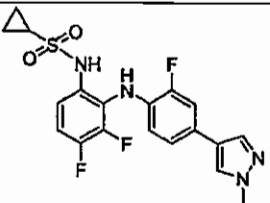
Compound Number	Structure	Activity μM
1018 (Racemic)		A
1019 (Racemic)		A
1020 (Racemic)		A
1021 (S isomer)		A

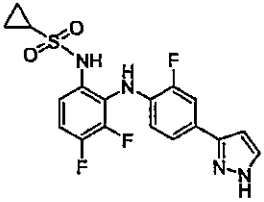
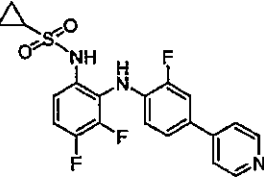
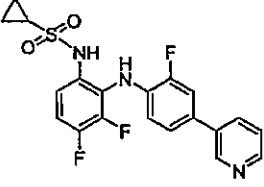
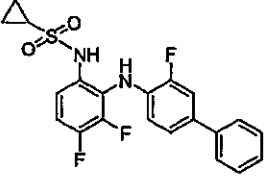
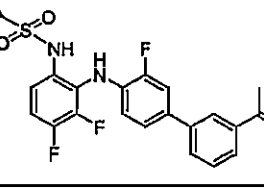
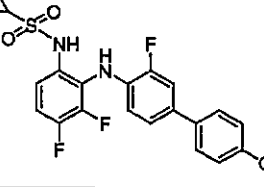
Compound Number	Structure	Activity μM
1022 (R isomer)		B
1023 (R isomer)		B
1024 (S isomer)		B
1025		B

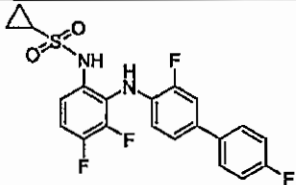
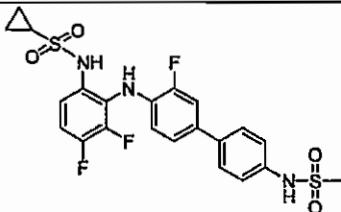
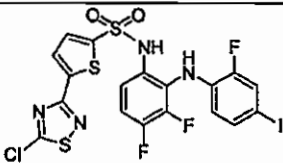
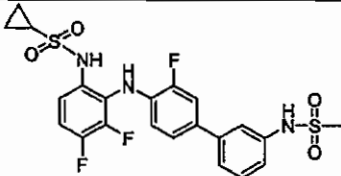
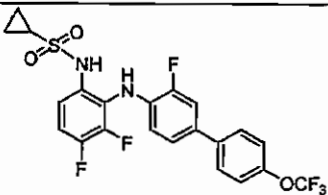
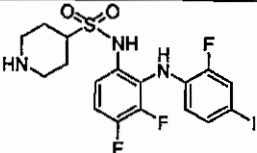
Compound Number	Structure	Activity μM
1026		A
1027		A
1028		A
1029		C

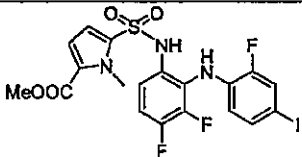
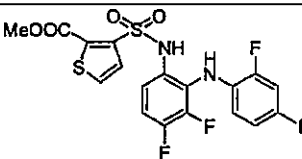
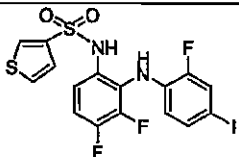
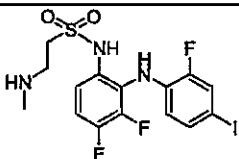
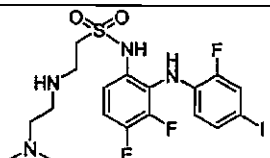
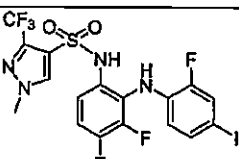
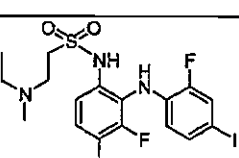
Compound Number	Structure	Activity μM
1030		C
1031		A

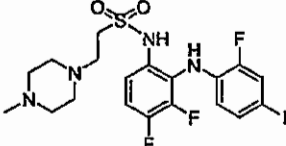
Legend: A, $\text{EC}_{50} < 2.0 \text{ nM}$; B, $\text{EC}_{50} = 2.0\text{-}15 \text{ nM}$; C, $\text{EC}_{50} = 15 \text{ nM}\text{-}100 \text{ nM}$;
D, $\text{EC}_{50} = 100 \text{ nM} - 200 \text{ nM}$; E, $\text{EC}_{50} > 200 \text{ nM}$; ND = not yet determined

CPD #	Structure	MDA pERK ELISA EC_{50}
0497618		E
0497620		E

0497654		D
0497688		E
0497689		E
0497692		E
0499266		E
0499267		ND

0499268		ND
0499271		E
0530701		D
0530716		ND
0530717		ND
0561599		C

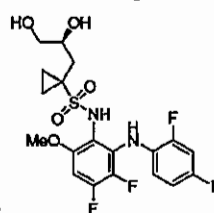
0561608		C
0620926		B
0620927		C
0621002		C
0621016		C
0621026		D
0621029		D

0621030		ND
---------	---	----

In vivo Biological Activity**Example 94**

[00480] The compounds and compositions described herein are useful for the treatment or prophylaxis of one or more diseases including but not limited to cancer, inflammatory bowel disease (IBD), psoriasis and rheumatoid arthritis (RA). The compounds and compositions described herein are also useful for the once- or twice-daily oral treatment or prophylaxis of one or more diseases including but not limited to cancer, IBD, psoriasis and RA.

10 [00481] *In vivo* tests of the compound of the structure below (Compound No. 1021 in the table shown in example 93 above, prepared as described herein), are described in this



example:

[00482] Human tumors were implanted in nu/nu mice. Compound no. 1021 was administered orally for 14 days once tumors were approximately 100 mm³ in size. Tumor growth inhibition (TGI) was determined after 14 days of treatment as the reduction in the size of tumors in treated groups versus vehicle controls. The time to endpoint (TTE) was calculated as the time for the tumor to reach the specified endpoint volume or the last day of the study, whichever came first. Treatment outcome was determined from percent tumor growth delay (%TGD), defined as the percent increase in median TTE of treated versus vehicle-treated control mice. Animals were also monitored for regression responses. Levels of pERK in tumors and brain were determined by Western blots and correlated with plasma levels of Compound no. 1021 for the pharmacodynamic/pharmacokinetic study. A number of tumor models were evaluated with different doses and dosing regimens. Treatment with 25 or 50 mg/kg once daily (QD) showed statistically significant %TGD in

A375 melanoma tumors, Colo205 colon cancer tumors, and A431 epidermoid tumors.

Statistically significant TGI was observed for oral dosing at 25 mg/kg QD for these tumor models as well as in HT29 colon cancer tumors. The effect of different dosing regimens was evaluated in A375 xenografts. Although 100 mg/kg Compound no. 1021 given orally once every two days showed statistically significant %TGD (91%), it was not as effective as QD treatments at 25 mg/kg (143% TGD) or 50 mg/kg (233% TGD). Twice daily (BID) dosing was also more effective than QD dosing as measured by %TGI. Dosing at 12.5 mg/kg BID resulted in 79.5% TGI compared to 51.7% for 25 mg/kg QD of Compound no. 1021. Dosing at 25 mg/kg BID resulted in 110.1% TGI compared to 69.9% TGI for 50 mg/kg QD. A pharmacodynamic/pharmacokinetic study in Colo205 xenografts show inhibition of pERK formation in tumors while minimal inhibition was observed in brain suggesting potent anti-tumor activity with limited CNS penetration.

[00483] Compound no. 1021 is a potent inhibitor of MEK1/2 that suppresses tumor cell growth *in vitro* and *in vivo*. BRAF status determines sensitivity to growth inhibition by the compound in anchorage-dependent growth but not anchorage-independent growth or in xenografts. Maintaining adequate MEK inhibition throughout the dosing interval appears to be more important than peak levels due to the greater efficacy with more frequent dosing. Compound no. 1021 has a favorable pk profile in humans, with the projected therapeutic dose, based on xenograft results, of 20-40mg/day in humans.

Example 94A

[00484] Inhibition of Cancer Cell Growth (GI₅₀)

Anchorage-dependent growth inhibition was measured using CellTiterGlo reagent after 48 hr treatment with Compound No. 1021 of cells grown in 384-well plates. Anchorage-independent growth assays used MTS (methanethiosulfonate) reagent after 7 days treatment of cells grown in media containing 0.15% agarose or on non-binding plates (A431). Growth inhibition values (GI₅₀) are shown in the table below.

Tumor Cell Line	BRAF status	Anchorage-Dependent GI ₅₀ (nM ± sd)	Anchorage-Independent GI ₅₀ (nM ± sd)
A375 Melanoma	V600E	67 ± 12	68 ± 34
Colo205 Colon	V600E	74 ± 45	33 ± 16
HT29 Colon	V600E	70 ± 12	Not determined
A431 Epidermoid	Normal	>10,000	65 ± 19

Example 94B**[00485] Anti-Tumor Xenograft Activity**

Female nu/nu mice were implanted with A375 Melanoma, Colo205 Colon Tumor, A431 Epidermoid Tumor or HT-29 Colon Tumor cells, which were allowed to grow to 100-200 mm³. Compound no. 1021 or vehicle was administered orally (25mg/kg, 50mg/kg or 100mg/kg), once a day, for 14 days. Average tumor volumes were graphed for vehicle and treated groups and are shown in Fig. 1.

Example 94C**10 [00486] Tumor Growth Inhibition (TGI) 25 mg/kg QD**

Tumor Growth Inhibition for the groups treated with 25 mg/kg Compound no. 1021 were calculated for the indicated tumor xenografts. Tumor Growth Inhibition was measured at the end of once daily dosing for 14 days and calculated according to:

$$\%TGI = 100 \times 1 - \frac{(\text{treated tumor volume}_{\text{final}} - \text{tumor volume}_{\text{initial}})}{(\text{vehicle treated tumor volume}_{\text{final}} - \text{tumor volume}_{\text{initial}})}$$

15 The range for A375 and Colo205 represent values from 2 separate studies.

Tumor Xenograft	% TGI	P value
A375 Melanoma	52-72**	<0.001
Colo205 Colon	70-123**	<0.001
HT29 Colon	56	<0.001
A431 Epidermoid	67	<0.001

**Regressions noted during course of experiment

Example 94D**20 [00487] ED₅₀ in Colo205 Xenografts**

Male nu/nu mice were implanted with Colo205 tumor cells. After 10 days animals were randomized by tumor size (range 126-256 mm³) and treated with paclitaxel (IV, QODx5), vehicle or Compound no. 1021 (PO, QDx14).

Pharmacokinetic parameters were obtained from dosing Balb/c mice with 25 mg/kg

25 Compound no. 1021 and extrapolating values for the lower dose groups and shown in the table below.

Group	n	Treatment Regimen		Initial Tumor Volume (mm ³)	Day 15 Tumor Volume (mm ³)	% TGI	C _{max} (μg/mL)	C _{min} (μg/mL)	AUC (μg-hr/mL)
		Agent	mg/kg						

1	10	Vehicle	-	185±11.1	2093±17 4	-	-	-	-
2	10	Paclitaxel	30	184±9.8	113±9.6	104*	-	-	-
3	10	Compound No. 1021	2.5	184±9.8	1187±12 7	47*	0.99	0.003	5.5
4	10		5	183.8±9.8	1175±10 4	48*	1.97	0.006	11.0
5	10		10	185.1±11. 7	1045±16 0	55*	3.94	0.012	22.0
6	10		25	185.1±11. 7	762±81	70*	9.85	0.029	55.0

*P<0.001

Example 94E**[00488] Tumor Growth Inhibition with A375 Xenografts**

- 5 A375 Xenograft mice were administered Compound no. 1021 50mg/kg QD, 25mg/kg BID, 50mg/kg QD and 12.5mg/kg BID. The %TGI was calculated and graphed and is shown in Fig. 2.

Example 94F**10 [00489] Plasma Concentrations in Mice**

Female nu/nu mice were implanted with A375 tumor cells, which were allowed to grow to 100-200 mm³. Compound no. 1021 or vehicle was administered orally once a day (QD) or twice a day (BID) (50mg/kg QD, 25mg/kg BID, 50mg/kg QD and 12.5mg/kg BID). Tumor Growth Inhibition was measured at the end of once daily dosing for 14 days and calculated

- 15 according to:

$$\%TGI = 100 \times 1 - \frac{(\text{treated tumor volume}_{\text{final}} - \text{tumor volume}_{\text{initial}})}{(\text{vehicle treated tumor volume}_{\text{final}} - \text{tumor volume}_{\text{initial}})}$$

AUC (µg·hr/ml)	132.5	117.0	66.5	78.0
C _{max} (µg/ml)	23.8	10.2	11.9	7.8
C _{min} (µg/ml)	0.06	1.24	0.03	0.49
C _{min} Free Fraction (ng/ml)	0.117	2.48	0.059	0.986

Statistical Significance = Logrank test

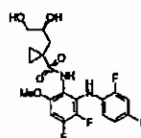
Example 94G**[00490] Mouse Xenograft Tumors and Inhibition of Brain MEK Activity**

Female nu/nu mice implanted with Colo205 tumor cells were given a single dose of vehicle or Compound no. 1021 at 2.5, 5, 10, or 25 mg/kg. Compound levels were determined in plasma samples and pERK levels were determined in tumor and brain samples collected at 2, 6, 12, and 24 hr post-dose. The pERK levels from Western blots were quantified using the LI-COR Odyssey, normalized to total ERK levels and compared to vehicle-treated levels to determine % MEK inhibition. MEK inhibition in tumor or brain for each mouse was graphed with the corresponding plasma concentration of Compound no. 1021 in the animal. Non-linear regression gave an EC_{50} of 73nM for MEK inhibition in tumors. The brain EC_{50} was >5000 nM.

A graph of plasma concentration (log nM) against pERK % inhibition is shown in Fig. 3.

Exemplary Preparation of Specific Capsules**[00491] Example 95A**

Blue size 1 hard gelatin capsules were prepared containing a dry powder blend composition in 1 mg and 10 mg strengths of Compound no. 1021 (see table shown in example 93 above) of structure:



Compound no. 1021 was prepared as described herein, and then micronized using a fluid energy mill (Spiral Jet Mill, electronically grounded, with a grinding chamber diameter of 50mm; a 50°. 4 x 0.8mm nozzle ring; an injector nozzle diameter of 0.8mm and injector nozzle distance of 3mm).. Compound no. 1021 and a portion of the microcrystalline cellulose were mixed and screened through a #20 mesh screen and added to a diffusion-tumble blender (V-blender). The remaining Microcrystalline Cellulose was screened through a #20 mesh screen, added to the materials in the blender and blended. The Croscarmellose Sodium and Sodium Lauryl Sulfate were screened through a #20 mesh screen, added to the materials in the blender and blended. The powder blend was passed through a rotating impeller mill (Quadro CoMil) and added back to the blender and blending continued. The Magnesium Stearate was screened through a #20 mesh screen and

blended with the milled powder blend. The powder blend was filled into size 1 capsules.

The 10 mg capsules were banded for identification.

[00492] The composition of the capsules is shown in the table below:

Component	1 mg capsule		10 mg capsule	
	mg/unit	%	mg/unit	%
Compound no. 1021	1.0	0.4	10.0	4.2
Microcrystalline Cellulose, NF (Avicel PH302)	222.2	92.6	213.2	88.8
Croscarmellose Sodium, NF (Ac-Di-Sol)	12.0	5.0	12.0	5.0
Sodium Lauryl Sulfate, NF	2.4	1.0	2.4	1.0
Magnesium Stearate, NF	2.4	1.0	2.4	1.0
Total ^a	240.0	100.0	240.0	100.0
Blue Size 1 Hard Gelatin Capsule Shell	1		1	

^aTarget fill weight adjusted based on actual potency of blend.

- 5 [00493] Typical batch formula for a 10,000 batch of 1 mg capsules were as follows:

Batch Formula Components	Quantity per batch (g) (for 10,000 units)
Compound no. 1021	10.0
Microcrystalline Cellulose, NF (Avicel PH302)	2222
Croscarmellose Sodium, NF (Ac-Di-Sol)	120.0
Sodium Lauryl Sulfate, NF	24.0
Magnesium Stearate, NF	24.0
Total Fill Weight ^a	2400
Blue Size 1 Hard Gelatin Capsule Shell	10,000

^aTarget fill weight adjusted based on actual potency of blend.

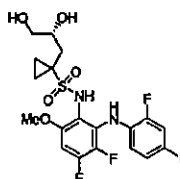
- [00494] Typical batch formula for a 10,000 batch of 10 mg capsules were as follows:

Batch Formula Components	Quantity per batch (g) (for 10,000 units)
Compound no. 1021	100.0
Microcrystalline Cellulose, NF (Avicel PH302)	2132
Croscarmellose Sodium, NF (Ac-Di-Sol)	120.0
Sodium Lauryl Sulfate, NF	24.0
Magnesium Stearate, NF	24.0
Total Fill Weight ^a	2400
Blue Size 1 Hard Gelatin Capsule Shell ^b	10,000

^aTarget fill weight adjusted based on actual potency of blend.

Example 95B

[00495] Blue size 1 hard gelatin capsules are prepared containing a dry powder blend composition in 1 mg and 10 mg strengths of Compound no. 1022 (see table shown in



example 93 above) of structure:

- Compound No. 1022 is prepared as described herein, and micronized using a fluid energy mill (Spiral Jet Mill, electronically grounded, with a grinding chamber diameter of 50mm; a 50°. 4 x 0.8mm nozzle ring; an injector nozzle diameter of 0.8mm and injector nozzle distance of 3mm).. Compound No. 1022 and a portion of the microcrystalline cellulose are mixed, screened through a #20 mesh screen and added to a diffusion-tumble blender (V-blender). The remaining Microcrystalline Cellulose is screened through a #20 mesh screen, added to the materials in the blender and blended. The Croscarmellose Sodium and Sodium Lauryl Sulfate are screened through a #20 mesh screen, added to the materials in the blender and blended. The powder blend is passed through a rotating impeller mill (Quadro CoMil), added back to the blender and blending continued. The Magnesium Stearate is screened through a #20 mesh screen and blended with the milled powder blend. The powder blend is filled into size 1 capsules. The 10 mg capsules are banded for identification.

[00496] The composition of the capsules is shown in the table below:

Component	1 mg capsule		10 mg capsule	
	mg/unit	%	mg/unit	%
Compound no. 1022	1.0	0.4	10.0	4.2
Microcrystalline Cellulose, NF (Avicel PH302)	222.2	92.6	213.2	88.8
Croscarmellose Sodium, NF (Ac-Di-Sol)	12.0	5.0	12.0	5.0
Sodium Lauryl Sulfate, NF	2.4	1.0	2.4	1.0
Magnesium Stearate, NF	2.4	1.0	2.4	1.0
Total ^a	240.0	100.0	240.0	100.0
Blue Size 1 Hard Gelatin Capsule Shell	1		1	

In vivo Activity in Humans**Example 96**

[00497] Administration of the capsules described in example 95A in Human Cancer Patients. Human cancer patients were administered a single dose of the 1 mg or 10 mg capsule composition described above in example 95A. For a 2mg dose, patients were given 2 x 1mg capsules; for a 4mg dose, patients were given 4 x 1mg capsules; for a 6mg dose, patients were given 6 x 1mg capsules; for a 10mg dose, patients were given 1 x 10mg capsule; for a 20mg dose, patients were given 2 x 10mg capsules.

[00498] The concentration-time profiles were monitored and are shown in Fig. 4 and in the table below:

Dose (mg)	Day	T _{max} (hr)	C _{max} (ng/mL)	C _{12hr} (ng/mL)	AUC _{0-12hr} (ng·hr/mL)	AUC _τ (ng·hr/mL)
2	1	2.0	0.111	0.0378	0.700	NA
	35	2.0	0.202	0.0756	NA	2.07
4	1	1.5	0.292	0.134	2.26	NA
	35	1.0	0.544	0.310	NA	5.12
10	35	NA	1.57	1.01	NA	14.3
20	35	NA	3.28	2.19	NA	29.5

Example 97: Administration Compound No.2021 in Human Cancer Patients

[00499] Advanced Human cancer patients were administered Compound No.2021 at doses of 2 mg, 4 mg, 6 mg, 10 mg, 20 mg, 30 mg and 40 mg once daily (QD) as follows:

Cohort	Dose Level (mg/subject /day)	# Patients Enrolled
1	2	6
2	4	3
3	6	3
4	10	5
5	20	4
6	30	3
7	40	3

[00500] Patients were suffering from a variety of cancers, such as ovarian, adrenal, colorectal or rectal.

[00501] Typical PK characteristics (T_{max}, C_{max}, C_{24hr}, AUC_{0-24hr} and t_{1/2}) of the patients were monitored and recorded (standard deviation in parentheses) and are shown in the table below:

Dose (mg/subject/day)	Day	N	T _{max} (hr)	C _{max} (μg/mL)	C _{24hr} (μg/mL)	AUC _{0-24hr} (μg·hr/mL)	t _{1/2} (hr)
2	35	3	1.33 (21.7)	0.0504 (49.2)	0.0093 8 (82.8)	0.517 (61.2)	11.4 (38.8)
4	≥22	3	1.50 (33.3)	0.105 (41.0)	0.0313 (41.1)	1.39 (42.7)	14.9 (0.992)
6	35	3	1.67 (69.3)	0.203 (16.6)	0.0369 (45.4)	1.98 (23.8)	13.2 (42.2)
10	≥22	3	1.67 (34.6)	0.218 (16.5)	0.0405 (49.7)	2.00 (29.4)	13.9 (28.9)
20	≥22	3	2.17 (35.3)	0.435 (35.6)	0.101 (68.8)	4.88 (34.2)	13.6 (43.3)
30	≥22	3	2.17 (35.3)	0.540 (83.6)	0.164 (53.6)	6.36 (68.6)	30.8 (96.9)
40	>33	2	2.00	0.909	0.151	10.1	10.5

T_{max} = time to maximum plasma concentration; C_{max} = maximum plasma concentration;

C_{24hr} = plasma concentration 24 hours after dosing; AUC area under curve and t_{1/2} = half life.

[00502] One patient was dosed at 60 mg/day and showed good absorption and a higher AUC than 40 mg dose.

5 [00503] Patients with stable disease states were observed, for example see below:

Cohort	Primary Tumor	# Courses	Response
Cohort 2 (4 mg/day)	Ovarian	10	Stable Disease
Cohort 3 (6 mg/day)	Adrenal	6	Stable Disease
	Colorectal	11	Stable Disease
Cohort 6 (30 mg/day)	Rectal	4	Stable Disease

Example 98: Administration Compound No.2021 in Human Cancer Patients

[00504] Advanced Human cancer patients (suffering from a variety of cancers) are administered Compound No.2021 at doses of 60mg, 80mg, 100mg, 150mg, 200mg,

10 300mg, 400mg and 500mg once daily (QD) as follows:

Cohort	Dose Level (mg/subject/day)
1	60
2	80
3	100
4	150
5	200
6	300
7	400
8	500

[00505] Patients are assessed for adverse reactions, clinical state and the like, and typical PK characteristics (T_{max} , C_{max} , C_{24hr} , AUC_{0-24hr} and $t_{1/2}$) are monitored and recorded.

Example 99: Administration Compound No.2021 in Human Cancer Patients

- 5 [00506] Advanced Human cancer patients (suffering from a variety of cancers) are administered Compound No.2021 at doses of 30mg, 40mg, 50mg, 75mg, 100mg, 150mg, 200mg and 250mg twice daily (BID) as follows:

Cohort	Dose Level (mg/subject)	Number of Doses/Day	Total Dose (mg/subject/day)
1	30	2	60
2	40	2	80
3	50	2	100
4	75	2	150
5	100	2	200
6	150	2	300
7	200	2	400
8	250	2	500

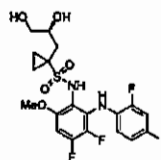
[00507] Patients are assessed for adverse reactions, clinical state and the like, and typical PK characteristics (T_{max} , C_{max} , C_{24hr} , AUC_{0-24hr} and $t_{1/2}$) are monitored and recorded.

10

Preparation of Exemplary Capsules

Example 100

[00508] Fifteen size 0 Swedish Orange capsules were prepared as described below, containing a composition in 50 mg strength of Compound No. 1021 of structure:



15

Procedure:

- A) Pass all materials through a No. 40 mesh sieve.
- B) Combine Compound No. 1021, SLS, and ~ 1/2 of the Prosolv 90 HD and blend.
- C) Add the remaining quantity of Prosolv 90 HD and blend.
- 20 D) Add the Croscarmellose Sodium and blend.
- E) Add the Magnesium Stearate and blend.
- F) Encapsulate into Size 0 Swedish Orange capsules at a target fill weight of 275 mg.

[00509] The composition of the capsules is shown below:

Component	50 mg capsule	
	mg/unit	%(w/w)
Compound no. 1021, Micronized	50.00	18.18
Sodium Lauryl Sulfate	12.00	4.36
Prosolv 90 HD	196.50	71.45
Croscarmellose Sodium	13.75	5.00
Magnesium Stearate	2.75	1.00
Total	275.00	100.00
Size 0 Swedish Orange Capsule Shell	1	

Example 101

[00510] Size 0 Swedish Orange capsules were prepared as described in example 100, containing a composition in 20 mg strength of Compound No. 1021, with the composition shown below:

Component	20 mg capsule	
	mg/unit	%(w/w)
Compound No. 1021, Micronized	20.00	18.18
Sodium Lauryl Sulfate	4.80	4.36
Prosolv 90 HD	78.60	71.45
Croscarmellose Sodium	5.50	5.00
Magnesium Stearate	1.10	1.00
Total	110.00	100.00
Size 0 Swedish Orange Capsule Shell	1	

Example 102

[00511] 5292 Size 0 Swedish Orange capsules were prepared as described below, containing a composition in 20 mg strength of Compound no. 1021, with the composition shown below:

Component	20 mg capsule	
	mg/unit	%(w/w)
Compound no. 1021, Micronized	20.00	4.17
Microcrystalline Cellulose		
Avicel PH302	426.40	88.83
Croscarmellose Sodium	24.00	5.00
Sodium Lauryl Sulfate	4.80	1.00

Component	20 mg capsule	
	mg/unit	%(w/w)
Magnesium Stearate	4.80	1.00
Total	480	100
Swedish orange opaque hard gelatin capsule (Size 00)	1	

Exemplary Batch Formula for 20 mg capsules:

Batch Formula Components	Amount per batch (g) (for 10,000 units)
Compound no. 1021	200
Microcrystalline Cellulose, NF (Avicel PH302)	4,264
Croscarmellose Sodium, NF	240
Sodium Lauryl Sulfate, NF	48
Magnesium Stearate, NF	48
Total	4,800
Swedish orange opaque hard gelatin capsule (Size 00)	10,000

5 Procedure:

A) Mix Compound No. 1021 and a portion of the Microcrystalline Cellulose and screen through a #20 mesh screen into a blender and blend.

B) Screen the remaining Microcrystalline Cellulose through a #20 mesh screen, add to materials in blender and blend.

10 C) Screen the Croscarmellose Sodium and Sodium Lauryl Sulfate through a # 20 mesh, add to materials in blender and blend.

D) Pass the powder blend through a mill.

E) Charge the material back into the blender and continue to blend.

F) Screen the Magnesium Stearate through a #20 mesh screen and blend with milled powder
15 blend.

G) Fill into size 00, Swedish orange capsules.

Examples 103A, 103B, 103C and 103D

[00512] 2 Piece capsules are prepared via either of two procedures, as described
20 below, containing a composition in 20 mg strength of Compound No. 1021.

Procedure A

A) Dissolve Compound No. 1021 and Hypromellose Acetate Succinate (or PVP, or Copovidone, or HPMC) in a suitable volume of solvent such as acetone.

B) Spray dry solution from Step (A) in a suitable spray drier.

- 5 C) Blend the powder collected from Step (B) with the Avicel PH302, Croscarmellose Sodium, Sodium Lauryl Sulfate, and Magnesium Stearate.

D) Encapsulate Blend from Step (C) into suitably sized two piece capsules.

Procedure B

- 10 A) Hot melt extrude Compound No. 1021 and Hypromellose Acetate Succinate (or PVP, or Copovidone, or HPMC) using a screw extruder. Collect and mill the extrudate.

B) Collect and mill the extrudate from Step (A)

C) Blend the powder collected from Step (B) with the Avicel PH302, Croscarmellose Sodium, Sodium Lauryl Sulfate, and Mg Stearate.

D) Encapsulate Blend from Step (C) into suitably sized two piece capsules.

- 15 [00513] Eg 103A - The composition of the capsules is shown below:

Component	20 mg capsule	
	mg/unit	%(w/w)
Compound No. 1021	20.00	4.17
Hypromellose Acetate Succinate	80.00	16.67
Avicel PH302	346.40	72.17
Croscarmellose Sodium	24.00	5.00
Sodium Lauryl Sulfate	4.80	1.00
Magnesium Stearate	4.80	1.00
Total	480.00	100.00
Capsule	1	

- [00514] Eg 103B - The composition of the capsules is shown below:

Component	20 mg capsule	
	mg/unit	%(w/w)
Compound No. 1021	20.00	4.17
PVP	80.00	16.67
Avicel PH302	346.40	72.17
Croscarmellose Sodium	24.00	5.00
Sodium Lauryl Sulfate	4.80	1.00
Magnesium Stearate	4.80	1.00
Total	480.00	100.00
Capsule	1	

- [00515] Eg 103C - The composition of the capsules is shown below:

Component	20 mg capsule
-----------	---------------

	mg/unit	%(w/w)
Compound No. 1021	20.00	4.17
Copovidone	80.00	16.67
Avicel PH302	346.40	72.17
Croscarmellose Sodium	24.00	5.00
Sodium Lauryl Sulfate	4.80	1.00
Magnesium Stearate	4.80	1.00
Total	480.00	100.00
Capsule	1	

[00516] Eg 103D - The composition of the capsules is shown below:

Component	20 mg capsule	
	mg/unit	%(w/w)
Compound No. 1021	20.00	4.17
HPMC	80.00	16.67
Avicel PH302	346.40	72.17
Croscarmellose Sodium	24.00	5.00
Sodium Lauryl Sulfate	4.80	1.00
Magnesium Stearate	4.80	1.00
Total	480.00	100.00
Capsule	1	

Examples 104A, 104B, 104C and 104D

[00517] 2 Piece capsules are prepared via either of two procedures, as described
 5 below, containing a composition in 50 mg strength of Compound No. 1021.

Procedure A

- A) Dissolve Compound No. 1021 and Hypromellose Acetate Succinate (or PVP, or Copovidone, or HPMC) in a suitable volume of solvent such as acetone.
 B) Spray dry solution from Step (A) in a suitable spray drier.
 10 C) Blend the powder collected from Step (B) with the Avicel PH302, Croscarmellose Sodium, Sodium Lauryl Sulfate, and Magnesium Stearate.
 D) Encapsulate Blend from Step (C) into suitably sized two piece capsules.

Procedure B

- A) Hot melt extrude Compound No. 1021 and Hypromellose Acetate Succinate (or PVP, or
 15 Copovidone, or HPMC) using a screw extruder. Collect and mill the extrudate.
 B) Collect and mill the extrudate from Step (A)
 C) Blend the powder collected from Step (B) with the Avicel PH302, Croscarmellose Sodium, Sodium Lauryl Sulfate, and Mg Stearate.
 D) Encapsulate Blend from Step (C) into suitably sized two piece capsules.

[00518] Eg 104A - The composition of the capsules is shown below:

Component	50 mg capsule	
	mg/unit	%(w/w)
Compound no. 1021	50.00	10.42
Hypromellose Acetate Succinate	150.00	31.25
Avicel PH302	246.40	51.33
Croscarmellose Sodium	24.00	5.00
Sodium Lauryl Sulfate	4.80	1.00
Magnesium Stearate	4.80	1.00
Total	480.00	100.00
Capsule	l	

[00519] Eg 104B - The composition of the capsules is shown below:

Component	50 mg capsule	
	mg/unit	%(w/w)
Compound no. 1021	50.00	10.42
PVP	150.00	31.25
Avicel PH302	246.40	51.33
Croscarmellose Sodium	24.00	5.00
Sodium Lauryl Sulfate	4.80	1.00
Magnesium Stearate	4.80	1.00
Total	480.00	100.00
Capsule	l	

[00520] Eg 104C - The composition of the capsules is shown below:

Component	50 mg capsule	
	mg/unit	%(w/w)
Compound no. 1021	50.00	10.42
Copovidone	150.00	31.25
Avicel PH302	246.40	51.33
Croscarmellose Sodium	24.00	5.00
Sodium Lauryl Sulfate	4.80	1.00
Magnesium Stearate	4.80	1.00
Total	480.00	100.00
Capsule	l	

5 [00521] Eg 104D - The composition of the capsules is shown below:

Component	50 mg capsule	
	mg/unit	%(w/w)
Compound no. 1021	50.00	10.42
HPMC	150.00	31.25
Avicel PH302	246.40	51.33
Croscarmellose Sodium	24.00	5.00
Sodium Lauryl Sulfate	4.80	1.00
Magnesium Stearate	4.80	1.00

Total	480.00	100.00
Capsule	1	

Examples 105A, 105B, 105C, 105D, 105E and 105F

[00522] 2 Piece capsules are prepared as described below, containing a composition in 50 mg strength of Compound No. 1021.

- 5 A) Hot melt extrude Compound No. 1021 and Gelucire 44/14 (or Poloxamer or Polyethylene Glycol) using a screw extruder. Collect and mill the extrudate.
- B) Collect and mill the extrudate from Step (A)
- C) Blend the powder collected from Step (B) with the PEG 400 (or Cremophor, or Polysorbate, or Vit E TPGS).
- 10 D) Encapsulate Blend from Step (C) into suitably sized two piece capsules.

[00523] Eg 105A - The composition of the capsules is shown below:

Component	50 mg capsule	
	mg/unit	%(w/w)
Compound no. 1021	50.00	6.25
Gelucire 44/14	675.00	84.38
PEG 400	75.00	9.38
Total	800.00	100.00
Capsule	1	

[00524] Eg 105B - The composition of the capsules is shown below:

Component	50 mg capsule	
	mg/unit	%(w/w)
Compound no. 1021	50.00	6.25
Poloxamer	675.00	84.38
PEG 400	75.00	9.38
Total	800.00	100.00
Capsule	1	

[00525] Eg 105C - The composition of the capsules is shown below:

Component	50 mg capsule	
	mg/unit	%(w/w)
Compound no. 1021	50.00	6.25
Polyethylene Glycol	675.00	84.38
PEG 400	75.00	9.38
Total	800.00	100.00
Capsule	1	

[00526] Eg 105D - The composition of the capsules is shown below:

Component	50 mg capsule	
	mg/unit	%(w/w)

Compound no. 1021	50.00	6.25
Gelucire 44/14	675.00	84.38
Cremophor	75.00	9.38
Total	800.00	100.00
Capsule	1	

[00527] Eg 105E - The composition of the capsules is shown below:

Component	50 mg capsule	
	mg/unit	%(w/w)
Compound no. 1021	50.00	6.25
Gelucire 44/14	675.00	84.38
Polysorbate	75.00	9.38
Total	800.00	100.00
Capsule	1	

[00528] Eg 105F - The composition of the capsules is shown below:

Component	50 mg capsule	
	mg/unit	%(w/w)
Compound no. 1021	50.00	6.25
Gelucire 44/14	675.00	84.38
Vit E TPGS	75.00	9.38
Total	800.00	100.00
Capsule	1	

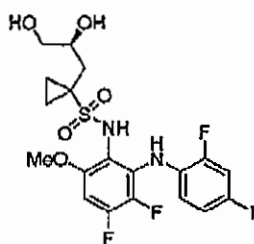
Example 106: Dissolution Studies

- 5 [00529] Capsules containing Compound No. 1021 were prepared as described in the above examples (95A and 95B). The following dissolution data was obtained using the USP<711> method for dissolution.

Time (min)	% Release (%RSD)	
	1mg form	10mg form
15	78 (8.3)	80 (7.3)
30	82 (7.1)	87 (9.2)
45	82 (6.7)	92 (9.6)
60	88 (6.3)	92 (7.2)
70	86 (5.7)	95 (5.4)

CLAIMS

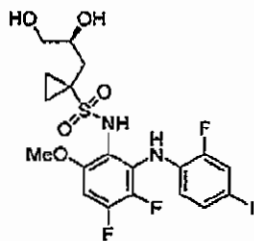
- 5 1. A pharmaceutical composition comprising:
i) from about 20mg to about 500mg of a compound of structure:



or a pharmaceutically acceptable salt thereof; and

ii) a pharmaceutically acceptable carrier or vehicle.

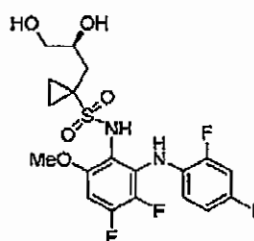
2. The pharmaceutical composition of claim 1, comprising:
10 i) from about 20mg to about 100mg of a compound of structure:



or a pharmaceutically acceptable salt thereof.

3. The pharmaceutical composition of claim 1, wherein the pharmaceutically acceptable carrier or vehicle is microcrystalline cellulose.
4. The pharmaceutical composition of claim 1, wherein the pharmaceutically acceptable carrier or vehicle is silicified microcrystalline cellulose.
- 15 5. The pharmaceutical composition of claim 1, in the form of a tablet, capsule, pill, powder, sustained release formulation, solution, suspension or emulsion, ointment or cream, or suppository.
6. The pharmaceutical composition of claim 1, further comprising: croscarmellose sodium; sodium lauryl sulfate; and magnesium stearate.
- 20 7. The pharmaceutical composition of claim 1 which is in the form of a capsule and which comprises:

20.00 mg of a compound of structure:



, which is micronized;

426.40 mg of microcrystalline cellulose;

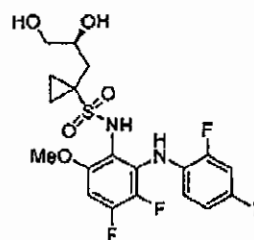
24.00 mg of croscarmellose sodium;

4.80 mg of sodium lauryl sulfate; and

4.80 mg of magnesium stearate.

8. A pharmaceutical composition comprising:

i) from about 2% to about 30% by weight of a compound of structure:



, or a pharmaceutically acceptable salt thereof; and

ii) from about 70% to about 98% by weight of a pharmaceutically acceptable carrier or vehicle.

9. The pharmaceutical composition of claim 8, wherein the pharmaceutically acceptable carrier or vehicle comprises microcrystalline cellulose.

10. The pharmaceutical composition of claim 8, wherein the pharmaceutically acceptable carrier or vehicle comprises silicified microcrystalline cellulose.

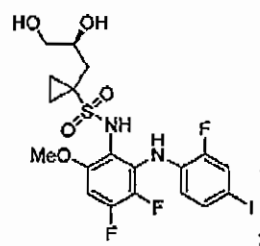
11. The pharmaceutical composition of claim 8, in the form of a tablet, capsule, pill, powder, sustained release formulation, solution, suspension or emulsion, ointment or cream, or suppository.

12. The pharmaceutical composition of claim 8, wherein the microcrystalline cellulose is from about 80% to about 95% by weight of the composition.

13. The pharmaceutical composition of claim 8, further comprising: from about 1% to about 6% by weight croscarmellose sodium; from about 0.1% to about 5% by weight sodium lauryl sulfate; and from about 0.25% to about 1.5% by weight magnesium stearate.

14. The pharmaceutical composition of claim 8, which is in the form of a capsule and which comprises:

10.0 mg of a compound of structure:



213.2 mg of microcrystalline cellulose;

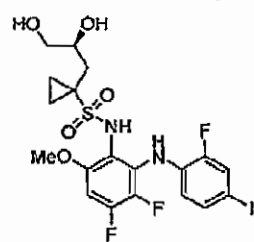
12.0 mg of croscarmellose sodium;

2.4 mg of sodium lauryl sulfate; and

2.4 mg of magnesium stearate.

15. A kit for treating a subject having cancer or an inflammatory disease, comprising:

i) from about 20mg to about 500mg of a compound of structure:



, or a pharmaceutically acceptable salt thereof; and

ii) instructions for administration of the compound or a pharmaceutically acceptable salt thereof to a subject to treat cancer or an inflammatory disease.