(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 June 2009 (11.06.2009)

PCT

(10) International Publication Number
WO 2009/073772 A1

(51) International Patent Classification:
A61K 31/535 (2006.01)

(21) International Application Number:
PCT/US2008/085505

(22) International Filing Date:
4 December 2008 (04.12.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/992,743 6 December 2007 (06.12.2007) US

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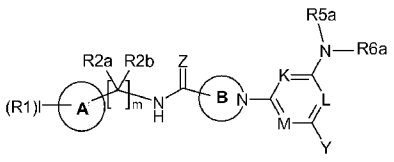
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report*

(54) **Title:** NOVEL SEH INHIBITORS AND THEIR USE



(I)

(57) **Abstract:** The invention is directed to novel sEH inhibitors and their use in the treatment of diseases mediated by the sEH enzyme. Specifically, the invention is directed to compounds according to Formula (I): wherein R1, R2a, R2b, R5a, R6a, A, B, K, L, M, Y, Z, I, and m are defined herein, and to pharmaceutically-acceptable salts thereof. The compounds of the invention are sEH inhibitors and can be used in the treatment of diseases mediated by the sEH enzyme, such as hypertension. Accordingly, the invention is further directed to pharmaceutical compositions comprising a compound of the invention. The invention is still further directed to methods of inhibiting sEH and treatment of conditions associated therewith using a compound of the invention or a pharmaceutical composition comprising a compound of the invention.

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NOVEL sEH INHIBITORS AND THEIR USE

FIELD OF THE INVENTION

The invention is directed to novel sEH inhibitors and their use in the treatment of diseases mediated by the sEH enzyme.

BACKGROUND OF THE INVENTION

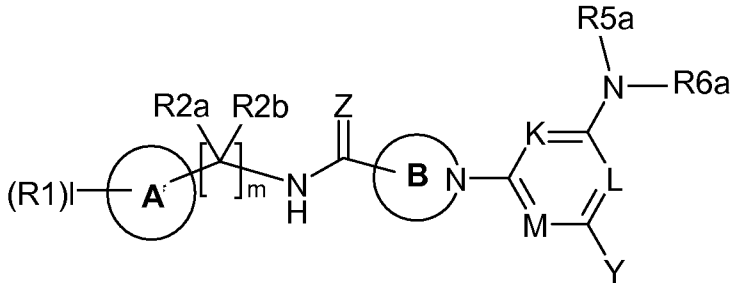
Epoxide functional groups may be found in drugs, xenobiotic materials, and endogenous biomolecules. Epoxide hydrolases, found in both plants and animals, are enzymes that convert epoxides to diols by hydrolysis. In mammals, soluble epoxide hydrolase ("sEH") is primarily responsible for the metabolism of arachidonic acid derivatives known as epoxyeicosatrienoic acids ("EETs"). sEH converts EETs into dihydroxyeicosatrienoic acids ("DHETs"). Several publications have described the beneficial vasodilatory, anti-inflamatory, and anti-thrombotic effects of EETs. Spector et al., *Prog. Lipid Res.,* **43,** 55-90, 2004; Imig, *Cardiovasc. Drug Rev.,* **24,** 169-188, 2006. DHETs are generally inactive and thus do not exhibit the beneficial effects of EETs.

Conversely, microsomal epoxide hydrolase ("mEH") catalyzes the hydrolysis of a broad range of epoxide substrates including carcinogenic polycyclic aromatic hydrocarbons and reactive epoxides, thus it provides an important detoxification pathway. Polymorphisms in mEH may lead to differences in bioactivation of pro-carcinogens and several human epidemiological studies suggest that mEH genotype is associated with altered cancer risk. Fretland & Omiecinski, *Chemico-Biol. Int.,* **129**, 41-59, 2000.

Pharmacological, knockout mouse phenotype and genetic polymorphism studies suggest that elevated EET levels are protective in numerous disorders including hypertension [*Cell Biochem Biophys.,* **47**, 87-98, 2007], heart failure [Xu *et al., Proc. Natl Acad. Sci. U.S.A.,***103**, 18733-18738, 2006], renal dysfunction / end organ damage [*Zhao et al., J. Am. Soc. Nephrol.,* **15**, 1244-1253, 2004; Imig et al., *Hypertension,* **46**, 975-981, 2005], stroke [Koerner *et al., J. Neurosci.,* **27**; 4642-4649, 2007], atherosclerosis and thrombosis [Wei *et al., Atherosclerosis,* **190**, 26-34, 2007; Krotz *et al*., *Arterioscler. Thromb. Vasc. Biol*., 24; 595-600, 2004] and inflammation [Inceoglu *et al., Life Sci.,* **79,** 2311-2319, 2006]. One approach to the treatment of such conditions designed to take advantage of the beneficial effect of EETs has been to search for compounds that inhibit sEH thereby preventing EET degradation.

SUMMARY OF THE INVENTION

The invention is directed to novel sEH inhibitors and their use in the treatment of diseases mediated by the sEH enzyme. Specifically, the invention is directed to compounds according to Formula I:



Formula I

wherein R1, R2a, R2b, R5a, R6a, A, B, K, L, M, Y, Z, l, and m are defined below, and to pharmaceutically-acceptable salts thereof.

In yet another aspect, this invention provides for the use of the compounds of Formula (I) for the treatment or prevention of hypertension, organ failure / damage (including heart failure, renal failure, cardiac and renal fibrosis, and liver failure), peripheral vascular disease (including ischemic limb disease, intermittent claudication, endothelial dysfunction, erectile dysfunction, Raynaud's disease, and diabetic vasculopathies e.g. retinopathy), atherosclerosis, atherothrombotic disorders (including coronary artery disease, coronary vasospasm, angina, stroke, myocardial ischemia, myocardial infarction, and hyperlipidemia), metabolic disorders (including diabetes, metabolic syndrome, hyperglycemia, and obesity), inflammation, inflammatory disorders (including arthritis, inflammatory pain, overactive bladder, asthma, and COPD), cognitive disorders (including cognitive impairment, dementia, and depression), glaucoma, osteoporosis, and polycystic ovary syndrome.

The compounds of this invention may be administered alone or in conjunction with one or more other therapeutic agents, eg. agents being selected from the group consisting of may be administered alone or in conjunction with one or more other therapeutic agents, eg. agents being selected from the group consisting of endothelin receptor antagonists, angiotensin converting enzyme (ACE) inhibitors, angiotension II receptor antagonists, vasopeptidase inhibitors, diuretics, digoxin, beta blocker, aldosterone antagonists, iontropes, NSAIDS, nitric oxide donors, calcium channel modulators, muscarinic antagonists, steroidal anti-inflammatory drugs, bronchodilators, Leukotriene antagonist, HMG-CoA reductase inhibitors, dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonists, type-5 phosphodiesterase inhibitors, and renin inhibitors.

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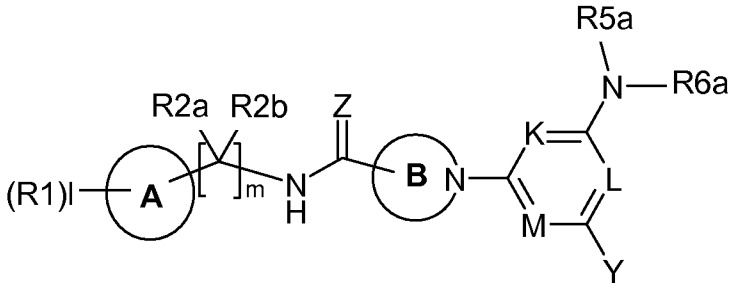
DETAILED DESCRIPTION OF THE INVENTION

Compounds

The invention is directed to compounds according to Formula I:



Formula I

wherein:

A is phenyl, monocyclic heteroaryl, or C5-C6 cycloalkyl;

when A is phenyl or monocyclic heteroaryl each R1 is selected from the group consisting of: halo, -CN, R14, R15, R16, R17, R18, R19, -ORb, -C(O)ORc, -C(O)NRcRc, -NRcRc, -NRcC(O)Rb, -NRcS(O_2)Ra, -SRb, -S(O_2)Ra, and -S(O_2)NRcRc;

when A is C5-C6 cycloalkyl each R1 is selected from the group consisting of: Ra, -ORb, -C(O)ORc, -C(O)NRcRc, -NRcRc, and -NRcC(O)Rb;

each R14 is C1-C6 alkyl optionally substituted with one or more substituents selected from the group consisting of: halo, -ORd, and -NRfRf;

each R15 is C3-C6 cycloalkyl optionally substituted with one or more substituents selected from the group consisting of: halo, -ORd, -NRfRf, C1-C3 alkyl, and C1-C3 haloalkyl;

each R16 is monocyclic heterocycloalkyl optionally substituted with one or more C1-C3 alkyl;

each R17 is phenyl optionally substituted with one or more substituents selected from the group consisting of: halo, -CN, C1-C3 alkyl, C1-C3 haloalkyl, -ORd, and -NRfRf;

each R18 is monocyclic heteroaryl optionally substituted with one or more substituents selected from the group consisting of: halo, -CN, C1-C3 alkyl, C1-C3 haloalkyl, -ORd, and -NRfRf;

each R19 is C1-C3 alkyl substituted with R13, R14, R15, or R16;
l is an integer from 0 to 5;

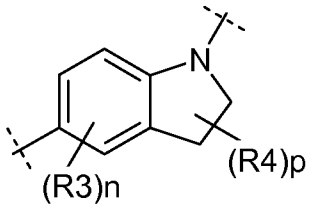
each R2a is H or C1-C3 alkyl;

each R2b is H or C1-C3 alkyl;

m is 1 or 2;

Z is O or S;

B is B1, B2, B3, B4, B5, B6, B7, B8, B9, B10, or B11 wherein

B1 is 

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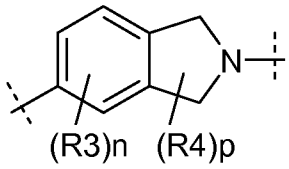
B2 is 

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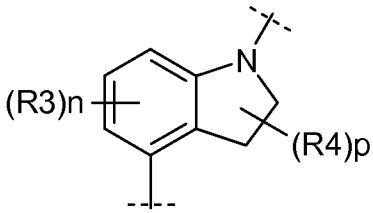
B3 is 

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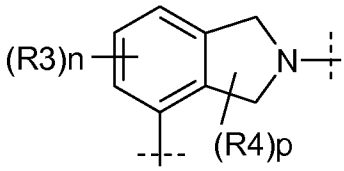
B4 is 

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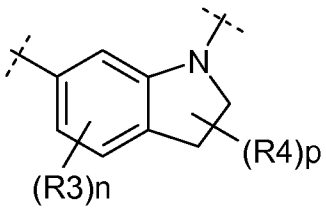
B5 is 

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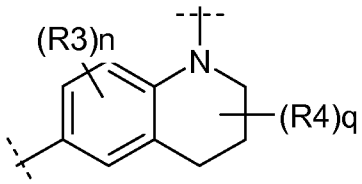
B6 is 

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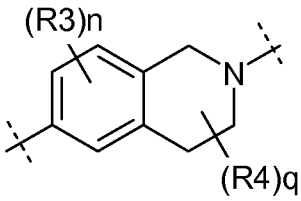
B7 is 

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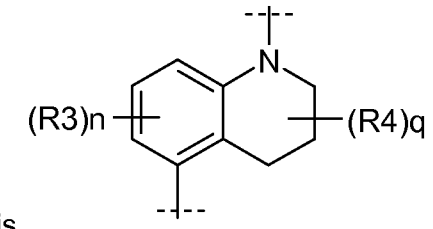
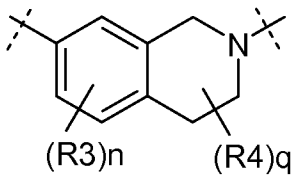
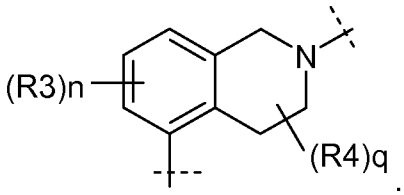
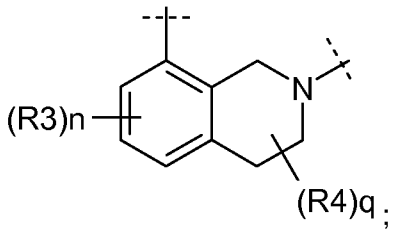
B8 is  ;

B9 is  ;

B10 is  ;

B11 is  ;

R3, if present, is a substituent on the phenyl ring of said B ring system and each R3 is selected from the group consisting of: halo and C1-C3 alkyl;

n is an integer from 0 to 3;

R4, if present, is a substituent on the Nitrogen-containing ring of said B ring system and each R4 is C1-C3 alkyl;

p is an integer from 0 to 2;

q is an integer from 0 to 4;

K, L, and M are each N or CR13 provided that one and only one of K, L and M is CR13;

Y is H, OH, R7, R8, R9, R10, R11, R12, or -NR5bR6b;

R5a and R5b are each H, R51, R52, R53, R54, R55, -C(O)Rb, -C(O)NRcRc, $-S(O_2)Ra$, or $-S(O_2)NRcRc$;

each R51 is C1-C6 alkyl optionally substituted with one or more substituents selected from the group consisting of: halo, -ORd, -SRk, -C(O)ORc, -C(O)NReRe, -NReRe, Rg, Rh, Ri, Rj;

each R52 is C3-C6 cycloalkyl optionally substituted with one or more substituents selected from the group consisting of: halo, -ORd, -SRd, -C(O)ORc, -C(O)NReRe,

-NReRe, C1-C3 alkyl, and C1-C3 haloalkyl;

R53 is monocyclic heterocycloalkyl optionally substituted with one or more C1-C3 alkyl;

R54 is phenyl optionally substituted with one or more substituents selected from the group consisting of: halo, CN, Ra, -ORb, -C(O)ORc, -C(O)NRcRc, -NRcRc, -NRcC(O)Rb, -NRcS(O_2)Ra, -SRb, -S(O_2)Ra, and -S(O_2)NReRe;

R55 is monocyclic heteroaryl optionally substituted with one or more substituents selected from the group consisting of: halo, -CN, C1-C3 alkyl, C1-C3 haloalkyl, -ORd, and -NReRe;

R6a and R6b are each H, R51, or R52; or

R5a and R6a and/or R5b and R6b, independently in each instance, taken together with the nitrogen atom to which they are attached form a saturated monocyclic ring having from 5 to 7 member atoms wherein said ring optionally contains one additional heteroatom as a member atom and wherein said ring is optionally substituted with one or more substituents selected from the group consisting of: C1-C3 alkyl, -ORd, and -NRfRf;

R7 is C1-C8 alkyl optionally substituted with one or more substituents selected from the group consisting of: halo, -ORd, -SRd, -NReRe, C3-C6 cycloalkyl, Ri, and Rj;

R8 is C3-C6 cycloalkyl optionally substituted with one or more substituents selected from the group consisting of: halo, -ORd, -SRd, -NReRe, C1-C3 alkyl, and C1-C3 haloalkyl;

R9 monocyclic heterocycloalkyl optionally substituted with one or more C1-C3 alkyl;

R10 is phenyl optionally substituted with one or more substituents selected from the group consisting of: halo, CN, Ra, -ORb, -C(O)ORc, -C(O)NReRe, -NReRe, -NRcC(O)Rb, -NRcS(O_2)Ra, -SRb, -S(O_2)Ra, and -S(O_2)NRcRc

R11 is heteroaryl optionally substituted with one or more substituents selected from the group consisting of: halo, CN, Ra, -ORb, -C(O)ORc, -C(O)NReRe, -NReRe, -NRcC(O)Rb, -NRcS(O_2)Ra, -SRb, -S(O_2)Ra, and -S(O_2)NRcRc;

R12 is -OR8, -OR9, -OR10, -OR11, -OR12, -SR8, -SR9, -SR10, SR11. –SR12;

R13 is H, R7, R8, R9, R10, R11, -CONRlRl, -NRlRl, -NRcCORm, -NRcSO_2Rm;

each Ra is C1-C6 alkyl or C1-C6 haloalkyl;

each Rb is H, C1-C6 alkyl or C1-C6 haloalkyl;

each Rc is H or C1-C6 alkyl;

each Rd is H, C1-C3 alkyl or C1-C3 haloalkyl;

each Re is H, C1-C3 alkyl, or -CH_2-CF_3; or

both Re groups, independently in each instance, taken together with the nitrogen atom to which they are attached form a saturated monocyclic ring having from 5 to 7 member atoms wherein said ring optionally contains one additional heteroatom as a member atom and wherein said ring is optionally substituted with one or more substituents selected from the group consisting of: C1-C3 alkyl, -ORd, and -NRfRf;

each Rf is H or C1-C3 alkyl.

each Rg is C3-C6 cycloalkyl optionally substituted with one or more substituents selected from the group consisting of: halo, -ORd, -SRd, -C(O)ORc, -C(O)NReRe, -NReRe, and C1-C3 alkyl;

each Rh is monocyclic heterocycloalkyl optionally substituted with one or more C1-C3 alkyl;

each Ri is phenyl optionally substituted with one or more substituents selected from the group consisting of: halo, -CN, C1-C3 alkyl, C1-C3 haloalkyl, -ORd, and -NReRe;

each Rj is monocyclic heteroaryl optionally substituted with one or more substituents selected from the group consisting of: halo, -CN, C1-C3 alkyl, C1-C3 haloalkyl, -ORd, and -NReRe;

each Rk is H, C1-C3 alkyl, C1-C3 haloalkyl, or benzyl optionally substituted with one or more substituents selected from the group consisting of: halo, -CN, C1-C3 alkyl, C1-C3 haloalkyl, -ORd, and -NReRe;

each Rl is H, Rh, Ri, Rj, or Rn; or

both Rl groups, independently in each instance, taken together with the nitrogen atom to which they are attached form a saturated monocyclic ring having from 5 to 7 member atoms wherein said ring optionally contains one additional heteroatom as a member atom and wherein said ring is optionally substituted with one or more substituents selected from the group consisting of: C1-C3 alkyl, -ORd, and -NRfRf;

Rm is Rh, Ri, Rj, or Rn; and

each Rn is -CH_2-C1-C4 haloalkyl or C1-C6 alkyl optionally substituted with one or more substituents selected from the group consisting of: Rh, Ri, and Rj;

or a pharmaceutically acceptable salt thereof.

The meaning of any functional group or substituent thereon at any one occurrence in Formula I, or any subformula thereof, is independent of its meaning, or any other functional group's or substituent's meaning, at any other occurrence, unless stated otherwise.

The compounds according to Formula I may contain one or more asymmetric centers (also referred to as a chiral center) and may, therefore, exist as individual enantiomers, diastereomers, or other stereoisomeric forms, or as mixtures thereof. Chiral centers, such as chiral carbon atoms, may also be present in a substituent such as an

alkyl group. Where the stereochemistry of a chiral center present in Formula I, or in any chemical structure illustrated herein, is not specified the structure is intended to encompass any stereoisomer and all mixtures thereof. Thus, compounds according to Formula I containing one or more chiral center may be used as racemic mixtures, enantiomerically enriched mixtures, or as enantiomerically pure individual stereoisomers.

Individual stereoisomers of a compound according to Formula I which contain one or more asymmetric center may be resolved by methods known to those skilled in the art. For example, such resolution may be carried out (1) by formation of diastereoisomeric salts, complexes or other derivatives; (2) by selective reaction with a stereoisomer-specific reagent, for example by enzamatic oxidation or reduction; or (3) by gas-liquid or liquid chromatography in a chiral enviornment, for example, on a chiral support such as silica with a bound chiral ligand or in the presence of a chiral solvent. The skilled artisan will appreciate that where the desired stereoisomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired form. Alternatively, specific stereoisomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer to the other by asymmetric transformation.

The compounds according to Formula I may also contain double bonds or other centers of geometric asymmetry. Where the stereochemistry of a center of geometric asymmetry present in Formula I, or in any chemical structure illustrated herein, is not specified, the structure is intended to encompass the trans (E) geometric isomer, the cis (Z) geometric isomer, and all mixtures thereof. Likewise, all tautomeric forms are also included in Formula I whether such tautomers exist in equilibrium or predominately in one form.

In certain embodiments, compounds according to Formula (I) may contain a basic functional group and are therefore capable of forming pharmaceutically acceptable acid addition salts by treatment with a suitable acid. Suitable acids include pharmaceutically acceptable inorganic acids and organic acids. Representative pharmaceutically acceptable acids include hydrogen chloride, hydrogen bromide, nitric acid, sulfuric acid, sulfonic acid, phosphoric acid, acetic acid, hydroxyacetic acid, phenylacetic acid, propionic acid, butyric acid, valeric acid, maleic acid, acrylic acid, fumaric acid, malic acid, malonic acid, tartaric acid, citric acid, salicylic acid, benzoic acid, tannic acid, formic acid, stearic acid, lactic acid, ascorbic acid, *p*-toluenesulfonic acid, oleic acid, lauric acid, and the like.

In certain embodiments, compounds according to Formula I may contain an acidic functional group and are therefore capable of forming pharmaceutically-acceptable base addition salts by treatment with a suitable base. Thus, the skilled artisan will appreciate that pharmaceutically-acceptable salts of the compounds according to Formula I may be prepared. Indeed, in certain embodiments of the invention, pharmaceutically-acceptable salts of the compounds according to Formula I may be preferred over the respective free base or free acid because such salts impart greater stability or solubility to the molecule thereby facilitating formulation into a dosage form. Accordingly, the invention is further directed to pharmaceutically-acceptable salts of the compounds according to Formula I.

As used herein, the term "pharmaceutically-acceptable salts" refers to salts that retain the desired biological activity of the subject compound and exhibit minimal undesired toxicological effects. These pharmaceutically-acceptable salts may be prepared *in situ* during the final isolation and purification of the compound, or by separately reacting the purified compound in its free acid or free base form with a suitable base or acid, respectively.

As used herein, the term "compounds of the invention" means both the compounds according to Formula I and the pharmaceutically-acceptable salts thereof. The term "a compound of the invention" also appears herein and refers to both a compound according to Formula I and its pharmaceutically-acceptable salts.

In the solid state, compounds of the invention can exist in crystalline, semi-crystalline and amorphous forms, as well as mixtures thereof. The skilled artisan will appreciate that pharmaceutically-acceptable solvates of a compound of the invention may be formed wherein solvent molecules are incorporated into the solid-state structure during crystallization. Solvates may involve water or nonaqueous solvents, or mixtures thereof. In addition, the solvent content of such solvates can vary in response to environment and upon storage. For example, water may displace another solvent over time depending on relative humidity and temperature.

Solvates wherein water is the solvent that is incorporated into the solid-state structure are typically referred to as "hydrates." Solvates wherein more than one solvent is incorporated into the solid-state structure are typically referred to as “mixed solvates”. Solvates include “stoichiometric solvates” as well as compositions containing variable amounts of solvent (referred to as “non-stoichiometric solvates”). Stoichiometric solvates wherein water is the solvent that is incorporated into the solid-state structure are typically referred to as "stoichiometric hydrates", and non-stoichiometric solvates wherein water is the solvent that is incorporated into the solid-state structure are typically referred to as "non-stoichiometric hydrates”. The invention includes both stoichiometric and non-stoichiometric solvates.

In addition, crystalline forms of a compound of the invention, including solvates thereof, may contain solvent molecules, which are not incorporated into the solid-state structure. For example, solvent molecules may become trapped in the crystals upon isolation. In addition, solvent molecules may be retained on the surface of the crystals. The invention includes such forms.

The skilled artisan will further appreciate that compounds of the invention, including solvates thereof, may exhibit polymorphism (i.e. the capacity to occur in different crystalline packing arrangements). These different crystalline forms are typically known as "polymorphs." The invention includes all such polymorphs. Polymorphs have the same chemical composition but differ in packing, geometrical arrangement, and other descriptive properties of the crystalline solid state. Polymorphs, therefore, may have different physical properties such as shape, density, hardness, deformability, stability, and dissolution properties. Polymorphs typically exhibit different IR spectra and X-ray powder

diffraction patterns, which may be used for identification. Polymorphs may also exhibit different melting points, which may be used for identification. The skilled artisan will appreciate that different polymorphs may be produced, for example, by changing or adjusting the reaction conditions or reagents, used in making the compound. For example, changes in temperature, pressure, or solvent may result in the production of different polymorphs. In addition, one polymorph may spontaneously convert to another polymorph under certain conditions.

Terms and Definitions

"Alkyl" refers to a monovalent saturated hydrocarbon chain having the specified number of member atoms. For example, C1-C8 alkyl refers to an alkyl group having from 1 to 8 member atoms. Alkyl groups may be optionally substituted with one or more substituents as defined herein. Alkyl groups may be straight or branched. Representative branched alkyl groups have one, two, or three branches. Alkyl includes methyl, ethyl, propyl (n-propyl and isopropyl), butyl (n-butyl, isobutyl, and t-butyl), pentyl (n-pentyl, isopentyl, and neopentyl), and hexyl.

"Cycloalkyl" refers to a monovalent saturated or unsaturated hydrocarbon ring having the specified number of member atoms. For example, C3-C6 cycloalkyl refers to a cycloalkyl group having from 3 to 6 member atoms. Unsaturated Cycloalkyl groups have one or more carbon-carbon double bonds within the ring. Cycloalkyl groups are not aromatic. Cycloalkyl groups having from 3 to 7 member atoms or less are monocyclic ring systems. Cycloalkyl groups having at least 7 member atoms may be monocyclic, bridged or fused bicyclic ring systems. Cycloalkyl groups may be optionally substituted with one or more substituents as defined herein. Cycloalkyl includes cyclopropyl, cyclopropenyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptanyl, and cycloheptenyl.

"Enantiomerically enriched" refers to products whose enantiomeric excess is greater than zero. For example, enantiomerically enriched refers to products whose enantiomeric excess is greater than 50% ee, greater than 75% ee, and greater than 90% ee.

"Enantiomeric excess" or **"ee"** is the excess of one enantiomer over the other expressed as a percentage. As a result, since both enantiomers are present in equal amounts in a racemic mixture, the enantiomeric excess is zero (0% ee). However, if one enantiomer was enriched such that it constitutes 95% of the product, then the enantiomeric excess would be 90% ee (the amount of the enriched enantiomer, 95%, minus the amount of the other enantiomer, 5%).

"Enantiomerically pure" refers to products whose enantiomeric excess is 99% ee or greater.

"Half-life" refers to the time required for half of a quantity of a substance to be converted to another chemically distinct specie *in vitro* or *in vivo*.

"Halo" refers to the halogen radical fluoro, chloro, bromo, or iodo.

"Haloalkyl" refers to an alkyl group that is substituted with one or more halo substituents. Haloalkyl includes trifluoromethyl.

"Heteroaryl" refers to a monovalent aromatic ring containing from 1 to 4 heteroatoms as member atoms in the ring. Heteroaryl groups containing more than one heteroatom may contain different heteroatoms. Heteroaryl groups may be optionally substituted with one or more substituents as defined herein. Unless otherwise specificed, heteroaryl groups are monocyclic ring systems or are fused, spiro, or bridged bicyclic ring systems. Monocyclic heteroaryl rings have 5 or 6 member atoms. Bicyclic heteroaryl rings have from 7 to 11 member atoms. Bicyclic heteroaryl rings include those rings wherein phenyl and a monocyclic heterocycloalkyl ring are attached forming a fused, spiro, or bridged bicyclic ring system, and those rings wherein a monocyclic heteroaryl ring and a monocyclic cycloalkyl, cycloalkenyl, heterocycloalkyl, or heteroaryl ring are attached forming a fused, spiro, or bridged bicyclic ring system. Heteroaryl includes pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, furanyl, furazanyl, thienyl, triazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, tetrazinyl, tetrazolyl, indolyl, isoindolyl, indolizinyl, indazolyl, purinyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, pteridinyl, cinnolinyl, benzimidazolyl, benzopyranyl, benzoxazolyl, benzisoxazolyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzisothiazolyl, benzothienyl, furopyridinyl, and napthyridinyl.

"Heteroatom" refers to a nitrogen, sulphur, or oxygen atom.

"Heterocycloalkyl" refers to a saturated or unsaturated ring containing from 1 to 4 heteroatoms as member atoms in the ring. However, heterocycloalkyl rings are not aromatic. Heterocycloalkyl groups containing more than one heteroatom may contain different heteroatoms. Heterocycloalkyl groups may be optionally substituted with one or more substituent as defined herein. Unless otherwise specified, heterocycloalkyl groups are monocyclic, bridged, or fused ring systems. Monocyclic heterocycloalkyl rings have from 4 to 7 member atoms. Bridged or bicyclic heterocycloalkyl rings have from 7 to 11 member atoms. In certain embodiments, heterocycloalkyl is saturated. In other embodiments, heterocycloalkyl is unsaturated but not aromatic. Heterocycloalkyl includes

pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, pyranyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothienyl, pyrazolidinyl, oxazolidinyl, thiazolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, thiamorpholinyl, azepinyl, 1,3-dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-oxathiolanyl, 1,3-oxathianyl, 1,3-dithianyl, azetidinyl, azabicylo[3.2.1]octyl, azabicylo[3.3.1]nonyl, azabicylo[4.3.0]nonyl, oxabicylo[2.2.1]heptyl, and pthalimidyl.

"Member atoms" refers to the atom or atoms that form a chain or ring. Where more than one member atom is present in a chain and within a ring, each member atom is covalently bound to an adjacent member atom in the chain or ring. Atoms that make up a substituent group on a chain or ring are not member atoms in the chain or ring.

"Optionally substituted" indicates that a group, such as alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heteroaryl, may be unsubstituted or substituted with one or more substituents as defined herein. **"Substituted"** in reference to a group indicates that a hydrogen atom attached to a member atom within a group is replaced. It should be understood that the term "substituted" includes the implicit provision that such substitution be in accordance with the permitted valence of the substituted atom and the substituent and that the substitution results in a stable compound (i.e. one that does not spontaneously undergo transformation such as by rearrangement, cyclization, or elimination). A single atom may be substituted with more than one substituent as long as such substitution is in accordance with the permitted valence of the atom. Suitable substituents are defined herein for each substituted or optionally substituted group.

"Pharmaceutically acceptable" refers to those compounds, materials, compositions, and dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

Representative Embodiments

In one embodiment:

A is phenyl, thiophenyl, or pyridyl;

R1 is CF_3, halo, OCF_3, CN, OC_1-C_6 alkyl, morpholino, CO_2H, or $N(CH_3)_2$;

l is 1, 2, or 3;

B is B1, B2, B6, and B7;

R2a and R2b and hydrogen;

n is 0;

m is 1;

Z is O;

Y is C1- C3 alkyl, phenyl, thiophenyl, or pyridyl; wherein the phenyl, thiophenyl or pyridyl may be substituted by -CO_2H, SO_2Me, CF_3, halo, or CN;

R5a is hydrogen or C1 – C6 alkyl; and

R6a is hydrogen or C1 – C6 alkyl;

or a pharmaceutically acceptable salt thereof.

In another embodiment:

A is phenyl;

R1 is CF_3, halo, OCF_3, CN, OC_1-C_6 alkyl, or $N(CH_3)_2$, or morpholino;

l is 1, or 2;

B is B2;

R2a and R2b and hydrogen;

L and M are N;

n is 0;

m is 1;

Z is O;

Y is methyl or phenyl;

R5a is hydrogen; and

R6a is hydrogen;

or a pharmaceutically acceptable salt thereof.

It is to be understood that the present invention covers all combinations of particular groups described hereinabove.

Compounds of Formula (I) include:

2-[4-(dimethylamino)-6-methyl-2-pyrimidinyl]-*N*-{[2-(trifluoromethyl)phenyl]methyl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide;

1-[2-methyl-6-(methylamino)-4-pyrimidinyl]-*N*-({2-[(trifluoromethyl)oxy]phenyl}methyl)-2,3-dihydro-1*H*-indole-5-carboxamide;

N-[(2,4-dichlorophenyl)methyl]-1-[6-(methylamino)-2-phenyl-4-pyrimidinyl]-2,3-dihydro-1*H*-indole-5-carboxamide;

N-[(2,4-dichlorophenyl)methyl]-1-[2-methyl-6-(methylamino)-4-pyrimidinyl]-2,3-dihydro-1H-indole-5-carboxamide;

1-[2-methyl-6-(methylamino)-4-pyrimidinyl]-*N*-{[2-(trifluoromethyl)phenyl]methyl}-2,3-dihydro-1*H*-indole-5-carboxamide;

1-[6-(methylamino)-2-phenyl-4-pyrimidinyl]-*N*-({2-[(trifluoromethyl)oxy]phenyl}methyl)-2,3-dihydro-1*H*-indole-5-carboxamide;

1-[6-(methylamino)-2-phenyl-4-pyrimidinyl]-*N*-{[2-(trifluoromethyl)phenyl]methyl}-2,3-dihydro-1*H*-indole-5-carboxamide;
N-[(2,4-dichlorophenyl)methyl]-2-[2-methyl-6-(methylamino)-4-pyrimidinyl]-2,3-dihydro-1H-isoindole-5-carboxamide;
2-[2-methyl-6-(methylamino)-4-pyrimidinyl]-N-{[2-(trifluoromethyl)phenyl]methyl}-2,3-dihydro-1H-isoindole-5-carboxamide;
2-[2-methyl-6-(methylamino)-4-pyrimidinyl]-N-({2-[(trifluoromethyl)oxy]phenyl}methyl)-2,3-dihydro-1H-isoindole-5-carboxamide;
N-[(2,4-dichlorophenyl)methyl]-2-[6-(methylamino)-2-phenyl-4-pyrimidinyl]-2,3-dihydro-1H-isoindole-5-carboxamide;
2-[6-(methylamino)-2-phenyl-4-pyrimidinyl]-N-{[2-(trifluoromethyl)phenyl]methyl}-2,3-dihydro-1H-isoindole-5-carboxamide;
2-[6-(methylamino)-2-phenyl-4-pyrimidinyl]-N-({2-[(trifluoromethyl)oxy]phenyl}methyl)-2,3-dihydro-1H-isoindole-5-carboxamide;
or a pharmaceutically acceptable salt thereof.

Compound Preparation

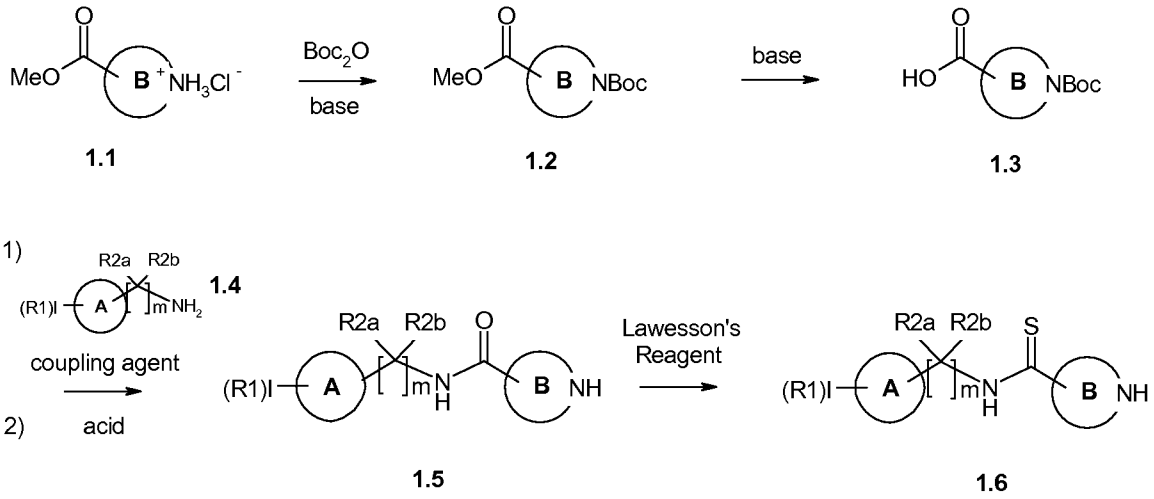
The compounds according to Formula I can be prepared using conventional organic syntheses. Suitable synthetic routes are depicted below in the following general reaction schemes. All functional groups are as defined in Formula I unless otherwise defined. Starting materials and reagents depicted below in the general reaction schemes are commercially available or can be made from commercially available starting materials using methods known by those skilled in the art.

The skilled artisan will appreciate that if a substituent described herein is not compatible with the synthetic methods described herein, the substituent may be protected with a suitable protecting group that is stable to the reaction conditions. The protecting group may be removed at a suitable point in the reaction sequence to provide a desired intermediate or target compound. Suitable protecting groups and methods for protecting and de-protecting different substituents using such suitable protecting groups are well known to those skilled in the art; examples of which may be found in T. Greene and P. Wuts, Protecting Groups in Chemical Synthesis (3rd ed.), John Wiley & Sons, NY (1999). In some instances, a substituent may be specifically selected to be reactive under the reaction conditions used. Under these circumstances, the reaction conditions convert the selected substituent into another substituent that is either useful as an intermediate compound or is a desired substituent in a target compound.

The skilled artisan will further appreciate that more than one of the pyrrimidinyl regioisomers provided for in Formula I (i.e. where K & L are N and M is CR13; K & M are N and L is CR13; or L & M are N and K is CR13) may be produced during the course of

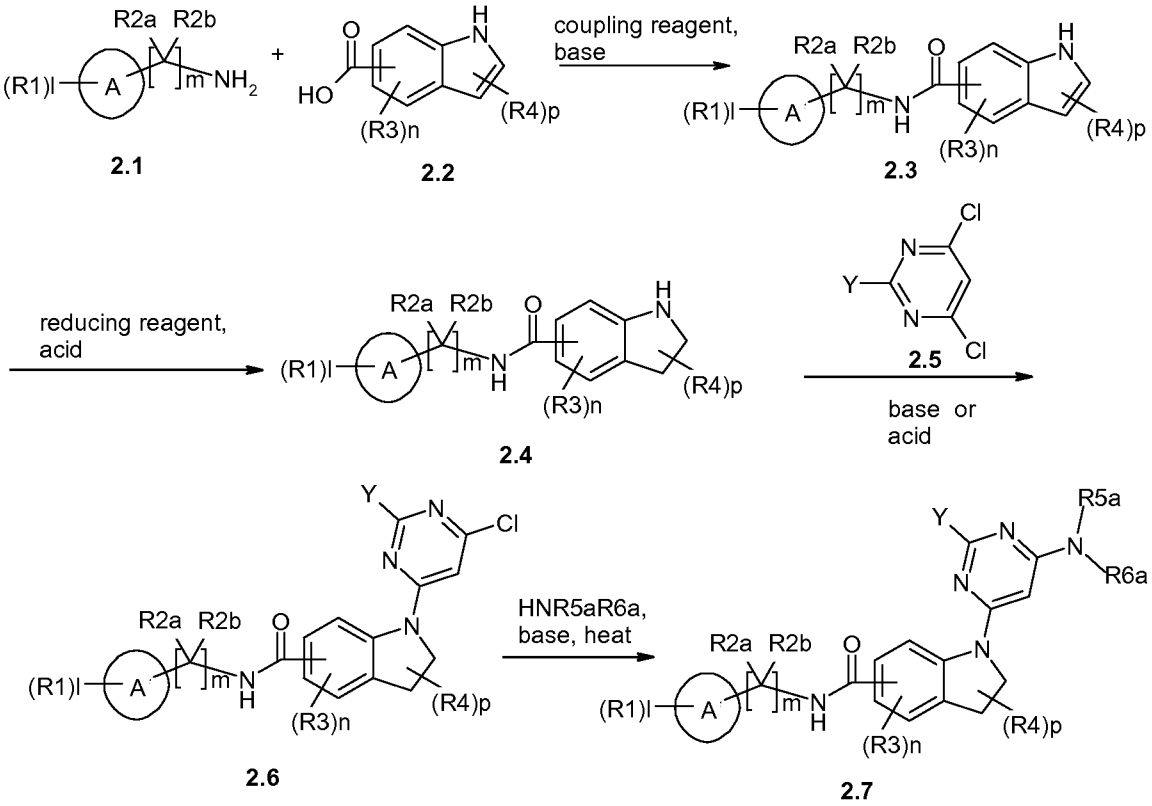
the syntheses provided below in the general reaction schemes. Such isomers can be isolated using methods known by those skilled in the art.

Scheme 1



Scheme 1 represents a general reaction scheme for preparing intermediates **1.5** and **1.6**. Treatment of compound **1.1** (commercially available or made from commercially available starting materials using methods known to those skilled in the art) with BOC anhydride in the presence of base (such as NaOH) in solvent (such as 1,4-dioxane and water) at temperatures between 0°C and 50°C provides intermediate **1.2**. Treatment of intermediate **1.2** with base (such as NaOH) in a solvent (such as MeOH) at temperatures between 25°C and 80°C provides intermediate **1.3**. Treatment of intermediate **1.3** with amine **1.4** (commercially available or made from commercially available starting materials using methods known to those skilled in the art) with a coupling reagent (such as EDCI) with a solvent (such as DMF) at temperatures between 25°C and 80°C provides intermediate **1.5**. Treatment of intermediate **1.5** with a thiolating agent (such as Lawesson's Reagent) with a solvent (such as toluene) at temperatures between 25°C and 80°C provides intermediate **1.6**.

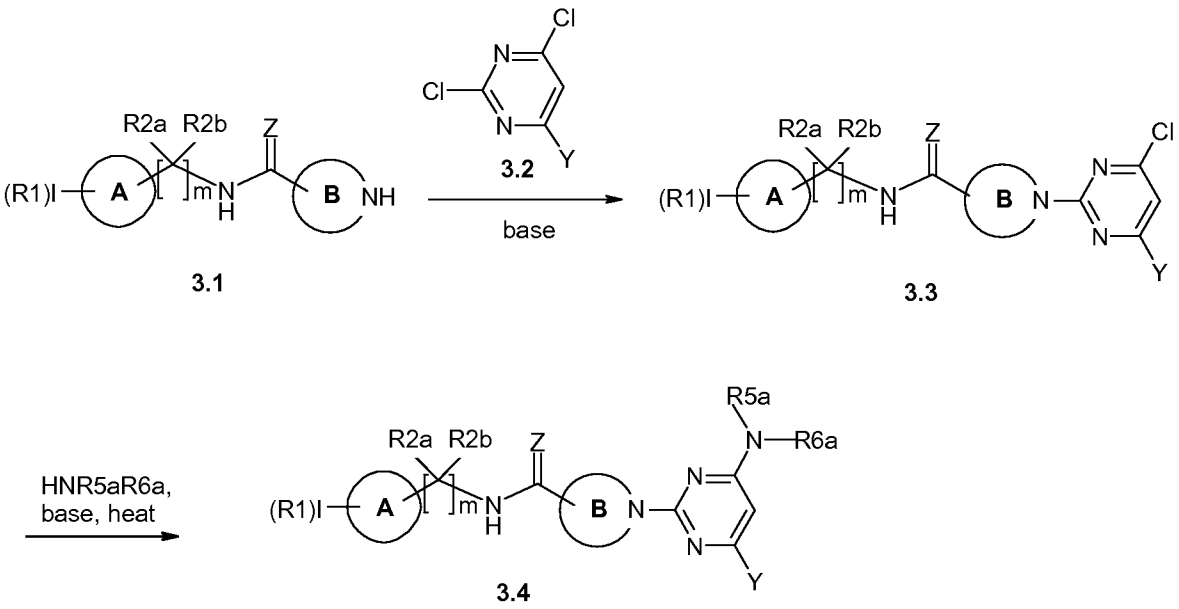
Scheme 2



Scheme 2 represents a general reaction scheme for preparing certain compounds according to Formula I. Treatment of intermediate **2.2** with amine **2.1** (commercially available or made from commercially available starting materials using methods known to those skilled in the art) and a coupling reagent (such as BOP) and a base (such as triethylamine) in a solvent (such as DMF) at temperatures between 25°C to 80°C provides intermediate **2.3**. Alternatively, the reduced form of intermediate **2.2** may be commercially available and may be used in place of **2.2** thus eliminating the need for the subsequent reduction step. Treatment of intermediate **2.3** with a reducing agent (such as Borane-THF complex in THF or triethylsilane in TFA) and optionally an acid (such as trifluoroacetic acid) in a solvent (such as THF) at temperatures between 25°C to 80°C provides intermediate **2.4**. Treatment of intermediate **2.4** with intermediate **2.5** (commercially available or made from commercially available starting materials using methods known to those skilled in the art) and a base (such as NaOH) or an acid (such as HCl) in a solvent (such as dioxane) at temperatures between 100°C to 200°C provides intermediate **2.6**. Treatment of intermediate **2.6** with HNR5aR6a (commercially available or made from commercially available starting materials using methods known to those skilled in the art)

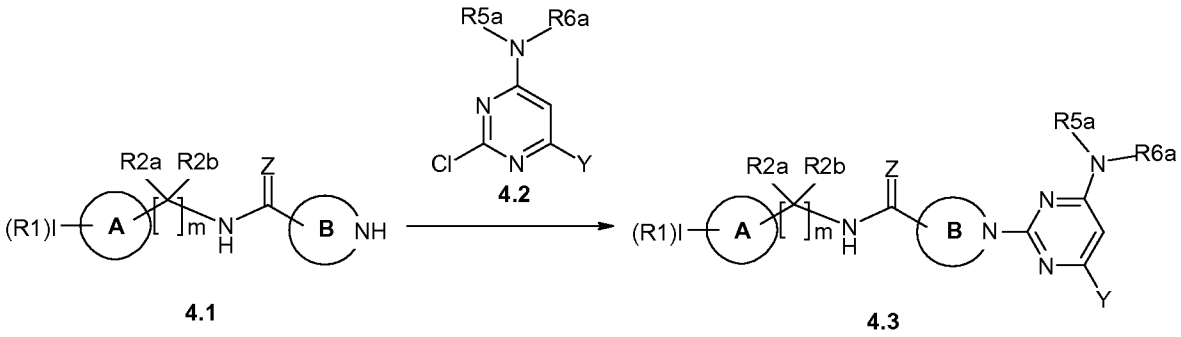
in a solvent (such as ethanol) at temperatures between 25°C to 80°C provides compounds according to Formula I wherein B is B1, B3, or B5 (depicted as compound **2.7**).

Scheme 3



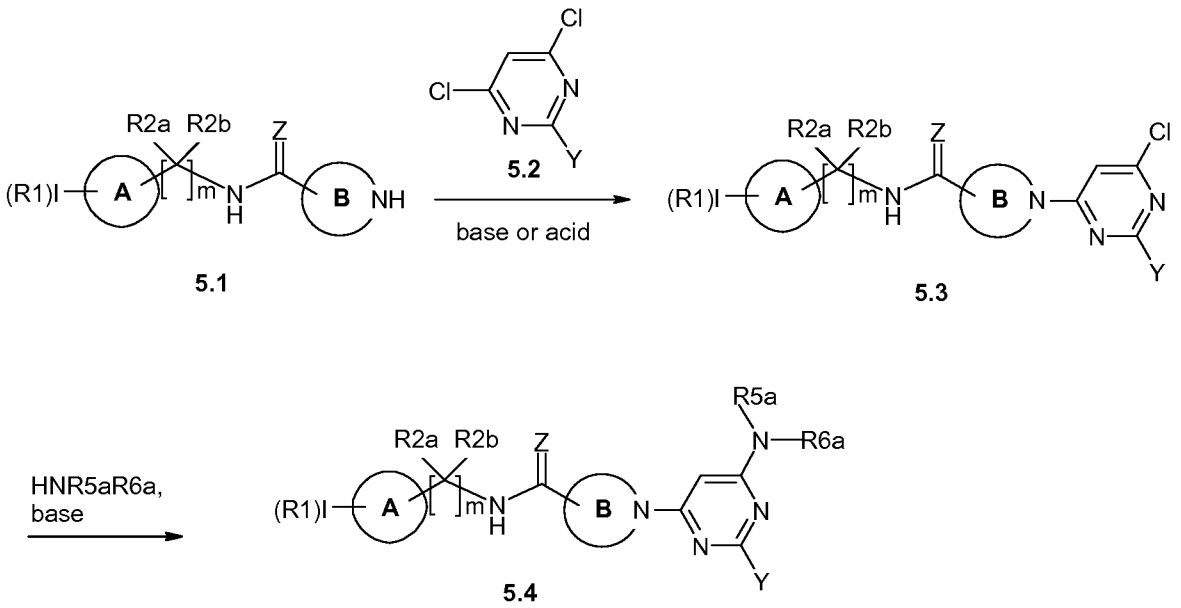
Scheme 3 represents a general reaction scheme for preparing certain compounds according to Formula 1. Treatment of intermediate **3.1** (depicted above as intermediate **1.5** or **1.6**) with intermediate **3.2** (commercially available or made from commercially available starting materials using methods known to those skilled in the art) and a base (such as NaOH) in a solvent (such as dioxane) at temperatures between 100°C to 200°C in a microwave reactor provides intermediate **3.3**. Treatment of intermediate **3.3** with HNR5aR6a (commercially available or made from commercially available starting materials using methods known to those skilled in the art) in a solvent (such as ethanol) at temperatures between 25°C to 80°C provides compounds according to Formula I (depicted as compound **3.4**).

Scheme 4



Scheme 4 represents a general reaction scheme for preparing certain compounds according to Formula 1. Treatment of intermediate **4.1** (depicted above as intermediate **1.5** or **1.6**) with intermediate **4.2** (commercially available or made from commercially available starting materials using methods known to those skilled in the art) in the presence of base such as NEt_3 in a solvent such as EtOH at temperatures between 85°C and 200°C in a microwave reactor provides compounds according to Formula I (depicted as compound **4.3**).

Scheme 5



Scheme 5 represents a general reaction scheme for preparing certain compounds according to Formula 1. Treatment of intermediate **5.1** (depicted above as intermediate **1.5** or **1.6**) with intermediate **5.2** (commercially available or made from commercially

available starting materials using methods known to those skilled in the art) and a base (such as NaOH) or an acid (such as HCl) in a solvent (such as dioxane) at temperatures between 50°C to 200°C provides intermediate **5.3**. Treatment of intermediate **5.3** with HNR5aR6a (commercially available or made from commercially available starting materials using methods known to those skilled in the art) in a solvent (such as ethanol) at temperatures between 25°C to 80°C provides compounds according to Formula I (depicted as compound **5.4**).

Examples

The following examples illustrate the invention. These examples are not intended to limit the scope of the present invention, but rather to provide guidance to the skilled artisan to prepare and use the compounds, compositions, and methods of the present invention. While particular embodiments of the present invention are described, the skilled artisan will appreciate that various changes and modifications can be made without departing from the spirit and scope of the invention.

1H NMR spectra were recorded on a Bruker Avance 400 megahertz NMR spectrometer. Chemical shifts are expressed in parts per million (ppm, units). Coupling constants (*J*) are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), dt (double triplet), m (multiplet), br (broad).

MS and liquid chromatography MS were recorded on a MDS Sciex liquid chromatography / mass spectroscopy system. All mass spectra were performed under electrospray ionization (ESI), chemical ionization (CI), electron impact (EI) or by fast atom bombardment (FAB) methods.

HPLC data was recorded on an Agilent 1100 series HPLC system with C-18 reverse phase column (Eclipse XDB-C18, 4.6 x 250 mm, 5 micron) running a gradient of 1-99% MeCN/H2O (+0.1% TFA) over 12 minutes.

All reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light, 5% ethanolic phosphomolybdic acid, p-anisaldehyde solution, aqueous potassium permanganate or potassium iodide / platinum chloride solution in water.

Flash column chromatography was performed on silica gel.

The naming program used is ACD Name Pro 6.02.

In describing the invention, chemical elements are identified in accordance with the Periodic Table of the Elements. Abbreviations and symbols utilized herein are in accordance with the common usage of such abbreviations and symbols by those skilled in the chemical and biological arts. For example, the following abbreviations are used herein:

"aq" is an abbreviation for aqueous

"BOC" is an abbreviation for *tert*-butoxycarbonyl

"BOP" is an abbreviation for (Benzotriazol-1-yloxy)tris (dimethylamino)phosphonium hexafluorophosphate

"°C" is an abbreviation for degrees Celsius

"DMAP" is an abbreviation for dimethylaminopyridine

"DMF" is an abbreviation for dimethylformamide

"DMSO" is an abbreviation for Dimethylsulfoxide

"EDCI" is an abbreviation for N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride

"equiv" is an abbreviation for equivalent

"HPLC" is an abbreviation for High Pressure Liquid Chromatography

"g" is an abbreviation for gram or grams

"L" is an abbreviation for liter or liters

"LC-MS" is an abbreviation for Liquid chromatography-Mass spectrometry

"mL" is an abbreviation for milliliter or milliliters

"min" is an abbreviation for minute or minutes

"mmol" is an abbreviation for millimole or millimolar

"N" is an abbreviation for Normal and refers to the number of equivalents of reagent per liter of solution

"Ph" is an abbreviation for phenyl

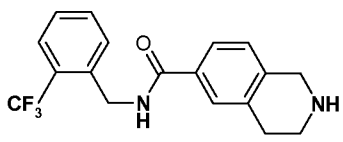
"sat" is an abbreviation for saturated

"TFA" is an abbreviation for trifluoroacetic acid

"THF" is an abbreviation for tetrahydrofuran

Intermediate 1

N-{[2-(trifluoromethyl)phenyl]methyl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide



Step 1: Preparation of 2-(1,1-dimethylethyl) 6-methyl 3,4-dihydro-2,6(1*H*)-isoquinoline-dicarboxylate

To a solution of methyl 1,2,3,4-tetrahydroisoquinoline-6-carboxylate hydrochloride (0.30 g, 1.32 mmol) in dioxane/H_2O (2:1, 5 mL) was added 1N NaOH (1.97 mL, 1.97 mmol) followed by Boc_2O (0.43 g, 1.97 mmol). The reaction was stirred at room temperature for 1 hour, at which time LCMS indicated complete conversion to product. The reaction was poured into H_2O (10 mL) and extracted with CH_2Cl_2 (3x10 mL). The organics were dried (Na_2SO_4) and evacuated. The crude carbamate was used directly in the next step.

Step 2: 2-{[(1,1-dimethylethyl)oxy]carbonyl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxylic acid

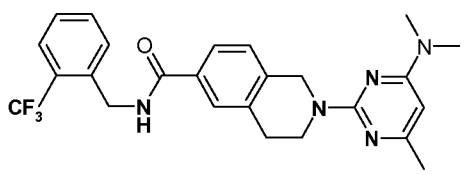
To a solution of the crude carbamate from Step 1 in MeOH/THF (1:1, 6 mL) was added 1N NaOH (1.97 mL, 1.97 mmol). The reaction was heated to 70°C for 1 hour. The reaction was cooled and the MeOH evacuated. The remaining aqueous solution was acidified to pH 4 with 1N HCl. The resulting precipitate was vacuum filtered and dried to afford the desired product (0.34 g, 93%) which was used without further purification. MS (ES+) m/e 222.0 $[M-t\text{Bu}]^+$

Step 3: *N*-{[2-(trifluoromethyl)phenyl]methyl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide

To a solution of aforementioned carboxylic acid (0.35 g, 1.27 mmol) in DMF (8 mL) was added DMAP (42.0 mg, 0.38 mmol) followed by 2-(trifluoromethoxy)benzylamine (178 □L, 1.27 mmol) and EDCI (292 mg, 1.52 mmol). After stirring overnight, the reaction was poured into H_2O (15 mL) and extracted with EtOAc (2x20 mL). The organics were dried (Na_2SO_4) and evacuated. The crude material was redissolved in CH_2Cl_2 (4mL) and treated with TFA (4 mL). After stirring for 30 minutes, the reaction was diluted with CH_2Cl_2 (15 mL) and poured into ice cold 1N NaOH (20 mL). The organics were extracted, dried (Na_2SO_4), and evacuated to afford the title compound (0.36 g, 85%), which was used without further purification. MS (ES+) m/e 334.9 $[M+1]^+$

Example 1

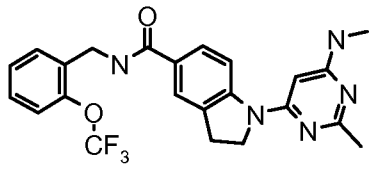
2-[4-(dimethylamino)-6-methyl-2-pyrimidinyl]-*N*-{[2-(trifluoromethyl)phenyl]methyl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide



A mixture of Intermediate 1 (50.0 mg, 0.15 mmol), NEt_3 (77.0 □L, 0.56 mmol), and 2-chloro-*N*,*N*,6-trimethyl-4-pyrimidinamine (38.0 mg, 0.22 mmol) in EtOH (2 mL) was heated to 150°C in a microwave for 15 minutes. The reaction mixture was purified directly by RP-HPLC (gradient 30-80% CH_3CN:H_2O (0.1% TFA)), to afford the title compound (55 mg, 79%). MS (ES+): m/e 470 $[M + H]^+$

Example 2

1-[2-methyl-6-(methylamino)-4-pyrimidinyl]-*N*-({2-[(trifluoromethyl)oxy]phenyl}methyl)-2,3-dihydro-1*H*-indole-5-carboxamide



Step 1: *N*-({2-[(trifluoromethyl)oxy]phenyl}methyl)-1*H*-indole-5-carboxamide

1H-indole-5-carboxylic acid (5 g, 31.0 mmol) and 1-{2-[(trifluoromethyl)oxy]phenyl}methanamine (5.22 ml, 34.1 mmol) were dissolved in dimethylformamide (DMF) (40 mL) at room temperature. Afterwards, triethylamine (4.32 ml, 31.0 mmol) was added and the solution was allowed to stir for several minutes before a separate solution of 1H-1,2,3-benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate (BOP reagent, 13.72 g, 31.0 mmol) dissolved in 15 mL of DMF was delivered to the mixture at room temperature. The reaction was maintained at that temperature for 2.5 hours before it was determined to be complete by LC/MS. The crude mixture was slowly poured into a vigorously stirring solution (550 mL) of saturated sodium bicarbonate and water (1:1) at room temperature which resulted in the precipitation of the desired product as an off-white solid. The mixture was allowed to stir for 18 hours before the solid was recovered by vacuum filtration and dried for 24 hours under vacuum at 65°C to give *N*-({2-[(trifluoromethyl)oxy]phenyl}methyl)-1*H*-indole-5-carboxamide (9.44 g, 28.0 mmol, 90 % yield). MS (ES) m/e 335 [M+H]+.

Step 2: *N*-({2-[(trifluoromethyl)oxy]phenyl}methyl)-2,3-dihydro-1*H*-indole-5-carboxamide, trifluoroacetate salt

A solution of *N*-({2-[(trifluoromethyl)oxy]phenyl}methyl)-1*H*-indole-5-carboxamide (2 g, 5.98 mmol) dissolved in trifluoroacetic acid (28.7 ml, 372 mmol) was prepared in a 25 mL round bottom flask equipped with a magnetic stir bar under argon. Triethylsilane (28.6 ml, 179 mmol) was delivered to the flask at room temperature. The mixture was allowed

to stir for 18 hours before the reaction was determined to be complete by LC-MS. The reaction mixture was concentrated under vacuum to provide *N*-({2-[(trifluoromethyl)oxy]phenyl}methyl)-2,3-dihydro-1*H*-indole-5-carboxamide, trifluoroacetate salt as a crude orange oil which was carried on to the next step without further purification. MS (ES) m/e 335 [M+H]+.

Step 3: 1-(6-chloro-2-methyl-4-pyrimidinyl)-*N*-({2-[(trifluoromethyl)oxy]phenyl}methyl)-2,3-dihydro-1*H*-indole-5-carboxamide

4,6-dichloro-2-methylpyrimidine (97 mg, 0.595 mmol) and *N*-({2-[(trifluoromethyl)oxy]phenyl}methyl)-2,3-dihydro-1*H*-indole-5-carboxamide, trifluoroacetate salt (200 mg, 0.445 mmol) were combined in a 5.0 mL glass reaction tube that was equipped with a magnetic stir bar. The contents of the tube were taken up in 1,4-dioxane (3 mL) and 6N sodium hydroxide (0.3 mL, 1.8 mmol). The tube was fitted with a rubber septum and hermetically sealed with a crimped metal foil seal. Using a Personal Chemistry Emrys Optimizer microwave unit, the reaction mixture was magnetically stirred and irradiated with microwave energy of dynamically adjusted power in order to maintain a temperature of 180°C for 2 hours. The reaction was determined to be complete by LC-MS. The reaction mixture was concentrated under vacuum and the crude residue was purified by prep HPLC (Sunfire, 35 x 150 mm, 40 mL/min, A: acetonitrile (0.1% TFA) B: water (0.1% TFA), A: 10 to 90% over 30 min, UV detection at 214 nm) to give 1-(6-chloro-2-methyl-4-pyrimidinyl) – N - ({2-[(trifluoromethyl)oxy] phenyl}methyl)-2,3-dihydro-1H-indole-5-carboxamide (27.2 mg, 0.046 mmol, 10 % yield), as the TFA salt in the form of a brown solid. MS (ES) m/e 463 [M+H]+.

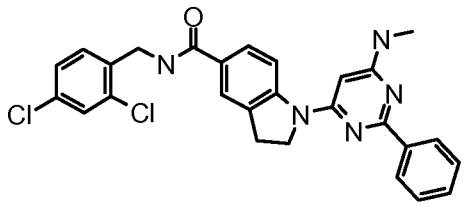
Step 4: 1-[2-methyl-6-(methylamino)-4-pyrimidinyl]-*N*-({2-[(trifluoromethyl)oxy]phenyl}methyl)-2,3-dihydro-1*H*-indole-5-carboxamide

1-(6-chloro-2-methyl-4-pyrimidinyl)-*N*-({2-[(trifluoromethyl)oxy]phenyl}methyl)-2,3-dihydro-1*H*-indole-5-carboxamide (27.2 mg, 0.046 mmol) and 33% methylamine in EtOH (0.71 mL, 5.7 mmol) were combined in a 5.0 mL glass reaction tube that was equipped with a magnetic stir bar. The tube was fitted with a rubber septum and hermetically sealed with a crimped metal foil seal. The mixture was stirred and heated to 70°C for 48 hours until the reaction was determined to be complete by LC-MS. Upon cooling, the product precipitated out of solution and was collected by vacuum filtration and rinsed with ethyl ether several times. After drying in a vacuum oven overnight, the title compound (15.9

mg, 0.035 mmol, 75 % yield) was recovered as the free base in the form of an off-white solid. MS (ES) m/e 458 [M+H]+.

Example 3

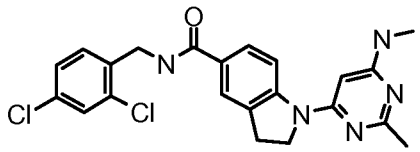
N-[(2,4-dichlorophenyl)methyl]-1-[6-(methylamino)-2-phenyl-4-pyrimidinyl]-2,3-dihydro-1*H*-indole-5-carboxamide



Example 3 was prepared using the general procedure described above in Example 2 substituting [(2,4-dichlorophenyl)methyl]amine for 1-{2-[(trifluoromethyl)oxy]phenyl} methanamine in Step 1 and 4,6-dichloro-2-phenylpyrimidine for 4,6-dichloro-2-methylpyrimidine in Step 3. MS (ES+): m/e 504 $[M + H]^+$.

Example 4

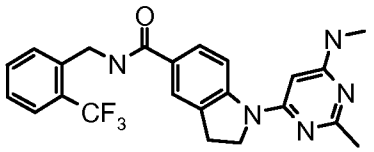
N-[(2,4-dichlorophenyl)methyl]-1-[2-methyl-6-(methylamino)-4-pyrimidinyl]-2,3-dihydro-1H-indole-5-carboxamide



Example 4 was prepared using the general procedure described above in Example 2 substituting [(2,4-dichlorophenyl)methyl]amine for 1-{2-[(trifluoromethyl)oxy]phenyl} methanamine in Step 1. MS (ES+): m/e 442 $[M + H]^+$.

Example 5

1-[2-methyl-6-(methylamino)-4-pyrimidinyl]-*N*-{[2-(trifluoromethyl)phenyl]methyl}-2,3-



dihydro-1*H*-indole-5-carboxamide

Step 1: *N*-{[2-(trifluoromethyl)phenyl]methyl}-1*H*-indole-5-carboxamide

1H-indole-5-carboxylic acid (5 g, 31.0 mmol) and {[2-(trifluoromethyl)phenyl] methyl}amine (4.78 ml, 34.1 mmol) were dissolved in DMF (40 mL) at room temperature. Afterwards, triethylamine (4.32 ml, 31.0 mmol) was added and the solution was allowed to stir for several minutes before a separate solution of BOP reagent (13.72 g, 31.0 mmol) dissolved in 15 mL of DMF was delivered to the mixture at room temperature. The reaction was maintained at that temperature for 2.5 hours, before it was determined to be complete by LC-MS. The crude mixture was slowly poured into a vigorously stirring solution (550 mL) of saturated sodium bicarbonate and water (1:1) at room temperature, which resulted in the precipitation of the desired product as an off-white solid. The mixture was allowed to stir for 18 hours, before the solid was recovered by vacuum filtration and dried for 24 hours under vacuum at 65°C to give *N*-{[2-(trifluoromethyl)phenyl]methyl}-1*H*-indole-5-carboxamide (9.43 g, 29.3 mmol, 95 % yield). MS (ES) m/e 319 $[M+H]^+$.

Step 2: *N*-{[2-(trifluoromethyl)phenyl]methyl}-2,3-dihydro-1*H*-indole-5-carboxamide

A solution of *N*-{[2-(trifluoromethyl)phenyl]methyl}-1*H*-indole-5-carboxamide (2 g, 6.28 mmol) dissolved in trifluoroacetic acid (30.1 ml, 391 mmol) was prepared in a 25 mL round bottom flask equipped with a magnetic stir bar under argon. Triethylsilane (30.0 ml, 189 mmol) was delivered to the flask at room temperature. The mixture was allowed to stir for 18 hours at room temperature, before it was determined to be complete by LC-MS. The crude mixture was concentrated under vacuum and the resulting crude oil was dissolved in 100 mL of EtOAc and washed with a saturated solution of sodium bicarbonate (3 x 100 mL), extracted, dried over sodium sulfate, and concentrated. The crude residue was absorbed onto a 120 g silica gel column and eluted with 100% DCM. The combined fractions were concentrated under vacuum to give *N*-{[2-(trifluoromethyl)phenyl]methyl}-2,3-dihydro-1*H*-indole-5-carboxamide (1.04 g, 3.1 mmol, 49 % yield) as the free base in the form of an off-white solid. MS (ES) m/e 321 $[M+H]^+$.

Step 3: 1-(6-chloro-2-methyl-4-pyrimidinyl)-*N*-{[2-(trifluoromethyl)phenyl]methyl}-2,3-dihydro-1*H*-indole-5-carboxamide, Hydrochloride salt

4,6-dichloro-2-methylpyrimidine (150 mg, 0.920 mmol) and N-{[2-(trifluoromethyl) phenyl]methyl}-2,3-dihydro-1H-indole-5-carboxamide (295 mg, 0.92 mmol) were combined in a 5.0 mL glass reaction tube that was equipped with a magnetic stir bar. The contents

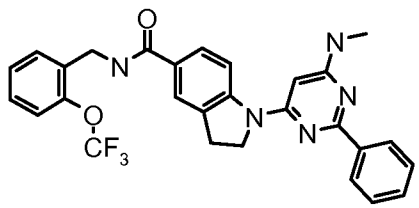
of the tube were taken up in 4M HCl in dioxane (2.3 mL, 9.2 mmol). The tube was fitted with a rubber septum and hermetically sealed with a crimped metal foil seal. The mixture was stirred and heated to 85°C for 1 hour until the reaction was determined to be complete by LC-MS. An off-white solid precipitated out of solution and was collected by vacuum filtration. After washing several times with small portions of both dioxane and ethyl ether the solid was collected and dried under vacuum at room temperature for several hours. The HCl salt form of the product, 1-(6-chloro-2-methyl-4-pyrimidinyl)-*N*-{[2-(trifluoromethyl)phenyl]methyl}-2,3-dihydro-1*H*-indole-5-carboxamide (317 mg, 0.65 mmol, 71 % yield), was recovered as an off-white solid. MS (ES) m/e 447 [M+H]+.

Step 4: 1-[2-methyl-6-(methylamino)-4-pyrimidinyl]-*N*-{[2-(trifluoromethyl)phenyl]methyl}-2,3-dihydro-1*H*-indole-5-carboxamide

1-(6-chloro-2-methyl-4-pyrimidinyl)-*N*-{[2-(trifluoromethyl)phenyl]methyl}-2,3-dihydro-1*H*-indole-5-carboxamide (100 mg, 0.207 mmol) and 33% methylamine in EtOH (3.1 mL, 24.8 mmol) were combined in a 5.0 mL glass reaction tube that was equipped with a magnetic stir bar. The tube was fitted with a rubber septum and hermetically sealed with a crimped metal foil seal. The mixture was stirred and heated to 70°C for 48 hours until the reaction was determined to be complete by LC-MS. An off-white solid precipitated out of solution during the reaction, which was collected by vacuum filtration and rinsed with ethyl ether several times. After drying in a vacuum oven overnight, the title compound (77.7 mg, 0.17 mmol, 83 % yield) was recovered as the free base in the form of an off-white solid. MS (ES) m/e 442 [M+H]+.

Example 6

1-[6-(methylamino)-2-phenyl-4-pyrimidinyl]-*N*-({2-[(trifluoromethyl)oxy]phenyl}methyl)-2,3-dihydro-1*H*-indole-5-carboxamide

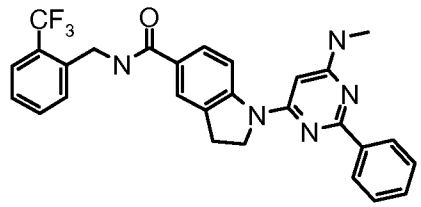


Example 6 was prepared using the general procedure described above in Example 5 substituting -{2-[(trifluoromethyl)oxy]phenyl}methanamine for {[2-(trifluoromethyl)phenyl]

methyl}amine in Step 1 and 4,6-dichloro-2-phenylpyrimidine for 4,6-dichloro-2-methylpyrimidine in Step 3. MS (ES+): m/e 520 $[M + H]^+$.

Example 7

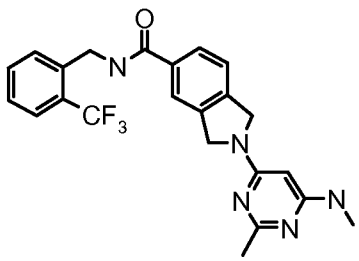
1-[6-(methylamino)-2-phenyl-4-pyrimidinyl]-*N*-{[2-(trifluoromethyl)phenyl]methyl}-2,3-dihydro-1*H*-indole-5-carboxamide



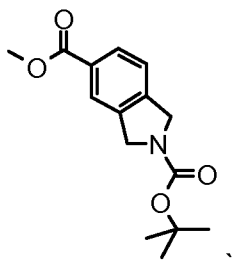
Example 7 was prepared using the general procedure described above in Example 5 substituting 4,6-dichloro-2-phenylpyrimidine for 4,6-dichloro-2-methylpyrimidine in Step 3.. MS (ES+): m/e 504 $[M + H]^+$.

Example 8

2-[2-methyl-6-(methylamino)-4-pyrimidinyl]-*N*-{[2-(trifluoromethyl)phenyl]methyl}-2,3-dihydro-1*H*-isoindole-5-carboxamide

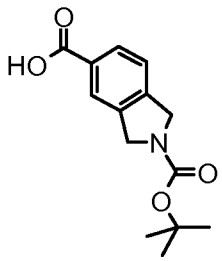


Step 1: <u>2-(1,1-dimethylethyl) 5-methyl 1,3-dihydro-2*H*-isoindole-2,5-dicarboxylate</u>



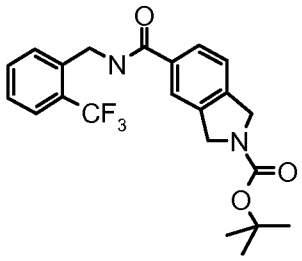
To a mixture of methyl 2,3-dihydro-1*H*-isoindole-5-carboxylate hydrochloride (1 g, 4.68 mmol) dissolved in 1,4-dioxane (10 ml) and water (5.0 ml) was added 1N NaOH (7.0 ml, 7.02 mmol) followed by BOC-anhydride (1.53 g, 7.02 mmol). The reaction was stirred at room temperature for 1 hour, before it was determined to be complete by TLC (eluted with 25% EtOAc in hexanes). The reaction was poured into 30 mL of water and extracted with methylene chloride (3x30mL). The organics were combined, dried (sodium sulfate) and concentrated under vacuum to give 2-(1,1-dimethylethyl) 5-methyl 1,3-dihydro-2H-isoindole-2,5-dicarboxylate (860 mg, 3.1 mmol, 66 % yield).

Step 2: 2-{[(1,1-dimethylethyl)oxy]carbonyl}-2,3-dihydro-1*H*-isoindole-5-carboxylic acid



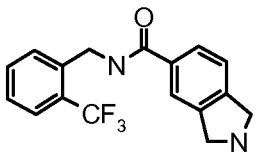
To a solution of 2-(1,1-dimethylethyl) 5-methyl 1,3-dihydro-2H-isoindole-2,5-dicarboxylate (860 mg, 3.1 mmol) dissolved in methanol (7.1 mL) and tetrahydrofuran (THF) (7.1 mL) was added 1N NaOH (4.4 mL, 4.4 mmol). The reaction was heated to 70 °C for 1.5 hr, after which it was determined to be complete by LC/MS. The reaction was allowed to cool to room temperature prior to removing the organics under vacuum using a rotary evaporator. The remaining aqueous solution was acidified to pH 4 with 1N HCl. The resulting precipitate (off-white solid) was allowed to stir for 18h before it was collected by vacuum filtration and dried under vacuum to give 2-{[(1,1-dimethylethyl)oxy]carbonyl}-2,3-dihydro-1*H*-isoindole-5-carboxylic acid (818 mg, 3.08 mmol, 99 % yield) as the free acid in the form of an off-white solid. MS (ES) m/e 164 [M-100]+.

Step 3: 1,1-dimethylethyl 5-[({[2-(trifluoromethyl)phenyl]methyl}amino)carbonyl]-1,3-dihydro-2*H*-isoindole-2-carboxylate



2-{[(1,1-dimethylethyl)oxy]carbonyl}-2,3-dihydro-1*H*-isoindole-5-carboxylic acid (272 mg, 1.03 mmol) and {[2-(trifluoromethyl)phenyl]methyl}amine (159 µl, 1.14 mmol) were dissolved in dimethylformamide (DMF) (1.45 mL) at room temperature. Afterwards, triethylamine (143 µl, 1.03 mmol) was added and the solution was allowed to stir for several minutes before a separate solution of (1H-1,2,3-benzotriazol-1-yloxy)[tris(dimethylamino)]phosphonium hexafluorophosphate (BOP reagent, 610 mg, 1.34 mmol) dissolved in 1.0 mL of DMF was delivered to the mixture at room temperature. The reaction was maintained at that temperature for 2.5 hours, after which it was determined to be complete by LC/MS. The crude mixture was slowly poured into a vigorously stirring solution (30 mL) of saturated sodium bicarbonate and water (1:1) at room temperature, which resulted in the precipitation of the desired product as an off-white solid. The mixture was allowed to stir for 2 hr, before the solid was isolated by vacuum filtration and dried under vacuum for 24 hours under to give 1,1-dimethylethyl 5-[({[2-(trifluoromethyl)phenyl]methyl}amino)carbonyl]-1,3-dihydro-2H-isoindole-2-carboxylate (406 mg, 0.966 mmol, 93 % yield). MS (ES) m/e 420 [M+H]+.

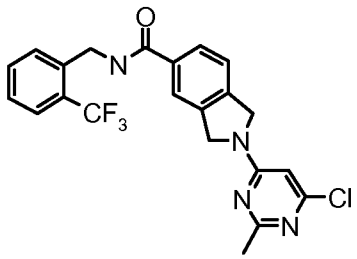
Step 4: <u>*N*-{[2-(trifluoromethyl)phenyl]methyl}-2,3-dihydro-1*H*-isoindole-5-carboxamide</u>



1,1-dimethylethyl 5-[({[2-(trifluoromethyl)phenyl]methyl}amino)carbonyl]-1,3-dihydro-2*H*-isoindole-2-carboxylate (406 mg, 0.966 mmol) was dissolved in dichloromethane (DCM) (3 mL) at room temperature. Afterwards, trifluoroacetic acid (TFA) (3.0 mL, 38.9 mmol) was added to the solution, and the reaction was allowed to stir for 30 minutes after which time it was determined to be complete by LC/MS. The mixture was diluted with 15 mL of DCM and poured into ice cold 1N NaOH (30 mL) and allowed to stir for several minutes in an

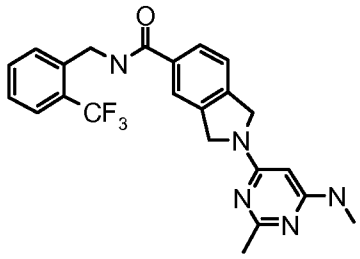
ice bath. The mixture was removed from the ice bath and the organics were extracted, dried (sodium sulfate) and concentrated to give *N*-{[2-(trifluoromethyl)phenyl]methyl}-2,3-dihydro-1*H*-isoindole-5-carboxamide (315 mg, 0.904 mmol, 94 % yield of 92% purity) in the form of a brown oil. MS (ES) m/e 321 [M+H]+.

Step 5: 2-(6-chloro-2-methyl-4-pyrimidinyl)-*N*-{[2-(trifluoromethyl)phenyl]methyl}-2,3-dihydro-1*H*-isoindole-5-carboxamide



4,6-dichloro-2-methylpyrimidine (40.3 mg, 0.247 mmol) and *N*-{[2-(trifluoromethyl)phenyl]methyl}-2,3-dihydro-1*H*-isoindole-5-carboxamide (66 mg, 0.206 mmol) were combined in a 5.0 mL glass reaction tube that was equipped with a magnetic stir bar. The contents of the tube were taken up in 1,4-Dioxane (2.1 mL) and treated with 6N NaOH (0.103 mL, 0.618 mmol). The tube was fitted with a rubber septum and hermetically sealed with a crimped metal foil seal. Using a heating-block, the reaction mixture was magnetically stirred and heated in order to maintain a temperature of 70 °C for 2 hr, after which time it was determined to be complete by LC/MS. The mixture was diluted 10-fold with water, which resulted in the precipitation of the product as an off-white solid. The solid was collected by vacuum filtration, washed several times with ether and allowed to dry under vacuum for several hours. The product, 2-(6-chloro-2-methyl-4-pyrimidinyl)-*N*-{[2-(trifluoromethyl)phenyl]methyl}-2,3-dihydro-1*H*-isoindole-5-carboxamide (73.7 mg, 0.163 mmol, 79 % yield) was recovered as an off-white solid. MS (ES) m/e 447 [M+H]+.

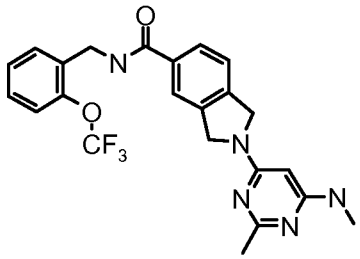
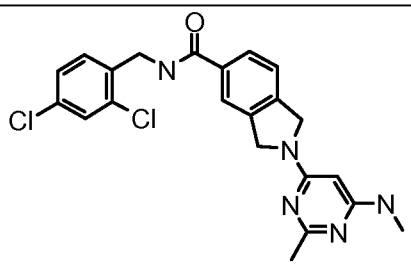
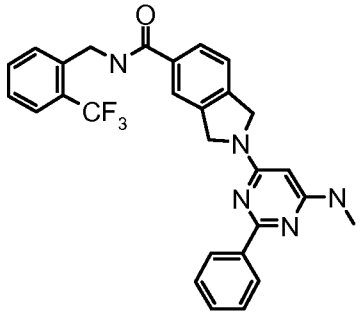
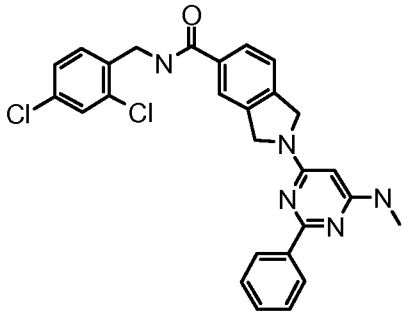
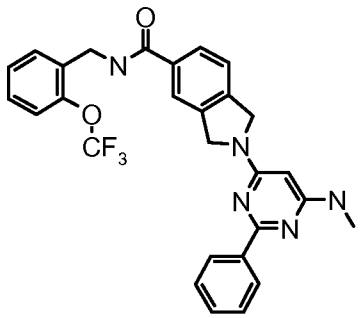
Step 6: 2-[2-methyl-6-(methylamino)-4-pyrimidinyl]-*N*-{[2-(trifluoromethyl)phenyl]methyl}-2,3-dihydro-1*H*-isoindole-5-carboxamide



2-(6-chloro-2-methyl-4-pyrimidinyl)-N-{[2-(trifluoromethyl)phenyl]methyl}-2,3-dihydro-1H-isoindole-5-carboxamide (73.7 mg, 0.163 mmol) and 33% methylamine in EtOH (2.5 mL, 19.8 mmol) were combined in a 5.0 mL glass reaction tube that was equipped with a magnetic stir bar. The tube was fitted with a rubber septum and hermetically sealed with a crimped metal foil seal. The mixture was stirred and heated to 70 °C for four days until the reaction was determined to be complete by LC/MS. The mixture was concentrated to dryness under vacuum and triturated with 6 mL of ether. The product was isolated by vacuum filtration and washed with ether several times. After drying under vacuum overnight, the title compound (51.0 mg, 0.114 mmol, 70 % yield) was obtained in the form of an off-white solid. MS (ES) m/e 442 [M+H]+.

Examples 9-13

The following compounds (Examples **9-13**) were prepared by a method similar to the one described for the preparation of 2-[2-methyl-6-(methylamino)-4-pyrimidinyl]-*N*-{[2-(trifluoromethyl)phenyl]methyl}-2,3-dihydro-1*H*-isoindole-5-carboxamide except using [(2,4-dichlorophenyl)methyl]amine or ({2-[(trifluoromethyl)oxy]phenyl}methyl)amine in place of {[2-(trifluoromethyl)phenyl]methyl}amine in Step 3, or using 4,6-dichloro-2-phenylpyrimidine in place of 4,6-dichloro-2-methylpyrimidine in Step 5. As is appreciated by those skilled in the art, these analogous examples may involve variations in synthetic procedure.

Ex	Structure	Compound Name	Mass LC/MS
9		2-[2-methyl-6-(methylamino)-4-pyrimidinyl]-*N*-({2-[(trifluoromethyl)oxy]phenyl}methyl)-2,3-dihydro-1*H*-isoindole-5-carboxamide	458
10		*N*-[(2,4-dichlorophenyl)methyl]-2-[2-methyl-6-(methylamino)-4-pyrimidinyl]-2,3-dihydro-1*H*-isoindole-5-carboxamide	442
11		2-[6-(methylamino)-2-phenyl-4-pyrimidinyl]-*N*-{[2-(trifluoromethyl)phenyl]methyl}-2,3-dihydro-1*H*-isoindole-5-carboxamide	504
12		*N*-[(2,4-dichlorophenyl)methyl]-2-[6-(methylamino)-2-phenyl-4-pyrimidinyl]-2,3-dihydro-1*H*-isoindole-5-carboxamide	504
13		2-[6-(methylamino)-2-phenyl-4-pyrimidinyl]-*N*-({2-[(trifluoromethyl)oxy]phenyl}methyl)-2,3-dihydro-1*H*-isoindole-5-carboxamide	520

As used above, the phrase "using the general procedure described above" indicates that the procedure used employs similar, but not necessarily identical, reaction conditions to those referred to.

Biological Activity

The compounds according to Formula I are sEH inhibitors. The compounds according to Formula I, therefore, are useful in the treatment of hypertension and other conditions involving sEH activity. As stated above, mEH provides an important detoxification pathway in mammals. Compounds that exhibit pharmacological selectivity for sEH over mEH therefore are desirable in the methods of treatment described below. Accordingly, in one embodiment the invention is directed to a compound according to Formula I wherein the compound exhibits a selectivity ratio (based on IC50) equal to or greater than 10:1 for sEH over mEH. In another embodiment the invention is directed to a compound according to Formula I wherein the compound exhibits a selectivity ratio (based on IC50) equal to or greater than 100:1 for sEH over mEH. In another embodiment the invention is directed to a compound according to Formula I wherein the compound exhibits a selectivity ratio (based on IC50) equal to or greater than 1000:1 for sEH over mEH.

The biological activity of the compounds according to Formula I can be determined using any suitable assay for determining the activity of a candidate compound as an sEH and / or mEH inhibitor, as well as suitable tissue and / or in vivo models.

<u>In vitro fluorescence assay</u>

Inhibition of Soluble Expoxide Hydrolase (sEH) activity is measured in a fluorescent assay based upon the format described by Wolf et al. (Analytical Biochemistry Vol. 355 (2006) pp. 71-80). In the presence of sEH, PHOME ((3-Phenyl-oxiranyl)-acetic acid cyano-(6-methoxy-naphthalen-2-yl)-methyl ester), is hydrolyzed to a diol which goes through an intramolecular cyclization and the release and decomposition of cyanohydrin (products = cyanide and 6-methoxy-2-naphthaldehyde). Production of 6-methoxy-2-naphthaldehyde is monitored at excitation of 360nm and an emission of 465nm.

The assay is used in a quenched assay format by sequentially adding enzyme (5 uL; 200 pM sEH in 25mM Hepes at pH 7.0, 0.01% CHAPS (w/v), 0.005% Casein (w/v); 10 minute ambient pre-incubation after addition) then PHOME substrate (5 ul; 10 uM PHOME substrate in 25mM Hepes at pH 7.0, 0.01% CHAPS (w/v), 0.005% Casein (w/v)) to a 384

well assay plate (Greiner 784076) pre-stamped with 25-100 nL compound at the desired concentration. The reaction is incubated for 30 minutes at room temperature, then quenched by the addition of stop solution (5 uL; 10 mM ZnSO4 in 25mM Hepes at pH 7.0, 0.01% CHAPS (w/v), 0.005% Casein (w/v)). Microtiter plates are centrifuged after each addition for 30 seconds at 500rpm. The fluorescence is measured on an EnVision plate reader platform (Perkin Elmer) using a 360 nm excitation filter, 465 nm emission filter, and 400 nm dichroic filter.

Compounds are first prepared in neat DMSO at a concentration of 10 mM, then diluted as required to achieve the desired assay concentration. For inhibition curves, compounds are diluted using a three fold serial dilution and tested at 11 concentrations (*e.g.* 50 μM-0.8 nM or 25 μM-0.42 nM or 2.5 μM to 42 pM). Curves are analysed using ActivityBase and XLfit, and results are expressed as pIC50 values.

Cell-based sEH inhibitor assay

Cell based sEH inhibition is measured using the 14,15-DHET immunoassay ELISA kit available from Detroit R&D (Cat. No. DH1), according to the following procedure:

- HEK293 cells (BioCat ID 80556) are transduced by sEH BacMam virus to increase sEH expression (other cell lines may be suitable) as follows: One day before the experiment, 1.5 million HEK293 cells (BioCat ID 80556) are seated in 3ml of DMEM/F12 (*with L-Glutamine, with 15mM HEPES, pH7.30, from Media Prep Lab*), with 10% fetal bovine serum (*from SAFC Biosciences, Cat. No.12176-1000M*), no antibiotic, in a 25 cm^2 flask (*from Corning Incorporated, Cat. No.430639*) and 30μL sEH BacMam virus is added. The cells are gently mixed then incubated at 37°C, 5% CO_2, for 24 hours.
- The cells are trypsinized to release them from the growth flask, washed once with PBS, then re-suspended in 5mL DMEM/F12 without phenol red (*from Media Prep lab*). Cell density should be approximately 3 * 10^5 cells/mL (= 300 cells/μL), counted using the Cedex AS^{20} (*from Innovatis*).
- The cells are then diluted in DMEM/F12 to 5.1cells/□L, and 98□L/well (= 500 cells/well) of this cell suspension is transfered to an assay plate (*96 well, clear polystyrene, flat bottom, from Whatman, Cat. No.7701-1350*).
- 2□L of the diluted test compound is then added to the cells in the assay plate. The reaction plate is shaken gently and incubated at room temperature for 30 min, after which 10□L of substrate solution is added (substrate solution is prepared by diluting 1.24□L of 14,15-EET from Cayman Chemical, Cat. No. 50651 with 8.24□L DMEM/F12). The assay plate is then incubated for one hour at room temperature.

- After the 1 hour reaction, the reaction mixture is diluted 3 fold with provided sample dilution buffer (ex. Add 220µL to the 110µL reaction mixture), mixed well, and spun for 5 min at 500rpm.
- 100µL of the diluted reaction mixture is then transferred from the reaction plates to the ELISA plates, and the ELISA is performed according to the instructions provided in the kit.
- IC50s and pIC50s are then calculated. The IC50 can be calculated directly using the 14, 15-DHET concentration or using the % inhibition [% inhibition = 100*(1- (sample DHET – 0 cell DHET) / (500 cells DHET – 0 cell DHET)].
- Compounds are first prepared in neat DMSO at a concentration of 0.5 mM, then diluted as required to achieve the desired assay concentration. For inhibition curves, compounds are diluted using a three fold serial dilution and tested at 9 concentrations (*e.g.* 10 µM-1.5 nM). Curves are analysed using ActivityBase and XLfit, and results are expressed as pIC50 values.

Biological Activity Results

Examples 1-7 were tested for activity as sEH inhibitors. Where the assay for a particular compound had been performed two or more times, the following conclusion regarding their activities is based on the average of individual experiments: All tested compounds (Examples 1–13) were found to have an IC50 in the range of 0.1 and 10,000 nM.

Methods of Use

The compounds of the invention inhibit the sEH enzyme and can be useful in the treatment of conditions wherein the underlying pathology is (at least in part) attributable to sEH involvement or in conditions wherein sEH inhibition offers some clinical benefit even though the underlying pathology is not (even in part) attributable to sEH involvement. Examples of such conditions include hypertension, organ failure / damage (including heart failure, renal failure, and liver failure), cardiac and renal fibrosis, peripheral vascular disease (including ischemic limb disease, intermittent claudication, endothelial dysfunction, erectile dysfunction, Raynaud's disease, and diabetic vasculopathies e.g. retinopathy), atherothrombotic disorders (including coronary artery disease, coronary vasospasm, angina, stroke, myocardial ischemia, myocardial infarction, and hyperlipidemia), metabolic disorders (including diabetes), and inflammatory disorders (including arthritis, inflammatory pain, overactive bladder, asthma, and COPD). Accordingly, in another aspect the invention is directed to methods of treating such conditions.

Essential hypertension is commonly associated with the development of significant end organ damage such as renal, endothelial, myocardial, and erectile dysfunction. Such conditions occur “secondary” to the elevated systemic arterial blood pressure. Secondary conditions may be prevented by treatment of the underlying (“primary”) cause. Accordingly, in another aspect the invention is directed to methods of preventing such secondary conditions.

Heart failure is a complex heterogenous disorder characterized by reduced cardiac output, resulting in the inability of the heart to meet perfusion demands of the body. Cardiac proinflammatory cytokine recruitment and maladaptive cardiac hypertrophy, fibrosis and apoptosis/necrosis are factors associated with the progression of heart failure. Compounds of the invention are directed to methods of treating such conditions.

In addition, sEH is indirectly involved in the regulation of platelet function through its effect on EETs. Drugs that inhibit platelet aggregation are believed to decrease the risk of atherthrombotic events, such as myocardial infarction and stroke, in patients with established cardiovascular atherosclerotic disease. Accordingly, in another aspect the invention is directed to methods of preventing atherothrombotic events, such as myocardial infarction and stroke in patients with a history of recent myocardial infarction, stroke, transient ischemic attacks, unstable angina, or atherosclerosis.

The methods of treating and the methods of preventing described above comprise administering a safe and effective amount of a compound of the invention to a patient in need thereof.

As used herein, "treatment" in reference to a condition means: (1) the amelioration or prevention of the condition being treated or one or more of the biological manifestations of the condition being treated, (2) the interference with (a) one or more points in the biological cascade that leads to or is responsible for the condition being treated or (b) one or more of the biological manifestations of the condition being treated, or (3) the alleviation of one or more of the symptoms or effects associated with the condition being treated.

As indicated above, “treatment” of a condition includes prevention of the condition. The skilled artisan will appreciate that "prevention" is not an absolute term. In medicine, "prevention" is understood to refer to the prophylactic administration of a drug to substantially diminish the likelihood or severity of a condition or biological manifestation thereof, or to delay the onset of such condition or biological manifestation thereof.

As used herein, "safe and effective amount" in reference to a compound of the invention or other pharmaceutically-active agent means an amount of the compound sufficient to significantly induce a positive modification in the condition to be treated but low enough to avoid serious side effects (at a reasonable benefit/risk ratio) within the scope of sound medical judgment. A safe and effective amount of a compound of the invention will vary with the particular compound chosen (e.g. consider the potency, efficacy, and half-life of the compound); the route of administration chosen; the condition

being treated; the severity of the condition being treated; the age, size, weight, and physical condition of the patient being treated; the medical history of the patient being treated; the duration of the treatment; the nature of concurrent therapy; the desired therapeutic effect; and like factors, but can nevertheless be determined by the skilled artisan.

As used herein, "patient" refers to a human or other animal.

The compounds of the invention may be administered by any suitable route of administration, including both systemic administration and topical administration. Systemic administration includes oral administration, parenteral administration, transdermal administration, rectal administration, and administration by inhalation. Parenteral administration refers to routes of administration other than enteral, transdermal, or by inhalation, and is typically by injection or infusion. Parenteral administration includes intravenous, intramuscular, and subcutaneous injection or infusion. Inhalation refers to administration into the patient's lungs whether inhaled through the mouth or through the nasal passages. Topical administration includes application to the skin as well as intraocular, otic, intravaginal, and intranasal administration.

The compounds of the invention may be administered once or according to a dosing regimen wherein a number of doses are administered at varying intervals of time for a given period of time. For example, doses may be administered one, two, three, or four times per day. Doses may be administered until the desired therapeutic effect is achieved or indefinitely to maintain the desired therapeutic effect. Suitable dosing regimens for a compound of the invention depend on the pharmacokinetic properties of that compound, such as absorption, distribution, and half-life, which can be determined by the skilled artisan. In addition, suitable dosing regimens, including the amount administered and the duration such regimens are administered, for a compound of the invention depend on the condition being treated, the severity of the condition being treated, the age and physical condition of the patient being treated, the medical history of the patient to be treated, the nature of concurrent therapy, the particular route of administration chosen, the desired therapeutic effect, and like factors within the knowledge and expertise of the skilled artisan. It will be further understood by such skilled artisans that suitable dosing regimens may require adjustment given an individual patient's response to the dosing regimen or over time as individual patient needs change. Typical daily dosages range from 1 mg to 1000 mg.

Additionally, the compounds of the invention may be administered as prodrugs. As used herein, a "prodrug" of a compound of the invention is a functional derivative of the compound which, upon administration to a patient, eventually liberates the compound of

the invention in vivo. Administration of a compound of the invention as a prodrug may enable the skilled artisan to do one or more of the following: (a) modify the onset of the compound in vivo; (b) modify the duration of action of the compound in vivo; (C) modify the transportation or distribution of the compound in vivo; (d) modify the solubility of the compound in vivo; and (e) overcome or overcome a side effect or other difficulty encountered with the compound. Typical functional derivatives used to prepare prodrugs include modifications of the compound that are chemically or enzymatically cleaved in vivo. Such modifications, which include the preparation of phosphates, amides, esters, thioesters, carbonates, and carbamates, are well known to those skilled in the art.

Compositions

The compounds of the invention will normally, but not necessarily, be formulated into a pharmaceutical composition prior to administration to a patient. Accordingly, in another aspect the invention is directed to pharmaceutical compositions comprising a compound of the invention and a pharmaceutically-acceptable excipient.

The pharmaceutical compositions of the invention may be prepared and packaged in bulk form wherein a safe and effective amount of a compound of the invention can be extracted and then given to the patient such as with powders, syrups, and solutions for injection. Alternatively, the pharmaceutical compositions of the invention may be prepared and packaged in unit dosage form wherein each physically discrete unit contains a safe and effective amount of a compound of the invention. When prepared in unit dosage form, the pharmaceutical compositions of the invention typically contain from 1 mg to 1000 mg.

The pharmaceutical compositions of the invention typically contain one compound of the invention. However, in certain embodiments, the pharmaceutical compositions of the invention contain more than one compound of the invention. For example, in certain embodiments the pharmaceutical compositions of the invention contain two compounds of the invention. In addition, the pharmaceutical compositions of the invention may optionally further comprise one or more additional pharmaceutically active compounds. Conversely, the pharmaceutical compositions of the invention typically contain more than one pharmaceutically-acceptable excipient. However, in certain embodiments, the pharmaceutical compositions of the invention contain one pharmaceutically-acceptable excipient.

As used herein, "pharmaceutically-acceptable excipient" means a pharmaceutically acceptable material, composition or vehicle involved in giving form or consistency to the pharmaceutical composition. Each excipient must be compatible with the other ingredients of the pharmaceutical composition when commingled such that

interactions which would substantially reduce the efficacy of the compound of the invention when administered to a patient and interactions which would result in pharmaceutical compositions that are not pharmaceutically acceptable are avoided. In addition, each excipient must of course be of sufficiently high purity to render it pharmaceutically-acceptable.

The compound of the invention and the pharmaceutically-acceptable excepient or excepients will typically be formulated into a dosage form adapted for administration to the patient by the desired route of administration. For example, dosage forms include those adapted for (1) oral administration such as tablets, capsules, caplets, pills, troches, powders, syrups, elixers, suspensions, solutions, emulsions, sachets, and cachets; (2) parenteral administration such as sterile solutions, suspensions, and powders for reconstitution; (3) transdermal administration such as transdermal patches; (4) rectal administration such as suppositories; (5) inhalation such as aerosols and solutions; and (6) topical administration such as creams, ointments, lotions, solutions, pastes, sprays, foams, and gels.

Suitable pharmaceutically-acceptable excipients will vary depending upon the particular dosage form chosen. In addition, suitable pharmaceutically-acceptable excipients may be chosen for a particular function that they may serve in the composition. For example, certain pharmaceutically-acceptable excipients may be chosen for their ability to facilitate the production of uniform dosage forms. Certain pharmaceutically-acceptable excipients may be chosen for their ability to facilitate the production of stable dosage forms. Certain pharmaceutically-acceptable excipients may be chosen for their ability to facilitate the carrying or transporting the compound or compounds of the invention once administered to the patient from one organ, or portion of the body, to another organ, or portion of the body. Certain pharmaceutically-acceptable excipients may be chosen for their ability to enhance patient compliance.

Suitable pharmaceutically-acceptable excipients include the following types of excipients: Diluents, fillers, binders, disintegrants, lubricants, glidants, granulating agents, coating agents, wetting agents, solvents, co-solvents, suspending agents, emulsifiers, sweetners, flavoring agents, flavor masking agents, coloring agents, anticaking agents, hemectants, chelating agents, plasticizers, viscosity increasing agents, antioxidants, preservatives, stabilizers, surfactants, and buffering agents. The skilled artisan will appreciate that certain pharmaceutically-acceptable excipients may serve more than one function and may serve alternative functions depending on how much of the excipient is present in the formulation and what other ingredients are present in the formulation.

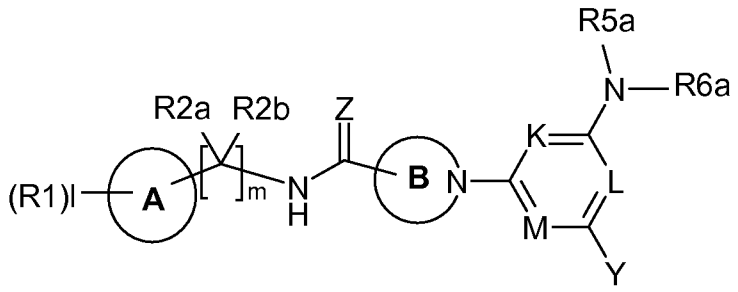
Skilled artisans possess the knowledge and skill in the art to enable them to select suitable pharmaceutically-acceptable excipients in appropriate amounts for use in the invention. In addition, there are a number of resources that are available to the skilled artisan which describe pharmaceutically-acceptable excipients and may be useful in selecting suitable pharmaceutically-acceptable excipients. Examples include Remington's Pharmaceutical Sciences (Mack Publishing Company), The Handbook of Pharmaceutical Additives (Gower Publishing Limited), and The Handbook of Pharmaceutical Excipients (the American Pharmaceutical Association and the Pharmaceutical Press).

The pharmaceutical compositions of the invention are prepared using techniques and methods known to those skilled in the art. Some of the methods commonly used in the art are described in Remington's Pharmaceutical Sciences (Mack Publishing Company).

In one aspect, the invention is directed to a solid oral dosage form such as a tablet or capsule comprising a safe and effective amount of a compound of the invention and a diluent or filler. Suitable diluents and fillers include lactose, sucrose, dextrose, mannitol, sorbitol, starch (e.g. corn starch, potato starch, and pre-gelatinized starch), cellulose and its derivatives (e.g. microcrystalline cellulose), calcium sulfate, and dibasic calcium phosphate. The oral solid dosage form may further comprise a binder. Suitable binders include starch (e.g. corn starch, potato starch, and pre-gelatinized starch), gelatin, acacia, sodium alginate, alginic acid, tragacanth, guar gum, povidone, and cellulose and its derivatives (e.g. microcrystalline cellulose). The oral solid dosage form may further comprise a disintegrant. Suitable disintegrants include crospovidone, sodium starch glycolate, croscarmelose, alginic acid, and sodium carboxymethyl cellulose. The oral solid dosage form may further comprise a lubricant. Suitable lubricants include stearic acid, magnesuim stearate, calcium stearate, and talc.

What is claimed is:

1. A compound according to Formula I:



Formula I

wherein:

A is phenyl, monocyclic heteroaryl, or C5-C6 cycloalkyl;

when A is phenyl or monocyclic heteroaryl each R1 is selected from the group consisting of: halo, -CN, R14, R15, R16, R17, R18, R19, -ORb, -C(O)ORc, -C(O)NRcRc, -NRcRc, -NRcC(O)Rb, -NRcS(O_2)Ra, -SRb, -S(O_2)Ra, and -S(O_2)NRcRc;

when A is C5-C6 cycloalkyl each R1 is selected from the group consisting of: Ra, -ORb, -C(O)ORc, -C(O)NRcRc, -NRcRc, and -NRcC(O)Rb;

each R14 is C1-C6 alkyl optionally substituted with one or more substituents selected from the group consisting of: halo, -ORd, and -NRfRf;

each R15 is C3-C6 cycloalkyl optionally substituted with one or more substituents selected from the group consisting of: halo, -ORd, -NRfRf, C1-C3 alkyl, and C1-C3 haloalkyl;

each R16 is monocyclic heterocycloalkyl optionally substituted with one or more C1-C3 alkyl;

each R17 is phenyl optionally substituted with one or more substituents selected from the group consisting of: halo, -CN, C1-C3 alkyl, C1-C3 haloalkyl, -ORd, and -NRfRf;

each R18 is monocyclic heteroaryl optionally substituted with one or more substituents selected from the group consisting of: halo, -CN, C1-C3 alkyl, C1-C3 haloalkyl, -ORd, and -NRfRf;

each R19 is C1-C3 alkyl substituted with R13, R14, R15, or R16;

l is an integer from 0 to 5;

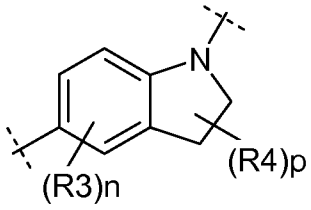
each R2a is H or C1-C3 alkyl;

each R2b is H or C1-C3 alkyl;

m is 1 or 2;

Z is O or S;

B is B1, B2, B3, B4, B5, B6, B7, B8, B9, B10, or B11 wherein

B1 is 

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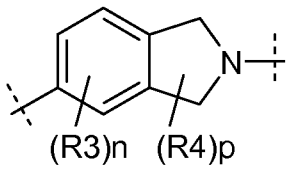
B2 is 

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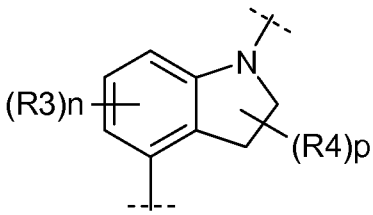
B3 is 

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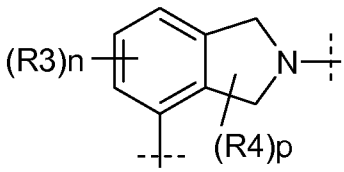
B4 is 

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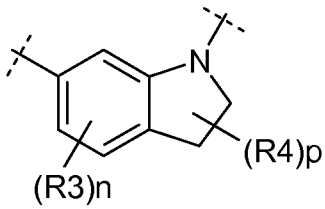
B5 is 

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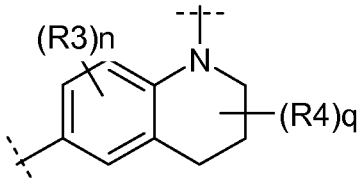
B6 is 

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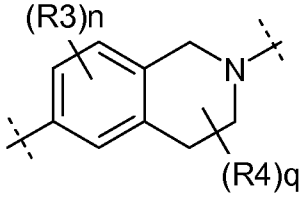
B7 is 

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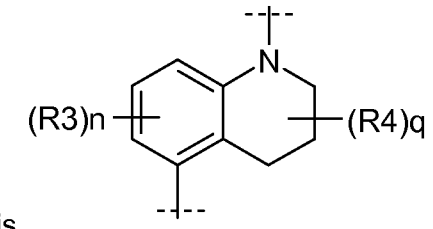
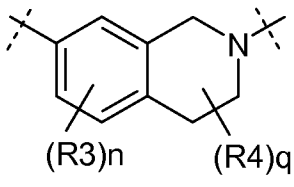
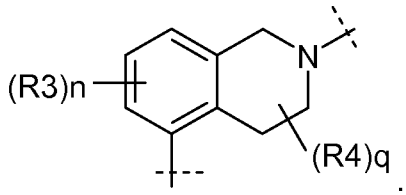
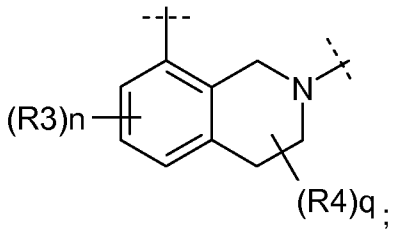
B8 is  ;

B9 is  ;

B10 is  ;

B11 is  ;

R3, if present, is a substituent on the phenyl ring of said B ring system and each R3 is selected from the group consisting of: halo and C1-C3 alkyl;

n is an integer from 0 to 3;

R4, if present, is a substituent on the Nitrogen-containing ring of said B ring system and each R4 is C1-C3 alkyl;

p is an integer from 0 to 2;

q is an integer from 0 to 4;

K, L, and M are each N or CR13 provided that one and only one of K, L and M is CR13;

Y is H, OH, R7, R8, R9, R10, R11, R12, or -NR5bR6b;

R5a and R5b are each H, R51, R52, R53, R54, R55, -C(O)Rb, -C(O)NRcRc, $-S(O_2)Ra$, or $-S(O_2)NRcRc$;

each R51 is C1-C6 alkyl optionally substituted with one or more substituents selected from the group consisting of: halo, -ORd, -SRk, -C(O)ORc, -C(O)NReRe, -NReRe, Rg, Rh, Ri, Rj;

each R52 is C3-C6 cycloalkyl optionally substituted with one or more substituents selected from the group consisting of: halo, -ORd, -SRd, -C(O)ORc, -C(O)NReRe, -NReRe, C1-C3 alkyl, and C1-C3 haloalkyl;

R53 is monocyclic heterocycloalkyl optionally substituted with one or more C1-C3 alkyl;

R54 is phenyl optionally substituted with one or more substituents selected from the group consisting of: halo, CN, Ra, -ORb, -C(O)ORc, -C(O)NRcRc, -NRcRc, -NRcC(O)Rb, -NRcS(O_2)Ra, -SRb, -S(O_2)Ra, and -S(O_2)NReRe;

R55 is monocyclic heteroaryl optionally substituted with one or more substituents selected from the group consisting of: halo, -CN, C1-C3 alkyl, C1-C3 haloalkyl, -ORd, and -NReRe;

R6a and R6b are each H, R51, or R52; or

R5a and R6a and/or R5b and R6b, independently in each instance, taken together with the nitrogen atom to which they are attached form a saturated monocyclic ring having from 5 to 7 member atoms wherein said ring optionally contains one additional heteroatom as a member atom and wherein said ring is optionally substituted with one or more substituents selected from the group consisting of: C1-C3 alkyl, -ORd, and -NRfRf;

R7 is C1-C8 alkyl optionally substituted with one or more substituents selected from the group consisting of: halo, -ORd, -SRd, -NReRe, C3-C6 cycloalkyl, Ri, and Rj;

R8 is C3-C6 cycloalkyl optionally substituted with one or more substituents selected from the group consisting of: halo, -ORd, -SRd, -NReRe, C1-C3 alkyl, and C1-C3 haloalkyl;

R9 monocyclic heterocycloalkyl optionally substituted with one or more C1-C3 alkyl;

R10 is phenyl optionally substituted with one or more substituents selected from the group consisting of: halo, CN, Ra, -ORb, -C(O)ORc, -C(O)NReRe, -NReRe, -NRcC(O)Rb, -NRcS(O_2)Ra, -SRb, -S(O_2)Ra, and -S(O_2)NRcRc

R11 is heteroaryl optionally substituted with one or more substituents selected from the group consisting of: halo, CN, Ra, -ORb, -C(O)ORc, -C(O)NReRe, -NReRe, -NRcC(O)Rb, -NRcS(O_2)Ra, -SRb, -S(O_2)Ra, and -S(O_2)NRcRc;

R12 is -OR8, -OR9, -OR10, -OR11, -OR12, -SR8, -SR9, -SR10, SR11. –SR12;

R13 is H, R7, R8, R9, R10, R11, -CONRlRl, -NRlRl, -NRcCORm, -NRcSO_2Rm;

each Ra is C1-C6 alkyl or C1-C6 haloalkyl;

each Rb is H, C1-C6 alkyl or C1-C6 haloalkyl;

each Rc is H or C1-C6 alkyl;

each Rd is H, C1-C3 alkyl or C1-C3 haloalkyl;

each Re is H, C1-C3 alkyl, or -CH_2-CF_3; or

both Re groups, independently in each instance, taken together with the nitrogen atom to which they are attached form a saturated monocyclic ring having from 5 to 7 member atoms wherein said ring optionally contains one additional heteroatom as a member atom and wherein said ring is optionally substituted with one or more substituents selected from the group consisting of: C1-C3 alkyl, -ORd, and -NRfRf;

each Rf is H or C1-C3 alkyl.

each Rg is C3-C6 cycloalkyl optionally substituted with one or more substituents selected from the group consisting of: halo, -ORd, -SRd, -C(O)ORc, -C(O)NReRe, -NReRe, and C1-C3 alkyl;

each Rh is monocyclic heterocycloalkyl optionally substituted with one or more C1-C3 alkyl;

each Ri is phenyl optionally substituted with one or more substituents selected from the group consisting of: halo, -CN, C1-C3 alkyl, C1-C3 haloalkyl, -ORd, and -NReRe;

each Rj is monocyclic heteroaryl optionally substituted with one or more substituents selected from the group consisting of: halo, -CN, C1-C3 alkyl, C1-C3 haloalkyl, -ORd, and -NReRe;

each Rk is H, C1-C3 alkyl, C1-C3 haloalkyl, or benzyl optionally substituted with one or more substituents selected from the group consisting of: halo, -CN, C1-C3 alkyl, C1-C3 haloalkyl, -ORd, and -NReRe;

each Rl is H, Rh, Ri, Rj, or Rn; or

both Rl groups, independently in each instance, taken together with the nitrogen atom to which they are attached form a saturated monocyclic ring having from 5 to 7 member atoms wherein said ring optionally contains one additional heteroatom as a member atom and wherein said ring is optionally substituted with one or more substituents selected from the group consisting of: C1-C3 alkyl, -ORd, and -NRfRf;

Rm is Rh, Ri, Rj, or Rn; and

each Rn is -CH_2-C1-C4 haloalkyl or C1-C6 alkyl optionally substituted with one or more substituents selected from the group consisting of: Rh, Ri, and Rj;

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 wherein:

A is phenyl, thiophenyl, or pyridyl;

R1 is CF_3, halo, OCF_3, CN, OC_1-C_6 alkyl, morpholino, CO_2H, or $N(CH_3)_2$;

l is 1, 2, or 3;

B is B1, B2, B6, and B7;

R2a and R2b and hydrogen;

n is 0;

m is 1;

Z is O;

Y is C1- C3 alkyl, phenyl, thiophenyl, or pyridyl; wherein the phenyl, thiophenyl or pyridyl may be substituted by -CO_2H, SO_2Me, CF_3, halo, or CN;

R5a is hydrogen or C1 – C6 alkyl; and

R6a is hydrogen or C1 – C6 alkyl;

or a pharmaceutically acceptable salt thereof.

3. A compound of claim 1 wherein:

A is phenyl;

R1 is CF_3, halo, OCF_3, CN, OC_1-C_6 alkyl, or $N(CH_3)_2$, or morpholino;

l is 1, or 2;

B is B2;

R2a and R2b and hydrogen;

L and M are N;

n is 0;

m is 1;

Z is O;

Y is methyl or phenyl;

R5a is hydrogen; and

R6a is hydrogen;

or a pharmaceutically acceptable salt thereof.

4. A compound of claim 1 chosen from:

2-[4-(dimethylamino)-6-methyl-2-pyrimidinyl]-*N*-{[2-(trifluoromethyl)phenyl]methyl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide;
1-[2-methyl-6-(methylamino)-4-pyrimidinyl]-*N*-({2-[(trifluoromethyl)oxy]phenyl}methyl)-2,3-dihydro-1*H*-indole-5-carboxamide;
N-[(2,4-dichlorophenyl)methyl]-1-[6-(methylamino)-2-phenyl-4-pyrimidinyl]-2,3-dihydro-1*H*-indole-5-carboxamide;
N-[(2,4-dichlorophenyl)methyl]-1-[2-methyl-6-(methylamino)-4-pyrimidinyl]-2,3-dihydro-1H-indole-5-carboxamide;

1-[2-methyl-6-(methylamino)-4-pyrimidinyl]-*N*-{[2-(trifluoromethyl)phenyl]methyl}-2,3-dihydro-1*H*-indole-5-carboxamide;
1-[6-(methylamino)-2-phenyl-4-pyrimidinyl]-*N*-({2-[(trifluoromethyl)oxy]phenyl}methyl)-2,3-dihydro-1*H*-indole-5-carboxamide;
1-[6-(methylamino)-2-phenyl-4-pyrimidinyl]-*N*-{[2-(trifluoromethyl)phenyl]methyl}-2,3-dihydro-1*H*-indole-5-carboxamide;
N-[(2,4-dichlorophenyl)methyl]-2-[2-methyl-6-(methylamino)-4-pyrimidinyl]-2,3-dihydro-1H-isoindole-5-carboxamide;
2-[2-methyl-6-(methylamino)-4-pyrimidinyl]-N-{[2-(trifluoromethyl)phenyl]methyl}-2,3-dihydro-1H-isoindole-5-carboxamide;
2-[2-methyl-6-(methylamino)-4-pyrimidinyl]-N-({2-[(trifluoromethyl)oxy]phenyl}methyl)-2,3-dihydro-1H-isoindole-5-carboxamide;
N-[(2,4-dichlorophenyl)methyl]-2-[6-(methylamino)-2-phenyl-4-pyrimidinyl]-2,3-dihydro-1H-isoindole-5-carboxamide;
2-[6-(methylamino)-2-phenyl-4-pyrimidinyl]-N-{[2-(trifluoromethyl)phenyl]methyl}-2,3-dihydro-1H-isoindole-5-carboxamide;
2-[6-(methylamino)-2-phenyl-4-pyrimidinyl]-N-({2-[(trifluoromethyl)oxy]phenyl}methyl)-2,3-dihydro-1H-isoindole-5-carboxamide;
or a pharmaceutically acceptable salt thereof.

5. A pharmaceutical composition comprising a compound or salt according to any of the preceding claims and one or more pharmaceutically-acceptable excipient.

6. A method of treating hypertension, heart failure, renal failure, liver failure, peripheral vascular disease, coronary artery disease, myocardial ischemia, angina, hyperlipidemia, diabetes, hypergylcemia, metabolic syndrome, obesity, myocardial infarction, diabetic nephropathy, diabetic heart failure, dyslipidemia, and stroke which comprises administering to a human in need thereof, a compound of Formula I of claims 1-5.

7. A method according to claim 6 wherein the compound of Formula I is administered orally.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/85505

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/535 (2009.01)
USPC - 514/231.2
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8)-A61K 31/535 (2009.01)
USPC-514/231.2, 235.8, 406; 546/124, 268.1, 275.7

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(PGPB,USPT,USOC,EPAB,JPAB); PubCHEM; Google Patents; Google Scholar
pyrimidinyl, carboxamide, methylamino, isoquinone, trifluoromethyl, epoxide, hydrolase, inhibitor, soluble, indole, isoindole, phenyl

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2006/0276515 A1 (CYWIN et al.) 07 December 2006 (07.12.2006) (para [0032], Table II)	1-5
A	US 6,890,925 B2 (INGRAHAM et al.) 10 May 2005 (10.05.2005) (cols 6-9)	1-5
A	US 6,831,082 B2 (INGRAHAM et al.) 14 December 2004 (14.12.2004) (cols 6-9)	1-5

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 January 2009 (17.01.2009)	10 FEB 2009

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/85505

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 6, 7
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.