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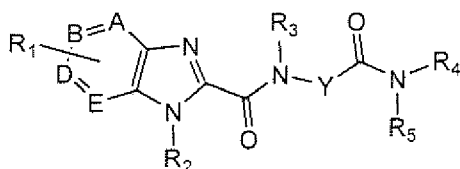
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(54) Title: BENZIMIDAZOLE CARBOXAMIDE DERIVATIVES



I

(57) Abstract: Benzimidazole carboxamide derivatives
of Formula I are provided: Formula (I) in which the
variables are as described herein. Such compounds may
be used to modulate bradykinin receptor activity *in vivo*
or *in vitro*, and are particularly useful in the treatment
of conditions responsive to B₁ modulation in humans,
domesticated companion animals and livestock animals,
including inflammation and pain. Pharmaceutical

compositions and methods for using them to treat such disorders are provided, as are methods for using such ligands for receptor
localization studies and various *in vitro* assays.



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BENZIMIDAZOLE CARBOXAMIDE DERIVATIVES

FIELD OF THE INVENTION

This invention relates generally to benzimidazole carboxamide derivatives, and to the use of
5 such compounds to treat conditions responsive to bradykinin receptor-1 (B_1) modulation. The
invention further relates to the use of such compounds as reagents for the identification of other
agents that bind to B_1 , and as probes for the detection and localization of B_1 .

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application 60/825,308, filed September
10 12, 2006, which is hereby incorporated by reference in its entirety.

DESCRIPTION OF THE SEQUENCE LISTING

SEQ ID NO:1	B_1 PCR primer number 1
SEQ ID NO:2	B_1 PCR primer number 2
SEQ ID NO:3	B_1 PCR primer number 3
15 SEQ ID NO:4	B_1 PCR primer number 4

BACKGROUND OF THE INVENTION

Millions of people throughout the world suffer debilitating and incapacitating pain. Current
treatments for pain can be beneficial, but such treatments are not completely effective, and typically
20 have undesirable side effects. For example, non-steroidal anti-inflammatory drugs are commonly
used, but are only moderately effective against pain, and have serious renal and gastrointestinal side
effects at high doses. Opiates, such as morphine, are potent analgesics, but their usefulness is limited
because of adverse side effects, such as physical addictiveness and withdrawal properties, as well as
respiratory depression, mood changes, and decreased intestinal motility with concomitant
25 constipation, nausea, vomiting, and alterations in the endocrine and autonomic nervous systems.
There is thus a need for effective agents for the treatment of pain.

Bradykinin (BK) is a nonapeptide (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg) that functions
in cardiovascular homeostasis, contraction and relaxation of smooth muscles, inflammation and pain.
The effects of BK are mediated by specific G protein-coupled BK receptors, of which there are at
30 least two distinct subtypes termed B_1 and B_2 . The B_2 receptor is expressed constitutively in a variety
of tissues. In contrast, the B_1 receptor is inducibly expressed in response to pathophysiological
conditions such as inflammation, pain, trauma, bacterial infection, burns and shock.

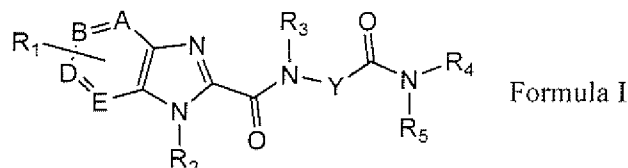
Accordingly, B_1 is a particularly attractive drug target for these and other conditions, and
agents that act at this receptor may be targeted specifically to injured tissues, with minimal effects in

normal tissues. In addition, compounds that bind to B₁ and/or modulate the activity of B₁ also find use as research tools.

There is thus a need in the art for small molecule modulators of B₁ activity. The present invention fulfills this need and provides further related advantages.

5 SUMMARY OF THE INVENTION

The present invention provides benzimidazole carboxamide derivatives that satisfy Formula I:



or are a pharmaceutically acceptable salt, solvate (*e.g.*, hydrate) or ester of such a compound.

Within Formula I:

A, B, D and E are each CH or N; preferably such that no more than one of A, B, D and E is N;

- 10 Y is a group of the formula (CH₂)_r-Q-(CH₂)_p, which is optionally substituted and is preferably substituted with from 0 to 4 substituents independently chosen from (i) amino, hydroxy, cyano, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl and C₁-C₆haloalkyl; and (ii) substituents of the same carbon atom or adjacent carbon atoms that are taken together to form C₃-C₆cycloalkyl, wherein:

- 15 Q is absent, CHR₁₀, CH=CH, O, S or NR₁₀; wherein R₁₀ is hydrogen, C₁-C₆alkyl or taken together with R₃ to form a 4- to 7-membered optionally substituted heterocycloalkyl; and r and p are independently chosen integers ranging from 0 to 6; preferably such that the sum of r and p ranges from 1 to 6;

- R₁ represents from 0 to 4 substituents; preferably each substituent is independently chosen from halogen, hydroxy, cyano, amino, nitro, aminocarbonyl, aminosulfonyl, -COOH, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, C₁-C₆alkoxy, C₁-C₆alkylthio, C₁-C₆alkylsulfinyl, C₁-C₆alkoxycarbonyl, C₁-C₆alkylsulfonylC₀-C₄alkyl, and mono- or di-(C₁-C₆alkyl)aminoC₀-C₄alkyl;

- 20 R₂ is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, mono- or di-(C₁-C₆alkyl)aminoC₁-C₄alkyl, (4- to 7-membered heterocycloalkyl)C₀-C₄alkyl, phenylC₀-C₄alkyl or (5- or 6-membered heteroaryl)C₀-C₄alkyl, each of which is substituted with from 0 to 4 substituents independently chosen from amino, halogen, hydroxy, cyano, oxo, C₁-C₆alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl and C₁-C₆alkoxy;

R₃ is hydrogen, C₁-C₆alkyl or taken together with R₁₀ to form a 4- to 7-membered optionally substituted heterocycloalkyl; and

- 30 R₄ and R₅ are:

(i) independently chosen from C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, (4- to 7-membered heterocycloalkyl)C₀-C₄alkyl, phenylC₀-C₄alkyl and (5- to 10-membered heteroaryl)C₀-C₄alkyl; or

(ii) taken together to form a 4- to 7-membered heterocycloalkyl;

each of which (i) and (ii) is optionally substituted and is preferably substituted with from 0 to 6 substituents independently chosen from:

(a) halogen, hydroxy, cyano, amino, nitro, -COOH, aminocarbonyl and oxo; and

(b) C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆alkoxy, (C₃-C₈cycloalkyl)C₀-C₄alkyl, mono- or di-(C₁-C₆alkyl)amino, (4- to 7-membered heterocycloalkyl)C₀-C₄alkyl, phenylC₀-C₄alkyl, (5- or 6-membered heteroaryl)C₀-C₄alkyl, and substituents that are taken together to form a fused or spiro 5- to 7-membered ring;

each of which (b) is substituted with from 0 to 4 substituents independently chosen from:

(1) amino, halogen, hydroxy, cyano, -COOH, aminocarbonyl and oxo; and

(2) C₁-C₆alkyl, C₁-C₆alkoxy, C₂-C₆alkyl ether, mono- or di-(C₁-C₆alkyl)aminoC₀-C₄alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, (4- to 7-membered heterocycloalkyl)C₀-C₄alkyl, phenylC₀-C₄alkyl and (5- or 6-membered heteroaryl)C₀-C₄alkyl, each of which is substituted with from 0 to 4 substituents independently chosen from halogen, oxo and C₁-C₄alkyl.

Within certain aspects, benzimidazole carboxamide derivatives of Formula I, and other Formulas provided herein, are B₁ modulators and exhibit a K_i of no greater than 5 micromolar, 2 micromolar, 1 micromolar, 500 nanomolar, 100 nanomolar, 50 nanomolar or 10 nanomolar in a B₁ binding assay and/or have an EC₅₀ or IC₅₀ value of no greater than 5 micromolar, 2 micromolar, 1 micromolar, 500 nanomolar, 100 nanomolar, 50 nanomolar or 10 nanomolar in an assay for determination of B₁ agonist or antagonist activity.

In certain embodiments, B₁ modulators provided herein are B₁ antagonists; preferably such antagonists exhibit no detectable B₁ agonist activity.

Within certain aspects, benzimidazole carboxamide derivatives of Formula I are labeled with a detectable marker (*e.g.*, radiolabeled or fluorescein conjugated).

The present invention further provides, within other aspects, pharmaceutical compositions comprising at least one benzimidazole carboxamide derivative of Formula I in combination with a physiologically acceptable carrier or excipient.

The present invention further provides, within other aspects, pharmaceutical compositions comprising at least one benzimidazole carboxamide derivative as described herein in combination with a physiologically acceptable carrier or excipient.

Methods are further provided for inhibiting agonist-induced B₁ activity. Within certain such aspects, the inhibition takes place *in vitro*. Such methods comprise contacting a B₁ receptor with at least one B₁ antagonist as described herein, under conditions and in an amount or concentration

sufficient to detectably inhibit agonist-induced B₁ activity. Within other such aspects, the B₁ receptor is in a patient. Such methods comprise contacting cells expressing a B₁ receptor in a patient with at least one B₁ antagonist as described herein in an amount or concentration that would be sufficient to detectably inhibit agonist-induced B₁ activity in cells expressing a cloned B₁ receptor *in vitro*.

5 The present invention further provides methods for treating a condition responsive to B₁ receptor modulation in a patient, comprising administering to the patient a therapeutically effective amount of at least one benzimidazole carboxamide derivative of Formula I.

10 Within other aspects, methods are provided for treating pain in a patient, comprising administering to a patient suffering from (or at risk for) pain a therapeutically effective amount of at least one benzimidazole carboxamide derivative of Formula I. Pain conditions that may be treated include, but are not limited to, inflammatory pain, acute pain, dental pain, back pain, surgical pain, headache, neuropathic pain, and pain associated with osteoarthritis or trauma.

15 Within further aspects, the present invention provides methods for determining the presence or absence of B₁ in a sample, comprising: (a) contacting a sample with a benzimidazole carboxamide derivative of Formula I under conditions that permit binding of the compound to B₁; and (b) detecting a signal indicative of a level of the compound bound to B₁.

In yet another aspect, the present invention provides methods of preparing the compounds disclosed herein, including the intermediates.

20 These and other aspects of the present invention will become apparent upon reference to the following detailed description.

DETAILED DESCRIPTION

As noted above, the present invention provides benzimidazole carboxamide derivatives, which may be used *in vitro* or *in vivo* in a variety of contexts, as described herein.

TERMINOLOGY

25 Compounds are generally described herein using standard nomenclature. For compounds having asymmetric centers, it should be understood that (unless otherwise specified) all of the optical isomers and mixtures thereof are encompassed. In addition, compounds with carbon-carbon double bonds may occur in Z- and E- forms, with all isomeric forms of the compounds being included in the present invention unless otherwise specified. If a compound exists in various tautomeric forms, a
30 recited compound is not limited to any one specific tautomer, but rather is intended to encompass all tautomeric forms. Certain compounds are described herein using a general formula that includes variables (*e.g.*, Y, R₁). Unless otherwise specified, each variable within such a formula is defined independently of any other variable, and any variable that occurs more than one time in a formula is defined independently at each occurrence.

The term "benzimidazole carboxamide derivative" encompasses any compound that satisfies Formula I. This term further includes pharmaceutically acceptable salts, solvates (*e.g.*, hydrates) and esters of such compounds.

A "pharmaceutically acceptable salt" of a compound recited herein is an acid or base salt that is suitable for use in contact with the tissues of human beings or animals without excessive toxicity or carcinogenicity, and preferably without irritation, allergic response, or other problem or complication. Such salts include mineral and organic acid salts of basic residues such as amines, as well as alkali or organic salts of acidic residues such as carboxylic acids. Specific pharmaceutically acceptable anions for use in salt formation include, but are not limited to, acetate, 2-acetoxybenzoate, ascorbate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, carbonate, chloride, citrate, dihydrochloride, diphosphate, edetate, estolate (ethylsuccinate), formate, fumarate, gluceptate, gluconate, glutamate, glycolate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroiodide, hydroxymaleate, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate, pantothenate, phenylacetate, phosphate, polygalacturonate, propionate, salicylate, stearate, subacetate, succinate, sulfamate, sulfanilate, sulfate, sulfonates including besylate (benzenesulfonate), camsylate (camphorsulfonate), edisylate (ethane-1,2-disulfonate), esylate (ethanesulfonate), 2-hydroxyethylsulfonate, mesylate (methanesulfonate), triflate (trifluoromethanesulfonate) and tosylate (*p*-toluenesulfonate), tannate, tartrate, teoclate and triethiodide. Similarly, pharmaceutically acceptable cations for use in salt formation include, but are not limited to ammonium, benzathine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, and metals such as aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Those of ordinary skill in the art will recognize further pharmaceutically acceptable salts for the compounds provided herein. In general, a pharmaceutically acceptable acid or base salt can be synthesized from a parent compound that contains a basic or acidic moiety by any conventional chemical method. Briefly, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, the use of nonaqueous media, such as ether, ethyl acetate, ethanol, methanol, isopropanol or acetonitrile, is preferred.

It will be apparent that each compound provided herein may, but need not, be formulated as a solvate (*e.g.*, a hydrate) or non-covalent complex. In addition, the various crystal forms and polymorphs are within the scope of the present invention. Also provided herein are prodrugs of the compounds provided herein. A "prodrug" is a compound that may not fully satisfy the structural requirements of a formula provided herein, but is modified *in vivo*, following administration to a patient, to produce a compound within the scope of such formula. For example, a prodrug may be an acylated derivative of a compound as provided herein. Prodrugs include compounds wherein hydroxy, amine or sulfhydryl groups are bonded to any group that, when administered to a

mammalian subject, cleaves to form a free hydroxy, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, phosphate and benzoate derivatives of alcohol and amine functional groups within the compounds provided herein. Prodrugs of the compounds provided herein may be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved *in vivo* to yield the parent compounds.

As used herein, the term "alkyl" refers to a straight or branched chain saturated aliphatic hydrocarbon. Alkyl groups include groups having from 1 to 8 carbon atoms (C₁-C₈alkyl), from 1 to 6 carbon atoms (C₁-C₆alkyl) and from 1 to 4 carbon atoms (C₁-C₄alkyl), such as methyl, ethyl, propyl, isopropyl, n-butyl, *sec*-butyl, *tert*-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl or 3-methylpentyl. "C₀-C₄alkyl" refers to a single covalent bond (C₀) or an alkylene group having 1, 2, 3 or 4 carbon atoms; "C₀-C₂alkyl" refers to a single covalent bond or a methylene or ethylene group.

"Alkylene" refers to a divalent alkyl group, as defined above. C₁-C₄alkylene is an alkylene group having 1, 2, 3 or 4 carbon atoms.

"Alkenyl" refers to straight or branched chain alkene groups, which comprise at least one unsaturated carbon-carbon double bond. Alkenyl groups include C₂-C₈alkenyl, C₂-C₆alkenyl and C₂-C₄alkenyl groups, which have from 2 to 8, 2 to 6 or 2 to 4 carbon atoms, respectively, such as ethenyl, allyl or isopropenyl. "Alkynyl" refers to straight or branched chain alkyne groups, which have one or more unsaturated carbon-carbon bonds, at least one of which is a triple bond. Alkynyl groups include C₂-C₈alkynyl, C₂-C₆alkynyl and C₂-C₄alkynyl groups, which have from 2 to 8, 2 to 6 or 2 to 4 carbon atoms, respectively.

A "cycloalkyl" is a saturated or partially saturated cyclic group in which all ring members are carbon, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and partially saturated variants thereof. Certain cycloalkyl groups are C₃-C₈cycloalkyl, in which the ring contains from 3 to 8 ring members, all of which are carbon. A "(C₃-C₈cycloalkyl)C₀-C₄alkyl" is a C₃-C₈cycloalkyl group linked via a single covalent bond or a C₁-C₄alkylene group.

By "alkoxy," as used herein, is meant an alkyl group attached via an oxygen bridge (*i.e.*, -O-alkyl). Alkoxy groups include C₁-C₆alkoxy and C₁-C₄alkoxy groups, which have from 1 to 6 or from 1 to 4 carbon atoms, respectively. Methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, *sec*-butoxy, *tert*-butoxy, n-pentoxy, 2-pentoxy, 3-pentoxy, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy are representative alkoxy groups.

Similarly, "alkylthio" refers to an alkyl group as attached via a sulfur bridge (*i.e.*, -S-alkyl). Alkylthio groups include C₁-C₆alkylthio and C₁-C₄alkylthio groups, which have from 1 to 6 or from 1 to 4 carbon atoms, respectively.

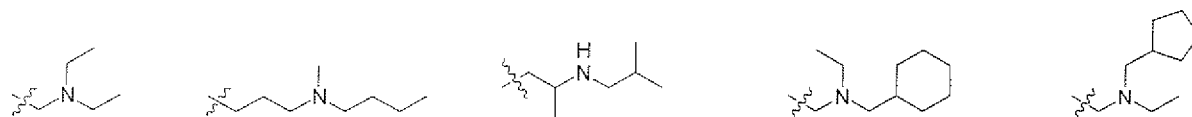
"Alkylsulfinyl" refers to groups of the formula -(SO)-alkyl, in which the sulfur atom is the point of attachment. Alkylsulfinyl groups include C₁-C₆alkylsulfinyl and C₁-C₄alkylsulfinyl groups, which have from 1 to 6 or from 1 to 4 carbon atoms, respectively.

"Alkylsulfonyl" refers to groups of the formula $-(SO_2)-alkyl$, in which the sulfur atom is the point of attachment. Alkylsulfonyl groups include C_1-C_6 alkylsulfonyl and C_1-C_4 alkylsulfonyl groups, which have from 1 to 6 or from 1 to 4 carbon atoms, respectively. The term " $(C_1-C_6$ alkylsulfonyl) C_0-C_4 alkyl" refers to a C_1-C_6 alkylsulfonyl that is linked via a single covalent bond or a C_1-C_4 alkylene group (*i.e.*, $-(C_0-C_4alkyl)-(SO_2)-(C_1-C_6alkyl)$).

The term "alkoxycarbonyl" refers to an alkoxy group linked via a carbonyl (*i.e.*, a group having the general structure $-C(=O)-O-alkyl$). Alkoxycarbonyl groups include C_1-C_8 , C_1-C_6 and C_1-C_4 alkoxycarbonyl groups, which have from 1 to 8, 6 or 4 carbon atoms, respectively, in the alkyl portion of the group. " C_1 alkoxycarbonyl" refers to $-C(=O)-O-CH_3$.

"Alkylamino" refers to a secondary or tertiary amine that has the general structure $-NH-alkyl$ or $-N(alkyl)(alkyl)$, wherein each alkyl is selected independently from alkyl, cycloalkyl and (cycloalkyl)alkyl groups. Such groups include, for example, mono- and di- (C_1-C_8alkyl) amino groups, in which each C_1-C_8alkyl may be the same or different, as well as mono- and di- (C_1-C_6alkyl) amino groups and mono- and di- (C_1-C_4alkyl) amino groups.

"Alkylaminoalkyl" refers to an alkylamino group linked via an alkylene moiety (*i.e.*, a group having the general structure $-alkylene-NH-alkyl$ or $-alkylene-N(alkyl)(alkyl)$) in which each alkyl is selected independently from alkyl, cycloalkyl and (cycloalkyl)alkyl groups. Alkylaminoalkyl groups include, for example, mono- and di- (C_1-C_8alkyl) amino C_1-C_6alkyl , and mono- and di- (C_1-C_6alkyl) amino C_1-C_4alkyl . "Mono- or di- (C_1-C_6alkyl) amino C_0-C_4alkyl " refers to a mono- or di- (C_1-C_6alkyl) amino group linked via a single covalent bond or a $C_1-C_4alkylene$ group. The following are representative alkylaminoalkyl groups:



It will be apparent that the definition of "alkyl" as used in the terms "alkylamino" and "alkylaminoalkyl" differs from the definition of "alkyl" used for all other alkyl-containing groups, in the inclusion of cycloalkyl and (cycloalkyl)alkyl groups (*e.g.*, $(C_3-C_7cycloalkyl)C_0-C_2alkyl$).

The term "aminocarbonyl" refers to an amide group (*i.e.*, $-C(=O)NH_2$).

Similarly, "aminosulfonyl" refers to a sulfonamide group (*i.e.*, $-SO_2NH_2$).

The term "halogen" refers to fluorine, chlorine, bromine or iodine.

The term "oxo," as used herein refers to an oxygen substituent of a carbon atom that results in the formation of a carbonyl group ($C=O$). An oxo group that is a substituent of a nonaromatic carbon atom results in a conversion of $-CH_2-$ to $-C(=O)-$. An oxo group that is a substituent of an aromatic carbon atom results in a conversion of $-CH-$ to $-C(=O)-$ and may result in a loss of aromaticity.

A "haloalkyl" is an alkyl group that is substituted with 1 or more independently chosen halogens (*e.g.*, " C_1-C_8 haloalkyl" groups have from 1 to 8 carbon atoms; " C_1-C_6 haloalkyl" groups have from 1 to 6 carbon atoms). Examples of haloalkyl groups include, but are not limited to, mono-, di- or

tri-fluoromethyl; mono-, di- or tri-chloromethyl; mono-, di-, tri-, tetra- or penta-fluoroethyl; mono-, di-, tri-, tetra- or penta-chloroethyl; and 1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl. Typical haloalkyl groups are trifluoromethyl and difluoromethyl.

A dash ("-") that is not between two letters or numbers is used to indicate a point of attachment for a substituent. For example, -C(=O)NH_2 is attached through the carbon atom.

Phenyl groups linked via a single covalent bond or $\text{C}_1\text{-C}_4$ alkylene group are designated phenyl $\text{C}_0\text{-C}_4$ alkyl (*e.g.*, phenyl $\text{C}_1\text{-C}_2$ alkyl, which includes benzyl, 1-phenyl-ethyl and 2-phenyl-ethyl). When substituted, it will be apparent that such groups may be substituted on the ring portion and/or on the alkylene portion of the group.

A "heterocycle" (also referred to herein as a "heterocyclic group") has from 1 to 3 fused, pendant or spiro rings, at least one of which is a heterocyclic ring (*i.e.*, one or more ring atoms is a heteroatom independently chosen from oxygen, sulfur and nitrogen, with the remaining ring atoms being carbon). Typically, a heterocyclic ring comprises 1, 2, 3 or 4 heteroatoms; within certain embodiments each heterocyclic ring has 1 or 2 heteroatoms per ring. Each heterocyclic ring generally contains from 3 to 8 ring members (rings having from 4 or 5 to 7 ring members are recited in certain embodiments) and heterocycles comprising fused, pendant or spiro rings typically contain from 9 to 14 ring members. Certain heterocycles comprise a sulfur atom as a ring member; in certain embodiments, the sulfur atom is oxidized to SO or SO_2 . Heterocycles may be optionally substituted with a variety of substituents, as indicated. Certain heterocycles are 4- to 10-membered and comprise one or two rings; in certain embodiments, such heterocycles are monocyclic (*e.g.*, 4- to 8-membered, 5- to 8-membered, 4- to 7-membered, or 5- or 6-membered).

Certain heterocycles are heteroaryl groups (*i.e.*, at least one heterocyclic ring within the group is aromatic), such as a 5- to 10-membered heteroaryl (which may be monocyclic or bicyclic) or a 5- or 6-membered heteroaryl (*e.g.*, thienyl, imidazolyl, pyridyl or pyrimidyl). Other heterocycles are heterocycloalkyl groups (*i.e.*, do not comprise an aromatic heterocyclic ring). Certain heterocycles may be linked by a single covalent bond or via an alkylene group, as indicated, for example, by the term "(4- to 7-membered heterocycloalkyl) $\text{C}_0\text{-C}_4$ alkyl." "(4- to 7-membered heterocycloalkyl) $\text{C}_1\text{-C}_2$ alkyl," for example, refers to a 4- to 7-membered heterocycloalkyl that is linked via a methylene or ethylene linker. When substituted, it will be apparent that substituent(s) may be attached on the ring and/or the alkylene linker.

A "substituent," as used herein, refers to a molecular moiety that is covalently bonded to an atom within a molecule of interest. For example, a "ring substituent" may be a moiety such as a halogen, alkyl group, haloalkyl group or other group discussed herein that is covalently bonded to an atom (such as a carbon or nitrogen atom) that is a ring member. The term "substitution" refers to replacing a hydrogen atom in a molecular structure with a substituent as described above, such that the valence on the designated atom is not exceeded, and such that a chemically stable compound (*i.e.*,

a compound that can be isolated, characterized, and tested for biological activity) results from the substitution.

Groups that are "optionally substituted" are unsubstituted or are substituted by other than hydrogen at one or more available positions, typically 1, 2, 3, 4 or 5 positions, by one or more suitable groups (which may be the same or different). Optional substitution is also indicated by the phrase "substituted with from 0 to X substituents," where X is the maximum number of possible substituents. Certain optionally substituted groups are substituted with from 0 to 2, 3 or 4 independently selected substituents (*i.e.*, are unsubstituted or substituted with up to the recited maximum number of substituents).

"B₁," as used herein, refers to the human B₁ bradykinin receptor reported by Menke et al. (1994) *J. Biol. Chem.* 269:21583-21586, as well as allelic variants thereof and homologues thereof found in other species (*e.g.*, GenBank Accession Number AAX14712 (*Macaca fascicularis*)).

The term "B₁ agonist" refers to a compound that binds B₁ and induces signal transduction mediated by B₁. B₁ agonists include, for example, bradykinin and kallidin (lysyl-bradykinin), as well as peptide portions or variants of bradykinin or kallidin that bind B₁ and retain activity. Representative B₁ agonists include, but are not limited to, desArg⁹bradykinin and desArg¹⁰kallidin.

A "B₁ antagonist" is a compound that detectably inhibits signal transduction mediated by B₁. Such inhibition may be determined using the representative calcium mobilization assay provided in Example 7. Preferred B₁ antagonists have an IC₅₀ of 5 μM or less in this assay, more preferably 2 μM or less, and still more preferably 1 μM or less, 500 nM or less, 100 nM or less or 10 nM or less. In certain embodiments, the B₁ antagonist is specific for B₁ (*i.e.*, the IC₅₀ value in a similar assay performed using the B₂ receptor is greater than 2 μM and/or the IC₅₀ ratio (B₂/B₁) is at least 10, preferably 100, and more preferably at least 1000). B₁ antagonists preferably have minimal agonist activity (*i.e.*, induce an increase in the basal activity of B₁ that is less than 5% of the increase that would be induced by one EC₅₀ of the peptide agonist desArg¹⁰kallidin, and more preferably have no detectable agonist activity within the assay described in Example 7). B₁ antagonists for use as described herein are generally non-toxic. B₁ antagonists include neutral antagonists and inverse agonists.

A "neutral antagonist" of B₁ is a compound that inhibits the activity of B₁ agonist (*e.g.*, desArg¹⁰kallidin) at B₁, but does not significantly change the basal activity of the receptor (*i.e.*, within a calcium mobilization assay as described in Example 7 performed in the absence of agonist, B₁ activity is reduced by no more than 10%, more preferably by no more than 5%, and even more preferably by no more than 2%; most preferably, there is no detectable reduction in activity). Neutral antagonists may, but need not, also inhibit the binding of agonist to B₁.

An "inverse agonist" of B₁ is a compound that reduces the activity of B₁ below its basal activity level in the absence of activating concentrations of agonist. Inverse agonists may also inhibit the activity of agonist at B₁, and/or may inhibit binding of B₁ agonist to B₁. The reduction in basal

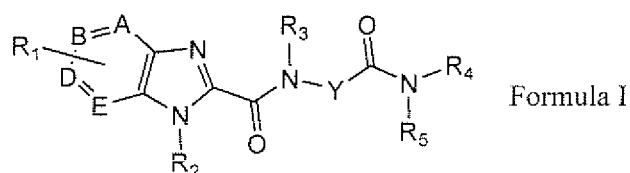
activity of B₁ produced by an inverse agonist may be determined from a calcium mobilization assay, such as the assay of Example 7.

A "therapeutically effective amount" (or dose) is an amount that, upon administration to a patient, results in a discernible patient benefit (e.g., provides detectable relief from a condition being treated). Such relief may be detected using any appropriate criteria. A therapeutically effective amount or dose generally results in a concentration of compound in a body fluid (such as blood, plasma, serum, CSF, synovial fluid, lymph, cellular interstitial fluid, tears or urine) that is sufficient to result in detectable alteration in B₁-mediated signal transduction (using an assay provided herein). The discernible patient benefit may be apparent after administration of a single dose, or may become apparent following repeated administration of the therapeutically effective dose according to a predetermined regimen, depending upon the indication for which the compound is administered. For the treatment of pain, a discernible patient benefit is generally apparent after administration of a single therapeutically effective dose, although further benefit may become apparent following repeated administrations.

A "patient" is any individual treated with a benzimidazole carboxamide derivative as provided herein. Patients include humans, as well as other animals such as companion animals (e.g., dogs and cats) and livestock. Patients may be experiencing one or more symptoms of a condition responsive to B₁ modulation or may be free of such symptom(s) (i.e., treatment may be prophylactic in a patient considered to be at risk for the development of such symptoms).

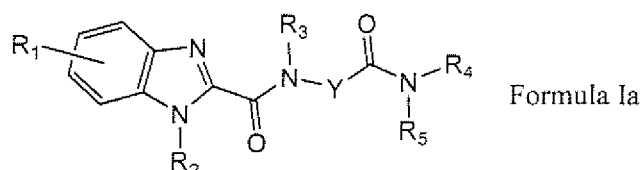
BENZIMIDAZOLE CARBOXAMIDE DERIVATIVES

As noted above, the present invention provides benzimidazole carboxamide derivatives of Formula I that may be used in a variety of contexts, including in the treatment of conditions responsive to B₁ modulation, as described herein.



Such compounds may also be used within *in vitro* assays (e.g., assays for B₁ activity), as probes for detection and localization of B₁ and within assays to identify other B₁ antagonists.

Within certain benzimidazole carboxamide derivatives of Formula I, the variables A, B, D and E are each CH. Such compounds satisfy Formula Ia:



It will be apparent that the substitution of a ring carbon atom in Formula I or Ia with a substituent represented by R₁ will result in the loss of the hydrogen atom at that ring carbon. Within

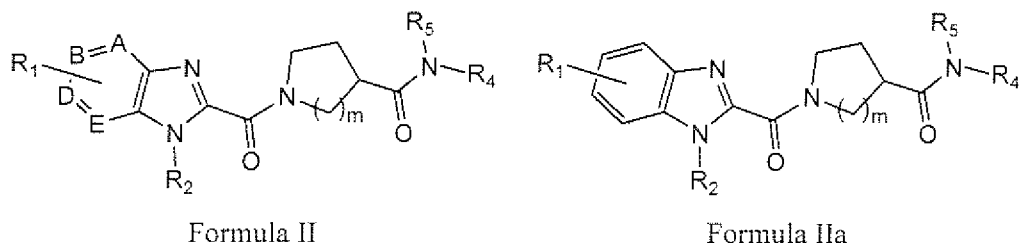
certain embodiments, R_1 represents from 0 to 2 substituents independently chosen from halogen, cyano and C_1 - C_4 alkyl.

The variable represented by R_2 is, within certain embodiments, phenyl C_1 - C_2 alkyl that is substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, cyano, C_1 - C_4 alkyl, and C_1 - C_4 alkoxy. Representative such R_2 moieties include, for example, benzyl that is substituted with from 0 to 3 substituents independently chosen from halogen, C_1 - C_4 alkyl, and C_1 - C_4 alkoxy. Within other embodiments, the variable represented by R_2 is (4- to 7-membered heterocycloalkyl) C_1 - C_4 alkyl that is substituted with from 0 to 3 substituents independently chosen from oxo and C_1 - C_4 alkyl.

Within the variable designated "Y," the sum of r and p ranges from 1 to 6 for certain benzimidazole carboxamide derivatives. Within certain such compounds, p is not zero. Certain Y groups satisfy the formula $(CH_2)_r-O-(CH_2)_p$, which is substituted with from 0 to 4 substituents independently chosen from amino, hydroxy, cyano, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 haloalkyl and substituents of the same carbon atom or adjacent carbon atoms that are taken together to form C_3 - C_6 cycloalkyl. Representative such Y groups include, for example, $-O-CH_2-$, $-CH_2-O-CH_2-$, $-O-CH_2-CH_2-$, $-CH_2-O-CH_2-CH_2-$ and $-CH_2-CH_2-O-CH_2-$. Other Y groups satisfy the formula $-N(R_{10})-CH_2-$. Yet another Y group is $-CH=CH-$.

Within other benzimidazole carboxamide derivatives of Formula I, Y is a group of the formula $(CH_2)_r-(CH_2)_p$ that is substituted with from 0 to 4 substituents independently chosen from amino, hydroxy, cyano, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 haloalkyl and substituents of the same carbon atom or adjacent carbon atoms that are taken together to form C_3 - C_6 cycloalkyl. Representative such Y groups include, for example, C_1 - C_6 alkylene groups such as methylene and ethylene, each of which is optionally substituted as indicated above (*e.g.*, unsubstituted or substituted with amino, hydroxy, cyano, C_1 - C_4 alkyl (*e.g.*, methyl or ethyl), C_2 - C_4 alkenyl or C_1 - C_4 haloalkyl).

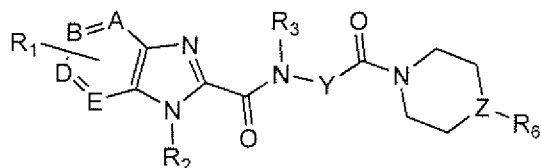
Within certain benzimidazole carboxamide derivatives of Formulas I and Ia, R_3 is hydrogen or C_1 - C_4 alkyl. Within certain other benzimidazole carboxamide derivatives of Formula I, Y is a group of the formula $(CH_2)_r-CHR_{10}-$, wherein R_{10} is taken together with R_3 to form a 4- to 7-membered heterocycloalkyl. Certain such compounds further satisfy Formula II or IIa:



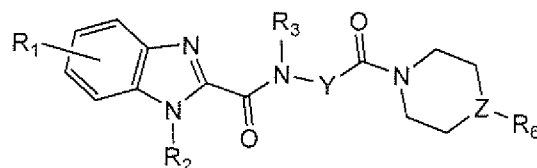
wherein m is 0, 1, 2 or 3 and the remaining variables are as described for Formula I.

Within certain benzimidazole carboxamide derivatives provided herein, the variables R_4 and R_5 are taken together to form a 4- to 7-membered heterocycloalkyl that is substituted with mono- or di- $(C_1$ - C_6 alkyl)amino C_0 - C_4 alkyl, (4- to 7-membered heterocycloalkyl) C_0 - C_4 alkyl, phenyl C_0 - C_4 alkyl or

(6-membered heteroaryl) C_0 - C_4 alkyl, each of which is unsubstituted or substituted with oxo, C_1 - C_4 alkyl or (5- or 6-membered heterocycle) C_0 - C_2 alkyl. Certain such compounds further satisfy Formula III or IIIa:



Formula III



Formula IIIa

wherein Z is N or CH; and R_6 is piperidinyl C_0 - C_4 alkyl, pyrrolidinyl C_0 - C_4 alkyl, pyridinyl C_0 - C_4 alkyl, pyrimidinyl C_0 - C_4 alkyl, tetrahydropyrimidinyl C_0 - C_4 alkyl, imidazolyl C_0 - C_4 alkyl, dihydroimidazolyl C_0 - C_4 alkyl, thiazolyl C_0 - C_4 alkyl, oxadiazolyl C_0 - C_4 alkyl, phenyl C_0 - C_4 alkyl, or di- $(C_1$ - C_4 alkyl)amino C_0 - C_4 alkyl, each of which is unsubstituted or substituted with one or two C_1 - C_4 alkyl. Within further such compounds:

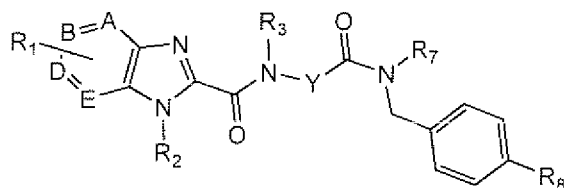
R_1 represents from 0 to 2 substituents independently chosen from halogen, cyano, and C_1 - C_4 alkyl;

R_2 is benzyl that is substituted with from 0 to 3 substituents independently chosen from halogen, C_1 - C_4 alkyl, and C_1 - C_4 alkoxy;

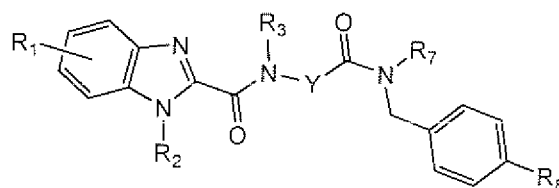
R_3 is hydrogen or C_1 - C_4 alkyl; and

Y is methylene or ethylene, each of which is unsubstituted or substituted with methyl or ethyl.

Within other benzimidazole carboxamide derivatives provided herein, R_4 is C_1 - C_4 alkyl; and R_5 is phenyl C_0 - C_2 alkyl that is substituted with mono- or di- $(C_1$ - C_6 alkyl)amino C_0 - C_4 alkyl, (4- to 7-membered heterocycloalkyl) C_0 - C_4 alkyl, phenyl C_0 - C_4 alkyl or (6-membered heteroaryl) C_0 - C_4 alkyl, each of which is unsubstituted or substituted with oxo, C_1 - C_4 alkyl, (5- or 6-membered heterocycle) C_0 - C_2 alkyl, or mono- or di- $(C_1$ - C_6 alkyl)amino C_0 - C_4 alkyl. Certain such compounds further satisfy Formula IV or IVa:



Formula IV



Formula IVa

wherein R_7 is methyl or ethyl; and R_8 is piperidinyl C_0 - C_4 alkyl, pyrrolidinyl C_0 - C_4 alkyl, pyridinyl C_0 - C_4 alkyl, pyrimidinyl C_0 - C_4 alkyl, tetrahydropyrimidinyl C_0 - C_4 alkyl, imidazolyl C_0 - C_4 alkyl, dihydroimidazolyl C_0 - C_4 alkyl, thiazolyl C_0 - C_4 alkyl, oxadiazolyl C_0 - C_4 alkyl, phenyl C_0 - C_4 alkyl, or di- $(C_1$ - C_4 alkyl)amino C_0 - C_4 alkyl, each of which is unsubstituted or substituted with one or two C_1 - C_4 alkyl. Within further such compounds:

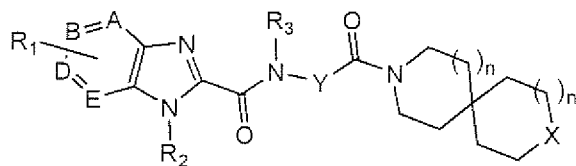
R_1 represents from 0 to 2 substituents independently chosen from halogen, cyano, and C_1 - C_4 alkyl;

R_2 is benzyl that is substituted with from 0 to 3 substituents independently chosen from halogen, C_1 - C_4 alkyl, and C_1 - C_4 alkoxy;

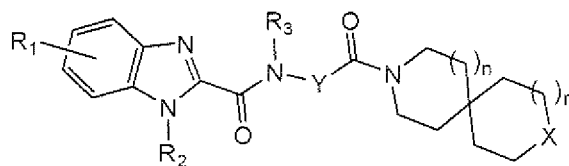
R₃ is hydrogen or C₁-C₄alkyl; and

Y is methylene or ethylene, each of which is unsubstituted or substituted with methyl or ethyl.

Within still further benzimidazole carboxamide derivatives provided herein, R₄ and R₅ are taken together to form a 8- to 14-membered spiro heterocycloalkyl that is unsubstituted or substituted with C₁-C₄alkyl, (C₃-C₇cycloalkyl)C₀-C₂alkyl or (5- or 6-membered heterocycle)C₀-C₂alkyl. Certain such compounds further satisfy Formula V or Va:



Formula V



Formula Va

wherein each n is independently 0 or 1; X is O or NR₉; and R₉ is C₁-C₄alkyl or (C₃-C₇cycloalkyl)C₀-C₂alkyl. Within further such compounds:

R₁ represents from 0 to 2 substituents independently chosen from halogen, cyano, and C₁-C₄alkyl;

R₂ is benzyl that is substituted with from 0 to 3 substituents independently chosen from halogen, C₁-C₄alkyl, and C₁-C₄alkoxy;

R₃ is hydrogen or C₁-C₄alkyl; and

Y is methylene or ethylene, each of which is unsubstituted or substituted with methyl or ethyl.

Representative benzimidazole carboxamide derivatives provided herein include, but are not limited to, those specifically described in the Examples below. It will be apparent that the specific compounds recited herein are representative only, and are not intended to limit the scope of the present invention. Further, as noted above, all compounds of the present invention may be present as a free acid or base or as a pharmaceutically acceptable salt, hydrate or ester.

As noted above, within certain aspects, benzimidazole carboxamide derivatives provided herein are B₁ modulators. In addition, certain benzimidazole carboxamide derivatives provided herein are specific for B₁. B₁ modulator activity may be confirmed using a calcium mobilization assay, such as the assay described in Example 7, herein.

If desired, B₁ binding activity of the benzimidazole carboxamide derivatives provided herein may be confirmed using the representative assay described in Example 6, herein, or using an assay described by Fox et al. (2005) *Br. J. Pharmacol.* 144:889-99. Preferred B₁ modulators exhibit a K_i within such an assay of 5 micromolar or less, more preferably 2 micromolar or less, 1 micromolar or less, 500 nanomolar or less, 100 nanomolar or less or 10 nanomolar or less.

In vivo activity of B₁ modulators provided herein may be confirmed using any of a variety of animal models including, but not limited to, those described in the following documents (each of which is hereby incorporated by reference for its disclosure of the recited animal model):

Wood et al. (2003) *J. Med. Chem.* 46:1803-06 – carrageenan-induced mechanical pressure hyperalgesia;

Conley et al. (2005) *Eur. J. Pharmacol.* 527:44-51 – thermal antinociception and carrageenan-induced mechanical pressure hypersensitivity;

Gougat et al. (2004) *J. Pharmacol. Exper. Therap.* 309:661-669 – UV irradiation-induced thermal hyperalgesia and chronic constriction of the sciatic nerve-induced neuropathy and in ischemia-induced injury;

Fox et al. (2005) *Br. J. Pharmacol.* 144:889-99 – complete Freund's adjuvant-induced mechanical pressure hypersensitivity;

Gabra et al. (2005) *J. Neuropathol. Exp. Neurol.* 64:782-89 – diabetes-induced peripheral neuropathic pain;

Pesquero et al. (2000) *Proc. Natl. Acad. Sci. USA* 97:8140-45 – carrageenan-induced pleurisy (inflammation around the lung);

Lawson et al. (2005) *Eur. J. Pharmacol.* 514:69-78 – diabetes-induced vascular disease;

Hirata et al. (2003) *Eur. J. Pharmacol.* 474:255-60 – ACE inhibitor-induced cough;

Mazzuferi et al. (2005) *Neuroscience*. 135:979-86 – neuronal hyperexcitability in epilepsy.

If desired, compounds provided herein may be evaluated for certain pharmacological properties including, but not limited to, oral bioavailability (preferred compounds are orally bioavailable to an extent allowing for therapeutically effective doses of less than 140 mg/kg, preferably less than 50 mg/kg, more preferably less than 30 mg/kg, even more preferably less than 10 mg/kg, still more preferably less than 1 mg/kg and most preferably less than 0.1 mg/kg), toxicity (a preferred compound is nontoxic when a therapeutically effective amount is administered to a subject), side effects (a preferred compound produces side effects comparable to placebo when a therapeutically effective amount of the compound is administered to a subject), serum protein binding and *in vitro* and *in vivo* half-life (a preferred compound exhibits an *in vivo* half-life allowing for Q.I.D. dosing, preferably T.I.D. dosing, more preferably B.I.D. dosing, and most preferably once-a-day dosing). In addition, differential penetration of the blood brain barrier may be desirable. Routine assays that are well known in the art may be used to assess these properties, and identify superior compounds for a particular use. For example, assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers. Penetration of the blood brain barrier of a compound in humans may be predicted from the brain levels of the compound in laboratory animals given the compound (*e.g.*, intravenously). Serum protein binding may be predicted from albumin binding assays. Compound half-life is inversely proportional to the frequency of dosage of a compound. *In vitro* half-lives of compounds may be predicted from assays of microsomal half-life as described herein.

As noted above, preferred compounds provided herein are nontoxic. In general, the term "nontoxic" as used herein shall be understood in a relative sense and is intended to refer to any substance that has been approved by the United States Food and Drug Administration ("FDA") for administration to mammals (preferably humans) or, in keeping with established criteria, is susceptible

to approval by the FDA for administration to mammals (preferably humans). In addition, a highly preferred nontoxic compound generally satisfies one or more of the following criteria: (1) does not substantially inhibit cellular ATP production; (2) does not significantly prolong heart QT intervals; (3) does not cause substantial liver enlargement, or (4) does not cause substantial release of liver enzymes.

As used herein, a compound that does not substantially inhibit cellular ATP production is a compound that satisfies the criteria set forth in Example 8, herein. In other words, cells treated as described in Example 8 with 100 μ M of such a compound exhibit ATP levels that are at least 50% of the ATP levels detected in untreated cells. In more highly preferred embodiments, such cells exhibit ATP levels that are at least 80% of the ATP levels detected in untreated cells.

A compound that does not significantly prolong heart QT intervals is a compound that does not result in a statistically significant prolongation of heart QT intervals (as determined by electrocardiography) in guinea pigs, minipigs or dogs upon administration of a dose that yields a serum concentration equal to the EC_{50} or IC_{50} for the compound. In certain preferred embodiments, a dose of 0.01, 0.05, 0.1, 0.5, 1, 5, 10, 40 or 50 mg/kg administered parenterally or orally does not result in a statistically significant prolongation of heart QT intervals. By "statistically significant" is meant results varying from control at the $p < 0.1$ level or more preferably at the $p < 0.05$ level of significance as measured using a standard parametric assay of statistical significance such as a student's T test.

A compound does not cause substantial liver enlargement if daily treatment of laboratory rodents (*e.g.*, mice or rats) for 5-10 days with a dose that yields a serum concentration equal to the EC_{50} or IC_{50} for the compound results in an increase in liver to body weight ratio that is no more than 100% over matched controls. In more highly preferred embodiments, such doses do not cause liver enlargement of more than 75% or 50% over matched controls. If non-rodent mammals (*e.g.*, dogs) are used, such doses should not result in an increase of liver to body weight ratio of more than 50%, preferably not more than 25%, and more preferably not more than 10% over matched untreated controls. Preferred doses within such assays include 0.01, 0.05, 0.1, 0.5, 1, 5, 10, 40 or 50 mg/kg administered parenterally or orally.

Similarly, a compound does not promote substantial release of liver enzymes if administration of twice the minimum dose that yields a serum concentration equal to the EC_{50} or IC_{50} for the compound does not elevate serum levels of ALT, LDH or AST in laboratory rodents by more than 100% over matched mock-treated controls. In more highly preferred embodiments, such doses do not elevate such serum levels by more than 75% or 50% over matched controls. Alternatively, a compound does not promote substantial release of liver enzymes if, in an *in vitro* hepatocyte assay, concentrations (in culture media or other such solutions that are contacted and incubated with hepatocytes *in vitro*) that are equal to the EC_{50} or IC_{50} for the compound do not cause detectable release of any of such liver enzymes into culture medium above baseline levels seen in media from matched mock-treated control cells. In more highly preferred embodiments, there is no detectable

release of any of such liver enzymes into culture medium above baseline levels when such compound concentrations are five-fold, and preferably ten-fold the EC₅₀ or IC₅₀ for the compound.

In other embodiments, certain preferred compounds do not inhibit or induce microsomal cytochrome P450 enzyme activities, such as CYP1A2 activity, CYP2A6 activity, CYP2C9 activity, CYP2C19 activity, CYP2D6 activity, CYP2E1 activity or CYP3A4 activity at a concentration equal to the EC₅₀ or IC₅₀ for the compound.

Certain preferred compounds are not clastogenic (*e.g.*, as determined using a mouse erythrocyte precursor cell micronucleus assay, an Ames micronucleus assay, a spiral micronucleus assay or the like) at a concentration equal the EC₅₀ or IC₅₀ for the compound. In other embodiments, certain preferred compounds do not induce sister chromatid exchange (*e.g.*, in Chinese hamster ovary cells) at such concentrations.

For detection purposes, as discussed in more detail below, compounds provided herein may be isotopically-labeled or radiolabeled. For example, such compounds may have one or more atoms replaced by an atom of the same element having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be present in the compounds provided herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ²H, ³H, ¹¹C, ¹³C, ¹⁴C, ¹⁵N, ¹⁸O, ¹⁷O, ³¹P, ³²P, ³³S, ¹⁸F and ³⁶Cl. In addition, substitution with heavy isotopes such as deuterium (*i.e.*, ²H) can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances.

PREPARATION OF BENZIMIDAZOLE CARBOXAMIDE DERIVATIVES

Compounds provided herein may generally be prepared using standard synthetic methods. In general, starting materials are commercially available from suppliers such as Sigma-Aldrich Corp. (St. Louis, MO), or may be synthesized from commercially available precursors using established protocols. By way of example, a synthetic route similar to that shown in any of the following Schemes may be used, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon appreciated by those skilled in the art. It will be apparent that the reagents and synthetic transformations in the following Schemes and in the art can be readily modified to produce additional compounds of Formula I. Each variable in the following Schemes refers to any group consistent with the description of the compounds provided herein.

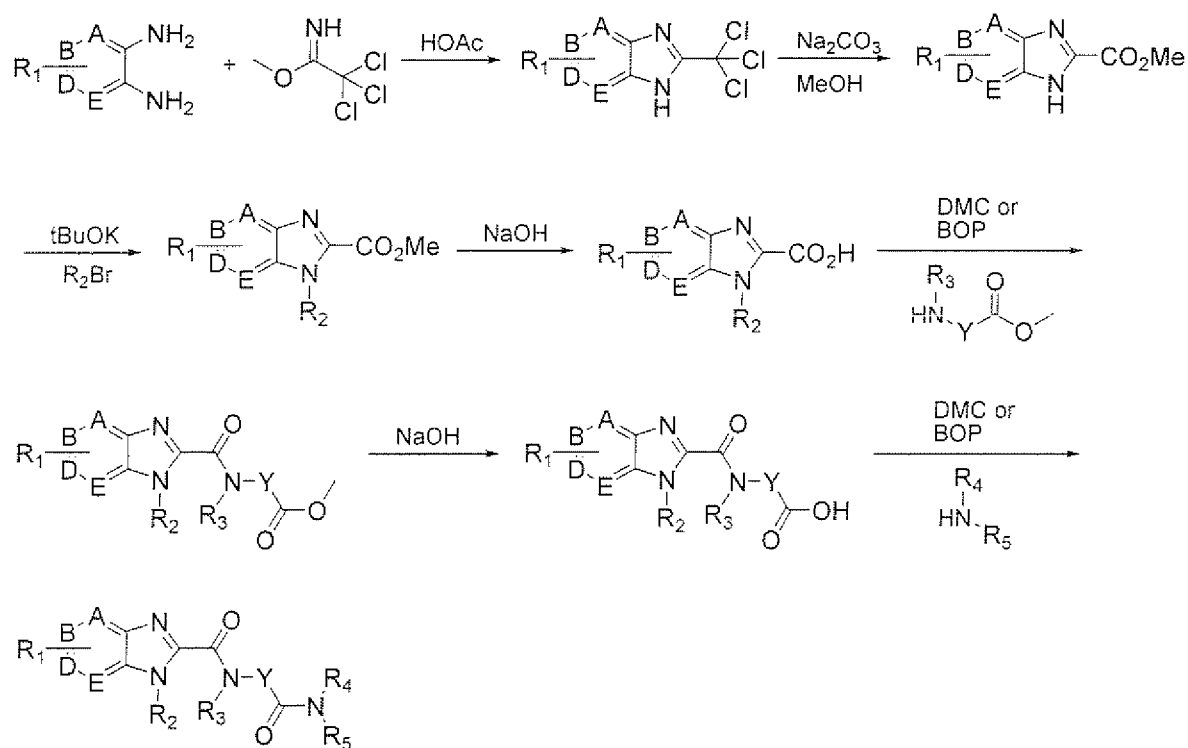
When a protecting group is required, an optional deprotection step may be employed. Suitable protecting groups and methodology for protection and deprotection, such as those described in *Protecting Groups in Organic Synthesis* by T. Greene, are well known. Compounds and intermediates requiring protection/deprotection will be readily apparent.

Certain abbreviations used in the following Schemes and in the Examples include:

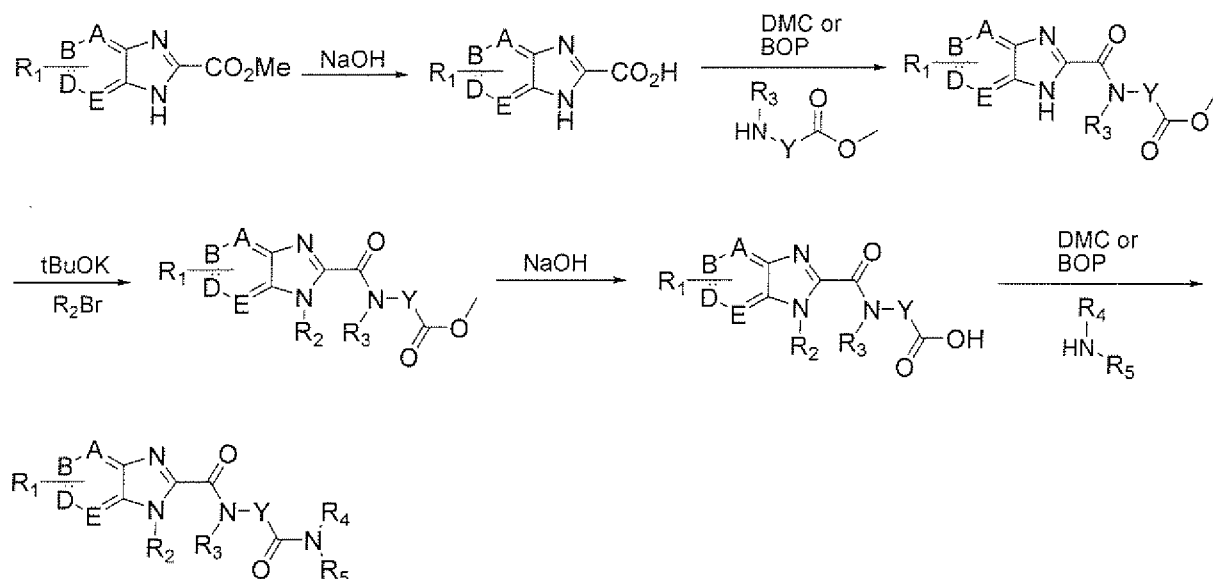
BOP	benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate
DIEA	N,N-diisopropylethylamine

	DMC	2-chloro-1,3-dimethylimidazolidinium chloride
	DMF	dimethylformamide
	DMSO	dimethylsulfoxide
	Eq.	equivalent(s)
5	EtOAc	ethyl acetate
	h	hour(s)
	¹ H NMR	proton nuclear magnetic resonance
	LC-MS	liquid chromatography/mass spectrometry
	MeOH	methanol
10	MHz	megahertz
	M+1	mass + 1
	min	minute(s)
	MS	mass spectrometry
	δ	chemical shift
15	rt	room temperature
	PTLC	preparative thin layer chromatography
	tBuOK	potassium <i>tert</i> -butoxide
	TFA	trifluoroacetic acid

Scheme 1



Scheme 2



In certain embodiments, a compound provided herein may contain one or more asymmetric carbon atoms, so that the compound can exist in different stereoisomeric forms. Such forms can be, for example, racemates or optically active forms. As noted above, all stereoisomers are encompassed by the present invention. Nonetheless, it may be desirable to obtain single enantiomers (*i.e.*, optically active forms). Standard methods for preparing single enantiomers include asymmetric synthesis and resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography using, for example a chiral HPLC column.

Compounds may be radiolabeled by carrying out their synthesis using precursors comprising at least one atom that is a radioisotope. Each radioisotope is preferably carbon (*e.g.*, ¹⁴C), hydrogen (*e.g.*, ³H), sulfur (*e.g.*, ³⁵S) or iodine (*e.g.*, ¹²⁵I). Tritium labeled compounds may also be prepared catalytically via platinum-catalyzed exchange in tritiated acetic acid, acid-catalyzed exchange in tritiated trifluoroacetic acid, or heterogeneous-catalyzed exchange with tritium gas using the compound as substrate. In addition, certain precursors may be subjected to tritium-halogen exchange with tritium gas, tritium gas reduction of unsaturated bonds, or reduction using sodium borotritide, as appropriate. Preparation of radiolabeled compounds may be conveniently performed by a radioisotope supplier specializing in custom synthesis of radiolabeled probe compounds.

PHARMACEUTICAL COMPOSITIONS

The present invention also provides pharmaceutical compositions comprising one or more benzimidazole carboxamide derivatives provided herein, together with at least one physiologically acceptable carrier or excipient. Pharmaceutical compositions may comprise, for example, one or more of water, buffers (*e.g.*, neutral buffered saline or phosphate buffered saline), ethanol, mineral oil, vegetable oil, dimethylsulfoxide, carbohydrates (*e.g.*, glucose, mannose, sucrose or dextrans), mannitol, proteins, adjuvants, polypeptides or amino acids such as glycine, antioxidants, chelating

agents such as EDTA or glutathione and/or preservatives. In addition, other active ingredients may (but need not) be included in the pharmaceutical compositions provided herein.

Pharmaceutical compositions may be formulated for any appropriate manner of administration, including, for example, topical, oral (including, but not limited to, sublingual), nasal, rectal or parenteral administration. The term parenteral as used herein includes subcutaneous, intradermal, intravascular (*e.g.*, intravenous), intramuscular, spinal, intracranial, intrathecal and intraperitoneal injection, as well as any similar injection or infusion technique. In certain embodiments, compositions suitable for oral use are preferred. Such compositions include, for example, tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs. Within yet other embodiments, compositions of the present invention may be formulated as a lyophilizate.

Compositions intended for oral use may further comprise one or more components such as sweetening agents, flavoring agents, coloring agents and/or preserving agents in order to provide appealing and palatable preparations. Tablets contain the active ingredient in admixture with physiologically acceptable excipients that are suitable for the manufacture of tablets. Such excipients include, for example, inert diluents (*e.g.*, calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate), granulating and disintegrating agents (*e.g.*, corn starch or alginic acid), binding agents (*e.g.*, starch, gelatin or acacia) and lubricating agents (*e.g.*, magnesium stearate, stearic acid or talc). The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent (*e.g.*, calcium carbonate, calcium phosphate or kaolin), or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium (*e.g.*, peanut oil, liquid paraffin or olive oil).

Aqueous suspensions contain the active material(s) in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include suspending agents (*e.g.*, sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia); and dispersing or wetting agents (*e.g.*, naturally-occurring phosphatides such as lecithin, condensation products of an alkylene oxide with fatty acids such as polyoxyethylene stearate, condensation products of ethylene oxide with long chain aliphatic alcohols such as heptadecaethyleneoxycetanol, condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides such as polyethylene sorbitan monooleate). Aqueous suspensions may also comprise one

or more preservatives, such as ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient(s) in a vegetable oil (e.g., arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and/or flavoring agents may be added to provide palatable oral preparations. Such suspensions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

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

Pharmaceutical compositions may also be formulated as oil-in-water emulsions. The oily phase may be a vegetable oil (e.g., olive oil or arachis oil), a mineral oil (e.g., liquid paraffin) or a mixture thereof. Suitable emulsifying agents include naturally-occurring gums (e.g., gum acacia or gum tragacanth), naturally-occurring phosphatides (e.g., soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol), anhydrides (e.g., sorbitan monoleate) and condensation products of partial esters derived from fatty acids and hexitol with ethylene oxide (e.g., polyoxyethylene sorbitan monoleate). An emulsion may also comprise one or more sweetening and/or flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, such as glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also comprise one or more demulcents, preservatives, flavoring agents and/or coloring agents.

Formulations for topical administration typically comprise a topical vehicle combined with active agent(s), with or without additional optional components. Suitable topical vehicles and additional components are well known in the art, and it will be apparent that the choice of a vehicle will depend on the particular physical form and mode of delivery. Topical vehicles include water; organic solvents such as alcohols (e.g., ethanol or isopropyl alcohol) or glycerin; glycols (e.g., butylene, isoprene or propylene glycol); aliphatic alcohols (e.g., lanolin); mixtures of water and organic solvents and mixtures of organic solvents such as alcohol and glycerin; lipid-based materials such as fatty acids, acylglycerols (including oils, such as mineral oil, and fats of natural or synthetic origin), phosphoglycerides, sphingolipids and waxes; protein-based materials such as collagen and gelatin; silicone-based materials (both non-volatile and volatile); and hydrocarbon-based materials such as microsponges and polymer matrices. A composition may further include one or more components adapted to improve the stability or effectiveness of the applied formulation, such as stabilizing agents, suspending agents, emulsifying agents, viscosity adjusters, gelling agents,

preservatives, antioxidants, skin penetration enhancers, moisturizers and sustained release materials. Examples of such components are described in Martindale--The Extra Pharmacopoeia (Pharmaceutical Press, London 1993) and Martin (ed.), Remington's Pharmaceutical Sciences. Formulations may comprise microcapsules, such as hydroxymethylcellulose or gelatin-microcapsules, liposomes, albumin microspheres, microemulsions, nanoparticles or nanocapsules.

A topical formulation may be prepared in a variety of physical forms including, for example, solids, pastes, creams, foams, lotions, gels, powders, aqueous liquids and emulsions. Typical modes of delivery for topical compositions include application using the fingers; application using a physical applicator such as a cloth, tissue, swab, stick or brush; spraying (including mist, aerosol or foam spraying); dropper application; sprinkling; soaking; and rinsing. Controlled release vehicles can also be used.

A pharmaceutical composition may be prepared as a sterile injectible aqueous or oleaginous suspension. The compound(s) provided herein, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Such a composition may be formulated according to the known art using suitable dispersing, wetting and/or suspending agents such as those mentioned above. Among the acceptable vehicles and solvents that may be employed are water, 1,3-butanediol, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils may be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectible compositions, and adjuvants such as local anesthetics, preservatives and/or buffering agents can be dissolved in the vehicle.

Compounds may also be formulated as suppositories (*e.g.*, for rectal administration). Such compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Pharmaceutical compositions may be formulated for release at a pre-determined rate. Instantaneous release may be achieved, for example, via sublingual administration (*i.e.*, administration by mouth in such a way that the active ingredient(s) are rapidly absorbed via the blood vessels under the tongue rather than via the digestive tract). Controlled release formulations (*i.e.*, formulations such as a capsule, tablet or coated tablet that slows and/or delays release of active ingredient(s) following administration) may be administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at a target site. In general, a controlled release formulation comprises a matrix and/or coating that delays disintegration and absorption in the gastrointestinal tract (or implantation site) and thereby provides a delayed action or a sustained action over a longer period. One type of controlled-release formulation is a sustained-release formulation, in which at least one active ingredient is continuously released over a period of time at a constant rate. Preferably, the therapeutic agent is released at such a rate that blood (*e.g.*, plasma) concentrations are

maintained within the therapeutic range, but below toxic levels, over a period of time that is at least 4 hours, preferably at least 8 hours, and more preferably at least 12 hours. Such formulations may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of modulator release. The amount of modulator contained within a sustained release formulation depends upon, for example, the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Controlled release may be achieved by combining the active ingredient(s) with a matrix material that itself alters release rate and/or through the use of a controlled-release coating. The release rate can be varied using methods well known in the art, including (a) varying the thickness or composition of coating, (b) altering the amount or manner of addition of plasticizer in a coating, (c) including additional ingredients, such as release-modifying agents, (d) altering the composition, particle size or particle shape of the matrix, and (e) providing one or more passageways through the coating. The amount of modulator contained within a sustained release formulation depends upon, for example, the method of administration (*e.g.*, the site of implantation), the rate and expected duration of release and the nature of the condition to be treated or prevented.

The matrix material, which itself may or may not serve a controlled-release function, is generally any material that supports the active ingredient(s). For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. Active ingredient(s) may be combined with matrix material prior to formation of the dosage form (*e.g.*, a tablet). Alternatively, or in addition, active ingredient(s) may be coated on the surface of a particle, granule, sphere, microsphere, bead or pellet that comprises the matrix material. Such coating may be achieved by conventional means, such as by dissolving the active ingredient(s) in water or other suitable solvent and spraying. Optionally, additional ingredients are added prior to coating (*e.g.*, to assist binding of the active ingredient(s) to the matrix material or to color the solution). The matrix may then be coated with a barrier agent prior to application of controlled-release coating. Multiple coated matrix units may, if desired, be encapsulated to generate the final dosage form.

In certain embodiments, a controlled release is achieved through the use of a controlled release coating (*i.e.*, a coating that permits release of active ingredient(s) at a controlled rate in aqueous medium). The controlled release coating should be a strong, continuous film that is smooth, capable of supporting pigments and other additives, non-toxic, inert and tack-free. Coatings that regulate release of the modulator include pH-independent coatings, pH-dependent coatings (which may be used to release modulator in the stomach) and enteric coatings (which allow the formulation to pass intact through the stomach and into the small intestine, where the coating dissolves and the contents are absorbed by the body). It will be apparent that multiple coatings may be employed (*e.g.*, to allow release of a portion of the dose in the stomach and a portion further along the gastrointestinal

tract). For example, a portion of active ingredient(s) may be coated over an enteric coating, and thereby released in the stomach, while the remainder of active ingredient(s) in the matrix core is protected by the enteric coating and released further down the GI tract. pH dependent coatings include, for example, shellac, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate, methacrylic acid ester copolymers and zein.

In certain embodiments, the coating is a hydrophobic material, preferably used in an amount effective to slow the hydration of the gelling agent following administration. Suitable hydrophobic materials include alkyl celluloses (*e.g.*, ethylcellulose or carboxymethylcellulose), cellulose ethers, cellulose esters, acrylic polymers (*e.g.*, poly(acrylic acid), poly(methacrylic acid), acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxy ethyl methacrylates, cyanoethyl methacrylate, methacrylic acid alkamide copolymer, poly(methyl methacrylate), polyacrylamide, ammonio methacrylate copolymers, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride) and glycidyl methacrylate copolymers) and mixtures of the foregoing. Representative aqueous dispersions of ethylcellulose include, for example, AQUACOAT® (FMC Corp., Philadelphia, PA) and SURELEASE® (Colorcon, Inc., West Point, PA), both of which can be applied to the substrate according to the manufacturer's instructions. Representative acrylic polymers include, for example, the various EUDRAGIT® (Rohm America, Piscataway, NJ) polymers, which may be used singly or in combination depending on the desired release profile, according to the manufacturer's instructions.

The physical properties of coatings that comprise an aqueous dispersion of a hydrophobic material may be improved by the addition of one or more plasticizers. Suitable plasticizers for alkyl celluloses include, for example, dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate and triacetin. Suitable plasticizers for acrylic polymers include, for example, citric acid esters such as triethyl citrate and tributyl citrate, dibutyl phthalate, polyethylene glycols, propylene glycol, diethyl phthalate, castor oil and triacetin.

Controlled-release coatings are generally applied using conventional techniques, such as by spraying in the form of an aqueous dispersion. If desired, the coating may comprise pores or channels to facilitate release of active ingredient. Pores and channels may be generated by well known methods, including the addition of organic or inorganic material that is dissolved, extracted or leached from the coating in the environment of use. Certain such pore-forming materials include hydrophilic polymers, such as hydroxyalkylcelluloses (*e.g.*, hydroxypropylmethylcellulose), cellulose ethers, synthetic water-soluble polymers (*e.g.*, polyvinylpyrrolidone, cross-linked polyvinylpyrrolidone and polyethylene oxide), water-soluble polydextrose, saccharides and polysaccharides and alkali metal salts. Alternatively, or in addition, a controlled release coating may include one or more orifices, which may be formed by methods such as those described in US Patent Nos. 3,845,770; 4,034,758; 4,077,407; 4,088,864; 4,783,337 and 5,071,607. Controlled-release may also be achieved through the use of transdermal patches, using conventional technology (*see, e.g.*, US Patent No. 4,668,232).

Further examples of controlled release formulations, and components thereof, may be found, for example, in US Patent Nos. 4,572,833; 4,587,117; 4,606,909; 4,610,870; 4,684,516; 4,777,049; 4,994,276; 4,996,058; 5,128,143; 5,202,128; 5,376,384; 5,384,133; 5,445,829; 5,510,119; 5,618,560; 5,643,604; 5,891,474; 5,958,456; 6,039,980; 6,143,353; 6,126,969; 6,156,342; 6,197,347; 6,387,394; 6,399,096; 6,437,000; 6,447,796; 6,475,493; 6,491,950; 6,524,615; 6,838,094; 6,905,709; 6,923,984; 6,923,988; and 6,911,217; each of which is hereby incorporated by reference for its teaching of the preparation of controlled release dosage forms.

In addition to or together with the above modes of administration, a compound provided herein may be conveniently added to food or drinking water (*e.g.*, for administration to non-human animals including companion animals (such as dogs and cats) and livestock). Animal feed and drinking water compositions may be formulated so that the animal takes in an appropriate quantity of the composition along with its diet. It may also be convenient to present the composition as a premix for addition to feed or drinking water.

Benzimidazole carboxamide derivatives provided herein are generally administered in a therapeutically effective amount. Preferred systemic doses are no higher than 50 mg per kilogram of body weight per day (*e.g.*, ranging from about 0.001 mg to about 50 mg per kilogram of body weight per day), with oral doses generally being about 5-20 fold higher than intravenous doses (*e.g.*, ranging from 0.01 to 40 mg per kilogram of body weight per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage unit will vary depending, for example, upon the patient being treated and the particular mode of administration. Dosage units will generally contain from about 10 μ g to about 500 mg of an active ingredient. Optimal dosages may be established using routine testing, and procedures that are well known in the art.

Pharmaceutical compositions provided herein may, but need not, further comprise one or more additional pharmaceutical agents, such as an anti-inflammatory agent or analgesic. Anti-inflammatory agents include, for example, non-steroidal anti-inflammatory drugs (NSAIDs), non-specific and cyclooxygenase-2 (COX-2) specific cyclooxygenase enzyme inhibitors, gold compounds, corticosteroids, methotrexate, leflunomide, cyclosporine A, IM gold, minocycline, azathioprine, tumor necrosis factor (TNF) receptor antagonists, soluble TNF alpha receptor (etanercept), anti-TNF alpha antibodies (*e.g.*, infliximab and adalimumab), anti-C5 antibodies, interleukin-1 (IL-1) receptor antagonists (*e.g.*, anakinra or IL-1 trap), IL-18 binding protein, CTLA4-Ig (*e.g.*, abatacept), anti-human IL-6 receptor monoclonal antibody (*e.g.*, tocilizumab), LFA-3-Ig fusion proteins (*e.g.*, alefacept), LFA-1 antagonists, anti-VLA4 monoantibody (*e.g.*, natalizumab), anti-CD11a monoclonal antibody, anti-CD20 monoclonal antibody (*e.g.*, rituximab), anti-IL-12 monoclonal antibody, anti-IL-15 monoclonal antibody, CDP 484, CDP 870, chemokine receptor antagonists, selective iNOS inhibitors, p38 kinase inhibitors, integrin antagonists, angiogenesis inhibitors, and TMI-1 dual inhibitors. Further anti-inflammatory agents include meloxicam, rofecoxib, celecoxib, etoricoxib, parecoxib, valdecoxib and tilicoxib.

NSAIDs include, but are not limited to, ibuprofen, flurbiprofen, naproxen or naproxen sodium, diclofenac, combinations of diclofenac sodium and misoprostol, sulindac, oxaprozin, diflunisal, piroxicam, indomethacin, etodolac, fenoprofen calcium, ketoprofen, sodium nabumetone, sulfasalazine, tolmetin sodium, and hydroxychloroquine. One class of NSAIDs consists of compounds that inhibit cyclooxygenase (COX) enzymes; such compounds include celecoxib and rofecoxib. NSAIDs further include salicylates such as acetylsalicylic acid or aspirin, sodium salicylate, choline and magnesium salicylates, and salsalate, as well as corticosteroids such as cortisone, dexamethasone, methylprednisolone, prednisolone, prednisolone sodium phosphate, and prednisone.

Certain analgesics for use in combination with B₁ modulators provided herein are also anti-inflammatory agents, and are listed above. Other such medications include narcotic agents which typically act at one or more opioid receptor subtypes (*e.g.*, μ , κ and/or δ), preferably as agonists or partial agonists. Such agents include opiates, opiate derivatives and opioids, as well as pharmaceutically acceptable salts and hydrates thereof. Specific examples of narcotic analgesics include, within preferred embodiments, alfentanil, alphaprodine, anileridine, bezitramide, buprenorphine, butorphanol, codeine, diacetyldihydromorphine, diacetylmorphine, dihydrocodeine, diphenoxylate, ethylmorphine, fentanyl, heroin, hydrocodone, hydromorphone, isomethadone, levomethorphan, levorphan, levorphanol, meperidine, metazocine, methadone, methorphan, metopon, morphine, nalbuphine, opium extracts, opium fluid extracts, powdered opium, granulated opium, raw opium, tincture of opium, oxycodone, oxymorphone, paregoric, pentazocine, pethidine, phenazocine, piminodine, propoxyphene, racemethorphan, racemorphan, sulfentanyl, thebaine and pharmaceutically acceptable salts and hydrates of the foregoing agents.

Other examples of narcotic analgesic agents include acetorphine, acetyldihydrocodeine, acetylmethadol, allylprodine, alphracetylmethadol, alphameprodine, alphamethadol, benzethidine, benzylmorphine, betacetylmethadol, betameprodine, betamethadol, betaprodine, clonitazene, codeine methylbromide, codeine-N-oxide, cyprenorphine, desomorphine, dextromoramide, diampromide, diethylthiambutene, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, drotebanol, ethanol, ethylmethylthiambutene, etonitazene, etorphine, etoxeridine, furethidine, hydromorphenol, hydroxypethidine, ketobemidone, levomoramide, levophenacymorphan, methyl-desorphine, methyldihydromorphine, morpheridine, morphine methylpromide, morphine methylsulfonate, morphine-N-oxide, myrophin, naloxone, naltrexone, nicocodeine, nicomorphine, noracymethadol, norlevorphanol, normethadone, normorphine, norpipanone, pentazocaine, phenadoxone, phenampromide, phenomorphan, phenoperidine, piritramide, pholcodine, proheptazoline, properidine, propiran, racemoramide, thebacon, trimeperidine and the pharmaceutically acceptable salts and hydrates thereof.

Further specific representative analgesic agents include, for example acetaminophen (paracetamol); aspirin and other NSAIDs described above; NR2B antagonists; capsaicin receptor

antagonists; anti-migraine agents; anticonvulsants such as oxcarbazepine and carbamazepine; antidepressants (such as TCAs, SSRIs, SNRIs, substance P antagonists, etc.); spinal blocks; pentazocine/naloxone; meperidine; levorphanol; buprenorphine; hydromorphone; fentanyl; sufentanyl; oxycodone; oxycodone/acetaminophen, nalbuphine and oxymorphone. Still further
5 analgesic agents include CB2-receptor agonists, such as AM1241, capsaicin receptor antagonists and compounds that bind to the $\alpha 2\delta$ subunit of voltage-gated calcium channels, such as gabapentin and pregabalin.

Representative anti-migraine agents for use in combination with a B₁ modulator provided herein include CGRP antagonists, ergotamines and 5-HT₁ agonists, such as sumatriptan, naratriptan,
10 zolmatriptan and rizatriptan.

Pharmaceutical compositions may be packaged for treating conditions responsive to B₁ modulation (*e.g.*, treatment of pain, inflammation or other disorder(s) recited herein). Packaged pharmaceutical preparations generally comprise a container holding a therapeutically effective amount of a pharmaceutical composition as described above and instructions (*e.g.*, labeling) indicating that
15 the composition is to be used for treating a condition responsive to B₁ modulation in a patient (*e.g.*, pain or other disorder as indicated herein). In certain embodiments, a packaged pharmaceutical preparation comprises one or more benzimidazole carboxamide derivatives provided herein and one or more additional agents in the same package, either in separate containers within the package or in the same container (*i.e.*, as a mixture). Preferred mixtures are formulated for oral administration (*e.g.*,
20 as pills, capsules, tablets or the like). In certain embodiments, the package comprises a label bearing indicia indicating that the components are to be taken together for the treatment of pain.

METHODS OF USE

Within certain aspects, the present invention provides methods for treating a condition responsive to B₁ modulation in a patient. The patient may be afflicted with such a condition, or may
25 be free of symptoms but considered at risk for developing such a condition. A condition is "responsive to B₁ modulation" if the condition or symptom(s) thereof are alleviated, attenuated, delayed or otherwise improved by modulation of B₁ activity. In general, such methods comprise administering to the patient a therapeutically effective amount of at least one benzimidazole carboxamide derivative as provided herein.

30 Conditions responsive to B₁ modulation include, for example pain; inflammation including neuroinflammation (such as atherosclerosis), inflammation associated with airway diseases (*e.g.*, asthma, including allergic asthma, exercise-induced bronchoconstriction, occupational asthma, and other non-allergic asthmas), and inflammatory skin disorders (*e.g.*, psoriasis and eczema)); respiratory disorders including bronchoconstriction, asthma, chronic obstructive pulmonary disease (*e.g.*,
35 emphysema), chronic cough (including ACE-inhibitor cough), adult respiratory distress syndrome, bronchitis, pneumonia, allergic rhinitis and vasomotor rhinitis; vascular edema (including diabetes-related vascular disease); and epilepsy.

Other conditions responsive to B₁ modulation include diabetes (*e.g.*, type II or non insulin dependent, as well as diabetic vasculopathy, diabetic neuropathy, diabetic retinopathy, post capillary resistance and symptoms associated with insulinitis), seizure disorders (*e.g.*, epilepsy), multiple sclerosis, liver disease, cardiovascular disorders (*e.g.*, atherosclerosis, congestive heart failure and myocardial infarction), neurodegenerative diseases (*e.g.*, Alzheimer's disease and Parkinson's disease) rheumatoid arthritis, infection, cancer, cranial trauma, rhinitis, septic shock, endotoxic and pancreatic shock, anaphylaxis, inflammatory bowel disease, irritable bowel syndrome, pancreatitis, cystitis, uveitis, vascular permeability, gingivitis, osteoporosis, benign prostatic hyperplasia, hyperactive bladder, cerebral edema, vasodilation, hypotension associated with sepsis, edema resulting from trauma associated with burns, sprains or fracture, cerebral edema, angiodema, Crohn's disease and ulcerative colitis. B₁ modulators may also be used as smooth muscle relaxants for treating spasms of the gastrointestinal tract of uterus. In certain embodiments, the condition responsive to B₁ modulation is pain or inflammation.

Pain that may be treated using the B₁ modulators provided herein may be chronic or acute and includes, but is not limited to, peripheral nerve-mediated pain (especially neuropathic pain, such as pain due to diabetes, postherpetic neuralgia, nerve injury, vulvodynia, root avulsions, painful traumatic neuropathy and painful polyneuropathy). Compounds provided herein may also be used in the treatment of, for example, visceral pain (*e.g.*, pancreatitis, interstitial cystitis and renal colic), persistent hyperalgesia, inflammatory pain, repetitive motion pain, carpal tunnel syndrome, perioperative pain, algesia, oral neuropathic pain, toothache (dental pain), denture pain, ocular pain, postherpetic neuralgia, diabetic neuropathy, chemotherapy-induced neuropathy, reflex sympathetic dystrophy, trigeminal neuralgia, bone and joint pain (*e.g.*, pain associated with osteoarthritis), rheumatoid arthritis, myofascial pain (*e.g.*, muscular injury and fibromyalgia), Guillain-Barre syndrome, meralgia paresthetica, burning-mouth syndrome and/or pain associated with nerve and root damage, including as pain associated with peripheral nerve disorders (*e.g.*, nerve entrapment and brachial plexus avulsions, amputation, peripheral neuropathies including bilateral peripheral neuropathy, tic douloureux, atypical facial pain, nerve root damage, and arachnoiditis). Additional neuropathic pain conditions include causalgia (reflex sympathetic dystrophy - RSD, secondary to injury of a peripheral nerve), neuritis (including, for example, sciatic neuritis, peripheral neuritis, polyneuritis, optic neuritis, postfebrile neuritis, migrating neuritis, segmental neuritis and Gombault's neuritis), neuronitis, neuralgias (*e.g.*, those mentioned above, cervicobrachial neuralgia, cranial neuralgia, geniculate neuralgia, glossopharyngeal neuralgia, migranous neuralgia, idiopathic neuralgia, intercostals neuralgia, mammary neuralgia, mandibular joint neuralgia, Morton's neuralgia, nasociliary neuralgia, occipital neuralgia, red neuralgia, Sluder's neuralgia, splenopalatine neuralgia, supraorbital neuralgia and vidian neuralgia), musculoskeletal pain, AIDS-related neuropathy, MS-related neuropathy, central nervous system pain (*e.g.*, pain due to brain stem damage, sciatica, and ankylosing spondylitis), and spinal pain, including spinal cord injury-related pain.

Headache, including headaches involving peripheral nerve activity may also be treated as described herein. Such headache pain includes, for example, sinus, cluster (*i.e.*, migranous neuralgia) and tension headaches, migraine, temporomandibular pain and maxillary sinus pain. For example, migraine headaches may be prevented by administration of a compound provided herein as soon as a pre-migrainous aura is experienced by the patient.

Further conditions that can be treated as described herein include Charcot's pains, intestinal gas pains, ear pain, heart pain, muscle pain, eye pain, orofacial pain (*e.g.*, odontalgia), abdominal pain, gynaecological pain (*e.g.*, menstrual pain, dysmenorrhoea, pain associated with cystitis, labor pain, chronic pelvic pain, chronic proctitis and endometriosis), acute and chronic back pain (*e.g.*, lower back pain), gout, scar pain, hemorrhoidal pain, dyspeptic pains, pain associated with angina, nerve root pain, "non-painful" neuropathies, complex regional pain syndrome, homotopic pain and heterotopic pain – including pain associated with carcinoma, often referred to as cancer pain (*e.g.*, in patients with bone cancer), pain (and inflammation) associated with venom exposure (*e.g.*, due to snake bite, spider bite, or insect sting) and trauma associated pain (*e.g.*, post-surgical pain such as postmastectomy, postthoracotomy and stump pain; phantom limb pain, episiotomy pain, pain from cuts, musculoskeletal pain, bruises and broken bones, and burn pain, especially primary hyperalgesia associated therewith). Additional pain conditions that may be treated as described herein include pain associated with respiratory disorders as described above, autoimmune diseases, immunodeficiency disorders, hot flashes, inflammatory bowel disease, gastroesophageal reflux disease (GERD), irritable bowel syndrome and/or inflammatory bowel disease.

In certain embodiments, pain treated with B₁ modulators provided herein is inflammatory pain, acute pain, dental pain, back pain, surgical pain, headache, neuropathic pain or pain from osteoarthritis or trauma.

It will be apparent that compounds provided herein may be administered alone or in combination with one or more additional agents that are suitable for treating the disorder of interest. Within such combination therapy, the compound(s) and additional agent(s) may be present in the same pharmaceutical composition, or may be administered separately in either order. Representative anti-inflammatory agents and analgesics for use in combination therapy include those indicated above.

Within other aspects, B₁ modulators provided herein may be used within combination therapy for the treatment of conditions involving pain and/or inflammatory components. Such conditions include, for example, autoimmune disorders and pathologic autoimmune responses known to have an inflammatory component including, but not limited to, arthritis (especially rheumatoid arthritis), psoriasis, Crohn's disease, lupus erythematosus, irritable bowel syndrome, tissue graft rejection, and hyperacute rejection of transplanted organs. Other such conditions include trauma (*e.g.*, injury to the head or spinal cord), cardio- and cerebro-vascular disease and certain infectious diseases. Within such combination therapy, a B₁ modulator is administered to a patient along with an additional analgesic and/or anti-inflammatory agent. The B₁ modulator and additional analgesic and/or anti-inflammatory

agent may be present in the same pharmaceutical composition, or may be administered separately in either order.

Administration to the patient can be by way of any means discussed above, including oral, topical, nasal or transdermal administration, or intravenous, intramuscular, subcutaneous, intrathecal, epidural, intracerebroventricular or like injection. Oral administration is preferred in certain
5 embodiments (*e.g.*, formulated as pills, capsules, tablets or the like).

Treatment regimens may vary depending on the compound used and the particular condition to be treated. In general, a dosage regimen of 4 times daily or less is preferred, with 1 or 2 times daily particularly preferred. It will be understood, however, that the specific dose and treatment regimen
10 for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex and diet of the patient, the time of administration, the route of administration, the rate of excretion, any drug combination and the severity of the particular disease undergoing therapy. Dosages are generally as described above; in general, the use of the minimum dose sufficient to provide effective therapy is preferred. Patients
15 may generally be monitored for therapeutic effectiveness using medical or veterinary criteria suitable for the condition being treated or prevented.

Suitable dosages for B₁ modulators (either alone or within such combination therapy) are generally as described above. Dosages and methods of administration of any additional agent(s) (*e.g.*, anti-inflammatory and/or analgesic agents) can be found, for example, in the manufacturer's
20 instructions or in the *Physician's Desk Reference*. In certain embodiments, combination administration results in a reduction of the dosage of the additional agent required to produce a therapeutic effect (*i.e.*, a decrease in the minimum therapeutically effective amount). Thus, preferably, the dosage of additional agent in a combination or combination treatment method of the invention is less than the maximum dose advised by the manufacturer for administration of the agent
25 without combination with a compound of Formula I. More preferably this dose is less than $\frac{3}{4}$, even more preferably less than $\frac{1}{2}$, and highly preferably less than $\frac{1}{4}$ of the maximum dose, while most preferably the dose is less than 10% of the maximum dose advised by the manufacturer for administration of the agent(s) when administered without combination administration as described herein. It will be apparent that the dose of compound as provided herein needed to achieve the
30 desired effect may similarly be affected by the dose and potency of the additional agent.

Within separate aspects, the present invention provides a variety of non-pharmaceutical *in vitro* and *in vivo* uses for the compounds provided herein. For example, such compounds may be labeled and used as probes for the detection and localization of B₁ (in samples such as cell preparations or tissue sections, preparations or fractions thereof). In addition, compounds provided
35 herein that comprise a suitable reactive group (such as an aryl carbonyl, nitro or azide group) may be used in photoaffinity labeling studies of receptor binding sites. In addition, compounds provided herein may be used as positive controls in assays for receptor activity, as standards for determining

the ability of a candidate agent to bind to B_1 , or as radiotracers for positron emission tomography (PET) imaging or for single photon emission computerized tomography (SPECT). Such methods can be used to characterize B_1 receptors in living subjects. For example, a compound may be labeled using any of a variety of well known techniques (*e.g.*, radiolabeled with a radionuclide such as tritium, as described herein), and incubated with a sample for a suitable incubation time (*e.g.*, determined by first assaying a time course of binding). Following incubation, unbound compound is removed (*e.g.*, by washing), and bound compound detected using any method suitable for the label employed (*e.g.*, autoradiography or scintillation counting for radiolabeled compounds; spectroscopic methods may be used to detect luminescent groups and fluorescent groups). As a control, a matched sample containing labeled compound and a greater (*e.g.*, 10-fold greater) amount of unlabeled compound may be processed in the same manner. A greater amount of detectable label remaining in the test sample than in the control indicates the presence of B_1 in the sample. Detection assays, including receptor autoradiography (receptor mapping) of B_1 in cultured cells or tissue samples may be performed as described by Kuhar in sections 8.1.1 to 8.1.9 of Current Protocols in Pharmacology (1998) John Wiley & Sons, New York.

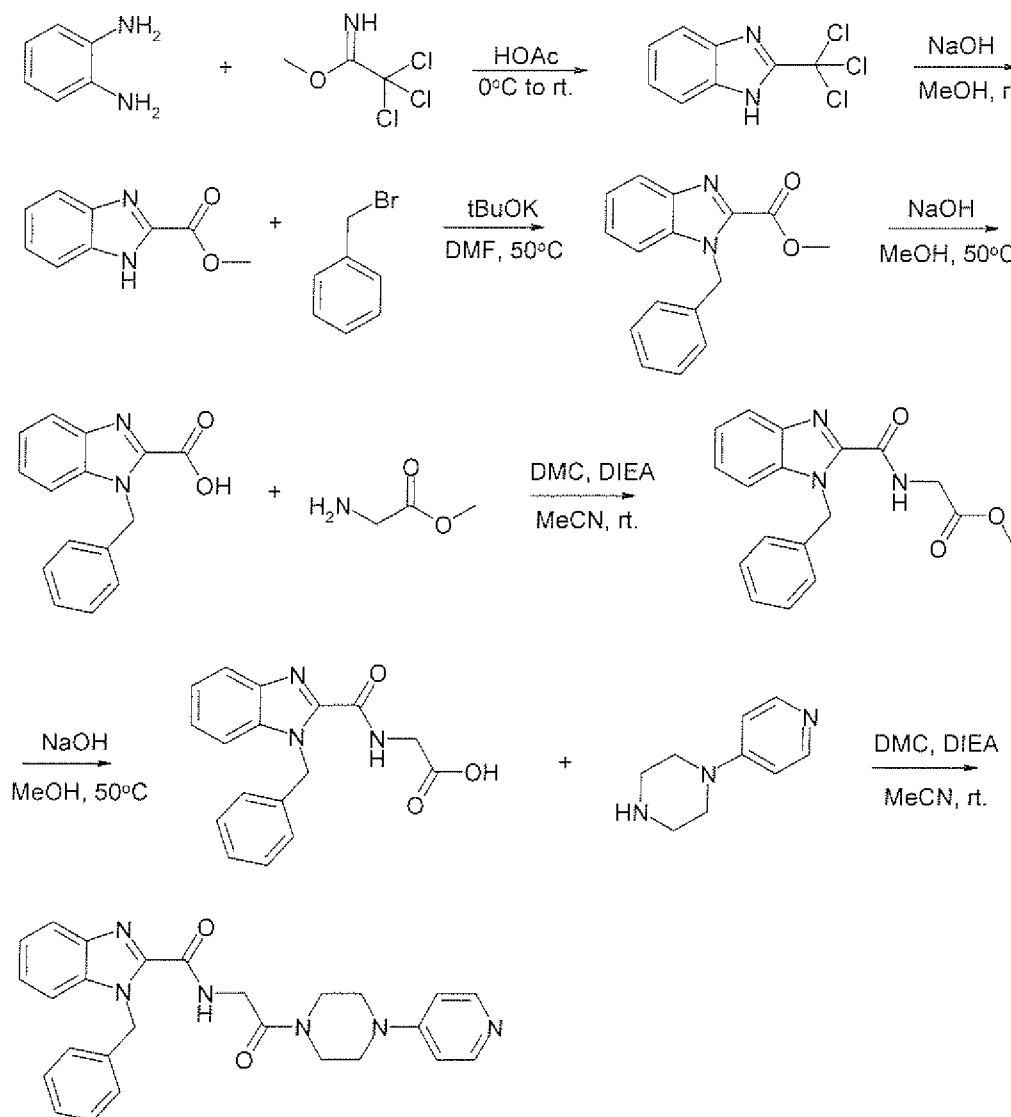
The following Examples are offered by way of illustration and not by way of limitation. Unless otherwise specified all reagents and solvent are of standard commercial grade and are used without further purification. Using routine modifications, the starting materials may be varied and additional steps employed to produce other compounds provided herein.

EXAMPLES

Mass spectroscopy data in the following Examples is Electrospray MS, obtained in positive ion mode using a Micromass Time-of-Flight LCT (Micromass, Beverly MA), equipped with a Waters 600 pump (Waters Corp.; Milford, MA), Waters 996 photodiode array detector, and a Gilson 215 autosampler (Gilson, Inc.; Middleton, WI). MassLynx (Advanced Chemistry Development, Inc; Toronto, Canada) version 4.0 software with OpenLynx Global Server™, OpenLynx™ and AutoLynx™ processing is used for data collection and analysis. MS conditions are as follows: capillary voltage = 3.5 kV; cone voltage = 30 V, desolvation and source temperature = 350°C and 120°C, respectively; mass range = 181-750 with a scan time of 0.22 seconds and an interscan delay of 0.05 min.

Sample volume of 1 microliter is injected onto a 50x4.6mm Chromolith SpeedROD RP-18e column (Merck KGaA, Darmstadt, Germany), and eluted using a 2-phase linear gradient at a flow rate of 6 ml/min. Sample is detected using total absorbance count over the 220-340nm UV range. The elution conditions are: Mobile Phase A - 95% water, 5% MeOH with 0.05% TFA; Mobile Phase B - 5% water, 95% MeOH with 0.025% TFA. The following gradient is used: 0-0.5 min 10-100%B, hold at 100%B to 1.2 min, return to 10%B at 1.21 min. Inject to inject cycle is 2.15 min.

EXAMPLE 1. SYNTHESIS OF 1-BENZYL-N-[2-OXO-2-(4-PYRIDIN-4-YLPIPERAZIN-1-YL)ETHYL]-1H-BENZIMIDAZOLE-2-CARBOXAMIDE



STEP 1. PREPARATION OF 2-TRICHLOROMETHYL-1H-BENZOIMIDAZOLE

- 5 Add methyl 2,2,2-trichloroacetimidate (31 mL, 0.25 mol) drop-wise to a solution of benzene-1,2-diamine (25 g, 0.23 mol) in HOAc (300 mL) at 0 °C and allow the solution to warm to rt. After 2 h, pour the mixture onto 500 mL ice-H₂O and stir for 1 h. Filter the solid and air-dry to give crude title compound.

STEP 2. PREPARATION OF 1H-BENZOIMIDAZOL-2-CARBOXYLIC ACID METHYL ESTER

- 10 Add Na₂CO₃ (9 g, 85 mmol) to a solution of 2-trichloromethyl-1H-benzimidazole (20 g, 85 mmol) in 500 mL MeOH at rt. Heat the mixture at reflux for 14 h and then cool to rt. Pour into 1 L H₂O and filter off the solid. Evaporate the volatiles and extract the residue with EtOAc. Combine the extracts, dry over Na₂SO₄ and evaporate to give the title compound.

STEP 3. PREPARATION OF 1-BENZYL-1H-BENZOIMIDAZOL-2-CARBOXYLIC ACID METHYL ESTER

Add tBuOK (2.02 g, 18 mmol) to a solution of 1H-benzoimidazol-2-carboxylic acid methyl ester (3 g, 17 mmol) in DMF (75 mL) and stir for 15 min at rt. Add benzyl chloride (800 mg, 18 mmol) in one portion. Heat the mixture at 50 °C for 5 h. Evaporate the solvent, add brine and extract
5 with EtOAc. Dry over Na₂SO₄ and remove the solvent to give crude title compound.

STEP 4. PREPARATION OF 1-BENZYL-1H-BENZOIMIDAZOL-2-CARBOXYLIC ACID

Add NaOH (3 mL of 10 N solution, 30 mmol) to a solution of 1-benzyl-1H-benzoimidazol-2-carboxylic acid methyl ester (4.3 g, 16 mmol) in MeOH (10 mL) at rt. Heat the mixture at 50 °C for 4 h. Evaporate to dryness. Add H₂O to dissolve the solid and adjust the pH to 3 with 6 N HCl. Collect
10 the solid by filtration and wash with H₂O, ether and dry to give the title compound.

STEP 5. PREPARATION OF [(1-BENZYL-1H-BENZOIMIDAZOLE-CARBONYL)-AMINO]-ACETIC ACID METHYL ESTER

Add DMC (1.3 g, 8 mmol) to a solution of 1-benzyl-1H-benzoimidazol-2-carboxylic acid (1 g, 4 mmol), DIEA (2.4 mL, 14 mmol) and glycine methyl ester HCl salt (515 mg, 4.1 mmol) in 120
15 mL MeCN at rt. Stir the mixture for 2 h at rt. Purify by flash column (elute with 1% MeOH in DCM) to give the title compound.

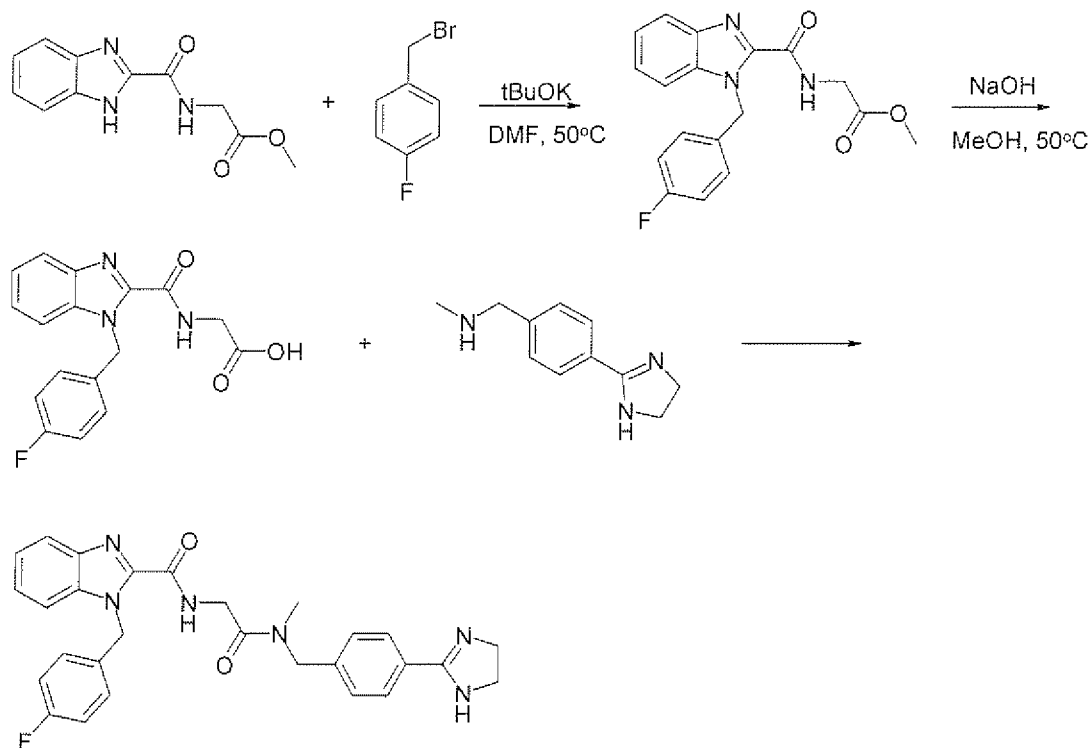
STEP 6. PREPARATION OF [(1-BENZYL-1H-BENZOIMIDAZOLE-CARBONYL)-AMINO]-ACETIC ACID

To NaOH (1 mL of 10N solution; 10 mmol) add a solution of [(1-benzyl-1H-benzoimidazole-carbonyl)-amino]-acetic acid methyl ester (1.1 g, 3.4 mmol) in MeOH (5 mL). Heat the mixture at 50
20 °C for 4 h. Evaporate and add H₂O to dissolve the solid and adjust the pH to 3 with 6 N HCl. Filter the solid and wash with H₂O and ether and dry to give the title compound.

STEP 7. PREPARATION OF 1-BENZYL-N-[2-OXO-2-(4-PYRIDIN-4-YLPIPERAZIN-1-YL)ETHYL]-1H-BENZIMIDAZOLE-2-CARBOXAMIDE

Add DMC (33 mg, 0.2 mmol) to a solution of [(1-benzyl-1H-benzoimidazole-carbonyl)-amino]-acetic acid (30 mg, 0.1 mmol), DIEA (61 µL, 0.35 mmol) and 1-(4-pyridyl)-piperazine (18.3
25 mg, 0.1 mmol) in 0.5 mL MeCN at rt. Stir the mixture for 2 h at rt. Purify the crude product by flash column (elute with 1% MeOH in DCM) to give the title compound. ¹H NMR (CDCl₃): 8.19-8.17 (d, 2H), 7.80-7.76 (d, 1H), 7.54-7.52 (d, 1H), 7.36-7.34 (m, 2H), 7.29-7.16 (m, 7H), 6.01 (s, 2H), 4.37 (s, 2H), 3.83-3.75 (m, 8H).

EXAMPLE 2. SYNTHESIS OF N-(2-{[4-(4,5-DIHYDRO-1H-IMIDAZOL-2-
YL)BENZYL](METHYL)AMINO}-2-OXOETHYL)-1-(4-FLUOROBENZYL)-1H-BENZIMIDAZOLE-2-
CARBOXAMIDE



5 STEP 1. PREPARATION OF [(1-BENZYL-1H-BENZOIMIDAZOLE-2-CARBONYL)-AMINO]-ACETIC ACID
METHYL ESTER

Add tBuOK (68 mg, 0.6 mmol) to a solution of 1H-benzoimidazol-2-carboxylic acid methyl
ester (150 mg, 0.54 mmol) in DMF (3 mL) at rt and stir for 15 min. Add 4-fluorobenzyl bromide (113
mg, 0.6 mmol) in one portion. Heat the mixture at 50 °C for 14 h. Evaporate, add brine and extract
10 with EtOAc. Dry over Na₂SO₄ and remove the solvent to give crude title compound.

STEP 2. PREPARATION OF [(1-BENZYL-1H-BENZOIMIDAZOLE-2-CARBONYL)-AMINO]-ACETIC ACID

Add NaOH (0.1 mL of 10 N solution, 1 mmol) to a solution of [(1-benzyl-1H-
benzoimidazole-2-carbonyl)-amino]-acetic acid methyl ester (50 mg, 0.13 mmol) in MeOH (1 mL) at
rt. Heat the mixture at 50 °C for 4 h. Evaporate and add H₂O to dissolve the solid and adjust the pH
15 to 3 with 6 N HCl. Collect the solid by filtration and wash with H₂O and ether and dry to give the title
compound.

STEP 3. PREPARATION OF N-(2-{[4-(4,5-DIHYDRO-1H-IMIDAZOL-2-YL)BENZYL](METHYL) AMINO}-2-
OXOETHYL)-1-(4-FLUOROBENZYL)-1H-BENZIMIDAZOLE-2-CARBOXAMIDE

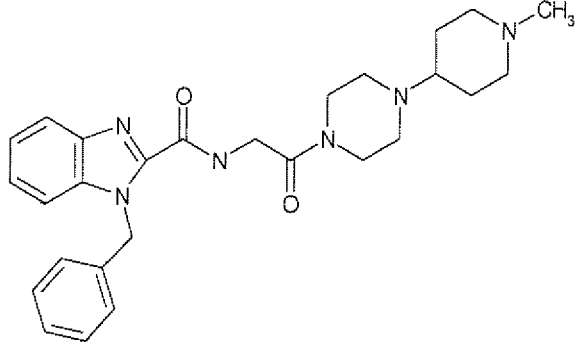
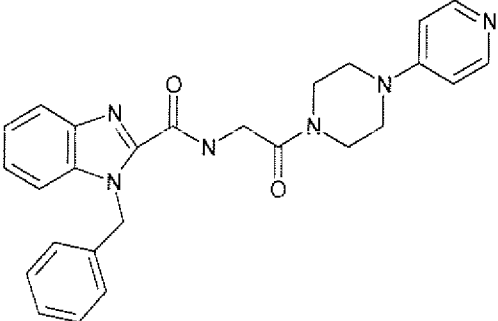
Add BOP (32 mg, 0.073 mmol) to a solution of [(1-benzyl-1H-benzoimidazole-2-carbonyl)-
amino]-acetic acid (16 mg, 0.049 mmol), [4-(4,5-dihydro-1H-imidazol-2-yl)-benzyl]-methylamine
20 (9.5 mg, 0.05 mmol), 1-hydroxybenzotriazole (1 mg, 0.008 mmol) and DIEA (20 µL, 0.12 mmol) in

DMF (0.2 mL) at rt. Stir the mixture for 14 h. Remove the solvent and purify by PTLC (elute with 10%MeOH/1%NH₃OH in DCM) to give the title compound. ¹H NMR (CD₃OD): 7.84-7.66 (m, 4H), 7.56-7.48 (m, 2H), 7.41-7.26 (m, 4H), 7.08-7-6.92 (m, 2H), 6.0-5.97 (m, 2H), 4.82-4.75 (m, 2H), 4.42-4.35 (m, 2H), 4.10-4.89 (m, 4H), 3.10-3.05 (m, 3H).

5 EXAMPLE 3. ADDITIONAL REPRESENTATIVE BENZIMIDAZOLE CARBOXAMIDE DERIVATIVES

Using routine modifications, the starting materials may be varied and additional steps employed to produce other compounds provided herein. Compounds listed in Table I are prepared using such methods. A "*" in the column headed "IC₅₀" indicates that the compound exhibits an IC₅₀ (determined as described in Example 7) that is 5 micromolar or less. Mass spectroscopy data is provided as M+1 in the column headed "MS," with the retention times ("Ret Time") given in minutes.

Table I
Representative Benzimidazole Carboxamide Derivatives

	<u>COMPOUND</u>	<u>NAME</u>	<u>MS</u>	<u>Ret Time</u>	<u>IC₅₀</u>
1		1-benzyl-N-{2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethyl}-1H-benzimidazole-2-carboxamide	475.2	1.1	*
2		1-benzyl-N-[2-oxo-2-(4-pyridin-4-ylpiperazin-1-yl)ethyl]-1H-benzimidazole-2-carboxamide	455.2	1.1	*

	<u>COMPOUND</u>	<u>NAME</u>	<u>MS</u>	<u>Ret</u> <u>Time</u>	<u>IC₅₀</u>
3		1-benzyl-N-{2-oxo-2-[4-(3-piperidin-1-yl)propyl]piperazin-1-yl}ethyl-1H-benzimidazole-2-carboxamide	503.2	1.1	*
4		1-benzyl-N-{3-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-3-oxopropyl}-1H-benzimidazole-2-carboxamide	489.3	1.1	*
5		1-benzyl-N-[3-oxo-3-(4-pyridin-4-yl)piperazin-1-yl]propyl]-1H-benzimidazole-2-carboxamide	469.2	1.1	*
6		1-benzyl-N-(3-{4-[4-(4,5-dihydro-1H-imidazol-2-yl)phenyl]piperazin-1-yl}-3-oxopropyl)-1H-benzimidazole-2-carboxamide	536.2	1.1	*
7		1-benzyl-N-[2-(1,4'-bipiperidin-1'-yl)-2-oxoethyl]-1H-benzimidazole-2-carboxamide	460.2	1.1	*

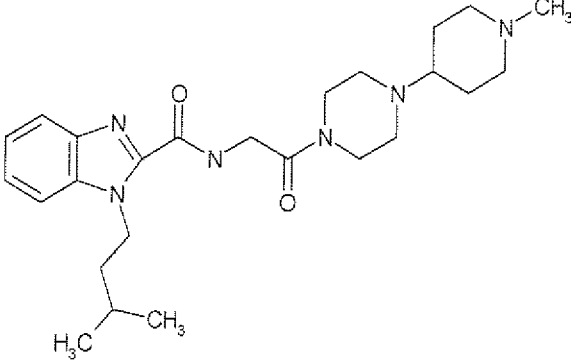
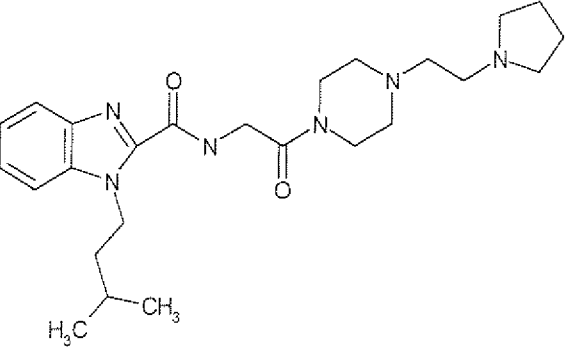
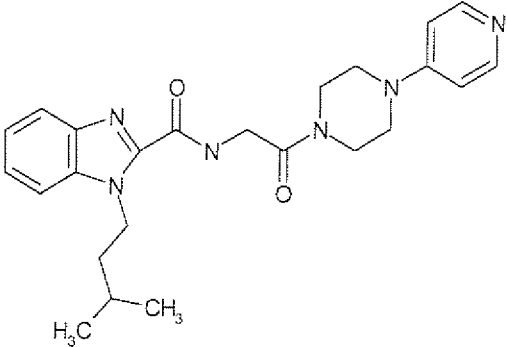
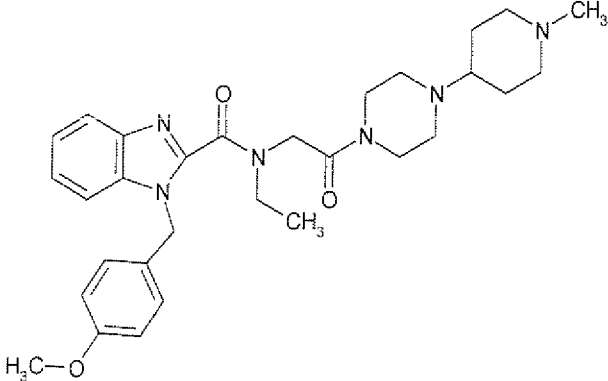
	COMPOUND	NAME	MS	Ret Time	IC ₅₀
8		1-benzyl-N-methyl-N-{2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethyl}-1H-benzimidazole-2-carboxamide	489.2	1.1	*
9		1-benzyl-N-methyl-N-[2-oxo-2-(4-pyridin-4-ylpiperazin-1-yl)ethyl]-1H-benzimidazole-2-carboxamide	469.2	1.1	*
10		1-benzyl-N-{2-oxo-2-[4-(pyridin-4-ylmethyl)piperazin-1-yl]ethyl}-1H-benzimidazole-2-carboxamide	469.2	1.1	
11		1-benzyl-N-{2-oxo-2-[4-(pyridin-3-ylmethyl)piperazin-1-yl]ethyl}-1H-benzimidazole-2-carboxamide	469.2	1.1	
12		1-benzyl-N-(2-{4-[2-(dimethylamino)-2-oxoethyl]piperazin-1-yl}-2-oxoethyl)-1H-benzimidazole-2-carboxamide	463.2	1.1	

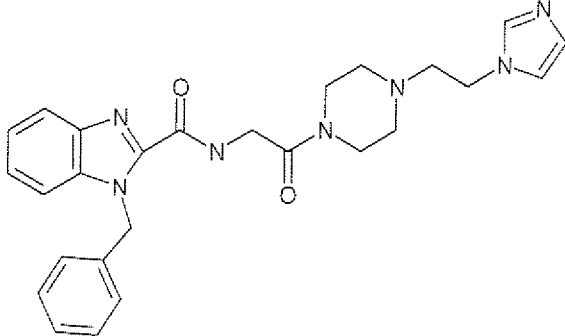
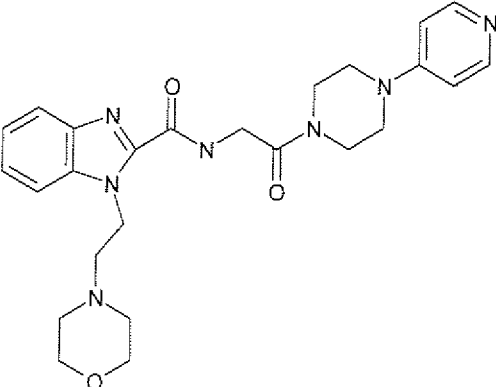
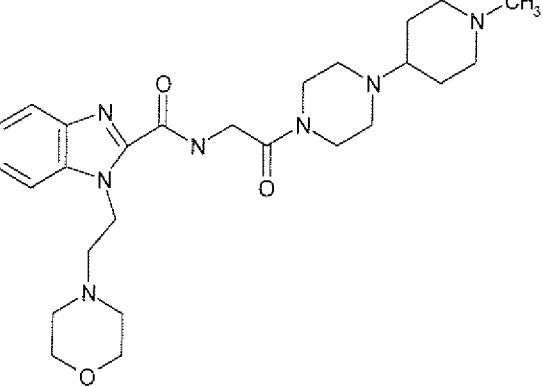
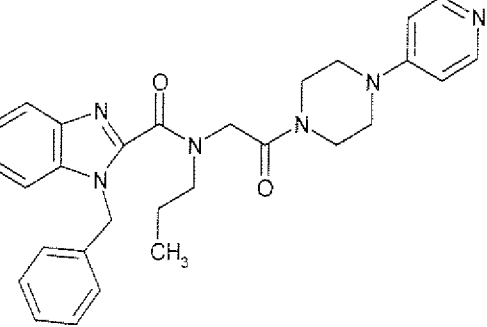
	COMPOUND	NAME	MS	Ret Time	IC ₅₀
13		1-benzyl-N-{2-oxo-2-[4-(2-oxo-2-pyrrolidin-1-ylethyl)piperazin-1-yl]ethyl}-1H-benzimidazole-2-carboxamide	489.2	1.1	
14		N-[2-oxo-2-(4-pyridin-4-ylpiperazin-1-yl)ethyl]-1-(2-phenylethyl)-1H-benzimidazole-2-carboxamide	469.2	1.1	*
15		N-{2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethyl}-1-(2-phenylethyl)-1H-benzimidazole-2-carboxamide	489.2	1.1	*
16		1-(4-methoxybenzyl)-N-[2-oxo-2-(4-pyridin-4-ylpiperazin-1-yl)ethyl]-1H-benzimidazole-2-carboxamide	485.5	1.1	*

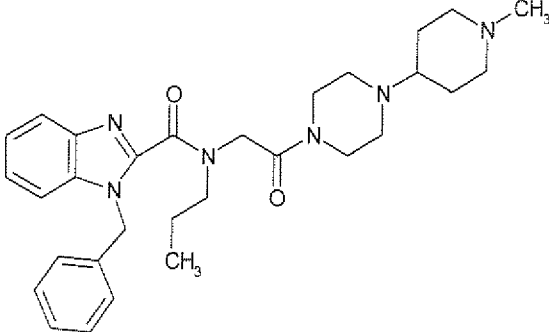
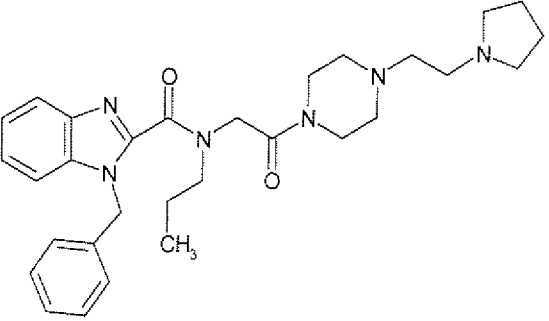
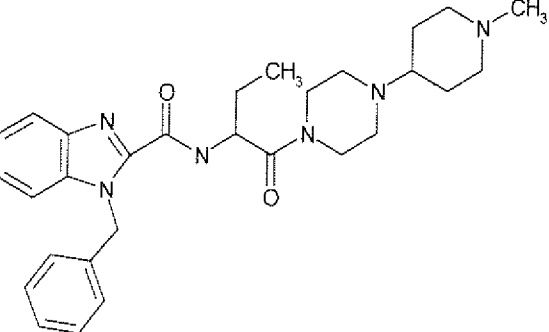
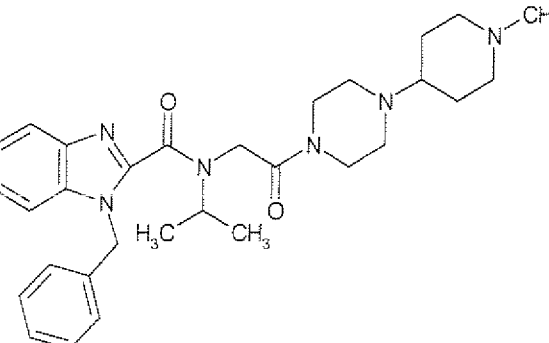
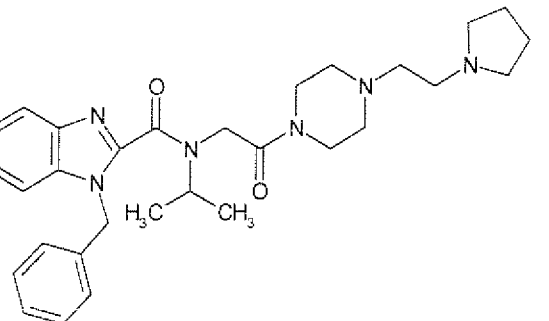
	<u>COMPOUND</u>	<u>NAME</u>	<u>MS</u>	<u>Ret</u> <u>Time</u>	<u>IC₅₀</u>
17		1-(4-methoxybenzyl)- N-{2-[4-(1- methylpiperidin-4- yl)piperazin-1-yl]-2- oxoethyl}-1H- benzimidazole-2- carboxamide	505.2	1.1	*
18		1-benzyl-N-(2-{4-[2- (diethylamino)ethyl]pip erazin-1-yl}-2- oxoethyl)-1H- benzimidazole-2- carboxamide	477.2	1.1	
19		1-benzyl-N-{2-oxo-2- [4-(2-pyrrolidin-1- ylethyl)piperazin-1- yl]ethyl}-1H- benzimidazole-2- carboxamide	475.2	1.1	*
20		1-[2-(4- methoxyphenyl)ethyl]- N-{2-[4-(1- methylpiperidin-4- yl)piperazin-1-yl]-2- oxoethyl}-1H- benzimidazole-2- carboxamide	519.2	1.1	*

	<u>COMPOUND</u>	<u>NAME</u>	<u>MS</u>	<u>Ret</u> <u>Time</u>	<u>IC₅₀</u>
21		1-benzyl-N-[2-oxo-2-(4-pyridin-4-ylpiperidin-1-yl)ethyl]-1H-benzimidazole-2-carboxamide	454.2	1.1	*
22		1-(4-methoxybenzyl)-N-[2-oxo-2-[4-(2-pyrrolidin-1-ylethyl)piperazin-1-yl]ethyl]-1H-benzimidazole-2-carboxamide	505.2	1.1	*
23		N-(2-{4-[2-(diethylamino)ethyl]piperazin-1-yl}-2-oxoethyl)-1-(4-methoxybenzyl)-1H-benzimidazole-2-carboxamide	507.2	1.1	*
24		1-benzyl-N-ethyl-N-[2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethyl]-1H-benzimidazole-2-carboxamide	503.2	1.1	*

	COMPOUND	NAME	MS	Ret Time	IC ₅₀
25		1-benzyl-N-ethyl-N-{2-oxo-2-[4-(2-pyrrolidin-1-ylethyl)piperazin-1-yl]ethyl}-1H-benzimidazole-2-carboxamide	503.2	1.1	*
26		1-(4-methoxybenzyl)-N-methyl-N-[2-oxo-2-(4-pyridin-4-yl)piperazin-1-yl]ethyl-1H-benzimidazole-2-carboxamide	499.1	1.1	*
27		1-(4-methoxybenzyl)-N-methyl-N-{2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethyl}-1H-benzimidazole-2-carboxamide	519.2	1.1	*
28		1-(4-methoxybenzyl)-N-methyl-N-{2-oxo-2-[4-(2-pyrrolidin-1-ylethyl)piperazin-1-yl]ethyl}-1H-benzimidazole-2-carboxamide	519.2	1.1	*

	COMPOUND	NAME	MS	Ret Time	IC ₅₀
29		1-(3-methylbutyl)-N-[2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethyl]-1H-benzimidazole-2-carboxamide	455.2	1.1	*
30		1-(3-methylbutyl)-N-[2-oxo-2-[4-(2-pyrrolidin-1-ylethyl)piperazin-1-yl]ethyl]-1H-benzimidazole-2-carboxamide	455.2	1.2	*
31		1-(3-methylbutyl)-N-[2-oxo-2-(4-pyridin-4-ylpiperazin-1-yl)ethyl]-1H-benzimidazole-2-carboxamide	435.2	1.2	*
32		N-ethyl-1-(4-methoxybenzyl)-N-[2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethyl]-1H-benzimidazole-2-carboxamide	533.2	1.1	*

COMPOUND	NAME	MS	Ret Time	IC ₅₀
33 	1-benzyl-N-(2-{4-[2-(1H-imidazol-1-yl)ethyl]piperazin-1-yl}-2-oxoethyl)-1H-benzimidazole-2-carboxamide	472.2	1.1	*
34 	1-(2-morpholin-4-ylethyl)-N-[2-oxo-2-(4-pyridin-4-yl)piperazin-1-yl]ethyl]-1H-benzimidazole-2-carboxamide	478.1	1.1	*
35 	N-[2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethyl]-1-(2-morpholin-4-ylethyl)-1H-benzimidazole-2-carboxamide	498.2	1.1	*
36 	1-benzyl-N-[2-oxo-2-(4-pyridin-4-yl)piperazin-1-yl]ethyl]-N-propyl-1H-benzimidazole-2-carboxamide	497.2	1.1	*

COMPOUND	NAME	MS	Ret Time	IC ₅₀
37 	1-benzyl-N-{2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethyl}-N-propyl-1H-benzimidazole-2-carboxamide	517.2	1.1	*
38 	1-benzyl-N-{2-oxo-2-[4-(2-pyrrolidin-1-ylethyl)piperazin-1-yl]ethyl}-N-propyl-1H-benzimidazole-2-carboxamide	517.2	1.2	*
39 	1-benzyl-N-(1-{[4-(1-methylpiperidin-4-yl)piperazin-1-yl]carbonyl}propyl)-1H-benzimidazole-2-carboxamide	503.2	1.1	*
40 	1-benzyl-N-isopropyl-N-{2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethyl}-1H-benzimidazole-2-carboxamide	517.2	1.1	*
41 	1-benzyl-N-isopropyl-N-{2-oxo-2-[4-(2-pyrrolidin-1-ylethyl)piperazin-1-yl]ethyl}-1H-benzimidazole-2-carboxamide	517.2	1.1	*

	COMPOUND	NAME	MS	Ret Time	IC ₅₀
42		1-benzyl-N-ethyl-N-{2-[2-methyl-4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethyl}-1H-benzimidazole-2-carboxamide	717.3	1.0	*
43		1-benzyl-N-{2-[3-methyl-4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethyl}-1H-benzimidazole-2-carboxamide	489.3	1.0	*
44		1-benzyl-N-ethyl-N-{2-[3-methyl-4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethyl}-1H-benzimidazole-2-carboxamide	517.3	1.0	*
45		1-benzyl-N-[2-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-2-oxoethyl]-N-ethyl-1H-benzimidazole-2-carboxamide	528.3	1.0	*

	<u>COMPOUND</u>	<u>NAME</u>	<u>MS</u>	<u>Ret</u> <u>Time</u>	<u>IC₅₀</u>
46		1-benzyl-N-[2-(2-cyclobutyl-2,8-diazaspiro[4.5]dec-8-yl)-2-oxoethyl]-N-ethyl-1H-benzimidazole-2-carboxamide	514.3	1.1	*
47		1-benzyl-N-[2-(8-cyclobutyl-2,8-diazaspiro[4.5]dec-2-yl)-2-oxoethyl]-N-ethyl-1H-benzimidazole-2-carboxamide	514.3	1.1	*
48		1-benzyl-2-({4-[(4-pyridin-4-yl)piperazin-1-yl]carbonyl}piperidin-1-yl)carbonyl)-1H-benzimidazole	509.3	1.1	*
49		1-benzyl-2-[(4-{[4-(1-methylpiperidin-4-yl)piperazin-1-yl]carbonyl}piperidin-1-yl)carbonyl]-1H-benzimidazole	529.3	1.1	*
50		1-benzyl-2-[(4-{[4-(2-pyrrolidin-1-ylethyl)piperazin-1-yl]carbonyl}piperidin-1-yl)carbonyl]-1H-benzimidazole	529.3	1.1	*

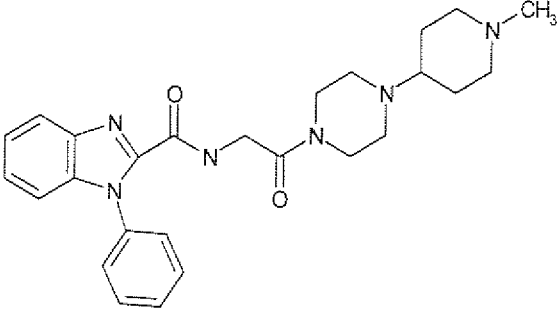
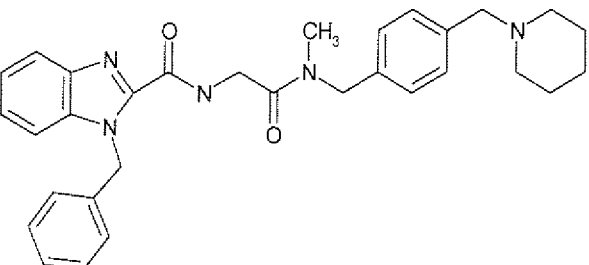
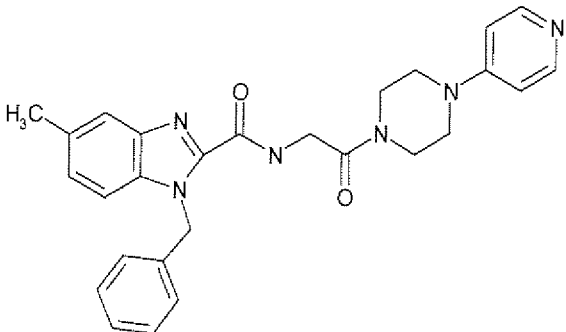
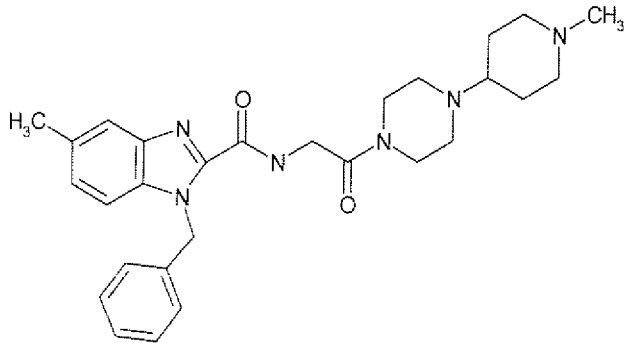
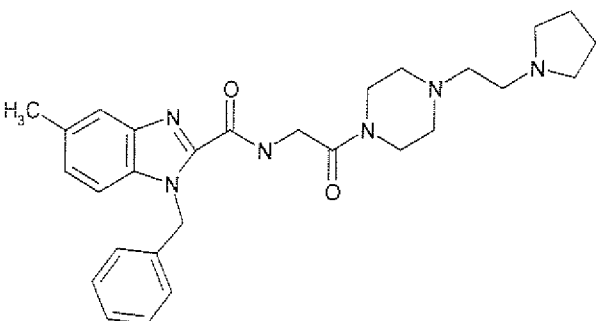
	COMPOUND	NAME	MS	Ret Time	IC ₅₀
51		1-((1-((1-benzyl-1H-benzimidazol-2-yl)carbonyl)piperidin-4-yl)carbonyl)-N,N-dimethylpiperidin-4-amine	474.3	1.1	*
52		1-benzyl-2-((4-((4-(3-piperidin-1-ylpropyl)piperazin-1-yl)carbonyl)piperidin-1-yl)carbonyl)-1H-benzimidazole	557.4	1.1	*
53		1-benzyl-2-((2-((4-(1-methylpiperidin-4-yl)piperazin-1-yl)carbonyl)pyrrolidin-1-yl)carbonyl)-1H-benzimidazole	515.3	1.1	*
54		1-benzyl-2-((2S)-2-((4-(3-piperidin-1-ylpropyl)piperazin-1-yl)carbonyl)pyrrolidin-1-yl)carbonyl)-1H-benzimidazole	543.2	1.1	*
55		1-benzyl-2-((2-((4-pyridin-4-yl)piperazin-1-yl)carbonyl)pyrrolidin-1-yl)carbonyl)-1H-benzimidazole	495.2	1.1	*

	COMPOUND	NAME	MS	Ret Time	IC ₅₀
56		1-benzyl-2-[(2-[(4-(1-methylpiperidin-4-yl)piperazin-1-yl)carbonyl]pyrrolidin-1-yl)carbonyl]-1H-benzimidazole	515.3	1.1	*
57		1-benzyl-N-(2-[[4-(4,5-dihydro-1H-imidazol-2-yl)benzyl](methyl)amino]-2-oxoethyl)-N-ethyl-1H-benzimidazole-2-carboxamide	509.3	1.0	*
58		1-benzyl-N-(2-[[4-(4,5-dihydro-1H-imidazol-2-yl)benzyl](methyl)amino]-2-oxoethyl)-1H-benzimidazole-2-carboxamide	481.2	1.1	*
59		1-benzyl-N-(3-[[4-(4,5-dihydro-1H-imidazol-2-yl)benzyl](methyl)amino]-3-oxopropyl)-1H-benzimidazole-2-carboxamide	495.2	1.0	*
60		N-[(1-benzyl-1H-benzimidazol-2-yl)methyl]-N-ethyl-2-oxo-2-[4-(2-pyrrolidin-1-ylethyl)piperazin-1-yl]ethanamine	489.3	1.1	*

	COMPOUND	NAME	MS	Ret Time	IC ₅₀
61		1-benzyl-5-fluoro-N-[2-oxo-2-(4-pyridin-4-yl)piperazin-1-yl]ethyl-1H-benzimidazole-2-carboxamide	473.2	1.2	*
62		1-benzyl-5-fluoro-N-{2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethyl}-1H-benzimidazole-2-carboxamide	492.2	1.1	*
63		1-benzyl-5-fluoro-N-{2-oxo-2-[4-(2-pyrrolidin-1-ylethyl)piperazin-1-yl]ethyl}-1H-benzimidazole-2-carboxamide	493.2	1.1	*
64		1-benzyl-N-ethyl-5-fluoro-N-{2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethyl}-1H-benzimidazole-2-carboxamide	521.3	1.1	*
65		1-benzyl-N-ethyl-5-fluoro-N-{2-oxo-2-[4-(2-pyrrolidin-1-ylethyl)piperazin-1-yl]ethyl}-1H-benzimidazole-2-carboxamide	521.3	1.2	*

	COMPOUND	NAME	MS	Ret Time	IC ₅₀
66		1-benzyl-N-(2-{methyl[4-(5-methyl-1,2,4-oxadiazol-3-yl)benzyl]amino}-2-oxoethyl)-1H-benzimidazole-2-carboxamide	495.2	1.1	*
67		1-benzyl-N-ethyl-N-(2-{methyl[4-(5-methyl-1,2,4-oxadiazol-3-yl)benzyl]amino}-2-oxoethyl)-1H-benzimidazole-2-carboxamide	523.2	1.1	*
68		5-fluoro-N-{2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethyl}-1-(2-morpholin-4-ylethyl)-1H-benzimidazole-2-carboxamide	516.2	1.1	
69		N-(2-{[4-(4,5-dihydro-1H-imidazol-2-yl)benzyl](methyl)amino}-2-oxoethyl)-5-fluoro-1-(2-morpholin-4-ylethyl)-1H-benzimidazole-2-carboxamide	522.3	1.0	*

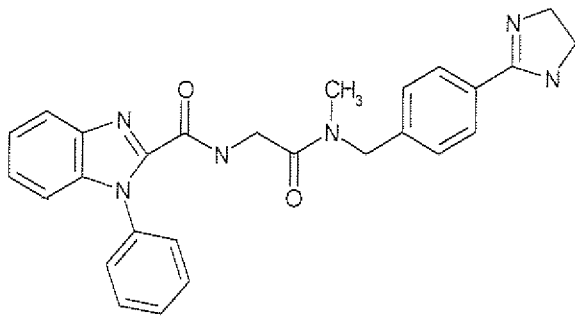
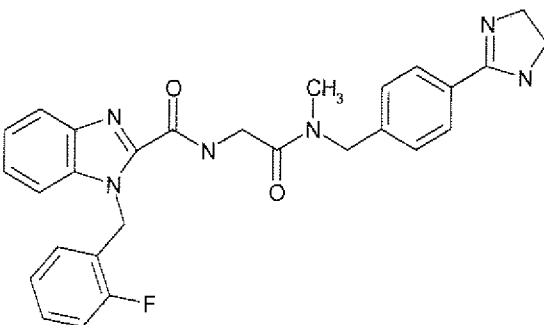
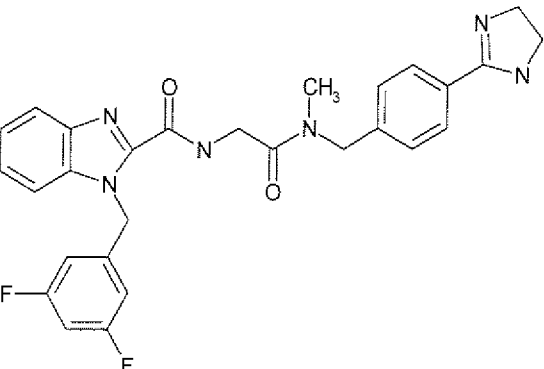
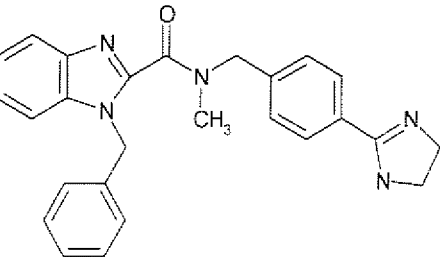
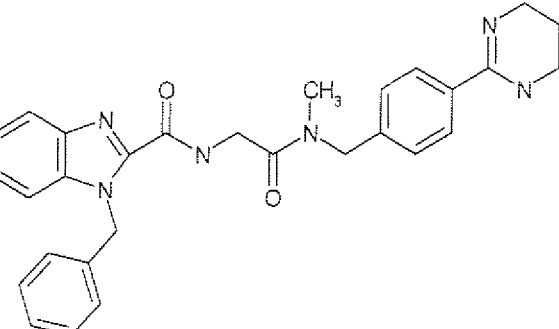
	COMPOUND	NAME	MS	Ret Time	IC ₅₀
70		N-(2-([4-(4,5-dihydro-1H-imidazol-2-yl)benzyl](methyl)amino)-2-oxoethyl)-1-(2-morpholin-4-ylethyl)-1H-benzimidazole-2-carboxamide	504.3	1.0	*
71		N-(2-([4-(4,5-dihydro-1H-imidazol-2-yl)benzyl](methyl)amino)-2-oxoethyl)-1-(4-fluorobenzyl)-1H-benzimidazole-2-carboxamide	499.2	1.1	*
72		N-(2-([4-(4,5-dihydro-1H-imidazol-2-yl)benzyl](methyl)amino)-2-oxoethyl)-1-(3-fluorobenzyl)-1H-benzimidazole-2-carboxamide	499.2	1.1	*
73		N-ethyl-N-(2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethyl)-1-phenyl-1H-benzimidazole-2-carboxamide	489.2	1.1	*

	COMPOUND	NAME	MS	Ret Time	IC ₅₀
74		N-{2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethyl}-1-phenyl-1H-benzimidazole-2-carboxamide	461.3	1.1	*
75		1-benzyl-N-(2-{methyl[4-(piperidin-1-yl)methyl]benzyl}amino)-2-oxoethyl)-1H-benzimidazole-2-carboxamide	510.3	1.1	*
76		1-benzyl-5-methyl-N-[2-oxo-2-(4-pyridin-4-yl)piperazin-1-yl]ethyl)-1H-benzimidazole-2-carboxamide	469.3	1.2	*
77		1-benzyl-5-methyl-N-{2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethyl}-1H-benzimidazole-2-carboxamide	489.3	1.1	*
78		1-benzyl-5-methyl-N-{2-oxo-2-[4-(2-pyrrolidin-1-ylethyl)piperazin-1-yl]ethyl}-1H-benzimidazole-2-carboxamide	489.3	1.1	*

COMPOUND	NAME	MS	Ret Time	IC ₅₀
79	1-benzyl-N-(2-{[4-(1H-imidazol-1-yl)benzyl](methyl)amino]-2-oxoethyl}-1H-benzimidazole-2-carboxamide	479.2	1.1	*
80	1-benzyl-N-{2-[methyl(4-pyridin-2-ylbenzyl)amino]-2-oxoethyl}-1H-benzimidazole-2-carboxamide	490.2	1.1	*
81	1-benzyl-N-(2-{methyl[4-(1,3-thiazol-2-yl)benzyl]amino}-2-oxoethyl)-1H-benzimidazole-2-carboxamide	496.2	1.1	*
82	1-benzyl-N-(2-[methyl(4-pyrimidin-2-ylbenzyl)amino]-2-oxoethyl)-1H-benzimidazole-2-carboxamide	491.2	1.2	*
83	1-benzyl-N-(2-{[4-(4,5-dihydro-1H-imidazol-2-yl)benzyl](methyl)amino]-2-oxoethyl}-5-methyl-1H-benzimidazole-2-carboxamide	495.2	1.1	*

	COMPOUND	NAME	MS	Ret	IC ₅₀
				Time	
84		1-benzyl-N-[2-(9-methyl-3,9-diazaspiro[5.5]undec-3-yl)-2-oxoethyl]-1H-benzimidazole-2-carboxamide	460.3	1.0	*
85		1-benzyl-N-[2-(2-methyl-2,8-diazaspiro[4.5]dec-8-yl)-2-oxoethyl]-1H-benzimidazole-2-carboxamide	446.2	1.1	*
86		1-benzyl-N-[2-(3-oxa-9-azaspiro[5.5]undec-9-yl)-2-oxoethyl]-1H-benzimidazole-2-carboxamide	447.2	1.4	*
87		1-benzyl-N-[3-(9-methyl-3,9-diazaspiro[5.5]undec-3-yl)-3-oxopropyl]-1H-benzimidazole-2-carboxamide	474.3	1.2	
88		1-benzyl-N-[3-(2-methyl-2,8-diazaspiro[4.5]dec-8-yl)-3-oxopropyl]-1H-benzimidazole-2-carboxamide	460.3	1.2	*

		COMPOUND							
				NAME	MS	Ret Time	IC ₅₀		
89				1-benzyl-N-[3-(3-oxa-9-azaspiro[5.5]undec-9-yl)-3-oxopropyl]-1H-benzimidazole-2-carboxamide	461.2	1.3	*		
90				1-benzyl-7-methyl-N-[2-oxo-2-(4-pyridin-4-ylpiperazin-1-yl)ethyl]-1H-benzimidazole-2-carboxamide	469.2	1.1	*		
91				1-benzyl-7-methyl-N-{2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethyl}-1H-benzimidazole-2-carboxamide	489.1	1.2	*		
92				1-benzyl-7-methyl-N-{2-oxo-2-[4-(2-pyrrolidin-1-ylethyl)piperazin-1-yl]ethyl}-1H-benzimidazole-2-carboxamide	489.3	1.1	*		
93				1-benzyl-N-(2-{[4-(4,5-dihydro-1H-imidazol-2-yl)benzyl](methyl)amino}-2-oxoethyl)-7-methyl-1H-benzimidazole-2-carboxamide	495.2	1.1	*		

COMPOUND	NAME	MS	Ret Time	IC ₅₀	
94		N-(2-([4-(4,5-dihydro-1H-imidazol-2-yl)benzyl](methyl)amino)-2-oxoethyl)-1-phenyl-1H-benzimidazole-2-carboxamide	467.2	1.1	*
95		N-(2-([4-(4,5-dihydro-1H-imidazol-2-yl)benzyl](methyl)amino)-2-oxoethyl)-1-(2-fluorobenzyl)-1H-benzimidazole-2-carboxamide	499.2	1.1	*
96		1-(3,5-difluorobenzyl)-N-(2-([4-(4,5-dihydro-1H-imidazol-2-yl)benzyl](methyl)amino)-2-oxoethyl)-1H-benzimidazole-2-carboxamide	517.2	1.1	*
97		1-benzyl-N-[4-(4,5-dihydro-1H-imidazol-2-yl)benzyl]-N-methyl-1H-benzimidazole-2-carboxamide	424.2	1.0	*
98		1-benzyl-N-(2-{methyl[4-(1,4,5,6-tetrahydropyrimidin-2-yl)benzyl]amino}-2-oxoethyl)-1H-benzimidazole-2-carboxamide	495.2	1.1	*

	COMPOUND	NAME	MS	Ret Time	IC ₅₀
99		1-benzyl-N-(2-([4-(5,5-dimethyl-1,4,5,6-tetrahydropyrimidin-2-yl)benzyl](methyl)amino)-2-oxoethyl)-1H-benzimidazole-2-carboxamide	523.3	1.1	*
100		1-benzyl-N-(2-{methyl[4-(1-methyl-4,5-dihydro-1H-imidazol-2-yl)benzyl]amino}-2-oxoethyl)-1H-benzimidazole-2-carboxamide	495.2	1.1	*
101		1-[(1-benzyl-1H-benzimidazol-2-yl)carbonyl]-N-[4-(4,5-dihydro-1H-imidazol-2-yl)benzyl]-N-methylpiperidine-4-carboxamide	535.3	1.0	*
102		1-benzyl-N-(2-{[4-(4,5-dihydro-1H-imidazol-2-yl)benzyl](ethyl)amino}-2-oxoethyl)-1H-benzimidazole-2-carboxamide	495.2	1.1	*
103		N-(2-{[4-(4,5-dihydro-1H-imidazol-2-yl)benzyl](ethyl)amino}-2-oxoethyl)-1-(2-fluorobenzyl)-1H-benzimidazole-2-carboxamide	513.2	1.1	*

COMPOUND	NAME	MS	Ret Time	IC ₅₀
	1-benzyl-N-(2-([4-(5-hydroxy-1,4,5,6-tetrahydropyrimidin-2-yl)benzyl](methylamino)-2-oxoethyl)-1H-benzimidazole-2-carboxamide	511.2	1.0	*
	N-(2-([4-(4,5-dihydro-1H-imidazol-2-yl)benzyl](ethylamino)-2-oxoethyl)-1-(2-fluorobenzyl)-5-methyl-1H-benzimidazole-2-carboxamide	527.2	1.2	*
	N-(2-([4-(4,5-dihydro-1H-imidazol-2-yl)benzyl](ethylamino)-2-oxoethyl)-1-(3-fluorobenzyl)-5-methyl-1H-benzimidazole-2-carboxamide	527.2	1.2	*
	1-benzyl-N-(2-([4-(4,5-dihydro-1H-imidazol-2-yl)benzyl](propylamino)-2-oxoethyl)-1H-benzimidazole-2-carboxamide	509.2	1.2	*
	N-(2-([4-(4,5-dihydro-1H-imidazol-2-yl)benzyl](methylamino)-2-oxoethyl)-1-(2-fluorobenzyl)-5-methyl-1H-benzimidazole-2-carboxamide	513.2	1.2	*

	COMPOUND	NAME	MS	Ret Time	IC ₅₀
109		N-(2-([4-(4,5-dihydro-1H-imidazol-2-yl)benzyl](methylamino)-2-oxoethyl)-1-(3-fluorobenzyl)-5-methyl-1H-benzimidazole-2-carboxamide	513.2	1.1	*
110		1-benzyl-N-{2-[9-(4,5-dihydro-1H-imidazol-2-ylmethyl)-3,9-diazaspiro[5.5]undec-3-yl]-2-oxoethyl}-1H-benzimidazole-2-carboxamide	528.3	1.1	*
111		1-benzyl-N-{2-[6-(4,5-dihydro-1H-imidazol-2-yl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-oxoethyl}-1H-benzimidazole-2-carboxamide	493.2	1.2	*
112		N-(2-[6-(4,5-dihydro-1H-imidazol-2-yl)-3,4-dihydroisoquinolin-2(1H)-yl]-2-oxoethyl)-1-(2-fluorobenzyl)-1H-benzimidazole-2-carboxamide	511.2	1.2	*

	COMPOUND	NAME	MS	Ret Time	IC ₅₀
113		1-(2,3-difluorobenzyl)- N-(2-([4-(4,5-dihydro- 1H-imidazol-2- yl)benzyl](methyl)amin o)-2-oxoethyl)-1H- benzimidazole-2- carboxamide	517.2	1.1	*
114		1-(2,5-difluorobenzyl)- N-(2-([4-(4,5-dihydro- 1H-imidazol-2- yl)benzyl](methyl)amin o)-2-oxoethyl)-1H- benzimidazole-2- carboxamide	517.2	1.1	*
115		1-(2,3-difluorobenzyl)- N-(2-([4-(4,5-dihydro- 1H-imidazol-2- yl)benzyl](ethyl)amino} -2-oxoethyl)-1H- benzimidazole-2- carboxamide	531.2	1.2	*
116		1-(2,5-difluorobenzyl)- N-(2-([4-(4,5-dihydro- 1H-imidazol-2- yl)benzyl](ethyl)amino} -2-oxoethyl)-1H- benzimidazole-2- carboxamide	531.2	1.1	*

	COMPOUND	NAME	MS	Ret Time	IC ₅₀
117		1-(2-fluorobenzyl)-5-methyl-N-{2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethyl}-1H-benzimidazole-2-carboxamide	507.3	1.1	*
118		1-benzyl-N-(3-[(2-chloro-6-(trifluoromethyl)pyridin-3-yl)amino]-3-oxopropyl)-1H-benzimidazole-2-carboxamide	502.1	1.1	
119		1-benzyl-N-(3-[(6-cyanopyridin-3-yl)amino]-3-oxopropyl)-1H-benzimidazole-2-carboxamide	425.2	1.1	
120		1-benzyl-N-(3-[(6-cyanopyridin-3-yl)amino]-3-oxopropyl)-1H-benzimidazole-2-carboxamide	425.2	0.8	*
121		1-benzyl-N-(2-[(6-cyanopyridin-3-yl)amino]-2-oxoethyl)-1H-benzimidazole-2-carboxamide	411.1	1.3	*

	COMPOUND	NAME	MS	Ret	IC ₅₀
				Time	
122		1-benzyl-N-(3-((6-(4,5-dihydro-1H-imidazol-2-yl)pyridin-3-yl)amino)-3-oxopropyl)-1H-benzimidazole-2-carboxamide	468.2	0.98	*
123		1-benzyl-N-(3-oxo-3-((5-(trifluoromethyl)pyridin-2-yl)amino)propyl)-1H-benzimidazole-2-carboxamide	468.2	0.73	*
124		1-benzyl-N-(3-oxo-3-((4-(trifluoromethyl)phenyl)amino)propyl)-1H-benzimidazole-2-carboxamide	467.2	0.73	*
125		ethyl 3-(N-((1-benzyl-1H-benzimidazol-2-yl)carbonyl)glycyl)-3-azaspiro[5.5]undecane-9-carboxylate	517.3	0.56	*
126		3-(N-((1-benzyl-1H-benzimidazol-2-yl)carbonyl)glycyl)-3-azaspiro[5.5]undecane-9-carboxylic acid	489.2	1.3	*

	COMPOUND	NAME	Ref		
			MS	Time	IC ₅₀
127		1-(2-fluorobenzyl)-N-(3-oxo-3-[[6-(trifluoromethyl)pyridin-3-yl]amino]propyl)-1H-benzimidazole-2-carboxamide	486.1	0.85	*
128		1-(2,3-difluorobenzyl)-N-(3-oxo-3-[[6-(trifluoromethyl)pyridin-3-yl]amino]propyl)-1H-benzimidazole-2-carboxamide	504.1	0.7	*
129		1-(2,6-difluorobenzyl)-N-(3-oxo-3-[[6-(trifluoromethyl)pyridin-3-yl]amino]propyl)-1H-benzimidazole-2-carboxamide	504.1	0.5	*
130		N-{3-[(5-cyanopyridin-2-yl)amino]-3-oxopropyl}-1-(2,3-difluorobenzyl)-1H-benzimidazole-2-carboxamide	461.1	0.57	*
131		N-{3-[(6-cyanopyridin-3-yl)amino]-3-oxopropyl}-1-(2,3-difluorobenzyl)-1H-benzimidazole-2-carboxamide	461.1	0.7	*

	COMPOUND	NAME	MS	Ret	IC ₅₀
				Time	
132		1-benzyl-N-(2-{methyl[4-(1H-pyrazol-5-yl)benzyl]amino}-2-oxoethyl)-1H-benzimidazole-2-carboxamide	479.2	0.5	*
133		1-benzyl-N-(2-{9-[(dimethylamino)methyl]-3-azaspiro[5.5]undec-3-yl}-2-oxoethyl)-1H-benzimidazole-2-carboxamide	502.3	1.13	*
134		N-(3-oxo-3-[[5-(trifluoromethyl)pyridin-2-yl]amino]propyl)-1-(pyridin-2-ylmethyl)-1H-benzimidazole-2-carboxamide	469.2	0.67	*
135		1-(2,3-difluorobenzyl)-N-(3-oxo-3-[[5-(trifluoromethyl)pyridin-2-yl]amino]propyl)-1H-benzimidazole-2-carboxamide	504.1	0.67	*
136		1-benzyl-N-(2-oxo-2-{4-[5-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}ethyl)-1H-benzimidazole-2-carboxamide	523.2	0.71	*

	COMPOUND	NAME	MS	Ret	IC ₅₀
				Time	
137		1-benzyl-N-(2-([4-(4,5-dihydro-1H-imidazol-2-yl)-3-methoxybenzyl])(methylamino)-2-oxoethyl)-1H-benzimidazole-2-carboxamide	511.2	0.89	*
138		1-(2,3-difluorobenzyl)-N-{2-([6-(4,5-dihydro-1H-imidazol-2-yl)pyridin-3-yl]methyl)(methylamino)-2-oxoethyl}-1H-benzimidazole-2-carboxamide	518.2	1.09	*
139		N-[3-(1H-benzimidazol-6-ylamino)-3-oxopropyl]-1-benzyl-1H-benzimidazole-2-carboxamide	439.1	1.18	*
140		1-benzyl-N-[3-(1H-indazol-6-ylamino)-3-oxopropyl]-1H-benzimidazole-2-carboxamide	439.2	1.27	*
141		1-benzyl-N-(3-oxo-3-{[2-(trifluoromethyl)-1H-benzimidazol-5-yl]amino}propyl)-1H-benzimidazole-2-carboxamide	507.1	1.3	*

	COMPOUND	NAME	MS	Ret	IC ₅₀
				Time	
142		N-(3-oxo-3-([4-(trifluoromethyl)phenyl]amino)propyl)-1-(pyridin-2-ylmethyl)-1H-benzimidazole-2-carboxamide	468.1	1.25	*
143		1-(2-fluorobenzyl)-5-methyl-N-(2-{methyl[4-(1-methyl-4,5-dihydro-1H-imidazol-2-yl)benzyl]amino}-2-oxoethyl)-1H-benzimidazole-2-carboxamide	527.2	1.2	*
144		1-(2,3-difluorobenzyl)-N-(2-{methyl[4-(1-methyl-4,5-dihydro-1H-imidazol-2-yl)benzyl]amino}-2-oxoethyl)-1H-benzimidazole-2-carboxamide	531.1	1.18	*
145		1-benzyl-N-(2-{[4-carbamoyl-4-(ethylamino)cyclohexyl]amino}-2-oxoethyl)-1H-benzimidazole-2-carboxamide	477.2	1.13	*
146		1-(3-fluorobenzyl)-5-methyl-N-(2-{methyl[4-(1-methyl-4,5-dihydro-1H-imidazol-2-yl)benzyl]amino}-2-oxoethyl)-1H-benzimidazole-2-carboxamide	527.2	1.2	*

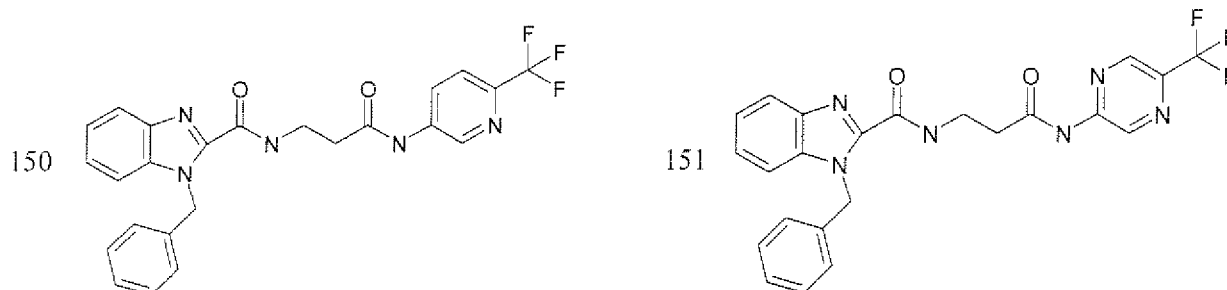
	COMPOUND	NAME	MS	Ret Time	IC ₅₀
147		N-ethyl-1-(3-fluorobenzyl)-5-methyl-N-(2-{methyl[4-(1-methyl-4,5-dihydro-1H-imidazol-2-yl)benzyl]amino}-2-oxoethyl)-1H-benzimidazole-2-carboxamide	555.3	1.28	*
148		1-(2,3-difluorobenzyl)-N-ethyl-N-(2-{methyl[4-(1-methyl-4,5-dihydro-1H-imidazol-2-yl)benzyl]amino}-2-oxoethyl)-1H-benzimidazole-2-carboxamide	559.3	1.25	*
149		methyl 4-[[[N-[(1-benzyl-1H-benzimidazol-2-yl)carbonyl]glycyl](methyl)amino]methyl]benzoate	471.1	1.29	*

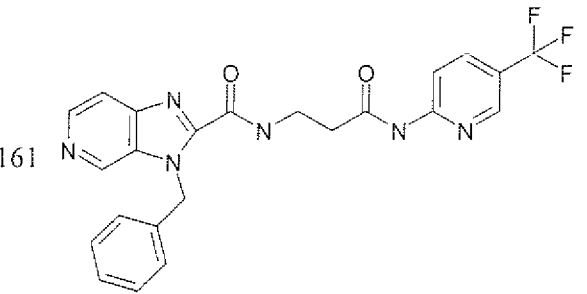
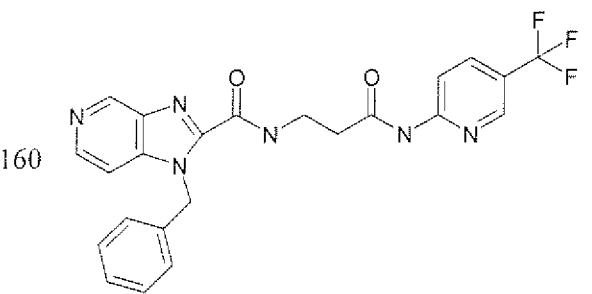
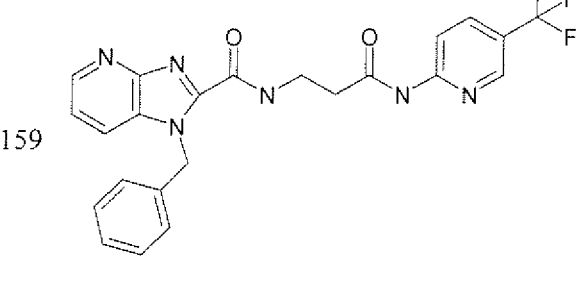
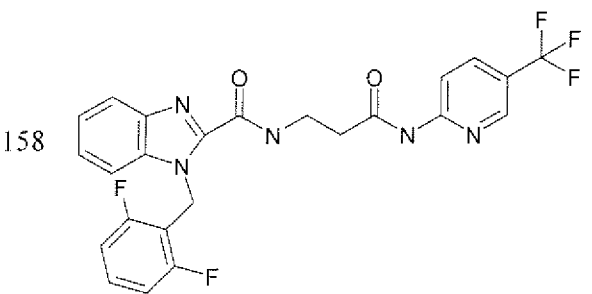
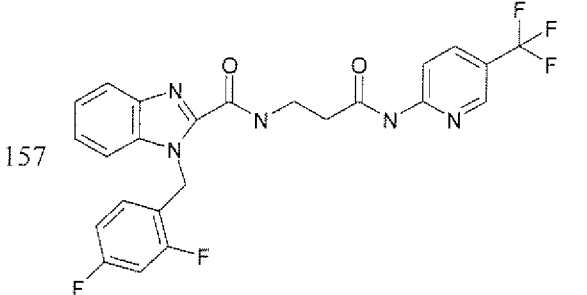
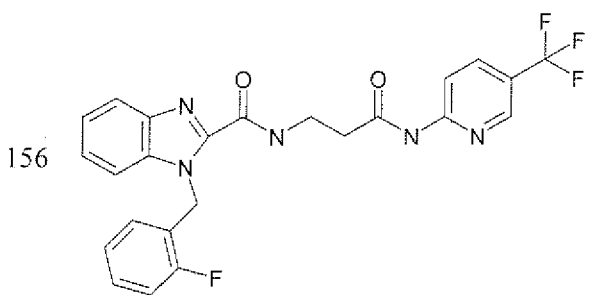
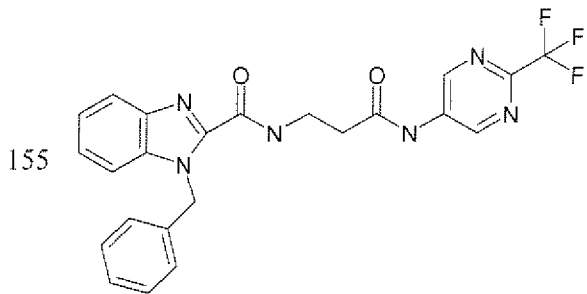
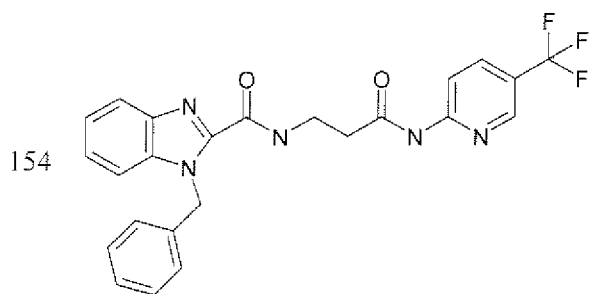
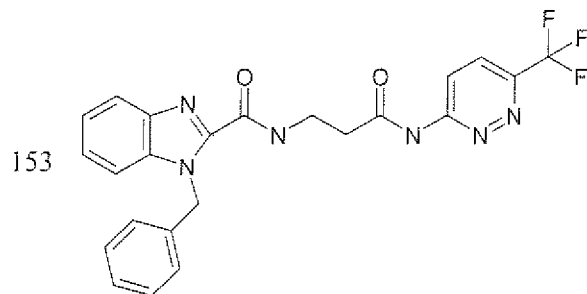
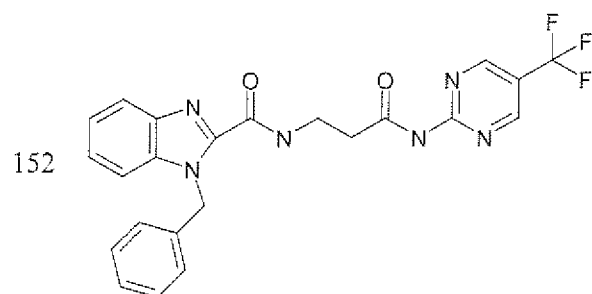
EXAMPLE 4. ADDITIONAL REPRESENTATIVE BENZIMIDAZOLE CARBOXAMIDE DERIVATIVES

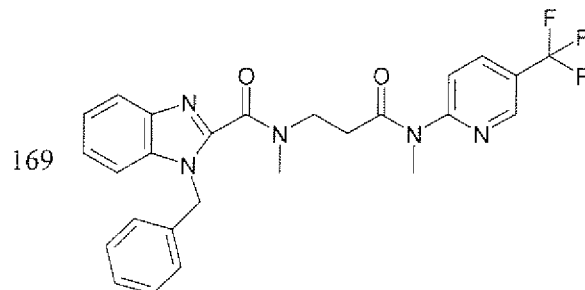
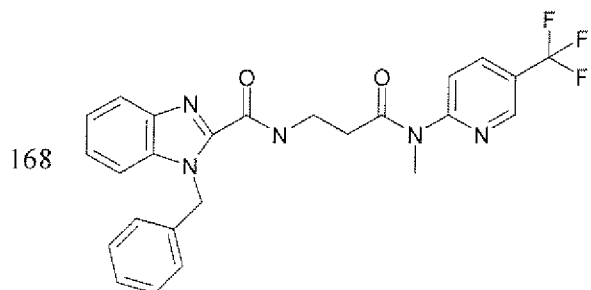
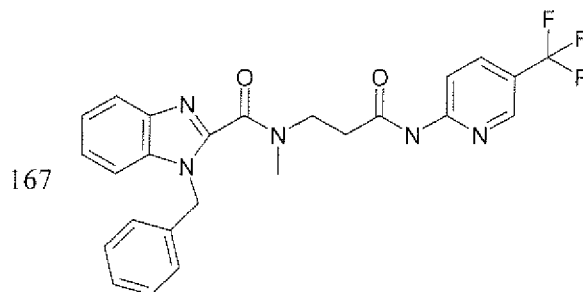
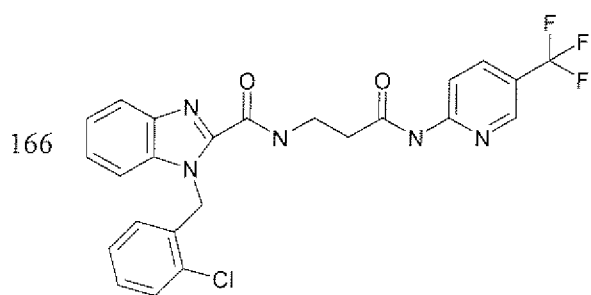
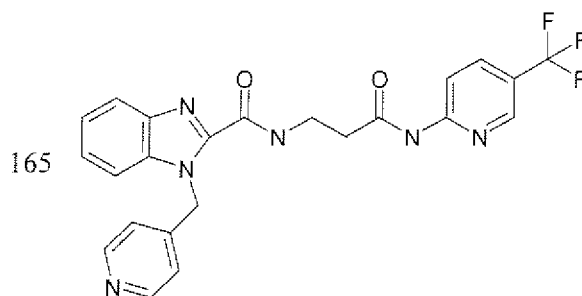
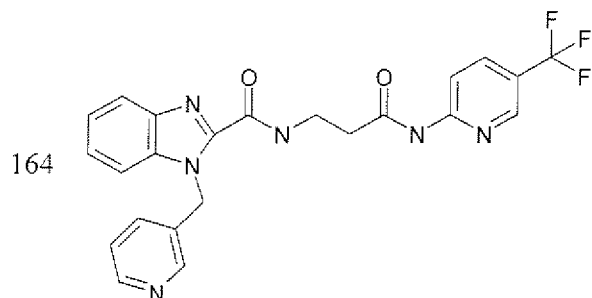
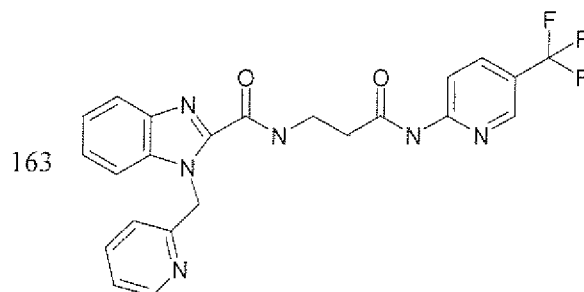
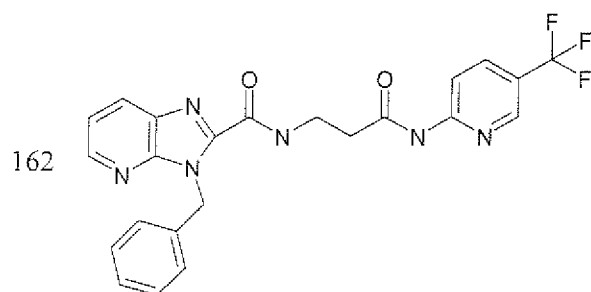
Using routine modifications, the starting materials may be varied and additional steps employed to produce other compounds provided herein. Compounds listed in Table II are prepared using such methods.

Table II

Additional Representative Benzimidazole Carboxamide Derivatives







EXAMPLE 5. PREPARATION OF B₁-TRANSFECTED CELLS

This Example illustrates the preparation of B₁-transfected cells for use in B₁ binding and modulation assays (Examples 6 and 7).

Cynomolgus macaque lung total RNA is isolated as described by Chomzynski et al. (1987) *Anal. Biochem.* 162:156-159. A cDNA encoding B₁ is cloned from the total RNA by reverse transcriptase-polymerase chain reaction (RT-PCR) with the following oligonucleotides:

Primer 1: GGCGCTAGCCACCATGGCATCCTGGCCCCCTC (SEQ ID NO:1)

Primer 2: AGCCGTCCCAGATCTGAAC (SEQ ID NO:2)

Primer 3: GATCTGGGACGGCTTGATG (SEQ ID NO:3)

Primer 4: CGGAGCTCTTAATTCCGCCAGAAAAGTTGGA (SEQ ID NO:4)

Primer pairs 1 & 2 and 3 & 4 are used to generate overlapping cDNA fragments corresponding to the entire protein coding sequence of cynomolgus macaque B₁ cDNA are isolated and linked to form the full-length coding sequence (GenBank Accession Number AY788905). The construct is cloned into pcDNA 3.1 (Invitrogen, Carlsbad, CA) and transfected into Chinese hamster ovary (CHO) cells using Lipofectamine (Invitrogen), resulting in cynomolgus macaque B₁-expressing CHO cells. Alternatively, the construct is cloned into pBAKPAK9 (Clontech, Mountain View, CA) and transfected into Sf9 cells to generate clonal baculovirus stocks. Clonal cell lines stably expressing the cynomolgus macaque B₁ receptor are selected in G418. A single clonal line that exhibits high levels of receptor expression is chosen for use in binding and calcium mobilization assays (Examples 6 and 7). Clonal baculovirus stocks are used to infect Sf9 cells such that the infected cells express high levels of recombinant B₁ receptors. These cells are used in radioligand binding assays (Example 6).

EXAMPLE 6. B₁ RECEPTOR BINDING ASSAYS

This Example illustrates a representative B₁ receptor binding assay that may be used to determine the binding affinity of compounds for B₁.

A. [3H]-DESARG¹⁰KALLIDIN BINDING TO INTACT IMR-90 CELLS OR CHO CELLS STABLY EXPRESSING RAT B₁

IMR-90 cells, which endogenously express human B₁, are seeded into 24 well plates at 65,000 cells per well, cultured overnight, and then treated for 3 h with 0.2 ng/mL interleukin-1 beta to induce B₁ expression (Menke, et al. (1994) *J. Biol. Chem.* 269:21583-86). CHO cells stably expressing rat B₁ are seeded into 24 well plates at 200,000 cells per well and cultured overnight. The cells are then washed 3 times with phosphate buffered saline (PBS). One hundred fifty microliters of binding buffer (50 mM Tris 7.4, 0.14 mg/mL, bacitracin, and 1 mg/mL BSA) is added to each well. Various concentrations of test compound are added to each well from DMSO solutions such the final DMSO concentration is 1% by volume; some wells receive DMSO only, and some wells receive DMSO plus 10 μ M desArg¹⁰Kallidin to define non-specific binding. All wells then receive 0.3 nM (final concentration) [3H]-desArg¹⁰Kallidin. The plates are allowed to sit for 2 h at room temperature. Cells are then washed three times, and lysed with 400 μ l Ultima Gold scintillation fluid (PerkinElmer; Boston, MA; 20 min incubation). The fluid is then transferred to counting vials counted in a Packard liquid scintillation counter (PerkinElmer). The number of counts present in the scintillation fluid is plotted as a function of antagonist compound concentration and fitted to a logistical equation using SigmaPlot (Systat Software, Point Richmond, CA) to determine each compound's IC₅₀ and K_i (e.g., as described by Szallasi, et al. (1993) *J. Pharmacol. Exp. Ther.* 266:678-83).

B. [3H]-DESARG¹⁰KALLIDIN BINDING TO MEMBRANE HOMOGENATES OF Sf9 CELLS EXPRESSING CYNOMOLGUS MACAQUE B₁

Sf9 cells infected with a baculovirus carrying the coding sequence for cynomolgus macaque B₁ are harvested by centrifugation and frozen at -80 °C. Pellets are subsequently resuspended on ice in Tris buffered saline (TBS; 50 mM Tris (pH 7.4), 120 mM NaCl), and cells are homogenized using a polytron for 30 seconds. The crude membrane fraction is collected by centrifugation at 20,000 rpm. Membranes are washed two times with TBS and collected by centrifugation each time. Protein content of the membranes is determined after the last wash and the concentration is adjusted to 0.7 µg/µL with binding buffer (50 mM Tris 7.4, 0.14 mg/mL bacitracin, and 1.0 mg/mL BSA). To perform the binding assay, 150 microliters of membrane fraction is added to each well of a 96-well plate along with 50 µl [³H]-desArg¹⁰Kallidin (0.3 nM final) and test compound in DMSO (final DMSO concentration = 1%). Some wells receive DMSO only, and some wells receive DMSO plus 10 µM desArg¹⁰Kallidin to define non-specific binding. The 96 well plates are allowed to sit for 2 h at room temperature. Membrane proteins are then harvested by filtration onto GF/C filtermats (PerkinElmer) pre-soaked for 1 hr in 0.5 % polyethylenimine. After filtration, filters are dried and then counted in a Beta plate counter. The number of counts present in the scintillation fluid is plotted as a function of antagonist compound concentration and fitted to a logistical equation using SigmaPlot (Systat Software, Point Richmond, CA) to determine each compound's IC₅₀ and K_i (e.g., as described by Szallasi, *et al.* (1993) *J. Pharmacol. Exp. Ther.* 266:678-83).

EXAMPLE 7. CALCIUM MOBILIZATION ASSAY

This Example illustrates representative calcium mobilization assays for use in evaluating test compounds for agonist and antagonist activity.

Cynomolgus macaque B₁-expressing CHO cells (Example 5) are plated in a 96 well plate. The cells are cultured for 1 day, after which culture media is emptied from the plate and replaced with 50 µl of KRH (Krebs-Ringer HEPES buffer: 25 mM HEPES, 5 mM KCl, 0.96 mM NaH₂PO₄, 1 mM MgSO₄, 2 mM CaCl₂, 5 mM glucose, 1 mM probenecid, pH 7.4) supplemented with the calcium-sensitive fluorescent dye Fluo4-AM (5 µg/ml; Teflabs, Austin, TX). The cells are then incubated at 37 °C in an environment containing 5% CO₂. After the 1 hour incubation, the dye solution is removed from the plate, the plate is washed once with KRH, and 100 µL KRH is added.

DETERMINATION OF B₁ AGONIST EC₅₀

100 µL KRH + 2% DMSO is added to each well of cells, such that the final volume in each well is 200 microliters and the final DMSO concentration is 1%. Various concentrations of the B₁ agonist desArg¹⁰Kallidin are added. Addition of desArg¹⁰Kallidin elicits a fluorescent response as consequence of increased intracellular calcium. This response is measured with a FLIPR instrument (Molecular Devices, Sunnyvale, CA) and determined to be desArg¹⁰Kallidin concentration dependent.

A plot of maximum fluorescent response as a function of desArg¹⁰Kalligin is generated and an EC₅₀ (concentration required to elicit a 50% of maximal response) for the response is determined using the equation:

$$y=a*(1/(1+(b/x)^c))$$

- 5 In this equation, y is the maximum fluorescence signal, x is the concentration of the B₁ agonist, a is the E_{max}, b corresponds to the EC₅₀ value and c is the Hill coefficient.

By replacing the desArg¹⁰Kallidin with a test compound, this assay is also used to assess B₁ agonist activity of the test compound.

DETERMINATION OF ANTAGONIST ACTIVITY

- 10 Various concentrations of test compounds are added to the cell plate prepared as described above in 100 µL KRH + 2% DMSO, such that the final volume in each well is 200 microliters and the final DMSO concentration is 1%. The EC₅₀ concentration of desArg¹⁰Kallidin is then added to each well of plates containing test compound to determine the extent to which each test compound inhibits an agonist-induced B₁ response. The maximum fluorescent response is plotted as a function of test compound concentration in order to determine the IC₅₀ (concentration required to inhibit 50% of the effect of agonist) for each compound at B₁. Antagonists of B₁ decrease this response by at least about 20%, preferably by at least about 50%, and most preferably by at least 80%, as compared to matched control (*i.e.*, cells treated with desArg¹⁰Kallidin at the EC₅₀ concentration in the absence of test compound), at a concentration of 10 micromolar or less, preferably 1 micromolar or less.

- 20 Alternatively, the data is analyzed as follows. First, the average maximum relative fluorescent unit (RFU) response from negative control wells (no agonist) is subtracted from the maximum response detected for each of the other experimental wells. Second, average maximum RFU response is calculated for the positive control wells (agonist wells). Then, percent inhibition for each compound tested is calculated using the equation:

$$\text{Percent Inhibition} = 100 - 100 \times \left[\frac{\text{Peak Signal in Test Wells}}{\text{Peak signal in Agonist Wells}} \right]$$

- 25 The % inhibition data is plotted as a function of test compound concentration and test compound IC₅₀ is determined using a linear regression in which x is ln(concentration of test compound) and y is ln(percent inhibition/(100 - percent inhibition)). Data with a percent inhibition that is greater than 90% or less than 15% are rejected and are not used in the regression. The IC₅₀ is $e^{(-\text{intercept}/\text{slope})}$.

30 EXAMPLE 8. MDCK CYTOTOXICITY ASSAY

This Example illustrates the evaluation of compound toxicity using a Madin Darby canine kidney (MDCK) cell cytotoxicity assay.

1 µL of test compound is added to each well of a clear bottom 96-well plate (Packard,

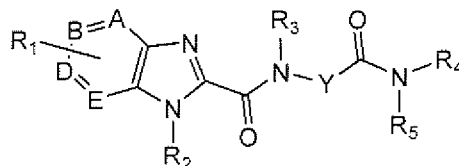
Meriden, CT) to give final concentration of compound in the assay of 10 μ M, 100 μ M or 200 μ M. Solvent without test compound is added to control wells.

MDCK cells, ATCC no. CCL-34 (American Type Culture Collection, Manassas, VA), are maintained in sterile conditions following the instructions in the ATCC production information sheet. Confluent MDCK cells are trypsinized, harvested, and diluted to a concentration of 0.1×10^6 cells/mL with warm (37°C) medium (VITACELL Minimum Essential Medium Eagle, ATCC catalog # 30-2003). 100 μ L of diluted cells is added to each well, except for five standard curve control wells that contain 100 μ L of warm medium without cells. The plate is then incubated at 37°C under 95% O₂, 5% CO₂ for 2 hours with constant shaking. After incubation, 50 μ L of mammalian cell lysis solution (from the Packard (Meriden, CT) ATP-LITE-M Luminescent ATP detection kit) is added per well, the wells are covered with PACKARD TOPSEAL stickers, and plates are shaken at approximately 700 rpm on a suitable shaker for 2 min.

Compounds causing toxicity will decrease ATP production, relative to untreated cells. The ATP-LITE-M Luminescent ATP detection kit is generally used according to the manufacturer's instructions to measure ATP production in treated and untreated MDCK cells. PACKARD ATP LITE-M reagents are allowed to equilibrate to room temperature. Once equilibrated, the lyophilized substrate solution is reconstituted in 5.5 mL of substrate buffer solution (from kit). Lyophilized ATP standard solution is reconstituted in deionized water to give a 10 mM stock. For the five control wells, 10 μ L of serially diluted PACKARD standard is added to each of the standard curve control wells to yield a final concentration in each subsequent well of 200 nM, 100 nM, 50 nM, 25 nM, and 12.5 nM. PACKARD substrate solution (50 μ L) is added to all wells, which are then covered, and the plates are shaken at approximately 700 rpm on a suitable shaker for 2 min. A white PACKARD sticker is attached to the bottom of each plate and samples are dark adapted by wrapping plates in foil and placing in the dark for 10 min. Luminescence is then measured at 22°C using a luminescence counter (*e.g.*, PACKARD TOPCOUNT Microplate Scintillation and Luminescence Counter or TECAN SPECTRAFLUOR PLUS), and ATP levels calculated from the standard curve. ATP levels in cells treated with test compound(s) are compared to the levels determined for untreated cells. Cells treated with 10 μ M of a preferred test compound exhibit ATP levels that are at least 80%, preferably at least 90%, of the untreated cells. When a 100 μ M concentration of the test compound is used, cells treated with preferred test compounds exhibit ATP levels that are at least 50%, preferably at least 80%, of the ATP levels detected in untreated cells.

What is claimed is:

1. A compound of the formula:



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

A, B, D and E are each CH or N, such that no more than one of A, B, D and E is N;

Y is a group of the formula $(CH_2)_r-Q-(CH_2)_p$, which is substituted with from 0 to 4 substituents independently chosen from (i) amino, hydroxy, cyano, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl and C_1 - C_6 haloalkyl; and (ii) substituents of the same carbon atom or adjacent carbon atoms that are taken together to form C_3 - C_6 cycloalkyl, wherein:

Q is absent, CHR_{10} , $CH=CH$, O, S or NR_{10} ; wherein R_{10} is hydrogen, C_1 - C_6 alkyl or taken together with R_3 to form a 4- to 7-membered heterocycloalkyl; and

r and p are independently chosen integers ranging from 0 to 6, such that the sum of r and p ranges from 1 to 6;

R_1 represents from 0 to 4 substituents independently chosen from halogen, hydroxy, cyano, amino, nitro, aminocarbonyl, aminosulfonyl, $-COOH$, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, $(C_3$ - C_8 cycloalkyl) C_0 - C_4 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkylthio, C_1 - C_6 alkylsulfinyl, C_1 - C_6 alkoxycarbonyl, C_1 - C_6 alkylsulfonyl C_0 - C_4 alkyl, and mono- or di- $(C_1$ - C_6 alkyl)amino C_0 - C_4 alkyl;

R_2 is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, $(C_3$ - C_8 cycloalkyl) C_0 - C_4 alkyl, mono- or di- $(C_1$ - C_6 alkyl)amino C_1 - C_4 alkyl, (4- to 7-membered heterocycloalkyl) C_0 - C_4 alkyl, phenyl C_0 - C_4 alkyl or (5- or 6-membered heteroaryl) C_0 - C_4 alkyl, each of which is substituted with from 0 to 4 substituents independently chosen from amino, halogen, hydroxy, cyano, oxo, C_1 - C_6 alkyl, $(C_3$ - C_8 cycloalkyl) C_0 - C_4 alkyl and C_1 - C_6 alkoxy;

R_3 is hydrogen, C_1 - C_6 alkyl or taken together with R_{10} to form a 4- to 7-membered heterocycloalkyl; and

R_4 and R_5 are:

- (i) independently chosen from C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, $(C_3$ - C_8 cycloalkyl) C_0 - C_4 alkyl, (4- to 7-membered heterocycloalkyl) C_0 - C_4 alkyl, phenyl C_0 - C_4 alkyl and (5- to 10-membered heteroaryl) C_0 - C_4 alkyl; or

- (ii) taken together to form a 4- to 7-membered heterocycloalkyl;

each of which (i) and (ii) is substituted with from 0 to 6 substituents independently chosen from:

- (a) halogen, hydroxy, cyano, amino, nitro, $-COOH$, aminocarbonyl and oxo; and

(b) C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆alkoxy, (C₃-C₈cycloalkyl)C₀-C₄alkyl, mono- or di-(C₁-C₆alkyl)amino, (4- to 7-membered heterocycloalkyl)C₀-C₄alkyl, phenylC₀-C₄alkyl, (5- or 6-membered heteroaryl)C₀-C₄alkyl, and substituents that are taken together to form a fused or spiro 5- to 7-membered ring;

each of which (b) is substituted with from 0 to 4 substituents independently chosen from:

- (1) amino, halogen, hydroxy, cyano, -COOH, aminocarbonyl and oxo; and
- (2) C₁-C₆alkyl, C₁-C₆alkoxy, C₂-C₆alkyl ether, mono- or di-(C₁-C₆alkyl)aminoC₀-C₄alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, (4- to 7-membered heterocycloalkyl)C₀-C₄alkyl, phenylC₀-C₄alkyl and (5- or 6-membered heteroaryl)C₀-C₄alkyl, each of which is substituted with from 0 to 4 substituents independently chosen from halogen, oxo and C₁-C₄alkyl.

2. A compound or salt or hydrate thereof according to claim 1, wherein R₁ represents from 0 to 2 substituents independently chosen from halogen, cyano, and C₁-C₄alkyl.

3. A compound or salt or hydrate thereof according to claim 1 or claim 2, wherein R₂ is phenylC₁-C₂alkyl that is substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, cyano, C₁-C₄alkyl, and C₁-C₄alkoxy.

4. A compound or salt or hydrate thereof according to claim 3, wherein R₂ is benzyl that is substituted with from 0 to 3 substituents independently chosen from halogen, C₁-C₄alkyl, and C₁-C₄alkoxy.

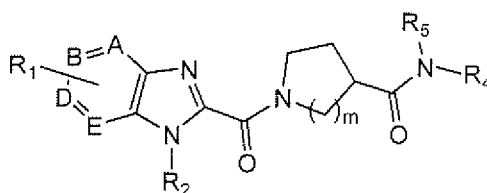
5. A compound or salt or hydrate thereof according to claim 1 or claim 2, wherein R₂ is (4- to 7-membered heterocycloalkyl)C₁-C₄alkyl that is substituted with from 0 to 3 substituents independently chosen from oxo and C₁-C₄alkyl.

6. A compound or salt or hydrate thereof according to any one of claims 1-5, wherein Y is C₁-C₆alkylene that is unsubstituted or substituted with amino, hydroxy, cyano, C₁-C₄alkyl, C₂-C₄alkenyl or C₁-C₄haloalkyl.

7. A compound or salt or hydrate thereof according to claim 6, wherein Y is methylene or ethylene, each of which is unsubstituted or substituted with methyl or ethyl.

8. A compound or salt or hydrate thereof according to any one of claims 1-5, wherein Y is (CH₂)_r-CHR₁₀-, and wherein R₁₀ is taken together with R₃ to form a 4- to 7-membered heterocycloalkyl.

9. A compound or salt or hydrate thereof according to claim 8, wherein the compound has the formula:

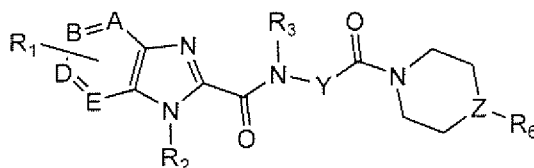


wherein m is 0, 1, 2 or 3.

10. A compound or salt or hydrate thereof according to any one of claims 1-7, wherein R₃ is hydrogen or C₁-C₄alkyl.

11. A compound or salt or hydrate thereof according to any one of claims 1-10, wherein R₄ and R₅ are taken together to form a 4- to 7-membered heterocycloalkyl that is substituted with mono- or di-(C₁-C₆alkyl)aminoC₀-C₄alkyl, (4- to 7-membered heterocycloalkyl)C₀-C₄alkyl, phenylC₀-C₄alkyl or (6-membered heteroaryl)C₀-C₄alkyl, each of which is unsubstituted or substituted with oxo, C₁-C₄alkyl or (5- or 6-membered heterocycle)C₀-C₂alkyl.

12. A compound or salt or hydrate thereof according to claim 11, wherein the compound satisfies the formula:



wherein:

Z is N or CH; and

R₆ is piperidinylC₀-C₄alkyl, pyrrolidinylC₀-C₄alkyl, pyridinylC₀-C₄alkyl, pyrimidinylC₀-C₄alkyl, tetrahydropyrimidinylC₀-C₄alkyl, imidazolylC₀-C₄alkyl, dihydroimidazolylC₀-C₄alkyl, thiazolylC₀-C₄alkyl, oxadiazolylC₀-C₄alkyl, phenylC₀-C₄alkyl, or di-(C₁-C₄alkyl)aminoC₀-C₄alkyl, each of which is unsubstituted or substituted with one or two C₁-C₄alkyl.

13. A compound or salt or hydrate thereof according to claim 11 or claim 12, wherein:

R₁ represents from 0 to 2 substituents independently chosen from halogen, cyano, and C₁-C₄alkyl;

R₂ is benzyl that is substituted with from 0 to 3 substituents independently chosen from halogen, C₁-C₄alkyl, and C₁-C₄alkoxy;

R₃ is hydrogen or C₁-C₄alkyl; and

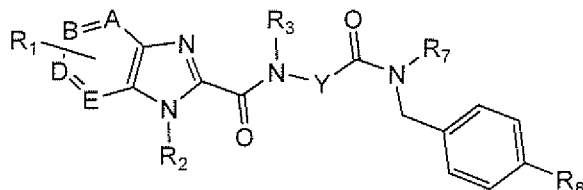
Y is methylene or ethylene, each of which is unsubstituted or substituted with methyl or ethyl.

14. A compound or salt or hydrate thereof according to any one of claims 1-10, wherein:

R₄ is C₁-C₄alkyl; and

R₅ is phenylC₀-C₂alkyl that is substituted with mono- or di-(C₁-C₆alkyl)aminoC₀-C₄alkyl, (4- to 7-membered heterocycloalkyl)C₀-C₄alkyl, phenylC₀-C₄alkyl or (6-membered heteroaryl)C₀-C₄alkyl, each of which is unsubstituted or substituted with a oxo, C₁-C₄alkyl, (5- or 6-membered heterocycle)C₀-C₂alkyl, or mono- or di-(C₁-C₆alkyl)aminoC₀-C₄alkyl.

15. A compound or salt or hydrate thereof according to claim 14, wherein the compound satisfies the formula:



wherein:

R₇ is methyl or ethyl; and

R₈ is piperidinylC₀-C₄alkyl, pyrrolidinylC₀-C₄alkyl, pyridinylC₀-C₄alkyl, pyrimidinylC₀-C₄alkyl, trihydroypyrimidinylC₀-C₄alkyl, imidazolylC₀-C₄alkyl, dihydroimidazolylC₀-C₄alkyl, thiazolylC₀-C₄alkyl, oxadiazolylC₀-C₄alkyl, phenylC₀-C₄alkyl, or di-(C₁-C₄alkyl)aminoC₀-C₄alkyl, each of which is unsubstituted or substituted with one or two C₁-C₄alkyl.

16. A compound or salt or hydrate thereof according to claim 14 or claim 15, wherein:

R₁ represents from 0 to 2 substituents independently chosen from halogen, cyano, and C₁-C₄alkyl;

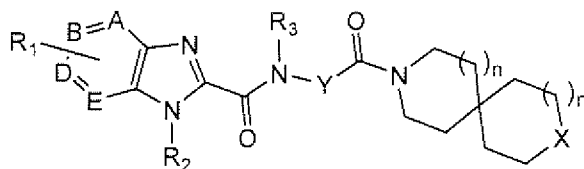
R₂ is benzyl that is substituted with from 0 to 3 substituents independently chosen from halogen, C₁-C₄alkyl, and C₁-C₄alkoxy;

R₃ is hydrogen or C₁-C₄alkyl; and

Y is methylene or ethylene, each of which is unsubstituted or substituted with methyl or ethyl.

17. A compound or salt or hydrate thereof according to any one of claims 1-10, wherein R₄ and R₅ are taken together to form a 8- to 14-membered spiro heterocycloalkyl that is unsubstituted or substituted with C₁-C₄alkyl, (C₃-C₇cycloalkyl)C₀-C₂alkyl or (5- or 6-membered heterocycle)C₀-C₂alkyl.

18. A compound or salt or hydrate thereof according to claim 17, wherein the compound satisfies the formula:



wherein:

each n is independently 0 or 1;

X is O or NR₉; and

R₉ is C₁-C₄alkyl or (C₃-C₇cycloalkyl)C₀-C₂alkyl.

19. A compound or salt or hydrate thereof according to claim 17 or claim 18, wherein:
R₁ represents from 0 to 2 substituents independently chosen from halogen, cyano, and C₁-C₄alkyl;
R₂ is benzyl that is substituted with from 0 to 3 substituents independently chosen from halogen, C₁-C₄alkyl, and C₁-C₄alkoxy;
R₃ is hydrogen or C₁-C₄alkyl; and
Y is methylene or ethylene, each of which is unsubstituted or substituted with methyl or ethyl.
20. A compound or salt or hydrate thereof according to any one of claims 1-19, wherein A, B, D and E are each CH.
21. A compound or salt or hydrate thereof according to any one of claims 1-20, wherein the compound exhibits no detectable agonist activity an *in vitro* assay of B₁ agonism.
22. A compound or salt or hydrate thereof according to any one of claims 1-21, wherein the compound has an IC₅₀ value of 1 micromolar or less in an *in vitro* assay of B₁ antagonism.
23. A pharmaceutical composition, comprising at least one compound or salt or hydrate thereof according to any one of claims 1-22, in combination with a physiologically acceptable carrier or excipient.
24. A pharmaceutical composition according to claim 23, wherein the composition is formulated as an injectible fluid, an aerosol, a cream, a gel, a pill, a capsule, a syrup or a transdermal patch.
25. A method for inhibiting induction of agonist-induced B₁ activity *in vitro*, the method comprising contacting B₁ receptor with at least one compound or salt or hydrate thereof according to any one of claims 1-22, under conditions and in an amount sufficient to detectably inhibit agonist-induced B₁ activity.
26. A method for inhibiting induction of agonist-induced B₁ activity in a patient, comprising contacting cells expressing B₁ receptor with at least one compound or salt or hydrate thereof according to any one of claims 1-22, in an amount sufficient to detectably inhibit agonist-induced B₁ activity in cells expressing a cloned B₁ receptor *in vitro*, and thereby inhibiting agonist-induced B₁ activity in the patient.
27. A method according to claim 26, wherein the patient is a human.
28. A method for treating a condition responsive to B₁ receptor modulation in a patient, comprising administering to the patient a therapeutically effective amount of at least one compound or

salt or hydrate thereof according to any one of claims 1-22, and thereby alleviating the condition in the patient.

29. A method according to claim 28, wherein the condition is inflammation or pain.

30. A method according to claim 28, wherein the condition is cough, asthma, vascular edema, or epilepsy.

31. A method for treating pain in a patient, comprising administering to a patient suffering from pain a therapeutically effective amount of at least one compound or salt or hydrate thereof according to any one of claims 1-22, and thereby alleviating pain in the patient.

32. A method according to claim 31, wherein the patient is suffering from inflammatory pain, acute pain, dental pain, back pain, surgical pain, headache, neuropathic pain or pain from osteoarthritis or trauma.

33. A method according to claim 31, wherein the patient is a human.

34. A compound or salt or hydrate thereof according to claim 1, wherein the compound is radiolabeled.

35. A method for determining the presence or absence of B₁ receptor in a sample, comprising the steps of:

- (a) contacting a sample with a compound or salt or hydrate thereof according to any one of claims 1-22, under conditions that permit binding of the compound to B₁ receptor; and
- (b) detecting a signal indicative of a level of the compound bound to B₁ receptor, and therefrom determining the presence or absence of B₁ receptor in the sample.

36. A method according to claim 35, wherein the compound is radiolabeled, and wherein the step of detection comprises the steps of:

- (i) separating unbound compound from bound compound; and
- (ii) detecting the presence or absence of bound radiolabel in the sample.

37. A packaged pharmaceutical preparation, comprising:

- (a) a pharmaceutical composition according to claim 23 in a container; and
- (b) instructions for using the composition to treat pain.

38. The use of a compound or salt or hydrate thereof according to any one of claims 1-22 for the manufacture of a medicament for the treatment of a condition responsive to B₁ receptor modulation.

39. A use according to claim 37, wherein the condition is an inflammatory condition or pain.