INDAZOLE-CARBOXAMIDE COMPOUNDS

BACKGROUND OF THE INVENTION

Field of the Invention

The invention is directed to indazole-carboxamide compounds which are useful as 5-HT_4 receptor agonists. The invention is also directed to pharmaceutical compositions comprising such compounds, methods of using such compounds for treating or preventing medical conditions mediated by 5-HT_4 receptor activity, and processes and intermediates useful for preparing such compounds.

State of the Art

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter that is widely distributed throughout the body, both in the central nervous system and in peripheral systems. At least seven subtypes of serotonin receptors have been identified and the interaction of serotonin with these different receptors is linked to a wide variety of physiological functions. There has been, therefore, substantial interest in developing therapeutic agents that target specific 5-HT receptor subtypes.

In particular, characterization of 5-HT_4 receptors and identification of pharmaceutical agents that interact with them has been the focus of significant recent activity. (See, for example, the review by Langlois and Fischmeister, *J. Med. Chem.* **2003**, *46*, 319-344.) 5-HT_4 receptor agonists are useful for the treatment of disorders of reduced motility of the gastrointestinal tract. Such disorders include irritable bowel syndrome (IBS), chronic constipation, functional dyspepsia, delayed gastric emptying, gastroesophageal reflux disease (GERD), gastroparesis, post-operative ileus, intestinal

pseudo-obstruction, and drug-induced delayed transit. In addition, it has been suggested that some 5-HT_4 receptor agonist compounds may be used in the treatment of central nervous system disorders including cognitive disorders, behavioral disorders, mood disorders, and disorders of control of autonomic function.

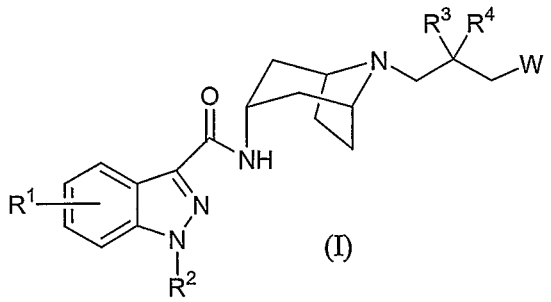
Despite the broad utility of pharmaceutical agents modulating 5-HT_4 receptor activity, few 5-HT_4 receptor agonist compounds are in clinical use at present.

Accordingly, there is a need for new 5-HT_4 receptor agonists that achieve their desired effects with minimal side effects. Preferred agents may possess, among other properties, improved selectivity, potency, pharmacokinetic properties, and/or duration of action.

SUMMARY OF THE INVENTION

The invention provides novel compounds that possess 5-HT_4 receptor agonist activity. Among other properties, compounds of the invention have been found to be potent and selective 5–HT_4 receptor agonists. In addition, compounds of the invention have been found to exhibit favorable pharmacokinetic properties which are predictive of good bioavailability upon oral administration.

Accordingly, the invention provides a compound of formula (I):



(I)

wherein:

R^1 is hydrogen, halo, hydroxy, C_{1-4}alkyl, or C_{1-4}alkoxy;

R^2 is C_{3-4}alkyl, or C_{3-6}cycloalkyl;

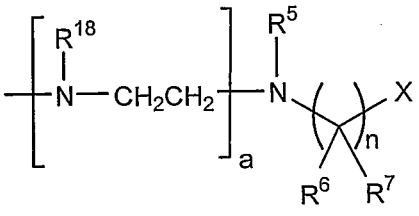
R^3 is hydroxy, C_{1-3}alkoxy, hydroxy-substituted C_{1-4}alkyl, or $-OC(O)NR^aR^b$;

R^4 is hydrogen or C_{1-4}alkyl;

W is selected from

(a) Y, wherein Y is selected from $-N(R^{8a})C(O)R^9$, $-N(R^{8a})S(O)_2R^{10}$, $-N(R^{8a})C(O)OR^{12}$, $-N(R^{8a})C(O)NR^{13}R^{14}$, and $-N(R^{8a})S(O)_2NR^{13}R^{14}$; and

(b) a moiety of formula (b):



(b);

wherein:

X is selected from -N(R^8)C(O)R^9, -N(R^8)S(O)$_2R^{10}$, -S(R^{11})O_2, -N(R^8)C(O)OR^{12}, -N(R^8)C(O)N$R^{13}R^{14}$, -N(R^8)S(O)$_2$N$R^{13}R^{14}$, -C(O)N$R^{13}R^{14}$, -OC(O)N$R^{13}R^{14}$, -C(O)OR^{12}, -OR^{15}, -NR^8R^{16}, cyano, -SR^{15}, CF_3, pyridinyl, pyrrolyl, pyrimidinyl, thiomorpholinyl, thiazolidinyl, 1,1-dioxo isothiazolidinyl, imidazolyl, indolyl, tetrahydrofuranyl, pyrrolidinyl and piperidinyl, wherein pyrrolidinyl is optionally substituted with oxo and piperidinyl is optionally substituted with 1 to 3 halo;

R^5 is hydrogen or C_{1-4}alkyl, wherein C_{1-4}alkyl is optionally substituted with hydroxy, C_{1-3}alkoxy, or cyano;

R^6 and R^7 at each occurrence are independently selected from hydrogen, hydroxy, halo, cyano, and C_{1-4}alkyl, wherein C_{1-4}alkyl is optionally substituted with 1 to 2 substituents selected from hydroxy, C_{1-3}alkoxy, halo, and cyano;

R^8 and R^{8a} are hydrogen or C_{1-4}alkyl;

or R^5 and R^8, R^5 and R^6, or R^6 and R^8 taken together form C_{2-5}alkylenyl, wherein C_{2-5}alkylenyl is optionally substituted with hydroxy, halo, hydroxy-substituted C_{1-3}alkyl, or C_{1-3}alkoxy;

or R^3 and R^5 or R^3 and R^{8a} taken together form -OCH_2CH_2-;

or R^5 and R^6 taken together form –$(CH_2)_q$-Q-$(CH_2)_q$, wherein Q is oxygen or sulfur and *q* is independently 0, 1, or 2;

or R^7 and X taken together form -NHC(O)NHC(O)- or -C(O)NHC(O)NH-;

R^9 is selected from hydrogen, furanyl, tetrahydrofuranyl, pyridinyl, or C_{1-4}alkyl, wherein C_{1-4}alkyl is optionally substituted with hydroxy or with from 1 to 3 halo;

R^{10} is selected from hydrogen, C_{1-4}alkyl, pyridinyl, and imidazolyl, wherein C_{1-4}alkyl is optionally substituted with -S(O)$_2R^c$, C_{3-6}cycloalkyl, or with from 1 to 3 halo, and imidazolyl is optionally substituted with C_{1-3}alkyl;

or R^8 and R^{10} taken together form C_3alkylenyl;

R^{11} is –NR^aR^b, or C_{1-4}alkyl, where C_{1-4}alkyl is optionally substituted with from 1 to 3 halo;

or R^5 and R^{11} or R^6 and R^{11} taken together form C_{2-5}alkylenyl;

R^{12} is C_{1-4}alkyl;

R^{13} and R^{14} are independently hydrogen or C_{1-4}alkyl;

R^{15} is hydrogen or C_{1-4}alkyl, wherein C_{1-4}alkyl is optionally substituted with hydroxy;

or when X is $-SR^{15}$, R^5 and R^{15} taken together form C_{1-4}alkylenyl;

R^{16} is $-(CH_2)_r-R^{17}$, wherein *r* is 0, 1, 2, or 3; and R^{17} is selected from hydrogen, hydroxy, C_{1-3}alkyl, C_{1-3}alkoxy, $-C(O)NR^aR^b$, -C(O)-morpholinyl, pyridinyl, pyrrolyl, pyrimidinyl, morpholinyl, and tetrahydrofuranyl, wherein C_{1-3}alkoxy is optionally substituted with hydroxy; provided that when *r* is 0, R^{17} is selected from hydrogen, C_{1-3}alkyl, pyridinyl, and pyrimidinyl; and when *r* is 1, R^{17} is hydrogen or R^{17} forms a carbon-carbon bond with the $-(CH_2)_r-$ carbon atom;

R^{18} is $-C(O)O-C_{1-3}$alkyl, $-S(O)_2-C_{1-3}$alkyl, or $-C(O)-C_{1-3}$alkyl;

R^a, R^b, and R^c are independently hydrogen or C_{1-3}alkyl;

a is 0 or 1; and

n is an integer of 1, 2, 3, 4, or 5; provided that when *n* is 1, X is $-SR^{15}$, or X forms a carbon-carbon bond with the carbon atom bearing the substituents R^6 and R^7;

or a pharmaceutically-acceptable salt or solvate or stereoisomer thereof.

The invention also provides a pharmaceutical composition comprising a compound of the invention and a pharmaceutically-acceptable carrier.

The invention also provides a method of treating a disease or condition associated with 5-HT_4 receptor activity, e.g. a disorder of reduced motility of the gastrointestinal tract, the method comprising administering to the mammal, a therapeutically effective amount of a compound of the invention.

Further, the invention provides a method of treating a disease or condition associated with 5-HT_4 receptor activity in a mammal, the method comprising administering to the mammal, a therapeutically effective amount of a pharmaceutical composition of the invention and a pharmaceutically acceptable carrier.

The compounds of the invention can also be used as research tools, i.e. to study biological systems or samples, or for studying the activity of other chemical compounds. Accordingly, in another of its method aspects, the invention provides a method of using a compound of formula (I), or a pharmaceutically acceptable salt or solvate or stereoisomer thereof, as a research tool for studying a biological system or sample or for discovering

new 5-HT_4 receptor agonists, the method comprising contacting a biological system or sample with a compound of the invention and determining the effects caused by the compound on the biological system or sample.

In separate and distinct aspects, the invention also provides synthetic processes and intermediates described herein, which are useful for preparing compounds of the invention.

The invention also provides a compound of the invention as described herein for use in medical therapy, as well as the use of a compound of the invention in the manufacture of a formulation or medicament for treating a disease or condition associated with 5-HT_4 receptor activity, e.g. a disorder of reduced motility of the gastrointestinal tract, in a mammal.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides novel indazole-carboxamide 5-HT_4 receptor agonists of formula (I), or pharmaceutically-acceptable salts or solvates or stereoisomers thereof. The following exemplary and preferred values for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

In a specific aspect of the invention, R^1 is hydrogen, halo, or C_{1-4}alkyl.

In other specific aspects, R^1 is hydrogen, fluoro, chloro, bromo, or methyl; R^1 is hydrogen or halo; or R^1 is hydrogen.

In a specific aspect of the invention, R^2 is C_{3-4}alkyl. Representative R^2 groups include *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, and *tert*-butyl.

In another specific aspect, R^2 is isopropyl, or C_{4-5}cycloalkyl.

In another specific aspect, R^2 is isopropyl.

In a specific aspect, R^3 is hydroxy, C_{1-3}alkoxy, or -$OC(O)NR^aR^b$.

In another specific aspect, R^3 is hydroxy, methoxy, hydroxymethyl, -$OC(O)NHCH_3$, or -$OC(O)N(CH_3)_2$.

In specific aspects, R^4 is hydrogen or methyl; or R^4 is hydrogen.

In one aspect of the invention, R^1 is hydrogen or halo, R^2 is isopropyl or C_{4-5}cycloalkyl, and R^4 is hydrogen.

In specific aspects, R^3 is hydroxy, C_{1-3}alkoxy, C_{1-3}alkyl terminally substituted with hydroxy, or -$OC(O)NR^aR^b$; R^3 is hydroxy, C_{1-3}alkoxy, or -$OC(O)NR^aR^b$; or R^3 is hydroxy.

In another specific aspect, R^3 is hydroxy, methoxy, hydroxymethyl, $-OC(O)NHCH_3$, or $-OC(O)N(CH_3)_2$, or R^3 and R^5 or R^3 and R^{8a} taken together form $-OCH_2CH_2-$.

In a specific aspect, R^5 is hydrogen, C_{1-3}alkyl, or C_{1-3}alkyl substituted at the terminal position with hydroxy, C_{1-3}alkoxy, or cyano. Representative R^5 groups include, but are not limited to, hydroxy, methyl, ethyl, 2-hydroxyethyl, 2-methoxyethyl, cyanomethyl, and 2-cyanoethyl.

In other specific aspects, R^5 is hydrogen, C_{1-3}alkyl, or C_{1-3}alkyl substituted at the terminal position with hydroxy; R^5 is hydrogen or C_{1-3}alkyl; or R^5 is hydrogen or methyl.

In another specific aspect, R^5 is hydrogen or C_{1-3}alkyl, or R^5 and R^8 form a C_{2-3}alkylenyl.

In a specific aspect, R^3 and R^5 taken together form $-OCH_2CH_2-$.

In a specific aspect, n is 1, 2 or 3 and R^5 and R^6 taken together form $-CH_2CH_2O-$ or $-CH_2CH_2OCH_2-$.

Alternatively, in another specific aspect, n is 2 and R^5 and R^6 taken together form C_{2-3}alkylenyl.

In a specific aspect, R^6 and R^7 are independently hydrogen, hydroxy, halo, C_{1-3}alkyl, or hydroxy-substituted C_{1-3}alkyl. Representative R^6 and R^7 groups include, but are not limited to, hydrogen, hydroxy, fluoro, chloro, hydroxyethyl, and hydroxymethyl.

In other specific aspects, R^6 and R^7 at each occurrence are independently hydrogen, hydroxy, halo or cyano; or R^6 and R^7 are each hydrogen.

In specific aspects, R^8 is hydrogen or C_{1-3}alkyl, or R^8 is hydrogen or methyl.

In another specific aspect, R^8 is hydrogen or C_{1-3}alkyl, or R^5 and R^8 taken together form C_{2-3}alkylenyl.

Alternatively, in another specific aspect, R^5 and R^8 taken together form C_{2-3}alkylenyl.

In a specific aspect, n is 2 and R^5 and R^8 taken together form C_2alkylenyl.

In a specific aspect, n is 2 and R^5 and R^8 taken together form C_3alkylenyl.

Alternatively, in another specific aspect, R^6 and R^8 taken together form C_{2-3}alkylenyl.

In specific aspects, R^{8a} is hydrogen or C_{1-3}alkyl, or R^3 and R^{8a} taken together form $-OCH_2CH_2-$; R^{8a} is hydrogen or C_{1-3}alkyl; or R^{8a} is hydrogen or methyl.

In a specific aspect, R^9 is hydrogen, tetrahydrofuranyl, pyridinyl, or C_{1-3}alkyl, wherein C_{1-3}alkyl is optionally substituted with hydroxy. Representative R^9 groups include, but are not limited to, hydrogen, tetrahydrofuran-2-yl, methyl, ethyl, propyl, isopropyl, and 1-hydroxyethyl.

In other specific aspects, R^9 is hydrogen, tetrahydrofuranyl, pyridinyl, or C_{1-3}alkyl, such as methyl; or R^9 is hydrogen or methyl.

In a specific aspect, R^{10} is hydrogen or C_{1-3}alkyl, wherein C_{1-3}alkyl is optionally substituted with $-SO_2R^c$, C_{3-6}cycloalkyl, or with from 1 to 3 halo, wherein R^c is C_{1-3}alkyl. Representative R^{10} groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, and methanesulfonylmethyl.

In another specific aspect, R^{10} is C_{1-3}alkyl, wherein C_{1-3}alkyl is optionally substituted with $-S(O)_2C_{1-3}$alkyl or with from 1 to 3 halo.

In other specific aspects, R^{10} is C_{1-3}alkyl; R^{10} is methyl or ethyl; or R^{10} is methyl.

In a specific aspect, R^{11} is $-NR^aR^b$, or C_{1-3}alkyl, where C_{1-3}alkyl is optionally substituted with from 1 to 3 halo.

In other specific aspects, R^{11} is $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$, methyl, ethyl, or $-CF_3$; or R^{11} is methyl.

In another specific aspect, n is 2 and R^5 and R^{11} taken together form C_2alkylenyl.

In yet another specific aspect, n is 2 or 3 and R^6 and R^{11} taken together form C_2alkylenyl.

In specific aspects, R^{12} is C_{1-3}alkyl; or R^{12} is methyl or ethyl.

In specific aspects, R^{13} and R^{14} are independently hydrogen or C_{1-3}alkyl; or R^{13} and R^{14} are independently hydrogen, methyl, or ethyl.

In a specific aspect, R^{15} is hydrogen, C_{1-3}alkyl, or C_{1-3}alkyl substituted at the terminal position with hydroxy. Representative R^{15} groups include, but are not limited to, hydrogen, methyl, ethyl, and 2-hydroxyethyl; such as hydrogen, methyl, and ethyl.

In other specific aspects, R^{15} is hydrogen or C_{1-3}alkyl; or R^{15} is hydrogen, methyl, or ethyl; or R^{15} is hydrogen or methyl.

In a specific aspect, R^{16} is $-(CH_2)_r-R^{17}$, wherein r is 0, 1, or 2. In another specific aspect R^{16} is $-(CH_2)_r-R^{17}$, wherein r is 1 or 2. Representative R^{16} groups include, but are not limited to, $-CH_2-C(O)NR^aR^b$, $-CH_2-C(O)$-morpholinyl, $-CH_2$-pyridinyl, $-CH_2$-pyrimidinyl, and $-CH_2$-tetrahydrofuranyl.

In a specific aspect, R^{17} is selected from hydroxy, C_{1-3}alkoxy, $-C(O)NR^aR^b$, -C(O)-morpholinyl, pyridinyl, pyrimidinyl, morpholinyl, and tetrahydrofuranyl.

In specific aspects, R^{18} is $-C(O)OCH_3$, $-S(O)_2CH_3$, or $-C(O)CH_3$; or R^{18} is $-C(O)OCH_3$.

In specific aspects, R^a, R^b, and R^c are independently hydrogen, methyl, or ethyl; or R^a, R^b, and R^c are independently hydrogen or methyl.

In a specific aspect, *a* is 0. In another specific aspect, *a* is 1.

In a specific aspect, *n* is an integer of 1, 2, 3, or 4, including 1, 2 or 3, such as 2 or 3. In another specific aspect, *n* is 2.

In a specific aspect of the invention, W is selected from:

(a) Y, wherein Y is selected from $-N(R^{8a})C(O)R^9$, $-N(R^{8a})S(O)_2R^{10}$, and $-N(R^{8a})C(O)NR^{13}R^{14}$; and

(b) a moiety of formula (b) wherein X is selected from $-N(R^8)C(O)R^9$, $-N(R^8)S(O)_2R^{10}$, $-N(R^8)C(O)OR^{12}$, $-N(R^8)C(O)NR^{13}R^{14}$, $-N(R^8)S(O)_2NR^{13}R^{14}$, $-C(O)NR^{13}R^{14}$, $-OR^{15}$, and cyano.

In yet another specific aspect, W is Y.

In specific aspects, W is selected from Y, whereinY is selected from $-N(R^{8a})C(O)R^9$, $-N(R^{8a})S(O)_2R^{10}$, $-N(R^{8a})C(O)OR^{12}$, and $-N(R^{8a})C(O)NR^{13}R^{14}$; or Y is selected from $-N(R^{8a})C(O)R^9$, $-N(R^{8a})S(O)_2R^{10}$, and $-N(R^{8a})C(O)NR^{13}R^{14}$. In other specific aspects, W is selected from Y, wherein Y is $-N(R^{8a})S(O)_2R^{10}$; Y is $-N(R^{8a})C(O)R^9$; or Y is $-N(R^{8a})S(O)_2R^{10}$.

In another aspect of the invention, W is selected from Y, wherein Y is as defined herein; R^{8a} is hydrogen or methyl; R^9 is hydrogen, tetrahydrofuranyl, pyridinyl, or methyl; R^{10} and R^{12} are methyl or ethyl; and R^{13} and R^{14} are independently hydrogen or methyl.

Alternatively, W is a moiety of formula (b). In a specific aspect, W is a moiety of formula (b) wherein (i) X is cyano; or (ii) *a* is 0, *n* is 2, R^6 and R^7 are hydrogen, R^5 and R^8 taken together form C_2alkylenyl, and X is selected from $-N(R^8)C(O)R^9$, $-N(R^8)S(O)_2R^{10}$, and $-N(R^8)C(O)NR^{13}R^{14}$.

In another specific aspect, W is a moiety of formula (b) wherein *a* is 0, *n* is 2, R^6 and R^7 are hydrogen, and R^5 and R^8 taken together form C_2alkylenyl. In this aspect, representative X values include, but are not limited to, $-N(R^8)C(O)R^9$, $-N(R^8)S(O)_2R^{10}$, and $-N(R^8)C(O)NR^{13}R^{14}$.

In still another aspect of the invention, W is a moiety of formula (b); *a* is 0 or 1; *n* is 1, 2 or 3; R^5 is hydrogen or methyl; or R^5 and R^8 together form a C_{2-5}alkylene; or R^3 and R^5 taken together are $-OCH_2CH_2-$; R^6 and R^7 are each hydrogen; or R^5 and R^6 together form a C_{2-5}alkylene; and X is as defined herein.

In yet another specific aspect, W is selected from -NHC(O)H, $-N(CH_3)C(O)H$, $-NHC(O)CH_3$, $-N(CH_3)C(O)CH_3$, $-N(CH_3)S(O)_2CH_3$, $-N(CH_3)C(O)NHCH_3$, $-N(CH_3)CH_2CH_2CN$, 1-methanesulfonylpiperazin-4-yl, 1-dimethylaminocarbonyl-piperazin-4-yl, 1-(tetrahydrofuran-2-yl)carbonylpiperazin-4-yl, 3-(methoxycarbonyl-amino)pyrrolidin-1-yl, and 2-(methoxymethylene)pyrrolidin-1-yl.

In a specific aspect, W is a moiety of formula (b), wherein X is selected from $-N(R^8)C(O)R^9$, $-N(R^8)S(O)_2R^{10}$, $-S(R^{11})O_2$, $-N(R^8)C(O)OR^{12}$, $-N(R^8)C(O)NR^{13}R^{14}$, $-N(R^8)S(O)_2NR^{13}R^{14}$, $-C(O)NR^{13}R^{14}$, $-OC(O)NR^{13}R^{14}$, $-C(O)OR^{12}$, $-OR^{15}$, $-NR^8R^{16}$, cyano, $-SR^{15}$, $-CF_3$, pyridinyl, pyrrolyl, 1,1-dioxoisothiazolidinyl, imidazolyl, and pyrrolidinyl, wherein pyrrolidinyl is optionally substituted with oxo.

In another specific aspect, W is a moiety of formula (b), wherein X is selected from $-N(R^8)C(O)R^9$, $-N(R^8)S(O)_2R^{10}$, $-S(R^{11})O_2$, $-N(R^8)C(O)OR^{12}$, $-N(R^8)C(O)NR^{13}R^{14}$, $-N(R^8)SO_2NR^{13}R^{14}$, $-C(O)NR^{13}R^{14}$, $-OC(O)NR^{13}R^{14}$, $-C(O)OR^{12}$, $-OR^{15}$, and cyano.

In other specific aspects, W is a moiety of formula (b), wherein X is selected from $-N(R^8)C(O)R^9$; $-N(R^8)S(O)_2R^{10}$, $-S(R^{11})O_2$, $-N(R^8)C(O)NR^{13}R^{14}$, $-C(O)NR^{13}R^{14}$, $-OC(O)NR^{13}R^{14}$, $-OR^{15}$, and cyano; or X is selected from $-N(R^8)C(O)R^9$, $-N(R^8)S(O)_2R^{10}$, $-N(R^8)C(O)NR^{13}R^{14}$, and cyano.

In still other specific aspects, W is a moiety of formula (b), wherein X is selected from $-N(R^8)C(O)R^9$, $-N(R^8)S(O)_2R^{10}$, and $-N(R^8)C(O)NR^{13}R^{14}$; or X is $-N(R^8)S(O)_2R^{10}$.

In one aspect of the invention, R^1, R^2, R^3, R^4, and *a* are as defined herein;

W is selected from Y and a moiety of formula (b), and

R^5 is hydrogen, C_{1-3}alkyl, or C_{1-3}alkyl substituted at the terminal position with hydroxy;

R^6 and R^7 at each occurrence are independently hydrogen, hydroxy, halo or cyano;

R^8 and R^{8a} are hydrogen or C_{1-3}alkyl;

or R^3 and R^5 or R^3 and R^{8a} taken together are $-OCH_2CH_2-$;

or R^5 and R^6 taken together form a C_{2-5}alkylene;

or R^5 and R^8 taken together form a C_{2-5}alkylene;

R^9 is hydrogen, tetrahydrofuranyl, pyridinyl, or C_{1-3}alkyl;

R^{10} is C_{1-3}alkyl, wherein C_{1-3}alkyl is optionally substituted with $-S(O)_2C_{1-3}$alkyl, or with from 1 to 3 halo;

R^{11} is $-NR^aR^b$ or C_{1-4}alkyl, where C_{1-4}alkyl is optionally substituted with from 1 to 3 halo;

or R^5 and R^{11} or R^6 and R^{11} taken together form C_{2-5}alkylenyl;

R^{12} is C_{1-3}alkyl;

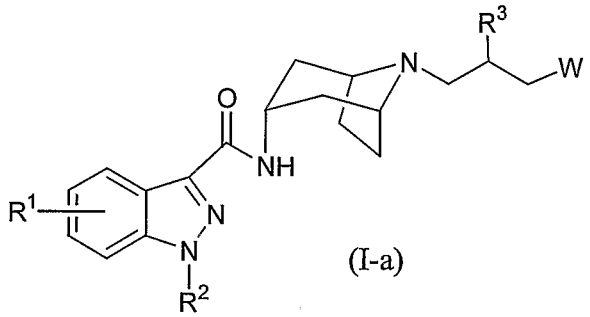
R^{13}, R^{14}, and R^{15} are independently hydrogen or C_{1-3}alkyl;

R^{16} is $-CH_2-C(O)NR^aR^b$, $-CH_2-C(O)$-morpholinyl, $-CH_2$-pyridinyl, $-CH_2$-pyrimidinyl, or $-CH_2$-tetrahydrofuran;

R^{18} is $—C(O)OCH_3$, $—S(O)_2CH_3$, or $-C(O)CH_3$; and

n is an integer of 1, 2, or 3.

In another aspect, the invention provides a compound of formula (I) which is a compound of formula (I-a):



(I-a)

wherein

R^1 is hydrogen, halo or C_{1-4}alkyl;

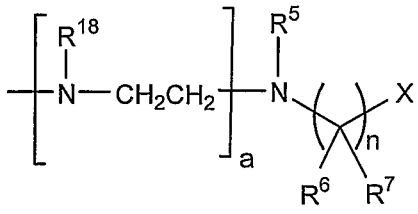
R^2 is isopropyl or C_{4-5}cycloalkyl;

R^3 is hydroxy, C_{1-3}alkoxy, or $OC(O)NR^aR^b$;

W is selected from

(a) Y, wherein Y is selected from $-N(R^{8a})C(O)R^9$, $-N(R^{8a})S(O)_2R^{10}$, $-N(R^{8a})C(O)OR^{12}$, $-N(R^{8a})C(O)NR^{13}R^{14}$, and $-N(R^{8a})S(O)_2NR^{13}R^{14}$; and

(b) a moiety of formula (b):



(b)

wherein

X is selected from -$N(R^8)C(O)R^9$, -$N(R^8)S(O)_2R^{10}$, -$S(R^{11})O_2$, -$N(R^8)C(O)OR^{12}$, -$N(R^8)C(O)NR^{13}R^{14}$, -$N(R^8)S(O)_2NR^{13}R^{14}$, -$C(O)NR^{13}R^{14}$, -$OC(O)NR^{13}R^{14}$, -$C(O)OR^{12}$, -$OR^{15}$, -$NR^8R^{16}$, cyano, -$SR^{15}$, CF_3, pyridinyl, pyrrolyl, 1,1-dioxo isothiazolidinyl, imidazolyl, and pyrrolidinyl, wherein pyrrolidinyl is optionally substituted with oxo;

R^5 is hydrogen, C_{1-3}alkyl, or C_{1-3}alkyl substituted at the terminal position with hydroxy;

R^6 and R^7 at each occurrence are independently hydrogen, hydroxy, halo or cyano;

R^8 and R^{8a} are hydrogen or C_{1-3}alkyl;

or R^5 and R^8 or R^5 and R^6 together form a C_{2-5}alkylene;

or R^3 and R^5 or R^3 and R^{8a} taken together are -OCH_2CH_2-;

R^9 is hydrogen, tetrahydrofuranyl, pyridinyl, or methyl;

R^{10} is C_{1-3}alkyl, wherein C_{1-3}alkyl is optionally substituted with -$S(O)_2C_{1-3}$alkyl, or with from 1 to 3 halo;

R^{11} is –NR^aR^b, or C_{1-3}alkyl, where C_{1-3}alkyl is optionally substituted with from 1 to 3 halo;

or R^5 and R^{11} or R^6 and R^{11} taken together form C_{2-5}alkylenyl;

R^{12} is C_{1-3}alkyl;

R^{13}, R^{14}, and R^{15} are independently hydrogen or C_{1-3}alkyl;

R^{16} is -CH_2-$C(O)NR^aR^b$, -CH_2-C(O)-morpholinyl, -CH_2-pyridinyl, -CH_2-pyrimidinyl, or -CH_2-tetrahydrofuranyl;

R^{18} is -$C(O)OCH_3$, -$S(O)_2CH_3$, or -$C(O)CH_3$;

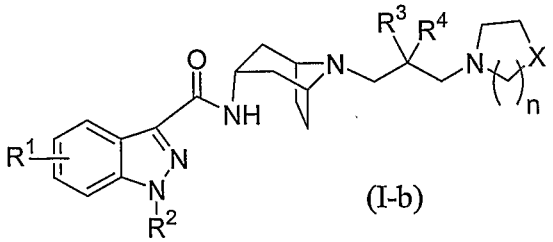
R^a and R^b are independently hydrogen or C_{1-3}alkyl;

a is 0 or 1; and

n is an integer of 1, 2, or 3; provided that when *n* is 1, X is -SR^{15}, or X forms a carbon-carbon bond with the carbon atom bearing the substituents R^6 and R^7;

or a pharmaceutically-acceptable salt or solvate or stereoisomer thereof.

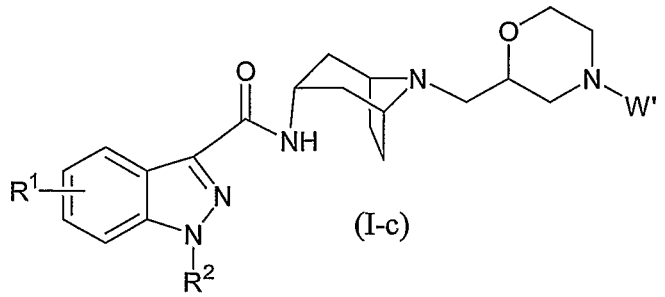
The invention further provides a compound of formula (I-b):



(I-b)

wherein R^1, R^2, R^3, R^4, *n* and X take any of the values defined herein.

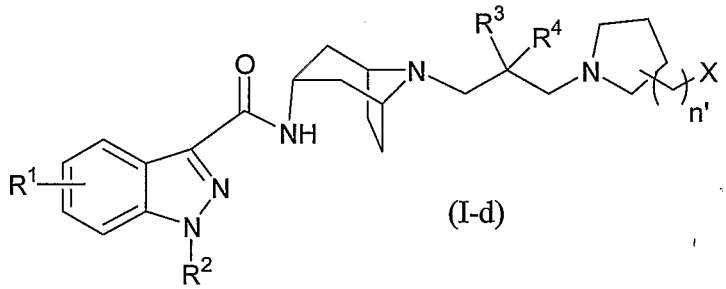
The invention further provides a compound of formula (I-c):



(I-c)

wherein W' is selected from $-C(O)R^9$, $-S(O)_2R^{10}$, $-C(O)OR^{12}$, $-C(O)NR^{13}R^{14}$, $-S(O)_2NR^{13}R^{14}$, and $-(CR^6R^7)_n-X$; and R^1, R^2, R^6, R^7, R^9, R^{10}, R^{12}, R^{13}, and R^{14} take any of the values defined herein.

The invention further provides a compound of formula (I-d):

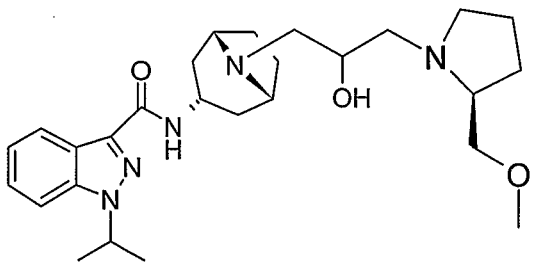


(I-d)

wherein *n'* is an integer of 0, 1, or 2, and R^1, R^2, R^3, R^4, and X take any of the values defined herein.

In yet another aspect, the invention provides the compounds listed in Tables I to X herein.

The chemical naming conventions used herein are illustrated for the compound of Example 1:



which is designated 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[2-hydroxy-3-((*S*)-2-methoxymethylpyrrolidin-1-yl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide according to the AutoNom software, provided by MDL Information Systems, GmbH (Frankfurt, Germany). The designation (1*S*,3*R*,5*R*) describes the relative

orientation of the bonds associated with the bicyclic ring system that are depicted as solid and dashed wedges. The compound is alternatively denoted as *N*-[(3-endo)-8-(3-((*S*)-2-methoxymethylpyrrolidin-1-yl)-2-hydroxypropyl)-8-azabicyclo[3.2.1]oct-3-yl]-1-(1-methylethyl)-1*H*-indazole-3-carboxamide.

Particular mention may be made of the following compounds:

1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[2-hydroxy-3-((*S*)-2-methoxymethylpyrrolidin-1-yl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide;

1-isopropyl-1*H*-indazole-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{3-[(2-cyano-ethyl)methylamino]-2-hydroxypropyl}-8-azabicyclo[3.2.1]oct-3-yl)amide;

1-isopropyl-1*H*-indazole-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{2-hydroxy-3-[4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl]propyl}-8-azabicyclo[3.2.1]oct-3-yl)-amide;

1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[2-hydroxy-3-(4-methanesulfonylpiperazin-1-yl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide;

1-isopropyl-1*H*-indazole-3-carboxylic acid [(1*S*,3*R*,5*R*)-8-(4-carbamoylmethylmorpholin-2-ylmethyl)-8-azabicyclo[3.2.1]oct-3-yl]amide;

1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[3-(4-dimethylcarbamoylpiperazin-1-yl)-2-hydroxypropyl]-8-azabicyclo[3.2.1]oct-3-yl}amide;

1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[3-(4-methanesulfonylpiperazin-1-yl)-2-methoxypropyl]-8-azabicyclo[3.2.1]oct-3-yl}amide;

1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[(*R*)-2-hydroxy-3-(4-methanesulfonylpiperazin-1-yl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide;

[1-(2-hydroxy-3-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-1*H*-indazole-3-carbonyl)-amino]-8-azabicyclo[3.2.1]oct-8-yl}propyl)pyrrolidin-3-yl]carbamic acid methyl ester;

1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[(*S*)-2-hydroxy-3-(4-methanesulfonylpiperazin-1-yl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide;

1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[2-hydroxy-3-(methanesulfonylmethylamino)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide;

1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[3-(acetyl-methylamino)-2-hydroxypropyl]-8-azabicyclo[3.2.1]oct-3-yl}amide;

1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[3-(formyl-methylamino)-2-hydroxypropyl]-8-azabicyclo[3.2.1]oct-3-yl}amide;

1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[3-(1,3-dimethylureido)-2-hydroxypropyl]-8-azabicyclo[3.2.1]oct-3-yl}amide;

1-isopropyl-1*H*-indazole-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{2-hydroxy-3-[(pyridine-4-carbonyl)amino]propyl}-8-azabicyclo[3.2.1]oct-3-yl)amide;

1-isopropyl-1*H*-indazole-3-carboxylic acid [(1*S*,3*R*,5*R*)-8-(3-formylamino-2-hydroxypropyl)-8-azabicyclo[3.2.1]oct-3-yl]-amide; and

1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[(*R*)-2-hydroxy-3-(methanesulfonylmethylamino)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide.

As illustrated above, the compounds of the invention may contain one or more chiral centers. Accordingly, the invention includes racemic mixtures, pure stereoisomers, and stereoisomer-enriched mixtures of such isomers, unless otherwise indicated. When a particular stereoisomer is shown, it will be understood by those skilled in the art, that minor amounts of other stereoisomers may be present in the compositions of the invention unless otherwise indicated, provided that the utility of the composition as a whole is not eliminated by the presence of such other isomers.

Definitions

When describing the compounds, compositions and methods of the invention, the following terms have the following meanings, unless otherwise indicated.

The term "alkyl" means a monovalent saturated hydrocarbon group which may be linear or branched or combinations thereof. Unless otherwise defined, such alkyl groups typically contain from 1 to 10 carbon atoms. Representative alkyl groups include, by way of example, methyl, ethyl, *n*-propyl (*n*-Pr), isopropyl (*i*-Pr), *n*-butyl (*n*-Bu), *sec*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, *n*-hexyl, *n*-heptyl, *n*-octyl, *n*-nonyl, *n*-decyl and the like.

The term "alkylenyl" or "alkylene" means a divalent saturated hydrocarbon group which may be linear or branched or combinations thereof. Representative "alkylenyl" groups include, by way of example, methylenyl, ethylenyl, *n*-propylenyl, isopropylenyl, *n*-butylenyl, *sec*-butylenyl, *tert*-butylenyl, and the like.

The term "alkoxy" means the monovalent group –O-alkyl, where alkyl is defined as above. Representative alkoxy groups include, by way of example, methoxy, ethoxy, propoxy, butoxy, and the like.

The term "compound" means a compound that was synthetically prepared or prepared in any other way, such as by metabolism.

The term "cycloalkyl" means a monovalent saturated carbocyclic group which may be monocyclic or multicyclic. Unless otherwise defined, such cycloalkyl groups

typically contain from 3 to 10 carbon atoms. Representative cycloalkyl groups include, by way of example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like.

The term "halo" means a fluoro, chloro, bromo or iodo.

The term "therapeutically effective amount" means an amount sufficient to effect treatment when administered to a patient in need of treatment.

The term "treatment" as used herein means the treatment of a disease, disorder, or medical condition in a patient, such as a mammal (particularly a human) which includes:

(a) preventing the disease, disorder, or medical condition from occurring, i.e., prophylactic treatment of a patient;

(b) ameliorating the disease, disorder, or medical condition, i.e., eliminating or causing regression of the disease, disorder, or medical condition in a patient;

(c) suppressing the disease, disorder, or medical condition, i.e., slowing or arresting the development of the disease, disorder, or medical condition in a patient; or

(d) alleviating the symptoms of the disease, disorder, or medical condition in a patient.

The term "pharmaceutically-acceptable salt" means a salt prepared from an acid or base which is acceptable for administration to a patient, such as a mammal. Such salts can be derived from pharmaceutically-acceptable inorganic or organic acids and from pharmaceutically-acceptable bases. Typically, pharmaceutically-acceptable salts of compounds of the present invention are prepared from acids.

Salts derived from pharmaceutically-acceptable acids include, but are not limited to, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic, xinafoic (1-hydroxy-2-naphthoic acid), napthalene-1,5-disulfonic acid and the like.

The term "solvate" means a complex or aggregate formed by one or more molecules of a solute, i.e. a compound of the invention or a pharmaceutically-acceptable salt thereof, and one or more molecules of a solvent. Such solvates are typically crystalline solids having a substantially fixed molar ratio of solute and solvent.

Representative solvents include by way of example, water, methanol, ethanol, isopropanol, acetic acid, and the like. When the solvent is water, the solvate formed is a hydrate.

It will be appreciated that the term "or a pharmaceutically-acceptable salt or solvate of stereoisomer thereof" is intended to include all permutations of salts, solvates and stereoisomers, such as a solvate of a pharmaceutically-acceptable salt of a stereoisomer of a compound of formula (I).

The term "amino-protecting group" means a protecting group suitable for preventing undesired reactions at an amino nitrogen. Representative amino-protecting groups include, but are not limited to, formyl; acyl groups, for example alkanoyl groups, such as acetyl; alkoxycarbonyl groups, such as *tert*-butoxycarbonyl (Boc); arylmethoxycarbonyl groups, such as benzyloxycarbonyl (Cbz) and 9-fluorenylmethoxycarbonyl (Fmoc); arylmethyl groups, such as benzyl (Bn), trityl (Tr), and 1,1-di-(4'-methoxyphenyl)methyl; silyl groups, such as trimethylsilyl (TMS) and *tert*-butyldimethylsilyl (TBDMS); and the like.

General Synthetic Procedures

Compounds of the invention can be prepared from readily available starting materials using the following general methods and procedures. Although a particular aspect of the present invention is illustrated in the schemes below, those skilled in the art will recognize that all aspects of the present invention can be prepared using the methods described herein or by using other methods, reagents and starting materials known to those skilled in the art. It will also be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

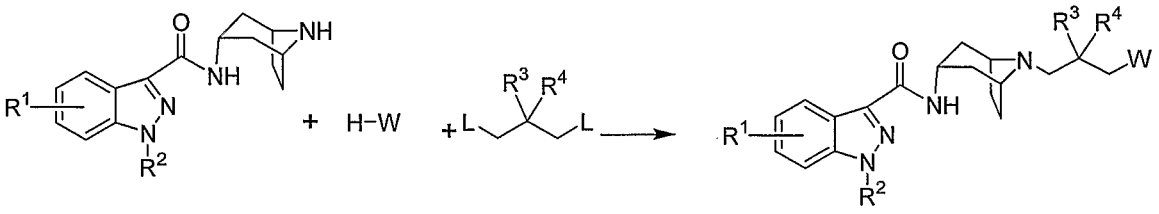
Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group, as well as suitable conditions for protection and deprotection, are well known in the art. For example, numerous protecting groups, and their introduction and removal, are described

in T. W. Greene and G. M. Wuts, *Protecting Groups in Organic Synthesis*, Third Edition, Wiley, New York, 1999, and references cited therein.

The substituents and variables shown in the following schemes have the definitions provided above unless otherwise indicated.

In one method of synthesis, compounds of formula (I) in which R^3 is defined as hydroxy or hydroxy-substituted C_{1-4}alkyl are prepared as illustrated in Scheme A:

Scheme A



1 2 3 (I)

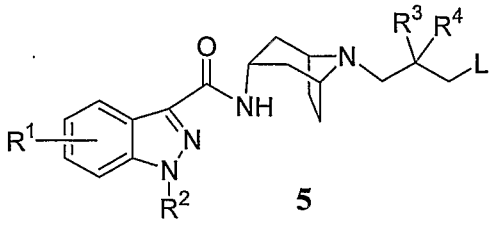
by reacting intermediate **1**, with intermediate **2** and intermediate **3**, wherein L is a leaving group, such as chloro, bromo, iodo, methanesulfonyloxy, *p*-toluenesulfonyloxy, or trifluoromethane-sulfonyloxy, to provide a compound of formula (I).

The reaction is typically conducted by contacting intermediate **1** with between about 1 and about 3 equivalents, each, of intermediates **2** and **3** in an inert diluent, such as methanol or ethanol, in the presence of an excess of base, for example between about 3 and about 6 equivalents, of base, such as *N,N*-diisopropylethylamine. The reaction is typically conducted at a temperature in the range of about 50 °C to about 80 °C for about 12 hours to about 24 hours, or until the reaction is substantially complete. Optionally, equal molar equivalents of intermediates **2** and **3** can be added in portions.

The product of formula (I) is isolated and purified by conventional procedures. For example, the product can be concentrated to dryness under reduced pressure, taken up in an aqueous weak acid solution and purified by HPLC chromatography.

It will be understood that in the process of Scheme A and in other processes described below using intermediate **1**, intermediate **1** can be supplied in the form of the freebase or in a salt form, with appropriate adjustment of reaction conditions, as necessary, as known to those skilled in the art.

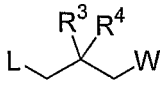
In Scheme A, the reaction of intermediate **1** with intermediates **2** and **3** is accomplished in a single step. Alternatively, the reaction can be performed in a stepwise manner. Using similar reaction conditions to those described above, intermediates **1** and **3** can first be coupled to form an intermediate **5**:



5

which is then reacted with intermediate **2** to provide a compound of formula (I).

Alternatively, intermediate **2** can first be coupled to intermediate **3** to form intermediate **10**:



10

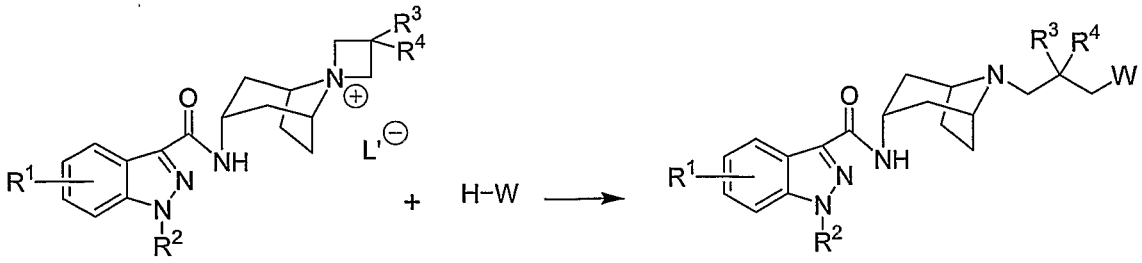
which is subsequently reacted with the indazole-carboxamide-tropane intermediate **1**, to provide a compound of formula (I).

Compounds of formula (I) can also be prepared by *N*-alkylating a compound of the form of formula (I) in which R^2 is defined as hydrogen, which can be prepared according to Scheme A. The *N*-alkylation reaction is typically conducted by contacting a compound of formula (I) in which R^2 is hydrogen with between about 1 and about 4 equivalents of a compound of the formula L'—R^2 in which L' is a leaving group such as iodo or bromo. This reaction is typically conducted in a polar aprotic solvent such as dimethylformamide in the presence of between about 2 and about 4 equivalents of strong base, such as potassium *tert*-butoxide or sodium hydride. Typically, the reaction is performed at a temperature of between about 60 °C and about 100 °C for between about 6 and about 24 hours, or until the reaction is substantially complete.

In yet another alternative, compounds of formula (I) in which R^1 is other than hydrogen are prepared by conventional processes such as aromatic halogenation from compounds of formula (I) in which R^1 is hydrogen.

In another method of synthesis, compounds of formula (I) in which R^3 is hydroxy, C_{1-3}alkoxy, or –OC(O)NR^aR^b and the carbon atom bearing the substituent R^3 is not chiral can be prepared by reacting an azetidine intermediate **11**, as illustrated in Scheme B:

Scheme B



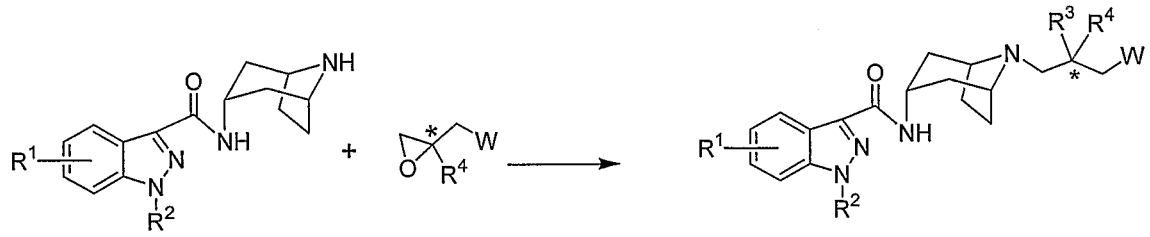
11 2 (I)

where L' is a counterion, such as halide, for example, Cl^-, Br^-, or trifluoroacetate, with intermediate **2**, H-W, to provide a compound of formula (I).

The reaction is typically conducted by contacting intermediate **11** with between about 1 and about 4 equivalents of intermediate **2** in an inert diluent, such as ethanol, methanol, or dimethylformamide, in the presence of an excess of base, for example between about 2 and about 4 equivalents, of base, such as *N,N*-diisopropylethylamine, 1,8-diazabicylco[5.4.0]undec-7-ene (DBU) or triethylamine. The reaction is typically conducted at a temperature in the range of about 50 °C to about 80 °C for about 1 hour to about 16 hours, or until the reaction is substantially complete. The product is isolated and purified by conventional means.

In yet another method of synthesis, compounds of formula (I) in which R^3 is hydroxy can be prepared as illustrated in Scheme C wherein an asterisk denotes a chiral center, by reacting intermediate **1** with intermediate **12** to provide a compound of formula (I).

Scheme C



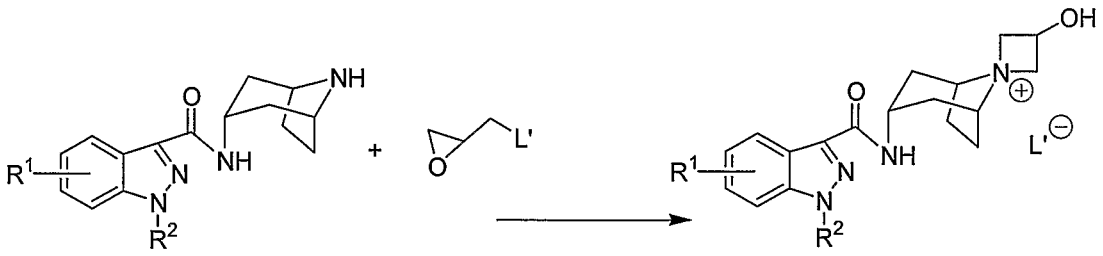
1 12 (I)

When a single enantiomer of the intermediate of formula **12** is employed, the reaction of Scheme C is useful to prepare single enantiomers of compounds of formula (I) having a chiral center at the carbon bearing the substituent R^4. Typically, in the reaction of Scheme C, intermediate **1** is contacted with between about 1 and about 1.2 equivalents of the epoxide **12** in an inert diluent such as ethanol or toluene. The reaction is typically

conducted at a temperature in the range of about 50 °C to about 100 °C for about 12 hours to about 24 hours, or until the reaction is substantially complete. The product is isolated and purified by conventional means.

The intermediates employed in Schemes A, B, and C above are prepared from readily available starting materials. For example, when R^3 is hydroxy, an azetidine intermediate of formula **13** can be prepared by the procedure illustrated in Scheme D.

Scheme D



1 **6** **13**

Intermediate **1** is reacted with intermediate **6**, an oxirane compound where L' represents a halo leaving group such as bromo, chloro, or iodo, (for instance, L' is bromo, and the oxirane compound is 2-bromomethyloxirane, commonly, epibromohydrin) to form intermediate **13**, an azetidine salt. This reaction is typically conducted by contacting **1** with between about 2 and about 4 equivalents of the oxirane compound in a polar diluent, such as ethanol. The reaction is typically conducted at ambient temperature for between about 24 and about 48 hours or until the reaction is substantially complete.

To form the azetidine intermediate **11** in which R^3 is C_{1-3}alkoxy, intermediate **13** above is contacted with from slightly less than one equivalent to about one equivalent of a C_{1-3}alkylhalide in an inert diluent in the presence of between about 1 and about 3 equivalents of a strong base, such as potassium *tert*-butoxide or sodium hydride. The reaction is typically conducted at ambient temperature for between about a quarter hour to an hour, or until the reaction is substantially complete. Suitable inert diluents include tetrahydrofuran, toluene, dimethylformamide, and the like.

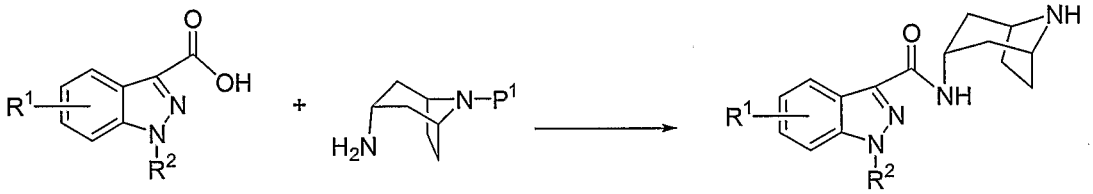
Intermediate **11** in which R^3 is a carbamic acid moiety of the form $-OC(O)NR^aR^b$ can be prepared from an intermediate of formula **13** in which R^3 is hydroxy. For example, to prepare a compound of formula **11** in which R^3 is $-OC(O)N(H)CH_3$ or $-OC(O)N(CH_3)_2$, intermediate **13** is contacted with between about 1 and about 3 equivalents of methylisocyanate or dimethylcarbamyl chloride, respectively, in an inert diluent in the presence of between about 1 and about 3 equivalents of base, such as *N,N*-diisopropyl-

ethylamine, and of a catalytic amount of a strong base, such as potassium *tert*-butoxide or sodium hydride. The reaction is typically conducted at ambient temperature for between about 4 hours and about 24 hours, or until the reaction is substantially complete.

Alternatively, compounds of formula (I) in which R^3 is a carbamic acid moiety of the form $-OC(O)NR^aR^b$ can be prepared from a compound of formula (I) in which R^3 is hydroxy. For example, to prepare a compound of formula (I) in which R^3 is $-OC(O)N(H)CH_3$ or $-OC(O)N(CH_3)_2$, a compound of formula (I) in which R^3 is hydroxy is contacted with between about 1 and about 3 equivalents of methylisocyanate or dimethylcarbamyl chloride, respectively, under conditions similar to those described above to prepare a compound of formula (I) in which R^3 is $-OC(O)NR^aR^b$.

A process for preparing intermediates of formula **1** is shown in Scheme E.

Scheme E



14 **15** **1**

Intermediate **1** can be prepared by reacting intermediate **14** with intermediate **15**, where P^1 represents an amino-protecting group, to provide intermediate **1**.

Typically, this reaction is conducted by first converting **14** to an acid chloride by contacting **14** with at least one equivalent, preferably between about 1 and about 2 equivalents of an activating agent, such as thionyl chloride or oxalyl chloride in an aromatic diluent, such as toluene, benzene, xylene, or the like. The reaction is typically conducted at a temperature ranging from about 80 °C to about 120 °C for about 15 minutes to about 4 hours, or until the reaction is substantially complete.

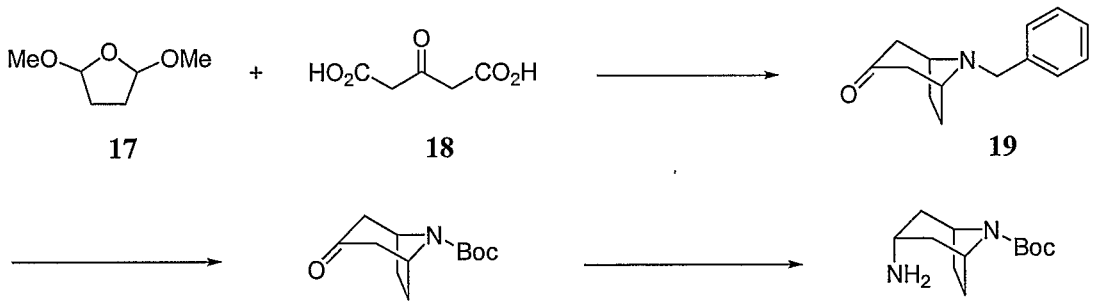
The acid chloride solution is typically added to a biphasic mixture of about 1 equivalent of the aminotropane **15** to form a protected intermediate, which is extracted by standard procedures. The biphasic mixture of **15** is generally prepared by dissolving **15** in an aromatic diluent, such as toluene, benzene, xylene, or the like, and adding an aqueous solution containing an excess of base, such as sodium hydroxide or potassium hydroxide, preferably about 2 to 5 equivalents of base. The reaction is typically conducted at a temperature ranging from about 80 °C to about 120 °C for about 15 minutes to about 4 hours, or until the reaction is substantially complete.

Alternatively, the amide coupling of intermediate **15** with the carboxylic acid **14** can be performed in the presence of a coupling agent such as 1,3 dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC), or benzotriazol-1-yloxytripyrrolidino-phosphonium hexafluorophosphate (PyBop), optionally combined with 1-hydroxy-7-azabenzotriazole (HOAt). In yet another alternative, the amide coupling of intermediate **15** with the carboxylic acid **14** can be performed by converting **14** to an activated ester.

The protecting group P^1 is removed by standard procedures to provide intermediate **1**. For example when the protecting group is Boc, typically removal is by treatment with an acid, such as trifluoroacetic acid, providing the acid salt of the intermediate. The acid salt of intermediate **1** can be converted to the free base by conventional treatment with base. The protecting group Cbz, for another example, is conveniently removed by hydrogenolysis over a suitable metal catalyst such as palladium on carbon.

The protected aminotropane **15** employed in the reactions described in this application is prepared from readily available starting materials. For example, when the protecting group P^1 is Boc, the protected aminotropane **16** can be prepared by the procedure illustrated in Scheme F.

Scheme F



17 **18** **19** **20** **16**

For example, the protected aminotropane intermediate **16** can be prepared by reacting 2,5-dimethoxy tetrahydrofuran **17** with 1,3-acetonedicarboxylic acid **18** to provide 8-benzyl-8-azabicyclo[3.2.1]octan-3-one **19**, commonly *N*-benzyltropanone. *N*-benzyltropanone is then reacted with a slight excess of di-*tert*-butyl dicarbonate in the presence of a transition metal catalyst to provide the protected Boc intermediate **20,** which is reduced to provide the protected aminotropane intermediate **16**.

First, 2,5-dimethoxy tetrahydrofuran **17** is contacted with between about 1 and 2 equivalents, preferably about 1.5 equivalents of benzyl amine and a slight excess, for example about 1.1 equivalents, of 1,3-acetonedicarboxylic acid **18** in an acidic aqueous solution in the presence of a buffering agent such as sodium hydrogen phosphate. The reaction mixture is heated to between about 60 °C and about 100 °C to ensure decarboxylation of any carboxylated intermediates in the product, 8-benzyl-8-azabicyclo[3.2.1]octan-3-one **19**, commonly *N*-benzyltropanone.

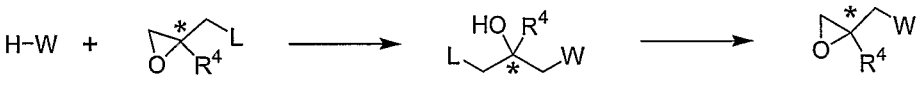
The intermediate **19** is typically reacted with a slight excess of di-*tert*-butyl dicarbonate, for example, about 1.1 equivalents, under a hydrogen atmosphere in the presence of a transition metal catalyst to provide the Boc protected intermediate **20**, 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester. The reaction is typically conducted at ambient temperature for about 12 to about 72 hours.

Finally, intermediate **20** is contacted with a large excess, for example more than 25 equivalents, of ammonium formate in an inert diluent, such as methanol, in the presence of a transition metal catalyst to provide intermediate **16** in the *endo* configuration. The product **16** can be purified by conventional procedures, such as alkaline extraction.

The 1*H*-indazole carboxylic acid, intermediate **14,** can be readily prepared by procedures similar to those reported in the literature in Harada *et al. Chem. and Pharm Bull.* **1995,** *43,* 1912-30 and described in the examples below.

The oxirane intermediate **12** used in Scheme C can be prepared as shown in Scheme G:

Scheme G



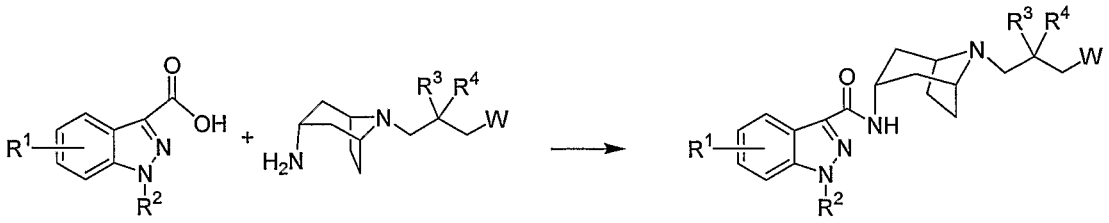
2 **7** **21** **12**

where intermediate **2** is reacted with intermediate 7, a substituted oxirane where L is a halo leaving group, to provide intermediate **21**, which is then recyclized to provide intermediate **12**. This reaction is typically conducted by contacting the amine intermediate **2** with between about 1 and about 2 equivalents of intermediate **7** in a polar diluent such as ethanol. The reaction is typically conducted at ambient temperature for between about 12 and about 24 hours, or until the reaction is substantially complete. The linear intermediate **21** is typically isolated by conventional procedures as a solid. The

solid **21** is typically dissolved in an inert diluent, for example tetrahydrofuran, in the presence of a molar excess of base, for example sodium hydroxide, to produce the cyclized intermediate **12**.

In yet another alternative method of synthesis, compounds of formula (I) can be prepared by coupling the substituted 1*H*-indazole carboxylic acid **14** with an intermediate of formula **22** as illustrated in Scheme H.

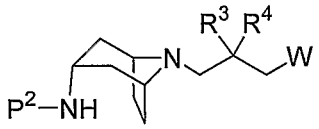
Scheme H



14 **22** **(I)**

The reaction of the carboxylic acid **14** with intermediate **22** is typically conducted under amide coupling conditions described above for Scheme E.

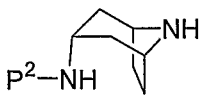
Intermediates of formula **22** can be prepared by deprotecting an intermediate of formula **23**:



23

where P^2 represents an amino-protecting group.

Intermediates of formula **23** can be prepared from readily available starting materials using procedures analogous to the reactions described above and/or using alternative reactions well known to those skilled in the art. For example, intermediate **23** can be prepared using an intermediate **24**:



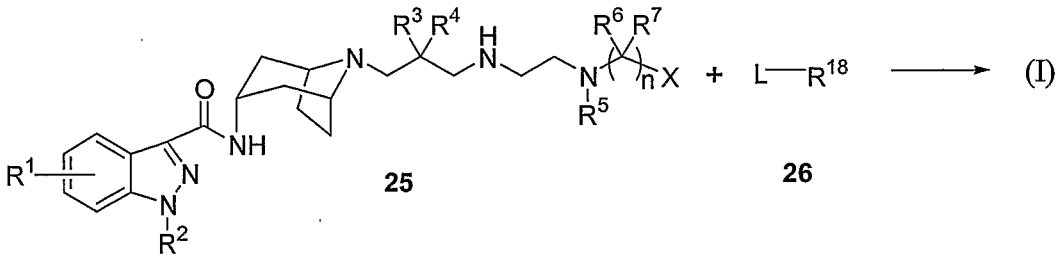
24

which may be formed by protecting the amino nitrogen of the aminoazobicyclooctane **15** with amino-protecting group P^2 and then removing P^1 from the nitrogen of the azabicyclooctane group. Protecting groups P^1 and P^2 are chosen such that they are removed under different conditions. For example when P^1 is chosen as Boc, then Cbz can

be used as P^2. Substituting the protected aminotropane **24** for intermediate **1** in the reactions described in Schemes A and C provides intermediates of formula **23**.

In yet another alternative method of synthesis, a compound of formula (I) in which W is a moiety of formula (b) and *a* is 1, can be prepared as shown below in Scheme J:

Scheme J



wherein intermediate **25** is reacted with intermediate **26**, wherein L is a leaving group, such as halo, for example, chloro, or ethoxy, or L-R^{18} is a carboxylic acid, i.e., L represents a hydroxy group, to provide a compound of formula (I).

Exemplary reagents of intermediate **26** include methanesulfonylchloride and acetylchloride, and the like. Optimal reaction conditions for the reaction of Scheme J may vary depending on the chemical properties of the reagents, as is well known to those skilled in the art.

For example, when L is a halo leaving group, such as chloro, the reaction is typically conducted by contacting intermediate **25** with between about 1 and about 4 equivalents of intermediate **26** in an inert diluent, such as dichloromethane, in the presence of an excess of a base, for example between about 3 and about 6 equivalents, of base, such as *N,N*-diisopropylethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Suitable inert diluents also include *N,N*-dimethylformamide (DMF), trichloromethane, 1,1,2,2-tetrachloroethane, tetrahydrofuran, and the like. The reaction is typically conducted at a temperature in the range of about -100 °C to about 30 °C for about a quarter hour to about 2 hours, or until the reaction is substantially complete.

When intermediate **26** is a carboxylic acid, Scheme J represents an amide coupling reaction which is typically conducted by contacting intermediate **25** with between about 1 and about 4 equivalents of a carboxylic acid in an inert diluent, for example, *N,N*-dimethylformamide, in the presence of a coupling agent such as benzotriazol-1-yloxytripyrrolidino-phosphonium hexafluorophosphate (PyBOP). The reaction is

typically conducted at ambient temperature, for about a quarter hour to about 2 hours, or until the reaction is substantially complete. Suitable alternative coupling agents include 1,3-dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC), and PyBOP combined with 1-hydroxy-7-azabenzotriazole (HOAt).

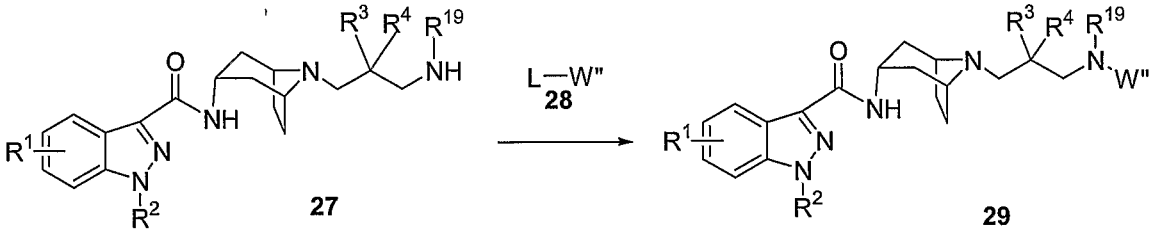
The amide coupling of intermediate **25** with a carboxylic acid alternatively can be performed by converting the carboxylic acid to an activated ester, such as an *N*-hydroxy succinimide (NHS) ester or a *p*-nitrophenyl ester, or an acid imidazole, which is then reacted with intermediate **25** to provide a compound of formula (I).

When intermediate **26** is a liquid, for example ethyl formate, the reaction can be performed by dissolving intermediate **25** in a large excess of intermediate **26**, and heating to a temperature of between about 50 °C and about 100 °C for about 12 to about 24 hours to provide a compound of formula (I). The product, a compound of formula (I), can then be isolated and purified by conventional procedures.

Intermediate **25** can be prepared from readily available starting materials using Schemes A, B, C, and H described herein, or using alternative reactions well known to those skilled in the art.

In another alternate synthesis, a compound of formula (I) wherein when *a* is 0, R^5 is hydrogen or optionally substituted C_{1-4}alkyl, or R^3 and R^5 taken together form $-OCH_2CH_2-$, can be prepared as shown below in Scheme K:

Scheme K



in which intermediate **27** (wherein R^{19} is R^5, R^{8a}, or R^{18}), is reacted with intermediate **28** (wherein L is a leaving group, such as halo, and W″ is a residue that, together with the terminal nitrogen atom of intermediate **27** will afford W) to provide a compound of formula (I). When R^{19} is R^{8a}, W″ is $-C(O)R^9$, $-S(O)_2R^{10}$, $-C(O)OR^{12}$, $-C(O)NR^{13}R^{14}$, or $-S(O)_2NR^{13}R^{14}$. When R^{19} is R^{18}, W″ is $-(CH_2)_2-N(R^5)(CR^6R^7)_n-X$. When *a* is 0, R^{19} is R^5, W″ is $-(CR^6R^7)_n-X$, and R^5 is hydrogen or C_{1-4}alkyl, wherein C_{1-4}alkyl is optionally substituted with hydroxy, C_{1-3}alkoxy, or cyano, or R^3 and R^5 taken together form $-OCH_2CH_2-$.

The reaction is typically conducted by contacting intermediate **27** with between about 1 and about 3 equivalents of intermediate **28** in an inert diluent, such as dichloromethane or the like, in the presence of a base, such as *N,N*-diisopropylethylamine or the like. The reaction is typically conducted at a temperature in the range of about 0 °C to about 100 °C for about 6 hours to about 24 hours, or until the reaction is substantially complete. The product, is isolated and purified by conventional procedures to provide a compound of formula (I).

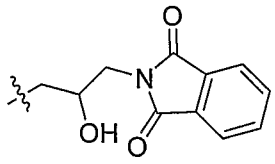
Intermediates of formula **27** can be prepared by reacting an azetidine intermediate **11** with an amine **30**:

H_2N——R^{19}

30

wherein R^{19} is R^5, R^{8a}, or R^{18}, to provide intermediate **27**. For example, intermediate **30** can be methylamine, or the like.

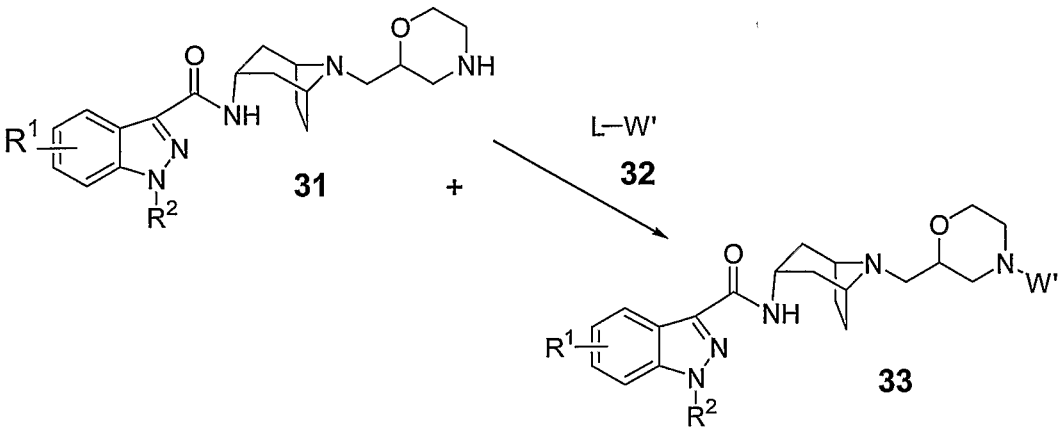
Alternatively, intermediates of formula **27** in which R^3 is –OH can be prepared by reacting intermediate **1** with an oxiranylmethyl compound having a protected nitrogen atom and then deprotecting. One useful reagent is 2-oxiranylmethyl-isoindole-1,3-dione, commonly epoxypropylphthalimide, which is reacted with intermediate **1** to form an intermediate in which a phthalimidyl-substituted 2-hydroxy propyl group:



is joined to the nitrogen of the azabicylcooctane ring of **1**. The phthalimidyl group is then removed by refluxing in hydrazine to form intermediate **27** in which R^3 is -OH and R^4 and R^{19} are hydrogen.

Further to the synthesis described above in Scheme K, a compound of formula (I) in which R^3 and R^5 or R^3 and R^{8a} taken together form $–OCH_2CH_2-$, and W is selected from Y or a moiety of formula (b) wherein *a* is 0, can be prepared as shown below in Scheme L:

Scheme L

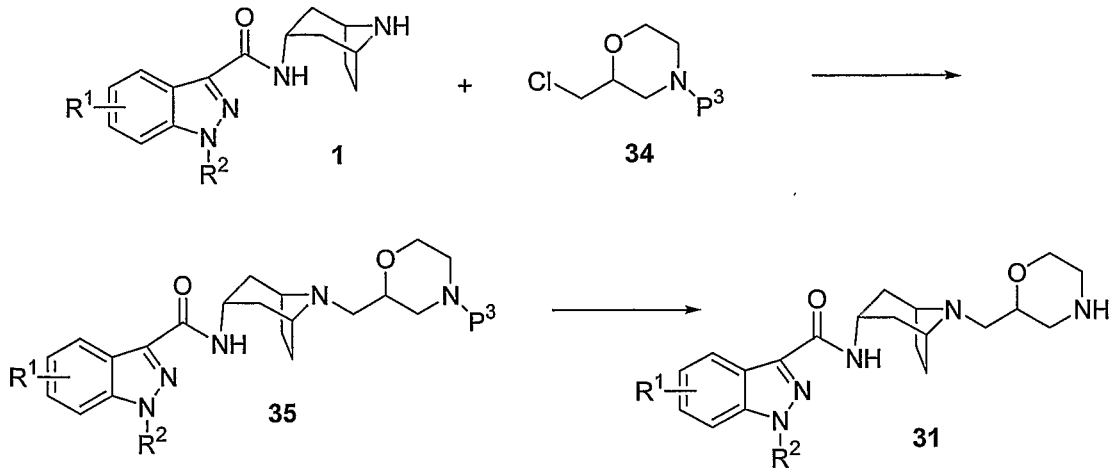


wherein intermediate **31** is reacted with intermediate **32**, (wherein L is a leaving group, such as halo, and W′ is selected from $-C(O)R^9$, $-S(O)_2R^{10}$, $-C(O)OR^{12}$, $-C(O)NR^{13}R^{14}$, $-S(O)_2NR^{13}R^{14}$, and $-(CR^6R^7)_n-X$, such that W′ represents a residue that, together with the nitrogen atom of the morpholine ring of intermediate **31** will afford W as defined herein) to provide a compound of formula (I).

The reaction is typically conducted by contacting intermediate **31** with between about 1 and about 3 equivalents of intermediate **32** in an inert diluent, such as methanol or ethanol, in the presence of a base, such as *N,N*-diisopropylethylamine. The reaction is typically conducted at a temperature in the range of about 60 °C to about 95 °C for about 6 hours to about 24 hours, or until the reaction is substantially complete. The product of formula (I) is isolated and purified by conventional procedures. For example, the product can be concentrated to dryness under reduced pressure, taken up in an aqueous weak acid solution and purified by HPLC chromatography.

A process for preparing intermediates of formula **31** is shown below in Scheme M:

Scheme M



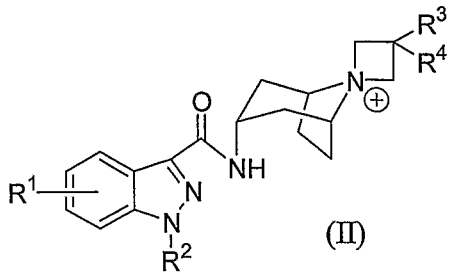
wherein intermediate **1** is reacted with intermediate **34**, wherein P^3 represents an amino-protecting group, such as BOC, to provide intermediate **35**, which is then deprotected to provide intermediate **31**. The reaction is typically conducted by contacting intermediate **1** with between about 1 and about 3 equivalents of intermediate **34,** in an inert diluent, such as acetonitrile, in the presence of potassium carbonate, at a temperature in the range of about 60 °C to about 95 °C for about 12 hours to about 24 hours, or until the reaction is substantially complete. Intermediate **35** is isolated, and then P^3 is removed to provide intermediate **31**.

The primary or secondary amines of intermediates **2**, **30**, **32**, and H-W are available commercially or are readily synthesized from common starting materials according to standard protocols described in the literature or in textbooks, such as J. March, *Advanced Organic Chemistry*, Fourth Edition, Wiley, New York, 1992, and as exemplified herein.

Further details regarding specific reaction conditions and other procedures for preparing representative compounds of the invention or intermediates thereto are described in the examples below.

Accordingly, in a method aspect, the invention provides a process for preparing a compound of formula (I), wherein R^1, R^2, R^3, R^4, and W are defined as in formula (I), or a salt or stereoisomer thereof, the process comprising:

(a) reacting a compound of formula (II):



(II)

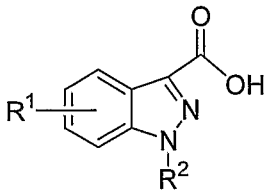
with a compound of formula (III):



(III) ;

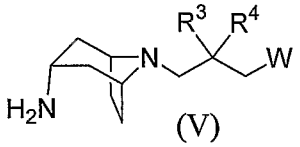
or

(b) reacting a compound of formula (IV):



(IV)

with a compound of formula (V):



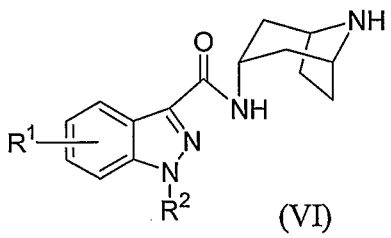
(V) ;

to provide a compound of formula (I), or a salt or stereoisomer thereof.

The invention also provides a process for preparing a compound of formula (I), wherein R^3 is hydroxy and R^1, R^2, R^4, and W are defined as in formula (I), or a salt or stereoisomer thereof, the process comprising:

step (a) or step (b) as defined above, or

(c) reacting a compound of formula (VI):



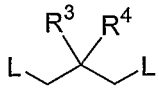
(VI)

or a salt thereof, with a compound of formula (III):

H–W

(III)

and a compound of formula (VII):

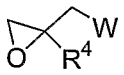


(VII)

wherein L is a leaving group;

or

(d) reacting a compound of formula (VI) with a compound of formula (VIII):

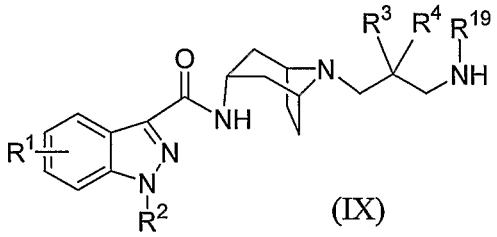


(VIII) ;

to provide a compound of formula (I), or a salt or stereoisomer thereof.

The invention also provides a process for preparing a compound of formula (I), wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{8a}, R^9, R^{10}, R^{12}, R^{13}, R^{14}, R^{18}, *a*, *n*, W and X are as defined in formula (I); provided that when *a* is 0, R^5 is hydrogen or C_{1-4}alkyl, wherein C_{1-4}alkyl is optionally substituted with hydroxy, C_{1-3}alkoxy, or cyano, or R^3 and R^5 taken together form $-OCH_2CH_2-$; or a salt or stereoisomer thereof, the process comprising:

reacting a compound of formula (IX):



(IX)

wherein R^{19} is R^5, R^{8a}, or R^{18};

with a compound of formula (X):

L–W"

(X)

wherein:

L is a leaving group; and

(a) when R^{19} is R^{8a}, W" is selected from $-C(O)R^9$, $-S(O)_2R^{10}$, $-C(O)OR^{12}$, $-C(O)NR^{13}R^{14}$, and $-S(O)_2NR^{13}R^{14}$;

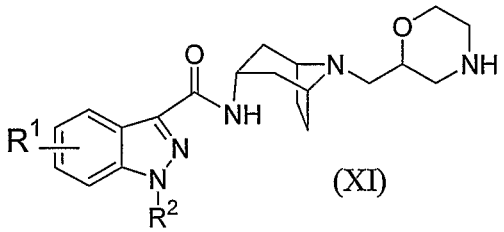
(b) when R^{19} is R^{18}, W″ is $-(CH_2)_2-N(R^5)(CR^6R^7)_n-X$; and

(c) when *a* is 0, R^{19} is R^5, W″ is $-(CR^6R^7)_n-X$, and R^5 is hydrogen or C_{1-4}alkyl, wherein C_{1-4}alkyl is optionally substituted with hydroxy, C_{1-3}alkoxy, or cyano, or R^3 and R^5 taken together form $-OCH_2CH_2-$;

to provide a compound of formula (I).

Further to the process described above, the invention also provides a process for preparing a compound of formula (I), wherein R^3 and R^5 or R^3 and R^{8a} taken together form $-OCH_2CH_2-$; W is selected from Y and a moiety of formula (b) wherein *a* is 0; and R^1, R^2, R^4, R^6, R^7, R^9, R^{10}, R^{12}, R^{13}, R^{14}, *n* and X are as defined for formula (I); or a salt or stereoisomer thereof, the process comprising:

reacting a compound of formula (XI):



(XI)

with a compound of formula (XII):

L–W'

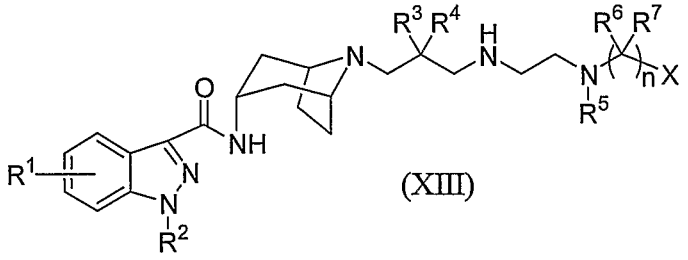
(XII)

wherein L is a leaving group, and W′ is selected from $-C(O)R^9$, $-S(O)_2R^{10}$, $-C(O)OR^{12}$, $-C(O)NR^{13}R^{14}$, $-S(O)_2NR^{13}R^{14}$, and $-(CR^6R^7)_n-X$;

to provide a compound of formula (I).

The invention further provides a process for preparing a compound of formula (I) wherein W is a moiety of formula (b) and *a* is 1; R^1, R^2, R^4, R^5, R^6, R^7, R^{18}, *n* and X are as defined for formula (I); or a salt or stereoisomer thereof, the process comprising:

reacting a compound of formula (XIII):



(XIII)

with a compound of formula (XIV):

(XIV)

wherein L is a leaving group;

to provide a compound of formula (I).

In other embodiments, this invention is directed to the other processes described herein; and to the products prepared by any of the processes described herein.

Pharmaceutical Compositions

The indazole-carboxamide compounds of the invention are typically administered to a patient in the form of a pharmaceutical composition. Such pharmaceutical compositions may be administered to the patient by any acceptable route of administration including, but not limited to, oral, rectal, vaginal, nasal, inhaled, topical (including transdermal) and parenteral modes of administration.

Accordingly, in one of its compositions aspects, the invention is directed to a pharmaceutical composition comprising a pharmaceutically-acceptable carrier or excipient and a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof. Optionally, such pharmaceutical compositions may contain other therapeutic and/or formulating agents if desired.

The pharmaceutical compositions of the invention typically contain a therapeutically effective amount of a compound of the present invention or a pharmaceutically-acceptable salt thereof. Typically, such pharmaceutical compositions will contain from about 0.1 to about 95% by weight of the active agent; preferably, from about 5 to about 70% by weight; and more preferably from about 10 to about 60% by weight of the active agent.

Any conventional carrier or excipient may be used in the pharmaceutical compositions of the invention. The choice of a particular carrier or excipient, or combinations of carriers or excipients, will depend on the mode of administration being used to treat a particular patient or type of medical condition or disease state. In this regard, the preparation of a suitable pharmaceutical composition for a particular mode of administration is well within the scope of those skilled in the pharmaceutical arts. Additionally, the ingredients for such compositions are commercially available from, for example, Sigma, P.O. Box 14508, St. Louis, MO 63178. By way of further illustration, conventional formulation techniques are described in *Remington: The Science and*

Practice of Pharmacy, 20th Edition, Lippincott Williams & White, Baltimore, Maryland (2000); and H.C. Ansel et al., *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 7th Edition, Lippincott Williams & White, Baltimore, Maryland (1999).

Representative examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, the following: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, such as microcrystalline cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical compositions.

The pharmaceutical compositions of the invention are typically prepared by thoroughly and intimately mixing or blending a compound of the invention with a pharmaceutically-acceptable carrier and one or more optional ingredients. If necessary or desired, the resulting uniformly blended mixture can then be shaped or loaded into tablets, capsules, pills and the like using conventional procedures and equipment.

The pharmaceutical compositions of the invention are preferably packaged in a unit dosage form. The term "unit dosage form" means a physically discrete unit suitable for dosing a patient, i.e., each unit containing a predetermined quantity of active agent calculated to produce the desired therapeutic effect either alone or in combination with one or more additional units. For example, such unit dosage forms may be capsules, tablets, pills, and the like.

In a preferred aspect, the pharmaceutical compositions of the invention are suitable for oral administration. Suitable pharmaceutical compositions for oral administration may be in the form of capsules, tablets, pills, lozenges, cachets, dragees, powders, granules; or as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil liquid emulsion; or as an elixir or syrup; and the like;

each containing a predetermined amount of a compound of the present invention as an active ingredient.

When intended for oral administration in a solid dosage form (i.e., as capsules, tablets, pills and the like), the pharmaceutical compositions of the invention will typically comprise a compound of the present invention as the active ingredient and one or more pharmaceutically-acceptable carriers, such as sodium citrate or dicalcium phosphate. Optionally or alternatively, such solid dosage forms may also comprise: (1) fillers or extenders, such as starches, microcrystalline cellulose, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and/or sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as cetyl alcohol and/or glycerol monostearate; (8) absorbents, such as kaolin and/or bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and/or mixtures thereof; (10) coloring agents; and (11) buffering agents.

Release agents, wetting agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the pharmaceutical compositions of the invention. Examples of pharmaceutically-acceptable antioxidants include: (1) water-soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfate sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal-chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like. Coating agents for tablets, capsules, pills and like, include those used for enteric coatings, such as cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), hydroxypropyl methylcellulose phthalate, methacrylic acid–methacrylic acid ester copolymers, cellulose acetate trimellitate (CAT), carboxymethyl ethyl cellulose (CMEC), hydroxypropyl methyl cellulose acetate succinate (HPMCAS), and the like.

If desired, the pharmaceutical compositions of the present invention may also be formulated to provide slow or controlled release of the active ingredient using, by way of

example, hydroxypropyl methyl cellulose in varying proportions; or other polymer matrices, liposomes and/or microspheres.

In addition, the pharmaceutical compositions of the present invention may optionally contain opacifying agents and may be formulated so that they release the active ingredient only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Suitable liquid dosage forms for oral administration include, by way of illustration, pharmaceutically-acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. Such liquid dosage forms typically comprise the active ingredient and an inert diluent, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (such as, for example, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Suspensions, in addition to the active ingredient, may contain suspending agents such as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Alternatively, the pharmaceutical compositions of the invention are formulated for administration by inhalation. Suitable pharmaceutical compositions for administration by inhalation will typically be in the form of an aerosol or a powder. Such compositions are generally administered using well-known delivery devices, such as a metered-dose inhaler, a dry powder inhaler, a nebulizer or a similar delivery device.

When administered by inhalation using a pressurized container, the pharmaceutical compositions of the invention will typically comprise the active ingredient and a suitable propellant, such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas.

Additionally, the pharmaceutical composition may be in the form of a capsule or cartridge (made, for example, from gelatin) comprising a compound of the invention and a powder suitable for use in a powder inhaler. Suitable powder bases include, by way of example, lactose or starch.

The compounds of the invention can also be administered transdermally using known transdermal delivery systems and excipients. For example, a compound of the invention can be admixed with permeation enhancers, such as propylene glycol, polyethylene glycol monolaurate, azacycloalkan-2-ones and the like, and incorporated into a patch or similar delivery system. Additional excipients including gelling agents, emulsifiers and buffers, may be used in such transdermal compositions if desired.

The following formulations illustrate representative pharmaceutical compositions of the present invention:

Formulation Example A

Hard gelatin capsules for oral administration are prepared as follows:

Ingredients	Amount
Compound of the invention	50 mg
Lactose (spray-dried)	200 mg
Magnesium stearate	10 mg

Representative Procedure: The ingredients are thoroughly blended and then loaded into a hard gelatin capsule (260 mg of composition per capsule).

Formulation Example B

Hard gelatin capsules for oral administration are prepared as follows:

Ingredients	Amount
Compound of the invention	20 mg
Starch	89 mg
Microcrystalline cellulose	89 mg
Magnesium stearate	2 mg

Representative Procedure: The ingredients are thoroughly blended and then passed through a No. 45 mesh U.S. sieve and loaded into a hard gelatin capsule (200 mg of composition per capsule).

Formulation Example C

Capsules for oral administration are prepared as follows:

Ingredients	Amount
Compound of the invention	10 mg
Polyoxyethylene sorbitan monooleate	50 mg
Starch powder	250 mg

Representative Procedure: The ingredients are thoroughly blended and then loaded into a gelatin capsule (310 mg of composition per capsule).

Formulation Example D

Tablets for oral administration are prepared as follows:

Ingredients	Amount
Compound of the invention	5 mg
Starch	50 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone (10 wt. % in water)	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg

Representative Procedure: The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resulting powders, and this mixture is then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50-60°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc (previously passed through a No. 60 mesh U.S. sieve) are then added to the granules. After mixing, the mixture is compressed on a tablet machine to afford a tablet weighing 100 mg.

Formulation Example E

Tablets for oral administration are prepared as follows:

Ingredients	Amount
Compound of the invention	25 mg
Microcrystalline cellulose	400 mg
Silicon dioxide fumed	10 mg
Stearic acid	5 mg

Representative Procedure: The ingredients are thoroughly blended and then compressed to form tablets (440 mg of composition per tablet).

Formulation Example F

Single-scored tablets for oral administration are prepared as follows:

Ingredients	Amount
Compound of the invention	15 mg
Cornstarch	50 mg
Croscarmellose sodium	25 mg
Lactose	120 mg
Magnesium stearate	5 mg

Representative Procedure: The ingredients are thoroughly blended and compressed to form a single-scored tablet (215 mg of compositions per tablet).

Formulation Example G

A suspension for oral administration is prepared as follows:

Ingredients	Amount
Compound of the invention	0.1 g
Fumaric acid	0.5 g
Sodium chloride	2.0 g
Methyl paraben	0.15 g
Propyl paraben	0.05 g
Granulated sugar	25.5 g
Sorbitol (70% solution)	12.85 g
Veegum k (Vanderbilt Co.)	1.0 g
Flavoring	0.035 mL
Colorings	0.5 mg
Distilled water	q.s. to 100 mL

Representative Procedure: The ingredients are mixed to form a suspension containing 10 mg of active ingredient per 10 mL of suspension.

Formulation Example H

A dry powder for administration by inhalation is prepared as follows:

Ingredients	Amount
Compound of the invention	1.0 mg
Lactose	25 mg

Representative Procedure: The active ingredient is micronized and then blended with lactose. This blended mixture is then loaded into a gelatin inhalation cartridge. The contents of the cartridge are administered using a powder inhaler.

Formulation Example I

A dry powder for administration by inhalation in a metered dose inhaler is prepared as follows:

Representative Procedure: A suspension containing 5 wt. % of a compound of the invention and 0.1 wt. % lecithin is prepared by dispersing 10 g of active compound as micronized particles with mean size less than 10 μm in a solution formed from 0.2 g of lecithin dissolved in 200 mL of demineralized water. The suspension is spray dried and the resulting material is micronized to particles having a mean diameter less than 1.5 μm. The particles are loaded into cartridges with pressurized 1,1,1,2-tetrafluoroethane.

Formulation Example J

An injectable formulation is prepared as follows:

Ingredients	Amount
Compound of the invention	0.2 g
Sodium acetate buffer solution (0.4 M)	40 mL
HCl (0.5 N) or NaOH (0.5 N)	q.s. to pH 4
Water (distilled, sterile)	q.s. to 20 mL

Representative Procedure: The above ingredients are blended and the pH is adjusted to 4 ± 0.5 using 0.5 N HCl or 0.5 N NaOH.

Formulation Example K

Capsules for oral administration are prepared as follows:

Ingredients	Amount
Compound of the Invention	4.05 mg
Microcrystalline cellulose (Avicel PH 103)	259.2 mg
Magnesium stearate	0.75 mg

Representative Procedure: The ingredients are thoroughly blended and then loaded into a gelatin capsule (Size #1, White, Opaque) (264 mg of composition per capsule).

Formulation Example L

Capsules for oral administration are prepared as follows:

Ingredients	Amount
Compound of the Invention	8.2 mg
Microcrystalline cellulose (Avicel PH 103)	139.05 mg
Magnesium stearate	0.75 mg

Representative Procedure: The ingredients are thoroughly blended and then loaded into a gelatin capsule (Size #1, White, Opaque) (148 mg of composition per capsule).

It will be understood that any form of the compounds of the invention, (i.e. free base, pharmaceutical salt, or solvate) that is suitable for the particular mode of administration, can be used in the pharmaceutical compositions discussed above.

Utility

The indazole-carboxamide compounds of the invention are 5-HT_4 receptor agonists and therefore are expected to be useful for treating medical conditions mediated by 5-HT_4 receptors or associated with 5-HT_4 receptor activity, i.e. medical conditions which are ameliorated by treatment with a 5-HT_4 receptor agonist. Such medical

conditions include, but are not limited to, irritable bowel syndrome (IBS), chronic constipation, functional dyspepsia, delayed gastric emptying, gastroesophageal reflux disease (GERD), gastroparesis, diabetic and idiopathic gastropathy, post-operative ileus, intestinal pseudo-obstruction, and drug-induced delayed transit. In addition, it has been suggested that some 5-HT_4 receptor agonist compounds may be used in the treatment of central nervous system disorders including cognitive disorders, behavioral disorders, mood disorders, and disorders of control of autonomic function.

In particular, the compounds of the invention are expected to increase motility of the gastrointestinal (GI) tract and thus are are expected to be useful for treating disorders of the GI tract caused by reduced motility in mammals, including humans. Such GI motility disorders include, by way of illustration, irritable bowel syndrome, chronic constipation, functional dyspepsia, diabetic gastroparesis, and idiopathic gastroparesis.

When used to treat disorders of reduced motility of the GI tract or other conditions mediated by 5-HT_4 receptors, the compounds of the invention will typically be administered orally in a single daily dose or in multiple doses per day, although other forms of administration may be used. The amount of active agent administered per dose or the total amount administered per day will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered and its relative activity, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

Suitable doses for treating disorders of reduced motility of the GI tract or other disorders mediated by 5-HT_4 receptors will range from about 0.0007 to about 20 mg/kg/day of active agent, preferably from about 0.0007 to about 1 mg/kg/day. For an average 70 kg human, this would amount to from about 0.05 to about 70 mg per day of active agent.

In one aspect of the invention, the compounds of the invention are used to treat chronic constipation. When used to treat chronic constipation, the compounds of the invention will typically be administered orally in a single daily dose or in multiple doses per day. Preferably, the dose for treating chronic constipation will range from about 0.05 to about 70 mg per day.

In another aspect of the invention, the compounds of the invention are used to treat irritable bowel syndrome. When used to treat irritable bowel syndrome, the compounds

of the invention will typically be administered orally in a single daily dose or in multiple doses per day. Preferably, the dose for treating irritable bowel syndrome will range from about 0.05 to about 70 mg per day.

In another aspect of the invention, the compounds of the invention are used to treat diabetic gastroparesis. When used to treat diabetic gastroparesis, the compounds of the invention will typically be administered orally in a single daily dose or in multiple doses per day. Preferably, the dose for treating diabetic gastroparesis will range from about 0.05 to about 70 mg per day.

In another aspect of the invention, the compounds of the invention are used to treat idiopathic gastroparesis. When used to treat idiopathic gastroparesis, the compounds of the invention will typically be administered orally in a single daily dose or in multiple doses per day. Preferably, the dose for treating diabetic gastroparesis will range from about 0.05 to about 70 mg per day.

In yet another aspect of the invention, the compounds of the invention are used to treat functional dyspepsia. When used to treat functional dyspepsia, the compounds of the invention will typically be administered orally in a single daily dose or in multiple doses per day. Preferably, the dose for treating functional dyspepsia will range from about 0.05 to about 70 mg per day.

The invention also provides a method of treating a mammal having a disease or condition associated with 5-HT_4 receptor activity, the method comprising administering to the mammal a therapeutically effective amount of a compound of the invention or of a pharmaceutical composition comprising a compound of the invention.

Since compounds of the invention are 5-HT_4 receptor agonists, such compounds are also useful as research tools for investigating or studying biological systems or samples having 5-HT_4 receptors, or for discovering new 5-HT_4 receptor agonists. Moreover, since compounds of the invention exhibit binding selectivity for 5-HT_4 receptors as compared with binding to receptors of other 5-HT subtypes, particularly 5-HT_3 receptors, such compounds are particularly useful for studying the effects of selective agonism of 5-HT_4 receptors in a biological system or sample. Any suitable biological system or sample having 5-HT_4 receptors may be employed in such studies which may be conducted either *in vitro* or *in vivo*. Representative biological systems or samples suitable for such studies include, but are not limited to, cells, cellular extracts,

plasma membranes, tissue samples, mammals (such as mice, rats, guinea pigs, rabbits, dogs, pigs, etc.) and the like.

In this aspect of the invention, a biological system or sample comprising a 5-HT_4 receptor is contacted with a 5-HT_4 receptor-agonizing amount of a compound of the invention. The effects of agonizing the 5-HT_4 receptor are then determined using conventional procedures and equipment, such as radioligand binding assays and functional assays. Such functional assays include ligand-mediated changes in intracellular cyclic adenosine monophosphate (cAMP), ligand-mediated changes in activity of the enzyme adenylyl cyclase (which synthesizes cAMP), ligand-mediated changes in incorporation of analogs of guanosine triphosphate (GTP), such as [^{35}S]GTPγS (guanosine 5'-O-(γ-thio)triphosphate) or GTP-Eu, into isolated membranes via receptor catalyzed exchange of GTP analogs for GDP analogs, ligand-mediated changes in free intracellular calcium ions (measured, for example, with a fluorescence-linked imaging plate reader or FLIPR® from Molecular Devices, Inc.), and measurement of mitogen activated protein kinase (MAPK) activation. A compound of the invention may agonize or increase the activation of 5-HT_4 receptors in any of the functional assays listed above, or assays of a similar nature. A 5-HT_4 receptor-agonizing amount of a compound of the invention will typically range from about 1 nanomolar to about 500 nanomolar.

Additionally, the compounds of the invention can be used as research tools for discovering new 5-HT_4 receptor agonists. In this aspect, 5-HT_4 receptor binding or functional data for a test compound or a group of test compounds is compared to the 5-HT_4 receptor binding or functional data for a compound of the invention to identify test compounds that have superior binding or functional activity, if any. This aspect of the invention includes, as separate aspects, both the generation of comparison data (using the appropriate assays) and the analysis of the test data to identify test compounds of interest.

Among other properties, compounds of the invention have been found to be potent agonists of the 5-HT_4 receptor and to exhibit selectivity for the 5-HT_4 receptor subtype over the 5-HT_3 receptor subtype in radioligand binding assays. Further, preferred compounds of the invention have demonstrated pharmacokinetic properties in a rat model.

These properties, as well as the utility of the compounds of the invention, can be demonstrated using various *in vitro* and *in vivo* assays well-known to those skilled in the art. Representative assays are described in further detail in the following examples.

EXAMPLES

The following synthetic and biological examples are offered to illustrate the invention, and are not to be construed in any way as limiting the scope of the invention. In the examples below, the following abbreviations have the following meanings unless otherwise indicated. Abbreviations not defined below have their generally accepted meanings.

Boc	=	*tert*-butoxycarbonyl
$(Boc)_2O$	=	di-*tert*-butyl dicarbonate
DCM	=	dichloromethane
DMF	=	*N*,*N*-dimethylformamide
DMSO	=	dimethyl sulfoxide
EtOAc	=	ethyl acetate
mCPBA	=	*m*-chloroperbenzoic acid
MeCN	=	acetonitrile
MTBE	=	*tert*-butyl methyl ether
PyBop	=	benzotriazol-1-yloxytripyrrolidino-phosphonium hexafluorophosphate
R_f	=	retention factor
RT	=	room temperature
TFA	=	trifluoroacetic acid
THF	=	tetrahydrofuran

Reagents (including secondary amines) and solvents were purchased from commercial suppliers (Aldrich, Fluka, Sigma, etc.), and used without further purification. Reactions were run under nitrogen atmosphere, unless noted otherwise. Progress of reaction mixtures was monitored by thin layer chromatography (TLC), analytical high performance liquid chromatography (anal. HPLC), and mass spectrometry, the details of which are given below and separately in specific examples of reactions. Reaction mixtures were worked up as described specifically in each reaction. Commonly the reaction mixtures were purified by extraction and other purification methods such as temperature-, and solvent-dependent crystallization, and precipitation. In addition, reaction mixtures were routinely purified by preparative HPLC. A general preparative HPLC protocol is described below. Characterization of reaction products was routinely carried out by mass and ^{1}H-NMR spectrometry. For NMR measurement, samples were dissolved in deuterated solvent (CD_3OD, $CDCl_3$, or DMSO-d_6), and ^{1}H-NMR spectra were acquired with a Varian Gemini 2000 instrument (300 MHz) under standard observation conditions. Mass spectrometric identification of compounds was performed

by an electrospray ionization method (ESMS) with a Perkin Elmer instrument (PE SCIEX API 150 EX).

General protocol for analytical HPLC

Crude compounds were dissolved in 50% MeCN/H_2O (with 0.1% TFA) at 0.5-1.0 mg/mL concentration, and analyzed using the following conditions:

Column:	Zorbax Bonus-RP (3.5 μm of particle size, 2.1 x 50 mm)
Flow rate:	0.5 mL/min
Gradient:	0.5-4.0 min (linear), 5% MeCN/H_2O containing 0.1% TFA to 75% MeCN/H_2O containing 0.1% TFA
Detector wavelength:	214, 254, and 280 nm.

General protocol for preparative HPLC purification

Crude compounds were dissolved in 50% acetic acid in water at 50-100 mg/mL concentration, filtered, and fractionated using the following procedure:

Column:	YMC Pack-Pro C18 (50a x 20 mm; ID = 5 μm)
Flow rate:	40 mL/min
Mobile Phases:	A = 90% MeCN/10% H_2O/0.1% TFA B = 98% H_2O/2% MeCN/0.1% TFA
Gradient:	10% A/90% B to 50% A/50% B over 30 min (linear)
Detector wavelength:	214 nm.

Preparation of secondary amines

Thiomorpholine-1,1-dioxide was prepared from thiomorpholine by protection of the secondary amine to *N*-Boc thiomorpholine ($(Boc)_2O$, MeOH), oxidation to sulfone (*m*CPBA, CH_2Cl_2, 0°C), and deprotection of the *N*-Boc group to provide the free amine (CF_3CO_2H, CH_2Cl_2). *(m/z)*: $[M+H]^+$ calcd for $C_4H_9NO_2S$, 136.04; found, 135.9.

The *N*-sulfonyl derivatives of piperazine were prepared from *N*-Boc piperazine by reacting with respective sulfonyl chloride (iPr_2NEt, CH_2Cl_2, 0°C), and deprotecting the *N*-Boc group (CF_3CO_2H, CH_2Cl_2). 1-Methanesulfonyl-piperazine: ^{1}H-NMR ($CDCl_3$; neutral): δ (ppm) 3.1 (t, 4H), 2.9 (t, 4H), 2.7 (s, 3H). 1-(Methylsulfonyl)methanesulfonyl-piperazine: ^{1}H-NMR (CD_3OD): δ (ppm) 2.90 (s, 3H), 3.02 (m, 4H), 3.38 (m, 4H), 4.61 (s, 2H).

The racemic or single chiral isomer forms of 3-acetylaminopyrrolidine were prepared by treating *N'*-Boc-3-aminopyrrolidine (racemate, 3R, or 3S) with acetyl chloride (iPr_2NEt, CH_2Cl_2, 0°C), and deprotecting the *N*-Boc group (CF_3CO_2H, CH_2Cl_2).

3-(Acetamido)pyrrolidine: ^{1}H-NMR (DMSO-d_6; TFA salt): δ (ppm) 4.2 (quin, 1H), 3.3-3.1 (m, 3H), 2.9 (m, 1H), 2.0 (m, 1H), 1.8 (br s, 4H).

3-((*R*)-2-Hydroxypropionamido)pyrrolidine was prepared after amidation of N^1-Boc-3-aminopyrrolidine (L-lactic acid, PyBOP, DMF, RT), and deprotection of *N*-Boc group (CF_3CO_2H, CH_2Cl_2). (*m/z*): $[M+H]^+$ calcd for $C_7H_{14}N_2O_2$, 159.11; found, 159.0. ^{1}H-NMR (CD_3OD; TFA salt): δ (ppm) 4.4 (quin, 1H), 4.1 (q, 1H), 3.5-3.4 (m, 2H), 3.3-3.2 (m, 2H), 2.3 (m, 1H), 2.0 (m, 1H), 1.3 (d, 3H).

The N^3-alkanesulfonyl derivatives of (3R)-aminopyrrolidine were obtained by treating N^1-Boc-(3R)-aminopyrrolidine with propionylsulfonyl chloride or cyclohexylmethylsulfonyl chloride (i-Pr_2NEt, CH_2Cl_2, 0°C), and deprotecting *N*-Boc group (CF_3CO_2H, CH_2Cl_2).

3-(*N*-Acetyl-*N*-methylamido)piperidine was prepared from N^3-Cbz protected 3-amino-piperidine-1-carboxylic acid *t*-butyl ester (De Costa, B., *et al. J. Med. Chem.* **1992**, *35*, 4334-43) after four synthetic steps: i) MeI, n-BuLi, THF, -78°c to rt; ii) H_2 (1 atm), 10% Pd/C, EtOH; iii) AcCl, i-Pr_2NEt, CH_2Cl_2; iv) CF_3CO_2H, CH_2Cl_2. *m/z*: $[M+H]^+$ calcd for $C_8H_{16}N_2O$: 157.13; found, 157.2. ^{1}H-NMR (CD_3OD; TFA salt): δ (ppm) 4.6 (m, 1H), 3.3 (m, 1H), 3.2 (m, 1H), 3.0 (m, 1H), 2.9 (s, 3H), 2.8 (m, 1H), 2.0 (s, 3H), 1.9-1.7 (m, 4H).

3-(*N*-Acetyl-amido)piperidine was prepared from 3-amino-piperidine-1-carboxylic acid *tert*-butyl ester after N-acetylation and deprotection of the *N*-Boc group: i) AcCl, i-Pr_2NEt, CH_2Cl_2; ii) CF_3CO_2H, CH_2Cl_2. ^{1}H-NMR (CD_3OD; TFA salt): δ (ppm) 3.9 (m, 1H), 3.3 (dd, 1H), 3.2 (m, 1H), 2.9 (dt, 1H), 2.75 (dt, 1H), 2.0-1.9 (m, 2H), 1.9 (s, 3H), 1.8-1.4 (m, 2H).

The N^3-alkanesulfonyl derivatives of 3-aminopiperidine were synthesized by reacting the chiral or racemic forms of 3-amino-piperidine-1-carboxylxic acid *tert*-butyl ester with the respective alkanesulfonyl chloride (i-Pr_2NEt, CH_2Cl_2) and deprotecting the *N*-Boc group (CF_3CO_2H, CH_2Cl_2). (3S)-3-(ethanesulfonylamido)piperidine: ^{1}H-NMR (CD_3OD): δ (ppm) 1.29(t, 3H, J_1 = 7.4 Hz),1.50-1.80 (m, 2H), 1.90-2.10 (m, 2H), 2.89 (m, 2H), 3.05 (q, 2H, J_1 = 7.4 Hz), 3.27 (m, 2H), 3.40 (d of d(br), 1H), 3.52 (m, 1H). 3S-Methylsulfonylmethanesulfonylamido-piperidine: ^{1}H-NMR (CD_3OD): δ (ppm) 2.13-2.30 (m, 2H), 2.40-2.57 (m, 2H), 2.98 (m, 2H), 3.15 (s, 3H), 3.21 (m, 2H), 3.30 (br d, 1H), 3.74 (m, 1H).

3-(Methylamino)-1-acetylpyrrolidine was prepared from 3-(methylamino)-1-benzylpyrrolidine (TCI America) after four steps: i) $(Boc)_2O$, MeOH, rt; ii) H_2 (1 atm), 10% Pd/C, EtOH; iii) AcCl, i-Pr_2NEt, CH_2Cl_2; iv) CF_3CO_2H, CH_2Cl_2. (*m/z*): $[M+H]^+$ calcd for $C_7H_{14}N_2O$: 143.12; found, 143.0.

3-(Methylamino)-1-(methanesulfonyl)pyrrolidine was prepared from 3-(methylamino)-1-benzylpyrrolidine after four steps: i) $(Boc)_2O$, MeOH, rt; ii) H_2 (1 atm), 10% Pd/C, EtOH; iii) $CH_3S(O)_2Cl$, i-Pr_2NEt, CH_2Cl_2; iv) CF_3CO_2H, CH_2Cl_2. (*m/z*): $[M+H]^+$ calcd for $C_6H_{14}N_2O_2S$: 179.08; found, 179.2. 3R-Methylamino-1-(methanesulfonyl)pyrrolidine was prepared in a similar manner from (3R)-(methylamino)-1-benzylpyrrolidine.

Derivatives of tetrahydro-3-thiophenamine-1,1-dioxide were prepared following the protocol of Loev, B. *J. Org. Chem.* **1961**, *26*, 4394-9 by reacting 3-sulfolene with a requisite primary amine in methanol (cat. KOH, rt). *N*-Methyl-3-tetrahydrothiophene-amine-1,1-dioxide (TFA salt): ^{1}H-NMR (DMSO-d_6): δ (ppm) 9.4 (br s, 2H), 4.0-3.8 (quin, 1H), 3.6-3.5 (dd, 1H), 3.4-3.3 (m, 1H), 3.2-3.1 (m, 2H), 2.5 (s, 3H), 2.4 (m, 1H), 2.1 (m, 1H). *N*-2-(1-hydroxy)ethyl-3-tetrahydrothiopheneamine-1,1-dioxide: (*m/z*): $[M+H]^+$ calcd for $C_6H_{13}NO_3S$: 180.07; found, 180.2.

N-Methyl-tetrahydro-2*H*-thiopyran-4-amine-1,1-dioxide was prepared from tetrahydro-4*H*-thiopyran-4-one: i) $MeNH_2$, $NaBH_4$; ii) $(Boc)_2O$, MeOH; iii) *m*CPBA, CH_2Cl_2, 0°C; iv) CF_3CO_2H, CH_2Cl_2. (*m/z*): $[M+H]^+$ calcd for $C_6H_{13}NO_2S$ 164.07; found, 164.9. ^{1}H-NMR (CD_3OD; TFA salt): δ (ppm) 3.4-3.1 (m, 5H), 2.7 (s, 3H), 2.4 (br d, 2H), 2.1 (br m, 2H).

1-Acetyl-3-(methylamino)piperidine was prepared from N^3-Cbz protected 3-methylamino-piperidine: i) AcCl, i-Pr_2NEt, CH_2Cl_2; ii) H_2 (1 atm), 10% Pd/C, EtOH. ^{1}H-NMR (CD_3OD): δ (ppm) 4.0 (m, 1H), 3.6 (m, 1H), 3.4-3.2 (m, 2H), 3.0 (m, 1H), 2.6 (s, 3H), 2.1 (s, 3H), 1.8-1.6 (m, 4H).

1-(Methanesulfonyl)-3-(methylamino)piperidine was prepared from N^3-Cbz protected 3-methylamino-piperidine: i) $CH_3S(O)_2Cl$, i-Pr_2NEt, CH_2Cl_2; ii) H_2 (1 atm), 10% Pd/C, EtOH. (*m/z*): $[M+H]^+$ calcd for $C_7H_{16}N_2O_2S$ 193.10; found, 193.0. ^{1}H-NMR (DMSO-d_6; TFA salt): δ (ppm) 3.4 (dd, 1H), 3.2 (m, 2H), 3.10 (s, 3H), 3.0-2.9 (m, 2H), 2.8 (s, 3H), 1.85-1.75 (m, 2H), 1.6-1.4 (m, 2H).

Proline dimethylamide, and iminodiacetonitrile were purchased from Bachem, and Aldrich, respectively.

The *N*-derivatives of piperazine such as 1-(methoxycarbonyl)piperazine, 1-(dimethylaminocarbonyl)piperazine, and 1-(dimethylaminosulfonyl)piperazine were prepared by reacting piperazine with methylchloroformate, dimethylaminochoroformate, or dimethylaminosulfamoyl chloride, respectively.

1-Methylamino-2-methylsulfonylethane was obtained by reacting methylamine with methyl vinyl sulfone in methanol. *N*-[2-(2-methoxyethylamino)ethyl], *N*-methyl-methanesulfonamide was synthesized starting from partially *N*-Boc protected ethanediamine after four steps of reactions in a sequence as follows: i) methylsulfonyl chloride, triethylamine; ii) MeI, Cs_2CO_3; iii) NaH, 1-bromo-2-methoxyethane; iv) CF_3CO_2H.

Isonipecotamide (piperidine-4-carboxamide), and proline amide were purchased from Aldrich. 2-Hydroxymethylmorpholine was available from Tyger Scientific Product.

Methyl 4-piperidinylcarbamate was prepared from the reaction of N_1-Boc protected 4-aminopiperidine with methylchloroformate followed by the deprotection of the *N*-Boc group.

4-Piperidinol-dimethylcarbamate, and *N*-dimethyl-*N*'-(3-piperidinyl)urea were prepared by reacting dimethylcarbamoyl chloride with *N*-Boc protected 4-piperidinol or N_1-Boc-3-aminopiperidine, respectively.

3-(Methylamino)-1-(dimethylaminosulfonyl)pyrrolidine was obtained by reacting 3-(*N*-methyl-*N*-Boc-amino)pyrrolidine with dimethylsulfamoyl chloride.

2-(3-Pyrrolidinyl)isothiazolidine-1,1-dioxide was synthesized by treating N_1-Boc protected 3-aminopyrrolidine with 3-chloropropylsulfonyl chloride in the presence of triethylamine, and followed by TFA treatment for the deprotection of the Boc group.

Example 1: Synthesis of 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[2-hydroxy-3-((*S*)-2-methoxymethylpyrrolidin-1-yl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide

a. Preparation of 8-benzyl-8-azabicyclo[3.2.1]octan-3-one

Concentrated hydrochloric acid (30 mL) was added to a heterogeneous solution of 2,5-dimethoxy tetrahydrofuran (82.2 g, 0.622 mol) in water (170 mL) while stirring. In a separate flask cooled to 0°C (ice bath), concentrated hydrochloric acid (92 mL) was added slowly to a solution of benzyl amine (100 g, 0.933 mol) in water (350 mL). The 2,5-dimethoxytetrahydrofuran solution was stirred for approximately 20 min, diluted with

water (250 mL), and then the benzyl amine solution was added, followed by the addition of a solution of 1,3-acetonedicarboxylic acid (100 g, 0.684 mol) in water (400 mL) and then the addition of sodium hydrogen phosphate (44 g, 0.31 mol) in water (200 mL). The pH was adjusted from pH 1 to pH ~ 4.5 using 40% NaOH. The resulting cloudy and pale yellow solution was stirred overnight. The solution was then acidified to pH 3 from pH 7.5 using 50% hydrochloric acid, heated to 85 °C and stirred for 2 hours. The solution was cooled to room temperature, basified to pH 12 using 40% NaOH, and extracted with DCM (3 x 500 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the title intermediate in quantitative yield as a viscous brown oil (~95% purity based on analytical HPLC). ^{1}H-NMR ($CDCl_3$) δ (ppm) 7.5-7.2 (m, 5H, C_6H_5), 3.7 (s, 2H, CH_2Ph), 3.45 (broad s, 2H, CH-NBn), 2.7-2.6 (dd, 2H, CH_2CO), 2.2-2.1 (dd, 2H, CH_2CO), 2.1-2.0 (m, 2H, CH_2CH_2), 1.6 (m, 2H, CH_2CH_2). (*m/z*): $[M+H]^+$ calcd for $C_{14}H_{17}NO$ 216.14; found, 216.0.

b. Preparation of 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester

To a solution of 8-benzyl-8-azabicyclo[3.2.1]octan-3-one (75 g, 0.348 mol) in EtOAc (300 mL) was added a solution of di-*tert*-butyl dicarbonate (83.6 g, 0.383 mol, 1.1 eq) in EtOAc (300 mL). The resulting solution and rinse (100 mL EtOAc) was added to a 1 L Parr hydrogenation vessel containing 23 g of palladium hydroxide (20 wt.% Pd, dry basis, on carbon, ~50% wet with water; e.g. Pearlman's catalyst) under a stream of nitrogen. The reaction vessel was degassed (alternating vacuum and N_2 five times) and pressurized to 60 psi of H_2 gas. The reaction solution was agitated for two days and recharged with H_2 as needed to keep the H_2 pressure at 60 psi until the reaction was complete as monitored by silica thin layer chromatography. The solution was then filtered through a pad of Celite® and concentrated under reduced pressure to yield the title intermediate quantitatively as a viscous, yellow to orange oil. It was used in the next step without further treatment. ^{1}H NMR ($CDCl_3$) δ(ppm) 4.5 (broad, 2H, CH-NBoc), 2.7 (broad, 2H, CH_2CO), 2.4-2.3 (dd, 2H, CH_2CH_2), 2.1 (broad m, 2H, CH_2CO), 1.7-1.6 (dd, 2H, CH_2CH_2), 1.5 (s, 9H, $(CH_3)_3COCON$)).

c. Preparation of (1*S*,3*R*,5*R*)-3-amino-8-azabicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester

To a solution of the product of the previous step (75.4 g, 0.335 mol) in methanol (1 L) was added ammonium formate (422.5 g, 6.7 mol), water (115 mL) and 65 g of

palladium on activated carbon (10% on dry basis, ~50% wet with water; Degussa type E101NE/W) under a stream of N_2 while stirring via mechanical stirrer. After 24 and 48 hours, additional portions of ammonium formate (132g, 2.1 mol) were added each time. Once reaction progression ceased, as monitored by anal. HPLC, Celite® (>500g) was added and the resulting thick suspension was filtered and then the collected solid was rinsed with methanol (~500 mL). The filtrates were combined and concentrated under reduced pressure until all methanol had been removed. The resulting cloudy, biphasic solution was then diluted with 1M phosphoric acid to a final volume of ~1.5 to 2.0 L at pH 2 and washed with dichloromethane (3 x 700 mL). The aqueous layer was basified to pH 12 using 40% aq. NaOH, and extracted with dichloromethane (3 x 700 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated by rotary evaporation, then high-vacuum leaving 52 g (70%) of the title intermediate, commonly *N*-Boc-*endo*-3-aminotropane, as a white to pale yellow solid. The isomer ratio of *endo* to. *exo* amine of the product was >99 based on ^{1}H-NMR analysis (>96% purity by analytical HPLC). ^{1}H NMR ($CDCl_3$) δ (ppm) 4.2-4.0 (broad d, 2H, CHNBoc), 3.25 (t, 1H, $CHNH_2$), 2.1-2.05 (m, 4H), 1.9 (m, 2H), 1.4 (s, 9H, $(CH_3)_3OCON$), 1.2-1.1 (broad, 2H). (*m/z*): $[M+H]^+$ calcd for $C_{12}H_{22}N_2O_2$) 227.18; found, 227.2. Analytical HPLC (isocratic method; 2:98 (A:B) to 90:10 (A:B) over 5 min): retention time = 3.68 min.

d. Preparation of 1-isopropyl-1*H*-indazole-3-carboxylic acid

Following the procedure of Harada *et al., Chemical & Pharmaceutical Bulletin* **1995**, *43*, 1912-30, first, indazole-1*H*-3-carboxylic acid was converted to the methyl ester (>95% purity) by refluxing the acid in methanol containing several drops of concentrated sulfuric acid. (*m/z*): $[M+H]^+$ 177.0; ^{1}H-NMR spectroscopy (CD_3OD; δ (ppm) 8.0 (1H, d), 7.5 (1H, d), 7.4 (1H, t), 7.2 (1H, t), 3.9 (3H, s)). This ester was treated with isopropyliodide and potassium *tert*-butoxide in refluxing THF, which afforded 1-isopropyl-1*H*-indazole-3-carboxylic acid methyl ester. TLC (R_f = 0.45 in 3/1 hexane/EtOAc). ^{1}H-NMR (CD_3OD): δ (ppm) 8.1-8.0 (1H, d), 7.6 (1H, d), 7.4 (1H, t), 7.2 (1H, t), 5.0 (1H, quin), 3.9 (s, 3H), 1.5 (6H, d). The N^1-isopropyl methyl ester was hydrolyzed in 1M NaOH/THF at ambient temperature to provide the title intermediate. (*m/z*): $[M+Na]^+$ 226.6. ^{1}H-NMR (CD_3OD): δ (ppm) 8.1-8.0 (1H, d), 7.6 (1H, d), 7.4 (1H, t), 7.2 (1H, t), 5.0 (1H, quin), 1.5 (6H, d).

e. Preparation of (1*S*,3*R*,5*R*)-3-[1-isopropyl-1*H*-indazole-3-carbonyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester

A suspension of 1-isopropyl-1*H*-indazole-3-carboxylic acid (56.35 g; 0.276 mol) in toluene (500 mL) was stirred and heated for 5 min prior to the addition of thionyl chloride (30.2 mL; 0.414 mol). After heating at 100 °C for 15 min, the mixture became a homogeneous solution, which continued to be stirred at the same temperature for an additional 90 min. In a separate reaction flask, (1*S*,3*R*,5*R*)-3-amino-8-azabicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester, prepared as in step c, (62.43 g; 0.276 mol) was dissolved in 250 mL of toluene and followed by addition of sodium hydroxide (66.3 g) dissolved in 250 mL of water. This biphasic mixture was cooled in an ice bath. The solution of indazole acid chloride prepared above was cooled to room temperature, and added over 15 min to the biphasic solution, which was stirred vigorously in an ice bath. After stirring for 1.5 h, the reaction mixture was transferred to a separatory funnel. First, the aqueous layer was separated from toluene layer (saved), and extracted with EtOAc (2 x 500 mL). The toluene layer was concentrated under reduced pressure, and the obtained residue was dissolved in the organic extract (1 L; EtOAc). The solution was washed with 1 M H_3PO_4 (400 mL), sat. $NaHCO_3$ (400 mL), and then brine solution (400 mL). After drying over $MgSO_4$, the organic solution was evaporated to dryness under reduced pressure, yielding 119.2 g of the title intermediate. ^{1}H-NMR (DMSO-d_6): δ (ppm) 1.41 (s, 9H), 1.51 (d, 6H), 1.82 (m, 2H), 1.97 (bs, 4H), 2.09 (m, 2H), 4.10 (m, 3H), 5.10 (sept, 1H), 7.23 (t, 1H), 7.42 (t, 1H), 7.79 (d, 1H), 7.82 (d, 1H), 8.18 (d, 1H). (*m/z*): $[M+H]^+$ calcd for $C_{23}H_{32}N_4O_3$, 413.26; found, 413.1. Retention time (anal. HPLC: 2-95% MeCN/H_2O over 6 min) = 4.85 min.

f. Preparation of 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-aza-bicyclo[3.2.1]oct-3-yl}amide

(1*S*,3*R*,5*R*)-3-[1-Isopropyl-1*H*-indazole-3-carbonyl)amino]-8-azabicyclo-[3.2.1]octane-8-carboxylic acid *tert*-butyl ester, the product of step (e), was solubilized in dichloromethane (200 mL), cooled in an ice bath, and then mixed with 200 mL of trifluoroacetic acid. The reaction mixture was stirred for 1 h at ambient temperature. It was then added dropwise to ethyl ether (2 L) in a flask while being stirred, which afforded 102.7 g of the title intermediate as its mono(trifluoroacetic acid) salt (87% yield over two steps). ^{1}H-NMR (DMSO-d_6): δ (ppm) 1.54 (d, 6H), 2.05 (m, 2H), 2.24 (m, 6H), 4.03 (s, 2H), 4.12 (q, 1H), 5.09 (sept, 1H), 7.28 (t, 1H), 7.45 (t, 1H), 7.81 (d, 1H), 8.00 (d, 1H),

8.11 (d, 1H), 8.54 (bd, 2H). (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{24}N_4O$, 313.20; found, 313.1 . Retention time (anal. HPLC: 2-95% MeCN/H_2O over 6 min) = 2.65 min.

g. Synthesis of 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[2-hydroxy-3-((*S*)-2-methoxymethylpyrrolidin-1-yl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide

(*S*)-2-Methoxymethylpyrrolidine (0.15 mmol) was added to a a stirred solution of 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-aza-bicyclo[3.2.1]oct-3-yl}amide monotrifluoroacetic acid salt (64 mg, 0.15 mmol) and diisopropylethylamine (0.078 mL, 0.45 mmol) in methanol (1.5 mL). 1,3-Dibromopropanol (0.015 mL, 0.15 mmol) was subsequently added and the reaction mixture heated to 65°C for 16 h. The reaction mixture was concentrated *in vacuo*, diluted with acetic acid/water 1:1 (1 mL) and purified by preparative HPLC, affording the bistrifluoroaceticacid salt of the title compound. (m/z): $[M+H]^+$ calcd for $C_{27}H_{41}N_5O_3$, 484.33; found 484.3. Retention time (anal. HPLC) = 2.04 min.

Examples 2-4

Using processes similar to those described in Example 1, except in step (g) replacing the (*S*)-2-methoxymethylpyrrolidine with the appropriate reagent, the compounds of Examples 2-4 were prepared.

Example 2: Synthesis of 1-isopropyl-1*H*-indazole-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{2-hydroxy-3-[4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl]propyl}-8-aza-bicyclo[3.2.1]oct-3-yl)amide; (m/z): $[M+H]^+$ calcd for $C_{30}H_{44}N_6O_4$, 553.35; found 553.7. Retention time (anal. HPLC) = 2.02 min.

Example 3: Synthesis of 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[2-hydroxy-3-(4-methanesulfonylpiperazin-1-yl)propyl]-8-azabicyclo-[3.2.1]oct-3-yl}amide; (m/z): $[M+H]^+$ calcd for $C_{26}H_{40}N_6O_4S$, 533.29; found 533.3. Retention time (anal. HPLC) = 2.03 min.

Example 4: Synthesis of 1-isopropyl-1*H*-indazole-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{3-[(2-cyano-ethyl)methylamino]-2-hydroxypropyl}-8-azabicyclo[3.2.1]oct-3-yl)amide; (m/z): $[M+H]^+$ calcd for $C_{25}H_{36}N_6O_2$, 453.30; found 453.2. Retention time (anal. HPLC) = 2.00 min.

Example 4: Alternate Synthesis of 1-isopropyl-1*H*-indazole-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{3-[(2-cyano-ethyl)methylamino]-2-hydroxypropyl}-8-azabicyclo[3.2.1]oct-3-yl)amide

a. Preparation of 3-Hydroxy-3'-{[1-isopropyl-1*H*-indazole-3-yl)carbonyl]amino}-spiro[azetidine-1,8'-(1*S*,3*R*,5*R*)-8-azabicyclo[3.2.1]octane

Epibromohydrin (0.06 mL, 0.70 mmol) was added to a stirred solution of 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-aza-bicyclo[3.2.1]oct-3-yl}amide trifluoroacetic acid salt, as prepared in step (f) of Example 1, (200 mg, 0.47 mmol) and DIPEA (0.082 ml, 0.47 mmol) in ethanol (4 mL) at room temperature. The reaction mixture was stirred for 12 h and then further epibromohydrin (2 x 0.06 mL, 0.70 mmol) was added. After a further 72 h, the reaction mixture was concentrated *in vacuo* to afford a crude oil which was used without further purification.

Alternatively, 3-hydroxy-3'-{[1-isopropyl-1*H*-indazole-3-yl)carbonyl]amino}-spiro[azetidine-1,8'-(1*S*,3*R*,5*R*)-8-azabicyclo[3.2.1]octane was also prepared in the following manner. Epibromohydrin (1.65 mL, 19.23 mmol) was added to a stirred solution of 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-aza-bicyclo[3.2.1]oct-3-yl}amide trifluoroacetic acid salt, as prepared in step (f) of Example 1, (3.00 g, 9.62 mmol) in ethanol (50 mL) at room temperature. The reaction mixture was stirred for 96 h and then further epibromohydrin (0.165 mL, 1.92 mmol) was added. After a further 4 h, the reaction mixture was concentrated *in vacuo* to afford a crude oil (4.29 g) which was used without further purification. (*m/z*): $[M+H]^+$ calcd for $C_{21}H_{29}N_4O_2$, 369.23; found 368.9. $[M]^+$1H NMR (DMSO): 1.47 (d, 6H), 2.19-2.40 (m, 8H), 3.85-4.05 (m, 3H), 4.21-4.43 (m, 3H), 4.57-4.73 (m, 2H), 5.10 (sept, 1H), 6.22 (d, 1H), 7.31 (m, 1H), 7.43 (m, 1H), 7.82 (d, 1H), 8.03 (m, 1H), 8.16 (d, 1H).

b. Synthesis of 1-isopropyl-1*H*-indazole-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{3-[(2-cyano-ethyl)methylamino]-2-hydroxypropyl}-8-azabicyclo[3.2.1]oct-3-yl)amide

3-Methylaminopropanenitrile (0.066 mL, 0.71 mmol) was added to 3-hydroxy-3'-{[1-isopropyl-1*H*-indazole-3-yl)carbonyl]amino}-spiro[azetidine-1,8'-(1*S*,3*R*,5*R*)-8-azabicyclo[3.2.1]octane, the product of the previous step, (0.47 mmol) and

diisopropylethylamine (0.245 mL, 1.41 mmol) in methanol (4 mL). The reaction mixture was shaken in a heating block at 65°C for 16 h. Further 3-methylaminopropanenitrile was added (2 x 0.066 mL, 0.71 mmol) and after 20 h the reaction mixture was cooled, concentrated *in vacuo*, diluted with acetic acid/water 1:1 (3 mL) and purified by preparative HPLC, to afford the bistrifluoroaceticacid salt of the title compound. (m/z): $[M+H]^+$ calcd for $C_{25}H_{36}N_6O_2$, 453.30; found 453.2. Retention time (anal. HPLC) = 2.00 min.

Example 5: Synthesis of 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[3-(4-dimethylcarbamoylpiperazin-1-yl)-2-hydroxypropyl]-8-azabicyclo[3.2.1]oct-3-yl}amide

Piperazine-4-dimethylurea (23 mg, 0.15 mmol) was dissolved in a solution of the 3-hydroxy-3'-{[1-isopropyl-1*H*-indazole-3-yl)carbonyl]amino}spiro[azetidine-1,8'-(1*S*,3*R*,5*R*)-8-azabicyclo[3.2.1]octane, prepared as in Example 4, step (a), (42 mg, 0.10 mmol) and diisopropylethylamine (0.017 mL, 0.15 mmol) in ethanol (2 mL). The reaction mixture was shaken on a heating block at 80°C for 16 h. The reaction mixture was concentrated *in vacuo*, diluted with 50% acetic acid in water (1.5 mL) and purified by preparative HPLC (5-75% gradient) to afford the bistrifluoroaceticacid salt of the title compound (56 mg) as a white solid. (m/z): $[M+H]^+$ calcd for $C_{28}H_{43}N_7O_3$, 526.35; found 526.4. Retention time (anal. HPLC) = 1.92 min.

Example 6: Synthesis of [1-(2-hydroxy-3-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-1*H*-indazole-3-carbonyl)-amino]-8-azabicyclo[3.2.1]oct-8-yl}propyl)pyrrolidin-3-yl]carbamic acid methyl ester

Pyrrolidine-3-NH-methylcarbamate (mono TFA salt; 39 mg, 0.15 mmol) was dissolved in a solution of the 3-hydroxy-3'-{[1-isopropyl-1*H*-indazole-3-yl)carbonyl]amino}spiro[azetidine-1,8'-(1*S*,3*R*,5*R*)-8-azabicyclo[3.2.1]octane, prepared in Example 4, step (a), (32mg, 0.075mmol) and diisopropylethylamine (0.065 mL, 0.37 mmol) in DMF (2 mL). The reaction mixture was shaken on a heating block at 80°C for 16 h. The reaction mixture was concentrated *in vacuo*, diluted with 50% acetic acid in water (1.5mL) and purified by preparative HPLC (5-75% gradient) to afford the

bistrifluoroaceticacid salt of the title compound (35 mg) as a white solid. (m/z): $[M+H]^+$ calcd for $C_{27}H_{40}N_6O_4$, 513.32; found 513.4. Retention time (anal. HPLC) = 1.98 min.

Example 7: Synthesis of 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[3-(4-methanesulfonylpiperazin-1-yl)-2-methoxypropyl]-8-azabicyclo[3.2.1]oct-3-yl}amide

a. Preparation of 3-methoxy-3'-{[1-isopropyl-1*H*-indazole-3-yl)carbonyl]-amino}spiro[azetidine-1,8'-(1*S*,3*R*,5*R*)-8-azabicyclo[3.2.1]octane

Epibromohydrin (2.81 mL, 32.86 mmol) was added to a stirred solution of 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-aza-bicyclo[3.2.1]oct-3-yl}amide TFA salt, prepared in Example 1, step (f), (7.00 g, 16.43 mmol) and diisopropylethylamine (2.86 mL, 16.43 mmol) at room temperature. The reaction mixture was stirred for 72 h and concentrated *in vacuo* to afford a crude oil (11.7 g, assume 63% product by mass) contaminated with diisopropylethylamine salts. A sample of the crude oil (1.5 g) was suspended in dichloromethane (45 mL) and cooled to 0 °C. Potassium *tert*-butoxide (472 mg, 4.21 mmol) was added and followed by methyl iodide (0.145 mL, 2.32 mmol) and the reaction mixture allowed to warm to room temperature. After 30 min the reaction mixture was cooled to 0 °C and a further amount of potassium *tert*-butoxide (2 x 236 mg, 2.10 mmol) and methyl iodide (2 x 0.145 mL, 2.32 mmol) was added. After 1 h, analytical HPLC indicated approx. 90% conversion of the starting material to a major product. The reaction mixture was quenched by the addition of water (20 mL) and diluted with dichloromethane (50 mL). The layers were separated and the aqueous layer was further extracted with dichloromethane (50 mL) and chloroform (25 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a crude product which was used without futher purification (1 g, 85% purity by HPLC).

b. Synthesis of 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[3-(4-methanesulfonylpiperazin-1-yl)-2-methoxypropyl]-8-azabicyclo[3.2.1]oct-3-yl}amide

N-Methylsulfonylpiperazine (70 mg, 0.252 mmol) was added to a solution of the crude product of the previous step (64 mg) and diisopropylethylamine (0.131 mL, 0.755 mmol) in ethanol (1.5 mL). The reaction mixture was shaken in a heating block at 80 °C for 16 h. The reaction mixture was concentrated *in vacuo*, diluted with acetic

acid/water 1:1 (1 mL) and purified by preparative HPLC to yield the bistrifluoroaceticacid salt of the title compound. (m/z): $[M+H]^+$ calcd for $C_{27}H_{42}N_6O_4S$,. 547.31; found 547.2.

Example 8: Synthesis of 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[(*R*)-2-hydroxy-3-(4-methanesulfonylpiperazin-1-yl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide

a. Preparation of 1-chloro-(*R*)-2-hydroxy-3-(4-methanesulfonylpiperazin-1-yl)propane

(*R*)-Epichlorohydrin (3.10 mL, 39.5 mmol) was added to a stirred solution of piperazine sulfonamide.TFA (10.0 g, 35.9 mmol) and diisopropylethylamine (6.26 mL, 35.9 mmol) in ethanol (150 mL) at room temperature. The reaction mixture was stirred for 18 h and a further amount of (*R*)-epichlorohydrin was added (0.28 mL, 3.6 mmol) and stirred for an additional 3 h. The reaction mixture was concentrated *in vacuo* and the white solid was suspended in ethanol (150 mL) and stirred for 2 days. The solid was collected by filtration and washed with cold ethanol to afford the title compound (5.69 g) as a white solid which was used without further purification. (m/z): $[M+H]^+$ calcd for $C_8H_{17}ClN_2O_3S$, 257.07; found 257.2. ^1H NMR (DMSO-d_6): δ (ppm) 2.37 (dd, 1H), 2.45 (dd, 1H), 2.50-2.58 (m, 4H), 2.86 (s, 3H), 3.09 (m, 4H), 3.55 (dd, 1H), 3.65 (dd, 1H), 3.84 (m, 1H), 5.09 (d, 1H).

b. Preparation of 1-[(2*R*)-oxiranylmethyl]-4-methanesulfonylpiperazine

Sodium hydroxide (1.07 g, 26.7 mmol) was added to a vigorously stirred solution of 1-chloro-(*R*)-2-hydroxy-3-(4-methanesulfonylpiperazin-1-yl)propane, the product of the previous step (5.69 g, 22.2 mmol) in THF/water (150mL/35mL). The reaction mixture was stirred for 35 min, concentrated *in vacuo* to approximately 50 mL volume, diluted with chloroform (200 mL), and washed with 1M NaOH (2 x 70 mL) and brine (70 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a white crystalline solid which was then recrystallised from hot EtOAc/hexane 1:1 (800 mL) to yield the title intermediate (2.62 g) as a white crystalline solid. (The filtrate could be further recrystallised to obtain additional product material.) ESMS ($C_8H_{16}N_2O_3S$): calcd. 221.10; found 221.3 (m/z): $[M+H]^+$; ^1H NMR (DMSO-d_6): δ (ppm) 2.22 (dd, 1H), 2.45-2.60 (m, 5H), 2.69-2.75 (m, 2H), 2.87 (s, 3H), 3.02 (m, 1H), 3.11 (m, 4H).

c. Synthesis of 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[(*R*)-2-hydroxy-3-(4-methanesulfonylpiperazin-1-yl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide

A solution of 1-[(2*R*)-oxiranylmethyl]-4-methanesulfonylpiperazine, the product of the previous step, (585 mg, 2.66 mmol) in toluene (12 mL) was added to 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-aza-bicyclo[3.2.1]oct-3-yl}amide (830 mg, 2.66 mmol) and the mixture stirred at 98°C for 16 h. The reaction mixture was cooled, concentrated *in vacuo*, diluted with 50% acetic acid in water containing 10% TFA (12 mL) and purified by preparative HPLC to afford the the bistrifluoroacetic acid salt of the title compound (525 mg) as a white solid. (m/z): $[M+H]^+$ calcd for $C_{26}H_{40}N_6O_4S$, 533.29; found 533.5. Retention time (anal. HPLC: 2-40% MeCN/H_2O over 6 min) = 4.03 min; ^1H NMR (CD_3OD): δ (ppm) 1.55 (d, 6H), 2.41 (m, 6H), 2.55-2.63 (m, 2H), 2.92 (s, 3H), 3.10-3.40 (m, 6H), 3.82 (bs, 4H), 4.16-4.24 (m, 3H), 4.66 (m, 1H), 4.99 (sept, 1H), 7.22 (t, 1H), 7.39 (t, 1H), 7.62 (d, 1H), 8.12 (d, 1H).

Example 9: Synthesis of 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[(*S*)-2-hydroxy-3-(4-methanesulfonylpiperazin-1-yl)propyl]-8-azabicyclo[3.2.1]-oct-3-yl}amide

a. Prepration of 1-chloro-(*S*)-2-hydroxy-3-(4-methanesulfonylpiperazin-1-yl)propane

(*S*)-Epichlorohydrin (48.0 mL, 0.612 mol) was added to a stirred solution of piperazine sulfonamide (87.3 g, 0.532 mol) in ethanol (1.33 L) at room temperature. The reaction mixture was stirred for 18 h and the white solid precipitate which formed was collected by filtration and washed with ethanol to afford the title intermediate (107.76 g) as a white solid which was used without further purification. (m/z): $[M+H]^+$ calcd for $C_8H_{17}ClN_2O_3S$, 257.07; found 257.2. ^1H NMR (DMSO-d_6): δ (ppm) 2.37 (dd, 1H), 2.45 (dd, 1H), 2.50-2.58 (m, 4H), 2.86 (s, 3H), 3.09 (m, 4H), 3.55 (dd, 1H), 3.65 (dd, 1H), 3.84 (m, 1H), 5.09 (d, 1H).

b. Prepration of 1-[(2*S*)-oxiranylmethyl]-4-methanesulfonylpiperazine

Sodium hydroxide (22.15 g, 0.534 mol) was added to a vigorously stirred solution of the product of the previous step (118.13 g, 0.461 mol) in THF/water (1200 mL/ 300 mL) at 0 °C. The reaction mixture was stirred for 90 min and the layers separated. The organic layer was concentrated *in vacuo* and diluted with dichloromethane (1500 mL)

and washed with a mixture of the previously separated aqueous layer and 1M NaOH (500 mL). The organic layer was further washed with 1M NaOH (500 mL) and brine (500 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a white crystalline solid which was recrystallised from hot EtOAc/hexane 1:1 (800 mL) to yield the title compound (43.33 g) as a white crystalline solid. (The filtrate could be further recrystallised to obtain additional product material.) (m/z): $[M+H]^+$ calcd for $C_8H_{16}N_2O_3S$), 221.10; found 221.3. ^1H NMR (DMSO-d_6): δ (ppm) 2.22 (dd, 1H), 2.45-2.60 (m, 5H), 2.69-2.75 (m, 2H), 2.87 (s, 3H), 3.02 (m, 1H), 3.11 (m, 4H).

c. Synthesis of 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[(*S*)-2-hydroxy-3-(4-methanesulfonylpiperazin-1-yl)propyl]-8-azabicyclo[3.2.1]-oct-3-yl}amide

A solution of the 1-[(2*S*)-oxiranylmethyl]-4-methanesulfonylpiperazine, the product of the previous step (0.44 g, 9.10 mmol) in toluene (30 mL) was added to 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-aza-bicyclo[3.2.1]oct-3-yl}amide (2.83 g, 9.10 mmol) and the mixture stirred at 98 °C for 16 h. The reaction mixture was cooled, concentrated *in vacuo*, diluted with 50% acetic acid in water containing 10% TFA (20 mL) and purified by preparative HPLC to afford the bistrifluoroacetic acid salt of the title compound (1.83 g) as a white solid. (m/z): $[M+H]^+$ calcd for $C_{26}H_{40}N_6O_4S$, 533.29; found 533.5. Retention time (anal. HPLC: 2-40% MeCN/H_2O over 6 min) = 4.03 min; ^1H NMR (CD_3OD): δ (ppm) 1.55 (d, 6H), 2.41 (m, 6H), 2.55-2.63 (m, 2H), 2.92 (s, 3H), 3.10-3.40 (m, 6H), 3.82 (bs, 4H), 4.16-4.24 (m, 3H), 4.66 (m, 1H), 4.99 (sept, 1H), 7.22 (t, 1H), 7.39 (t, 1H), 7.62 (d, 1H), 8.12 (d, 1H).

Example 10: Synthesis of 1-isopropyl-1*H*-indazole-3-carboxylic acid [(1*S*,3*R*,5*R*)-8-(4-carbamoylmethylmorpholin-2-ylmethyl)-8-azabicyclo[3.2.1]oct-3-yl]amide

a. Preparation of 2-chloromethylmorpholine

2-Chloromethylmorpholine was synthesized according to the procedures reported in literature (Araki, K. et al., *J. Med. Chem.* **1993**, *36*, 1356-63; Nishimura, Y. et al., *Chem. & Pharm. Bull.* **1990**, *38*, 2190-6), and its secondary amine was protected as *N*-Boc group by treating with $(Boc)_2O$ (dissolved in methanol, at room temperature).

b. Preparation of 1-isopropyl-1*H*-indazole-3-carboxylic acid [(1*S*,3*R*,5*R*)-8-(4-(tert-butoxycarbonyl)morpholin-2-ylmethyl)-8-azabicyclo[3.2.1]oct-3-yl]amide

To a solution of 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-aza-bicyclo[3.2.1]oct-3-yl}amide monotrifluoroacetic acid salt, prepared in Example 1, step (f), (2 g; 4.7 mmol) dissolved in 50 mL of acetonitrile was added potassium carbonate (1.3 g, 9.4 mmol) and 2-chloromethylmorpholine, the product of the previous step (1.2 g, 5.1 mmol). The reaction mixture was stirred at 85 °C for 24 h, and cooled to room temperature prior to being quenched by water (100 mL). The mixture was diluted with dichloromethane (300 mL), and transferred to a separatory funnel. After shaking, the organic layer was collected, and washed with brine solution (100 mL). It was dried over $MgSO_4$, and evaporated *in vacuo*, to afford the title intermediate as a pale yellow oil which was used without further purification. (m/z): $[M+H]^+$ calcd for $C_{28}H_{41}N_5O_4$, 512.33; found 512.4.

c. Preparation of 1-isopropyl-1*H*-indazole-3-carboxylic acid [(1*S*,3*R*,5*R*)-8-(morpholin-2-ylmethyl)-8-azabicyclo[3.2.1]oct-3-yl]amide

1-Isopropyl-1*H*-indazole-3-carboxylic acid [(1*S*,3*R*,5*R*)-8-(4-(tert-butoxy-carbonyl)morpholin-2-ylmethyl)-8-azabicyclo[3.2.1]oct-3-yl]amide, the product of the previous step, was dissolved in dichloromethane (20 mL), and followed by addition of trifluoroacetic acid. After stirring for 30 min at room temperature, the mixture was evaporated *in vacuo*, yielding a pale yellow oil. It was dissolved in 50% aqueous acetonitrile (5% TFA), and fractionated by preparative HPLC, affording a trifluoroacetic acid salt of the title intermediate. (m/z): $[M+H]^+$ calcd for $C_{23}H_{33}N_5O_2$, 412.27; found 412.6. Retention time (anal. HPLC: 10-40% MeCN/H_2O over 6 min) = 3.9 min.

d. Synthesis of 1-isopropyl-1*H*-indazole-3-carboxylic acid [(1*S*,3*R*,5*R*)-8-(4-carbamoylmethylmorpholin-2-ylmethyl)-8-azabicyclo[3.2.1]oct-3-yl]amide

1-Isopropyl-1*H*-indazole-3-carboxylic acid [(1*S*,3*R*,5*R*)-8-(morpholin-2-ylmethyl)-8-azabicyclo[3.2.1]oct-3-yl]amide, the product of the previous step, (0.1 g, 0.19 mmol) was dissolved in ethanol (10 mL) containing diisopropylethylamine (0.066 mL, 0.38 mmol), and followed by the addition of bromoacetamide (26 mg, 0.21 mmol). The mixture was heated at 90 °C for 12 h, and concentrated *in vacuo*, yielding a pale yellow

oil. It was fractionated to afford a bistrifluoroacetic acid salt of the title compound. (m/z): $[M+H]^+$ calcd for $C_{25}H_{36}N_6O_3$, 469.29; found 469.2. Retention time (anal. HPLC) = 2.28 min.

Example 11: Synthesis of 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[2-hydroxy-3-(methanesulfonylmethylamino)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide

a. Preparation of 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[2-hydroxy-3-methylamino)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide

To a solution of ethanol (5 mL) containing 3-hydroxy-3'-{[1-isopropyl-1*H*-indazole-3-yl)carbonyl]amino}spiro[azetidine-1,8'-(1*S*,3*R*,5*R*)-8-azabicyclo[3.2.1]octane, prepared in Example 4, step (a), (0.365 g, 0.8 mmol) was added methylamine in THF (41%, 0.27 mL). The mixture was stirred at 90 °C for three days, and concentrated *in vacuo*, to yield the title intermediate. The product was used in the next step without further purification.

b. Synthesis of 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[2-hydroxy-3-(methanesulfonylmethylamino)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide

To a cold solution of dichloromethane (5 mL) containing 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[2-hydroxy-3-methylamino)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide, the product of the previous step, (0.4 g, 1 mmol) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.18 mL, 1.2 mmol) and then methanesulfonyl chloride (0.082 mL, 1.05 mmol). The mixture was stirred in an ice bath for 1 h prior to being quenched by water, and concentrated *in vacuo*. The residue was dissolved in 50% aqueous acetic acid, and purified by prep HPLC to afford the monotrifluoroacetic acid salt of the title compound. (m/z): $[M+H]^+$ calcd for $C_{23}H_{35}N_5O_4S$, 478.25; found 478.2. Retention time (anal. HPLC) = 3.0 min.

Example 12: Synthesis of 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[3-(acetyl-methylamino)-2-hydroxypropyl]-8-azabicyclo[3.2.1]oct-3-yl}amide

To a cold solution of DMF (5 mL) containing 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[2-hydroxy-3-methylamino)propyl]-8-azabicyclo[3.2.1]oct-

3-yl}amide, the product of Example 11, step (a), (0.4 g, 1 mmol) was added diisopropylethylamine (0.21 mL, 1.2 mmol) and then acetyl chloride (0.075 mL, 1.05 mmol). The mixture was stirred in an ice bath for 1 h prior to being quenched by water, and concentrated *in vacuo*. The residue was dissolved in 50% aqueous acetic acid, and purified by prep HPLC to provide the monotrifluoracetic acid salt of the title compound. (m/z): $[M+H]^+$ calcd for $C_{24}H_{35}N_5O_3$, 442.28; found 442.2. Retention time (anal. HPLC) = 2.9 min.

Example 13: Synthesis of 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[3-(formyl-methylamino)-2-hydroxypropyl]-8-azabicyclo[3.2.1]oct-3-yl}amide

A solution of neat ethyl formate (5 mL) containing 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[2-hydroxy-3-methylamino)propyl]-8-azabicyclo-[3.2.1]oct-3-yl}amide, the product of Example 11, step (a), (0.4 g, 1 mmol) was stirred at 80 °C for 2 h. The mixture was concentrated *in vacuo*, dissolved in 50% aqueous acetic acid, and purified by prep HPLC to yield the monotrifluoroacetic acid salt of the title compound. (m/z): $[M+H]^+$ calcd for $C_{23}H_{33}N_5O_3$, 428.27; found 428.2. Retention time (anal. HPLC) = 1.4 min.

Example 14: Synthesis of 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[(*R*)-2-hydroxy-3-(methanesulfonylmethylamino)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide

a. Preparation of (*S*)-1-(benzyl-methyl-amino)-3-chloropropan-2-ol

N-Benzylmethylamine (13.95 mL, 108.1 mmol) and (*S*)-2-chloromethyloxirane, commonly (*S*)-epichlorohydrin (8.48 mL, 108.1 mmol) were dissolved in hexane (40 mL), and stirred for 16 h. The solution was then flash chromatographed (SiO_2, eluting with 10 % methanol/90 % dichloromethane). Fractions containing product were concentrated to afford the title intermediate as an oil (19.7 g). ^{1}H-NMR (DMSO *d6*, 299.96 MHz): δ (ppm) 2.01 (s, 3H), 2.2-2.4 (m, 2H), 3.21-3.5 (m, 3H), 3.53-3.6 (m, 1H), 3.65-3.75 (m, 1H), 4.95 (d, 1H), 7.0-7.25 (m, 5H). (*m/z*): $[M+H]^+$ calcd for $C_{11}H_{16}ClNO$, 214.10; found 214.1.

b. Preparation of ((*S*)-3-chloro-2-hydroxypropyl)methylcarbamic acid *tert*-butyl ester

(*S*)-1-(benzyl-methyl-amino)-3-chloropropan-2-ol, the product of the previous step (8.4 g, 39.3 mmol) was dissolved in ethyl acetate (75 mL), and then di-*tert*-butyl dicarbonate (9.3 g, 43.23 mmol) and palladium hydroxide (2.5 g) were added. The mixture was shaken for 12 h under hydrogen (60 atm). The mixture was filtered through a bed of Celite®, and concentrated to dryness under reduced pressure. The resulting oil was filtered through silica, eluted with hexane, followed by dichloromethane, followed by diethyl ether. The ether layer was concentrated to give the title intermediate (7.1 g) as an oil. ^{1}H-NMR (DMSO d_6, 299.96 MHz): δ (ppm) 1.35-1.46 (s, 9H), 2.81-2.85 (s, 3H), 2.95-3.1 (m, 1H), 3.3-3.6 (m, 3H), 3.67-3.85 (m, 1H), 5.25-5.4 (m, 1H). (*m/z*): [M+H-Boc]$^+$ calcd for $C_9H_{18}ClNO_3$, 123.10; found 123.1.

c. Preparation of 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[(*R*)-2-hydroxy-3-(*N*-tert-butoxycarbonyl-*N*-methylamino)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide

To a solution of 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-aza-bicyclo[3.2.1]oct-3-yl}amide monotrifluoroacetic acid salt (1.3 g, 3.0 mmol) dissolved in 12 mL of methanol was added diisopropylethylamine (1.57 mL, 9.0 mmol) and ((*S*)-3-chloro-2-hydroxypropyl)methylcarbamic acid *tert*-butyl ester, the product of the previous step (1 g, 4.49 mmol). The mixture was stirred at 90 °C for 32 h, and evaporated *in vacuo*, yielding a pale yellow oil. It was purified by flash silica column chromatography eluting with 10% methanol in dichloromethane, to afford the title intermediate (1.2 g).

d. Preparation of 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[(*S*)-2-hydroxy-3-(methylamino)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide

1-Isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[(*R*)-2-hydroxy-3-(*N*-tert-butoxycarbonyl-*N*-methylamino)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide, the product of the previous step, was dissolved in 10 mL of dichloromethane followed by the addition of trifluoroacetic acid (10 mL). The mixture was stirred for 10 min, and concentrated *in vacuo*. The concentrate was washed with ether, dried *in vacuo*, to afford the bistrifluoroacetic acid salt of the title intermediate, which was used in the next step without further treatment.

e. Synthesis of 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[(*R*)-2-hydroxy-3-(methanesulfonylmethylamino)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide

To a cold solution of dichloromethane (4 mL) containing the product of the previous step (0.54 g, 0.86 mmol) was added 1,8-diazabicyclo[5.4.0]unde-7-cene (0.448 mL, 3 mmol) and then methanesulfonyl chloride (0.07 mL, 0.9 mmol). The mixture was stirred in an ice bath for 1 h prior to being quenched by water, and concentrated *in vacuo*. The residue was dissolved in 50% aqueous acetic acid, and purified by prep HPLC to yield the monotrifluoroacetic acid salt of the title compound. (*m/z*): $[M+H]^+$ calcd for $C_{23}H_{35}N_5O_4S$,. 478.25; found 478.2. Retention time (anal. HPLC) = 3.0 min.

Example 15: Synthesis of 1-isopropyl-1*H*-indazole-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{2-hydroxy-3-[(pyridine-4-carbonyl)amino]propyl}-8-azabicyclo[3.2.1]oct-3-yl)amide

a. Preparation of 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-2-hydroxy-propyl]-8-aza-bicyclo[3.2.1]oct-3-yl}amide

An ethanol solution (100 mL) of 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-aza-bicyclo[3.2.1]oct-3-yl}amide (3.15 g, 10 mmol) was stirred at 22 °C in a 250 mL flask. 2-Oxiranylmethyl-isoindole-1,3-dione, commonly epoxypropyl-phthalimide (3.07 g, 15 mmol) was added and the solution was heated to 80 °C for 48 h. The reaction mixture was cooled to room temperature and ethyl acetate (200 mL) was added. After completing aqueous washings with saturated $NaHCO_3$ and saturated NaCl solution, the organics were combined and dried over $MgSO_4$. After filtration, volatiles were removed *in vacuo* to afford the title intermediate (5.5 g) as a yellow solid. (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{39}N_5O_4$, 516.26; found 516.5. Retention time (anal. HPLC: 10-70% MeCN/H_2O over 6 min) = 3.18 min.

b. Preparation of 1-isopropyl-1H-indazole-3-carboxylic acid [(1*S*,3*R*,5*R*)-8-(2-hydroxy-3-methylaminopropyl)-8-azabicyclo[3.2.1]oct-3-yl]amide

An ethanol solution (80 mL) of 1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-2-hydroxy-propyl]-8-aza-bicyclo[3.2.1]oct-3-yl}amide, the product of the previous step, (3.0 g, 5.8 mmol) was stirred at 22 °C in a 250 mL flask. Hydrazine solution as neat (3.07 g, 15 mmol) was added and the mixture was heated to 80 °C for 16 h. The reaction mixture was cooled to room temperature and filtered to remove insoluble material. Evaporation of the filtrate *in vacuo* yielded the title intermediate (2.5 g) as a yellow solid. (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{39}N_5O_4$, calcd. 386.26; found 386.2. Retention time (anal. HPLC: 10-70% MeCN/H_2O over 6 min) = 1.85 min.

c. Synthesis of 1-isopropyl-1*H*-indazole-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{2-hydroxy-3-[(pyridine-4-carbonyl)amino]propyl}-8-azabicyclo[3.2.1]oct-3-yl)amide

To a stirred dichloromethane solution (5 mL) of 1-isopropyl-1H-indazole-3-carboxylic acid [(1*S*,3*R*,5*R*)-8-(2-hydroxy-3-methylaminopropyl)-8-azabicyclo[3.2.1]oct-3-yl]amide, the product of the previous step, (42 mg, 0.10 mmol) cooled at 0 °C was added pyridine-4-carboxylic acid chloride (21 mg, 0.12 mmol) as a solid and diisopropylethylamine (0.021 mL, 0.12 mmol) via micropipette. The reaction mixture was stirred at 0 °C for 5 min then warmed to room temperature and stirred for 16 h. It was concentrated *in vacuo*, diluted with 50% aqueous acetic acid (1.5 mL) and purified by preparative HPLC (5-75% gradient) to afford the monotrifluoroacetic acid salt of the title compound (22 mg) as a white solid. (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{34}N_6O_3$, 491.28; found 491.1. Retention time (anal. HPLC) = 1.91 min.

Example 16: Synthesis of 1-isopropyl-1*H*-indazole-3-carboxylic acid [(1*S*,3*R*,5*R*)-8-(3-formylamino-2-hydroxypropyl)-8-azabicyclo[3.2.1]oct-3-yl]-amide

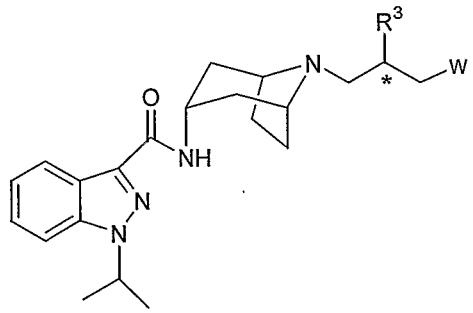
To a DMF solution (5 mL) of 1-isopropyl-1*H*-indazole-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{2-hydroxy-3-[(pyridine-4-carbonyl)amino]propyl}-8-azabicyclo[3.2.1]oct-3-yl)amide, the product of Example 15, (42 mg, 0.10 mmol) was added ethyl formate (0.01 mL, 1.2 mmol) via micropipette. The reaction mixture was sealed and shaken at 80 °C for 16 h. It was concentrated *in vacuo*, diluted with 50% aqueous acetic acid (1.5mL) and purified by preparative HPLC (5-75% gradient) to yield the

monotrifluoroacetic acid of the title compound (35 mg) as a white solid. (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{31}N_5O_3$, 414.25; found 414.1. Retention time (anal. HPLC) = 2.04 min.

Example 17: Compounds of the Invention

Using the procedures of Examples 1-16 and variations thereof, the compounds of Table I to X were prepared and characterized by mass spectrometry. In tables containing compounds prepared as pure stereoisomers, the chirality of the carbon atom marked with an asterisk is indicated in the column headed by an asterisk. In the compounds of Tables I to X, the indazole-carboxamide group is in the endo configuration with respect to the azabicylo-octane group.

Table I



No.	R^3	*	W	Molecular Formula	Calc'd [M+H]	Obsd [M+H]
1	OH		$N(CH_3)(CH_2)_2OH$	$C_{24}H_{37}N_5O_3$	444.30	444.2
2	OH		$N(CH_3)CH_2C(O)NH_2$	$C_{24}H_{36}N_6O_3$	457.29	457.2
3	OH		$N(CH_3)(CH_2)_2CN$	$C_{25}H_{36}N_6O_2$	453.30	453.2
4	OH		$N(CH_3)(CH_2)_2OCH_3$	$C_{25}H_{39}N_5O_3$	458.32	458.3
5	OH		$N(CH_3)(CH_2)_2$-pyridin-2-yl	$C_{29}H_{40}N_6O_2$	505.33	505.3
6	OH		$N(CH_2CH_2OH)(CH_2)_2OH$	$C_{25}H_{39}N_5O_4$	474.31	474.3
7	OH		$N(CH_2CH_2OCH_3)(CH_2)_2OCH_3$	$C_{27}H_{43}N_5O_4$	502.34	502.3
8	OH		$N(CH_3)(CH_2)_2N(CH_3)SO_2CH_3$	$C_{26}H_{42}N_6O_4S$	535.31	535.4
9	OCH_3		$N(CH_3)(CH_2)_2CN$	$C_{26}H_{38}N_6O_2$	467.32	467.2
10	OH		$N(CH_3)S(O)_2CH_3$	$C_{23}H_{35}N_5O_4S$	478.25	478.2
11	OH		$N(CH_3)C(O)CH_3$	$C_{24}H_{35}N_5O_4$	442.28	442.2
12	OH		$N(CH_3)C(O)N(CH_3)_2$	$C_{25}H_{38}N_6O_3$	471.31	471.2
13	OH		$N(CH_3)C(O)OCH_3$	$C_{24}H_{35}N_5O_4$	458.28	458.2

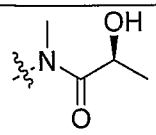
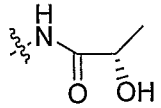
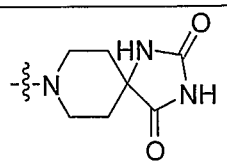
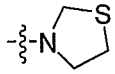
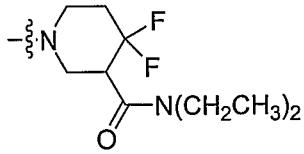
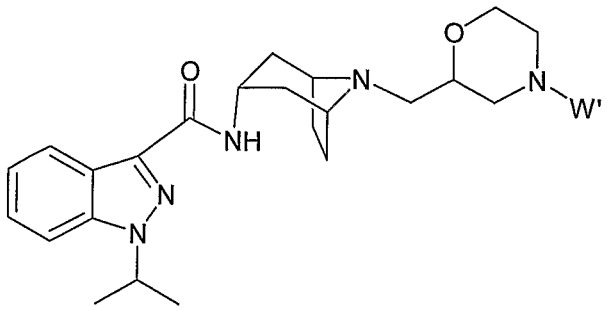
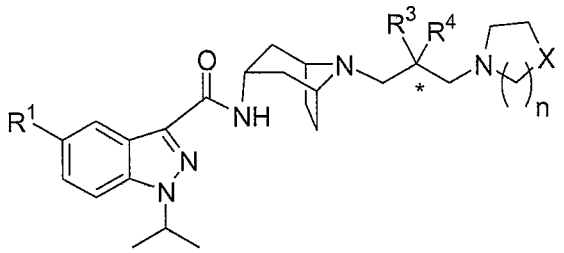
14	OH		$N(CH_3)C(O)$-pyridin-4-yl	$C_{28}H_{36}N_6O_3$	505.29	505.2
15	OH		$N(CH_3)C(O)H$	$C_{23}H_{33}N_5O_3$	428.27	428.2
16	OH		$N(CH_3)C(O)NHCH_3$	$C_{24}H_{36}N_6O_3$	457.29	457.2
17	OH		$N(CH_3)C(O)NH_2$	$C_{23}H_{34}N_6O_3$	443.28	443.2
18	OH			$C_{25}H_{37}N_5O_4$	472.29	472.2
19	OH		NHC(O)-pyridin-4-yl	$C_{27}H_{34}N_6O_3$	491.28	491.1
20	OH		$NHC(O)OCH_3$	$C_{23}H_{33}N_5O_4$	444.26	444.2
21	OH		$NHC(O)CH_3$	$C_{23}H_{33}N_5O_3$	428.27	428.1
22	OH		$NHS(O)_2$-1-methylimidazol-4-yl	$C_{25}H_{35}N_7O_4S$	530.26	530.1
23	OH		$NHS(O)_2N(CH_3)_2$	$C_{23}H_{36}N_6O_4S$	493.26	493.1
24	OH		$NHC(O)N(CH_3)_2$	$C_{24}H_{36}N_6O_3$	457.29	457.2
25	OH		$NHC(O)NHCH_3$	$C_{23}H_{34}N_6O_3$	443.28	443.2
26	OH		$NHC(O)NH_2$	$C_{22}H_{32}N_6O_3$	429.26	429.1
27	OH		NHC(O)H	$C_{22}H_{31}N_5O_3$	414.25	414.1
28	OH			$C_{24}H_{35}N_5O_4$	458.28	458.2
29	OH	*R*	$N(CH_3)S(O)_2CH_3$	$C_{23}H_{35}N_5O_4S$	478.25	478.2
30	OH	*S*	$N(CH_3)S(O)_2CH_3$	$C_{23}H_{35}N_5O_4S$	478.25	478.2
31	OH	*R*	$N(CH_3)C(O)CH_3$	$C_{24}H_{35}N_5O_3$	442.28	442.2
32	OH	*S*	$N(CH_3)C(O)CH_3$	$C_{24}H_{35}N_5O_4$	442.28	442.2
33	OH		$NHS(O)_2$-pyridin-3-yl	$C_{26}H_{34}N_6O_4S$	527.25	527.2
34	OH		$NHS(O)_2CH_3$	$C_{22}H_{33}N_5O_4S$	464.24	464.2
35	OH			$C_{28}H_{39}N_7O_4$	538.32	538.4
36	OH			$C_{24}H_{35}N_5O_2S$	458.26	458.2
37	OH			$C_{31}H_{46}F_2N_6O_3$	589.37	589.4

Table II



No.	W'	Molecular Formula	Calc'd [M+H]	Obsd [M+H]
1	$(CH_2)_2NHC(O)OCH_3$	$C_{27}H_{40}N_6O_4$	513.32	513.2
2	$(CH_2)_3S(O)_2N(CH_3)_2$	$C_{28}H_{44}N_6O_4S$	561.32	561.2
3	$(CH_2)_2OCH_3$	$C_{26}H_{39}N_5O_3$	470.32	470.2
4	$(CH_2)_2$-pyrrol-1-yl	$C_{29}H_{40}N_6O_2$	505.33	505.2
5	$(CH_2)_2N(CH_3)S(O)_2CH_3$	$C_{27}H_{42}N_6O_4S$	547.31	547.2
6	$(CH_2)_2OC(O)N(CH_3)_2$	$C_{28}H_{42}N_6O_4$	527.34	527.3
7	$(CH_2)_2C(O)NHCH_2CH_3$	$C_{28}H_{42}N_6O_3$	511.34	511.3
8	$(CH_2)_2C(O)NH_2$	$C_{26}H_{38}N_6O_3$	483.31	483.2
9	$(CH_2)_3C(O)N(CH_3)_2$	$C_{29}H_{44}N_6O_3$	525.36	525.3
10	$(CH_2)_2OH$	$C_{25}H_{37}N_5O_3$	456.30	456.2
11	$(CH_2)_2CF_3$	$C_{26}H_{36}F_3N_5O_2$	508.29	508.2
12	$(CH_2)_2CN$	$C_{26}H_{36}N_6O_2$	465.30	465.2
13	$CH_2C(O)N(CH_3)_2$	$C_{27}H_{40}N_6O_3$	497.33	497.2
14	CH_2CN	$C_{25}H_{34}N_6O_2$	451.28	451.2
15	$CH_2C(O)NH_2$	$C_{25}H_{36}N_6O_3$	469.29	469.2
16	$CH(CN)C(O)N(CH_3)_2$	$C_{28}H_{39}N_7O_3$	522.32	522.2
17	$S(O)_2CH_3$	$C_{24}H_{35}N_5O_4S$	490.25	490.2
18	$C(O)OCH_3$	$C_{25}H_{35}N_5O_4$	470.28	470.2
19	$S(O)_2CF_3$	$C_{24}H_{32}F_3N_5O_4S$	544.22	544.1
20	$C(O)CH_3$	$C_{25}H_{35}N_5O_3$	454.28	454.2

Table III

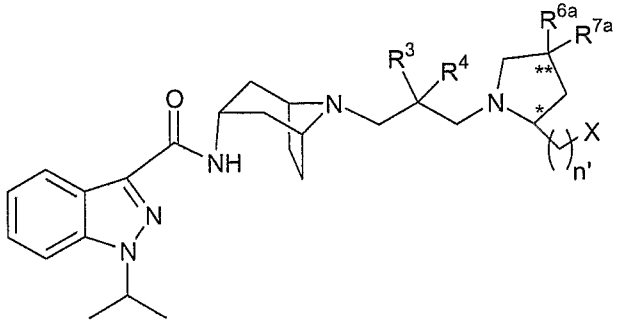


No.	R^1	R^3	*	R^4	n	X	Molecular Formula	Calc'd [M+H]	Obsd [M+H]
1	H	OH		H	2	S	$C_{25}H_{37}N_5O_2S$	472.28	472.2
2	H	OH		H	2	N-pyridin-2-yl	$C_{30}H_{41}N_7O_2$	532.34	532.3
3	H	OH		H	2	NCH_2-pyridin-4-yl	$C_{31}H_{43}N_7O_2$	546.36	546.3
4	H	OH		H	2	N-pyrimidin-2-yl	$C_{29}H_{40}N_8O_2$	533.34	533.3
5	H	OH		H	2	N-pyridin-4-yl	$C_{30}H_{41}N_7O_2$	532.34	532.3
6	H	OH		H	2	NC(O)-tetrahydrofuran-2-yl	$C_{30}H_{44}N_6O_4$	553.35	553.3
7	H	OH		H	2	$NCH_2C(O)N(CH_3)_2$	$C_{29}H_{45}N_7O_3$	540.37	540.3
8	H	OH		H	2	NCH_2-tetrahydrofuran-2-yl	$C_{30}H_{46}N_6O_3$	539.37	539.3
9	H	OH		H	2	$NS(O)_2CH_3$	$C_{26}H_{40}N_6O_4S$	533.29	533.3
10	H	OH		H	2	$NC(O)OCH_2CH_3$	$C_{28}H_{42}N_6O_4$	527.34	527.3
11	H	OH		H	2	$NCH_2C(O)$-morpholin-4-yl	$C_{28}H_{47}N_7O_4$	582.38	582.3
12	H	OH		H	3	$NS(O)_2CH_3$	$C_{27}H_{42}N_6O_4S$	547.31	547.4
13	H	OH		H	2	$NS(O)_2CH_2CH_3$	$C_{27}H_{42}N_6O_4S$	547.31	547.2

No.	R^1	R^3	*	R^4	n	X	Molecular Formula	Calc'd [M+H]	Obsd [M+H]
14	H	OH		H	2	$NS(O)_2CH_2$-cyclohexane	$C_{32}H_{50}N_6O_4S$	615.37	615.4
15	H	OH		H	2	$NS(O)_2N(CH_3)_2$	$C_{27}H_{43}N_7O_4S$	562.32	562.4
16	H	OH		H	2	$NS(O)_2CH(CH_3)_2$	$C_{28}H_{44}N_6O_4S$	561.32	561.4
17	H	OH		H	2	$NS(O)_2CH_2S(O)_2CH_3$	$C_{27}H_{42}N_6O_6S_2$	611.27	611.2
18	H	OH		H	2	$NC(O)N(CH_3)_2$	$C_{28}H_{43}N_7O_3$	526.35	526.4
19	H	OCH_3		H	2	$NS(O)_2CH_3$	$C_{27}H_{42}N_6O_4S$	547.31	547.2
20	H	OH	R	H	2	$NS(O)_2CH_3$	$C_{26}H_{40}N_6O_4S$	533.29	533.5
21	H	OH		H	2	$NC(O)OCH_3$	$C_{27}H_{40}N_6O_4$	513.32	513.4
22	H	OH		H	2	$S(O)_2$	$C_{25}H_{37}N_5O_4S$	504.27	504.2
23	H	OH	S	H	2	$NS(O)_2CH_3$	$C_{26}H_{40}N_6O_4S$	533.29	533.5
24	H	OH		H	2	$NS(O)_2CH_2CF_3$	$C_{27}H_{39}F_3N_6O_4S$	601.28	601.2
25	H	OH		CH_3	2	$NS(O)_2CH_3$	$C_{27}H_{42}N_6O_4S$	547.31	547.6
26	Br	OH	S	H	2	$NS(O)_2CH_3$	$C_{26}H_{39}BrN_6O_4S$	611.20	611.4
27	H	OH		CH_3	2	$NC(O)OCH_3$	$C_{28}H_{42}N_6O_4$	527.34	527.2
28	H	$OC(O)N(CH_3)_2$		H	2	NC(O)-tetrahydrofuran-2-yl	$C_{33}H_{49}N_7O_5$	624.39	624.4
29	H	$OC(O)N(CH_3)_2$		H	2	$S(O)_2$	$C_{28}H_{42}N_6O_5S$	575.30	575.2
30	H	$OC(O)N(CH_3)_2$		H	2	$NC(O)OCH_3$	$C_{30}H_{45}N_7O_5$	584.36	584.2
31	H	$OC(O)N(CH_3)_2$		H	2	$NC(O)CH_3$	$C_{30}H_{45}N_7O_4$	568.36	568.4

No.	R^1	R^3	*	R^4	n	X	Molecular Formula	Calc'd [M+H]	Obsd [M+H]
32	H	$OC(O)N(CH_3)_2$		H	2	$NC(O)N(CH_3)_2$	$C_{31}H_{48}N_8O_4$	597.39	597.4
33	H	OH		H	2	$NC(O)NH_2$	$C_{26}H_{39}N_7O_3$	498.32	498.2
34	H	OH		H	2	$NC(O)NHCH_3$	$C_{27}H_{41}N_7O_3$	512.34	512.4
35	H	$OC(O)NHCH_3$	R	H	2	$NS(O)_2CH_3$	$C_{28}H_{43}N_7O_5S$	590.31	590.6
36	H	$OC(O)NHCH_3$	S	H	2	$NS(O)_2CH_3$	$C_{28}H_{43}N_7O_5S$	590.31	590.6

Table IV



No.	R^3	R^4	n'	X	*	**	R^{6a}	R^{7a}	Molecular Formula	Calc'd [M+H]	Obsd [M+H]
1	OH	H	0	$C(O)N(CH_3)_2$	S		H	H	$C_{28}H_{42}N_6O_3$	511.34	511.3
2	OH	H	1	OCH_3	*S*		H	H	$C_{27}H_{41}N_5O_3$	484.33	484.3
3	OH	H	0	pyridin-4-yl			H	H	$C_{30}H_{40}N_6O_2$	517.33	517.3

No.	R^3	R^4	n'	X	*	**	R^{6a}	R^{7a}	Molecular Formula	Calc'd [M+H]	Obsd [M+H]
4	OH	H	0	$C(O)NH_2$	*R*		H	H	$C_{26}H_{38}N_6O_3$	483.31	484.3
5	OH	H	0	$C(O)NH\text{-}C(CH_3)_3$	*S*		F	F	$C_{30}H_{44}F_2N_6O_4$	575.35	575.2
6	OH	H	0	$C(O)N(CH_2CH_3)_2$	*S*	*S*	F	H	$C_{30}H_{45}FN_6O_3$	557.36	557.2
7	OH	H	0	$C(O)N(CH_2CH_3)_2$	*S*		F	F	$C_{30}H_{44}F_2N_6O_3$	575.35	575.4
8	OH	H	0	$C(O)NHC(CH_3)_3$	*S*	*S*	F	H	$C_{30}H_{45}FN_6O_3$	557.36	557.4
9	OCH_3	H	0	$C(O)NH_2$	*R*		H	H	$C_{27}H_{40}N_6O_3$	497.33	497.4
10	OH	CH_3	0	$C(O)NH_2$	*R*		H	H	$C_{27}H_{40}N_6O_3$	497.33	497.4
11	OH	CH_3	0	$C(O)N(CH_3)_2$	*R*		H	H	$C_{29}H_{44}N_6O_3$	525.36	525.4
12	$OC(O)N(CH_3)_2$	H	0	$C(O)NH_2$	*R*		H	H	$C_{29}H_{43}N_7O_4$	554.35	554.2
13	$OC(O)N(CH_3)_2$	H	0	$C(O)N(CH_3)_2$	*S*		H	H	$C_{31}H_{47}N_7O_4$	582.38	582.4
14	$OC(O)N(CH_3)_2$	H	1	OH	*S*		H	H	$C_{29}H_{44}N_6O_5$	541.35	541.4

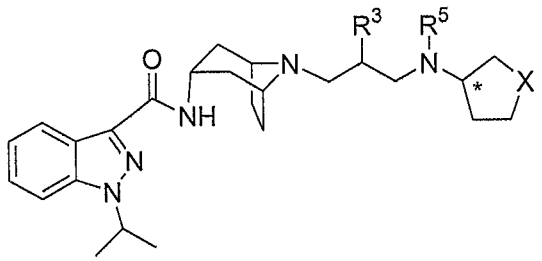
Table V

No.	R^3	R^4	n'	X	*	**	R^{6a}	R^{7a}	Molecular Formula	Calc'd [M+H]	Obsd [M+H]
1	OH	H	0	$N(CH_3)C(O)CH_3$			H	H	$C_{28}H_{42}N_6O_3$	511.34	511.3
2	OH	H	0	$NHC(O)CH_3$	R		H	H	$C_{27}H_{40}N_6O_3$	497.33	497.4
3	OH	H	0	$NHC(O)CH_3$	*S*		H	H	$C_{27}H_{40}N_6O_3$	497.33	497.4
4	OH	H	0	$NHS(O)_2CH_3$	*R*		H	H	$C_{26}H_{40}N_6O_4S$	533.29	533.2
5	OH	H	0	$NHS(O)_2CH_2CH_3$	*R*		H	H	$C_{27}H_{42}N_6O_4S$	547.31	547.2
6	OH	H	0	$NHS(O)_2N(CH_3)_2$	*R*		H	H	$C_{27}H_{43}N_7O_4S$	562.32	562.2
7	OH	H	0	$NHS(O)_2CH_2C_6H_{11}$	*R*		H	H	$C_{32}H_{50}N_6O_4S$	615.37	615.4
8	OH	H	1	$NHS(O)_2CH_3$			H	H	$C_{27}H_{42}N_6O_4S$	547.31	547.2
9	OH	H	1	$NHS(O)_2CH_2CH_3$			H	H	$C_{28}H_{44}N_6O_4S$	561.32	561.2
10	OH	H	1	$NHS(O)_2N(CH_3)_2$			H	H	$C_{28}H_{45}N_7O_4S$	576.34	576.4

No.	R^3	R^4	n'	X	*	**	R^{6a}	R^{7a}	Molecular Formula	Calc'd [M+H]	Obsd [M+H]
11	OH	H	1	$NHS(O)_2CH_2S(O)_2CH_3$			H	H	$C_{28}H_{44}N_6O_6S_2$	625.29	625.2
12	OCH_3	H	0	$N(CH_3)C(O)CH_3$			H	H	$C_{29}H_{44}N_6O_3$	525.36	525.4
13	OH	H	1	$NHC(O)OCH_3$			H	H	$C_{28}H_{42}N_6O_4$	527.34	527.4
14	OH	H	0	$NHC(O)OCH_3$			H	H	$C_{27}H_{40}N_6O_4$	513.32	513.4
15	OH	H	0	$NHC(O)N(CH_3)_2$			H	H	$C_{28}H_{43}N_7O_3$	526.35	526.4
16	OH	H	0	$NHC(O)CH_3$			H	H	$C_{27}H_{40}N_6O_3$	497.33	497.4
17	OH	H	0	$NHC(O)CF_3$	*R*		H	H	$C_{27}H_{37}F_3N_6O_3$	551.30	551.2
18	OH	H	0	$NHC(O)CF_3$	*S*		H	H	$C_{27}H_{37}F_3N_6O_3$	551.30	551.2
19	OH	H	0	$NHC(O)CF_3$	*S*		H	H	$C_{27}H_{37}F_3N_6O_3$	551.30	551.2
20	OH	H	0	$N(CH_3)S(O)_2CH_3$			H	H	$C_{27}H_{42}N_6O_4S$	547.31	547.2
21	OH	H	0	$N(CH_3)S(O)_2N(CH_3)_2$			H	H	$C_{28}H_{45}N_7O_4S$	576.34	576.2
22	OH	CH_3	0	$N(CH_2CH_3)C(O)CH_3$			H	H	$C_{30}H_{46}N_6O_3$	539.37	539.4
23	OH	H	0	$N(CH_3)C(O)OCH_3$			H	H	$C_{28}H_{42}N_6O_4$	527.34	527.2
24	OH	H	0	$N(CH_3)C(O)N(CH_3)_2$			H	H	$C_{29}H_{45}N_7O_3$	540.37	540.4
25	OH	H	1	$NHC(O)N(CH_3)_2$			H	H	$C_{29}H_{45}N_7O_3$	540.37	540.4
26	OH	H	0	$NHS(O)_2CH_3$			H	H	$C_{26}H_{40}N_6O_4S$	533.29	533.2
27	OH	H	0				H	H	$C_{28}H_{42}N_6O_4$	527.34	527.4

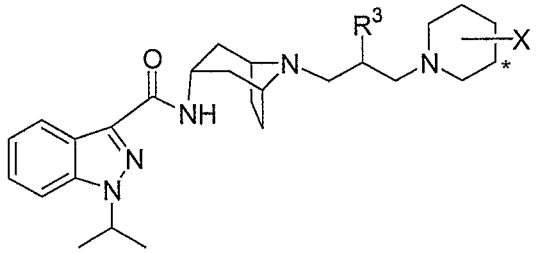
No.	R^3	R^4	n'	X	*	**	R^{6a}	R^{7a}	Molecular Formula	Calc'd [M+H]	Obsd [M+H]
28	OH	H	0	$NHS(O)_2N(CH_3)_2$			H	H	$C_{27}H_{43}N_7O_4S$	562.32	562.4
29	$OC(O)N(CH_3)_2$	H	0	$N(CH_2CH_3)C(O)CH_3$			H	H	$C_{32}H_{49}N_7O_4$	596.39	596.2
30	$OC(O)N(CH_3)_2$	H	0	$N(CH_3)S(O)_2CH_3$			H	H	$C_{30}H_{47}N_7O_5S$	618.35	618.4
31	OH	H	0	$N(CH_3)S(O)_2CH_3$	*S*	*S*	H	OH	$C_{27}H_{42}N_6O_5S$	563.30	563.2
32	OH	H	0	$N(CH_3)C(O)OCH_3$	*S*	*S*	H	OH	$C_{28}H_{42}N_6O_5$	543.33	543.4
33	OH	H	0	$N(CH_3)C(O)N(CH_3)_2$	*S*	*S*	H	OH	$C_{29}H_{45}N_7O_4$	556.36	556.4
34	OH	H	0	$OC(O)N(CH_3)_2$			H	H	$C_{28}H_{42}N_6O_4$	527.34	527.2
35	OH	H	0				H	H	$C_{28}H_{42}N_6O_4S$	559.31	559.3

Table VI



No.	R^3	R^5	*	X	Molecular Formula	Calc'd [M+H]	Obsd [M+H]
1	OH	CH_3		$S(O)_2$	$C_{26}H_{39}N_5O_4S$	518.28	518.2
2	OH	CH_3		$NS(O)_2CH_3$	$C_{27}H_{42}N_6O_4S$	547.31	547.4
3	OH	CH_3		$NC(O)OCH_3$	$C_{28}H_{42}N_6O_4$	527.34	527.4
4	OH	CH_3		$NC(O)N(CH_3)_2$	$C_{29}H_{45}N_7O_3$	540.37	540.4
5	OH	CH_3		$NS(O)_2CH_2CH_3$	$C_{28}H_{44}N_6O_4S$	561.32	561.8
6	$OC(O)N(CH_3)_2$	CH_3		$NS(O)_2CH_3$	$C_{30}H_{47}N_7O_5S$	618.35	618.4
7	OH	CH_2CH_2OH		$S(O)_2$	$C_{27}H_{41}N_5O_5S$	548.29	548.2
8	OH	CH_3		$NC(O)CH_3$	$C_{28}H_{42}N_6O_3$	511.34	511.4
9	OH	CH_3	*R*	$NS(O)_2CH_3$	$C_{27}H_{42}N_6O_4S$	547.31	547.2

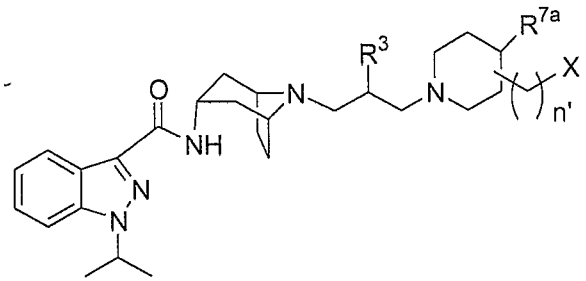
Table VII



No.	R^3	X	*	Molecular Formula	Calc'd [M+H]	Obsd [M+H]
1	OH	4-OH		$C_{26}H_{39}N_5O_3$	470.32	470.3
2	OH	4-pyrrolidin-1-yl		$C_{30}H_{46}N_6O_2$	523.38	523.3
3	OH	4-$N(CH_3)S(O)_2CH_3$		$C_{28}H_{44}N_6O_4S$	561.32	561.2
4	OH	3-$NHS(O)_2CH_3$	*S*	$C_{27}H_{42}N_6O_4S$	547.31	547.4
5	OH	3-$NHS(O)_2CH_2$-$S(O)_2CH_3$	*S*	$C_{28}H_{44}N_6O_6S_2$	625.29	625.2
6	OH	3-$C(O)NH_2$		$C_{27}H_{40}N_6O_3$	497.33	497.4
7	OH	4-$NHS(O)_2CH_3$		$C_{27}H_{42}N_6O_4S$	547.31	547.2
8	OH	3-$NHC(O)CH_3$		$C_{28}H_{42}N_6O_3$	511.34	511.4
9	OH	3-$NHC(O)OCH_3$		$C_{28}H_{42}N_6O_4$	527.34	527.4
10	OH	3-$NHC(O)N(CH_3)_2$		$C_{29}H_{45}N_7O_3$	540.37	540.4
11	OH	3-$N(CH_3)C(O)CH_3$		$C_{29}H_{44}N_6O_3$	525.36	525.4
12	OH	3-$N(CH_3)C(O)OCH_3$		$C_{29}H_{44}N_6O_4$	541.35	541.4

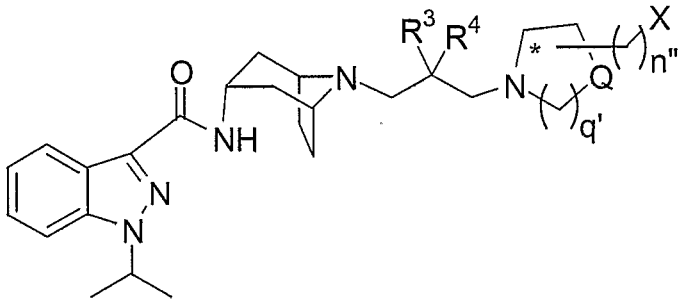
No.	R^3	X	*	Molecular Formula	Calc'd [M+H]	Obsd [M+H]
13	OH	3-$N(CH_3)S(O)_2CH_3$		$C_{28}H_{44}N_6O_4S$	561.32	561.4
14	OH	3-$OC(O)N(CH_3)_2$		$C_{29}H_{44}N_6O_4$	541.35	541.4
15	OH	3-$NHS(O)_2CH_3$		$C_{27}H_{42}N_6O_4S$	547.31	547.4
16	OH	3-$NHS(O)_2N(CH_3)_2$	*S*	$C_{28}H_{45}N_7O_4S$	576.34	576.3
17	OH	3-$NHS(O)_2CH(CH_3)_2$	*S*	$C_{29}H_{46}N_6O_4S$	575.34	575.3
18	OH	3-$NHS(O)_2CH_2CH_3$	*S*	$C_{28}H_{44}N_6O_4S$	561.32	561.2
19	$OC(O)N(CH_3)_2$	3-$C(O)N(CH_2CH_3)_2$		$C_{34}H_{53}N_7O_4$	624.43	624.4
20	$OC(O)N(CH_3)_2$	3-$C(O)NH_2$		$C_{30}H_{45}N_7O_4$	568.36	568.4
21	$OC(O)N(CH_3)_2$	4-OH		$C_{29}H_{44}N_6O_4$	541.35	541.4
22	$OC(O)N(CH_3)_2$	4-(2-oxopyrrolidin-1-yl)		$C_{33}H_{49}N_7O_4$	608.39	608.4
23	OH	3-$N(CH_3)S(O)_2N(CH_3)_2$		$C_{29}H_{47}N_7O_4S$	590.35	590.4
24	OH	3-$N(CH_3)C(O)N(CH_3)_2$		$C_{30}H_{47}N_7O_3$	554.38	554.4
25	OH	2-$C(O)NH_2$		$C_{27}H_{40}N_6O_3$	497.33	498.2
26	OH	3-$NHS(O)_2N(CH_3)_2$		$C_{28}H_{45}N_7O_4S$	576.34	576.2

Table VIII



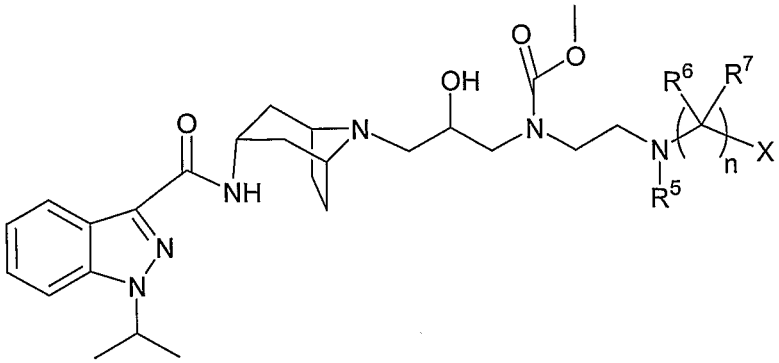
No.	R^3	$(CH_2)_{n'}$	X	R^{7a}	Molecular Formula	Calc'd [M+H]	Obsd [M+H]
1	OH	2-CH_2	OH	H	$C_{27}H_{41}N_5O_3$	484.33	484.3
2	OH	2-$(CH_2)_2$	OH	H	$C_{28}H_{43}N_5O_3$	498.35	498.3
3	OH	4-$(CH_2)_2$	OH	H	$C_{28}H_{43}N_5O_3$	498.35	498.3
4	OH	4-CH_2	$NHS(O)_2CH_3$	OH	$C_{28}H_{44}N_6O_5S$	577.32	577.2
5	OCH_3	4-CH_2	$NHS(O)_2CH_3$	H	$C_{29}H_{46}N_6O_4S$	575.35	575.2
6	OH	4-CH_2	$N(CH_3)S(O)_2CH_3$	H	$C_{29}H_{46}N_6O_4S$	575.34	575.4
7	OH	4-CH_2	$NHS(O)_2CH_3$	H	$C_{28}H_{44}N_6O_4S$	561.32	561.2
8	$OC(O)N(CH_3)_2$	4-CH_2	$NHS(O)_2CH_3$	H	$C_{31}H_{49}N_7O_5S$	632.36	632.4
9	$OC(O)N(CH_3)_2$	2-CH_2	OH	H	$C_{30}H_{46}N_6O_4$	555.37	555.4

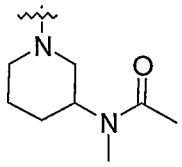
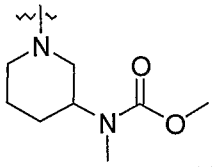
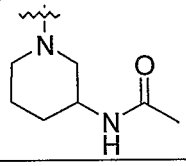
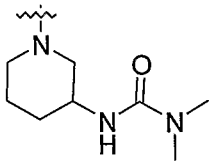
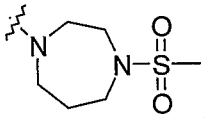
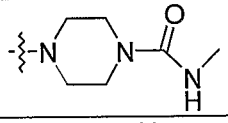
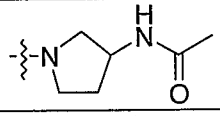
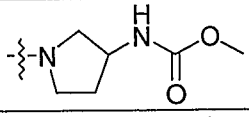
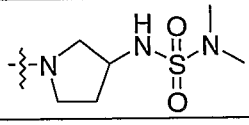
Table IX

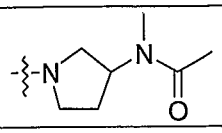
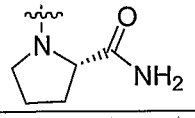
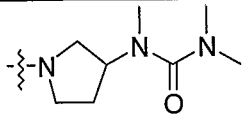
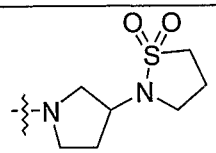


No.	R^3	R^4	q'	Q	*	$(CH_2)_{n''}$	X	Molecular Formula	Calc'd [M+H]	Obsd [M+H]
1	OH	H	2	S		bond	3-C(O)N(CH_2CH_3)$_2$	$C_{30}H_{46}N_6O_3S$	571.35	571.3
2	OH	H	1	S	*R*	bond	4-C(O)N(CH_2CH_3)$_2$	$C_{29}H_{44}N_6O_3S$	557.33	557.4
3	OH	H	2	O		2-CH_2	NHS(O)$_2CH_3$	$C_{27}H_{42}N_6O_5S$	563.30	563.2
4	OH	H	2	O		3-CH_2	N(CH_3)S(O)$_2CH_3$	$C_{28}H_{44}N_6O_5S$	577.32	577.2
5	OH	CH_3	2	O		2-CH_2	NHS(O)$_2CH_3$	$C_{28}H_{44}N_6O_5S$	577.32	577.2
6	OH	H	2	O		3-CH_2	OH	$C_{26}H_{39}N_5O_4$	486.31	486.4
7	OC(O)N(CH_3)$_2$	H	2	O		3-CH_2	OH	$C_{29}H_{44}N_6O_5$	557.35	557.4

Table X



No.	-N(R^5)(CR^{6}R^7)$_n$-X	Molecular Formula	Calc'd [M+H]	Obsd [M+H]
1		$C_{33}H_{51}N_7O_5$	626.41	626.4
2		$C_{33}H_{51}N_7O_6$	642.40	642.4
3		$C_{32}H_{49}N_7O_5$	612.39	612.4
4		$C_{33}H_{52}N_8O_5$	641.42	641.4
5		$C_{31}H_{49}N_7O_6S$	648.36	648.4
6		$C_{31}H_{48}N_8O_5$	613.38	613.4
7		$C_{31}H_{47}N_7O_5$	598.37	598.4
8		$C_{31}H_{47}N_7O_6$	614.37	614.4
9		$C_{31}H_{50}N_8O_6S$	663.37	663.4

No.	-N(R^5)(CR^{6}R^7)$_n$-X	Molecular Formula	Calc'd [M+H]	Obsd [M+H]
10		$C_{32}H_{49}N_7O_5$	612.39	612.4
11		$C_{30}H_{45}N_7O_5$	584.36	584.1
12		$C_{33}H_{52}N_8O_5$	641.42	641.4
13		$C_{32}H_{49}N_7O_6S$	660.36	660.4
14	-N(CH$_3$)(CH$_2$)$_2$NHS(O)$_2$CH$_3$	$C_{29}H_{47}N_7O_6S$	622.34	622.4

Example 18: Radioligand Binding Assay on 5-HT$_{4(c)}$ Human Receptors

a. Membrane Preparation 5-HT$_{4(c)}$

HEK-293 (human embryonic kidney) cells stably-transfected with human 5-HT$_{4(c)}$ receptor cDNA (Bmax = ~ 6.0 pmol/mg protein, as determined using [^{3}H]-GR113808 membrane radioligand binding assay) were grown in T-225 flasks in Dulbecco's Modified Eagles Medium (DMEM) containing 4,500 mg/L D-glucose and pyridoxine hydrochloride (GIBCO-Invitrogen Corp., Carlsbad CA: Cat #11965) supplemented with 10% fetal bovine serum (FBS) (GIBCO-Invitrogen Corp.: Cat #10437), 2 mM L-glutamine and (100 units) penicillin-(100 μg) streptomycin/ml (GIBCO-Invitrogen Corp.: Cat #15140) in a 5% CO_2, humidified incubator at 37 °C. Cells were grown under continuous selection pressure by the addition of 800 μg/mL geneticin (GIBCO-Invitrogen Corp.: Cat #10131) to the medium.

Cells were grown to roughly 60-80% confluency (< 35 subculture passages). At 20-22 hours prior to harvesting, cells were washed twice and fed with serum-free DMEM. All steps of the membrane preparation were performed on ice. The cell monolayer was lifted by gentle mechanical agitation and trituration with a 25 mL pipette. Cells were collected by centrifugation at 1000 rpm (5 min).

For the membrane preparation, cell pellets were resuspended in ice-cold 50 mM 4-(2-hydroxyethyl)-1-piperazineethanesulphonic acid (HEPES), pH 7.4 (membrane

preparation buffer) (40 mL/total cell yield from 30-40 T225 flasks) and homogenized using a polytron disrupter (setting 19, 2 x 10 s) on ice. The resultant homogenates were centrifuged at 1200 g for 5 min at 4°C. The pellet was discarded and the supernatant centrifuged at 40,000 g (20 min). The pellet was washed once by resuspension with membrane preparation buffer and centrifugation at 40,000 g (20 min). The final pellet was resuspended in 50 mM HEPES, pH 7.4 (assay buffer) (equivalent 1 T225 flask/1 mL). Protein concentration of the membrane suspension was determined by the method of Bradford (Bradford, 1976). Membranes were stored frozen in aliquots at -80 °C.

b. Radioligand Binding Assays

Radioligand binding assays were performed in 1.1 mL 96- deep well polypropylene assay plates (Axygen) in a total assay volume of 400 µL containing 2 µg membrane protein in 50 mM HEPES pH 7.4, containing 0.025% bovine serum albumin (BSA). Saturation binding studies for determination of K_d values of the radioligand were performed using [^{3}H]-GR113808 (Amersham Inc., Bucks, UK: Cat #TRK944; specific activity ~82 Ci/mmol) at 8-12 different concentrations ranging from 0.001 nM – 5.0 nM. Displacement assays for determination of pK_i values of compounds were performed with [^{3}H]-GR113808 at 0.15 nM and eleven different concentrations of compound ranging from 10 pM - 100 µM.

Test compounds were received as 10 mM stock solutions in DMSO and diluted to 400 µM into 50 mM HEPES pH 7.4 at 25°C, containing 0.1% BSA, and serial dilutions (1:5) then made in the same buffer. Non-specific binding was determined in the presence of 1 µM unlabeled GR113808. Assays were incubated for 60 min at room temperature, and then the binding reactions were terminated by rapid filtration over 96-well GF/B glass fiber filter plates (Packard BioScience Co., Meriden, CT) presoaked in 0.3% polyethyleneimine. Filter plates were washed three times with filtration buffer (ice-cold 50mM HEPES, pH7.4) to remove unbound radioactivity. Plates were dried, 35 µL Microscint-20 liquid scintillation fluid (Packard BioScience Co., Meriden, CT) was added to each well and plates were counted in a Packard Topcount liquid scintillation counter (Packard BioScience Co., Meriden, CT).

Binding data were analyzed by nonlinear regression analysis with the GraphPad Prism Software package (GraphPad Software, Inc., San Diego, CA) using the 3-parameter

model for one-site competition. The BOTTOM (curve minimum) was fixed to the value for nonspecific binding, as determined in the presence of 1 μM GR113808. K_i values for test compounds were calculated, in Prism, from the best-fit IC_{50} values, and the K_d value of the radioligand, using the Cheng-Prusoff equation (Cheng and Prusoff, *Biochemical Pharmacology,* **1973**, *22,* 3099-108): $K_i = IC_{50} / (1 + [L]/K_d)$ where [L] = concentration [^{3}H]-GR113808. Results are expressed as the negative decadic logarithm of the K_i values, pK_i.

Test compounds having a higher pK_i value in this assay have a higher binding affinity for the 5-HT_4 receptor. The compounds of the invention which were tested in this assay had a pK_i value ranging from about 6.9 to about 9.5, typically ranging from about 7.0 to about 8.6.

Example 19: Radioligand Binding Assay on 5-HT_{3A} Human Receptors: Determination of Receptor Subtype Selectivity

a. Membrane Preparation 5-HT_{3A}

HEK-293 (human embryonic kidney) cells stably-transfected with human 5-HT_{3A} receptor cDNA were obtained from Dr. Michael Bruess (University of Bonn, GDR) (Bmax = ~ 9.0 pmol/mg protein, as determined using [^{3}H]-GR65630 membrane radioligand binding assay). Cells were grown in T-225 flasks or cell factories in 50% Dulbecco's Modified Eagles Medium (DMEM) (GIBCO-Invitrogen Corp., Carlsbad, CA: Cat #11965) and 50% Ham's F12 (GIBCO-Invitrogen Corp.: Cat #11765) supplemented with 10% heat inactivated fetal bovine serum (FBS) (Hyclone, Logan, UT: Cat #SH30070.03) and (50 units) penicillin-(50 μg) streptomycin/ml (GIBCO-Invitrogen Corp.: Cat #15140) in a 5% CO_2, humidified incubator at 37 °C.

Cells were grown to roughly 70-80% confluency (< 35 subculture passages). All steps of the membrane preparation were performed on ice. To harvest the cells, the media was aspirated and cells were rinsed with Ca^{2+}, Mg^{2+}-free Dulbecco's phosphate buffered saline (dPBS). The cell monolayer was lifted by gentle mechanical agitation. Cells were collected by centrifugation at 1000 rpm (5 min). Subsequent steps of the membrane preparation followed the protocol described above for the membranes expressing 5-$HT_{4(c)}$ receptors.

b. Radioligand Binding Assays

Radioligand binding assays were performed in 96-well polypropylene assay plates in a total assay volume of 200 µL containing 1.5-2 µg membrane protein in 50 mM HEPES pH 7.4, containing 0.025% BSA assay buffer. Saturation binding studies for determination of K_d values of the radioligand were performed using [^{3}H]-GR65630 (PerkinElmer Life Sciences Inc., Boston, MA: Cat #NET1011, specific activity ~85 Ci/mmol) at twelve different concentrations ranging from 0.005 nM to 20 nM. Displacement assays for determination of pK_i values of compounds were performed with [^{3}H]-GR65630 at 0.50 nM and eleven different concentrations of compound ranging from 10 pM to 100 µM. Compounds were received as 10 mM stock solutions in DMSO (see section 3.1), diluted to 400 µM into 50 mM HEPES pH 7.4 at 25°C, containing 0.1% BSA, and serial (1:5) dilutions then made in the same buffer. Non-specific binding was determined in the presence of 10 µM unlabeled MDL72222. Assays were incubated for 60 min at room temperature, then the binding reactions were terminated by rapid filtration over 96-well GF/B glass fiber filter plates (Packard BioScience Co., Meriden, CT) presoaked in 0.3% polyethyleneimine. Filter plates were washed three times with filtration buffer (ice-cold 50mM HEPES, pH7.4) to remove unbound radioactivity. Plates were dried, 35 µL Microscint-20 liquid scintillation fluid (Packard BioScience Co., Meriden, CT) was added to each well and plates were counted in a Packard Topcount liquid scintillation counter (Packard BioScience Co., Meriden, CT).

Binding data were analyzed using the non-linear regression procedure described above to determine K_i values. The BOTTOM (curve minimum) was fixed to the value for nonspecific binding, as determined in the presence of 10 µM MDL72222. The quantity [L] in the Cheng-Prusoff equation was defined as the concentration [^{3}H]-GR65630.

Selectivity for the 5-HT_4 receptor subtype with respect to the 5-HT_3 receptor subtype was calculated as the ratio K_i(5-HT_{3A})/K_i(5-$HT_{4(c)}$). The compounds of the invention which were tested in this assay typically had a 5-HT_4/5-HT_3 receptor subtype selectivity ranging from about 10 to about 40,000, more typically, between from about 100 to about 4000.

Example 20: Whole-cell cAMP Accumulation Flashplate Assay with HEK-293 cells expressing human 5-HT$_{4(c)}$ Receptors

In this assay, the functional potency of a test compound was determined by measuring the amount of cyclic AMP produced when HEK-293 cells expressing 5-HT$_4$ receptors were contacted with different concentrations of test compound.

a. Cell Culture

HEK-293 (human embryonic kidney) cells stably-transfected with cloned human 5-HT$_{4(c)}$ receptor cDNA were prepared expressing the receptor at two different densities: (1) at a density of about 0.5-0.6 pmol/mg protein, as determined using a [^{3}H]-GR113808 membrane radioligand binding assay, and (2) at a density of about 6.0 pmol/mg protein. The cells were grown in T-225 flasks in Dulbecco's Modified Eagles Medium (DMEM) containing 4,500 mg/L D-glucose (GIBCO-Invitrogen Corp.: Cat #11965) supplemented with 10% fetal bovine serum (FBS) (GIBCO-Invitrogen Corp.: Cat #10437) and (100 units) penicillin-(100 μg) streptomycin/ml (GIBCO-Invitrogen Corp.: Cat #15140) in a 5% CO_2, humidified incubator at 37°C. Cells were grown under continuous selection pressure by the addition of geneticin (800 μg/mL: GIBCO-Invitrogen Corp.: Cat #10131) to the medium.

b. Cell Preparation

Cells were grown to roughly 60-80% confluency. Twenty to twenty-two hours prior to assay, cells were washed twice, and fed, with serum-free DMEM containing 4,500 mg/L D-glucose (GIBCO-Invitrogen Corp.: Cat #11965). To harvest the cells, the media was aspirated and 10 mL Versene (GIBCO-Invitrogen Corp.: Cat #15040) was added to each T-225 flask. Cells were incubated for 5 min at RT and then dislodged from the flask by mechanical agitation. The cell suspension was transferred to a centrifuge tube containing an equal volume of pre-warmed (37°C) dPBS and centrifuged for 5 min at 1000 rpm. The supernatant was discarded and the pellet was re-suspended in pre-warmed (37°C) stimulation buffer (10mL equivalent per 2-3 T-225 flasks). This time was noted and marked as time zero. The cells were counted with a Coulter counter (count above 8 μm, flask yield was 1-2 x 10^7 cells/flask). Cells were resuspended at a concentration of 5 x 10^5 cells/ml in pre-warmed (37°C) stimulation buffer (as provided in the flashplate kit) and preincubated at 37°C for 10 min.

cAMP assays were performed in a radioimmunoassay format using the Flashplate Adenylyl Cyclase Activation Assay System with ^{125}I-cAMP (SMP004B, PerkinElmer Life Sciences Inc., Boston, MA), according to the manufacturer's instructions.

Cells were grown and prepared as described above. Final cell concentrations in the assay were 25 x 10^3 cells/well and the final assay volume was 100 µL. Test compounds were received as 10 mM stock solutions in DMSO, diluted to 400 µM into 50 mM HEPES pH 7.4 at 25°C, containing 0.1% BSA, and serial (1:5) dilutions then made in the same buffer. Cyclic AMP accumulation assays were performed with 11 different concentrations of compound ranging from 10 pM to 100 µM (final assay concentrations). A 5-HT concentration-response curve (10 pM to 100 µM) was included on every plate. The cells were incubated, with shaking, at 37°C for 15 min and the reaction terminated by addition of 100 µl of ice-cold detection buffer (as provided in the flashplate kit) to each well. The plates were sealed and incubated at 4°C overnight. Bound radioactivity was quantified by scintillation proximity spectroscopy using the Topcount (Packard BioScience Co., Meriden, CT).

The amount of cAMP produced per mL of reaction was extrapolated from the cAMP standard curve, according to the instructions provided in the manufacturer's user manual. Data were analyzed by nonlinear regression analysis with the GraphPad Prism Software package using the 3-parameter sigmoidal dose-response model (slope constrained to unity). Potency data are reported as pEC_{50} values, the negative decadic logarithm of the EC_{50} value, where EC_{50} is the effective concentration for a 50 % maximal response.

Test compounds exhibiting a higher pEC_{50} value in this assay have a higher potency for agonizing the 5-HT_4 receptor. The compounds of the invention which were tested in this assay, for example, in the cell line (1) having a density of about 0.5-0.6 pmol/mg protein, had a pEC_{50} value ranging from about 6.5 to about 9.0, typically ranging from about 7.5 to about 8.5.

Example 21: *In vitro* Model of Oral Bioavailability: Caco-2 Permeation Assay

The Caco-2 permeation assay was performed to model the ability of test compounds to pass through the intestine and get into the blood stream after oral administration. The rate at which test compounds in solution permeate a cell monolayer

designed to mimic the tight junction of human small intestinal monolayers was determined.

Caco-2 (colon, adenocarcinoma; human) cells were obtained from ATCC (American Type Culture Collection; Rockville, MD). For the permeation study, cells were seeded at a density of 63,000 cells/cm^2 on pre-wetted transwells polycarbonate filters (Costar; Cambridge, MA). A cell monolayer was formed after 21 days in culture. Following cell culture in the transwell plate, the membrane containing the cell monolayer was detached from the transwell plate and inserted into the diffusion chamber (Costar; Cambridge, MA). The diffusion chamber was inserted into the heating block which was equipped with circulating external, thermostatically regulated 37 °C water for temperature control. The air manifold delivered 95% O_2/5% CO_2 to each half of a diffusion chamber and created a laminar flow pattern across the cell monolayer, which was effective in reducing the unstirred boundary layer.

The permeation study was performed with test compound concentrations at 100 μM and with ^{14}C-mannitol to monitor the integrity of the monolayer. All experiments were conducted at 37 °C for 60 min. Samples were taken at 0, 30 and 60 min from both the donor and receiver sides of the chamber. Samples were analyzed by HPLC or liquid scintillation counting for test compound and mannitol concentrations. The permeation coefficient (K_p) in cm/sec was calculated.

In this assay, a K_p value greater than about 10 x 10^{-6} cm/sec is considered indicative of favorable bioavailability. The compounds of the invention that were tested in this assay typically exhibited K_p values of between about 5 x 10^{-6} cm/sec and about 50 x 10^{-6} cm/sec, more typically between about 15 x 10^{-6} cm/sec and about 40 x 10^{-6} cm/sec.

Example 22: Pharmacokinetic Study in the Rat

Aqueous solution formulations of test compounds were prepared in 0.1 % lactic acid at a pH of between about 5 and about 6. Male Sprague-Dawley rats (CD strain, Charles River Laboratories, Wilmington, MA) were dosed with test compounds via intravenous administration (IV) at a dose of 2.5 mg/kg or by oral gavage (PO) at a dose of 5 mg/kg. The dosing volume was 1 mL/kg for IV and 2 mL/kg for PO administration. Serial blood samples were collected from animals pre-dose, and at 2 (IV only), 5, 15, and 30 min, and at 1, 2, 4, 8, and 24 hours post-dose. Concentrations of test compounds in blood plasma were determined by liquid chromatography-mass spectrometry analysis

(LC-MS/MS) (MDS SCIEX, API 4000, Applied Biosystems, Foster City, CA) with a lower limit of quantitation of 1 ng/mL.

Standard pharmacokinetic parameters were assessed by non-compartmental analysis (Model 201 for IV and Model 200 for PO) using WinNonlin (Version 4.0.1, Pharsight, Mountain View, CA). The maximum in the curve of test compound concentration in blood plasma vs. time is denoted C_{max}. The area under the concentration vs. time curve from the time of dosing to the last measurable concentration (AUC(0-t)) was calculated by the linear trapezoidal rule. Oral bioavailability (F(%)), i.e. the dose-normalized ratio of AUC(0-t) for PO administration to AUC(0-t) for IV administration, was calculated as:

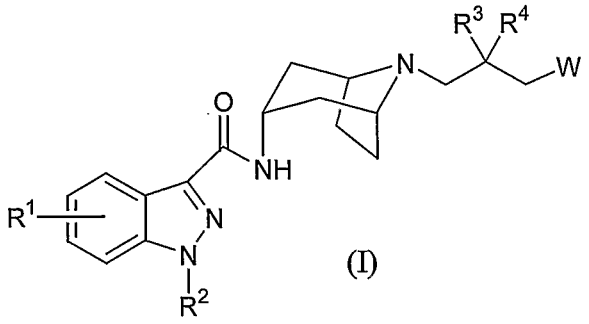
$$F(\%) = AUC_{PO}/AUC_{IV} \times Dose_{IV}/Dose_{PO} \times 100\%$$

Test compounds which exhibit larger values of the parameters C_{max}, AUC(0-t), and F(%) in this assay are expected to have greater bioavailability when administered orally. The compounds of the invention that were tested in this assay typically had C_{max} values ranging from about 0.05 to about 0.45 μg/mL, more typically ranging from about 0.10 to about 0.35 μg/mL; and AUC(0-t) values ranging from about 0.05 to about 0.9 μg·hr/mL, typically ranging from about 0.25 to about 0.8 μg·hr/mL. By way of example, the compound of Example 2 had a C_{max} value of 0.055 μg/mL, an AUC(0-t) value of 0.427 μg·hr/mL and oral bioavailability (F(%)) in the rat model of about 30 %.

While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto. Additionally, all publications, patents, and patent documents cited hereinabove are incorporated by reference herein in full, as though individually incorporated by reference.

WHAT IS CLAIMED IS:

1. A compound of formula (I):



(I)

wherein:

R^1 is hydrogen, halo, hydroxy, C_{1-4}alkyl, or C_{1-4}alkoxy;

R^2 is C_{3-4}alkyl, or C_{3-6}cycloalkyl;

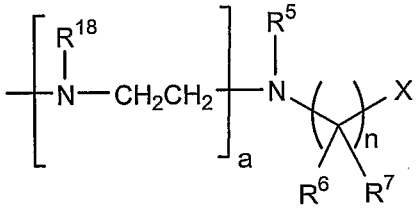
R^3 is hydroxy, C_{1-3}alkoxy, hydroxy-substituted C_{1-4}alkyl, or $-OC(O)NR^aR^b$;

R^4 is hydrogen or C_{1-4}alkyl;

W is selected from

(a) Y, wherein Y is selected from $-N(R^{8a})C(O)R^9$, $-N(R^{8a})S(O)_2R^{10}$, $-N(R^{8a})C(O)OR^{12}$, $-N(R^{8a})C(O)NR^{13}R^{14}$, and $-N(R^{8a})S(O)_2NR^{13}R^{14}$; and

(b) a moiety of formula (b):



(b);

wherein:

X is selected from $-N(R^8)C(O)R^9$, $-N(R^8)S(O)_2R^{10}$, $-S(R^{11})O_2$, $-N(R^8)C(O)OR^{12}$, $-N(R^8)C(O)NR^{13}R^{14}$, $-N(R^8)S(O)_2NR^{13}R^{14}$, $-C(O)NR^{13}R^{14}$, $-OC(O)NR^{13}R^{14}$, $-C(O)OR^{12}$, $-OR^{15}$, $-NR^8R^{16}$, cyano, $-SR^{15}$, CF_3, pyridinyl, pyrrolyl, pyrimidinyl, thiomorpholinyl, thiazolidinyl, 1,1-dioxo isothiazolidinyl, imidazolyl, indolyl, tetrahydrofuranyl, pyrrolidinyl and piperidinyl, wherein pyrrolidinyl is optionally substituted with oxo and piperidinyl is optionally substituted with 1 to 3 halo;

R^5 is hydrogen or C_{1-4}alkyl, wherein C_{1-4}alkyl is optionally substituted with hydroxy, C_{1-3}alkoxy, or cyano;

R^6 and R^7 at each occurrence are independently selected from hydrogen, hydroxy, halo, cyano, and C_{1-4}alkyl, wherein C_{1-4}alkyl is optionally substituted with 1 to 2 substituents selected from hydroxy, C_{1-3}alkoxy, halo, and cyano;

R^8 and R^{8a} are hydrogen or C_{1-4}alkyl;

or R^5 and R^8, R^5 and R^6, or R^6 and R^8 taken together form C_{2-5}alkylenyl, wherein C_{2-5}alkylenyl is optionally substituted with hydroxy, halo, hydroxy-substituted C_{1-3}alkyl, or C_{1-3}alkoxy;

or R^3 and R^5 or R^3 and R^{8a} taken together form $-OCH_2CH_2-$;

or R^5 and R^6 taken together form $-(CH_2)_q-Q-(CH_2)_q$, wherein Q is oxygen or sulfur and *q* is independently 0, 1, or 2;

or R^7 and X taken together form -NHC(O)NHC(O)- or -C(O)NHC(O)NH-;

R^9 is selected from hydrogen, furanyl, tetrahydrofuranyl, pyridinyl, or C_{1-4}alkyl, wherein C_{1-4}alkyl is optionally substituted with hydroxy or with from 1 to 3 halo;

R^{10} is selected from hydrogen, C_{1-4}alkyl, pyridinyl, and imidazolyl, wherein C_{1-4}alkyl is optionally substituted with $-S(O)_2R^c$, C_{3-6}cycloalkyl, or with from 1 to 3 halo, and imidazolyl is optionally substituted with C_{1-3}alkyl;

or R^8 and R^{10} taken together form C_3alkylenyl;

R^{11} is hydrogen, $-NR^aR^b$, or C_{1-4}alkyl, where C_{1-4}alkyl is optionally substituted with from 1 to 3 halo;

or R^5 and R^{11} or R^6 and R^{11} taken together form C_{2-5}alkylenyl;

R^{12} is C_{1-4}alkyl;

R^{13} and R^{14} are independently hydrogen or C_{1-4}alkyl;

R^{15} is hydrogen or C_{1-4}alkyl, wherein C_{1-4}alkyl is optionally substituted with hydroxy;

or when X is $-SR^{15}$, R^5 and R^{15} taken together form C_{1-4}alkylenyl;

R^{16} is $-(CH_2)_r-R^{17}$, wherein *r* is 0, 1, 2, or 3; and R^{17} is selected from hydrogen, hydroxy, C_{1-3}alkyl, C_{1-3}alkoxy, $-C(O)NR^aR^b$, -C(O)-morpholinyl, pyridinyl, pyrrolyl, pyrimidinyl, morpholinyl, and tetrahydrofuranyl, wherein C_{1-3}alkoxy is optionally substituted with hydroxy; provided that when *r* is 0, R^{17} is selected from hydrogen, C_{1-3}alkyl, pyridinyl, and pyrimidinyl; and when *r* is 1, R^{17} is hydrogen or R^{17} forms a carbon-carbon bond with the $-(CH_2)_r-$ carbon atom;

R^{18} is $-C(O)O-C_{1-3}$alkyl, $-S(O)_2-C_{1-3}$alkyl, or $-C(O)-C_{1-3}$alkyl;

R^a, R^b, and R^c are independently hydrogen or C_{1-3}alkyl;

a is 0 or 1; and

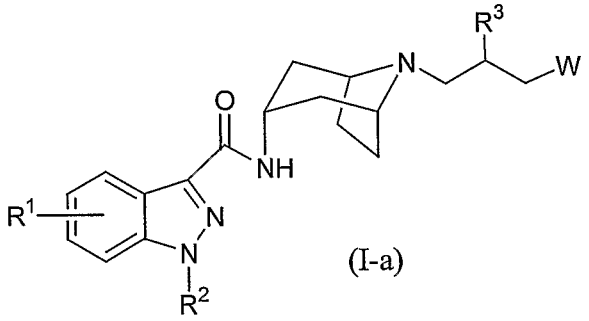
n is an integer of 1, 2, 3, 4, or 5; provided that when *n* is 1, X is -SR^{15}, or X forms a carbon-carbon bond with the carbon atom bearing the substituents R^6 and R^7;

or a pharmaceutically-acceptable salt or solvate or stereoisomer thereof.

2. The compound of Claim 1 wherein R^1 is hydrogen or halo, R^2 is isopropyl or C_{4-5}cycloalkyl, and R^4 is hydrogen.

3. The compound of of Claim 1 or 2 wherein R^3 is hydroxy, methoxy, hydroxymethyl, -$OC(O)NHCH_3$, or -$OC(O)N(CH_3)_2$, or R^3 and R^5 or R^3 and R^{8a} taken together form -OCH_2CH_2-.

4. The compound of Claim 1, which is a compound of formula (I-a):



(I-a)

wherein:

R^1 is hydrogen, halo or C_{1-4}alkyl;

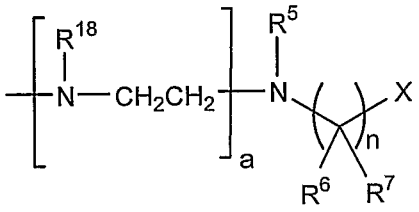
R^2 is isopropyl or C_{4-5}cycloalkyl;

R^3 is hydroxy, C_{1-3}alkoxy, or $OC(O)NR^aR^b$;

W is selected from

(a) Y, wherein Y is selected from -$N(R^{8a})C(O)R^9$, -$N(R^{8a})S(O)_2R^{10}$, -$N(R^{8a})C(O)OR^{12}$, -$N(R^{8a})C(O)NR^{13}R^{14}$, and -$N(R^{8a})S(O)_2NR^{13}R^{14}$; and

(b) a moiety of formula (b):



(b)

wherein

X is selected from $-N(R^8)C(O)R^9$, $-N(R^8)S(O)_2R^{10}$, $-S(R^{11})O_2$, $-N(R^8)C(O)OR^{12}$, $-N(R^8)C(O)NR^{13}R^{14}$, $-N(R^8)S(O)_2NR^{13}R^{14}$, $-C(O)NR^{13}R^{14}$, $-OC(O)NR^{13}R^{14}$, $-C(O)OR^{12}$, $-OR^{15}$, $-NR^8R^{16}$, cyano, $-SR^{15}$, CF_3, pyridinyl, pyrrolyl, 1,1-dioxoisothiazolidinyl, imidazolyl, and pyrrolidinyl, wherein pyrrolidinyl is optionally substituted with oxo;

R^5 is hydrogen, C_{1-3}alkyl, or C_{1-3}alkyl substituted at the terminal position with hydroxy;

R^6 and R^7 at each occurrence are independently hydrogen, hydroxy, halo or cyano;

R^8 and R^{8a} are hydrogen or C_{1-3}alkyl;

or R^5 and R^8 or R^5 and R^6 together form a C_{2-5}alkylene;

or R^3 and R^5 or R^3 and R^{8a} taken together are $-OCH_2CH_2-$;

R^9 is hydrogen, tetrahydrofuranyl, pyridinyl, or C_{1-3}alkyl;

R^{10} is C_{1-3}alkyl, wherein C_{1-3}alkyl is optionally substituted with $-S(O)_2C_{1-3}$alkyl, or with from 1 to 3 halo;

R^{11} is hydrogen, $-NR^aR^b$, or C_{1-3}alkyl, where C_{1-3}alkyl is optionally substituted with from 1 to 3 halo;

or R^5 and R^{11} or R^6 and R^{11} taken together form C_{2-5}alkylenyl;

R^{12} is C_{1-3}alkyl;

R^{13}, R^{14}, and R^{15} are independently hydrogen or C_{1-3}alkyl;

R^{16} is $-CH_2-C(O)NR^aR^b$, $-CH_2-C(O)$-morpholinyl, $-CH_2$-pyridinyl, $-CH_2$-pyrimidinyl, or $-CH_2$-tetrahydrofuranyl;

R^{18} is $-C(O)OCH_3$, $-S(O)_2CH_3$, or $-C(O)CH_3$;

R^a and R^b are independently hydrogen or C_{1-3}alkyl;

a is 0 or 1; and

n is an integer of 1, 2, or 3; provided that when *n* is 1, X is $-SR^{15}$, or X forms a carbon-carbon bond with the carbon atom bearing the substituents R^6 and R^7;

or a pharmaceutically-acceptable salt or solvate or stereoisomer thereof.

5. The compound of any one of Claims 1 to 4 wherein W is selected from:

(a) Y, wherein Y is selected from $-N(R^{8a})C(O)R^9$, $-N(R^{8a})S(O)_2R^{10}$, and $-N(R^{8a})C(O)NR^{13}R^{14}$; and

(b) a moiety of formula (b) wherein X is selected from $-N(R^8)C(O)R^9$, $-N(R^8)S(O)_2R^{10}$, $-N(R^8)C(O)OR^{12}$, $-N(R^8)C(O)NR^{13}R^{14}$, $-N(R^8)S(O)_2NR^{13}R^{14}$, $-C(O)NR^{13}R^{14}$, $-OR^{15}$, and cyano.

6. The compound of any one of Claims 1 to 5 wherein W is selected from Y, wherein R^{8a} is hydrogen or methyl; R^9 is hydrogen, tetrahydrofuranyl, pyridinyl, or methyl; R^{10} and R^{12} are methyl or ethyl; and R^{13} and R^{14} are independently hydrogen or methyl.

7. The compound of any one of Claims 1 to 5 wherein W is a moiety of formula (b) wherein:

(i) X is cyano; or

(ii) *a* is 0, *n* is 2, R^6 and R^7 are hydrogen, R^5 and R^8 taken together form C_2alkylenyl, and X is selected from $-N(R^8)C(O)R^9$, $-N(R^8)S(O)_2R^{10}$, and $-N(R^8)C(O)NR^{13}R^{14}$.

8. The compound of any one of Claims 1 to 4 wherein W is selected from $-NHC(O)H$, $-N(CH_3)C(O)H$, $-NHC(O)CH_3$, $-N(CH_3)C(O)CH_3$,$-N(CH_3)S(O)_2CH_3$, $-N(CH_3)C(O)NHCH_3$, $-N(CH_3)CH_2CH_2CN$, 1-methanesulfonylpiperazin-4-yl, 1-dimethylaminocarbonylpiperazin-4-yl, 1-(tetrahydrofuran-2-yl)carbonylpiperazin-4-yl, 3-(methoxycarbonylamino)pyrrolidin-1-yl, and 2-(methoxymethylene)pyrrolidin-1-yl.

9. The compound of Claim 1 wherein the compound is selected from the group consisting of:

1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[2-hydroxy-3-((*S*)-2-methoxymethylpyrrolidin-1-yl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide;

1-isopropyl-1*H*-indazole-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{3-[(2-cyano-ethyl)methylamino]-2-hydroxypropyl}-8-azabicyclo[3.2.1]oct-3-yl)amide;

1-isopropyl-1*H*-indazole-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{2-hydroxy-3-[4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl]propyl}-8-azabicyclo[3.2.1]oct-3-yl)-amide;

1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[2-hydroxy-3-(4-methanesulfonylpiperazin-1-yl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide;

1-isopropyl-1*H*-indazole-3-carboxylic acid [(1*S*,3*R*,5*R*)-8-(4-carbamoylmethylmorpholin-2-ylmethyl)-8-azabicyclo[3.2.1]oct-3-yl]amide;

1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[3-(4-dimethylcarbamoylpiperazin-1-yl)-2-hydroxypropyl]-8-azabicyclo[3.2.1]oct-3-yl}amide;

1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[3-(4-methanesulfonylpiperazin-1-yl)-2-methoxypropyl]-8-azabicyclo[3.2.1]oct-3-yl}amide;

1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[(*R*)-2-hydroxy-3-(4-methanesulfonylpiperazin-1-yl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide;

[1-(2-hydroxy-3-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-1*H*-indazole-3-carbonyl)-amino]-8-azabicyclo[3.2.1]oct-8-yl}propyl)pyrrolidin-3-yl]carbamic acid methyl ester;

1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[(*S*)-2-hydroxy-3-(4-methanesulfonylpiperazin-1-yl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide;

1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[2-hydroxy-3-(methanesulfonylmethylamino)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide;

1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[3-(acetyl-methylamino)-2-hydroxypropyl]-8-azabicyclo[3.2.1]oct-3-yl}amide;

1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[3-(formyl-methylamino)-2-hydroxypropyl]-8-azabicyclo[3.2.1]oct-3-yl}amide;

1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[3-(1,3-dimethylureido)-2-hydroxypropyl]-8-azabicyclo[3.2.1]oct-3-yl}amide;

1-isopropyl-1*H*-indazole-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{2-hydroxy-3-[(pyridine-4-carbonyl)amino]propyl}-8-azabicyclo[3.2.1]oct-3-yl)amide;

1-isopropyl-1*H*-indazole-3-carboxylic acid [(1*S*,3*R*,5*R*)-8-(3-formylamino-2-hydroxypropyl)-8-azabicyclo[3.2.1]oct-3-yl]-amide; and

1-isopropyl-1*H*-indazole-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[(*R*)-2-hydroxy-3-(methanesulfonylmethylamino)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide; and

pharmaceutically-acceptable salts and solvates and stereoisomers thereof.

10. A pharmaceutical composition comprising a therapeutically effective amount of the compound of any one of Claims 1 to 9 and a pharmaceutically acceptable carrier.

11. A compound as claimed in any one of Claims 1 to 9 for use in therapy.

12. Use of a compound of any one of Claims 1 to 9 for manufacture of a medicament.

13. The use of Claim 12 wherein the medicament is for the treatment of a medical condition in a mammal associated with 5-HT_4 receptor activity.

14. The use of Claim 13 wherein the disease or condition is a disorder of reduced motility of the gastrointestinal tract.

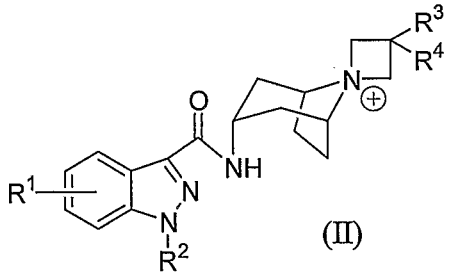
15. A method of treating a mammal having a medical condition associated with 5-HT_4 receptor activity, the method comprising administering to the mammal, a therapeutically effective amount of a pharmaceutical composition comprising a pharmaceutically-acceptable carrier and a compound of any one of Claims 1 to 9.

16. The method of Claim 15 wherein the medical condition is selected from the group consisting of irritable bowel syndrome, chronic constipation, functional dyspepsia, delayed gastric emptying, gastroesophageal reflux disease, gastroparesis, post-operative ileus, intestinal pseudo-obstruction, and drug-induced delayed transit.

17. A method of treating a disorder of reduced motility of the gastrointestinal tract in a mammal, the method comprising administering to the mammal, a therapeutically effective amount of a pharmaceutical composition comprising a pharmaceutically-acceptable carrier and a compound of any one of Claims 1 to 9.

18. A process for preparing a compound of formula (I), wherein R^1, R^2, R^3, R^4, and W are defined as in Claim 1, or a salt or stereoisomer thereof, the process comprising:

(a) reacting a compound of formula (II):



(II)

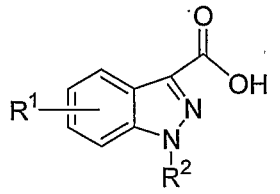
with a compound of formula (III):

H–W

(III) ;

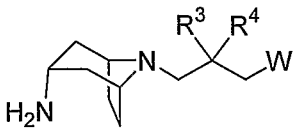
or

(b) reacting a compound of formula (IV) :



(IV)

with a compound of formula (V):

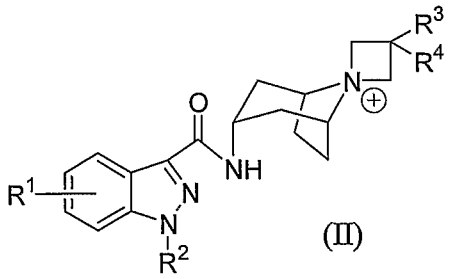


(V) ;

to provide a compound of formula (I), or a salt or stereoisomer thereof.

19. A process for preparing a compound of formula (I), wherein R^3 is hydroxy and R^1, R^2, R^4, and W are defined as in Claim 1, or a salt or stereoisomer thereof, the process comprising:

(a) reacting a compound of formula (II):



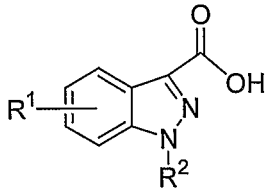
(II)

with a compound of formula (III):

H-W

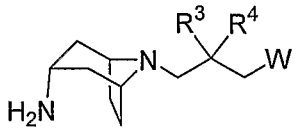
(III) ;

(b) reacting a compound of formula (IV) :



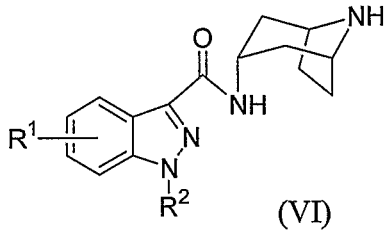
(IV)

with a compound of formula (V):



(V) ;

(c) reacting a compound of formula (VI):



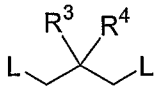
(VI)

or a salt thereof, with a compound of formula (III):



(III)

and a compound of formula (VII):

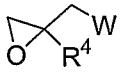


(VII)

wherein L is a leaving group;

or

(d) reacting a compound of formula (VI) with a compound of formula (VIII):

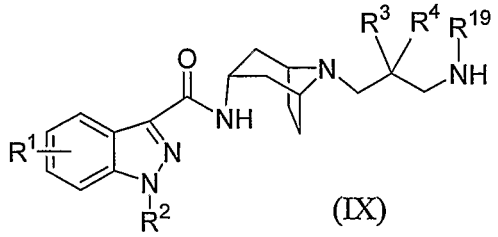


(VIII) ;

to provide a compound of formula (I), or a salt or stereoisomer thereof.

20. A process for preparing a compound of formula (I), wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{8a}, R^9, R^{10}, R^{12}, R^{13}, R^{14}, R^{18}, *a*, *n*, W and X are as defined in Claim 1; provided that when *a* is 0, R^5 is hydrogen or C_{1-4}alkyl, wherein C_{1-4}alkyl is optionally substituted with hydroxy, C_{1-3}alkoxy, or cyano, or R^3 and R^5 taken together form $-OCH_2CH_2-$; or a salt or stereoisomer thereof, the process comprising:

reacting a compound of formula (IX):



(IX)

wherein R^{19} is R^5, R^{8a}, or R^{18};

with a compound of formula (X):

L—W"

(X)

wherein:

L is a leaving group; and

(a) when R^{19} is R^{8a}, W" is selected from $-C(O)R^9$, $-S(O)_2R^{10}$, $-C(O)OR^{12}$, $-C(O)NR^{13}R^{14}$, and $-S(O)_2NR^{13}R^{14}$;

(b) when R^{19} is R^{18}, W" is $-(CH_2)_2-N(R^5)(CR^6R^7)_n-X$; and

(c) when *a* is 0, R^{19} is R^5, W" is $-(CR^6R^7)_n-X$, and R^5 is hydrogen or C_{1-4}alkyl, wherein C_{1-4}alkyl is optionally substituted with hydroxy, C_{1-3}alkoxy, or cyano, or R^3 and R^5 taken together form $-OCH_2CH_2-$;

to provide a compound of formula (I).

21. The product prepared by the process of any one of Claims 18, 19 and 20.

22. A method of studying a biological system or sample comprising a 5-HT_4 receptor, the method comprising:

(a) contacting the biological system or sample with a compound of any one of Claims 1 to 9; and

(b) determining the effects caused by the compound on the biological system