QUINOLINONE COMPOUNDS AS 5-HT$_4$ RECEPTOR AGONISTS

BACKGROUND OF THE INVENTION

Field of the Invention

The invention is directed to quinolinone-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 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.) For example, 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.

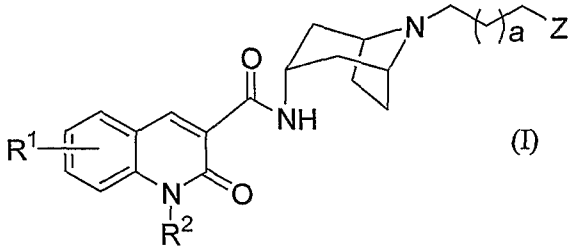
Despite the potential broad utility of pharmaceutical agents modulating 5-HT_4 receptor activity, few 5-HT_4 receptor agonist compounds are in clinical use at present. One agent, cisapride, that was utilized extensively for treatment of motility disorders of the gastrointestinal tract was withdrawn from the market, reportedly due to cardiac side effects. Late stage clinical trials of another agent, prucalopride, have been suspended.

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.

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



(I)

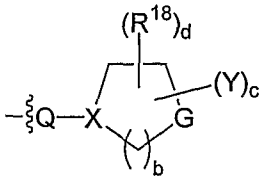
wherein

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

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

a is 0 or 1;

Z is a moiety of formula (a):



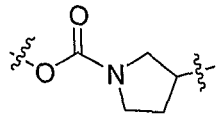
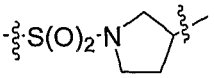
(a)

wherein:

b is 1, 2 or 3;

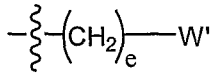
d is 0 or 1;

X is carbon and Q is selected from -A-, $-A(CH_2)_2N(R^4)-$, and $-S(O)_2(CH_2)_2N(R^4)-$;

or X is nitrogen and Q is selected from $-S(O)_2CH_2C(O)-$, $-SCH_2C(O)-$, -OC(O)-, $-S(O)_2-$, $-S(O)_2(CH_2)_2-$, $-A(CH_2)_2-$,  , and  ;

G is W and *c* is 0, wherein W is selected from $-N\{C(O)R^9\}-$, $-N\{S(O)_2R^{10}\}-$, $-N\{C(O)OR^{12}\}-$, $-N\{C(O)NR^{13}R^{14}\}-$, $-N\{S(O)_2NR^{13}R^{14}\}-$, $-N\{R^{16}\}-$, $-S(O)_2-$, -O-, and -S-; provided that when G is W, *c* is 0, and *b* is 1, then X is carbon;

or G is carbon, *c* is 1, and Y is a moiety of formula (b):



(b)

wherein:

e is 0 or 1;

W' is selected from $-N(R^8)C(O)R^9$, $-N(R^8)S(O)_2R^{10}$, $-S(R^{11})(O)_2$, $-N(R^8)C(O)OR^{12}$, $-N(R^8)C(O)NR^{13}R^{14}$, $-N(R^8)S(O)_2NR^{13}R^{14}$, $-C(O)NR^{13}R^{14}$, $-OC(O)NR^{13}R^{14}$, $-C(O)OR^{12}$, $-OR^{15}$, and $-N(R^8)R^{16}$; provided that when X is nitrogen, *e* is 0, and W' is attached to a carbon atom bonded to X, then W' is $-C(O)NR^{13}R^{14}$ or $-C(O)OR^{12}$;

A is selected from $-S(O)_2CH_2C(O)N(R^3)-$, $-N\{C(O)R^5\}-$, $-N\{C(O)NR^{6a}R^{6b}\}-$, $-N\{S(O)_2C_{1-3}alkyl\}-$, $-N\{S(O)_2NR^{6a}R^{6b}\}-$, $-S(O)_2N(R^{7a})-$, and $-OC(O)N(R^{7b})-$;

R^3 and R^4 are independently C_{1-4}alkyl;

R^5 is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, C_{4-6}cycloalkyl, or pyrimidin-4-yl;

R^{6a} and R^{6b} are independently hydrogen, C_{5-6}cycloalkyl, or C_{1-4}alkyl, wherein C_{1-4}alkyl is optionally substituted with hydroxy, C_{1-3}alkoxy, or cyano;

R^{7a} and R^{7b} are independently hydrogen or C_{1-4}alkyl;

R^8 is hydrogen or C_{1-4}alkyl;

R^9 is hydrogen, furanyl, tetrahydrofuranyl, pyridinyl, or C_{1-4}alkyl;

R^{10} is C_{1-4}alkyl, optionally substituted with $S(O)_2C_{1-3}$alkyl, or with from 1 to 3 halo;

R^{11} is $-NR^{13}R^{14}$, or C_{1-4}alkyl;

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

R^{13}, R^{14}, and R^{15} are independently hydrogen or C_{1-4}alkyl;

R^{16} is $-(CH_2)_r-R^{17}$, wherein *r* is 0, 1, 2, or 3;

R^{17} is hydrogen, hydroxy, cyano, C_{1-3}alkyl, C_{1-3}alkoxy, $-C(O)NR^{13}R^{14}$, $-CF_3$, pyrrolyl, pyrrolidinyl, pyridinyl, tetrahydrofuranyl, $-N(R^8)C(O)OR^{12}$, $-OC(O)NR^{13}R^{14}$, $-N(R^8)S(O)_2CH_3$, $-S(O)_2NR^{13}R^{14}$, or 2-oxoimidazolidin-1-yl, 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, and pyridinyl; 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_{1-3}alkyl optionally substituted with hydroxy;

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 comprising a pharmaceutically-acceptable carrier and a compound of the invention.

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 quinolinone-carboxamide 5-HT_4 receptor agonists of formula (I), or pharmaceutically-acceptable salts or solvates or stereoisomers thereof. These compounds may contain one or more chiral centers and, when such a chiral center or centers are present, this invention is directed to 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 any utility of the composition as a whole is not eliminated by the presence of such other isomers.

The compounds of this invention also contain several basic groups (e.g., amino groups) and therefore, the compounds of formula (I) and its intermediates can exist in various salt forms. All such salt forms are included within the scope of this invention. Also, included within the scope of this invention are pharmaceutically-acceptable solvates of the compounds of formula (I) or the salts thereof.

Representative Embodiments

The following substituents and values are intended to provide representative examples and embodiments of various aspects of this invention. These representative values are intended to further define such aspects and embodiments and are not intended to exclude other embodiments or limit the scope of this invention. In this regard, the representation herein that a particular value or substituent is preferred is not intended in any way to exclude other values or substituents from this invention unless specifically indicated.

In a specific aspect, R^1 is hydrogen or halo.

In another specific aspect, R^1 is hydrogen, bromo, fluoro, or methyl. In another specific aspect, R^1 is hydrogen.

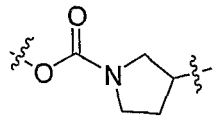
In a specific aspect, R^2 is *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, *tert*-butyl, cyclobutyl or cyclopentyl.

In another specific aspect, R^2 is C_{3-4}alkyl.

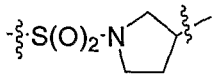
In still another specific aspect, R^2 is isopropyl.

In a specific aspect, X is carbon. In specific aspects, X is carbon and Q is $-A(CH_2)_2N(R^4)-$; or X is carbon and Q is -A-. When X is carbon, representative Q groups include $-N\{C(O)R^5\}-$, $-N\{C(O)NR^{6a}R^{6b}\}-$, $-N\{S(O)_2C_{1-3}alkyl\}-$, and $-S(O)_2N(R^{7a})-$, such as $-N\{C(O)C_{1-3}alkoxy\}-$, $-N\{C(O)NR^{6a}R^{6b}\}-$, $-N\{S(O)_2C_{1-3}alkyl\}-$, and $-S(O)_2N(R^{7a})-$.

In another specific aspect, X is nitrogen. In specific aspects, X is nitrogen and Q is selected from -OC(O)-, $-S(O)_2-$, $-S(O)_2(CH_2)_2-$, $-A(CH_2)_2-$,



, and



; or X is nitrogen and Q is selected from -OC(O)-, $-S(O)_2-$, $-S(O)_2(CH_2)_2-$, and $-A(CH_2)_2-$.

In another aspect, when X is nitrogen, Q is selected from -OC(O)-, $-S(O)_2-$, $-S(O)_2(CH_2)_2-$, $-S(O)_2N(R^{7a})(CH_2)_2-$, $-N\{C(O)R^5\}(CH_2)_2-$, and $-N\{S(O)_2C_{1-3}alkyl\}(CH_2)_2-$. When X is nitrogen, representative Q moieties include -OC(O)-, $-S(O)_2-$, $-S(O)_2(CH_2)_2-$, $-S(O)_2N(CH_3)(CH_2)_2-$, $-N\{C(O)CH_3\}(CH_2)_2-$, $-N\{C(O)OCH_3\}(CH_2)_2-$ and $-N\{S(O)_2CH_3\}(CH_2)_2-$.

In yet another aspect, when X is nitrogen, Q is selected from -OC(O)-, $-S(O)_2-$, $-S(O)_2(CH_2)_2-$, $-S(O)_2N(R^{7a})(CH_2)_2-$, $-N\{C(O)C_{1-3}alkoxy\}(CH_2)_2-$, and $-N\{S(O)_2C_{1-3}alkyl\}(CH_2)_2-$.

In a specific aspect, A is selected from $-N\{C(O)R^5\}-$, $-N\{C(O)NR^{6a}R^{6b}\}-$, $-N\{S(O)_2C_{1-3}alkyl\}-$, and $-S(O)_2N(R^{7a})-$.

In another specific aspect, A is selected from $-N\{C(O)C_{1-3}alkyl\}-$, $-N\{C(O)C_{1-3}alkoxy\}-$, $-N\{C(O)NR^{6a}R^{6b}\}-$, $-N\{S(O)_2C_{1-3}alkyl\}-$, and $-S(O)_2N(R^{7a})-$.

In still another specific aspect, A is selected from $-N\{C(O)CH_3\}-$, $-N\{C(O)OCH_3\}-$; $-N\{C(O)NH_2\}-$, $-N\{C(O)NHCH_3\}-$, $-N\{C(O)N(CH_3)_2\}-$, $-N\{S(O)_2CH_3\}-$, and $-S(O)_2N(CH_3)-$.

In a specific aspect, G is W and *c* is 0, wherein W is as defined in formula (I). In another specific aspect, G is W, *c* is 0, *b* is 1, and X is carbon.

In a specific aspect, W is selected from -N{C(O)R^9}-, -N{$S(O)_2R^{10}$}-, -N{C(O)$NR^{13}R^{14}$}-, -N{R^{16}}-, and -$S(O)_2$-, such as -N{C(O)-tetrahydrofuran-2-yl}-, -N{$C(O)CH_3$}-, -N{$C(O)CH_2CH_3$}-, -N{$S(O)_2CH_3$}-, -N{$S(O)_2CH_2CH_3$}-, -N{$C(O)NH_2$}-, -N{$C(O)NHCH_3$}-, -N{$C(O)N(CH_3)_2$}-, -N{CH_3}-, -N{$(CH_2)_2CN$}-, -N{$(CH_2)_2CH_3$}-, and -$S(O)_2$-. In another specific aspect, W is selected from -$S(O)_2$-, -N{C(O)R^9}-, -N{$S(O)_2R^{10}$}-, -N{C(O)$NR^{13}R^{14}$}-, and -N{R^{16}}-.

Alternatively, in another specific aspect, G is carbon, *c* is 1, and Y is a moiety of formula (b). In another specific aspect, G is carbon, *c* is 1, X is nitrogen, and Y is a moiety of formula (b).

In a specific aspect, W' 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)$NR^{13}R^{14}$, -OR^{15}, and -N(R^8)R^{16}, such as -N(CH_3)C(O)CH_3, -NHC(O)CH_3, -N(CH_3)C(O)H, -N(CH_3)C(O)CH_2CH_3, -N(CH_3)$S(O)_2CH_3$, -N(CH_3)$S(O)_2CH_2CH_3$, -$S(O)_2CH_3$, -N(CH_3)$C(O)NH_2$, -N(CH_3)C(O)$NHCH_3$, -N(CH_3)C(O)$N(CH_3)_2$, -OH, -OCH_3, -N(CH_3)$_2$, -N(CH_3)$(CH_2)_2CN$, and -N(CH_3)$(CH_2)_2CH_3$. In another specific aspect, W' is selected from -OR^{15} and -N(R^8)R^{16}.

In a specific aspect, R^3 and R^4 are independently C_{1-3}alkyl, such as methyl or ethyl. In another specific aspect, R^3 and R^4 are methyl.

In a specific aspect, R^5 is hydrogen, C_{1-3}alkyl, or C_{1-3}alkoxy, such as hydrogen, methyl, or methoxy. In other specific aspects, R^5 is C_{1-3}alkyl, such as methyl; or R^5 is C_{1-3}alkoxy, such as methoxy.

In a specific aspect, R^{6a} and R^{6b} are independently hydrogen or C_{1-4}alkyl, for instance, R^{6a} and R^{6b} are independently hydrogen or methyl.

In a specific aspect, R^{7a} and R^{7b} are independently hydrogen or C_{1-4}alkyl, such as hydrogen or methyl. In another specific aspect, R^{7a} and R^{7b} are methyl.

In a specific aspect, R^8 is hydrogen or C_{1-3}alkyl, such as hydrogen, methyl, or ethyl. In a specific aspect, R^8 is hydrogen. In another specific aspect, R^8 is methyl.

In a specific aspect, R^9 is tetrahydrofuranyl, methyl, or ethyl.

In specific aspects, R^{10}, R^{11}, and R^{12} are independently methyl or ethyl; or R^{10}, R^{11}, and R^{12} are methyl.

In a specific aspect, R^{13}, and R^{14} are independently hydrogen, methyl or ethyl. In another specific aspect, R^{13}, and R^{14} are independently hydrogen or methyl.

In a specific aspect, R^{15} is hydrogen or C_{1-3}alkyl, such as hydrogen or methyl. In a specific aspect, R^{15} is hydrogen. In another specific aspect, R^{15} is methyl.

In a specific aspect, R^{16} is $-(CH_2)_r-R^{17}$, wherein *r* is 0, or 1, or 2. In other specific aspects, *r* is 0; *r* is 1; or *r* is 2.

In a specific aspect, R^{17} is selected from hydroxy, cyano, C_{1-3}alkyl, and C_{1-3}alkoxy. In other specific aspects, R^{17} is selected from hydroxy, cyano, methyl, ethyl, propyl, methoxy, and ethoxy; or R^{17} is selected from cyano, methyl, ethyl, and propyl.

In a specific aspect, R^{18} is methyl or ethyl, wherein methyl or ethyl is optionally substituted with hydroxy.

In specific aspects, *a* is 0; or *a* is 1.

In specific aspects, *b* is 1 or 2; or *b* is 1; or *b* is 2.

In a specific aspect, *b* is 1 or 2, X is carbon, G is W, c is 0, and W is $-S(O)_2-$.

In another specific aspect, *b* is 2, G is W and c is 0, and W is selected from $-S(O)_2-$, $-N\{C(O)R^9\}-$, $-N\{S(O)_2R^{10}\}-$, $-N\{C(O)NR^{13}R^{14}\}-$, and $-N\{R^{16}\}-$.

In specific aspects, *c* is 0; or *c* is 1.

In a specific aspect, *d* is 0.

In specific aspects, *e* is 0; or *e* is 1.

The invention further provides a compound of formula (I), wherein R^1 is hydrogen or halo, R^2 is C_{3-4}alkyl, and *d* is 0.

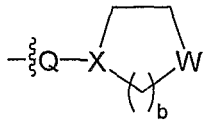
The invention further provides a compound of formula (I), wherein X is carbon and Q is -A-; or X is nitrogen and Q is selected from $-OC(O)-$, $-S(O)_2-$, $-S(O)_2(CH_2)_2-$, and $-A(CH_2)_2-$.

The invention further provides a compound of formula (I), wherein X is carbon and Q is selected from $-N\{C(O)R^5\}-$, $-N\{C(O)NR^{6a}R^{6b}\}-$, $-N\{S(O)_2C_{1-3}\text{alkyl}\}-$, and $-S(O)_2N(R^{7a})-$; or X is nitrogen and Q is selected from $-OC(O)-$, $-S(O)_2-$, $-S(O)_2(CH_2)_2-$, $-S(O)_2N(R^{7a})(CH_2)_2-$, $-N\{C(O)R^5\}(CH_2)_2-$, and $-N\{S(O)_2C_{1-3}\text{alkyl}\}(CH_2)_2-$.

The invention further provides a compound of formula (I), wherein G is W and *c* is 0, wherein W is selected from $-N\{C(O)R^9\}-$, $-N\{S(O)_2R^{10}\}-$, $-N\{C(O)NR^{13}R^{14}\}-$, $-N\{R^{16}\}-$, and $-S(O)_2-$; or G is carbon, *c* is 1, and Y is a moiety of formula (b), wherein W' is selected from $-N(R^8)C(O)R^9$, $-N(R^8)S(O)_2R^{10}$, $-S(R^{11})(O)_2$, $-N(R^8)C(O)NR^{13}R^{14}$, $-OR^{15}$, and $-N(R^8)R^{16}$.

Additionally, the invention provides a compound of formula (I), wherein Z is:

(i) a moiety of formula (c):



(c)

wherein:

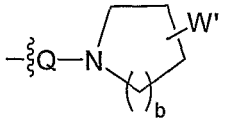
X is carbon and Q is -A-;

or X is nitrogen and Q is selected from -OC(O)-, $-S(O)_2-$, $-S(O)_2(CH_2)_2-$, and $-A(CH_2)_2-$;

b is 1, X is carbon, and W is $-S(O)_2-$;

or *b* is 2, X is carbon or nitrogen, and W is selected from $-S(O)_2-$, $-N\{C(O)R^9\}-$, $-N\{S(O)_2R^{10}\}-$, $-N\{C(O)NR^{13}R^{14}\}-$, and $-N\{R^{16}\}-$; or

(ii) a moiety of formula (d):



(d)

wherein:

Q is selected from -OC(O)-, $-S(O)_2-$, $-S(O)_2(CH_2)_2-$, and $-A(CH_2)_2-$;

b is 1 or 2; and

W' is selected from $-N(R^8)C(O)R^9$, $-N(R^8)S(O)_2R^{10}$, $-S(R^{11})(O)_2$, $-N(R^8)C(O)NR^{13}R^{14}$, $-OR^{15}$, and $-N(R^8)R^{16}$; and

R^8 is hydrogen, methyl, or ethyl;

R^9 is tetrahydrofuranyl, methyl, or ethyl;

R^{10} is methyl or ethyl;

R^{11} is methyl or ethyl;

R^{13} and R^{14} are independently hydrogen, methyl or ethyl;

R^{15} is hydrogen or methyl;

R^{16} is $-(CH_2)_r-R^{17}$, wherein *r* is 0, 1, or 2; and

R^{17} is selected from hydroxy, cyano, C_{1-3}alkyl, and C_{1-3}alkoxy.

The invention also provides a compound of formula (I):

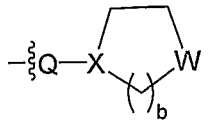
wherein:

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

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

a is 0 or 1;

Z is a moiety of formula (c):



(c)

wherein:

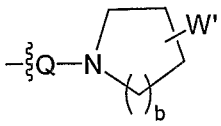
X is carbon and Q is -A-;

or X is nitrogen and Q is selected from -OC(O)-, -$S(O)_2$-, -$S(O)_2(CH_2)_2$-, and -$A(CH_2)_2$-;

b is 1, X is carbon, and W is -$S(O)_2$-;

or *b* is 2, X is carbon or nitrogen, and W is selected from -$S(O)_2$-, -$N\{C(O)R^9\}$-, -$N\{S(O)_2R^{10}\}$-, -$N\{C(O)NR^{13}R^{14}\}$-, and -$N\{R^{16}\}$-; or

Z is a moiety of formula (d):



(d)

wherein:

Q is selected from -OC(O)-, -$S(O)_2$-, -$S(O)_2(CH_2)_2$-, and -$A(CH_2)_2$-;

b is 1 or 2; and

W' is selected from -$N(R^8)C(O)R^9$, -$N(R^8)S(O)_2R^{10}$, -$S(R^{11})(O)_2$, -$N(R^8)C(O)NR^{13}R^{14}$, -OR^{15}, and -$N(R^8)R^{16}$; provided that when W' is attached to a carbon atom bonded to the nitrogen atom of the ring, then W' is -$C(O)NR^{13}R^{14}$; and

A is selected from -$S(O)_2CH_2C(O)N(R^3)$-, -$N\{C(O)R^5\}$-, -$N\{C(O)NR^{6a}R^{6b}\}$-, -$N\{S(O)_2C_{1-3}alkyl\}$-, -$N\{S(O)_2NR^{6a}R^{6b}\}$-, -$S(O)_2N(R^{7a})$-, and -$OC(O)N(R^{7b})$-;

R^3 is C_{1-4}alkyl;

R^5 is hydrogen, C_{1-3}alkyl, or C_{1-3}alkoxy;

R^{6a} and R^{6b} are independently hydrogen or C_{1-4}alkyl;

R^{7a} and R^{7b} are independently hydrogen or C_{1-4}alkyl;

R^8 is hydrogen, methyl, or ethyl;

R^9 is tetrahydrofuranyl, methyl, or ethyl;

R^{10} is methyl or ethyl;

R^{11} is methyl or ethyl;

R^{13} and R^{14} are independently hydrogen, methyl or ethyl;

R^{15} is hydrogen or methyl;

R^{16} is $-(CH_2)_r-R^{17}$, wherein *r* is 0, 1, or 2; and R^{17} is selected from hydroxy, cyano, C_{1-3}alkyl, and C_{1-3}alkoxy; provided that when r is 0, R^{17} is selected from C_{1-3}alkyl; and when r is 1, R^{17} is cyano or C_{1-3}alkyl;

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

In a specific aspect, Z is a moiety of formula (c).

In specific aspects, Z is a moiety of formula (c), wherein X is nitrogen and Q is selected from -OC(O)-, $-S(O)_2-$, $-S(O)_2(CH_2)_2-$, $-S(O)_2N(R^{7a})(CH_2)_2-$, $-N\{C(O)C_{1-3}alkoxy\}(CH_2)_2-$ and $-N\{S(O)_2C_{1-3}alkyl\}(CH_2)_2-$; or Z is a moiety of formula (c), wherein X is nitrogen and Q is selected from -OC(O)-, $-S(O)_2-$, $-S(O)_2(CH_2)_2-$, and $-N\{C(O)C_{1-3}alkoxy\}(CH_2)_2-$.

In other specific aspects, Z is a moiety of formula (c), wherein X is nitrogen, *b* is 2, and Q is -OC(O)-; Z is a moiety of formula (c), wherein X is nitrogen, *b* is 2, and Q is $-S(O)_2-$; or Z is a moiety of formula (c), wherein X is nitrogen, *b* is 2, and Q is $-S(O)_2(CH_2)_2-$.

In another aspect, Z is a moiety of formula (c), wherein X is nitrogen, Q is as defined herein, *b* is 2, and W is selected from $-N\{C(O)R^9\}-$, and $-N\{S(O)_2R^{10}\}-$.

In another aspect, Z is a moiety of formula (c), wherein X is carbon and Q is selected from $-N\{C(O)C_{1-3}alkoxy\}-$, $-N\{C(O)NR^{6a}R^{6b}\}-$, $-N\{S(O)_2C_{1-3}alkyl\}-$, and $-S(O)_2N(R^{7a})-$.

In other specific aspects, Z is a moiety of formula (c), wherein X is carbon and Q is $-N\{C(O)C_{1-3}alkoxy\}-$; Z is a moiety of formula (c), wherein X is carbon and Q is $-N\{C(O)NR^{6a}R^{6b}\}-$; or Z is a moiety of formula (c), wherein X is carbon and Q is $-N\{S(O)_2R^{10}\}-$.

In still another specific aspect, Z is a moiety of formula (c), wherein X is carbon, Q is as defined herein, and W is $-S(O)_2-$.

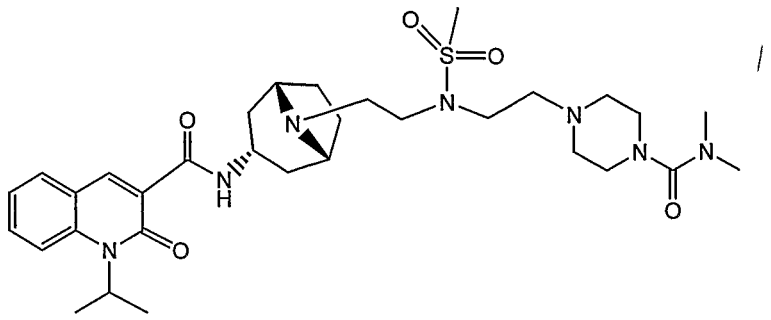
In a specific aspect, Z is a moiety of formula (d).

In yet another aspect, Z is a moiety of formula (d), wherein Q is selected from -OC(O)- and $-S(O)_2-$.

In another specific aspect, Z is a moiety of formula (d), wherein W' is selected from $-OR^{15}$ and $-N(R^8)R^{16}$.

Included within the invention are the compounds listed in Tables 1 to 5 herein.

The chemical naming conventions used herein are illustrated for the compound of Example 28:



which is designated 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid [(1*R*,3*R*,5*S*)-8-(2-{[2-(4-dimethylcarbamoylpiperazin-1-yl)ethyl]methanesulfonyl-amino}ethyl)-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-(2-{[2-(4-dimethylcarbamoylpiperazin-1-yl)ethyl]methane-sulfonylamino}ethyl)-8-azabicyclo-[3.2.1]oct-3-yl]-1-(1-methylethyl)-2-oxo-1,2-dihydro-3-quinolinecarboxamide. In all of the compounds of the invention listed by name below, the quinolinone-carboxamide is endo to the azabicyclooctyl group.

Particular mention may be made of the following compounds:

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[3-(4-methanesulfonylpiperazine-1-sulfonyl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide;

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[3-(3-dimethylaminopyrrolidine-1-sulfonyl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide;

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{3-[4-(2-hydroxyethyl)piperazine-1-sulfonyl]propyl}-8-azabicyclo[3.2.1]oct-3-yl)amide;

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[3-(4-methylpiperazine-1-sulfonyl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide;

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{2-[methanesulfonyl-(1-propylpiperidin-4-yl)amino]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-amide;

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid [(1*S*,3*R*,5*R*)-8-(3-{[1-(2-methoxyethyl)piperidin-4-yl]methylsulfamoyl}propyl)-8-azabicyclo[3.2.1]oct-3-yl]amide;

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{3-[(1-methanesulfonylpiperidin-4-yl)methylsulfamoyl]propyl}-8-azabicyclo[3.2.1]oct-3-yl)amide;

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid [(1*S*,3*R*,5*R*)-8-(3-{[1-(2-cyanoethyl)piperidin-4-yl]methylsulfamoyl}propyl)-8-azabicyclo[3.2.1]oct-3-yl]amide;

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{2-[(1,1-dioxotetrahydro-1λ^6-thiophen-3-yl)methanesulfonylamino]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)amide;

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{2-[1-(1,1-dioxotetrahydro-1λ^6-thiophen-3-yl)-3,3-dimethylureido]ethyl}-8-azabicyclo[3.2.1]-oct-3-yl)amide;

(1,1-dioxo-tetrahydro-1λ^6-thiophen-3-yl)-(2-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}ethyl)-carbamic acid methyl ester;

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid [(1*S*,3*R*,5*R*)-8-(2-{[2-(4-dimethylcarbamoylpiperazin-1-yl)ethyl]methanesulfonylamino}ethyl)-8-azabicyclo-[3.2.1]oct-3-yl]amide;

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{2-[2-(4-methanesulfonylpiperazin-1-yl)ethanesulfonyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)amide;

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid [(1*S*,3*R*,5*R*)-8-(2-{2-[4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl]ethanesulfonyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]amide;

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{2-[2-(4-ethanesulfonylpiperazin-1-yl)ethanesulfonyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)amide;

(1,1-dioxo-hexahydro-1λ^6-thiopyran-4-yl)-(2-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}ethyl)-carbamic acid methyl ester;

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{2-[1-(1,1-dioxotetrahydro-1λ^6-thiophen-3-yl)-3-methylureido]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)amide;

(2-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)-amino]-8-azabicyclo[3.2.1]oct-8-yl}ethyl)-[2-(4-methanesulfonylpiperazin-1-ylethyl]-carbamic acid methyl ester;

[2-(4-dimethylcarbamoylpiperazin-1-yl)ethyl]-(2-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}-ethyl)-carbamic acid methyl ester;

[2-(4-acetyl-piperazin-1-yl)ethyl]-(2-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}ethyl)-carbamic acid methyl ester;

[2-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)ethyl]-(2-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}ethyl)-carbamic acid methyl ester;

(1,1-dioxo-tetrahydro-1λ^6-thiophen-3-yl)-(3-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}propyl)-carbamic acid methyl ester;

((*S*)-1,1-dioxo-tetrahydro-1λ^6-thiophen-3-yl)-(2-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}ethyl)-carbamic acid methyl ester;

1-isopropyl-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[3-(methyl-{2-[4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl]ethyl}sulfamoyl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide;

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{3-[4-(tetrahydrofuran-2-carbonyl)piperazine-1-sulfonyl]propyl}-8-aza-bicyclo-[3.2.1]oct-3-yl)amide;

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[3-(4-acetylpiperazine-1-sulfonyl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide;

4-methanesulfonyl-piperazine-1-carboxylic acid 3-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}propyl ester;

4-(tetrahydrofuran-2-carbonyl)piperazine-1-carboxylic acid 3-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-aza-bicyclo[3.2.1]oct-8-yl}propyl ester;

4-acetyl-piperazine-1-carboxylic acid 3-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}propyl ester; and

4-hydroxypiperidine-1-carboxylic acid 3-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}-propyl ester.

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. Examples of particular values for a C_{1-4}alkyl group include, by way of example, methyl, ethyl, *n*-propyl (*n*-Pr), isopropyl (*i*-Pr), *n*-butyl (*n*-Bu), *sec*-butyl, isobutyl, and *tert*-butyl.

The term "alkylene" means a divalent saturated hydrocarbon group which may be linear or branched or combinations thereof. Examples of particular values for a C_{2-5}alkylene include ethylene, propylene, isopropylene, butylene, and pentylene, and the like.

The term "alkoxy" means a 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 "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 C_{3-6}cycloalkyl groups include, by way of example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

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

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

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 "leaving group" means a functional group or atom which can be displaced by another functional group or atom in a substitution reaction, such as a nucleophilic substitution reaction. By way of example, representative leaving groups include halo, such as chloro, bromo and iodo groups; sulfonic ester groups, such as mesylate, tosylate, brosylate, nosylate and the like; and acyloxy groups, such as acetoxy, trifluoroacetoxy and the like.

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.

The term "hydroxy protecting group" means a protecting group suitable for preventing undesired reactions of a hydroxyl group. The term "hydroxyl-protecting group" means a protecting group suitable for preventing undesirable reactions at a hydroxyl group. Representative hydroxyl-protecting groups include, but are not limited to, silyl groups including tri(1-6C)alkylsilyl groups, such as trimethylsilyl (TMS), triethylsilyl (TES), *tert*-butyldimethylsilyl (TBS) and the like; esters (acyl groups) including (1-6C)alkanoyl groups, such as formyl, acetyl and the like; arylmethyl groups, such as benzyl (Bn), *p*-methoxybenzyl (PMB), 9-fluorenylmethyl (Fm), diphenylmethyl (benzhydryl, DPM) and the like. Additionally, two hydroxyl groups can also be protected as an alkylidene group, such as prop-2-ylidine, formed, for example, by reaction with a ketone, such as acetone.

General Synthetic Procedures

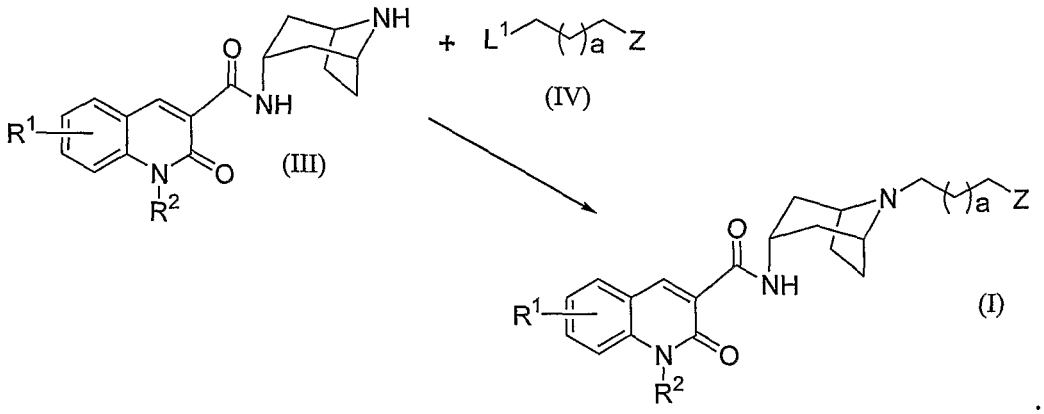
Compounds of the invention can be prepared from readily available starting materials using the following general methods and procedures. Although a particular aspect of the present invention is illustrated in the schemes below, those skilled in the art will recognize that all aspects of the present invention 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 herein unless otherwise indicated.

In one method of synthesis, compounds of formula (I) are prepared as illustrated in Scheme A:

Scheme A



As shown in Scheme A, a compound of formula (III) is reacted with a compound of formula (IV) wherein L^1 is a leaving group, such as halo, for example, chloro, or a sulfonic ester group, such as mesylate, tosylate, brosylate, nosylate and the like, to provide a compound of formula (I) or a salt or solvate or stereoisomer thereof.

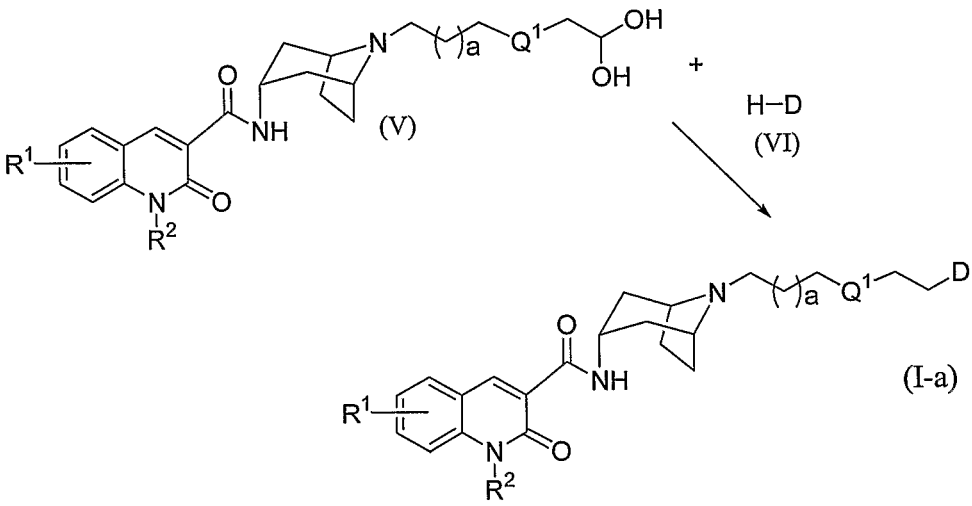
When L^1 is a halo leaving group, such as chloro, the reaction is typically conducted by contacting a compound of formula (III) with between about 1 and about 4 equivalents of a compound of formula (IV) in an inert diluent, such as *N,N*-dimethyl-formamide (DMF), in the presence of an excess of a base, 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), in the presence of a catalyst, such as sodium iodide. Suitable inert diluents also include DMF, dichloromethane, trichloromethane, 1,1,2,2-tetrachloroethane, tetrahydrofuran, methanol, ethanol, and the like. Suitable catalysts include, for example, sodium iodide, potassium iodide, and tetrabutylammonium iodide.

The reaction is typically conducted at a temperature in the range of about 15 °C to about 90 °C for about 4 hours to about 48 hours, or until the reaction is substantially complete.

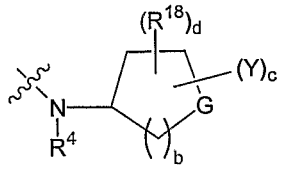
The product of formula (I) is isolated and purified by conventional procedures. For example, the product can be concentrated to dryness under reduced pressure, taken up in an aqueous weak acid solution and purified by HPLC chromatography.

Alternatively, compounds of formula (I), wherein X is carbon and Q is selected from $-A(CH_2)_2N(R^4)-$ and $-S(O)_2(CH_2)_2N(R^4)-$; or X is nitrogen and Q is selected from $-S(O)_2(CH_2)_2-$ and $-A(CH_2)_2-$; can be prepared as illustrated in Scheme B shown below, to provide a compound of formula (I-a).

Scheme B

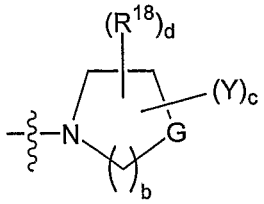


As shown in Scheme B, a compound of formula (V), wherein Q^1 is selected from $-S(O)_2-$ and -A-, is reacted with H-D, an amine compound of formula (VI), wherein D is selected from a moiety of formula (D1):



(D1)

and a moiety of formula (D2):



(D2)

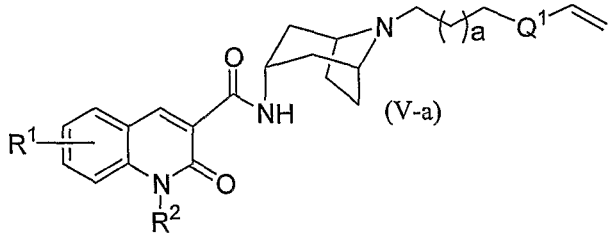
to provide a compound of formula (I-a) or a salt or solvate or stereoisomer thereof.

It will be understood that while intermediate compound (V) is shown in the form of an aldehyde hydrate, intermediate (V) can equivalently be depicted in the form of an aldehyde.

In scheme B, intermediate compound (V) is reductively coupled with an amine of formula (VI) to provide a compound of formula (I-a). Typically, a solution is prepared of between about 1 and about 3 equivalents of the amine of formula (VI) and a reducing agent in an inert diluent in the presence of a base, such as, for example, *N,N*-diisopropyl-ethylamine or 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU). Suitable reducing agents, for example, include hydrogen in the presence of a Group VIII metal catalyst, such as palladium on charcoal, or a borohydride, such as sodium triacetoxyborohydride, sodium cyanoborohydride, lithium cyanoborohydride, and the like. Suitable inert diluents include acetonitrile, halogenated hydrocarbons, such as dichloromethane (DCM) and dichloroethane, alcohols, such as methanol, ethanol, and isopropyl alcohol, or mixtures thereof.

Intermediate (V) is added slowly to the amine mixture. Generally, this reaction is conducted at a temperature ranging from about 0 °C to about 50 °C for a period of about 10 minutes to about 12 hours or until the reaction is substantially complete. The reaction product is then isolated using conventional procedures, such as extraction, recrystallization, chromatography and the like.

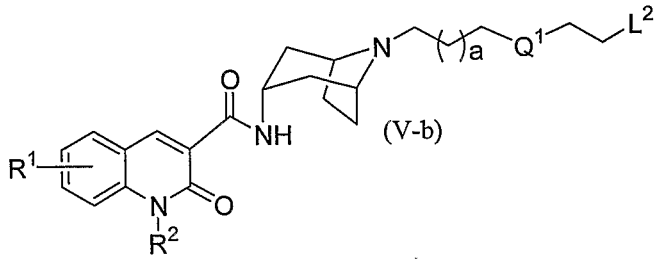
Alternatively, a compound of formula (I-a), wherein Q^1 is $-S(O)_2-$, can be prepared by reacting an intermediate compound (V-a):



with a compound of formula (VI), to provide a compound of formula (I-a), wherein Q^1 is $-S(O)_2-$, or a salt or solvate or stereoisomer thereof. This reaction is typically conducted either in the presence of a base, such as *N,N'*-diisopropylethylamine or inorganic bases, such as sodium hydroxide, and potassium hydroxide when the reacting amines are given in salt form, or in the absence of a base when the reacting amines are given in neutral form. Generally, this reaction is conducted in an inert diluent, such as dichloromethane,

methanol, ethanol, DMF, or water, at a temperature ranging from about 0 °C to about 100°C until the reaction is substantially complete. The reaction product is then isolated using conventional procedures, such as extraction, recrystallization, chromatography and the like.

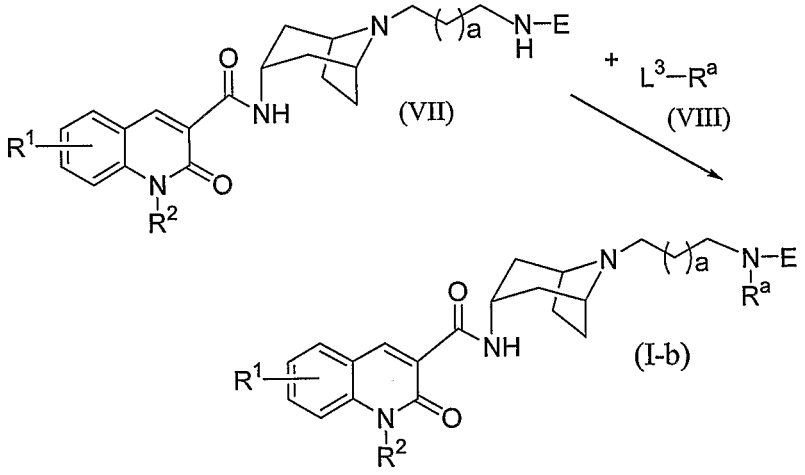
A compound of formula (I-a) can also be prepared by reacting an intermediate compound (V-b):



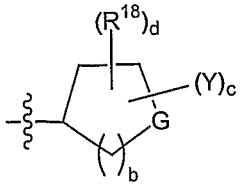
in which L^2 is a leaving group, with a compound of formula (VI), to provide a compound of formula (I-a). Typical conditions for this coupling reaction are described in Scheme A.

Alternatively, compounds of formula (I), wherein X is carbon and Q is selected from $-A^1-$ and $-A^1(CH_2)_2N(R^4)-$; or X is nitrogen and Q is selected from $-A^1(CH_2)_2-$, wherein A^1 is selected from $-N\{C(O)R^5\}-$, $-N\{C(O)NR^{6a}R^{6b}\}-$, $-N\{S(O)_2C_{1-3}alkyl\}-$, and $-N\{S(O)_2NR^{6a}R^{6b}\}-$; can be prepared as illustrated in Scheme C shown below:

Scheme C



As shown in Scheme C, a compound of formula (VII), wherein E is selected from a moiety of formula (E1):



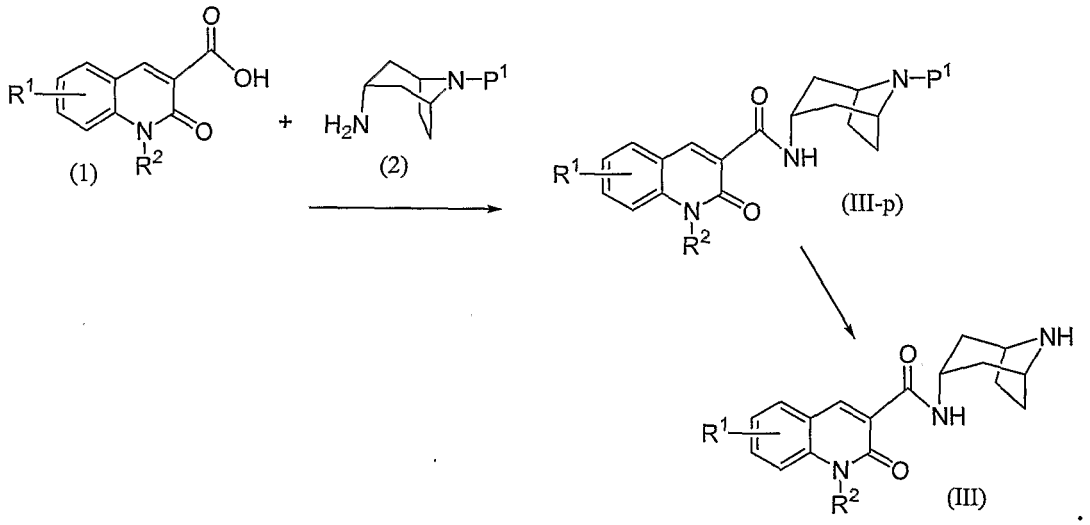
(E1)

and a moiety of formula $-CH_2CH_2-D$, wherein D is selected from a moiety of formula (D1) and a moiety of formula (D2); is reacted with a compound of formula (VIII), wherein L^3-R^a is C_{1-4}alkylisocyanate, or L^3 is a leaving group, such as halo, *p*-nitrophenol, or a sulfonic ester group, and R^a is $-C(O)R^5$, $-C(O)NR^{6a}R^{6b}$, $-S(O)_2C_{1-3}$alkyl, or $-S(O)_2NR^{6a}R^{6b}$; to provide a compound of formula (I-b) or a salt or solvate or stereoisomer thereof.

Typically, compound (VII) is contacted with between about 1 and about 6 equivalents of compound (VIII) in an inert diluent, such as dichloromethane, chloroform, *N*-methylpyrrolidinone, DMF, or the like, in the presence of 2 to 3 equivalents of a base, such as *N,N*-diisopropylethylamine, triethylamine, potassium carbonate, sodium hydroxide, and the like. The reaction is typically conducted at a temperature of between about 0 °C and about 120 °C for between about 10 minutes and about 24 hours, or until the reaction is substantially complete to provide a compound of formula (I-b).

A compound of formula (III) can be prepared as illustrated in Scheme D:

Scheme D



In Scheme D, a substituted quinolinone carboxylic acid (1) is reacted with a protected aminotropane (2), wherein P^1 is an amino-protecting group, to provide a protected intermediate (III-p), which is then de-protected to provide a compound of formula (III).

A substituted quinolinone carboxylic acid (1) can be readily prepared by procedures similar to those reported in the literature in Suzuki *et al, Heterocycles*, **2000**, *53*, 2471-2485 and described in the examples below.

A protected aminotropane (2) or aminoazabicyclooctane can be prepared from readily available starting materials. For example, when the protecting group P^1 is Boc,

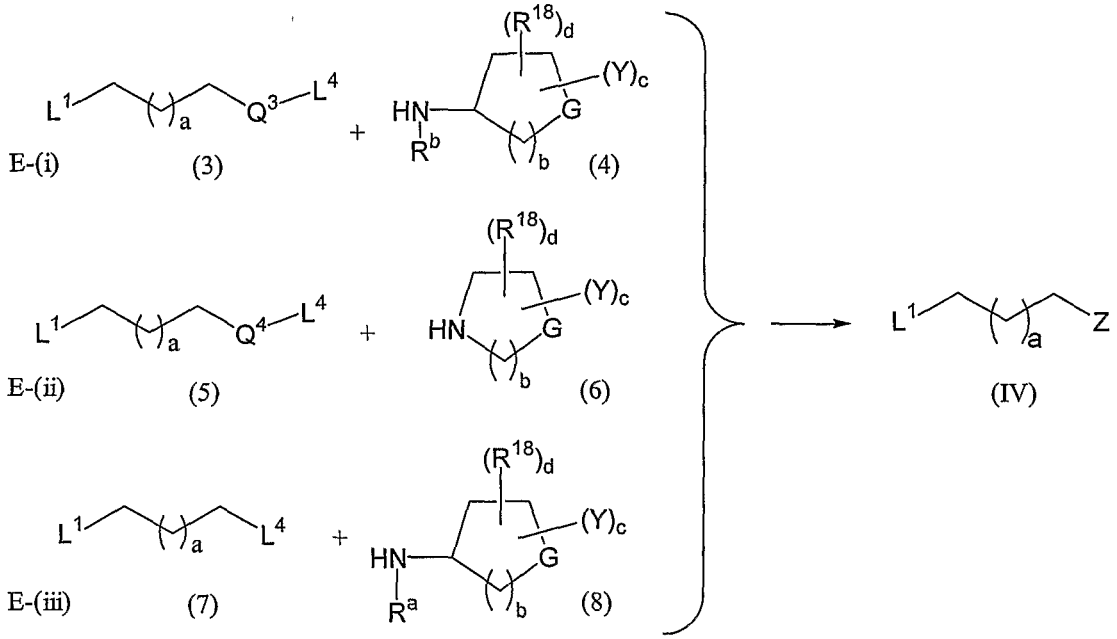
the protected tropane can be prepared by contacting 2,5-dimethoxy tetrahydrofuran with between about 1 and 2 equivalents, preferably about 1.5 equivalents of benzyl amine and a slight excess, for example about 1.1 equivalents, of 1,3-acetonedicarboxylic acid in an acidic aqueous solution in the presence 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, commonly *N*-benzyltropanone.

The resulting *N*-benzyltropanone is typically reacted with a slight excess of di-*tert*-butyl dicarbonate (commonly $(Boc)_2O$), for example, about 1.1 equivalents, under a hydrogen atmosphere in the presence of a transition metal catalyst to provide a Boc protected intermediate, 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, 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester is contacted with a large excess, for example at least about 25 equivalents, of ammonium formate in an inert diluent, such as methanol, in the presence of a transition metal catalyst to provide intermediate (2) where P^1 is Boc, in the *endo* configuration with high stereospecificity, for example, *endo* to *exo* ratio of >99:1. The reaction is typically conducted at ambient temperature for about 12 to about 72 hours or until the reaction is substantially complete. It is advantageous to add the ammonium formate reagent in portions. For example, 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester is contacted with an initial portion of ammonium formate of about 15 to about 25 equivalents. After an interval of about 12 to about 36 hours, an additional portion of about 5 to about 10 equivalents of ammonium formate is added. The subsequent addition can be repeated after a similar interval. The product can be purified by conventional procedures, such as alkaline extraction.

Intermediate compound (III) can be prepared by coupling a substituted quinolinone carboxylic acid (1), with a protected aminotropane (2) under conditions similar to those described in Scheme A for amide bond formation. The protecting group P^1 can be removed by standard procedures to provide an intermediate compound (III). 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 protecting group Cbz, for another example, is conveniently removed by hydrogenolysis over a suitable metal catalyst such as palladium on carbon.

An intermediate compound of formula (IV) can be prepared as illustrated below in Scheme E:

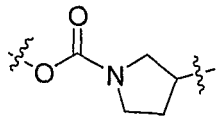
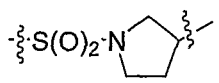
Scheme E

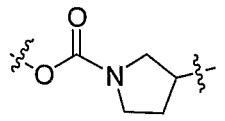
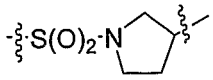


As shown in Scheme E, a compound of formula (IV) can be prepared by reacting an amine, intermediate (4), (6), or (8), with intermediate (3), (5), or (7) respectively, containing L^4, a leaving group, to provide a compound of formula (IV). Q^3 and Q^4 are defined below.

For example, a compound of formula (IV) wherein X is carbon and Q is selected from $-S(O)_2CH_2C(O)N(R^3)-$, $-S(O)_2(CH_2)_2N(R^4)-$, $-S(O)_2N(R^{7a})-$, $-OC(O)N(R^{7b})-$, and $-A(CH_2)_2N(R^4)-$, can be prepared by Scheme E-(i), by reacting intermediate (3) wherein L^1 and L^4 are leaving groups, and Q^3 is selected from $-S(O)_2CH_2C(O)-$, $-S(O)_2(CH_2)_2-$, $-S(O)_2-$, $-OC(O)-$, and $-A(CH_2)_2-$, with intermediate (4) wherein R^b is selected from R^3, R^4, R^{7a}, and R^{7b} as defined herein; to provide a compound of formula (IV).

Similarly, a compound of formula (IV) wherein X is nitrogen and Q is selected from $-S(O)_2CH_2C(O)-$, $-SCH_2C(O)-$, $-S(O)_2-$, $-S(O)_2(CH_2)_2-$, $-OC(O)-$, $-A(CH_2)_2-$,


, and

; can be prepared by Scheme E-(ii) by reacting intermediate (5) wherein L^1 and L^4 are leaving groups, and Q^4 is selected from $-S(O)_2CH_2C(O)-$, $-SCH_2C(O)-$, $-S(O)_2-$, $-S(O)_2(CH_2)_2-$, $-OC(O)-$, $-A(CH_2)_2-$,

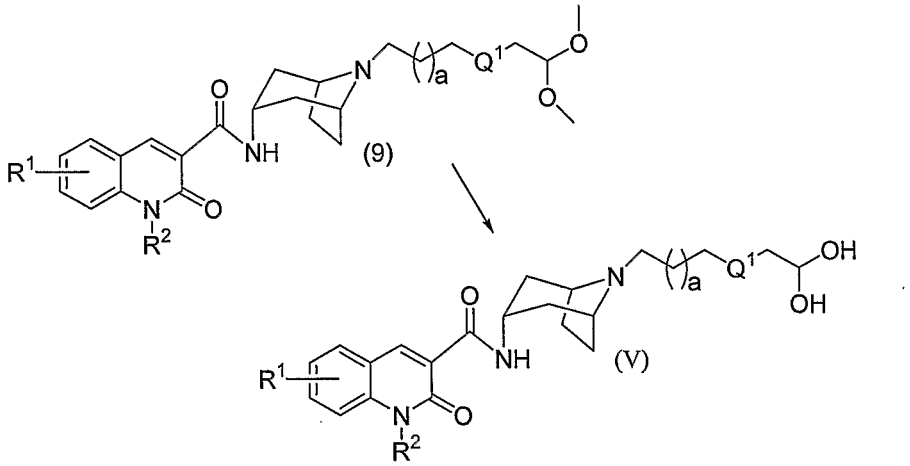

, and 
; with intermediate (6), to provide a compound of formula (IV).

Similarly, a compound of formula (IV) where X is carbon and Q is -A^1- , wherein A^1 is selected from -N{C(O)R^5}-, -N{C(O)N$R^{6a}R^{6b}$}-, -N{$S(O)_2C_{1-3}$alkyl}-, and -N{$S(O)_2NR^{6a}R^{6b}$}-; can be prepared by Scheme E-(iii); by reacting intermediate (7) wherein L^1 and L^4 are leaving groups, with intermediate compound (8), wherein R^a is -C(O)R^5, -C(O)N$R^{6a}R^{6b}$, -$S(O)_2C_{1-3}$alkyl, or -$S(O)_2NR^{6a}R^{6b}$; to provide a compound of formula (IV).

The reactions of Scheme E are typically conducted under the conditions described above for Scheme A, and are further illustrated in the Examples herein.

A compound of formula (V) can be prepared as illustrated in Scheme F:

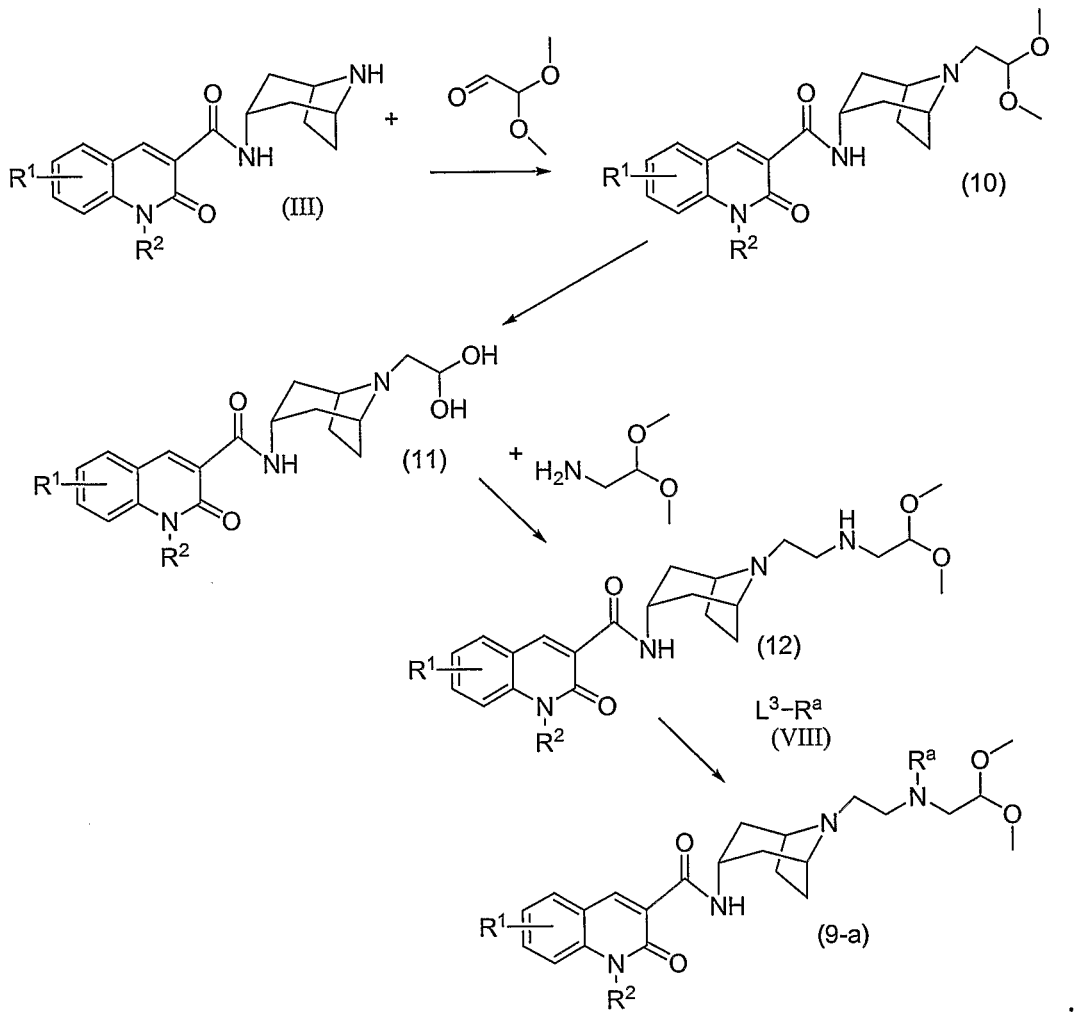
Scheme F



wherein a dimethoxy acetal intermediate compound (9) (wherein Q^1 is selected from -$S(O)_2$- and -A-) is hydrolyzed in an aqueous solution of a strong acid, for example, 3N or 6N HCl, to provide a compound of formula (V). While intermediate compound (V) is shown in the form of an aldehyde hydrate, it can equivalently be depicted in the form of an aldehyde.

An intermediate compound (9-a), representative of intermediate (9), wherein *a* is 0, and Q^1 is selected from -N{C(O)R^5}-, -N{C(O)N$R^{6a}R^{6b}$}-, -N{$S(O)_2C_{1-3}$alkyl}-, and -N{$S(O)_2NR^{6a}R^{6b}$}-, can be prepared as illustrated in Scheme G:

Scheme G



As shown in Scheme G, intermediate (III) is reductively N-alkylated by reaction with dimethoxyacetaldehyde to provide an intermediate of formula (10). This reaction is typically conducted by contacting intermediate (III) with between about 1 and about 4 equivalents of dimethoxyacetaldehyde in an inert diluent in the presence of a base, such as *N,N'*-diisopropylethylamine, and between about 1 and about 2 equivalents of a reducing agent. The reaction is typically conducted at ambient temperature for about 1 to about 2 hours, or until the reaction is substantially complete. Suitable inert diluents include dichloromethane, trichloromethane, 1,1,2,2-tetrachloroethane, and the like. Typical reducing agents include sodium triacetoxyborohydride, sodium borohydride, and sodium cyanoborohydride. The product (10) is isolated by standard procedures.

Next, the dimethoxy intermediate (10) is hydrolyzed in an aqueous solution of a strong acid, for example 3N or 6H HCl, to provide the dihydroxyethyl intermediate (11). The reaction is typically conducted at a temperature in the range of about 25 °C to about

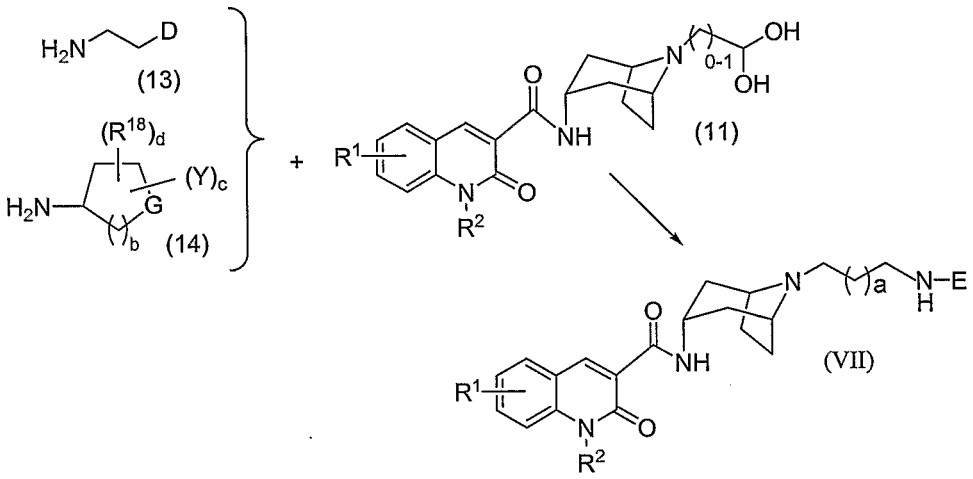
100 °C for about 15 minutes to about 2 hours, or until the reaction is substantially complete.

Next, intermediate (11) is reductively coupled with aminoacetaldehyde dimethyl acetal, to provide intermediate (12). Typically a solution is prepared of between about 1 and about 2 equivalents of the aminoacetaldehyde dimethyl acetal and a reducing agent in an inert diluent. The intermediate (11) is added slowly to the amine mixture. The reaction is typically conducted at ambient temperature for about 15 minutes to about 2 hours, or until the reaction is substantially complete.

Finally intermediate (12) is reacted with a compound of formula (VIII) to provide intermediate (9-a). Typical conditions for this reaction are described in Scheme C herein.

A compound of formula (VII) can be prepared as shown in Scheme H:

Scheme H

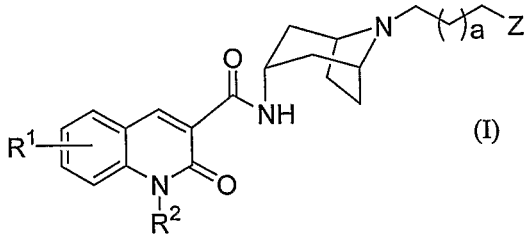


by reductively coupling a dihydroxy acetal intermediate (11) with intermediate (13) or (14), to provide a compound of formula (VII). For example, a compound of formula (VII) wherein E is a moiety of formula (E1) can be prepared by reductively coupling intermediate (11) with intermediate (14). Whereas a compound of formula (VII) wherein E is a moiety of the formula -CH_2CH_2-D can be prepared by reductively coupling intermediate (11) with intermediate (13). Typical conditions for these reactions are described above in Scheme B.

Compounds of formulae (VI) and (VIII), and intermediates (3), (4), (5),(6), (7), (8), (13), and (14) employed in the reactions described in this application are available commercially or are readily prepared by standard procedures from common starting materials.

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.

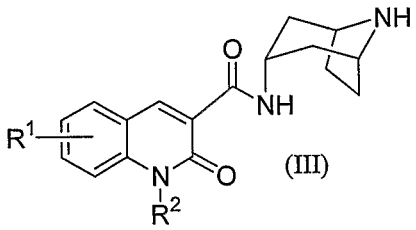
Accordingly, the invention provides a process for preparing a compound of formula (I):



(I)

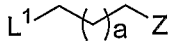
wherein R^1, R^2, *a* and Z are as defined herein for a compound of formula (I), or a pharmaceutically-acceptable salt or solvate or stereoisomer thereof,

the process comprising reacting a compound of formula (III):



(III)

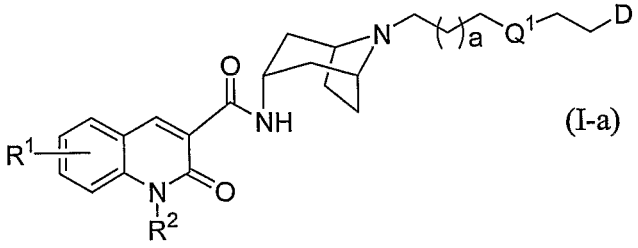
or a salt or stereoisomer thereof, with a compound of formula (IV):



(IV)

wherein L^1 is a leaving group, to provide a compound of formula (I) or a pharmaceutically-acceptable salt or solvate or stereoisomer thereof.

The invention further provides a process for preparing a compound of formula (I-a):

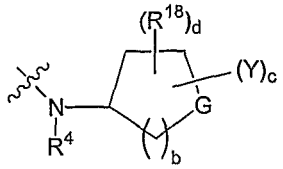


(I-a)

wherein:

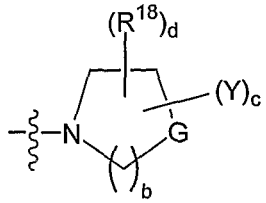
Q^1 is selected from $-S(O)_2-$, and -A-; and

D is selected from a moiety of formula (D1):



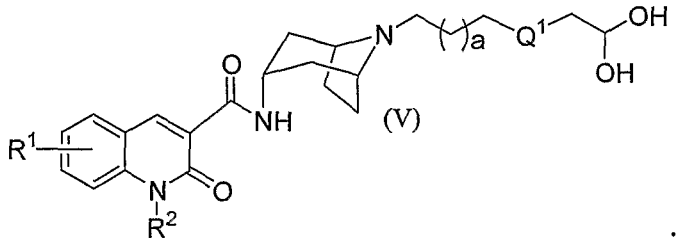
(D1) ; and

a moiety of formula (D2):



(D2)

wherein R^1, R^2, R^4, R^{18}, A, Y, G, *a*, *b*, *c*, and *d* are as defined herein for a compound of formula (I); or a pharmaceutically-acceptable salt or solvate or stereoisomer thereof, the process comprising reacting a compound of formula (V):



(V) ;

with a compound of formula (VI):

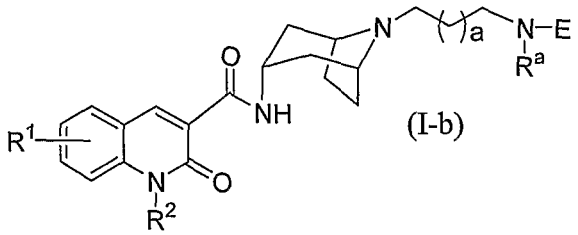
H–D

(VI)

to provide a compound of formula (I-a) or a pharmaceutically-acceptable salt or solvate or stereoisomer thereof.

Accordingly, the invention further provides a compound of formula (I-a).

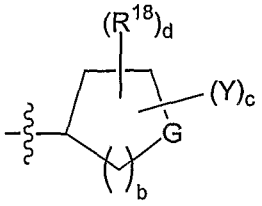
The invention also provides a process for preparing a compound of formula (I-b):



(I-b)

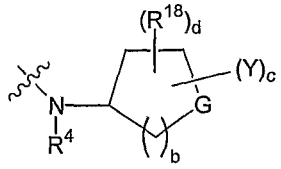
wherein R^a is $-C(O)R^5$, $-C(O)NR^{6a}R^{6b}$, $-S(O)_2C_{1-3}$alkyl, or $-S(O)_2NR^{6a}R^{6b}$; and

E is selected from a moiety of formula (E1):



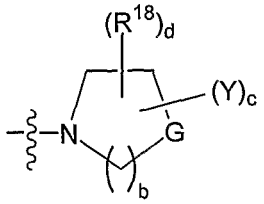
(E1)

and a moiety of formula $-CH_2CH_2-D$, wherein D is selected from a moiety of formula (D1):



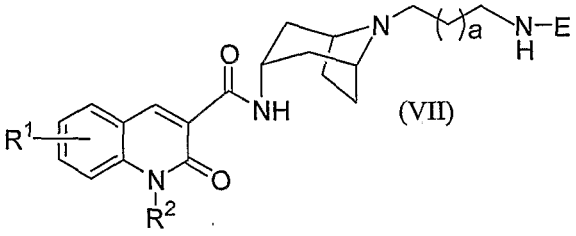
(D1)

and a moiety of formula (D2):



(D2) ;

wherein R^1, R^2, R^4, R^5, R^{6a}, R^{6b}, R^{18}, Y, G, *a*, *b*, *c*, and *d* are as defined herein for a compound of formula (I); or a pharmaceutically-acceptable salt or solvate or stereoisomer thereof, the process comprising reacting a compound of formula (VII):



(VII)

with a compound of formula (VIII):

$$L^3—R^a$$

(VIII)

wherein L^3-R^a is C_{1-4}alkylisocyanate, or L^3 is a leaving group, and R^a is $-C(O)R^5$, $-C(O)NR^{6a}R^{6b}$, $-S(O)_2C_{1-3}$alkyl, or $-S(O)_2NR^{6a}R^{6b}$; to provide a compound of formula (I-b) or a pharmaceutically-acceptable salt, solvate, or stereoisomer thereof.

In addition, the invention provides a compound of formula (I-b).

The invention further provides the product of the processes described herein.

Pharmaceutical Compositions

The quinolinone-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 embodiment, 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 quinolinone-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 increase motility of the gastrointestinal (GI) tract are thus 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, chronic constipation, constipation-predominant irritable bowel syndrome (C-IBS), diabetic and idiopathic gastroparesis, and functional dyspepsia.

In one aspect, therefore, the invention provides a method of increasing 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 the invention.

In another aspect, the invention provides 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 the invention.

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, including 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 is expected to 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 constipation-predominant 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 constipation-

predominant irritable bowel syndrome is expected to 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 is expected to 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 is expected to 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 the compounds of the invention are 5-HT_4 receptor agonists, such compounds 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 1000 nanomolar.

Additionally, the compounds of the invention can be used as research tools for discovering new 5-HT$_4$ receptor agonists. In this embodiment, 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 embodiments, 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 substantial selectivity for the 5-HT$_4$ receptor subtype over the 5-HT$_3$ receptor subtype in radioligand binding assays. Further, compounds of the invention which have been tested in a rat model have typically demonstrated superior pharmacokinetic properties in a rat model. Compounds of the invention are thus expected to be bioavailable upon oral administration. In addition, these compounds typically have been shown to exhibit an acceptable level of inhibition of the potassium ion current in an *in vitro* voltage-clamp model using isolated whole cells expressing the hERG cardiac potassium channel. The voltage-clamp assay is an accepted pre-clinical method of assessing the potential for pharmaceutical agents to change the pattern of cardiac repolarization, specifically to cause, so-called QT prolongation, which has been associated with cardiac arrhythmia. (Cavero *et al.*, *Opinion on Pharmacotherapy*, **2000**, *1*, 947-73, Fermini *et al.*, *Nature Reviews Drug Discovery*,

2003, *2*, 439-447) Accordingly, pharmaceutical compositions comprising compounds of the invention are expected to have an acceptable cardiac profile.

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 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 they 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 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
Mobile Phases:	5% MeCN/H_2O containing 0.1% TFA (isocratic; 0-0.5 min); 5% MeCN/H_2O containing 0.1% TFA to 75% MeCN/H_2O containing 0.1% TFA (linear gradient 0.5-4 min);
Detector wavelength:	214, 254, and 280 nm.

Other conditions, when used, are indicated explicitly.

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

Preparation of various secondary amines used as intermediates in the synthesis of a compound of formula (I) are described below.

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-Methanesulfonylpiperazine: ^{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). Methanesulfonylpiperazine was also prepared by reacting methanesulfonyl chloride with excess piperazine (>2 equivalents) in water.

The racemic or single chiral isomer forms of 3-acetylaminopyrrolidine were prepared by treating N^1-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_3SO_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-tetrahydrothiopheneamine-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.

(*S*)-1,1-Dioxo-tetrahydro-1λ^6-thiophen-3-ylamine was prepared as follows: 1) *N*-Boc protection of (*S*)-3-tetrahydrothiophenamine (Dehmlow, E. V.; Westerheide, R. *Synthesis* **1992**, *10*, 947-9) by treating with $(Boc)_2O$ in methanol at room temperature for about 12 h; 2) oxidation by treating with *m*CPBA in dichloromethane to *N*-Boc protected (*S*)-1,1-dioxo-tetrahydro-1λ^6-thiophen-3-ylamine at 0 °C for about 5 h; and 3) *N*-Boc deprotection of the sulfone derivative with TFA in dichloromethane at room temperature

for 1h to the free amine which was isolated as a TFA salt. (*R*)-1,1-dioxo-tetrahydro-1λ^6-thiophen-3-ylamine was prepared using the same method, but replacing the (*S*)-3-tetrahydrothiophenamine with (*R*)-3-tetrahydrothiophenamine.

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_3SO_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

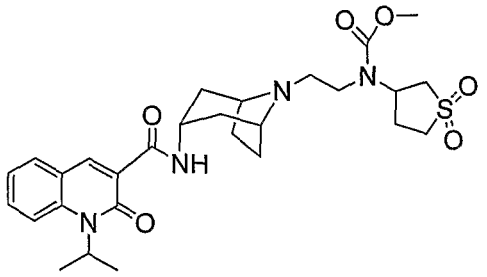
protected 4-aminopiperidine with methylchloroformate followed by the deprotection of the *N*-Boc group.

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 (1,1-dioxotetrahydro-1λ^6-thiophen-3-yl)-(2-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}ethyl)carbamic acid methyl ester



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 dichloromethane (3 x 500 mL). The combined organic layers were washed with brine,

dried ($MgSO_4$), filtered and concentrated under reduced pressure to produce the crude title intermediate as a viscous brown oil (52 g).

To a solution of the crude intermediate in methanol (1000 mL) was added di-*tert*-butyl dicarbonate (74.6 g, 0.342 mol) at 0 °C. The solution was allowed to warm to room temperature and stirred overnight. The methanol was removed under reduced pressure and the resulting oil was dissolved in dichloromethane (1000 mL). The intermediate was extracted into 1 M H_3PO_4 (1000 mL) and washed with dichloromethane (3 x 250 mL). The aqueous layer was basified to pH 12 using aqueous NaOH, and extracted with dichloromethane (3 x 500 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to produce the title intermediate as a viscous, light brown oil. ^{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 (51 g). 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 >99:1 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-2-oxo-1,2-dihydroquinoline-3-carboxylic acid

Acetone (228.2 mL, 3.11 mol) was added to a stirred suspension of 2-aminophenylmethanol (255.2 g, 2.07 mol) and acetic acid (3.56 mL, 62 mmol) in water (2 L) at room temperature. After 4 h, the suspension was cooled to 0 °C and stirred for an additional 2.5 h and then filtered. The solid was collected and washed with water and the wet solid cooled and dried by lyophilisation to yield 2,2,-dimethyl-1,4-dihydro-2*H*-benzo[1,3]oxazine (332.2 g, 98 %) as an off-white solid. ^{1}H NMR ($CDCl_3$; 300MHz): 1.48 (s, 6H, $C(C\underline{H}_3)_2$), 4.00 (bs, 1H, N<u>H</u>), 4.86 (s, 2H, $C\underline{H}_2$), 6.66 (d, 1H, Ar<u>H</u>), 6.81 (t, 1H, Ar<u>H</u>), 6.96 (d, 1H, Ar<u>H</u>), 7.10 (t, 1H, Ar<u>H</u>).

A solution of 2,2,-dimethyl-1,4-dihydro-2*H*-benzo[1,3]oxazine (125 g, 0.77 mol) in THF (1 L) was filtered through a scintillation funnel and then added dropwise via an addition funnel, over a period of 2.5 h, to a stirred solution of 1.0 M $LiAlH_4$ in THF (800 mL) at 0 °C. The reaction was quenched by slow portionwise addition of $Na_2SO_4 \cdot 10H_2O$ (110 g), over a period of 1.5 h, at 0 °C. The reaction mixture was stirred

overnight, filtered and the solid salts were washed thoroughly with THF. The filtrate was concentrated under reduced pressure to yield 2-isopropylaminophenylmethanol (120 g, 95 %) as a yellow oil. ^{1}H NMR ($CDCl_3$; 300MHz): 1.24 (d, 6H, $CH(C\underline{H}_3)_2$), 3.15 (bs, 1H, O<u>H</u>), 3.61 (sept, 1H, $C\underline{H}(CH_3)_2$), 4.57 (s, 2H, $C\underline{H}_2$), 6.59 (t, 1H, Ar<u>H</u>), 6.65 (d, 1H, Ar<u>H</u>), 6.99 (d, 1H, Ar<u>H</u>), 7.15 (t, 1H, Ar<u>H</u>).

Manganese dioxide (85 % 182.6 g, 1.79 mol) was added to a stirred solution of 2-isopropylaminophenylmethanol (118 g, 0.71 mol) in toluene (800 mL) and the reaction mixture was heated to 117 °C for 4 h. The reaction mixture was allowed to cool to room temperature overnight and then filtered through a pad of Celite which was eluted with toluene. The filtrate was concentrated under reduced pressure to yield 2-isopropylaminobenzaldehyde (105 g, 90 %) as an orange oil. ^{1}H NMR ($CDCl_3$; 300MHz): 1.28 (d, 6H, $CH(C\underline{H}_3)_2$), 3.76 (sept, 1H, $C\underline{H}(CH_3)_2$), 6.65 (t, 1H, Ar<u>H</u>), 6.69 (d, 1H, Ar<u>H</u>), 7.37 (d, 1H, Ar<u>H</u>), 7.44 (t, 1H, Ar<u>H</u>), 9.79 (s, 1H, C<u>H</u>O).

2,2-Dimethyl-[1,3]dioxane-4,6-dione, commonly Meldrum's acid, (166.9 g, 1.16 mol) was added to a stirred solution of 2-isopropylaminobenzaldehyde (105 g, 0.64 mol), acetic acid (73.6 mL, 1.29 mol) and ethylenediamine (43.0 mL, 0.64 mol) in methanol (1 L) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and then at room temperature overnight. The resulting suspension was filtered and the solid washed with methanol and collected to yield the title intermediate, 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (146 g, 98 %) as an off-white solid. ^{1}H NMR ($CDCl_3$; 300MHz): 1.72 (d, 6H, $CH(C\underline{H}_3)_2$), 5.50 (bs, 1H, $C\underline{H}(CH_3)_2$), 7.44 (t, 1H, Ar<u>H</u>), 7.75-7.77 (m, 2H, Ar<u>H</u>), 7.82 (d, 1H, Ar<u>H</u>), 8.89 (s, 1H, C<u>H</u>).

e. <u>Preparation of (1*S*,3*R*,5*R*)-3-[1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester</u>

Thionyl chloride (36.6 mL, 0.52 mol) was added to a stirred suspension of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (80 g, 0.35 mol) in toluene (600 mL) at 85 °C and the reaction mixture then heated to 95 °C for 2 h. The reaction mixture was cooled to room temperature and then added over 25 min to a vigorously stirred biphasic solution of (1*S*,3*R*,5*R*)-3-amino-8-azabicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester (78.2 g, 0.35 mol) and sodium hydroxide (69.2 g, 1.73 mol) in toluene/water (1:1) (1L) at °C. After 1 h, the layers were allowed to separate and the organic phase concentrated under reduced pressure. The aqueous phase was washed with EtOAc (1 L) and then (500 mL) and the combined organic extracts used to dissolve the

concentrated organic residue. This solution was washed with 1M H_3PO_4 (500 mL), saturated aqueous $NaHCO_3$ (500 mL) and brine (500 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the title intermediate (127.9 g, approx. 84 %) as a yellow solid. ^1H NMR ($CDCl_3$): 1.47 (s, 9H), 1.67 (d, 6H), 1.78-1.84 (m, 2H), 2.04-2.18 (m, 6H), 4.20-4.39 (m, 3H), 5.65 (bs, 1H), 7.26 (dd. 1H), 7.63 (m, 2H), 7.75 (dd, 1H), 8.83 (s, 1H), 10.63 (d, 1H).

f. Preparation of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-azabicyclo[3.2.1]oct-3-yl}amide

TFA (300 mL) was added to a stirred solution of the product of the previous step (127.9 g) in CH_2Cl_2 (600 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h and then concentrated under reduced pressure. The oily brown residue was then poured into a vigorously stirred solution of ether (3 L) and a solid precipitate formed immediately. The suspension was stirred overnight and then the solid collected by filtration and washed with ether to yield the title intermediate as its trifluoroacetic acid salt (131.7 g, 86% over two steps) as a light yellow solid. ^1H NMR ($CDCl_3$): 1.68 (d, 6H), 2.10 (d, 2H), 2.33-2.39 (m, 4H), 2.44-2.61 (m, 2H), 4.08 (bs, 2H), 4.41 (m, 1H), 5.57 (bs, 1H), 7.31 (m. 1H), 7.66 (m, 2H), 7.77 (d, 1H), 8.83 (s, 1H), 9.38 (bd, 2H), 10.78 (d, 1H).

g. Preparation of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {(1*S*, 3*R*, 5*R*)-8-[(2,2-dimethoxy)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}amide

N,N'-diisopropylethylamine (4.3 mL) and dimethoxyacetaldehyde in *tert*-butyl methyl ether (conc 45%; 4.5 mL, 17 mmol) were added to a solution of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {(1*S*, 3*R*, 5*R*)-8-azabicyclo[3.2.1]oct-3-yl}amide mono trifluoroacetic acid salt (5.44 g; 12 mmol) dissolved in 50 mL of dichloromethane. After stirring 35 minutes at ambient temperature, sodium triacetoxyborohydride (3.7 g; 17.3 mmol) was added to the reaction mixture. After 90 minutes, water (50 mL) and saturated $NaHCO_3$ solution (100 mL) was slowly added to the reaction mixture in an ice bath to quench the reaction. The mixture was diluted with 500 mL of dichloromethane, and transferred to a separatory funnel. The organic layer was collected, and washed with saturated $NaHCO_3$ (250 mL), and brine solution (350 mL). It was dried over $MgSO_4$, and evaporated *in vacuo*, to yield the title intermediate. (*m/z*): $[M+H]^+$ calcd for $C_{24}H_{33}N_3O_4$ 428.25; found, 428.4.

h. Preparation of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {(1*S*, 3*R*, 5*R*)-8-[(2,2-dihydroxy)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}amide

1-Isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {(1*S*, 3*R*, 5*R*)-8-[(2,2-dimethoxy)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}amide (5.5 g) was suspended in 50 mL of 6M hydrochloric acid, then heated at 70°C for 1 h. The reaction mixture was cooled to 0°C, and diluted with dichloromethane (100 mL) prior to basification of the aqueous layer by slow addition of 6M NaOH (80 mL). It was further mixed with 80 mL of dichloromethane, and transferred to a separatory funnel. The organic layer was collected, washed with brine, dried over $MgSO_4$, and evaporated to dryness to yield the title intermediate as an aldehyde hydrate. (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{29}N_3O_4$ 400.22; found, 400.5.

i. Preparation of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {(1*S*, 3*R*, 5*R*)-{8-[2-(1,1-dioxotetrahydro-1λ^6-thiophen-3-ylamino)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-amide

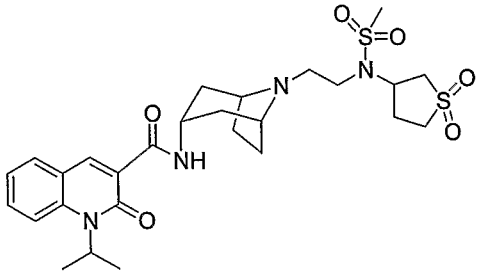
1,1-dioxotetrahydro-1λ^6-thiophen-3-ylamine trifluoroacetic acid salt (500 mg; 2 mmol), *N,N'*-diisopropylethylamine (0.35 mL), and sodium triacetoxyborohydride (422 mg; 2 mmol) was added to a vial containing 10 mL of dichloromethane. The mixture was stirred for 5 minutes prior to the addition of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {(1*S*, 3*R*, 5*R*)-8-[(2,2-dihydroxy)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}amide (0.427 g). The final mixture was stirred for 1 h, at which time the reaction was judged to be complete based on HPLC and mass spectrometric analysis. Water (20 mL) was slowly added to quench the remaining reducing agent. The mixture was diluted with 100 mL of dichloromethane, and shaken in a funnel before collecting the organic layer. The organic layer was washed with 1M NaOH (40 mL) and brine (50 mL), dried over $MgSO_4$, and evaporated to yield the title intermediate as a colorless solid. This crude product was used in the next step without further treatment.

j. Synthesis of (1,1-dioxo-tetrahydro-1λ^6-thiophen-3-yl)-(2-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-aza-bicyclo[3.2.1]oct-8-yl}ethyl)-carbamic acid methyl ester

N,N'-diisopropylethylamine (0.07 mL, 0.4 mmol) and methyl chloroformate (0.02 mL, 0.26 mmol) was added to a solution of DMF (1 mL) containing the product of the previous step, 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {(1*S*, 3*R*, 5*R*)-{8-[2-(1,1-dioxotetrahydro-1λ^6-thiophen-3-ylamino)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-amide (65 mg, 0.13 mmol). The reaction mixture was shaken at room temperature for 30 minutes, and concentrated in vacuo, yielding an oily residue. The residue was dissolved

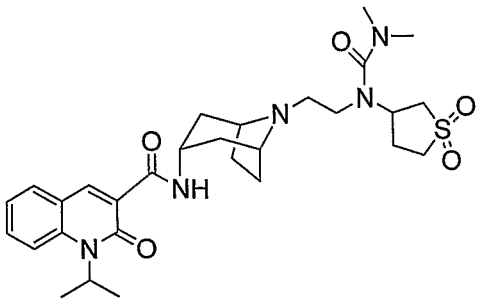
in 50% aqueous acetic acid (1 mL), and purified by preparative HPLC, to yield the title compound. (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{38}N_4O_6S$ 559.25; found, 559.2. Retention time (anal. HPLC: 10-40% MeCN/H_2O over 6 min) = 2.56 min.

Example 2: Synthesis of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{2-[(1,1-dioxotetrahydro-1λ^6-thiophen-3-yl)methanesulfonylamino]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)amide



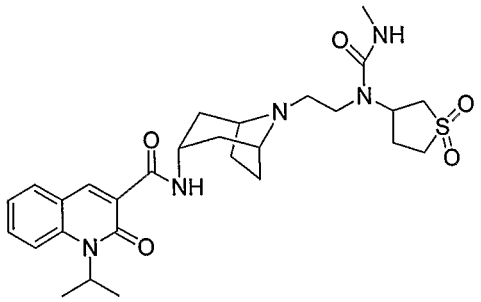
Following the procedure described in Example 1, step (j), the title compound was prepared by replacing methyl chloroformate, *N,N'*-diisopropylethylamine, and DMF with methylsulfonyl chloride, DBU, and dichloromethane, respectively. (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{38}N_4O_6S_2$ 579.22; found. 579.2. Retention time (anal. HPLC: 10-40% MeCN/ H_2O over 6 min) = 2.62 min.

Example 3: Synthesis of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{2-[1-(1,1-dioxotetrahydro-1λ^6-thiophen-3-yl)-3,3-dimethylureido]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)amide



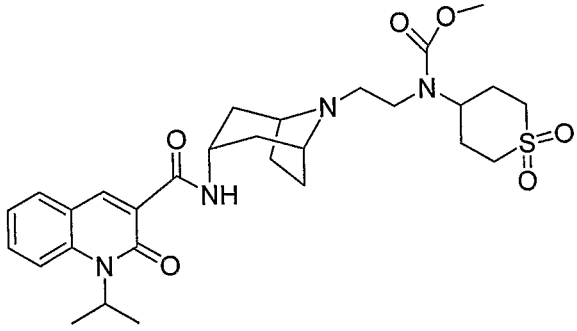
Following the procedure described in Example 1, step (j), the title compound was prepared by replacing methyl chloroformate with *N,N'*-dimethylcarbamoyl chloride. (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{41}N_5O_5S$ 572.28; found, 572.2. Retention time (anal. HPLC: 10-40% MeCN/H_2O over 6 min) = 2.55 min.

Example 4: Synthesis of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{2-[1-(1,1-dioxotetrahydro-1λ^6-thiophen-3-yl)-3-methylureido]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)amide



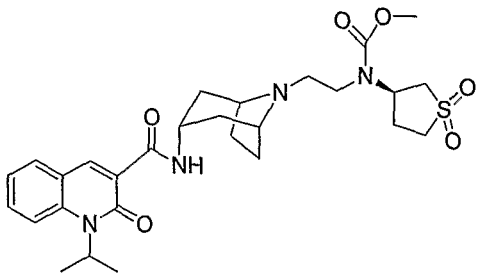
Following the procedure described in Example 1, step (j), the title compound was prepared by replacing methyl chloroformate with methyl isocyanate. (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{39}N_5O_5S$ 558.27; found 558.2 $[M+H]^+$. Retention time (anal. HPLC: 10-40% MeCN/H_2O over 6 min) = 2.69 min.

Example 5: Synthesis of (1,1-dioxohexahydro-1λ^6-thiopyran-4-yl)-(2-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}ethyl)-carbamic acid methyl ester



Following the procedure described in Example 1, the title compound was prepared by replacing 1,1-dioxotetrahydro-1λ^6-thiophen-3-ylamine trifluoroacetic acid salt in Example 1, step (i), with 1,1-dioxohexahydro-1λ^6-thiopyran-4-ylamine. (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{40}N_4O_6S$ 573.27; found, 573.2. Retention time (anal. HPLC: 10-40% MeCN/H_2O over 6 min) = 2.70 min.

Example 6: Synthesis of ((*R*)-1,1-dioxotetrahydro-1λ^6-thiophen-3-yl)-(2-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}-ethyl)carbamic acid methyl ester



a. Preparation of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {8-(1*S*,3*R*,5*R*)-[2-((*R*)-1,1-dioxotetrahydro-1λ^6-thiophen-3-ylamino)ethyl]-8-aza-bicyclo[3.2.1]oct-3-yl}amide

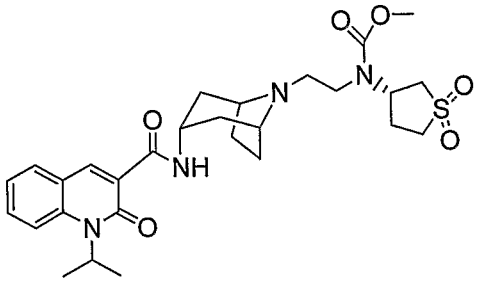
(*R*)-1,1-dioxotetrahydro-1λ^6-thiophen-3-ylamine trifluoroacetic acid salt (278 mg; 1.1 mmol), and sodium triacetoxyborohydride (254 mg; 1.2 mmol) was added to a vial containing 4 mL of dichloromethane. The mixture was stirred for 5 min prior to the addition of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {(1*S*, 3*R*, 5*R*)-8-[(2,2-dihydroxy)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}amide (0.420 g; 1.1 mmol), the product of Example 1, step (h). The mixture was stirred for 1 h, at which time the reaction was judged to be complete based on HPLC and mass spectrometric analysis. Water (10 mL) was slowly added to quench the remaining reducing agent. The mixture was diluted with 50 mL of dichloromethane, and shaken in a funnel before collecting the organic layer. It was washed with 1M NaOH (20 mL) and brine (20 mL), dried over $MgSO_4$, and evaporated to yield the title intermediate as a colorless solid. This crude product was used in the next step without further purification. (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{36}N_4O_4S$ calcd. 501.25; found, 501.6.

b. Synthesis of ((*R*)-1,1-dioxotetrahydro-1λ^6-thiophen-3-yl)-(2-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}-ethyl)carbamic acid methyl ester

N,*N*'-diisopropylethylamine (0.38 mL, 2.2 mmol) and methyl chloroformate (0.11 mL, 1.4 mmol) was added to a solution of DMF (1 mL) containing 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {8-(1*S*,3*R*,5*R*)-[2-((*R*)-1,1-dioxotetrahydro-1λ^6-thiophen-3-ylamino)ethyl]-8-aza-bicyclo[3.2.1]oct-3-yl}amide (365 mg, 0.73 mmol) prepared in step (a) above. The reaction mixture was shaken at room temperature for about 30 minutes, then concentrated *in vacuo*, yielding an oily residue. The residue was dissolved in 50% aqueous acetic acid (1 mL), and purified by preparative HPLC, to yield

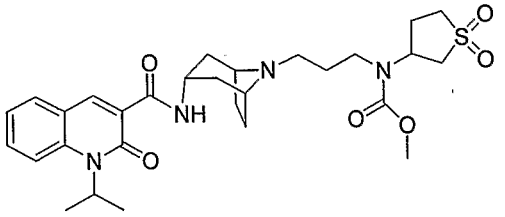
the title compound. (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{38}N_4O_6S$ 559.27; found, 559.4. Retention time (anal. HPLC: 10-40% MeCN/H_2O over 6 min) = 2.56 min.

Example 7: Synthesis of ((*S*)-1,1-dioxo-tetrahydro-1λ^6-thiophen-3-yl)-(2-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}-ethyl)carbamic acid methyl ester



The title compound, an (*S*)-enantiomer of the compound of Example 6, was prepared using the process described in Example 6, by replacing in Example 6, step (a), (*R*)-1,1-dioxotetrahydro-1λ^6-thiophen-3-ylamine with (*S*)-1,1-dioxotetrahydro-1λ^6-thiophen-3-ylamine. (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{38}N_4O_6S$ 559.27; found, 559.4. Retention time (anal. HPLC: 10-40% MeCN/H_2O over 6 min) = 2.56 min.

Example 8: Synthesis of (1,1-dioxotetrahydro-1λ^6-thiophen-3-yl)-(3-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}propyl)-carbamic acid methyl ester



a. Preparation of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid [8-(1*S*,3*R*,5*R*)-(3-aminopropyl)-8-azabicyclo[3.2.1]oct-3-yl]amide

N,*N*'-diisopropylethylamine (15.7 mL, 90 mmol), and *N*-Boc-3-bromo-propanamine (14.2 g, 60 mmol) was added to a solution of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-azabicyclo[3.2.1]oct-3-yl}amide mono trifluoroacetic acid salt (13.6 g; 30 mmol) (the product of Example 1, step (f)) dissolved in 120 mL of methanol. The mixture was refluxed for 16 h, followed by the addition of a second portion of *N*-Boc-3-bromopropanamine (7 g, 30 mmol). The mixture was refluxed for an additional 16 h, concentrated *in vacuo*, and purified by flash column

chromatography (eluant, 10% MeOH/CH_2Cl_2). The product was dissolved in dichloromethane (50 mL), then trifluoroacetic acid (50 mL) was added. After stirring at room temperature for 30 minutes, the solution was concentrated *in vacuo*, and the resulting residue was suspended in ether (200 mL). The solidified residue was collected by filtration, to yield the title intermediate as a TFA salt, which was converted to a netural form by dissolving the salt in dichloromethane, then washing with aqueous NaOH solution.

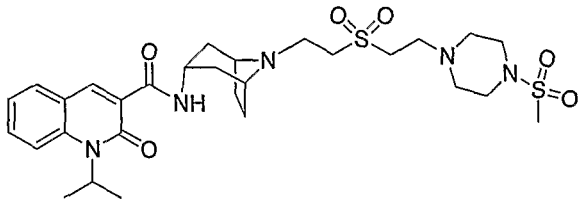
b. Preparation of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {8-(1*S*,3*R*,5*R*)-[3-(1,1-dioxotetrahydro-1λ^6-thiophen-3-ylamino)propyl]-8-aza-bicyclo[3.2.1]oct-3-yl}amide

Potasium hydroxide (3 mg) dissolved in water (0.1 mL) and 2,5-dihydrothiophene-1,1-dioxide (0.236 g, 2 mmol) was added to a solution of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid [8-(1*S*,3*R*,5*R*)-(3-aminopropyl)-8-azabicyclo-[3.2.1]oct-3-yl]amide (free base; 0.16 g, 0.4 mmol) in DMF (1 mL). The mixture was stirred at 75 °C for 16 h under nitrogen atmosphere. Evaporation *in vacuo* yielded the title intermediate, which was used in the next step without further purification.

c. Synthesis of (1,1-dioxotetrahydro-1λ^6-thiophen-3-yl)-(3-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}propyl)-carbamic acid methyl ester

N,*N*'-diisopropylethylamine (0.28 mL, 1.6 mmol) and methyl chloroformate (75 mg, 0.8 mmol) was added to a solution of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {8-(1*S*,3*R*,5*R*)-[3-(1,1-dioxotetrahydro-1λ^6-thiophen-3-ylamino)propyl]-8-aza-bicyclo[3.2.1]oct-3-yl}-amide (0.206 g, 0.4 mmol) dissolved in DMF (2 mL). The reaction mixture was stirred at room temperature for about 30 minutes, then concentrated *in vacuo*. The residue was dissolved in 50% aqueous acetic acid (1 mL), and purified by preparative HPLC to yield the title compound. (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{40}N_4O_6S$ 573.27; found, 573.6.

Example 9: Synthesis of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{2-[2-(4-methanesulfonylpiperazin-1-yl)ethanesulfonyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-amide



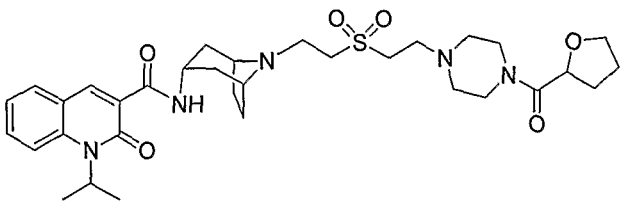
a. Preparation of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid [(1*S*,3*R*,5*R*)-8-(2-ethenesulfonylethyl)-8-azabicyclo[3.2.1]oct-3-yl]amide

Vinylsulfone (1.1 g, 9.32 mmol) was added dropwise to a stirred solution of dichloromethane (25 mL) containing 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {(1*S*, 3*R*, 5*R*)-8-azabicyclo[3.2.1]oct-3-yl}amide (1.58 g, 4.64 mmol), the product of Example 1, step (f). The reaction mixture was stirred at room temperature overnight, then concentrated *in vacuo*, to yield the title intermediate as an oily residue which was used in the next step without further purification.

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

1-methylsulfonylpiperazine (656 mg, 0.4 mmol) was added to a solution of 1-isopropyl-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid [(1*S*,3*R*,5*R*)-8-(2-ethenesulfonyl-ethyl)-8-aza-bicyclo[3.2.1]oct-3-yl]-amide (45 mg, 0.1 mmol) in 1 mL of dichloromethane. The reaction mixture was shaken at room temperature overnight, and concentrated *in vacuo*, yielding an oily residue. The residue was dissolved in 50% aqueous acetic acid (1 mL), then purified by preparative HPLC, to yield the title compound. (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{43}N_5O_6S_2$ 622.27; found, 622.2. Retention time (anal. HPLC: 10-40% MeCN/H_2O over 6 min) = 2.35 min.

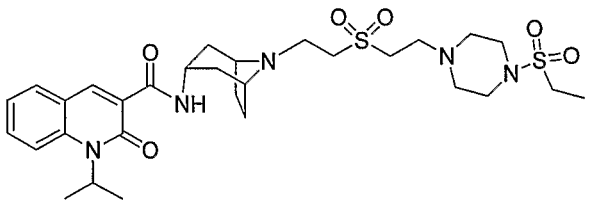
Example 10: Synthesis of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid [(1*S*,3*R*,5*R*)-8-(2-{2-[4-(tetrahydrofuran-2-carbonyl)-piperazin-1-yl]ethanesulfonyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]amide



The title compound was prepared using the method described in Example 9 by replacing, in Example 9, Step (b), 1-methylsulfonylpiperazine with piperazin-1-yl-(tetra-

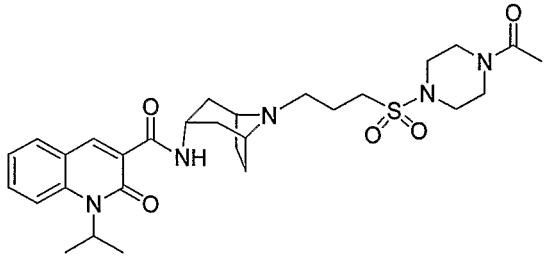
hydrofuran-2-yl)methanone. (*m/z*): $[M+H]^+$ calcd for $C_{33}H_{47}N_5O_6S$ 642.32; found, 642.2. Retention time (anal. HPLC: 10-40% MeCN/H_2O over 6 min) = 2.30 min.

Example 11: Synthesis of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{2-[2-(4-ethanesulfonylpiperazin-1-yl)-ethanesulfonyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-amide



The title compound was prepared using the method described in Example 9 by replacing in Example 9, Step (b) 1-methylsulfonylpiperazine with 1-ethylsulfonyl-piperazine. (*m/z*): $[M+H]^+$ calcd for $C_{30}H_{45}N_5O_6S_2$ 636.28; found, 636.2. Retention time (anal. HPLC: 10-40% MeCN/H_2O over 6 min) = 2.41 min.

Example 12: Synthesis of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[3-(4-acetylpiperazine-1-sulfonyl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide



a. Preparation of 1-{4-(3-chloropropane-1-sulfonyl)piperazin-1-yl}ethanone

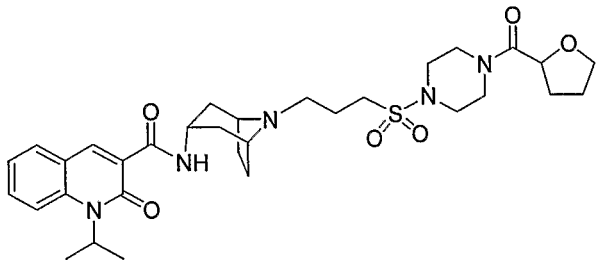
N,N'-diisopropylethylamine (0.10 mL, 6 mmol) and then 3-chloropropyl-1-sulfonyl chloride (53.1 mg, 0.3 mmol) were added to a 5 mL glass vial containing *N*-acetylpiperazine (38 mg, 0.3 mmol) dissolved in dichloromethane (1 mL). The reaction mixture was shaken at room temperature for about 0.5 h, then evaporated *in vacuo*, to yield the title intermediate as an oily residue which was used without further treatment.

b. Synthesis of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[3-(4-acetylpiperazine-1-sulfonyl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide

Sodium iodide (14 mg), *N,N'*-diisopropylethylamine (0.05 mL, 0.3 mmol), and 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {(1*S*, 3*R*, 5*R*)-8-azabicyclo[3.2.1]oct-3-yl}amide (45.3 mg, 0.1 mmol) were added to the product of the previous step dissolved in DMF (1 mL). The mixture was shaken at 85°C for 24 h, then

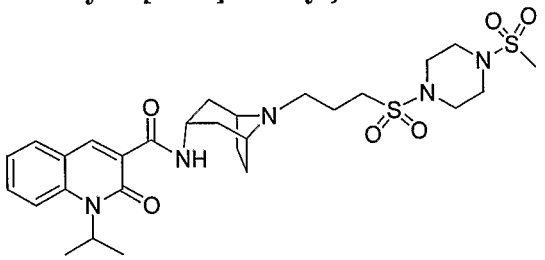
concentrated *in vacuo*. The concentrated residue was dissolved in 50% aqueous acetic acid (1 mL), then purified by preparative HPLC to yield the title compound. (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{41}N_5O_5S$ 572.28; found 572.2. Retention time (anal. HPLC: 10-40% MeCN/H_2O over 6 min) = 1.66 min.

Example 13: Synthesis of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{3-[4-(tetrahydrofuran-2-carbonyl)piperazine-1-sulfonyl]propyl}-8-azabicyclo-[3.2.1]oct-3-yl)amide



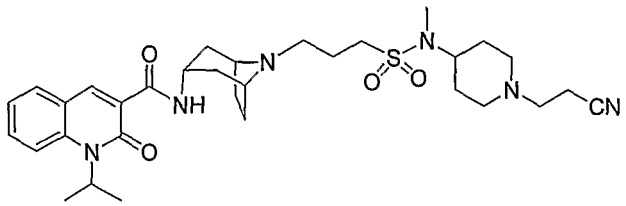
The title compound was prepared using the method described in Example 12 by replacing in Example 12, Step (a), *N*-acetylpiperazine with piperazin-1-yl-(tetrahydro-furan-2-yl)-methanone. (*m/z*): $[M+H]^+$ calcd for $C_{32}H_{45}N_5O_6S$ 628.31; found, 628.2. Retention time (anal. HPLC: 10-40% MeCN/H_2O over 6 min) = 1.69 min.

Example 14: Synthesis of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[3-(4-methanesulfonyl-piperazine-1-sulfonyl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide



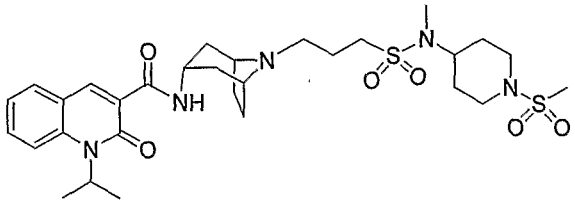
The title compound was prepared using the method described in Example 12 by replacing in Example 12, Step (a), *N*-acetylpiperazine with 1-methylsulfonylpiperazine. (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{41}N_5O_6S_2$ 607.25; found, 608.2. Retention time (anal. HPLC: 10-40% MeCN/H_2O over 6 min) = 1.61 min.

Example 15: Synthesis of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid [(1*S*,3*R*,5*R*)-8-(3-{[1-(2-cyanoethyl)piperidin-4-yl]methylsulfamoyl}propyl)-8-azabicyclo[3.2.1]oct-3-yl]amide



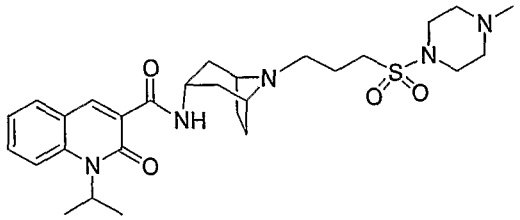
The title compound was prepared using the method described in Example 12 by replacing in Example 12, Step (a), *N*-acetylpiperazine with 3-(4-methylaminopiperidin-1-yl)propanenitrile. (*m/z*): $[M+H]^+$ calcd for $C_{32}H_{46}N_6O_4S$ 611.33; found, 611.20. Retention time (anal. HPLC: 10-40% MeCN/H_2O over 6 min) = 2.32 min.

Example 16: Synthesis of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{3-[(1-methanesulfonylpiperidin-4-yl)-methylsulfamoyl]-propyl}-8-azabicyclo[3.2.1]oct-3-yl)amide



The title compound was prepared using the method described in Example 12 by replacing in Example 12, Step (a), *N*-acetylpiperazine with (1-methanesulfonylpiperidin-4-yl)methylamine. (*m/z*): $[M+H]^+$ calcd for $C_{30}H_{45}N_5O_6S_2$ 636.28; found, 636.20. Retention time (anal. HPLC: 10-40% MeCN/H_2O over 6 min) = 2.57 min.

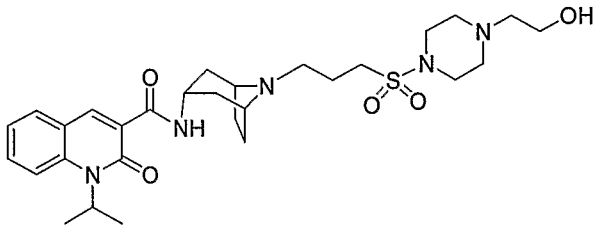
Example 17: Synthesis of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[3-(4-methylpiperazine-1-sulfonyl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide



The title compound was prepared using the method described in Example 12 by replacing in Example 12, Step (a), *N*-acetylpiperazine with 1-methylpiperazine. (*m/z*):

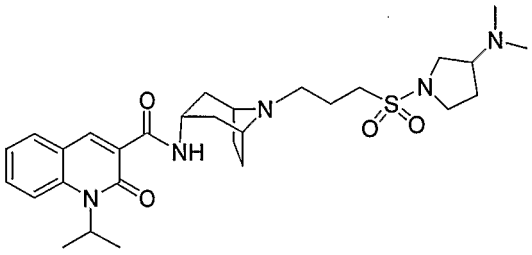
$[M+H]^+$ calcd for$C_{28}H_{41}N_5O_4S$ 544.29; found, 544.3. Retention time (anal. HPLC: 10-40% MeCN/H_2O over 6 min) = 2.21 min.

Example 18: Synthesis of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{3-[4-(2-hydroxyethyl)piperazine-1-sulfonyl]propyl}-8-azabicyclo[3.2.1]oct-3-yl)amide



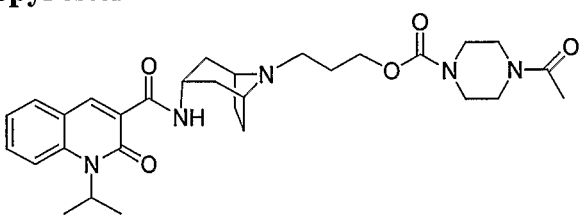
The title compound was prepared using the method described in Example 12 by replacing in Example 12, Step (a), *N*-acetylpiperazine with 2-piperazin-1-ylethanol. (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{43}N_5O_5S$ 574.30; found, 574.2. Retention time (anal. HPLC: 10-40% MeCN/H_2O over 6 min) = 1.19 min.

Example 19: Synthesis of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[3-(3-dimethylaminopyrrolidine-1-sulfonyl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide



The title compound was prepared using the method described in Example 12 by replacing in Example 12, Step (a), *N*-acetylpiperazine with dimethylpyrrolidin-3-ylamine. (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{43}N_5O_4S$ 558.30; found, 558.3. Retention time (anal. HPLC: 10-40% MeCN/H_2O over 6 min) = 2.20 min.

Example 20: Synthesis of 4-acetylpiperazine-1-carboxylic acid 3-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo-[3.2.1]oct-8-yl}propyl ester



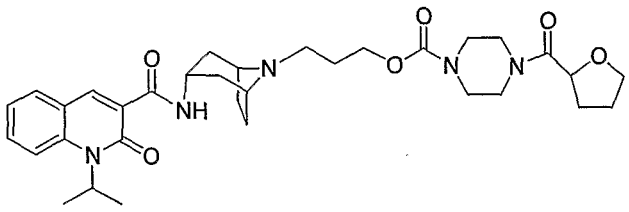
a. Preparation of 4-acetylpiperazine-1-carboxylic acid 3-chloropropyl ester

N,N'-diisopropylethylamine (0.10 mL, 6 mmol), followed by 3-chloropropane chloroformate (47.1 mg, 0.3 mmol) was added to a 5 mL glass vial containing 1-piperazin-1-yl-ethanone (38 mg, 0.3 mmol) dissolved in dichloromethane (1 mL). The reaction mixture was shaken at room temperature for about 0.5 h, then evaporated *in vacuo* to yield the title intermediate as an oily residue which was used without further treatment.

b. Synthesis of 4-acetylpiperazine-1-carboxylic acid 3-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo-[3.2.1]oct-8-yl}propyl ester

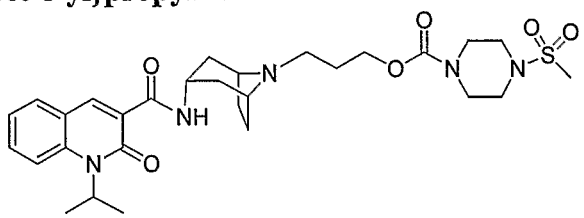
Sodium iodide (14 mg), followed by *N,N'*-diisopropylethylamine (0.05 mL, 0.3 mmol), and 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {(1*S*, 3*R*, 5*R*)-8-azabicyclo[3.2.1]oct-3-yl}amide (45.3 mg, 0.1 mmol) were added to the product of the previous step dissolved in DMF (1 mL). The mixture was shaken at 85 °C for 24 h, then concentrated *in vacuo*. The residue was dissolved in 50% aqueous acetic acid (1 mL), then purified by preparative HPLCto yield the title compound. (*m/z*): $[M+H]^+$ calcd for $C_{30}H_{41}N_5O_5$ 552.31; found, 552.4. Retention time (anal. HPLC: 10-40% MeCN/H_2O over 6 min) = 1.56 min.

Example 21: Synthesis of 4-(tetrahydrofuran-2-carbonyl)piperazine-1-carboxylic acid 3-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}propyl ester



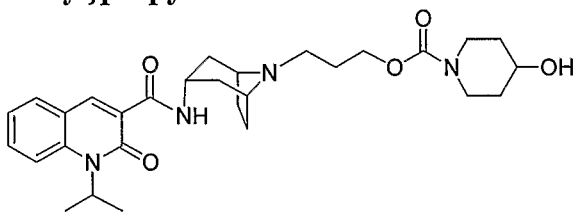
The title compound was prepared using the method described in Example 20 by replacing, in Example 20, Step (a), 1-piperazin-1-ylethanonewith piperazin-1-yl-(tetrahydrofuran-2-yl)-methanone. (*m/z*): $[M+H]^+$ calcd for $C_{33}H_{45}N_5O_6$ 607.34; found, 608.4. Retention time (anal. HPLC: 10-40% MeCN/H_2O over 6 min) = 1.7 min.

Example 22: Synthesis of 4-methanesulfonylpiperazine-1-carboxylic acid 3-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}propyl ester



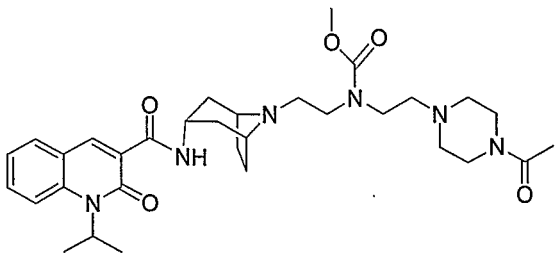
The title compound was prepared using the method described in Example 20 by replacing in Example 20, Step (a), 1-piperazin-1-yl-ethanone with 1-methylsulfonyl-piperazine. (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{41}N_5O_6S$ 588.28; found, 588.2. Retention time (anal. HPLC: 10-40% MeCN/H_2O over 6 min) = 1.74 min.

Example 23: Synthesis of 4-hydroxypiperidine-1-carboxylic acid 3-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}propyl ester



The title compound was prepared using the method described in Example 20 by replacing in Example 20, Step (a), 1-piperazin-1-yl-ethanone with 4-hydroxy-piperidine. (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{39}N_5O_6$ 526.30; found, 525.2. Retention time (anal. HPLC: 10-40% MeCN/H_2O over 6 min) = 2.64 min.

Example 24: Synthesis of [2-(4-acetyl-piperazin-1-yl)ethyl]-(2-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo-[3.2.1]oct-8-yl}ethyl)-carbamic acid methyl ester



a. Preparation of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[2-(2,2-dimethoxyethylamino)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}amide

2,2-Dimethoxy-1-ethylamine (4.2 mL, 39 mmol) and *N,N'*-diisopropylethylamine (4.53 mL, 26 mmol) were added to a solution of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {(1*S*, 3*R*,5*R*)-8-[(2,2-dihydroxy)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}amide *hydrochloride salt* (5.43 g, 13.0 mmol) in 30 mL of dichloromethane. After the mixture was stirred at room temperature for about 45 minutes, sodium triacetoxyborohydride (3.86 g; 18.2 mmol) was added. The mixture was stirred for about 4 h, then the remaining reducing agent was quenched by adding water (20 mL) slowly to the reaction mixture in an ice bath. The mixture was diluted with 200 mL of dichloromethane, and shaken in a funnel before collecting the organic layer. The organic layer was washed with brine (50 mL) and a saturated sodium bicarbonate solution, dried over $MgSO_4$, and evaporated to yield the title intermediate which was used in the next step without further treatment. (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{38}N_4O_4$ 471.29; found, 472.0.

b. Preparation of (2,2-dimethoxyethyl)-(2-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydro-quinoline-3-carbonyl)amino]}-8-azabicyclo[3.2.1]oct-8-yl}ethyl)-carbamic acid methyl ester

Methyl chloroformate (0.275 mL, 3.58 mmol) and *N,N'*-diisopropylethylamine (0.62 mL, 3.58 mmol) were added to a cold solution of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[2-(2,2-dimethoxyethylamino)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}amide (1.53 g, 3.25 mmol) dissolved in dichloromethane (25 mL) in an ice bath. The mixture was stirred at 0 °C for 2 h, then stirred at room temperature overnight. The mixture was diluted with dichloromethane (200 mL), and washed with brine and a saturated sodium carbonate solution. After drying over $MgSO_4$, the organic solution was evaporated *in vacuo*, to yield an oily residue that was dissolved in 50% aqueous acetonitrile, then purified by preparative HPLC to yield the title intermediate. (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{40}N_4O_6$ 529.29; found, 529.3.

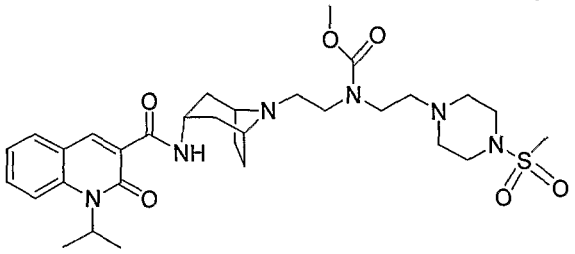
c. Preparation of (2,2-dihydroxy-ethyl)-(2-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-8-aza-bicyclo[3.2.1]oct-8-yl}-ethyl)-carbamic acid methyl ester

A solution of (2,2-dimethoxyethyl)-(2-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydro-quinoline-3-carbonyl)amino]}-8-azabicyclo[3.2.1]oct-8-yl}ethyl)-carbamic acid methyl ester (236 mg, 0.367 mmol) in 6M HCl (5 mL) was stirred at room temperature overnight. It was lyophilized to yield the title intermediate as a hydrochloride salt.

d. Synthesis of [2-(4-acetyl-piperazin-1-yl)ethyl]-(2-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo-[3.2.1]oct-8-yl}ethyl)-carbamic acid methyl ester

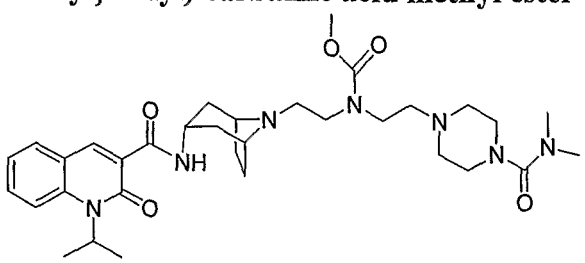
1-Piperazin-1-ylethanone (25.6 mg, 0.2 mmol), *N,N'*-diisopropyl-ethylamine (0.07 mL, 0.4 mmol), and sodium triacetoxyborohydride (29.7 mg, 0.14 mmol) were added to a solution of (2,2-dihydroxyethyl)-(2-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}ethyl)carbamic acid methyl ester (52 mg, 0.1 mmol) in 2 mL of dichloromethane. The mixture was shaken at room temperature for 2 h, then concentrated *in vacuo*, yielding an oily residue. The residue was dissolved in 50% aqueous acetic acid (1 mL), purified by preparative HPLC, to yield the title compound. (*m/z*): $[M+H]^+$ calcd for $C_{32}H_{46}N_6O_5$ 595.35; found, 595.2. Retention time (anal. HPLC: 10-40% MeCN/H_2O over 6 min) = 2.02 min

Example 25: Synthesis of (2-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-8-azabicyclo[3.2.1]oct-8-yl}ethyl)-[2-(4-methanesulfonylpiperazin-1-ylethyl]-carbamic acid methyl ester



The title compound was prepared using the method described in Example 24 by replacing in Example 24, Step (d), 1-piperazin-1-ylethanone with 1-methylsulfonyl-piperazine. (*m/z*): $[M+H]^+$ calcd for $C_{31}H_{46}N_6O_6S$ 631.32; found, 631.2. Retention time (anal. HPLC: 10-40% MeCN/H_2O over 6 min) = 2.11 min.

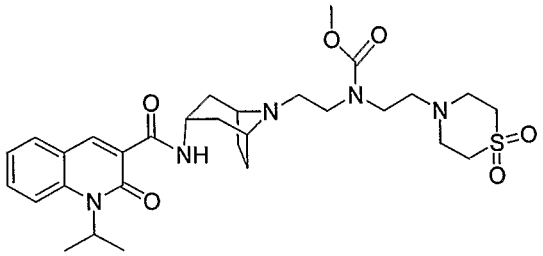
Example 26: Synthesis of [2-(4-dimethylcarbamoylpiperazin-1-yl)-ethyl]-(2-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}-ethyl)-carbamic acid methyl ester



The title compound was prepared using the method described in Example 24 by replacing in Example 24, Step (d), 1-piperazin-1-ylethanone with piperazine-1-carboxylic

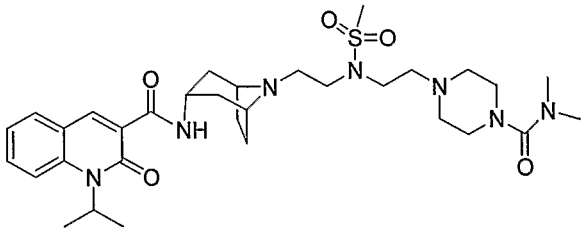
acid dimethylamide. (*m/z*): $[M+H]^+$ calcd for $C_{33}H_{49}N_7O_5S$ 624.38; found, 624.3. Retention time (anal. HPLC: 10-40% MeCN/H_2O over 6 min) = 2.07 min.

Example 27: Synthesis of [2-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-ethyl]-(2-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}ethyl)-carbamic acid methyl ester



The title compound was prepared using the method described in Example 24 by replacing in Example 24, Step (d), 1-piperazin-1-ylethanone with thiomorpholine-1,1-dioxide. (*m/z*): $[M+H]^+$ calcd for $C_{30}H_{43}N_5O_6S$ 602.29; found, 602.2. Retention time (anal. HPLC: 10-40% MeCN/H_2O over 6 min) = 2.16 min.

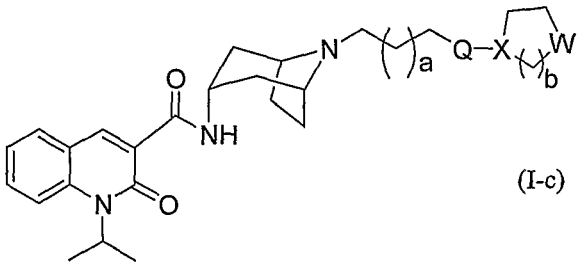
Example 28: Synthesis of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid [(1*S*,3*R*,5*R*)-8-(2-{[2-(4-dimethylcarbamoylpiperazin-1-yl)-ethyl]methanesulfonylamino}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]amide



The title compound was prepared using the method described in Example 24 substituting the appropriate reagents. In Example 24, Step (b), methyl chloroformate was replaced with methylsulfonyl chloride. In Example 24, Step (d), 1-piperazin-1-ylethanone was replaced with piperazine-1-carboxylic acid dimethylamide to yield the title compound. (*m/z*): $[M+H]^+$ calcd for $C_{32}H_{49}N_7O_5S$ 644.35; found, 644.4. Retention time (anal. HPLC: 10-40% MeCN/H_2O over 6 min) = 2.77 min.

Using the methods described in Examples 1-28, and substituting the appropriate reagents, the following compounds listed in Tables 1-5 were prepared. In all of the compounds of the invention, the quinolinone-carboxamide is *endo* to the azabicyclooctanyl group.

Table 1



(I-c)

No.	a	b	X	Q	W	Mol. Formula	Calc'd [M+H]	Obsd [M+H]
1	1	2	N	$S(O)_2$	$NS(O)_2CH_3$	$C_{28}H_{41}N_5O_6S_2$	608.25	608.2
2	1	2	C	$S(O)_2N(CH_3)$	$NC(O)OCH_2CH_3$	$C_{30}H_{43}N_5O_6S$	602.31	602.2
3	1	2	C	$N\{S(O)_2CH_3\}$	NCH_3	$C_{30}H_{45}N_5O_4S$	572.34	572.3
4	1	2	N	$S(O)_2$	$N(CH_2)_2OH$	$C_{29}H_{43}N_5O_5S$	574.30	574.2
5	1	2	N	$S(O)_2$	NCH_2-pyridin-4-yl	$C_{33}H_{44}N_6O_4S$	621.33	621.3
6	1	2	N	$S(O)_2$	NCH_2-tetrahydro-furan-2-yl	$C_{32}H_{47}N_5O_5S$	614.35	614.3
7	1	2	N	$S(O)_2$	$NCH_2C(O)N(CH_3)_2$	$C_{31}H_{46}N_6O_5S$	615.34	615.3
8	1	2	N	$S(O)_2$	$N(CH_2)_3CH_3$	$C_{31}H_{47}N_5O_4S$	586.35	586.3
9	1	2	C	$S(O)_2NH$	NH	$C_{28}H_{41}N_5O_4S$	544.30	544.3
10	1	2	N	$S(O)_2$	NCH_3	$C_{28}H_{41}N_5O_4S$	544.29	544.3
11	0	2	C	$N\{S(O)_2CH_3\}$	$N(CH_2)_2CH_3$	$C_{31}H_{47}N_5O_4S$	586.33	586.3
12	0	2	C	$N\{S(O)_2CH_3\}$	$N(CH_2)_2OH$	$C_{30}H_{45}N_5O_5S$	588.33	588.3
13	0	2	C	$N\{S(O)_2CH_3\}$	$N(CH_2)_2OCH_3$	$C_{31}H_{47}N_5O_5S$	602.35	600.3
14	0	2	C	$N\{S(O)_2CH_3\}$	$N(CH_2)_2$-pyrrol-1-yl	$C_{34}H_{48}N_6O_4S$	637.36	637.3
15	0	2	C	$N\{S(O)_2CH_3\}$	NCH_2-pyridin-3-yl	$C_{34}H_{46}N_6O_4S$	635.35	635.3
16	0	2	C	$N\{S(O)_2CH_3\}$	$N(CH_2)_2NHC(O)OCH_3$	$C_{32}H_{48}N_6O_6S$	645.35	645.3
17	0	2	C	$N\{S(O)_2CH_3\}$	$N(CH_2)_2OC(O)N(CH_3)_2$	$C_{33}H_{50}N_6O_6S$	659.37	659.3
18	0	2	C	$N\{S(O)_2CH_3\}$	$N(CH_2)_2C(O)NHCH_3$	$C_{33}H_{50}N_6O_5S$	643.37	643.3
19	0	2	C	$N\{S(O)_2CH_3\}$	$N(CH_2)_3C(O)N(CH_3)_2$	$C_{34}H_{52}N_6O_5S$	657.39	657.3
20	0	2	C	$N\{S(O)_2CH_3\}$	$N(CH_2)_2NHS(O)_2CH_3$	$C_{31}H_{48}N_6O_6S_2$	665.32	665.3
21	0	2	C	$N\{S(O)_2CH_3\}$	$N(CH_2)_2N(CH_3)S(O)_2$ -CH_3	$C_{32}H_{50}N_6O_6S_2$	679.34	679.3
22	0	2	C	$N\{S(O)_2CH_3\}$	$N(CH_2)_2S(O)_2N(CH_3)_2$	$C_{33}H_{52}N_6O_6S_2$	693.36	693.3
23	1	2	C	$S(O)_2N(CH_3)$	$N(CH_2)_2CH_3$	$C_{32}H_{49}N_5O_4S$	600.37	600.3
24	1	2	C	$S(O)_2N(CH_3)$	$N(CH_2)_2OH$	$C_{31}H_{47}N_5O_5S$	602.35	602.3
25	1	2	C	$S(O)_2N(CH_3)$	$N(CH_2)_2OCH_3$	$C_{32}H_{49}N_5O_5S$	616.35	616.2
26	1	2	C	$S(O)_2N(CH_3)$	$N(CH_2)_2$-pyrrol-1-yl	$C_{35}H_{50}N_6O_4S$	651.38	651.3

No.	a	b	X	Q	W	Mol. Formula	Calc'd [M+H]	Obsd [M+H]
27	1	2	C	$S(O)_2N(CH_3)$	NCH_2-pyridin-3-yl	$C_{35}H_{48}N_6O_4S$	649.36	649.3
28	1	2	C	$S(O)_2N(CH_3)$	$N(CH_2)_2OC(O)N(CH_3)_2$	$C_{34}H_{52}N_6O_6S$	673.38	673.3
29	1	2	C	$S(O)_2N(CH_3)$	$N(CH_2)_2OC(O)NH$-CH_2CH_3	$C_{34}H_{52}N_6O_5S$	657.39	657.3
30	1	2	C	$S(O)_2N(CH_3)$	$N(CH_2)_3C(O)N(CH_3)_2$	$C_{35}H_{54}N_6O_5S$	671.41	671.4
31	1	2	C	$S(O)_2N(CH_3)$	$N(CH_2)_2NHS(O)_2CH_3$	$C_{32}H_{50}N_6O_6S_2$	679.32	679.3
32	1	2	C	$S(O)_2N(CH_3)$	$N(CH_2)_2N(CH_3)S(O)_2$-CH_3	$C_{33}H_{52}N_6O_6S_2$	693.36	693.3
33	1	2	C	$S(O)_2N(CH_3)$	$N(CH_2)_3S(O)_2N(CH_3)_2$	$C_{34}H_{54}N_6O_6S_2$	707.37	707.3
34	1	2	C	$S(O)_2N(CH_3)$	$NS(O)_2CH_3$	$C_{30}H_{45}N_5O_6S_2$	636.28	636.2
35	0	2	N	$S(O)_2$	$NS(O)_2CH_3$	$C_{27}H_{39}N_5O_6S_2$	594.25	594.2
36	0	2	N	$S(O)_2$	$NC(O)OCH_2CH_3$	$C_{29}H_{41}N_5O_6S$	588.29	588.2
37	0	2	N	$S(O)_2$	O	$C_{26}H_{36}N_4O_5S$	517.26	517.2
38	0	2	N	$S(O)_2$	NCH_2-tetrahydro-furan-2-yl	$C_{31}H_{45}N_5O_5S$	600.33	600.3
39	0	2	N	$S(O)_2$	$NCH_2C(O)N(CH_3)_2$	$C_{30}H_{44}N_6O_5S$	601.33	601.3
40	0	2	N	$S(O)_2$	NC(O)-tetrahydro-furan-2-yl	$C_{31}H_{43}N_5O_6S$	614.31	614.3
41	0	2	N	$S(O)_2$	N-pyridin-4-yl	$C_{31}H_{40}N_6O_4S$	593.30	593.2
42	0	2	N	$S(O)_2$	NCH_2-pyridin-4-yl	$C_{32}H_{42}N_6O_4S$	607.31	607.2
43	0	2	N	$S(O)_2$	$N(CH_2)_2OH$	$C_{28}H_{41}N_5O_5S$	560.30	560.2
44	0	2	N	$S(O)_2$	NCH_3	$C_{27}H_{39}N_5O_4S$	530.29	530.2
45	0	2	C	$N\{S(O)_2CH_3\}$	$NC(O)OCH_3$	$C_{30}H_{43}N_5O_6S$	602.31	602.2
46	0	2	C	$N\{S(O)_2CH_3\}$	$NC(O)CH_3$	$C_{30}H_{43}N_5O_5S$	586.31	586.3
47	0	2	C	$N\{S(O)_2CH_3\}$	$NS(O)_2CF_3$	$C_{29}H_{40}F_3N_5O_6S_2$	676.25	676.2
48	0	2	C	$N\{S(O)_2CH_3\}$	NCH_2CF_3	$C_{30}H_{42}F_3N_5O_4S$	626.31	626.2
49	0	2	C	$N\{S(O)_2CH_3\}$	$N(CH_2)_2C(O)NH_2$	$C_{31}H_{46}N_6O_5S$	615.34	615.3
50	0	2	C	$N\{S(O)_2CH_3\}$	$N(CH_2)_2CF_3$	$C_{31}H_{44}F_3N_5O_4S$	640.32	640.2
51	0	2	C	$N\{S(O)_2CH_3\}$	$N(CH_2)_2CN$	$C_{31}H_{44}N_6O_4S$	597.33	597.2
52	0	2	C	$N\{S(O)_2CH_3\}$	$N(CH_2)_2S(O)_2N(CH_3)_2$	$C_{32}H_{50}N_6O_6S_2$	679.34	679.2
53	0	2	C	$N\{S(O)_2CH_3\}$	$NCH_2C(O)NH_2$	$C_{30}H_{44}N_6O_5S$	601.33	601.2
54	0	2	C	$N\{S(O)_2CH_3\}$	$NCH_2C(O)N(CH_3)_2$	$C_{32}H_{48}N_6O_5S$	629.36	629.3
55	1	2	C	$S(O)_2N(CH_3)$	$NCH_2C(O)N(CH_3)_2$	$C_{33}H_{50}N_6O_5S$	643.37	643.2
56	1	2	C	$S(O)_2N(CH_3)$	$NCH_2C(O)NH_2$	$C_{31}H_{46}N_6O_5S$	615.34	615.2
57	1	2	C	$S(O)_2N(CH_3)$	NCH_2CF_3	$C_{31}H_{44}F_3N_5O_4S$	640.32	640.2
58	1	2	C	$S(O)_2N(CH_3)$	$N(CH_2)_2CF_3$	$C_{32}H_{46}F_3N_5O_4S$	654.34	654.2

No.	a	b	X	Q	W	Mol. Formula	Calc'd [M+H]	Obsd [M+H]
59	1	3	C	$S(O)_2N(CH_3)$	$N(CH_2)_2C(O)NH_2$	$C_{32}H_{48}N_6O_5S$	629.36	629.2
60	1	2	C	$S(O)_2N(CH_3)$	$N(CH_2)_2CN$	$C_{32}H_{46}N_6O_4S$	611.33	611.2
61	1	2	C	$S(O)_2N(CH_3)$	$NC(O)CH_2OCH_3$	$C_{32}H_{47}N_5O_6S$	630.34	630.2
62	1	2	C	$S(O)_2N(CH_3)$	NCH_2CN	$C_{31}H_{44}N_6O_4S$	597.33	597.2
63	0	1	C	$N\{S(O)_2CH_3\}$	$S(O)_2$	$C_{27}H_{38}N_4O_6S_2$	579.22	579.2
64	0	1	C	$N\{C(O)CH_3\}$	$S(O)_2$	$C_{28}H_{38}N_4O_5S$	543.27	543.2
65	0	1	C	$N\{C(O)N(CH_3)_2\}$	$S(O)_2$	$C_{29}H_{41}N_5O_5S$	572.28	572.2
66	0	1	C	$N\{C(O)OCH_3\}$	$S(O)_2$	$C_{28}H_{38}N_4O_6S$	559.25	559.2
67	0	1	C	N{C(O)-pyridin-4-yl}	$S(O)_2$	$C_{32}H_{39}N_5O_5S$	606.28	606.2
68	0	2	N	$N\{S(O)_2CH_3\}(CH_2)_2$	$NS(O)_2CH_2CF_3$	$C_{31}H_{45}F_3N_6O_6S_2$	719.30	719.2
69	0	2	N	$N\{S(O)_2CH_3\}(CH_2)_2$	$S(O)_2$	$C_{29}H_{43}N_5O_6S_2$	622.28	622.2
70	0	2	N	$N\{S(O)_2CH_3\}(CH_2)_2$	$NC(O)N(CH_3)_2$	$C_{32}H_{49}N_7O_5S$	644.35	644.4
71	0	2	N	$N\{S(O)_2CH_3\}(CH_2)_2$	$NS(O)_2N(CH_3)_2$	$C_{31}H_{49}N_7O_6S_2$	680.34	680.2
72	0	2	N	$N\{S(O)_2CH_3\}(CH_2)_2$	$NC(O)NHCH_3$	$C_{31}H_{47}N_7O_5S$	630.35	630.4
73	0	2	N	$S(O)_2(CH_2)_2$	$NS(O)_2N(CH_3)_2$	$C_{28}H_{41}N_5O_5S$	560.30	560.2
74	0	1	C	$S(O)_2(CH_2)_2N(CH_3)$	$NC(O)N(CH_3)_2$	$C_{32}H_{48}N_6O_5S$	629.36	629.2
75	0	2	N	$S(O)_2(CH_2)_2$	$S(O)_2$	$C_{28}H_{40}N_4O_6S_2$	593.25	593.2
76	0	1	C	$S(O)_2(CH_2)_2N(CH_3)$	$S(O)_2$	$C_{29}H_{42}N_4O_6S_2$	607.27	607.2
77	0	2	N	$S(O)_2(CH_2)_2$	$NS(O)_2CH_3$	$C_{29}H_{43}N_5O_6S_2$	622.27	622.2
78	0	2	N	$S(O)_2(CH_2)_2$	NC(O)-tetrahydro-furan-2-yl	$C_{33}H_{47}N_5O_6S$	642.32	642.2
79	0	2	N	$S(O)_2(CH_2)_2$	$NS(O)_2CH_2CF_3$	$C_{30}H_{42}F_3N_5O_6S_2$	690.27	690.2
80	0	2	N	$S(O)_2(CH_2)_2$	$NS(O)_2CH_2CH_3$	$C_{30}H_{45}N_5O_6S_2$	636.28	636.2
81	0	2	N	$S(O)_2(CH_2)_2$	$NS(O)_2CH(CH_3)_2$	$C_{31}H_{47}N_5O_6S_2$	650.31	650.2
82	0	2	N	$S(O)_2(CH_2)_2$	$NC(O)OCH_3$	$C_{30}H_{43}N_5O_6S$	602.31	602.2
83	0	2	N	$S(O)_2(CH_2)_2$	$NC(O)N(CH_3)_2$	$C_{31}H_{46}N_6O_5S$	615.34	615.2
84	0	3	N	$S(O)_2(CH_2)_2$	$NC(O)CH_3$	$C_{31}H_{45}N_5O_5S$	600.33	600.2
85	0	1	C	$S(O)_2(CH_2)_2N(CH_3)$	$NC(O)OCH_3$	$C_{31}H_{45}N_5O_6S$	616.33	616.2
86	0	1	C	$S(O)_2(CH_2)_2N(CH_3)$	$NS(O)_2CH_3$	$C_{30}H_{45}N_5O_6S_2$	636.30	636.2
87	0	2	C	$N\{S(O)_2CH_3\}$	$S(O)_2$	$C_{28}H_{40}N_4O_6S_2$	593.25	593.1
88	0	2	C	$N\{C(O)CH_3\}$	$S(O)_2$	$C_{29}H_{40}N_4O_5S$	557.29	557.2
89	0	2	C	$N\{C(O)OCH_3\}$	$S(O)_2$	$C_{29}H_{40}N_4O_6S$	573.27	573.2
90	0	2	C	N{C(O)-pyridin-4-yl}	$S(O)_2$	$C_{33}H_{41}N_5O_5S$	620.30	620.2
91	0	1	C	$N\{C(O)H\}$	$S(O)_2$	$C_{27}H_{36}N_4O_5S$	529.26	529.2

No.	a	b	X	Q	W	Mol. Formula	Calc'd [M+H]	Obsd [M+H]
92	0	1	C	N{C(O)NHCH$_3$}	S(O)$_2$	$C_{28}H_{39}N_5O_5S$	558.27	558.2
93	0	1	C	N{C(O)NH$_2$}	S(O)$_2$	$C_{27}H_{37}N_5O_5S$	544.27	544.2
94	0	2	N	N{S(O)$_2$N(CH$_3$)$_2$}(CH$_2$)$_2$	NS(O)$_2$CH$_3$	$C_{31}H_{49}N_7O_6S_2$	680.34	680.2
95	0	2	N	N{S(O)$_2$N(CH$_3$)$_2$}(CH$_2$)$_2$	NC(O)N(CH$_3$)$_2$	$C_{33}H_{52}N_8O_5S$	673.40	673.2
96	0	2	N	N{S(O)$_2$N(CH$_3$)$_2$}(CH$_2$)$_2$	NC(O)OCH$_3$	$C_{32}H_{49}N_7O_6S$	660.36	660.2
97	0	2	N	N{S(O)$_2$N(CH$_3$)$_2$}(CH$_2$)$_2$	NC(O)CH$_3$	$C_{32}H_{49}N_7O_5S$	644.37	644.2
98	0	2	N	N{S(O)$_2$N(CH$_3$)$_2$}(CH$_2$)$_2$	NS(O)$_2$N(CH$_3$)$_2$	$C_{32}H_{52}N_8O_6S_2$	709.36	709.2
99	0	2	N	N{S(O)$_2$N(CH$_3$)$_2$}(CH$_2$)$_2$	S(O)$_2$	$C_{30}H_{46}N_6O_6S_2$	651.31	651.2
100	0	2	N	N{C(O)OCH$_3$}(CH$_2$)$_2$	NS(O)$_2$CH$_3$	$C_{31}H_{46}N_6O_6S$	631.32	631.2
101	0	2	N	N{C(O)OCH$_3$}(CH$_2$)$_2$	NC(O)N(CH$_3$)$_2$	$C_{33}H_{49}N_7O_5$	624.38	624.3
102	0	2	N	N{C(O)OCH$_3$}(CH$_2$)$_2$	NC(O)OCH$_3$	$C_{32}H_{46}N_6O_6$	611.31	611.2
103	0	2	N	N{C(O)OCH$_3$}(CH$_2$)$_2$	NC(O)CH$_3$	$C_{32}H_{46}N_6O_5$	595.35	595.2
104	0	2	N	N{C(O)OCH$_3$}(CH$_2$)$_2$	NS(O)$_2$N(CH$_3$)$_2$	$C_{32}H_{49}N_7O_6S$	660.36	660.2
105	0	2	N	N{C(O)OCH$_3$}(CH$_2$)$_2$	NC(O)-tetrahydro-furan-2-yl	$C_{35}H_{50}N_6O_6$	651.40	651.3
106	0	2	N	N{C(O)OCH$_3$}(CH$_2$)$_2$	S(O)$_2$	$C_{30}H_{43}N_5O_6S$	602.29	602.2
107	0	1	C	N{C(O)OCH$_3$}-(CH$_2$)$_2$N(CH$_3$)	S(O)$_2$	$C_{31}H_{45}N_5O_6S$	616.33	616.2
108	0	2	N	N{C(O)N(CH$_3$)$_2$}(CH$_2$)$_2$	NS(O)$_2$CH$_3$	$C_{32}H_{49}N_7O_5S$	644.37	644.2
109	0	2	N	N{C(O)N(CH$_3$)$_2$}(CH$_2$)$_2$	NC(O)N(CH$_3$)$_2$	$C_{34}H_{52}N_8O_4$	637.43	637.3
110	0	2	N	N{C(O)N(CH$_3$)$_2$}(CH$_2$)$_2$	NC(O)OCH$_3$	$C_{33}H_{49}N_7O_5$	624.40	624.3
111	0	2	N	N{C(O)N(CH$_3$)$_2$}(CH$_2$)$_2$	NC(O)CH$_3$	$C_{33}H_{49}N_7O_4$	608.40	608.3
112	0	2	N	N{C(O)N(CH$_3$)$_2$}(CH$_2$)$_2$	NS(O)$_2$N(CH$_3$)$_2$	$C_{33}H_{52}N_8O_5S$	673.40	673.2
113	0	2	N	N{C(O)N(CH$_3$)$_2$}(CH$_2$)$_2$	NC(O)-tetrahydro-furan-2-yl	$C_{36}H_{53}N_7O_5$	664.43	664.3
114	0	1	C	N{C(O)N(CH$_3$)$_2$}-(CH$_2$)$_2$N(CH$_3$)	S(O)$_2$	$C_{32}H_{48}N_6O_5S$	629.36	629.2
115	0	2	C	N{C(O)H}	S(O)$_2$	$C_{28}H_{38}N_4O_5S$	543.27	543.1
116	0	2	C	N{C(O)NHCH$_3$}	S(O)$_2$	$C_{29}H_{41}N_5O_5S$	572.30	572.2
117	0	2	C	N{C(O)NH$_2$}	S(O)$_2$	$C_{28}H_{39}N_5O_5S$	558.28	558.1
118	1	1	C	N{C(O)OCH$_3$}	S(O)$_2$	$C_{29}H_{40}N_4O_6S$	573.27	573.6
119	1	2	N	N{C(O)OCH$_3$}(CH$_2$)$_2$	NS(O)$_2$CH$_3$	$C_{32}H_{48}N_6O_6S$	645.35	645.4
120	1	2	N	N{C(O)OCH$_3$}(CH$_2$)$_2$	NC(O)N(CH$_3$)$_2$	$C_{34}H_{51}N_7O_5$	638.41	638.4
121	1	2	N	N{C(O)OCH$_3$}(CH$_2$)$_2$	NC(O)OCH$_3$	$C_{33}H_{48}N_6O_6$	625.38	625.4
122	1	2	N	N{C(O)OCH$_3$}(CH$_2$)$_2$	NC(O)CH$_3$	$C_{33}H_{48}N_6O_5$	609.39	609.4
123	1	2	N	N{C(O)OCH$_3$}(CH$_2$)$_2$	NS(O)$_2$N(CH$_3$)$_2$	$C_{33}H_{51}N_7O_6S$	674.38	674.4

No.	a	b	X	Q	W	Mol. Formula	Calc'd [M+H]	Obsd [M+H]
124	1	2	N	$N\{C(O)OCH_3\}(CH_2)_2$	NC(O)-tetrahydro-furan-2-yl	$C_{36}H_{52}N_6O_6$	665.41	665.4
125	1	3	N	$N\{C(O)OCH_3\}(CH_2)_2$	$NS(O)_2CH_3$	$C_{33}H_{50}N_6O_6S$	659.37	659.4
126	1	3	N	$N\{C(O)OCH_3\}(CH_2)_2$	$NC(O)CH_3$	$C_{34}H_{50}N_6O_5$	623.40	623.4
127	1	2	N	$N\{C(O)OCH_3\}(CH_2)_2$	$NC(O)NHCH_3$	$C_{33}H_{49}N_7O_5$	624.40	624.4
128	1	2	N	$N\{C(O)OCH_3\}(CH_2)_2$	$S(O)_2$	$C_{31}H_{45}N_5O_6S$	616.33	616.4
129	1	2	C	$N\{C(O)OCH_3\}$-$(CH_2)_2N(CH_3)$	$S(O)_2$	$C_{33}H_{49}N_5O_6S$	644.36	644.4
130	1	1	C	$N\{C(O)OCH_3\}$-$(CH_2)_2N(CH_3)$	$S(O)_2$	$C_{32}H_{47}N_5O_6S$	630.34	630.4
131	1	1	C	$N\{C(O)OCH_3\}$-$(CH_2)_2N(CH_3)$	$NS(O)_2N(CH_3)_2$	$C_{34}H_{53}N_7O_6S$	688.40	688.4
132	1	1	C	$N\{C(O)OCH_3\}$-$(CH_2)_2N(CH_3)$	$NC(O)OCH_3$	$C_{34}H_{50}N_6O_6$	639.40	639.4
133	1	1	C	$N\{C(O)OCH_3\}$-$(CH_2)_2N(CH_3)$	$NS(O)_2CH_3$	$C_{33}H_{50}N_6O_6S$	659.37	659.4
134	1	2	N	$N\{C(O)CH_3\}(CH_2)_2$	$NS(O)_2CH_3$	$C_{32}H_{48}N_6O_5S$	629.36	629.4
135	1	2	N	$N\{C(O)CH_3\}(CH_2)_2$	$NC(O)N(CH_3)_2$	$C_{34}H_{51}N_7O_4$	622.42	622.4
136	1	2	N	$N\{C(O)CH_3\}(CH_2)_2$	$NC(O)OCH_3$	$C_{33}H_{48}N_6O_5$	609.39	609.4
137	1	2	N	$N\{C(O)CH_3\}(CH_2)_2$	$NC(O)CH_3$	$C_{33}H_{48}N_6O_4$	593.39	593.4
138	1	2	N	$N\{C(O)CH_3\}(CH_2)_2$	$NS(O)_2N(CH_3)_2$	$C_{33}H_{51}N_7O_5S$	658.38	658.4
139	1	2	N	$N\{C(O)CH_3\}(CH_2)_2$	NC(O)-tetrahydro-furan-2-yl	$C_{36}H_{52}N_6O_5$	649.42	649.4
140	1	2	N	$N\{C(O)CH_3\}(CH_2)_2$	$NS(O)_2CH_2S(O)_2$-CH_3	$C_{33}H_{50}N_6O_7S_2$	707.34	707.2
141	1	3	N	$N\{C(O)CH_3\}(CH_2)_2$	$NS(O)_2CH_3$	$C_{33}H_{50}N_6O_5S$	643.37	643.4
142	1	3	N	$N\{C(O)CH_3\}(CH_2)_2$	$NC(O)CH_3$	$C_{34}H_{50}N_6O_4$	607.41	607.4
143	1	2	N	$N\{C(O)CH_3\}(CH_2)_2$	$NC(O)NHCH_3$	$C_{33}H_{49}N_7O_4$	608.40	608.4
144	1	2	N	$N\{C(O)CH_3\}(CH_2)_2$	$S(O)_2$	$C_{31}H_{45}N_5O_5S$	600.33	600.4
145	1	2	C	$N\{C(O)CH_3\}(CH_2)_2$	$S(O)_2$	$C_{33}H_{49}N_5O_5S$	628.36	628.4
146	1	1	C	$N\{C(O)CH_3\}(CH_2)_2$ -$N(CH_3)$	$S(O)_2$	$C_{32}H_{47}N_5O_5S$	614.35	614.4
147	1	1	C	$N\{C(O)CH_3\}(CH_2)_2$ -$N(CH_3)$	$NS(O)_2N(CH_3)_2$	$C_{34}H_{53}N_7O_5S$	672.40	672.4
148	1	1	C	$N\{C(O)CH_3\}(CH_2)_2$ -$N(CH_3)$	$NC(O)OCH_3$	$C_{34}H_{50}N_6O_5$	623.40	623.4
149	1	1	C	$N\{C(O)CH_3\}(CH_2)_2$ -$N(CH_3)$	$NS(O)_2CH_3$	$C_{33}H_{50}N_6O_5S$	643.37	643.4
150	1	2	N	$S(O)_2N(CH_3)(CH_2)_2$	$NS(O)_2CH_3$	$C_{31}H_{48}N_6O_6S_2$	665.32	665.2
151	1	2	N	$S(O)_2N(CH_3)(CH_2)_2$	$NS(O)_2N(CH_3)_2$	$C_{33}H_{51}N_7O_5S$	658.38	658.3
152	1	2	N	$S(O)_2N(CH_3)(CH_2)_2$	$NC(O)OCH_3$	$C_{32}H_{48}N_6O_6S$	645.35	645.3

No.	a	b	X	Q	W	Mol. Formula	Calc'd [M+H]	Obsd [M+H]
153	1	2	N	$S(O)_2N(CH_3)(CH_2)_2$	$NC(O)CH_3$	$C_{32}H_{48}N_6O_5S$	629.36	629.3
154	1	2	N	$S(O)_2N(CH_3)(CH_2)_2$	$NS(O)_2N(CH_3)_2$	$C_{32}H_{51}N_7O_6S_2$	694.35	694.3
155	1	3	N	$S(O)_2N(CH_3)(CH_2)_2$	$NC(O)CH_3$	$C_{33}H_{50}N_6O_5S$	643.37	643.3
156	1	2	N	$S(O)_2N(CH_3)(CH_2)_2$	$NC(O)NHCH_3$	$C_{32}H_{49}N_7O_5S$	644.37	644.3
157	1	1	C	$S(O)_2N(CH_3)(CH_2)_2$-$N(CH_3)$	$NS(O)_2N(CH_3)_2$	$C_{33}H_{53}N_7O_6S_2$	708.37	708.3
158	1	2	N	$S(O)_2N(CH_3)(CH_2)_2$	NC(O)-tetrahydro-furan-2-yl	$C_{35}H_{52}N_6O_6S$	685.37	685.3
159	1	2	N	$S(O)_2N(CH_3)(CH_2)_2$	$NS(O)_2CH_2S(O)_2CH_3$	$C_{32}H_{50}N_6O_8S_3$	743.30	743.2
160	1	3	N	$S(O)_2N(CH_3)(CH_2)_2$	$NS(O)_2CH_3$	$C_{32}H_{50}N_6O_6S_2$	679.34	679.3
161	1	2	C	$S(O)_2N(CH_3)(CH_2)_2$-$N(CH_3)$	$S(O)_2$	$C_{32}H_{49}N_5O_6S_2$	664.33	664.3
162	1	1	C	$S(O)_2N(CH_3)(CH_2)_2$-$N(CH_3)$	$S(O)_2$	$C_{31}H_{47}N_5O_6S_2$	650.31	650.3
163	1	1	C	$S(O)_2N(CH_3)(CH_2)_2$-$N(CH_3)$	$NC(O)OCH_3$	$C_{33}H_{50}N_6O_6S$	659.37	659.3
164	0	2	C	$N\{S(O)_2CH_3\}$	$NC(O)N(CH_3)_2$	$C_{31}H_{46}N_6O_5S$	615.34	615.4
165	0	2	C	$N\{S(O)_2CH_3\}$	$NC(O)NHCH_3$	$C_{30}H_{44}N_6O_5S$	601.33	601.2
166	0	2	C	$N\{C(O)N(CH_3)_2\}$	$NC(O)OCH_3$	$C_{32}H_{46}N_6O_5$	595.37	595.4
167	0	2	C	$N\{C(O)N(CH_3)_2\}$	$NC(O)CH_3$	$C_{32}H_{46}N_6O_4$	579.37	579.4
168	0	2	C	$N\{C(O)N(CH_3)_2\}$	$NC(O)N(CH_3)_2$	$C_{33}H_{49}N_7O_4$	608.40	608.4
169	0	2	C	$N\{C(O)N(CH_3)_2$	$NC(O)NHCH_3$	$C_{32}H_{47}N_7O_4$	594.39	594.4
170	0	2	C	$N\{C(O)N(CH_3)_2\}$	$NS(O)_2CH_3$	$C_{31}H_{46}N_6O_5S$	615.34	615.4
171	0	2	C	$N\{S(O)_2CH_3\}$	$NC(O)NH_2$	$C_{29}H_{42}N_6O_5S$	587.31	587.2
172	0	2	C	$N\{C(O)N(CH_3)_2\}$	$NC(O)NH_2$	$C_{31}H_{45}N_7O_4$	580.37	580.2
173	1	2	N	$S(O)_2N(CH_3)(CH_2)_2$	$S(O)_2$	$C_{30}H_{45}N_5O_6S_2$	636.30	636.2
174	1	2	N	$OC(O)N(CH_3)(CH_2)_2$	$NC(O)CH_3$	$C_{33}H_{48}N_6O_5$	609.39	609.4
175	1	2	N	$OC(O)N(CH_3)(CH_2)_2$	$NC(O)N(CH_3)_2$	$C_{34}H_{51}N_7O_5$	638.41	638.4
176	1	2	N	$OC(O)N(CH_3)(CH_2)_2$	$NC(O)OCH_3$	$C_{33}H_{48}N_6O_6$	625.38	625.4
177	1	2	N	$OC(O)N(CH_3)(CH_2)_2$	NC(O)tetrahydro-furan-2-yl	$C_{36}H_{52}N_6O_6$	665.41	665.4
178	1	2	N	$OC(O)N(CH_3)(CH_2)_2$	$NS(O)_2CH_3$	$C_{32}H_{48}N_6O_6S$	645.35	645.4
179	1	2	N	$OC(O)N(CH_3)(CH_2)_2$	$NS(O)_2N(CH_3)_2$	$C_{33}H_{51}N_7O_6S$	674.38	674.4
180	1	2	N	$OC(O)N(CH_3)(CH_2)_2$	$NC(O)NHCH_3$	$C_{33}H_{49}N_7O_5$	624.40	624.4
181	1	3	N	$OC(O)N(CH_3)(CH_2)_2$	$NC(O)CH_3$	$C_{34}H_{50}N_6O_5$	623.40	623.4
182	1	3	N	$OC(O)N(CH_3)(CH_2)_2$	$NS(O)_2CH_3$	$C_{33}H_{50}N_6O_6S$	659.37	659.4
183	1	2	N	$OC(O)N(CH_3)(CH_2)_2$	$S(O)_2$	$C_{31}H_{45}N_5O_6S$	616.33	616.4

No.	a	b	X	Q	W	Mol. Formula	Calc'd [M+H]	Obsd [M+H]
184	1	2	C	$OC(O)N(CH_3)(CH_2)_2$-$N(CH_3)$	$S(O)_2$	$C_{33}H_{49}N_5O_6S$	644.36	643.9
185	1	1	C	$OC(O)N(CH_3)(CH_2)_2$-$N(CH_3)$	$S(O)_2$	$C_{32}H_{47}N_5O_6S$	630.34	630.4
186	1	1	C	$OC(O)N(CH_3)(CH_2)_2$-$N(CH_3)$	$NS(O)_2N(CH_3)_2$	$C_{34}H_{53}N_7O_6S$	688.40	688.4
187	0	2	N	$OC(O)N(CH_3)(CH_2)_2$	$NC(O)CH_3$	$C_{32}H_{46}N_6O_5$	595.37	595.4
188	0	2	N	$OC(O)N(CH_3)(CH_2)_2$	$NC(O)N(CH_3)_2$	$C_{33}H_{49}N_7O_5$	624.40	624.4
189	0	2	N	$OC(O)N(CH_3)(CH_2)_2$	$NC(O)OCH_3$	$C_{32}H_{46}N_6O_6$	611.36	611.4
190	0	2	N	$OC(O)N(CH_3)(CH_2)_2$	NC(O)-tetrahydro-furan-2-yl	$C_{35}H_{50}N_6O_6$	651.40	651.4
191	0	2	N	$OC(O)N(CH_3)(CH_2)_2$	$NS(O)_2CH_3$	$C_{31}H_{46}N_6O_6S$	631.34	631.4
192	0	2	N	$OC(O)N(CH_3)(CH_2)_2$	$NS(O)_2N(CH_3)_2$	$C_{32}H_{49}N_7O_6S$	660.36	660.4
193	0	2	N	$OC(O)N(CH_3)(CH_2)_2$	$NC(O)NHCH_3$	$C_{32}H_{47}N_7O_5$	610.38	610.4
194	0	3	N	$OC(O)N(CH_3)(CH_2)_2$	$NC(O)CH_3$	$C_{33}H_{48}N_6O_5$	609.39	609.4
195	0	3	N	$OC(O)N(CH_3)(CH_2)_2$	$NS(O)_2CH_3$	$C_{32}H_{48}N_6O_6S$	645.35	645.4
196	0	2	N	$OC(O)N(CH_3)(CH_2)_2$	$S(O)_2$	$C_{30}H_{43}N_5O_6S$	602.31	602.2
197	0	1	C	$OC(O)N(CH_3)$-$(CH_2)_2N(CH_3)$	$S(O)_2$	$C_{31}H_{45}N_5O_6S$	616.33	616.2
198	0	1	C	$OC(O)N(CH_3)$-$(CH_2)_2N(CH_3)$	$NS(O)_2N(CH_3)_2$	$C_{33}H_{51}N_7O_6S$	674.38	674.4
199	1	2	N	$SCH_2C(O)$	$NC(O)CH_3$	$C_{31}H_{43}N_5O_4S$	582.32	582.2
200	1	2	N	$SCH_2C(O)$	$NC(O)N(CH_3)_2$	$C_{32}H_{46}N_6O_4S$	611.35	611.4
201	1	2	N	$S(O)_2(CH_2)_2$	$NC(O)OCH_3$	$C_{31}H_{45}N_5O_6S$	616.33	616.2
202	1	2	N	$S(O)_2(CH_2)_2$	$NC(O)CH_3$	$C_{31}H_{45}N_5O_5S$	600.31	600.4
203	1	2	N	$S(O)_2(CH_2)_2$	$NS(O)_2CH_3$	$C_{30}H_{45}N_5O_6S_2$	636.30	636.2
204	1	2	N	$S(O)_2(CH_2)_2$	$NC(O)N(CH_3)_2$	$C_{32}H_{48}N_6O_5S$	629.36	629.4
205	1	2	N	$S(O)_2(CH_2)_2$	$S(O)_2$	$C_{29}H_{42}N_4O_6S_2$	607.27	607.2
206	1	2	N	$S(O)_2CH_2C(O)$	$NC(O)CH_3$	$C_{31}H_{43}N_5O_6S$	614.31	614.2
207	1	1	C	$S(O)_2CH_2C(O)N(CH_3)$	$S(O)_2$	$C_{30}H_{42}N_4O_7S_2$	635.26	635.2
208	1	2	N	$S(O)_2CH_2C(O)$	$NC(O)OCH_3$	$C_{31}H_{43}N_5O_7S$	630.30	630.2
209	1	2	N	$S(O)_2CH_2C(O)$	NC(O)-tetrahydro-furan-2-yl	$C_{34}H_{47}N_5O_7S$	670.34	670.2
210	1	2	N	$S(O)_2CH_2C(O)$	$S(O)_2$	$C_{29}H_{40}N_4O_7S_2$	621.25	621.2
211	1	1	C	$S(O)_2CH_2C(O)N(CH_3)$	$NS(O)_2N(CH_3)_2$	$C_{32}H_{48}N_6O_7S_2$	693.32	693.2
212	1	2	N	$S(O)_2$	NC(O)tetrahydro-furan-2-yl	$C_{32}H_{45}N_5O_6S$	628.31	628.2
213	1	2	N	$S(O)_2$	$NC(O)CH_3$	$C_{29}H_{41}N_5O_5S$	572.28	572.2
214	1	1	C	$S(O)_2N(CH_3)$	$S(O)_2$	$C_{28}H_{40}N_4O_6S_2$	593.25	593.2

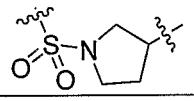
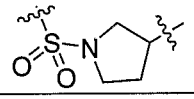
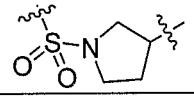
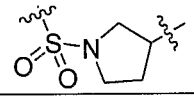
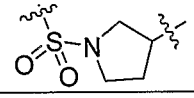
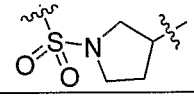
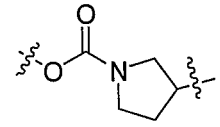
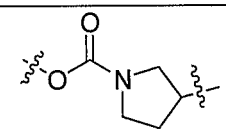
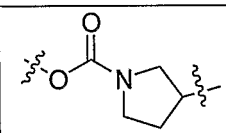
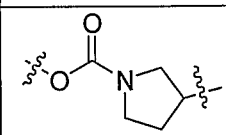
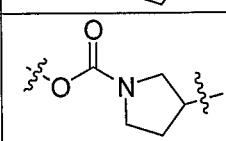
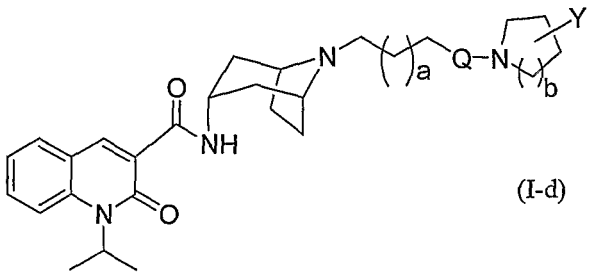
No.	a	b	X	Q	W	Mol. Formula	Calc'd [M+H]	Obsd [M+H]
215	1	2	N	$S(O)_2$	$S(O)_2$	$C_{27}H_{38}N_4O_6S_2$	579.24	579.2
216	1	1	C	$S(O)_2N(CH_3)$	$NS(O)_2N(CH_3)_2$	$C_{30}H_{46}N_6O_6S_2$	651.31	651.2
217	1	2	N	$S(O)_2$	$NC(O)OCH_3$	$C_{29}H_{41}N_5O_6S$	588.29	588.2
218	1	2	N	OC(O)	$NS(O)_2CH_3$	$C_{29}H_{41}N_5O_6S$	588.28	588.2
219	1	2	N	OC(O)	NC(O)tetrahydro-furan-2-yl	$C_{33}H_{45}N_5O_6$	608.34	608.4
220	1	1	C	$OC(O)N(CH_3)$	$S(O)_2$	$C_{29}H_{40}N_4O_6S$	573.28	573.2
221	1	1	C	$OC(O)N(CH_3)$	$NS(O)_2N(CH_3)_2$	$C_{31}H_{46}N_6O_6S$	631.34	631.2
222	1	2	N	OC(O)	$NC(O)OCH_3$	$C_{30}H_{41}N_5O_6$	568.32	568.2
223	1	2	N	OC(O)	$NC(O)CH_3$	$C_{30}H_{41}N_5O_5$	552.31	552.4
224	1	2	N		$NC(O)OCH_3$	$C_{33}H_{48}N_6O_6S$	657.35	657.4
225	1	2	N		NC(O)tetrahydro-furan-2-yl	$C_{36}H_{52}N_6O_6S$	697.38	697.4
226	1	2	N		$NC(O)CH_3$	$C_{33}H_{48}N_6O_5S$	641.36	641.4
227	1	2	N		$NS(O)_2CH_3$	$C_{32}H_{48}N_6O_6S_2$	677.32	677.2
228	1	3	N		$NC(O)CH_3$	$C_{34}H_{50}N_6O_5S$	655.37	655.4
229	1	3	N		$NS(O)_2CH_3$	$C_{33}H_{50}N_6O_6S_2$	691.34	691.4
230	1	2	N		NC(O)tetrahydro-furan-2-yl	$C_{37}H_{52}N_6O_6$	677.41	677.4
231	1	2	N		$NC(O)CH_3$	$C_{34}H_{48}N_6O_5$	621.39	621.4
232	1	2	N		$NS(O)_2CH_3$	$C_{33}H_{48}N_6O_6S$	657.35	657.4
233	1	3	N		$NC(O)CH_3$	$C_{35}H_{50}N_6O_5$	635.40	635.4
234	1	3	N		$NS(O)_2CH_3$	$C_{34}H_{50}N_6O_6S$	671.37	671.4

Table 2

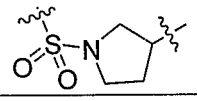
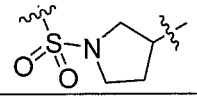
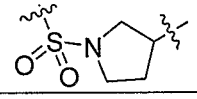
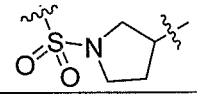
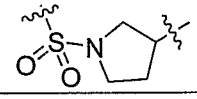
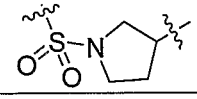
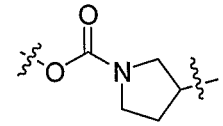
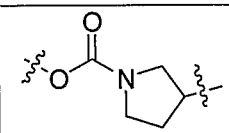
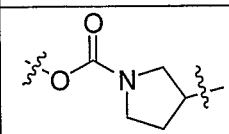


(I-d)

No.	*a*	*b*	Q	Y	Molecular Formula	Calc'd [M+H]	Obsd [M+H]
235	1	1	$S(O)_2$	3-$N(CH_3)_2$	$C_{29}H_{43}N_5O_4S$	558.30	558.3
236	1	2	$S(O)_2$	4-$CH_2NHS(O)_2CH_3$	$C_{30}H_{45}N_5O_6S_2$	636.30	636.3
237	0	1	$S(O)_2$	3-$N(CH_3)C(O)CH_3$	$C_{29}H_{41}N_5O_5S$	572.30	572.2
238	0	1	$S(O)_2$	3-$N(CH_3)_2$	$C_{28}H_{41}N_5O_4S$	544.30	544.2
239	0	2	$S(O)_2$	4-OH	$C_{27}H_{38}N_4O_5S$	531.27	531.1
240	0	2	$N\{S(O)_2CH_3\}(CH_2)_2$	3-$OC(O)N(CH_3)_2$	$C_{33}H_{50}N_6O_6S$	659.37	659.4
241	0	2	$N\{S(O)_2CH_3\}(CH_2)_2$	3-$NHC(O)CH_3$	$C_{32}H_{48}N_6O_5S$	629.36	629.4
242	0	2	$N\{S(O)_2CH_3\}(CH_2)_2$	2-$C(O)NH_2$	$C_{31}H_{46}N_6O_5S$	615.34	615.2
243	0	2	$N\{S(O)_2CH_3\}(CH_2)_2$	3-$N(CH_3)S(O)_2CH_3$	$C_{32}H_{50}N_6O_6S_2$	679.34	679.2
244	0	2	$S(O)_2(CH_2)_2$	3-$N(CH_3)C(O)OCH_3$	$C_{32}H_{47}N_5O_6S$	630.34	630.2
245	0	2	$S(O)_2(CH_2)_2$	3-$N(CH_3)C(O)N(CH_3)_2$	$C_{33}H_{50}N_6O_5S$	643.37	643.4
246	0	2	$S(O)_2(CH_2)_2$	3-$NHC(O)CH_3$	$C_{31}H_{45}N_5O_5S$	600.33	600.2
247	0	2	$S(O)_2(CH_2)_2$	4-$CH_2NHS(O)_2CH_3$	$C_{31}H_{47}N_5O_6S_2$	650.31	650.2
248	0	2	$S(O)_2(CH_2)_2$	3-$OC(O)N(CH_3)_2$	$C_{32}H_{47}N_5O_6S$	630.34	630.2
249	1	2	$N\{C(O)OCH_3\}(CH_2)_2$	3-$N(CH_3)S(O)_2CH_3$	$C_{34}H_{52}N_6O_6S$	673.38	673.4
250	1	2	$N\{C(O)OCH_3\}(CH_2)_2$	3-$N(CH_3)C(O)OCH_3$	$C_{35}H_{52}N_6O_6$	653.41	653.4
251	1	2	$N\{C(O)OCH_3\}(CH_2)_2$	3-$N(CH_3)C(O)CH_3$	$C_{35}H_{52}N_6O_5$	637.42	637.4
252	1	2	$N\{C(O)OCH_3\}(CH_2)_2$	3-$NHS(O)_2N(CH_3)_2$	$C_{34}H_{53}N_7O_6S$	688.40	688.4
253	1	2	$N\{C(O)OCH_3\}(CH_2)_2$	3-$NHC(O)OCH_3$	$C_{34}H_{50}N_6O_6$	639.40	639.4
254	1	2	$N\{C(O)OCH_3\}(CH_2)_2$	3-$NHC(O)CH_3$	$C_{34}H_{50}N_6O_5$	623.40	623.4
255	1	2	$N\{C(O)OCH_3\}(CH_2)_2$	3-$NHC(O)N(CH_3)_2$	$C_{35}H_{53}N_7O_5$	652.43	652.4
256	1	2	$N\{C(O)OCH_3\}(CH_2)_2$	3-$C(O)NH_2$	$C_{33}H_{48}N_6O_5$	609.39	609.4
257	1	2	$N\{C(O)OCH_3\}(CH_2)_2$	4-$OC(O)N(CH_3)_2$	$C_{35}H_{52}N_6O_6$	653.41	653.4
258	1	2	$N\{C(O)OCH_3\}(CH_2)_2$	4-$CH_2NHS(O)_2CH_3$	$C_{34}H_{52}N_6O_6S$	673.38	673.4
259	1	1	$N\{C(O)OCH_3\}(CH_2)_2$	3-$NHC(O)CH_3$	$C_{33}H_{48}N_6O_5$	609.39	609.4

No.	*a*	*b*	Q	Y	Molecular Formula	Calc'd [M+H]	Obsd [M+H]
260	1	1	$N\{C(O)OCH_3\}(CH_2)_2$	$3\text{-}NHC(O)OCH_3$	$C_{33}H_{48}N_6O_6$	625.38	625.4
261	1	1	$N\{C(O)OCH_3\}(CH_2)_2$	$3\text{-}NHS(O)_2N(CH_3)_2$	$C_{33}H_{51}N_7O_6S$	674.38	674.4
262	1	1	$N\{C(O)OCH_3\}(CH_2)_2$	$3\text{-}OC(O)N(CH_3)_2$	$C_{34}H_{50}N_6O_6$	639.40	639.4
263	1	1	$N\{C(O)OCH_3\}(CH_2)_2$	$3\text{-}N(CH_3)C(O)CH_3$	$C_{34}H_{50}N_6O_5$	623.40	623.4
264	1	1	$N\{C(O)OCH_3\}(CH_2)_2$	$3\text{-}N(CH_3)S(O)_2N(CH_3)_2$	$C_{34}H_{53}N_7O_6S$	688.40	688.4
265	1	1	$N\{C(O)OCH_3\}(CH_2)_2$	$3\text{-}N(CH_3)C(O)N(CH_3)_2$	$C_{35}H_{53}N_7O_5$	652.43	652.4
266	1	2	$N\{C(O)CH_3\}(CH_2)_2$	$3\text{-}N(CH_3)S(O)_2CH_3$	$C_{34}H_{52}N_6O_5S$	657.39	657.4
267	1	2	$N\{C(O)CH_3\}(CH_2)_2$	$3\text{-}N(CH_3)C(O)OCH_3$	$C_{35}H_{52}N_6O_5$	637.42	637.4
268	1	2	$N\{C(O)CH_3\}(CH_2)_2$	$3\text{-}NHS(O)_2N(CH_3)_2$	$C_{34}H_{53}N_7O_5S$	672.40	672.4
269	1	2	$N\{C(O)CH_3\}(CH_2)_2$	$3\text{-}NHC(O)OCH_3$	$C_{34}H_{50}N_6O_5$	623.40	623.4
270	1	2	$N\{C(O)CH_3\}(CH_2)_2$	$3\text{-}NHC(O)CH_3$	$C_{34}H_{50}N_6O_4$	607.41	607.4
271	1	2	$N\{C(O)CH_3\}(CH_2)_2$	$3\text{-}NHC(O)N(CH_3)_2$	$C_{35}H_{53}N_7O_4$	636.43	636.4
272	1	2	$N\{C(O)CH_3\}(CH_2)_2$	$3\text{-}C(O)NH_2$	$C_{33}H_{48}N_6O_4$	593.39	593.4
273	1	2	$N\{C(O)CH_3\}(CH_2)_2$	$4\text{-}OC(O)N(CH_3)_2$	$C_{35}H_{52}N_6O_5$	637.42	637.4
274	1	2	$N\{C(O)CH_3\}(CH_2)_2$	$4\text{-}CH_2NHS(O)_2CH_3$	$C_{34}H_{52}N_6O_5S$	657.39	657.4
275	1	1	$N\{C(O)CH_3\}(CH_2)_2$	$3\text{-}NHC(O)CH_3$	$C_{33}H_{48}N_6O_4$	593.39	593.4
276	1	1	$N\{C(O)CH_3\}(CH_2)_2$	$3\text{-}NHC(O)OCH_3$	$C_{33}H_{48}N_6O_5$	609.39	609.4
277	1	1	$N\{C(O)CH_3\}(CH_2)_2$	$3\text{-}NHS(O)_2N(CH_3)_2$	$C_{33}H_{51}N_7O_5S$	658.38	658.4
278	1	1	$N\{C(O)CH_3\}(CH_2)_2$	$3\text{-}OC(O)N(CH_3)_2$	$C_{34}H_{50}N_6O_5$	623.40	623.4
279	1	1	$N\{C(O)CH_3\}(CH_2)_2$	$3\text{-}N(CH_3)C(O)CH_3$	$C_{34}H_{50}N_6O_4$	607.41	607.4
280	1	1	$N\{C(O)CH_3\}(CH_2)_2$	$3\text{-}N(CH_3)S(O)_2N(CH_3)_2$	$C_{34}H_{53}N_7O_5S$	672.40	672.4
281	1	1	$N\{C(O)CH_3\}(CH_2)_2$	$3\text{-}N(CH_3)C(O)N(CH_3)_2$	$C_{35}H_{53}N_7O_4$	636.43	636.4
282	1	2	$S(O)_2N(CH_3)(CH_2)_2$	$3\text{-}N(CH_3)S(O)_2CH_3$	$C_{33}H_{52}N_6O_6S_2$	693.36	693.3
283	1	2	$S(O)_2N(CH_3)(CH_2)_2$	$3\text{-}N(CH_3)C(O)OCH_3$	$C_{34}H_{52}N_6O_6S$	673.38	673.3
284	1	2	$S(O)_2N(CH_3)(CH_2)_2$	$3\text{-}N(CH_3)C(O)CH_3$	$C_{34}H_{52}N_6O_5S$	657.39	657.3
285	1	2	$S(O)_2N(CH_3)(CH_2)_2$	$3\text{-}NHS(O)_2N(CH_3)_2$	$C_{33}H_{53}N_7O_6S_2$	708.37	708.3
286	1	2	$S(O)_2N(CH_3)(CH_2)_2$	$3\text{-}NHC(O)OCH_3$	$C_{33}H_{50}N_6O_6S$	659.37	659.3
287	1	2	$S(O)_2N(CH_3)(CH_2)_2$	$3\text{-}NHC(O)CH_3$	$C_{33}H_{50}N_6O_5S$	643.37	643.3
288	1	2	$S(O)_2N(CH_3)(CH_2)_2$	$3\text{-}NHC(O)N(CH_3)_2$	$C_{34}H_{53}N_7O_5S$	672.40	672.3
289	1	2	$S(O)_2N(CH_3)(CH_2)_2$	$3\text{-}C(O)NH_2$	$C_{32}H_{48}N_6O_5S$	629.36	629.3
290	1	2	$S(O)_2N(CH_3)(CH_2)_2$	$4\text{-}CH_2NHS(O)_2CH_3$	$C_{33}H_{52}N_6O_6S_2$	693.36	693.2
291	1	1	$S(O)_2N(CH_3)(CH_2)_2$	$3\text{-}NHC(O)CH_3$	$C_{32}H_{48}N_6O_5S$	629.36	629.3
292	1	1	$S(O)_2N(CH_3)(CH_2)_2$	$3\text{-}NHC(O)OCH_3$	$C_{32}H_{48}N_6O_6S$	645.35	645.3

No.	*a*	*b*	Q	Y	Molecular Formula	Calc'd [M+H]	Obsd [M+H]
293	1	1	$S(O)_2N(CH_3)(CH_2)_2$	$3\text{-}NHS(O)_2N(CH_3)_2$	$C_{32}H_{51}N_7O_6S_2$	694.35	694.3
294	1	1	$S(O)_2N(CH_3)(CH_2)_2$	$3\text{-}N(CH_3)C(O)CH_3$	$C_{33}H_{50}N_6O_5S$	643.37	643.3
295	1	1	$S(O)_2N(CH_3)(CH_2)_2$	$3\text{-}N(CH_3)S(O)_2N(CH_3)_2$	$C_{33}H_{53}N_7O_6S_2$	708.37	708.3
296	1	2	$S(O)_2N(CH_3)(CH_2)_2$	$3\text{-}OC(O)N(CH_3)_2$	$C_{34}H_{52}N_6O_6S$	673.38	673.4
297	1	2	$S(O)_2N(CH_3)(CH_2)_2$	$3\text{-}OC(O)N(CH_3)_2$	$C_{30}H_{45}N_5O_6S_2$	636.30	636.2
298	1	2	$OC(O)N(CH_3)(CH_2)_2$	$3\text{-}C(O)NH_2$	$C_{33}H_{48}N_6O_5$	609.39	609.4
299	1	2	$OC(O)N(CH_3)(CH_2)_2$	$3\text{-}N(CH_3)S(O)_2CH_3$	$C_{34}H_{52}N_6O_6S$	673.38	673.4
300	1	2	$OC(O)N(CH_3)(CH_2)_2$	$4\text{-}CH_2NHS(O)_2CH_3$	$C_{34}H_{52}N_6O_6S$	673.38	673.4
301	1	2	$OC(O)N(CH_3)(CH_2)_2$	4-OH	$C_{32}H_{47}N_5O_5$	582.37	582.4
302	1	2	$OC(O)N(CH_3)(CH_2)_2$	$4\text{-}OC(O)N(CH_3)_2$	$C_{35}H_{52}N_6O_6$	653.41	653.4
303	1	1	$OC(O)N(CH_3)(CH_2)_2$	$3\text{-}OC(O)N(CH_3)_2$	$C_{34}H_{50}N_6O_6$	639.40	639.4
304	1	1	$OC(O)N(CH_3)(CH_2)_2$	$3\text{-}N(CH_3)S(O)_2CH_3$	$C_{33}H_{50}N_6O_6S$	659.37	659.4
305	1	1	$OC(O)N(CH_3)(CH_2)_2$	$3\text{-}N(CH_3)S(O)_2N(CH_3)_2$	$C_{34}H_{53}N_7O_6S$	688.40	688.4
306	1	1	$OC(O)N(CH_3)(CH_2)_2$	$3\text{-}N(CH_3)C(O)CH_3$	$C_{34}H_{50}N_6O_5$	623.40	623.4
307	0	2	$OC(O)N(CH_3)(CH_2)_2$	$3\text{-}C(O)NH_2$	$C_{32}H_{46}N_6O_5$	595.37	595.4
308	0	2	$OC(O)N(CH_3)(CH_2)_2$	$3\text{-}N(CH_3)S(O)_2CH_3$	$C_{33}H_{50}N_6O_6S$	659.37	659.4
309	0	2	$OC(O)N(CH_3)(CH_2)_2$	$4\text{-}CH_2NHS(O)_2CH_3$	$C_{33}H_{50}N_6O_6S$	659.37	659.4
310	0	2	$OC(O)N(CH_3)(CH_2)_2$	4-OH	$C_{31}H_{45}N_5O_5$	568.36	568.4
311	0	2	$OC(O)N(CH_3)(CH_2)_2$	$4\text{-}OC(O)N(CH_3)_2$	$C_{34}H_{50}N_6O_6$	639.40	639.4
312	0	1	$OC(O)N(CH_3)(CH_2)_2$	$3\text{-}OC(O)N(CH_3)_2$	$C_{33}H_{48}N_6O_6$	625.38	625.4
313	0	1	$OC(O)N(CH_3)(CH_2)_2$	$3\text{-}N(CH_3)S(O)_2CH_3$	$C_{32}H_{48}N_6O_6S$	645.35	645.4
314	0	1	$OC(O)N(CH_3)(CH_2)_2$	$3\text{-}N(CH_3)S(O)_2N(CH_3)_2$	$C_{33}H_{51}N_7O_6S$	674.38	674.4
315	0	1	$OC(O)N(CH_3)(CH_2)_2$	$3\text{-}N(CH_3)C(O)CH_3$	$C_{33}H_{48}N_6O_5$	609.39	609.4
316	1	2	$SCH_2C(O)$	$4\text{-}N(CH_3)S(O)_2CH_3$	$C_{32}H_{47}N_5O_5S_2$	646.32	646.2
317	1	2	$S(O)_2(CH_2)_2$	$4\text{-}N(CH_3)S(O)_2CH_3$	$C_{32}H_{49}N_5O_6S_2$	664.33	664.2
318	1	2	$S(O)_2CH_2C(O)$	$4\text{-}N(CH_3)S(O)_2CH_3$	$C_{32}H_{47}N_5O_7S_2$	678.31	678.2
319	1	2	$S(O)_2CH_2C(O)$	$3\text{-}C(O)NH_2$	$C_{31}H_{43}N_5O_6S$	614.31	614.2
320	1	2	$S(O)_2$	$4\text{-}CH_2NHC(O)OCH_3$	$C_{31}H_{45}N_5O_6S$	616.33	616.2
321	1	2	$S(O)_2$	$4\text{-}CH_2N(CH_3)S(O)_2CH_3$	$C_{31}H_{47}N_5O_6S_2$	650.31	650.2
322	1	2	$S(O)_2$	4-OH	$C_{28}H_{40}N_4O_5S$	545.29	545.2
323	1	2	$S(O)_2$	$4\text{-}OC(O)N(CH_3)_2$	$C_{31}H_{45}N_5O_6S$	616.33	616.2
324	1	2	$S(O)_2$	$3\text{-}C(O)NH_2$	$C_{29}H_{41}N_5O_5S$	572.30	572.2
325	1	2	$S(O)_2$	$3\text{-}N(CH_3)S(O)_2CH_3$	$C_{30}H_{45}N_5O_6S_2$	636.30	636.2

No.	*a*	*b*	Q	Y	Molecular Formula	Calc'd [M+H]	Obsd [M+H]
326	1	1	$S(O)_2$	3-$N(CH_3)C(O)CH_3$	$C_{30}H_{43}N_5O_5S$	586.31	586.2
327	1	1	$S(O)_2$	3-$OC(O)N(CH_3)_2$	$C_{30}H_{43}N_5O_6S$	602.31	602.2
328	1	2	OC(O)	4-$CH_2NHC(O)OCH_3$	$C_{32}H_{45}N_5O_6$	596.35	596.4
329	1	2	OC(O)	4-$CH_2NHS(O)_2CH_3$	$C_{31}H_{45}N_5O_6S$	616.33	616.2
330	1	2	OC(O)	4-$CH_2N(CH_3)S(O)_2CH_3$	$C_{32}H_{47}N_5O_6S$	630.34	630.4
331	1	2	OC(O)	4-$OC(O)N(CH_3)_2$	$C_{32}H_{45}N_5O_6$	596.35	596.4
332	1	2	OC(O)	3-$C(O)NH_2$	$C_{30}H_{41}N_5O_5$	552.33	552.2
333	1	2	OC(O)	3-$N(CH_3)C(O)CH_3$	$C_{32}H_{45}N_5O_5$	580.36	580.4
334	1	2	OC(O)	3-$N(CH_3)S(O)_2CH_3$	$C_{31}H_{45}N_5O_6S$	616.33	616.2
335	1	1	OC(O)	3-$N(CH_3)C(O)CH_3$	$C_{31}H_{43}N_5O_5$	566.34	566.4
336	1	1	OC(O)	3-$OC(O)N(CH_3)_2$	$C_{31}H_{43}N_5O_6$	582.34	582.4
337	1	2	OC(O)	3-CH_2OH	$C_{30}H_{42}N_4O_5$	539.33	539.4
338	1	2	OC(O)	4-OH	$C_{29}H_{40}N_4O_5$	525.30	525.2
339	1	2		4-OH	$C_{32}H_{47}N_5O_5S$	614.35	614.2
340	1	2		4-$CH_2NHS(O)_2CH_3$	$C_{34}H_{52}N_6O_6S_2$	705.36	705.4
341	1	2		3-$C(O)NH_2$	$C_{33}H_{48}N_6O_5S$	641.36	641.4
342	1	1		3-$N(CH_3)S(O)_2CH_3$	$C_{33}H_{50}N_6O_6S_2$	691.34	691.2
343	1	1		3-$N(CH_3)CH_2$-$C(O)N(CH_3)_2$	$C_{32}H_{48}N_6O_5S$	629.36	629.4
344	1	2		4-$OC(O)N(CH_3)_2$	$C_{35}H_{52}N_6O_6S$	685.38	685.4
345	1	2		4-OH	$C_{33}H_{47}N_5O_5$	594.37	594.4
346	1	2		4-$OC(O)N(CH_3)_2$	$C_{36}H_{52}N_6O_6$	665.41	665.4
347	1	2		4-$CH_2NHS(O)_2CH_3$	$C_{35}H_{52}N_6O_6S$	685.38	685.4

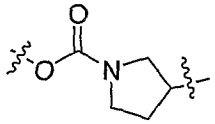
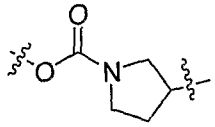
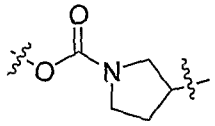
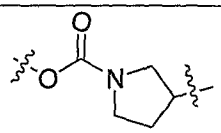
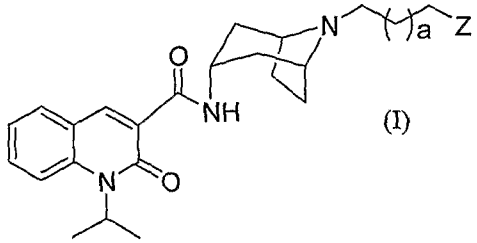
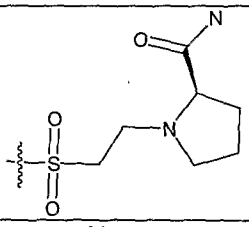
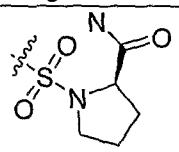
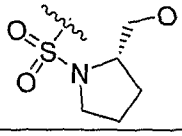
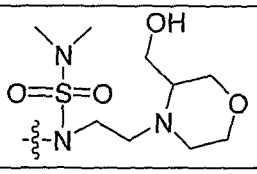
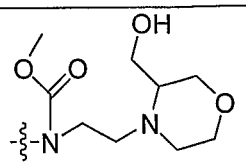
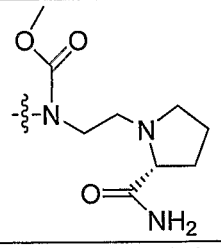
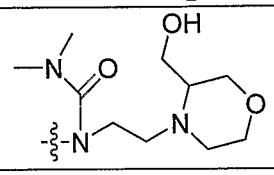
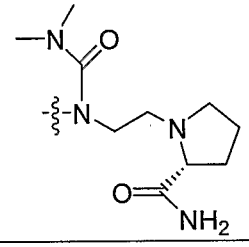
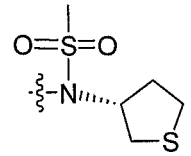
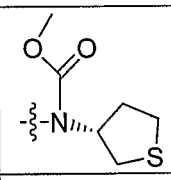
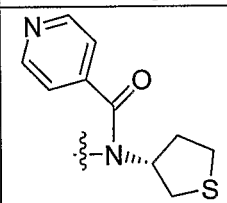
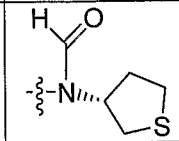
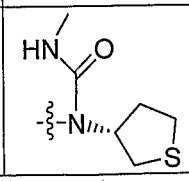
No.	*a*	*b*	Q	Y	Molecular Formula	Calc'd [M+H]	Obsd [M+H]
348	1	2		4-$CH_2NHC(O)OCH_3$	$C_{36}H_{52}N_6O_6$	665.41	665.4
349	1	1		3-$N(CH_3)S(O)_2CH_3$	$C_{34}H_{50}N_6O_6S$	671.37	671.4
350	1	1		3-$OC(O)N(CH_3)_2$	$C_{35}H_{50}N_6O_6$	651.40	651.4
351	1	1		3-$N(CH_3)CH_2$-$C(O)N(CH_3)_2$	$C_{33}H_{48}N_6O_5$	609.39	609.4

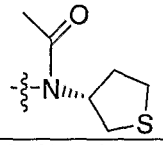
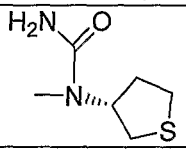
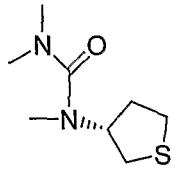
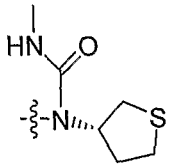
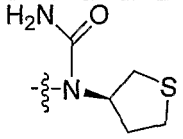
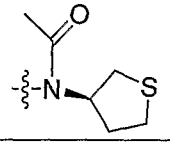
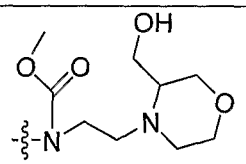
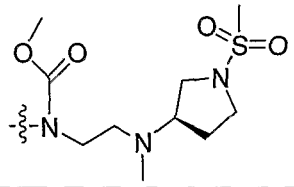
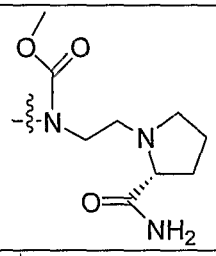
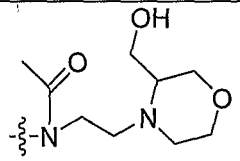
Table 3

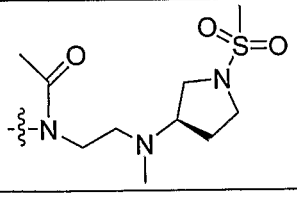
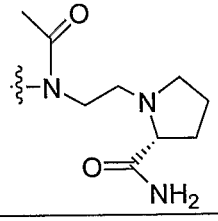
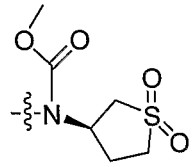
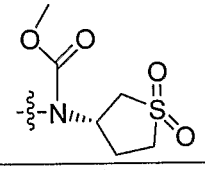
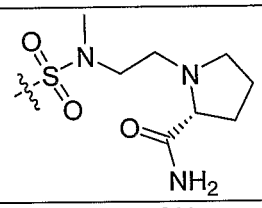
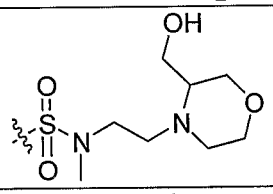
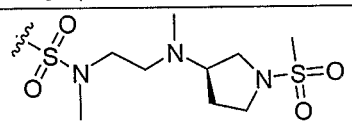
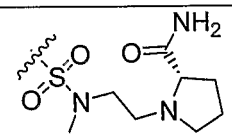
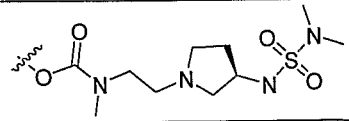
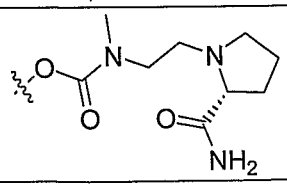


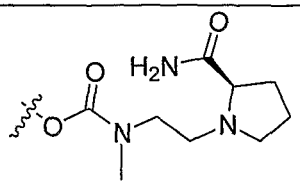
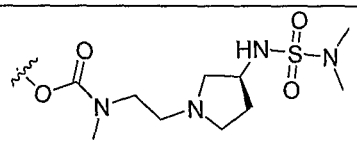
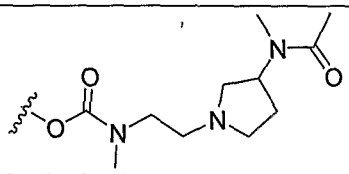
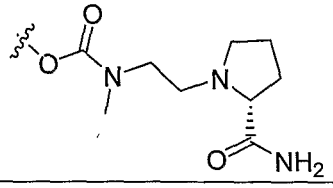
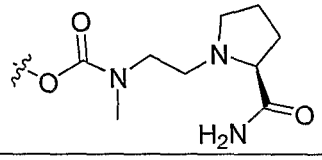
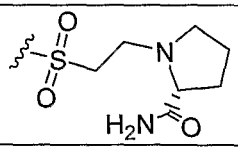
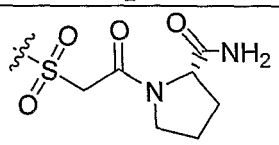
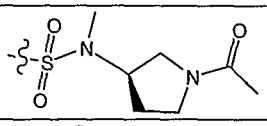
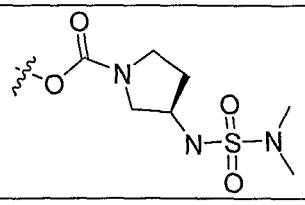
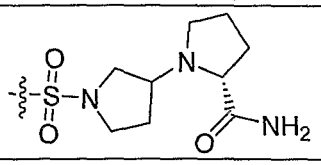
(I)

No.	a	Z	Molecular Formula	Calc'd [M+H]	Obsd [M+H]
352	0		$C_{29}H_{41}N_5O_5S$	572.30	572.3
353	1		$C_{28}H_{39}N_5O_5S$	558.28	558.3
354	0		$C_{27}H_{38}N_4O_5S$	531.27	531.2
355	0		$C_{31}H_{48}N_6O_6S$	633.35	633.2

No.	a	Z	Molecular Formula	Calc'd [M+H]	Obsd [M+H]
356	0		$C_{31}H_{45}N_5O_6$	584.35	584.2
357	0		$C_{31}H_{44}N_6O_5$	581.35	581.2
358	0		$C_{32}H_{48}N_6O_5$	597.39	597.3
359	0		$C_{32}H_{47}N_7O_4$	594.39	594.3
360	0		$C_{27}H_{38}N_4O_4S_2$	547.25	547.2
361	0		$C_{28}H_{38}N_4O_4S$	527.28	527.2
362	0		$C_{32}H_{39}N_5O_3S$	574.29	574.2
363	0		$C_{27}H_{36}N_4O_3S$	497.27	497.2
364	0		$C_{28}H_{39}N_5O_3S$	526.29	526.2

No.	a	Z	Molecular Formula	Calc'd [M+H]	Obsd [M+H]
365	0		$C_{28}H_{38}N_4O_3S$	511.28	511.2
366	0		$C_{27}H_{37}N_5O_3S$	512.28	512.2
367	0		$C_{29}H_{41}N_5O_3S$	540.31	540.2
368	0		$C_{28}H_{39}N_5O_3S$	526.29	526.2
369	0		$C_{27}H_{37}N_5O_3S$	512.28	512.2
370	0		$C_{28}H_{38}N_4O_3S$	511.28	511.2
371	1		$C_{32}H_{47}N_5O_6$	598.37	598.4
372	1		$C_{33}H_{50}N_6O_6S$	659.37	659.4
373	1		$C_{32}H_{46}N_6O_5$	595.37	595.4
374	1		$C_{32}H_{47}N_5O_5$	582.37	582.4

No.	a	Z	Molecular Formula	Calc'd [M+H]	Obsd [M+H]
375	1		$C_{33}H_{50}N_6O_5S$	643.37	643.4
376	1		$C_{32}H_{46}N_6O_4$	579.37	579.4
377	0		$C_{28}H_{38}N_4O_6S$	559.27	559.4
378	0		$C_{28}H_{38}N_4O_6S$	559.27	559.4
379	1		$C_{31}H_{46}N_6O_5S$	615.34	615.3
380	1		$C_{31}H_{47}N_5O_6S$	618.34	618.3
381	1		$C_{32}H_{50}N_6O_6S_2$	679.34	679.3
382	1		$C_{31}H_{46}N_6O_5S$	615.34	615.2
383	1		$C_{33}H_{51}N_7O_6S$	674.38	674.4
384	1		$C_{32}H_{46}N_6O_5$	595.37	595.4

No.	a	Z	Molecular Formula	Calc'd [M+H]	Obsd [M+H]
385	1		$C_{32}H_{46}N_6O_5$	595.37	595.4
386	0		$C_{32}H_{49}N_7O_6S$	660.36	660.4
387	0		$C_{33}H_{48}N_6O_5$	609.39	609.4
388	0		$C_{31}H_{44}N_6O_5$	581.35	581.4
389	0		$C_{31}H_{44}N_6O_5$	581.35	581.4
390	1		$C_{30}H_{43}N_5O_5S$	586.31	586.2
391	1		$C_{30}H_{41}N_5O_6S$	600.29	600.2
392	1		$C_{30}H_{43}N_5O_5S$	586.31	586.2
393	1		$C_{30}H_{44}N_6O_6S$	617.32	617.2
394	1		$C_{32}H_{46}N_6O_5S$	627.34	627.4

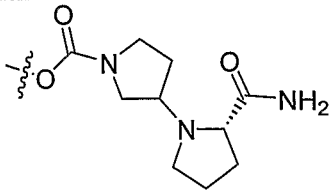
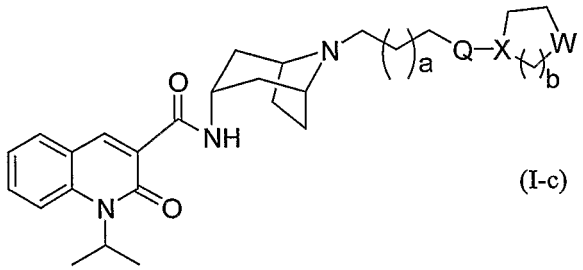
No.	a	Z	Molecular Formula	Calc'd [M+H]	Obsd [M+H]
395	1		$C_{33}H_{46}N_6O_5$	607.37	607.4

Table 4

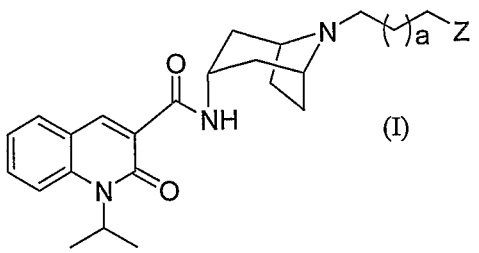


(I-c)

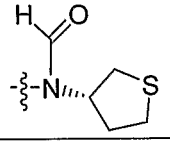
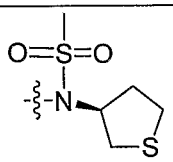
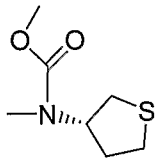
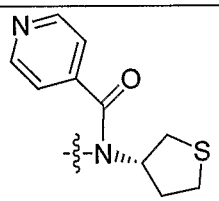
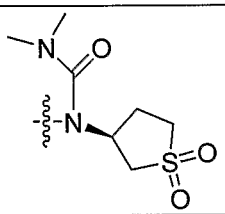
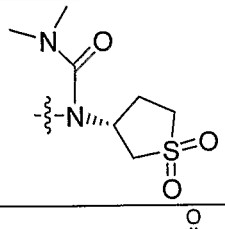
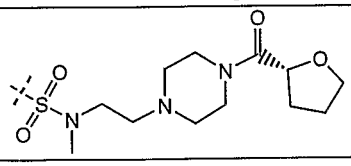
No.	a	b	X	Q	W
396	0	2	C	N{$S(O)_2CH_3$}	NH
397	1	2	C	$S(O)_2N(CH_3)$	NH
398	0	2	C	N{$C(O)N(CH_3)_2$}	$S(O)_2$
399	0	1	C	N{C(O)-pyridin-4-yl}	S
400	0	2	C	N{$S(O)_2CH_3$}	$NS(O)_2CH_3$
401	0	2	C	N{$C(O)CH_3$}	$NC(O)CH_3$
402	0	2	C	N{C(O)H}	NC(O)H
403	0	1	C	N{$S(O)_2CH_3$}	$NS(O)_2CH_3$
404	0	1	C	N{$C(O)CH_3$}	$NC(O)CH_3$
405	0	1	C	N{C(O)H}	NC(O)H
406	1	2	C	N{$C(O)CH_3$}	$NC(O)CH_3$
407	1	2	C	N{C(O)H}	NC(O)H
408	1	1	C	N{$C(O)CH_3$}	$NC(O)CH_3$
409	1	1	C	N{C(O)H}	NC(O)H
410	0	2	C	N{$C(O)N(CH_3)_2$}	NC(O)H
411	1	1	C	$S(O)_2N(CH_3)(CH_2)_2N(CH_3)$	$NS(O)_2CH_3$
412	1	2	N	$SCH_2C(O)$	$NS(O)_2CH_3$
413	1	2	N	$S(O)_2CH_2C(O)$	$NS(O)_2CH_3$

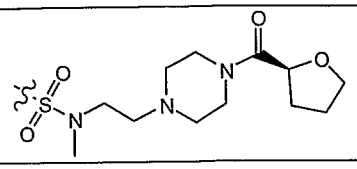
No.	a	b	X	Q	W
414	1	2	N	OC(O)	$N(CH_2)_2OH$
415	1	2	N	OC(O)	$S(O)_2$

Table 5



(I)

No.	a	Z
416	0	
417	0	
418	0	
419	0	
420	0	
421	0	
422	1	

No.	a	Z
423	1	

Example 29: 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 6.3 to about 9.4, typically ranging from about 6.5 to about 8.5.

Example 30: 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 had a 5-HT_4/5-HT_3 receptor subtype selectivity ranging from about 10 to about 95,000, typically ranging from about 100 to about 4000.

Example 31: 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 7.0 to about 9.5, typically ranging from about 7.5 to about 8.5.

Example 32: *In vitro* Voltage Clamp Assay of Inhibition of Potassium Ion Current in Whole Cells Expressing the hERG Cardiac Potassium Channel

CHO-K1 cells stably transfected with hERG cDNA were obtained from Gail Robertson at the University of Wisconsin. Cells were held in cryogenic storage until needed. Cells were expanded and passaged in Dulbecco's Modified Eagles Medium/F12 supplemented with 10 % fetal bovine serum and 200 µg/mL geneticin. Cells were seeded onto poly-D-lysine (100 µg/mL) coated glass coverslips, in 35 mm^2 dishes (containing 2 mL medium) at a density that enabled isolated cells to be selected for whole cell voltage-clamp studies. The dishes were maintained in a humidified, 5% CO_2 environment at 37°C.

Extracellular solution was prepared at least every 7 days and stored at 4°C when not in use. The extracellular solution contained (mM): NaCl (137), KCl (4), $CaCl_2$ (1.8), $MgCl_2$ (1), Glucose (10), 4-(2-hydroxyethyl)-1-piperazineethanesulphonic acid (HEPES) (10), pH 7.4 with NaOH. The extracellular solution, in the absence or presence of test compound, was contained in reservoirs, from which it flowed into the recording chamber at approximately 0.5 mL/min. The intracellular solution was prepared, aliquoted and stored at -20°C until the day of use. The intracellular solution contained (mM): KCl (130), $MgCl_2$ (1), ethylene glycol-bis(beta-aminoethyl ether) *N,N,N',N'*-tetra acetic acid salt (EGTA) (5), MgATP (5), 4-(2-hydroxyethyl)-1-piperazineethanesulphonic acid (HEPES) (10), pH 7.2 with KOH. All experiments were performed at room temperature (20-22°C).

The coverslips on which the cells were seeded were transferred to a recording chamber and perfused continuously. Gigaohm seals were formed between the cell and the patch electrode. Once a stable patch was achieved, recording commenced in the voltage clamp mode, with the initial holding potential at -80 mV. After a stable whole-cell current was achieved, the cells were exposed to test compound. The standard voltage protocol was: step from the holding potential of -80 mV to +20 mV for 4.8 sec, repolarize to -50 mV for 5 sec and then return to the original holding potential (-80 mV). This voltage protocol was run once every 15 sec (0.067 Hz). Peak current amplitudes during the repolarization phase were determined using pClamp software. Test compounds at a concentration of 3 μM were perfused over the cells for 5 minutes, followed by a 5-minute washout period in the absence of compound. Finally a positive control (cisapride, 20 nM) was added to the perfusate to test the function of the cell. The step from -80 mV to +20 mV activates the hERG channel, resulting in an outward current. The step back to -50 mV results in an outward tail current, as the channel recovers from inactivation and deactivates.

Peak current amplitudes during the repolarization phase were determined using pCLAMP software. The control and test article data were exported to Origin® (OriginLab Corp., Northampton MA) where the individual current amplitudes were normalized to the initial current amplitude in the absence of compound. The normalized current means and standard errors for each condition were calculated and plotted versus the time course of the experiment.

Comparisons were made between the observed K^+ current inhibitions after the five-minute exposure to either the test article or vehicle control (usually 0.3 % DMSO). Statistical comparisons between experimental groups were performed using a two-population, independent t-test (Microcal Origin v. 6.0). Differences were considered significant at $p < 0.05$.

The smaller the percentage inhibition of the potassium ion current in this assay, the smaller the potential for test compounds to change the pattern of cardiac repolarization when used as therapeutic agents. The compounds of the invention which were tested in this assay at a concentration of 3 μM typically exhibited an inhibition of the potassium ion current of less than about 20 %. For example, the compound of Example 17 when tested in this assay exhibited an inhibition of the potassium ion current of less than about 15 %.

Example 33: 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:

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

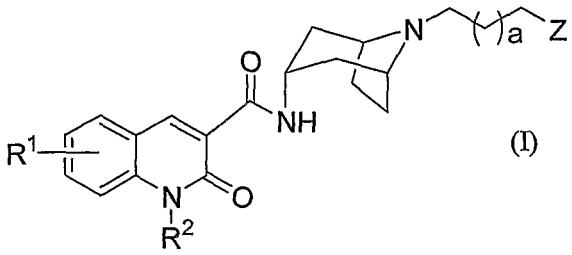
Test compounds which exhibit larger values of the parameters C_{max}, AUC(0-t), and F(%) in this assay are expected to have greater bioavailability when administered orally. The compounds of the invention that were tested in this assay typically had C_{max} values ranging from about 0.01 to about 1.2 μg/mL, more typically ranging from about 0.1 to about 0.5 μg/mL, and AUC(0-t) values typically ranging from about 0.15 to about 1.4 μg·hr/mL, more typically ranging from about 0.2 to about 0.8 μg·hr/mL. By way of example, the compound of Example 17 when tested in this assay had a C_{max} value of 0.06 μg/mL, an AUC(0-t) value of 0.45 μg·hr/mL and oral bioavailability (F(%)) in the rat model of about 20 %.

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)

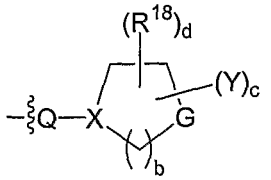
wherein

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

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

a is 0 or 1;

Z is a moiety of formula (a):



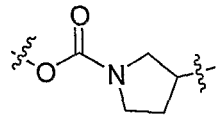
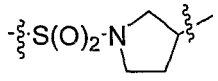
(a)

wherein:

b is 1, 2 or 3;

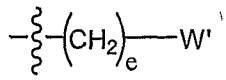
d is 0 or 1;

X is carbon and Q is selected from -A-, $-A(CH_2)_2N(R^4)-$, and $-S(O)_2(CH_2)_2N(R^4)-$;

or X is nitrogen and Q is selected from $-S(O)_2CH_2C(O)-$, $-SCH_2C(O)-$, $-OC(O)-$, $-S(O)_2-$, $-S(O)_2(CH_2)_2-$, $-A(CH_2)_2-$, , and ;

G is W and *c* is 0, wherein W is selected from $-N\{C(O)R^9\}-$, $-N\{S(O)_2R^{10}\}-$, $-N\{C(O)OR^{12}\}-$, $-N\{C(O)NR^{13}R^{14}\}-$, $-N\{S(O)_2NR^{13}R^{14}\}-$, $-N\{R^{16}\}-$, $-S(O)_2-$, -O-, and -S-; provided that when G is W, *c* is 0, and *b* is 1, then X is carbon;

or G is carbon, *c* is 1, and Y is a moiety of formula (b):



(b)

wherein:

e is 0 or 1;

W' 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}, and -N(R^8)R^{16}; provided that when X is nitrogen, *e* is 0, and W' is attached to a carbon bonded to X, then W' is -C(O)N$R^{13}R^{14}$ or -C(O)OR^{12};

A is selected from -S(O)$_2$CH_2C(O)N(R^3)-, -N{C(O)R^5}-, -N{C(O)N$R^{6a}R^{6b}$}-, -N{S(O)$_2$C$_{1-3}$alkyl}-, -N{S(O)$_2$N$R^{6a}R^{6b}$}-, -S(O)$_2$N(R^{7a})-, and -OC(O)N(R^{7b})-;

R^3 and R^4 are independently C$_{1-4}$alkyl;

R^5 is hydrogen, C$_{1-3}$alkyl, C$_{1-3}$alkoxy, C$_{4-6}$cycloalkyl, or pyrimidin-4-yl;

R^{6a} and R^{6b} are independently hydrogen, C$_{5-6}$cycloalkyl, or C$_{1-4}$alkyl, wherein C$_{1-4}$alkyl is optionally substituted with hydroxy, C$_{1-3}$alkoxy, or cyano;

R^{7a} and R^{7b} are independently hydrogen or C$_{1-4}$alkyl;

R^8 is hydrogen or C$_{1-4}$alkyl;

R^9 is hydrogen, furanyl, tetrahydrofuranyl, pyridinyl, or C$_{1-4}$alkyl;

R^{10} is C$_{1-4}$alkyl, optionally substituted with S(O)$_2$C$_{1-3}$alkyl, or with from 1 to 3 halo;

R^{11} is –N$R^{13}R^{14}$, or C$_{1-4}$alkyl;

R^{12} is C$_{1-4}$alkyl;

R^{13}, R^{14}, and R^{15} are independently hydrogen or C$_{1-4}$alkyl;

R^{16} is –(CH_2)$_r$-R^{17}, wherein *r* is 0, 1, 2, or 3;

R^{17} is hydrogen, hydroxy, cyano, C$_{1-3}$alkyl, C$_{1-3}$alkoxy, -C(O)N$R^{13}R^{14}$, -CF_3, pyrrolyl, pyrrolidinyl, pyridinyl, tetrahydrofuranyl, -N(R^8)C(O)OR^{12}, -OC(O)N$R^{13}R^{14}$, -N(R^8)S(O)$_2$CH_3, -S(O)$_2$N$R^{13}R^{14}$, or 2-oxoimidazolidin-1-yl, 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, and pyridinyl; 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$_{1-3}$alkyl optionally substituted with hydroxy;

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 C$_{3-4}$alkyl, and *d* is 0.

3. The compound of Claim 1 or Claim 2, wherein:

X is carbon and Q is -A-;

or X is nitrogen and Q is selected from -OC(O)-, -$S(O)_2$-, -$S(O)_2(CH_2)_2$-, and -$A(CH_2)_2$-.

4. The compound of any one of Claims 1 to 3, wherein:

X is carbon and Q is selected from -$N\{C(O)R^5\}$-, -$N\{C(O)NR^{6a}R^{6b}\}$-, -$N\{S(O)_2C_{1-3}alkyl\}$-, and -$S(O)_2N(R^{7a})$-;

or X is nitrogen and Q is selected from -OC(O)-, -$S(O)_2$-, -$S(O)_2(CH_2)_2$-, -$S(O)_2N(R^{7a})(CH_2)_2$-, -$N\{C(O)R^5\}(CH_2)_2$-, and -$N\{S(O)_2C_{1-3}alkyl\}(CH_2)_2$-.

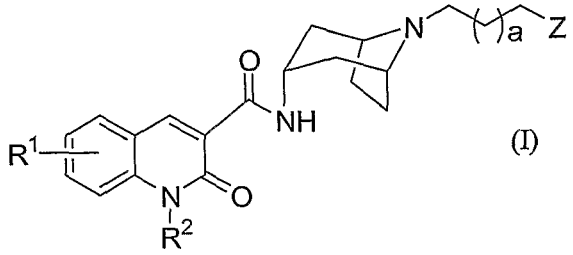
5. The compound of any one of Claims 1 to 4, wherein:

G is W and *c* is 0, wherein W is selected from -$N\{C(O)R^9\}$-, -$N\{S(O)_2R^{10}\}$-, -$N\{C(O)NR^{13}R^{14}\}$-, -$N\{R^{16}\}$-, and -$S(O)_2$-;

or G is carbon, *c* is 1, and Y is a moiety of formula (b), wherein W' is selected from -$N(R^8)C(O)R^9$, -$N(R^8)S(O)_2R^{10}$, -$S(R^{11})(O)_2$, -$N(R^8)C(O)NR^{13}R^{14}$, -OR^{15}, and -$N(R^8)R^{16}$.

6. The compound of any one of Claims 1 to 5, wherein G is W and *c* is 0.

7. A compound of formula (I):



(I)

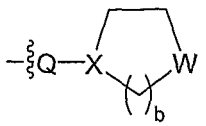
wherein:

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

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

a is 0 or 1;

Z is a moiety of formula (c):



(c)

wherein:

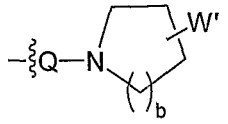
X is carbon and Q is -A-;

or X is nitrogen and Q is selected from -OC(O)-, -$S(O)_2$-, -$S(O)_2(CH_2)_2$-, and -$A(CH_2)_2$-;

b is 1, X is carbon, and W is -$S(O)_2$-;

or *b* is 2, X is carbon or nitrogen, and W is selected from -$S(O)_2$-, -$N\{C(O)R^9\}$-, -$N\{S(O)_2R^{10}\}$-, -$N\{C(O)NR^{13}R^{14}\}$-, and -$N\{R^{16}\}$-; or

Z is a moiety of formula (d):



(d)

wherein:

Q is selected from -OC(O)-, -$S(O)_2$-, -$S(O)_2(CH_2)_2$-, and -$A(CH_2)_2$-;

W' is selected from -$N(R^8)C(O)R^9$, -$N(R^8)S(O)_2R^{10}$, -$S(R^{11})(O)_2$, -$N(R^8)C(O)NR^{13}R^{14}$, -OR^{15}, and -$N(R^8)R^{16}$; provided that when W' is attached to a carbon atom bonded to the nitrogen atom of the ring, that W' is -$C(O)NR^{13}R^{14}$; and

b is 1 or 2;

A is selected from -$S(O)_2CH_2C(O)N(R^3)$-, -$N\{C(O)R^5\}$-, -$N\{C(O)NR^{6a}R^{6b}\}$-, -$N\{S(O)_2C_{1\text{-}3}alkyl\}$-, -$N\{S(O)_2NR^{6a}R^{6b}\}$-, -$S(O)_2N(R^{7a})$-, and -$OC(O)N(R^{7b})$-;

R^3 is $C_{1\text{-}4}$alkyl;

R^5 is hydrogen, $C_{1\text{-}3}$alkyl, or $C_{1\text{-}3}$alkoxy;

R^{6a} and R^{6b} are independently hydrogen or $C_{1\text{-}4}$alkyl;

R^{7a} and R^{7b} are independently hydrogen or $C_{1\text{-}4}$alkyl;

R^8 is hydrogen, methyl, or ethyl;

R^9 is tetrahydrofuranyl, methyl, or ethyl;

R^{10} is methyl or ethyl;

R^{11} is methyl or ethyl;

R^{13} and R^{14} are independently hydrogen, methyl or ethyl;

R^{15} is hydrogen or methyl;

R^{16} is $-(CH_2)_r$-R^{17}, wherein *r* is 0, 1, or 2; and R^{17} is selected from hydroxy, cyano, $C_{1\text{-}3}$alkyl, and $C_{1\text{-}3}$alkoxy; provided that when r is 0, R^{17} is selected from $C_{1\text{-}3}$alkyl; and when r is 1, R^{17} is cyano or $C_{1\text{-}3}$alkyl;

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

8. The compound of Claim 7, wherein Z is a moiety of formula (c), wherein X is nitrogen and Q is selected from -OC(O)-, -$S(O)_2$-, -$S(O)_2(CH_2)_2$-, -$S(O)_2N(R^{7a})(CH_2)_2$-, -N{C(O)C_{1-3}alkoxy}$(CH_2)_2$-, and -N{$S(O)_2C_{1-3}$alkyl}$(CH_2)_2$-.

9. The compound of Claim 7, wherein Z is a moiety of formula (c), wherein X is carbon and Q is selected from -N{C(O)C_{1-3}alkoxy}-, -N{C(O)$NR^{6a}R^{6b}$}-, -N{$S(O)_2C_{1-3}$alkyl}-, and -$S(O)_2N(R^{7a})$-.

10. The compound of Claim 7, wherein Z is a moiety of formula (d), wherein Q is selected from -OC(O)- and -$S(O)_2$-.

11. The compound of Claim 7, wherein the compound is selected from:

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[3-(4-methanesulfonylpiperazine-1-sulfonyl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide;

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[3-(3-dimethylaminopyrrolidine-1-sulfonyl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide;

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{3-[4-(2-hydroxyethyl)piperazine-1-sulfonyl]propyl}-8-azabicyclo[3.2.1]oct-3-yl)amide;

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[3-(4-methylpiperazine-1-sulfonyl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide;

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{2-[methanesulfonyl-(1-propylpiperidin-4-yl)amino]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-amide;

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid [(1*S*,3*R*,5*R*)-8-(3-{[1-(2-methoxyethyl)piperidin-4-yl]methylsulfamoyl}propyl)-8-azabicyclo[3.2.1]oct-3-yl]amide;

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{3-[(1-methanesulfonylpiperidin-4-yl)methylsulfamoyl]propyl}-8-azabicyclo[3.2.1]oct-3-yl)amide;

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid [(1*S*,3*R*,5*R*)-8-(3-{[1-(2-cyanoethyl)piperidin-4-yl]methylsulfamoyl}propyl)-8-azabicyclo[3.2.1]oct-3-yl]amide;

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{2-[(1,1-dioxotetrahydro-1λ^6-thiophen-3-yl)methanesulfonylamino]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)amide;

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{2-[1-(1,1-dioxotetrahydro-1λ^6-thiophen-3-yl)-3,3-dimethylureido]ethyl}-8-azabicyclo[3.2.1]-oct-3-yl)amide;

(1,1-dioxo-tetrahydro-1λ^6-thiophen-3-yl)-(2-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}ethyl)-carbamic acid methyl ester;

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid [(1*S*,3*R*,5*R*)-8-(2-{[2-(4-dimethylcarbamoylpiperazin-1-yl)ethyl]methanesulfonylamino}ethyl)-8-azabicyclo-[3.2.1]oct-3-yl]amide;

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{2-[2-(4-methanesulfonylpiperazin-1-yl)ethanesulfonyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)amide;

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid [(1*S*,3*R*,5*R*)-8-(2-{2-[4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl]ethanesulfonyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]amide;

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{2-[2-(4-ethanesulfonylpiperazin-1-yl)ethanesulfonyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)amide;

(1,1-dioxo-hexahydro-1λ^6-thiopyran-4-yl)-(2-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}ethyl)-carbamic acid methyl ester;

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{2-[1-(1,1-dioxotetrahydro-1λ^6-thiophen-3-yl)-3-methylureido]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)amide;

(2-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)-amino]-8-azabicyclo[3.2.1]oct-8-yl}ethyl)-[2-(4-methanesulfonylpiperazin-1-ylethyl]-carbamic acid methyl ester;

[2-(4-dimethylcarbamoylpiperazin-1-yl)ethyl]-(2-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}-ethyl)-carbamic acid methyl ester;

[2-(4-acetyl-piperazin-1-yl)ethyl]-(2-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}ethyl)-carbamic acid methyl ester;

[2-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)ethyl]-(2-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}ethyl)-carbamic acid methyl ester;

(1,1-dioxo-tetrahydro-1λ^6-thiophen-3-yl)-(3-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}propyl)-carbamic acid methyl ester;

((*S*)-1,1-dioxo-tetrahydro-1λ^6-thiophen-3-yl)-(2-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}ethyl)-carbamic acid methyl ester;

1-isopropyl-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[3-(methyl-{2-[4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl]ethyl}sulfamoyl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide;

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid ((1*S*,3*R*,5*R*)-8-{3-[4-(tetrahydrofuran-2-carbonyl)piperazine-1-sulfonyl]propyl}-8-azabicyclo-[3.2.1]oct-3-yl)amide;

1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {(1*S*,3*R*,5*R*)-8-[3-(4-acetylpiperazine-1-sulfonyl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide;

4-methanesulfonyl-piperazine-1-carboxylic acid 3-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}propyl ester;

4-(tetrahydrofuran-2-carbonyl)piperazine-1-carboxylic acid 3-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-aza-bicyclo[3.2.1]oct-8-yl}propyl ester;

4-acetyl-piperazine-1-carboxylic acid 3-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}propyl ester; and

4-hydroxypiperidine-1-carboxylic acid 3-{(1*S*,3*R*,5*R*)-3-[(1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carbonyl)amino]-8-azabicyclo[3.2.1]oct-8-yl}-propyl ester;

and pharmaceutically-acceptable salts and solvates and stereoisomers thereof.

12. A pharmaceutical composition comprising a therapeutically effective amount of the compound of any one of Claims 1 to 11 and a pharmaceutically-acceptable carrier.

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

14. Use of a compound of any one of Claims 1 to 11 for manufacture of a medicament.

15. The use of Claim 14 wherein the medicament is for the treatment of a medical condition in a mammal associated with 5-HT_4 receptor activity.

16. The use of Claim 15 wherein the disease or condition is a disorder of reduced motility of the gastrointestinal tract.

17. The method of Claim 16, wherein the disorder of reduced motility is constipation-predominant irritable bowel syndrome.

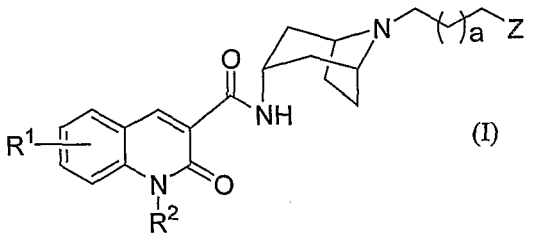
18. A method of treating a mammal having a medical condition associated with 5-HT_4 receptor activity, the method comprising administering to the mammal, a therapeutically effective amount of a pharmaceutical composition comprising a pharmaceutically-acceptable carrier and a compound of any one of Claims 1 to 11.

19. The method of Claim 18 wherein the medical condition is selected from the group consisting of 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.

20. 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 11.

21. The method of Claim 20, wherein the disorder of reduced motility is selected from the group consisting of chronic constipation, constipation-predominant irritable bowel syndrome, diabetic and idiopathic gastroparesis, and functional dyspepsia.

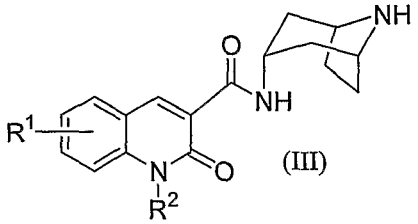
22. A process for preparing a compound of formula (I):



(I)

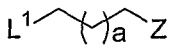
wherein R^1, R^2, *a* and Z are defined as in Claim 1; or a pharmaceutically-acceptable salt or solvate or stereoisomer thereof,

the process comprising reacting a compound of formula (III):



(III)

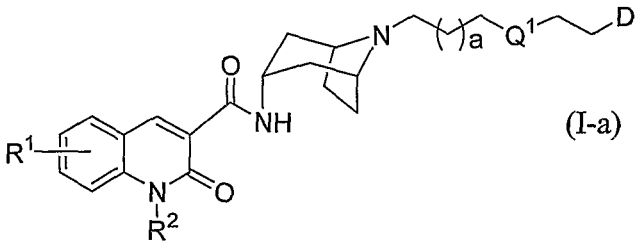
or a salt or stereoisomer thereof, with a compound of formula (IV):



(IV)

wherein L^1 is a leaving group, to provide a compound of formula (I) or a pharmaceutically-acceptable salt or solvate or stereoisomer thereof.

23. A process for preparing a compound of formula (I-a):

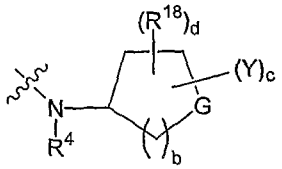


(I-a)

wherein:

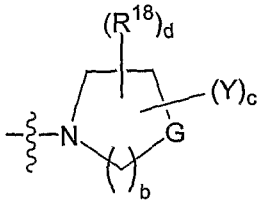
Q^1 is selected from $-S(O)_2-$ and -A-; and

D is selected from a moiety of formula (D1):



(D1) ; and

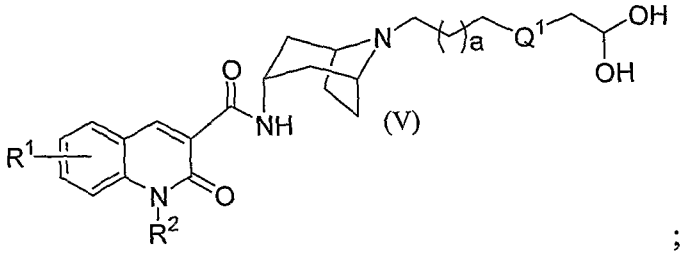
a moiety of formula (D2):



(D2)

wherein R^1, R^2, R^4, R^{18}, A, Y, G, *a*, *b*, *c*, and *d* are defined as in Claim 1; or a pharmaceutically-acceptable salt or solvate or stereoisomer thereof,

the process comprising reacting a compound of formula (V):



(V) ;

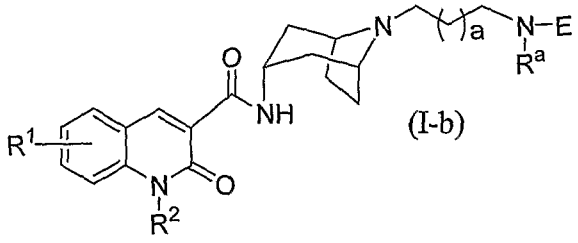
with a compound of formula (VI):

H–D

(VI) ;

to provide a compound of formula (I-a) or a pharmaceutically-acceptable salt or solvate or stereoisomer thereof.

24. A process for preparing a compound of formula (I-b):

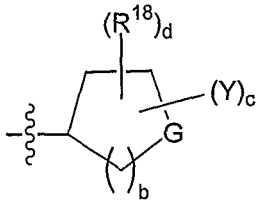


(I-b)

wherein:

R^a is $-C(O)R^5$, $-C(O)NR^{6a}R^{6b}$, $-S(O)_2C_{1-3}$alkyl, or $-S(O)_2NR^{6a}R^{6b}$; and

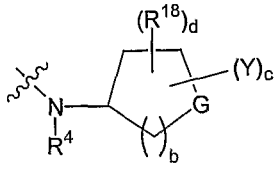
E is selected from a moiety of formula (E1):



(E1)

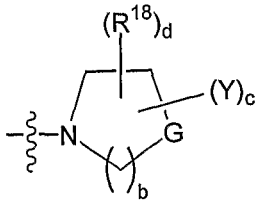
and a moiety of formula -CH_2CH_2-D,

wherein D is selected from a moiety of formula (D1):



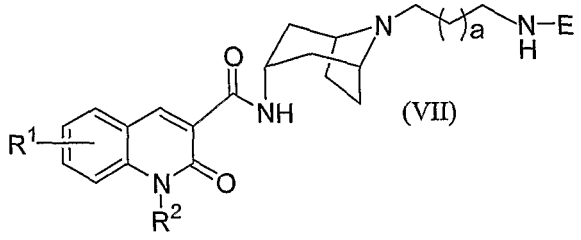
(D1)

and a moiety of formula (D2):



(D2) ;

wherein R^1, R^2, R^4, R^5, R^{6a}, R^{6b}, R^{18}, Y, G, *a*, *b*, *c*, and *d* are as defined in Claim 1; or a pharmaceutically-acceptable salt or solvate or stereoisomer thereof, the process comprising reacting a compound of formula (VII):



(VII)

with a compound of formula (VIII):

L^3–R^a

(VIII)

wherein L^3-R^a is C_{1-4}alkylisocyanate, or L^3 is a leaving group, and R^a is -C(O)R^5, -C(O)$NR^{6a}R^{6b}$, -$S(O)_2C_{1-3}$alkyl, or -$S(O)_2NR^{6a}R^{6b}$;

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

25. The product prepared by the process of any one of Claims 22 to 24.

26. 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 any one of Claims 1 to 11; and

(b) determining the effect caused by the compound on the biological system or sample.