1-(4-PIPERIDINYL)BENZIMIDAZOLONES AS HISTAMINE H3 ANTAGONISTS

FIELD OF THE INVENTION

The present invention relates to novel substituted benzimidazolones, and aza- and diaza-derivatives thereof, useful as histamine H_3 antagonists. The invention also relates to pharmaceutical compositions comprising said compounds and their use in treating inflammatory diseases, allergic conditions and central nervous system disorders. The invention also relates to the use of a combination of novel histamine H_3 antagonists of this invention with histamine H_1 compounds for the treatment of inflammatory diseases and allergic conditions, as well as pharmaceutical compositions comprising a combination of one or more novel histamine H_3 antagonist compounds of the invention with one or more histamine H_1 compounds.

BACKGROUND OF THE INVENTION

The histamine receptors, H_1, H_2 and H_3 are well-identified forms. The H_1 receptors are those that mediate the response antagonized by conventional antihistamines. H_1 receptors are present, for example, in the ileum, the skin, and the bronchial smooth muscle of humans and other mammals. Through H_2 receptor-mediated responses, histamine stimulates gastric acid secretion in mammals and the chronotropic effect in isolated mammalian atria.

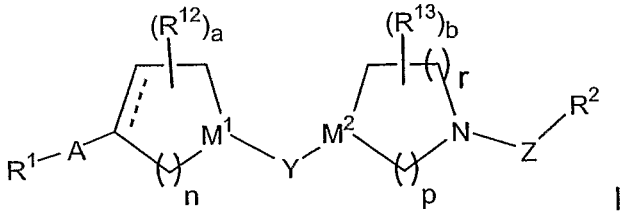
H_3 receptor sites are found on sympathetic nerves, where they modulate sympathetic neurotransmission and attenuate a variety of end organ responses under control of the sympathetic nervous system. Specifically, H_3 receptor activation by histamine attenuates nonepinephrine outflow to resistance and capacitance vessels, causing vasodilation.

Imidazole H_3 receptor antagonists are well known in the art. More recently, non-imidazole H_3 receptor antagonists have been disclosed in WO 02/32893 and WO 02/072,570.

US 5,869,479 discloses compositions for the treatment of the symptoms of allergic rhinitis using a combination of at least one histamine H_1 receptor antagonist and at least one histamine H_3 receptor antagonist.

SUMMARY OF THE INVENTION

The present invention provides novel compounds of formula I:



I

or a pharmaceutically acceptable salt or solvate thereof, wherein:

the dotted line represents an optional double bond;

a is 0 to 3;

b is 0 to 3;

n is 1, 2 or 3;

p is 1, 2 or 3 with the proviso that when M^2 is N, then p is not 1;

r is 1, 2, or 3 with the proviso that when r is 2 or 3, then M^2 is $C(R^3)$ and p is 2 or 3;

A is a bond or C_1-C_6 alkylene;

M^1 is $C(R^3)$ or N;

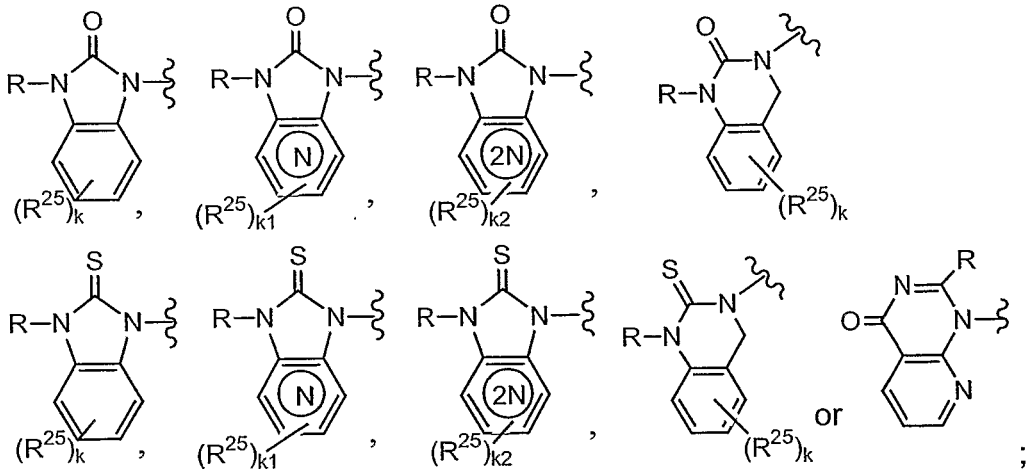
M^2 is $C(R^3)$ or N;

Y is –C(=O)-, -C(=S)-, $-(CH_2)_q$ -, $–NR^4C(=O)$-, $-C(=O)NR^4$-, $-C(=O)CH_2$-, $-CH_2(C=O)$-, $-SO_{1-2}$-, -NH-C(=N-CN)- or –C(=N-CN)-NH-; with the provisos that when M^1 is N, Y is not $–NR^4C(=O)$- or -NH-C(=N-CN)-; and when M^2 is N, Y is not $-C(=O)NR^4$- or –C(=N-CN)-NH-;

q is 1 to 5, provided that when M^1 and M^2 are both N, q is not 1 ;

Z is a bond, C_1-C_6 alkylene, C_1-C_6 alkenylene, -C(=O)-, -CH(CN)-, or $–CH_2C(=O)NR^4$-;

R^1 is



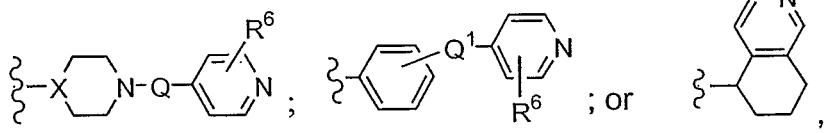
k is 0, 1, 2, 3 or 4;

k1 is 0, 1, 2 or 3;

k2 is 0, 1 or 2;

R is H, C_1-C_6 alkyl, hydroxy-(C_2-C_6)alkyl-, halo-(C_1-C_6)alkyl-, halo-(C_1-C_6)-alkoxy-(C_1-C_6)alkyl-, R^{29}-O-C(O)-(C_1-C_6)alkyl-, (C_1-C_6)alkoxy-(C_1-C_6)alkyl-, N(R^{30})(R^{31})-(C_1-C_6)alkyl-, (C_1-C_6)alkoxy-(C_1-C_6)alkoxy-(C_1-C_6)alkyl-, R^{32}-aryl, R^{32}-aryl(C_1-C_6)alkyl-, R^{32}-aryloxy(C_1-C_6)alkyl-, R^{32}-heteroaryl, R^{32}-heteroaryl(C_1-C_6)alkyl-, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl-, N(R^{30})(R^{31})-C(O)-(C_1-C_6)alkyl-, or heterocycloalkyl(C_1-C_6)alkyl-;

R^2 is a six-membered heteroaryl ring having 1 or 2 heteroatoms independently selected from N or N-O, with the remaining ring atoms being carbon; a five-membered heteroaryl ring having 1, 2, 3 or 4 heteroatoms independently selected from N, O or S, with the remaining ring atoms being carbon; R^{32}-quinolyl; R^{32}-aryl; heterocycloalkyl; (C_3-C_6)cycloalkyl; (C_1-C_6)alkyl; hydrogen;



wherein said six-membered heteroaryl ring or said five-membered heteroaryl ring is optionally substituted by R^6;

X is CH or N;

Q is a bond or C_1-C_6 alkylene;

Q^1 is a bond, C_1-C_6 alkylene or –N(R^4)-;

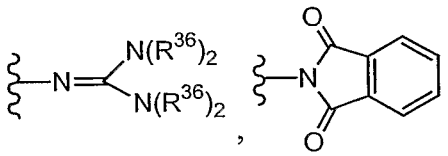
R^3 is H, halogen, C_1-C_6 alkyl, -OH or (C_1-C_6)alkoxy;

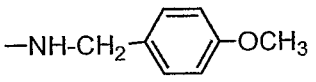
R^4 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, R^{33}-aryl, R^{33}-aryl(C_1-C_6)alkyl, and R^{32}-heteroaryl;

R^5 is hydrogen, C_1-C_6 alkyl, -C(O)R^{20}, -C(O)$_2R^{20}$, –C(O)N(R^{20})$_2$ or (C_1-C_6)alkyl-SO_2-;

or R^4 and R^5, together with the nitrogen to which they are attached, form an azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl ring;

R^6 is 1 to 3 substituents independently selected from the group consisting of -OH, halogen, C_1-C_6 alkyl-, C_1-C_6 alkoxy, C_1-C_6 alkylthio, -CF_3, -NR^4R^5, NO_2, -CO_2R^4, -CON(R^4)$_2$, -CH_2-NR^4R^5, -CN,



, and 

,

or 2 R^6 substituents together on the same carbon are =O;

R^{12} is independently selected from the group consisting of C_1-C_6 alkyl, hydroxy, C_1-C_6 alkoxy, or fluoro, provided that when R^{12} is hydroxy or fluoro, then R^{12} is not bound to a carbon adjacent to a nitrogen; or two R^{12} substituents together form a C_1 to C_2 alkyl bridge from one ring carbon to another non-adjacent ring carbon; or R^{12} is =O;

R^{13} is independently selected from the group consisting of C_1-C_6 alkyl, hydroxy, C_1-C_6 alkoxy, or fluoro, provided that when R^{13} is hydroxy or fluoro then R^{13} is not bound to a carbon adjacent to a nitrogen; or two R^{13} substituents together form a C_1 to C_2 alkyl bridge from one ring carbon to another non-adjacent ring carbon; or R^{13} is =O;

R^{20} is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, or aryl, wherein said aryl group is optionally substituted with from 1 to 3 groups independently selected from halogen, -CF_3, -OCF_3, hydroxyl, or methoxy; or when two R^{20} groups are present, said two R^{20} groups taken together with the nitrogen to which they are bound can form a five or six membered heterocyclic ring;

R^{22} is C_1-C_6 alkyl, R^{34}-aryl or heterocycloalkyl;

R^{24} is H, C_1-C_6 alkyl, -SO_2R^{22} or R^{34}-aryl;

R^{25} is independently selected from the group consisting of C_1-C_6 alkyl, -CN, -NO_2, halogen, –CF_3, -OH, C_1-C_6 alkoxy, (C_1-C_6)alkyl-C(O)-, aryl-C(O)-, N(R^4)(R^5)-C(O)-, N(R^4)(R^5)-S(O)$_{1\text{-}2}$-, halo-(C_1-C_6)alkyl- or halo-(C_1-C_6)alkoxy-(C_1-C_6)alkyl-;

R^{29} is H, C_1-C_6 alkyl, R^{35}-aryl or R^{35}-aryl(C_1-C_6)alkyl-;

R^{30} is H, C_1-C_6 alkyl-, R^{35}-aryl or R^{35}-aryl(C_1-C_6)alkyl-;

R^{31} is H, C_1-C_6 alkyl-, R^{35}-aryl, R^{35}-aryl(C_1-C_6)alkyl-, (C_1-C_6)alkyl-C(O)-, R^{35}-aryl-C(O)-, N(R^4)(R^5)-C(O)-, (C_1-C_6)alkyl-S(O)$_2$- or R^{35}-aryl-S(O)$_2$-;

or R^{30} and R^{31} together are -$(CH_2)_{4-5}$-, –$(CH_2)_2$-O-$(CH_2)_2$- or –$(CH_2)_2$-N(R^{29})-$(CH_2)_2$- and form a ring with the nitrogen to which they are attached;

R^{32} is 1 to 3 substituents independently selected from the group consisting of H, -OH, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, -SR^{22}, -CF_3, -OCF_3, -$OCHF_2$, -$NR^{37}R^{38}$, -NO_2, -CO_2R^{37}, -$CON(R^{37})_2$, -$S(O)_2R^{22}$, -$S(O)_2N(R^{20})_2$, -$N(R^{24})S(O)_2R^{22}$, -CN, hydroxy-(C_1-C_6)alkyl- and -$OCH_2CH_2OR^{22}$;

R^{33} is 1 to 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, -CN, -NO_2, -$OCHF_2$ and –O-(C_1-C_6)alkyl;

R^{34} is 1 to 3 substituents independently selected from the group consisting of H, halogen, -CF_3, -OCF_3, -OH and –OCH_3.

R^{35} is 1 to 3 substituents independently selected from hydrogen, halo, C_1-C_6 alkyl, hydroxy, C_1-C_6 alkoxy, phenoxy, -CF_3, -$N(R^{36})_2$, -$COOR^{20}$ and –NO_2;

R^{36} is independently selected form the group consisting of H and C_1-C_6 alkyl;

R^{37} is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, R^{33}-aryl, R^{33}-aryl(C_1-C_6)alkyl, and R^{32}-heteroaryl; and

R^{38} is hydrogen, C_1-C_6 alkyl, -$C(O)R^{20}$, -$C(O)_2R^{20}$, –$C(O)N(R^{20})_2$ or (C_1-C_6)alkyl-SO_2-;

or R^{37} and R^{38}, together with the nitrogen to which they are attached, form an azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl ring.

This invention also provides a pharmaceutical composition comprising an effective amount of compound of at least one compound of formula I and a pharmaceutically acceptable carrier.

This invention further provides a method of treating allergy, allergy-induced airway (e.g., upper airway) responses, congestion (e.g., nasal congestion), hypotension, cardiovascular disease, diseases of the GI tract, hyper- and hypo-motility and acidic secretion of the gastro-intestinal tract, obesity, sleeping disorders (e.g., hypersomnia, somnolence, and narcolepsy), disturbances of the central nervous system, attention deficit hyperactivity disorder (ADHD), hypo and

hyperactivity of the central nervous system (for example, agitation and depression), and/or other CNS disorders (such as Alzheimer's, schizophrenia, and migraine) comprising administering to a patient in need of such treatment an effective amount of at least one compound of formula I.

Compounds of this invention are particularly useful for treating allergy, allergy-induced airway responses and/or congestion.

This invention further provides a pharmaceutical composition comprising an effective amount of a combination of at least one compound of formula I and at least one H_1 receptor antagonist in combination with a pharmaceutically acceptable carrier.

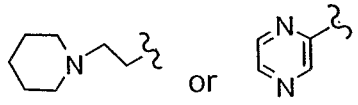
This invention further provides a method of treating allergy, allergy-induced airway (e.g., upper airway) responses, and/or congestion (e.g., nasal congestion) comprising administering to a patient in need of such treatment (e.g., a mammal, such as a human being) an effective amount of a combination of at least one compound of formula I and at least one H_1 receptor antagonist.

Kits comprising a compound of formula I in a pharmaceutical composition, and a separate H_1 receptor antagonist in a pharmaceutical compositions in a single package are also contemplated.

DETAILED DESCRIPTION OF THE INVENTION

Preferred definitions of the variables in the structure of formula I are as follows:

R^1 is preferably R-substituted benzimidazolone, wherein R is preferably H, alkyl, alkoxyalkyl, R^{32}-aryl, R^{32}-heteroaryl or heterocycloalkylalkyl. More preferably, R is $-CH_3$, phenyl, 4-fluorophenyl, CH_3-O-$(CH_2)_2$-,



R^{25} is preferably halogen or $-CF_3$ and k is 0 or 1. When R^1 is an aza- or diaza derivative of benzimidazolone, R is preferably as defined for benzimidazolone, and k_1 and k_2 are preferably zero.

R^2 is preferably a six-membered heteroaryl ring, optionally substituted with one substituent. More preferably, R^2 is pyridyl, pyrimidinyl or pyridazinyl, each optionally substituted with halogen or $-NR^4R^5$, wherein $R^4$and R^5 are independently selected from the group consisting of H and $(C_1$-$C_6)$alkyl, or $R^4$and R^5 together with the nitrogen to which they are attached form a pyrrolidinyl, piperidinyl or morpholinyl ring.

A is preferably a bond.

Y is preferably –C(O)-.

Z is preferably straight or branched C_1-C_3 alkyl.

M^1 is preferably N; a is preferably 0; and n is preferably 2; the optional double bond is preferably not present (i.e., a single bond is present).

M^2 is preferably $C(R^3)$ wherein R^3 is hydrogen or halogen, especially fluorine; b is preferably 0; r is preferably 1; and p is preferably 2.

As used herein, the following terms have the following meanings, unless indicated otherwise:

alkyl (including, for example, the alkyl portions of arylalkyl and alkoxy) represents straight and branched carbon chains and contains from one to six carbon atoms;

alkylene represents a divalent straight or branched alkyl chain, e.g., ethylene ($-CH_2CH_2-$) or propylene ($–CH_2CH_2CH_2-$);

Haloalkyl or haloalkoxy represent alkyl or alkoxy chains as defined above wherein one or more hydrogen atoms are replaced by halogen atoms, e.g., $-CF_3$, $CF_3CH_2CH_2-$, CF_3CF_2- or CF_3O-;

aryl (including the aryl portion of arylalkyl) represents a carbocyclic group containing from 6 to 14 carbon atoms and having at least one aromatic ring (e.g., aryl is a phenyl or naphthyl ring), with all available substitutable carbon atoms of the carbocyclic group being intended as possible points of attachment;

arylalkyl represents an aryl group, as defined above, bound to an alkyl group, as defined above, wherein said alkyl group is bound to the compound;

cycloalkyl represents saturated carbocyclic rings of from 3 to 6 carbon atoms;

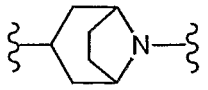
halogen (halo) represents fluoro, chloro, bromo and iodo;

heteroaryl represents cyclic groups, having at least one heteroatom selected from O, S or N, said heteroatom interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, with the aromatic heterocyclic groups preferably containing from 2 to 14 carbon atoms; examples include but are not limited to isothiazolyl, isoxazolyl, oxazolyl, furazanyl, triazolyl, tetrazolyl, thiazolyl, thiadiazolyl, isothiadiazolyl, thienyl, furanyl (furyl), pyrrolyl, pyrazolyl, pyranyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyridyl (e.g., 2-, 3-, or 4-pyridyl), pyridyl N-oxide (e.g., 2-, 3-, or 4-pyridyl N-oxide), triazinyl, pteridinyl, indolyl (benzopyrrolyl), pyridopyrazinyl, isoquinolinyl, quinolinyl, naphthyridinyl; the 5- and 6-membered heteroaryl groups included in the definition of R^2 are exemplified by the

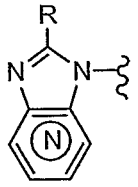
heteroaryl groups listed above; all available substitutable carbon and nitrogen atoms can be substituted as defined.

heterocycloalkyl represents a saturated, carbocylic ring containing from 3 to 15 carbon atoms, preferably from 4 to 6 carbon atoms, which carbocyclic ring is interrupted by 1 to 3 hetero groups selected from -O-, -S-, -SO-, $-SO_2$ or $-NR^{40}-$ wherein R^{40} represents H, C_1 to C_6 alkyl, arylalkyl, $-C(O)R^{20}$, $-C(O)OR^{20}$, or $-C(O)N(R^{20})_2$ (wherein each R^{20} is independently selected); examples include but are not limited to 2- or 3-tetrahydrofuranyl, 2- or 3- tetrahydrothienyl, 2-, 3- or 4-piperidinyl, 2- or 3-pyrrolidinyl, 2- or 3-piperazinyl, 2- or 4-dioxanyl, 1,3-dioxolanyl, 1,3,5-trithianyl, pentamethylene sulfide, perhydroisoquinolinyl, decahydroquinolinyl, trimethylene oxide, azetidinyl, 1-azacycloheptanyl, 1,3-dithianyl, 1,3,5-trioxanyl, morpholinyl, thiomorpholinyl, 1,4-thioxanyl, and 1,3,5-hexahydrotriazinyl, thiazolidinyl, tetrahydropyranyl.

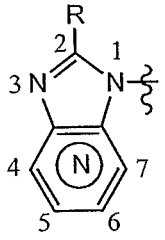
When R^{12} or R^{13} is said to be =O, this means that two hydrogen atoms on the same carbon atom of the ring can be replaced by =O. When two R^{12} or R^{13} groups are said to form a bridge between non-adjacent carbon atoms, the bridge will not include carbon atoms in M^1or M^2, not the carbon joined to "A". An example of a bridged ring is



Ⓝ , for example in the structure



represents a nitrogen atom that is located at one of the 4 non-fused positions of the ring, i.e., positions 4, 5, 6 or 7 indicated below:



Similarly, Ⓝ2 means that two nitrogens are located at any two of the 4 non-fused positions of the ring, e.g., the 4 and 6 positions, the 4 and 7 positions, or the 5 and 6 positions.

"Patient" means a mammal, typically a human, although veterinary use is also contemplated.

Also, as used herein, "upper airway" usually means the upper respiratory system--i.e., the nose, throat, and associated structures.

Also, as used herein, "effective amount" generally means a therapeutically effective amount.

A line drawn into a ring means that the indicated bond may be attached to any of the substitutable ring carbon atoms.

Certain compounds of the invention may exist in different isomeric (e.g., enantiomeric, diastereoisomeric and geometric) forms. The invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures. Enol forms and tautomers are also included.

The compounds of this invention are ligands for the histamine H_3 receptor. The compounds of this invention can also be described as antagonists of the H_3 receptor, or as H_3 antagonists.

The compounds of the invention are basic and form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for such salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those skilled in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium hydroxide, potassium carbonate, ammonia and sodium bicarbonate. The free base forms can differ from their corresponding salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the salts are otherwise equivalent to their corresponding free base forms for purposes of this invention.

Depending upon the substituents on the inventive compounds, one may be able to form salts with bases. Thus, for example, if there is a carboxylic acid substituent in the molecule, a salt may be formed with an inorganic as well as organic base such as, for example, NaOH, KOH, NH_4OH, tetraalkylammonium hydroxide, and the like.

The compounds of formula I can exist in unsolvated as well as solvated forms, including hydrated forms, e.g., hemi-hydrate. In general, the solvated form, with pharmaceutically acceptable solvents such as water, ethanol and the like are equivalent to the unsolvated form for purposes of the invention.

The compounds of this invention can be combined with an H_1 receptor antagonist (i.e., the compounds of this invention can be combined with an H_1 receptor antagonist in a pharmaceutical composition, or the compounds of this invention can be administered with an H_1 receptor antagonist).

Numerous chemical substances are known to have histamine H_1 receptor antagonist activity and can therefore be used in the methods of this invention. Many H_1 receptor antagonists useful in the methods of this invention can be classified as ethanolamines, ethylenediamines, alkylamines, phenothiazines or piperidines. Representative H_1 receptor antagonists include, without limitation: astemizole, azatadine, azelastine, acrivastine, brompheniramine, cetirizine, chlorpheniramine, clemastine, cyclizine, carebastine, cyproheptadine, carbinoxamine, descarboethoxyloratadine, diphenhydramine, doxylamine, dimethindene, ebastine, epinastine, efletirizine, fexofenadine, hydroxyzine, ketotifen, loratadine, levocabastine, meclizine, mizolastine, mequitazine, mianserin, noberastine, norastemizole, picumast, pyrilamine, promethazine, terfenadine, tripelennamine, temelastine, trimeprazine and triprolidine. Other compounds can readily be evaluated to determine activity at H_1 receptors by known methods, including specific blockade of the contractile response to histamine of isolated guinea pig ileum. See for example, WO98/06394 published February 19, 1998.

Those skilled in the art will appreciate that the H_1 receptor antagonist is used at its known therapeutically effective dose, or the H_1 receptor antagonist is used at its normally prescribed dosage.

Preferably, said H_1 receptor antagonist is selected from: astemizole, azatadine, azelastine, acrivastine, brompheniramine, cetirizine, chlorpheniramine, clemastine, cyclizine, carebastine, cyproheptadine, carbinoxamine, descarboethoxyloratadine, diphenhydramine, doxylamine, dimethindene, ebastine, epinastine, efletirizine, fexofenadine, hydroxyzine, ketotifen, loratadine, levocabastine, meclizine, mizolastine, mequitazine, mianserin, noberastine, norastemizole, picumast, pyrilamine, promethazine, terfenadine, tripelennamine, temelastine, trimeprazine or triprolidine.

More preferably, said H_1 receptor antagonist is selected from: astemizole, azatadine, azelastine, brompheniramine, cetirizine, chlorpheniramine, clemastine, carebastine, descarboethoxyloratadine, diphenhydramine, doxylamine, ebastine, fexofenadine, loratadine, levocabastine, mizolastine, norastemizole, or terfenadine.

Most preferably, said H_1 receptor antagonist is selected from: azatadine, brompheniramine, cetirizine, chlorpheniramine, carebastine, descarboethoxy-loratadine, diphenhydramine, ebastine, fexofenadine, loratadine, or norastemizole.

Even more preferably, said H_1 antagonist is selected from loratadine, descarboethoxyloratadine, fexofenadine or cetirizine. Most preferably, said H_1 antagonist is loratadine or descarboethoxyloratadine.

In one preferred embodiment, said H_1 receptor antagonist is loratadine.

In another preferred embodiment, said H_1 receptor antagonist is descarboethoxyloratadine.

In still another preferred embodiment, said H_1 receptor antagonist is fexofenadine.

In yet another preferred embodiment, said H_1 receptor antagonist is cetirizine.

Preferably, in the above methods, allergy-induced airway responses are treated.

Also, preferably, in the above methods, allergy is treated.

Also, preferably, in the above methods, nasal congestion is treated.

In the methods of this invention wherein a combination of an H_3 antagonist of this invention (compound of formula I) is administered with an H_1 antagonist, the antagonists can be administered simultaneously or sequentially (first one and then the other over a period of time). In general, when the antagonists are administered sequentially, the H_3 antagonist of this invention (compound of formula I) is administered first.

Compounds of the present invention can be prepared by a number of ways evident to one skilled in the art. Preferred methods include, but are not limited to, the general synthetic procedures described herein. One skilled in the art will recognize that one route will be optimal depending on the choice of appendage substituents. Additionally, one skilled in the art will recognize that in some cases the order of steps has to be controlled to avoid functional group incompatibilities. One such method for the preparation of compounds of formula I wherein R^1 is benzimidazolone is shown in Scheme 1 below. Similar procedures can be used to prepare the aza-

benzimidazolones (i.e., compounds wherein R^1 is other than benzimidazolone as defined above) and R^{25}-substituted benzimidazolones and aza-benzimidazolones. In the scheme, Prot is a protecting group and the variables are as defined above or in the following description.

The starting material and reagents used in preparing compounds described are either available from commercial suppliers such as Aldrich Chemical Co. (Wisconsin, USA) and Acros Organics Co. (New Jersey, USA) or were prepared by literature methods known to those skilled in the art.

Henning et al have reported a synthesis of compounds **XIV** in Scheme I, below, where M^1 of formula I is a nitrogen atom in *J. Med. Chem. 30*, (1987) 814.

One skilled in the art will recognize that the synthesis of compounds of formula **XVI** may require the need for the protection of certain functional groups (i.e. derivatization for the purpose of chemical compatibility with a particular reaction condition). Suitable protecting groups for an amine are methyl, benzyl, ethoxyethyl, t-butoxycarbonyl, phthaloyl and the like which can appended to and removed by literature methods known to those skilled in the art.

One skilled in the art will recognize that the synthesis of compounds of formula **XVI** may require the construction of an amide bond. Methods include but are not limited to the use of a reactive carboxy derivative (e.g. acid halide) or the use of an acid with a coupling reagent (e.g. DECI, DCC) with an amine at 0 °C to 100 °C. Suitable solvents for the reaction are halogenated hydrocarbons, ethereal solvents, dimethylformamide and the like.

One skilled in the art will recognize that the synthesis of compounds of formula **XVI** may require the construction of an amine bond. Methods include but are not limited to the reaction of an amine with a reactive carbonyl (e.g. aldehyde or ketone) under reductive amination conditions. Suitable reducing reagents for the reaction include $NaBH_3CN$, sodium triacetoxyborohydride and the like at 0 °C to 100 °C. Suitable solvents for the reaction are halogenated hydrocarbons, ethereal solvents, dimethylformamide and the like.

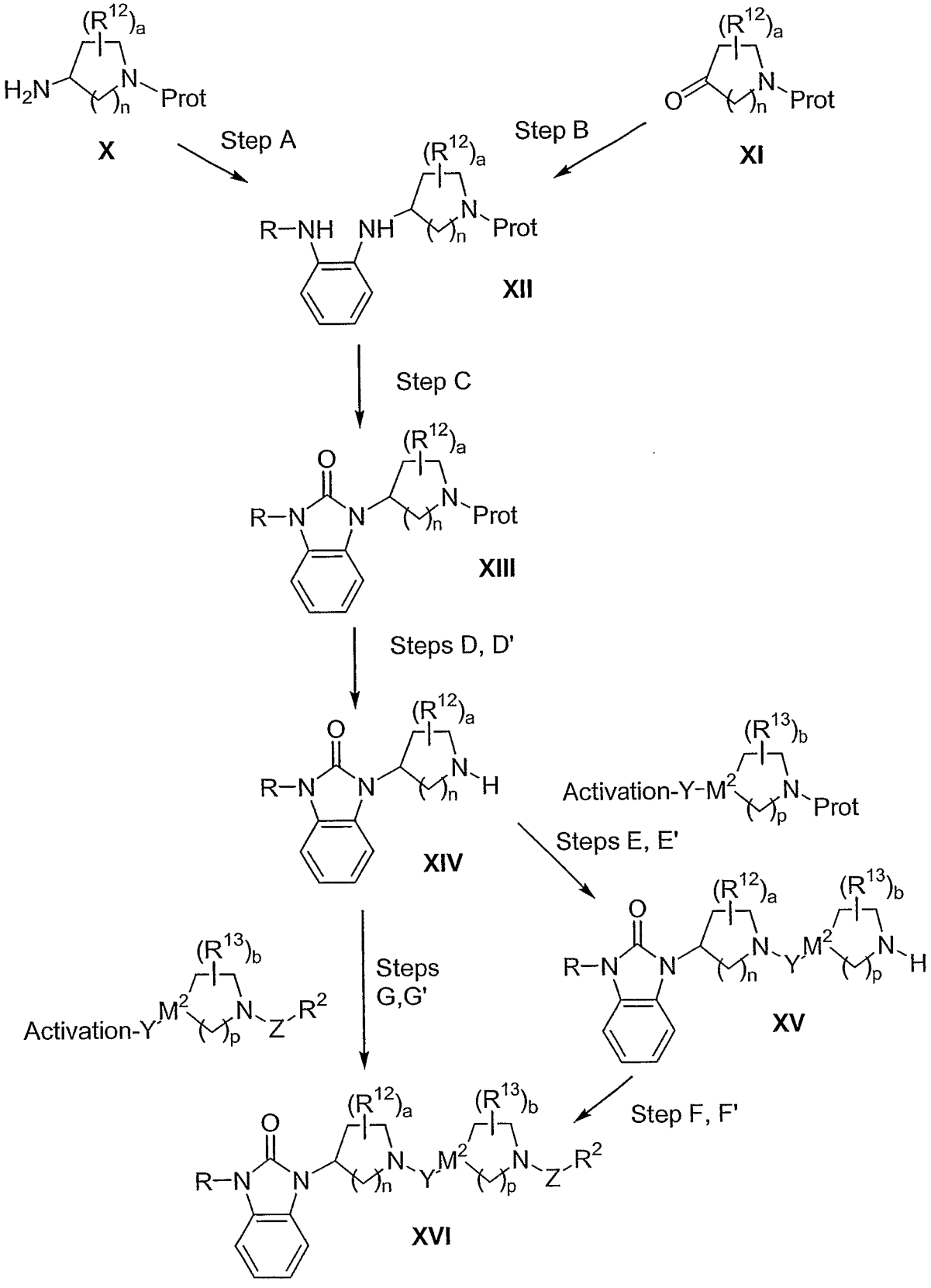
One skilled in the art will recognize that the synthesis of compounds of formula **XVI** may require the reduction of a reducible functional group. Suitable reducing reagents include $NaBH_4$, $LiAlH_4$, diborane and the like at -20 °C to 100 °C. Suitable

solvents for the reaction are halogenated hydrocarbons, ethereal solvents, dimethylformamide, alcohols and alike.

One skilled in the art will recognize that the synthesis of compounds of formula **XVI** may require the oxidation of a functional group. Suitable oxidizing reagents include oxygen, hydrogen peroxide, m-chloroperoxybenzoic acid and the like at -20 °C to 100 °C. Suitable solvents for the reaction are halogenated hydrocarbons, ethereal solvents, water and the like.

The starting materials and the intermediates of a reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography and the like. Such materials can be characterized using conventional means, including physical constants and spectral data.

SCHEME 1. General Method for Preparation of Compounds of Formula **XVI**



(Steps D', E', F', G' are optional)

Step A: A suitably mono-protected amine of formula **X** is alkylated with a halide to form a compound of formula **XII**. A suitable halide for alkylation is a substituted 2-bromo nitrobenzene as described by Henning et al, *J. Med. Chem. 30*, (1987) 814. Suitable amine protecting groups are methyl, benzyl, ethoxycarbonyl or the like.

Step B: A suitably protected ketone of formula **XI** is reductively alkylated with an amine to form a compound of formula **XII**. Suitable amine protecting groups are methyl, benzyl, ethoxycarbonyl or the like

Step C: An intermediate diamine of formula **XII** is then cyclized with an appropriate carbonyl equivalent such as phosgene, triphosgene or carbonyl diimidazole (CDI) to form a compound of formula **XIII**. Methods for cyclization have been described by Henning et al, *J. Med. Chem. 30*, (1987) 814.

Steps D & D': The protected amine of formula **XIII** is deprotected using methods known to those skilled in the art. See, for example, Green et al, *Protective Groups in Organic Synthesis*. A suitable method for methyl deprotection is reaction with a haloformate or the like. A suitable method for benzyl deprotection is cleavage with hydrogen at or above atmospheric pressure and a catalyst such as palladium. A suitable method for carbamate deprotection is treatment with an acid such as HCl.

Optionally, when R is H in formula **XIII**, derivatization can be accomplished before other steps by methods known to those skilled in the art. Preferred methods include, but are not limited to, alkylation with a halide under phase transfer conditions (e.g. biphasic basic conditions) or arylation with an aryl or heteroarylboronic acid under metal catalyzed conditions.

Steps E & E': An amine of formula **XIV** is reacted with an activated functional group to form the bond between the nitrogen and functional group Y in formula **XV**. When Y is a carbonyl group and M^2 is carbon, activation can be via a halide (i.e. acid chloride intermediate) and suitable reaction conditions may require a base such as triethylamine. When Y is a methylene and M^2 is a carbon, activation can be via a halide (i.e. iodomethyl intermediate) or an acid chloride as above followed by treatment with a reducing agent such as LAH. When Y is a sulfonyl and M^2 is a carbon, activation can be via a sulfonyl halide (i.e. sulfonyl chloride intermediate).

Optionally, when R is H in formula **XIV**, derivatization can be accomplished before other steps by methods known to those skilled in the art.

Steps F & F': The protected amine of formula **XV** is deprotected using methods known to those skilled in the art. A suitable method for methyl deprotection is reaction

with a haloformate or the like. A suitable method for benzyl deprotection is cleavage with hydrogen at or above atmospheric pressure and a catalyst such as palladium. A suitable method for carbamate deprotection is treatment with an acid such as hydrochloric acid. The deprotected amine intermediate formed above is then alkylated with a suitable reagent such as halide-Z-R^2 to form the bond between nitrogen and Z in compound **XVI.**

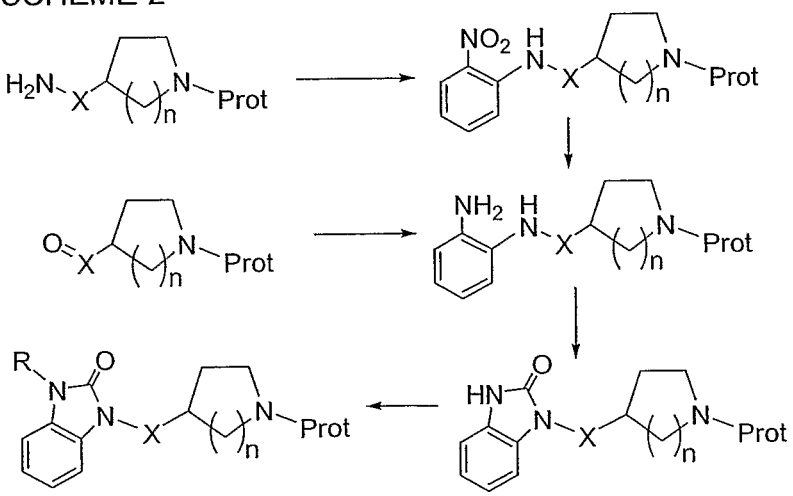
Optionally, when R is H in formula **XV**, derivatization can be accomplished before other steps by methods known to those skilled in the art.

Steps G & G': An amine of formula **XIV** is reacted with an activated functional group to form the bond between the nitrogen and functional group Y in formula **XV**. When Y is a carbonyl group and M^2 is carbon, activation can be via a halide (i.e. acid chloride intermediate) and suitable reaction conditions may require a base such as triethylamine. When Y is a methylene and M^2 is a carbon, activation can be via a halide (i.e. iodomethyl intermediate) or an acid chloride as above followed by treatment with a reducing agent such as LAH. When Y is a sulfonyl and M^2 is a carbon, activation can be via a sulfonylhalide (i.e. sulfonyl chloride intermediate).

Optionally, when R is H in formula **XIV**, derivatization can be accomplished before other steps by methods known to those skilled in the art.

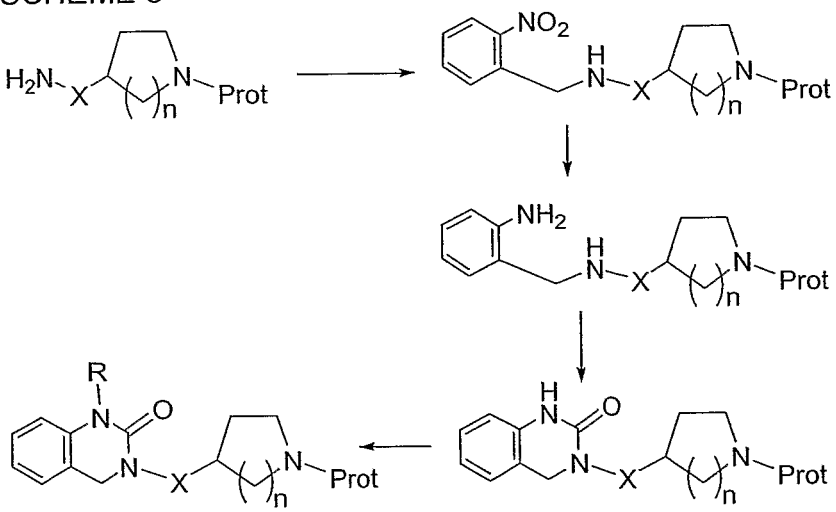
The preparation of intermediates of formula **XIII** is further elaborated in the following Schemes 2 and 3. Preparation of benzimidazoles is shown, but aza and diaza derivatives can be similarly prepared.

SCHEME 2



These procedures are described by Henning et al and in *J. Med. Chem.*, *41* (1998), p. 74.

SCHEME 3



This procedure is described in *J. Heterocyclic Chem.*, *20* (1983), p. 565.

Compounds of formula I can be prepared by the general methods outlined in Schemes 1-3. Specifically exemplified compounds were prepared as described in the examples below, from starting materials known in the art or prepared as described below. These examples are being provided to further illustrate the present invention. They are for illustrative purposes only; the scope of the invention is not to be considered limited in any way thereby.

Unless otherwise stated, the following abbreviations have the stated meanings in the Examples below:

Me=methyl; Et=ethyl; Bu=butyl; Pr=propyl; Ph=phenyl; t-BOC=tert-butoxycarbonyl; CBZ=carbobenzyloxy; and Ac=acetyl

DCC= dicyclohexylcarbodiimide

DMAP=4-dimethylaminopyridine

DMF=dimethylformamide

EDCI= 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

HATU=O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate

HOBT= 1-hydroxybenzotriazole

LAH= lithium aluminum hydride

$NaBH(OAc)_3$= sodium triacetoxyborohydride

NBS=N-bromosuccinimide

TBAF=tetrabutylammonium fluoride

TBDMS=t-butyldimethylsilyl

TMEDA=N,N,N',N'-tetramethylethylenediamine

TEMPO=2,2,6,6-tetramethyl-1-piperidinyloxy, free radical

TLC=thin layer chromatography

HRMS= High Resolution Mass Spectrometry

LRMS= Low Resolution Mass Spectrometry

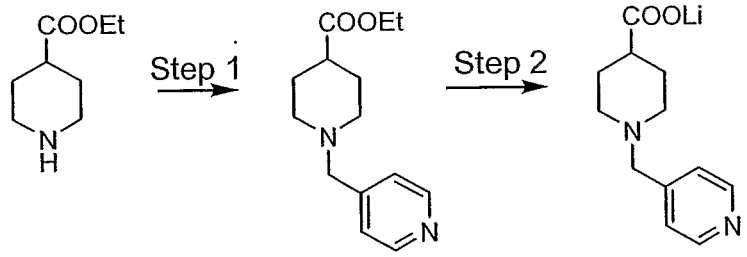
nM= nanomolar

Ki= Dissociation Constant for substrate/receptor complex

pA2= -logEC_{50}, as defined by J. Hey, *Eur. J. Pharmacol.,* (1995), Vol. 294, 329-335.

Ci/mmol= Curie/mmol (a measure of specific activity)

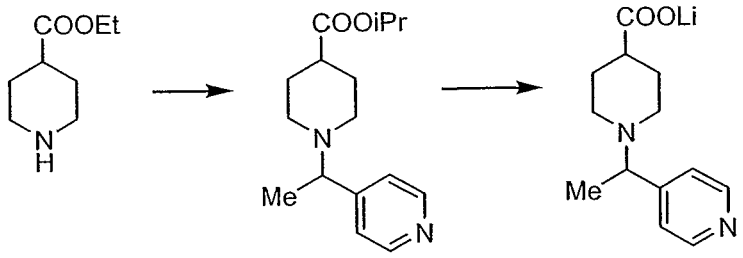
Preparation 1



Step 1: To a solution of ethyl isonipecotate (147 g, 0.93 mol) in dichloroethane (1300 ml) was added 4-pyridinecarboxaldehyde (50.0 g, 0.47 mol) and crushed 3 Å molecular sieves (35 g). After 10 min., $NaBH(OAc)_3$ (198 g, 0.93 mol) was added, portionwise, and the reaction stirred at 23 °C. After 16 h, water (300 ml) was slowly added, the organic layer separated, and the aqueous layer extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The crude product was distilled under vacuum to afford 101.5 g (0.409 mol, 91%) of the desired compound as an oil (bp 148-150 °C @ 3 mm Hg). MS (ES) m/e 249 (MH^+).

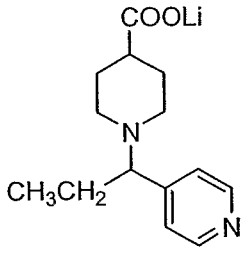
Step 2: To a solution of the product of Step 1 (101.5 g, 0.409 mol) in CH_3OH (1000 ml) was added LiOH monohydrate in H_2O (1.0 M, 860 ml, 0.86 mol). The reaction was heated at reflux for 16 h, then concentrated. The remaining water was removed azeotropically with EtOH (3 x 300 ml) to give 104.5 g (0.384 mol, 94%) of the compound of Preparation 1 with LiOH as a white solid. MS (ES): m/e 221 (MH^+).

Preparation 2



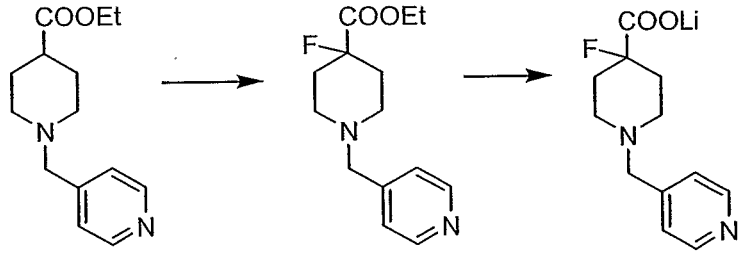
To a solution of ethyl isonipecotate (15.0 g, 95.4 mmol), was added 4-acetylpyridine (9.25 g, 76.3 mmol) and titanium isopropoxide (27.12 g, 95.4 mmol). The reaction was stirred at 23 °C for 16 h, and then EtOH (300 ml) and $NaCNBH_3$ (6.00 g, 95.4 mmol) were added. After an additional 24 h, water (300 ml) and CH_2Cl_2 (300 ml) were added. The reaction was filtered through celite and washed with water (300 ml) and CH_2Cl_2 (300 ml). The filtrate was transferred to a separatory funnel, 1 N NaOH was added and the organic layer separated. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Further purification by silica gel chromatography (eluant: 3% CH_3OH – CH_2Cl_2 then 6% CH_3OH - CH_2Cl_2) afforded 8 g (28.9 mol, 38% yield) of the desired compound as a yellow oil. MS (FAB for M+1): m/e 277. This compound was hydrolyzed with LiOH monohydrate as in Preparation 1 to afford the compound of Preparation 2.

The following compound was prepared according to the same above procedure:



Preparation 2A: MS (ES): m/e 291 (MH^+).

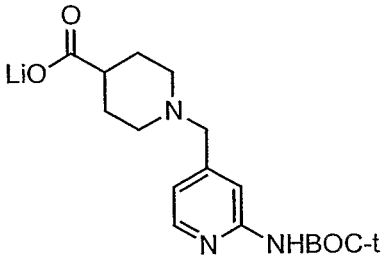
Preparation 3



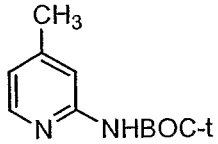
To a solution of diisopropylamine (2.28 g, 3.2 ml, 22.55 mmol) in dry THF (50 mL) at 0 °C under N_2 was added n-butyl lithium (2.5 M, 8.4 ml, 20.94 mmol) via syringe. After 10 min, the reaction was cooled to -78 °C and the product of Prearation 1, Step 1(4.00 g, 16.11 mmol) in dry THF (10 ml) was added dropwise via an addition funnel. After 3 h at -78 °C, N-fluorobenzenesulfonimide (6.60 g, 20.94 mmol) was added, and the reaction was then allowed to warm slowly to 23 °C overnight. The reaction was quenched by addition of 0.5 N NaOH (100 ml) and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 2% CH_3OH –

CH_2Cl_2 then 3% CH_3OH – CH_2Cl_2) afforded 0.63 g (2.37 mmol, 15%) of the desired compound as a yellow oil. MS (FAB for M+1): m/e 267. This compound was hydrolyzed with LiOH monohydrate as in Preparation 1 to afford the compound of Preparation 3.

Preparation 4

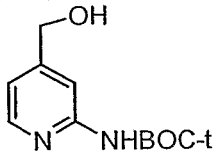


Step 1:



To a solution of 2-amino-4-methylpyridine (10.81 g, 100 mmol) in tert-butanol (250 ml) was added t-BOC anhydride (26.19 g, 120 mmol). The reaction mixture was stirred at 23 °C overnight, and then concentrated to an oil. The crude product was dry loaded onto a silica gel column and flash chromatographed (eluant: 30% hexanes-CH_2Cl_2 to 0-2% acetone-CH_2Cl_2) to obtain 15.25 g (73.32 mmol; 73%) of the desired product as a white solid.

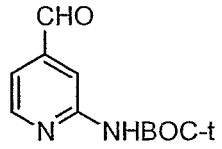
Step 2:



To a solution of the product of Step 1 (35.96 g, 173 mmol) in THF (1.4 l) at -78 °C was added n-BuLi (1.4 M, 272 ml, 381 mmol) in hexanes portionwise over 30 min. The reaction mixture was then allowed to warm slowly and was stirred for 2 h at 23 °C, which resulted in the formation of an orange precipitate. The mixture was then recooled to –78 °C, and pre-dried oxygen (passed through a Drierite column) was bubbled through the suspension for 6 h while the temperature was maintained at -78 °C. The color of the reaction mixture changed from orange to yellow during this time. The reaction was quenched at -78 °C with $(CH_3)_2S$ (51.4 ml, 700 mmol) followed by AcOH (22 ml, 384 mmol) and allowed to warm slowly to room temperature. After 48 h, water was added and the product extracted into EtOAc. Purification by silica gel

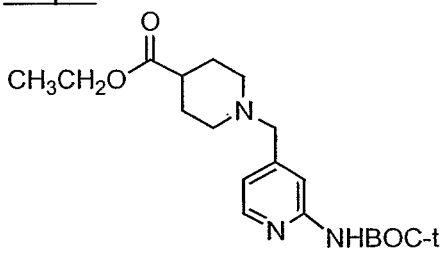
flash chromatography (eluant: 0–15% acetone/ CH_2Cl_2) provided 20.15 g (90 mmol; 52%) of the alcohol as a pale yellow solid.

Step 3:



To a solution of the product of Step 2 (19.15 g, 85.5 mmol) in CH_2Cl_2 (640 ml) was added a saturated aqueous solution of $NaHCO_3$ (8.62 g, 103 mmol) and NaBr (444 mg, 4.3 mmol). The reaction mixture was cooled to 0 °C, and TEMPO (140 mg, 0.90 mmol) was introduced. Upon vigorous stirring, commercial bleach solution (122 ml, 0.7 M, 85.4 mmol) (5.25% in NaOCl) was added portionwise over 40 min. After an additional 20 min at 0 °C, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ and allowed to warm to 23 °C. Dilution with water and extraction with CH_2Cl_2, followed by concentration and flash chromatography (eluant: 30% hexanes-CH_2Cl_2 to 0-2% acetone-CH_2Cl_2) afforded 15.97 g (71.9 mmol; 84% yield) of the aldehyde as an off-white solid.

Step 4:



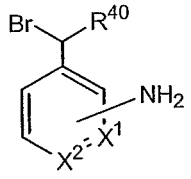
To a solution of the product of Step 3 (11.87 g, 53.5 mmol) in CH_2Cl_2 (370 ml) was added ethyl isonipecotate (9.07 ml, 58.8 mmol) followed by four drops of AcOH. The reaction mixture was then stirred for 40 min at 23 °C, after which $NaB(OAc)_3H$ (22.68 g, 107 mmol) was added. The reaction mixture was stirred overnight at 23 °C, neutralized with saturated aqueous $NaHCO_3$, diluted with water and extracted with CH_2Cl_2. Concentration of the organic extracts, followed by silica gel flash chromatography (eluant: 0–4% sat. NH_3 in CH_3OH-CH_2Cl_2) provided 19.09 g (52.6 mmol; 98%) of the ester as an off-white solid.

Step 5:

To a solution of the product of Step 5 (1.57 g, 4.33 mmol) in THF-water-CH_3OH (10 ml of a 3:1:1 mixture) was added LiOH monohydrate (0.125 g, 5.21 mmol). The reaction mixture was stirred overnight at 23 °C, concentrated and dried

under high vacuum to obtain 1.59 g of crude title compound as a yellowish solid which was used without purification.

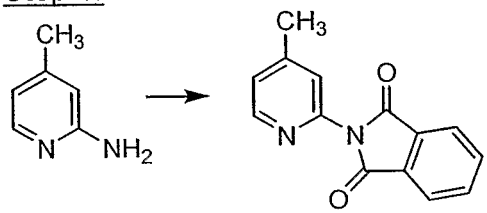
Preparation 5



R^{40} = H, -CH_3

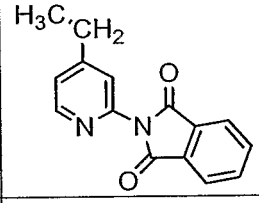
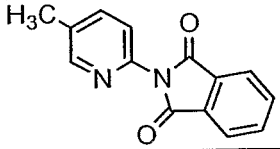
X^1, X^2 = C or N

Step 1:

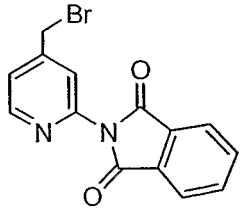


To a solution of the substituted pyridine (30 g, 277 mmol) and DMAP (100 mg, 0.82 mmol) in CH_2Cl_2 (800 ml) was added a solution of phthaloyl dichloride (56.3 g, 277 mmol) in CH_2Cl_2 (70 ml) via an addition funnel. The reaction mixture was stirred at 23 °C for 2 h, and then aqueous $NaHCO_3$ was added slowly. The organic layer was separated, and the aqueous layer further extracted with CH_2Cl_2. The combined organic layers were washed with water, dried, and concentrated to provide the desired compound as an off-white solid (61.2 g, 92%). MS (CI): 239 (MH^+)

The following compounds were prepared using a similar procedure and the appropriate starting materials:

	Compounds	MS (CI)
5-1A		253 (MH^+)
5-1B		239 (MH^+)

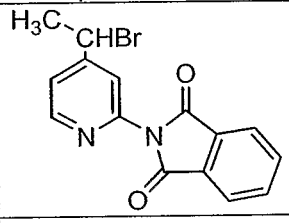
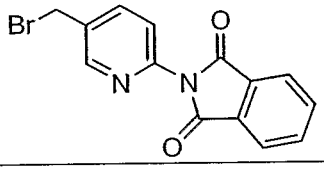
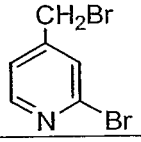
Step 2:



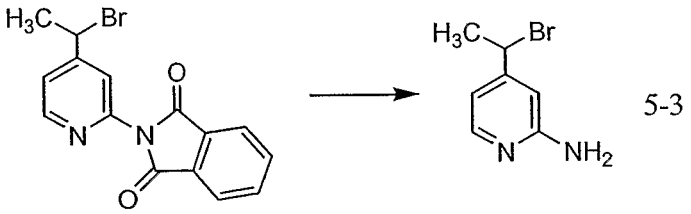
A suspension of the compound of Step 1 (10.94 g, 45.92 mmol), NBS (25 g, 140.5 mmol) and benzoyl peroxide (1.15 g, 4.75 mmol) in CCl_4 (300 ml) was refluxed

for 20 h, cooled to 23 °C, and filtered. The filtrate was concentrated. The resulting crude product was purified by silica gel flash chromatography (eluant: 40% EtOAc-hexanes) to give a tan solid (5.20 g). ^{1}H NMR revealed this was a mixture of the starting material and product with a ratio 1.4:1. The calculated yield is 15%. MS (CI): 317 (M+1).

The following compounds were prepared using a similar procedure and the appropriate starting materials:

	Compounds	MS (CI)
5-2A		--
5-2B		317 (MH^+)
5-2C		250 (MH^+)

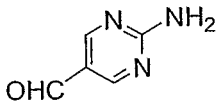
Step 3:



5-3

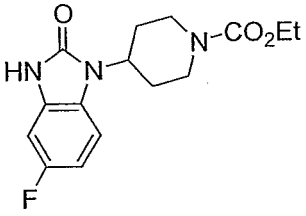
To a solution of Preparation 5-2A (4.5 g, 13.6 mmol) in EtOH (55 ml) was added hydrazine (0.48 g, 14.9 mmol). The reaction mixture was stirred at 23 °C for 2 h, concentrated, treated with water and CH_2Cl_2. The organic layer was separated, dried, and concentrated. Silica gel flash chromatography of the crude product (eluant: 2% CH_3OH-CH_2Cl_2) provided the desired compound as a white solid. (1.0 g, 37%).

Preparation 6

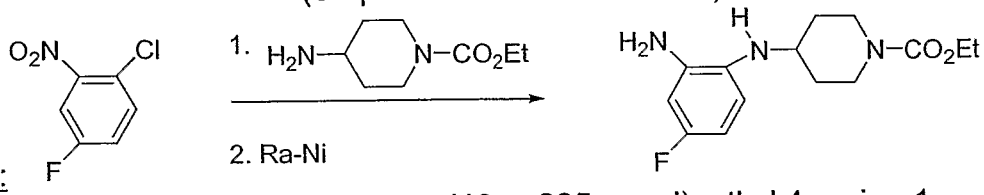


The compound is prepared according to the procedure described in JP Patent 63227573, 1988.

Intermediate 1



(Steps A and C of Scheme 1)



Step A:

2-Chloro-5-fluoro nitrobenzene (40 g, 225 mmol), ethyl 4-amino-1-piperidinecarboxylate (39 g, 226 mmol), K_2CO_3 (65 g, 470 mmol) were combined and heated to 150 °C. After 16 h the reaction was cooled, diluted with CH_2Cl_2, washed with water and the organic layer concentrated to a brown semi-solid. Further purification by silica gel chromatography (20:80 EtOAc:hexanes) afforded the nitro-aromatic intermediate (42 g, 60% yield, m/e 311).

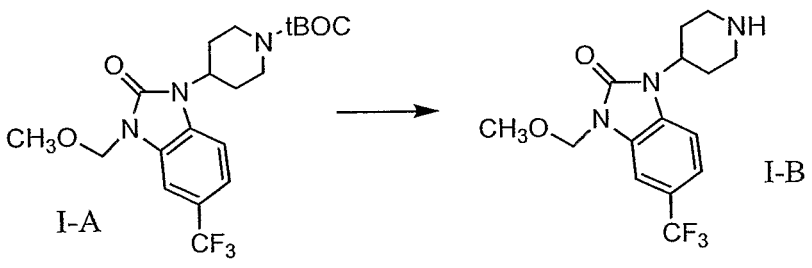
The nitro-aromatic intermediate (10 g, 32 mmol) was dissolved in a mixture of ethanol (36 ml) and THF (72 ml) in a Parr pressure vessel. Raney Nickel (~ 3.3 g wet) was added and the reaction was shaken under H_2 at 40 psi for 2 h. TLC (1:1 EtOAc:hexanes) indicated reaction was complete. The reaction mixture was filtered through celite and the filtrate concentrated to afford the desired product (8.6 g, 96% yield, m/e 281).

Step C:

The product of Step A (18 g, 64 mmol) was dissolved in CH_2Cl_2 (700 ml) and cooled to 0 °C. Triphosgene (16 g, 54 mmol) was added slowly followed by Et_3N (18 ml, 245 mmol). The reaction was allowed to warm slowly to 23 °C over 3 h. The reaction was washed with 1 N HCl, then water. The organic layer was dried over Na_2SO_4 to afford the product as an off-white solid (11.2 g, 60% yield, m/e 307).

Intermediate 2

(Step D of Scheme 1)

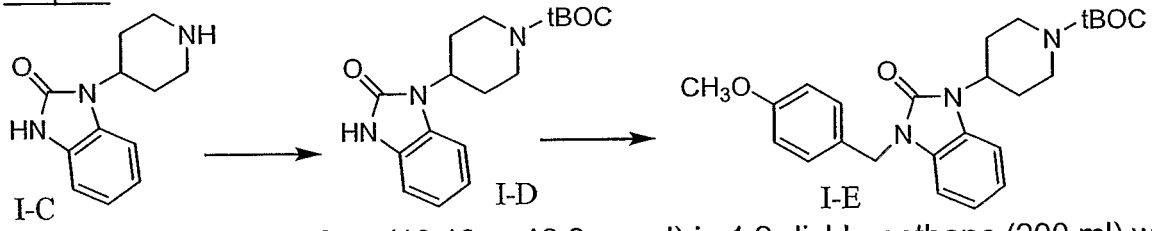


To a suspension of anhydrous $ZnBr_2$ (1.0 g, 4.4 mmol) in CH_2Cl_2 (15 ml) was added a solution of compound I-A (432 mg, 1.0 mmol) in CH_2Cl_2 (15 ml) and the reaction was stirred at 23 °C for 16 h. Saturated $NaHCO_3$ and 1 N NaOH solution were added, and the product extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification by silica gel chromatography (eluant: 1:1 CH_2Cl_2:4% NH_3 in CH_3OH) afforded 0.22 g (0.67 mmol, 67%) of I-B as a white solid. MS: m/e 330 (MH^+)

Intermediate 3

(Steps D' and D of Scheme 1)

Step D':

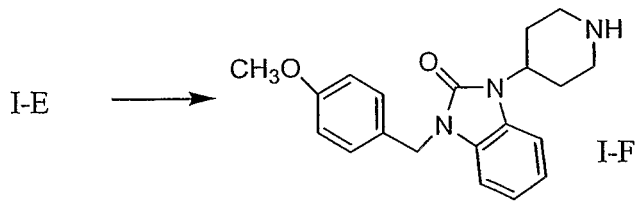


I-C I-D I-E

To a solution of I-C (10.19 g, 46.9 mmol) in 1,2-dichloroethane (200 ml) was added di-t-butyl dicarbonate (10.24 g, 47 mmol). The reaction was heated at reflux for 20 min. and then stirred at 23 °C for 1 h. The solvent was evaporated to give 14.89 g (46.9 mmol, 100% yield) of the N-Boc protected intermediate, I-D, as a white foam. MS (FAB for M+1): m/e 318.

To a solution of I-D (1.0 g, 3.15 mmol) in toluene (20 ml) was added NaOH (0.44 g, 11.0 mmol), K_2CO_3 (0.87 g, 6.30 mmol), tetra-n-butylammonium sulfate (0.21 g, 0.63 mmol) and 4-methoxybenzyl chloride (0.74 g, 4.73 mmol). The reaction was heated at reflux for 16 h and then cooled to 23 °C. Water (30 ml) was added, and the crude product isolated by extraction with EtOAc. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 3% CH_3OH – CH_2Cl_2) gave 1.26 g (2.88 mmol, 91%) of I-E as a white foam. MS (FAB for M+1): m/e 438.

Step D:



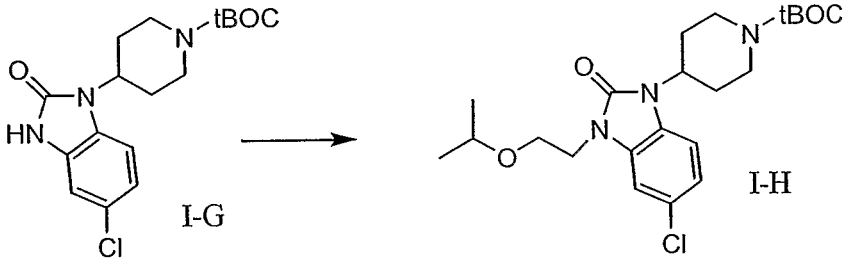
To a solution of compound I-E (1.25 g, 2.86 mmol) in CH_2Cl_2 (20 ml) was added HCl in dioxane (4 N, 2.9 ml, 11.4 mmol). The reaction was stirred for 16 h at

23 °C, concentrated, 1 N NaOH (30 ml) was added, and the product extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to give 0.96 g (2.86 mmol, 100%) of I-F as a colorless oil. MS (FAB for M+1): m/e 338.

Other R-substituted benzimidazolone derivatives were made in a similar manner.

Intermediate 4

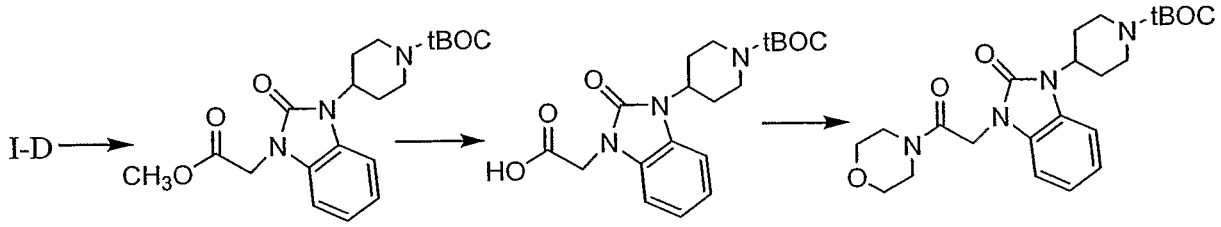
(Step D' of Scheme 1)



To a solution of I-G (1.0 g, 2.84 mmol) in DMF (20 ml) was added NaH (60 wt %, 0.082 g, 3.41 mmol). After 1 h at 23 °C excess methylsulfonyloxyethylisopropyl ether was added, and the reaction was then heated to 100 °C. After 16 h, the reaction was cooled, water (50 ml) was added and the product extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 20% EtOAc – CH_2Cl_2) afforded 1.20 g (2.74 mmol, 100% yield) of I-H as a foam. MS (ES for M+1): m/e 438.

Intermediate 5

(Step D' of Scheme 1)



To a solution of I-D (4.0 g, 12.7 mmol) in dry DMF (40 ml) at -78 °C was added lithium bis(trimethylsilyl)amide (1.0 M in THF, 16.5 ml, 16.5 mmol) dropwise via syringe. The reaction was stirred at -78 °C for 60 min., methyl bromoacetate (2.90 g, 1.8 ml, 19.0 mmol) was then added and the reaction warmed slowly to 23 °C. After 16 h the solvent was evaporated, saturated NH_4Cl (60 ml) added, and the product extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 40% EtOAc –

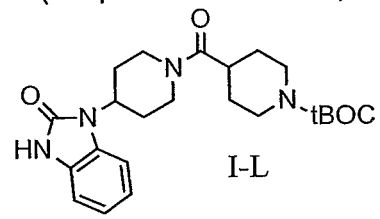
hexane) afforded 3.37 g (8.66 mmol, 69%) of I-I as a white foam. MS (CI for M+1): m/e 390.

To a solution of I-I (3.36 g, 8.66 mmol) in 1:1 CH_3OH:H_2O by volume (50 ml) was added $LiOH•H_2O$ (0.76 g, 17.3 mmol) and the reaction was heated to reflux for 3 h. The reaction was cooled and the solvent evaporated to give 3.49 g (8.62 mmol, 99%) of I-J (with 1 equivalent of LiOH) as a white solid. MS (FAB for M+1): m/e 382.

To a solution of compound I-J (1.64 g, 4.30 mmol) in 1:1 CH_2Cl_2:DMF by volume (40 ml) was added HOBT (0.88 g, 6.50 mmol), EDCI (1.25 g, 6.50 mmol), and morpholine (0.49 g, 5.60 mmol). After 0.5 h the reaction was heated to reflux for 16 h. The reaction was cooled, concentrated, 0.5 N NaOH (30 ml) was then added, and the product extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 5% CH_3OH – CH_2Cl_2) gave 1.91 g (4.30 mmol, 100%) of I-K as an oil. MS (ES for M+1): m/e 445.

Intermediate 6

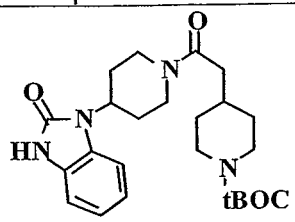
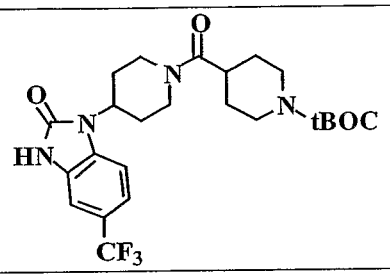
(Step E of Scheme 1)



I-L

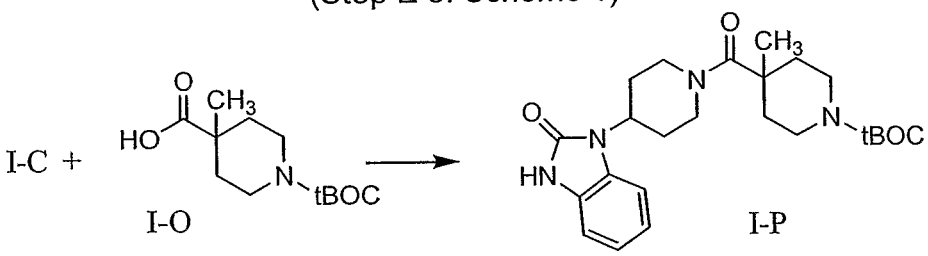
To a solution of I-C (4.52 g, 20.8 mmol) in CH_2Cl_2 (100 ml) was added t-BOC-isonipecotic acid (5.25 g, 22.9 mmol), DCC (5.37 g, 26.0 mmol), and HOBT (3.51 g, 26.0 mmol) and the reaction stirred at 23 °C for 16 h. The solids were filtered, and the filtrate transferred to a separatory funnel. 0.5 N NaOH (200 ml) was added, and the product extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 5% CH_3OH-CH_2Cl_2, then 8% CH_3OH-CH_2Cl_2) afforded 8.51 g (19.9 mmol, 95% yield) of I-L as a white foam. MS (ES for M+1): m/e 429.

The following compounds were prepared using a similar procedure and the appropriate starting materials:

	Compound	MS (CI, FAB, or ES)
I-M		443 (MH^+)
I-N		497 (MH^+)

Intermediate 7

(Step E of Scheme 1)

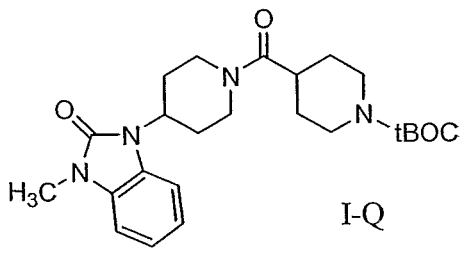


I-C + I-O → I-P

To a mixture of Intermediate I-C (4.45g, 20.48 mmol), I-O (5.00 g, 20.55 mmol), and DMAP (5.10g, 41.75 mmol) in DMF (200 ml) was added HATU (7.90 g, 20.78 mmol). The resulting solution was stirred at 23 °C for 16 h, and quenched with cold water (250 ml). The reaction mixture was transferred to separatory funnel, and the product extracted with ether. The combined organic layers were washed with saturated brine (2 X 200 ml), dried over $MgSO_4$, and concentrated. Purification by silica chromatography (10% CH_3OH in CH_2Cl_2) gave a yellow gel, which was crystallized from ether to provide a white solid (6.93 g). The mother liquid was concentrated and recrystallization from 100 ml of ether delivered another portion of white solid (0.20 g). Combined yield of I-P was 79%.

Intermediate 8

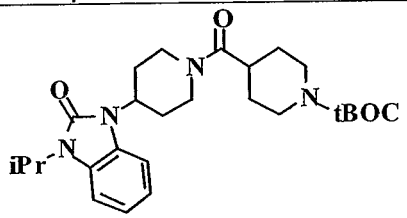
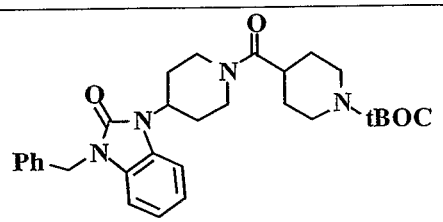
(Step E' of Scheme 1)



I-Q

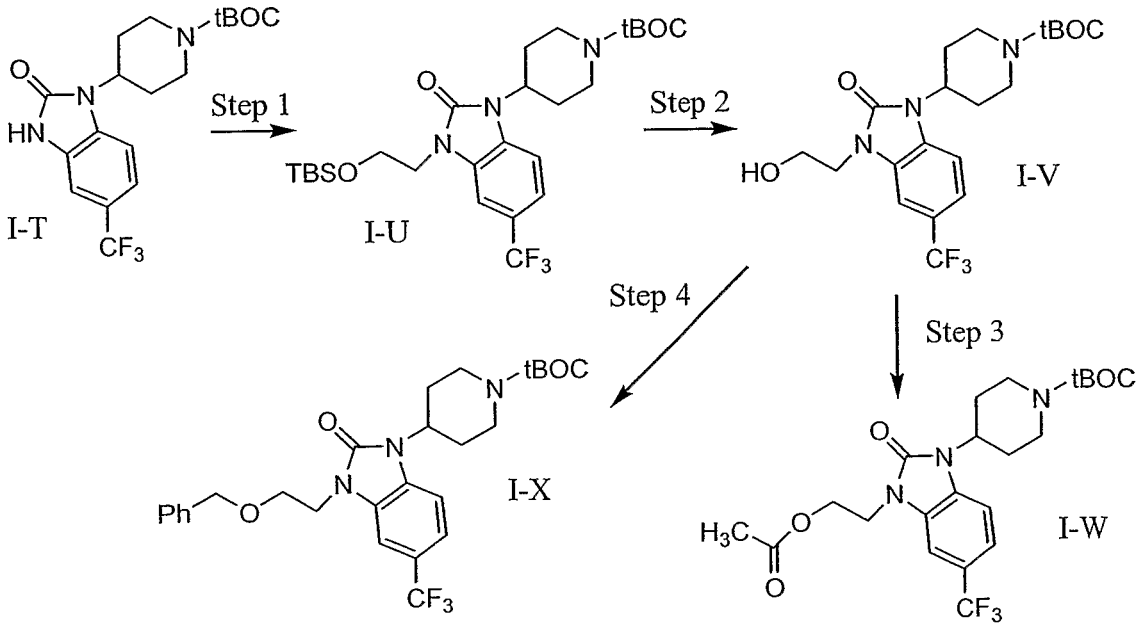
To a solution of I-L (1.00 g, 2.33 mmol) in toluene (20 ml) was added NaOH (0.33 g, 8.17 mmol), K_2CO_3 (0.64 g, 4.67 mmol), tetrabutylammonium hydrogensulfate (0.16 g, 0.467 mmol), and dimethylsulfate (0.44 g, 0.33 ml, 3.50 mmol). The reaction was heated at reflux for 16 h then cooled. Water (40 ml) was added, and the product extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 5% CH_3OH–CH_2Cl_2) gave 0.99 g (2.24 mmol, 96%) of I-Q as a white foam. MS (ES for M+1): m/e 443.

The following compounds were prepared according to the same above procedure:

	Compound	MS (CI, FAB, or ES)
I-R		485 (MH^+)
I-S		519 (MH^+)

Intermediate 9

(Step F' of Scheme 1)

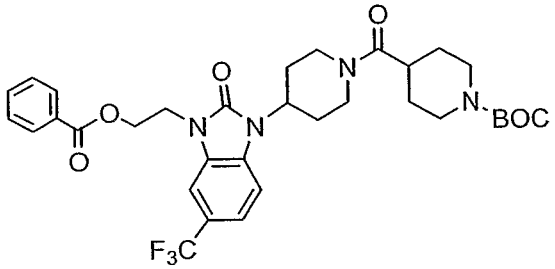


Step 1: To a solution of I-T (1.42 g, 2.86 mmol) in dry DMF (7.2 ml) was added 60% NaH (458 mg, 11.4 mmol) portionwise. After 10 min, 2-bromoethyl t-butyldimethylsilyl ether (1.23 ml, 5.7 mmol) was added and the reaction stirred for 15 h at 23 °C, then heated at 45 °C for 7 h. The reaction was quenched by slow addition into cold NH_4Cl solution and the product extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification by silica gel chromatography (eluant: EtOAc) afforded 1.0 g (1.53 mmol, 53%) of product I-U as a white solid. MS: m/e 655 (MH^+).

Step 2: To a solution of I-U (1.0 g, 1.53 mmol) in THF (7.6 ml) was added TBAF (3.1 ml, 3.1 mmol, 1 M in THF) and the reaction stirred at 23 °C. After 2.5 h, EtOAc was added and the organic layer washed with brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated to give 0.67 g (1.25 mmol, 82%) of the product I-V as a white solid. MS: m/e 541 (MH^+).

Step 3: To a solution of I-V (250 mg, 0.46 mmol) in CH_2Cl_2 (3.2 ml) at 0 °C was added Et_3N (97 µl, 0.69 mmol), DMAP (68 mg, 0.55 mmol), and Ac_2O (65 µl, 0.69 mmol). The reaction was allowed to warm to 23 °C. After 2 h, saturated $NaHCO_3$ solution was added and the product extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification by silica gel chromatography (eluant: EtOAc) afforded 0.173 g (0.30 mmol, 64% yield) of I-W as a white solid. MS: m/e 583 (MH^+).

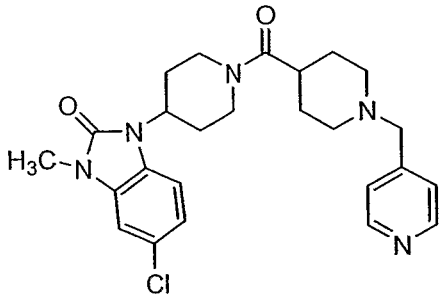
The following compound was prepared according to the same above procedure:



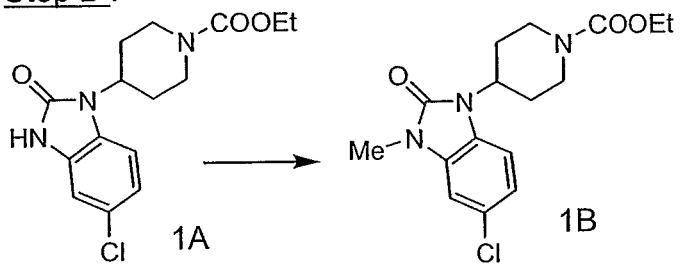
I-Y: MS: m/e 645 (MH^+)

Step 4: To a solution of I-V (173 mg, 0.32 mmol) in dry THF (3.2 ml) was added 60 wt % NaH (38 mg, 0.96 mmol) portionwise at 23 °C. After 10 min., benzylbromide (144 µl, 0.96 mmol) was added. After 3.5 h, the reaction was poured slowly into cold NH_4Cl solution and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification by silica gel chromatography (eluant: EtOAc) afforded 0.166 g (0.26 mmol, 82% yield) of I-X as a white solid. MS: m/e 631 (MH^+).

Example 1



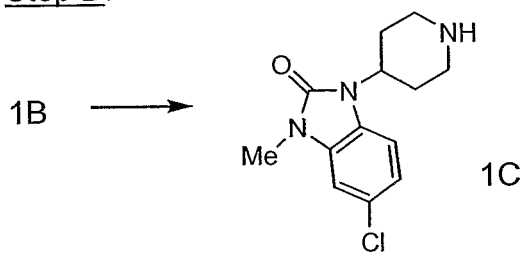
Step D':



1A 1B

To a suspension of compound 1A (0.3 g, 4.02 mmol) in dry toluene (30 ml), was added NaOH (0.56 g, 14.05 mmol), K_2CO_3 (1.11 g, 8.00 mmol), tetra-n-butylammonium sulfate (0.27 g, 0.80 mmol) and dimethylsulfate (0.76 g, 0.57 ml, 6.02 mmol). The reaction was refluxed for 16 h and then cooled to 23 °C. The solvent was evaporated, water added (50 ml), and the product extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to afford 1.0 g (2.96 mmol, 71% yield) of the product 1B as a cream solid (mp 138-139 °C). MS (CI) m/e 338 (MH^+)

Step D:



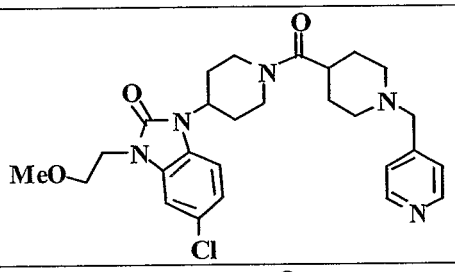
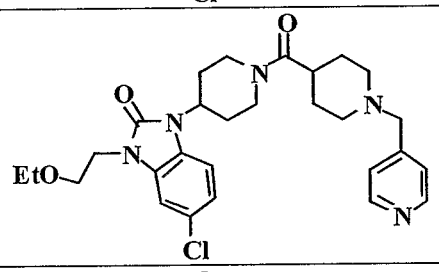
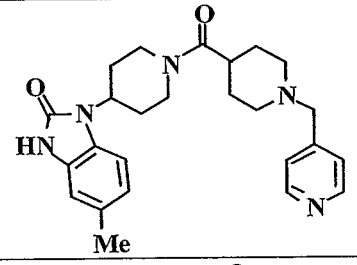
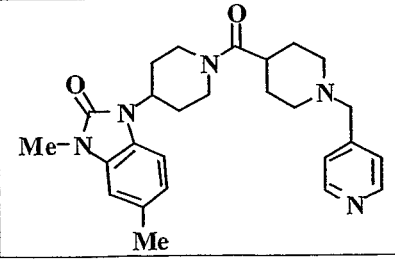
1B 1C

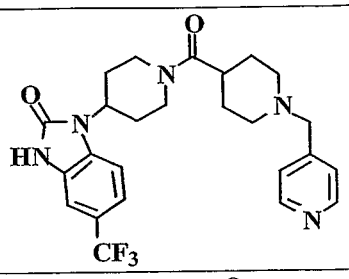
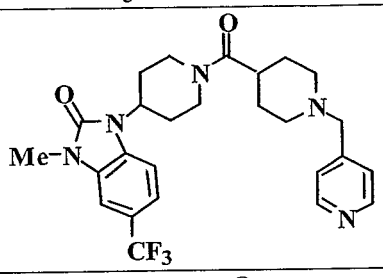
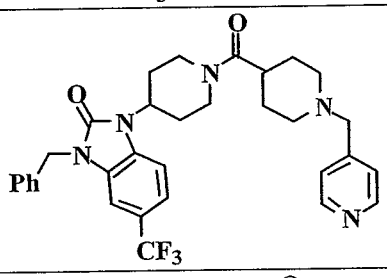
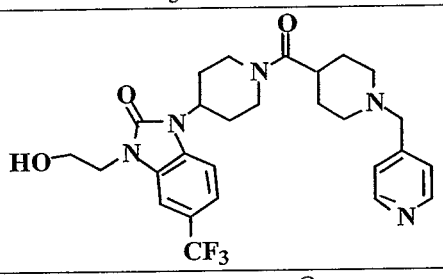
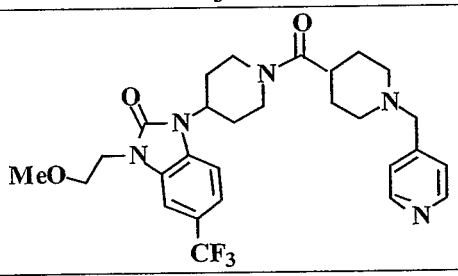
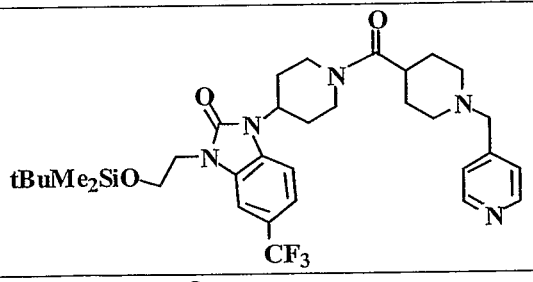
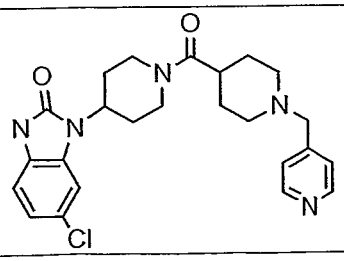
To a solution of 1B (1.0 g, 2.96 mmol) in ethanol (75 ml) was added 25% NaOH in water (12 ml). The reaction was heated at reflux for 16 h and then cooled to 23 °C. The solvent was evaporated, and the product partitioned between saturated NaCl and CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to give 0.77 g (2.90 mmol, 97%) of 1C as a white solid (mp 194-195 °C). MS (CI) m/e 266 (MH^+).

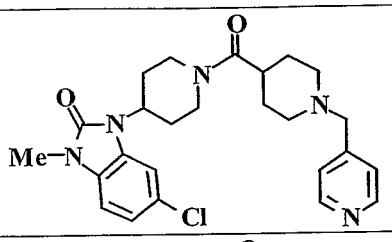
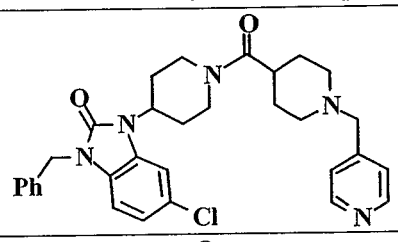
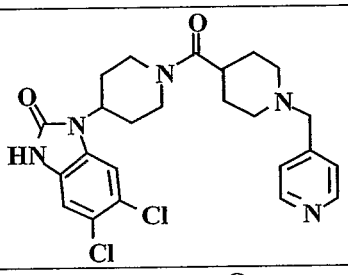
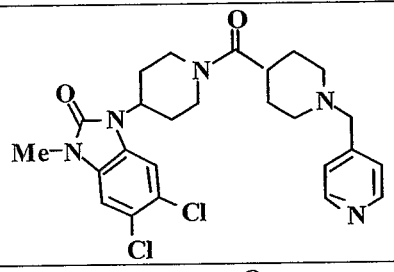
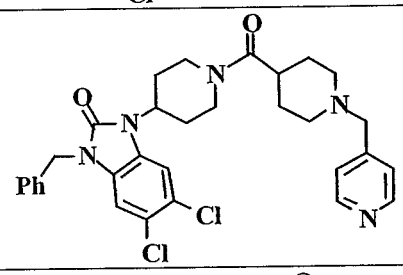
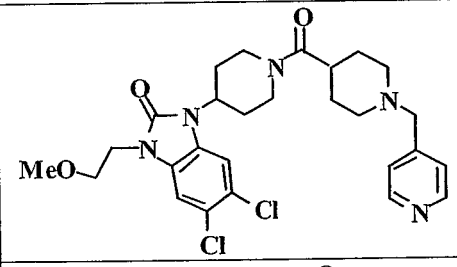
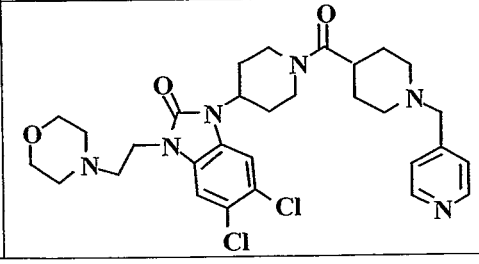
Step G:

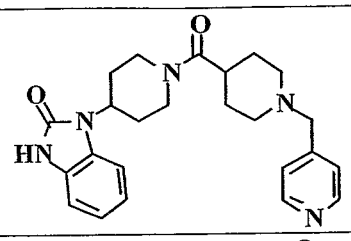
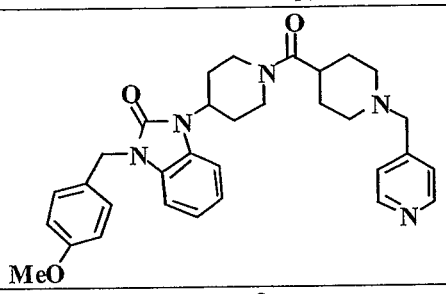
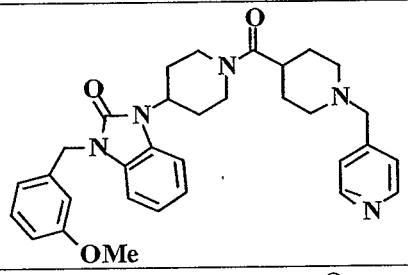
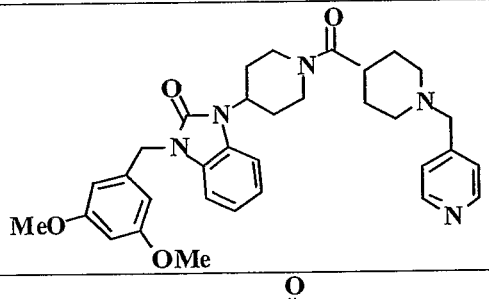
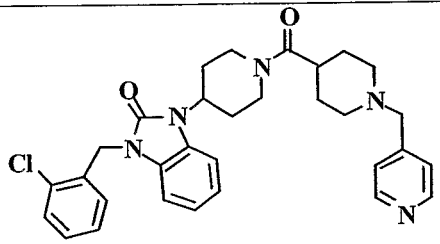
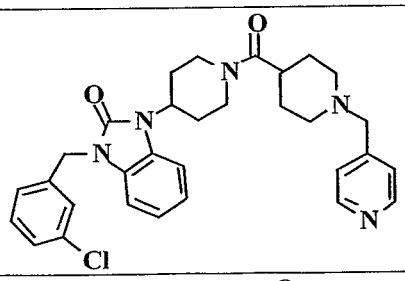
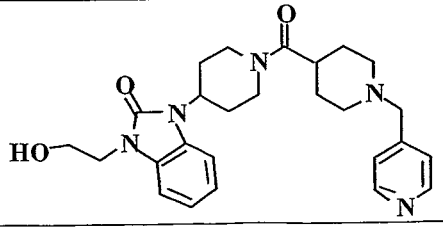
Compound 1C (0.50 g, 1.88 mmol) was dissolved in a 1:1 CH_2Cl_2:DMF (20 ml) mixture and HOBT (0.38 g, 2.82 mmol), EDCI (0.54 g, 2.82 mmol), and the product of Preparation 1 (0.53 g, 2.35 mmol) were added. After 0.5 h, the reaction was heated to reflux for 16 h. The reaction was then cooled, quenched with 0.5 N NaOH (30 ml) and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 5% CH_3OH with NH_3-CH_2Cl_2) gave 0.70 g (1.50 mmol, 80% yield) of Example 1 as a foam. MS (CI) m/e 468 (MH^+).

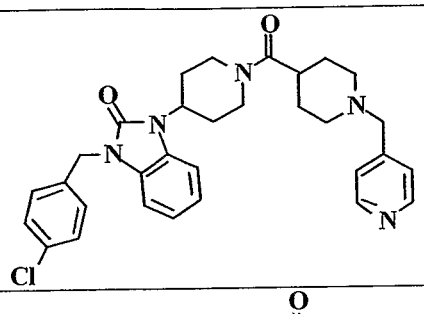
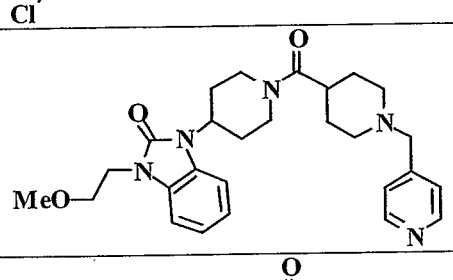
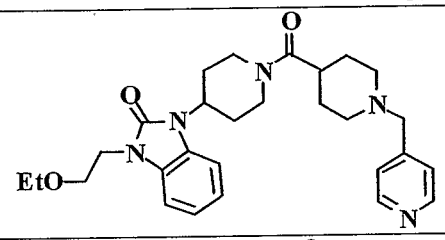
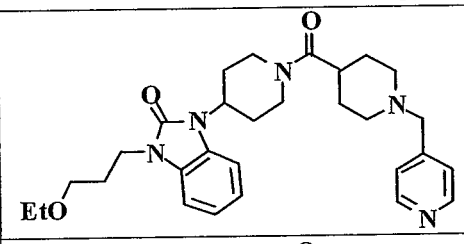
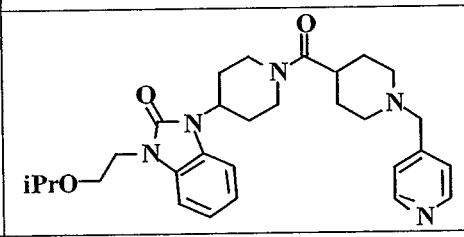
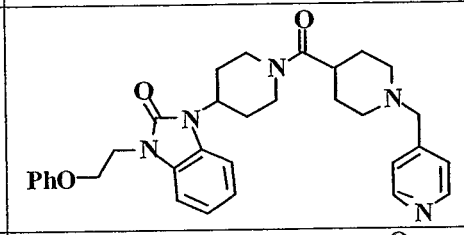
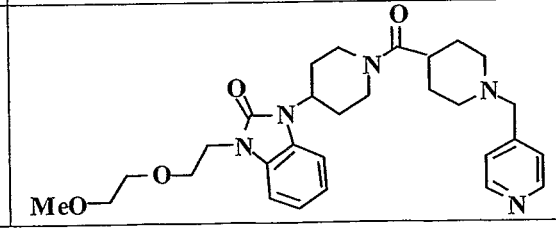
The following compounds were prepared in a similar fashion.

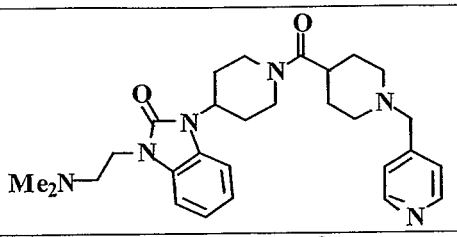
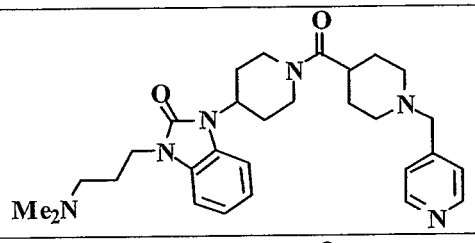
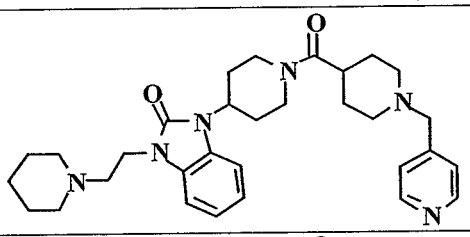
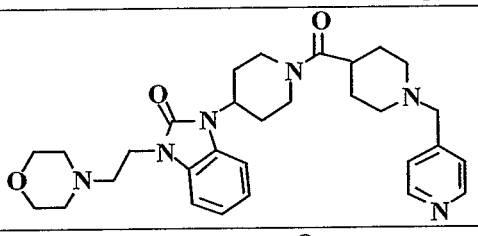
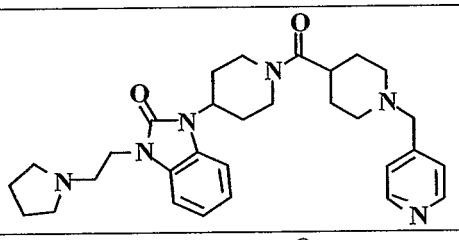
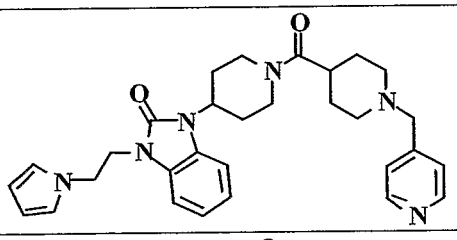
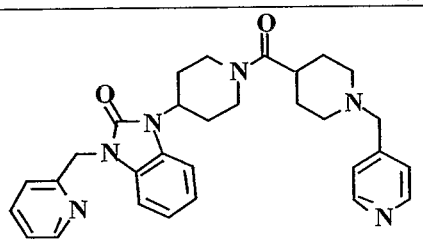
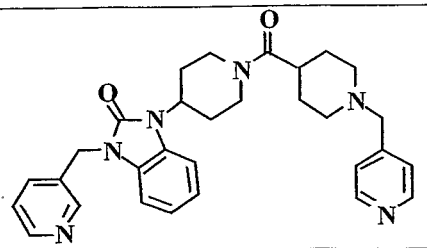
	Compound	MS (CI, FAB, ES)
1A		512 (MH^+)
1B		526 (MH^+)
1C		434 (MH^+)
1D		448 (MH^+)

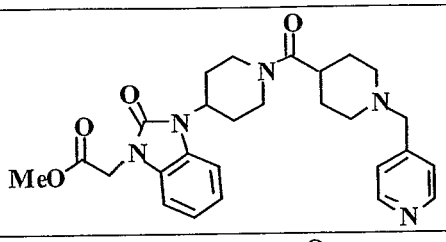
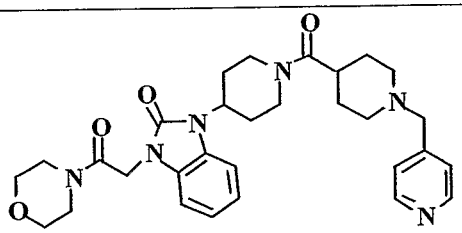
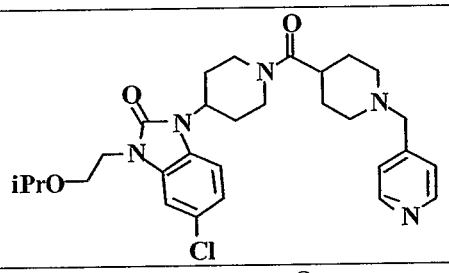
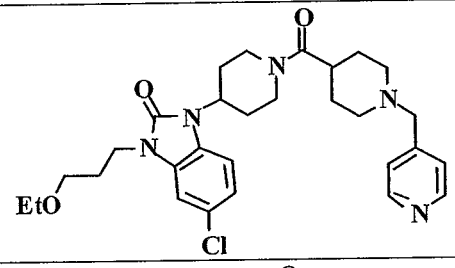
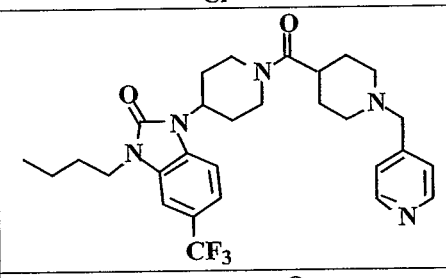
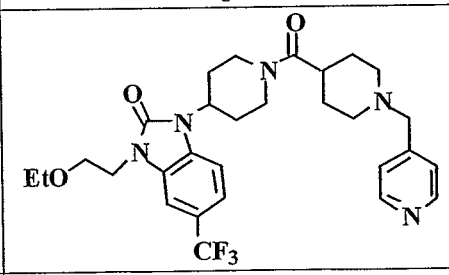
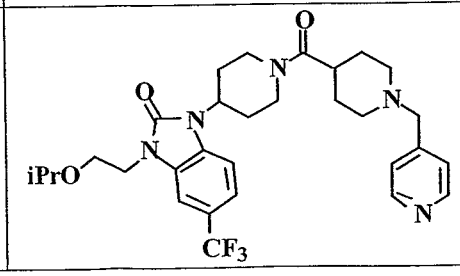
1E		488 (MH^+)
1F		502 (MH^+)
1G		578 (MH^+)
1H		532 (MH^+)
1I		546 (MH^+)
1J		532 (M-$SiMe_2tBu$+1)
1K		454 (MH^+)

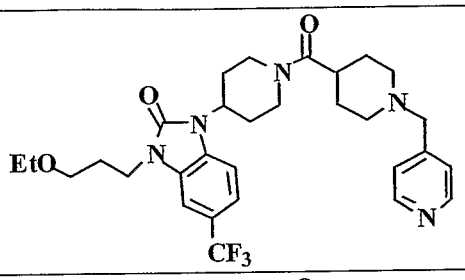
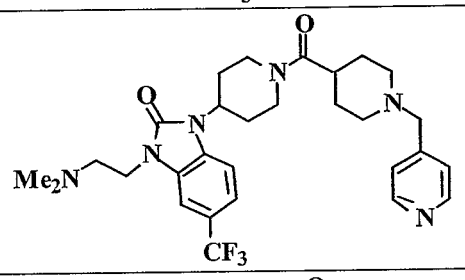
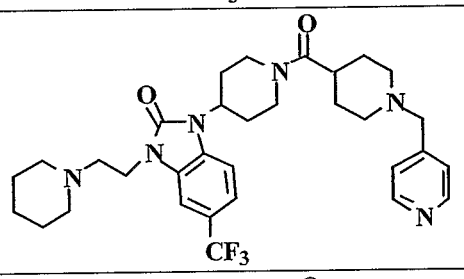
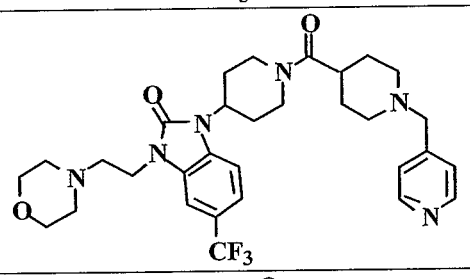
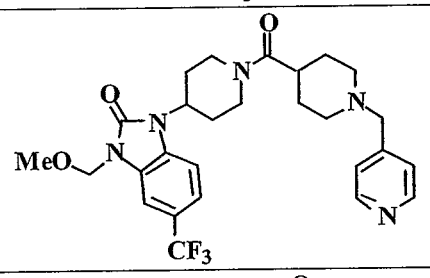
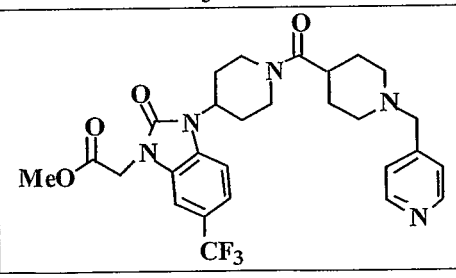
1L		468 (MH^+)
1M		544 (MH^+)
1N		488 (MH^+)
1O		502 (MH^+)
1P		578 (MH^+)
1Q		546 (MH^+)
1R		601 (MH^+)

1S		420 (MH^+)
1T		540 (MH^+)
1U		540 (MH^+)
1V		570 (MH^+)
1W		544 (MH^+)
1X		544 (MH^+)
1Y		464 (MH^+)

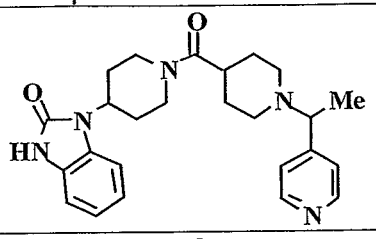
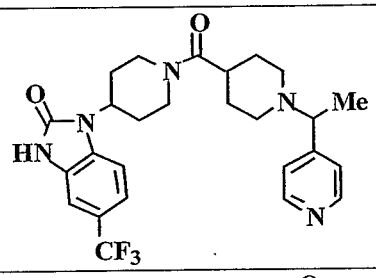
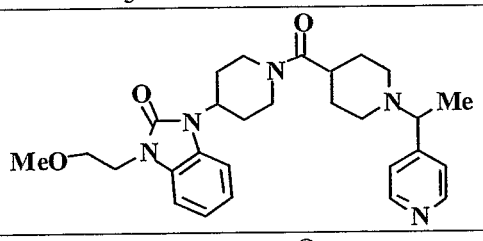
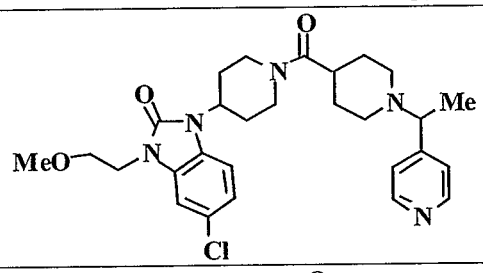
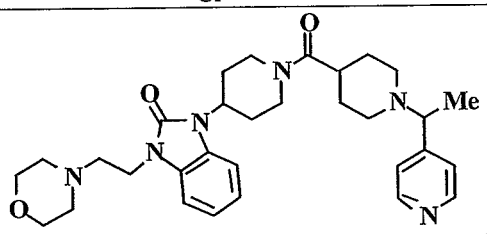
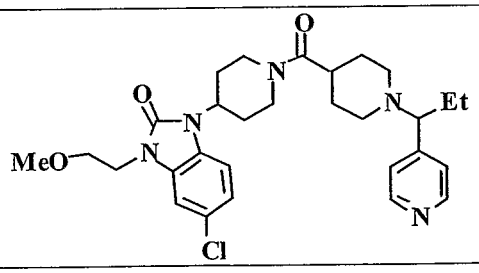
1Z		544 (MH^+)
1AA		478 (MH^+)
1AB		492 (MH^+)
1AC		506 (MH^+)
1AD		506 (MH^+)
1AE		540 (MH^+)
1AF		522 (MH^+)

1AG		491 (MH^+)
1AH		505 (MH^+)
1AI		531 (MH^+)
1AJ		533 (MH^+)
1AK		517 (MH^+)
1AL		513 (MH^+)
1AM		511 (MH^+)
1AN		511 (MH^+)

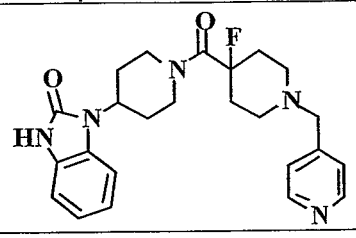
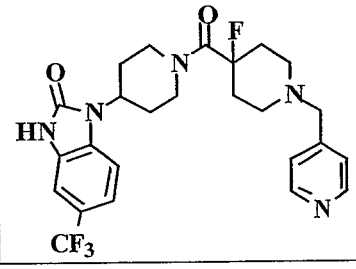
1AO		492 (MH^+)
1AP		547 (MH^+)
1AQ		540 (MH^+)
1AR		540 (MH^+)
1AS		544 (MH^+)
1AT		560 (MH^+)
1AU		574 (MH^+)

1AV		574 (MH^+)
1AW		559 (MH^+)
1AX		599 (MH^+)
1AY		601 (MH^+)
1AZ		532 (MH^+)
1AAA		560 (MH^+)

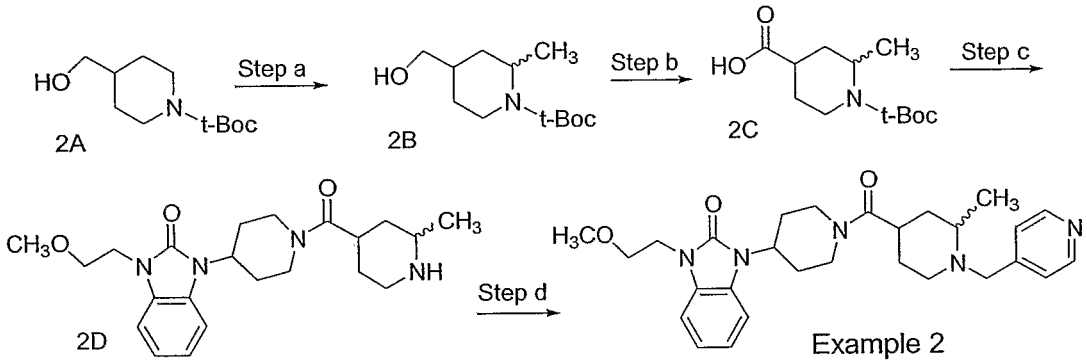
The following compounds were prepared using a procedure similar to the above, but using Preparation 2 as starting material. The enantiomers were separated on a Chiralcel OD column (eluant: isopropanol – hexane with diethylamine).

	Compound	MS (CI, FAB, ES)
1BA		434 (MH^+)
1BB		502 (MH^+)
!BC		492 (MH^+)
1BD		526 (MH^+)
1BE		581 (MH^+)
1BF		540 (MH^+)

The following compounds were prepared using a procedure similar to the above but using Preparation 3 as starting material.

	Compound	MS (CI, FAB, ES)
1CA		438 (MH^+)
1CB		506 (MH^+)

Example 2



Step a: A flask was charged with alcohol 2A (5.40 g, 25.08 mmol) and DMF (50 ml). Imidazole (1.88 g, 27.59 mmol) and TBDMS chloride (3.40 g, 22.57 mmol) were added at 23 °C. After 16 h, saturated NH_4Cl (500 ml) was added and the product extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification by silica gel chromatography (eluant: hexane, then 8:1 hexane:EtOAc) afforded 6.54 g (19.85 mmol, 79%) of the TBMDS protected alcohol. MS (FAB for M+1): m/e 230.

The TBDMS protected alcohol (5.54 g, 16.8 mmol) was dissolved in Et_2O (50 ml) and cooled to –78 °C under N_2. TMEDA (2.44 g, 3.2 ml, 21.0 mmol) and sec-BuLi (1.3 M, 16.2 ml, 21.0 mmol) were added via syringe and the reaction stirred at –78 °C. After 3 h, dimethylsulfate (3.18 g, 2.4 ml, 25.2 mmol) was added via syringe, and the reaction was allowed to warm slowly over 2 h to 23 °C and stirred for an additional 2 h. The reaction was quenched by addition of water (100 ml) and the product extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 5% EtOAc–

hexane then 10% EtOAc–hexane) gave 4.59 g (13.36 mmol, 79%) of the 2-methylated product as a colorless oil. MS (FAB for M+1): m/e 344.

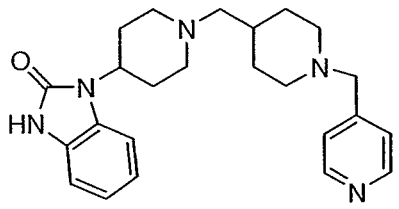
The 2-methylated product (4.58 g, 13.3 mmol) was dissolved in THF (30 ml) and n-Bu_4NF (1.0 M in THF, 20.0 ml, 20.0 mmol) was added. After 16 h at 23 °C, water (100 ml) was added and the product extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 5% CH_3OH–CH_2Cl_2 then 10% CH_3OH-CH_2Cl_2) gave 3.06 g (13.3 mmol, 100%) of 2B as a colorless oil. MS (FAB for M+1): m/e 230.

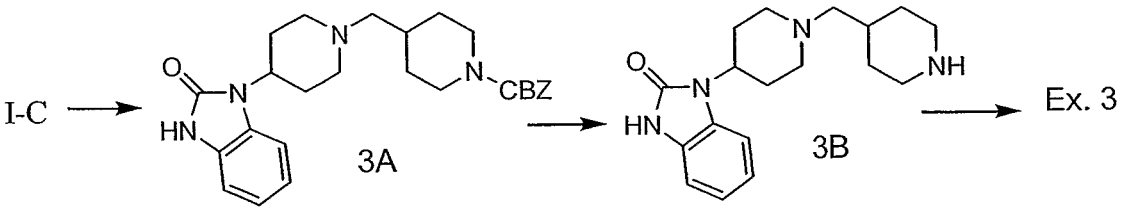
Step b: Oxalyl chloride (2.57 g, 1.8 ml, 20.3 mmol) and dry CH_2Cl_2 (60 ml) were cooled to –78 °C under N_2. DMSO (3.16 g, 2.9 ml, 40.5 mmol) in CH_2Cl_2 (5 ml) was added dropwise via an addition funnel. After 15 min at –78 °C, compound 2B as a solution in CH_2Cl_2 (20 ml) was added dropwise. After 1 h at –78 °C, Et_3N (5.46 g, 7.5 ml, 54.0 mmol) was added and the reaction allowed to warm up to 23 °C. After 2 h, water (100 ml) was added and the product extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to give 3.07 g (13.5 mmol, 100%) of the corresponding aldehyde as a yellow oil. MS (ES for M+1): m/e 228.

To the aldehyde (3.07 g, 13.5 mmol) dissolved in t-BuOH (60 ml) was added 2-methyl-2-butene (6 ml), sodium chlorite (7.33 g, 81.0 mmol), and potassium phosphate (9.19 g, 67.5 mmol) in H_2O (60 ml). The reaction was stirred at 23 °C. After 2h, the solvent was removed, 0.5 N HCl added and the product extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to give 3.29 g (13.5 mmol, 100%) of the acid 2C as a yellow oil. MS (FAB for M+1): m/e 244.

Step c: 2C was coupled with the appropriate piperidine to afford intermediate 2D, which was transformed into the title compound using the procedure of Example 1, Step G. (ES for M+1): m/e 492.

Example 3



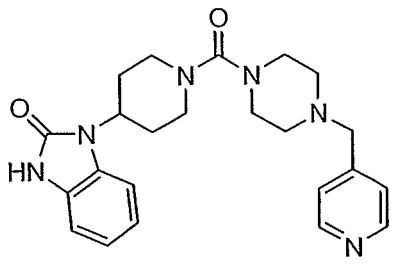


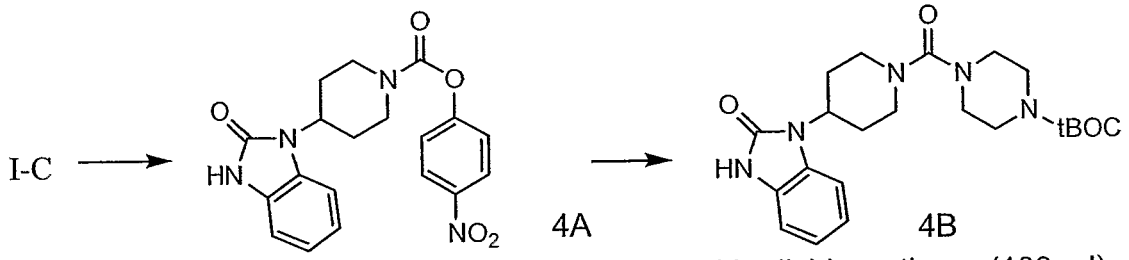
Compound I-C (2.64 g, 12.13 mmol), N-CBZ-4-piperidinecarboxaldehyde (2.00 g, 8.09 mmol), crushed 3Å molecular sieves (2.5 g), and $NaBH(OAc)_3$ (2.57 g, 12.13 mmol) were combined in CH_2Cl_2:CF_3CH_2OH (1:1, 50 ml) at 23 °C. The reaction was stirred for 16 h and then quenched with 1 N NaOH (50 ml). The reaction mixture was then filtered, the solid washed with CH_2Cl_2 and the filtrate transferred to a separatory funnel. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Further purification by silica gel chromatography (eluant: 5% CH_3OH–CH_2Cl_2 then 10% CH_3OH–CH_2Cl_2) gave 3.34 g (7.45 mmol, 92%yield) of the product 3A as a white foam. MS (FAB for M+1): m/e 449.

Compound 3A (3.33 g, 7.42 mmol) was dissolved in DMF (50 ml) and shaken on Parr hydrogenation apparatus under 50 psi hydrogen pressure with 10% Pd/C catalyst (0.75 g). After 20 h, the reaction was filtered through celite and washed with CH_3OH. The filtrate was concentrated to give 2.16 g (6.87 mmol, 93%yield) of 3B as a white solid. MS (CI for M+1): m/e 315.

3B (1.00 g, 3.18 mmol) was added to trifluoroethanol (25 ml), 4-pyridine-carboxaldehyde (0.31 g, 2.89 mmol), crushed 3Å molecular sieves (1.0 g) and $NaBH(OAc)_3$ (0.92 g, 4.34 mmol) at 23 °C. After 16 h, 1 N NaOH (50 ml) was added, the reaction mixture filtered and the filtrate transferred to a separatory funnel. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 5% CH_3OH with NH_3–CH_2Cl_2 then 7% CH_3OH with NH_3–CH_2Cl_2) gave 0.54 g (1.33 mmol, 46%) of the title compound as a white foam. MS (ES for M+1): m/e 406.

Example 4



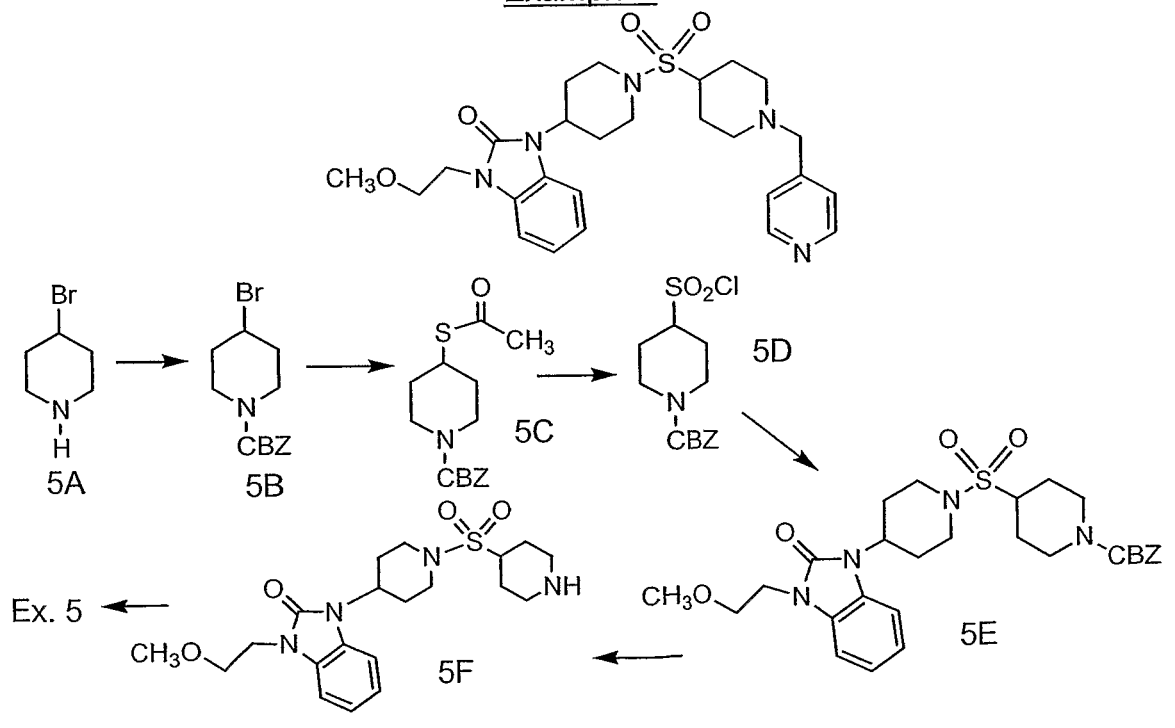


Compound I-C(4.00 g, 18.4 mol) was dissolved in dichloroethane (100 ml) and Et_3N (2.79 g, 3.8 ml, 27.6 mmol) and 4-nitrophenyl chloroformate (3.71 g, 18.4 mmol) were added. The reaction was heated at reflux for 1 h, cooled, and 0.5 N NaOH (100 ml) was added. The product was extracted with CH_2Cl_2, the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to give 7.04 g (18.4 mmol, 100%) of 4A as a yellow foam.

Compound 4A (3.5 g, 9.2 mmol) was dissolved in DMF (50 ml) and mono-N-tBOC-piperazine (1.7 g, 9.2 mmol) was added. The reaction was heated at 120 °C for 16 h, concentrated, and the residue dissolved in water. The product was extracted with CH_2Cl_2 and the combined extracts were dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 5% CH_3OH-CH_2Cl_2) gave 1.6 g (3.73 mmol, 41% yield) of 4B as a yellow foam. MS (FAB for M+1): m/e 430.

Compound 4B was deprotected as in Intermediate 3, Step D and reacted with the pyridinecarboxaldehyde as in Example 3 to obtain the title compound.

Example 5



A flask was charged with compound 5A (HBr salt) (5.0 g, 20.4 mmol), CH_2Cl_2 (80 ml), saturated $NaHCO_3$ (160 ml) and benzyl chloroformate (3.7 ml, 24.5 mmol) at 23 °C. After 22 h, the biphasic reaction mixture was transferred to a separatory funnel, and the product extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification by silica gel chromatography (eluant: 8:1 hexane:EtOAc) gave 3.02 g (10.1 mmol, 50% yield) of 5B as a colorless oil. MS: m/e 298.

To a solution of 5B (2.13 g, 7.14 mmol) in dry DMSO (12 ml) was added potassium thioacetate (1.23 g, 10.7 mmol). After 21.5 h, water was added and the product extracted into EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification by silica gel chromatography (eluant: 5:1 hexane:EtOAc) gave 1.36 g (4.7 mmol, 66% yield) of 5C as a yellow oil. MS: m/e 294.

Cl_2 (gas) was bubbled into a suspension of 5C (1.05 g, 3.58 mmol) in water (30 ml) at 0 °C. After 35 min, additional water was added, and the product extracted with Et_2O. The combined organic extracts were washed sequentially with 5% $Na_2S_2O_5$ (100 ml), saturated $NaHCO_3$ (50 ml), and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. Purification by silica gel chromatography (eluant: 5:1 hexane:EtOAc, followed by hexane:EtOAc 3.5:1) gave 0.909 g (2.86 mmol, 80% yield) of 5D as a yellow solid. MS: m/e 318.

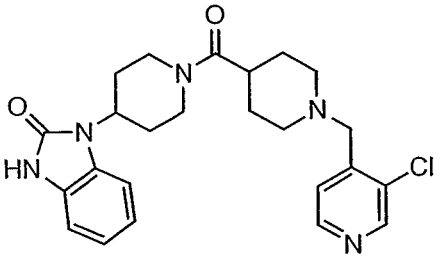
To a solution of 5D (227 mg, 0.714 mmol) in CH_2Cl_2 (8 ml) at 0 °C was added Et_3N (0.30 ml, 2.14 mmol) and 4-(2-keto-3-methoxyethyl-1-benzimidazolinyl)-piperidine (289 mg, 0.93 mmol). After 1 h at 0° C, water was added and the product extracted with CH_2Cl_2. The combined organic extracts were washed with 1 N HCl, brine and then dried (Na_2SO_4), filtered, and concentrated. The crude product 5E (0.54 mmol, 76% yield) was used without further purification. MS: m/e 557.

To a solution of 5E (300 mg, 53.9 mmol) in CH_3OH (10 ml) was added palladium on charcoal (50 mg) in a pressure vessel. The reaction mixture was shaken under hydrogen (50 psi) for 14 h. The catalyst was removed by filtration, the filtrate concentrated and purified by silica gel chromatography (eluant: 18:1 CH_2Cl_2:4% NH_3 in CH_3OH) to give 0.198 g (0.47 mmol, 87% yield) of 5F as a white solid. MS: m/e 423 (M+1).

To a solution of 5F (180 mg, 0.426 mmol) in CH_2Cl_2 (4 ml) was added 3 Å molecular sieves (400 mg), 4-pyridinecarboxyaldehyde (137 mg, 1.28 mmol) and

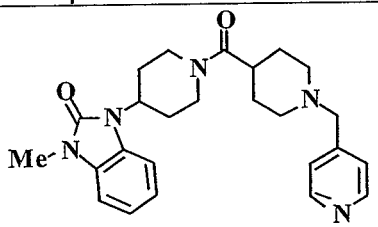
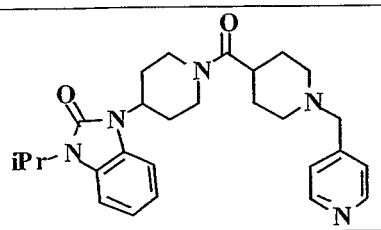
$NaB(OAc)_3H$ (271 mg, 1.28 mmol). After 24 h at 23 °C the reaction was filtered, additional CH_2Cl_2 added, and the organic phase washed with 1 N NaOH, and brine. The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated. Purification by silica gel chromatography (eluant: 18:1 CH_2Cl_2:4% NH_3 in CH_3OH) afforded 0.064 g (0.124 mmol, 30% yield) of the title compound as a white solid. MS: m/e 514 (M+1).

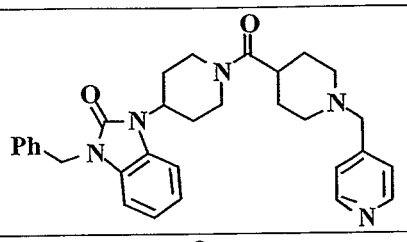
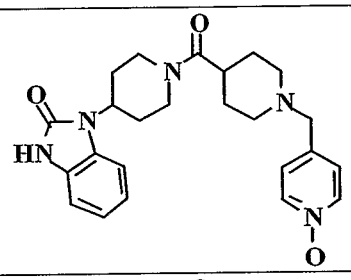
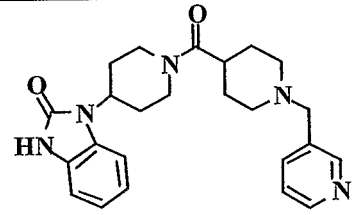
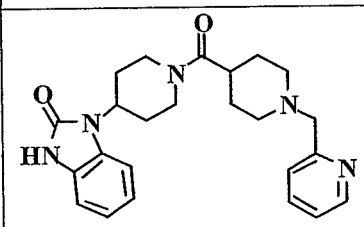
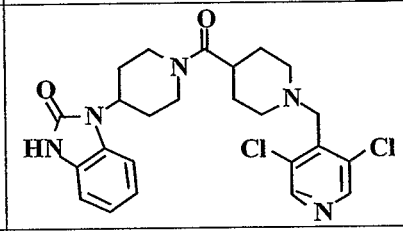
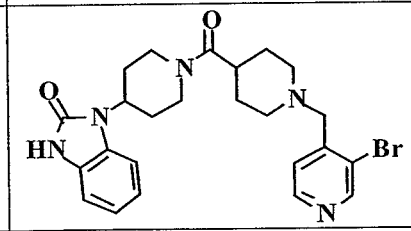
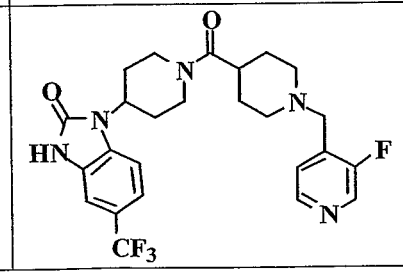
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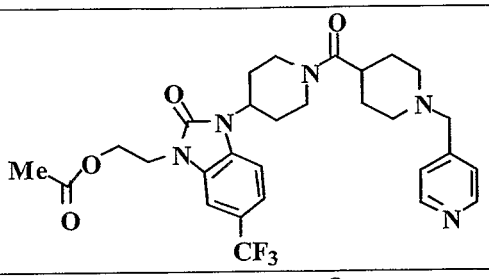
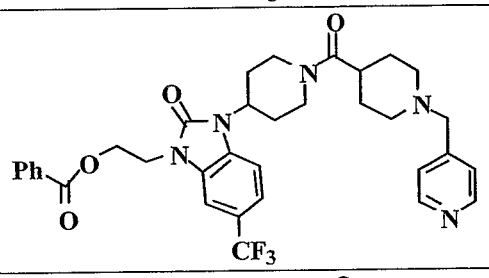
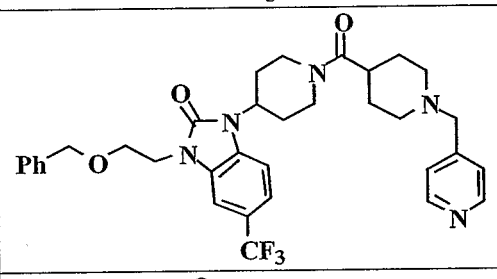
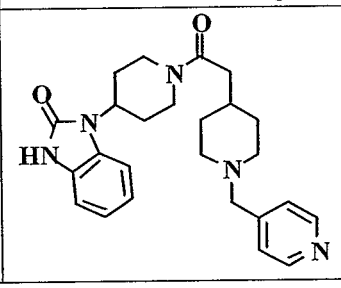


Intermediate 6 (I-L) was deprotected using the procedure of Intermediate 3, Step D. To a solution of the hydrochloride salt of the resulting compound (1.50 g, 4.11 mmol) in trifluoroethanol (20 ml) was added potassium t-butoxide (0.37 g, 3.29 mmol), crushed 3Å molecular sieves (1.5 g), 3-chloro-4-pyridinecarboxaldehyde (0.39 g, 2.74 mmol), and $NaBH(OAc)_3$ (0.87 g, 4.11 mmol). After 16 h, the reaction was filtered, the solvent evaporated, and the residue redissolved in CH_2Cl_2. 0.5 N NaOH (30 ml) was added and the product extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 5% MeOH – CH_2Cl_2) gave 0.85 g (1.87 mmol, 65% yield) of the title compound as a light yellow foam. MS (FAB for M+1): m/e 454.

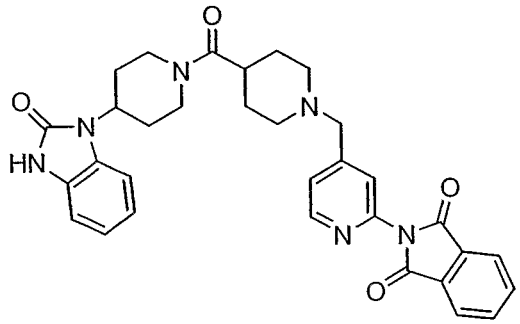
The following compounds were prepared using a similar above procedure with the appropriate pyridinecarboxaldehyde analog:

	Compound	MS (CI, FAB, or ES)
6A		434 (MH^+)
6B		476 (MH^+)

6C		510 (MH^+)
6D		436 (MH^+)
6E		420 (MH^+)
6F		420 (MH^+)
6G		488 (MH^+)
6H		498 (MH^+)
6I		505 (MH^+)

6J		574 (MH^+)
6K		636 (MH^+)
6L		622 (MH^+)
6M		434 (MH^+)

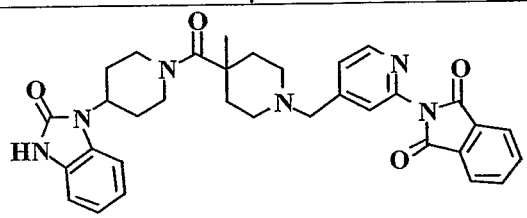
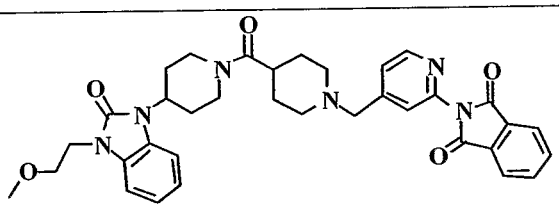
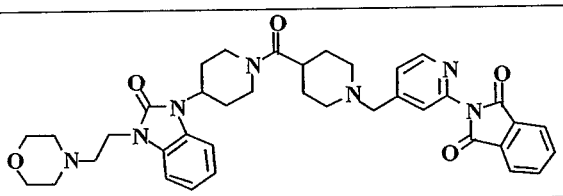
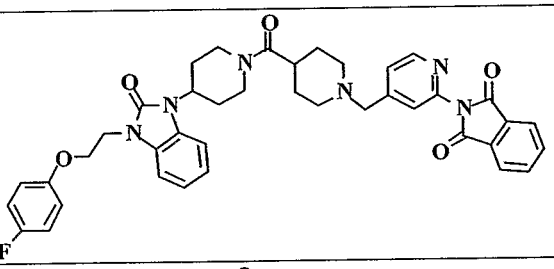
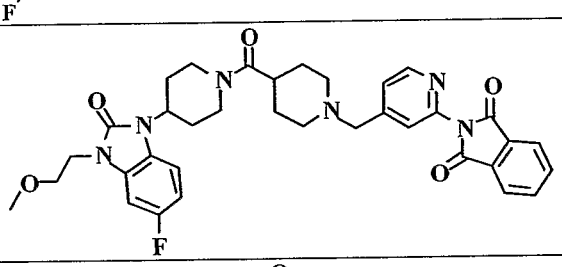
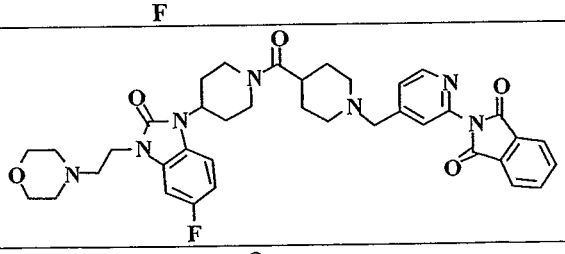
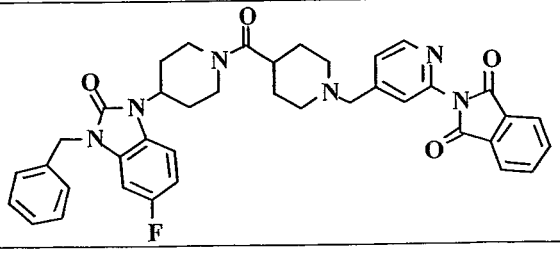
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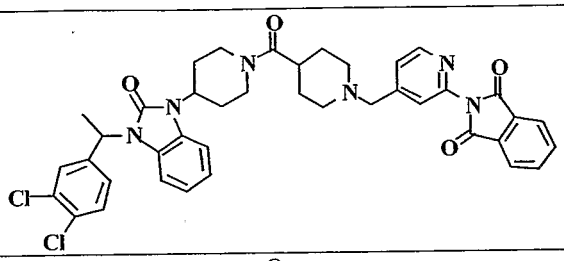
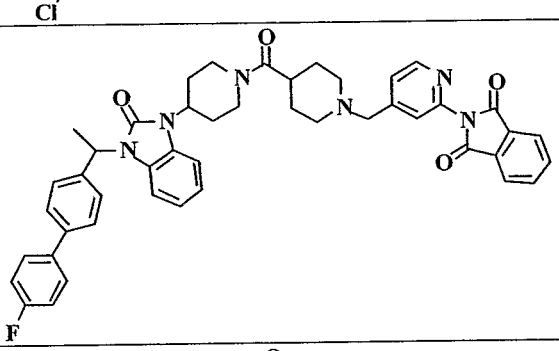
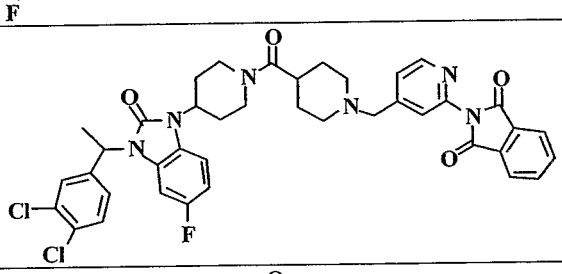
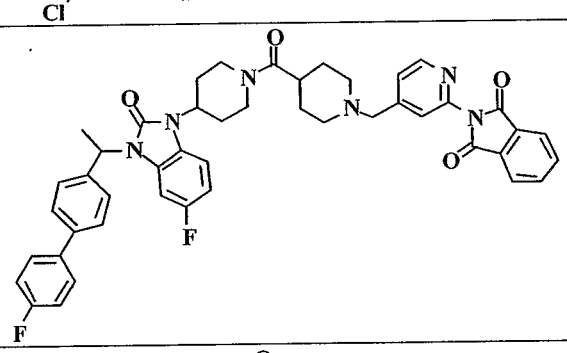
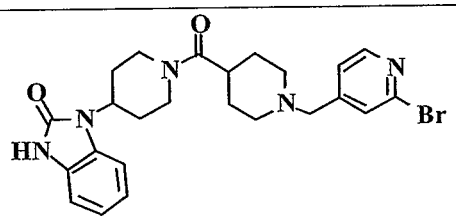
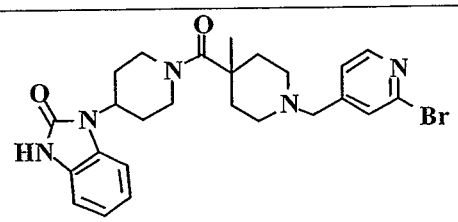
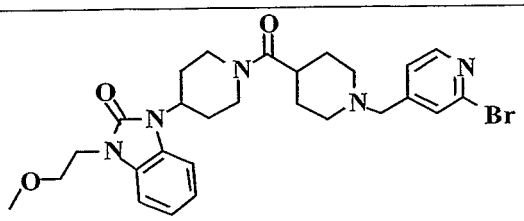


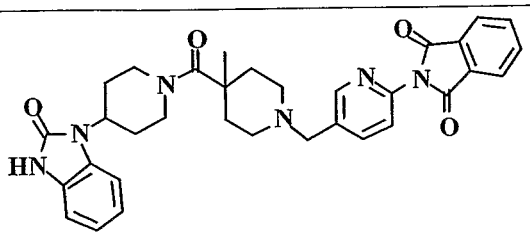
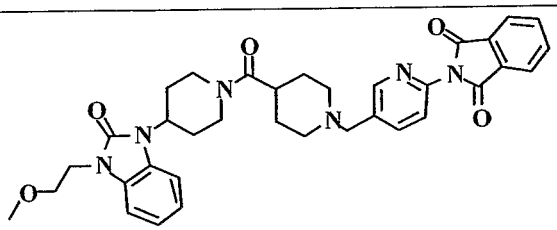
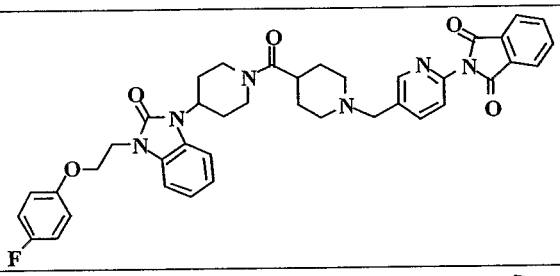
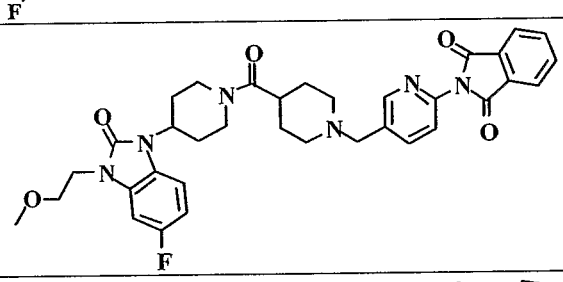
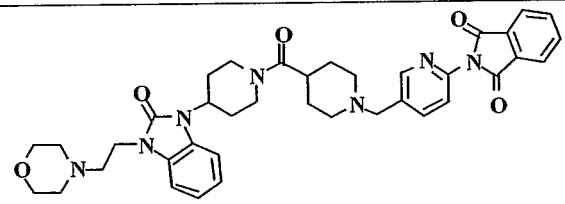
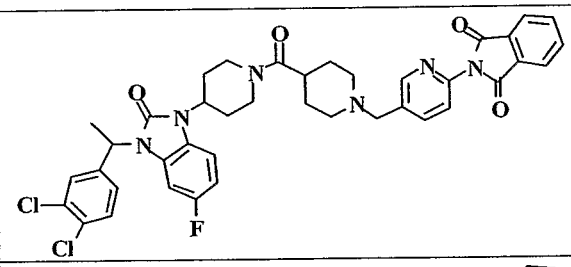
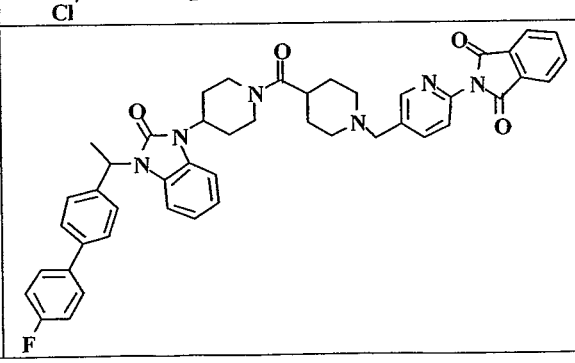
To a solution of deprotected I-L (100 mg, 0.271 mmol) and Preparation 5-2B (250 mg of mixture, ~0.33 mmol) in DMF was added Et_3N (0.5 ml, ~3.6 mmol). The reaction mixture was stirred at 23 °C for 15 h, water was added, and the mixture extracted with CH_2Cl_2. The combined organic extracts were washed with water, dried, and concentrated. Purification by silica gel chromatography (eluant: 10%

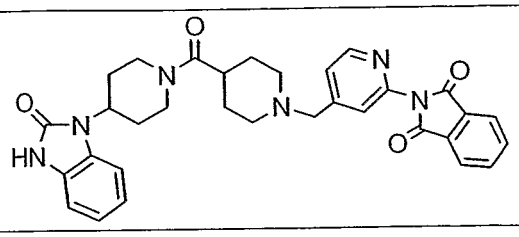
CH_3OH-CH_2Cl_2) provided the title compound as a slightly yellow solid. (62 mg, 41% yield). MS (CI): 597 (MH^++CH_3OH).

The following compounds were prepared in a similar manner:

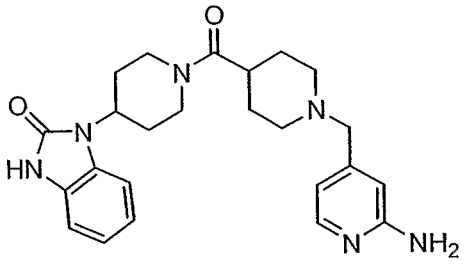
	Compounds	MS (CI)
7A		579 (MH^+)
7B		655 (MH^++CH_3OH)
7C		710 (MH^++CH_3OH)
7D		735 (MH^++CH_3OH)
7E		641 (MH^+)
7F		696 (MH^+)
7G		673 (MH^+)

7H		719 (MH^+)
7I		--
7J		--
7K		--
7L		500 (MH^+)
7M		512 (MH^+)
7N		556 (MH^+)

7O		--
7P		--
7Q		--
7R		--
7S		--
7T		--
7U		--

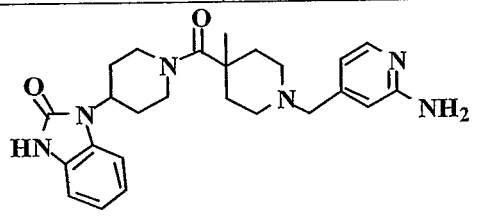
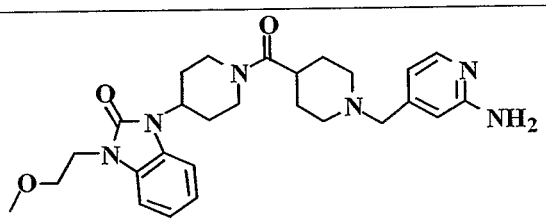
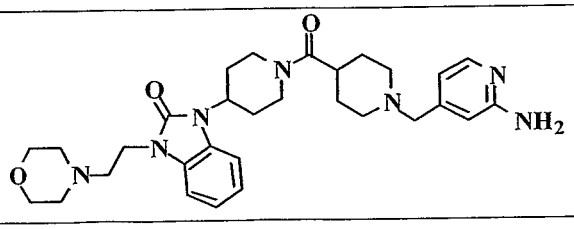
7V		564 (MH^+)

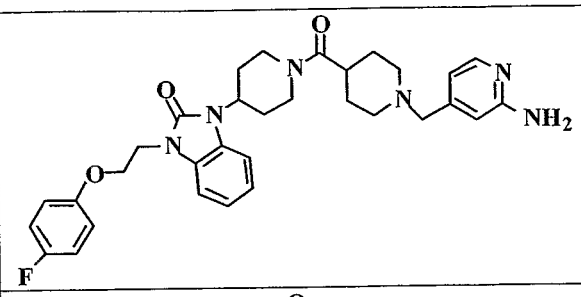
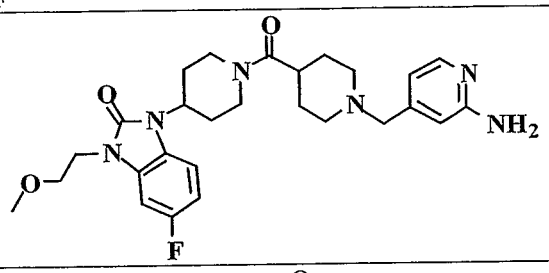
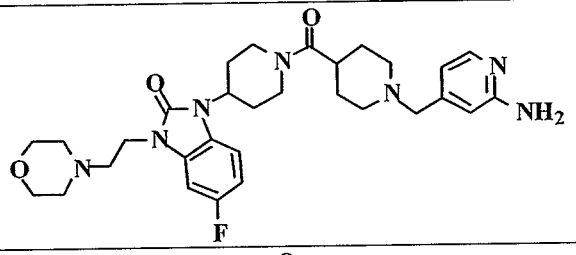
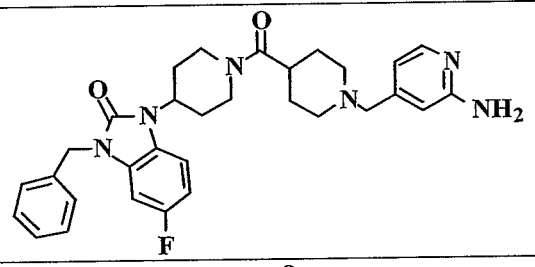
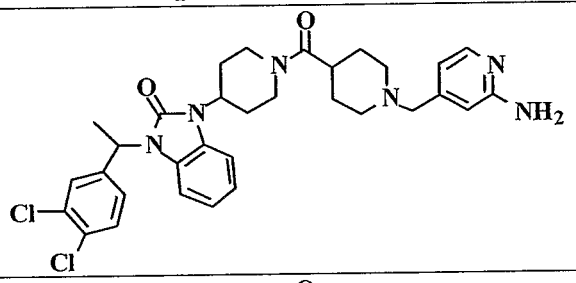
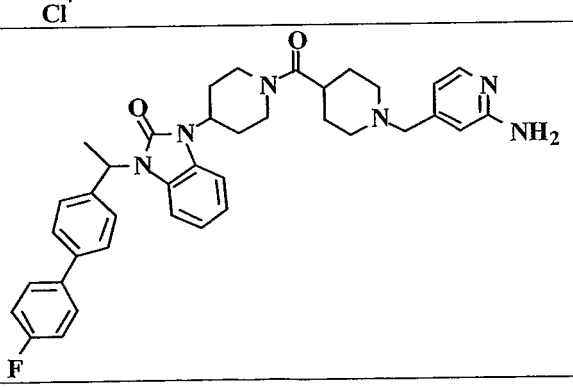
Example 8

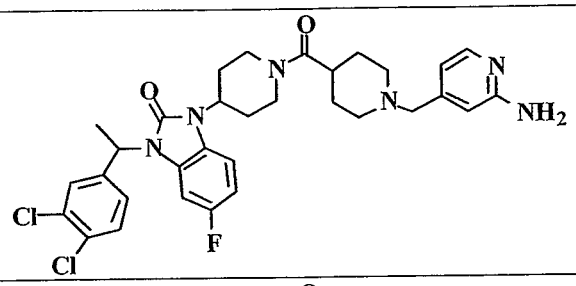
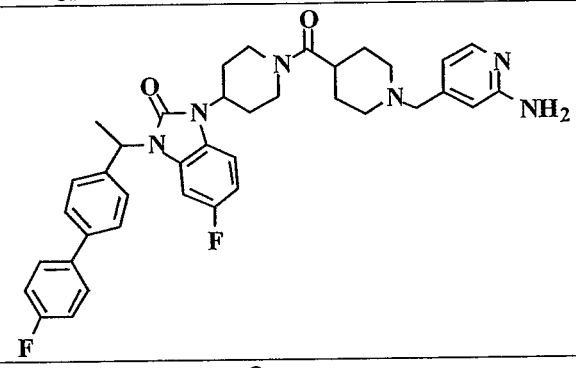
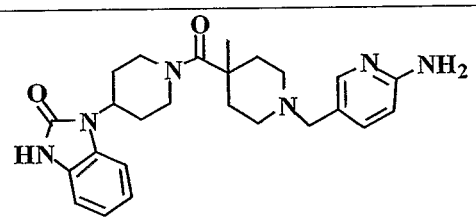
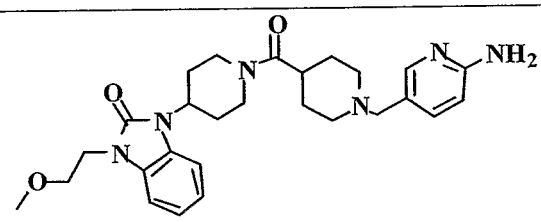
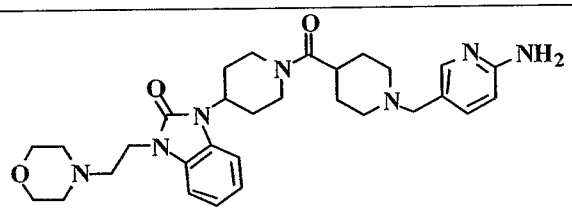
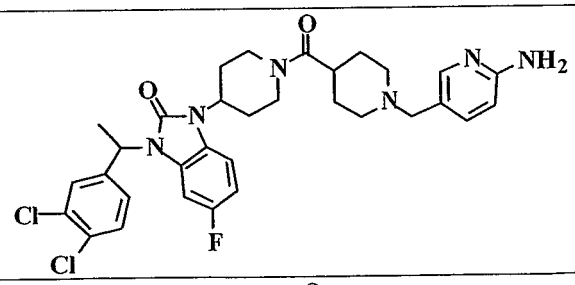
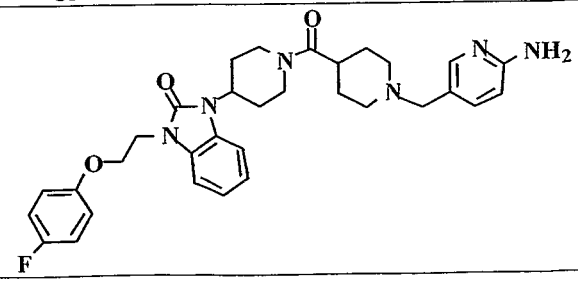


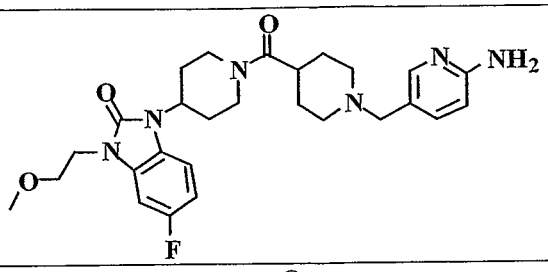
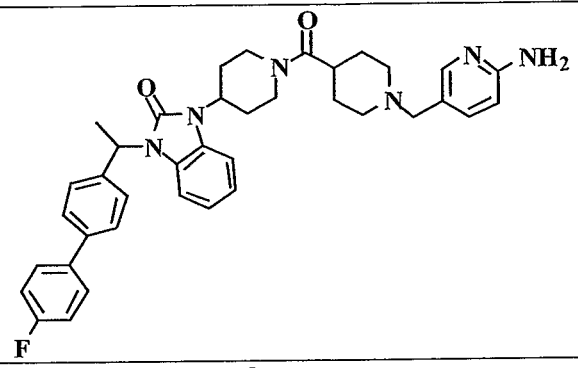
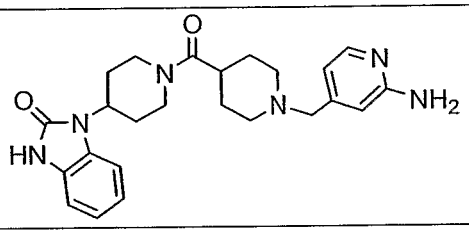
To a solution of hydrazine (1 ml of 0.5 M, 0.50 mmol) in ethanol was added the compound of Example 7 (51 mg, 0.090 mmol). The reaction mixture was stirred at 23 °C for 1.5 h, diluted with aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic extracts were washed with water, dried, and concentrated. Purification by silica gel chromatography (eluant: 10:90:1 CH_3OH: CH_2Cl_2:NH_4OH) gave the title compound as a white solid (20.4 mg, 52% yield). MS (CI) 435 (MH^+).

Using the compounds of Example 7, the following compounds were prepared according to a similar procedure.

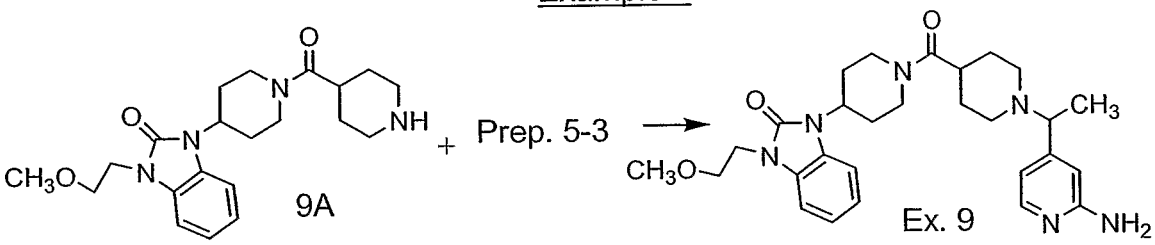
	Compounds	MS (CI)
8A		449 (MH^+)
8B		493 (MH^+)
8C		548 (MH^+)

8D		573 (MH^+)
8E		511 (MH^+)
8F		566 (MH^+)
8G		543 (MH^+)
8H		607 (MH^+)
8I		633 (MH^+)

8J		625 (MH^+)
8K		651 (MH^+)
8L		449 (MH^+)
8M		493 (MH^+)
8N		548 (MH^+)
8O		607 ($M-NH_3$)
8P		573 (MH^+)

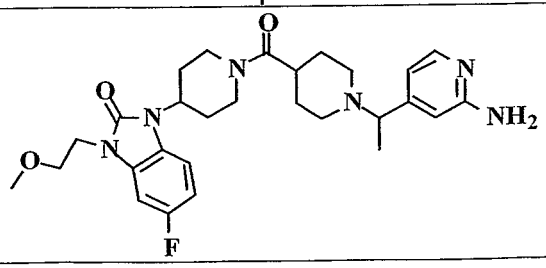
8Q		511 (MH^+)
8R		633 (MH^+)
8S		435 (MH^+)

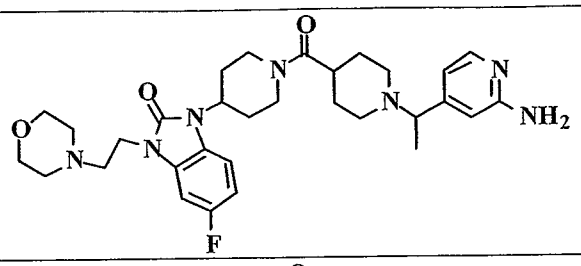
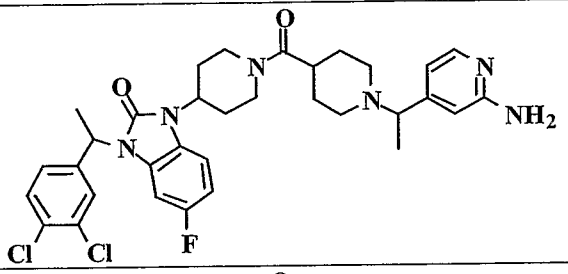
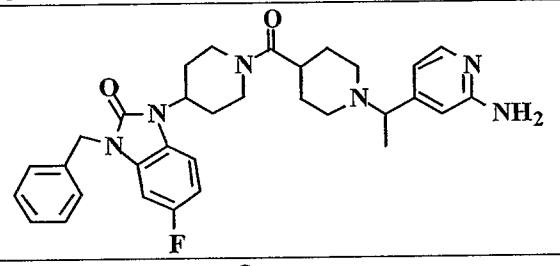
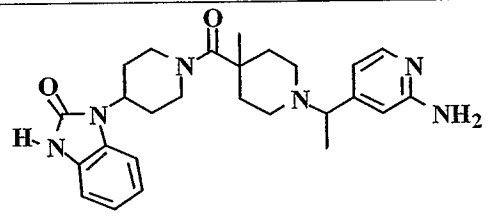
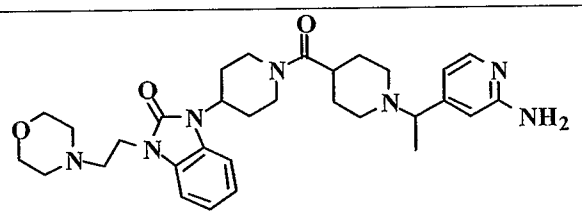
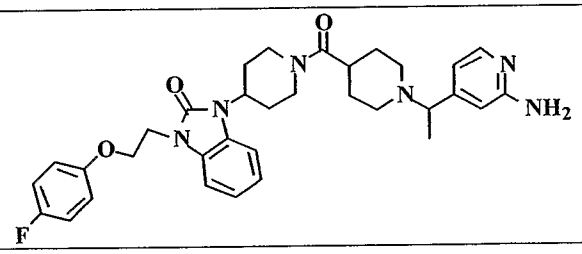
Example 9



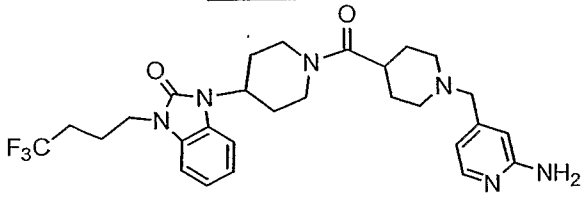
To a solution of 9A (115 mg, 0.250 mmol) and the product of Preparation 5-3 (50 mg, 0.249 mmol) in DMF (2 ml) was added Et_3N. The reaction mixture was stirred at 23 °C for 12 h, diluted with CH_2Cl_2, washed with water, dried, and concentrated. Purification of the residue by preparative TLC (10% CH_3OH-CH_2Cl_2) afforded a white solid. (34 mg, 27% yield). MS (CI) 507 (MH^+).

The following compounds were synthesized using a similar procedure.

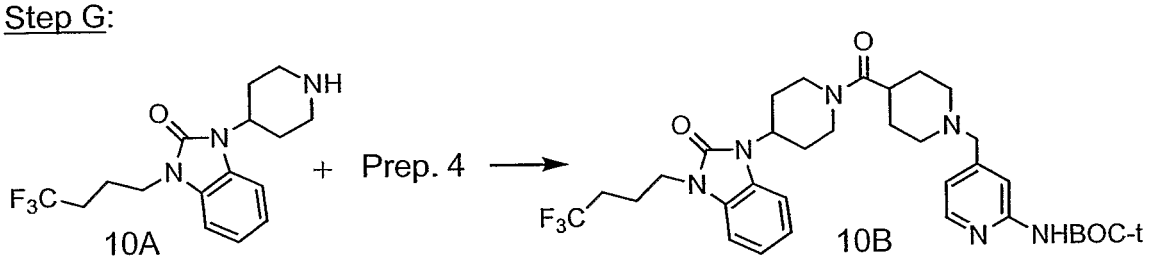
	Compound	MS (CI)
9B		525 (MH^+)

9C		580 (MH^+)
9D		639 (MH^+)
9E		557 (MH^+)
9F		463 (MH^+)
9G		561 (M)
9H		587 (MH^+)

Example 10



Step G:



10A 10B

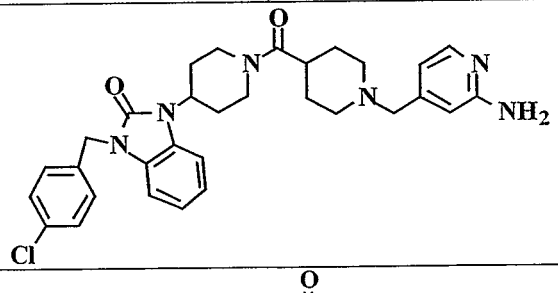
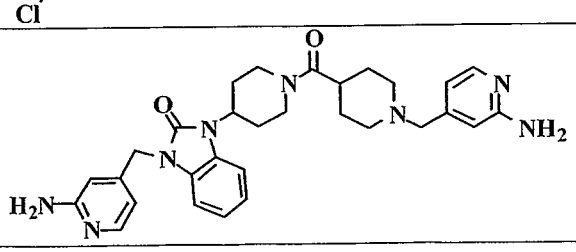
A flask was charged with amine 10A (222 mg, 0.68 mmol), Preparation 4 (232 mg, 0.68 mmol), EDCI (163 mg, 0.85 mmol), HOBT (115 mg, 0.85 mmol), Hunig's base (176 mg, 1.36 mmol) and DMF-CH_2Cl_2 (1:1, 4.5 ml). The reaction was stirred at 70 °C for 15 h, cooled, diluted with CH_2Cl_2, and washed with 1 N $NaHCO_3$ and then water. The combined organic extracts were dried and concentrated. Purification of the crude product by silica gel flash chromatography (eluant: 5% CH_3OH-CH_2Cl_2) gave 10B as a white solid (243 mg, 55% yield).

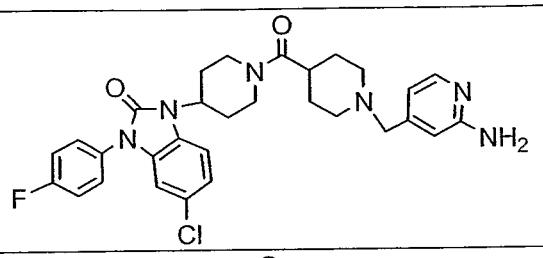
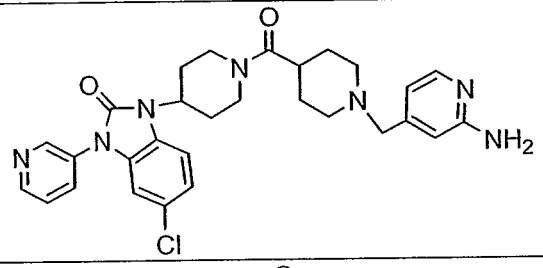
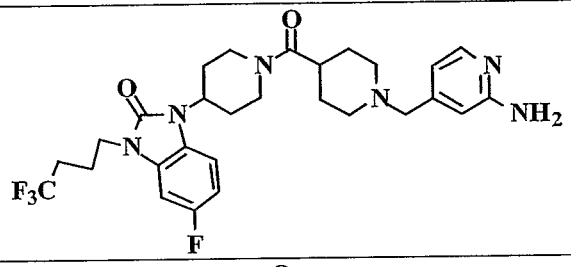
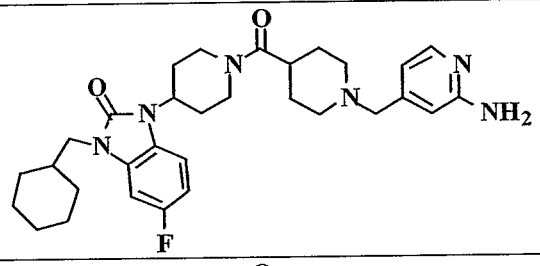
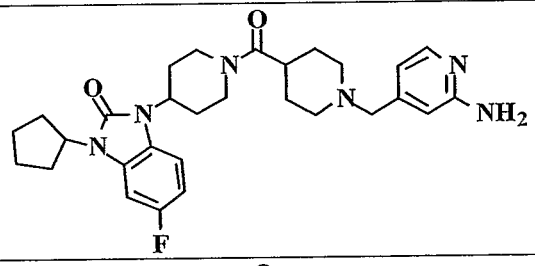
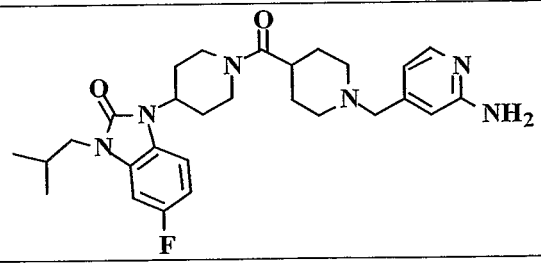
Compounds with different substituents on the benzimidazolone portion were similarly prepared.

Step G':

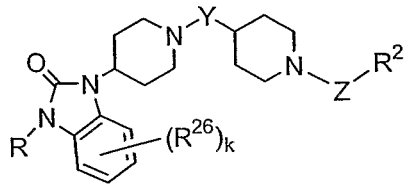
TFA (2 ml) was added to a solution of 10B (230 mg, 0.36 mmol) in CH_2Cl_2 (4 ml). The resulting mixture was stirred at 23 °C for two days, diluted with CH_2Cl_2, and washed with 1 N NaOH. The organic layer was dried and concentrated to afford the crude product. Purification of the residue via preparative TLC plate (10% CH_3OH-CH_2Cl_2) afforded the title compound as a white solid (177 mg, 90% yield).

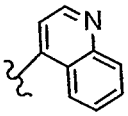
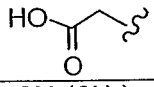
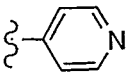
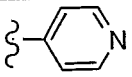
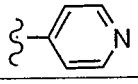
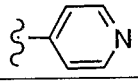
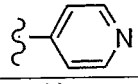
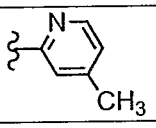
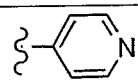
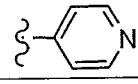
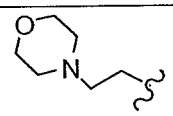
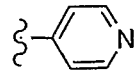
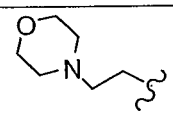
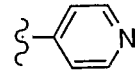
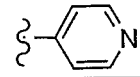
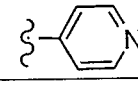
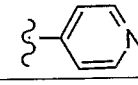
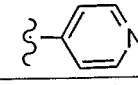
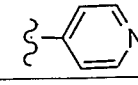
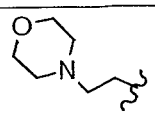
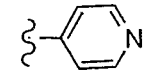
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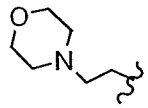
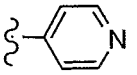
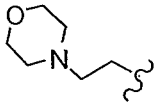
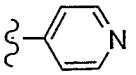
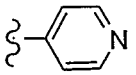
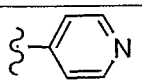
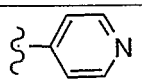
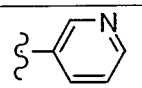
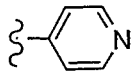
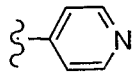
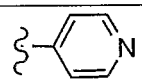
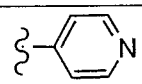
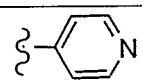
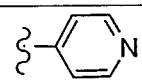
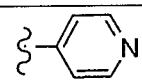
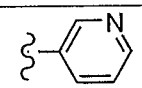
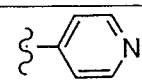
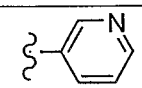
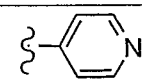
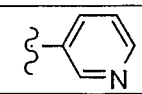
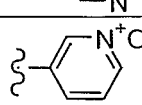
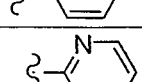
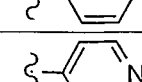
	Compound	MS (CI)
10C		560 (MH^+)
10D		541 (MH^+)

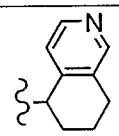
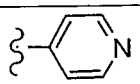
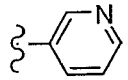
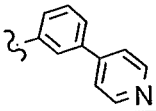
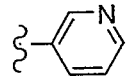
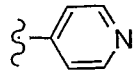
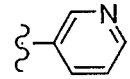
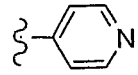
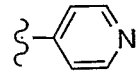
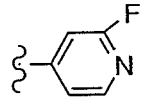
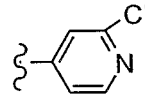
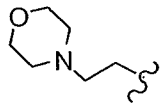
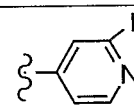
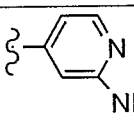
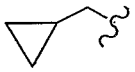
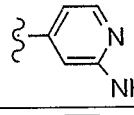
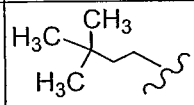
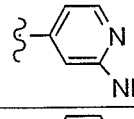
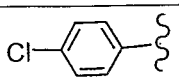
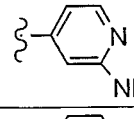
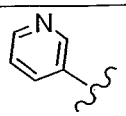
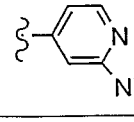
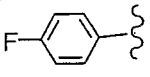
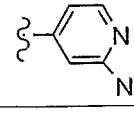
10E		564 (MH^+)
10F		549 (MH^+)
10G		563 (MH^+)
10H		549 (MH^+)
10I		521 (MH^+)
10J		509 (MH^+)

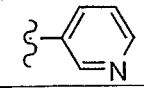
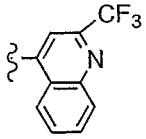
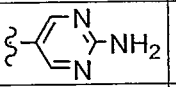
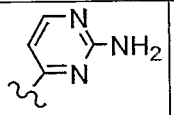
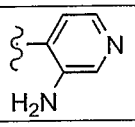
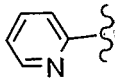
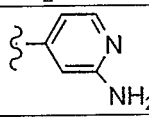
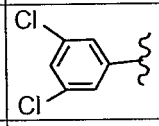
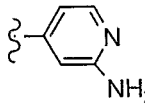
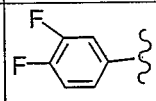
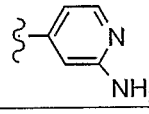
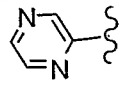
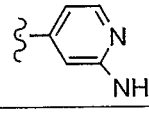
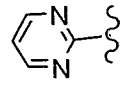
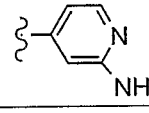
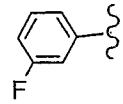
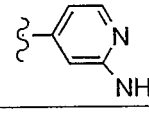
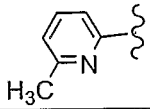
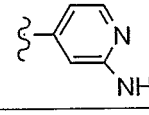
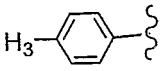
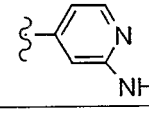
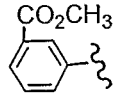
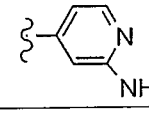
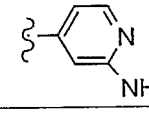
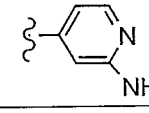
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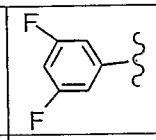
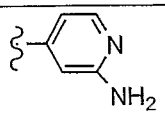
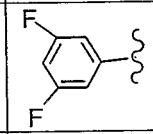
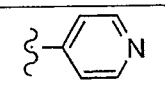
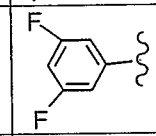
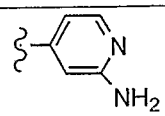
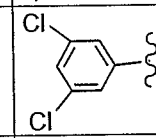
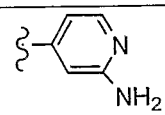
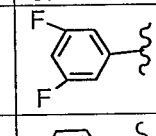
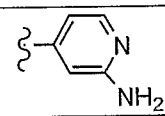
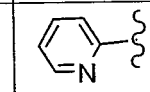
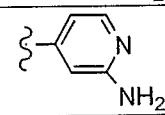
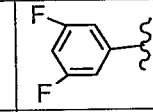
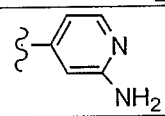
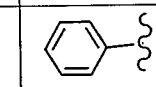
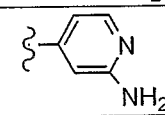
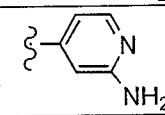


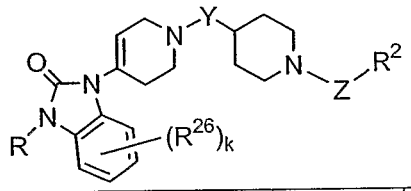
Ex.	R	$(R^{26})_k$	Y	Z	R^2	Physical Data
11	H	H	-C(O)-	$-CH_2-$		470 (MH^+)
12		H	-C(O)-	$-CH_2-$		478 (MH^+)
13	$CH_3(CH_2)_3-$	H	-C(O)-	$-CH(CH_3)-$		490 (MH^+) isomer 1
14	$CH_3(CH_2)_3-$	H	-C(O)-	$-CH(CH_3)-$		490 (MH^+) isomer 2
15	$CH_3O(CH_2)_2-$	H	-C(O)-	-CH(CN)-		503 (MH^+)
16	$CH_3O(CH_2)_2-$	H	-C(O)-	$-C(CH_3)_2-$		506 (MH^+)
17	H	H	-C(O)-	bond		420 (MH^+)
18	$CH_3O(CH_2)_2-$	5-F	-C(O)-	$-CH_2-$		496 (MH^+)
19	$CH_3O(CH_2)_2-$	5-F	-C(O)-	$-CH(CH_3)-$		510 (MH^+)
20		5-F	-C(O)-	$-CH_2-$		551 (MH^+)
21		5-F	-C(O)-	$-CH(CH_3)-$		565 (MH^+)
22	H	5-F	-C(O)-	$-CH_2-$		438 (MH^+)
23	H	5-F	-C(O)-	$-CH(CH_3)-$		452 (MH^+)
24	H	5-Cl	-C(O)-	$-CH_2-$		454 (MH^+)
25	CH_3-	5-F	-C(O)-	$-CH_2-$		469 (MH^+)
26	$C_6H_5-CH_2-$	5-Cl	-C(O)-	$-CH_2-$		545 (MH^+)
27		5-Cl	-C(O)-	$-CH_2-$		568 (MH^+)

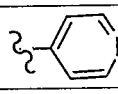
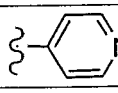
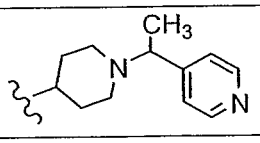
28		5-Cl	-C(O)-	-CH(CH_3)-		582 (MH^+) isomer 1
29		5-Cl	-C(O)-	-CH(CH_3)-		582 (MH^+) isomer 2
30	H	5-CF_3-	-C(O)-	-CH_2-		488 (MH^+)
31	H	H	-C(O)CH_2-	-CH_2-		434 (MH^+)
32	$CH_3O(CH_2)_2$-	H	-C(O)CH_2-	bond		478 (MH^+)
33	$CH_3O(CH_2)_2$-	H	-C(O)CH_2-	bond		478 (MH^+)
34	H	5-CF_3	-C(O)NH-	-CH_2-		503 (MH^+)
35	H	5-CF_3	-SO_2-	-CH_2-		523 (MH^+)
36	H	5-CF_3	(=N-CN)-NH-	-CH_2-		527 (MH^+)
37	H	H	-C(O)-	bond		406 (MH^+)
38	H	H	-C(O)-	-C(O)-		434 (MH^+)
39	H	H	-C(O)-	-$(CH_2)_2$-		434 (MH^+)
40	H	H	-C(O)-	-C(O)CH_2-		448 (MH^+)
41	H	5-CF_3	-C(O)-	bond		474 (MH^+)
42	$CH_3O(CH_2)_2$-	H	-C(O)-	-C(=NH)-		491 (MH^+)
43	$CH_3O(CH_2)_2$-	H	-C(O)-	-C(O)-		492 (MH^+)
44	H	5-CF_3	-C(O)-	-C(O)-		502 (MH^+)
45	$CH_3O(CH_2)_2$-	H	-C(O)-	-C(O)NH-		507 (MH^+)
46	$CH_3O(CH_2)_2$-	H	-C(O)-	-C(O)-		508 (MH^+)
47	H	5-CF_3	-C(O)-	-NH-C(O)-		517 (MH^+)
48	H	5-CF_3	-C(O)-	-NH-C(O)-		517 (MH^+)

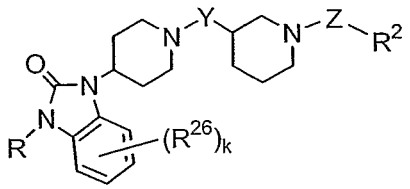
49	$CH_3O(CH_2)_2$-	H	-C(O)-	bond		518 (MH^+)
50	$CH_3O(CH_2)_2$-	H	-C(O)-	-CH_2-C(=O)-NH-		521 (MH^+)
51	$CH_3O(CH_2)_2$-	H	-C(O)-	-C(=O)-NH-CH_2-		521 (MH^+)
52	$CH_3O(CH_2)_2$-	H	-C(O)-	bond		540 (MH^+)
53	$CH_3O(CH_2)_2$-	H	-C(O)-	N(CN)=C-NH-CH_2-		507 (MH^+)
54	$CH_3O(CH_2)_2$-	5-CF_3	-C(O)-	-$(CH_2)_3$-		574 (MH^+)
55	$CH_3O(CH_2)_2$-	5-CF_3	-C(O)-	-$(CH_2)_3$-		574 (MH^+)
56	$CH_3O(CH_2)_2$-	5-CF_3	-C(O)-	-C(O)-$(CH_2)_2$-		588 (MH^+)
57	$CH_3O(CH_2)_2$-	5-CF_3	-C(O)-	-$(CH_2)_4$-		588 (MH^+)
58	$CH_3O(CH_2)_2$-	H	-C(O)-	-CH_2-		496 (MH^+)
59	H	5-CF_3	-C(O)-	-$(CH_2)_4$-		502 (MH^+)
60		H	-C(O)-	-CH_2-		551 (MH^+)
61	H	H	-C(O)-	-$CH(CH_3)$-		449 (MH^+)
62		5-F	-C(O)-	-CH_2-		507 (MH^+)
63		5-F	-C(O)-	-CH_2-		537 (MH^+)
64		H	-C(O)-	-CH_2-		546 (MH^+)
65		5-Cl	-C(O)-	-CH_2-		547 (MH^+)
66		5-Cl	-C(O)-	-CH_2-		564 (MH^+)

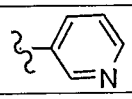
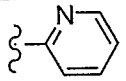
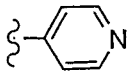
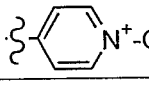
67	H	5-CF_3-	-C(O)-	-NH-C(O)-		517 (MH^+)
68	$CH_3O(CH_2)_2$-	5-CF_3-	-C(O)-	bond		650 (MH^+)
69	$CH_3O(CH_2)_2$-	H	-C(O)-	-CH_2-		494 (MH^+)
70	$CH_3O(CH_2)_2$-	H	-C(O)-	-CH_2-		494 (MH^+)
71	$CH_3O(CH_2)_2$-	H	-C(O)-	-CH_2-		493 (MH^+)
72		5-F	-C(O)-	-CH_2-		530 (MH^+)
73		5-F	-C(O)-	-CH_2-		598 (MH^+)
74		5-F	-C(O)-	-CH_2-		565 (MH^+)
75		5-F	-C(O)-	-CH_2-		531 (MH^+)
76		5-F	-C(O)-	-CH_2-		531 (MH^+)
77		5-F	-C(O)-	-CH_2-		547 (MH^+)
78		5-F	-C(O)-	-CH_2-		544 (MH^+)
79		5-F	-C(O)-	-CH_2-		544 (MH^+)
80		5-F	-C(O)-	-CH_2-		587 (MH^+)
81	H	5-F	-C(O)-	-CH_2-		453 (MH^+)
82	CF_3CH_2-	5-F	-C(O)-	-CH_2-		535 (MH^+)

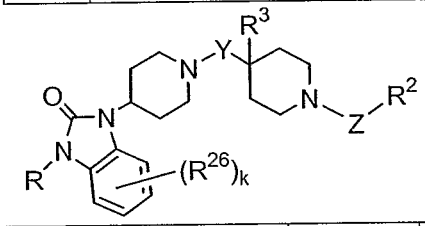
83		5-F	-C(O)-	$-CH_2-$		565 (MH^+)
84		5-Cl	-C(O)-	$-CH_2-$		567 (MH^+)
85		5-Cl	-C(O)-	$-CH_2-$		582 (MH^+)
86		5-Cl	-C(O)-	$-CH_2-$		614 (MH^+)
87		5-Cl	-C(O)-	$-CH(CH_3)-$		596 (MH^+)
88		$5-CF_3-$	-C(O)-	$-CH_2-$		580 (MH^+)
89		$5-CF_3-$	-C(O)-	$-CH_2-$		615 (MH^+)
90		$5-CF_3-$	-C(O)-	$-CH_2-$		579 (MH^+)
91	H	$5-CF_3-$	-C(O)-	$-CH_2-$		503

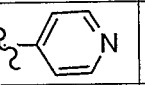
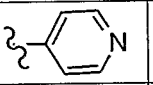
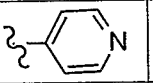
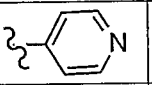
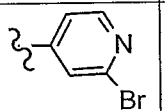
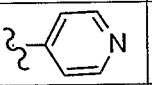
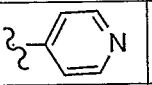
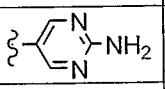
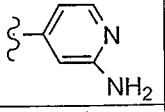
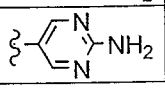


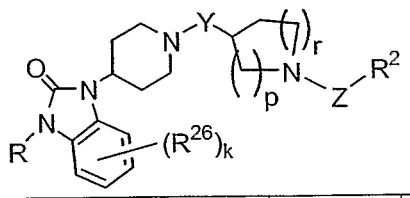
Ex.	R	$(R^{26})_k$	Y	Z	R^2	Physical Data
92	H	H	-C(O)-	$-CH_2-$		418 (MH^+)
93	$N(CH_3)_2-(CH_2)_2-$	H	-C(O)-	$-CH_2-$		489 (MH^+)
94	H	H	-C(O)-	-C(O)-		543 (MH^+)

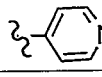
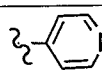
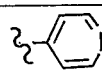


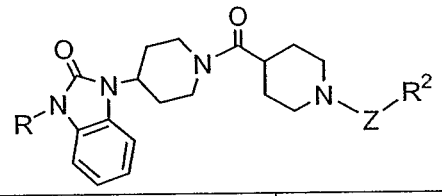
Ex.	R	$(R^{26})_k$	Y	Z	R^2	Physical Data
94	H	5-CF_3-	-C(O)-	-CH_2-		488 (MH^+)
96	H	5-CF_3-	-C(O)-	-CH_2-		488 (MH^+)
97	H	5-CF_3-	-C(O)-	-C(O)-		502 (MH^+)
98	H	5-CF_3-	-C(O)-	-CH_2-		500 (MH^+)

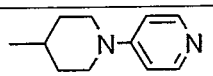
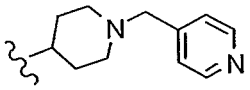
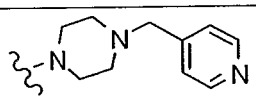
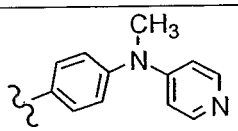
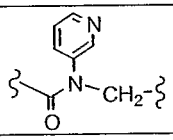
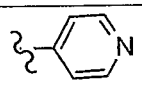
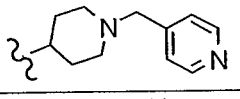
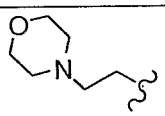
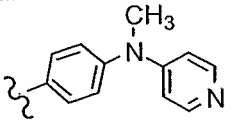
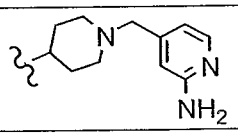
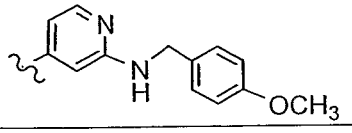


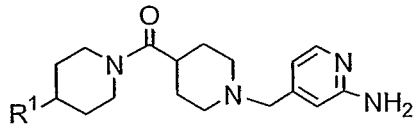
Ex.	R	$(R^{26})_k$	Y	R^3	Z	R^2	Physical Data
99	H	H	-C(O)-	-CH_3	-$CH(CH_3)$-		448 (MH^+)
100	H	5-CF_3-	-C(O)-	-CH_3	-CH_2-		502 (MH^+)
101	H	5-CF_3-	-C(O)-	-OH	-CH_2-		504 (MH^+)
102	$CH_3O(CH_2)_2$-	H	-C(O)-	F	-$CH(CH_3)$-		510 (MH^+)
103	H	H	-C(O)-	-CH_3	-CH_2-		512 (MH^+)
104	$CH_3O(CH_2)_2$-	5-Cl	-C(O)-	F	-$CH(CH_3)$-		544 (MH^+)
105	$CH_3C(O)(CH_2)_2$-	5-CF_3-	-C(O)-	-CH_3	-CH_2-		572 (MH^+)
106	$CH_3O(CH_2)_2$-	H	-C(O)-	F	-CH_2-		512 (MH^+)
107	$CH_3O(CH_2)_2$-	H	-C(O)-	F	-CH_2-		511 (MH^+)
108	H	5-F	-C(O)-	F	-CH_2-		472 (MH^+)

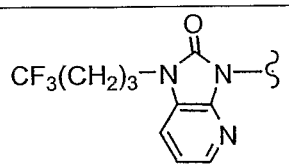
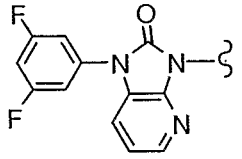
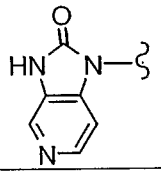
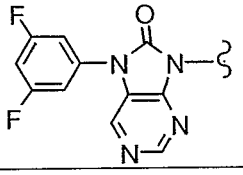
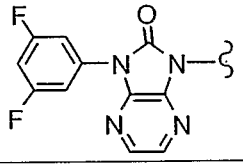
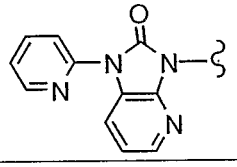


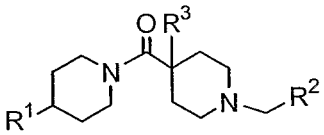
Ex.	R	$(R^{26})_k$	Y	r	p	Z	R^2	Physical Data
109	$CH_3O(CH_2)_2$-	H	-C(O)-	0	1	$-CH_2$-		450 (MH^+)
110	$CH_3O(CH_2)_2$-	H	-C(O)-	1	1	$-CH_2$-		464 (MH^+)
111	$CH_3O(CH_2)_2$-	H	-C(O)-	1	3	$-CH_2$-		492 (MH^+)

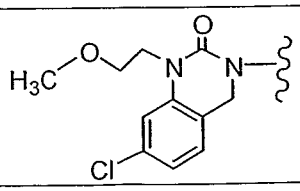
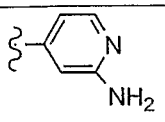
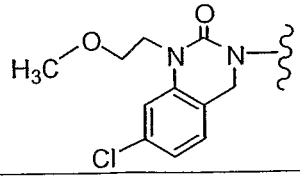
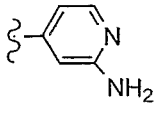


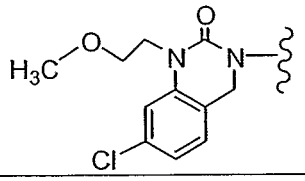
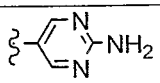
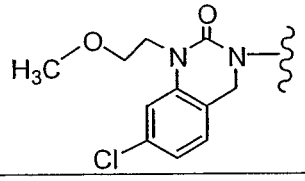
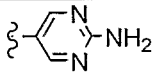
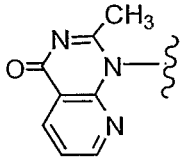
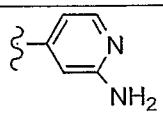
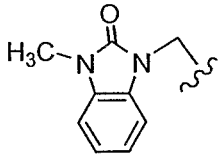
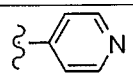
Ex.	R	Z	R^2	Physical Data
112	$CH_3O(CH_2)_2$-	-C(O)-		575 (MH^+)
113	$CH_3O(CH_2)_2$-	-C(O)-		589 (MH^+)
114	$CH_3O(CH_2)_2$-	-C(O)-		590 (MH^+)
115	$CH_3O(CH_2)_2$-	-C(O)-		597 (MH^+)
116	$CH_3O(CH_2)_2$-			611 (MH^+)
117	$CH_3O(CH_2)_2$-	-C(O)-NH-		604 (MH^+)
118		-C(O)-		652 (MH^+)
119	$CH_3O(CH_2)_2$-	-C(O)-		604 (MH^+)
120	H	$-CH_2$-		555 (MH^+)



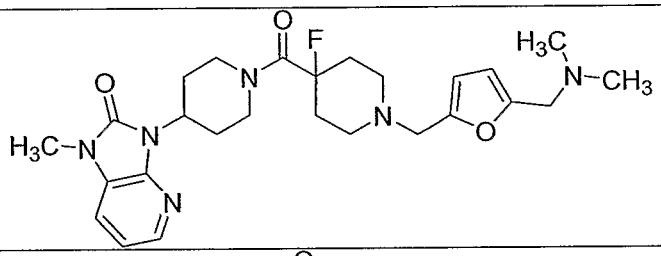
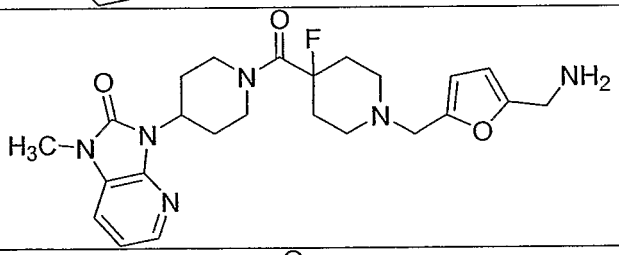
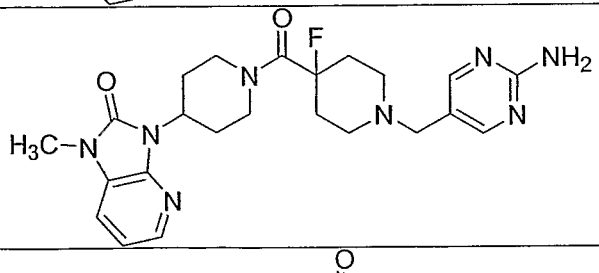
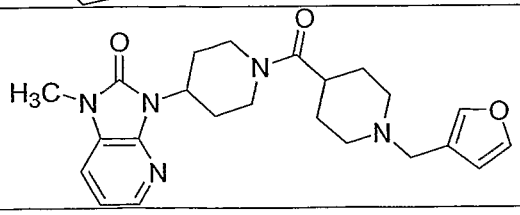
Ex.	R^1	Physical Data
121		546 (MH^+)
122		548 (MH^+)
123		536 (MH^+)
124		549 (MH^+)
125		549 (MH^+)
126		586 (MH^+)

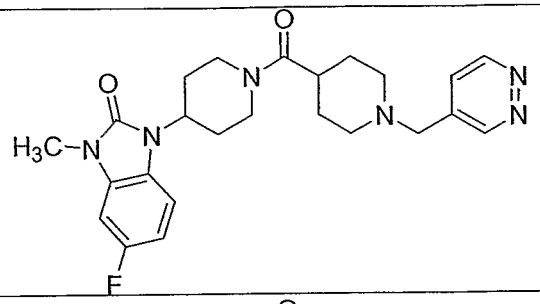
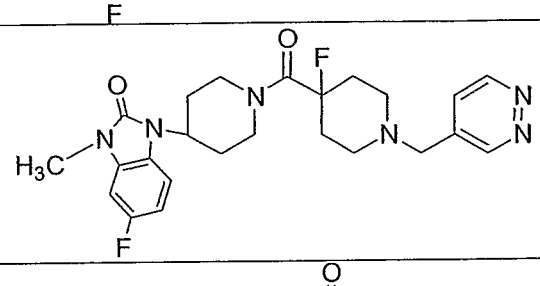
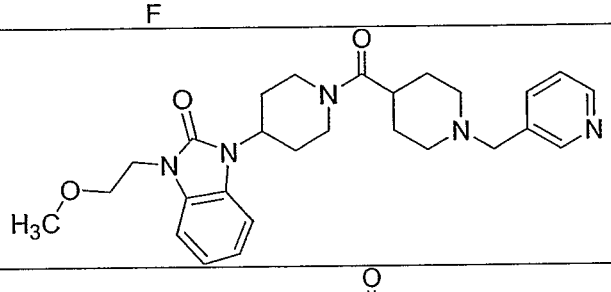
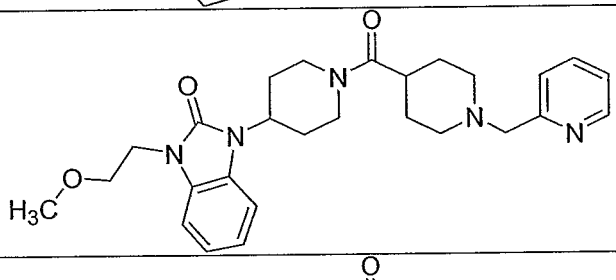
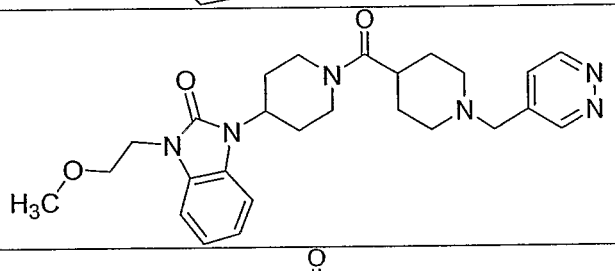
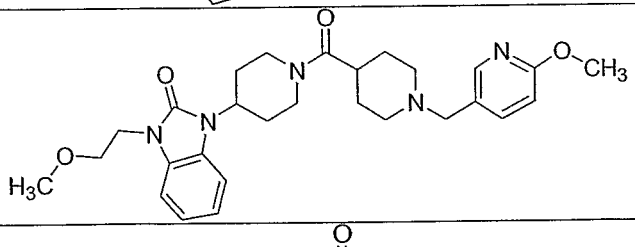
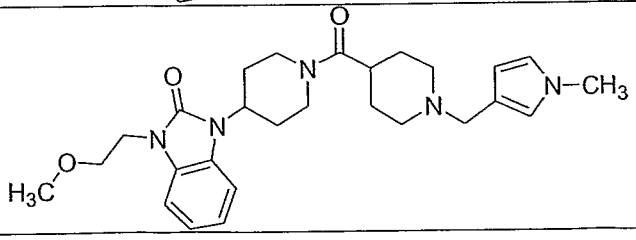


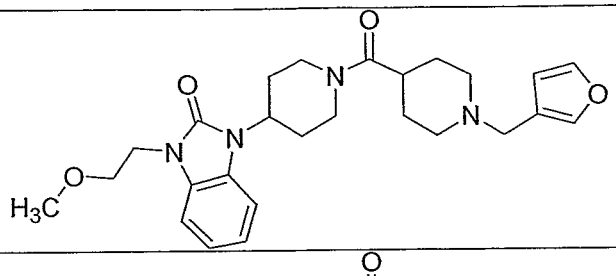
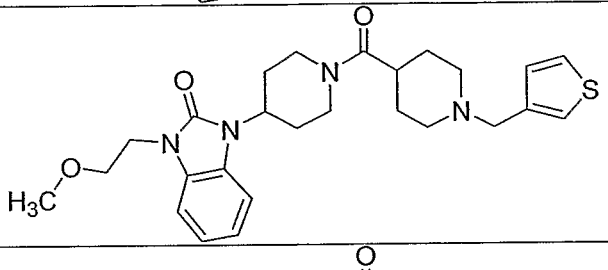
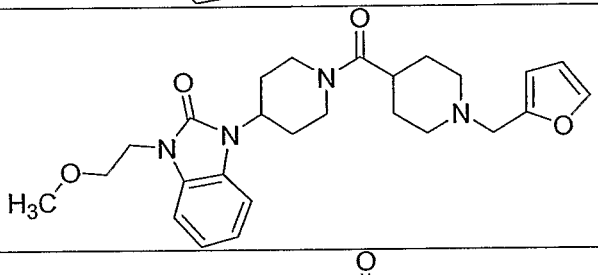
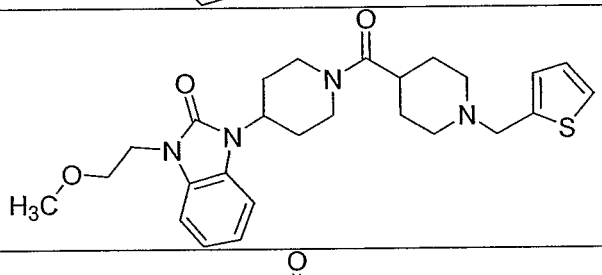
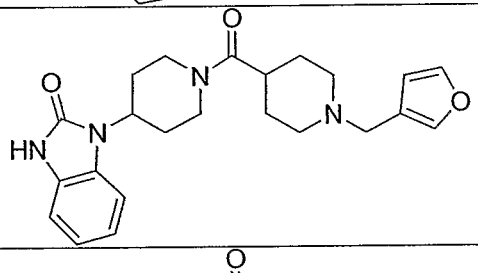
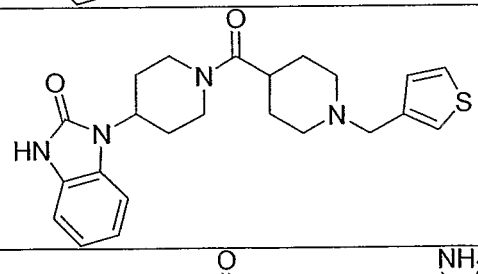
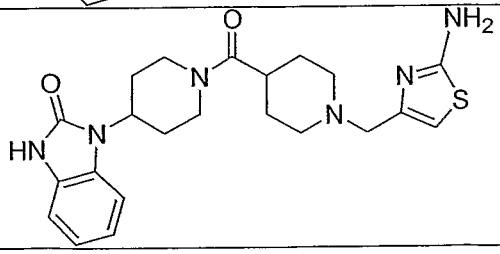
Ex.	R^1	R^3	R^2	Physical Data
127		F		559 (MH^+)
128		H		541 (MH^+)

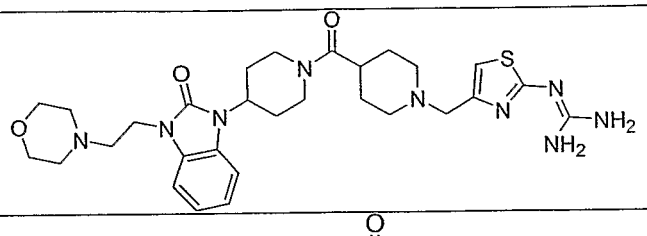
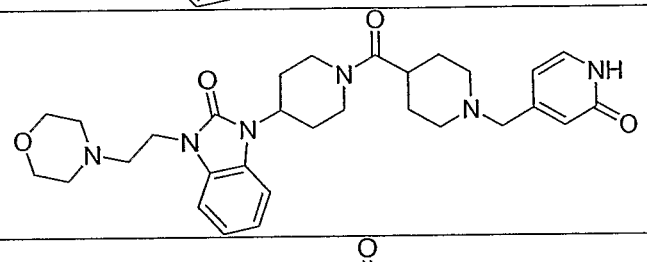
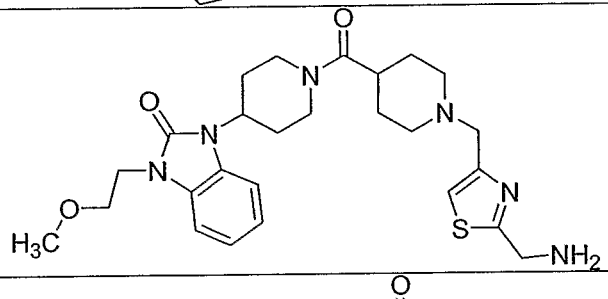
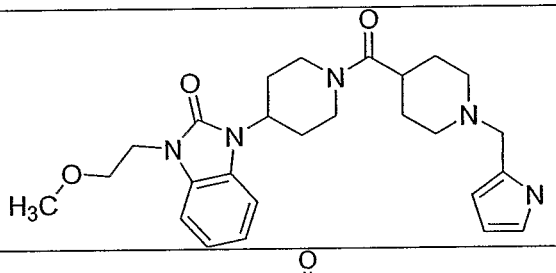
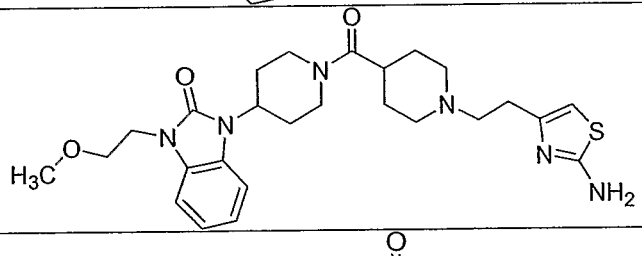
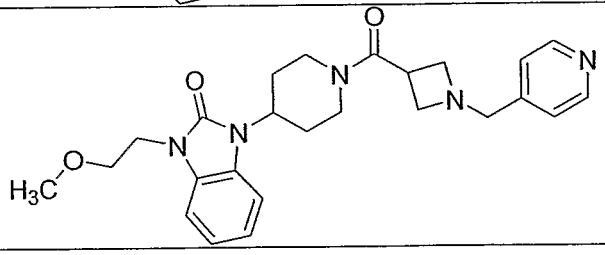
129		H		542 (MH^+)
130		F		560 (MH^+)
131		H		462 (MH^+)
132		H		448 (MH^+)

compounds of the formula:

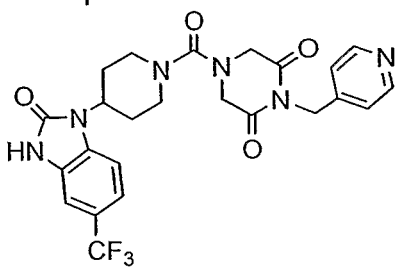
Ex.	Compound	MS (M+H)
133		499
134		471
135		469
136		424

137		453
138		471
139		478
140		478
141		479
142		507
143		479

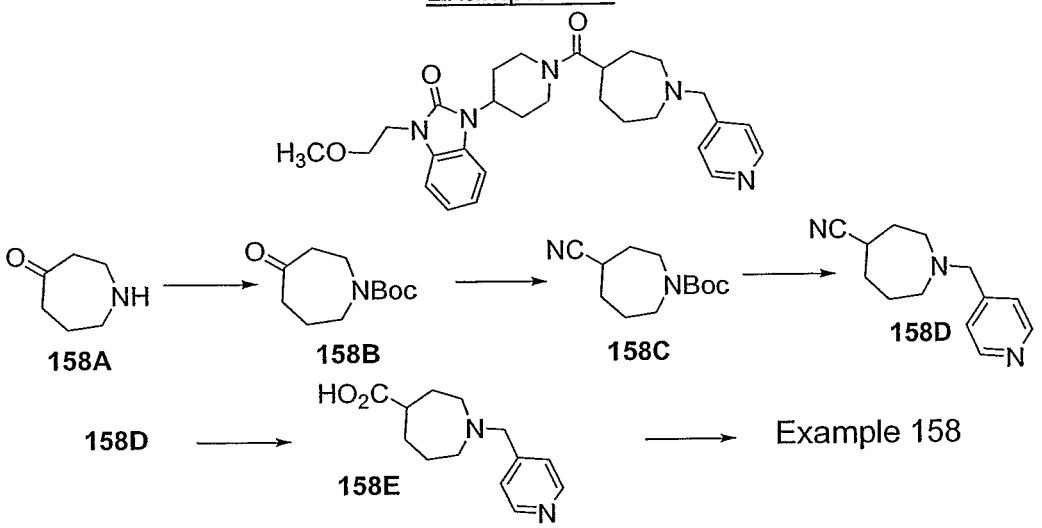
144		467
145		483
146		467
147		483
148		409
149		425
150		441

151		596
152		549
153		513
154		466
155		513
156		450

and
Example 157:



Example 158



In a manner similar to that described for Intermediate 3, Step D', compound 158A was converted to compound 158B.

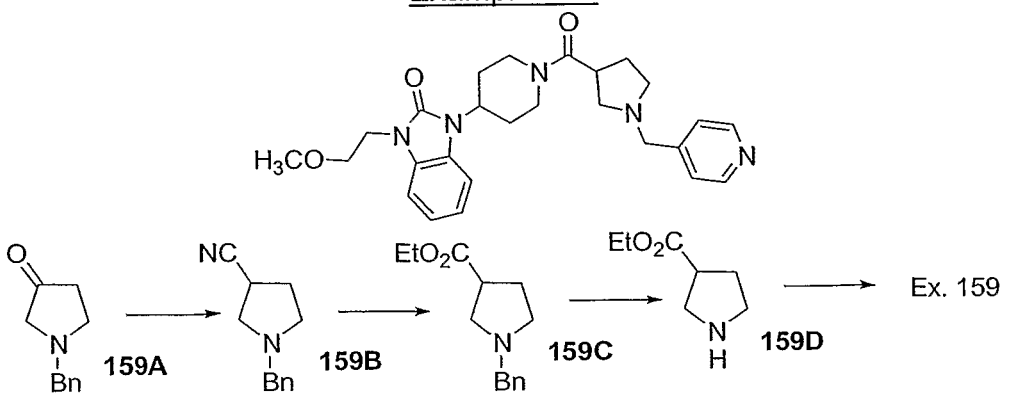
A solution of 158B (1.7g, 8.0 mmol) in ethylene glycol dimethyl ether (12 ml) was treated with tosylmethyl isocyanide (1.6 g, 8.0 mmol) and EtOH (1 ml), cooled to 0 °C, and treated with t-BuOK (2.2g, 16.0 mmol). The reaction mixture was stirred at 20 °C overnight, filtered through celite with EtOAc, and concentrated. Filtration through a plug of SiO_2 with EtOAc provided 158C as a yellow oil.

In a manner similar to that described for Intermediate 3, Step D, and then Preparation 4, Step 4, compound 158C was converted to compound 158D.

A solution of 158D (100 mg, 0.47 mmol) in EtOH (12 ml) was treated with NaOH (310 mg, 8.0 mmol) and H_2O (1 ml) and refluxed for 4 days. The reaction mixture was concentrated, slurried in EtOAc (20 ml), taken up in 4M HCl-dioxane and CH_3OH, and concentrated to provide 158E.

In a manner similar to that described in Example 1, Step G, compound 158E was converted to Example 158.

Example 159



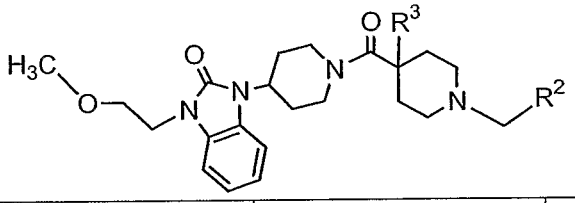
In a manner similar to that described for Example 158, compound 159A was converted to compound 159B.

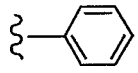
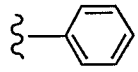
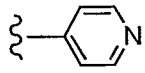
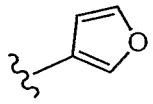
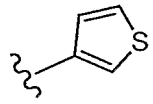
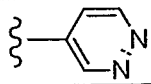
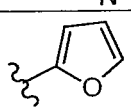
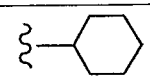
A solution of 159B (1.5g, 7.9 mmol) in EtOH (40 ml) was treated with 4M HCl-dioxane (20 ml) and stirred overnight. The reaction mixture was cooled to 0 °C, treated with saturated aqueous $NaHCO_3$ until neutralized, and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated. Flash chromatography (35-50% EtOAc/hexane) provided 159C (1.1 g, 58%).

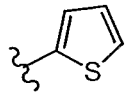
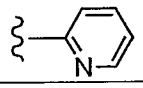
A solution of 159C (210 mg, 0.85 mmol) in AcOH (10 ml) was treated with $Pd(OH)_2$ (100 mg) and stirred under H_2 overnight. The reaction mixture was filtered through celite and concentrated to provide 159D.

In a manner similar to that described in Preparation 4, Step 4-5 and Example 1, Step G, compound 159D was converted to compound Example 159.

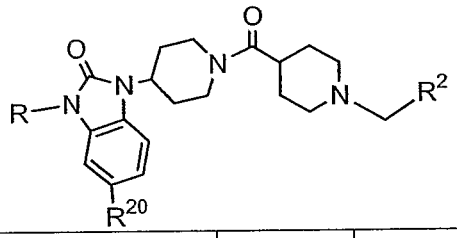
Using the procedures described above for Examples 1-159, compounds of the following structure were prepared:

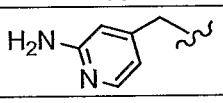
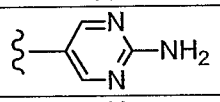
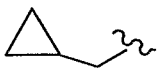
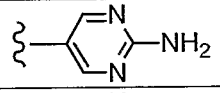
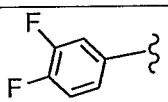
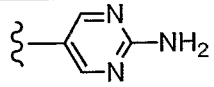
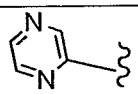
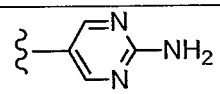
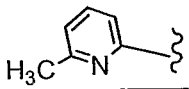
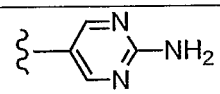
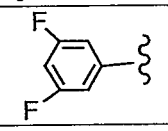
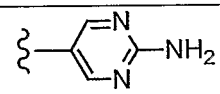
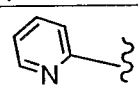
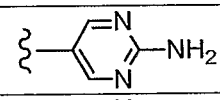
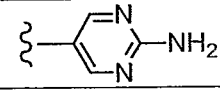
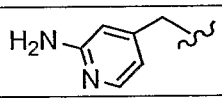
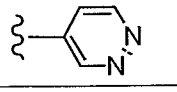
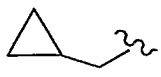
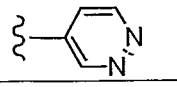
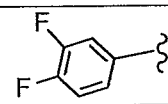
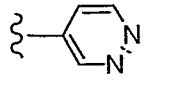
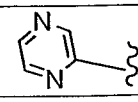
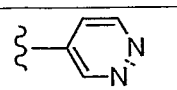


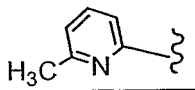
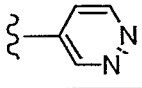
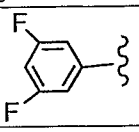
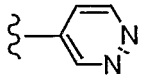
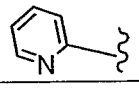
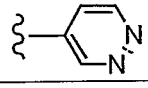
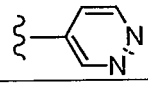
Ex.	R^3	R^2	Physical Data
160	H		477 (MH^+)
161	F		495 (MH^+)
162	F		496 (MH^+)
163	F		485 (MH^+)
164	F		501 (MH^+)
165	F		497 (MH^+)
166	F		485 (MH^+)
167	F		501 (MH^+)

168	F		501 (MH^+)
169	F		496 (MH^+)

Using the procedures described above for Examples 1-159, compounds of the following structure can be prepared:



Ex.	R	R^{20}	R^2
170		H	
171		F	
172		F	
173		F	
174		F	
175		F	
176		$-CF_3$	
177	$CF_3(CH_2)_3$-	F	
178		H	
179		F	
180		F	
181		F	

182		F	
183		F	
184		$-CF_3$	
185	$CF_3(CH_2)_3$-	F	

General Procedure for H_3-Receptor Binding Assay

The source of the H_3 receptors in this experiment was guinea pig brain. The animals weighed 400-600 g. The brain tissue was homogenized with a solution of 50 mM Tris, pH 7.5. The final concentration of tissue in the homogenization buffer was 10% w/v. The homogenates were centrifuged at 1,000 x g for 10 min. in order to remove clumps of tissue and debris. The resulting supernatants were then centrifuged at 50,000 x g for 20 min. in order to sediment the membranes, which were next washed three times in homogenization buffer (50,000 x g for 20 min. each). The membranes were frozen and stored at -70°C until needed.

All compounds to be tested were dissolved in DMSO and then diluted into the binding buffer (50 mM Tris, pH 7.5) such that the final concentration was 2 µg/ml with 0.1% DMSO. Membranes were then added (400 µg of protein) to the reaction tubes. The reaction was started by the addition of 3 nM [^{3}H]R-α-methyl histamine (8.8 Ci/mmol) or 3 nM [^{3}H]N$^{\alpha}$-methyl histamine (80 Ci/mmol) and continued under incubation at 30°C for 30 min. Bound ligand was separated from unbound ligand by filtration, and the amount of radioactive ligand bound to the membranes was quantitated by liquid scintillation spectrometry. All incubations were performed in duplicate and the standard error was always less than 10%. Compounds that inhibited more than 70% of the specific binding of radioactive ligand to the receptor were serially diluted to determine a K_i (nM).

Compounds of formula I have a K_i within the range of about 0.1 to about 1000 nM. Preferred compounds of formula I have a K_i within the range of about 0.1 to about 100 nM. More preferred compounds of formula I have a K_i within the range of about 0.1 to about 20 nM. Example 1AI has a Ki of 0.2 nM, Example 83 has a Ki of 1.0 nM, and Example 10G has a Ki of 3.9 nM.

General Procedure for rHu H_3 Binding Assay

[^{3}H]N$^{\alpha}$-methylhistamine (82 Ci/mmole) was obtained from Dupont NEN. Thioperamide was obtained from the Chemical Research Department, Schering-Plough Research Institute.

HEK-293 human embryonic kidney cells stably expressing the human histamine H_3 receptor were cultured in Dulbecco's modified Eagle's medium/10% fetal calf serum/penicillin (100 U/ml)/streptomycin (100 µg/ml)/Geneticin (0.5 mg/ml) at 37° C in a humidified 5% CO_2 atmosphere. Cells were harvested between passages five and twenty at 37° C in 5 mM EDTA/Hank's balanced salt solution and processed for membrane preparation. After low-speed centrifugation, ten min at 1000 xg, they were put into ten volumes of ice-cold buffer and disrupted with a Polytron (PTA 35/2 tip, 30 sec at setting 6). After subsequent low-speed centrifugation, supernatant was centrifuged ten min at 50,000 x*g*. The high-speed pellet was resuspended in the original volume of buffer, a sample was taken for protein assay (bicinchoninic acid, Pierce) and the suspension was centrifuged again at 50,000 x*g*. Membranes were resuspended at 1 mg of protein/ml of buffer and frozen at -80° C until use.

Membrane (15 µg of protein) was incubated with 1.2 nM [^{3}H]N$^{\alpha}$-methyl-histamine, without or with inhibitor compounds, in a total volume of 200 µl of buffer. Nonspecific binding was determined in the presence of 10^{-5} M thioperamide. Assay mixtures were incubated for 30 min at 30° C in polypropylene, 96-well, deep-well plates, then filtered through 0.3% polyethylenimine-soaked GF/B filters. These were washed three times with 1.2 ml of 4° C buffer, dried in a microwave oven, impregnated with Meltilex wax scintillant and counted at 40% efficiency in a Betaplate scintillation counter (Wallac).

IC_{50} values were interpolated from the data or were determined from curves fit to the data with Prism nonlinear least squares curve-fitting program (GraphPad Software, San Diego, CA). K_i values were determined from IC_{50} values according to the Cheng and Prusoff equation.

In this specification, the term "at least one compound of formula I" means that one to three different compounds of formula I may be used in a pharmaceutical composition or method of treatment. Preferably one compound of formula I is used.

Similarly, "at least one H_1 receptor antagonist " means that one to three different H_1 antagonists may be used in a pharmaceutical composition or method of treatment. Preferably, one H_1 antagonist is used.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), *The Science and Practice of Pharmacy*, 20th Edition, (2000), Lippincott Williams & Wilkins, Baltimore, MD.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 1 mg to about 350 mg, preferably from about 1 mg to about 150 mg, more preferably from about 1 mg to about 50 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 1 mg/day to about 300 mg/day, preferably 1 mg/day to 75 mg/day, in two to four divided doses.

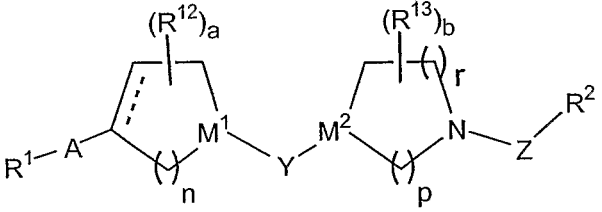
When the invention comprises a combination of H_3 antagonist and H_1 antagonist compounds, the two active components may be co-administered simultaneously or sequentially, or a single pharmaceutical composition comprising a H_3 antagonist and an H_1 antagonist in a pharmaceutically acceptable carrier can be administered. The components of the combination can be administered individually or together in any conventional dosage form such as capsule, tablet, powder, cachet, suspension, solution, suppository, nasal spray, etc. The dosage of the H_1 antagonist can be determined from published material, and may range from 1 to 1000 mg per dose.

When separate H_3 and H_1 antagonist pharmaceutical compositions are to be administered, they can be provided in a kit comprising in a single package, one container comprising an H_3 antagonist in a pharmaceutically acceptable carrier, and a separate container comprising an H_1 antagonist in a pharmaceutically acceptable carrier, with the H_3 and H_1 antagonists being present in amounts such that the combination is therapeutically effective. A kit is advantageous for administering a combination when, for example, the components must be administered at different time intervals or when they are in different dosage forms.

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

WHAT IS CLAIMED IS:

1. A compound represented by the structural formula



or a pharmaceutically acceptable salt or solvate thereof, wherein:

the dotted line represents an optional double bond;

a is 0 to 3;

b is 0 to 3;

n is 1, 2 or 3;

p is 1, 2 or 3 with the proviso that when M^2 is N, then p is not 1;

r is 1, 2, or 3 with the proviso that when r is 2 or 3, then M^2 is $C(R^3)$ and p is 2 or 3;

A is a bond or C_1-C_6 alkylene;

M^1 is $C(R^3)$ or N;

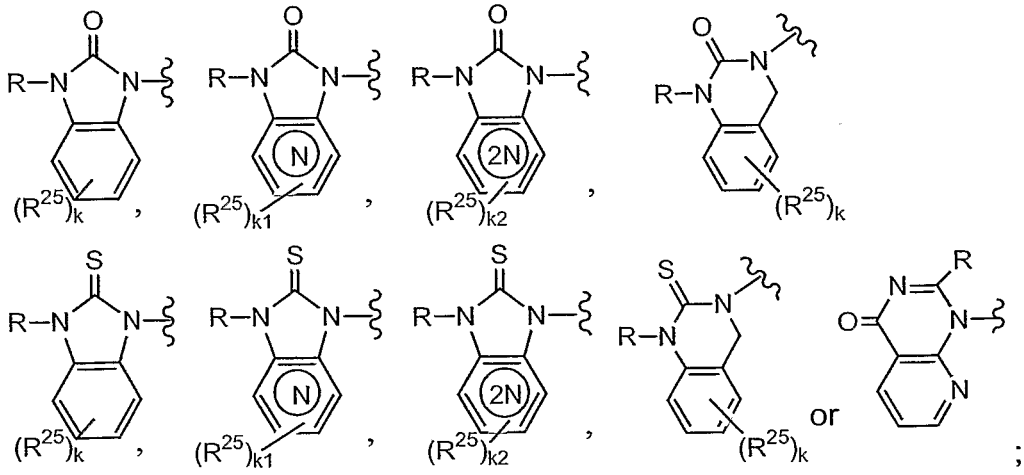
M^2 is $C(R^3)$ or N;

Y is –C(=O)-, -C(=S)-, $-(CH_2)_q$ -, $–NR^4C(=O)$-, $-C(=O)NR^4$-, $-C(=O)CH_2$-, $-CH_2(C=O)$-, $-SO_{1-2}$-, -NH-C(=N-CN)- or –C(=N-CN)-NH-; with the provisos that when M^1 is N, Y is not $–NR^4C(=O)$- or -NH-C(=N-CN)-; and when M^2 is N, Y is not $-C(=O)NR^4$- or –C(=N-CN)-NH-;

q is 1 to 5, provided that when M^1 and M^2 are both N, q is not 1 ;

Z is a bond, C_1-C_6 alkylene, C_1-C_6 alkenylene, -C(=O)-, -CH(CN)-, or $–CH_2C(=O)NR^4$-;

R^1 is



;

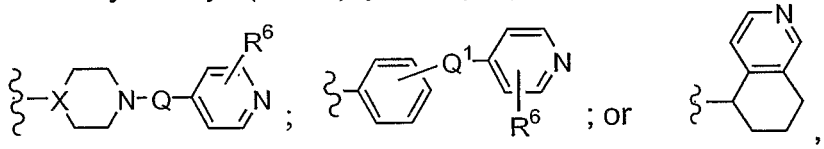
k is 0, 1, 2, 3 or 4;

k1 is 0, 1, 2 or 3;

k2 is 0, 1 or 2;

R is H, C_1-C_6 alkyl, hydroxy-(C_2-C_6)alkyl-, halo-(C_1-C_6)alkyl-, halo-(C_1-C_6)-alkoxy-(C_1-C_6)alkyl-, R^{29}-O-C(O)-(C_1-C_6)alkyl-, (C_1-C_6)alkoxy-(C_1-C_6)alkyl-, N(R^{30})(R^{31})-(C_1-C_6)alkyl-, (C_1-C_6)alkoxy-(C_1-C_6)alkoxy-(C_1-C_6)alkyl-, R^{32}-aryl, R^{32}-aryl(C_1-C_6)alkyl-, R^{32}-aryloxy(C_1-C_6)alkyl-, R^{32}-heteroaryl, R^{32}-heteroaryl(C_1-C_6)alkyl-, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl-, N(R^{30})(R^{31})-C(O)-(C_1-C_6)alkyl-, or heterocycloalkyl(C_1-C_6)alkyl-;

R^2 is a six-membered heteroaryl ring having 1 or 2 heteroatoms independently selected from N or N-O, with the remaining ring atoms being carbon; a five-membered heteroaryl ring having 1, 2, 3 or 4 heteroatoms independently selected from N, O or S, with the remaining ring atoms being carbon; R^{32}-quinolyl; R^{32}-aryl; heterocycloalkyl; (C_3-C_6)cycloalkyl; (C_1-C_6)alkyl; hydrogen;



wherein said six-membered heteroaryl ring or said five-membered heteroaryl ring is optionally substituted by R^6;

X is CH or N;

Q is a bond or C_1-C_6 alkylene;

Q^1 is a bond, C_1-C_6 alkylene or –N(R^4)-;

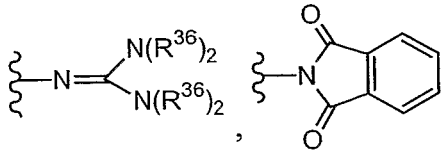
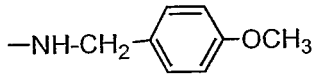
R^3 is H, halogen, C_1-C_6 alkyl, -OH or (C_1-C_6)alkoxy;

R^4 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, R^{33}-aryl, R^{33}-aryl(C_1-C_6)alkyl, and R^{32}-heteroaryl;

R^5 is hydrogen, C_1-C_6 alkyl, -C(O)R^{20}, -C(O)$_2R^{20}$, –C(O)N(R^{20})$_2$ or (C_1-C_6)alkyl-SO_2-;

or R^4 and R^5, together with the nitrogen to which they are attached, form an azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl ring;

R^6 is 1 to 3 substituents independently selected from the group consisting of -OH, halogen, C_1-C_6 alkyl-, C_1-C_6 alkoxy, C_1-C_6 alkylthio, -CF_3, -NR^4R^5, NO_2, -CO_2R^4, -CON(R^4)$_2$, -CH_2-NR^4R^5, -CN,


, and 
,

or 2 R^6 substituents together on the same carbon are =O;

R^{12} is independently selected from the group consisting of C_1-C_6 alkyl, hydroxy, C_1-C_6 alkoxy, or fluoro, provided that when R^{12} is hydroxy or fluoro, then R^{12} is not bound to a carbon adjacent to a nitrogen; or two R^{12} substituents together form a C_1 to C_2 alkyl bridge from one ring carbon to another non-adjacent ring carbon; or R^{12} is =O;

R^{13} is independently selected from the group consisting of C_1-C_6 alkyl, hydroxy, C_1-C_6 alkoxy, or fluoro, provided that when R^{13} is hydroxy or fluoro then R^{13} is not bound to a carbon adjacent to a nitrogen; or two R^{13} substituents together form a C_1 to C_2 alkyl bridge from one ring carbon to another non-adjacent ring carbon; or R^{13} is =O;

R^{20} is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, or aryl, wherein said aryl group is optionally substituted with from 1 to 3 groups independently selected from halogen, $-CF_3$, $-OCF_3$, hydroxyl, or methoxy; or when two R^{20} groups are present, said two R^{20} groups taken together with the nitrogen to which they are bound can form a five or six membered heterocyclic ring;

R^{22} is C_1-C_6 alkyl, R^{34}-aryl or heterocycloalkyl;

R^{24} is H, C_1-C_6 alkyl, $-SO_2R^{22}$ or R^{34}-aryl;

R^{25} is independently selected from the group consisting of C_1-C_6 alkyl, -CN, $-NO_2$, halogen, $-CF_3$, -OH, C_1-C_6 alkoxy, (C_1-C_6)alkyl-C(O)-, aryl-C(O)-, $N(R^4)(R^5)$-C(O)-, $N(R^4)(R^5)$-$S(O)_{1-2}$-, halo-(C_1-C_6)alkyl- or halo-(C_1-C_6)alkoxy-(C_1-C_6)alkyl-;

R^{29} is H, C_1-C_6 alkyl, R^{35}-aryl or R^{35}-aryl(C_1-C_6)alkyl-;

R^{30} is H, C_1-C_6 alkyl-, R^{35}-aryl or R^{35}-aryl(C_1-C_6)alkyl-;

R^{31} is H, C_1-C_6 alkyl-, R^{35}-aryl, R^{35}-aryl(C_1-C_6)alkyl-, (C_1-C_6)alkyl-C(O)-, R^{35}-aryl-C(O)-, $N(R^4)(R^5)$-C(O)-, (C_1-C_6)alkyl-$S(O)_2$- or R^{35}-aryl-$S(O)_2$-;

or R^{30} and R^{31} together are $-(CH_2)_{4-5}$-, $-(CH_2)_2$-O-$(CH_2)_2$- or $-(CH_2)_2$-$N(R^{29})$-$(CH_2)_2$- and form a ring with the nitrogen to which they are attached;

R^{32} is 1 to 3 substituents independently selected from the group consisting of H, -OH, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-SR^{22}$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-NR^{37}R^{38}$, $-NO_2$, $-CO_2R^{37}$, $-CON(R^{37})_2$, $-S(O)_2R^{22}$, $-S(O)_2N(R^{20})_2$, $-N(R^{24})S(O)_2R^{22}$, -CN, hydroxy-(C_1-C_6)alkyl- and $-OCH_2CH_2OR^{22}$;

R^{33} is 1 to 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, -CN, -NO_2, -$OCHF_2$ and –O-(C_1-C_6)alkyl;

R^{34} is 1 to 3 substituents independently selected from the group consisting of H, halogen, -CF_3, -OCF_3, -OH and –OCH_3.

R^{35} is 1 to 3 substituents independently selected from hydrogen, halo, C_1-C_6 alkyl, hydroxy, C_1-C_6 alkoxy, phenoxy, -CF_3, -$N(R^{36})_2$, -$COOR^{20}$ and –NO_2;

R^{36} is independently selected form the group consisting of H and C_1-C_6 alkyl;

R^{37} is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, R^{33}-aryl, R^{33}-aryl(C_1-C_6)alkyl, and R^{32}-heteroaryl; and

R^{38} is hydrogen, C_1-C_6 alkyl, -$C(O)R^{20}$, -$C(O)_2R^{20}$, –$C(O)N(R^{20})_2$ or (C_1-C_6)alkyl-SO_2-;

or R^{37} and R^{38}, together with the nitrogen to which they are attached, form an azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl ring.

2. A compound of claim 1 wherein A is a bond, M^1 is N, a is 0, n is 2, and the optional double bond is not present.

3. A compound of claim 2 wherein M^2 is $C(R^3)$ wherein R^3 is hydrogen or halogen, b is 0; r is 1 and p is 2.

4. A compound of claim 3 wherein Y is –C(O)-.

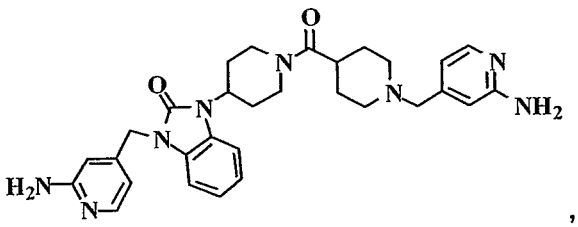
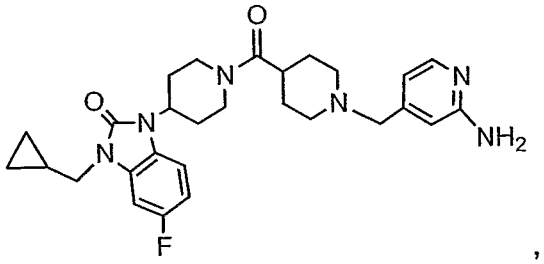
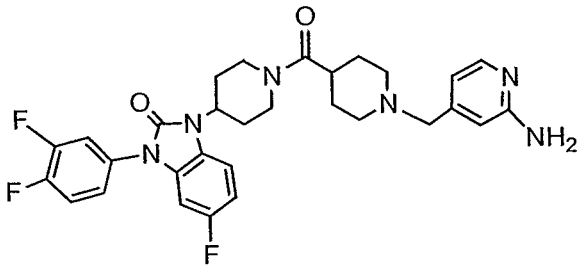
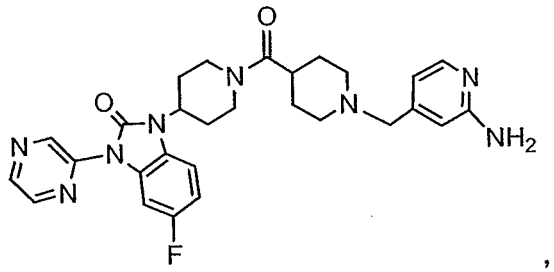
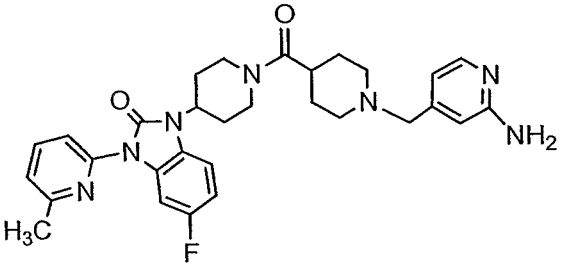
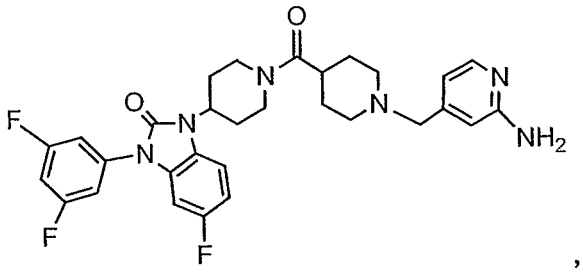
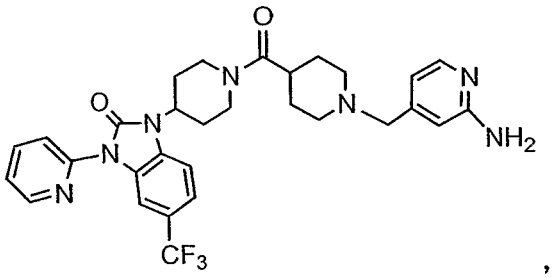
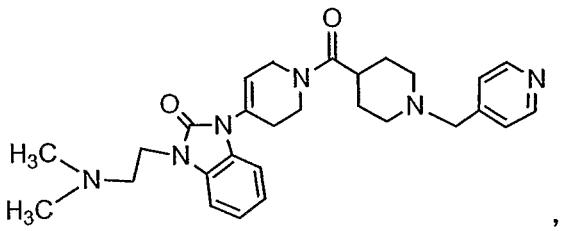
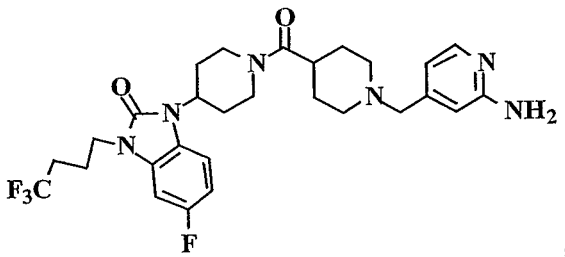
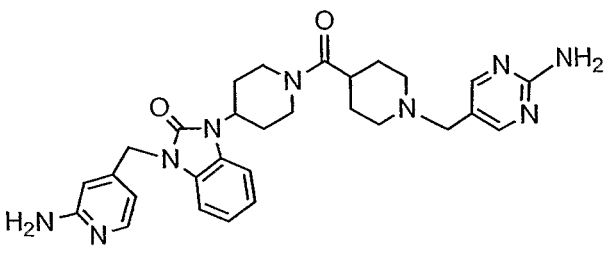
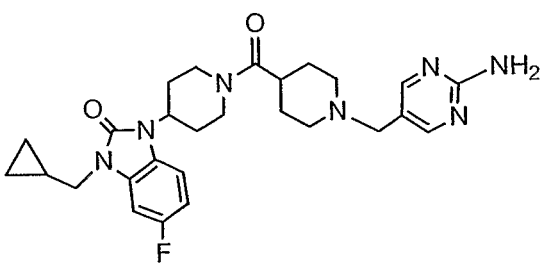
5. A compound of claim 4 wherein Z is straight or branched C_1-C_3 alkyl.

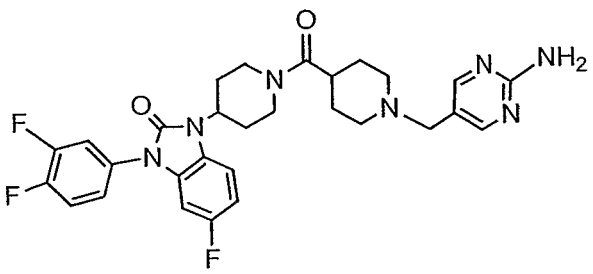
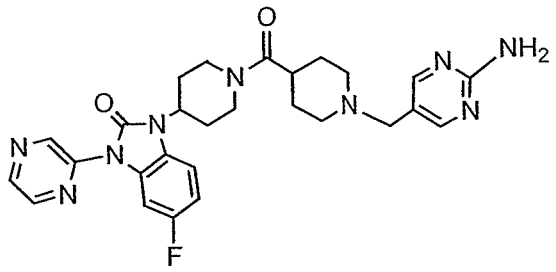
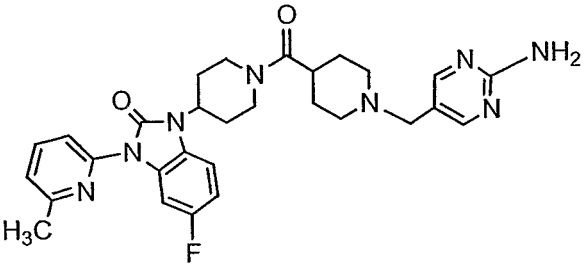
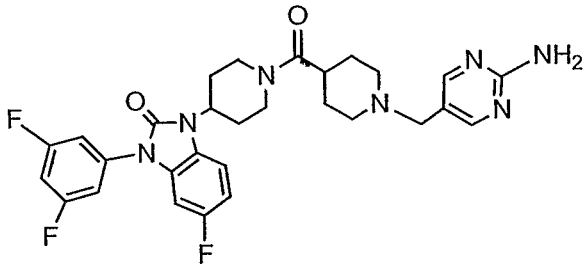
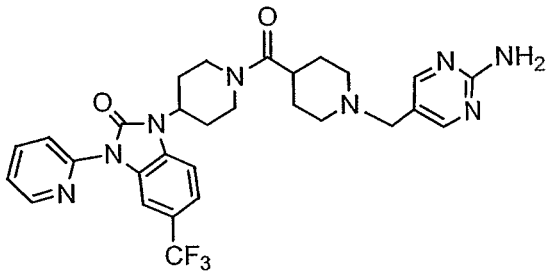
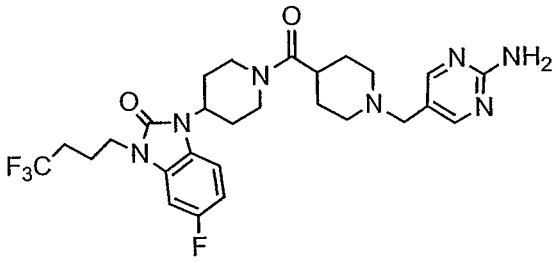
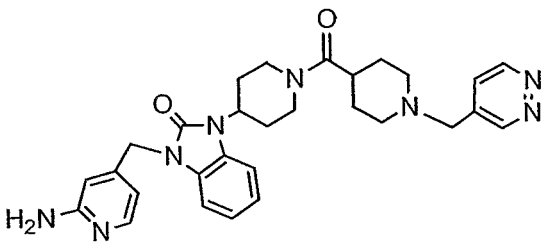
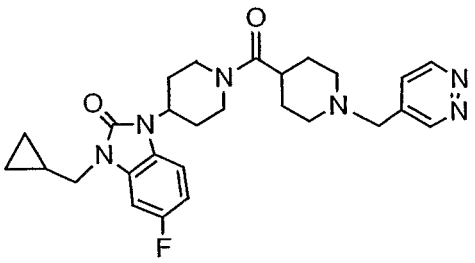
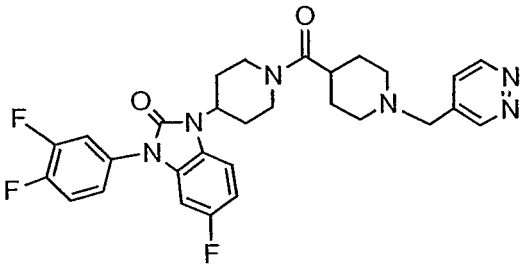
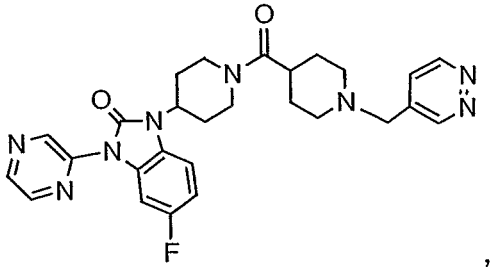
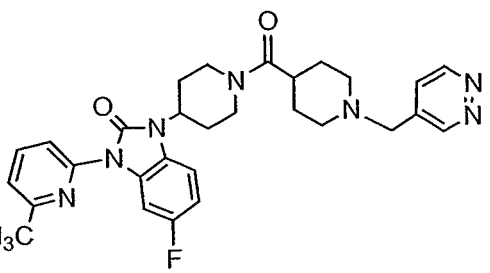
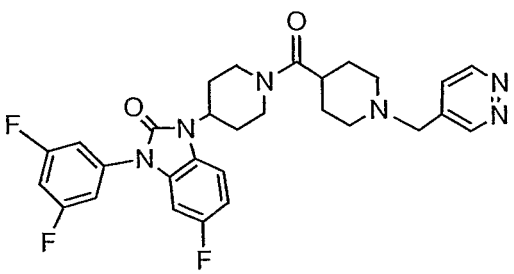
6. A compound of claim 5 wherein R^2 is a six-membered heteroaryl ring, optionally substituted with one R^6 substituent.

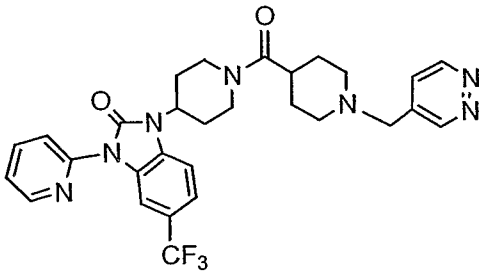
7. A compound of claim 6 wherein R^1 is R-substituted benzimidazolone, wherein R is H, (C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, R^{32}-aryl, R^{32}-heteroaryl or heterocycloalkyl(C_1-C_6)alkyl.

8. A compound of claim 7 wherein R^{25} is halogen or –CF_3 and k is 0 or 1.

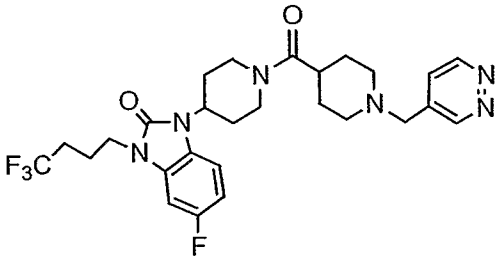
9. A compound of claim 1 selected from the group consisting of


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10. A pharmaceutical composition comprising an effective amount of a compound of claim 1 and a pharmaceutically effective carrier.

11. The use of a compound of claim 1 for the preparation of a medicament for treating allergy, allergy-induced airway responses, congestion, hypotension, cardiovascular disease, diseases of the GI tract, hyper or hypo motility or acidic secretion of the gastro-intestinal tract, obesity, sleeping disorders, disturbances of the central nervous system, attention deficit hyperactivity disorder, hypo or hyperactivity of the central nervous system, Alzheimer's disease, schizophrenia, or migraine.

12. The use of claim 14 wherein allergy-induced airway responses, allergy or nasal congestion are treated.

13. A pharmaceutical composition comprising an effective amount of a compound of claim 1, and an effective amount of H_1 receptor antagonist, and a pharmaceutically effective carrier.

14. The use of a compound of claim 1 for the preparation of a medicament for use in combination with an H_1 receptor antagonist for treating allergy, allergy-induced airway responses, or congestion.

15. The use of claim 14 wherein said H_1 receptor antagonist is selected from the group consisting of astemizole, azatadine, azelastine, acrivastine, brompheniramine, cetirizine, chlorpheniramine, clemastine, cyclizine, carebastine, cyproheptadine, carbinoxamine, descarboethoxyloratadine, diphenhydramine, doxylamine, dimethindene, ebastine, epinastine, efletirizine, fexofenadine, hydroxyzine, ketotifen, loratadine, levocabastine, meclizine, mizolastine, mequitazine, mianserin, noberastine, norastemizole, picumast, pyrilamine, promethazine, terfenadine, tripelennamine, temelastine, trimeprazine and triprolidine.