(1-4-PIPERIDINYL)BENZIMIDAZOLE DERIVATIVES USEFUL AS HISTAMINE H3 ANTAGONISTS

FIELD OF THE INVENTION

The present invention relates to novel substituted benzimidazoles 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.

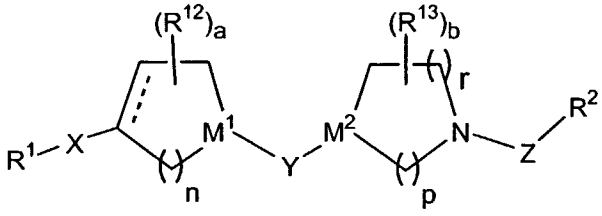
H_3 receptor sites are found on sympathetic nerves, where they modulate sympathetic neurotransmission and attenuate a variety of end organ responses under control of the sympathetic nervous system. Specifically, H_3 receptor activation by histamine attenuates norepinephrine outflow to resistance and 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 PCT US01/32151, filed October 15, 2001, and US Provisional Application 60/275,417, filed March 13, 2001.

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 2;

b is 0 to 2;

n is 1, 2 or 3;

p is 1, 2 or 3;

r is 0, 1, 2, or 3;

with the provisos that when M^2 is N, p is not 1; and that when r is 0, M^2 is $C(R^3)$; and that the sum of p and r is 1 to 4;

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

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

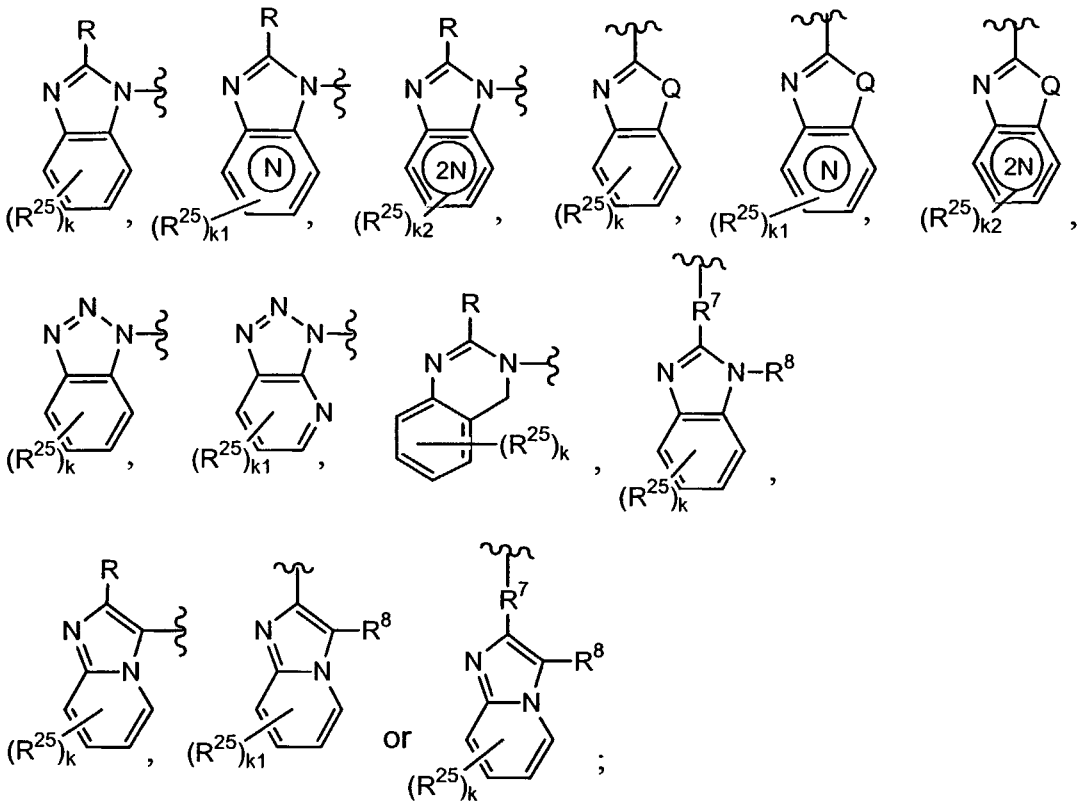
X is a bond or C_1-C_6 alkylene;

Y is –C(O)-, -C(S)-, $-(CH_2)_q$ -, $-NR^4C(O)$-, $-C(O)NR^4$-, $-C(O)CH_2$-, $-SO_2$-, $-N(R^4)$-, -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)-; when M^2 is N, Y is not $-C(O)NR^4$- or –C(=N-CN)-NH-; and when Y is $-N(R^4)$-, M^1 is CH and M^2 is $C(R^3)$;

q is 1 to 5, provided that when both M^1 and M^2 are N, q is 2 to 5;

Z is a bond, C_1-C_6 alkylene, C_1-C_6 alkenylene, -C(O)-, -CH(CN)-, $-SO_2$- or $-CH_2C(O)NR^4$-;

R^1 is



Q is $-N(R^8)-$, -S- or –O-;

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

k1 is 0, 1, 2 or 3;

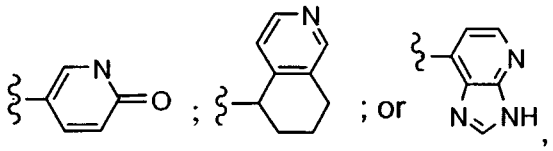
k2 is 0, 1 or 2;

R is H, C_1-C_6 alkyl, halo(C_1-C_6)alkyl-, C_1-C_6 alkoxy, (C_1-C_6)alkoxy-(C_1-C_6)alkyl-, (C_1-C_6)-alkoxy-(C_1-C_6)alkoxy, (C_1-C_6)alkoxy-(C_1-C_6)alkyl-SO_{0-2}, R^{32}-aryl(C_1-C_6)alkoxy-, R^{32}-aryl(C_1-C_6)alkyl-, R^{32}-aryl, R^{32}-aryloxy, R^{32}-heteroaryl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl-oxy-, R^{37}-heterocycloalkyl, R^{37}-heterocycloalkyl-oxy-, R^{37}-heterocycloalkyl-(C_1-C_6)alkoxy, $N(R^{30})(R^{31})$-(C_1-C_6)alkyl-, $-N(R^{30})(R^{31})$, -NH-(C_1-C_6)alkyl-O-(C_1-C_6)alkyl, $-NHC(O)NH(R^{29})$; R^{29}-$S(O)_{0-2}$-, halo(C_1-C_6)alkyl-$S(O)_{0-2}$-, $N(R^{30})(R^{31})$-(C_1-C_6)alkyl-$S(O)_{0-2}$- or benzoyl;

R^8 is H, C_1-C_6 alkyl, halo(C_1-C_6)alkyl-, (C_1-C_6)alkoxy-(C_1-C_6)alkyl-, R^{32}-aryl(C_1-C_6)alkyl-, R^{32}-aryl, R^{32}-heteroaryl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkyl, R^{37}-heterocycloalkyl, $N(R^{30})(R^{31})$-(C_1-C_6)alkyl-, R^{29}-$S(O)_2$-, halo(C_1-C_6)alkyl-$S(O)_2$-, R^{29}-$S(O)_{0-1}$-(C_2-C_6)alkyl-, halo(C_1-C_6)alkyl-$S(O)_{0-1}$-(C_2-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; thianaphthenyl;



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

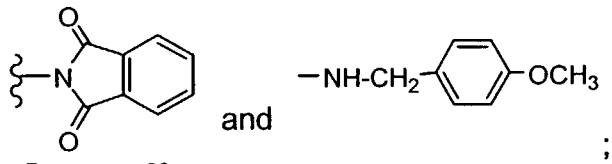
R^3 is H, halogen, C_1-C_6 alkyl, -OH, (C_1-C_6)alkoxy or $-NHSO_2$-(C_1-C_6)alkyl;

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

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, $-CF_3$, $-NR^4R^5$, $-CH_2-NR^4R^5$, $-NHSO_2R^{22}$, $-N(SO_2R^{22})_2$, phenyl, R^{33}-phenyl, NO_2, $-CO_2R^4$, $-CON(R^4)_2$,



;

R^7 is $-N(R^{29})$-, -O- or $-S(O)_{0-2}$-;

R^{12} is independently selected from the group consisting of C_1-C_6 alkyl, hydroxyl, 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 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, hydroxyl, 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 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, halogen, -CN, $-NO_2$, $-CF_3$, -OH, C_1-C_6 alkoxy, (C_1-C_6)alkyl-C(O)-, aryl-C(O)-, $-C(O)OR^{29}$, $-N(R^4)(R^5)$, $N(R^4)(R^5)$-C(O)-, $N(R^4)(R^5)$-$S(O)_{1-2}$-, R^{22}-$S(O)_{0-2}$-, 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, C_3-C_6 cycloalkyl, 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-, R^{35}-heteroaryl, (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 $-(CH_2)_2$-$N(R^{38})$-$(CH_2)_2$- 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, R^{35}-aryl-O-, $-SR^{22}$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-NR^{39}R^{40}$, phenyl, R^{33}-phenyl, NO_2, $-CO_2R^{39}$, $-CON(R^{39})_2$, $-S(O)_2R^{22}$, $-S(O)_2N(R^{20})_2$, $-N(R^{24})S(O)_2R^{22}$, -CN, hydroxy-(C_1-C_6)alkyl-, $-OCH_2CH_2OR^{22}$, and R^{35}-aryl(C_1-C_6)alkyl-O-, or two R^{32} groups on adjacent carbon atoms together form a $-OCH_2O$- or $-O(CH_2)_2O$- group;

R^{33} is 1 to 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, -CN, $-NO_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$ 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 1 to 3 substituents independently selected from hydrogen, halo, C_1-C_6 alkyl, hydroxy, C_1-C_6 alkoxy, phenoxy, $-CF_3$, $-N(R^{36})_2$, $-COOR^{20}$, $-C(O)N(R^{29})_2$ and $-NO_2$, or R^{37} is one or two =O groups;

R^{38} is H, C_1-C_6 alkyl, R^{35}-aryl, R^{35}-aryl(C_1-C_6)alkyl-, (C_1-C_6)alkyl-SO_2 or halo(C_1-C_6)alkyl-SO_2-;

R^{39} 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^{40} is hydrogen, C_1-C_6 alkyl, -C(O)R^{20}, -C(O)$_2R^{20}$, –C(O)N(R^{20})$_2$, (C_1-C_6)alkyl-SO_2-, or (C_1-C_6)alkyl-SO_2-NH-;

or R^{39} and R^{40}, 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 (e.g., a mammal, such as a human being) 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 optionally substituted benzimidazolyl or 7-azabenzimidazolyl, wherein R is preferably alkyl, alkoxy, alkoxyalkoxy, alkylthio, heteroaryl or R^{32}-aryl. More preferably, R is $-CH_3$, $-CH_2CH_3$, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2CH_3$, $-OCH((CH_3)_2$, $-SCH_3$, $-SCH_2CH_3$, pyridyl (especially 2-pyridyl), pyrimidyl, pyrazinyl, furanyl, oxazolyl or R^{32}-phenyl.

R^{25} is preferably halogen or $-CF_3$ and k is 0 or 1.

R^2 is preferably a six-membered heteroaryl ring, optionally substituted with one substituent. More preferably, R^2 is pyrimidyl, R^6-pyrimidyl, pyridyl, R^6-pyridyl or pyridazinyl, wherein R^6 is $-NR^4R^5$, 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. More preferably, R^6 is $-NH_2$.

X 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 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 and haloalkoxy represent alkyl or alkoxy chains wherein one or more hydrogen atoms are replaced by halogen atoms, e.g., $-CF_3$, $CF_3CH_2CH_2-$, CF_3CF_2- or CF_3S;

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;

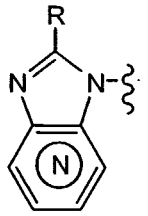
halogen (halo) represents fluoro, chloro, bromo and iodo;

heteroaryl represents cyclic groups, having 1 to 4 heteroatoms 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, isoqinolinyl, 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;

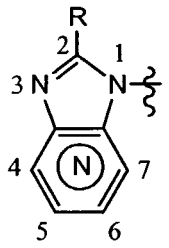
heterocycloalkyl represents a saturated, carbocylic ring containing from 3 to 15 carbon atoms, preferably from 4 to 6 carbon atoms; examples include but are not limited to 2- or 3-tetrahydrofuranyl, 2- or 3- tetrahydrothienyl, 2-, 3- or 4-piperidinyl, 2- or 3-pyrrolidinyl, 2- or 3-piperazinyl, 2- or 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.

In the definition of R^{32}, when two R^{32} groups on adjacent carbon atoms of an aryl or heteroaryl ring are said to be taken together form a $-OCH_2O-$ or $-O(CH_2)_2O-$ group, this means that the two R^{32} groups form a methylenedioxy or ethylenedioxy ring fused to the aryl or heteroaryl ring. When R^{12}, R^{13} or R^{37} is said to be one or two =O groups, this means that two hydrogen atoms on the same carbon atom of the ring can be replaced by =O; two such groups can be present on a ring.


, 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,  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.

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.

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

Lines drawn into the rings indicate 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 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 are carboxylic acid substituents in the molecule, salts may be formed with inorganic as well as organic bases 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 forms, with pharmaceutically acceptable solvents such as water, ethanol and the like are equivalent to the unsolvated forms 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 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. Still even more 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 a 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.

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.

One skilled in the art will recognize that the synthesis of compounds of formula I may require the construction of carbon-nitrogen bond. Methods include but are not limited to the use of a substituted aromatic compound or heteroaromatic compound and amine at 0 °C to 200 °C. The reaction may be carried out neat or in a solvent. Suitable solvents for the reaction are halogenated hydrocarbons, ethereal solvents, toluene, dimethylformamide and the like.

One skilled in the art will recognize that the synthesis of compounds of formula I may require the construction of heterocycle. Methods include but are not limited to the use of a diamino compound and a carbonyl equivalent at 0 °C to 200 °C. The reaction may be carried out in acidic, basic or neutral conditions. Suitable solvents for the reaction are water, halogenated hydrocarbons, ethereal solvents, alcoholic solvents, toluene, ketones, dimethylformamide and the like.

One skilled in the art will recognize that the synthesis of compounds of formula I 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). See, for example, Green et al, *Protective Groups in Organic Synthesis*. A suitable protecting group for an amine is 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.

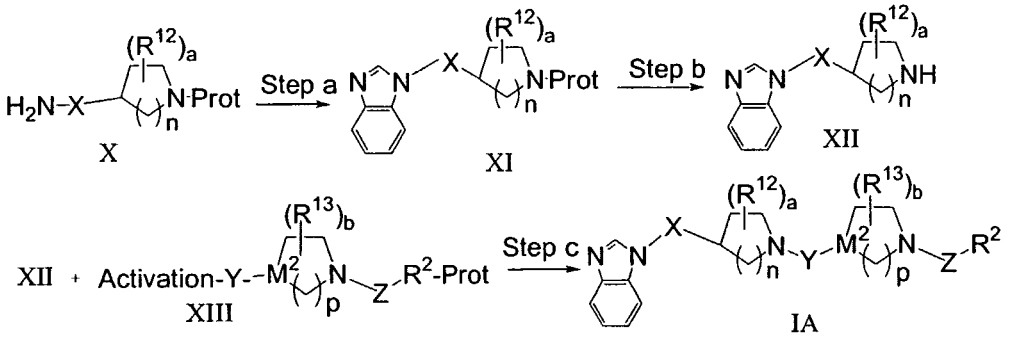
One skilled in the art will recognize that the synthesis of compounds of formula I may require the construction of an amide bond. Methods include but are not limited to the use of a reactive carboxy derivative (e.g. acid halide) or the use of an acid with a coupling reagent (e.g. EDCI, DCC, HATU) with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

One skilled in the art will recognize that the synthesis of compounds of formula I may require the reduction of a functional group. Suitable reducing reagents for the reaction include $NaBH_4$, lithium aluminum hydride, diborane and the like at -20 °C to 100 °C. Suitable solvents for the reaction are halogenated hydrocarbons, ethereal solvents, and the like.

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

One method shown in Scheme 1, below, is for the preparation of compounds of formula IA wherein R^1 is 1-benzimidazolyl or 2-benzamidazolyl and X is a bond or alkyl. Similar procedures can be used to prepare compounds wherein the benzene ring of the benzimidazolyl group is substituted, as well as the aza-benzimidazoles compounds (i.e., compounds wherein R^1 is other than benzimidazolyl as defined above) and the benzoxazolyl and benzothiazolyl derivatives.

SCHEME 1.



Step a: A suitably monoprotected diamine of formula **X**, wherein X is a bond or alkyl, Prot is a protecting group, and the remaining variables are as defined above is alkylated or arylated with a halide. The intermediate diamine is then cyclized with an appropriate carbonyl or formyl equivalent to form a compound of formula **XI**. Suitable

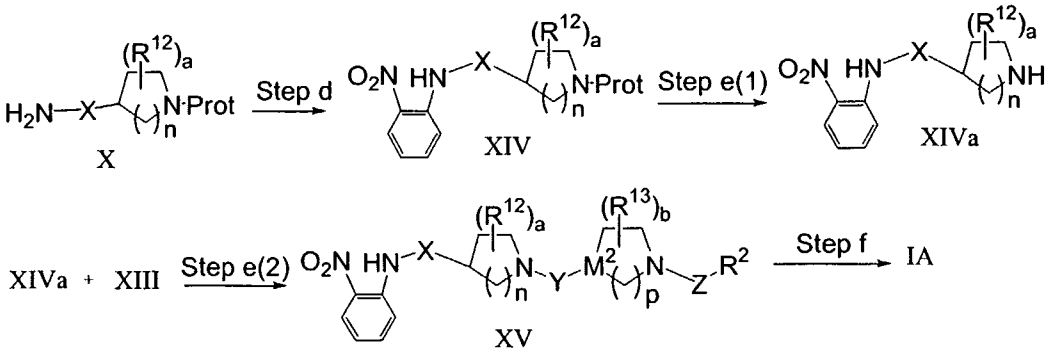
protecting groups are methyl, benzyl, butoxycarbonyl, or ethoxycarbonyl. A suitable halide for alkylation is a substituted aromatic compound or a substituted hetero-aromatic compound as described by Henning et al, *J. Med. Chem. 30*, (1987), 814-819.

Step b: The protected amine of formula **XI** 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. Suitable methods for carbamate deprotection are treatment with an acid, base or trimethylsilyl iodide.

Step c: An amine of formula **XII** is reacted with an activated functional group Y of formula **XIII** to form the bond between the nitrogen and functional group Y in formula IA. When Y is a carbonyl group and M^2 is carbon, activation can be via a halide (i.e. acid chloride intermediate) or other coupling reagents (EDCI, DCC, HATU, or like). Suitable reaction conditions may require a base such as triethylamine or N,N-diisopropylethylamine.

Another method for the preparation of compounds of formula IA wherein R^1 is 1-benzimidazolyl or 2-benzimidazolyl and X is a bond or alkyl is shown in Scheme 2, below. Similar procedures can be used to prepare compounds wherein the benzene ring of the benzimidazolyl group is substituted, as well as the aza-benzimidazoles compounds (i.e., compounds wherein R^1 is other than benzimidazolyl as defined above).

Scheme 2.



Step d: A suitably monoprotected diamine of formula **X**, wherein X is a bond or alkyl, Prot is a protecting group, and the remaining variables are as defined above, is alkylated or arylated with a halide to form a compound of formula **XIV**. Suitable protecting groups are methyl, benzyl, butoxycarbonyl, and ethoxycarbonyl. A suitable

halide for alkylation is a substituted aromatic compound or a substituted hetero-aromatic compound as described by Henning et al.

Step e:

(1) The protected amine of formula **XIV** 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. Suitable methods for carbamate deprotection are treatment with an acid, base or trimethylsilyl iodide.

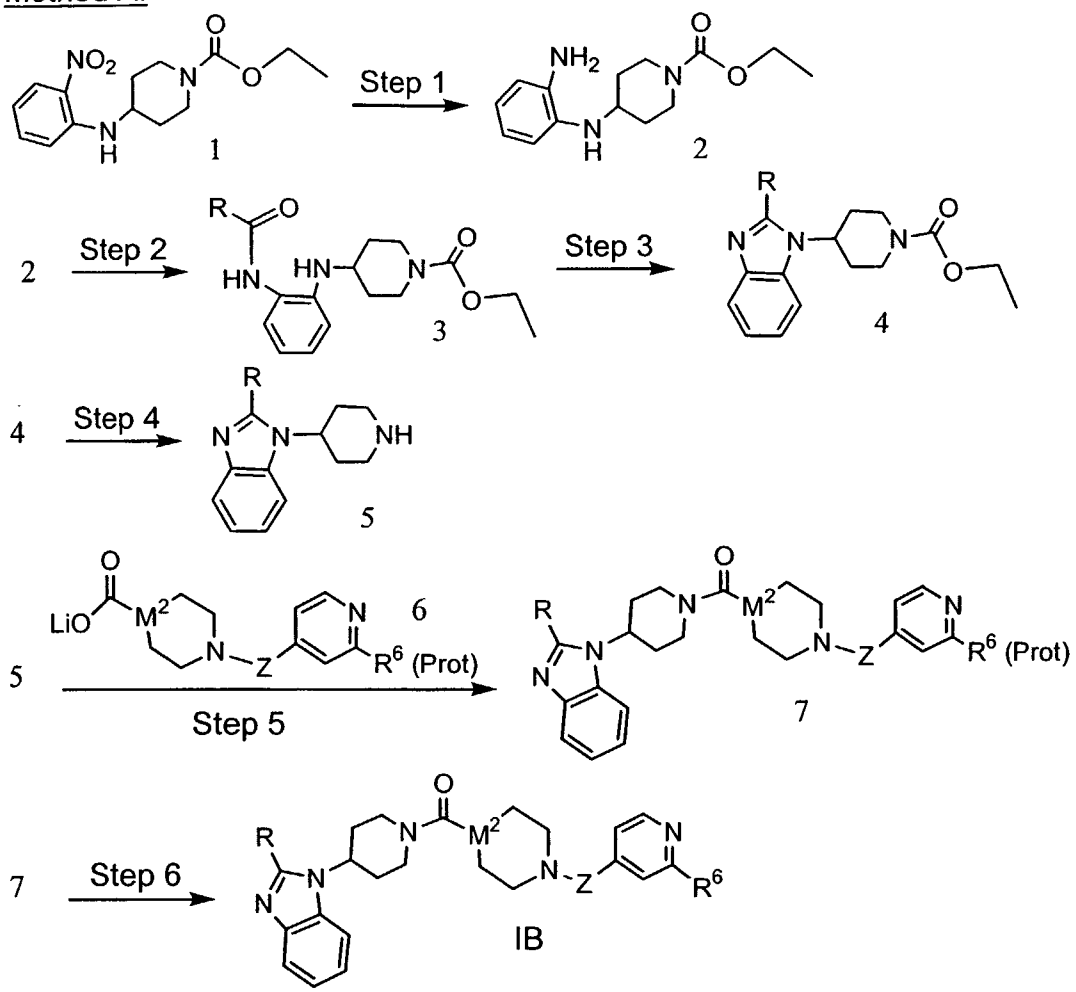
(2) The resulting amine from Step e(1) is reacted with an activated functional group Y of formula **XIII** to form the bond between the nitrogen and functional group Y to obtain the compound of formula **XV**. When Y is a carbonyl group and M^2 is carbon, activation can be via a halide (i.e. acid chloride intermediate) or other coupling reagents (EDCI, DCC, HATU, or the like). Suitable reaction conditions may require a base such as triethylamine, N,N-diisopropylethylamine, pyridine, or the like.

Step f: After reduction of formula **XV**, the resulting compound is reacted with a carbonyl equivalent to give the cyclized compound of formula IA. The reduction conditions can be hydrogen in the presence of catalyst, metal in the presence of an acid or a base, or other reduction reagent. The cyclization can be performed in acidic or basic conditions.

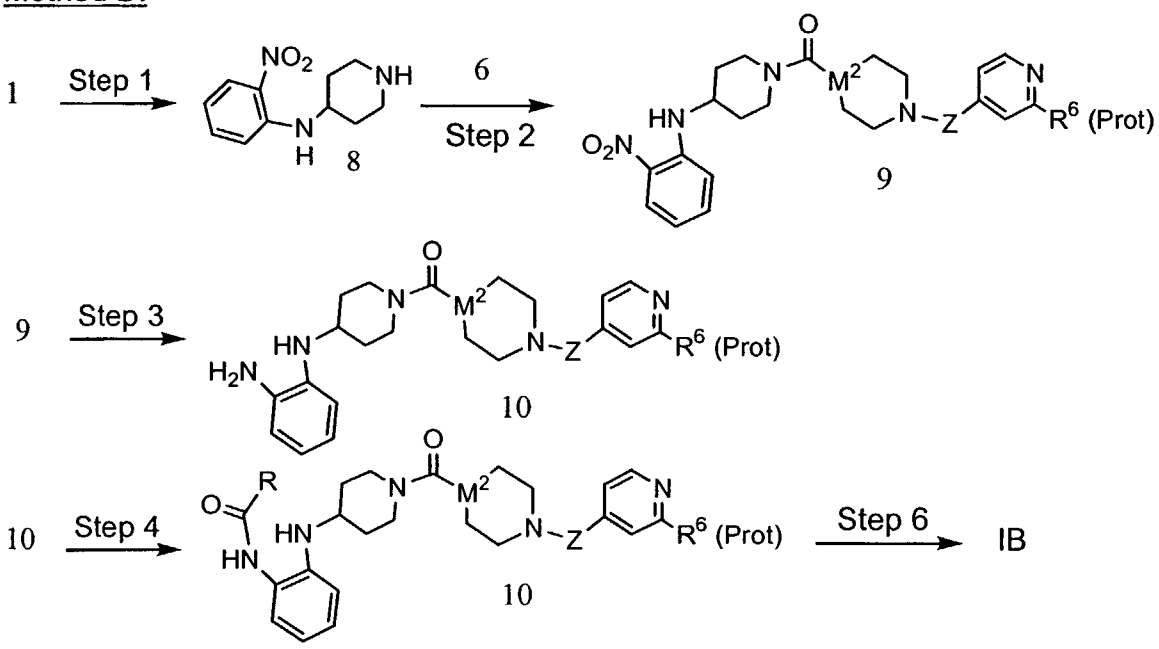
More detailed methods for synthesis of compounds are shown in **Scheme 3** below. The preparation of compounds of formula IB wherein R^1 is 1-benzimidazolyl (Methods A, B, C and F), Y is –C(O)- and R^2 is substituted pyridyl, and compounds of formulas IC and IC' wherein R^1 is 2-benzimidazolyl (Methods D and E), Y is –C(O)- and R^2 is substituted pyridyl are shown, but those skilled in the art will recognize that similar procedures can be used to prepare compounds wherein the benzene ring of the benzimidazolyl group is substituted, R^2 is other than pyridyl, and aza-benzimidazoles compounds (i.e., compounds wherein R^1 is other than benzimidazolyl as defined above).

Scheme 3.

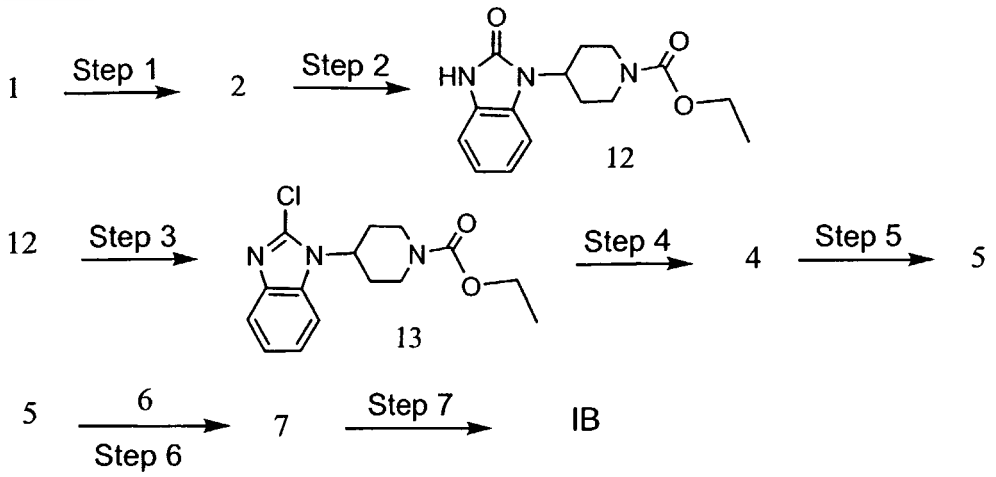
Method A:



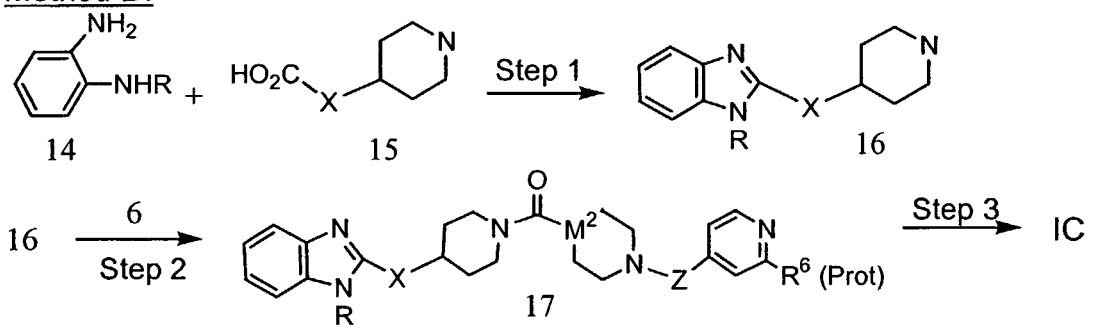
Method B:



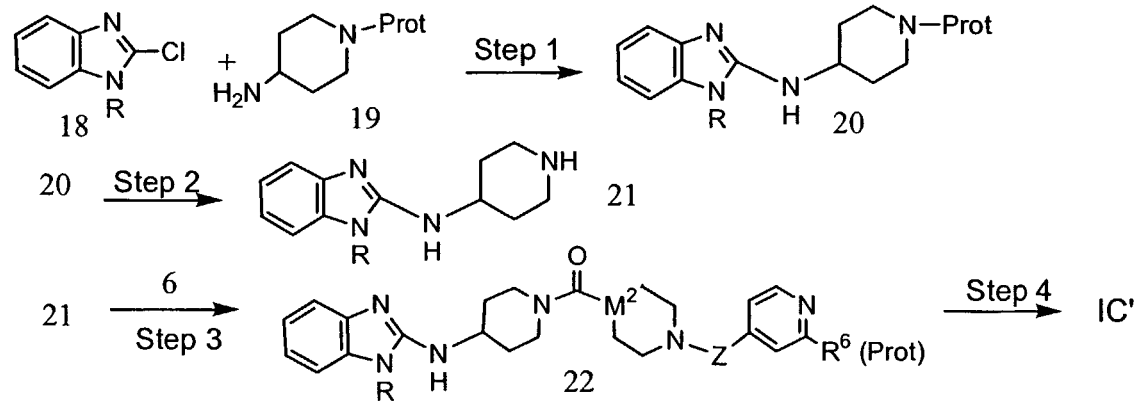
Method C:



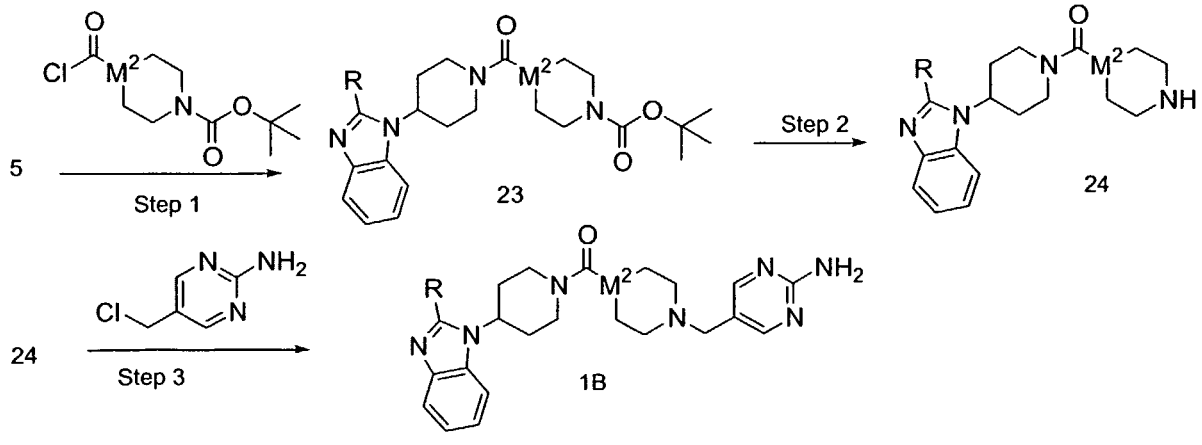
Method D:



Method E:



Method F:



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-butyloxycarbonyl; CBZ=carbobenzyloxy; and Ac=acetyl

DCC= dicyclohexylcarbodiimide

DMAP=4-dimethylaminopyridine

DMF=dimethylformamide

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

ESMS=Electron spray mass spectroscopy

FAB=Fast atom bombardment mass spectroscopy

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

HOBT= 1-hydroxybenzotriazole

LAH= lithium aluminum hydride

LDA= lithium diisopropylamide

$NaBH(OAc)_3$= sodium triacetoxyborohydride

NBS=N-bromosuccinimide

PPA= polyphosphoric acid

RT=room temperature

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

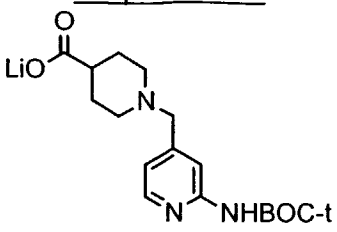
nM= nanomolar

Ki= Dissociation Constant for substrate/receptor complex

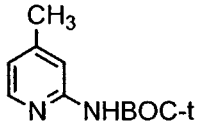
pA2= $-\log EC_{50}$, as defined by J. Hey, *Eur. J. Pharmacol.,* (1995), Vol. 294, 329-335.

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

Preparation 1

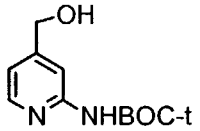


Step 1:



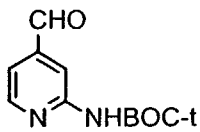
To a solution of 2-amino-4-methylpyridine (10.81 g, 100 mmol) in tert-butanol (250 ml) was added t-BOC anhydride (26.19 g, 120 mmol). The reaction mixture was stirred at 23 °C overnight, and then concentrated to an oil. The crude product was dry loaded onto a silica gel column and flash chromatographed (eluant: 30% hexanes-CH_2Cl_2 to 0-2% acetone-CH_2Cl_2) to produce 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 a n-BuLi solution (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 cooled back 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 with stirring to 23 °C. 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.

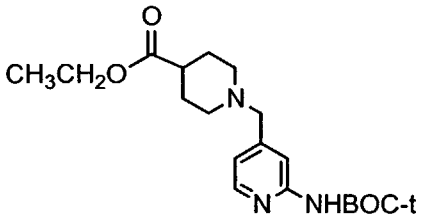
Step 3:



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:

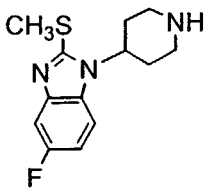


To a solution of the product of Step 3 (11.87 g, 53.5 mmol) in CH_2Cl_2 (370 ml) was added ethyl isonipecotate (9.07 ml, 58.8 mmol) followed by four drops of AcOH. The reaction mixture was then stirred for 40 min at 23 °C, after which $NaB(OAc)_3H$ (22.68 g, 107 mmol) was added. The reaction mixture 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.

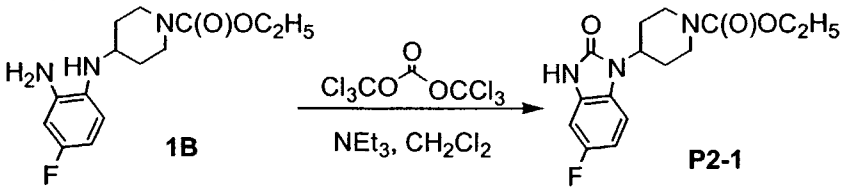
Step 5:

To a solution of the product of Step 4 (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 exposed to high vacuum to obtain 1.59 g of crude title compound as a yellowish solid which was used without purification.

Preparation 2

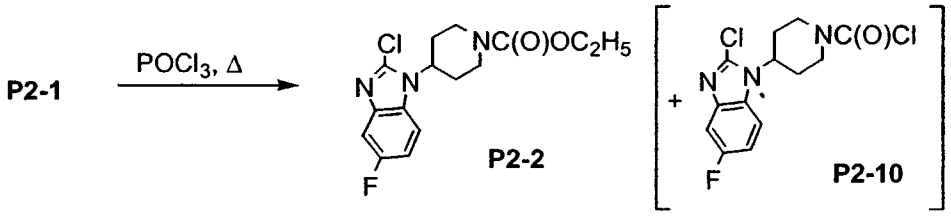


Step 1:



A solution of diamine **1B** (see Method A, Step 1) (20g, 71.1mmol) and Et_3N (30 ml, 213 mmol) in CH_2Cl_2 (400 ml) was cooled to 0 °C in an ice-water bath. To the well-stirred solution was added triphosgene (14.2 g, 47.3 mmol) cautiously (exotherm!) and portionwise over a period of 30 min. When addition was complete, stirring was continued at 0 °C for 1 h, then at RT for 16 h. The mixture was washed with 0.5N NaOH (200 ml), the organic layer was dried over anhydrous $MgSO_4$ and concentrated under vacuum. Hot EtOAc (200 ml) was added to the semi-solid residue, and the resultant mixture was cooled to RT. Filtration yielded compound **P2-1** as a white solid (16.5g); and silica gel flash chromatography [CH_2Cl_2/CH_3OH (2N NH_3) = 40:1] of the filtrate provided additional product as a white solid (2.7 g) [combined yield: 88%]. FABMS: 308 (MH^+; 100%).

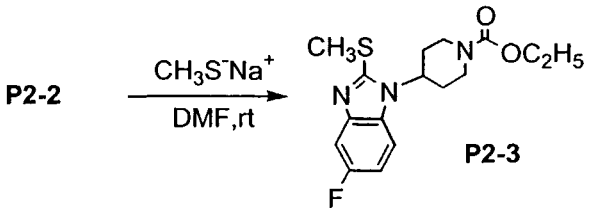
Step 2:



$POCl_3$ (100 ml) was added to **P2-1** (17.2 g; 56 mmol) in a round-bottomed flask flushed with dry N_2. The mixture was placed in an oil bath heated to 108 °C and was maintained at reflux for 6 h. $POCl_3$ was then removed in vacuo. The residue was adjusted to pH ~ 9-10 with 7N methanolic ammonia and was concentrated to dryness under vacuum. CH_2Cl_2 was added to the residue, insoluble material was filtered off, and the filtrate was again concentrated in vacuo. The residue was crystallized from EtOH to obtain compound **P2-2** as a white solid (12.6 g; 67%). ES-MS: 326.1 (MH^+; 100%).

Varying amounts of compound **P2-10** may be formed in this process and can be converted to desired product **P2-2** by careful in situ treatment in CH_2Cl_2 solution at 0 °C with one equivalent each of EtOH and NaH, followed by workup with ice-water and CH_2Cl_2. Low temperature is maintained in order to minimize reaction at the 2-position of the benzimidazole nucleus.

Step 3:

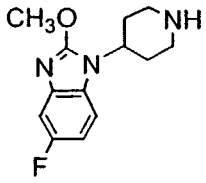


Sodium thiomethoxide (1.05 g; 15.0 mmol) was added to DMF (15 ml) in a round-bottomed flask flushed with N_2. After stirring at RT for 30 min, solid chloride **P2-2** (3.25 g, 10 mmol) was added, and the resultant mixture was kept stirring at RT for 16 h. EtOAc (100 ml) and water (50 ml) were added to the reaction mixture. The aqueous layer was separated and further extracted with EtOAc (50 ml). The combined extracts were dried over anhydrous $MgSO_4$ and concentrated under vacuum. The residue was purified via flash chromatography on silica gel, eluting with EtOAc-hexanes (3:4), to obtain compound **P2-3** as a white solid (2.12 g; 63%). FABMS: 338.3 (MH^+; 100%).

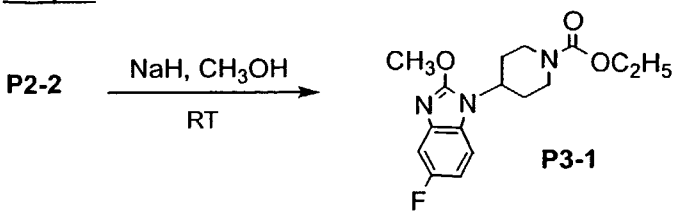
Step 4 :

To a stirred solution of **P2-3** (300 mg, 12.5 mmol) in EtOH (40 ml)-isopropyl alcohol (40 ml) was added 25% (w/w) aqueous NaOH solution (20 ml). The resultant mixture was stirred at 85 °C for 24 h, then at 100 °C for an additional 4 h. Alcohols were removed under vacuum, and the aqueous residue was extracted sequentially with CH_2Cl_2 (2 x 40 ml), then EtOAc (30 ml). Combined extracts were dried over anhydrous $MgSO_4$. Drying agent was removed by filtration, and the filtrate was concentrated under vacuum. The residue was purified by silica gel flash chromatography (CH_2Cl_2/2N methanolic ammonia = 12:1) to obtain Preparation 2 as an off-white solid (2.85 g, 70%). ES-MS: 266 (MH^+; 100%).

Preparation 3



Step 1:

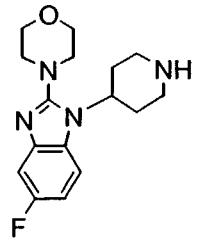


NaH (60 mg of a 60% dispersion; 1.48 mmol) was added to CH_3OH (4 ml) in a flask charged with N_2. After stirring at RT for 30 min, chloride **P2-2** (400 mg, 1.23 mmol) was added, and the resultant mixture was stirred at RT for 16 h. CH_3OH was removed in vacuo, and to the residue were added CH_2Cl_2 (30 ml) and water (10 ml). The organic layer was dried over anhydrous $MgSO_4$, filtered, and the filtrate concentrated under vacuum. The residue was purified via flash chromatography on silica gel, eluting with EtOAc-hexanes (3:2) to obtain **P3-1** as a white foam (0.232g; 59%). ES-MS: 322.1 (MH^+; 100%).

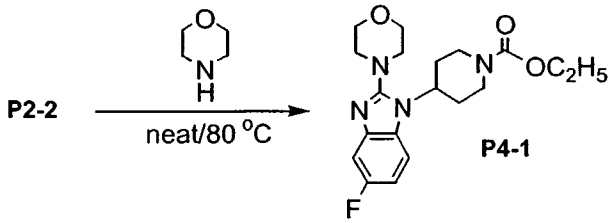
Step 2:

1N aqueous KOH (4.82 mL; 4.82 mmol) was added to a solution of **P3-1** in EtOH (15 ml), and the resultant mixture was stirred at 80 °C for 48 h. The mixture was concentrated under vacuum. Water (3 ml) and CH_2Cl_2 (15 ml) were added to the residue, and the organic layer was separated and dried over anhydrous $MgSO_4$. Drying agent was filtered, and the filtrate was concentrated in vacuo to obtain Preparation 3 as a colorless glass (160mg; 95%). FABMS: 250.2 (MH^+; 100%).

Preparation 4



Step 1:

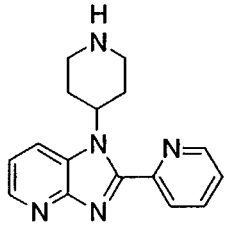


P2-2 (300 mg; 0.923 mmol) and morpholine (3 ml) were mixed in a round-bottomed flask under N_2, and the resultant mixture was heated to 80 °C for 16 h. Morpholine was removed under vacuum, and the residue was dissolved in CH_2Cl_2 (20 ml). An insoluble white precipitate was filtered off, and the filtrate was concentrated and purified by means of flash chromatography on silica gel, eluting with CH_2Cl_2/2N methanolic ammonia (45:1), to obtain **P4-1** as a colorless glass (0.325g; 94%). ES-MS: 377.1 (MH^+; 100%).

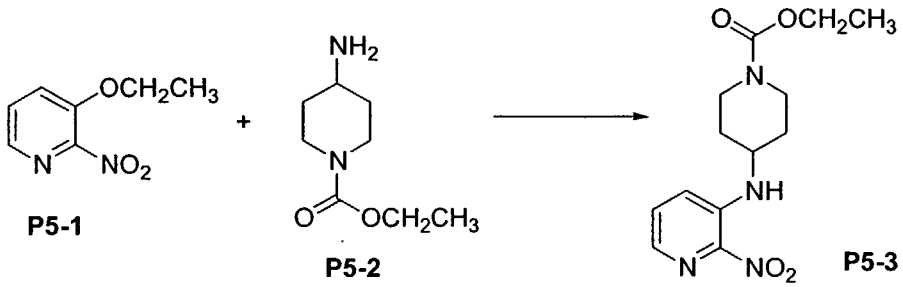
Step 2:

Trimethylsilyl iodide (240 microliters; 1.64mmol) was added to a solution of **P4-1** (316 mg; 0.843 mmol) in $CHCl_3$ (2 ml) under N_2, and the resultant solution was stirred at 55 °C for 7 h. The reaction was quenched with EtOH (2 ml), and the mixture was concentrated to dryness under vacuum. The residue was basified with a 1:1 (v/v) mixture of concentrated NH_4OH and water to pH ~10 and extracted with CH_2Cl_2 (2 x 5 ml). The combined extracts were dried over anhydrous $MgSO_4$. Drying agent was filtered, and the filtrate was concentrated under vacuum. The residue was purified via flash chromatography on silica gel, eluting with CH_2Cl_2-2N methanolic ammonia (13:1), to obtain compound Preparation 4 as a colorless glass. (181 mg; 70%). ES-MS: 305.1 (MH^+; 100%).

Preparation 5



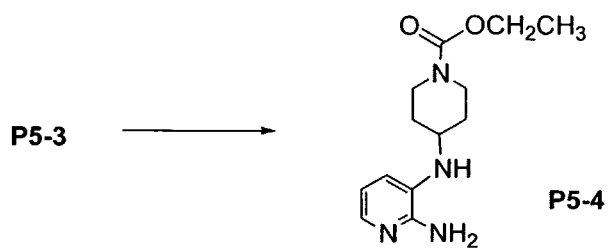
Step 1:



P5-1 **P5-2** **P5-3**

A solution of **P5-1** (3.5 g, 21 mmol) and **P5-2** (6.5 g, 38 mmol) in CH_2Cl_2 (3 ml) was heated to 110° C for 24 h and RT for 24 h. The reaction was diluted with CH_2Cl_2, washed with water and brine, and dried (Na_2SO_4). Purification on a flash column (SiO_2, 40% to 60% EtOAc in hexanes) gave **P5-3** (1.3 g, 21%; M+H = 295).

Step 2:

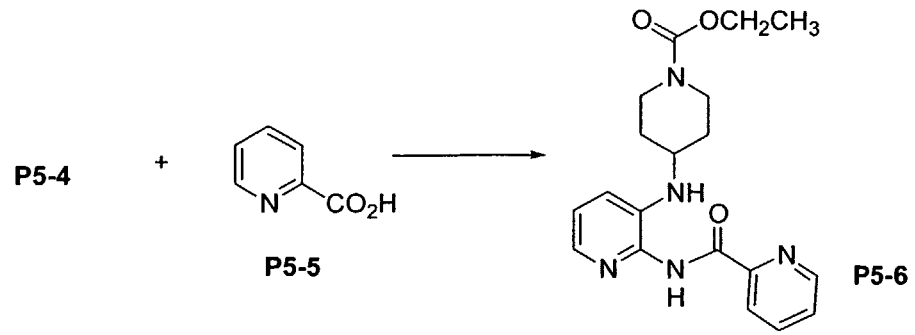


P5-3 **P5-4**

To a solution of **P5-3** (1.3 g, 4.4 mmol) in CH_3OH (30 ml) was added Ra-Ni (0.5 g) and the mixture was hydrogenated under a H_2 atmosphere (50 psi) for 18 h.

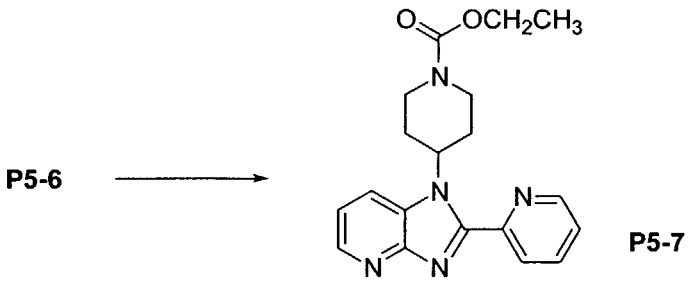
Filtration through a pad of celite gave **P5-4** as a grey solid that was used without further purification (1.05 g, 90%; M+H = 265).

Step 3:



A solution of **P5-4** (1.05 g, 3.97 mmol), **P5-5** (0.49 g, 3.97 mmol), DEC (1.14 g, 5.96 mmol) and HOBT (0.8 g, 5.96 mmol) in CH_2Cl_2 (10 ml) were stirred for 18 h at RT. The crude reaction mixture was diluted with additional CH_2Cl_2 and washed with 5% aqueous NaOH and brine and dried (Na_2SO_4). Purification using flash chromatography (SiO, 8% EtOAc in hexane to 10% CH_3OH in EtOAc) gave **P5-6** (0.35 g, 24%; M+H = 370).

Step 4:

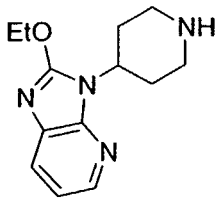


Compound **P5-6** (0.7 g, 1.89 mmol) was dissolved in HOAc (10 ml) and heated to 120° C for 3.5 h. The reaction was cooled to RT, concentrated in vacuo, neutralized by the addition of 10% aqueous NaOH and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated to give **P5-7** (0.58 g, 87%; M+H = 352) which was used in the next step without further purification.

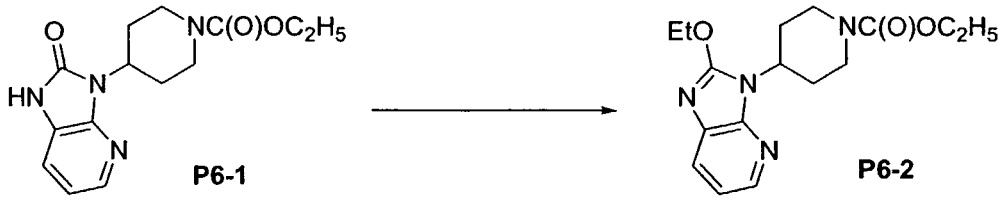
Step 5:

A solution of **P5-7** (0.58 g, 1.65 mmol) and NaOH (0.43 g, 13.2 mmol) in EtOH/H_2O (9/1, 10 ml) was heated to 100° C for 18 h. The reaction was cooled and concentrated and the residue purified on a flash column (SiO_2, 10% CH_3OH saturated with ammonia in CH_2Cl_2) to give Preparation 5 (0.42 g, 91%; M+H = 280).

Preparation 6



Step 1:

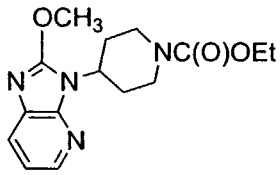


A solution of compound **P6-1** (prepared by procedures analogous to P2-1) (10.5 g, 36.2 mmol) and 2,6-di-*tert*-butylpyridine (12.2 ml, 54.4 mmol) in CH_2Cl_2 (400 ml) was treated with 1M sol. of $Et_3O^+BF_4^-$ (in CH_2Cl_2, 55 ml, 55 mmol). The reaction mixture was stirred at RT for 2h, quenched with 1N NaOH (100 ml), extracted with CH_2Cl_2 (3x), dried with Na_2SO_4 and concentrated. Purification by silica gel chromatography (eluant: 5-10% acetone/ CH_2Cl_2) to give 6.37 g of **P6-2** (20.0 mmol, 55%).

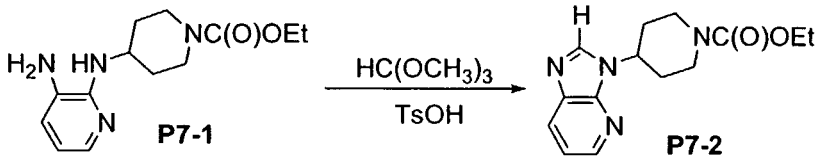
Step 2:

In a manner similar to that described in Preparation 3, Step 2, **P6-2** was converted to Preparation 6.

Preparation 7



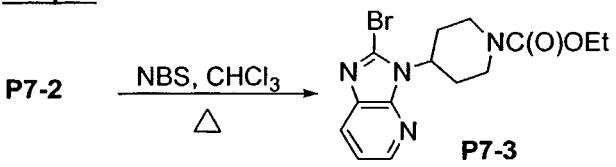
Step 1:



A mixture of **P7-1** (40g, 150 mmol), trimethyl orthoformate (66 ml, 64.0 g, 600 mmol) and a catalytic amount of *p*-toluenesulfonic acid monohydrate (300 mg, 1.58 mmol) was stirred under N_2 at 120 °C for 3 h. Excess orthoformate was removed under vacuum. The residue was partitioned between EtOAc (200 ml) and 1N NaOH (100 ml). The organic layer was washed with brine (100 ml) and dried over anhydrous $MgSO_4$. Drying agent was removed by filtration, and the filtrate was concentrated

under vacuum. The residue was purified by silica gel flash chromatography (CH_2Cl_2/CH_3OH (2N NH_3) = 45:1) to obtain **P7-2** as a dark purple syrup (27.2 g, 66%), which solidified upon standing. ES-MS: 275 (MH^+; 100%).

Step 2:

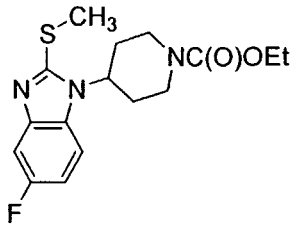


NBS was added portionwise (exotherm) to a solution of **P7-2** (27 g, 100 mmol) in $CHCl_3$ (300 ml), and the resultant solution was stirred at 60 °C for 16 h. Solvent was then removed under vacuum, and the residue was partitioned between EtOAc (200 ml) and 0.7N $Na_2S_2O_4$ (250 ml). The organic layer was washed with brine (150 ml) and dried over anhydrous $MgSO_4$. Drying agent was removed by filtration, and the filtrate was concentrated under vacuum. The residue was purified by silica gel flash chromatography [CH_2Cl_2/acetone = 45:1] to obtain **P7-3** as a yellow solid (24.2 g, 69%). ES-MS: 353 (MH^+; 100%).

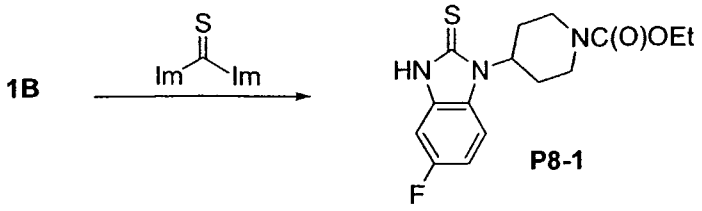
Step 3:

NaH (544 mg of a 60% dispersion, 13.6 mmol) was added to a solution of CH_3OH (0.551 ml, 436 mg, 13.6 mmol) in DMF (5 ml). The resultant mixture was stirred at RT for 30 min before adding solid bromide **P7-3** (3.99 g, 11.3 mmol). The reaction suspension was stirred at RT for 16 h. The mixture was then partitioned between EtOAc (800 ml) and water (40 ml). The aqueous layer was extracted with EtOAc (40 ml). Combined extracts were washed with brine (30 ml) and dried over anhydrous $MgSO_4$. Drying agent was removed by filtration, and the filtrate was concentrated under vacuum to obtain Preparation 7 as a white syrup (2.81 g, 81%), which was used without further purification. ES-MS: 305 (MH^+; 100%).

Preparation 8



Step 1:

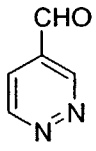


A solution of **1B** (15 g, 52.8 mmol) and 1,1'-thiocarbonyldiimidazole (25 g, 140 mmol) in THF (300 ml) was stirred at 72 °C under N_2 for 16 h, during which time a precipitate formed. THF was removed under vacuum, and the residue was purified by silica gel flash chromatography (CH_2Cl_2/acetone = 20:1) to obtain **P8-1** as a light yellow solid (16.7 g, >95%). ES-MS: 324 (MH^+; 100%).

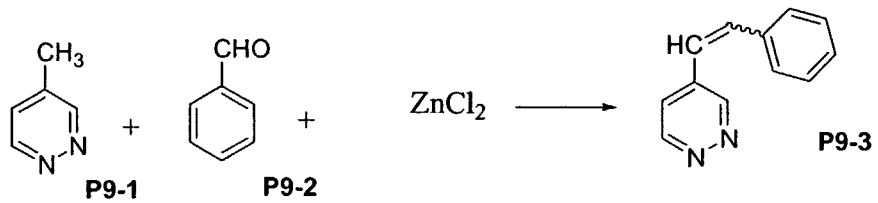
Step 2:

To a stirred mixture of **P8-1** (4.00 g, 12.5 mmol) and K_2CO_3 (2.05 g, 13.6 mmol) in DMF (40 ml) under a N_2 atmosphere was added CH_3I (0.85 ml, 1.94 g, 13.6 mmol). The resultant mixture was stirred at RT for 16 h before partitioning between EtOAc (100 ml) and water (40 ml). The aqueous layer was extracted with EtOAc (40 ml). Combined extracts were washed with brine (30 ml) and dried over anhydrous $MgSO_4$. Drying agent was removed by filtration, and the filtrate was concentrated under vacuum to obtain Preparation 8 as a foamy white solid (4.20 g, >95%; contained a small amount of DMF), which was used without further purification. ES-MS: 338 (MH^+; 100%).

Preparation 9



Step 1:



(Modified published procedure: G. Heinisch, E. Luszczak, and M. Pailer: *Monatshefte für Chemie*, 1973 (104), 1372.

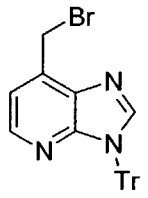
P9-1 (4.5 g, 47.8 mmoles), **P9-2** (8.12g, 76.5 mmoles), and anhydrous $ZnCl_2$ were heated, under N_2, in a dry apparatus, at a bath temperature of 160 °C for 5 h.

The resulting oil was purified by flash chromatography on silica gel using 30% Hexanes/EtOAc, yielding 5.92 grams (67%) of the product.

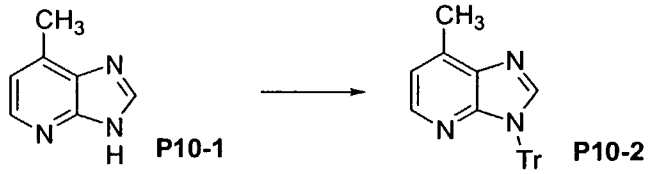
Step 2:

OsO_4 (5.0 ml in t-butanol, 2.5% w/w) was added to **P9-3** (5.9 g, 32.38 mmoles) dissolved in p-dioxane (87 ml) and water (29 ml). $NaIO_4$ (14.1 g, 65.92 mmoles) was added, with good stirring, in small portions, over a period of 6 h. The mixture was then diluted with p-dioxane and filtered. After removing most of the solvent under reduced pressure, the residue was taken in CH_2Cl_2 (600 ml) and dried over anhydrous Na_2SO_4. After removal of the solvent, the mixture was purified by flash chromatography on silica gel using 5% CH_3OH/CH_2Cl_2 as eluent to obtain Preparation 9. Yield: 2.89 g (82%).

Preparation 10



Step 1:



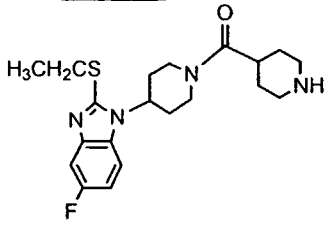
P10-1 **P10-2**

A solution of **P10-1** (2 g, 15 mmol) in CH_2Cl_2 (50 ml) was treated with Et_3N (3 g, 30 mmol) and triphenylmethyl chloride (TrCl, 4.25 g, 15.3 mmol) and stirred at RT overnight. The solvent was removed in vacuo and the residue purified via flash column chromatography (SiO_2, 20% EtOAc in hexane) to give **P10-2** (5.2 g, 46%).

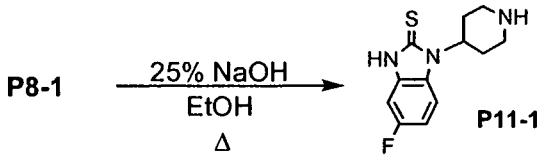
Step 2:

A solution of **P10-2** (5.2 g, 14.6 mmol) in CCl_4 (80 ml) was treated with NBS (7.8 g, 43 mmol) and the reaction heated to 80° C overnight. The reaction was cooled, filtered and concentrated, and the residue was purified via flash column chromatography (SiO_2, 20% to 30% EtOAc in hexane) to give Preparation 10 (2.8 g, 42%, M+H = 453, 455)

Preparation 11

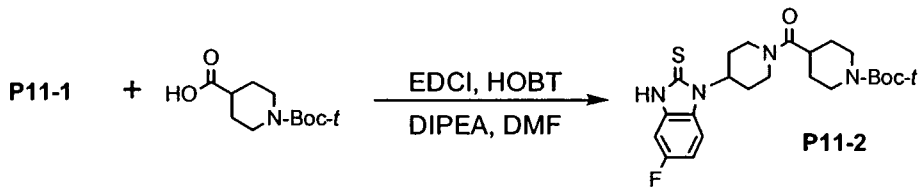


Step 1:



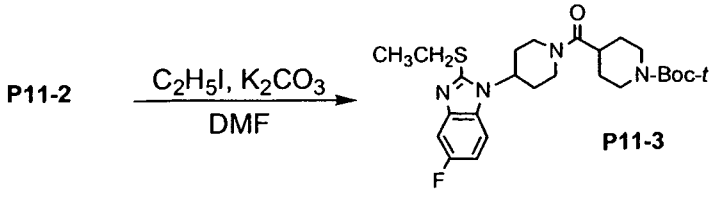
To a stirred solution of **P8-1** (6.5 g, 20.1 mmol) in EtOH (80 ml) was added 25% (w/w) aqueous NaOH solution (20 ml). The resultant mixture was stirred at 90 °C for 16 h. EtOH was removed under vacuum, and the residue was adsorbed directly onto silica gel and subjected to flash chromatography (CH_2Cl_2/2N methanolic ammonia = 9:1) to obtain **P11-1** as a white solid (4.46 g, 70%). ES-MS: 252 (MH^+; 100%).

Step 2:



A mixture of **P11-1** (3.95 g; 15.7 mmol), BOC-isonipecotic acid (3.60 g; 15.7 mmol), HOBT (3.19 g; 23.6 mmol), DIPEA (3ml; 2.23g; 17.2 mmol) and EDCI (4.50 g; 23.6 mmol) in DMF (30 ml) was stirred under N_2 at RT for 16 h. The reaction mixture was partitioned between EtOAc (60 ml) and water (40 ml). The aqueous phase was extracted with EtOAc (40 ml), and the combined extracts were washed with brine (40 ml) and dried over anhydrous $MgSO_4$. Drying agent was removed by filtration, and the filtrate was concentrated under vacuum. The residue was purified by silica gel flash chromatography (CH_2Cl_2/CH_3OH (2N NH_3) = 40:1) to obtain **P11-2** as a white solid (~7.3 g, ~100%), containing a small amount of DMF, used without further purification in Step 3 below. ES-MS: 463 (MH^+; 70%); 407 (100%).

Step 3:

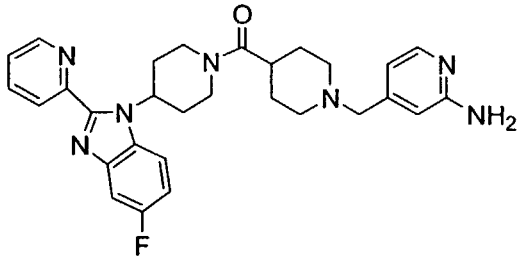


To a stirred mixture of **P11-2** (460 mg; 1 mmol) and K_2CO_3 (165 mg; 1.20 mmol) in DMF (4 ml) under a N_2 atmosphere was added EtI (92 microliters; 179 mg; 1.15 mmol). The resultant mixture was stirred at RT for 16 h and was then partitioned between EtOAc (20 ml) and water (10 ml). The aqueous phase was extracted with EtOAc (10 ml), and the combined extracts were washed with brine (20 ml) and dried over anhydrous $MgSO_4$. Drying agent was removed by filtration, and the filtrate was concentrated under vacuum to obtain **P11-3** as a pale yellow foam (471 mg, 96%), containing a small amount of DMF, used without further purification in Step 4 below. ES-MS: 463 (MH^+; 85%); 435 (100%).

Step 4:

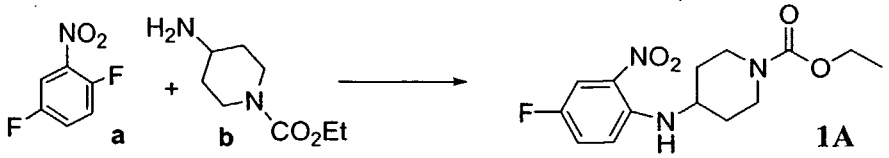
To a solution of **P11-3** (465 mg; 0.949 mmol) in CH_2Cl_2 (4 ml) was added TFA (1 ml; 1.54 g; 13.5 mmol). The resultant solution was stirred for 2 h at RT and was then partitioned between CH_2Cl_2 (20 ml) and 1:1 (v/v) concentrated NH_4OH:water (5 ml). The aqueous phase was extracted successively with 95:5 CH_2CL_2:EtOH (5 ml) and EtOAc (5 ml). The combined extracts were dried over anhydrous $MgSO_4$. Drying agent was removed by filtration, and the filtrate was concentrated under vacuum to obtain Preparation 11 as a pale white foam (353 mg, 95%), used without further purification. ES-MS: 391 (MH^+; 100%).

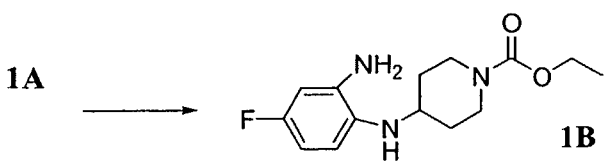
Example 1



Method A

Step 1:



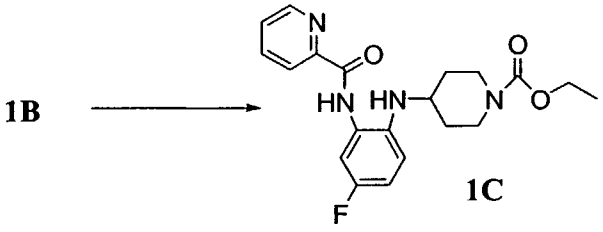


A mixture of **a** (25 g, 0.16 mol), **b** (27 g, 0.16 mol), K_2CO_3 (26 g, 0.19 mol), and NaI (2.4g, 0.016 mol) in dimethylacetamide (50 ml) was heated at 140 °C for 3.5 h.

The reaction mixture was concentrated to one-third volume, poured onto saturated aqueous $NaHCO_3$, and extracted with EtOAc (4×). The combined organic layers were washed with water (2×) and brine, dried over Na_2SO_4, and concentrated. Recrystallization with EtOH provided **1A** (48 g, 98%).

A suspension of **1A** (20.00 g, 64.2 mmol,) and Raney® 2800 Nickel (5.0 g) in ethanol (70 ml) and THF (140 ml) was shaken under H_2 (40 psi) for 2 h. The mixture was filtered through a short pad of celite. The filtrate was concentrated and dried on vacuum to deliver a tan solid (18.20 g, ~100%).

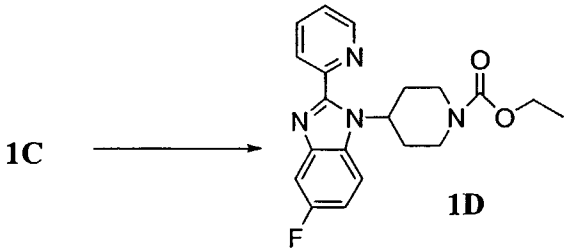
Step 2:



1C

A solution of **1B** (5.00 g, 17.77 mmol) and picolinoyl chloride hydrochloride (3.16g, 17.75 mmol) in CH_2Cl_2 (400 ml) and Et_3N (15 ml) was stirred at RT. After 15 h, the reaction was diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4, concentrated, and dried on vacuum to provide a brown foam (6.47g, 94%).

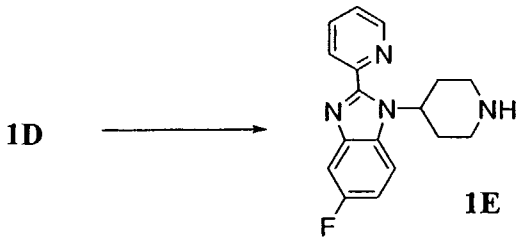
Step 3:



1D

A solution of **1C** (1.77g, 4.58 mmol) in ethanol (50 ml) and concentrated H_2SO_4 (5.0 ml) was refluxed for 3 h, cooled to RT, and neutralized with 1.0 M NaOH until pH = 10. The resulting mixture was extracted with CH_2Cl_2. The combined organic solutions were dried over Na_2SO_4 and concentrated on reduced pressure. The residue was purified by flash chromatography (silica gel, 5% CH_3OH in CH_2Cl_2 as eluent) to provide a tan foam (1.58g, 94%).

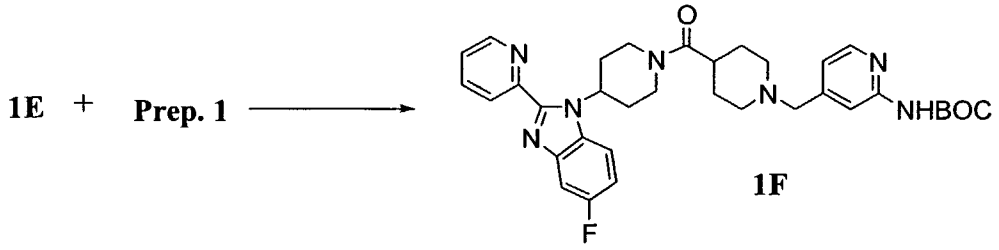
Step 4:



1E

Iodotrimethylsilane (6.30g, 31.48 mmol) was added to a solution of **1D** (3.88g, 10.53 mmol) in anhydrous 1,2-dichloroethane (40 ml). The resulting solution was stirred at 75 °C for 4 hours, cooled to RT, and treated with 1.0 M NaOH solution. The mixture was then extracted with CH_2Cl_2. The combined extracts were washed with water, dried over Na_2SO_4, and the solvent evaporated. Purification of the residue by flash chromatography (silica gel, 10% CH_3OH in CH_2Cl_2 as eluent) delivered an off-white foam (2.10g, 67%).

Step 5:



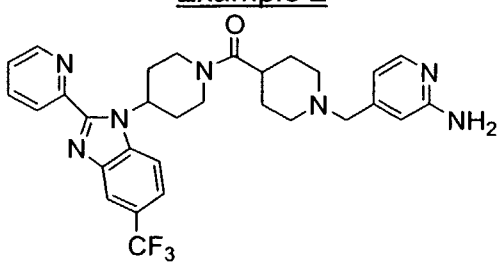
1F

Amine **1E** (5.80g, 19.6 mmol) and Preparation 1 (5.32g, 23.4 mmol) were dissolved in DMF (60 ml) and CH_2Cl_2 (60 ml). To the resulting solution, EDCI hydrochloride (5.70g, 24.50 mmol), HOBT (1.30g, 24.50 mmol), and diisopropylethylamine (5.08g, 39.6 mmol) were added successively. The resulting reaction mixture was stirred at 70°C for 4 hours, cooled to RT, diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4, and concentrated. Flash chromatography (SiO_2, 5% CH_3OH in CH_2Cl_2 → 90:10:0.5 CH_2Cl_2:CH_3OH:NH_4OH) of the residue provided a tan foam (7.89g, 65%).

Step 6:

A solution of **1F** (7.89g, 12.88 mmol) and TFA (29g, 257 mmol) in CH_2Cl_2 (65 ml) was stirred at RT for 12 h, neutralized with 1.0 M NaOH, and extracted with CH_2Cl_2. The combined organic layers were washed with water, dried over Na_2SO_4 and concentrated. Purification of the crude product by flash chromatography (SiO_2, 5% CH_3OH in CH_2Cl_2 to 90:10:0.5 CH_2Cl_2:CH_3OH:NH_4OH) provided the title compound as a white solid (5.80g, 88%). MS: 514 (MH^+).

Example 2



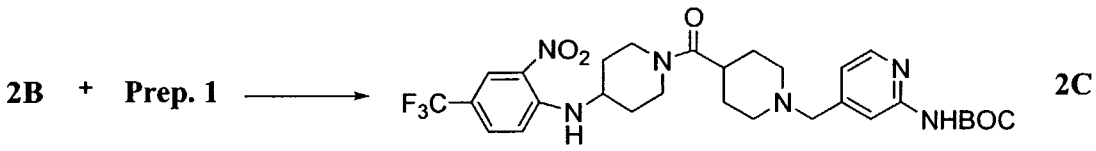
Method B

Step 1:



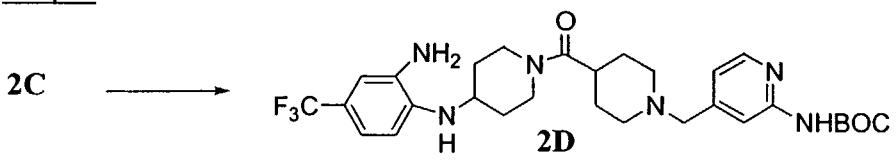
TFA (200 ml, 2.596 mol) was added to a solution of **2A** (20g, 51.36 mmol) in CH_2Cl_2 (100 ml). The resulting reaction mixture was stirred at RT for 6 h, neutralized with 1.0 M NaOH, and extracted. The combined extracts were washed with water, dried over Na_2SO_4, and concentrated. Flash chromatography gave an orange solid (13.50g, 91%).

Step 2:



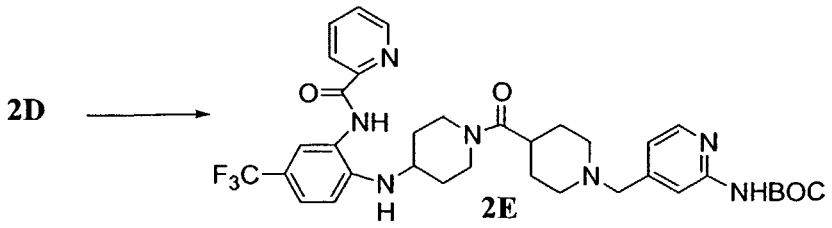
Amine **2B** (1.50g, 5.19 mmol) and Preparation 1 (1.75g, 5.13 mmol) were dissolved in DMF (10 ml) and CH_2Cl_2 (10 ml). To the resulting solution, EDCI hydrochloride (1.50g, 7.83 mmol), HOBT (1.05g, 7.82 mmol), and diisopropylethylamine (3.71g, 28.70 mmol) were added successively. The resulting reaction mixture was stirred at 70°C for 18 h, cooled to RT, diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4, and concentrated. Flash chromatography of the residue provided an orange gel (2.31g, 74%).

Step 3:



A suspension of **2C** (2.10 g, 3.46 mmol,) and Raney® 2800 Nickel (1.0 g) in CH_3OH (100 ml) was shaken under H_2 (30 psi) for 6 h. The mixture was filtered through a short pad packed with celite. The filtrate was concentrated and dried on vacuum to deliver an orange solid (1.80 g, 90%).

Step 4:

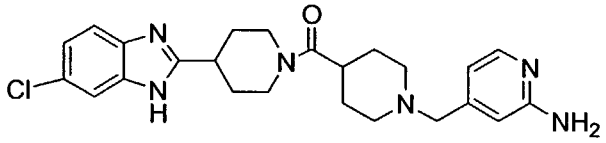


Amine **2D** (200 mg, 0.347 mmol) and picolinoyl chloride hydrochloride (62 mg, 0.348 mmol) were dissolved in CH_2Cl_2. Et_3N was then introduced via a syringe. The resulting solution was stirred at RT for 6 h, treated with 1.0 M NaOH solution, and extracted. The extracts were washed with water, dried over Na_2SO_4, and concentrated. Purification of the residue by flash chromatography gave a white foam (167 mg, 71% yield).

Step 5:

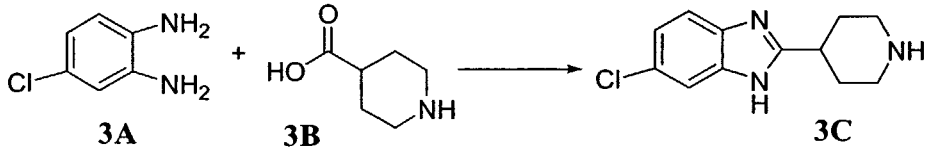
A solution of **2E** (160 mg, 0.235 mmol) and H_2SO_4 (concentrated, 0.50 ml) in ethanol (10 ml) was refluxed for 2.5 h, cooled to RT, and neutralized with 1.0 M NaOH. After extraction of the mixture, the combined organic layers were washed with water, dried over Na_2SO_4, and concentrated. Purification of the crude product using prep TLC (10% CH_3OH in CH_2Cl_2) provided the title compound as a white solid (88 mg, 66%). MS: 564 (MH^+)

Example 3



Method D

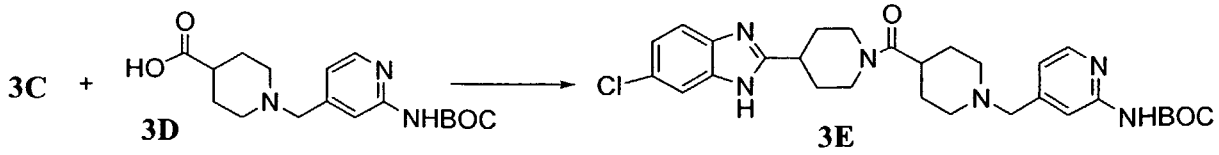
Step 1:



3A **3B** **3C**

Diamine **3A** (1.43 g, 10 mmol) and isonipecotic acid **3B** (1.29 g, 10 mmol) were mixed, and PPA (20 g) was added. The resulting mixture was heated at 180 °C for 3.5 h, cooled to RT and diluted with water to 100 ml. The solution was then basified with solid NaOH to pH 14. The resultant copious precipitate was filtered off. The precipitate was washed repeatedly with CH_3OH, and combined CH_3OH extracts were concentrated-dry loaded on silica gel and flash chromatographed (25-40% 5N NH_3 in CH_3OH/ CH_2Cl_2) to provide **3C** as a dark solid (1.90 g, 81%).

Step 2:



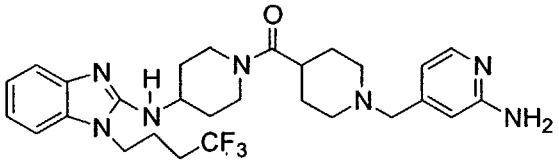
3C **3D** **3E**

To the mixture of acid **3D** (181mg, 0.54 mmol), HATU (247 mg, 0.65 mmol) and Et_3N (84 μl, 0.6 mmol) in DMF (12 ml) was added amine **3C** (126 mg, 0.54 mmol). The resulting mixture was stirred at RT for 24 h, concentrated, redissolved in CH_3OH, concentrated-dry loaded on silica gel and flash chromatographed (5-10% 5N NH_3 in CH_3OH/ CH_2Cl_2) to provide **3E** as a yellow oil (210mg, 70%).

Step 3:

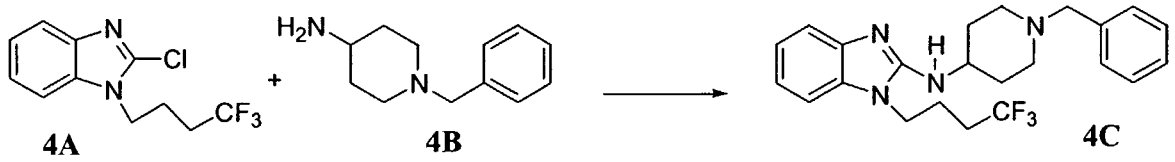
A solution of **3E** (96 mg, 0.174 mmol) in 15 ml of 1M HCl in 25% CH_3OH/ dioxane was stirred at RT for 48 h. The mixture was concentrated, exposed to high vacuum, redissolved in CH_3OH, concentrated-dry loaded on silica gel and flash chromatographed (10-15% 5N NH_3 in CH_3OH/ CH_2Cl_2) to provide the title compound as a colorless oil (48 mg, 61%). MS: 453 (MH^+)

Example 4



Method E

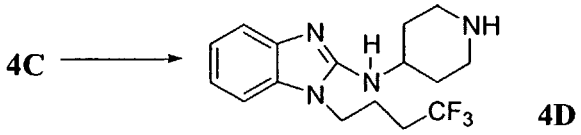
Step 1:



4A **4B** **4C**

A mixture of neat **4A** (1.75g, 6.66 mmol) and **4B** (2.93g, 15.07 mmol) was stirred at 120 °C for 2 days, cooled to RT, treated with 1.0 M NaOH solution (30 ml), and extracted with EtOAc. The combined organic layers were washed with water and dried over Na_2SO_4. After evaporation to dryness, the crude residue was flash chromatographed (silica gel, 50% EtOAc in hexanes as eluent) to give 510 mg of **4C** (18%).

Step 2:

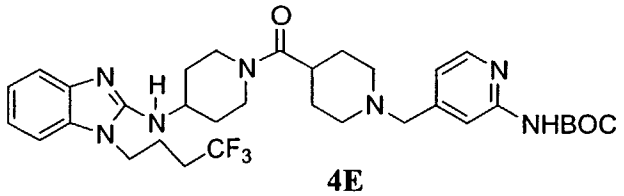


4C **4D**

To a 500 ml pressure bottle was added **4C** (490 mg, 1.18 mmol) in CH_3OH (20 ml). Under N_2 stream, palladium hydroxide (300 mg, 20 wt.% on carbon) solid was added. The reaction mixture was shaken under 55 psi of hydrogen for 40 h and

filtered. The filtrate was concentrated and dried on vacuum to deliver a yellow solid (340 mg, 88%).

Step 3:

4D + **Prep. 1** ⟶ 

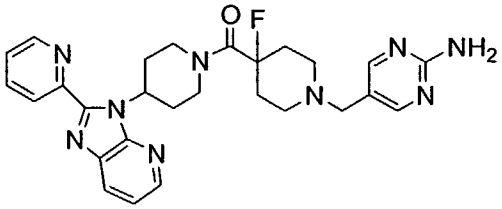
4E

To a 50 ml round-bottomed flask were successively added **4D** (287 mg, 0.88 mmol), Preparation 1 (300 mg, 0.88 mmol), EDCI hydrochloride (210 mg, 1.10 mmol), HOBT (149 mg, 1.10 mmol), and diisopropylethylamine (228 mg, 1.76 mmol). DMF (3 ml) and CH_2Cl_2 (3 ml) were introduced via a syringe. The resulting reaction mixture was stirred at 70 °C for 15 h and cooled to RT. After addition of 1 N $NaHCO_3$ solution, the resulting mixture was extracted with CH_2Cl_2. The combined organic solutions were dried over Na_2SO_4 and concentrated. Purification of the crude product by flash chromatography on silica gel with 10% CH_3OH in CH_2Cl_2 as the eluent provided **4E** as a solid (231 mg, 41%).

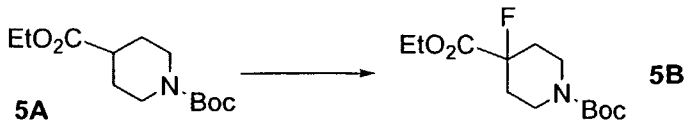
Step 4:

To a 25 ml round-bottomed flask was added **4E** (200 mg, 0.31 mmol) in CH_2Cl_2 (2.5 ml). TFA was then introduced via a syringe. The resulting solution was stirred at RT for 15 h, diluted with CH_2Cl_2, neutralized with 1.0 M NaOH solution, and separated. The organic solution was washed with water and dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified on a preparative TLC plate with 10% CH_3OH in CH_2Cl_2 as the eluent to provide the title compound as a white solid (85 mg, 50%). MS: 544 (MH^+).

Example 5



Step 1:

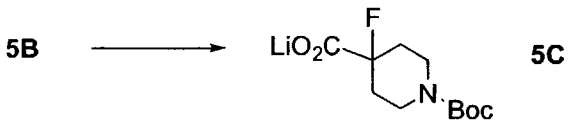


5A **5B**

A solution of compound **5A** (100g, 0.389 mol) in THF (400 ml) was added dropwise over 1.0 h to a solution of LDA (233 mL, 2.0 M in THF/heptane/ethyl-

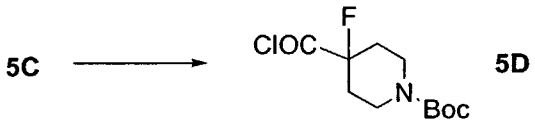
benzene, 0.466 mol) in THF (300ml) at 0 °C. The red-orange solution was stirred at 0 °C for 30 min, and then transferred by cannula to a pre-cooled (0 °C) solution of N-fluorobenzenesulfonimide (153 g, 0.485 mol) in dry THF (600 ml). The reaction mixture was stirred at 0 °C for 30 min, and then at 20 °C for 18 h. The total solvent volume was reduced to approximately one third, and EtOAc (1l) was added. The solution was washed successively with water, 0.1 N aq. HCl, saturated aq. $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield a crude liquid. Separation by flash chromatography (6:1 hexanes-EtOAc) gave compound **5B** (93.5 g, 87%).

Step 2:



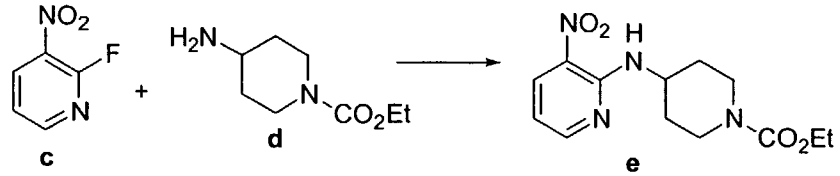
A solution of **5B** (50g, 0.181 mol) in THF (300 ml) and CH_3OH (200 ml) was treated with a solution of $LiOH-H_2O$ (9.2 g, 0.218 mol) in water (100 ml) and then heated to 45 °C for 6 h. The mixture was then concentrated and dried in vacuo to provide **5C** (45 g, 100%).

Step 3:

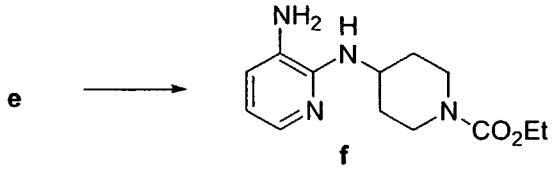


Compound **5C** (20.4 g, 0.081 mol) was added slowly to a stirred flask of CH_2Cl_2 (250 ml) at 20 °C. The resulting white slurry was cooled to 0 °C and treated slowly with oxalyl chloride (6.7 ml, 0.075 mol) and a drop of DMF. After stirring at 20 °C for 0.5 h, the mixture was concentrated and dried in vacuo to provide **5D**.

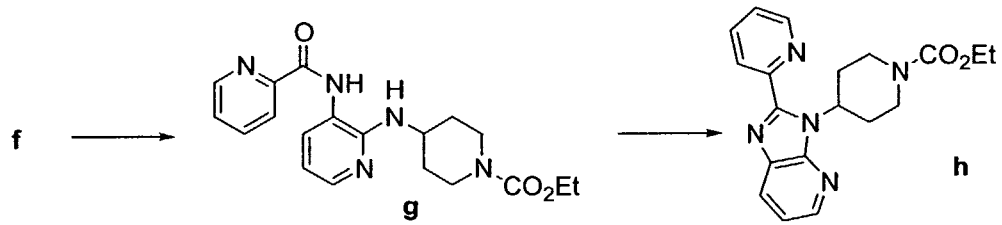
Step 4A:



A mixture of **c** (64 g, 0.40 mol), **d** (84 ml, 0.52 mol), and K_2CO_3 (66 g, 0.48 mol) in anhydrous toluene (350 ml) was heated at reflux overnight. The reaction mixture was diluted with CH_2Cl_2, washed three times with 5% aqueous NaOH, dried over Na_2SO_4, and concentrated. Recrystallization with MeOH provided **e** (121 g, ~100%) as a yellow solid.

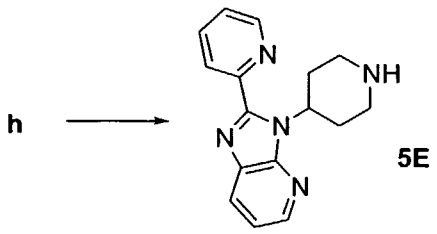


A suspension of **e** (121 g, 0.41 mol) and Raney Nickel (10 g) in EtOH (400 ml) was shaken under H_2 (40 psi) for 4 h. The mixture was filtered through a short pad of Celite (washing with CH_3OH). The filtrate was concentrated and dried in vacuo to provide **f** (109 g, ~100%) as a dark brown solid.



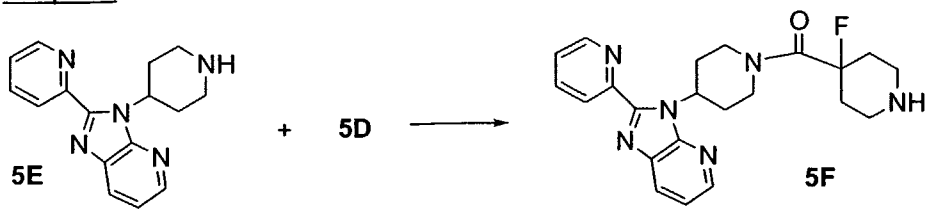
A solution of **f** (109 g, 0.41 mol) in CH_2Cl_2-DMF (1:1, 500 ml) was treated with picolinic acid (61 g, 0.50 mol), EDCI (119 g, 0.62 mol), HOBt (84 g, 0.62 mol) and iPr_2NEt (141 ml, 1.03 mol). The mixture was stirred at 70 °C for 6 h and then overnight at 20 °C. The reaction mixture was diluted with EtOAc, washed 3 times with 5% aqueous NaOH, dried over Na_2SO_4, and concentrated. Flash chromatography (0–100% EtOAc/hexane) provided **g** (131 g, 86%).

A solution of **g** (131 g, 0.36 mol) in AcOH (200 ml) was heated at 120 °C overnight. The reaction mixture was cooled, carefully basified with 5% aqueous NaOH and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated. Flash chromatography (0–80% EtOAc/hexane) provided **h** (95 g, 76%) as a yellow solid.



A solution of **h** (95 g, 0.27 mol) in anhydrous $CHCl_3$ (300 ml) was treated with iodotrimethylsilane (272 g, 1.36 mol) and heated at 70 °C for 5 h. The reaction mixture was cooled, quenched with cold 10% aqueous NaOH, and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated. Flash chromatography (2N NH_3-CH_3OH/EtOAc) provided **5E** (43 g, 57%) as a pale yellow solid.

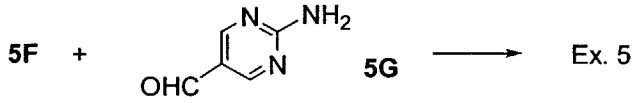
Step 4B:



A mixture of **5D** (0.075 mol) in CH_2Cl_2 (250 ml) was treated with **5E** (15 g, 0.054 mol) and iPr_2NEt (25 ml, 0.135 mol) while maintaining a temperature of 20 °C. After 1 h, the mixture was concentrated and then stirred in CH_3OH (200 ml)/CH_2Cl_2 (200 ml)/H_2O (1 ml) for 1 h at 20 °C. The solvent was then evaporated. Treatment with TFA (200 ml) in CH_2Cl_2 (250 ml) at 20 °C followed by flash chromatography (0–7% 7N NH_3-CH_3OH/CH_2Cl_2) provided **5F** (80–90% from **5C**).

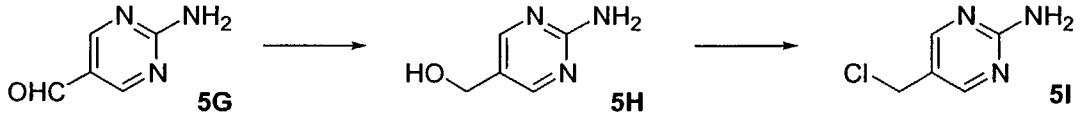
Step 5:

Method A:



A solution of **5F** (0.41 g, 1.0 mmol) in CH_2Cl_2 (20 ml) was treated with **5G** (0.31 g, 2.5 mmol, JP Patent 63227573, 1988), $NaBH(OAc)_3$ (0.53 g, 2.5 mmol) and few drops of AcOH and then stirred overnight at 20 °C. The mixture was partitioned between 10% NaOH and CH_2Cl_2. The organic layer was dried with Na_2SO_4 and concentrated. Flash chromatography (0–5% 7N NH_3-CH_3OH/CH_2Cl_2) provided the title compound (0.45g, 87%). MS: 516 (M+H).

Method B:

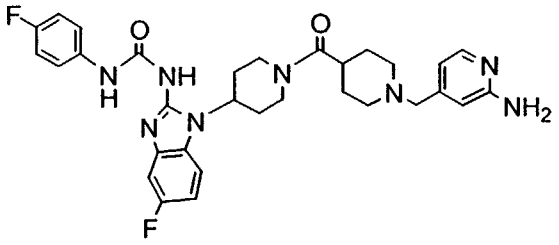


A solution of **5G** (50 g, 0.41 mol) in CH_3OH (300 ml) was cooled to 0 °C and carefully treated with $NaBH_4$ (20g, 0.53 mol in 6 batches) over 20 min. The reaction was then allowed to warm to 20 °C and was stirred for 4 h. The mixture was again cooled to 0 °C, carefully quenched with saturated aqueous NH_4Cl, and concentrated. Flash chromatography (5–10% 7N NH_3-CH_3OH/CH_2Cl_2) provided **5H** (31g, 62%) as a light yellow solid.

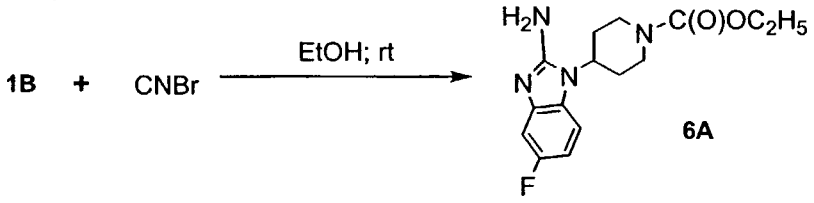
A slurry of **5H** (31 g, 0.25 mol) in CH_2Cl_2 (500 ml) was cooled to 0 °C and slowly treated with $SOCl_2$ (55ml, 0.74 mol over 30 min). The reaction was then stirred overnight at 20 °C. The material was concentrated, slurried in acetone, and then filtered. The resulting beige solid **5I** was dried overnight in vacuo (38.4g, 52%, HCl salt).

A homogeneous solution of **5F** (16.4 g, 40 mmol) in anhydrous DMF (200 ml) was cooled to 0 °C, carefully treated with NaH (8g, 200 mmol), and stirred at 20 °C for 20 min. The reaction mixture was then cooled to 0 °C, treated with NaI (6g, 40 mmol) and **5I** (14.5g, 80 mmol), and then stirred overnight at 20 °C. The reaction was diluted with CH_2Cl_2 (500 ml), washed with 1N aqueous NaOH, washed with brine, filtered through Celite, and concentrated. Flash chromatography (0–4% 7N NH_3-CH_3OH/CH_2Cl_2) provided Ex. 5 (16.9g, 82%) as a beige solid.

Example 6

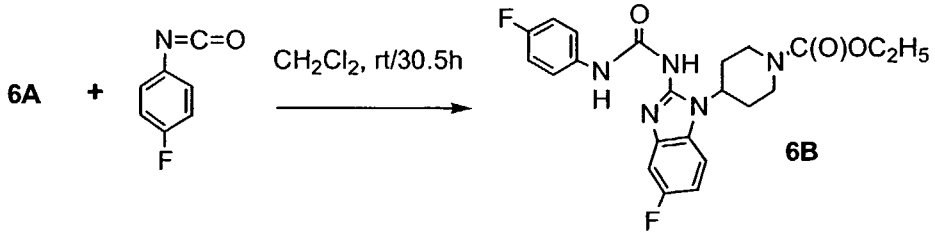


Step 1:



To a stirred solution of diamine **1B** (1.0g, 3.55 mmol) in C_2H_5OH (25 ml), at RT was added portionwise solid CNBr (564 mg; 5.33 mmol). The resultant solution was allowed to stir at RT for 5 days before removing solvent under vacuum. The residual oil was partitioned between EtOAc (30 ml) and 2M Na_2CO_3 (10 ml). The aqueous layer was adjusted to pH ~10 by addition of a few drops of 6N NaOH and was then re-extracted with EtOAc (2 x 10 ml). Combined extracts were washed with brine (5 ml) and filtered through anhydrous $MgSO_4$. The filtrate was stripped in vacuo to obtain compound **6A** as brown powder (1.03 g; 94%) sufficiently pure for use without purification. FABMS: 307 (MH^+; 100%).

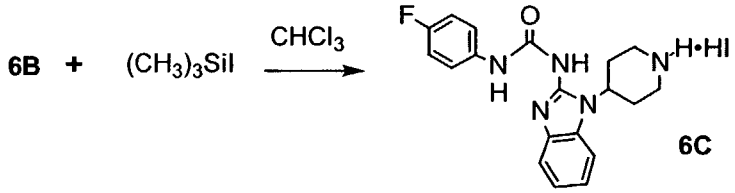
Step 2:



In a dry flask, under an inert atmosphere, a mixture of compound **6A** (369 mg; 1.20 mmol) and CH_2Cl_2 (11 ml) was stirred and sonicated until the formation of a

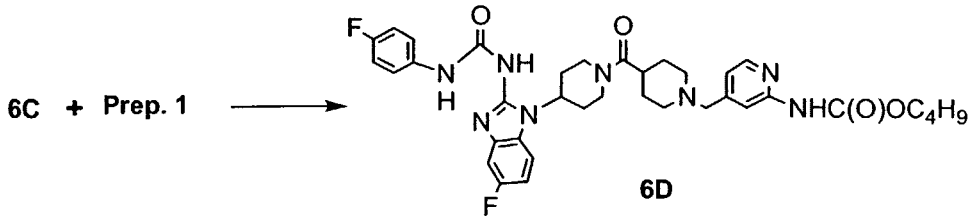
clear, amber solution to which was added via syringe 4-fluorophenyl isocyanate (158 microliters; 190 mg; 1.38 mmol). After 30.5 h at RT, a few drops of CH_3OH were added to the reaction solution, and solvent was removed under vacuum. The residual solid was dissolved in boiling Et_2O (~30 ml). Insoluble matter was filtered, and the filtrate was diluted to a volume of ~60 ml with hot hexanes. The solution was concentrated on a steam bath to a volume of ~30 ml, by which point precipitation had begun. The mixture was allowed to stand at RT for ~3 h. Filtration and washing with Et_2O-hexanes (1:1 v/v) yielded compound **6B** as a reddish-brown powder (394 mg; 74%). FABMS: 444 (MH^+; 100%). Although TLC and NMR indicated the presence of minor impurities, the product was sufficiently pure for use in Step 3 below.

Step 3:



To a stirred suspension of compound **6B** (333 mg; 0.751 mmol) in $CHCl_3$ (2 ml), contained in a flask equipped for reflux under an inert atmosphere, was added via syringe $(CH_3)_3SiI$ (214 microliters; 301 mg; 1.51 mmol). Solids dissolved rapidly to produce a dark reddish-brown solution. Stirring was continued at RT for 20 min before placing the reaction mixture in an oil bath preheated to 50 °C. After 5 h at 50 °C, a second portion of $(CH_3)_3SiI$ (54 microliters; 75 mg; 0.378 mmol) was added and heating continued at 50 °C for another 2.5 h. The reaction mixture (consisting of solid and solution phases) was removed from the heating bath and was treated with CH_3OH (2.5 ml) added in two portions. The reaction mixture was stirred and warmed to 50 °C for a few minutes, allowed to cool and was then filtered. Collected solids were washed with 1:1 (v/v) CH_3OH-EtOAc to obtain the hydriodide salt form of **6C** as a pale reddish-brown powder (356 mg) wich was used in the next step without further purification. FABMS: 372 (MH^+; 100%).

Step 4:



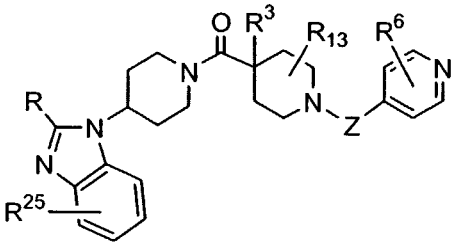
To a stirred suspension of **6C** (340 mg; 0.681 mmol), Prep. 1 (228 mg; 0.681 mmol), HOBT (9.2 mg; 0.0681 mmol) and NEt_3 (379 microliters; 275 mg; 2.72 mmol)

in DMF (13 ml) was added solid EDCI (163 mg; 0.851 mmol). The cloudy reaction mixture was placed in a preheated oil bath and was stirred at 50 °C for 30 min, after which the resultant clear, amber solution was stirred for 23.5 h at RT. A few drops of water were added, and the reaction mixture was concentrated at 60 °C under vacuum. The concentrate was partitioned between EtOAc (20 ml) and water (5 ml)-brine (2.5 ml). The aqueous phase was extracted with EtOAc (2 x 5 ml). Combined extracts were washed with brine (2.5 ml) and filtered through anhydrous $MgSO_4$. The filtrate was evaporated under vacuum, and the residue was purified by flash chromatography on silica gel, eluting with a gradient of CH_2Cl_2-CH_3OH-NH_4OH (97:3:0.5 -> 96:4:0.5). Product **6D** (222 mg; 47%) was obtained as pale yellow powder. FABMS: 689 (MH^+; ~93%); 578 (~58%); 478 (100%).

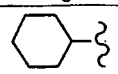
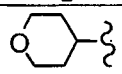
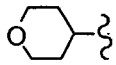
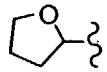
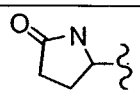
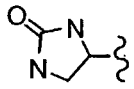
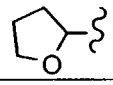
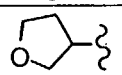
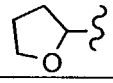
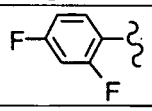
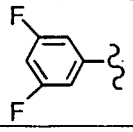
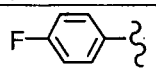
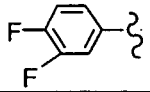
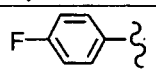
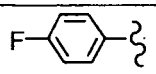
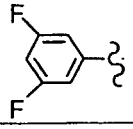
Step 5:

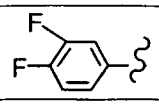
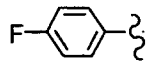
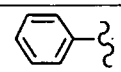
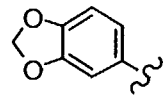
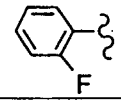
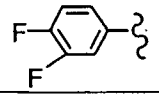
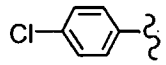
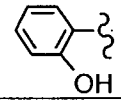
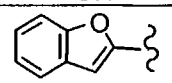
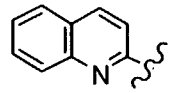
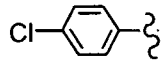
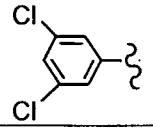
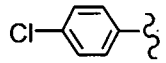
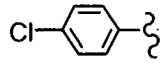
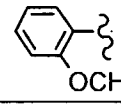
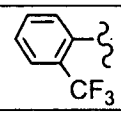
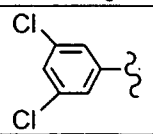
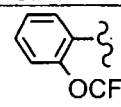
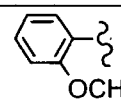
To a solution of **6D** (208 mg; 0.302 mmol) in CH_2Cl_2 (3 ml) was added TFA (928 microliters; 1.37 g; 12.1 mmol) with swirling of the flask, which was then flushed with dry N_2, sealed and allowed to stand at RT for 6 h. The reaction solution was evaporated under vacuum, and the residue was partitioned between EtOAc (20 ml) and 2M Na_2CO_3 (3 ml) plus sufficient water to produce two clear phases. The aqueous phase was extracted with EtOAc (3 x 5 ml). Combined extracts were washed with brine (3 ml) and filtered through anhydrous $MgSO_4$. The filtrate was stripped of solvent in vacuo, and the residue was subjected to flash chromatography on silica gel, eluting with CH_2Cl_2-CH_3OH-NH_4OH (97:3:0.5). The title compound (130 mg; 72%) was obtained as pale yellow powder. FABMS: 589 (MH^+; ~64%); 478 (100%).

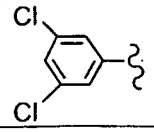
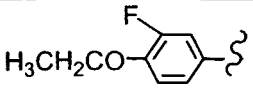
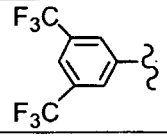
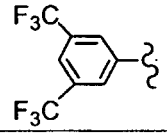
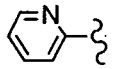
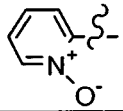
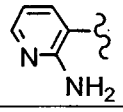
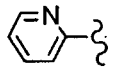
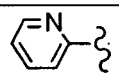
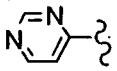
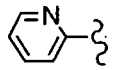
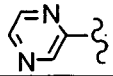
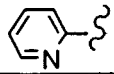
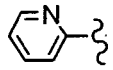
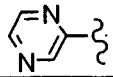
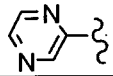
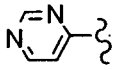
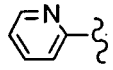
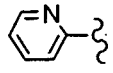
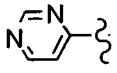
Using procedures similar to those described above, employing the appropriate starting materials, compounds in the following tables are prepared:

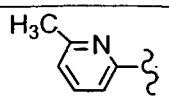
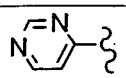
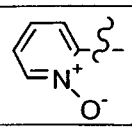
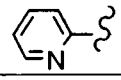
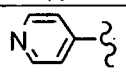
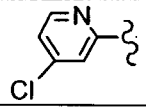
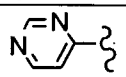
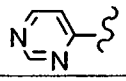
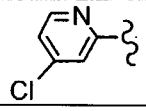
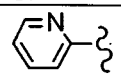
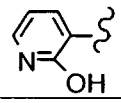
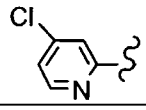
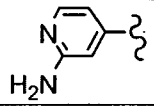
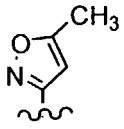
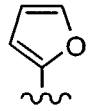
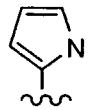
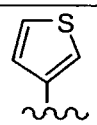
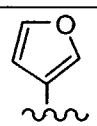


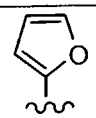
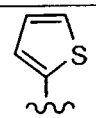
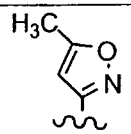
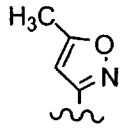
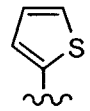
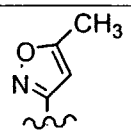
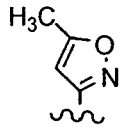
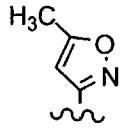
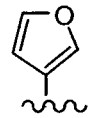
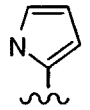
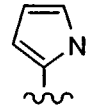
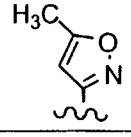
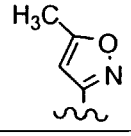
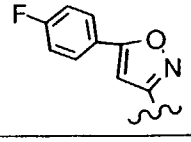
No.	R	R^{25}	R^3	R^{13}	Z	R^6	Physical Data MS (MH^+)
7	$-CH_3$	5-OCH_3	H	H	$-CH_2-$	2-NH_2	463
8	$-CH_3$	6-Cl	H	H	$-CH_2-$	2-NH_2	467
9	$-CH_3$	5-Cl	H	H	$-CH_2-$	2-NH_2	467

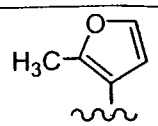
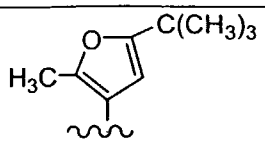
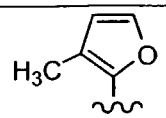
10	$-CH_3$	5-Br	H	H	$-CH_2-$	$2-NH_2$	512
11		5-Cl	H	H	$-CH_2-$	$2-NH_2$	535
12	benzyl	5-F	H	H	$-CH_2-$	$2-NH_2$	527
13	$-CH(CH_3)_2$	5-Br	H	H	$-CH_2-$	$2-NH_2$	540
14	$-CH_2NH_2$	H	H	H	$-CH_2-$	$2-NH_2$	488
15	$-CH_2NHSO_2CH_3$	H	H	H	$-CH_2-$	$2-NH_2$	526
16	$-CH_2NHC(O)CH_3$	5-Cl	H	H	$-CH_2-$	$2-NH_2$	524
17	$-CH_2OCH_3$	5-F	H	H	$-CH_2-$	$2-NH_2$	481
18	$-CH_2NH_2$	5-Cl	H	H	$-CH_2-$	$2-NH_2$	482
19	$-CH_2OCH_3$	6,7-di-F	H	H	$-CH_2-$	$2-NH_2$	499
20		6-F	H	H	$-CH_2-$	$2-NH_2$	521
21		5-F	H	H	$-CH_2-$	$2-NH_2$	521
22		6-F	H	H	$-CH_2-$	$2-NH_2$	507
23		5-F	H	H	$-CH_2-$	$2-NH_2$	520
24		5-F	H	H	$-CH_2-$	$2-NH_2$	521
25		5-Br	H	H	$-CH_2-$	$2-NH_2$	568
26		5-F	H	H	$-CH_2-$	$2-NH_2$	507
27		5-F	H	H	$-CH_2-$	$2-NH_2$	507
28		H	H	H	$-CH_2-$	$2-NH_2$	531
29		5-F	H	H	$-CH_2-$	$2-NH_2$	549
30		6-F	H	H	$-CH_2-$	$2-NH_2$	531
31		6,7-di-F	H	H	$-CH_2-$	$2-NH_2$	567
32		6-Cl	H	H	$-CH_2-$	$2-NH_2$	547
33		5-F	H	H	$-CH_2-$	$2-NH_2$	531
34		5-Cl	H	H	$-CH_2-$	$2-NH_2$	565

35		H	H	H	$-CH_2-$	$2-NH_2$	531
36		5-Cl	H	H	$-CH_2-$	$2-NH_2$	547
37		5-Cl	H	H	$-CH_2-$	$2-NH_2$	529
38		6-F	H	H	$-CH_2-$	$2-NH_2$	557
39		5-Br	H	H	$-CH_2-$	$2-NH_2$	592
40		5-Br	H	H	$-CH_2-$	$2-NH_2$	610
41		5-F	H	H	$-CH_2-$	$2-NH_2$	547
42		5-F	H	H	$-CH_2-$	$2-NH_2$	529
43		6-F	H	H	$-CH_2-$	$2-NH_2$	553
44		6-F	H	H	$-CH_2-$	$2-NH_2$	564
45		H	H	H	$-CH_2-$	$2-NH_2$	529
46		5-F	H	H	$-CH_2-$	$2-NH_2$	581
47		5-Cl	H	H	$-CH_2-$	$2-NH_2$	563
48		6-Cl	H	H	$-CH_2-$	$2-NH_2$	563
49		5-F	H	H	$-CH_2-$	$2-NH_2$	543
50		5-F	H	H	$-CH_2-$	$2-NH_2$	581
51		5-Cl	H	H	$-CH_2-$	$2-NH_2$	597
52		5-F	H	H	$-CH_2-$	$2-NH_2$	597
53		5-Br	H	H	$-CH_2-$	$2-NH_2$	604

54		6-Cl	H	H	$-CH_2-$	$2-NH_2$	597
55		$5-CH_3$	H	H	$-CH_2-$	$2-NH_2$	571
56		5-Cl	H	H	$-CH_2-$	$2-NH_2$	665
57		5-Br	H	H	$-CH_2-$	$2-NH_2$	710
58		6-ethoxy	H	H	$-CH_2-$	$2-NH_2$	540
59		5-Cl	H	H	$-CH_2-$	$2-NH_2$	546
60		H	H	H	$-CH_2-$	$2-NH_2$	511
61		5-F	H	H	$-CH_2-$	H	499
62		6-Cl	H	H	$-CH_2-$	$2-NH_2$	530
63		5-F	H	H	$-CH_2-$	$2-NH_2$	515
64		6-F	H	H	$-CH_2-$	$2-NH_2$	514
65		6-F	H	H	$-CH_2-$	$2-NH_2$	515
66		7-Cl	H	H	$-CH_2-$	$2-NH_2$	531
67		H	H	H	$-CH_2-$	$2-NH_2$	496
68		5-F	H	H	$-CH_2-$	$2-NH_2$	515
69		5-Cl	H	H	$-CH_2-$	$2-NH_2$	531
70		5-Cl	H	H	$-CH_2-$	$2-NH_2$	531
71		5,6-di-F	H	H	$-CH_2-$	$2-NH_2$	532
72		5-Br	H	H	$-CH_2-$	$2-NH_2$	575
73		6-ethoxy	H	H	$-CH_2-$	$2-NH_2$	541

74		5-F	H	H	$-CH_2-$	$2-NH_2$	528
75		6-F	H	H	$-CH_2-$	$2-NH_2$	515
76		5-Br	H	H	$-CH_2-$	$2-NH_2$	591
77		5-Cl	H	H	$-CH_2-$	$2-NH_2$	530
78		5-Cl	H	H	$-CH_2-$	$2-NH_2$	530
79		5-F	H	H	$-CH_2-$	$2-NH_2$	548
80		$5-CF_3$	H	H	$-CH_2-$	$2-NH_2$	565
81		H	H	H	$-CH_2-$	$2-NH_2$	497
82		6,7-di-F	H	H	$-CH_2-$	$2-NH_2$	567
83		6,7-di-F	H	H	$-CH_2-$	$2-NH_2$	532
84		5-F	H	H	$-CH_2-$	$2-NH_2$	530
85		$5-CF_3$,7-F	H	H	$-CH_2-$	$2-NH_2$	617
86		5-F	H	H	$-CH_2-$	$2-NH_2$	529
87		H	H	H	$-CH_2-$	$2-NH_2$	500
88		H	H	H	$-CH_2-$	$2-NH_2$	485
89		H	H	H	$-CH_2-$	$2-NH_2$	489
90		6-F	H	H	$-CH_2-$	$2-NH_2$	514
91		6-F	H	H	$-CH_2-$	$2-NH_2$	503

92		5-F	H	H	$-CH_2-$	$2-NH_2$	503
93		H	H	H	$-CH_2-$	$2-NH_2$	501
94		5-F	H	H	$-CH_2-$	$2-NH_2$	518
95		5-Cl	H	H	$-CH_2-$	$2-NH_2$	534
96		5-F	H	H	$-CH_2-$	$2-NH_2$	519
97		6,7-di-F	H	H	$-CH_2-$	$2-NH_2$	536
98		5-Br	H	H	$-CH_2-$	$2-NH_2$	579
99		6-ethoxy	H	H	$-CH_2-$	$2-NH_2$	544
100		5-F	H	H	$-CH_2-$	$2-NH_2$	503
101		5-Br	H	H	$-CH_2-$	$2-NH_2$	563
102		5-F	H	H	$-CH_2-$	$2-NH_2$	502
103		$5-CF_3$	H	H	$-CH_2-$	$2-NH_2$	568
104		$5-CF_3$,7-F	H	H	$-CH_2-$	$2-NH_2$	586
105		5-F	H	H	$-CH_2-$	$2-NH_2$	598

106		5-F	H	H	-CH_2-	2-NH_2	517
107		5-F	H	H	-CH_2-	2-NH_2	573
108		5-F	H	H	-CH_2-	2-NH_2	517
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110	CH_3-CH_2-S-	5-F	H	H	-CH_2-	2-NH_2	497
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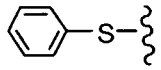
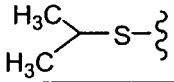
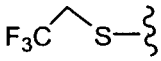
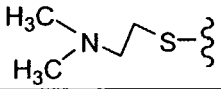
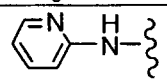
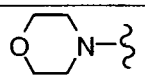
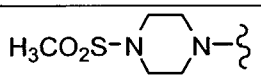
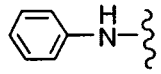
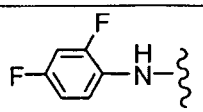
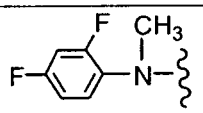
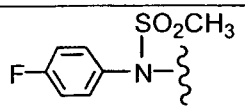
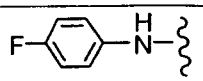
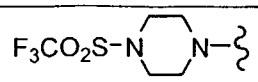
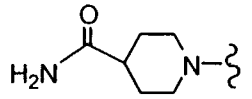
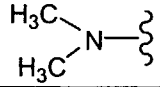
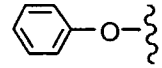
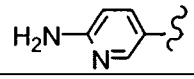
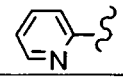
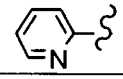
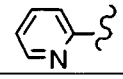
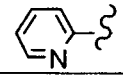
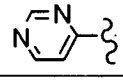
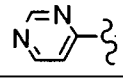
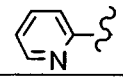
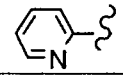
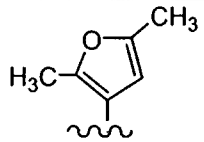
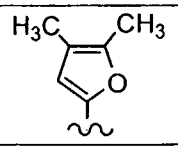
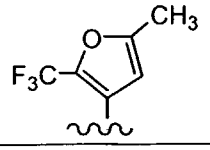
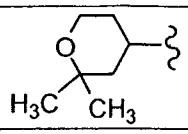
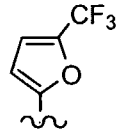
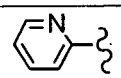
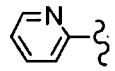
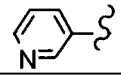
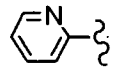
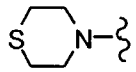
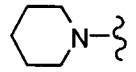
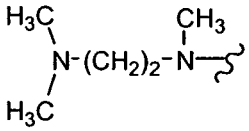
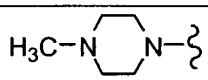
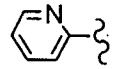
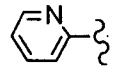
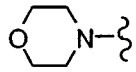
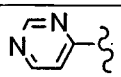
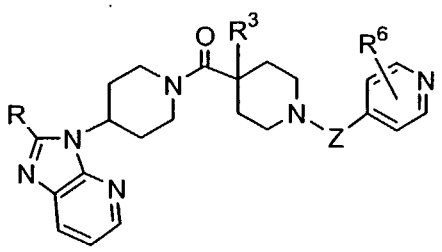
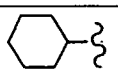
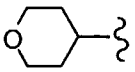
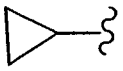
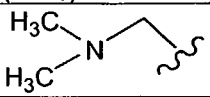
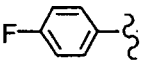
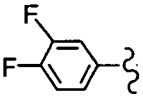
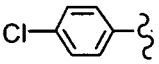
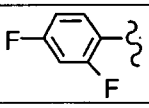
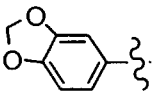
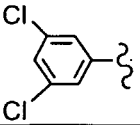
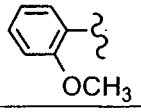
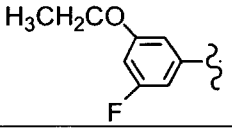
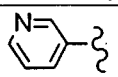
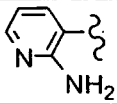
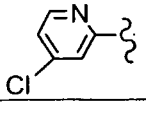
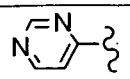
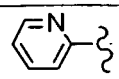
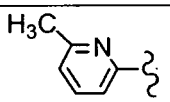
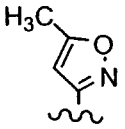
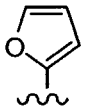
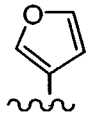
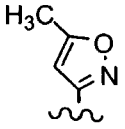
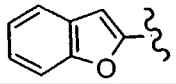
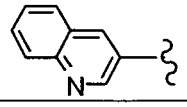
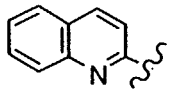
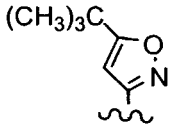
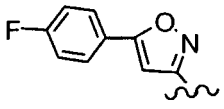
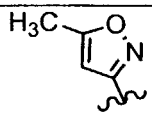
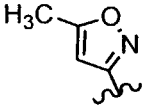
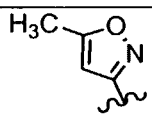
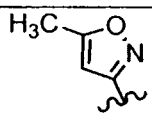
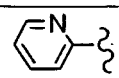
112		5-F	H	H	-CH_2-	2-NH_2	545
113		5-F	H	H	-CH_2-	2-NH_2	511
114		5-F	H	H	-CH_2-	2-NH_2	551
115		5-F	H	H	-CH_2-	2-NH_2	540
116	HS-	5-F	H	H	-CH_2-	2-NH_2	469
117	CH_3-S-	5-F	H	2-CH_3	-CH_2-	2-NH_2	497
118	CH_3-S-	5-F	F	H	-CH_2-	2-NH_2	501
119		5-F	H	H	-CH_2-	2-NH_2	529
120		5-F	H	H	-CH_2-	2-NH_2	522
121		5-F	H	H	-CH_2-	2-NH_2	599
123		5-F	H	H	-CH_2-	2-NH_2	528
124		5-F	H	H	-CH_2-	2-NH_2	564
125		5-F	H	H	-CH_2-	2-NH_2	578
126		5-F	H	H	-CH_2-	2-NH_2	624
127		5-F	H	H	-CH_2-	2-NH_2	546

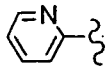
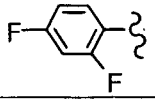
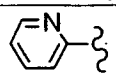
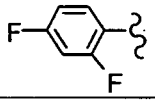
128		5-F	H	H	$-CH_2-$	$2-NH_2$	653
129	$CH_3-O-(CH_2)_2-NH-$	5-F	H	H	$-CH_2-$	$2-NH_2$	510
130		5-F	H	H	$-CH_2-$	$2-NH_2$	563
131		5-F	H	H	$-CH_2-$	$2-NH_2$	480
132	CH_3-O-	5-F	H	H	$-CH_2-$	$2-NH_2$	467
133	CH_3-CH_2-O-	5-F	H	H	$-CH_2-$	$2-NH_2$	481
134	$CH_3-O-(CH_2)_2-O-$	5-F	H	H	$-CH_2-$	$2-NH_2$	511
135	$(CH_3)_2-CH-O-$	5-F	H	H	$-CH_2-$	$2-NH_2$	495
136		5-F	H	H	$-CH_2-$	$2-NH_2$	529
137		H	H	H	$-CH_2-$	$2-NH_2$	511
138		$5-CF_3,7-F$	H	H	$-CH_2-$	$2-NH_2$	582
139		5-F	H	H		$2-NH_2$	528
140		5-F	F	H	$-CH_2-$	$2-NH_2$	532
141		5-F	OH	H	$-CH_2-$	$2-NH_2$	530
142		5-F	H	H		$2-NH_2$	529
143		5-F	H	H		$2-NH_2$	529
144		5-F	$-CH_3$	H	$-CH_2-$	$2-NH_2$	528
145		6-F	H	H		$2-NH_2$	528
146	H	5-F	H	H	$-CH_2-$	$2-NH_2$	437
147		5-F	H	H	$-CH_2-$	$2-NH_2$	531
148		5-F	H	H	$-CH_2-$	$2-NH_2$	531
149		5-F	H	H	$-CH_2-$	$2-NH_2$	585

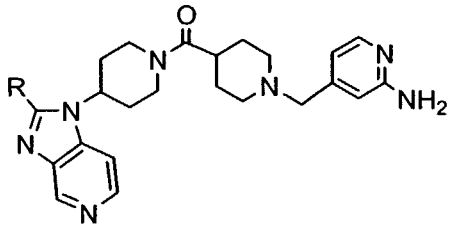
150		5-F	H	H	$-CH_2-$	$2-NH_2$	549
151		5-F	H	H	$-CH_2-$	$2-NH_2$	571
152		H	F	H	$-CH_2-$	$2-NH_2$	514
153	$(CH_3)_2N-(CH_2)_2-NH-$	5-F	H	H	$-CH_2-$	$2-NH_2$	523
154	CH_3-S-	5-F	H	H	$-\overset{CH_3}{\overset{\vert}{CH}}-$	$2-NH_2$	497
155		5-F	H	2-CH_3	$-CH_2-$	$2-NH_2$	528
156		5-F	H	H	$-CH_2-$	$2-NH_2$	514
157		5-F	H	H	$-CH_2-$	$3-NH_2$	514
158		5-F	H	H	$-CH_2-$	$2-NH_2$	589
159		5-F	H	H	$-CH_2-$	$2-NH_2$	520
160	CH_3CH_2O-	5-F	F	H	$-CH_2-$	$2-NH_2$	499
161		5-F	H	H	$-CH_2-$	$2-NH_2$	537
162		5-F	H	H	$-CH_2-$	$2-NH_2$	535
163		5-F	H	5-OH	$-CH_2-$	$2-NH_2$	530
164		5-F	F	H	$-CH_2-$	$3-NH_2$	532
165		5-F	F	H	$-CH_2-$	$2-NH_2$	540
166		5-F	H	H	$-CH_2-$	$3-NH_2$	515



No.	R	R^3	Z	R^6	Physical Data MS (MH^+)
167		H	$-CH_2-$	2-NH_2	502
168	$-CH_2OCH_3$	H	$-CH_2-$	2-NH_2	464
169		H	$-CH_2-$	2-NH_2	504
170		H	$-CH_2-$	2-NH_2	460
171	$(CH_3)_2$-CH-	H	$-CH_2-$	2-NH_2	462
172		H	$-CH_2-$	2-NH_2	477
173		H	$-CH_2-$	2-NH_2	514
174		H	$-CH_2-$	2-NH_2	532
175		H	$-CH_2-$	2-NH_2	530
176		H	$-CH_2-$	2-NH_2	532
177		H	$-CH_2-$	2-NH_2	540
178		H	$-CH_2-$	2-NH_2	564
179		H	$-CH_2-$	2-NH_2	526
180		H	$-CH_2-$	2-NH_2	558
181		H	$-CH_2-$	2-NH_2	497
182		H	$-CH_2-$	2-NH_2	512
183		H	$-CH_2-$	2-NH_2	531

184		H	$-CH_2-$	$2-NH_2$	498
185		H	$-CH_2-$	$2-NH_2$	497
186		H	$-CH_2-$	$2-NH_2$	511
187		H	$-CH_2-$	$3-NH_2$	501
188		H	$-CH_2-$	$2-NH_2$	486
189		H	$-CH_2-$	$2-NH_2$	486
190		H	$-CH_2-$	$2-NH_2$	501
191		H	$-CH_2-$	$2-NH_2$	536
192		H	$-CH_2-$	$2-NH_2$	547
193		H	$-CH_2-$	$2-NH_2$	547
194		H	$-CH_2-$	$2-NH_2$	543
195		H	$-CH_2-$	$2-NH_2$	581
196		F	$-CH_2-$	$2-NH_2$	519
197		H	$-\overset{CH_3}{\overset{\vert}{CH}}-$	$2-NH_2$	515
198		OH	$-CH_2-$	$2-NH_2$	517
199			$-CH_2-$	$2-NH_2$	577
200		F	$-CH_2-$	$2-NH_2$	515

201		F	$-CH_2-$	$2-NH_2$	504
202		H	$-CH_2-$	$3-NH_2$	497
203		H	$-CH_2-$	$3-NH_2$	532
204		F	$-CH_2-$	$3-NH_2$	515
205		F	$-CH_2-$	$3-NH_2$	550



No.	R	Physical Data MS (MH^+)
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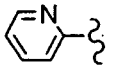
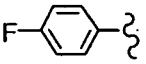
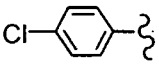
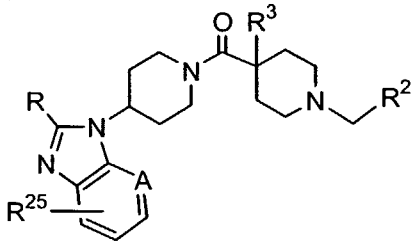
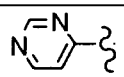
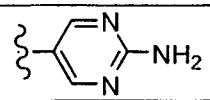
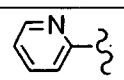
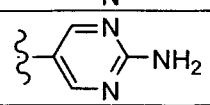
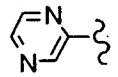
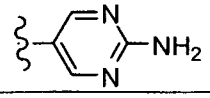
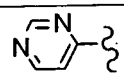
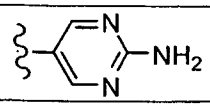
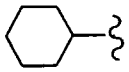
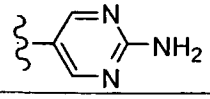
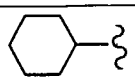
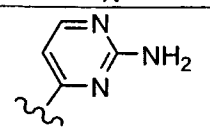
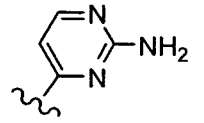
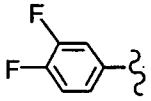
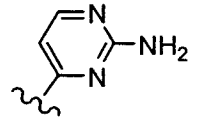
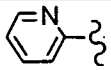
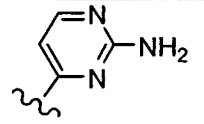
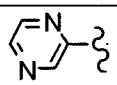
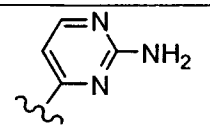
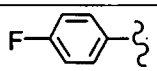
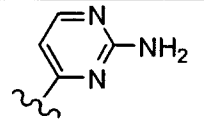
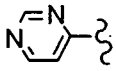
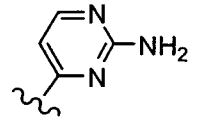
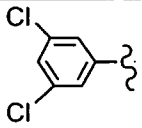
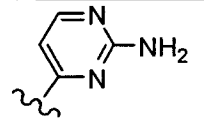
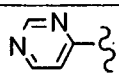
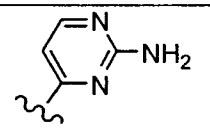
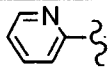
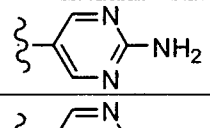
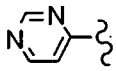
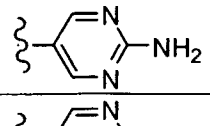
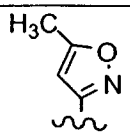
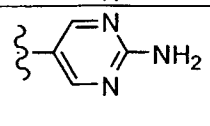
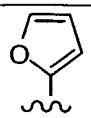
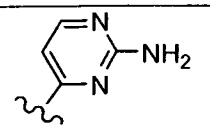
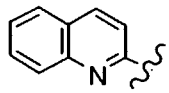
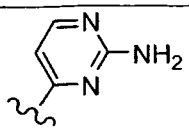
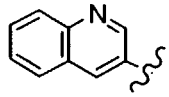
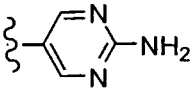
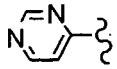
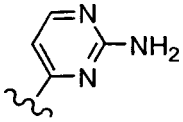
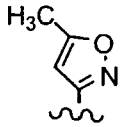
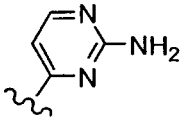
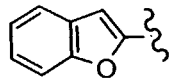
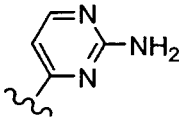
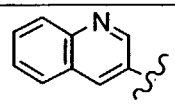
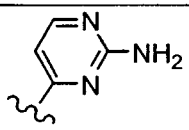
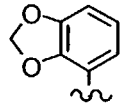
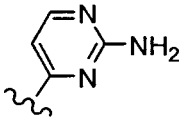
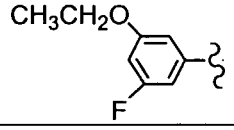
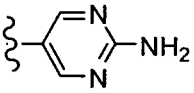
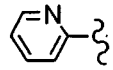
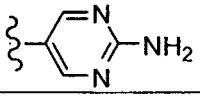
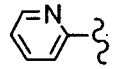
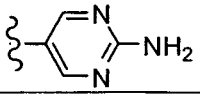
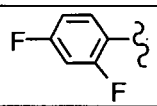
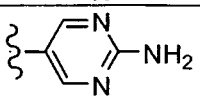
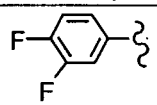
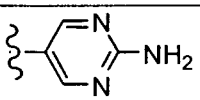
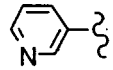
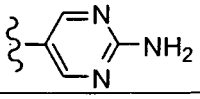
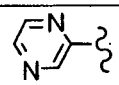
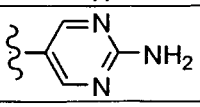
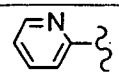
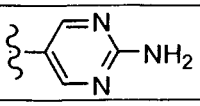
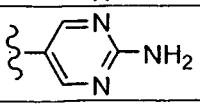
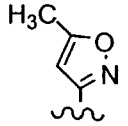
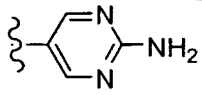
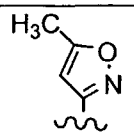
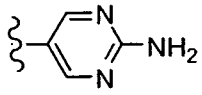
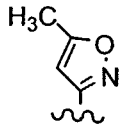
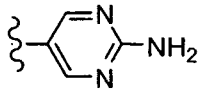
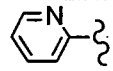
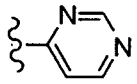
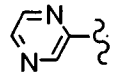
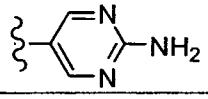
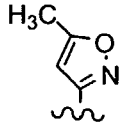
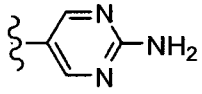
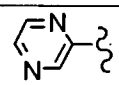
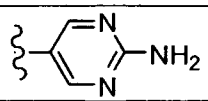
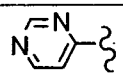
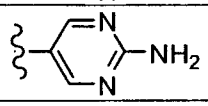
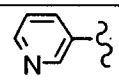
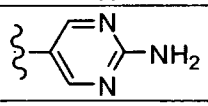
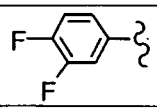
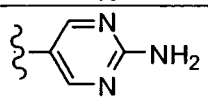
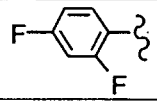
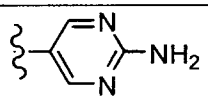
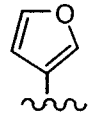
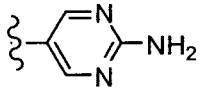
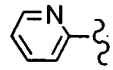
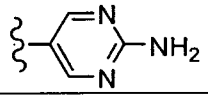
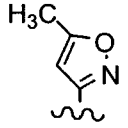
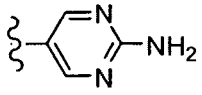
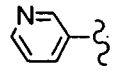
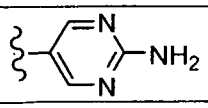
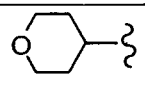
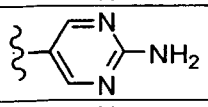
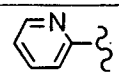
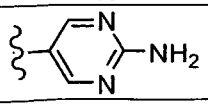
207		497
208		514
209		530

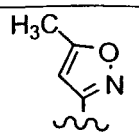
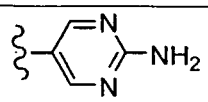
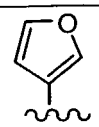
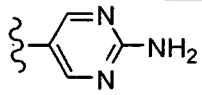
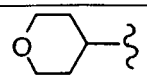
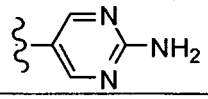
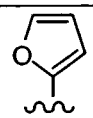
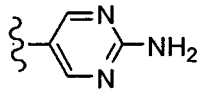
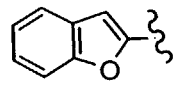
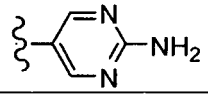
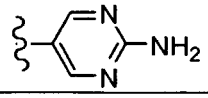
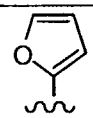
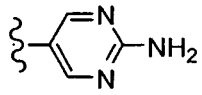
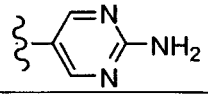
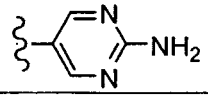
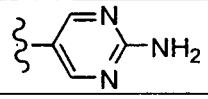
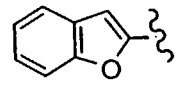
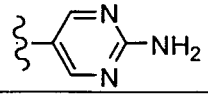
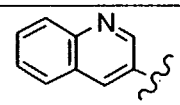
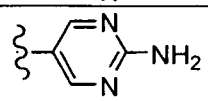
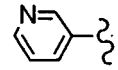
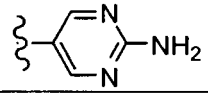
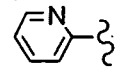
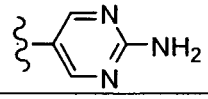
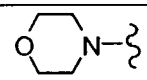
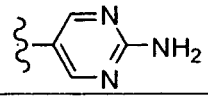
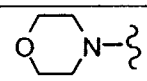
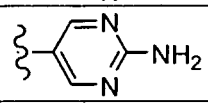
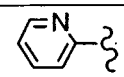
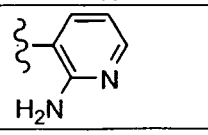


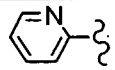
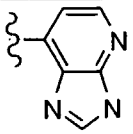
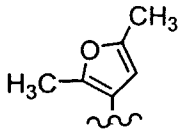
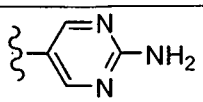
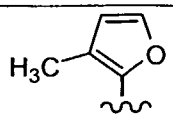
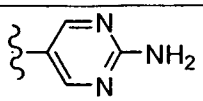
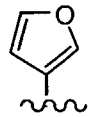
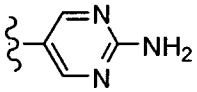
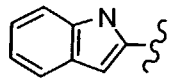
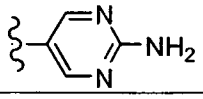
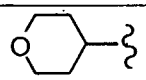
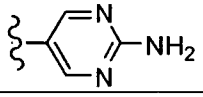
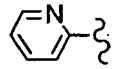
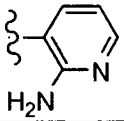
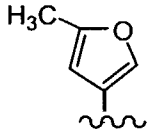
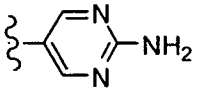
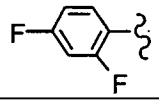
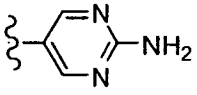
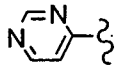
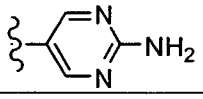
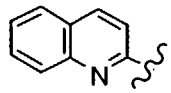
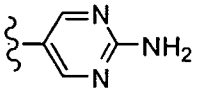
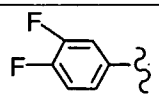
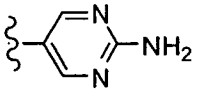
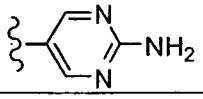
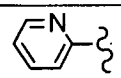
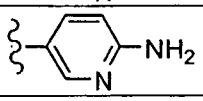
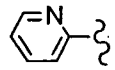
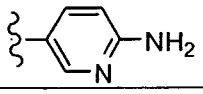
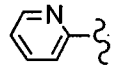
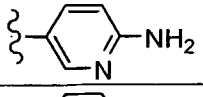
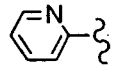
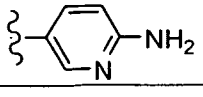
No.	R	R^{25}	A	R^3	R^2	Physical Data MS (MH^+)
210		5-Cl	C	H		532
211		5-F	C	H		515
212		5-Cl	C	H		532

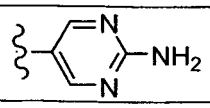
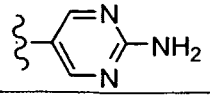
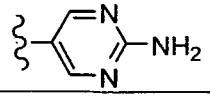
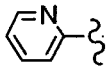
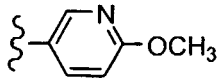
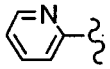
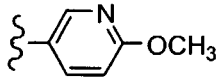
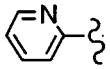
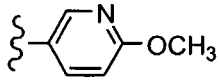
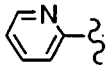
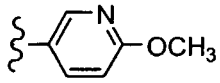
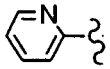
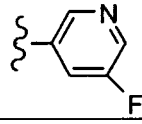
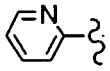
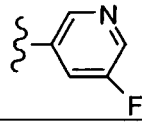
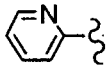
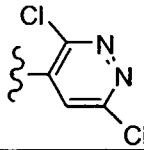
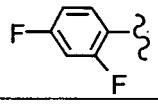
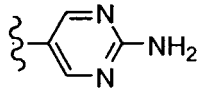
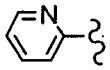
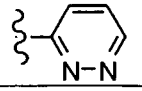
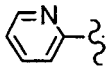
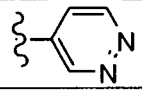
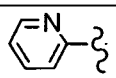
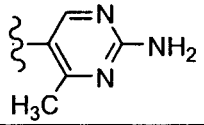
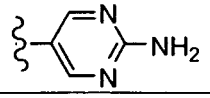
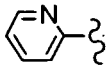
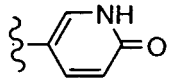
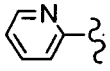
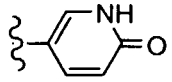
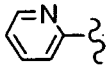
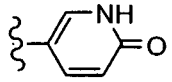
213		5-F	C	H		516
214		H	N	H		503
215		H	N	H		503
216	$(CH_3)_2CH$-	H	N	H		463
217		5-F	C	H		550
218		5-F	C	H		515
219		5-Cl	C	H		532
220		6-Cl	C	H		548
221		5-F	C	H		516
222		6-Cl	C	H		600
223		5-Cl	C	H		532
224		6-F	C	H		515
225		H	N	H		499
226		H	N	H		502
227		H	N	H		487

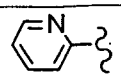
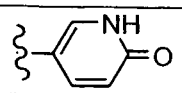
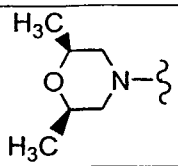
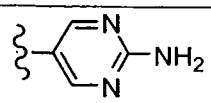
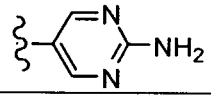
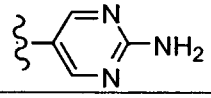
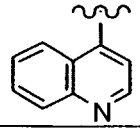
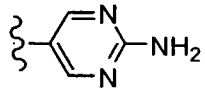
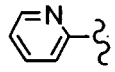
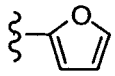
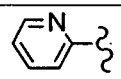
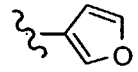
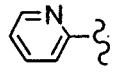
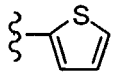
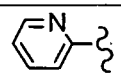
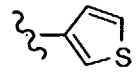
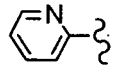
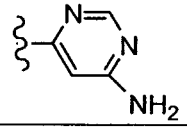
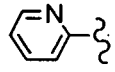
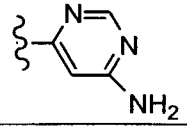
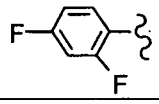
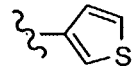
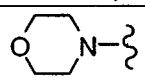
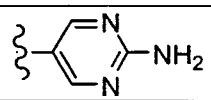
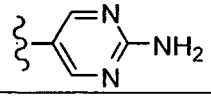
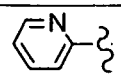
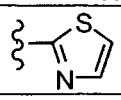
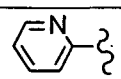
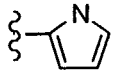
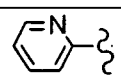
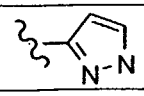
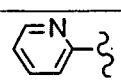
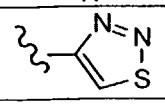
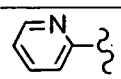
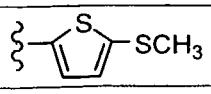
228		H	N	H		548
229		H	N	H		548
230		H	N	H		499
231		H	N	H		502
232		H	N	H		537
233		H	N	H		548
234		H	N	H		541
235		H	N	H		559
236		H	N	H		498
237		5-F	C	F		533
238		5-F	C	H		550
239		5-F	C	H		550
240		5-F	C	H		515
241		5-F	C	H		516
242		H	C	H		497
243	$(CH_3)_2N\text{-}CH_2\text{-}$	H	N	H		478

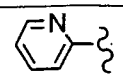
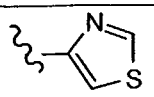
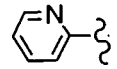
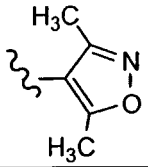
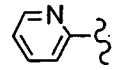
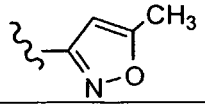
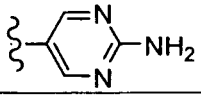
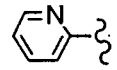
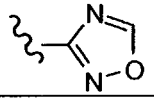
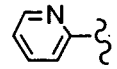
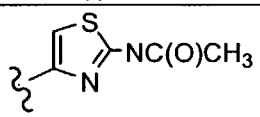
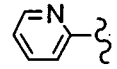
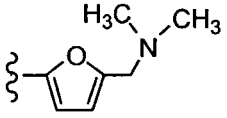
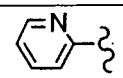
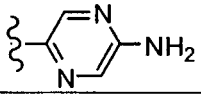
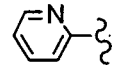
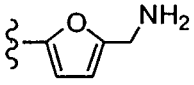
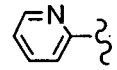
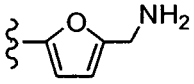
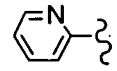
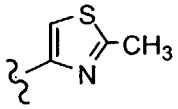
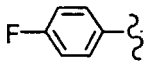
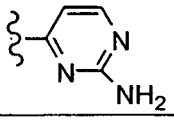
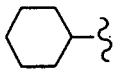
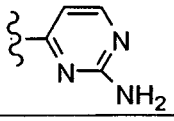
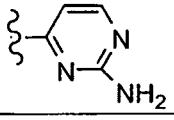
244		5-F	C	H		519
245		H	C	H		501
246		5,6-di-F	C	H		537
247		5-F	C	H		500
248		5,6-di-F	C	H		534
249		5-F	C	F		537
250		5-F	C	F		534
251		5-F	C	F		534
252		5-F	C	F		533
253		5-F	C	F		568
254		5-F	C	F		568
255		H	N	H		487
256		H	C	F		515
257		H	C	F		519
258		H	N	F		516
259		H	N	H		505
260		H	N	F		516

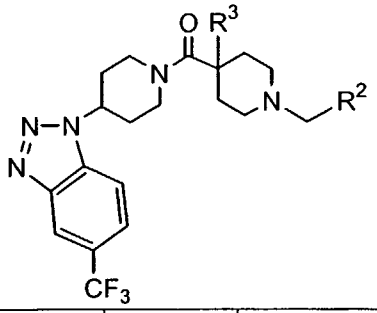
261		H	N	F		520
262		5-F	C	H		504
263		5-F	C	H		522
264		5-F	C	H		504
265		H	N	H		537
266	$(CH_3)_2N-CH_2-$	H	N	F		496
267		H	N	F		505
268	CH_3CH_2-O-	5-F	C	H		482
269	CH_3-S-	5-F	C	H		484
270	CH_3CH_2-O-	5-F	C	F		500
271		H	N	F		555
272		H	N	F		566
273		H	N	H		498
274		5,6-di-F	C	F		551
275		5-F	C	F		541
276		5-F	C	H		523
277		5-F	C	H		514

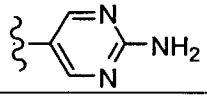
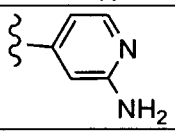
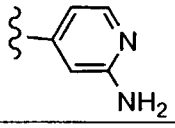
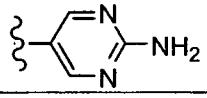
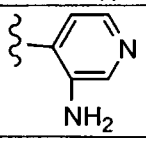
278		5-F	C	H		539
279		H	N	H		515
280		H	N	H		501
281		H	N	F		505
282		H	N	H		536
283		H	N	F		523
284		5-F	C	F		532
285		H	N	H		501
286		H	N	H		533
287		H	N	F		517
288		H	N	H		548
289		H	N	H		533
290	CH_3S-	5-F	C	F		502
291		H	N	F		515
292		5-F	C	F		532
293		5-F	C	H		514
294		H	N	H		497

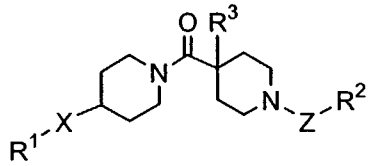
295	$(CH_3)_2N$-	5-F	C	F		499
296	CH_3CH_2-S-	5-F	C	F		516
297	CH_3-O-	5-F	C	F		486
298		H	N	H		512
299		H	N	F		530
300		5-F	C	F		547
301		5-F	C	H		529
302		5-F	C	H		517
303		5-F	C	F		535
304		H	N	H		551
305		H	N	F		551
306		5-F	C	H		500
307		5-F	C	H		500
308		5-F	C	F		547
309	$(CH_3CH_2)_2N$-	5-F	C	F		527
310		H	N	H		498
311		H	N	F		516
312		5-F	C	H		515

313		5-F	C	F		533
314		5-F	C	F		569
315	CH_3-S-	H	N	F		485
316	CH_3CH_2-O-	H	N	F		483
317		H	N	F		566
318		H	N	F		489
319		H	N	F		489
320		H	N	F		505
321		H	N	F		505
322		5-F	C	F		533
323		H	N	F		516
325		H	N	F		540
325		H	N	F		524
326	$(CH_3)_2CH$-O-	5-F	C	F		514
327		H	N	F		506
328		H	N	F		488
329		H	N	F		489
330		H	N	F		507
331		H	N	F		551

332		H	N	F		506
333		H	N	F		518
334		H	N	F		504
335	CH_3-O-	H	N	F		464
336		H	N	F		491
337		H	N	F		563
338		5-F	C	H		545
339		5-F	C	F		533
340		H	N	F		518
341		5-F	C	H		535
342		H	N	F		520
343		6-Cl	C	H		548
345		H	N	H		503
346	$(CH_3)_2$-CH-	H	N	H		463



No.	R^3	R^2	Physical Data MS (MH^+)
347	H		489
348	F		506
349	F		488
350	F		507
351	F		506



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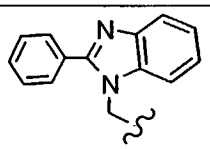
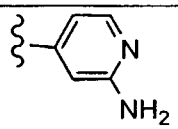
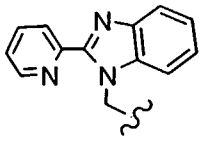
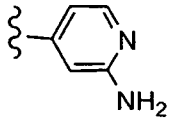
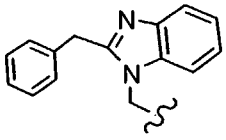
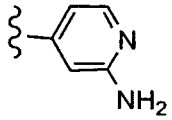
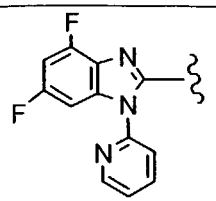
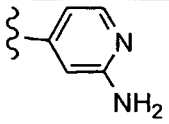
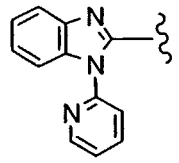
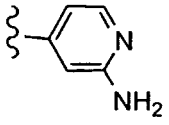
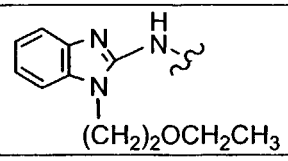
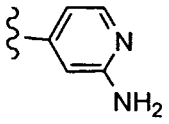
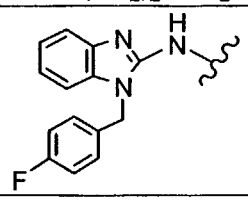
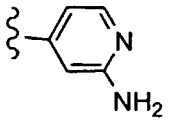
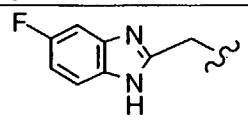
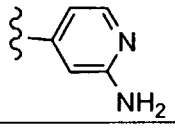
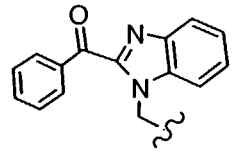
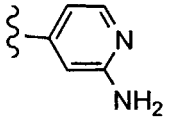
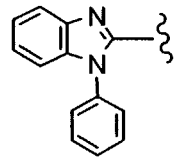
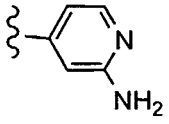
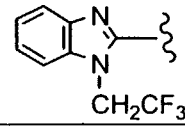
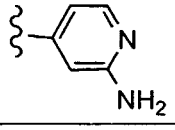
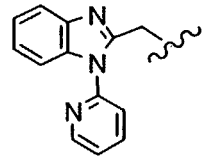
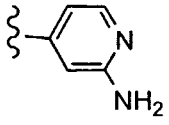
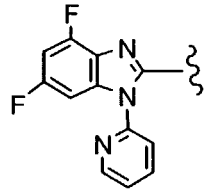
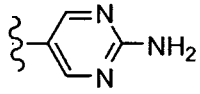
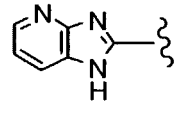
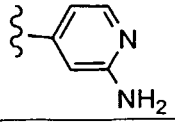
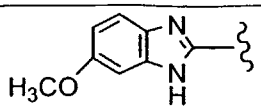
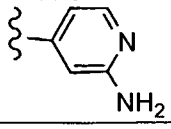
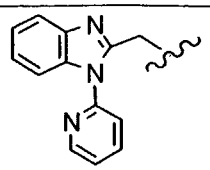
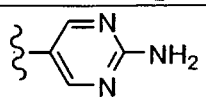
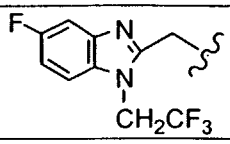
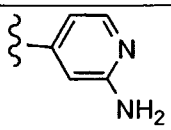
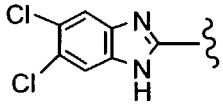
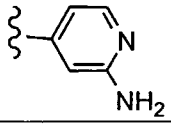
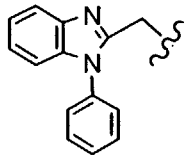
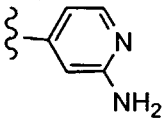
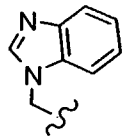
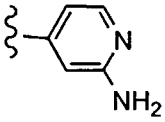
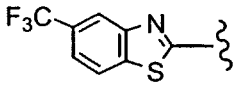
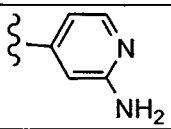
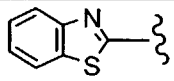
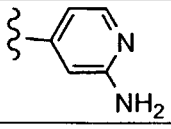
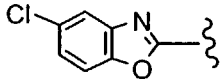
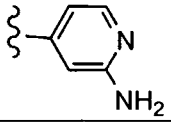
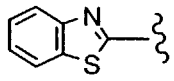
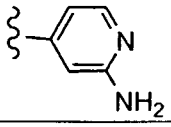
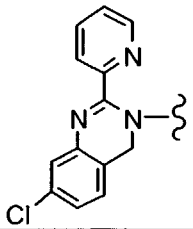
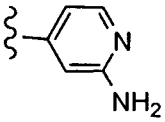
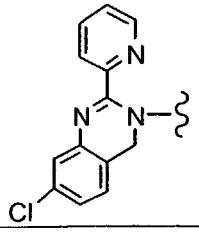
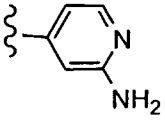
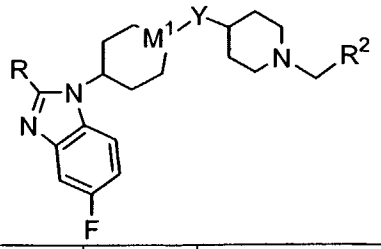
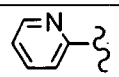
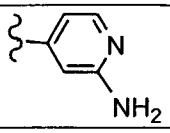
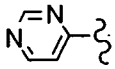
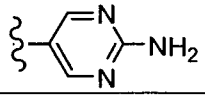
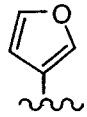
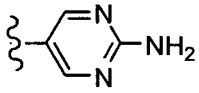
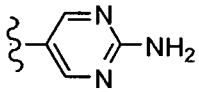
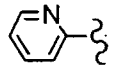
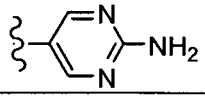
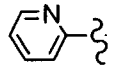
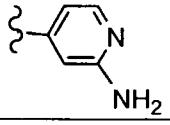
352		$-CH_2-$	H		509
353		$-CH_2-$	H		510
354		$-CH_2-$	H		523

355		-CH_2-	H		532
356		-CH_2-	H		496
357		-CH_2-	H		506
358		-CH_2-	H		542
359		-CH_2-	H		451
360		-CH_2-	H		537
361		-CH_2-	H		495
362		-CH_2-	H		501
363		-CH_2-	H		510
364		-CH_2-	H		533
365		-CH_2-	H		420

366		-CH_2-	H		449
367		-CH_2-	H		497
368		-CH_2-	H		533
369		-CH_2-	H		487
370		-CH_2-	H		509
371		-CH_2-	H		433
372		-CH_2-	H		504
373		-CH_2-	H		436
374		-CH_2-	H		472
375		-$(CH_2)_3$-	H		464
376		-CH_2-	H		544
377		-CH_2-	F		562



No.	R	M^1	Y	R^2	Physical Data MS (MH^+)
378		CH	$-CH_2-$		500
379		N	-NH-		502
380		N	-NH-		490
381		N	-NH-		494
382		N	-NH-		501
383		N	-NH-		500

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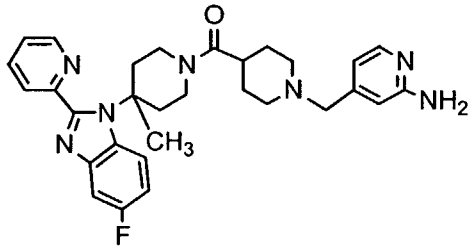
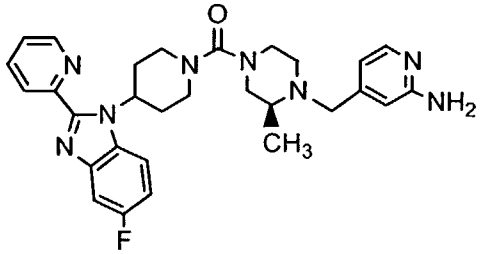


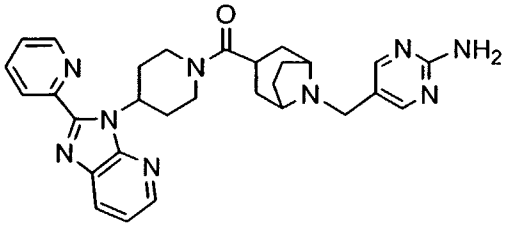
MS: 528 (MH^+)

385:



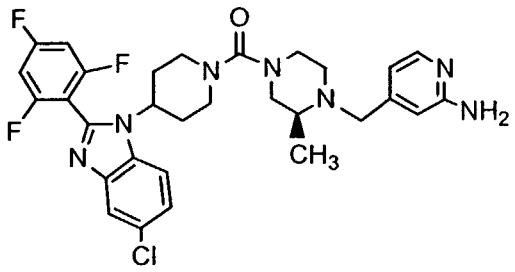
MS 385 (MH^+)

386:



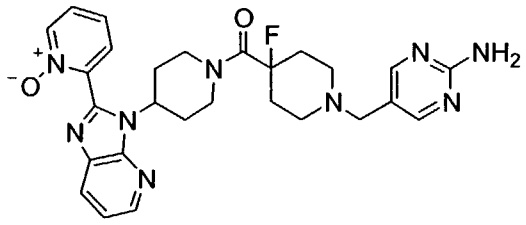
MS 529 (MH+)

387:

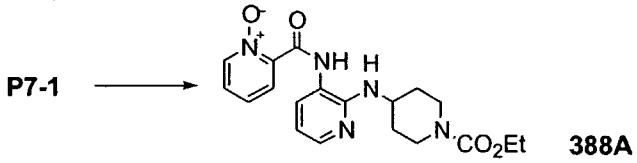


MS 583 (MH^+)

Example 388

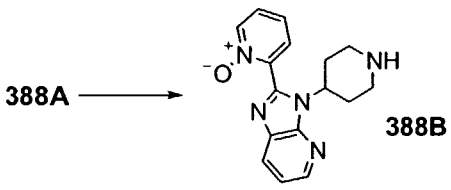


Step 1:



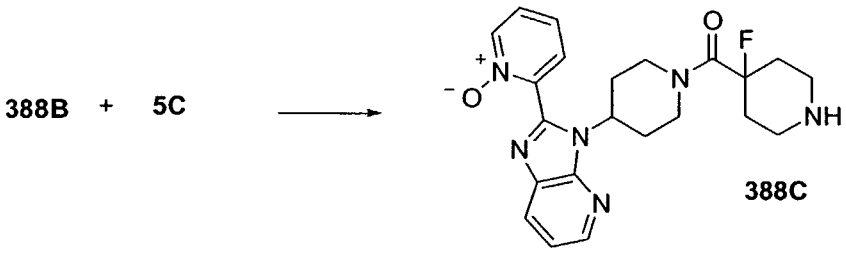
A solution of **P7-1** (2.3 g, 8.9 mmol) in CH_2Cl_2-DMF (1:1, 50 ml) was treated with picolinic acid N-oxide (1.5 g, 10.6 mmol), EDCI (2.6 g, 13.3 mmol) and HOBT (1.8 g, 13.3 mmol). The mixture was stirred at 70 °C overnight. The reaction mixture was concentrated, diluted with EtOAc, washed three times with 5% aqueous NaOH, dried over Na_2SO_4, and concentrated. Flash chromatography (50% EtOAc/hexane) provided **388A** (2.5 g, 74%).

Step 2:



In a manner similar to that described in Preparation 5, Step 4, compound **388A** was converted to compound **388B.**

Step 3:

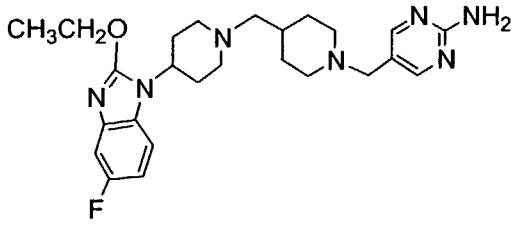


A solution of **388B** (0.66 g, 2.2 mmol) in DMF (15 ml) was treated with **5C** (0.62 g, 2.5 mmol), 1-propanephosphonic acid cyclic anhydride (3.3 ml, 11.2 mmol, 50 wt. % in EtOAc) and N-ethylmorpholine (1.4 ml, 10.7 mmol). The mixture was stirred at 50 °C for 3h. The reaction mixture was concentrated and diluted with EtOAc. The solution was washed three times with 5% aqueous NaOH, dried over Na_2SO_4, concentrated and subjected to flash chromatography (10% 2N NH_3-CH_3OH/EtOAc). The material was then taken up in CH_2Cl_2 (20 ml) and treated with 4 M HCl-dioxane (4 ml). After stirring overnight at 20 °C, the reaction was carefully basified with 10% aqueous NaOH and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated and subjected to flash chromatography (30% 2N NH_3-CH_3OH/EtOAc) to provide **388C** as a white solid (0.08g, 10%).

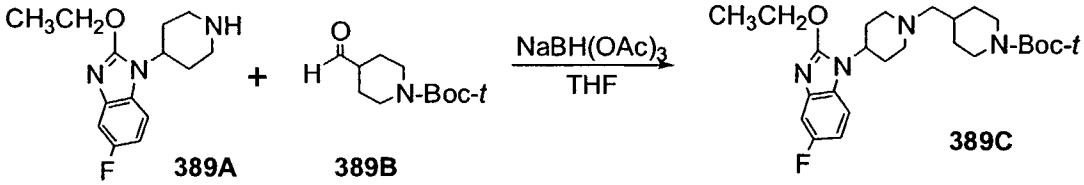
Step 4:

In a manner similar to that described in Example 5, Step 5, compound **388C** was converted to Example 388.

Example 389



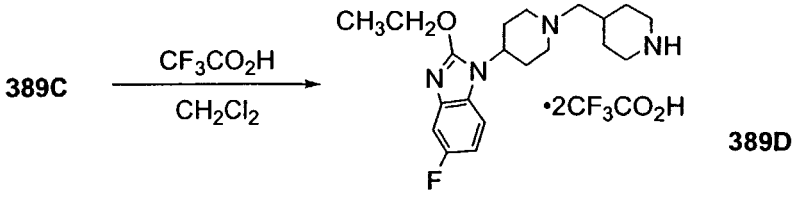
Step 1:



To a stirred, cloudy solution of **389A** (300 mg, 1.14 mmol) in THF (15 ml) were added a solution of **389B** (292 mg, 1.37 mmol) in THF (1 ml), followed by $NaBH(OAc)_3$ (483 mg, 2.28 mmol). After stirring at RT for 39 h, TLC revealed the presence of unchanged starting materials in the cloudy white reaction suspension. Therefore, another quantity of $NaBH(OAc)_3$ (242 mg, 1.14 mmol) was added and stirring at RT continued for a total of 113 h. The reaction mixture was then filtered and collected solids washed thoroughly with CH_2Cl_2. The combined filtrate and washings were stripped of solvent under vacuum, and the residue was partitioned between EtOAc (60 ml) and a solution consisting of water (2.5 ml), 2M Na_2CO_3 (6.5 ml) and 6N NaOH (5

ml). The aqueous layer was further extracted with EtOAc (3 x 15 ml). The combined extracts were washed with brine (5 ml) and dried over anhydrous $MgSO_4$. Drying agent was removed by filtration, and the filtrate was concentrated under vacuum. The residue was purified by silica gel flash chromatography (EtOAc/hexanes = 1:1) to obtain **389C** as a mixture of colorless gum and white foam (368 mg, 70%), homogeneous to TLC, which solidified upon standing. ES-MS: 461 (MH^+; 100%).

Step 2:

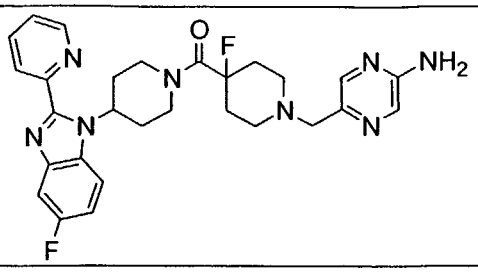
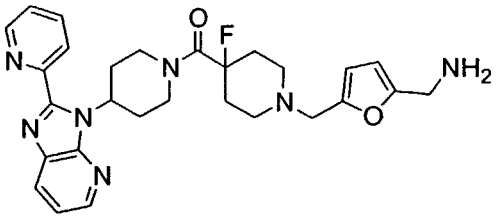
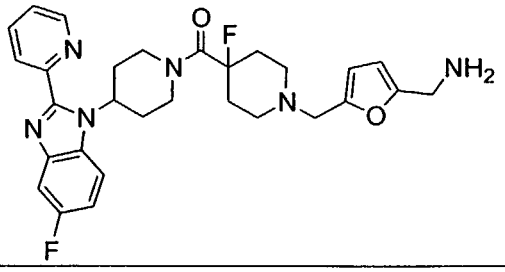
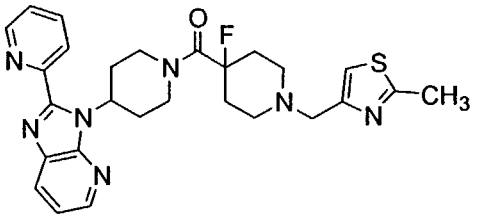
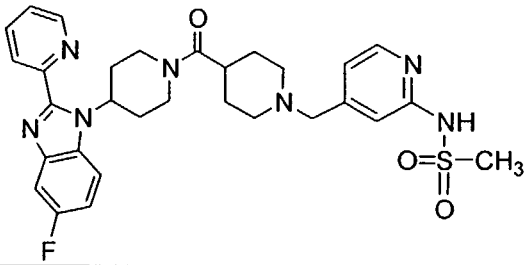
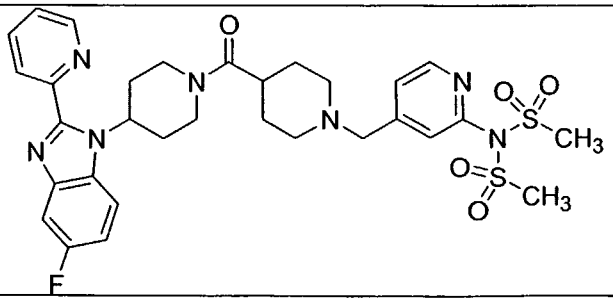


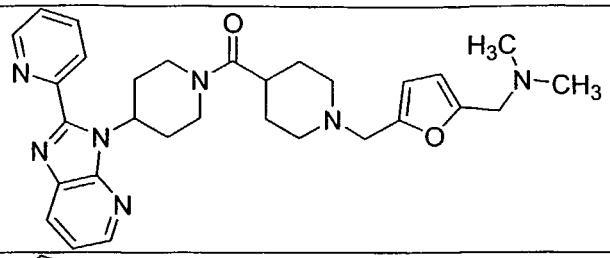
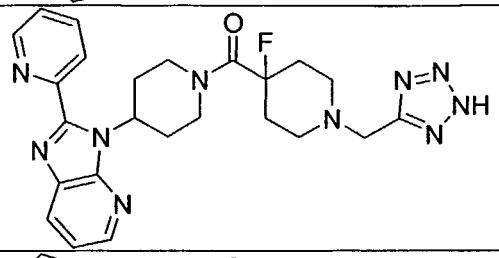
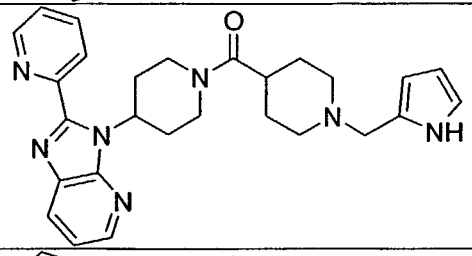
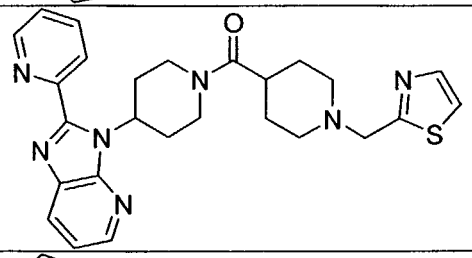
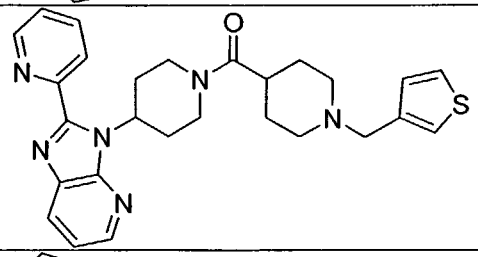
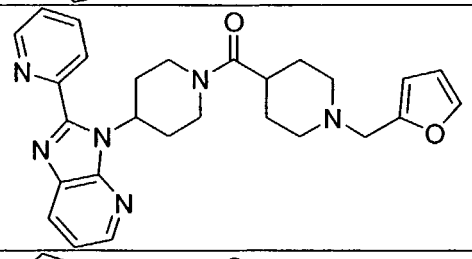
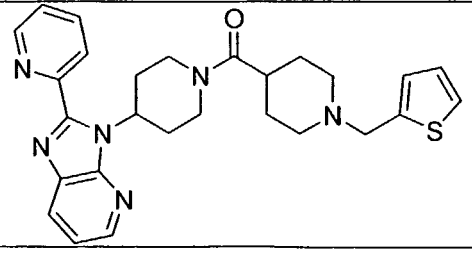
To a stirred, ice-cold solution of **389C** (358 mg, 0.777 ml) in CH_2Cl_2 (7 ml) was added via syringe cold, neat TFA (576 microliters, 886 mg, 7.77 mmol). The resultant solution was stirred in an ice-water bath for 30 min, then at RT for 29.5 h. Volatiles were removed under vacuum, and the gummy residue was triturated (magnetic stirrer) with Et_2O (35 ml) for 16 h. Filtration and washing with Et_2O yielded the bis-trifluoroacetate salt of **389D** as a white powder (449 mg, 98%).

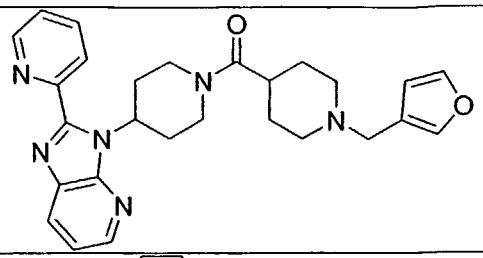
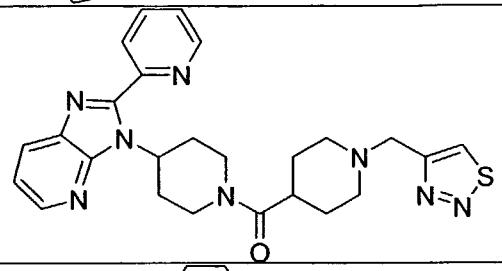
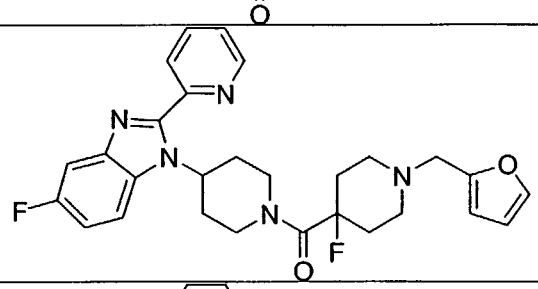
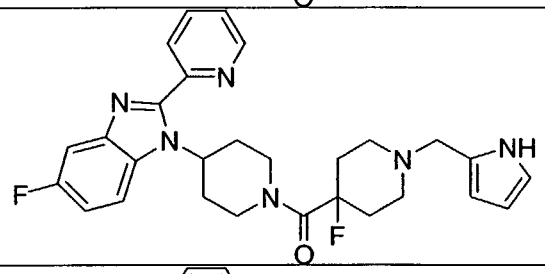
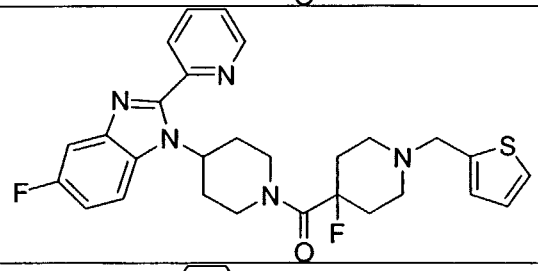
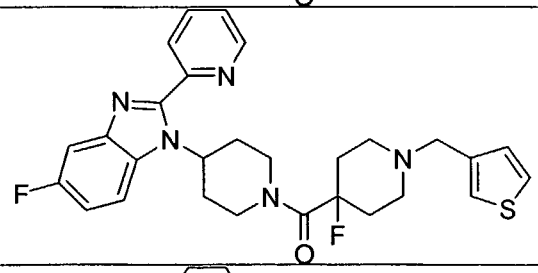
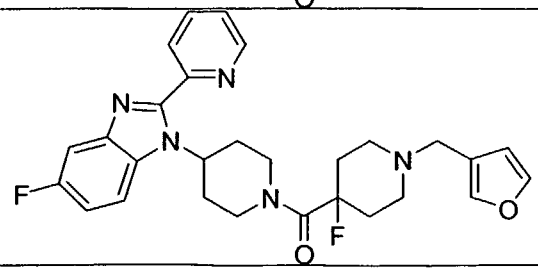
Step 3:

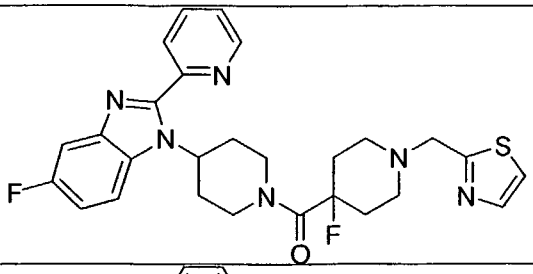
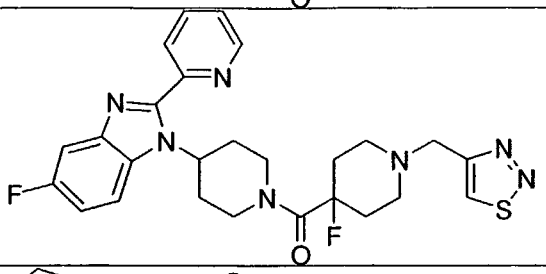
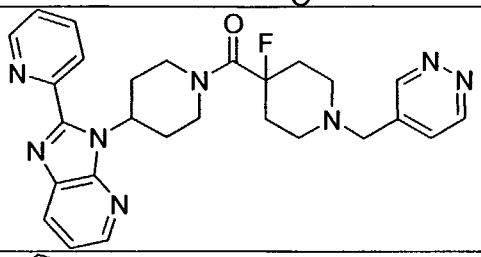
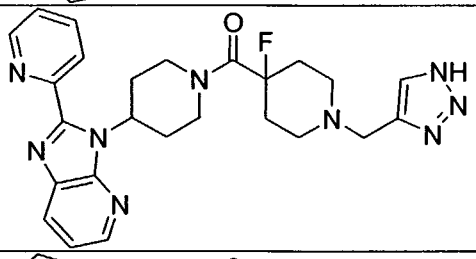
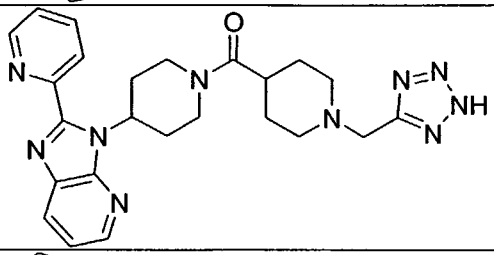
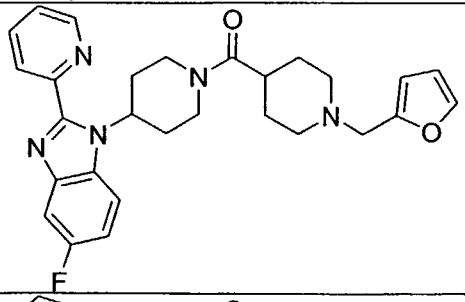
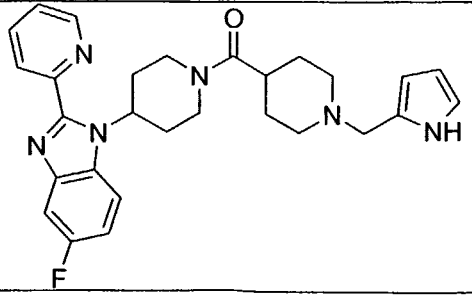
To a stirred suspension of **389D** (100 mg, 0.170 mmol) in CH_2Cl_2 (5 ml) was added Et_3N (47.4 microliters, 34.4 mg, 0.340 mmol), whereupon all solids dissolved. To the stirred solution were then added **5G** (25.1 mg, 0.204 mmol), followed by $NaBH(OAc)_3$ (72.1 mg, 0.340 mmol). After stirring at RT for 66 h, TLC revealed the presence of unchanged starting materials in the light yellow reaction suspension. Therefore, another quantity of $NaBH(OAc)_3$ (72.1 mg, 0.340 mmol) was added and stirring at RT continued for a total of 90 h. The reaction mixture was then filtered and collected solids washed thoroughly with CH_2Cl_2. The combined filtrate and washings were stripped of solvent under vacuum, and the residue was partitioned between EtOAc (20 ml) and a solution consisting of water (0.6 ml), 2M Na_2CO_3 (1.5 ml) and 6N NaOH (1.2 ml). The aqueous layer was further extracted with EtOAc (3 x 5 ml). The combined extracts were washed with brine (2 ml) and dried over anhydrous $MgSO_4$. Drying agent was removed by filtration, and the filtrate was concentrated under vacuum. The residue was purified by preparative TLC (silica gel; CH_2Cl_2/CH_3OH/conc. NH_4OH = 90:9:1) to obtain the title compound as a light beige foam (36 mg, 45%). FABMS: 468 (MH^+; 100%).

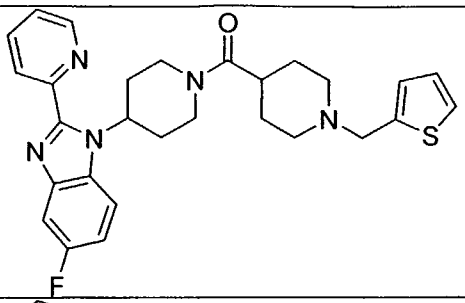
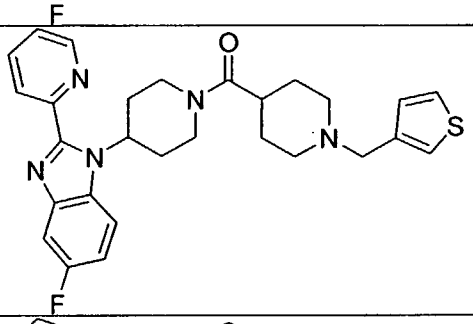
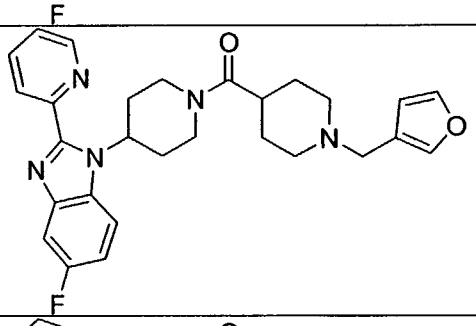
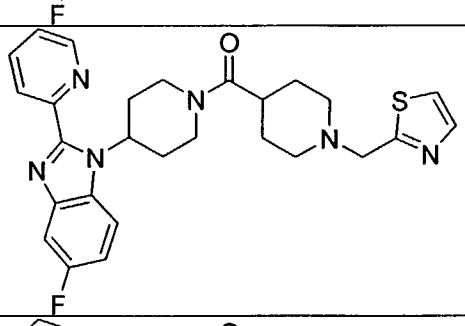
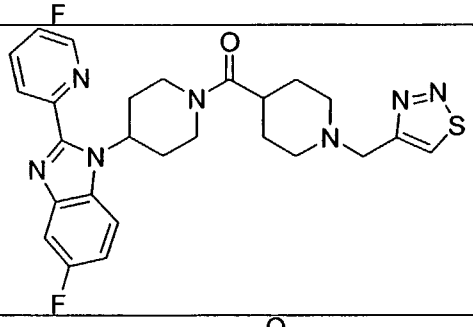
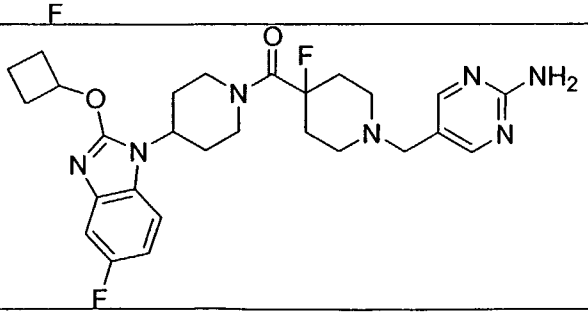
Using procedures similar to those described above in Examples 1-6 and 388-389, the following compounds were prepared:

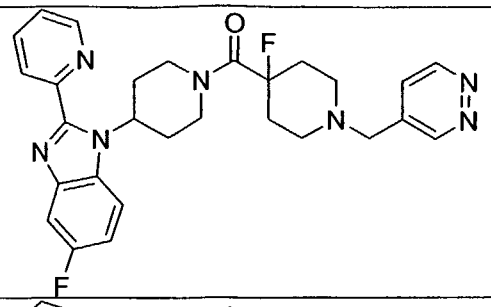
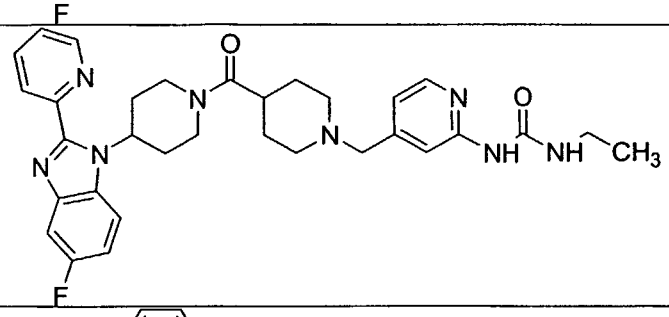
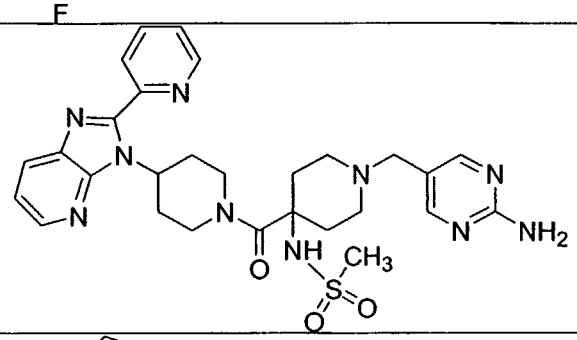
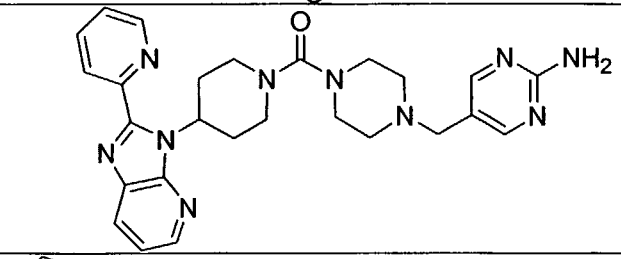
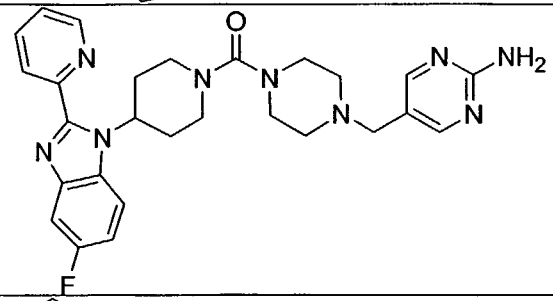
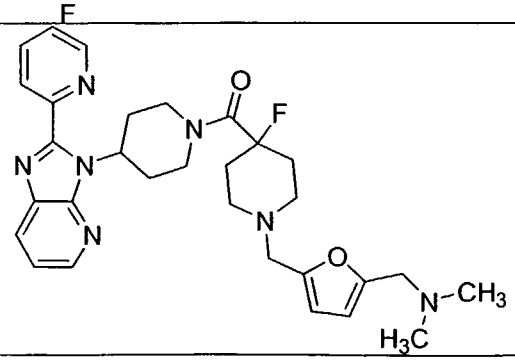
Ex.	Structure	Mass Spec (M+H)
390		533 (ESMS)
391		518 (ESMS)
392		535 (ESMS)
393		520 (ESMS)
394		592 (FAB)
395		670 (FAB)

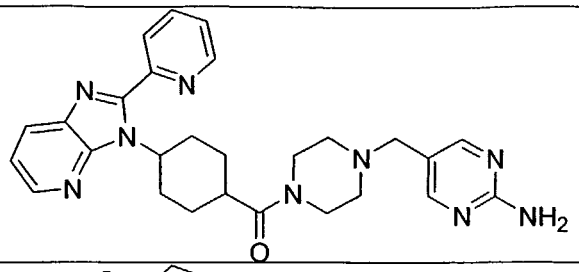
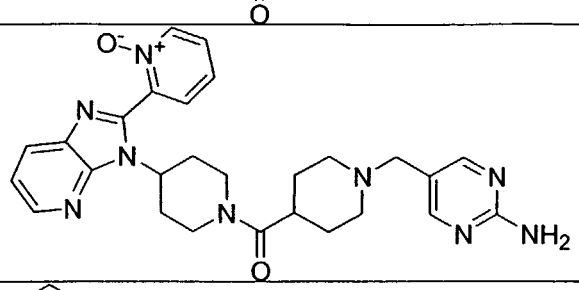
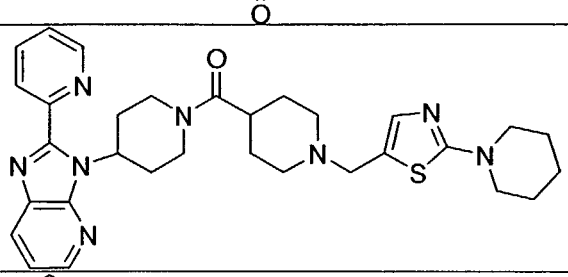
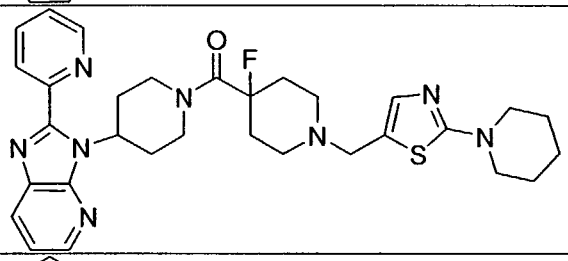
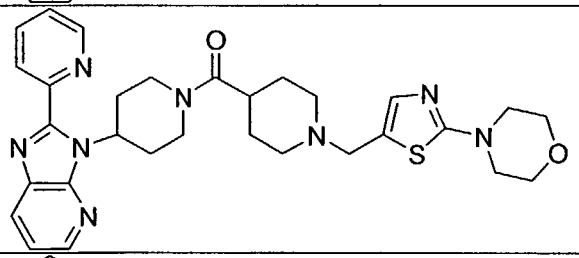
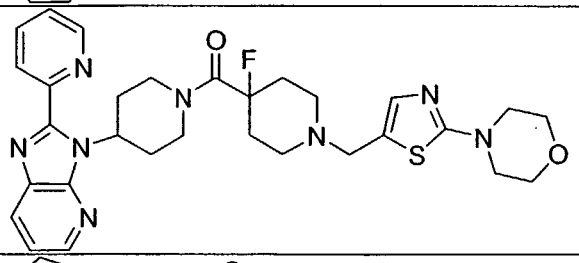
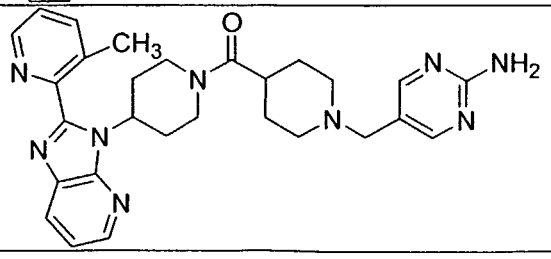
396		528 (ESMS)
397		491 (ESMS)
398		470 (ESMS)
399		488 (ESMS)
400		487 (ESMS)
401		471 (ESMS)
402		487 (ESMS)

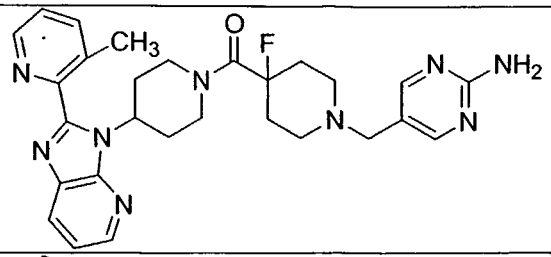
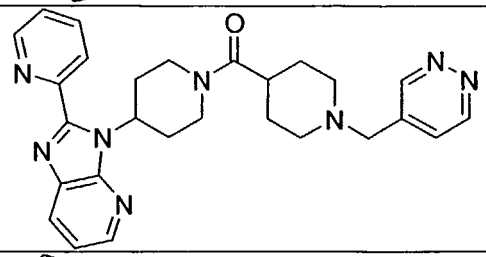
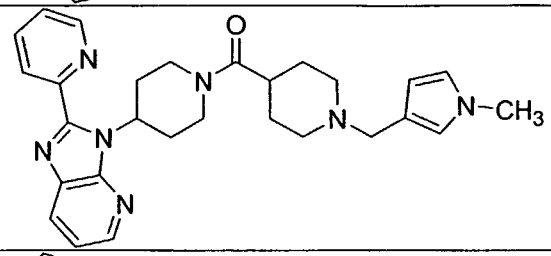
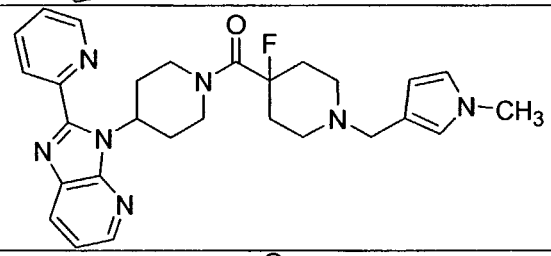
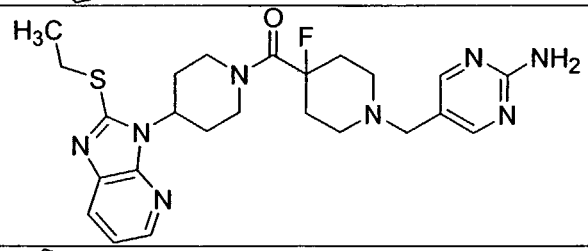
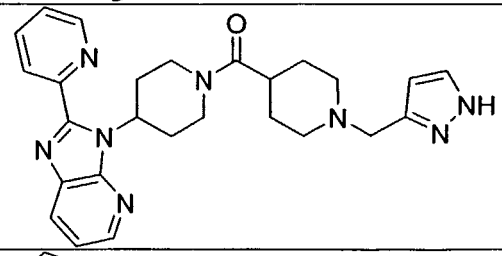
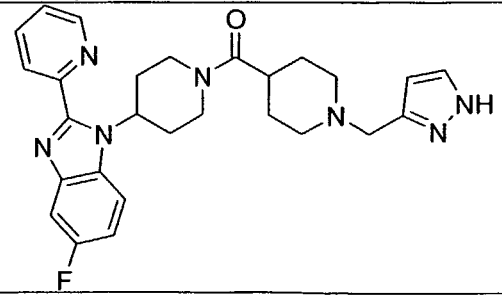
403		471 (ESMS)
404		489 (ESMS)
405		506 (ESMS)
406		505 (ESMS)
407		522 (ESMS)
408		522 (ESMS)
409		506 (ESMS)

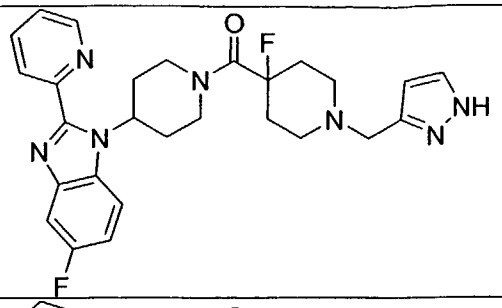
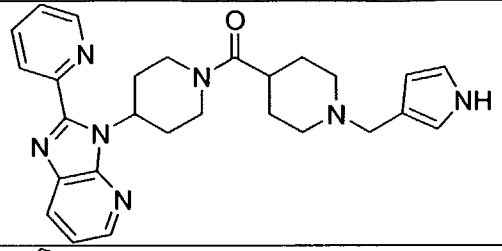
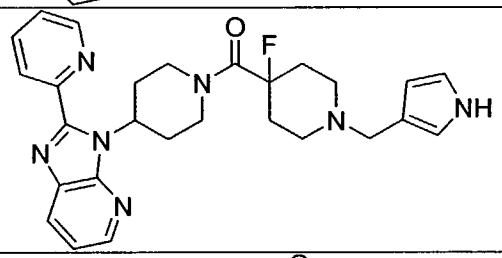
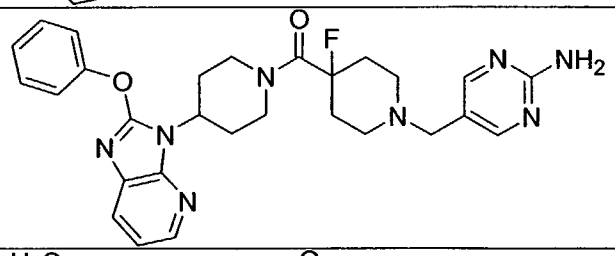
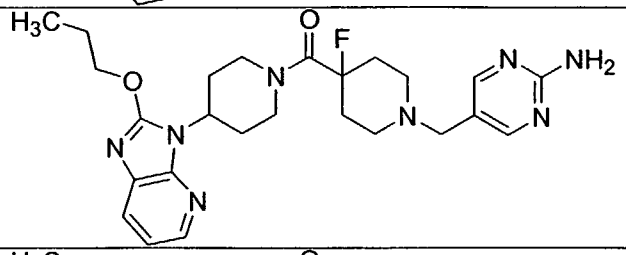
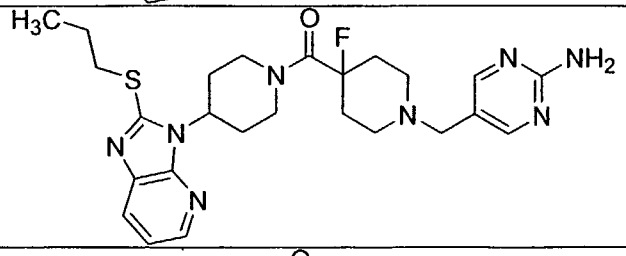
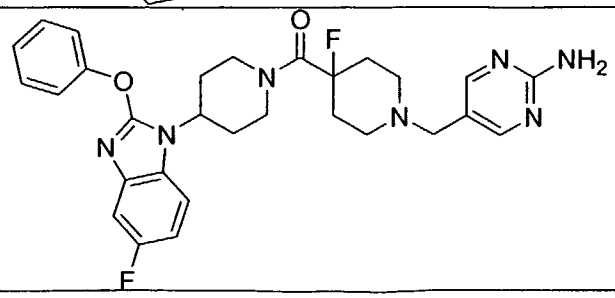
410		523 (ESMS)
411		524 (ESMS)
412		501 (ESMS)
413		490 (ESMS)
414		473 (ESMS)
415		488 (ESMS)
416		487 (ESMS)

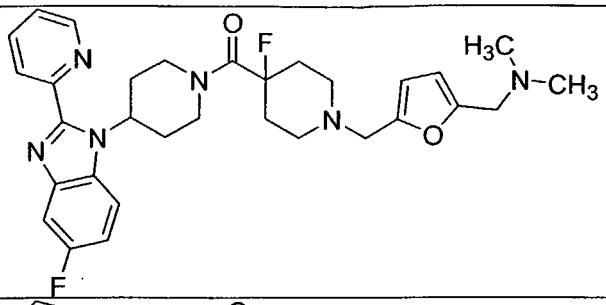
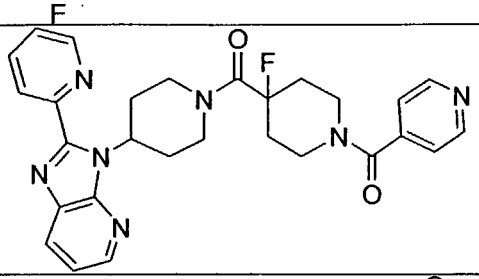
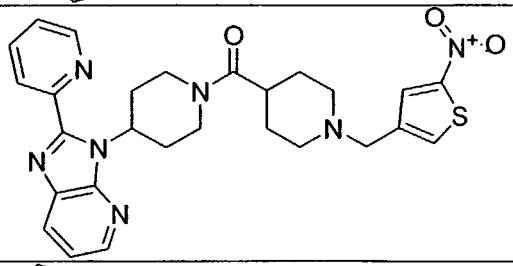
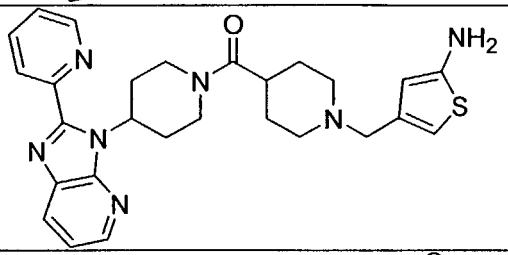
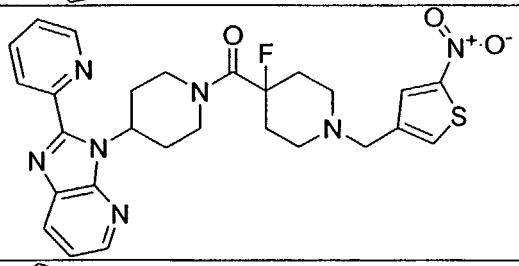
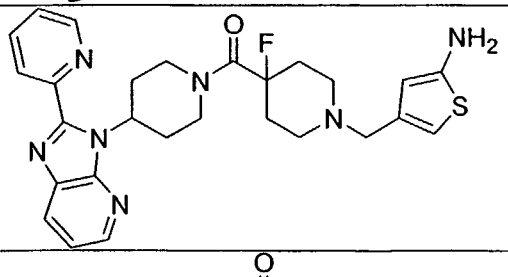
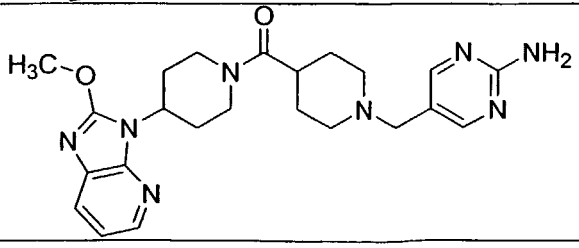
417		504 (ESMS)
418		504 (ESMS)
419		488 (ESMS)
420		505 (ESMS)
421		506 (ESMS)
422		526 (FAB)

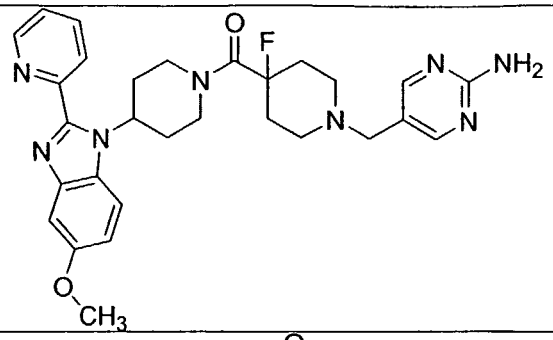
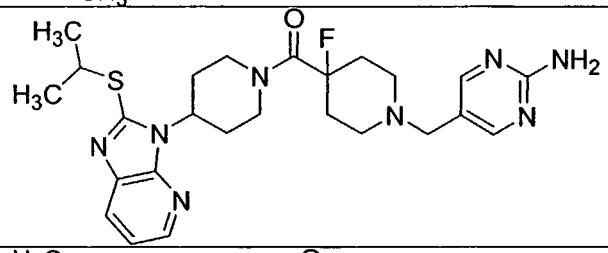
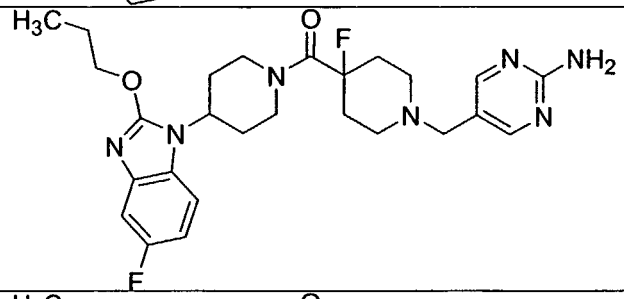
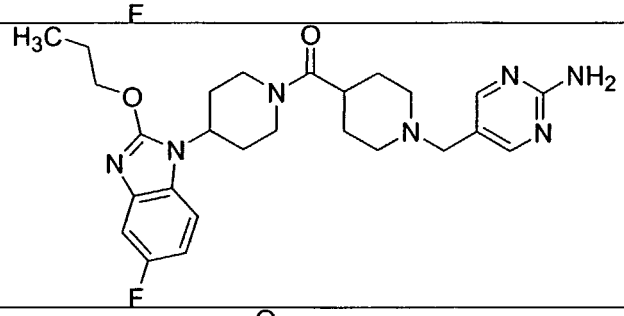
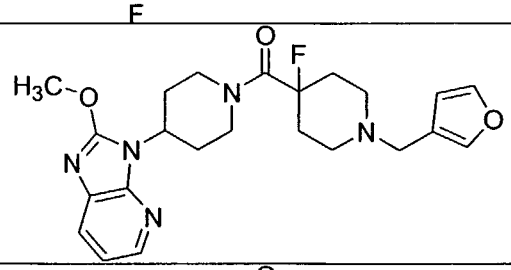
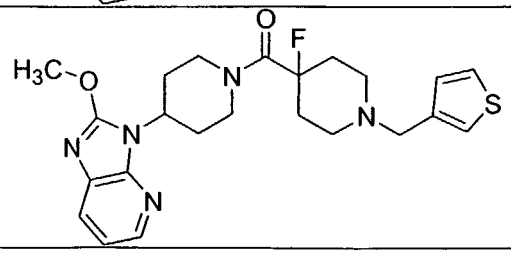
423		518 (ESMS)
424		585 (FAB)
425		591 (ESMS)
426		499 (ESMS)
427		516 (ESMS)
428		546 (ESMS)

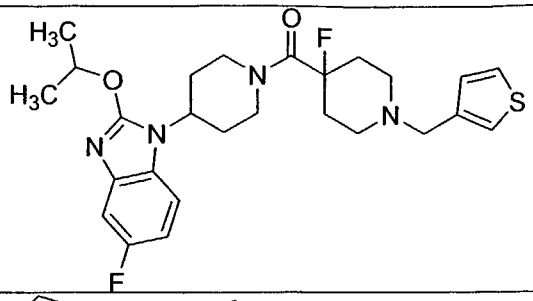
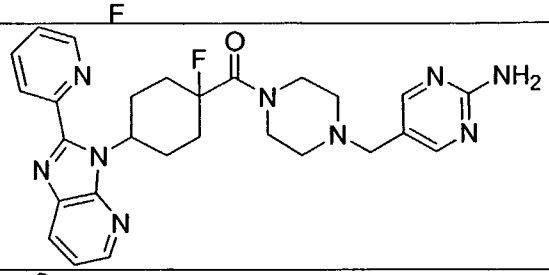
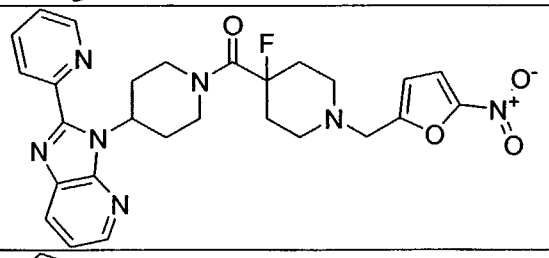
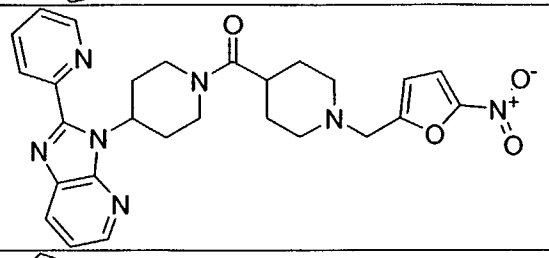
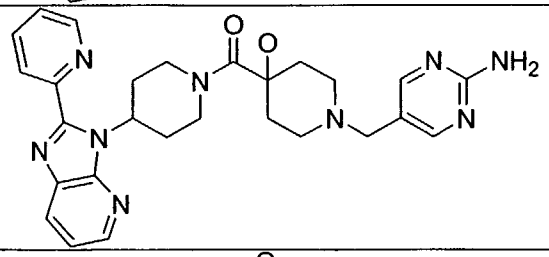
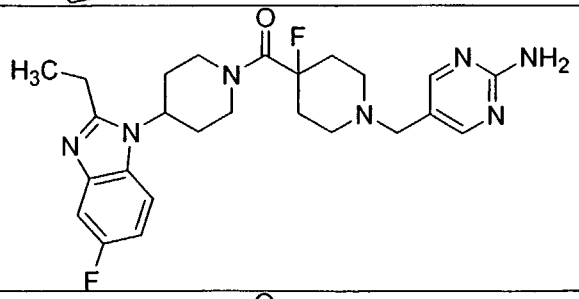
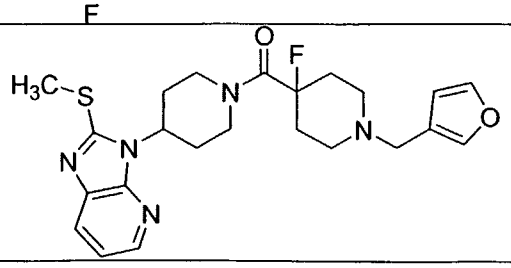
429		498 (ESMS)
430		514 (ESMS)
431		571 (ESMS)
432		589 (ESMS)
433		573 (ESMS)
434		591 (ESMS)
435		512 (ESMS)

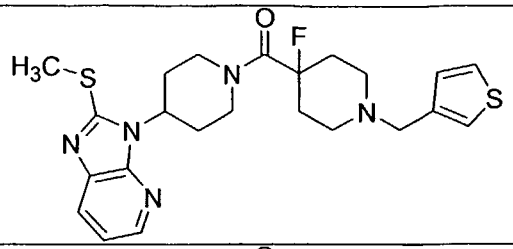
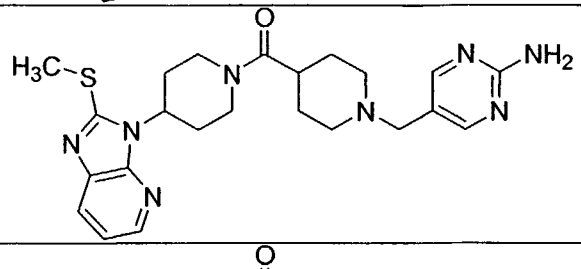
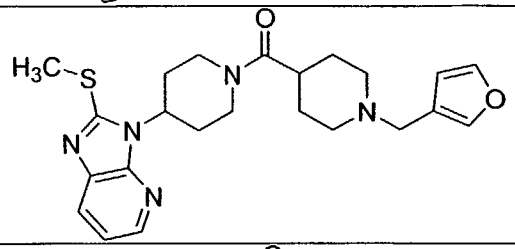
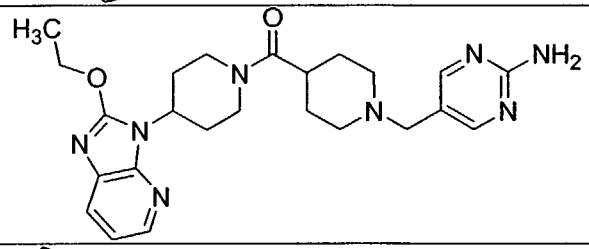
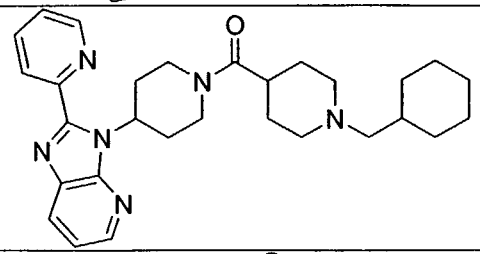
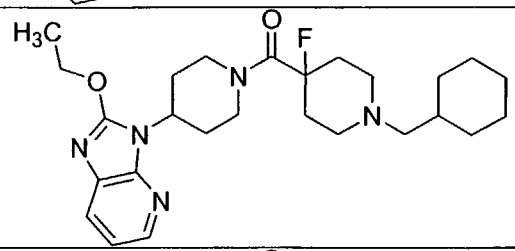
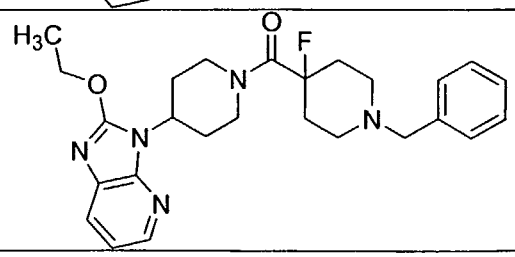
436		530 (ESMS)
437		483 (ESMS)
438		484 (ESMS)
439		502 (ESMS)
440		499 (FAB)
441		471 (ESMS)
442		488 (ESMS)

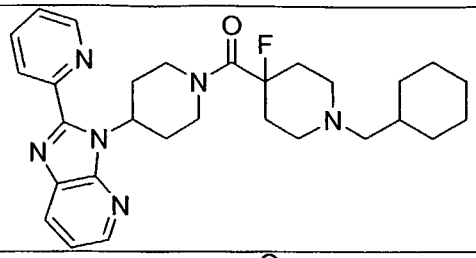
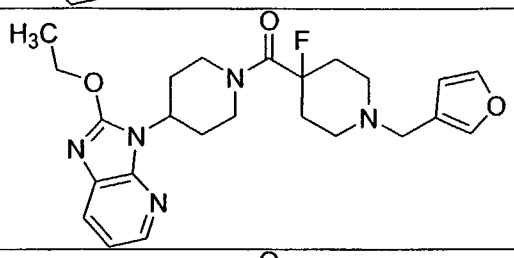
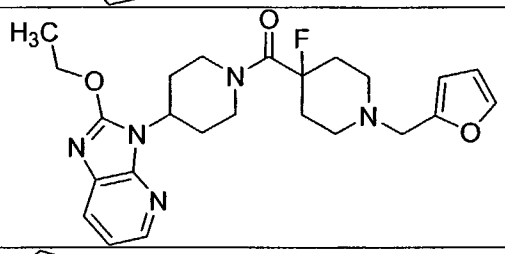
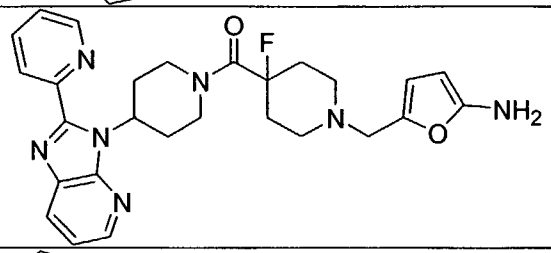
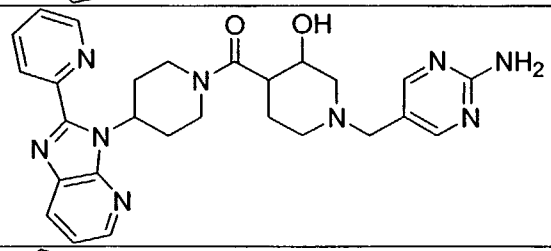
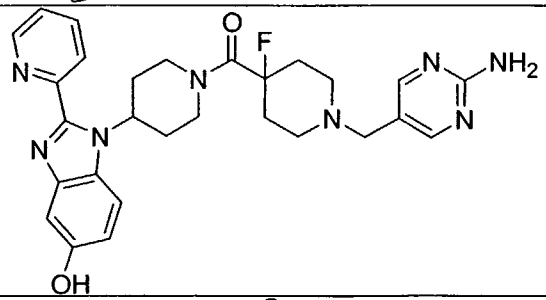
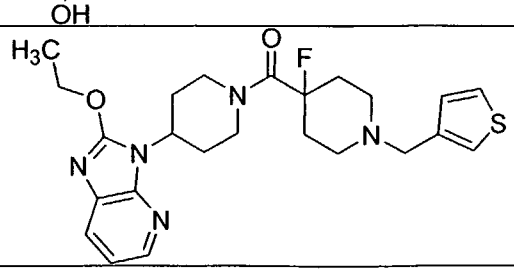
443		506 (ESMS)
444		470 (ESMS)
445		488 (ESMS)
446		531 (FAB)
447		497 (FAB)
448		513 (FAB)
449		548 (FAB)

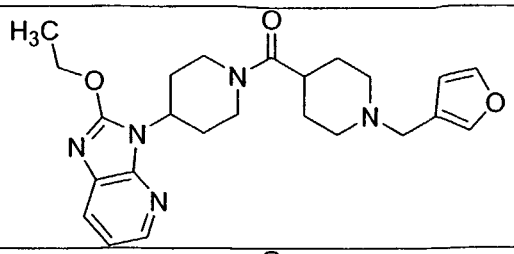
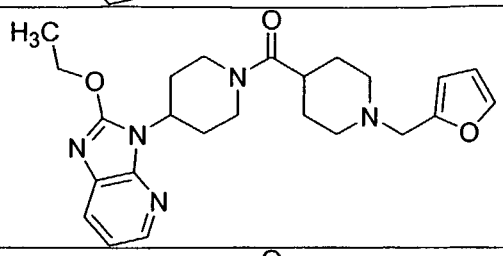
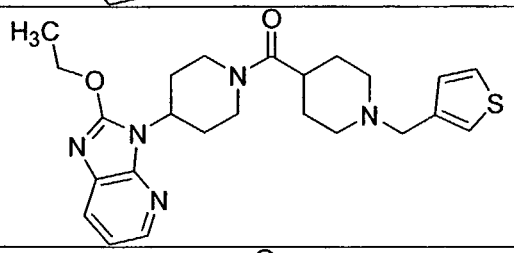
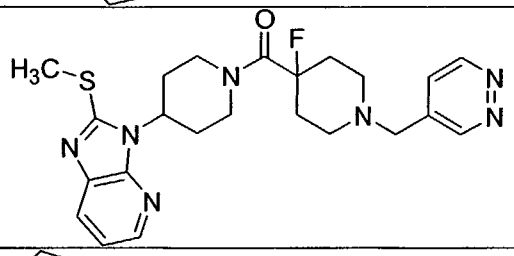
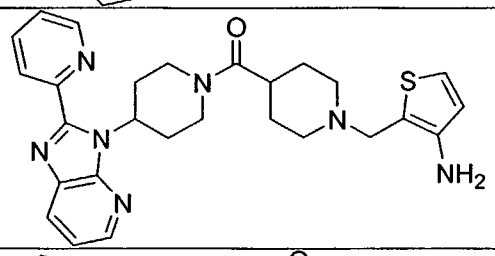
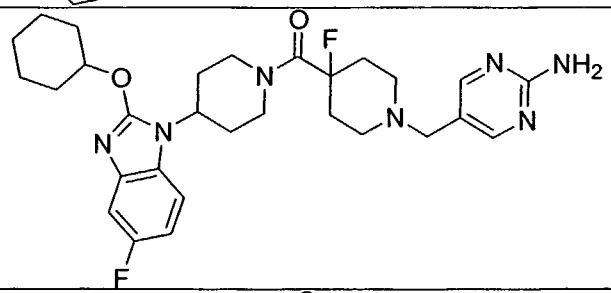
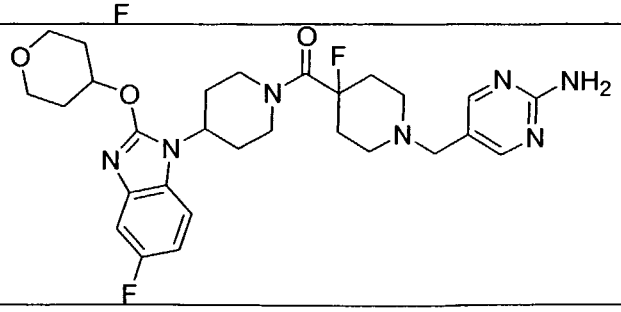
450		563 (ESMS)
451		514(ESMS)
452		532 (ESMS)
453		502 (ESMS)
454		550 (ESMS)
455		520 (ESMS)
456		451 (ESMA)

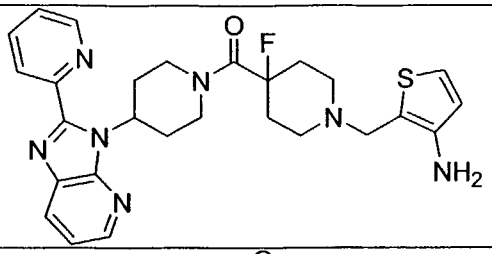
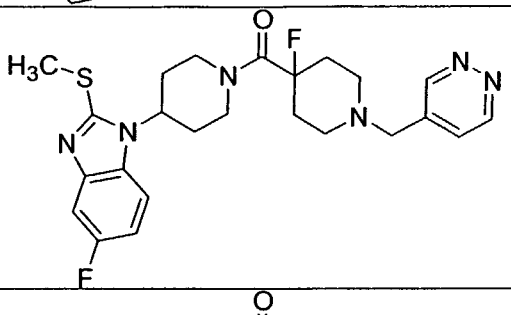
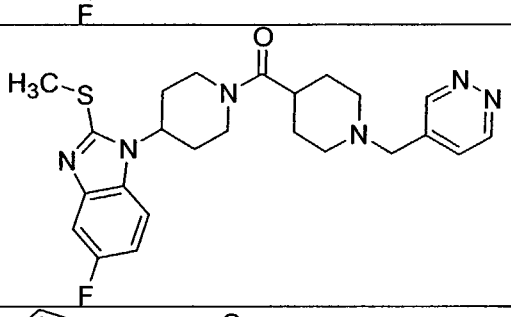
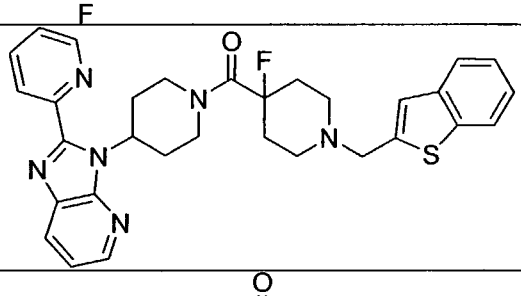
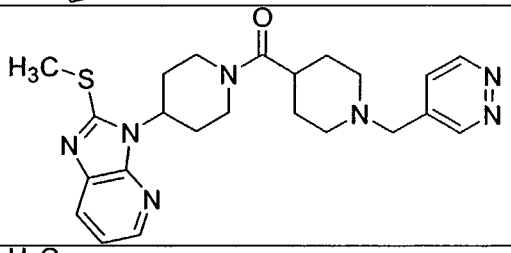
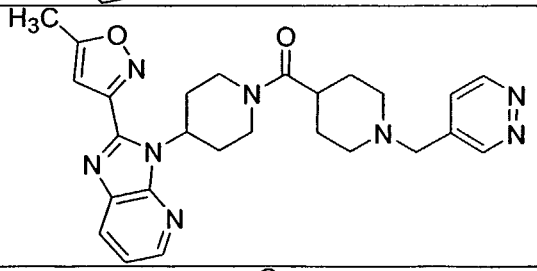
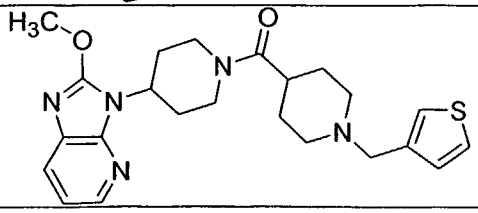
457		545 (ESMS)
458		513 (ESMS)
459		514 (FAB)
460		496 (FAB)
461		442 (ESMS)
462		458 (ESMS)

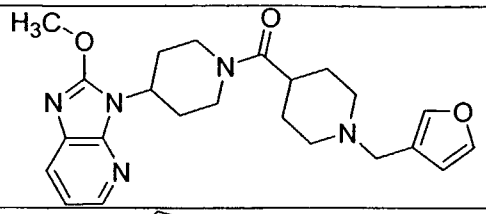
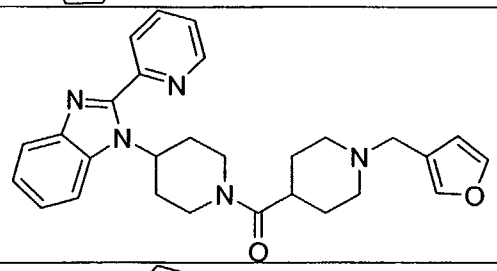
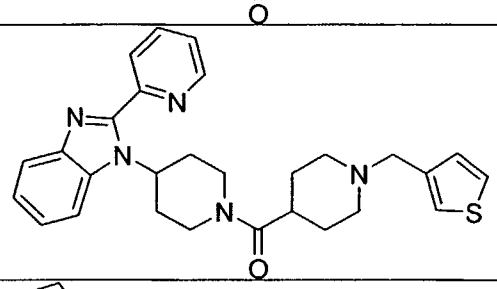
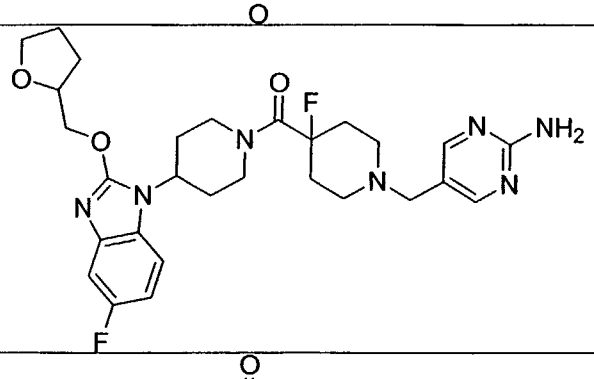
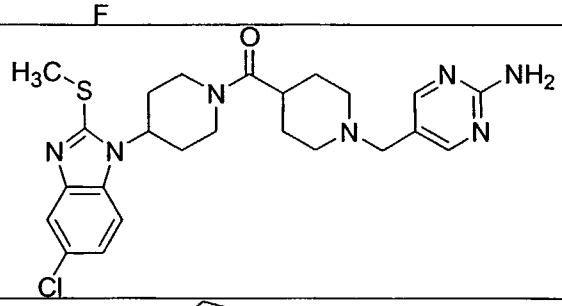
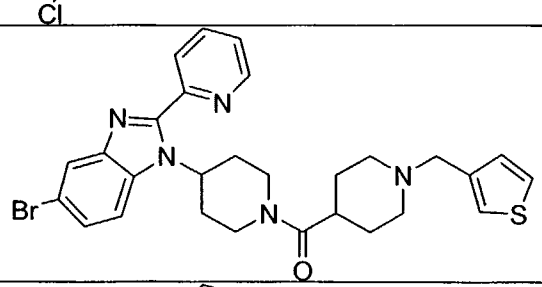
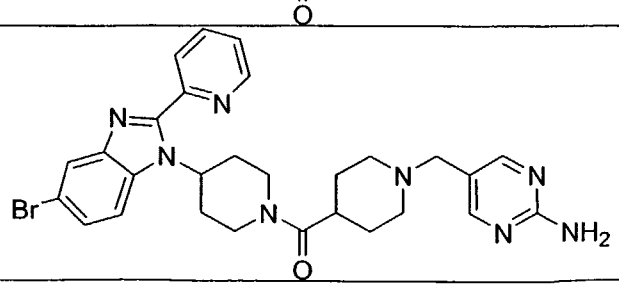
463		503 (ESMS)
464		407 (ESMS)
465		534 (ESMS)
466		516 (ESMS)
467		514 (ESMS)
468		484 (ESMS)
469		458 (ESMS)

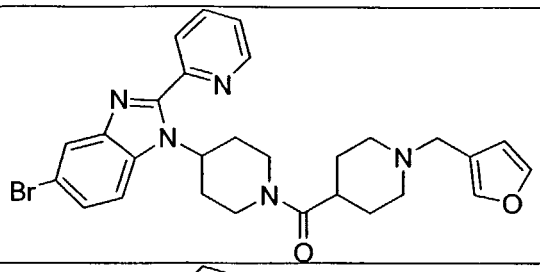
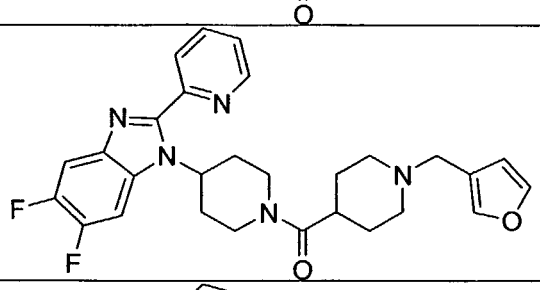
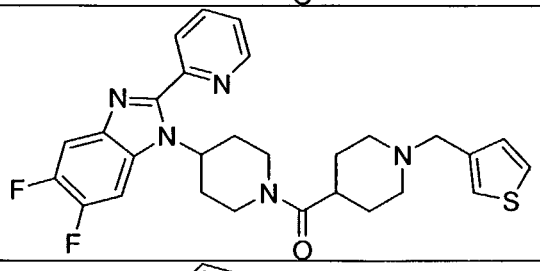
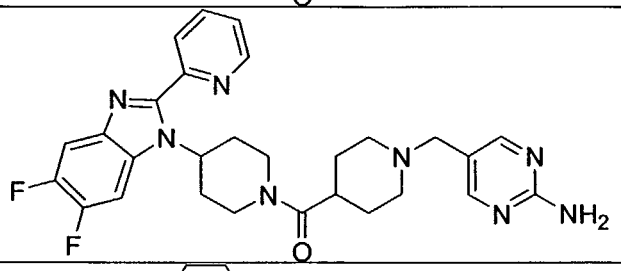
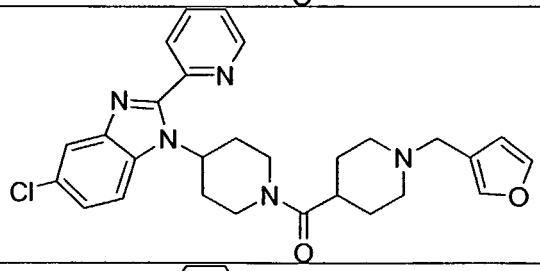
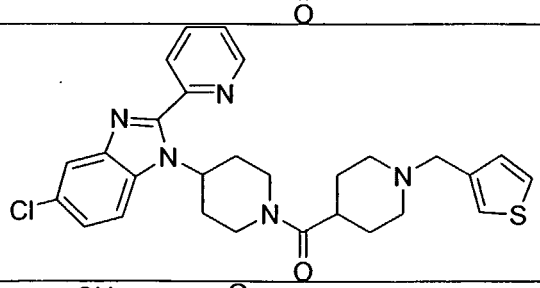
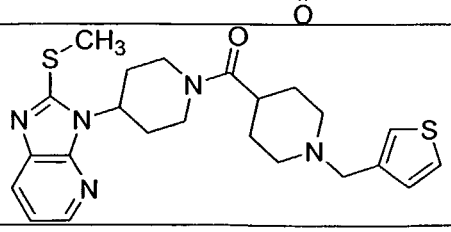
470		474 (ESMS)
471		467 (ESMA)
472		440 (ESMS)
473		465 (ESMS)
474		487 (ESMS)
475		472 (ESMS)
476		466 (ESMS)

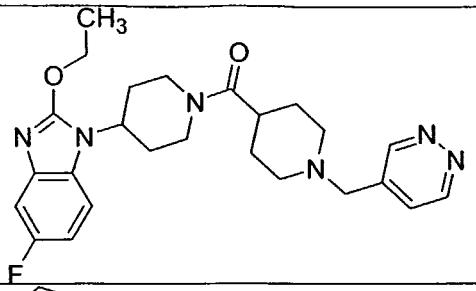
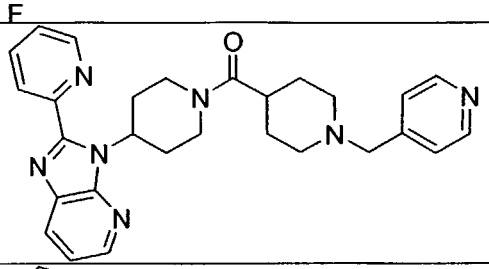
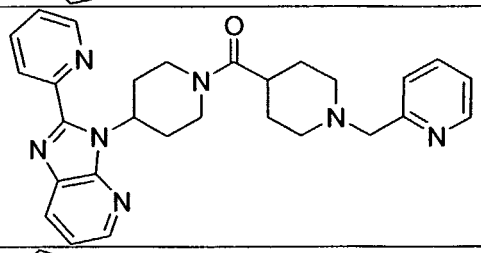
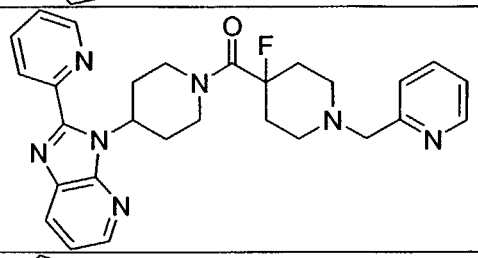
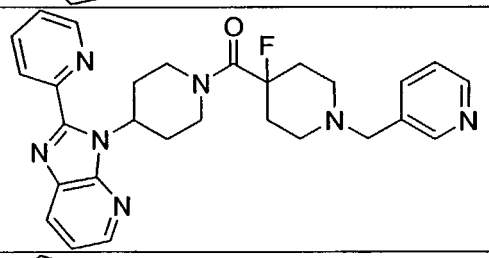
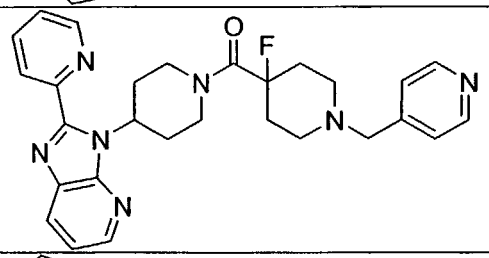
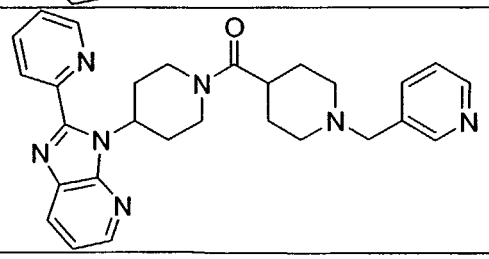
477		505 (ESMS)
478		456 (ESMS)
479		456 (ESMS)
480		504 (ESMS)
481		514 (ESMS)
482		531 (FAB)
483		472 (ESMS)

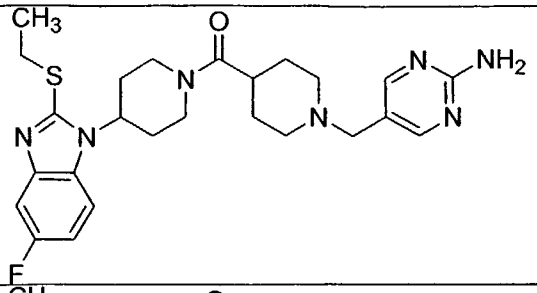
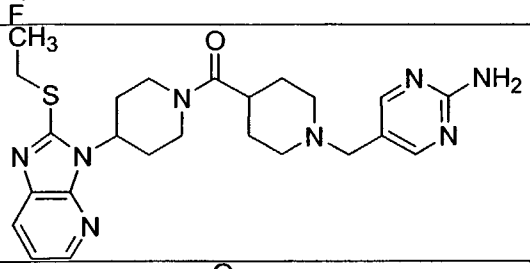
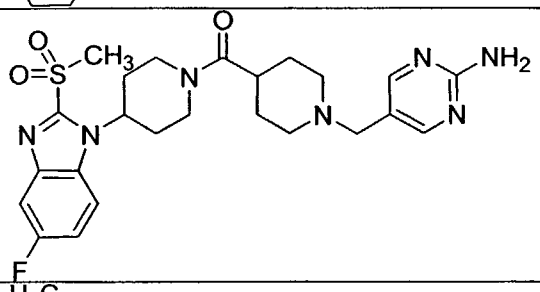
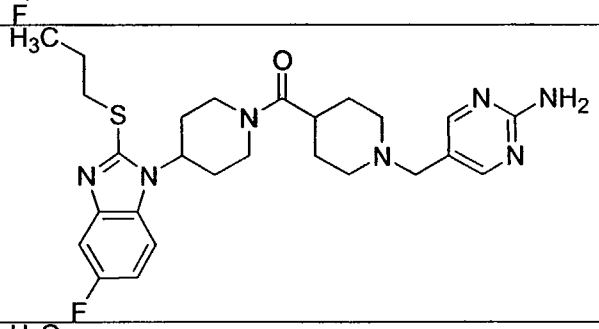
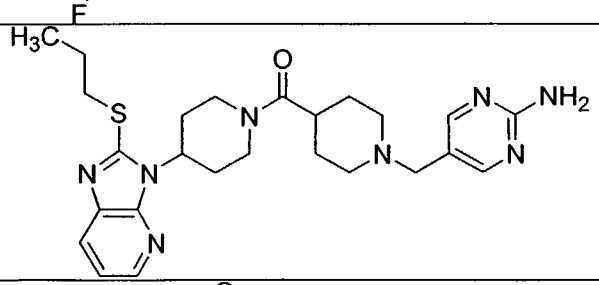
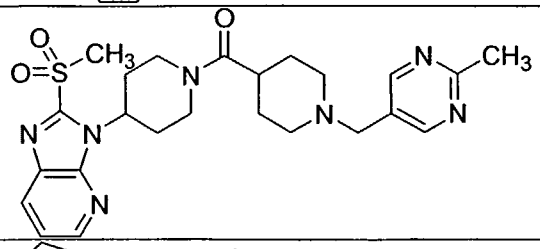
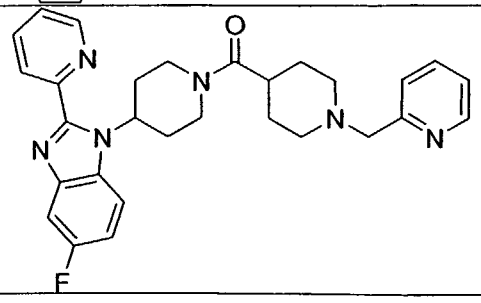
484		438 (ESMS)
485		438 (ESMS)
486		454 (ESMS)
487		470 (ESMS)
488		502 (ESMS)
489		554 (FAB)
490		556 (FAB)

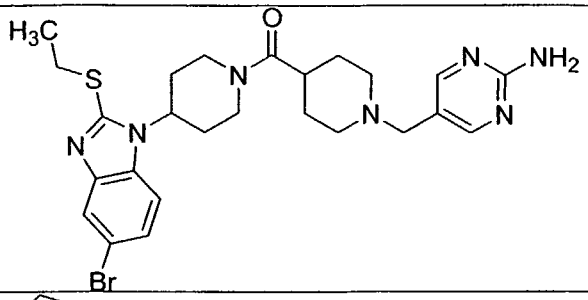
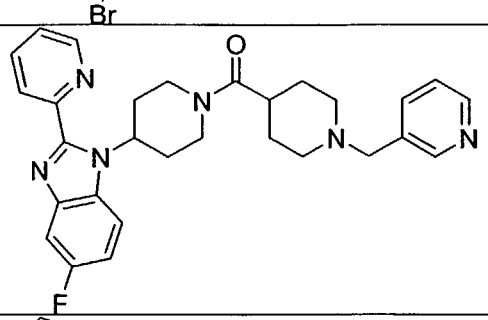
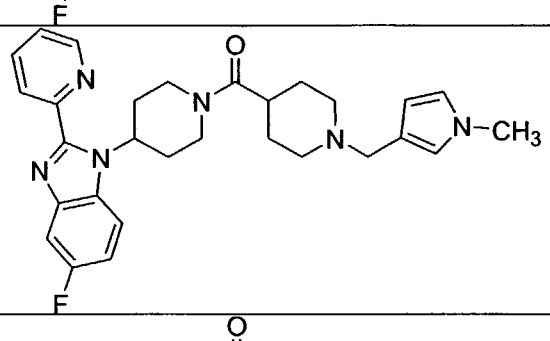
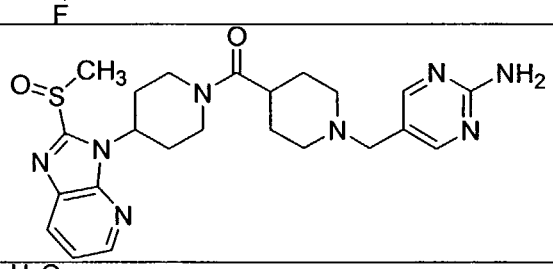
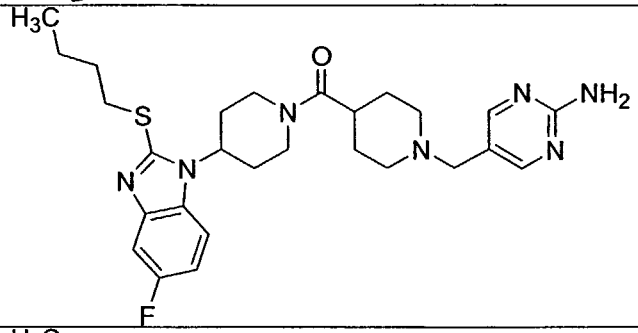
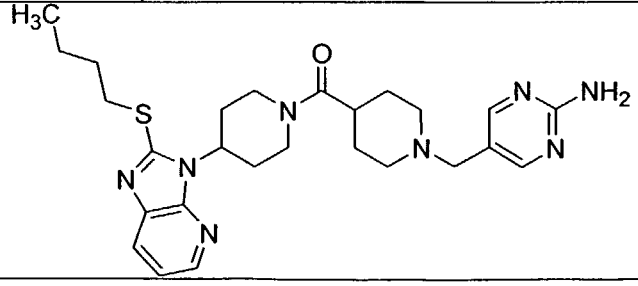
491		470 (ESMS)
492		487 (ESMS)
493		469 (ESMS)
44		555 (ESMS)
495		452 (ESMS)
496		487 (ESMS)
497		440 (ESMS)

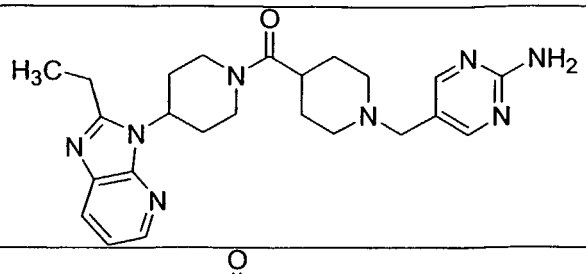
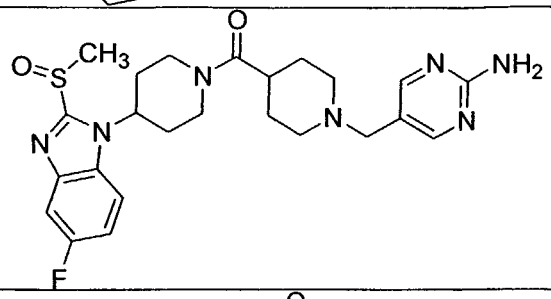
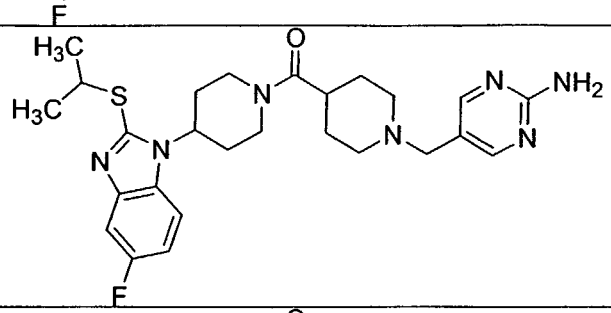
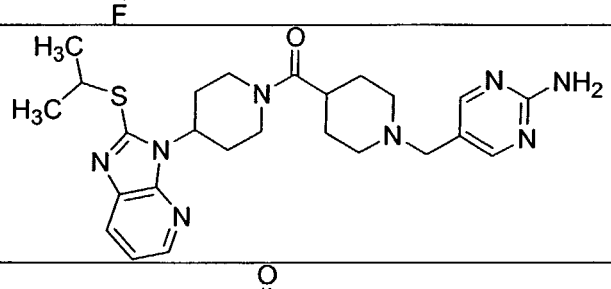
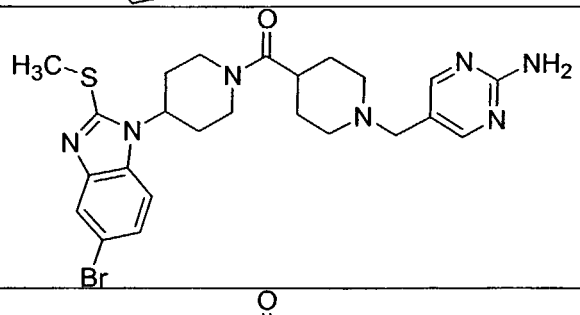
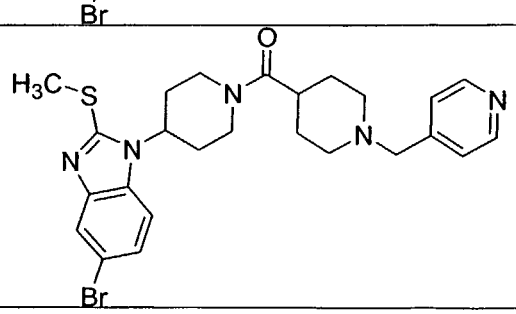
498		424 (ESMS)
499		470 (ESMS)
500		486 (ESMS)
501		556 (ESMS)
502		500 (ESMS)
503		566 (ESMS)
504		577 (ESMS)

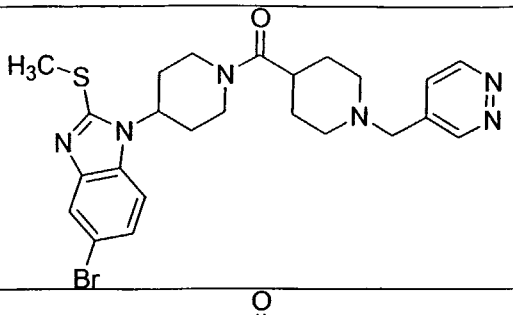
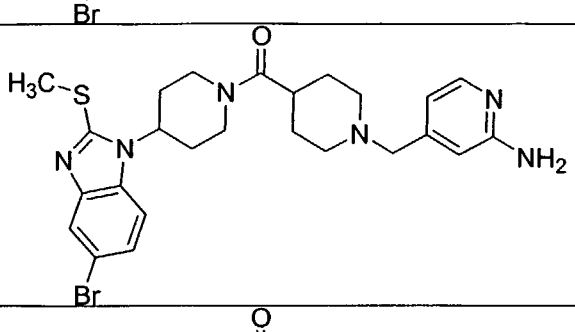
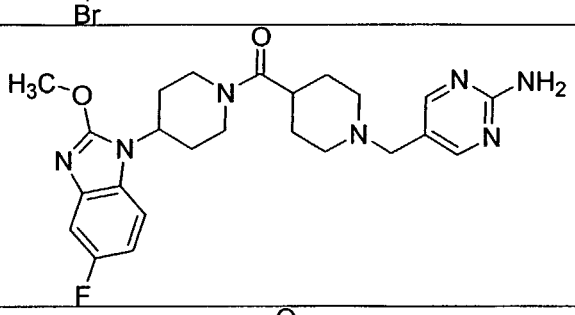
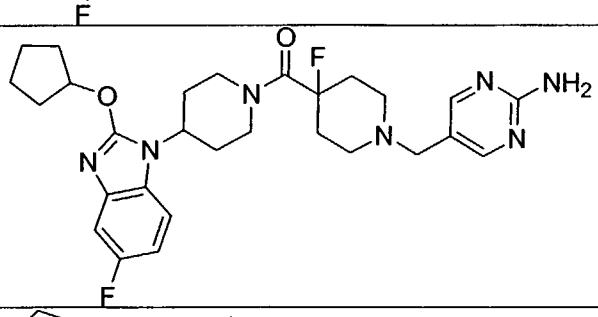
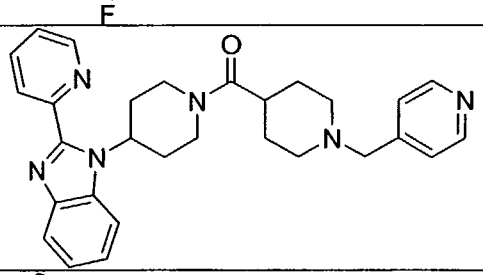
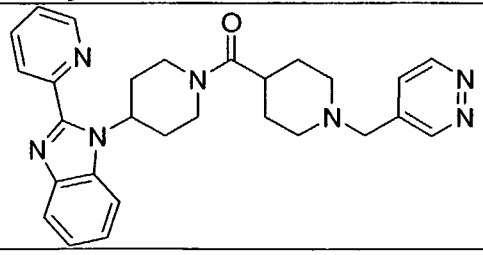
505		550 (ESMS)
506		506 (ESMS)
507		522 (ESMS)
508		533 (ESMS)
509		504 (ESMS)
510		520 (ESMS)
511		456 (ESMS)

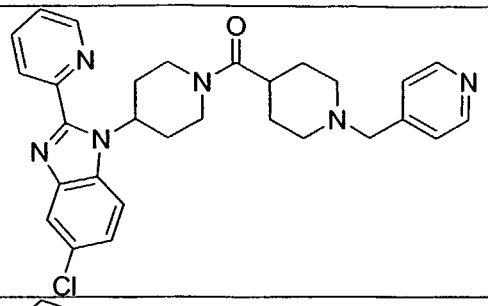
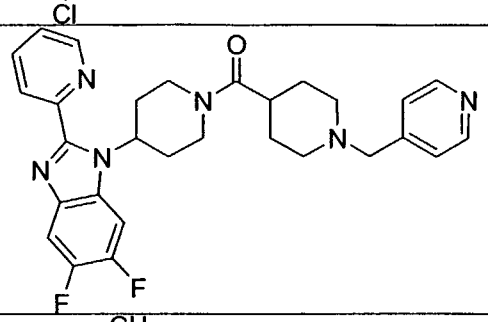
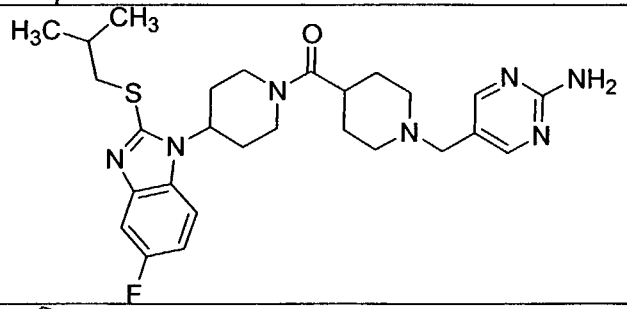
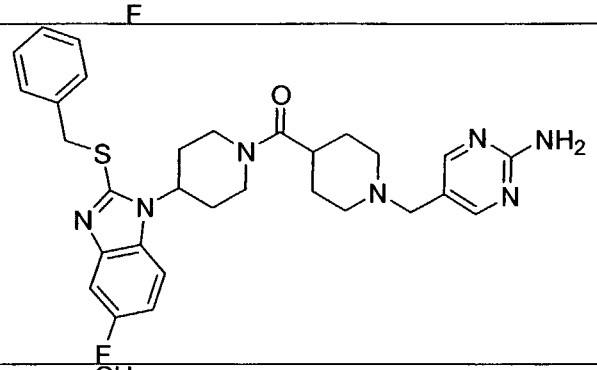
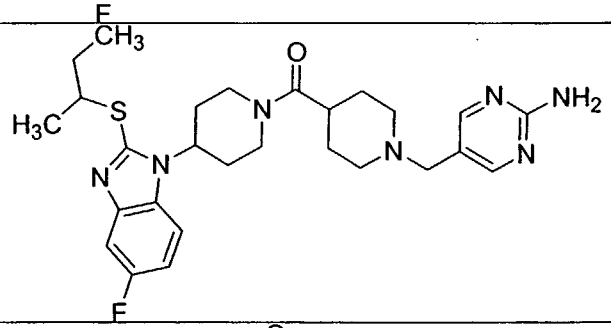
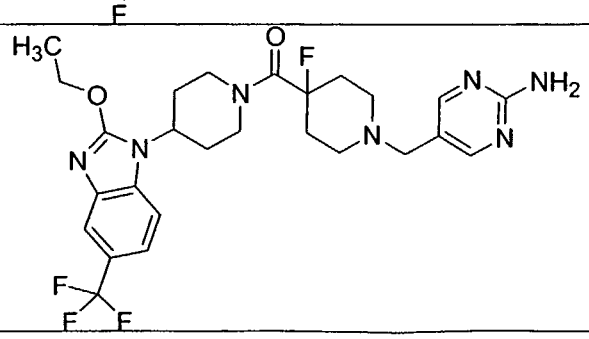
512		467 (ESMS)
513		482 (ESMS)
514		482 (ESMS)
515		500 (ESMS)
516		500 (ESMS)
517		500 (ESMS)
518		482 (ESMS)

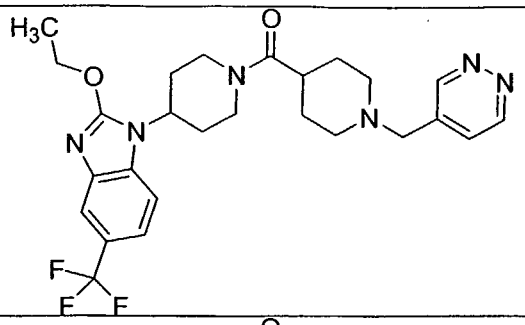
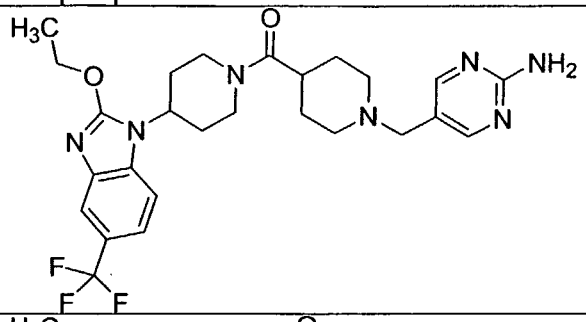
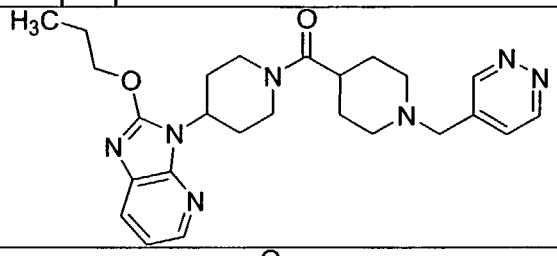
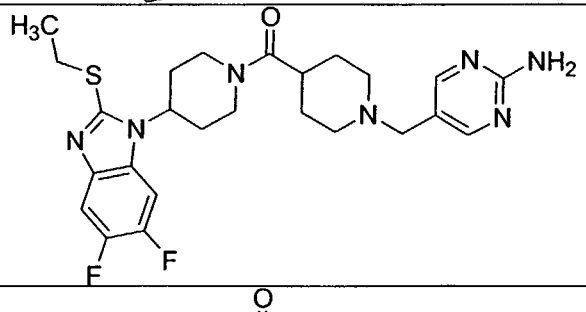
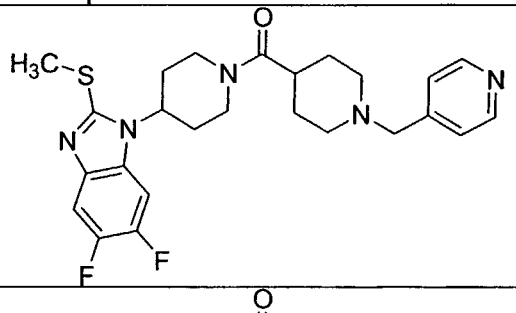
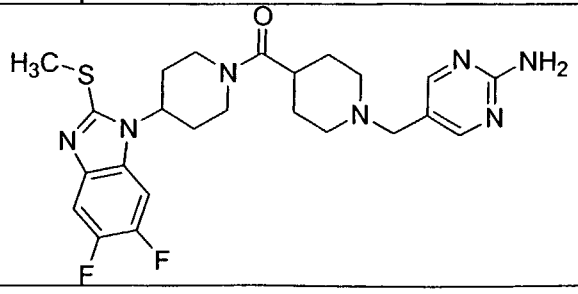
519		498 (ESMS)
520		481 (ESMS)
521		516 (ESMS)
522		512 (FAB)
523		495 (FAB)
524		499 (FAB)
525		499 (ESMS)

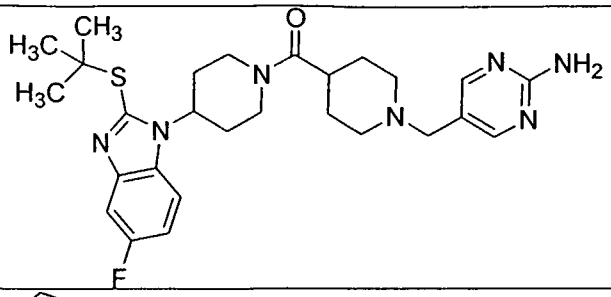
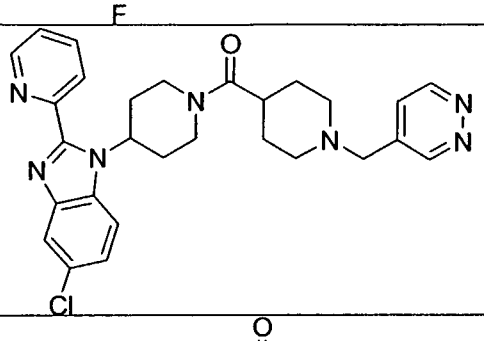
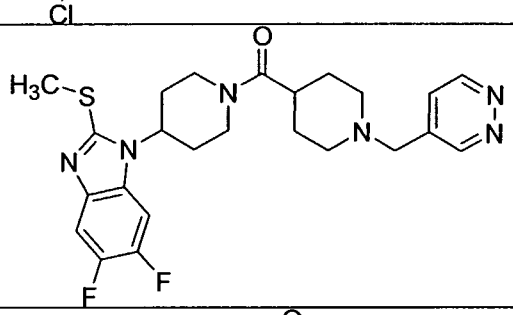
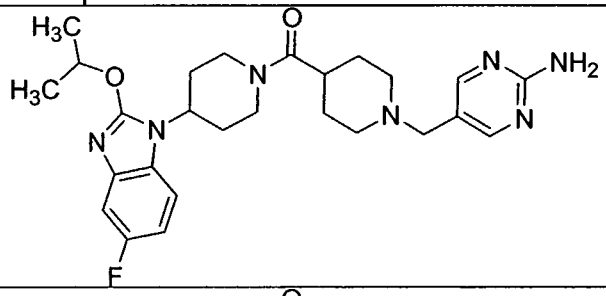
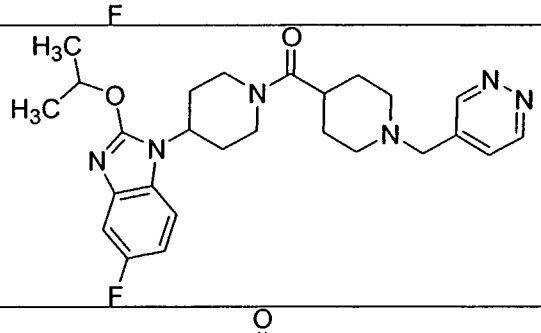
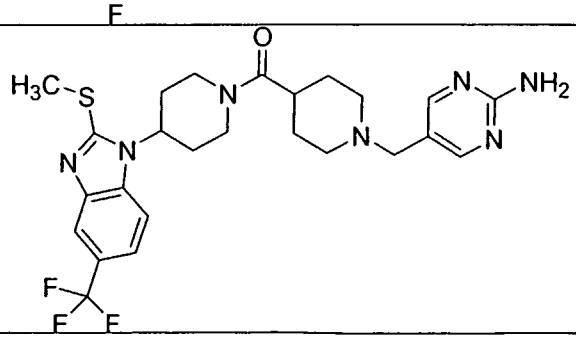
526		560 (ESMS)
527		499 (ESMS)
528		501(ESMS)
529		483 (ESMS)
530		526 (ESMS)
531		509 (ESMS)

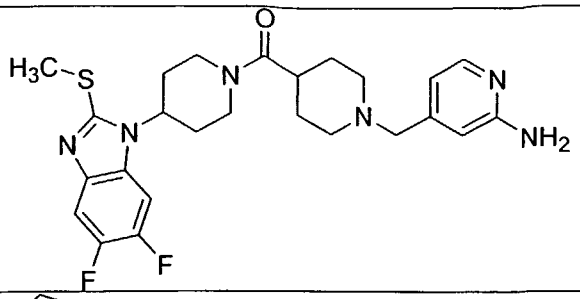
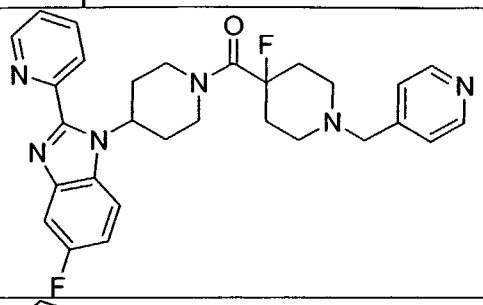
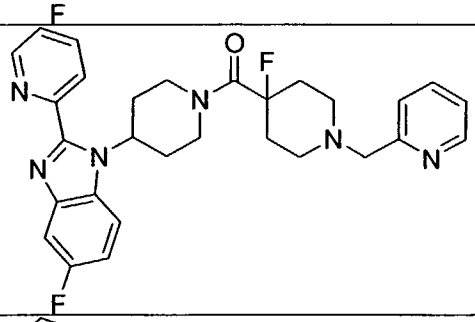
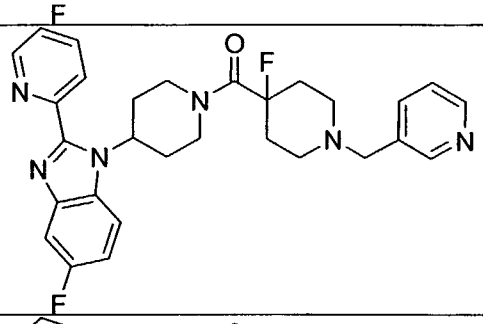
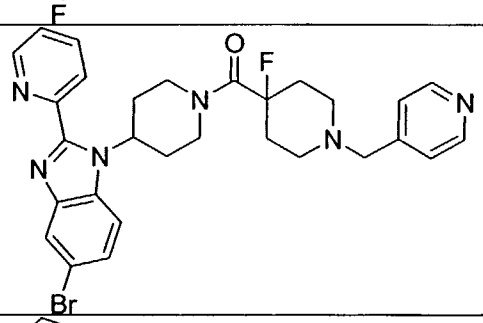
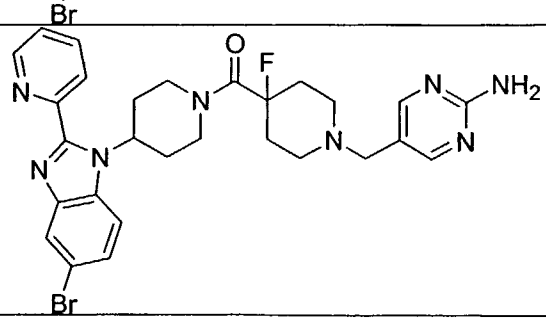
532		449 (ESMS)
533		500 (ESMS)
534		512 (ESMS)
535		495 (ESMS)
536		546 (ESMS)
537		530 (ESMS)

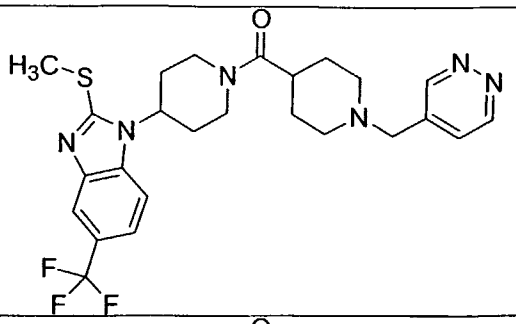
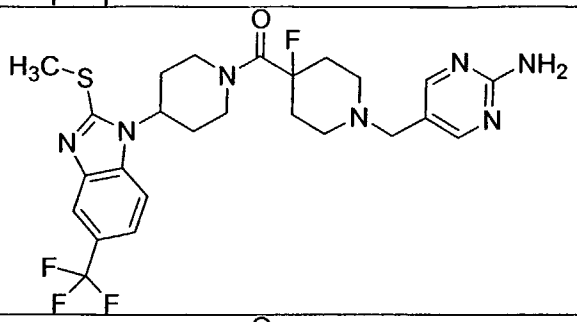
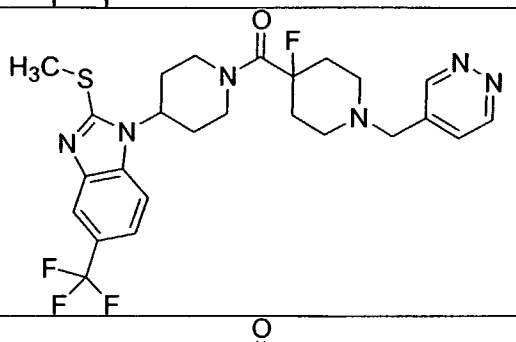
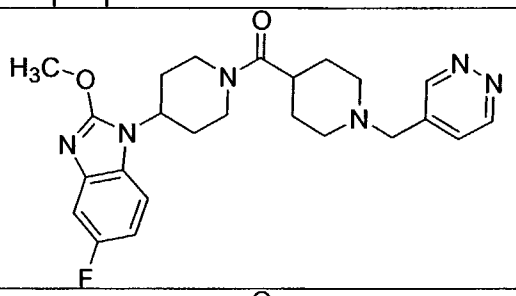
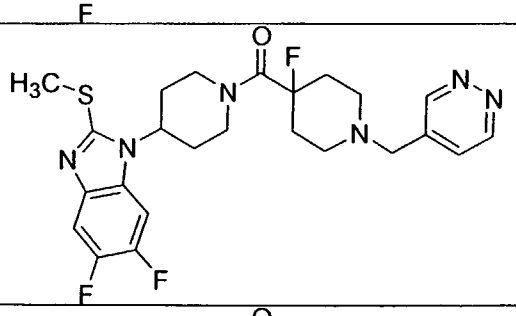
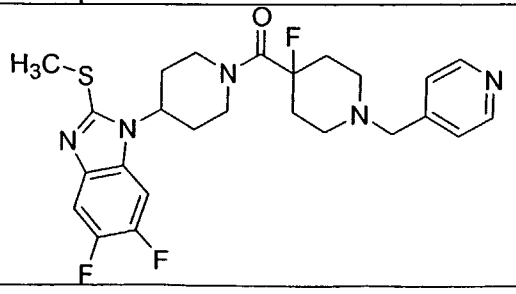
538		531 (ESMS)
539		545 (ESMS)
540		468 (ESMS)
541		540 (ESMS)
542		481 (ESMS)
543		482 (ESMS)

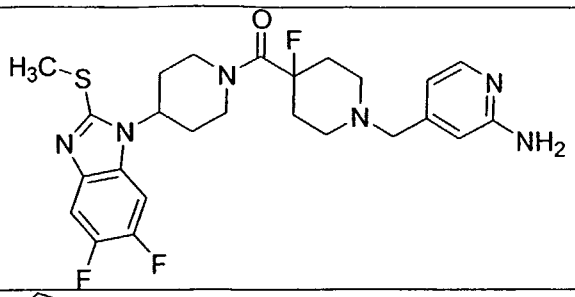
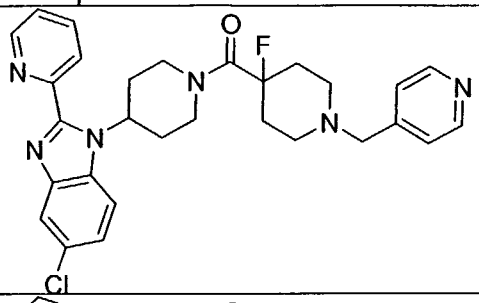
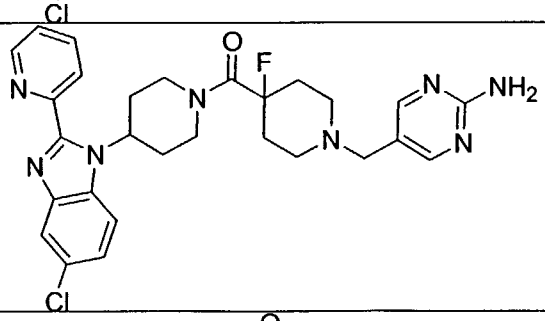
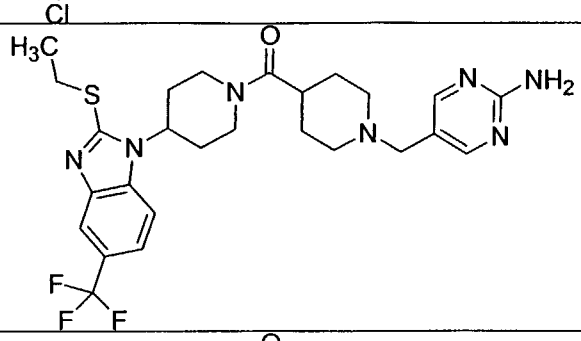
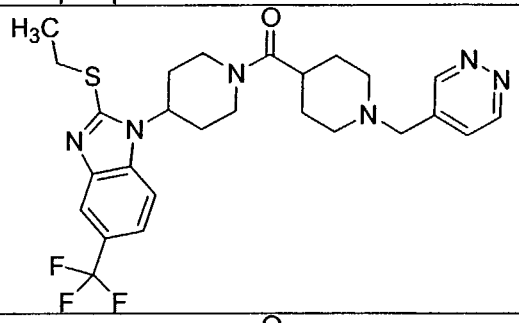
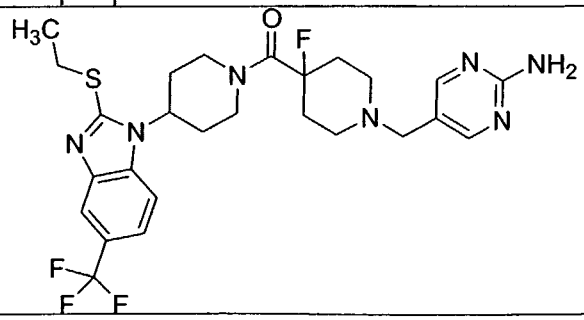
544		515 (ESMS)
545		517 (ESMS)
546		526 (ESMS)
547		5560 (ESMS)
548		526 (ESMS)
549		550 (ESMS)

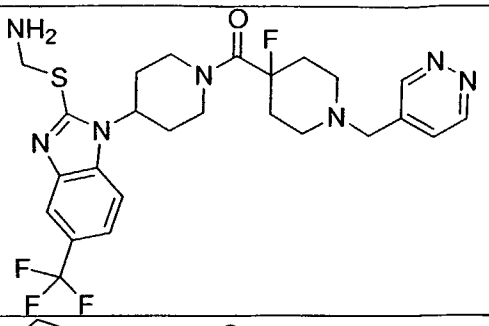
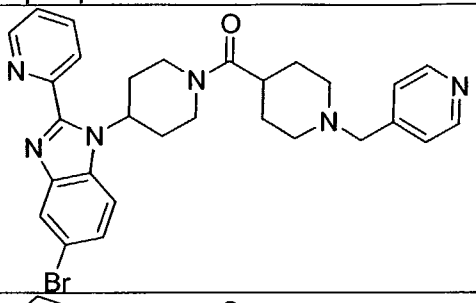
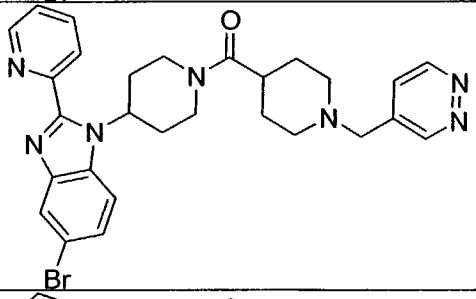
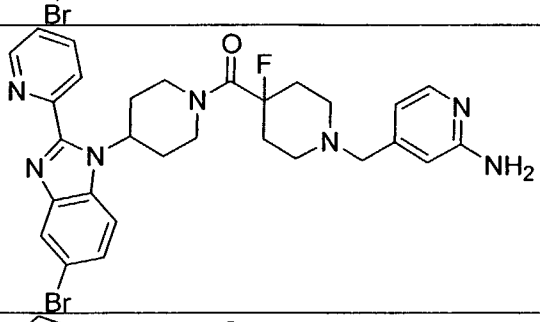
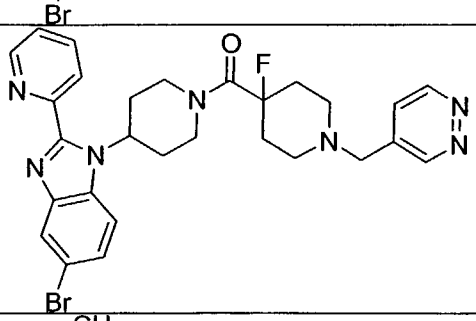
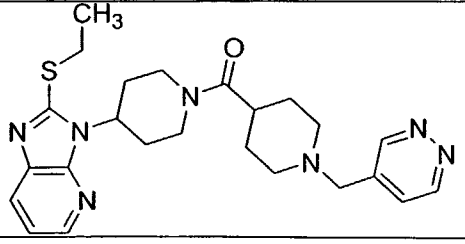
550		517 (ESMS)
551		532 (ESMS)
552		464 (ESMS)
553		516 (ESMS)
554		486 (ESMS)
555		502 (ESMS)

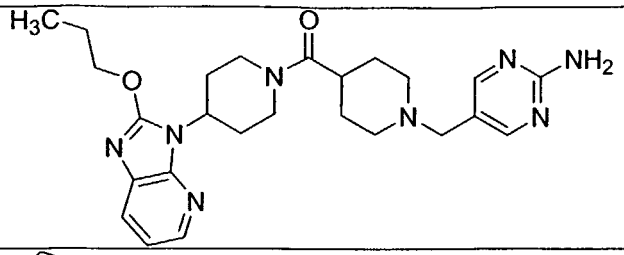
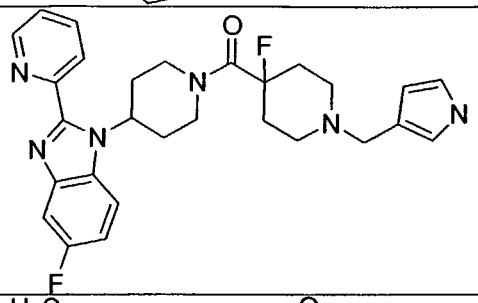
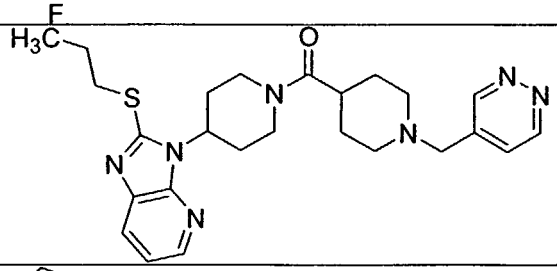
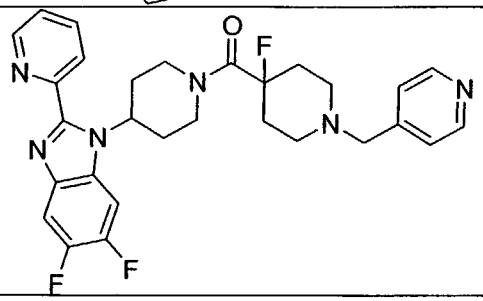
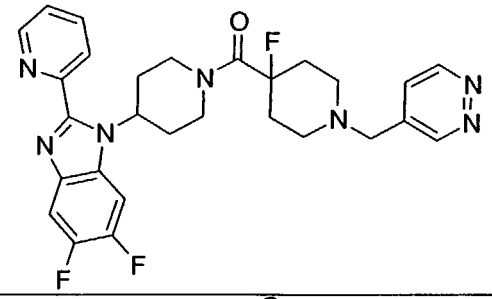
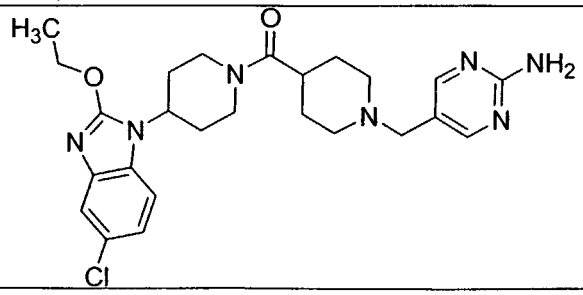
556		526 (ESMS)
557		516 (ESMS)
558		487 (ESMS)
559		496 (ESMS)
560		481 (FAB)
561		534 (ESMS)

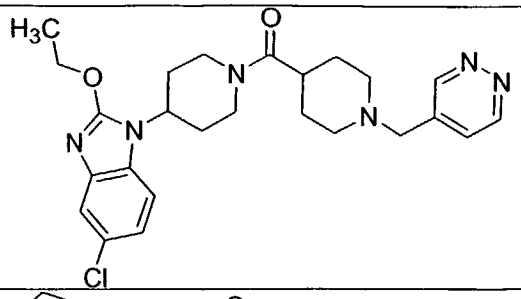
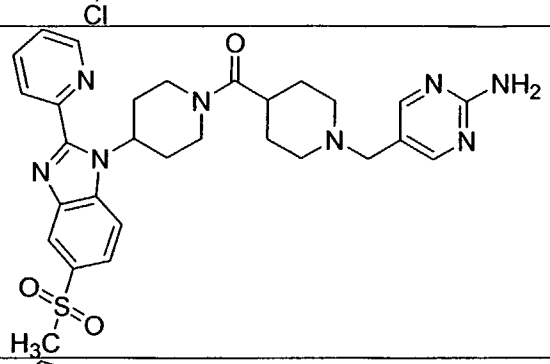
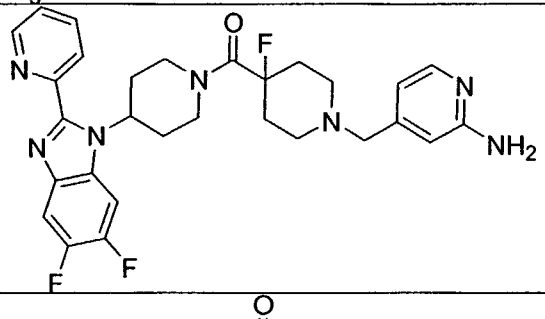
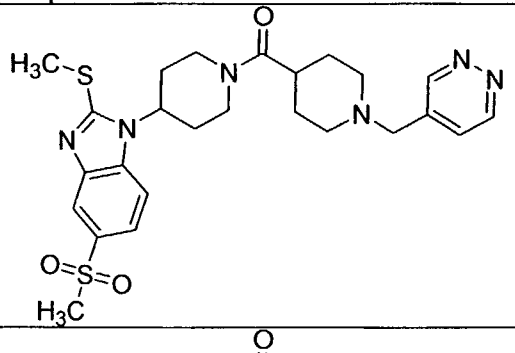
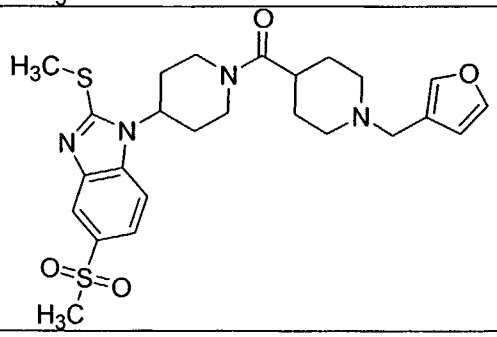
562		501 (ESMS)
563		517 (ESMS)
564		517 (ESMS)
565		517 (ESMS)
566		577 (ESMS)
567		592 (ESMS)

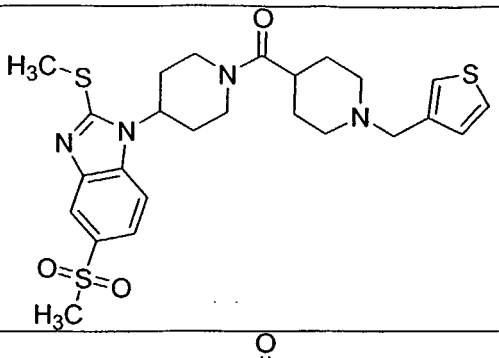
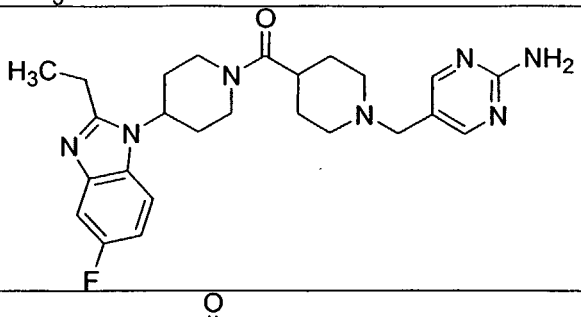
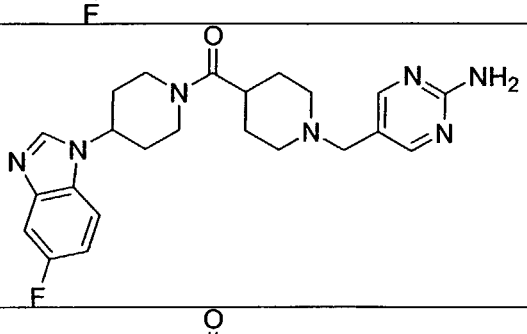
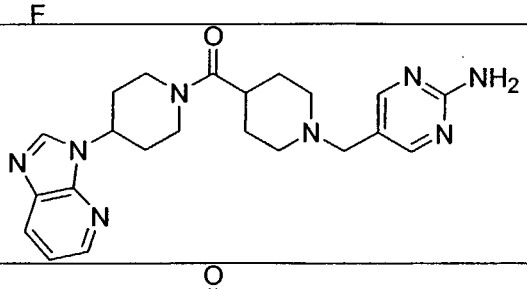
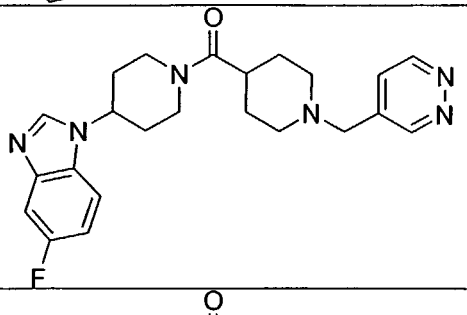
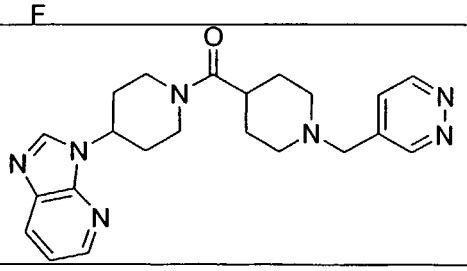
568		519 (ESMS)
569		552 (ESMS)
570		537 (ESMS)
571		453 (ESMS)
572		505 (ESMS)
573		504 (ESMS)

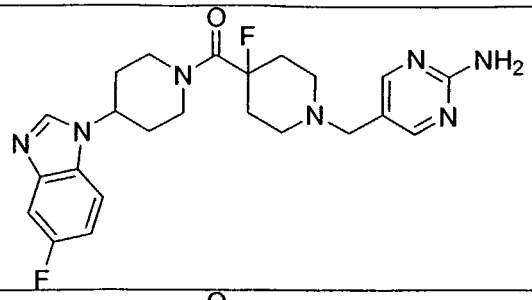
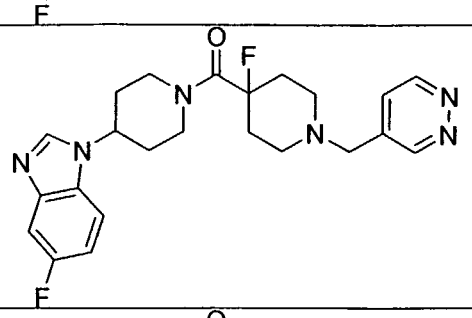
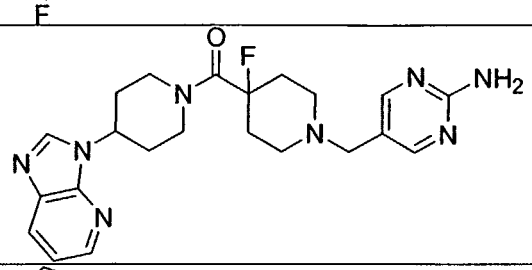
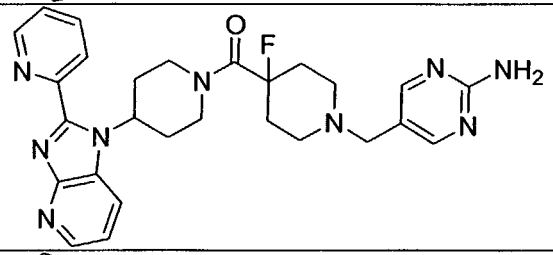
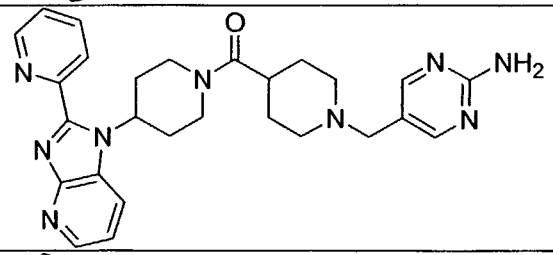
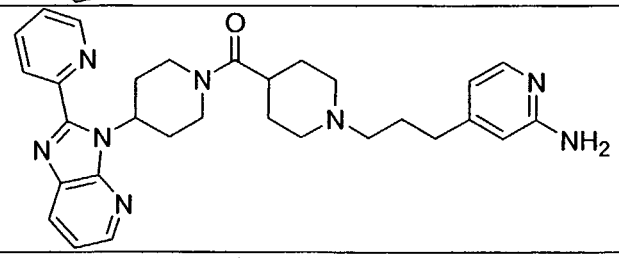
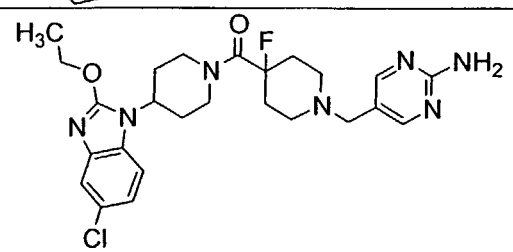
574		519 (ESMS)
575		533 (ESMS)
576		549 (ESMS)
577		548 (ESMS)
578		533 (ESMS)
579		566 (ESMS)

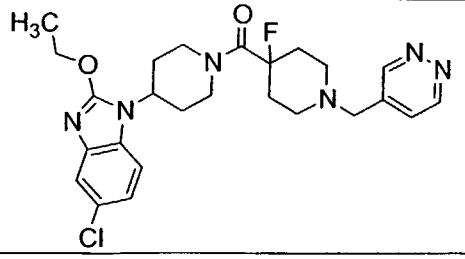
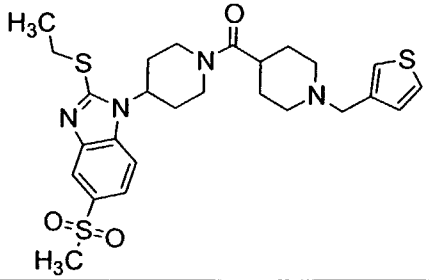
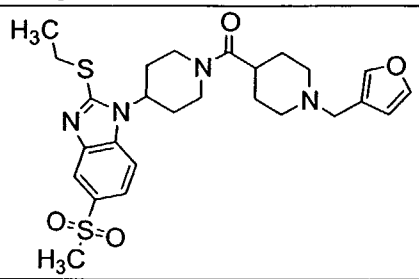
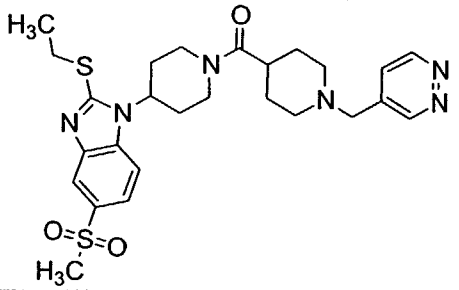
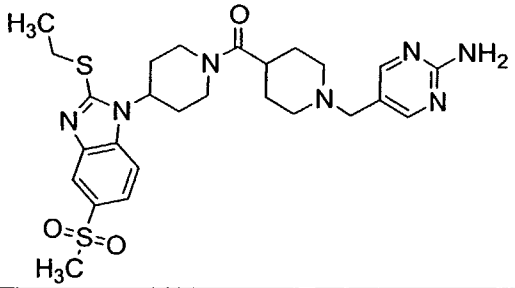
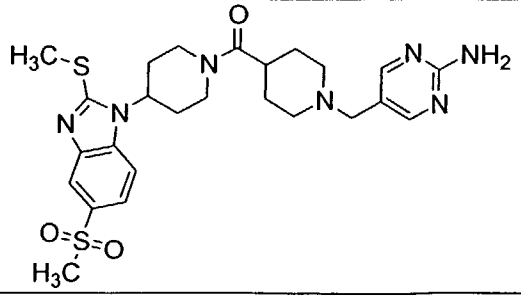
580		551 (ESMS)
581		559 (ESMS)
582		560 (ESMS)
583		592 (ESMS)
584		579 (ESMS)
585		466 (ESMS)

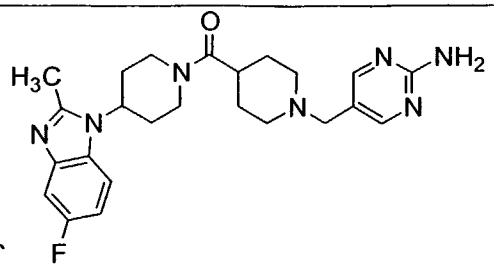
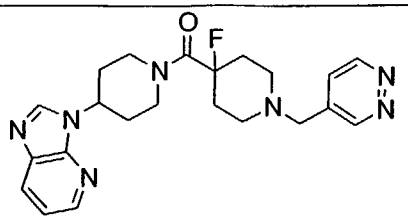
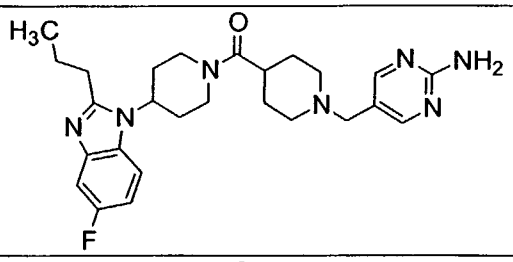
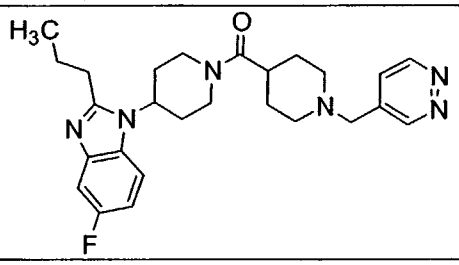
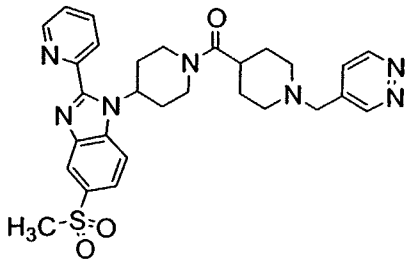
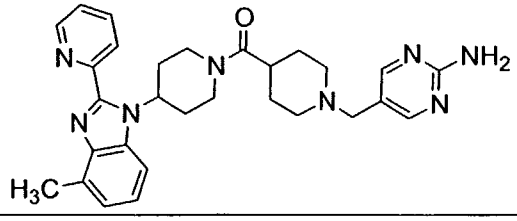
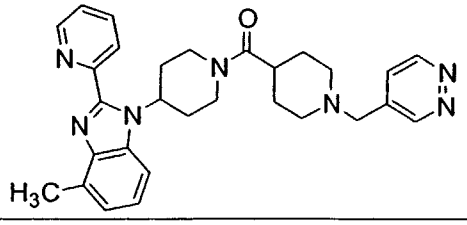
586		479 (FAB)
587		505 (ESMS)
588		480 (ESMS)
589		535 (ESMS)
590		536 (ESMS)
591		498 (ESMS)

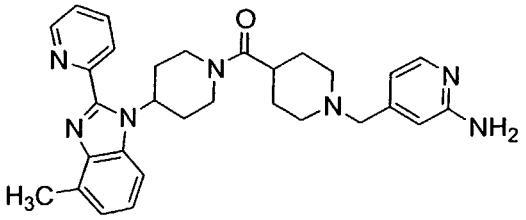
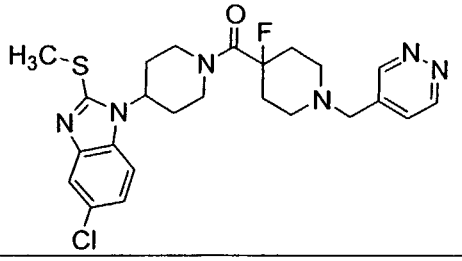
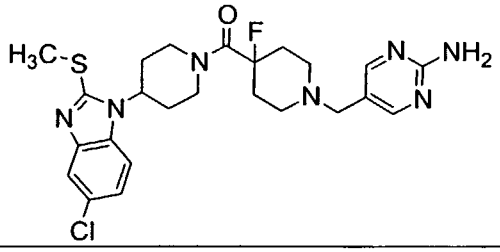
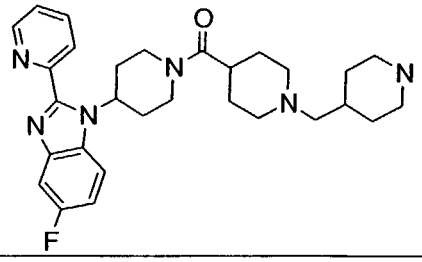
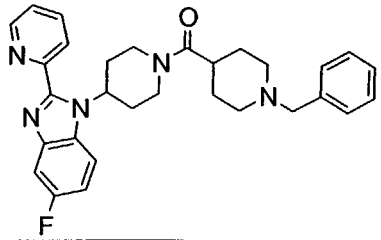
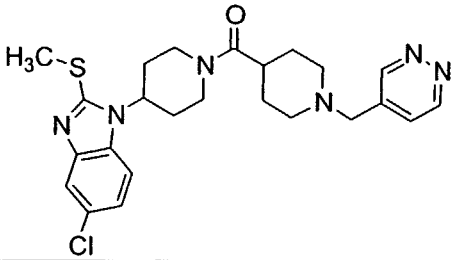
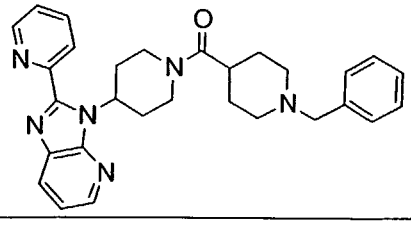
592		483 (ESMS)
593		575 (ESMS)
594		550 (ESMS)
595		529 (ESMS)
596		517 (ESMS)

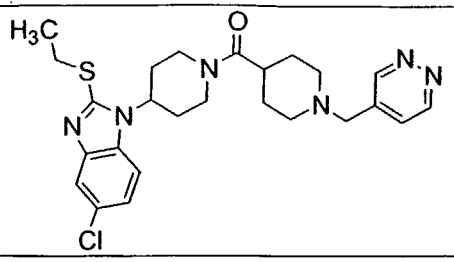
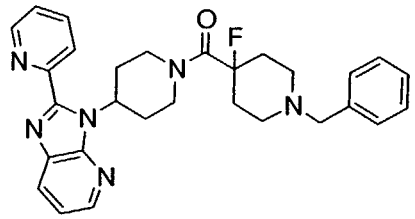
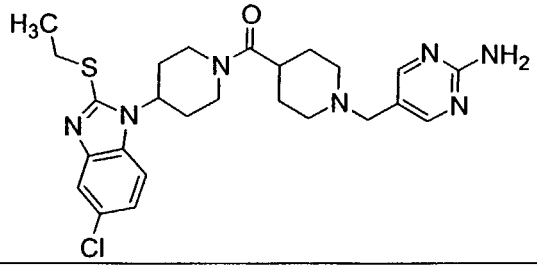
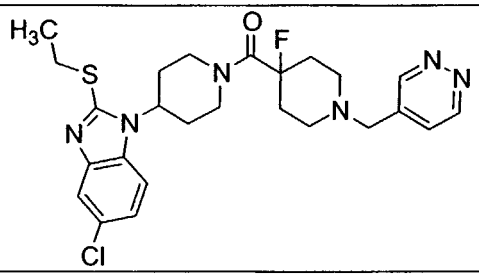
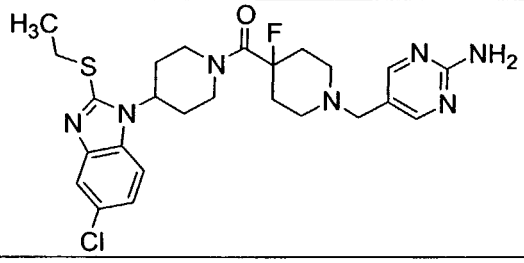
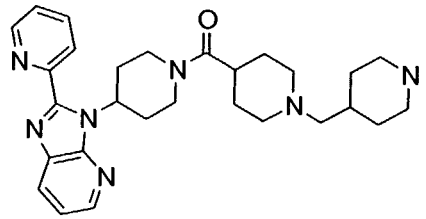
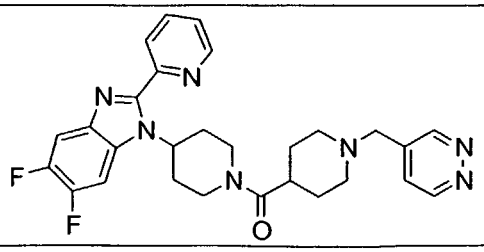
597		533 (ESMS)
598		466 (ESMS)
599		438 (ESMS)
600		421 (ESMS)
601		423 (ESMS)
602		406 (ESMS)

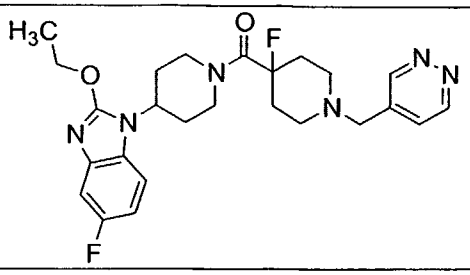
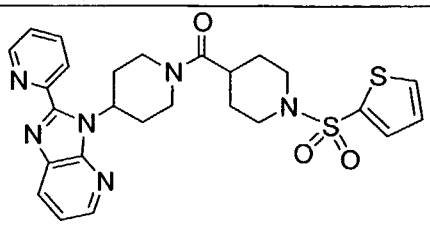
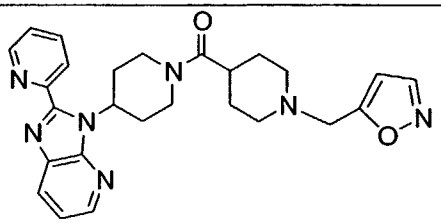
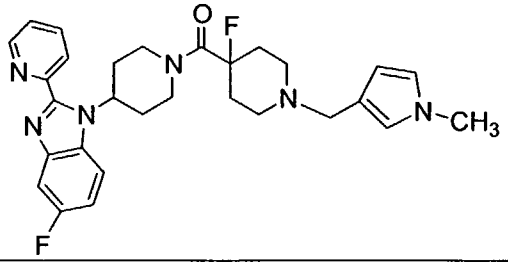
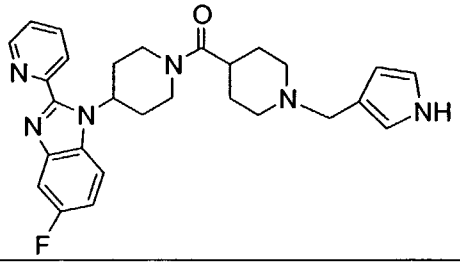
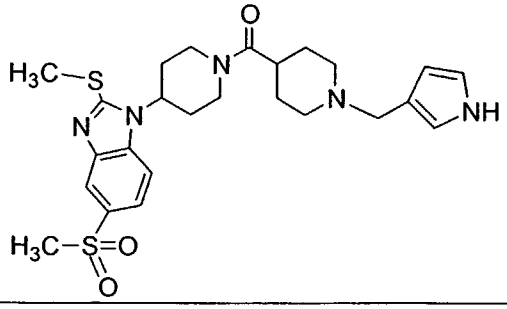
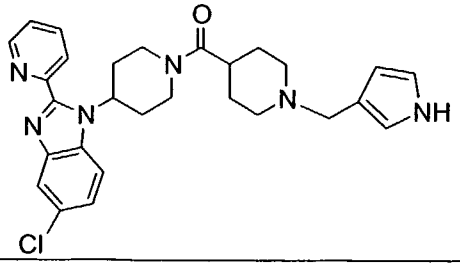
603		456 (ESMS)
604		441 (ESMS)
605		439 (ESMS)
606		516 (ESMS)
607		498 (ESMS)
608		525 (ESMS)
609		516 (ESMS)

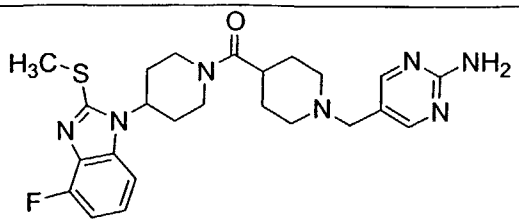
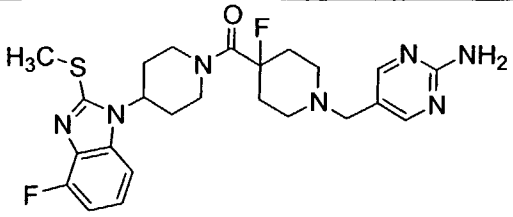
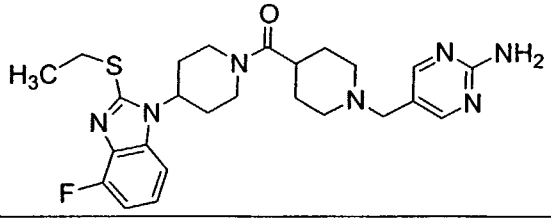
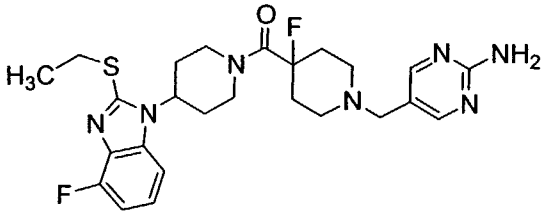
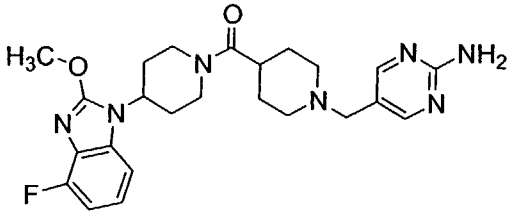
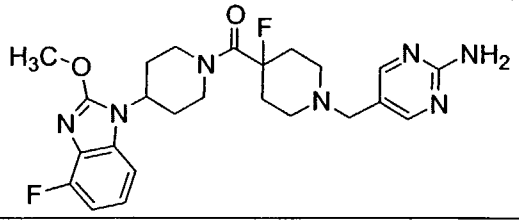
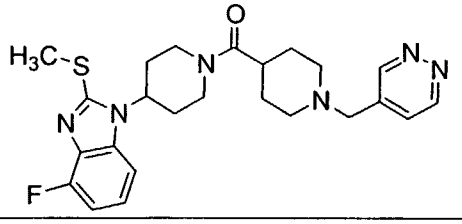
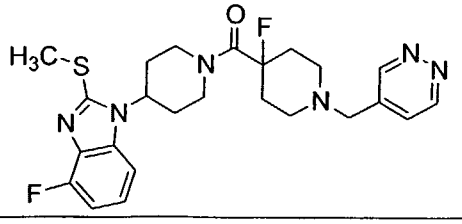
610		501 (ESMS)
611		547 (ESMS)
612		531 (ESMS)
613		543 (ESMS)
614		558 (ESMS)
615		544 (ESMS)

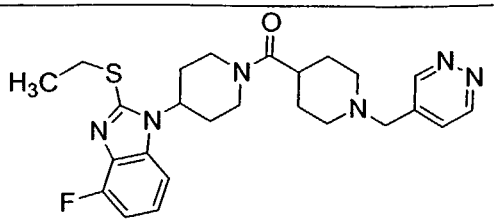
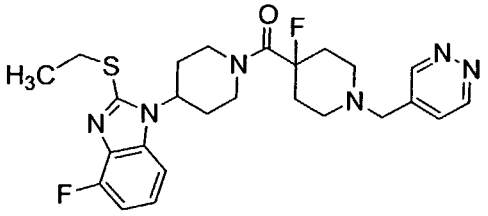
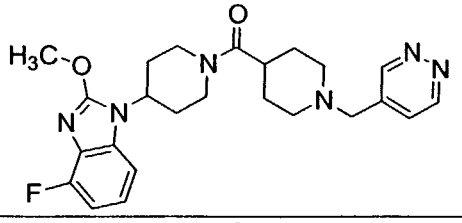
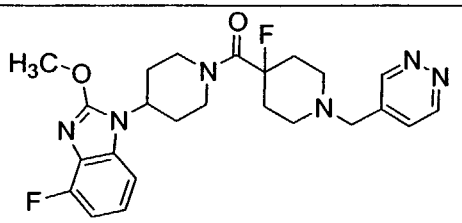
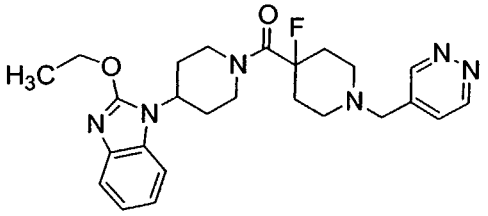
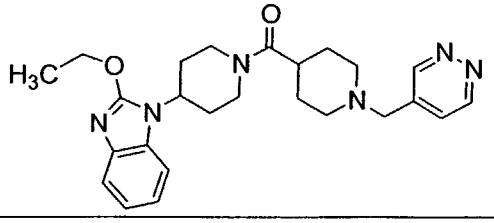
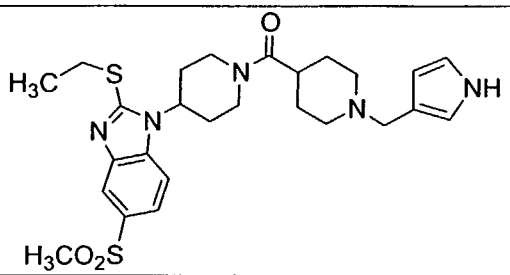
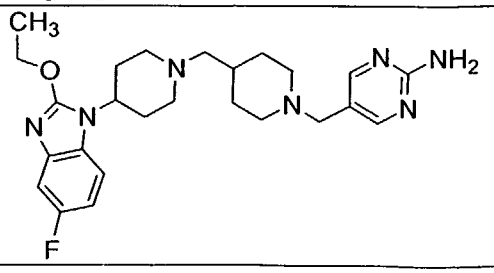
616		452 (FAB)
617		424 (ESMS)
618		480 (ESMS)
619		465 (ESMS)
620		560 (ESMS)
621		511 (ESMS)
622		496 (ESMS)

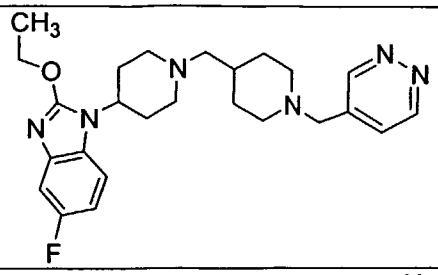
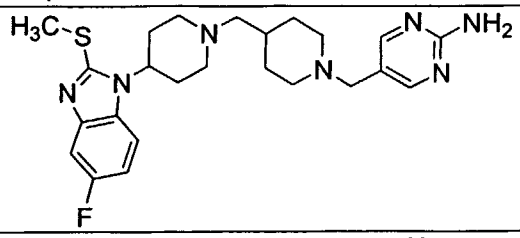
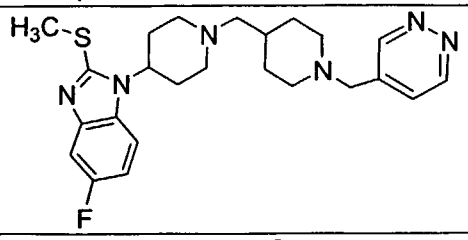
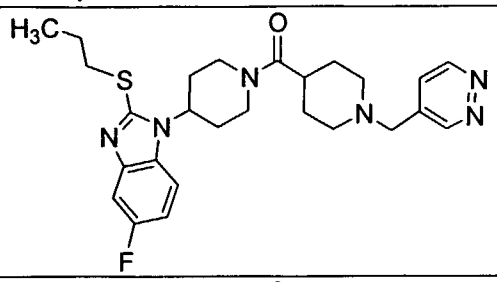
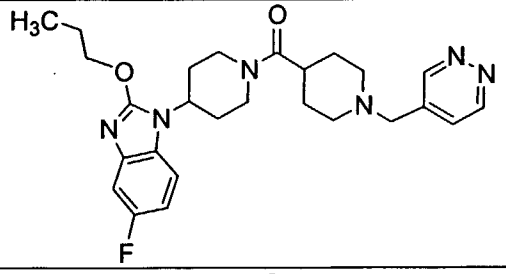
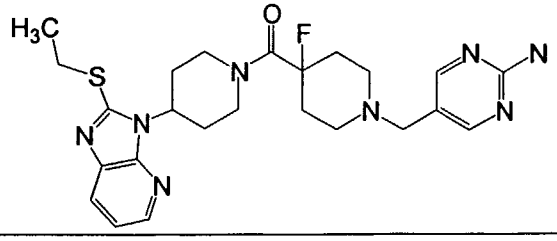
623		510 (ESMS)
624		503 (ESMS)
625		518 (ESMS)
626		505 (ESMS)
627		498 (ESMS)
628		485 (ESMS)
629		481 (ESMS)

630		499 (ESMS)
631		499 (ESMS)
632		514 (ESMS)
633		517 (ESMS)
634		532 (ESMS)
635		488 (ESMS)
636		518 (ESMS)

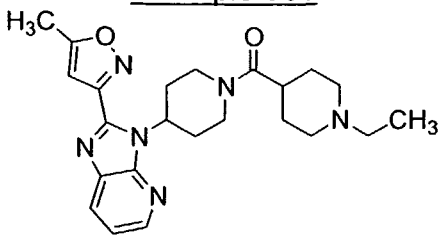
637		451 (ESMS)
638		537 (MH+)
639		472 (MH+)
640		519 (MH+)
641		487 (MH+)
642		516 (MH+)
643		503 (MH+)

644		484 (ESMS)
645		503 (ESMS)
646		498 (ESMS)
647		516 (ESMS)
648		468 (ESMS)
649		486 (ESMS)
650		469 (ESMS)
651		487 (ESMS)

652		483 (ESMS)
653		501 (ESMS)
654		453 (ESMS)
655		471 (ESMS)
656		468 (ESMS)
657		450 (ESMS)
658		530 (ESMS)
659		

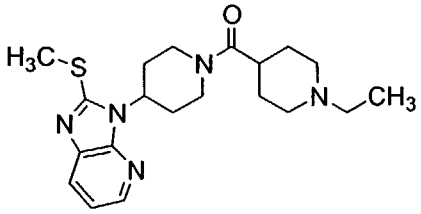
660		453 (FAB)
661		470 (FAB)
662		455 (FAB)
663		497 (ESMS)
664		481 (FAB)
664A		499 (FAB)

Example 665



4-[[4-[2-(5-methyl-3-isoxazolyl)-3H-imidazo[4,5-b]pyridine-3-yl]-1-(4-piperidinylcarbonyl)piperidine (0.99 g, 2.51 mmoles) and pyridazine 4-carboxaldehyde (0.35 g, 3.26 mmoles) were stirred at RT in dry CH_2Cl_2 (25 ml) containing activated 3Å molecular sieves (6.5 g). After 5 h, triacetoxy borohydride (3.2 g, 15 mmoles) was added and the mixture was stirred for 70 h. The mixture was diluted with CH_2Cl_2 and the solid filtered through a pad of Celite. The filtrate was stirred for 20 min. with saturated aqueous $NaHCO_3$, then separated, washed with brine, and dried over anahydrous Na_2SO_4. The reaction mixture was purified by preparative TLC. The plates were eluted with EtOAc:Hexanes:$CH_3OH(NH_3)$ (75:20:5). Extraction of the bands with 13% $CH_3OH(NH_3)$/EtOAc gave a mixture of Example 665 and Example 496. Example 658: MS (M+H): 423.

In a similar manner, using 4-[[4-[2-(methylthio)-3H-imidazo[4,5-b]pyridine-3-yl]-1-(4-piperidinylcarbonyl)piperidine (0.88 gr.;2.44 mmoles), pyridazine 4-carboxaldehyde (0.34 g, 3.18 mmoles), and triacetoxy borohydride, a mixture of Example 666 and Example 495 was prepared:



Example 666: MS (M+H): 388

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).

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 these assays, compounds of formula I have a K_i within the range of about 0.1 to about 600 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.

Representative compounds of the present invention tested according to the above procedures have the following Ki values:

Ex.	Receptor Source	K_i
1	rHu	1
3	Guinea pig	13
5	rHu	9
13	Guinea Pig	27
54	Guinea Pig	30
71	Guinea Pig	1
94	Guinea Pig	1
109	rHu	1
120	Guinea Pig	0.3
165	rHu	2
170	Guinea Pig	0.5
173	Guinea Pig	0.4
195	Guinea Pig	10
211	Guinea Pig	7
254	Guinea Pig	13
269	rHu	4
270	rHu	4
281	rHu	4
290	rHu	3
290	rHu	3
297	rHu	4
297	rHu	4
315	rHu	5
316	rHu	5
316	rHu	5
326	rHu	2

Ex.	Receptor Source	Ki
335	rHu	12
388	rHu	30
423	rHu	5
442	rHu	1
449	rHu	1
459	rHu	4
460	rHu	4
468	rHu	10
493	rHu	1
502	rHu	7
512	rHu	2
547	rHu	14
552	rHu	4
557	rHu	19
571	rHu	2
574	rHu	2
577	rHu	44
588	rHu	6
592	rHu	9
595	rHu	41
598	rHu	17
608	rHu	1
618	rHu	9
619	rHu	2
625	rHu	10
628	rHu	4

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.

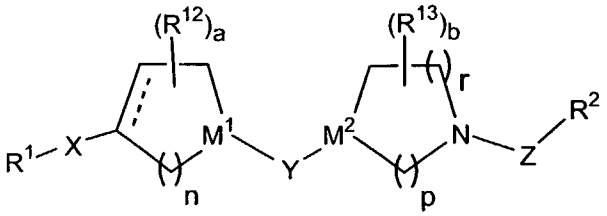
When separate H_3 and H_1 antagonist pharmaceutical compositions are to be administered, they can be provided in a kit comprising in a single package, one container comprising an H_3 antagonist in a pharmaceutically acceptable carrier, and a separate container comprising an H_1 antagonist in a pharmaceutically 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 2;

b is 0 to 2;

n is 1, 2 or 3;

p is 1, 2 or 3;

r is 0, 1, 2, or 3;

with the provisos that when M^2 is N, p is not 1; and that when r is 0, M^2 is $C(R^3)$; and that the sum of p and r is 1 to 4;

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

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

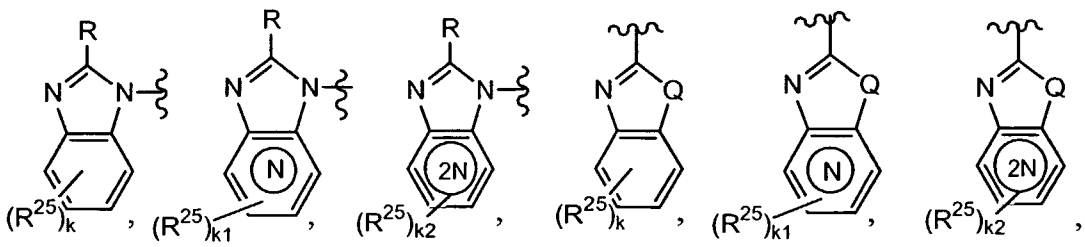
X is a bond or C_1-C_6 alkylene;

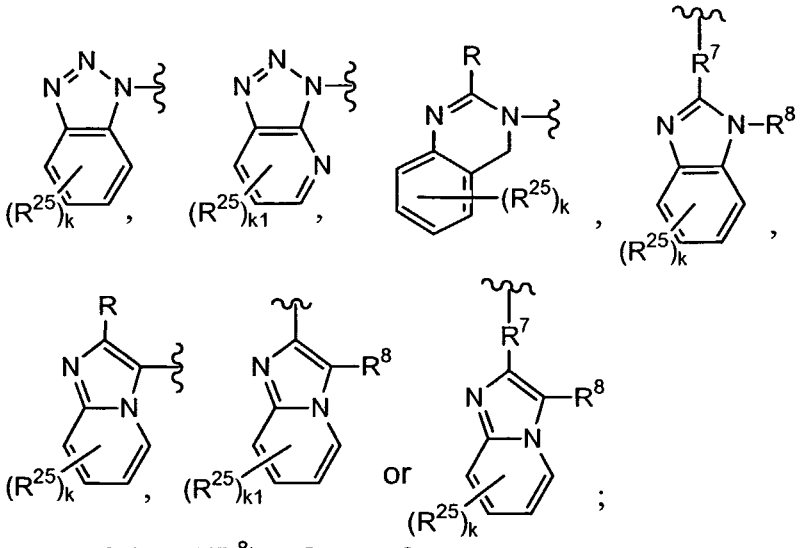
Y is –C(O)-, -C(S)-, $-(CH_2)_q$ -, $-NR^4C(O)$-, $-C(O)NR^4$-, $-C(O)CH_2$-, $-SO_2$-, $-N(R^4)$-, -NH-C(=N-CN)- or –C(=N-CN)-NH-; with the provisos that when M^1 is N, Y is not $-NR^4C(O)$- or -NH-C(=N-CN)-; when M^2 is N, Y is not $-C(O)NR^4$- or –C(=N-CN)-NH-; and when Y is $-N(R^4)$-, M^1 is CH and M^2 is $C(R^3)$;

q is 1 to 5, provided that when both M^1 and M^2 are N, q is 2 to 5;

Z is a bond, C_1-C_6 alkylene, C_1-C_6 alkenylene, -C(O)-, -CH(CN)-, $-SO_2$- or $-CH_2C(O)NR^4$-;

R^1 is





Q is –N(R^8)-, -S- or –O-;

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

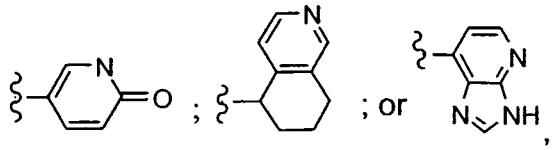
k1 is 0, 1, 2 or 3;

k2 is 0, 1 or 2;

R is H, C_1-C_6 alkyl, halo(C_1-C_6)alkyl-, C_1-C_6 alkoxy, (C_1-C_6)alkoxy-(C_1-C_6)alkyl-, (C_1-C_6)-alkoxy-(C_1-C_6)alkoxy, (C_1-C_6)alkoxy-(C_1-C_6)alkyl-SO_{0-2}, R^{32}-aryl(C_1-C_6)alkoxy-, R^{32}-aryl(C_1-C_6)alkyl-, R^{32}-aryl, R^{32}-aryloxy, R^{32}-heteroaryl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl-oxy-, R^{37}-heterocycloalkyl, R^{37}-heterocycloalkyl-oxy-, R^{37}-heterocycloalkyl-(C_1-C_6)alkoxy, N(R^{30})(R^{31})-(C_1-C_6)alkyl-, -N(R^{30})(R^{31}), -NH-(C_1-C_6)alkyl-O-(C_1-C_6)alkyl, -NHC(O)NH(R^{29}); R^{29}-$S(O)_{0-2}$-, halo(C_1-C_6)alkyl-$S(O)_{0-2}$-, N(R^{30})(R^{31})-(C_1-C_6)alkyl-$S(O)_{0-2}$- or benzoyl;

R^8 is H, C_1-C_6 alkyl, halo(C_1-C_6)alkyl-, (C_1-C_6)alkoxy-(C_1-C_6)alkyl-, R^{32}-aryl(C_1-C_6)alkyl-, R^{32}-aryl, R^{32}-heteroaryl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkyl, R^{37}-heterocycloalkyl, N(R^{30})(R^{31})-(C_1-C_6)alkyl-, R^{29}-$S(O)_2$-, halo(C_1-C_6)alkyl-$S(O)_2$-, R^{29}-$S(O)_{0-1}$-(C_2-C_6)alkyl-, halo(C_1-C_6)alkyl-$S(O)_{0-1}$-(C_2-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; thianaphthenyl;



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

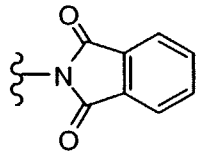
R^3 is H, halogen, C_1-C_6 alkyl, -OH, (C_1-C_6)alkoxy or –$NHSO_2$-(C_1-C_6)alkyl;

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

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, -CH_2-NR^4R^5, -$NHSO_2R^{22}$, -$N(SO_2R^{22})_2$, phenyl, R^{33}-phenyl, NO_2, -CO_2R^4, -$CON(R^4)_2$,



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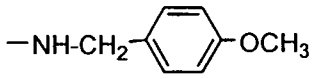


;

R^7 is -$N(R^{29})$-, -O- or –$S(O)_{0\text{-}2}$-;

R^{12} is independently selected from the group consisting of C_1-C_6 alkyl, hydroxyl, 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 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, hydroxyl, 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 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, halogen, -CN, -NO_2, –CF_3, -OH, C_1-C_6 alkoxy, (C_1-C_6)alkyl-C(O)-, aryl-C(O)-, -$C(O)OR^{29}$,

-N(R^4)(R^5), N(R^4)(R^5)-C(O)-, N(R^4)(R^5)-S(O)$_{1-2}$-, R^{22}-S(O)$_{0-2}$-, 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, C_3-C_6 cycloalkyl, 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-, R^{35}-heteroaryl, (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^{38})-(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, R^{35}-aryl-O-, -SR^{22}, -CF_3, -OCF_3, -$OCHF_2$, -$NR^{39}R^{40}$, phenyl, R^{33}-phenyl, NO_2, -CO_2R^{39}, -CON(R^{39})$_2$, -S(O)$_2R^{22}$, -S(O)$_2$N(R^{20})$_2$, -N(R^{24})S(O)$_2R^{22}$, -CN, hydroxy-(C_1-C_6)alkyl-, -$OCH_2CH_2OR^{22}$, and R^{35}-aryl(C_1-C_6)alkyl-O-, or two R^{32} groups on adjacent carbon atoms together form a –OCH_2O- or –O(CH_2)$_2$O- group;

R^{33} is 1 to 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen, -CN, -NO_2, -CF_3, -OCF_3, -$OCHF_2$ 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 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})$_2$, -$COOR^{20}$, -C(O)N(R^{29})$_2$ and –NO_2, or R^{37} is one or two =O groups;

R^{38} is H, C_1-C_6 alkyl, R^{35}-aryl, R^{35}-aryl(C_1-C_6)alkyl-, (C_1-C_6)alkyl-SO_2 or halo(C_1-C_6)alkyl-SO_2-;

R^{39} 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^{40} is hydrogen, C_1-C_6 alkyl, -C(O)R^{20}, -C(O)$_2R^{20}$, –C(O)N(R^{20})$_2$, (C_1-C_6)alkyl-SO_2-, or (C_1-C_6)alkyl-SO_2-NH-;

or R^{39} and R^{40}, 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 M^1 is N, a is 0, and 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 fluorine, b is 0, r is 1, and p is 2.

4. A compound of claim 3 wherein X is a bond.

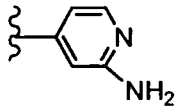
5. A compound of claim 4 wherein Y is –C(O)-.

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

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

8. A compound of claim 7 wherein R^2 is pyrimidy, R^6-pyrimidyl, pyridyl, R^6-pyridyl or pyridazinyl and R^6 is $-NH_2$.

9. A compound of claim 8 wherein R^2 is



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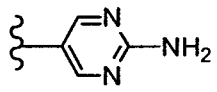

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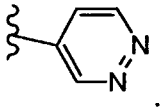

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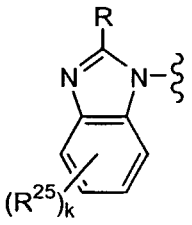
10. A compound of claim 2 wherein R^1 is



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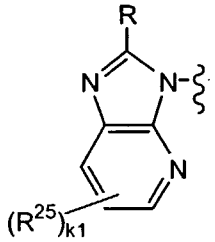
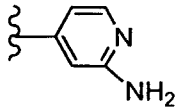
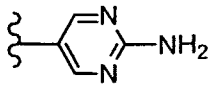
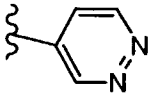


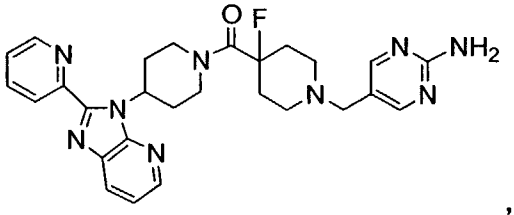
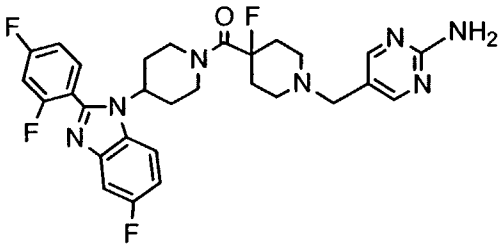
11. A compound of claim 10 wherein R is (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkoxy, (C_1-C_6)alkylthio, heteroaryl or R^{32}-aryl; R^{25} is halogen or –CF_3; and k and k1 are 0 or 1.

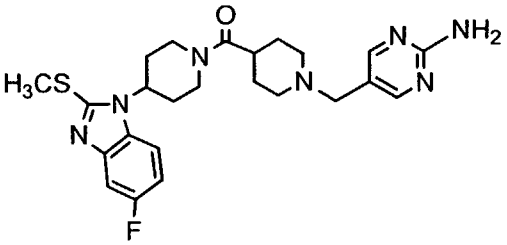
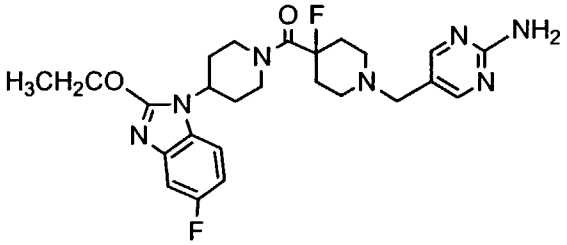
12. A compound of claim 11 wherein R is $–CH_3$, $-CH_2CH_3$, $–OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2CH_3$, $-OCH((CH_3)_2$, $-CH_2CH_3$, $-SCH_3$, $-SCH_2CH_3$, pyridyl, pyrimidyl, pyrazinyl, furanyl, oxazolyl or R^{32}-phenyl.

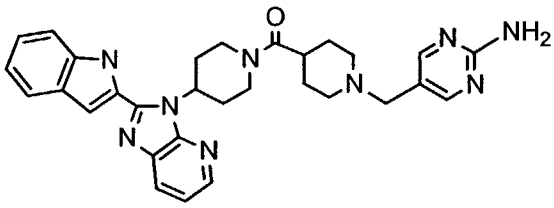
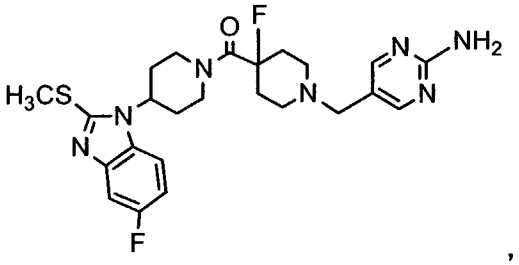
13. A compound of claim 12 wherein R^2 is

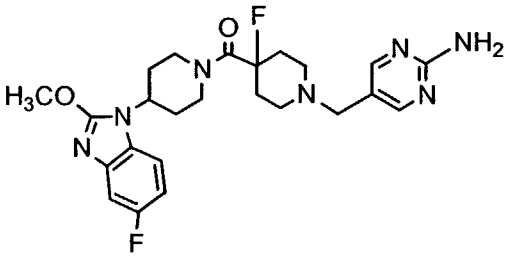
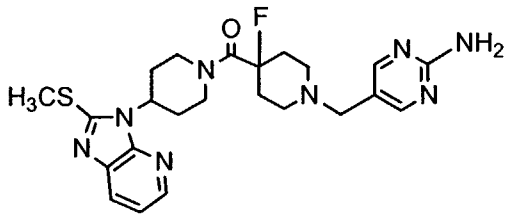
 ,  or 

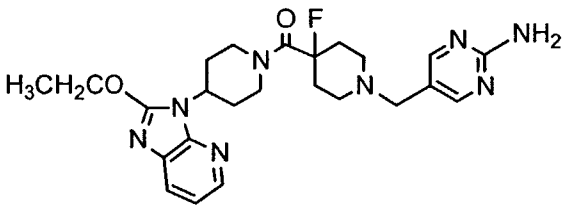
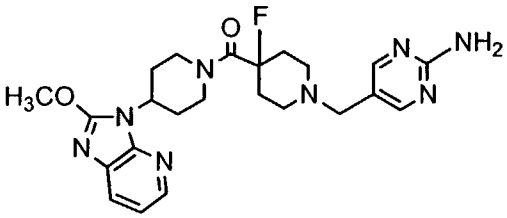
14. A compound of claim 1 selected from the group consisting of

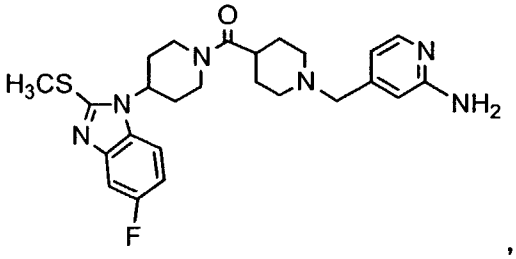
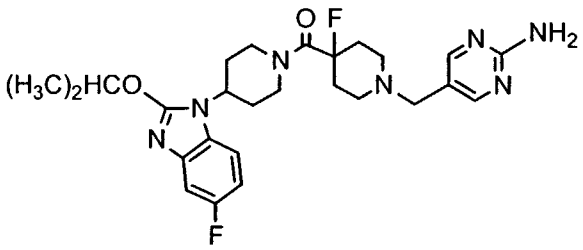
 ,  ,

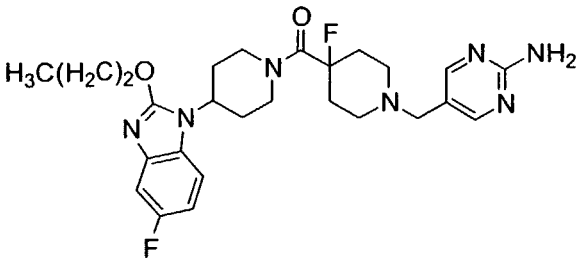
 ,  ,

 ,  ,

 ,  ,

 ,  ,

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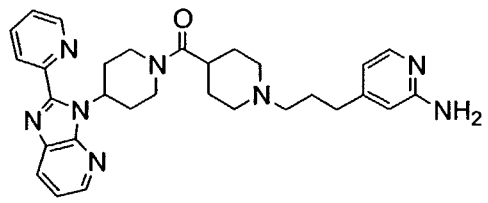
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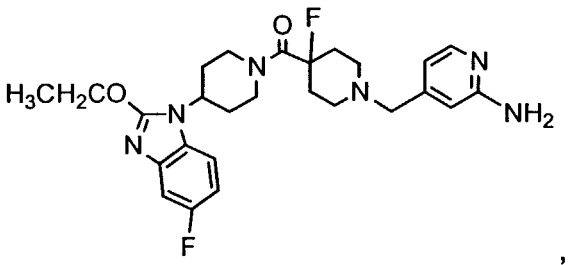
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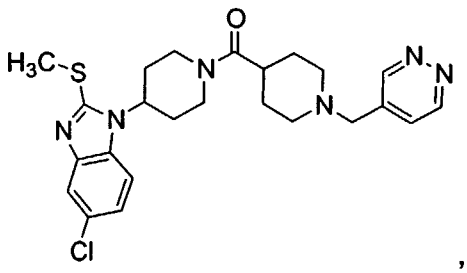
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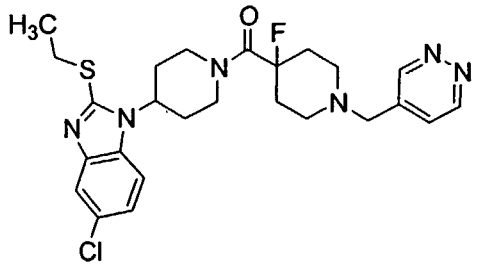
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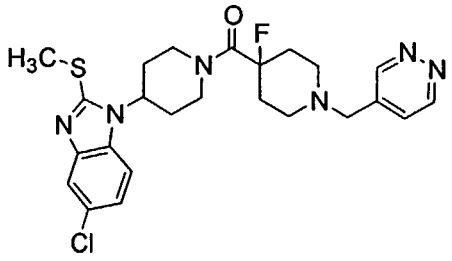
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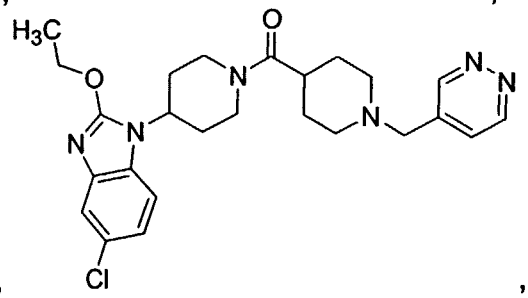
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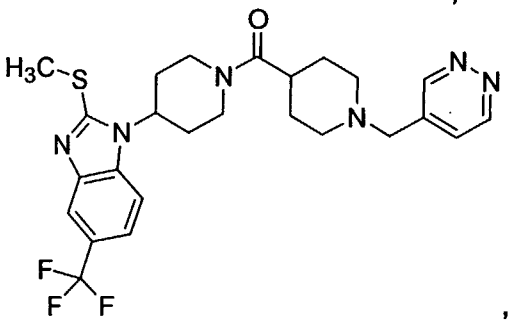
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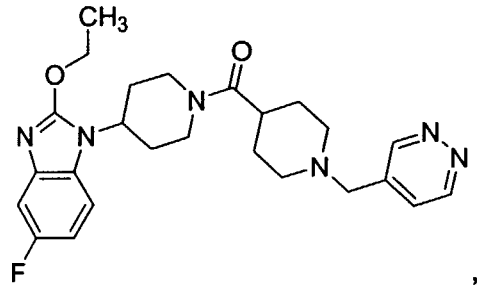
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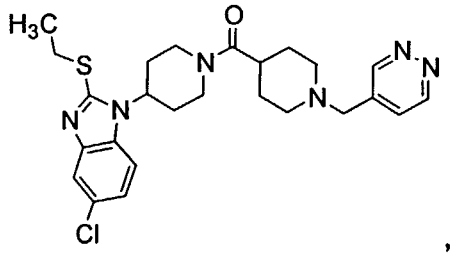
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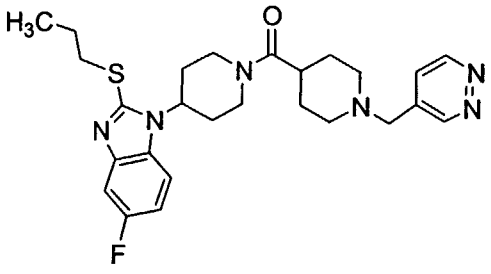
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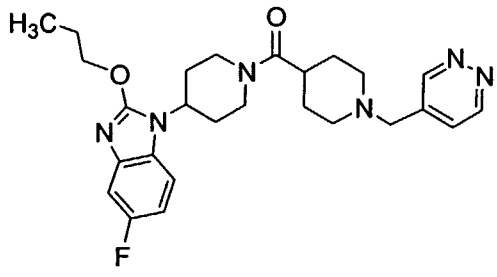
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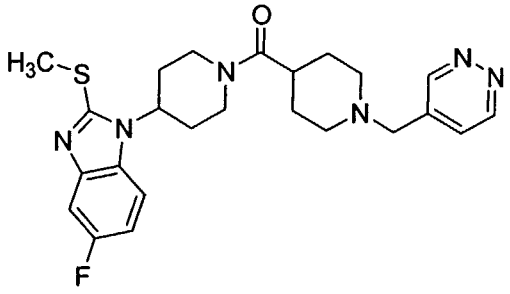
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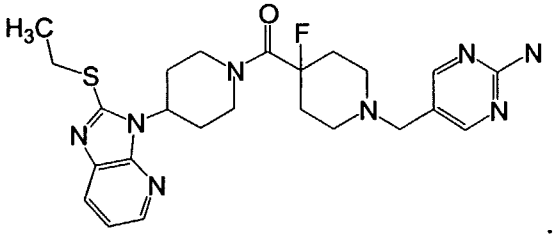
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15. A pharmaceutical composition comprising an effective amount of a compound of claim 1 and a pharmaceutically effective carrier.

16. 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 and hypo motility and acidic secretion of the gastro-intestinal tract, obesity, sleeping disorders, disturbances of the central nervous system, attention deficit hyperactivity disorder, hypo and hyperactivity of the central nervous system, Alzheimer's disease, schizophrenia, and migraine.

17. 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.

18. 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, and congestion.

19. The use of claim 19 wherein 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.