COMBINATION OF AN H_3 ANTAGONIST/INVERSE AGONIST AND AN APPETITE SUPPRESSANT

FIELD OF THE INVENTION

The present invention relates to pharmaceutical compositions comprising therapeutic combinations comprising: one or more H_3 antagonists/inverse agonists; one or more appetite suppressants selected from the group consisting of CB_1 antagonists/inverse agonists, sibutramine, phentermine and topiramate; and optionally one or more HMG-CoA reductase inhibitors. The invention also relates to medicaments and kits comprising the pharmaceutical compositions of the present invention, and methods of treating obesity, obesity related disorders and diabetes using the pharmaceutical compositions of the present invention.

BACKGROUND OF THE INVENTION

The histamine receptors, H_1, H_2, H_3 and H_4 have been characterized by their pharmacological behavior. 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. The most prominent H_2 receptor-mediated responses are the secretion of gastric acid in mammals and the chronotropic effect in isolated mammalian atria. H_4 receptors are expressed primarily on eosinophils and mast cells and have been shown to be involved in the chemotaxis of both cell types.

In the periphery, 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. In addition, in rodents, peripheral H_3

receptors are expressed in brown adipose tissue, suggesting that they may be involved in thermogenesis regulation.

H_3 receptors are also present in the CNS. H_3 receptor expression is observed in cerebral cortex, hippocampal formation, hypothalamus and other parts of the human and animal brain. H_3 receptors are expressed on histaminergic neurons where they function as autoreceptors and, on neurons involved in other neurotransmitter systems, where they function as heteroreceptors. In both cases H_3 receptor activation results in presynaptic inhibition of neurotransmitter release. In the particular case of histaminergic neurons, H_3 receptors have been implicated in the regulation of hypothalamic histamine tone, which in turn has been associated with the modulation of sleeping, feeding and cognitive processes in the human brain (see, for example, Leurs et al., *Nature Reviews, Drug Discovery*, 4, (2005), 107).

It is also known and has been described in the literature that histamine is involved in regulation of cognitive and memory processes in the human brain (see, for example, *Life Sciences*, 72, (2002), 409-414). Consequently, indirect modulation of histaminergic brain function through the central H_3 receptors may be a means to modulate these processes. Different classes of H_3 receptor ligands have been described and their use for neurological and psychiatric diseases has been suggested (see, e.g., US Patent Publication No. 20040224953, International Publication No. WO2004089373, International Publication No. WO2004101546). H_3 receptor antagonists may be useful in treating various neuropsychiatric conditions, where cognitive deficits are an integral part of the disease, specifically ADHD, schizophrenia and Alzheimer's disease.

Imidazole H_3 receptor antagonists are well known in the art. More recently, non-imidazole H_3 receptor antagonists have been disclosed in US Patents 6,720,328 and 6,849,621, and in US Published Applications 2004/0097483, 2004/0048843 and 2004/0019099.

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.

WO 95/14007 discloses H3 receptor antagonists of the imidazole type.

WO 99/24405 discloses H_3 receptor ligands of the imidazole type.

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.

HMG-CoA reductase inhibitors, e.g., statins such as lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin, and resuvastatin, slow the progression of atherosclerotic lesions in the coronary and carotid arteries. Simvastatin, atorvastatin and pravastatin have also been shown to reduce the risk of coronary heart disease events in patients with hypercholesterolemia and/or atherosclerotic coronary heart disease (CHD).

Simvastatin is marketed worldwide, and sold in the U.S. under the tradename ZOCOR®. Methods for making it are described in U.S Patent Nos. 4,444,784; 4,916,239; 4,820,850; among other patent and literature publications.

The CB_1 receptor is one of the most abundant neuromodulatory receptors in the brain, and is expressed at high levels in the hippocampus, cortex, cerebellum, and basal ganglia (e.g., Wilson et al., *Science*, 2002, vol. 296, 678-682). Selective CB_1 receptor antagonists, for example pyrazole derivatives such as rimonabant, can be used to treat various conditions, such as obesity and metabolic syndrome (e.g., Bensaid et al., *Molecular Pharmacology*, 2003 vol. 63, no. 4, pp. 908-914; Trillou et al., *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 2002 vol. 284, R345-R353; Kirkham, *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 2002 vol. 284, R343-R344; Sanofi-Aventis Publication, Bear Stearns Conference, New York, September 14, 2004; Nicole Cranois and Jean-Marc Podvin, Sanofi-Synthelabo, press release reporting results of RIO-LIPIDS AND STRATUS-US Study results, American College of Cardiology Annual Meeting, New Orleans, March 9, 2004;), neuroinflammatory disorders (e.g., Adam, et al., *Expert Opin. Ther. Patents*, 2002, vol. 12, no. 10, 1475-1489), cognitive disorders, psychosis, addiction, gastrointestinal disorders (e.g., Lange et al., *J. Med. Chem.* 2004, vol. 47, 627-643) and cardiovascular conditions (e.g., Porter et al., *Pharmacology and Therapeutics*, 2001 vol. 90, 45-60).

Recently, it has been shown that treatment of subjects with CB_1 receptor antagonists (e.g., rimonabant) can increase serum high density lipoprotein cholesterol (HDL-C) levels, decrease triglyceride levels and decrease waist circumference in patients (Sanofi-Aventis Publication, Bear Stearns Conference, New York, September 14, 2004, pages 19-24).

Sibutramine has been shown to reduce food intake (e.g., Halford et al., British Journal of Pharmacology 1994, 114: Proc Suppl (387P); Stricker-Krongrad et al., *International Journal of Obesity* 1995, 19: Suppl 2 (145)) and increase oxygen consumption and body core temperature (Connoley et al., *British Journal of Pharmacology* 1994, 114:Proc Suppl (388P)).

Phentermine is an appetite suppressant used for treating obesity (e.g., D. Craddock, *Drugs* 1976; 11:378).

WO 2004/110368 describes combination therapies for the treatment of hypertension comprising the combination of an anti-obesity agent and an anti-hypertensive agent.

WO 2005/000217 describes combination therapies for the treatment of dyslipidemia comprising the administration of a combination of an anti-obesity agent and an anti-dyslipidemic agent.

WO 2004/110375 describes combination therapies for the treatment of diabetes comprising the administration of a combination of an anti-obesity agent and an anti-diabetic agent.

US 2004/0122033 describes combination therapies for the treatment of obesity comprising the administration of a combination of an appetite suppressant and/or metabolic rate enhancers and/or nutrient absorption inhibitors. US 2004/0229844 describes combination therapies for treating atherosclerosis comprising the administration of a combination of nicotinic acid or another nicotinic acid receptor agonist and a DP receptor antagonist.

However, none of the above patents, published patent applications or articles expressly describes the combination of an H_3 antagonist/inverse agonist with an appetite suppressant selected from the group consisting of a CB_1 antagonist (e.g., rimonabant), sibutramine, phentermine and topiramate

U.S. 6,437,147, 6,756,384, and 2003/0135056 describe combinations of imidazo heterocyclic compounds which bind to the H_3 receptor with antiobesity agents or appetite regulating agents, including sibutramine, phentermine, topiramate, lovastatin, pravastatin, and simvastatin. However, the compounds of U.S. 6,437,147, 6,756,384, and 2003/0135056 which bind to the H_3 receptor are different from the H_3 antagonists/inverse agonists of Formulae (I)-(VI) of the present invention.

U.S. 6,673,829 and 2003/0130253 describe combinations of aminoazetidine, pyrrolidine, and piperidine derivatives which bind to the H_3 receptor with antiobesity agents or appetite regulating agents, including sibutramine, phentermine, topiramate, lovastatin, pravastatin, and simvastatin. However, the compounds of U.S. 6,673,829 and 2003/0130253 which bind to the H_3 receptor are different from the H_3 antagonists/inverse agonists of Formulae (I)-(VI) of the present invention.

U.S. 6,417,218 and 2002/0058659 describe combinations of imidazole compounds which bind to the H_3 receptor with antiobesity agents or appetite regulating agents, including sibutramine, phentermine, topiramate, lovastatin, pravastatin, and simvastatin. However, the compounds of U.S. 6,417,218 and 2002/0058659 which bind to the H_3 receptor are different from the H_3 antagonists/inverse agonists of Formulae (I)-(VI) of the present invention.

U.S. 2004/0248938 and 2003/0186963 describe combinations of substituted piperidines which bind to the H_3 receptor with antiobesity agents or appetite regulating agents, including sibutramine, phentermine, topiramate, lovastatin, pravastatin, and simvastatin. However, the compounds of U.S. 2004/0248938 and 2003/0186963 which bind to the H_3 receptor are different from the H_3 antagonists/inverse agonists of Formulae (I)-(VI) of the present invention.

SUMMARY OF THE INVENTION

In one embodiment, the present invention is directed to a composition comprising one or more appetite suppressants selected from the group consisting of CB_1 antagonists/inverse agonists (e.g., rimonabant), sibutramine, phentermine, and topiramate, in combination with one or more metabolic rate enhancers comprising an H_3 antagonist/inverse agonist of Formula (I)-(VIII) (as defined herein).

In another embodiment, the present invention is directed to a pharmaceutical composition comprising one or more appetite suppressants selected from the group consisting of CB_1 antagonists/inverse agonists (e.g., rimonabant), sibutramine, phentermine, and topiramate, in combination with one or more metabolic rate enhancers comprising an H_3 antagonist/inverse agonist of Formula (I)-(VIII) (as defined herein), and at least one pharmaceutically acceptable carrier.

In another embodiment, the present invention is directed to a pharmaceutical composition comprising one or more appetite suppressants selected from the group

consisting of CB_1 antagonists/inverse agonists (e.g., rimonabant), sibutramine, phentermine, and topiramate, in combination with one or more metabolic rate enhancers comprising an H_3 antagonist/inverse agonist, and one or more HMG-CoA reductase inhibitors.

In another embodiment, the present invention is directed to a method of treating obesity or an obesity-related disorder. The method comprises administering to the patient an effective amount of a composition comprising one or more appetite suppressants selected from the group consisting of CB_1 antagonists/inverse agonists (e.g., rimonabant), sibutramine, phentermine, and topiramate, in combination with one or more metabolic rate enhancers comprising an H_3 antagonist/inverse agonist of Formula (I)-(VIII) (as defined herein).

In another embodiment, the present invention is directed to a method of treating obesity or an obesity-related disorder. The method comprises administering to the patient an effective amount of one or more appetite suppressants selected from the group consisting of CB_1 antagonists/inverse agonists (e.g., rimonabant), sibutramine, phentermine, and topiramate, in combination with one or more metabolic rate enhancers comprising an H_3 antagonist/inverse, and one or more HMG-CoA reductase inhibitors.

DETAILED DESCRIPTION OF THE INVENTION

As used above, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

A "patient" is a human or non-human mammal. In one embodiment, a patient is a human. In another embodiment, a patient is a non-human mammal, including, but not limited to, a monkey, dog, baboon, rhesus, mouse, rat, horse, cat or rabbit. In another embodiment, a patient is a companion animal, including but not limited to a dog, cat, rabbit, horse or ferret. In one embodiment, a patient is a dog. In another embodiment, a patient is a cat.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. The alkyl groups can contain about 1 to about 12 carbon atoms in the chain, and in another embodiment, the alkyl groups can contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or

propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. The term "substituted alkyl" means that the alkyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)$_2$, carboxy and -C(O)O-alkyl. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl.

"Alkylene" means a difunctional group obtained by removal of a hydrogen atom from an alkyl group that is defined above. Non-limiting examples of alkylene include methylene (i.e., -CH_2-), ethylene (i.e., -CH_2CH_2- or –$CH(CH_3)$-), propylene (i.e., -$CH_2CH_2CH_2$-, –$CH_2CH(CH_3)$-, –$CH(CH_3)CH_2$-, or –$CH(CH_2CH_3)$-), butylene (i.e., -$CH_2CH_2CH_2CH_2$-, –$CH_2CH_2CH(CH_3)$-, -$CH_2CH(CH_3)CH_2$-,–$CH(CH_2CH_2CH_3)$-, etc.). "Lower alkylene" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched.

"Alkenyl" means a hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Alkenyl groups can have about 2 to about 12 carbon atoms in the chain; and in another embodiment, about 2 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. The term "substituted alkenyl" means that the alkenyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, cyano, alkoxy, and -S(alkyl). Non-limiting examples of suitable alkenyl groups include ethenyl, propenyl (i.e., allyl), n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl.

"Alkenylene" means a difunctional group obtained by removal of a hydrogen from an alkenyl group that is defined above. Non-limiting examples of alkenylene include –CH=CH-, -$C(CH_3)$=CH-, and –CH=$CHCH_2$-.

"Alkynyl" means a hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15

carbon atoms in the chain. Alkynyl groups can have about 2 to about 12 carbon atoms in the chain, and in another embodiment, about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyl. The term "substituted alkynyl" means that the alkynyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, aryl and cycloalkyl.

"Alkynylene" means a difunctional group obtained by removal of a hydrogen from an alkynyl group that is defined above. Non-limiting examples of alkenylene include -C≡C- and $-CH_2C≡C-$.

"Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, an in another embodiment, about 6 to about 10 carbon atoms. The aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, and in another embodiment, about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Heteroaryls can contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl,

quinazolinyl, thienopyrimidinyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like. The term "heteroaryl" also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl, indazolyl, and the like, in which there is at least one aromatic ring.

"Alkylene-aryl" (or aryl-alkylene-) means a group in which the aryl and alkylene are as previously described. The bond to the parent moiety is through the alkylene. The alkylene moiety can be bonded to one or more aryl moieties. Alkylene-aryls can comprise a lower alkylene group. Non-limiting examples of suitable alkylene-aryl groups include benzyl, 2-phenethyl, 2,2-diphenylethylene and naphthalenylmethyl.

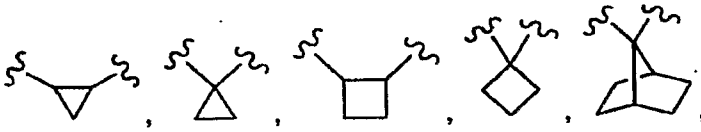
"Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as previously described. Alkylaryls can comprise a lower alkyl group. Non-limiting examples of suitable alkylaryl groups include tolyl and xylyl. The bond to the parent moiety is through the aryl.

"Alkylheteroaryl" means an alkyl-heteroaryl- group in which the alkyl and heteroaryl are as previously described. Alkylheteroaryls can comprise a lower alkyl group. A non-limiting example of a suitable alkylheteroaryl group includes 2-methylpyridine. The bond to the parent moiety is through the heteroaryl.

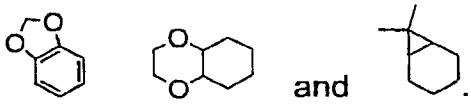
"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, and in another embodiment, about 5 to about 10 carbon atoms. Cycloalkyl rings can contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like, as well as partially saturated species such as, for example, indanyl, tetrahydronaphthyl and the like.

"Cycloalkenyl" means an unsaturated, non-aromatic mono- or multicyclic ring system having at least 1 carbon-carbon double bond, and comprising about 3 to about 10 carbon atoms, an in another embodiment, about 5 to about 10 carbon atoms. Cycloalkenyl rings can contain about 5 to about 7 ring atoms. The cycloalkenyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable

monocyclic cycloalkenyls include cyclopropenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include norbornenyl, adamantenyl and the like.

"Cycloalkylene" means a difunctional group obtained by removal of a hydrogen atom from a cycloalkyl group that is defined above. Non-limiting examples of cycloalkylene include  , and 

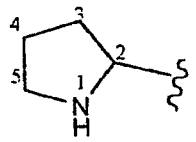
"Halogen" or "halo" means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine and bromine.

"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, alkylene-aryl, alkylaryl, alkylene-heteroaryl, heteroaryl-alkenylene-, heteroaryl-alkynylene-, alkylheteroaryl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aryl-alkoxy-, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aryl-alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylthio, arylthio, heteroarylthio, aryl-alkylthio, heteroaryl-alkylthio, cycloalkyl, heterocyclyl, -C(=N-CN)-NH_2, -C(=NH)-NH_2, -C(=NH)-NH(alkyl), Y^1Y^2N-, Y^1Y^2N-alkyl-, $Y^1Y^2NC(O)$-, $Y^1Y^2NSO_2$- and $-SO_2NY^1Y^2$, wherein Y^1 and Y^2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, and aryl-alkylene-. "Ring system substituent" may also mean a single moiety which simultaneously replaces two available hydrogens on two adjacent carbon atoms (one H on each carbon) on a ring system. Examples of such moiety are methylenedioxy, ethylenedioxy, $-C(CH_3)_2$- and the like which form moieties such as, for example:  .

"Heterocyclyl" or "heterocyclic" means a monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms,

for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Heterocyclyls may be completely saturated, partially unsaturated, or aromatic. Aromatic heterocyclyls are termed "heteroaryl", as defined above. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. Any -NH in a heterocyclyl ring may exist protected such as, for example, as an -N(Boc), -N(CBn), -N(Tos) group and the like; such protections are also considered part of this invention. The heterocyclyl can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include saturated heterocyclyls, for example piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, lactams, lactones, and the like. Non-limiting examples of partially unsaturated monocyclic heterocyclyl rings include, for example, thiazolinyl, and the like.

It should be noted that in hetero-atom containing ring systems of this invention, there are no hydroxyl groups on carbon atoms adjacent to a N, O or S, as well as there are no N or S groups on carbon adjacent to another heteroatom. Thus, for example, in the ring:



there is no -OH attached directly to carbons marked 2 and 5.

"Alkynylalkyl" means an alkynyl-alkyl- group in which the alkynyl and alkyl are as previously described. Alkynylalkyls can contain a lower alkynyl and a lower alkyl group. The bond to the parent moiety is through the alkyl. Non-limiting examples of suitable alkynylalkyl groups include propargylmethyl.

"Heteroarylalkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. Heteroaralkyls can contain a lower alkyl group. Non-limiting examples of suitable aralkyl groups include pyridylmethyl, and quinolin-3-ylmethyl. The bond to the parent moiety is through the alkyl.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Hydroxyalkyls can contain lower alkyl. Non-limiting examples of suitable hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Acyl" means an H-C(O)-, alkyl-C(O)- or cycloalkyl-C(O)-, group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Acyls can contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl and propanoyl.

"Aroyl" means an aryl-C(O)- group in which the aryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include benzoyl and 1- naphthoyl.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy and n-butoxy. The bond to the parent moiety is through the ether oxygen.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Non-limiting examples of suitable aryloxy groups include phenoxy and naphthoxy. The bond to the parent moiety is through the ether oxygen.

"Aryl-alkyloxy" (or arylalkoxy) means an aryl-alkyl-O- group in which the aryl-alkyl group is as previously described. Non-limiting examples of suitable aryl-alkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy. The bond to the parent moiety is through the ether oxygen.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkylthio groups include methylthio and ethylthio. The bond to the parent moiety is through the sulfur.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Non-limiting examples of suitable arylthio groups include phenylthio and naphthylthio. The bond to the parent moiety is through the sulfur.

"Aryl-alkylthio" (or arylalkylthio) means an aryl-alkyl-S- group in which the aryl-alkyl group is as previously described. Non-limiting example of a suitable aryl-alkylthio group is benzylthio. The bond to the parent moiety is through the sulfur.

"Alkoxycarbonyl" means an alkyl-O-C(O)- group. Non-limiting examples of suitable alkoxycarbonyl groups include methoxycarbonyl and ethoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aryloxycarbonyl" means an aryl-O-C(O)- group. Non-limiting examples of suitable aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Arylalkoxycarbonyl" means an aryl-alkyl-O-C(O)- group. Non-limiting example of a suitable aralkoxycarbonyl group is benzyloxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Alkylsulfonyl" means an alkyl-$S(O_2)$- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfonyl.

"Arylsulfonyl" means an aryl-$S(O_2)$- group. The bond to the parent moiety is through the sulfonyl.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound' or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties. An optionally substituted moiety may be unsubstituted or substituted with one or more substituents.

The term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being isolated from a synthetic process or natural source or combination thereof. Thus, the term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being obtained from a purification process or processes described herein or well known to the skilled artisan, in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

The term "metabolic rate enhancer" refers to compounds which improve energy expenditure.

It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and Tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in Organic Synthesis* (1991), Wiley, New York.

When any variable (e.g., aryl, heterocycle, R^1, etc.) occurs more than one time in any constituent or in Formula I, its definition on each occurrence is independent of its definition at every other occurrence.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design,* (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press. The term "prodrug" means a compound (e.g, a drug precursor) that is transformed *in vivo* to yield a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (e.g., by metabolic or chemical processes), such as, for example, through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For example, if the appetite suppressant, metabolic rate enhancer, or HMG-CoA reductase inhibitor contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as, for example, $(C_1–C_8)$alkyl, $(C_2$-$C_{12})$alkanoyloxymethyl, 1-

(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_1-C_2)alkylamino(C_2-C_3)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di (C_1-C_2)alkylcarbamoyl-(C_1-C_2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-C_3)alkyl, and the like.

Similarly, if the appetite suppressant, metabolic rate enhancer, or HMG-CoA reductase inhibitor contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as, for example, (C_1-C_6)alkanoyloxymethyl, 1-((C_1-C_6)alkanoyloxy)ethyl, 1-methyl-1-((C_1-C_6)alkanoyloxy)ethyl, (C_1-C_6)alkoxycarbonyloxymethyl, N-(C_1-C_6)alkoxycarbonylaminomethyl, succinoyl, (C_1-C_6)alkanoyl, α-amino(C_1-C_4)alkanyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$, $-P(O)(O(C_1-C_6)alkyl)_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate), and the like.

If the appetite suppressant, metabolic rate enhancer, or HMG-CoA reductase inhibitor incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as, for example, R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently (C_1-C_{10})alkyl, (C_3-C_7) cycloalkyl, benzyl, or R-carbonyl is a natural α-aminoacyl or natural α-aminoacyl, $-C(OH)C(O)OY^1$ wherein Y^1 is H, (C_1-C_6)alkyl or benzyl, $-C(OY^2)Y^3$ wherein Y^2 is (C_1-C_4) alkyl and Y^3 is (C_1-C_6)alkyl, carboxy (C_1-C_6)alkyl, amino(C_1-C_4)alkyl or mono-N- or di-N,N-(C_1-C_6)alkylaminoalkyl, $-C(Y^4)Y^5$ wherein Y^4 is H or methyl and Y^5 is mono-N- or di-N,N-(C_1-C_6)alkylamino morpholino, piperidin-1-yl or pyrrolidin-1-yl, and the like.

One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and

the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

One or more compounds of the invention may optionally be converted to a solvate. Preparation of solvates is generally known. Thus, for example, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describes the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder *et al*, *AAPS PharmSciTech.*, 5(1), article 12 (2004); and A. L. Bingham *et al*, *Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example I. R. spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

The term "obesity" as used herein, refers to a patient being overweight and having a body mass index (BMI) of 25 or greater. In one embodiment, an obese patient has a BMI of 25 or greater. In another embodiment, an obese patient has a BMI from 25 to 30. In another embodiment, an obese patient has a BMI greater than 30. In still another embodiment, an obese patient has a BMI greater than 40.

The term "obesity-related disorder" as used herein refers to any disorder which results from a patient having a BMI of 25 or greater. Non-limiting examples of an obesity-related disorder include edema, shortness of breath, sleep apnea, skin disorders and high blood pressure.

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in inhibiting

the diseases or conditions noted below, and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

The appetite suppressant, metabolic rate enhancer, or HMG-CoA reductase inhibitor of the present invention can form salts which are also within the scope of this invention. Reference to the appetite suppressant or metabolic rate enhancer of the present invention herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when the appetite suppressant, metabolic rate enhancer, or HMG-CoA reductase inhibitor of the present invention contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the appetite suppressant, metabolic rate enhancer, or HMG-CoA reductase inhibitor of the present invention may be formed, for example, by reacting the appetite suppressant, metabolic rate enhancer, HMG-CoA reductase inhibitor of the present invention with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use.* (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in

The Orange Book (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g. methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Pharmaceutically acceptable esters of the appetite suppressant, metabolic rate enhancer, or HMG-CoA reductase inhibitor of the present invention include the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted with, for example, halogen, $(C_1$-$C_4)$alkyl, or $(C_1$-$C_4)$alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a $(C_1$-$C_{20})$ alcohol or reactive derivative thereof, or by a 2,3-di-$(C_6$-$C_{24})$acyl glycerol.

The appetite suppressant, metabolic rate enhancer, or HMG-CoA reductase inhibitor of the present invention may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the appetite suppressant, metabolic rate enhancer, or HMG-CoA reductase inhibitor of the present invention as well as mixtures thereof, including racemic

mixtures, (and including those of the salts, solvates, esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs) form part of the present invention. In addition, the present invention embraces all geometric and positional isomers, as well as enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers (e.g., substituted biaryls), and diastereomeric forms. For example, if the appetite suppressant, metabolic rate enhancer, or HMG-CoA reductase inhibitor of the present invention incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention.

Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate", "ester", "prodrug" and the like, is intended to equally apply to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Enantiomers can also be separated by use of a chiral HPLC column.

The present invention also embraces isotopically-labeled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

Certain isotopically labeled compounds of the present invention (e.g., those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labeled compounds of the present invention can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples herein below, by substituting an appropriate isotopically labeled reagent for a non-isotopically labeled reagent.

Polymorphic forms of the appetite suppressant, metabolic rate enhancer, or HMG-CoA reductase inhibitor of the present invention, and of the salts, solvates, esters and prodrugs of the appetite suppressant or metabolic rate enhancer of the present invention, are intended to be included in the present invention.

The term "pharmaceutical composition" is also intended to encompass both the bulk composition and individual dosage units comprised of more than one (e.g., two) pharmaceutically active agents such as, for example, a compound of the present invention and an additional agent selected from the lists of the additional agents described herein, along with any pharmaceutically inactive excipients. The bulk composition and each individual dosage unit can contain fixed amounts of the afore-said "more than one pharmaceutically active agents". The bulk composition is material that has not yet been formed into individual dosage units. An illustrative dosage unit is an oral dosage unit such as tablets, pills and the like. Similarly, the herein-described method of treating a patient by administering a pharmaceutical composition of the present invention is also intended to encompass the administration of the afore-said bulk composition and individual dosage units.

The compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof are useful in treating obesity or obesity related disorders.

The appetite suppressant, metabolic rate enhancer, or HMG-CoA reductase inhibitor of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, can be administered in any suitable form, e.g., alone, or in combination with a pharmaceutically acceptable carrier, excipient or diluent in a pharmaceutical

composition, according to standard pharmaceutical practice. The compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, can be administered orally or parenterally, including intravenous, intramuscular, interperitoneal, subcutaneous, rectal, or topical routes of administration.

Pharmaceutical compositions comprising the appetite suppressant or metabolic rate enhancer of the present invention, or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof can be in a form suitable for oral administration, e.g., as tablets, troches, capsules, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, syrups, or elixirs. Oral compositions may be prepared by any conventional pharmaceutical method, and may also contain sweetening agents, flavoring agents, coloring agents, and preserving agents.

The amount of the appetite suppressant or metabolic rate enhancer of the present invention, or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof, administered to a patient can be determined by a physician based on the age, weight, and response of the patient, as well as by the severity of the condition treated. For example, the amount of the appetite suppressant or metabolic rate enhancer of the present invention, or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof, administered to the patient can range from about 0.1 mg/kg body weight per day to about 60 mg/kg/d, preferably about 0.5 mg/kg/d to about 40 mg/kg/d.

Non-limiting examples of HMG CoA reductase inhibitor compounds useful in combination with the nicotinic acid receptor agonists of the present invention are lovastatin (for example MEVACOR® which is available from Merck & Co.), simvastatin (for example ZOCOR® which is available from Merck & Co.), pravastatin (for example PRAVACHOL® which is available from Bristol Meyers Squibb), atorvastatin (for example LIPITOR® which is available from Pfizer), atorvastatin, fluvastatin (for examples LESCOL® which is available from Novartis), cerivastatin, CI-981, rivastatin (sodium 7-(4-fluorophenyl)-2,6-diisopropyl-5-methoxymethylpyridin-3-yl)-3,5-dihydroxy-6-heptanoate), rosuvastatin calcium (CRESTOR® from AstraZeneca Pharmaceuticals), pitavastatin (such as NK-104 of Negma Kowa of Japan).

H_3 receptors have been implicated in thermogenesis regulation in rodents and in feeding behavior in humans. Various H_3 receptor antagonists/inverse agonists

have been disclosed as useful for modulating histaminergic function, and thereby can be useful in treating obesity and obesity-related conditions. H_3 receptor antagonists/inverse agonists have been disclosed in U.S. 2002/183309, 2002/177589, 2002/111340, 2004/0122033, 2003/0186963, 2003/0130253, 2004/0248938, 2002/0058659, 2003/0135056, 2003/134835, 2003/153548, 2004/0019099, 2004/0097483, 2004/0048843, 2004/087573, 2004/092521, 2004/214856, 2004/248899, 2004/224953, 2004/224952, 2005/222151, 2005/222129, 2005/182045, 2005/171181, 6,620,839, 6,515,013, 6,559,140, 6,316,475, 6,166,060, 6,448,282, 6,008,240, 5,652,258, 6,417,218, 6,673,829, 6,756,384, 6,437,147, 6,720,328, 5,869,479, 6,849,621, 6,908,929, 6,908,926, 6,906,060, 6,884,809, 6,884,803, 6,878,736, 6,638,967, 6,610,721, 6,528,522, 6,518,287, 6,506,756, 6,489,337, 6,436,939, 6,448,282, 6,407,132, 6,355,665, 6,248,765, 6,133,291, 6,103,735, 6,080,871, 5,932,596, 5,929,089, 5,837,718, 5,821,259, 5,807,872, 5,639,775, 5,708,171, 5,578,616, 5,990,147, 6,906,081, WO 95/14007, WO 99/24405 (each of which is herein incorporated by reference).

In one embodiment, the present invention is directed to compositions comprising one or more metabolic rate enhancer which is an H_3 receptor antagonist/inverse agonist described generically (i.e., a compound according to Formula (I)-(VIII) as described herein) or specifically exemplified in U.S. 6,720,328, 6,849,621, 2004/0019099, 2004/0097483, 2004/0048843, or 2005/0113383 (each of which is herein incorporated by reference); and one or more appetite suppressant selected from the group consisting of a CB_1 antagonist (e.g., rimonabant), phentermine, sibutramine, and topiramate.

In another embodiment, the present invention is directed to compositions comprising one or more H_3 receptor antagonist/inverse agonist; one or more appetite suppressant selected from the group consisting of a CB_1 antagonist (e.g., rimonabant), phentermine, sibutramine, and topiramate; and one or more HMG-CoA reductase inhibitor.

In another embodiment, the present invention is directed to compositions comprising one or more H_3 receptor antagonist/inverse agonists and one or more anti-diabetic agents. The compositions are useful for treating or preventing diabetes.

There are two major forms of diabetes: Type I diabetes (also referred to as insulin-dependent diabetes or IDDM) and Type II diabetes (also referred to as

noninsulin dependent diabetes or NIDDM). In one embodiment, the compositions are useful for treating Type I diabetes. In another embodiment, the compositions are useful for treating Type II diabetes.

Examples of anti-diabetic agents useful in the present methods for treating diabetes include sulfonylureas, insulin sensitizers (such as PPAR agonists, DPPIV inhibitors, PTP-1B inhibitors and glucokinase activators), α-glucosidase inhibitors, insulin secretagogues, hepatic glucose output lowering compounds, anti-obesity agents, antihypertensive agents, meglitinides, insulin and insulin-containing compositions.

In one embodiment, the anti-diabetic agent is an insulin sensitizer or a sulfonylurea.

Non-limiting examples of sulfonylureas include glipizide, tolbutamide, glyburide, glimepiride, chlorpropamide, acetohexamide, gliamilide, gliclazide, glibenclamide and tolazamide. Insulin sensitizers include PPAR-γ agonists described in detail above, preferably troglitazone, rosiglitazone, pioglitazone and englitazone; biguanidines such as metformin and phenformin; DPPIV inhibitors such as sitagliptin, saxagliptin, denagliptin and vildagliptin; PTP-1B inhibitors; and glucokinase activators. α-Glucosidase inhibitors that can be useful in treating type II diabetes include miglitol, acarbose, and voglibose. Hepatic glucose output lowering drugs include Glucophage and Glucophage XR. Insulin secretagogues include sulfonylurea and non-sulfonylurea drugs such as GLP-1, exendin, GIP, secretin, glipizide, chlorpropamide, nateglinide, meglitinide, glibenclamide, repaglinide and glimepiride. Insulin includes all formualtions of insulin, including long acting and short acting forms of insulin.

Non-limiting examples of anti-obesity agents useful in the present methods for treating diabetes include CB1 antagonists or inverse agonists such as rimonabant, neuropeptide Y antagonists, MCR4 agonists, MCH receptor antagonists, histamnine H3 receptor antagonists or inverse agonists, leptin, appetite suppressants such as sibutramine, and lipase inhibitors such as xenical.

Non-limiting examples of antihypertensive agents useful in the present methods for treating diabetes include β-blockers and calcium channel blockers (for example diltiazem, verapamil, nifedipine, amlopidine, and mybefradil), ACE inhibitors (for example captopril, lisinopril, enalapril, spirapril, ceranopril, zefenopril, fosinopril,

cilazopril, and quinapril), AT-1 receptor antagonists (for example losartan, irbesartan, and valsartan), renin inhibitors and endothelin receptor antagonists (for example sitaxsentan).

Non-limiting examples of meglitinides useful in the present methods for treating diabetes include repaglinide and nateglinide.

Non-limiting examples of insulin sensitizers include biguanides, such as metformin and thiazolidinediones.

In one embodiment, the insulin sensitizer is a thiazolidinedione.

Non-limiting examples of antidiabetic agents that slow or block the breakdown of starches and certain sugars and are suitable for use in the compositions and methods of the present invention include alpha-glucosidase inhibitors and certain peptides for increasing insulin production. Alpha-glucosidase inhibitors help the body to lower blood sugar by delaying the digestion of ingested carbohydrates, thereby resulting in a smaller rise in blood glucose concentration following meals. Non-limiting examples of suitable alpha-glucosidase inhibitors include acarbose; miglitol; camiglibose; certain polyamines as disclosed in WO 01/47528 (incorporated herein by reference); voglibose. Non-limiting examples of suitable peptides for increasing insulin production including amlintide (CAS Reg. No. 122384-88-7 from Amylin; pramlintide, exendin, certain compounds having Glucagon-like peptide-1 (GLP-1) agonistic activity as disclosed in WO 00/07617 (incorporated herein by reference).

Non-limiting examples of orally administrable insulin and insulin containing compositions include AL-401 from Autolmmune, and the compositions disclosed in U.S. Patent Nos. 4,579,730; 4,849,405; 4,963,526; 5,642,868; 5,763,396; 5,824,638; 5,843,866; 6,153,632; 6,191,105; and International Publication No. WO 85/05029, each of which is incorporated herein by reference.

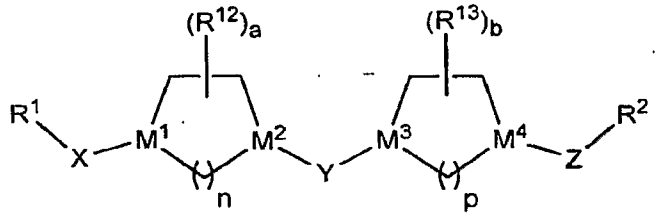
In another embodiment, the compositions comprising one or more H_3 receptor antagonist/inverse agonists and one or more anti-diabetic agents are useful for treating or preventing obesity or an obesity-related disorder.

Anti-diabetic agents useful in the present methods for treating obesity or an obesity-related disorder include; but are not limited to the anti-diabetic agents listed above herein.

In the combination therapies of the present invention, the one or more H_3 receptor antagonist/inverse agonists and the one or more additional therapeutic

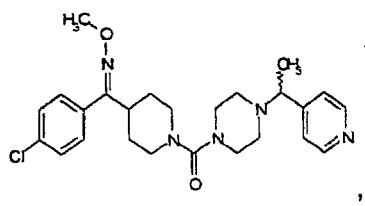
agents can be administered simultaneously (at the same time, in a single dosage form or in separate dosage forms) or sequentially (first one and then another, etc... over a period of time) in any order.

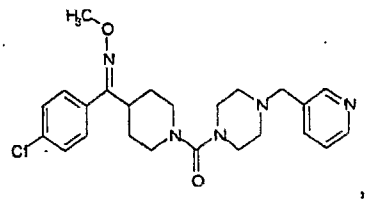
In one embodiment, the H_3 antagonists/inverse agonists of the present invention can have a structure according to Formula (I):

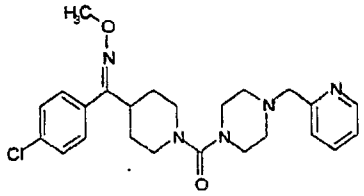


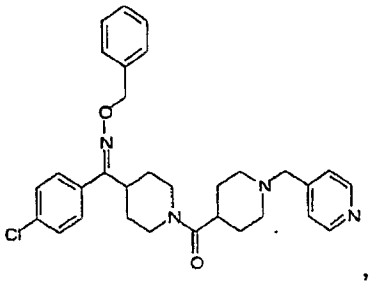
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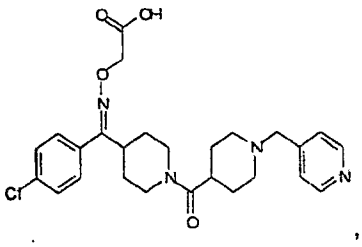
as described in U.S. Patent No. 6,720,328, which is herein incorporated by reference in its entirety. Non-limiting examples of compounds of Formula (I) include:

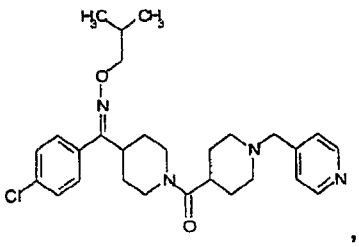


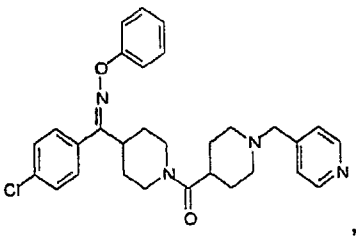


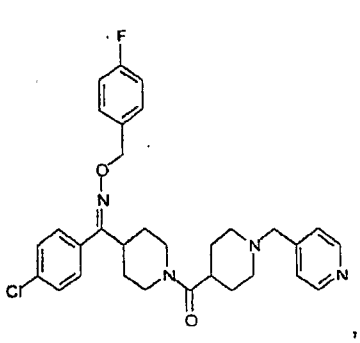


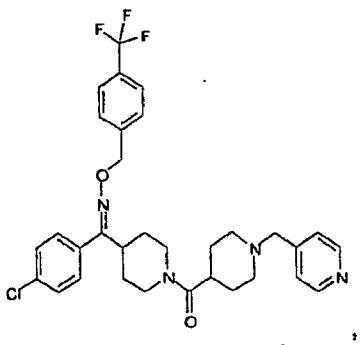


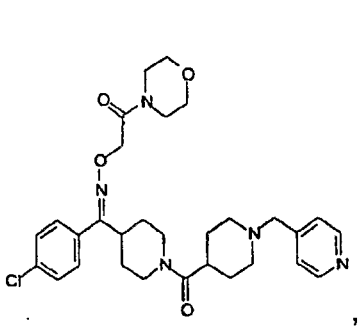
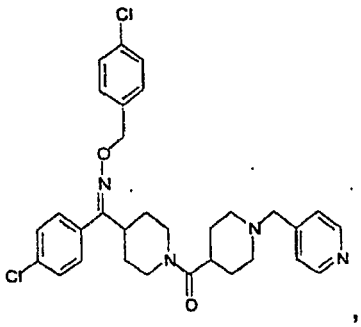
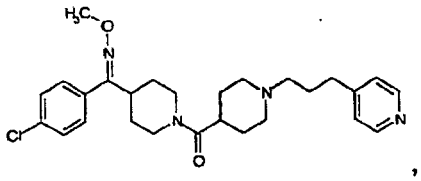
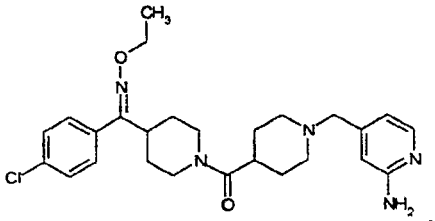
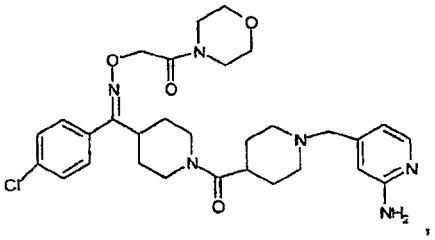
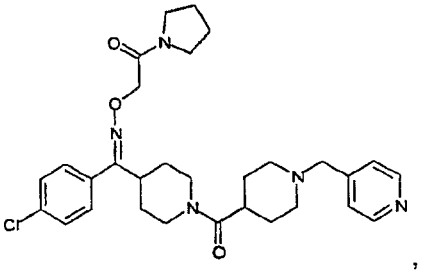
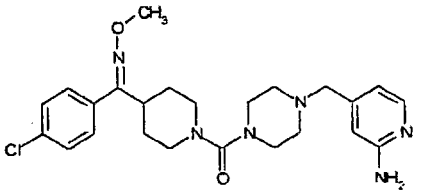
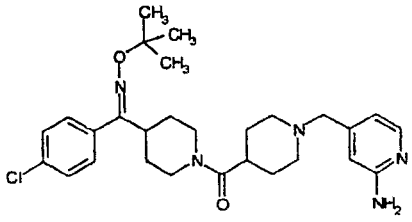
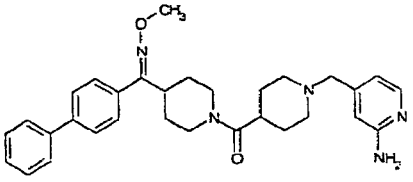
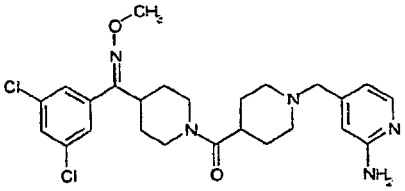
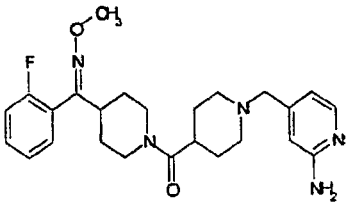
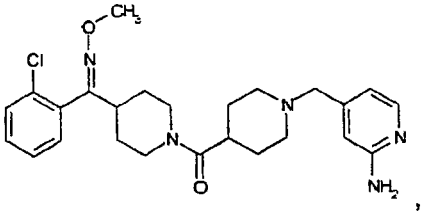
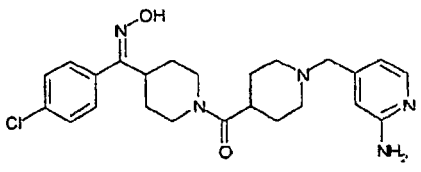
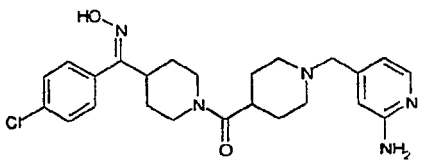
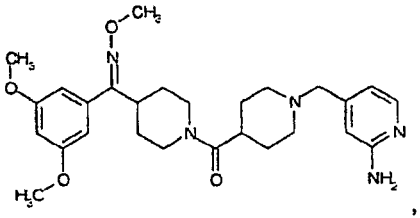
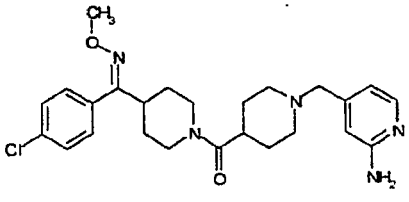




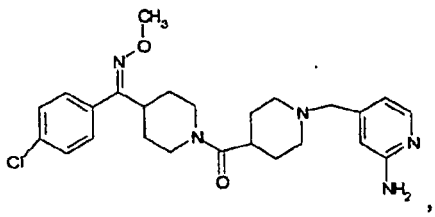


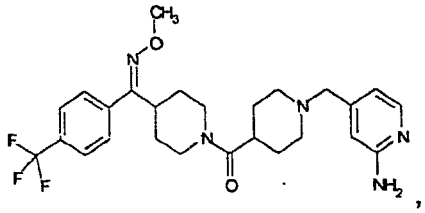


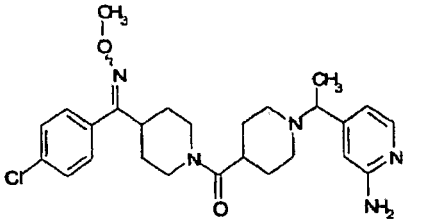


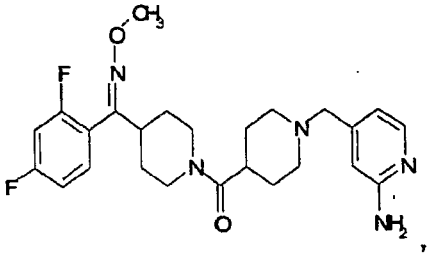

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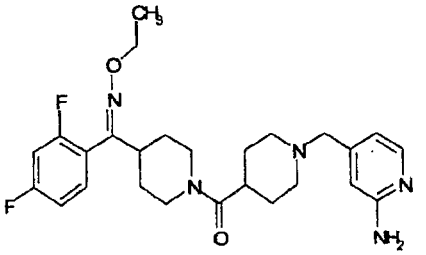
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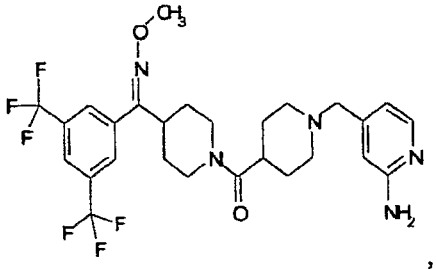


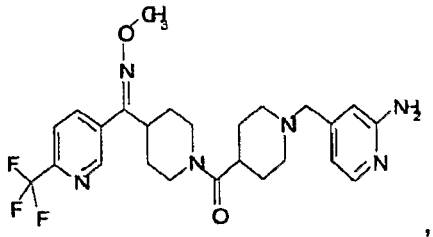


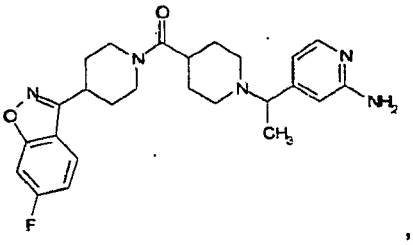


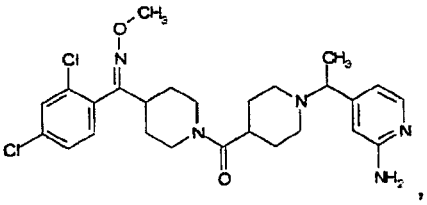


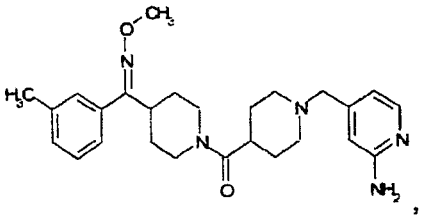


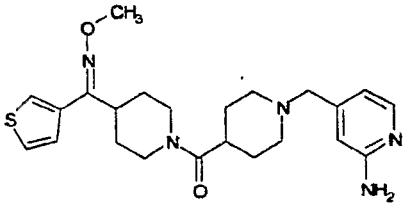


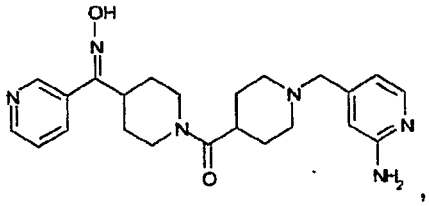


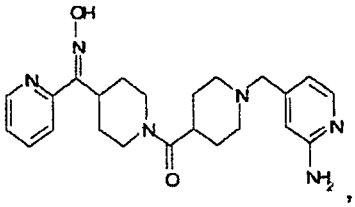


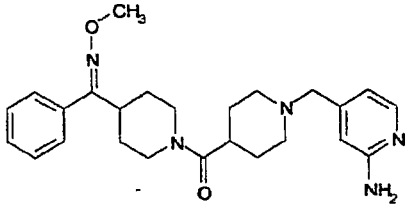


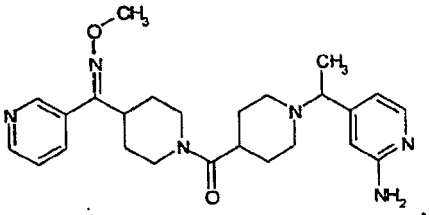


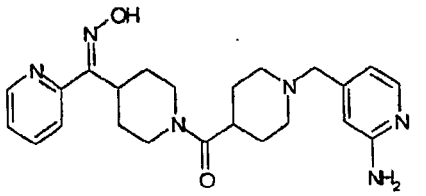


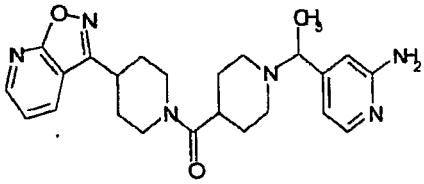


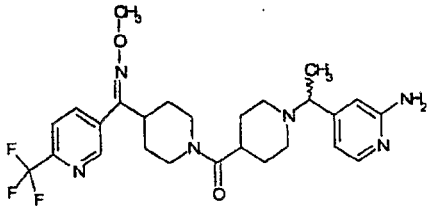


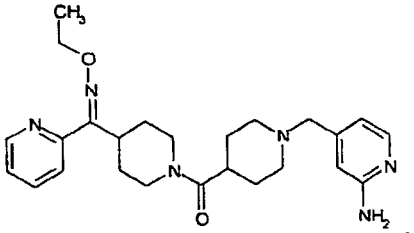


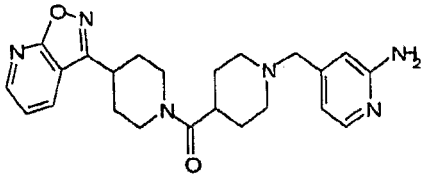


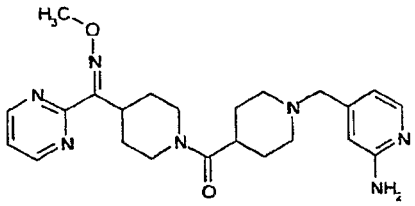


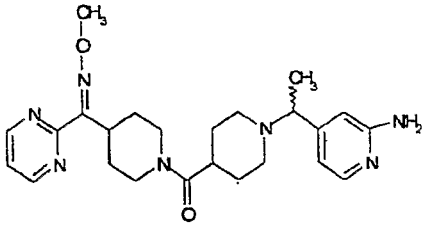


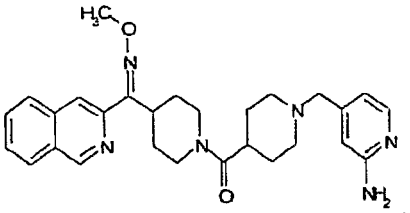


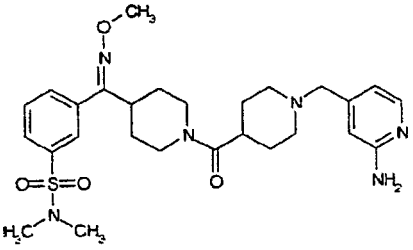


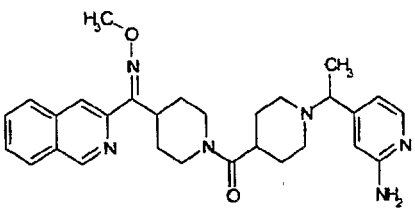


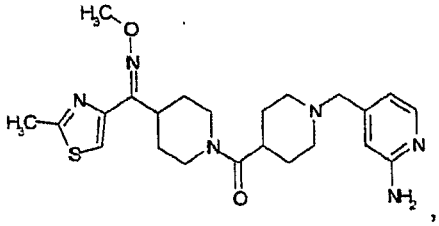


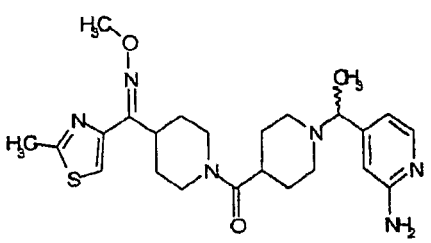
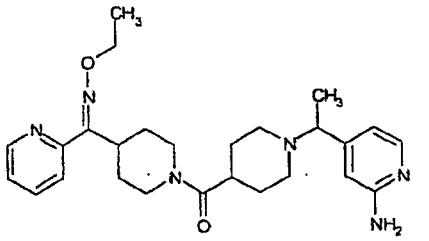
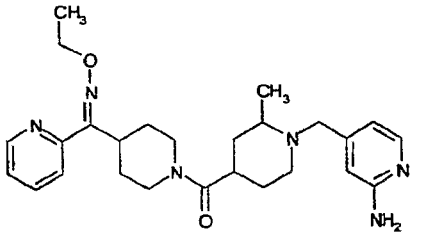
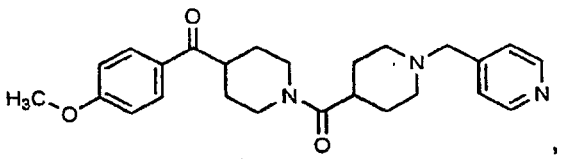
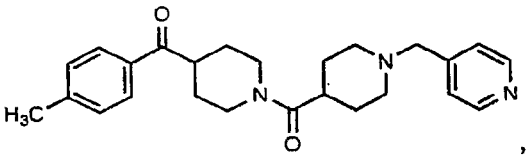
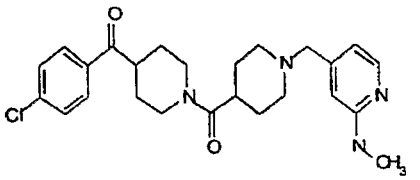
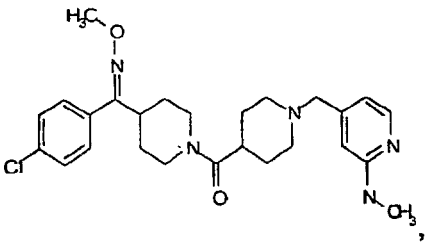
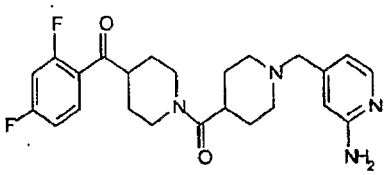
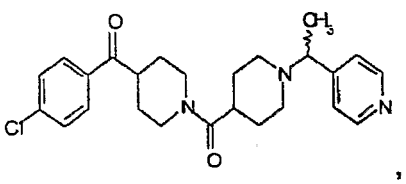
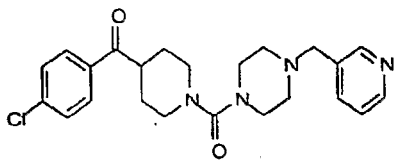
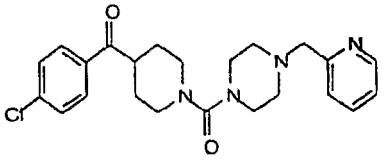
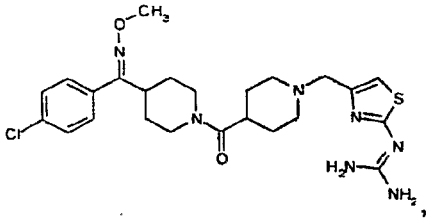
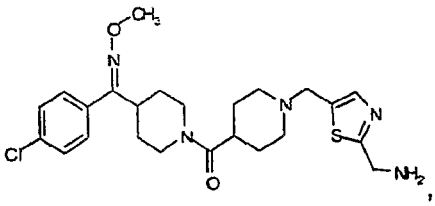
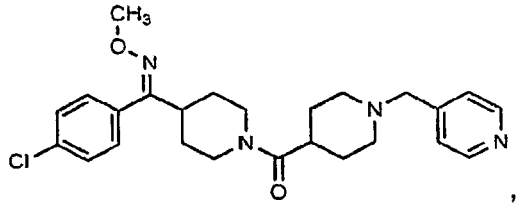
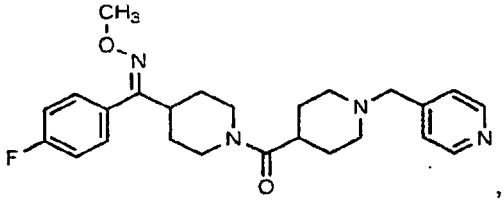
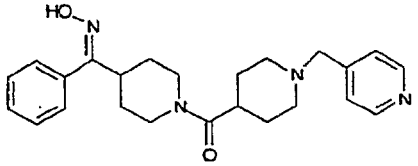




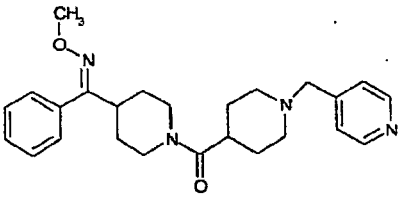
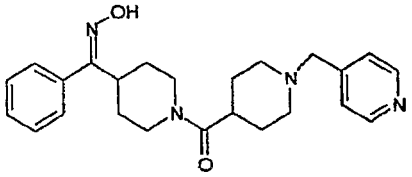
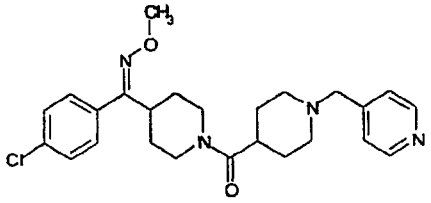
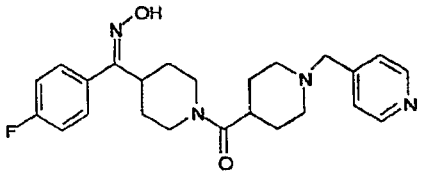
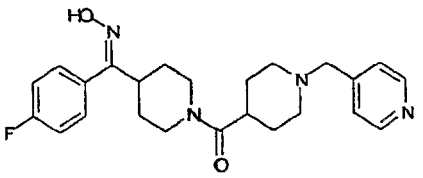
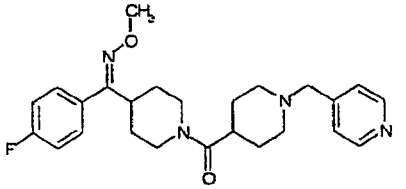
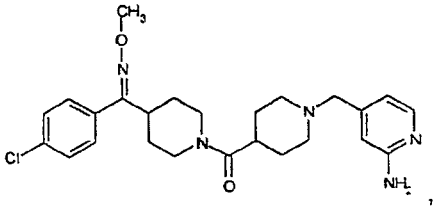
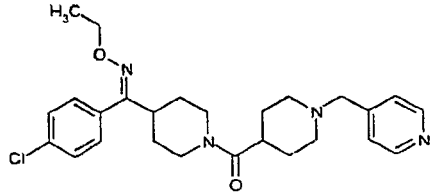
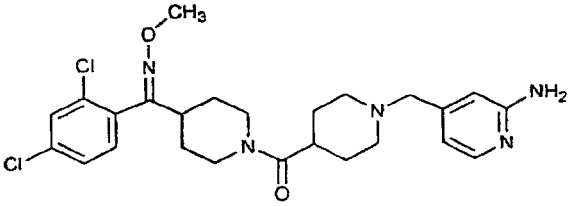
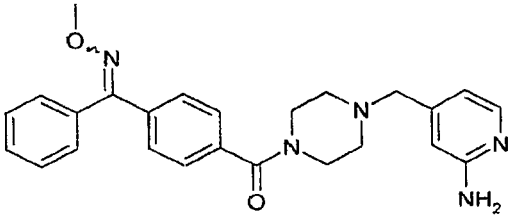
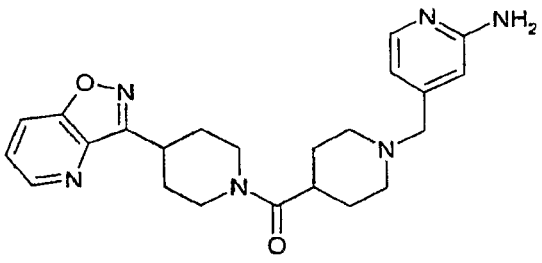
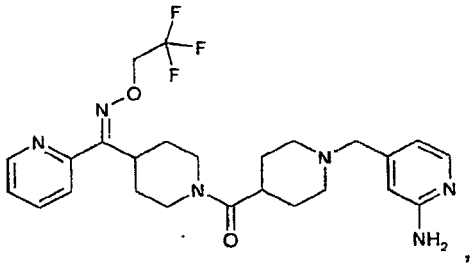


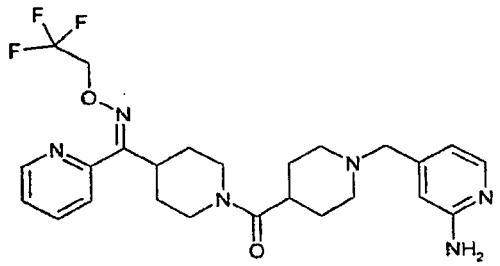


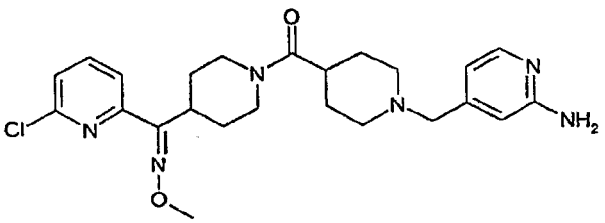


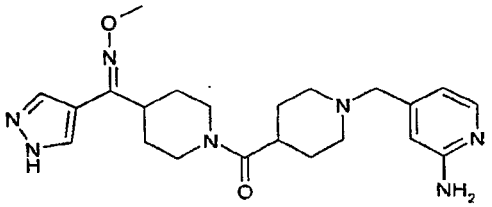

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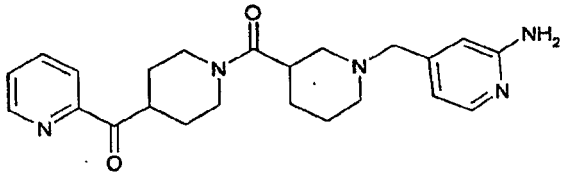
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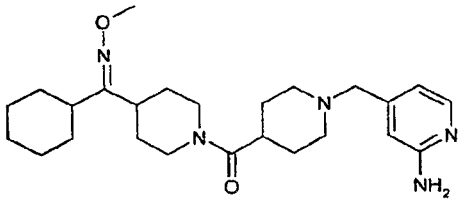

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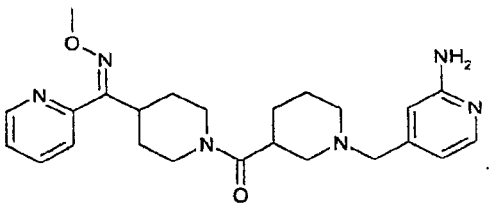


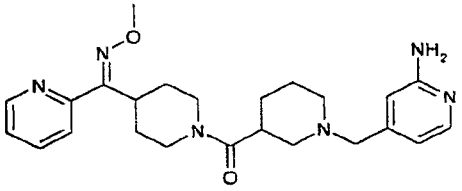


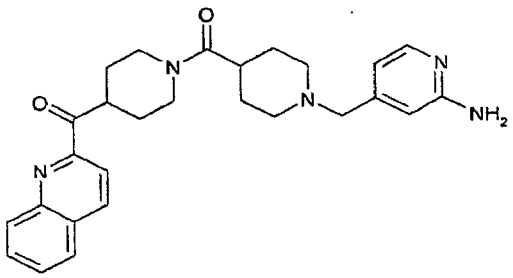


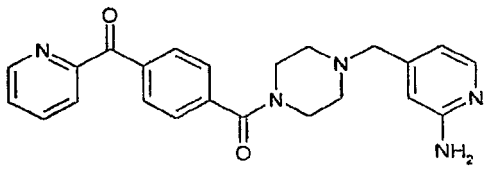


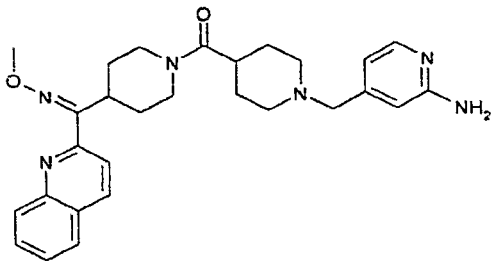


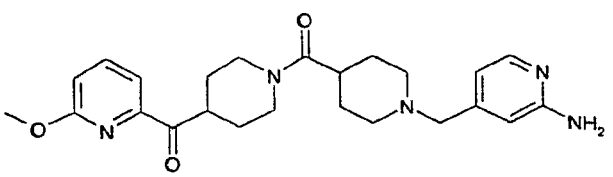


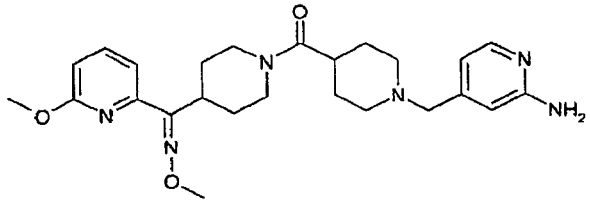


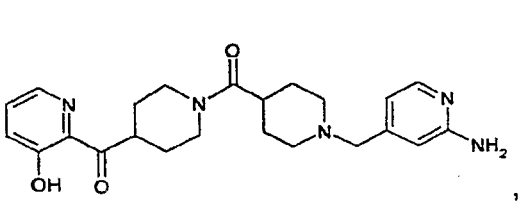


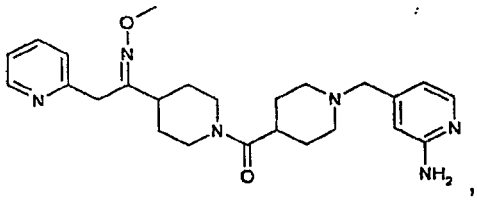


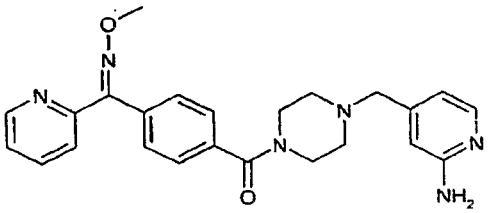


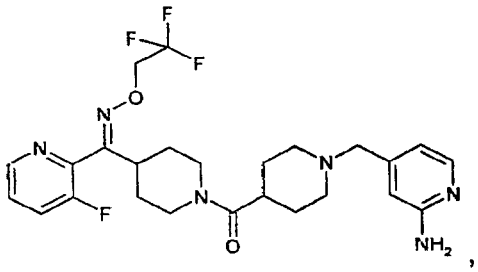


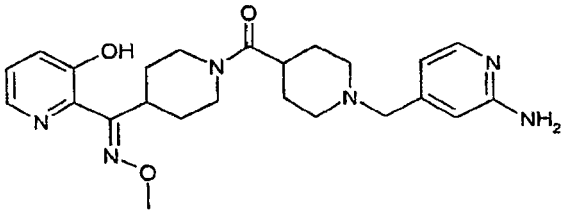


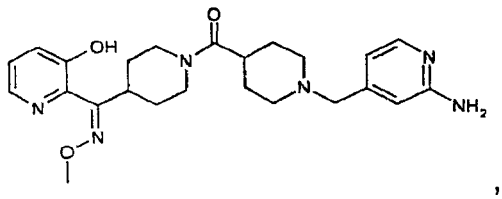


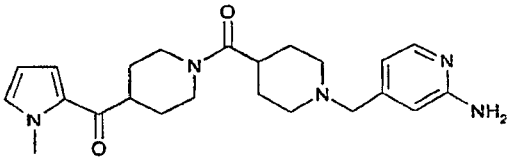


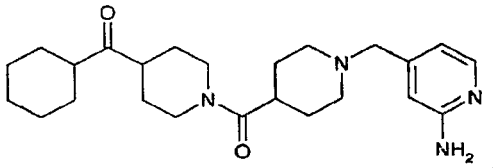


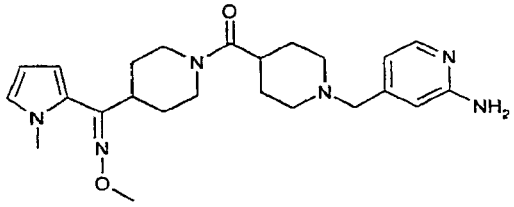


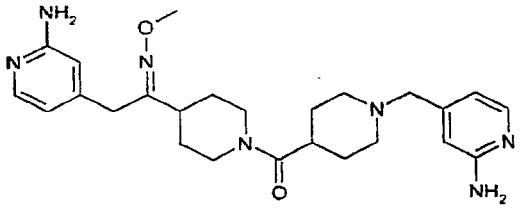


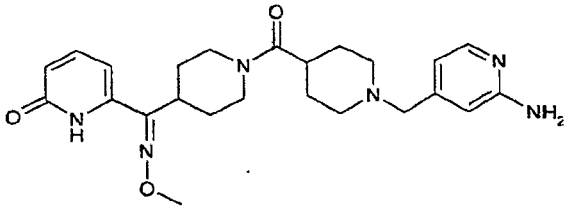


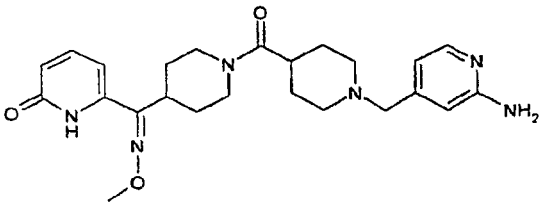


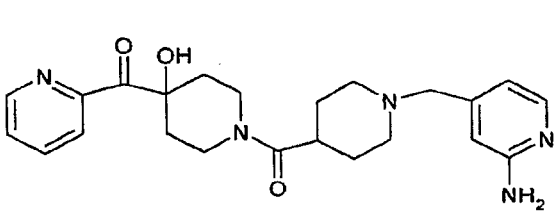


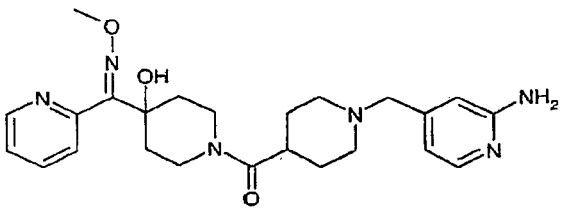


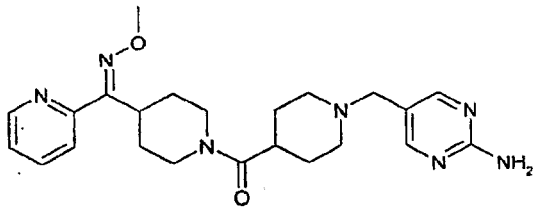


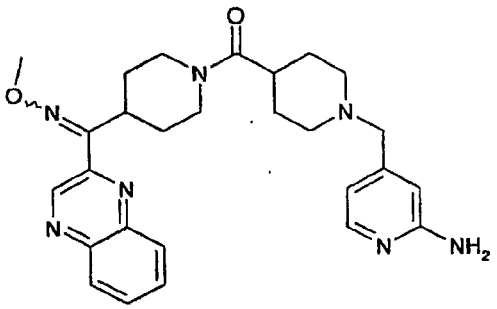


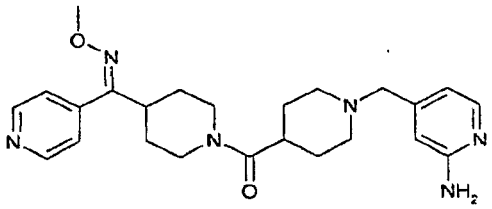


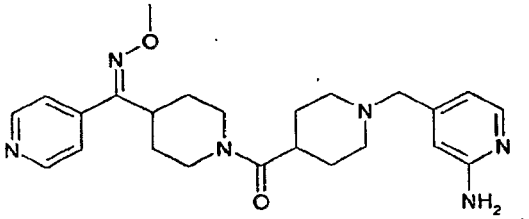


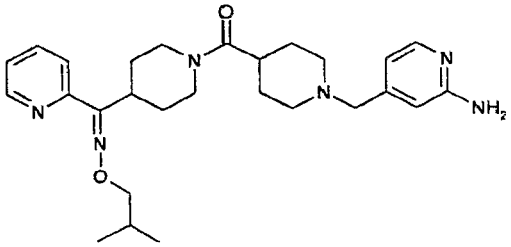


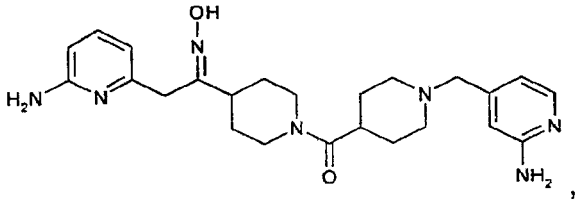


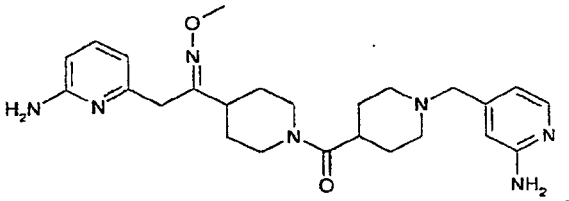


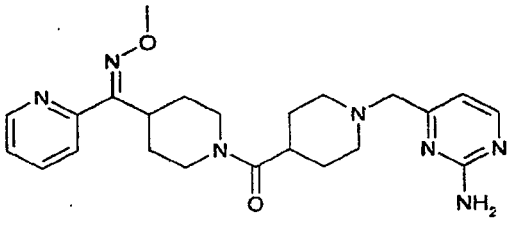


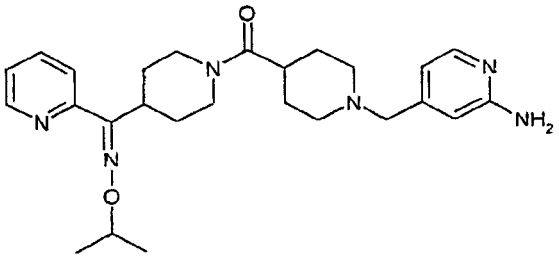


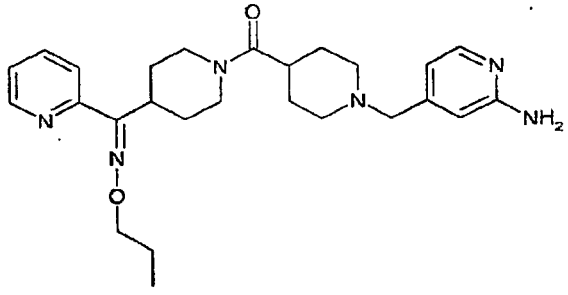




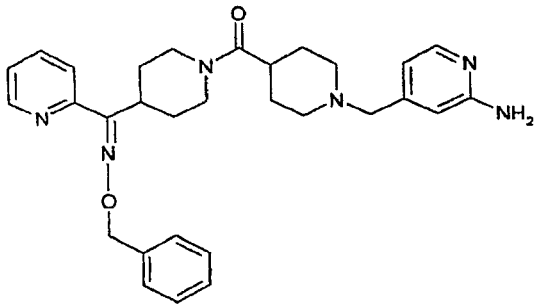


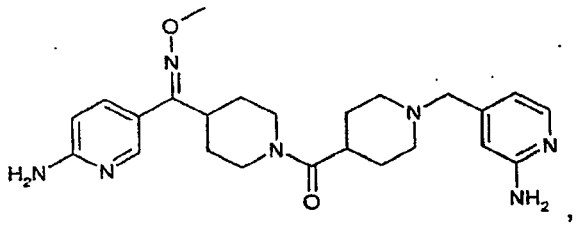


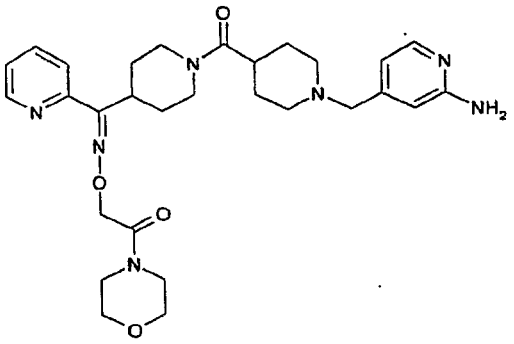


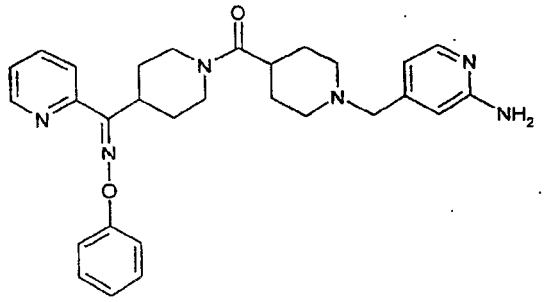


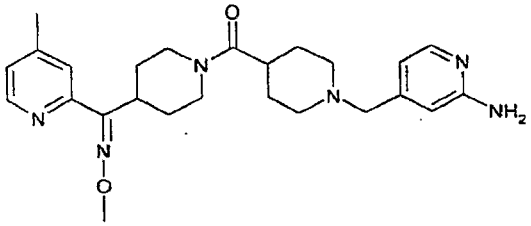
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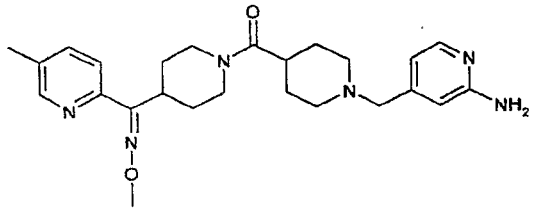


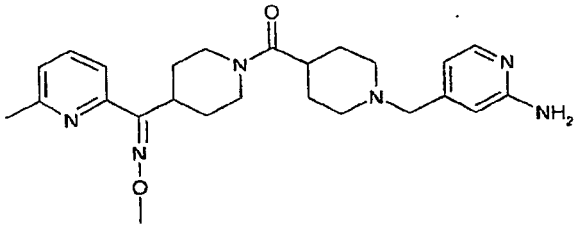


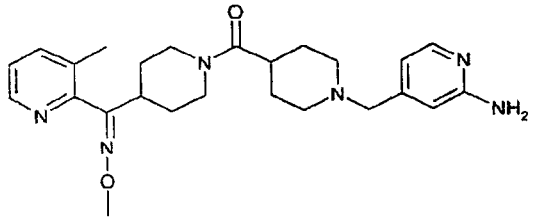


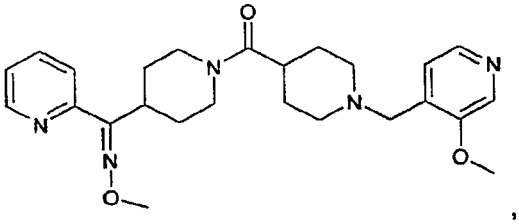


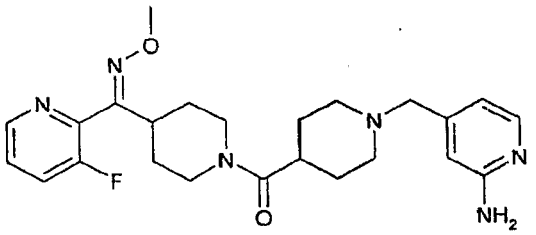




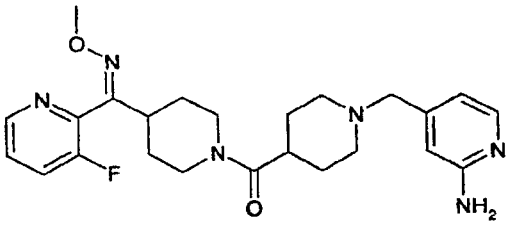


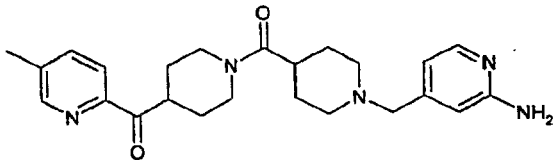


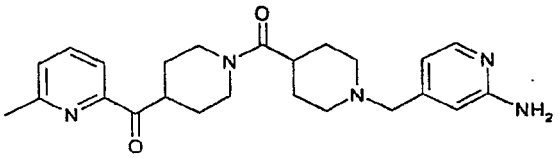


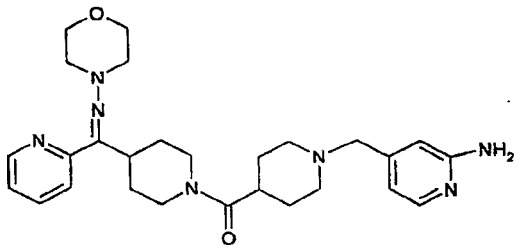


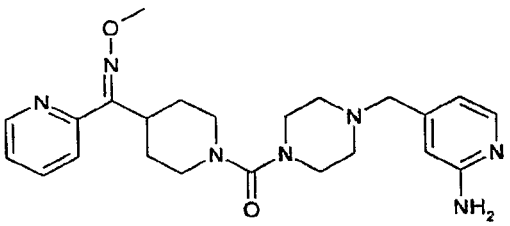
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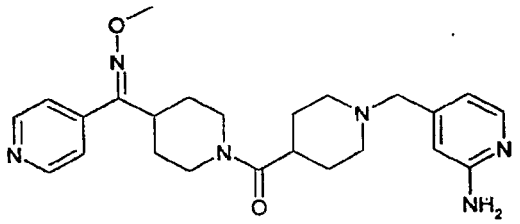


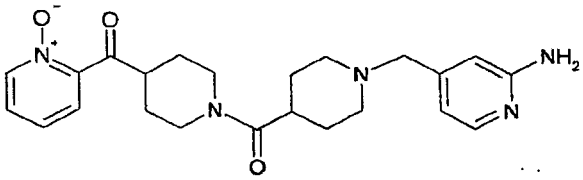


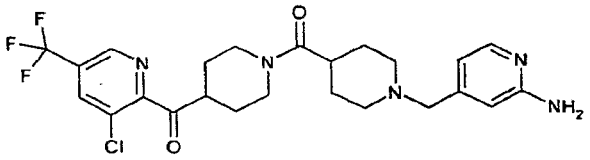


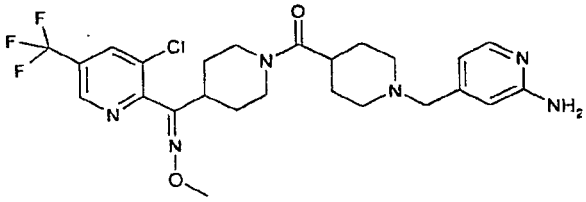


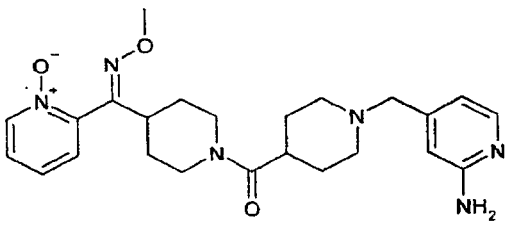


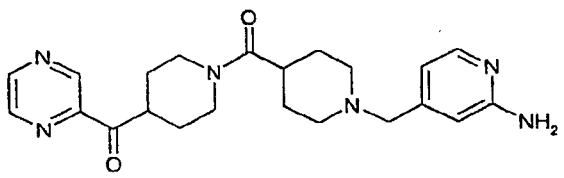


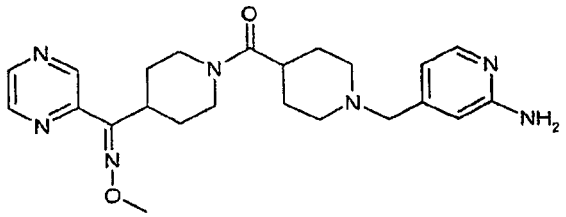


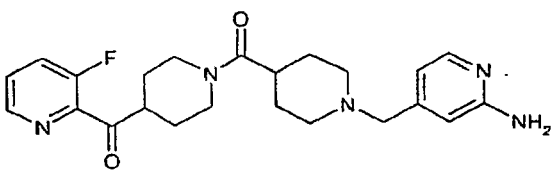


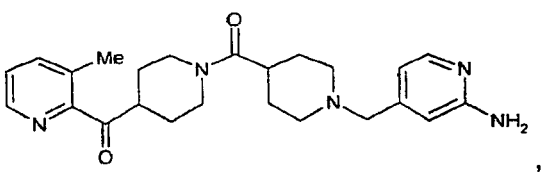


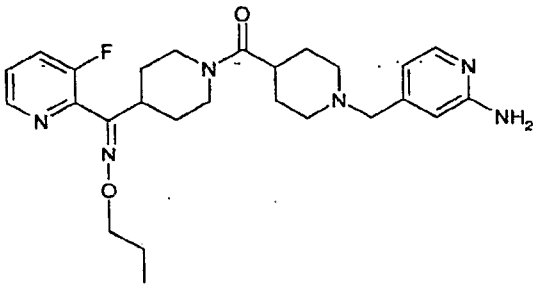


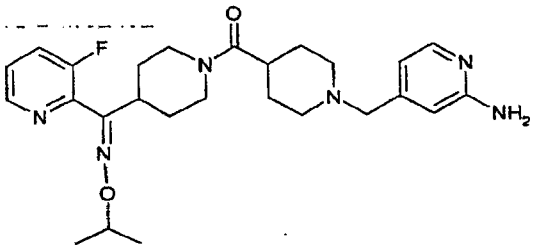


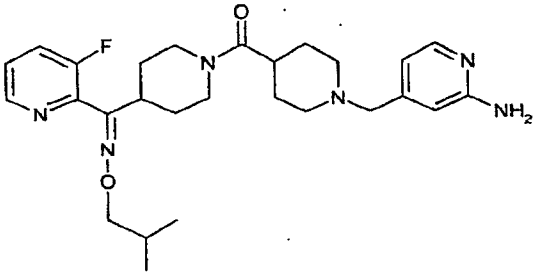


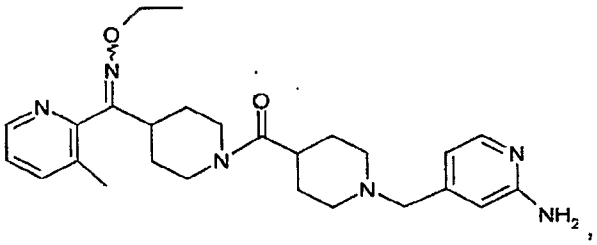


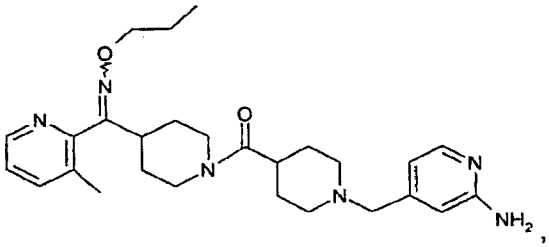


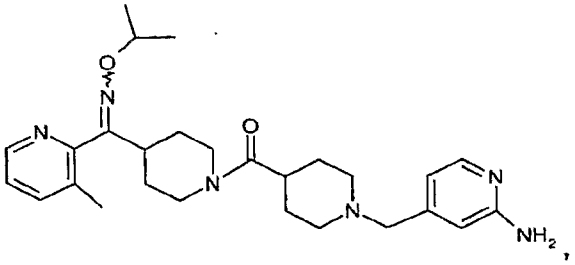


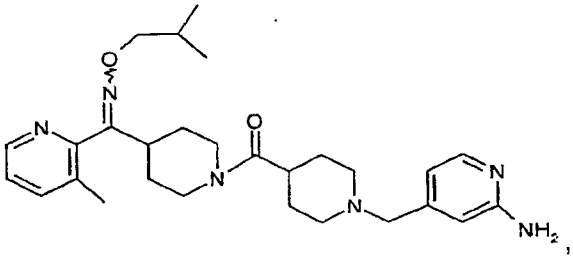


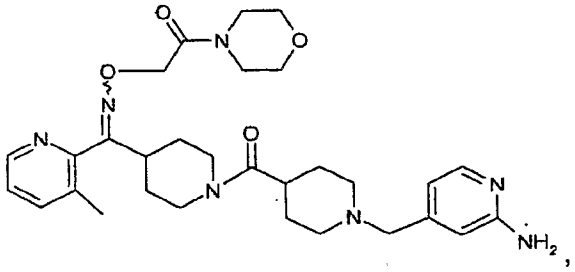


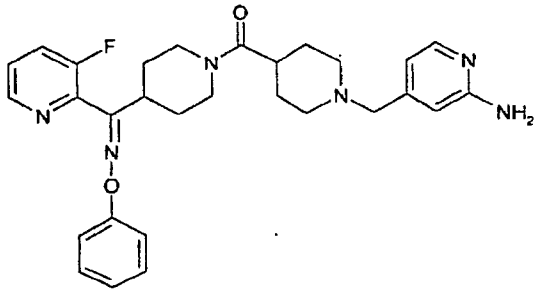


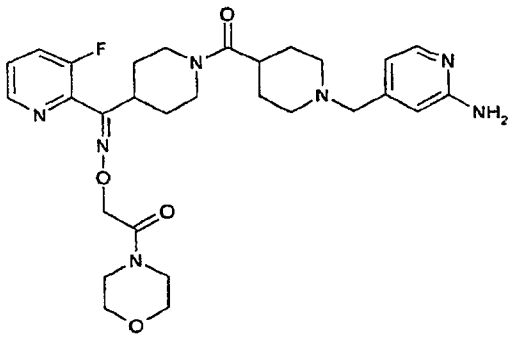




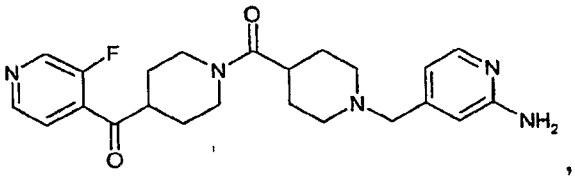


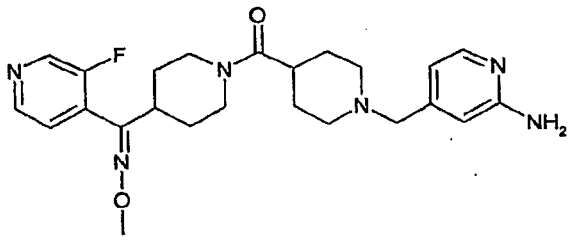


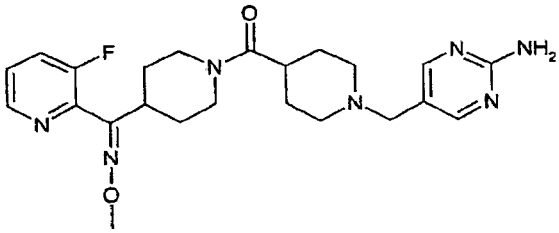


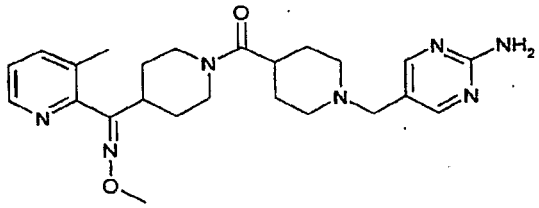


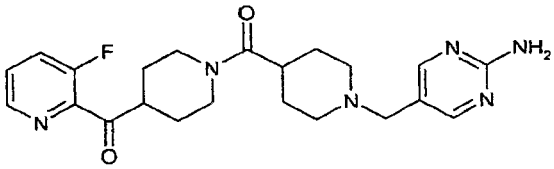
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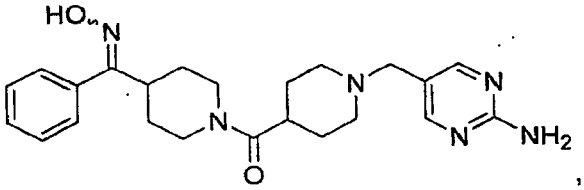


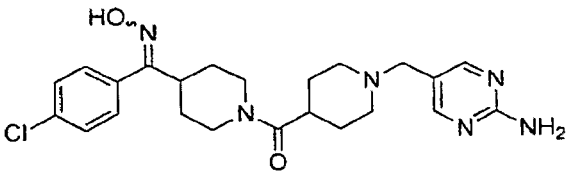


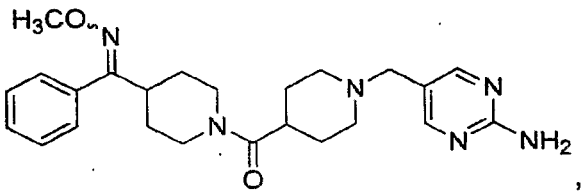


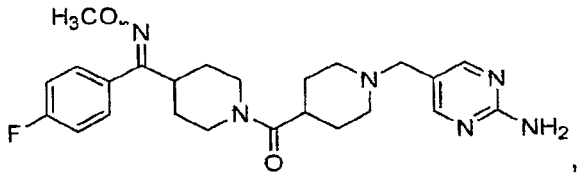


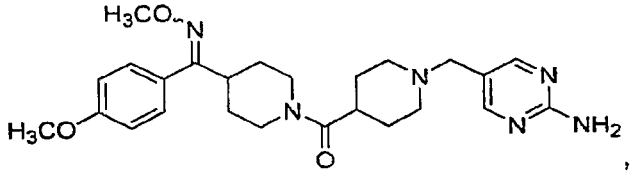


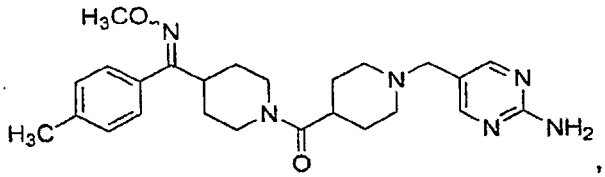


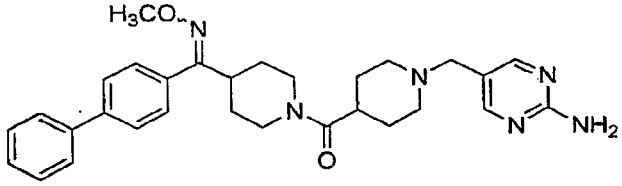


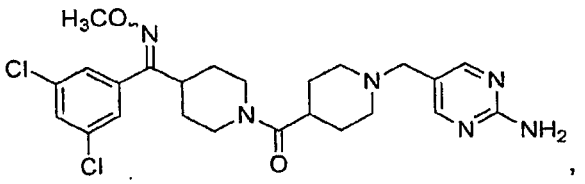


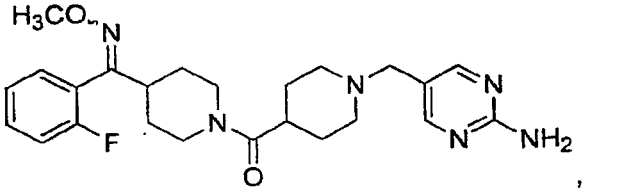


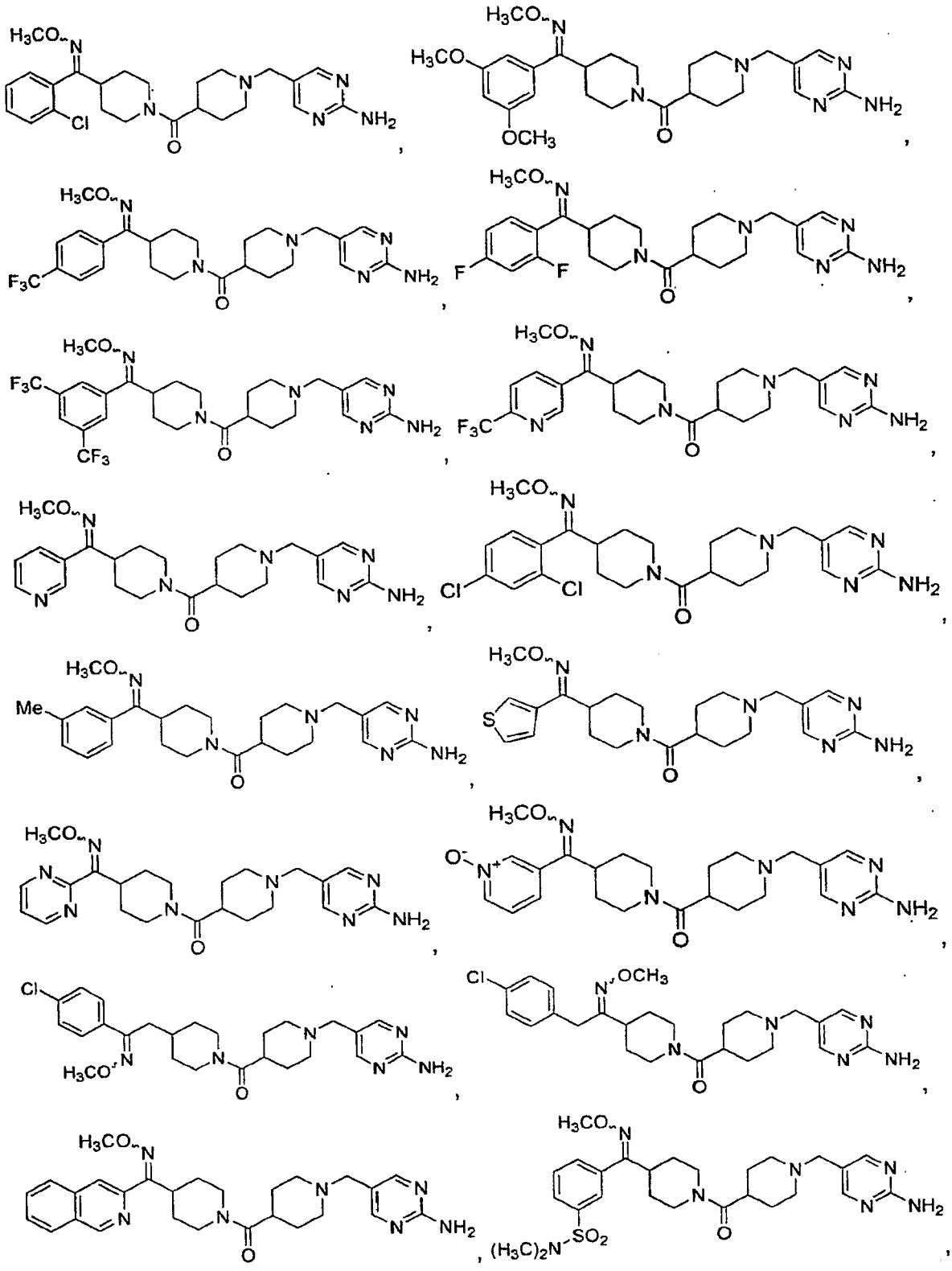


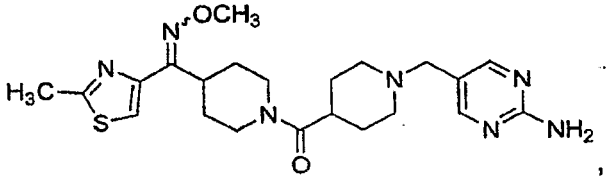


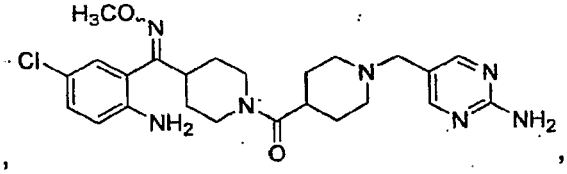


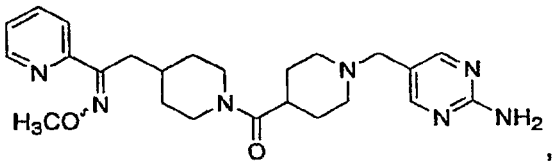


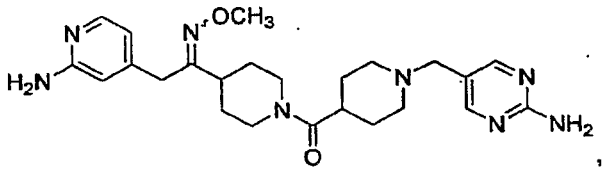


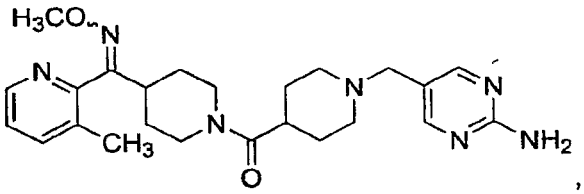


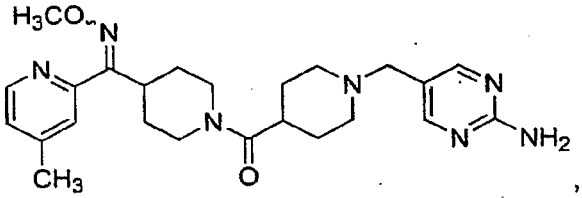


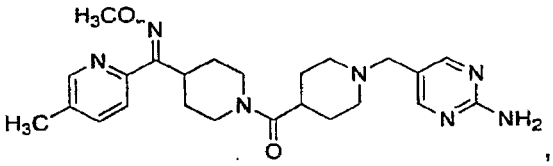


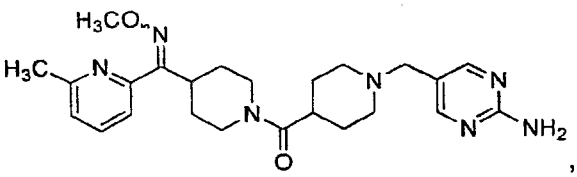


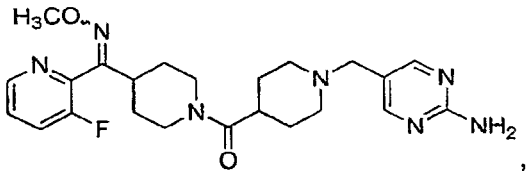


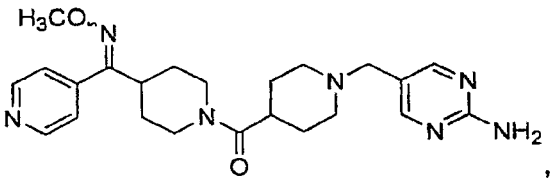


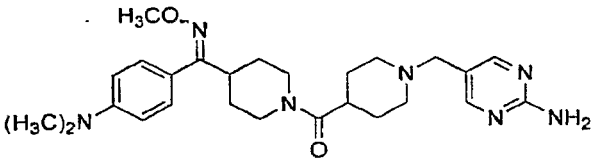


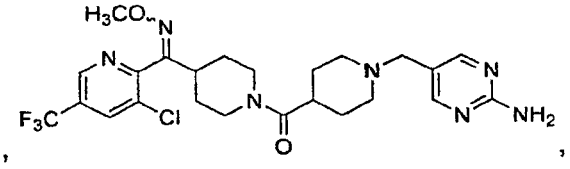


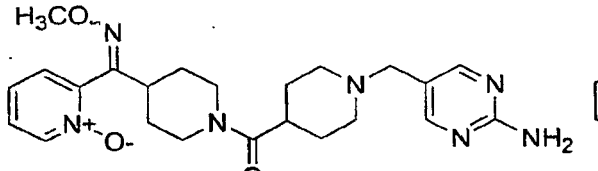


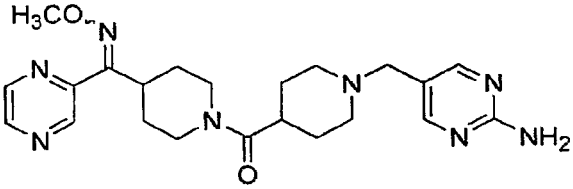


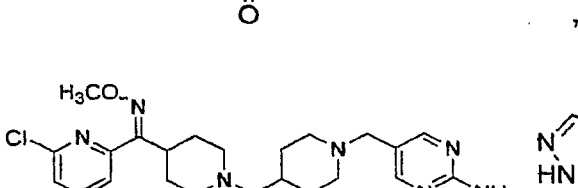


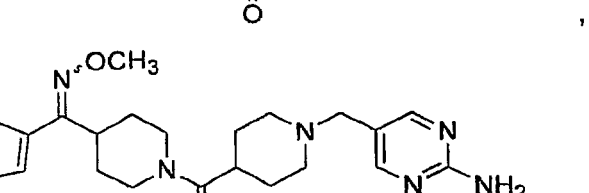


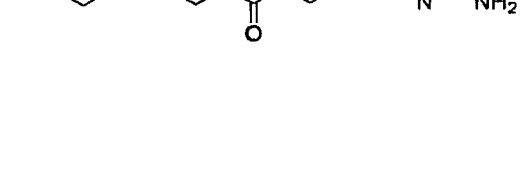


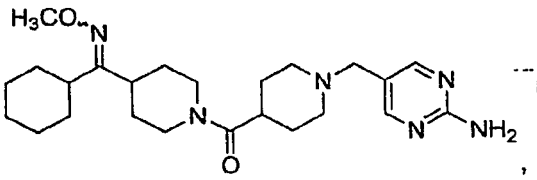


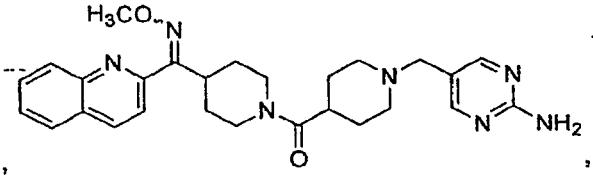


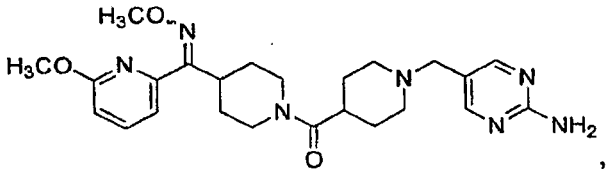


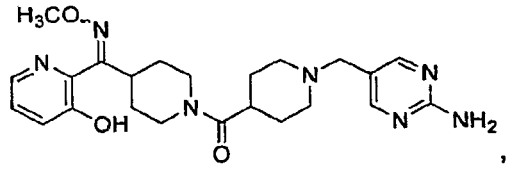


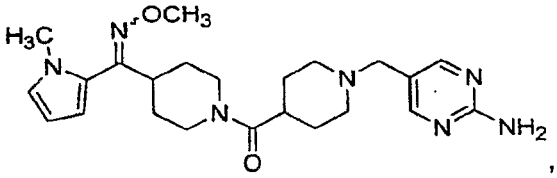


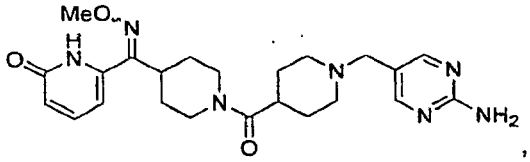


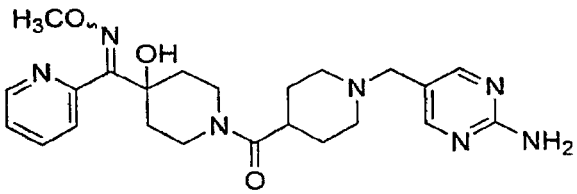


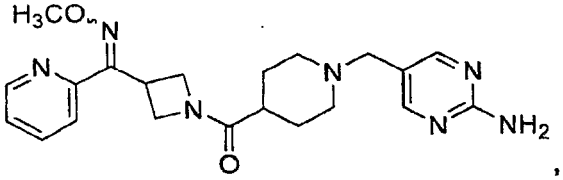


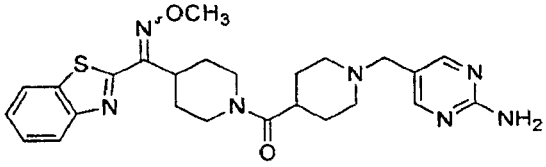


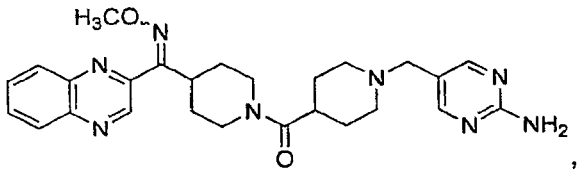




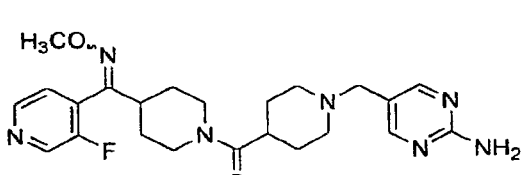


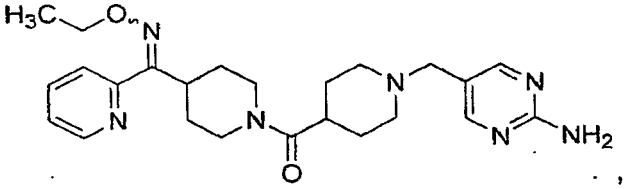


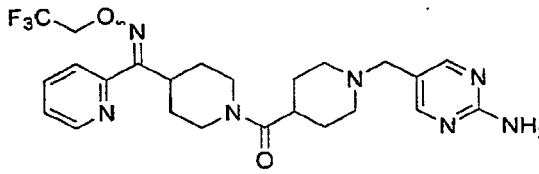


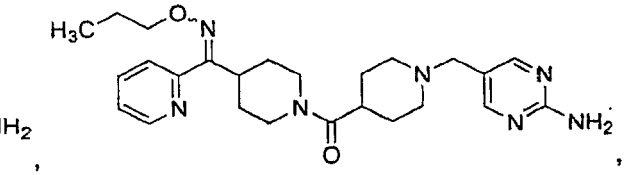


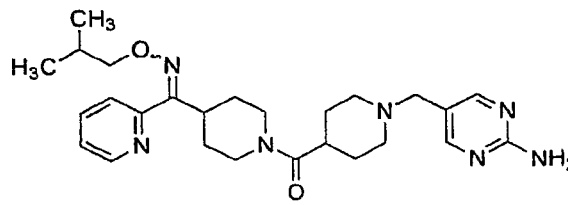
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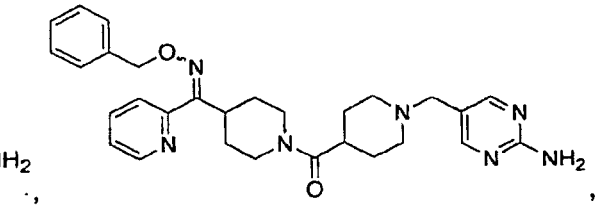


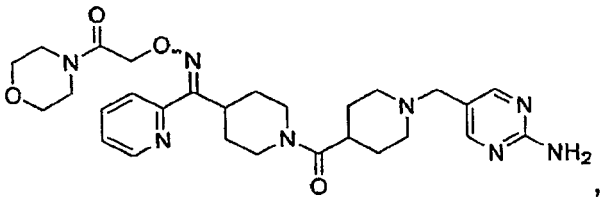
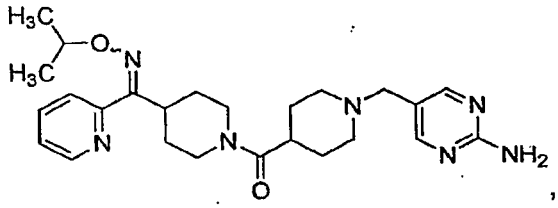
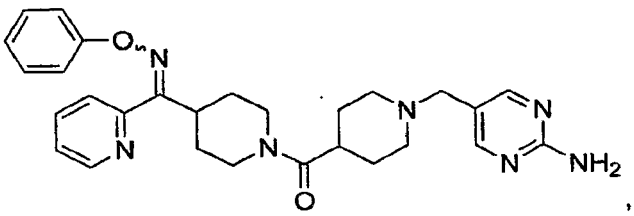
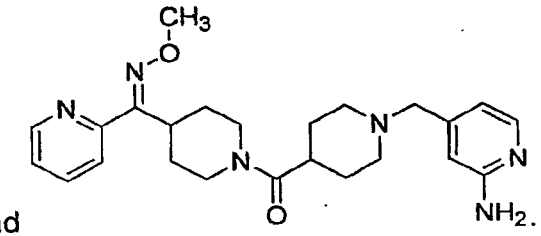




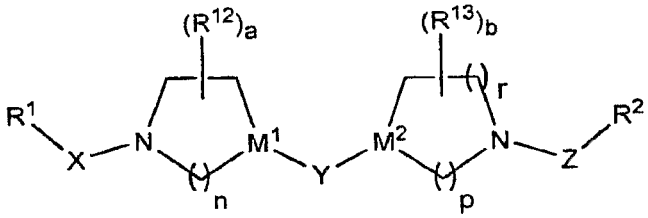




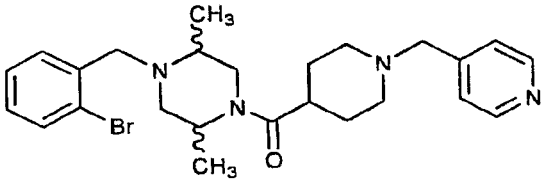
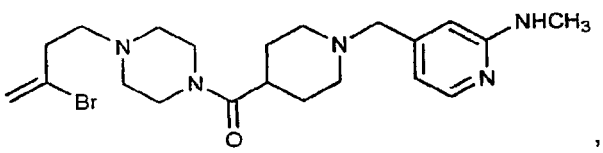
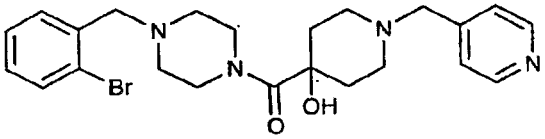
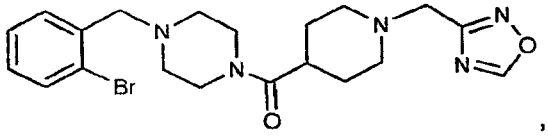
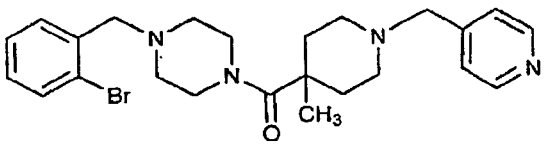
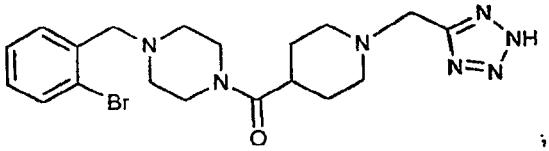
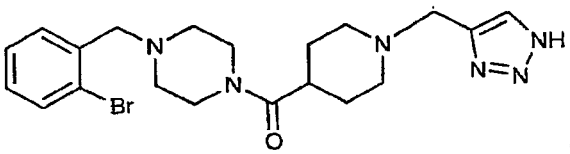
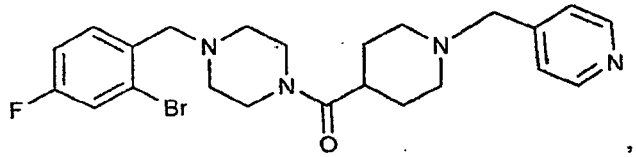


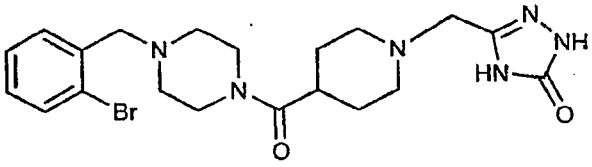

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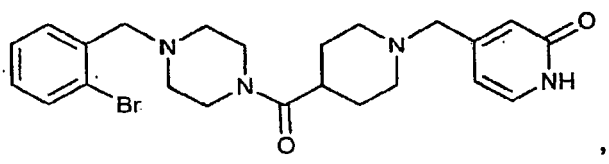
In one embodiment, the H_3 antagonists/inverse agonists of the present invention can have a structure according to Formula (II):

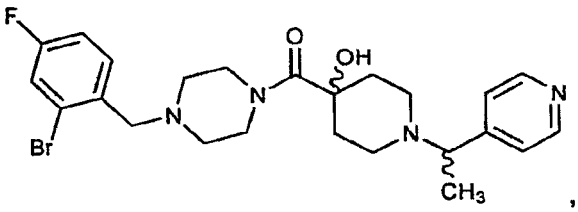

(II)

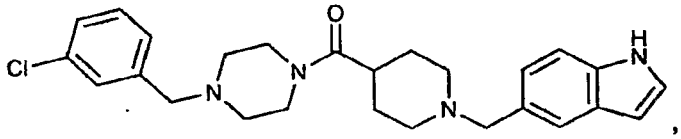
as described in U.S. 6,849,621 and U.S. 2005/0113383, both of which are herein incorporated by reference in their entirety. Non-limiting examples of compounds of Formula (II) include:

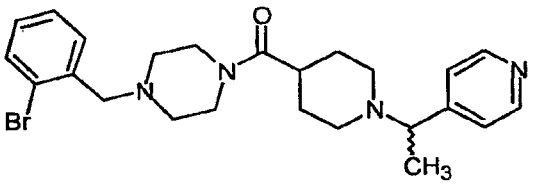

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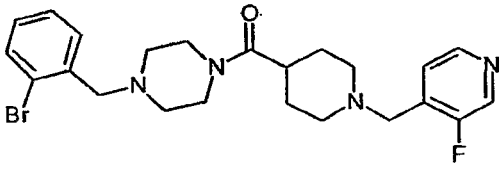


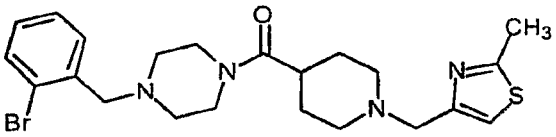


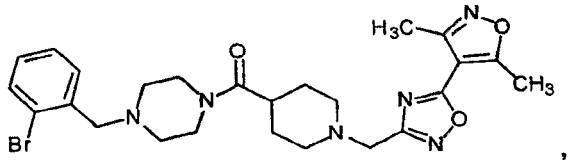


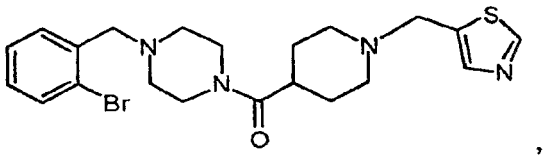


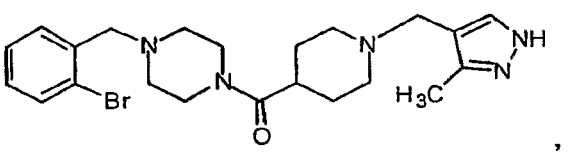


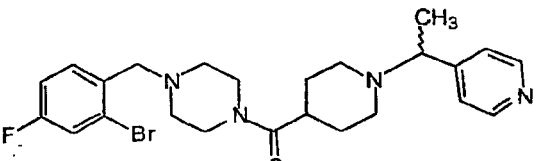


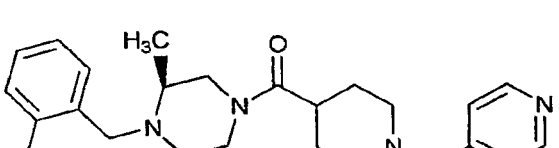


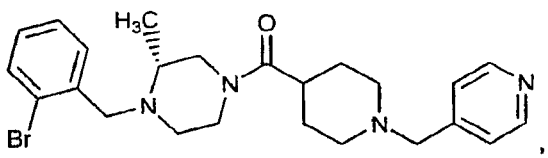


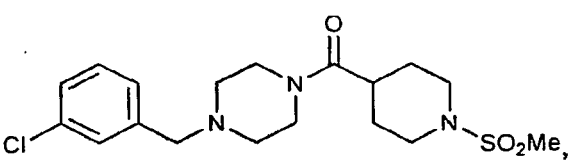


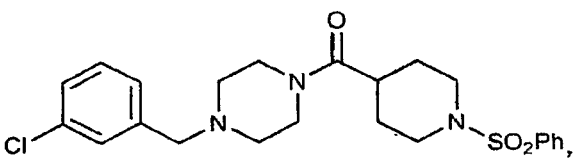


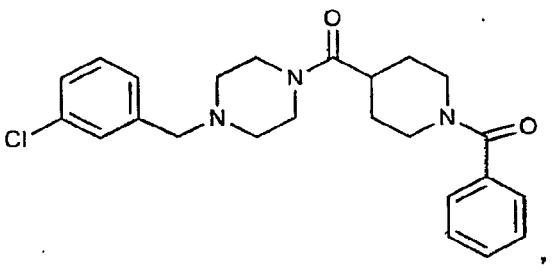


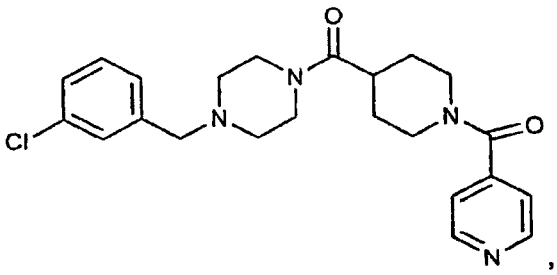


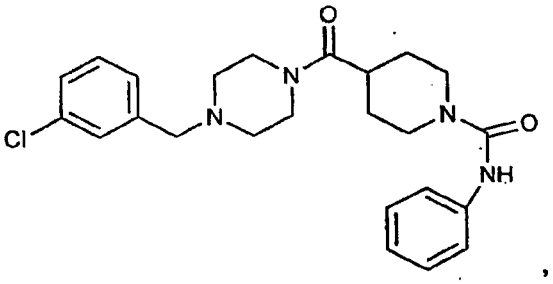


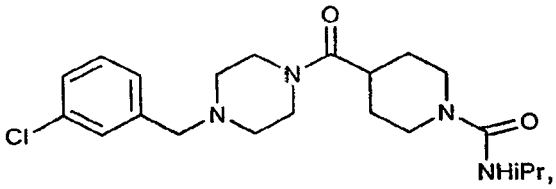


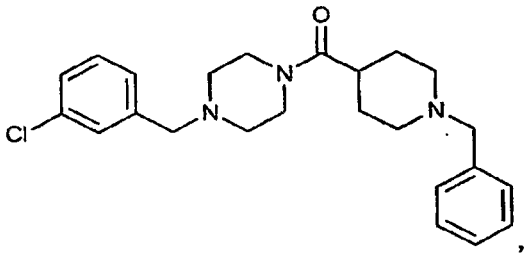


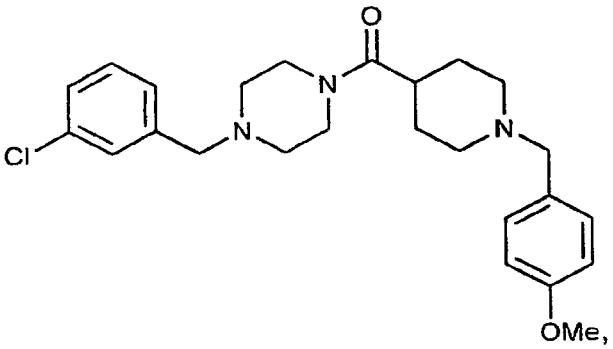


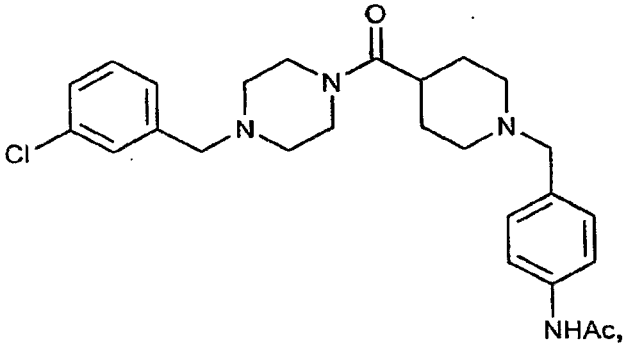


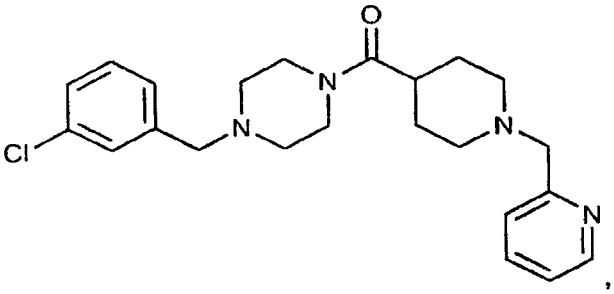


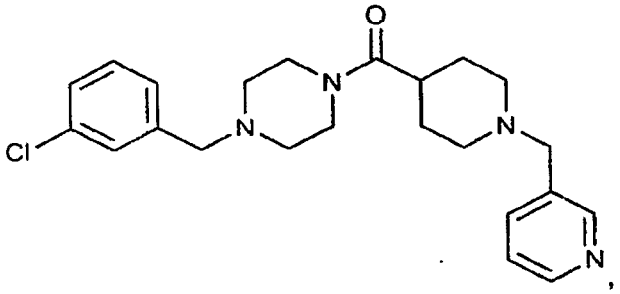


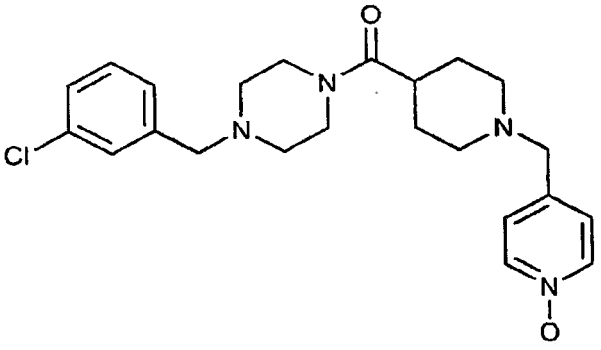


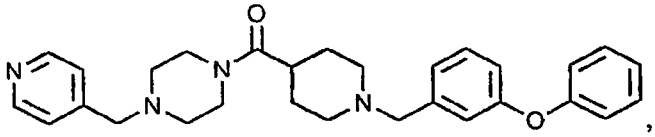




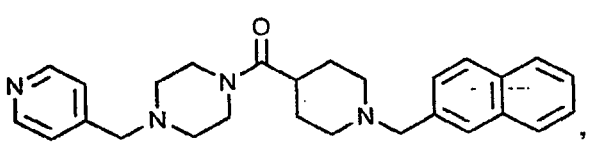


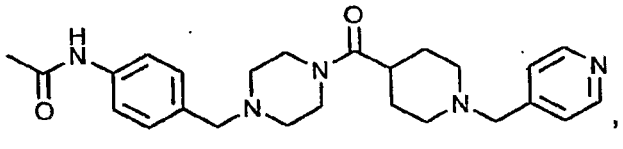


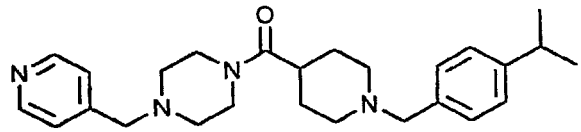


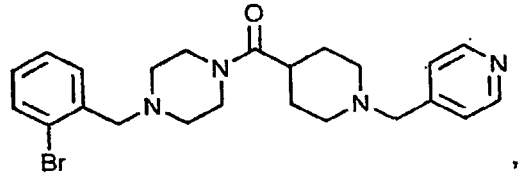


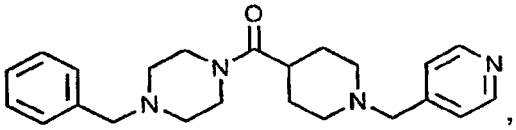
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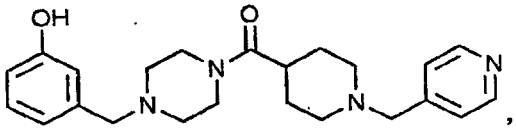


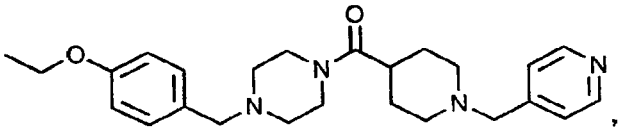


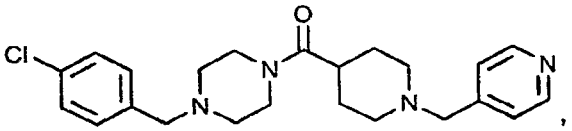


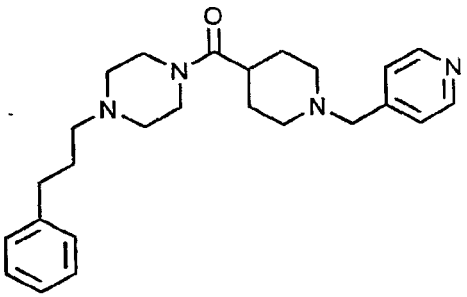


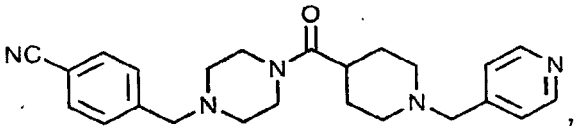


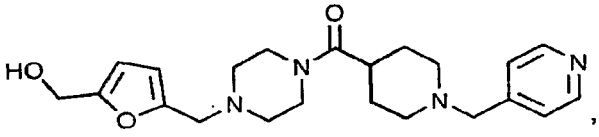


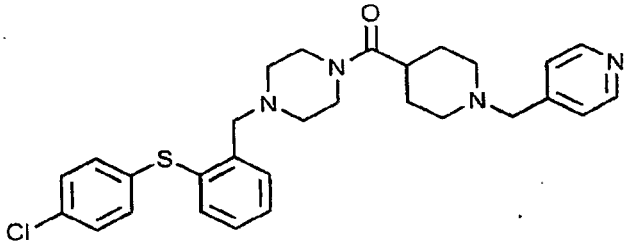


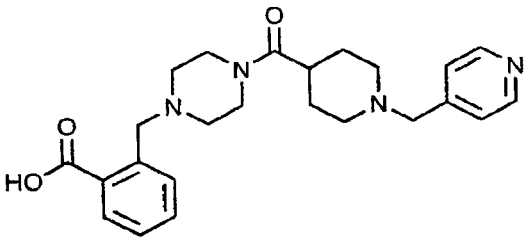


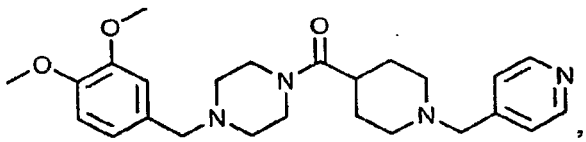


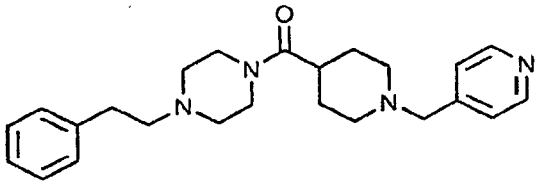


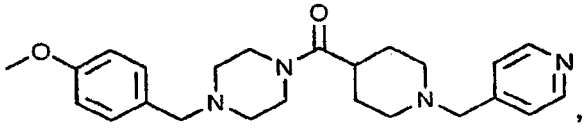


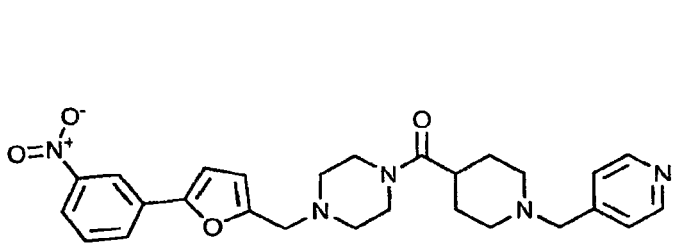


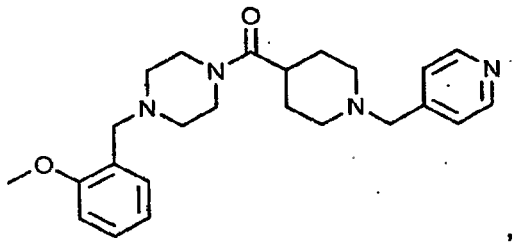


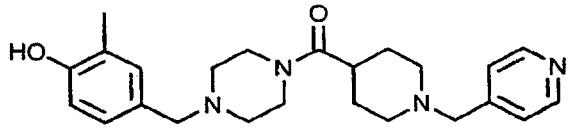


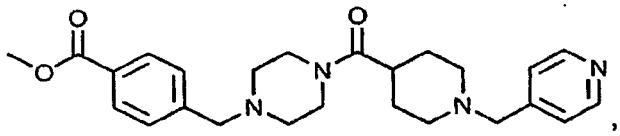


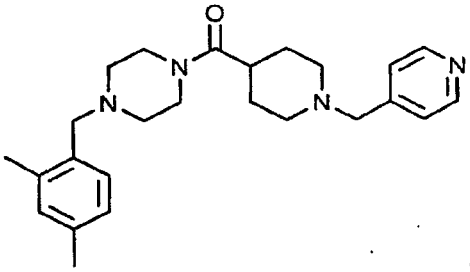


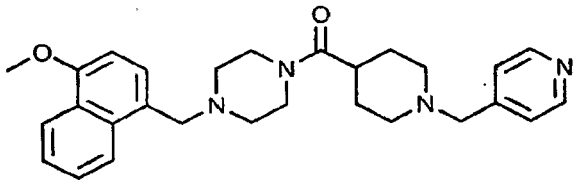


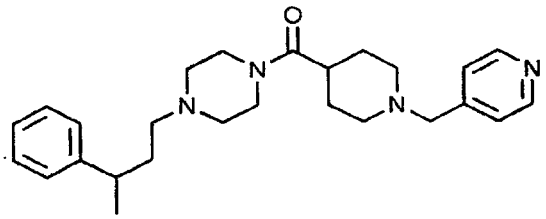


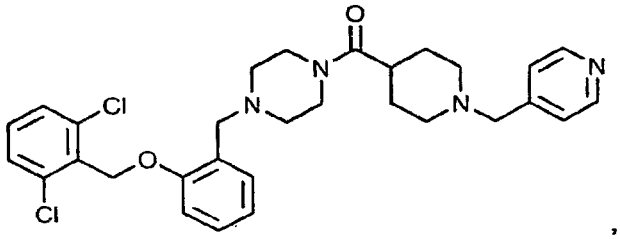


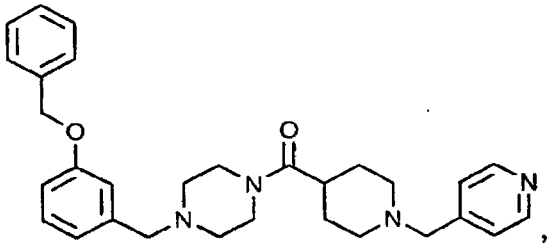


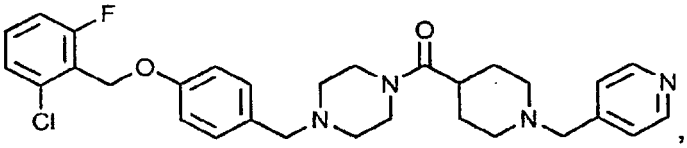


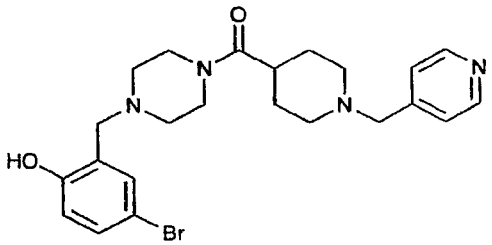


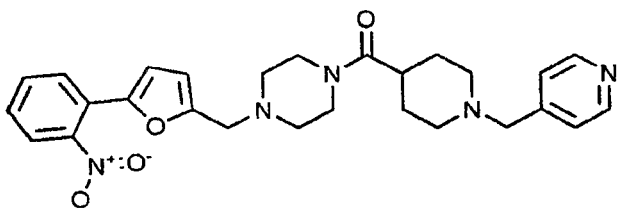


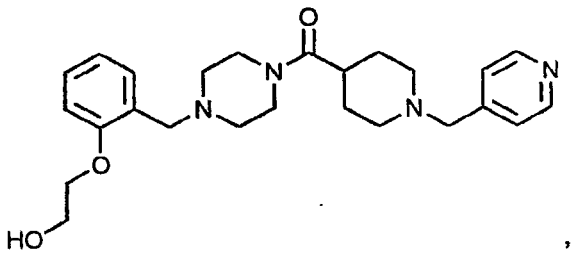


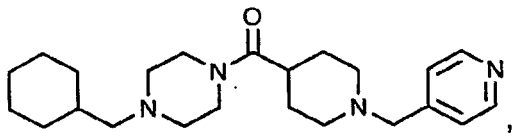


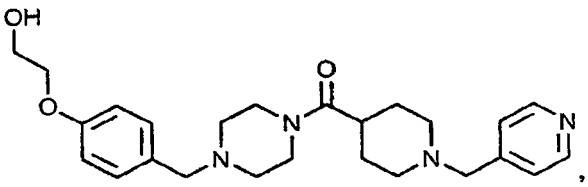


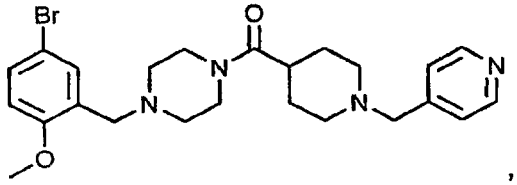


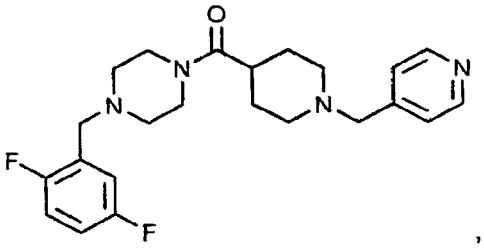


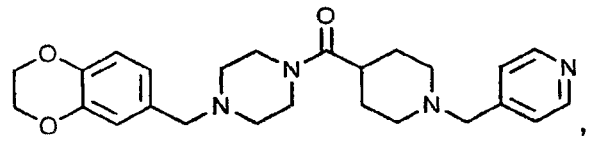


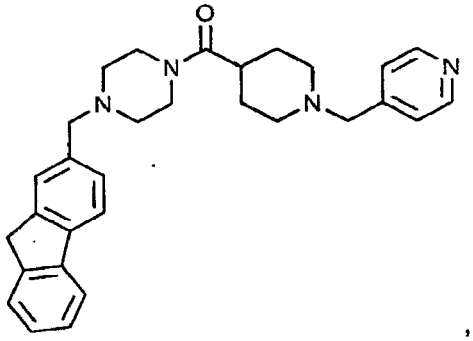


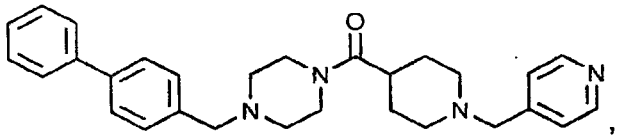


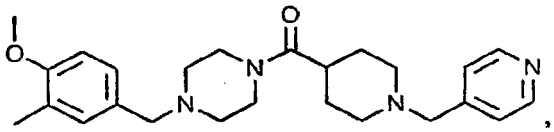


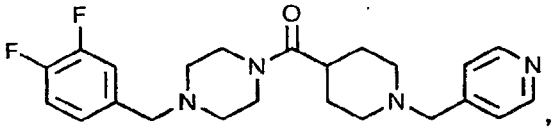


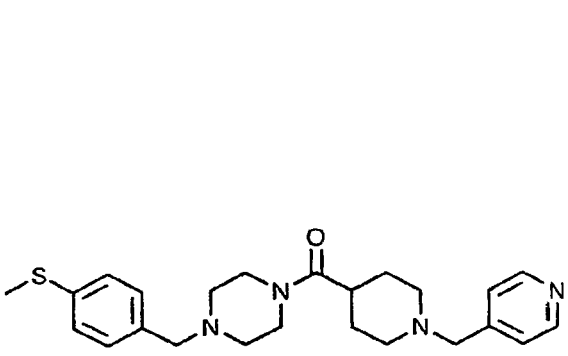


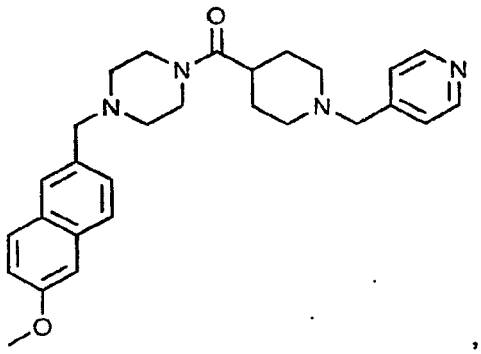


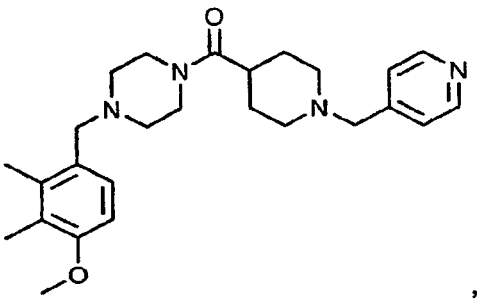


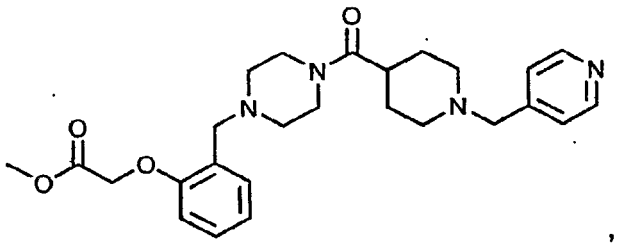


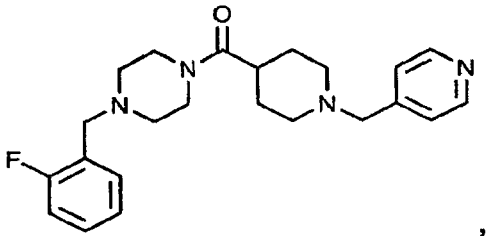


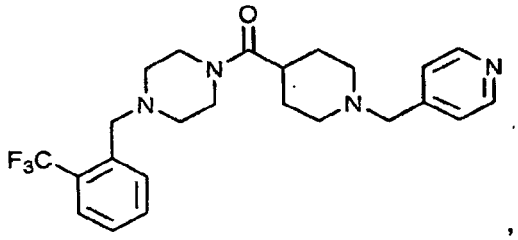


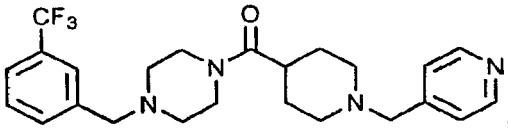


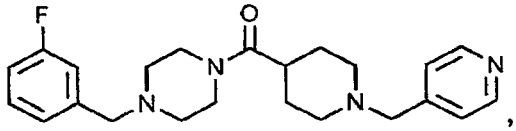


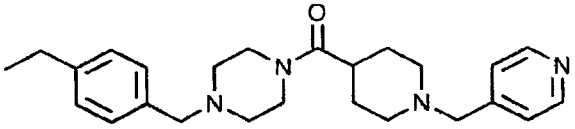


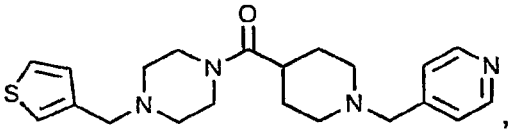


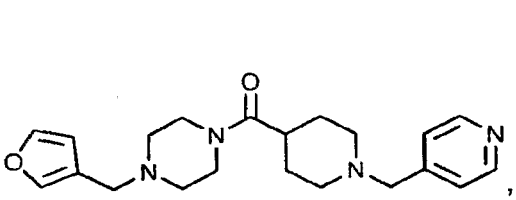


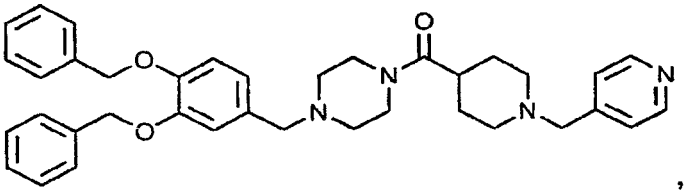


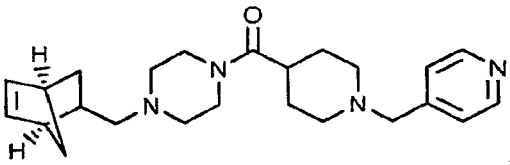


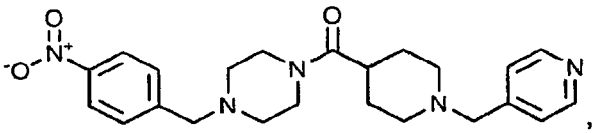


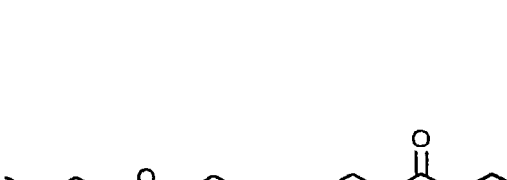


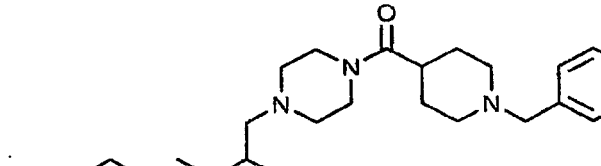


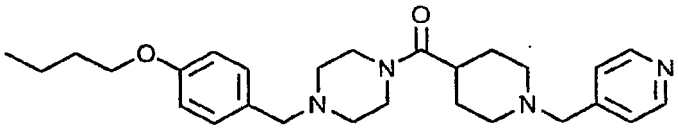


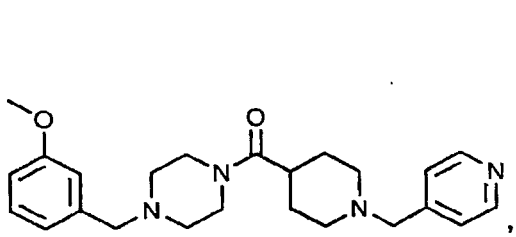


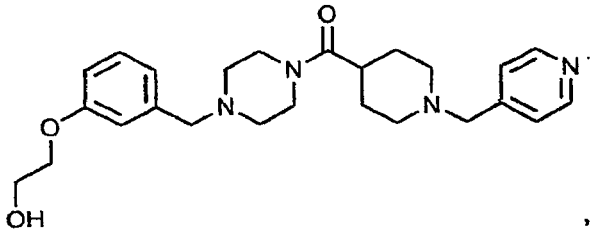


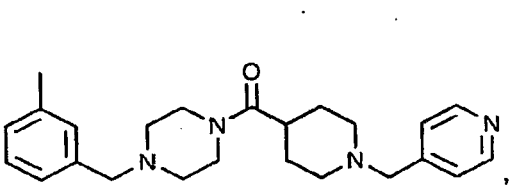


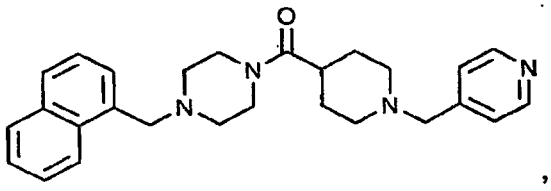


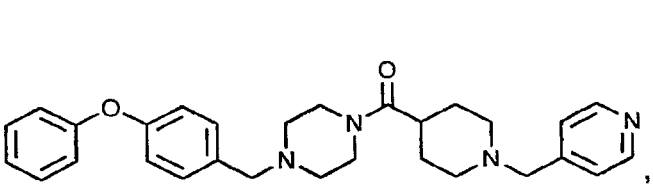


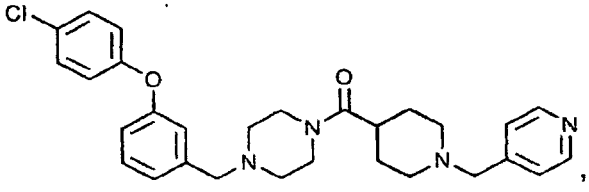


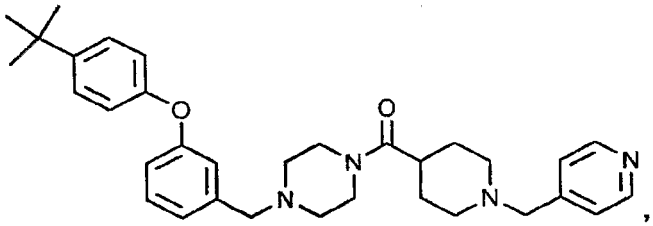


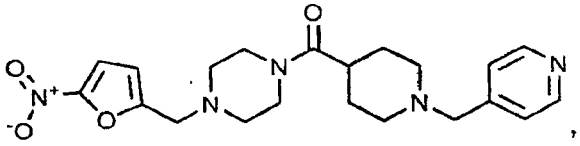


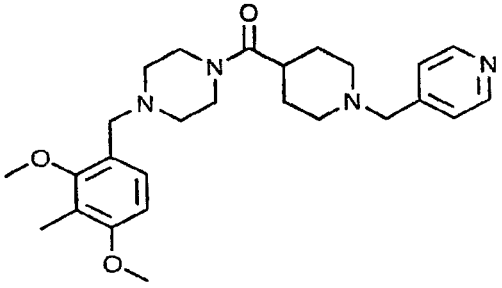


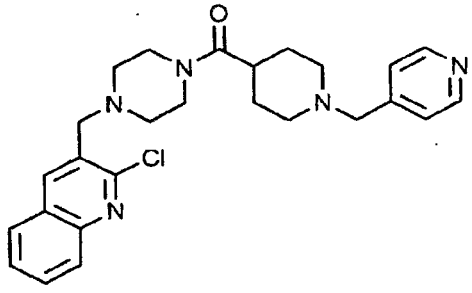




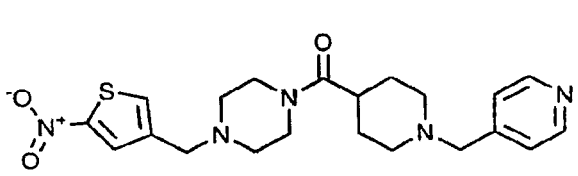


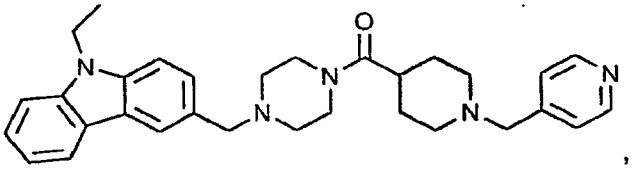


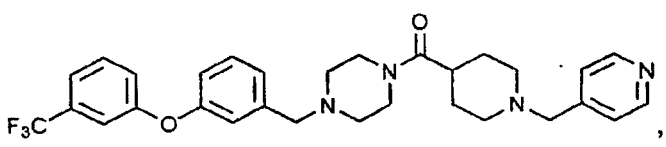


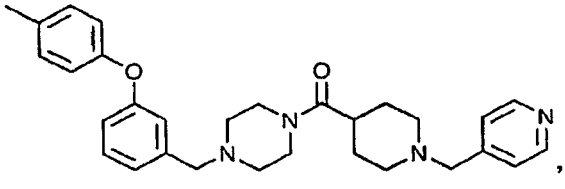


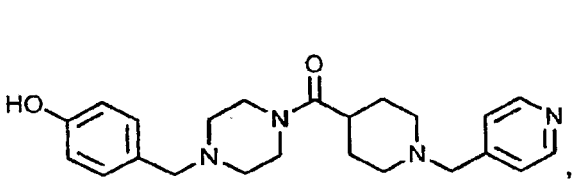
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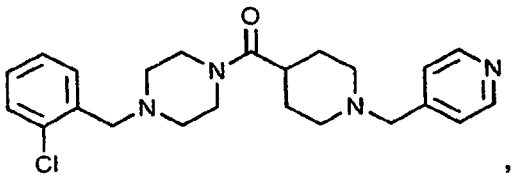


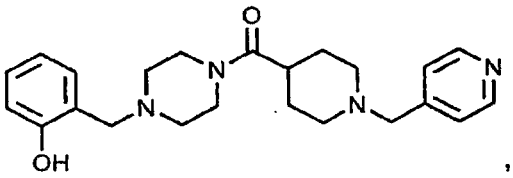


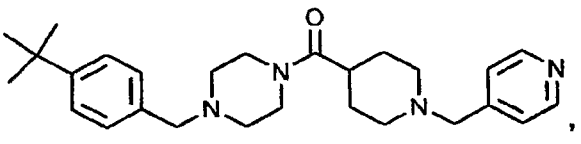


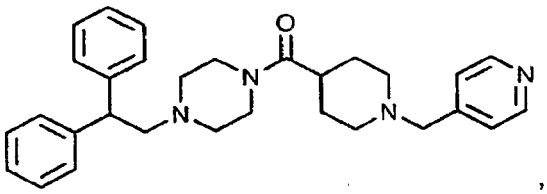


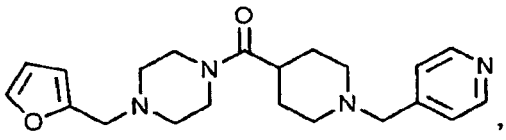


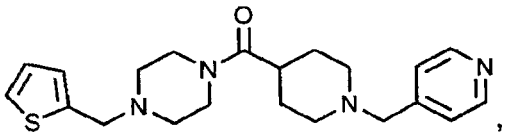


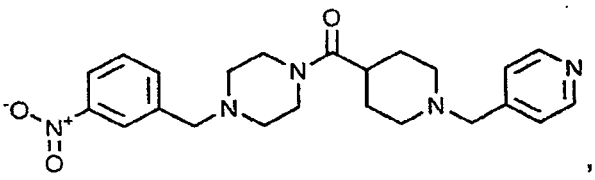


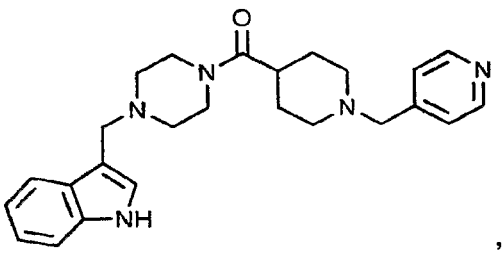


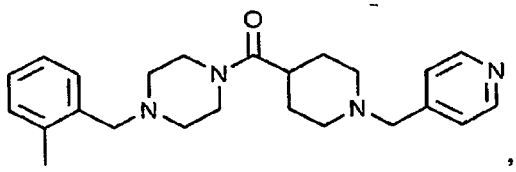


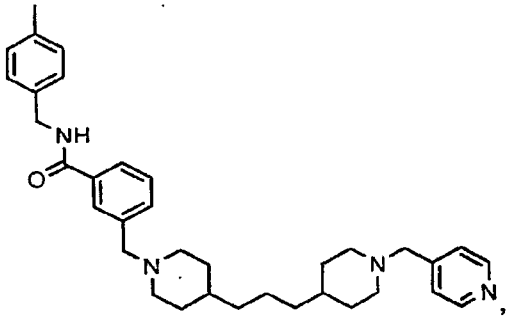


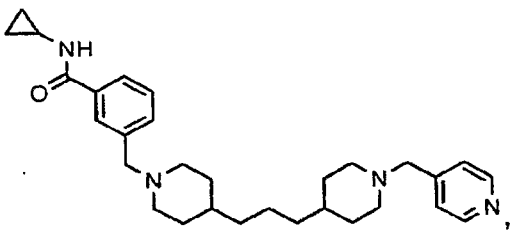


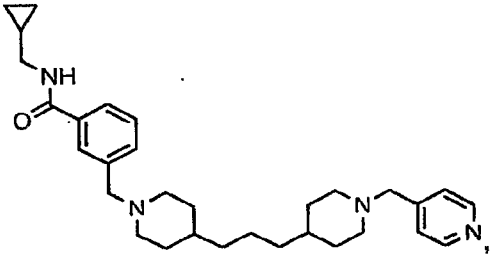


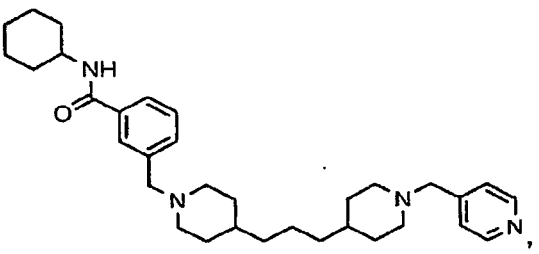


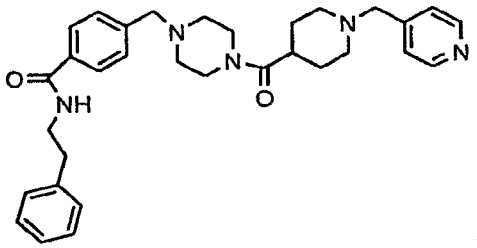


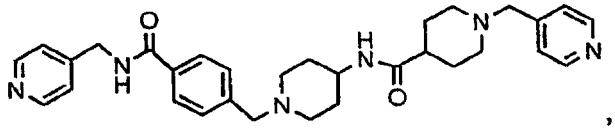


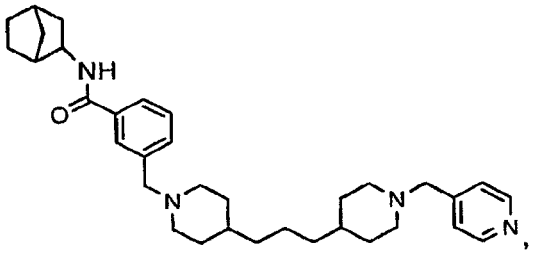


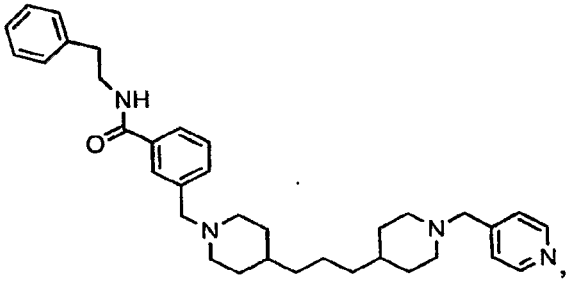


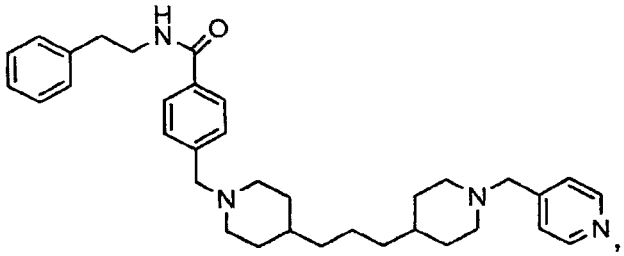


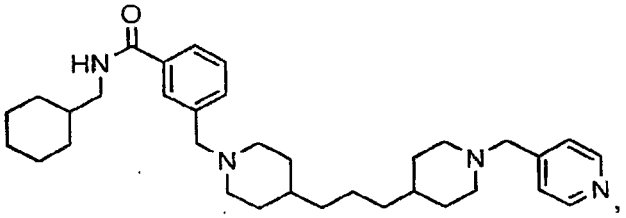


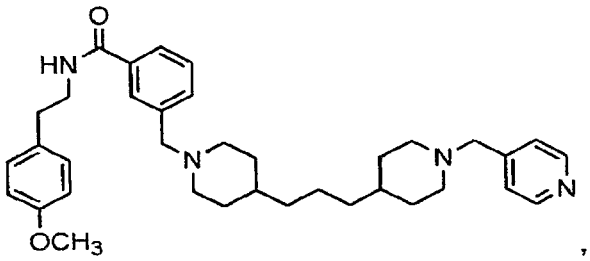


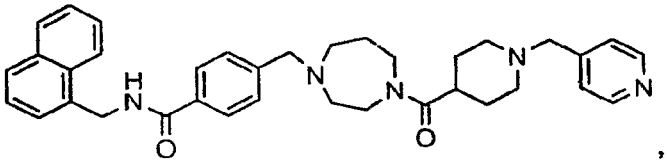


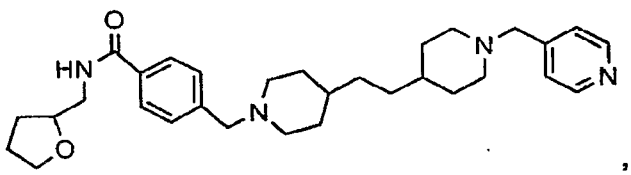


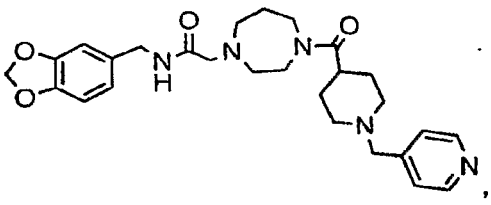


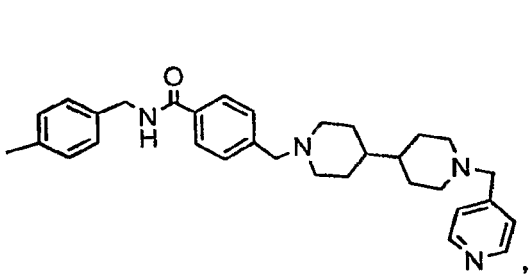


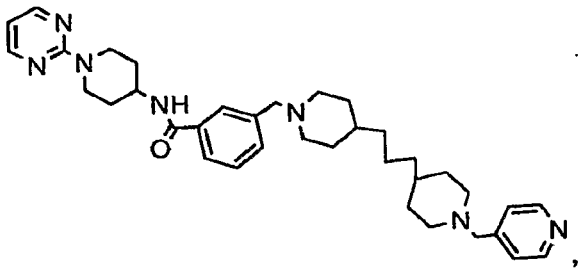


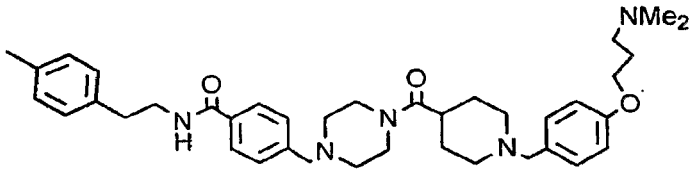


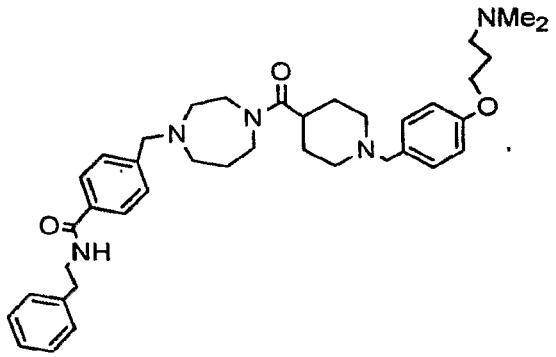


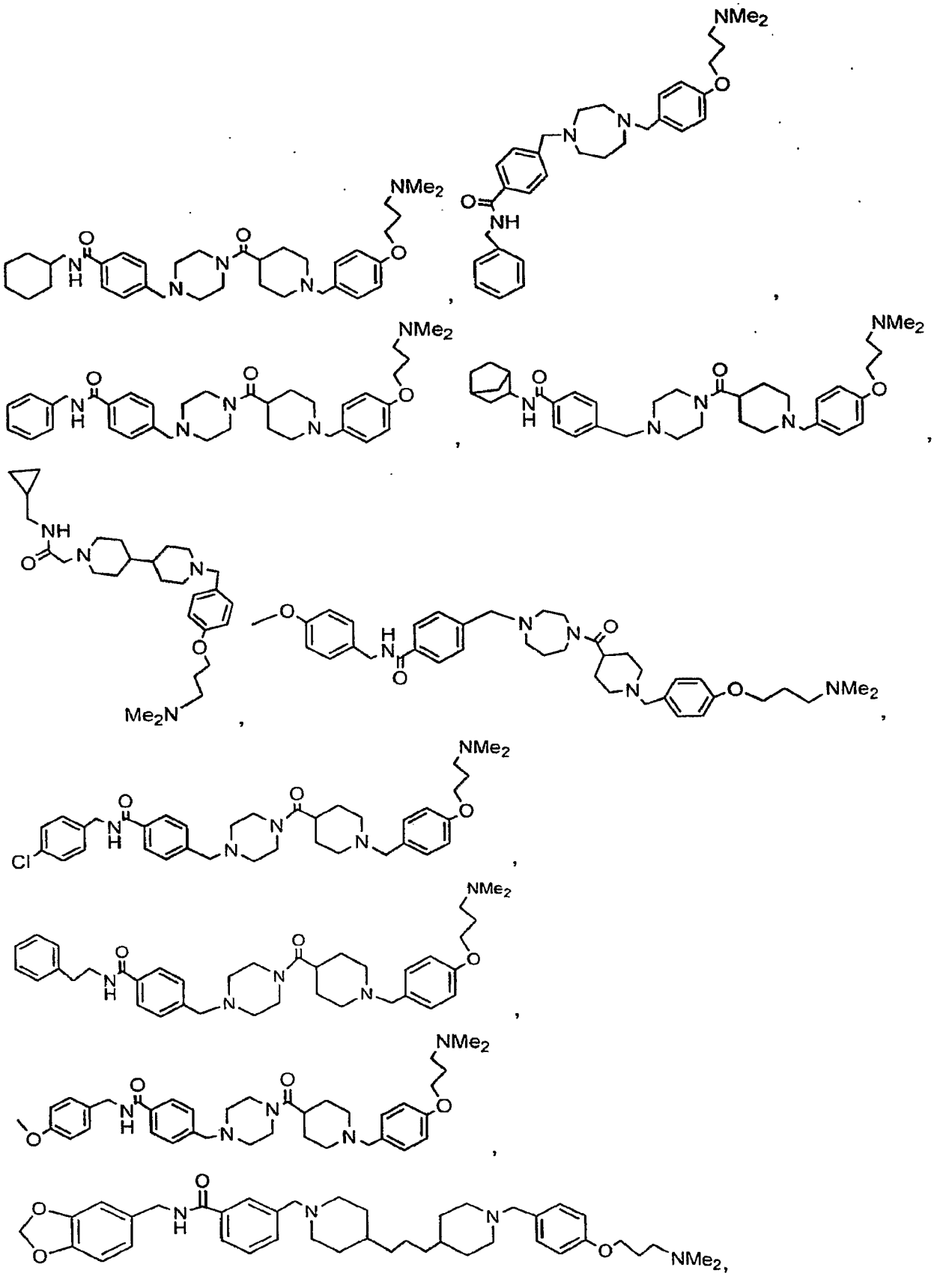


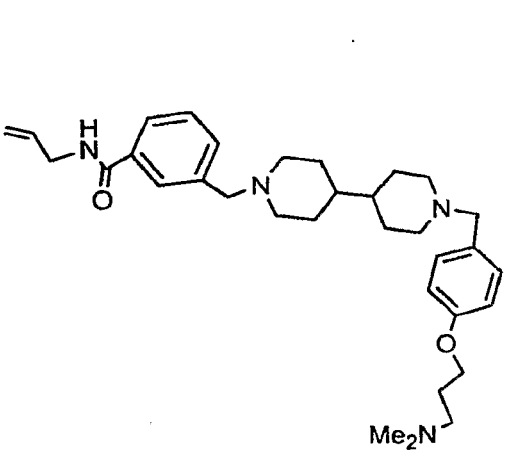


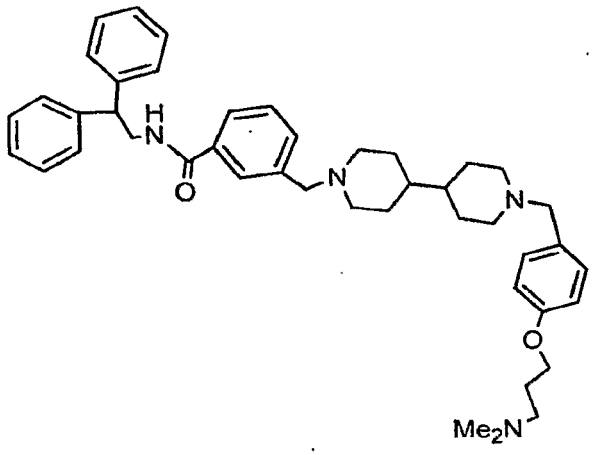


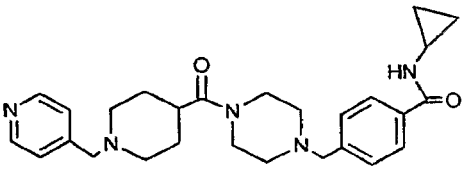


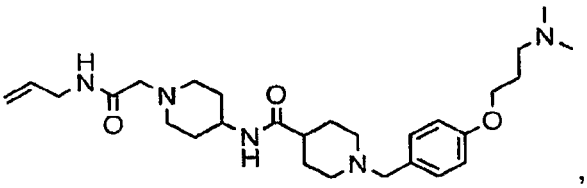


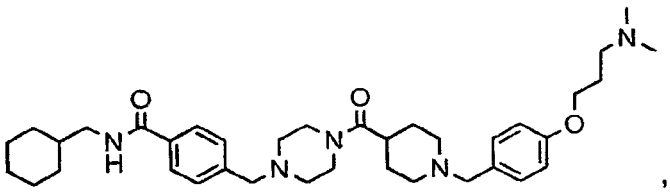


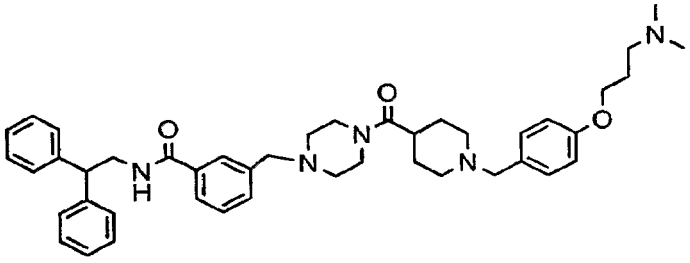


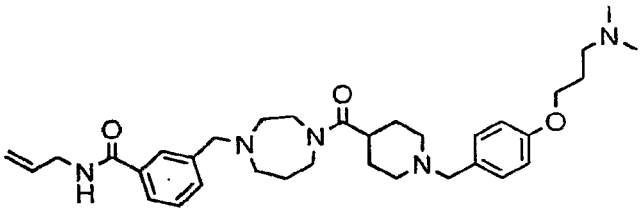


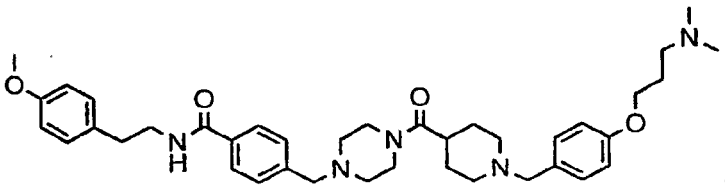


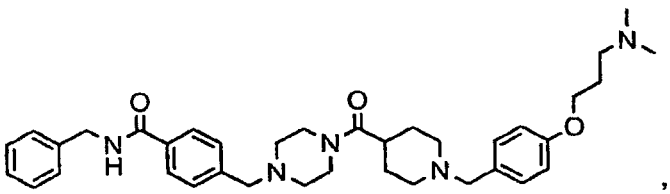


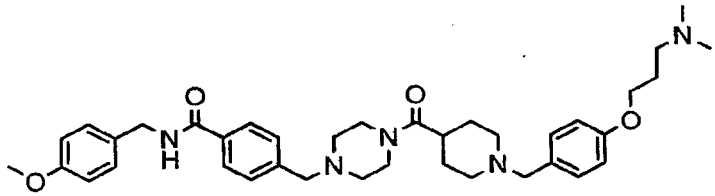


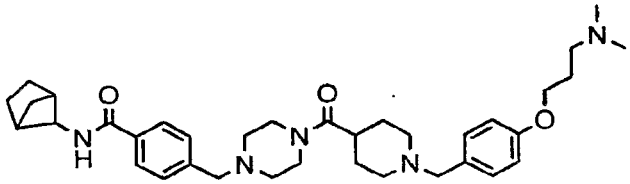


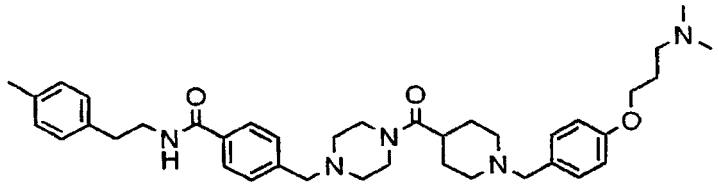


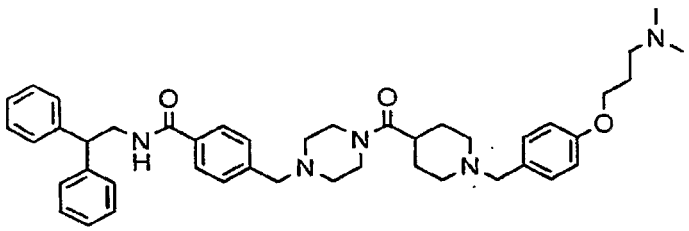


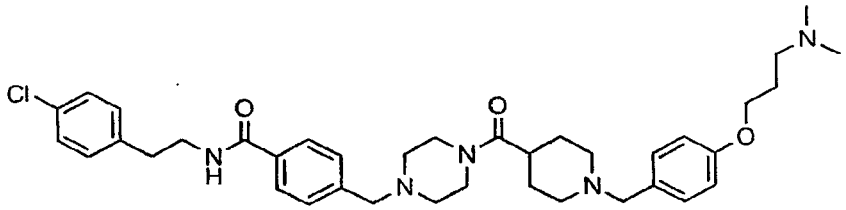


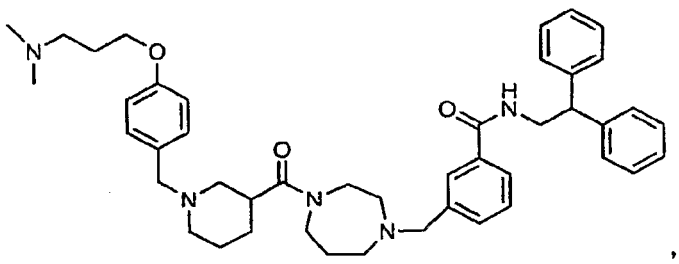


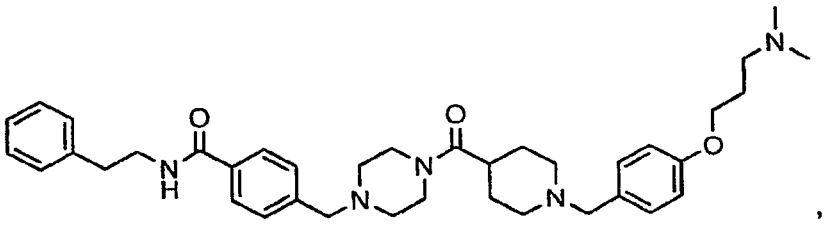


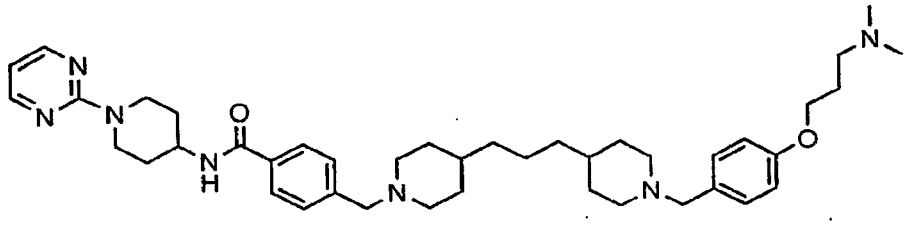


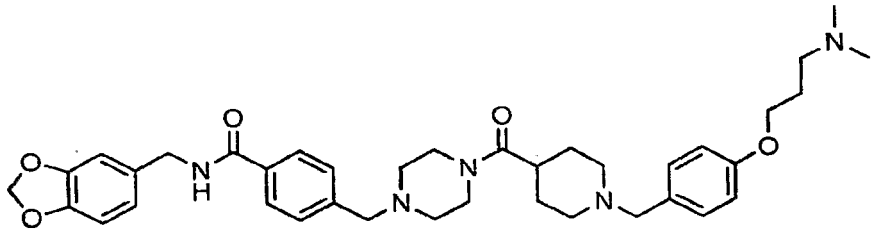


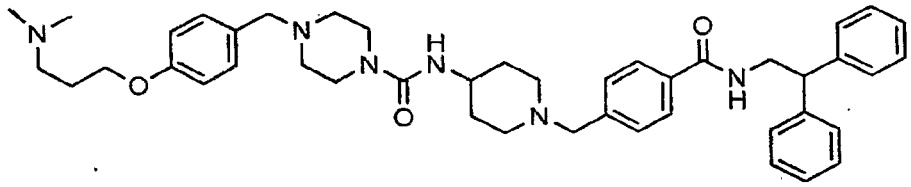


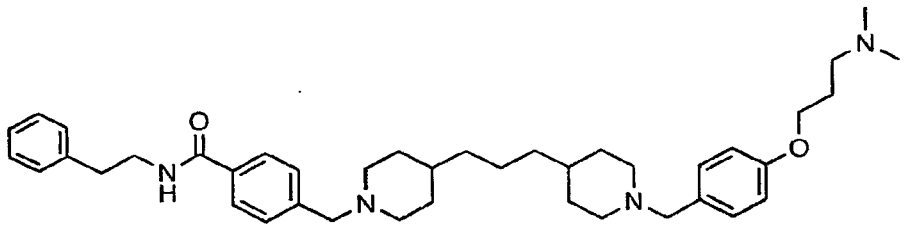


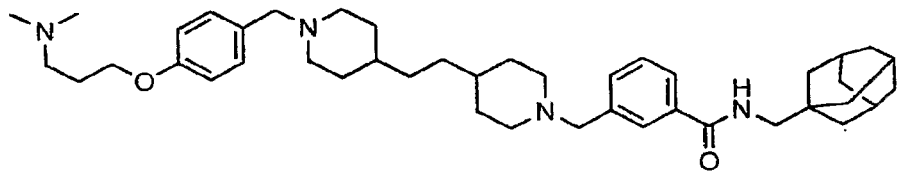


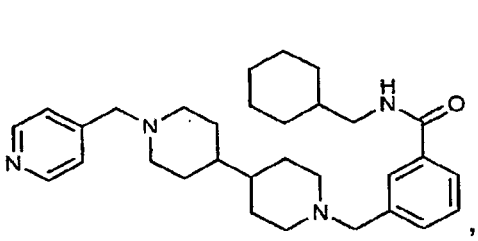


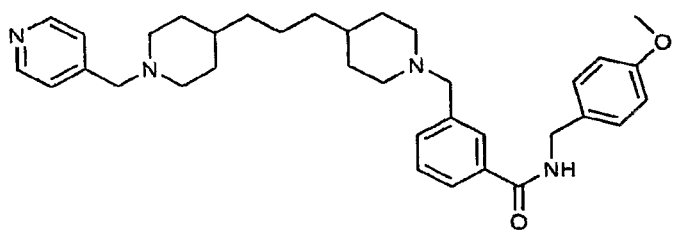


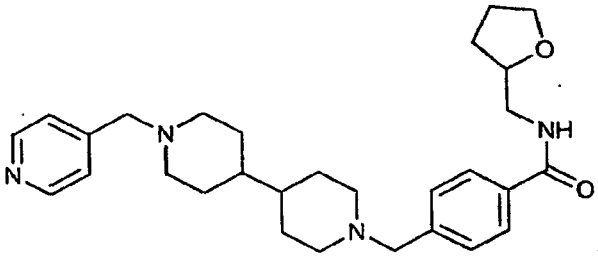


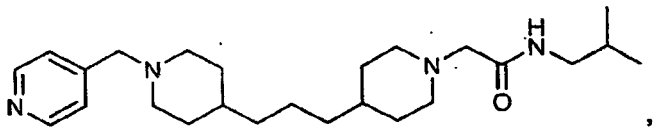


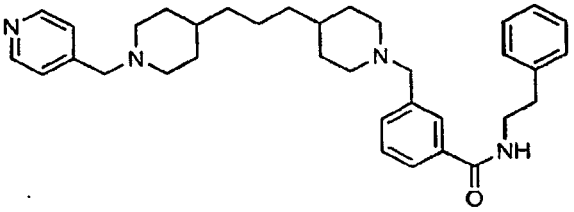


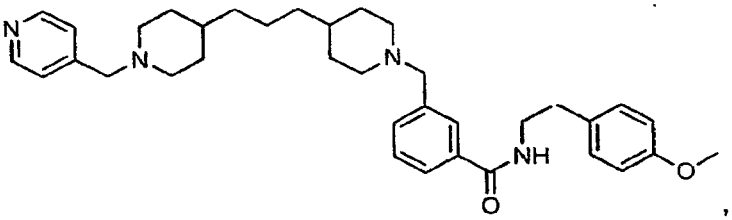


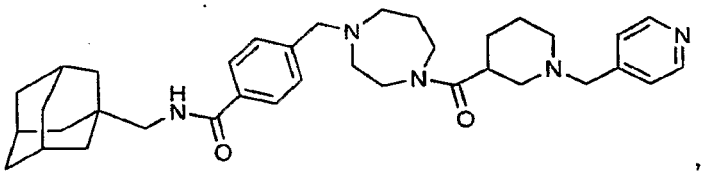


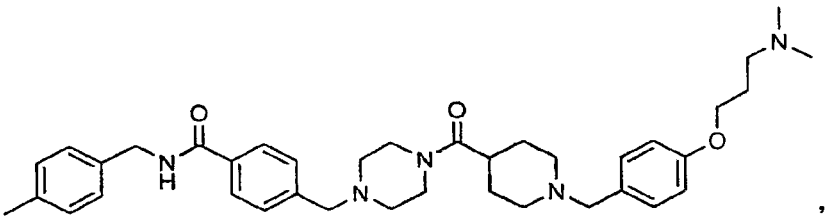


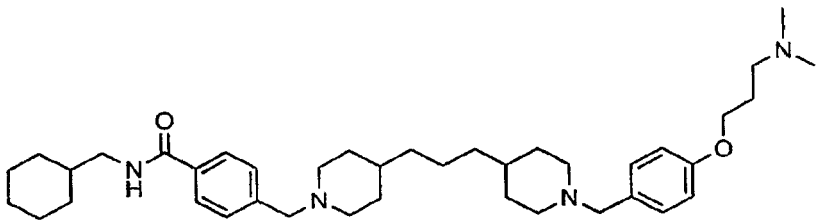


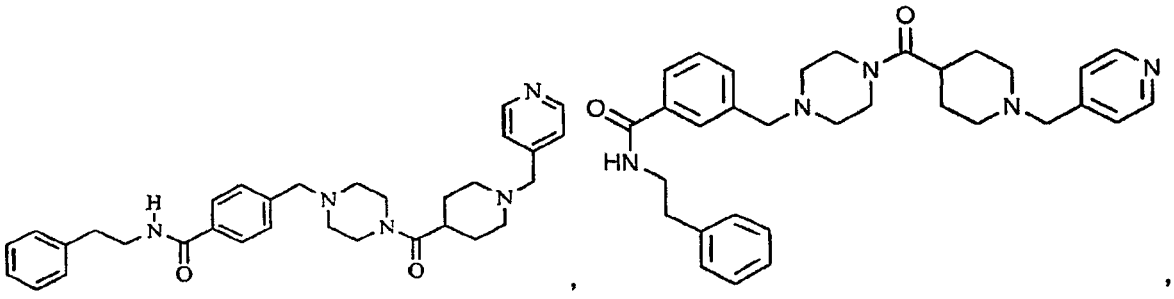


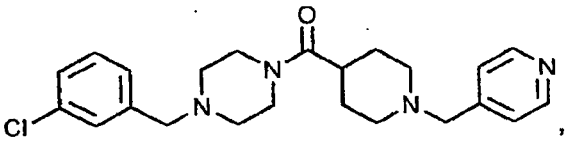
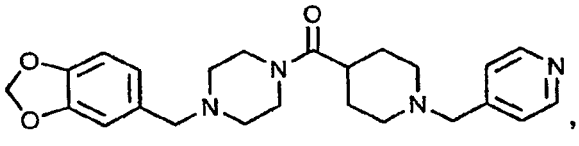
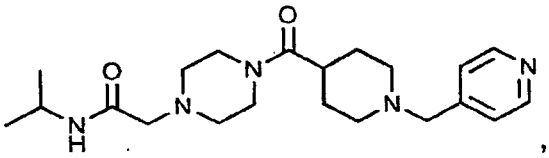
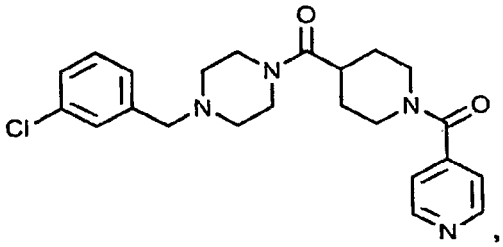
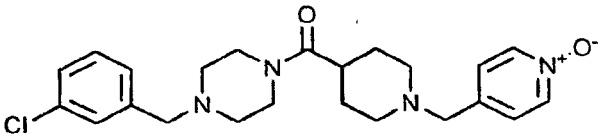
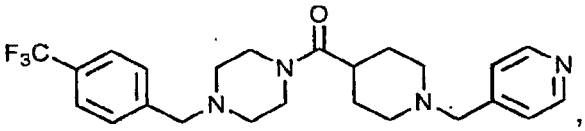
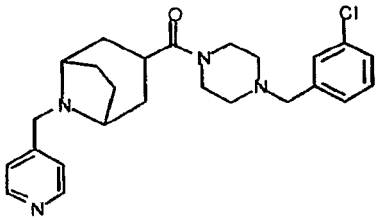
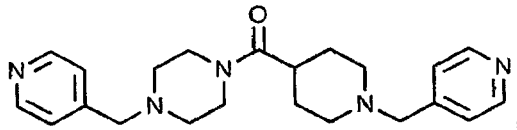
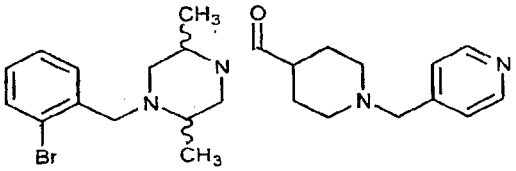


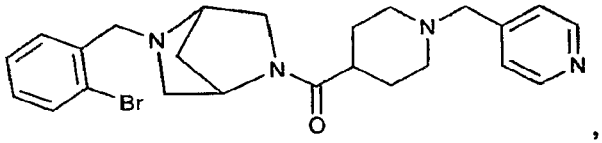
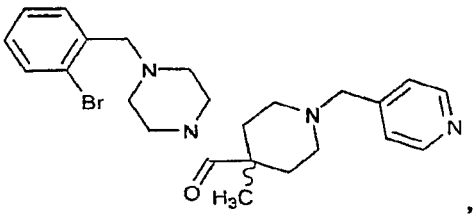
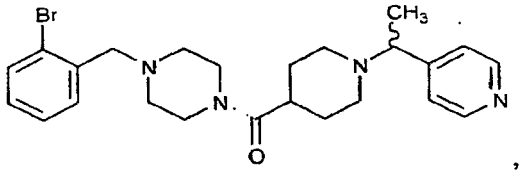
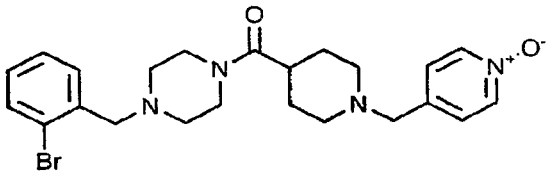
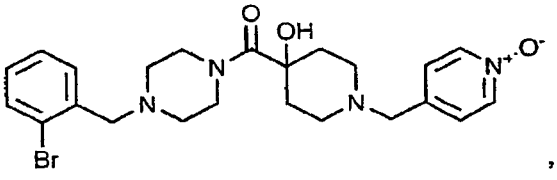
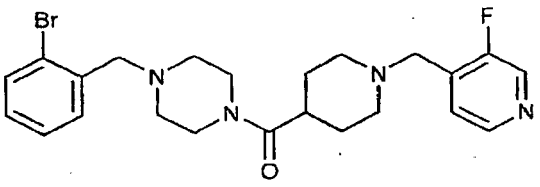
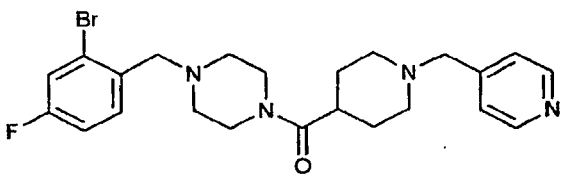




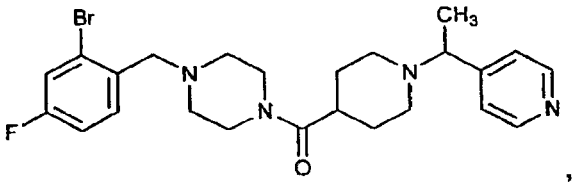
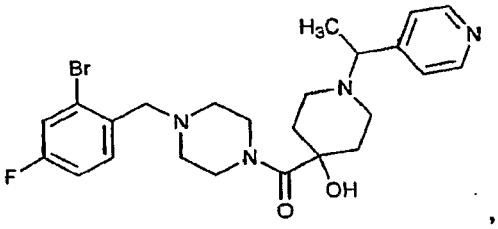
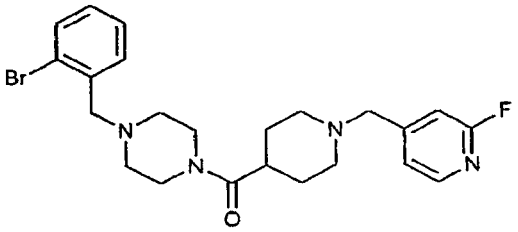
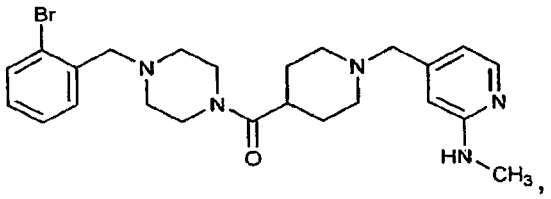
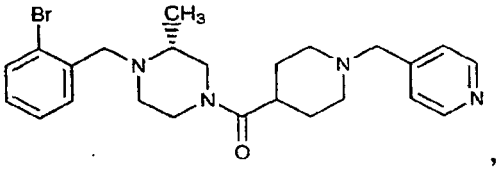
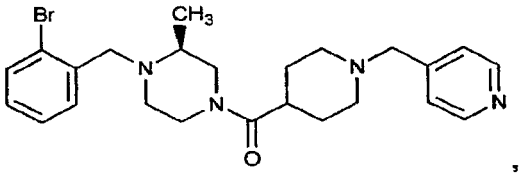
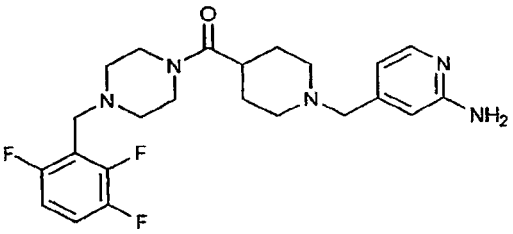
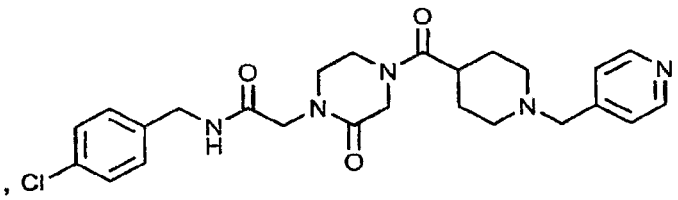
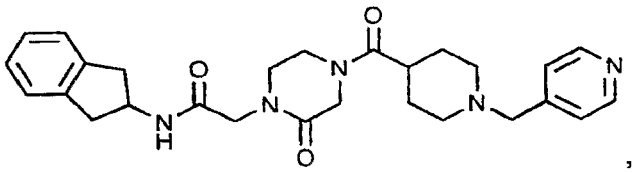
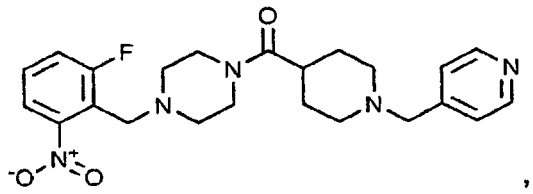
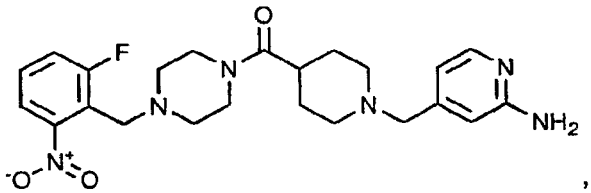
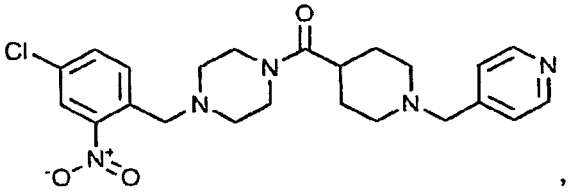
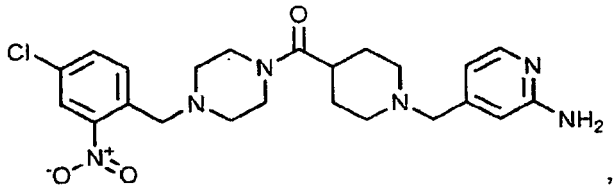
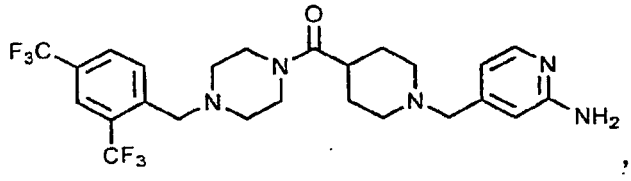




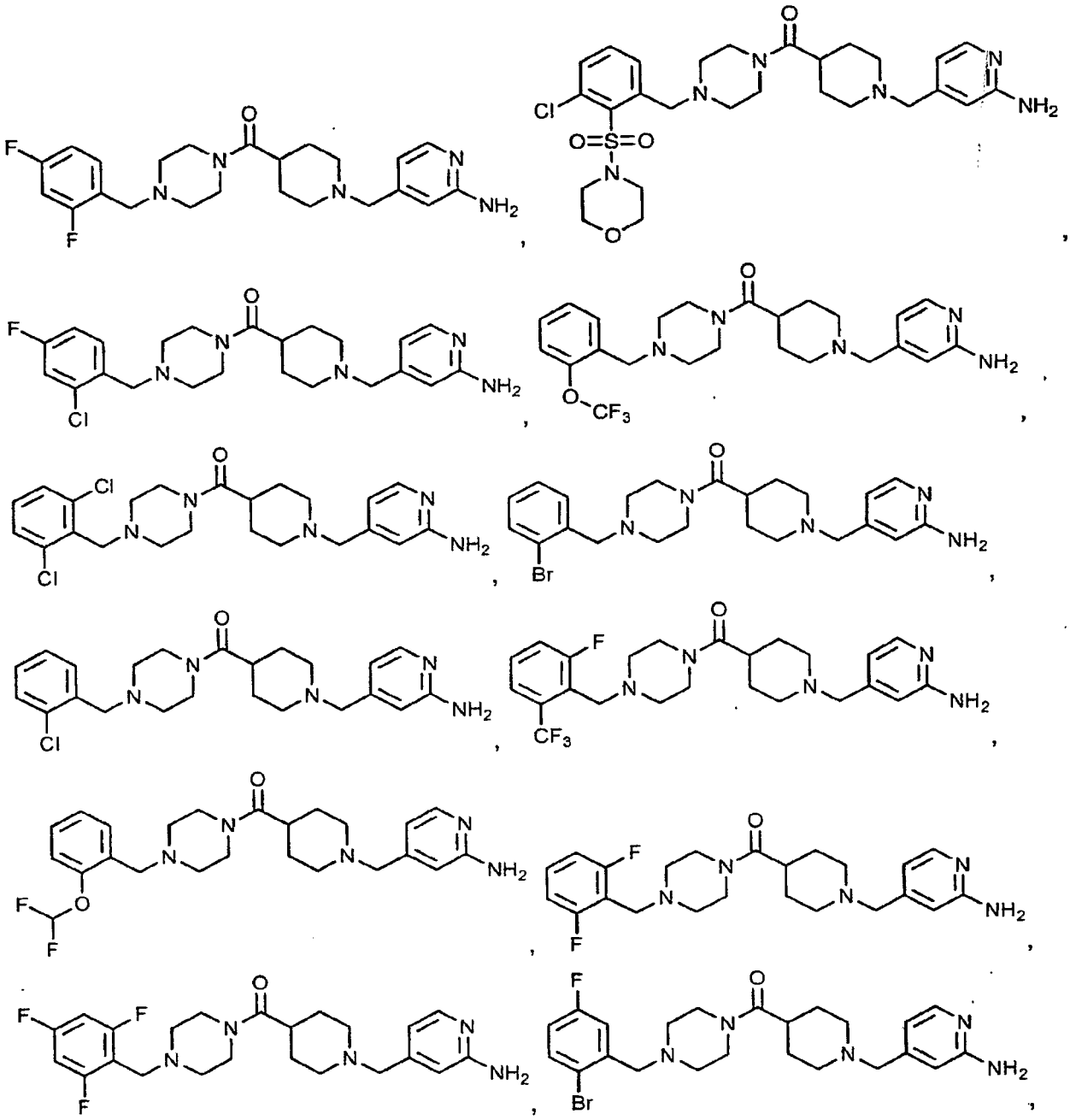








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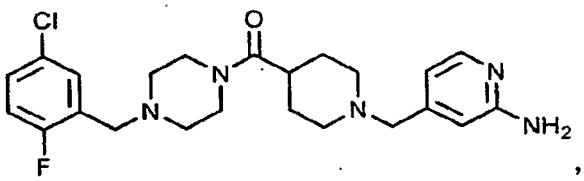

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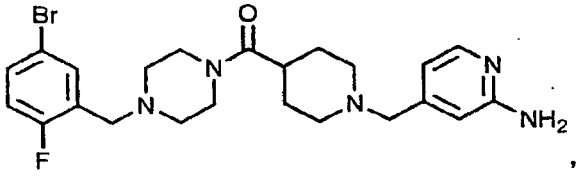
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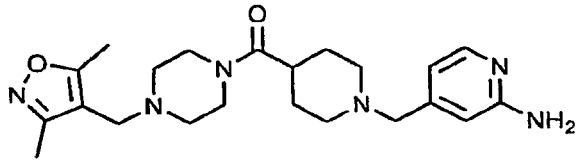
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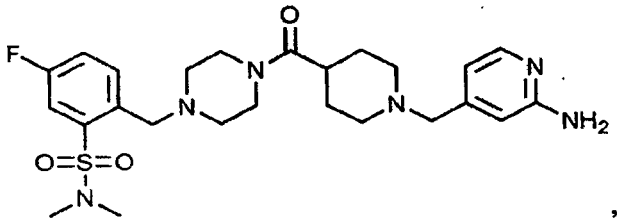
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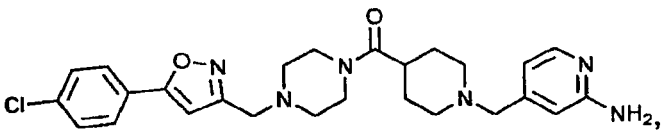
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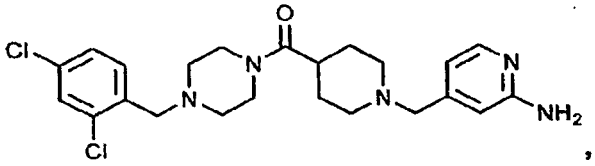

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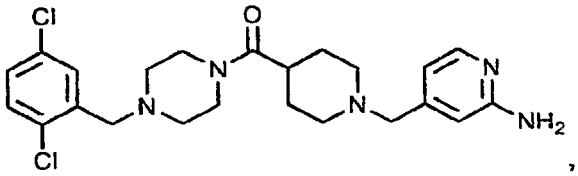
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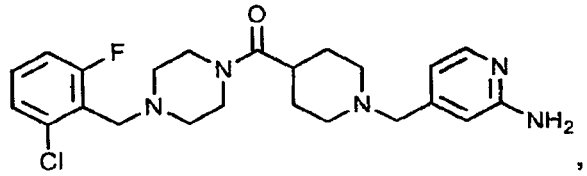

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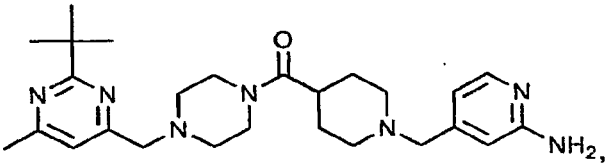
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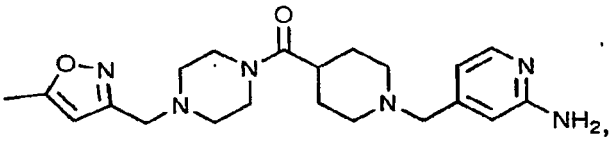


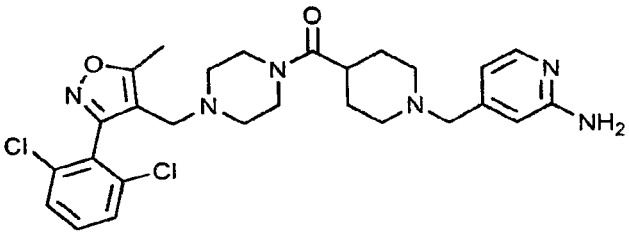


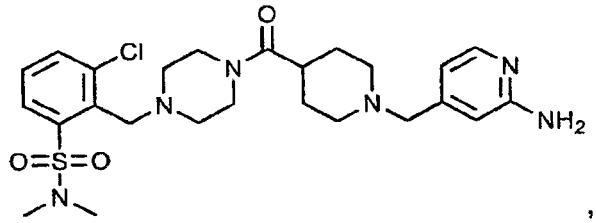


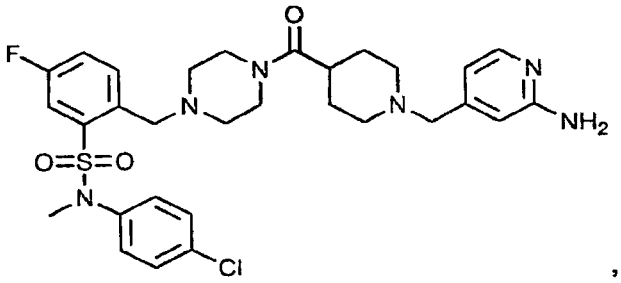


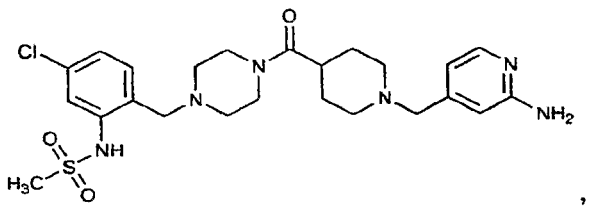


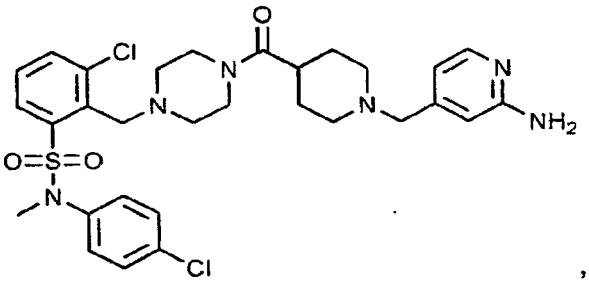


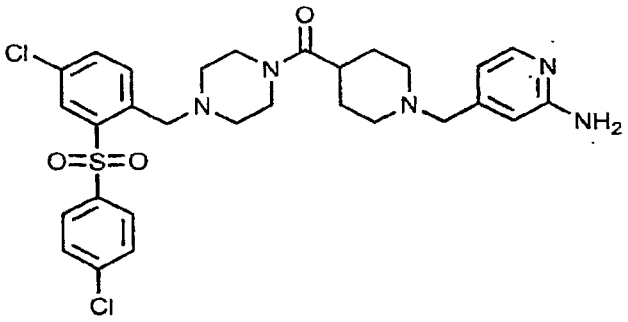


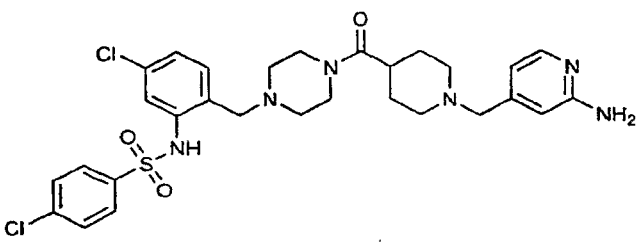


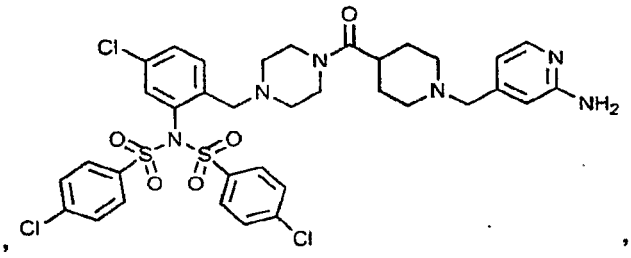


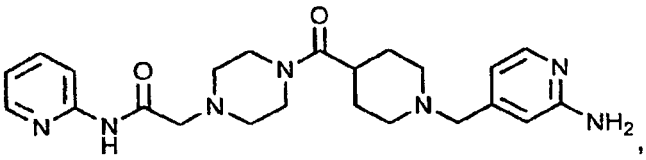


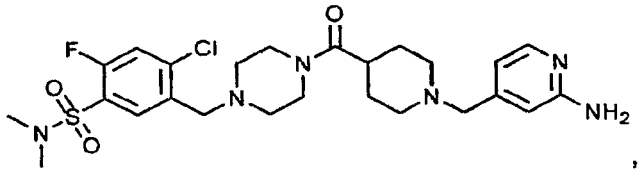


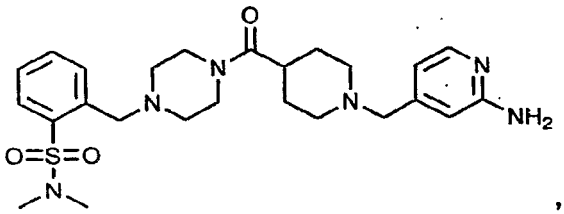


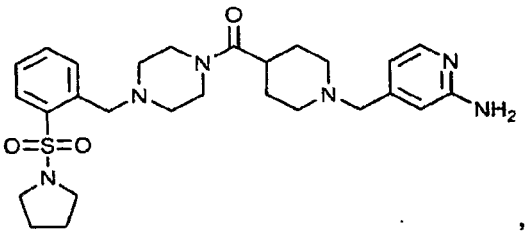


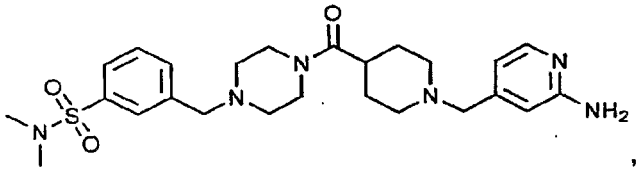


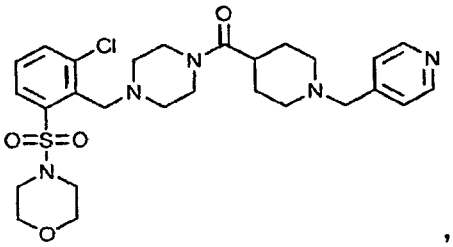


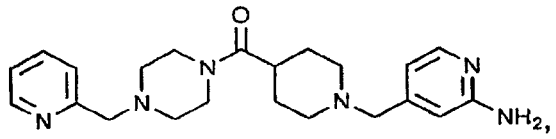


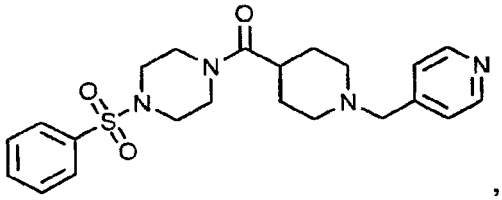


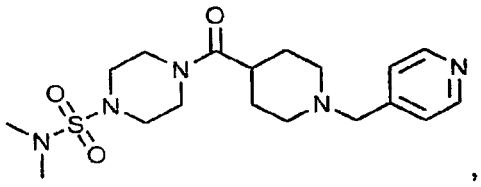


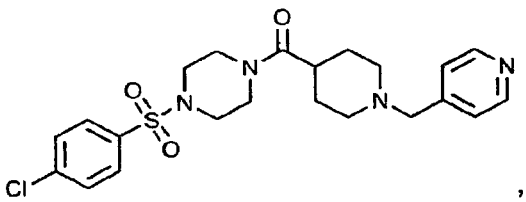


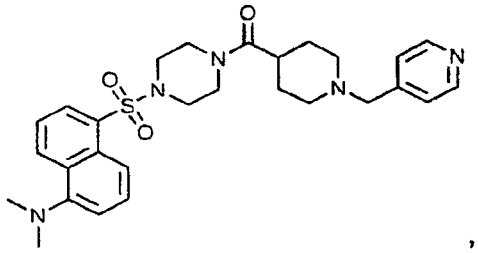


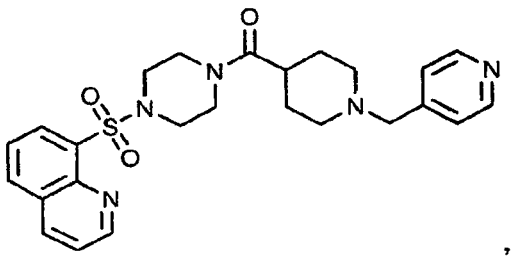


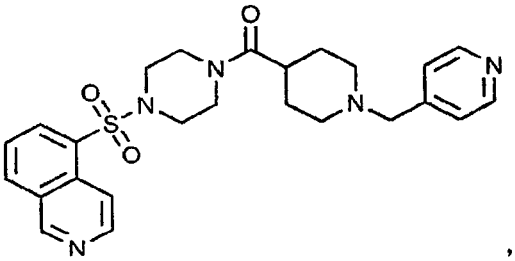


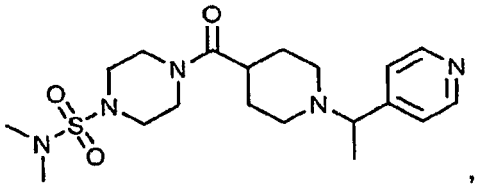


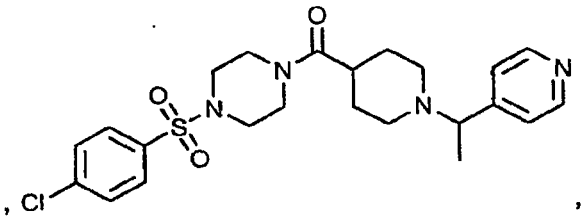


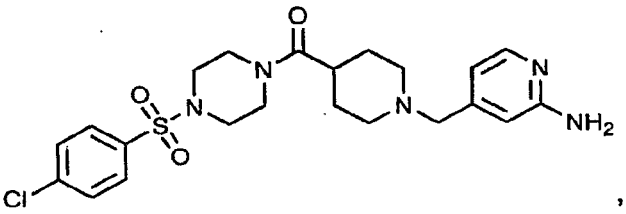


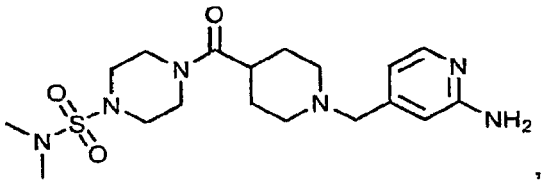


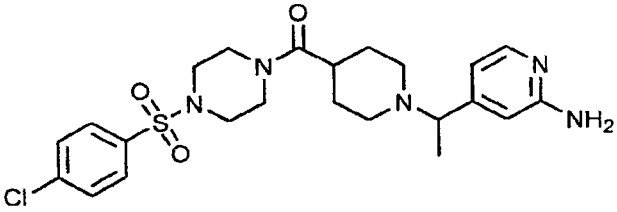


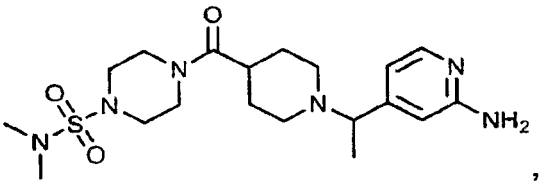


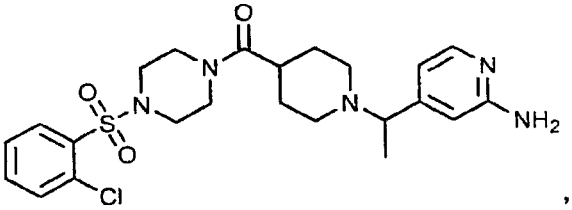


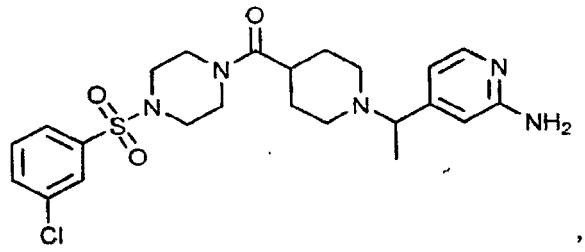


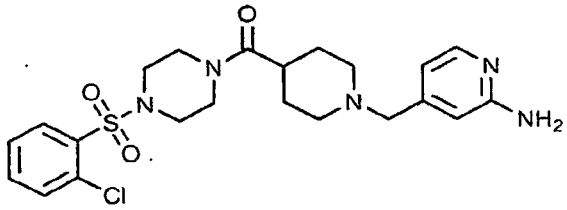


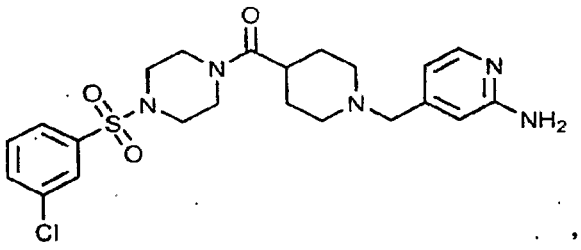


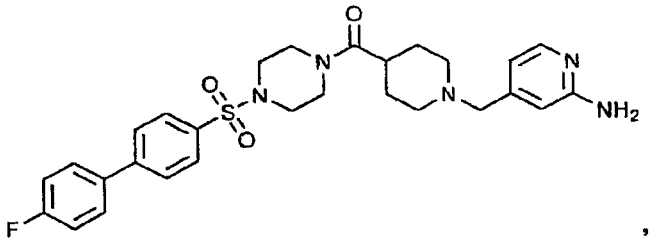


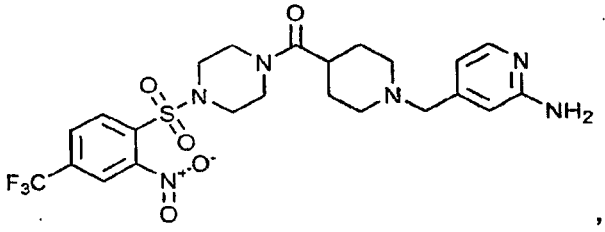


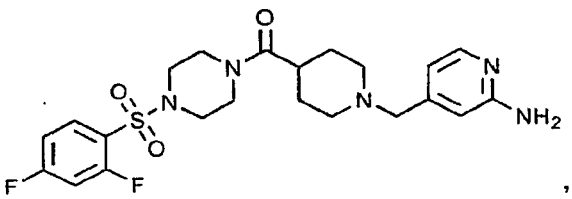


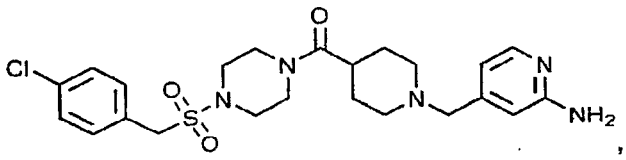


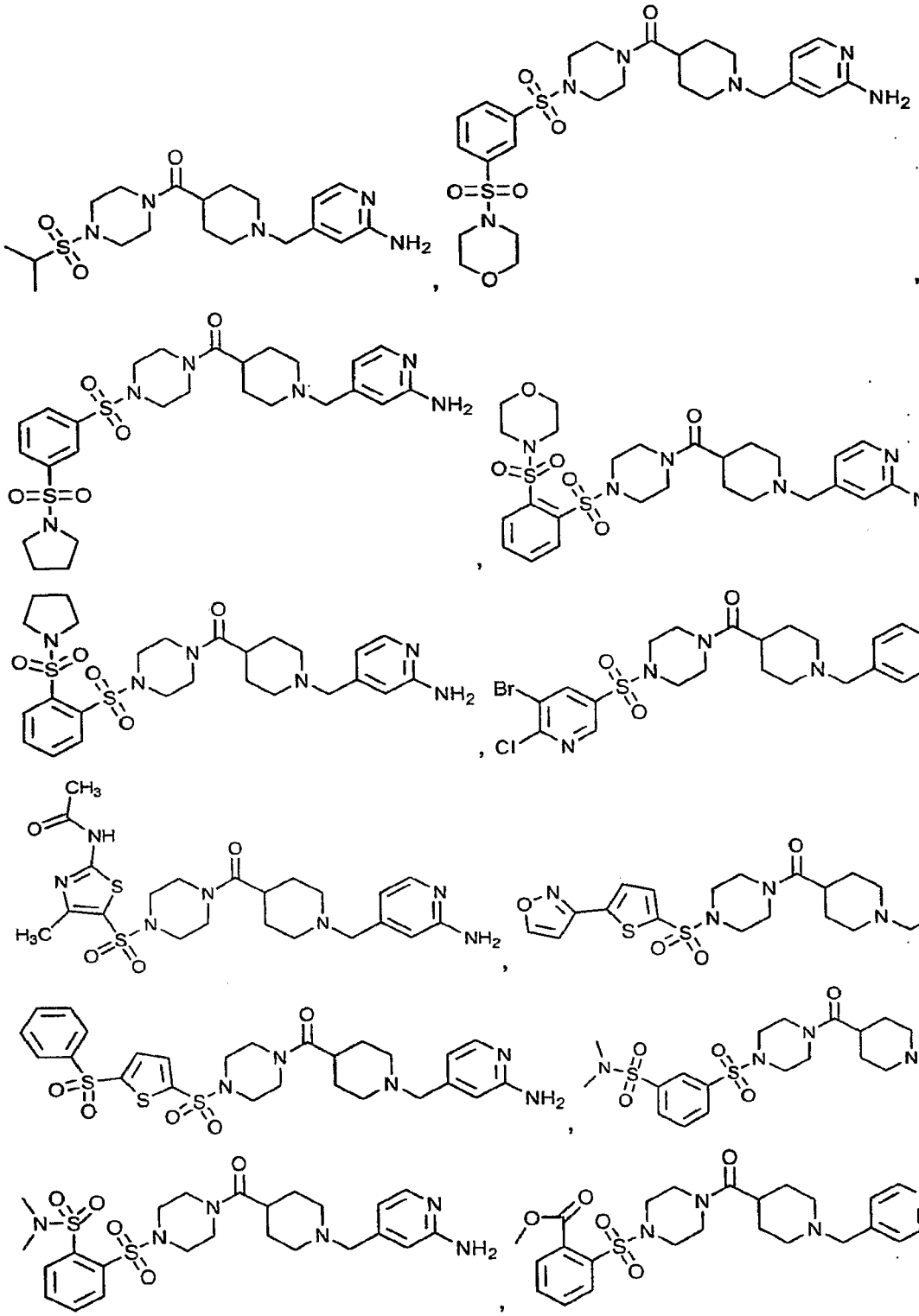


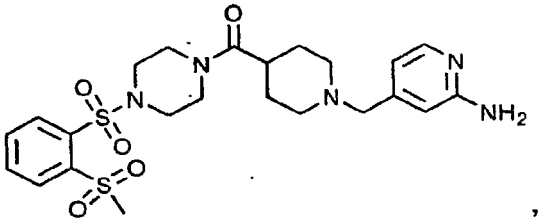




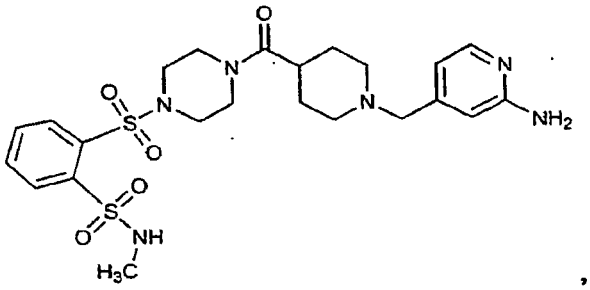




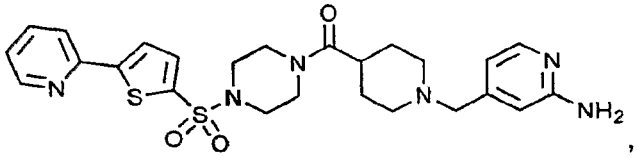




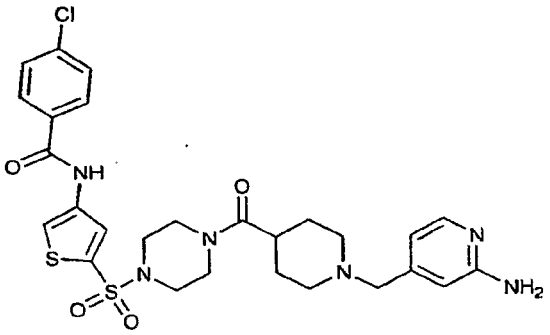
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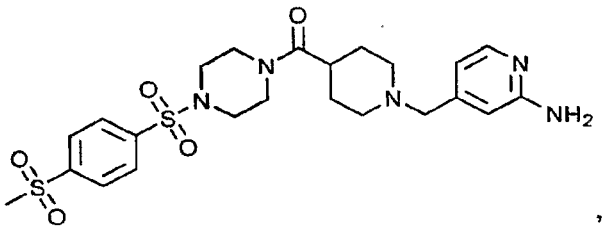
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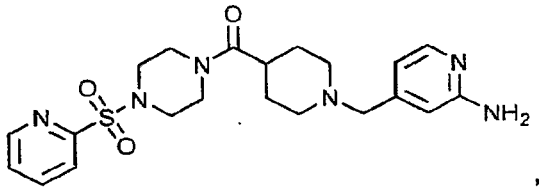
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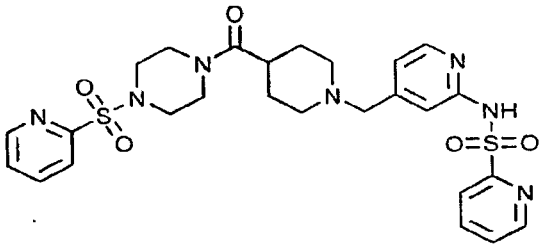
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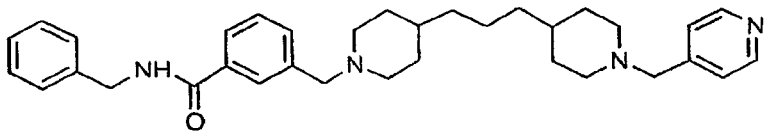
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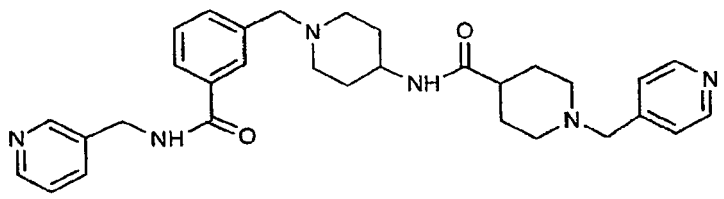
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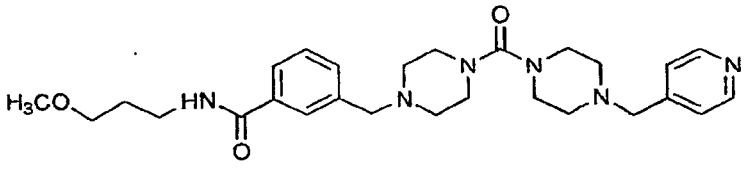
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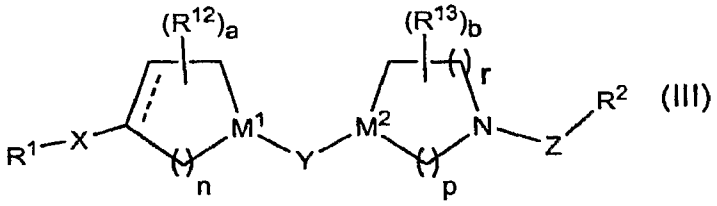


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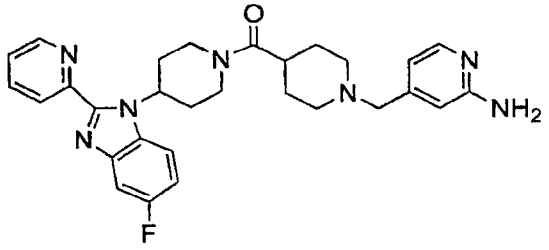
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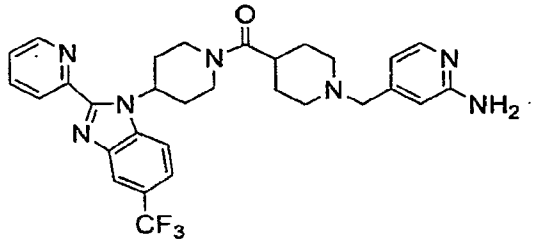
In one embodiment, the H_3 antagonists/inverse agonists of the present invention can have a structure according to Formula (III):

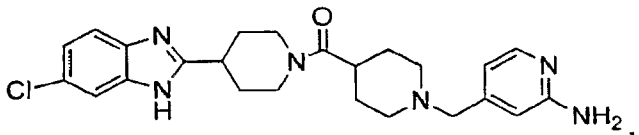


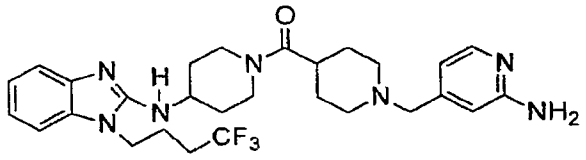
(III)

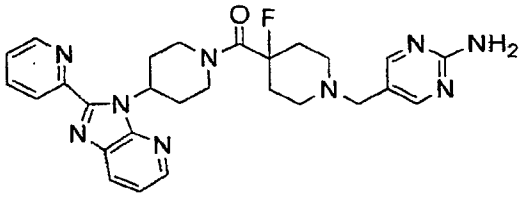
as described in U.S. Patent Publication No. 2004/0097483, which is herein incorporated by reference in its entirety. Non-limiting examples of compounds of Formula (III) include:

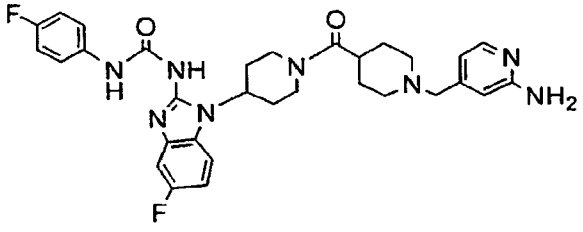




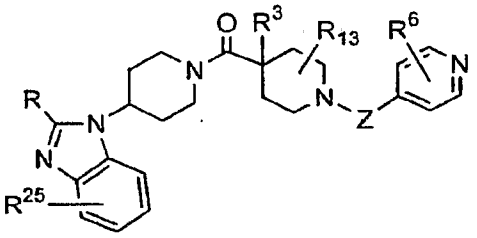






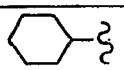
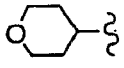
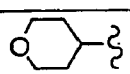
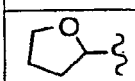


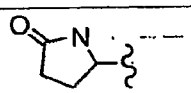
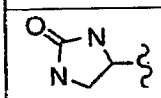
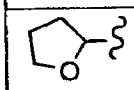
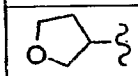
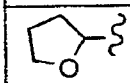
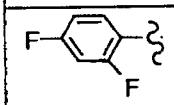
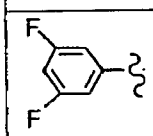
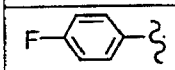
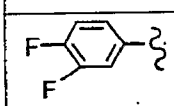
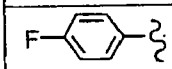
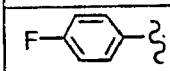
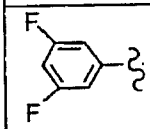
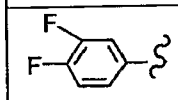
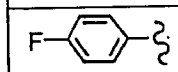
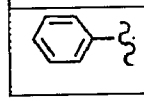
compounds of the following general formula:

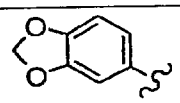
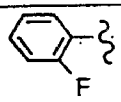
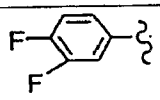
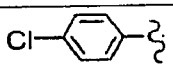
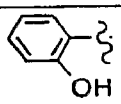
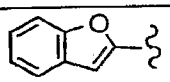
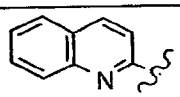
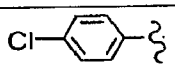
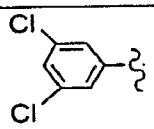
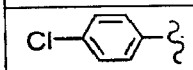
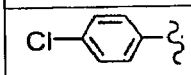
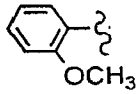
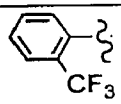


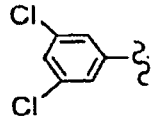
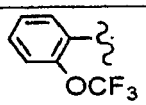
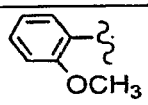
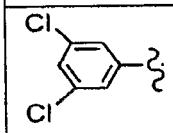
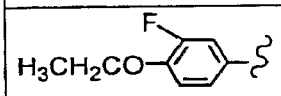
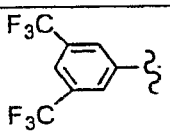
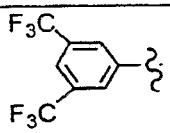
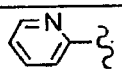
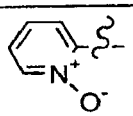
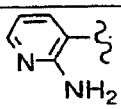
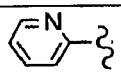
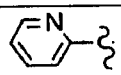
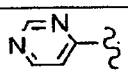
wherein R, R^{25}, R^3, R^{13}, Z, and R^6 are as shown in the following Table:

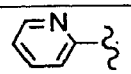
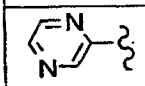
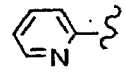
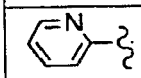
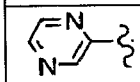
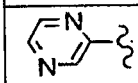
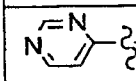
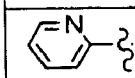
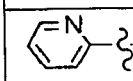
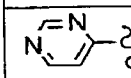
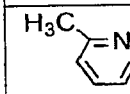
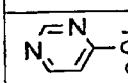
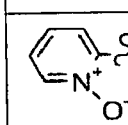
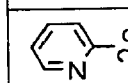
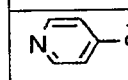
R	R^{25}	R^3	R^{13}	Z	R^6
$-CH_3$	5-OCH_3	H	H	$-CH_2-$	2-NH_2

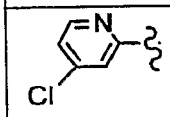
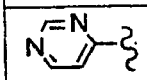
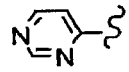
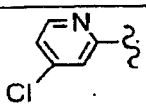
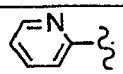
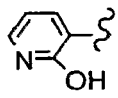
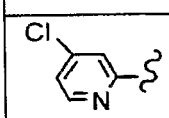
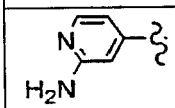
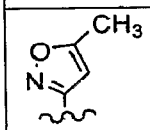
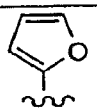
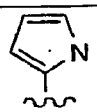
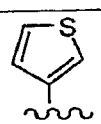
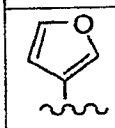
R	R^{25}	R^3	R^{13}	Z	R^6
$-CH_3$	6-Cl	H	H	$-CH_2-$	2-NH_2
$-CH_3$	5-Cl	H	H	$-CH_2-$	2-NH_2
$-CH_3$	5-Br	H	H	$-CH_2-$	2-NH_2
	5-Cl	H	H	$-CH_2-$	2-NH_2
benzyl	5-F	H	H	$-CH_2-$	2-NH_2
$-CH(CH_3)_2$	5-Br	H	H	$-CH_2-$	2-NH_2
$-CH_2NH_2$	H	H	H	$-CH_2-$	2-NH_2
$-CH_2NHSO_2CH_3$	H	H	H	$-CH_2-$	2-NH_2
$-CH_2NHC(O)CH_3$	5-Cl	H	H	$-CH_2-$	2-NH_2
$-CH_2OCH_3$	5-F	H	H	$-CH_2-$	2-NH_2
$-CH_2NH_2$	5-Cl	H	H	$-CH_2-$	2-NH_2
$-CH_2OCH_3$	6,7-di-F	H	H	$-CH_2-$	2-NH_2
	6-F	H	H	$-CH_2-$	2-NH_2
	5-F	H	H	$-CH_2-$	2-NH_2
	6-F	H	H	$-CH_2-$	2-NH_2

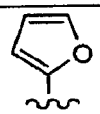
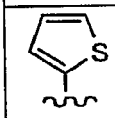
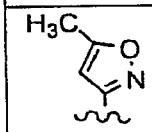
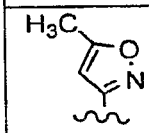
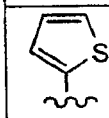
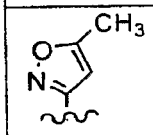
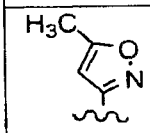
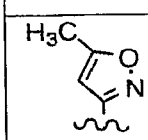
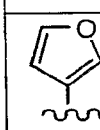
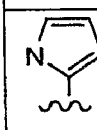
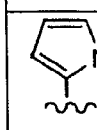
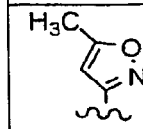
R	R^{25}	R^3	R^{13}	Z	R^6
	5-F	H	H	$-CH_2-$	2-NH_2
	5-F	H	H	$-CH_2-$	2-NH_2
	5-Br	H	H	$-CH_2-$	2-NH_2
	5-F	H	H	$-CH_2-$	2-NH_2
	5-F	H	H	$-CH_2-$	2-NH_2
	H	H	H	$-CH_2-$	2-NH_2
	5-F	H	H	$-CH_2-$	2-NH_2
	6-F	H	H	$-CH_2-$	2-NH_2
	6,7-di-F	H	H	$-CH_2-$	2-NH_2
	6-Cl	H	H	$-CH_2-$	2-NH_2
	5-F	H	H	$-CH_2-$	2-NH_2
	5-Cl	H	H	$-CH_2-$	2-NH_2
	H	H	H	$-CH_2-$	2-NH_2
	5-Cl	H	H	$-CH_2-$	2-NH_2
	5-Cl	H	H	$-CH_2-$	2-

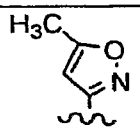
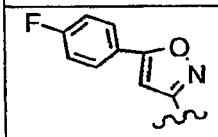
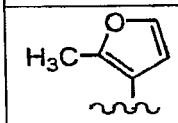
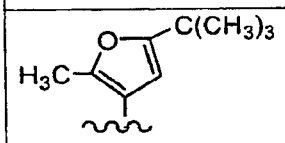
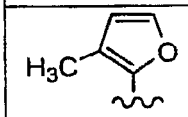
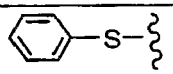
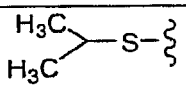
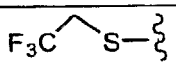
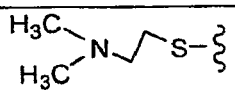
R	R^{25}	R^3	R^{13}	Z	R^6
					NH_2
	6-F	H	H	$-CH_2-$	2-NH_2
	5-Br	H	H	$-CH_2-$	2-NH_2
	5-Br	H	H	$-CH_2-$	2-NH_2
	5-F	H	H	$-CH_2-$	2-NH_2
	5-F	H	H	$-CH_2-$	2-NH_2
	6-F	H	H	$-CH_2-$	2-NH_2
	6-F	H	H	$-CH_2-$	2-NH_2
	H	H	H	$-CH_2-$	2-NH_2
	5-F	H	H	$-CH_2-$	2-NH_2
	5-Cl	H	H	$-CH_2-$	2-NH_2
	6-Cl	H	H	$-CH_2-$	2-NH_2
	5-F	H	H	$-CH_2-$	2-NH_2
	5-F	H	H	$-CH_2-$	2-NH_2

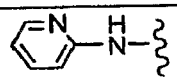
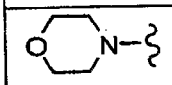
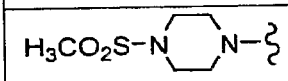
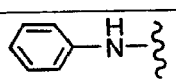
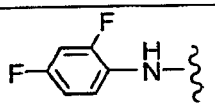
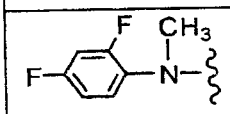
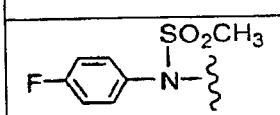
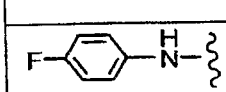
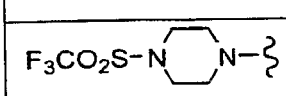
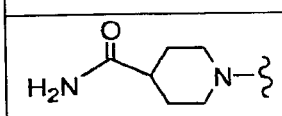
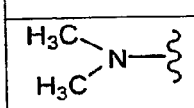
R	R^{25}	R^3	R^{13}	Z	R^6
	5-Cl	H	H	$-CH_2-$	2-NH_2
	5-F	H	H	$-CH_2-$	2-NH_2
	5-Br	H	H	$-CH_2-$	2-NH_2
	6-Cl	H	H	$-CH_2-$	2-NH_2
	5-CH_3	H	H	$-CH_2-$	2-NH_2
	5-Cl	H	H	$-CH_2-$	2-NH_2
	5-Br	H	H	$-CH_2-$	2-NH_2
	6-ethoxy	H	H	$-CH_2-$	2-NH_2
	5-Cl	H	H	$-CH_2-$	2-NH_2
	H	H	H	$-CH_2-$	2-NH_2
	5-F	H	H	$-CH_2-$	H
	6-Cl	H	H	$-CH_2-$	2-NH_2
	5-F	H	H	$-CH_2-$	2-NH_2

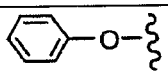
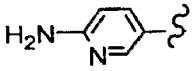
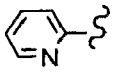
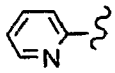
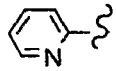
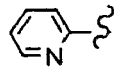
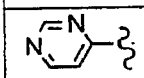
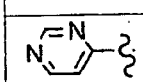
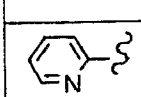
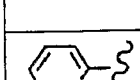
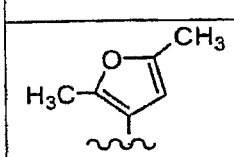
R	R^{25}	R^3	R^{13}	Z	R^6
	6-F	H	H	$-CH_2-$	2-NH_2
	6-F	H	H	$-CH_2-$	2-NH_2
	7-Cl	H	H	$-CH_2-$	2-NH_2
	H	H	H	$-CH_2-$	2-NH_2
	5-F	H	H	$-CH_2-$	2-NH_2
	5-Cl	H	H	$-CH_2-$	2-NH_2
	5-Cl	H	H	$-CH_2-$	2-NH_2
	5,6-di-F	H	H	$-CH_2-$	2-NH_2
	5-Br	H	H	$-CH_2-$	2-NH_2
	6-ethoxy	H	H	$-CH_2-$	2-NH_2
	5-F	H	H	$-CH_2-$	2-NH_2
	6-F	H	H	$-CH_2-$	2-NH_2
	5-Br	H	H	$-CH_2-$	2-NH_2
	5-Cl	H	H	$-CH_2-$	2-NH_2
	5-Cl	H	H	$-CH_2-$	2-NH_2

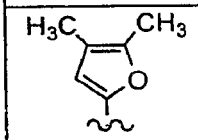
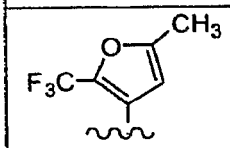
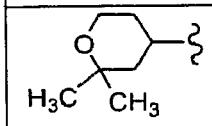
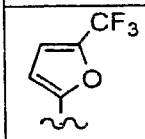
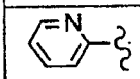
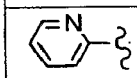
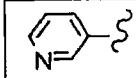
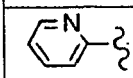
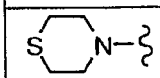
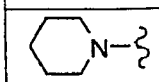
R	R^{25}	R^3	R^{13}	Z	R^6
	5-F	H	H	$-CH_2-$	2-NH_2
	5-CF_3	H	H	$-CH_2-$	2-NH_2
	H	H	H	$-CH_2-$	2-NH_2
	6,7-di-F	H	H	$-CH_2-$	2-NH_2
	6,7-di-F	H	H	$-CH_2-$	2-NH_2
	5-F	H	H	$-CH_2-$	2-NH_2
	5-CF_3,7-F	H	H	$-CH_2-$	2-NH_2
	5-F	H	H	$-CH_2-$	2-NH_2
	H	H	H	$-CH_2-$	2-NH_2
	H	H	H	$-CH_2-$	2-NH_2
	H	H	H	$-CH_2-$	2-NH_2
	6-F	H	H	$-CH_2-$	2-NH_2
	6-F	H	H	$-CH_2-$	2-NH_2

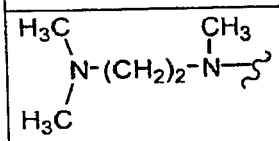
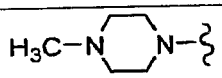
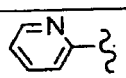
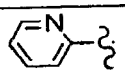
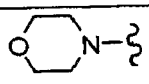
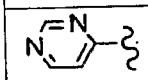
R	R^{25}	R^3	R^{13}	Z	R^6
	5-F	H	H	$-CH_2-$	2-NH_2
	H	H	H	$-CH_2-$	2-NH_2
	5-F	H	H	$-CH_2-$	2-NH_2
	5-Cl	H	H	$-CH_2-$	2-NH_2
	5-F	H	H	$-CH_2-$	2-NH_2
	6,7-di-F	H	H	$-CH_2-$	2-NH_2
	5-Br	H	H	$-CH_2-$	2-NH_2
	6-ethoxy	H	H	$-CH_2-$	2-NH_2
	5-F	H	H	$-CH_2-$	2-NH_2
	5-Br	H	H	$-CH_2-$	2-NH_2
	5-F	H	H	$-CH_2-$	2-NH_2
	5-CF_3	H	H	$-CH_2-$	2-NH_2

R	R^{25}	R^3	R^{13}	Z	R^6
	5-CF_3,7-F	H	H	-CH_2-	2-NH_2
	5-F	H	H	-CH_2-	2-NH_2
	5-F	H	H	-CH_2-	2-NH_2
	5-F	H	H	-CH_2-	2-NH_2
	5-F	H	H	-CH_2-	2-NH_2
CH_3-S-	5-F	H	H	-CH_2-	2-NH_2
CH_3-CH_2-S-	5-F	H	H	-CH_2-	2-NH_2
CH_3-SO_2-	5-F	H	H	-CH_2-	2-NH_2
	5-F	H	H	-CH_2-	2-NH_2
	5-F	H	H	-CH_2-	2-NH_2
	5-F	H	H	-CH_2-	2-NH_2
	5-F	H	H	-CH_2-	2-NH_2
HS-	5-F	H	H	-CH_2-	2-NH_2
CH_3-S-	5-F	H	2-CH_3	-CH_2-	2-NH_2

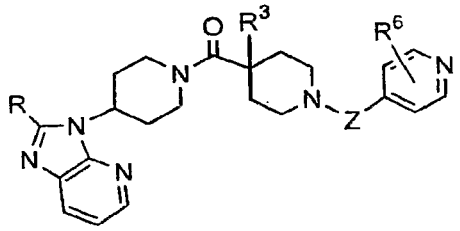
R	R^{25}	R^3	R^{13}	Z	R^6
CH_3-S-	5-F	F	H	-CH_2-	2-NH_2
	5-F	H	H	-CH_2-	2-NH_2
	5-F	H	H	-CH_2-	2-NH_2
	5-F	H	H	-CH_2-	2-NH_2
	5-F	H	H	-CH_2-	2-NH_2
	5-F	H	H	-CH_2-	2-NH_2
	5-F	H	H	-CH_2-	2-NH_2
	5-F	H	H	-CH_2-	2-NH_2
	5-F	H	H	-CH_2-	2-NH_2
	5-F	H	H	-CH_2-	2-NH_2
CH_3-O-(CH_2)$_2$-NH-	5-F	H	H	-CH_2-	2-NH_2
	5-F	H	H	-CH_2-	2-NH_2
	5-F	H	H	-CH_2-	2-NH_2
CH_3-O-	5-F	H	H	-CH_2-	2-NH_2
CH_3-CH_2-O-	5-F	H	H	-CH_2-	2-

R	R^{25}	R^3	R^{13}	Z	R^6
					NH_2
CH_3-O-$(CH_2)_2$-O-	5-F	H	H	-CH_2-	2-NH_2
$(CH_3)_2$-CH-O-	5-F	H	H	-CH_2-	2-NH_2
	5-F	H	H	-CH_2-	2-NH_2
	H	H	H	-CH_2-	2-NH_2
	5-CF_3,7-F	H	H	-CH_2-	2-NH_2
	5-F	H	H		2-NH_2
	5-F	F	H	-CH_2-	2-NH_2
	5-F	OH	H	-CH_2-	2-NH_2
	5-F	H	H		2-NH_2
	5-F	H	H		2-NH_2
	5-F	-CH_3	H	-CH_2-	2-NH_2
	6-F	H	H		2-NH_2
H	5-F	H	H	-CH_2-	2-NH_2
	5-F	H	H	-CH_2-	2-NH_2

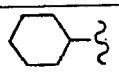
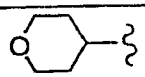
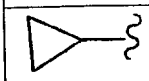
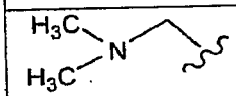
R	R^{25}	R^3	R^{13}	Z	R^6
	5-F	H	H	$-CH_2-$	2-NH_2
	5-F	H	H	$-CH_2-$	2-NH_2
	5-F	H	H	$-CH_2-$	2-NH_2
	5-F	H	H	$-CH_2-$	2-NH_2
	H	F	H	$-CH_2-$	2-NH_2
$(CH_3)_2N-(CH_2)_2-NH-$	5-F	H	H	$-CH_2-$	2-NH_2
CH_3-S-	5-F	H	H		2-NH_2
	5-F	H	2-CH_3	$-CH_2-$	2-NH_2
	5-F	H	H	$-CH_2-$	2-NH_2
	5-F	H	H	$-CH_2-$	3-NH_2
	5-F	H	H	$-CH_2-$	2-NH_2
	5-F	H	H	$-CH_2-$	2-NH_2
CH_3CH_2O-	5-F	F	H	$-CH_2-$	2-NH_2

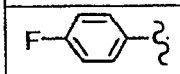
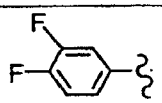
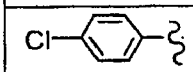
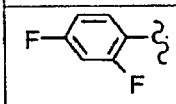
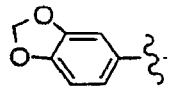
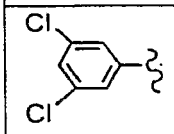
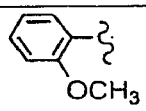
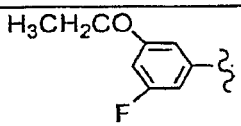
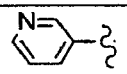
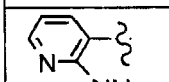
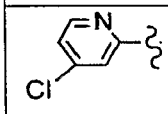
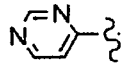
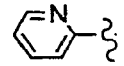
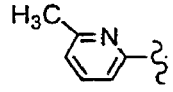
R	R^{25}	R^3	R^{13}	Z	R^6
	5-F	H	H	$-CH_2-$	2-NH_2
	5-F	H	H	$-CH_2-$	2-NH_2
	5-F	H	5-OH	$-CH_2-$	2-NH_2
	5-F	F	H	$-CH_2-$	3-NH_2
	5-F	F	H	$-CH_2-$	2-NH_2
	5-F	H	H	$-CH_2-$	3-NH_2

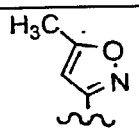
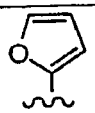
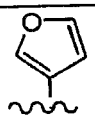
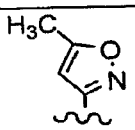
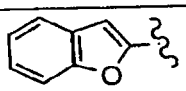
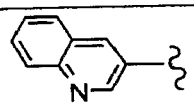
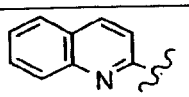
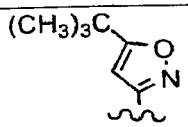
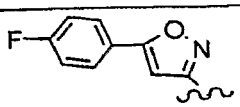
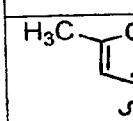
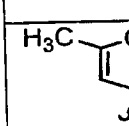
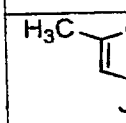
compounds having the following general formula:

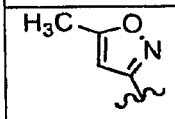
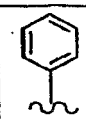
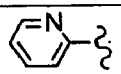
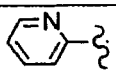
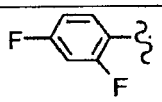
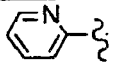
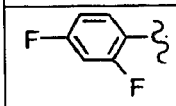


wherein R, R^3, Z, and R^6 are as defined in the following Table:

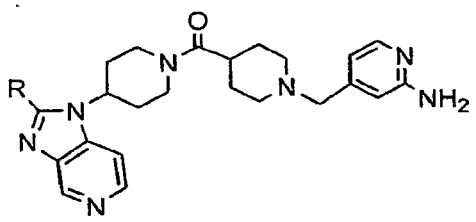
R	R^3	Z	R^6
	H	$-CH_2-$	2-NH_2
$-CH_2OCH_3$	H	$-CH_2-$	2-NH_2
	H	$-CH_2-$	2-NH_2
	H	$-CH_2-$	2-NH_2
$(CH_3)_2$-CH-	H	$-CH_2-$	2-NH_2
	H	$-CH_2-$	2-NH_2

R	R^3	Z	R^6
	H	$-CH_2-$	2-NH_2
	H	$-CH_2-$	2-NH_2
	H	$-CH_2-$	2-NH_2
	H	$-CH_2-$	2-NH_2
	H	$-CH_2-$	2-NH_2
	H	$-CH_2-$	2-NH_2
	H	$-CH_2-$	2-NH_2
	H	$-CH_2-$	2-NH_2
	H	$-CH_2-$	2-NH_2
	H	$-CH_2-$	2-NH_2
	H	$-CH_2-$	2-NH_2
	H	$-CH_2-$	2-NH_2
	H	$-CH_2-$	2-NH_2
	H	$-CH_2-$	2-NH_2

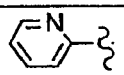
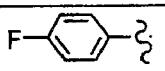
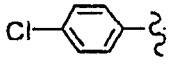
R	R^3	Z	R^6
	H	$-CH_2-$	3-NH_2
	H	$-CH_2-$	2-NH_2
	H	$-CH_2-$	2-NH_2
	H	$-CH_2-$	2-NH_2
	H	$-CH_2-$	2-NH_2
	H	$-CH_2-$	2-NH_2
	H	$-CH_2-$	2-NH_2
	H	$-CH_2-$	2-NH_2
	H	$-CH_2-$	2-NH_2
	F	$-CH_2-$	2-NH_2
	H	$-\underset{CH_3}{\underset{\vert}{CH}}-$	2-NH_2
	OH	$-CH_2-$	2-NH_2

R	R^3	Z	R^6
		$-CH_2-$	$2-NH_2$
	F	$-CH_2-$	$2-NH_2$
	F	$-CH_2-$	$2-NH_2$
	H	$-CH_2-$	$3-NH_2$
	H	$-CH_2-$	$3-NH_2$
	F	$-CH_2-$	$3-NH_2$
	F	$-CH_2-$	$3-NH_2$

compounds of the following general formula:

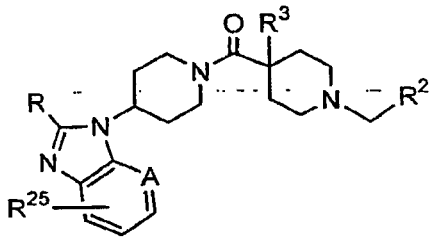


wherein R is as defined in the following Table:

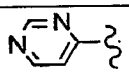
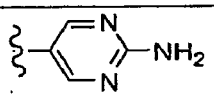
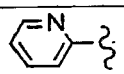
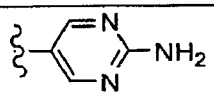
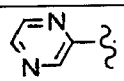
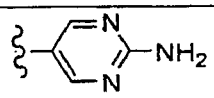
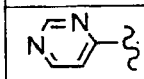
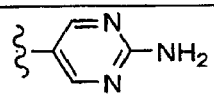
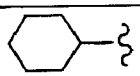
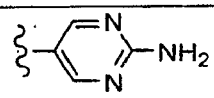
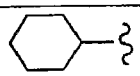
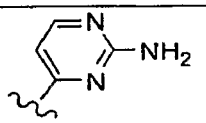
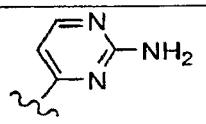
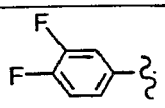
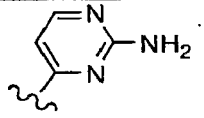
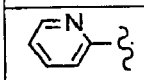
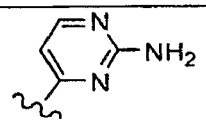
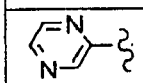
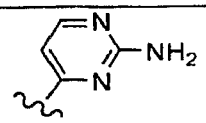
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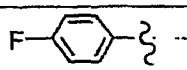
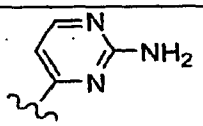
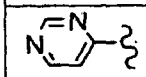
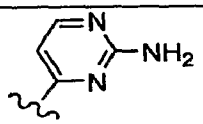
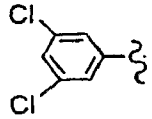
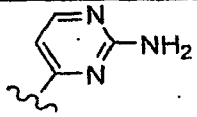
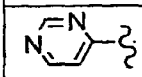
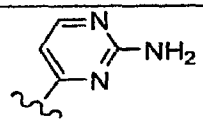
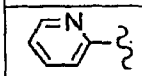
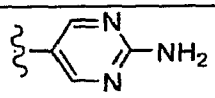
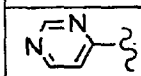
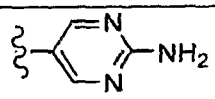
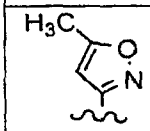
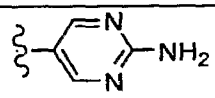
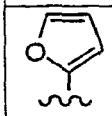
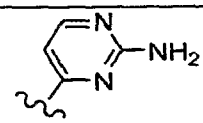
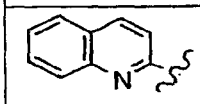
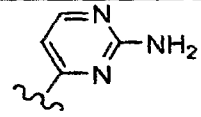
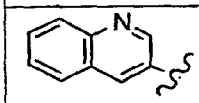
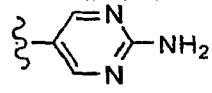
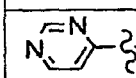
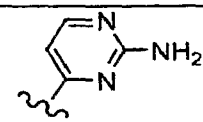
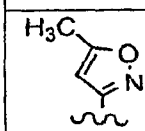
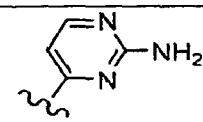
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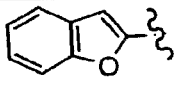
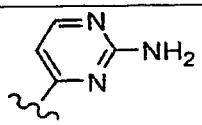
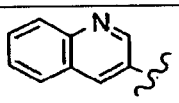
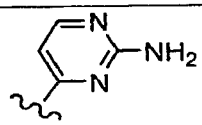
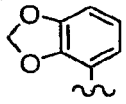
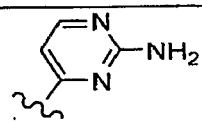
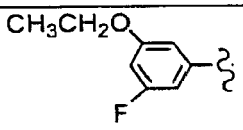
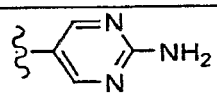
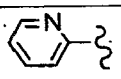
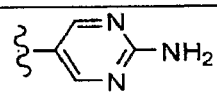
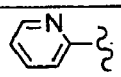
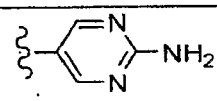
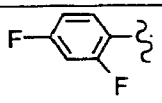
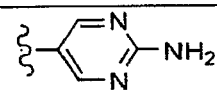
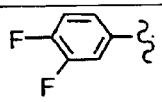
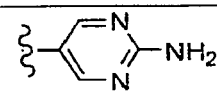
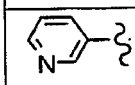
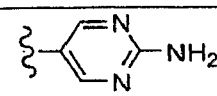
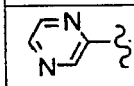
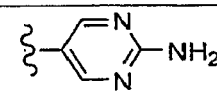
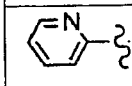
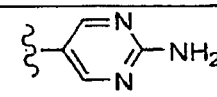
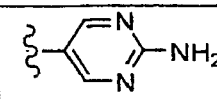
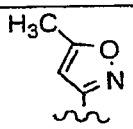
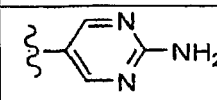
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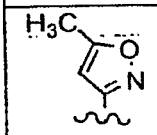
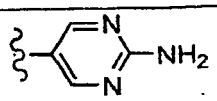
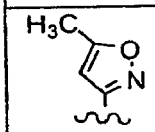
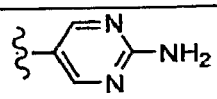
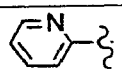
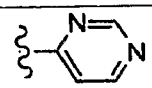
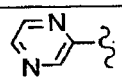
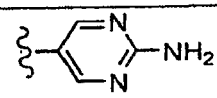
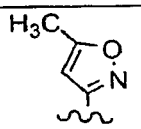
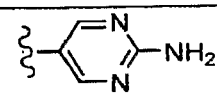
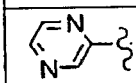
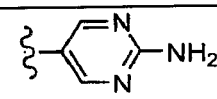
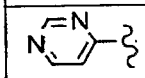
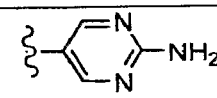
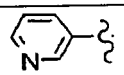
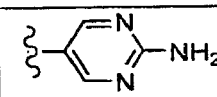
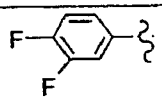
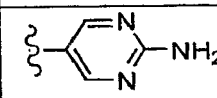
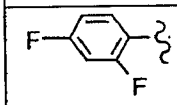
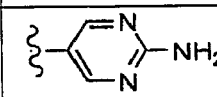
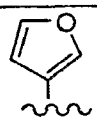
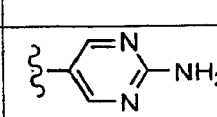
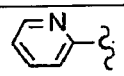
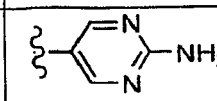
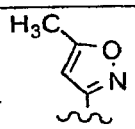
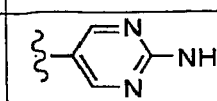


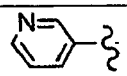
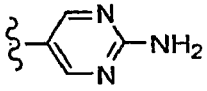
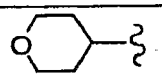
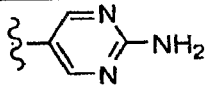
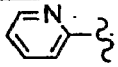
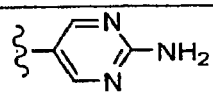
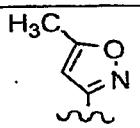
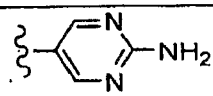
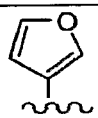
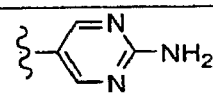
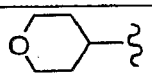
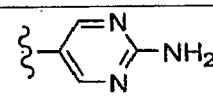
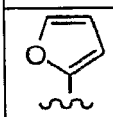
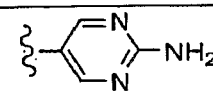
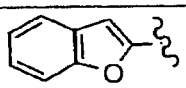
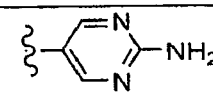
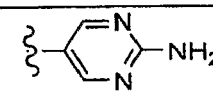
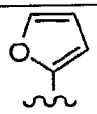
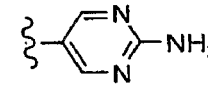
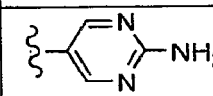
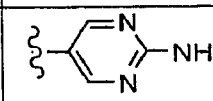
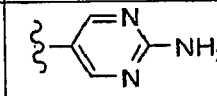
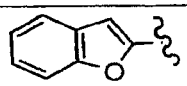
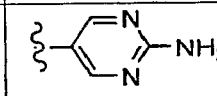
wherein R, R^{25}, A, R^3, and R^2 are as defined in the following Table:

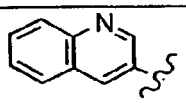
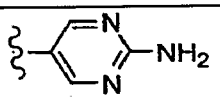
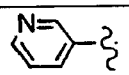
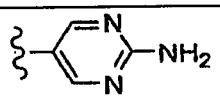
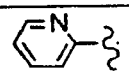
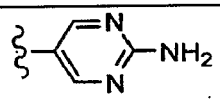
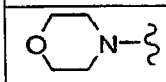
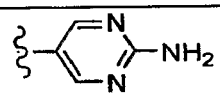
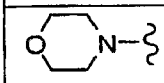
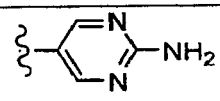
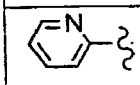
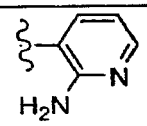
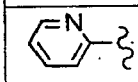
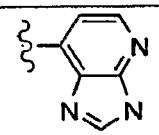
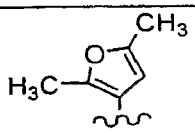
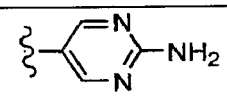
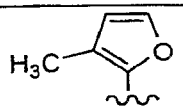
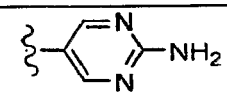
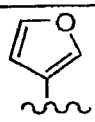
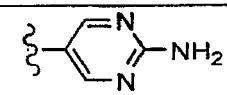
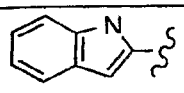
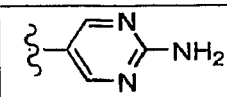
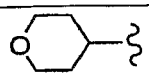
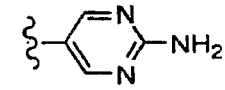
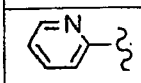
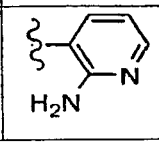
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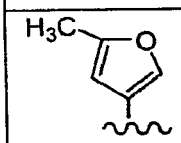
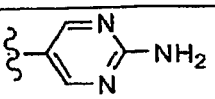
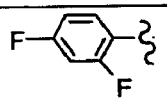
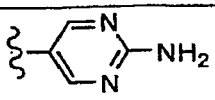
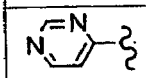
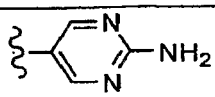
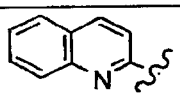
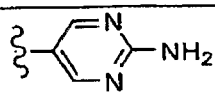
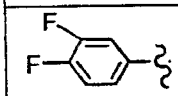
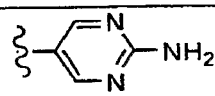
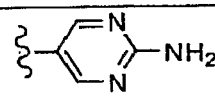
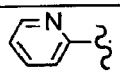
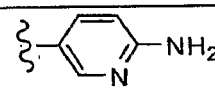
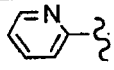
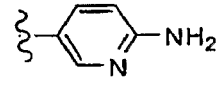
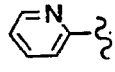
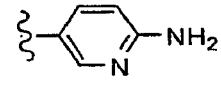
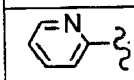
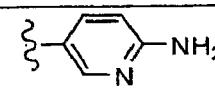
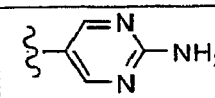
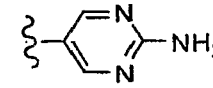
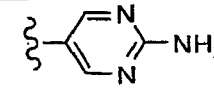
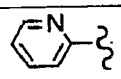
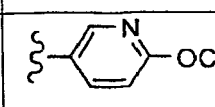
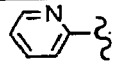
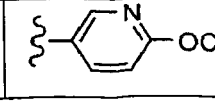
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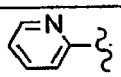
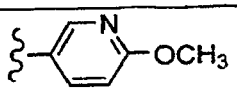
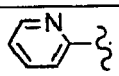
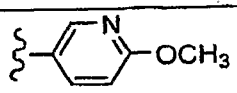
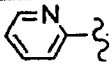
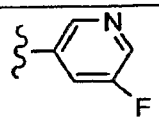
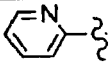
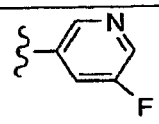
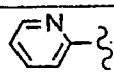
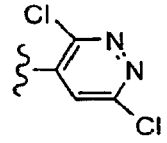
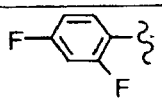
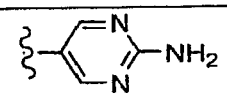
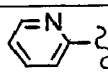
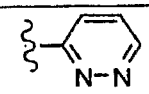
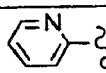
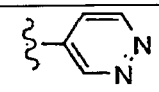
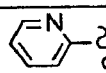
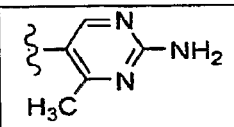
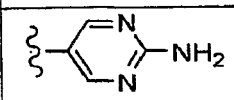
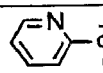
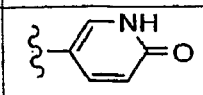
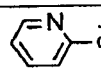
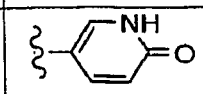
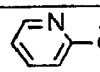
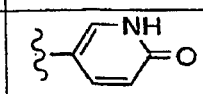
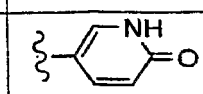
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	H	N	H	
	H	N	H	
	H	N	H	
	5-F	C	F	
	5-F	C	H	
	5-F	C	H	
	5-F	C	H	
	5-F	C	H	
	H	C	H	
$(CH_3)_2N\text{-}CH_2\text{-}$	H	N	H	
	5-F	C	H	

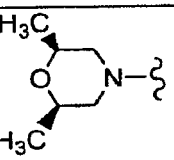
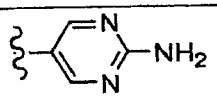
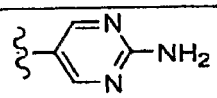
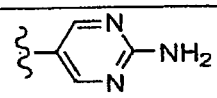
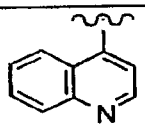
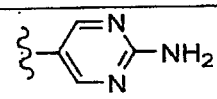
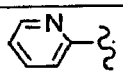
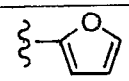
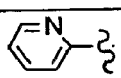
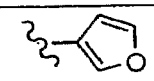
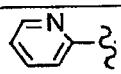
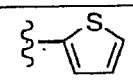
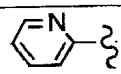
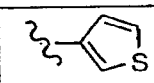
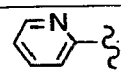
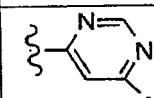
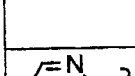
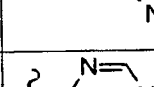
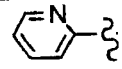
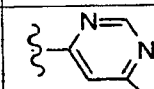
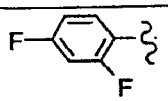
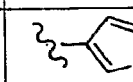
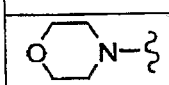
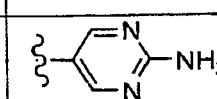
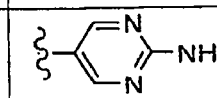
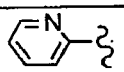
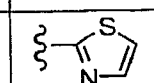
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	5-F	C	H	
	5,6-di-F	C	H	
	5-F	C	F	
	5-F	C	F	
	5-F	C	F	
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	5-F	C	F	
	5-F	C	F	
	H	N	H	
	H	C	F	
	H	C	F	

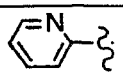
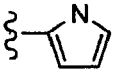
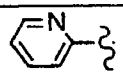
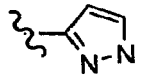
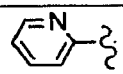
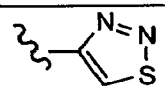
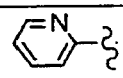
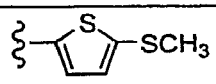
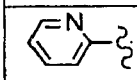
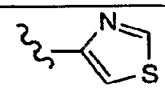
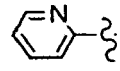
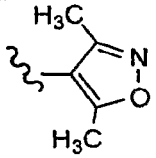
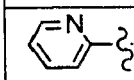
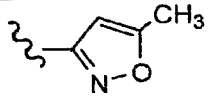
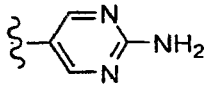
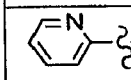
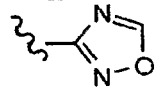
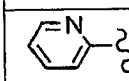
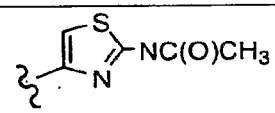
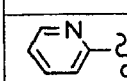
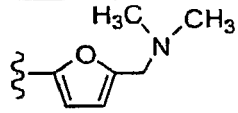
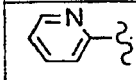
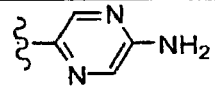
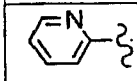
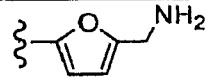
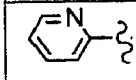
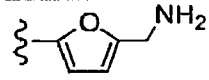
R	R^{25}	A	R^3	R^2
	H	N	F	
	H	N	H	
	H	N	F	
	H	N	F	
	5-F	C	H	
	5-F	C	H	
	5-F	C	H	
	H	N	H	
$(CH_3)_2N\text{-}CH_2\text{-}$	H	N	F	
	H	N	F	
$CH_3CH_2\text{-}O\text{-}$	5-F	C	H	
$CH_3\text{-}S\text{-}$	5-F	C	H	
$CH_3CH_2\text{-}O\text{-}$	5-F	C	F	
	H	N	F	

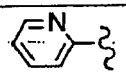
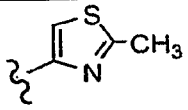
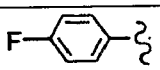
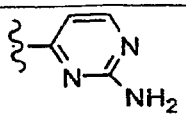
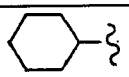
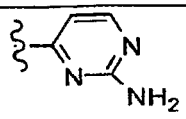
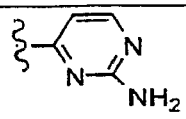
R	R^{25}	A	R^3	R^2
	H	N	F	
	H	N	H	
	5,6-di-F	C	F	
	5-F	C	F	
	5-F	C	H	
	5-F	C	H	
	5-F	C	H	
	H	N	H	
	H	N	H	
	H	N	F	
	H	N	H	
	H	N	F	
	5-F	C	F	

R	R^{25}	A	R^3	R^2
	H	N	H	
	H	N	H	
	H	N	F	
	H	N	H	
	H	N	H	
CH_3S-	5-F	C	F	
	H	N	F	
	5-F	C	F	
	5-F	C	H	
	H	N	H	
$(CH_3)_2N$-	5-F	C	F	
CH_3CH_2-S-	5-F	C	F	
CH_3-O-	5-F	C	F	
	H	N	H	
	H	N	F	

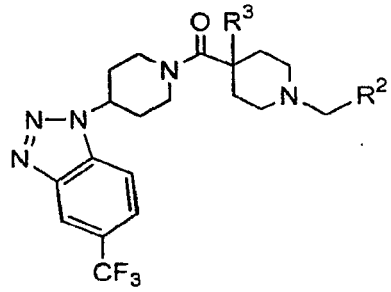
R	R^{25}	A	R^3	R^2
	5-F	C	F	
	5-F	C	H	
	5-F	C	H	
	5-F	C	F	
	H	N	H	
	H	N	F	
	5-F	C	H	
	5-F	C	H	
	5-F	C	F	
$(CH_3CH_2)_2N$-	5-F	C	F	
	H	N	H	
	H	N	F	
	5-F	C	H	
	5-F	C	F	

R	R^{25}	A	R^3	R^2
	5-F	C	F	
CH_3-S-	H	N	F	
CH_3CH_2-O-	H	N	F	
	H	N	F	
	H	N	F	
	H	N	F	
	H	N	F	
	H	N	F	
	H	N	F	
	5-F	C	F	
	H	N	F	
	H	N	F	
	H	N	F	
$(CH_3)_2CH$-O-	5-F	C	F	
	H	N	F	

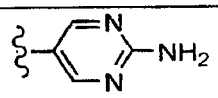
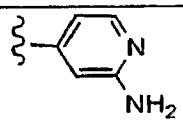
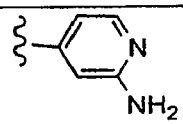
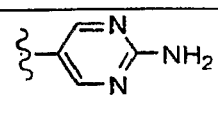
R	R^{25}	A	R^3	R^2
	H	N	F	
	H	N	F	
	H	N	F	
	H	N	F	
	H	N	F	
	H	N	F	
	H	N	F	
CH_3-O-	H	N	F	
	H	N	F	
	H	N	F	
	5-F	C	H	
	5-F	C	F	
	H	N	F	
	5-F	C	H	

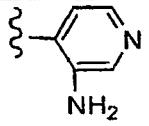
R	R^{25}	A	R^3	R^2
	H	N	F	
	6-Cl	C	H	
	H	N	H	
$(CH_3)_2$-CH-	H	N	H	

compounds of the following general formula:

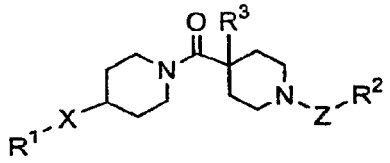


wherein R^3 and R^2 are as defined in the following Table:

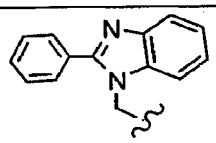
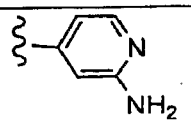
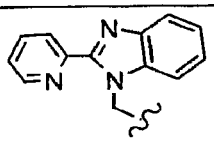
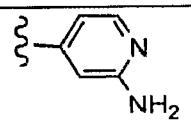
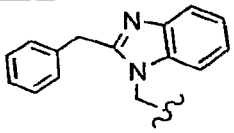
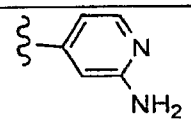
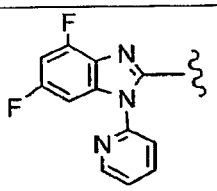
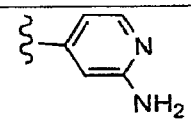
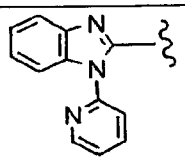
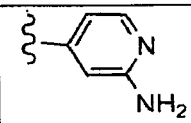
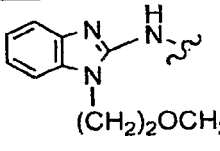
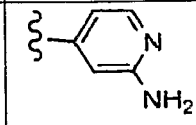
R^3	R^2
H	
F	
F	
F	

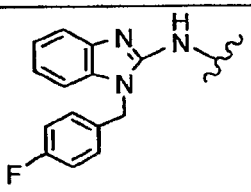
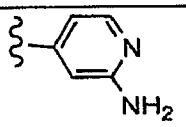
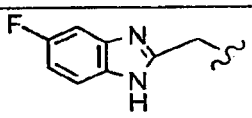
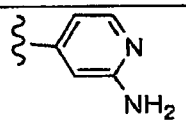
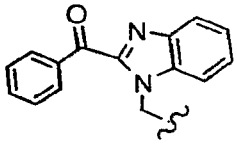
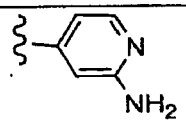
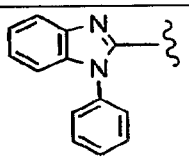
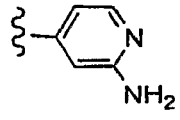
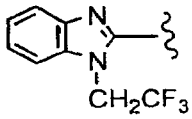
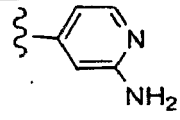
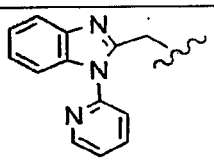
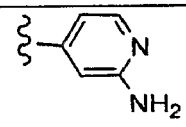
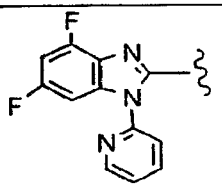
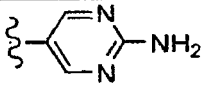
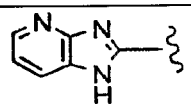
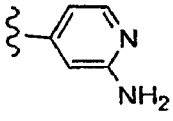
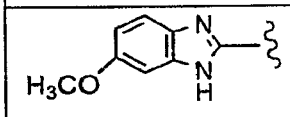
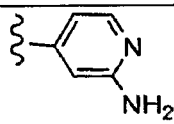
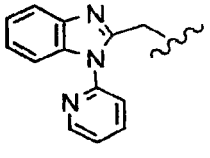
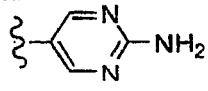
R^3	R^2
F	

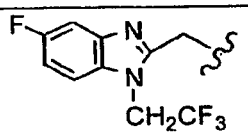
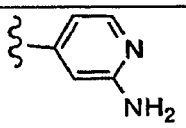
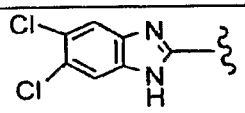
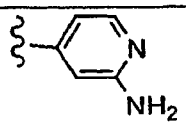
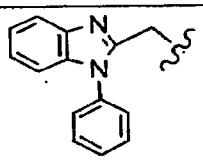
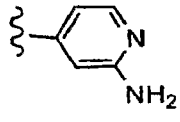
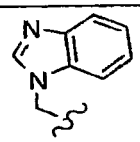
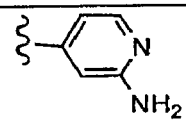
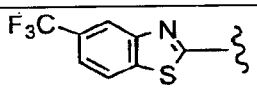
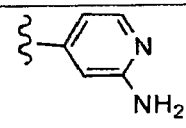
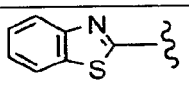
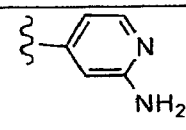
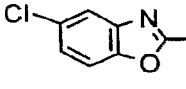
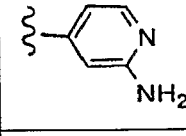
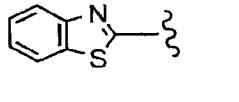
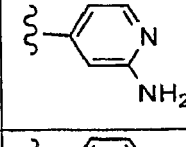
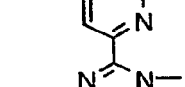
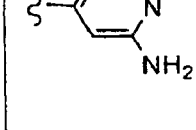
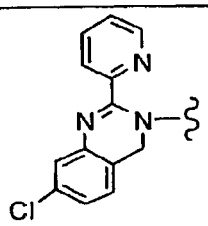
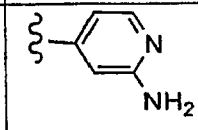
compounds of the following general formula:



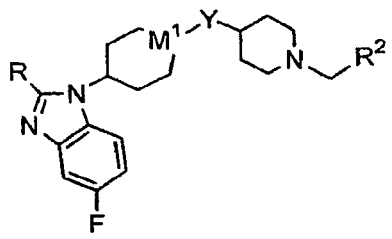
wherein R^1-X-, Z, R^3, and R^2 are defined as shown in the following Table:

R^1-X-	Z	R^3	R^2
	-CH_2-	H	
	-CH_2-	H	
	-CH_2-	H	
	-CH_2-	H	
	-CH_2-	H	
	-CH_2-	H	

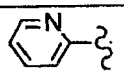
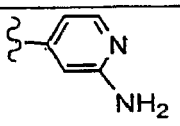
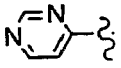
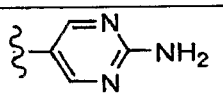
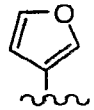
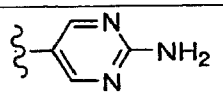
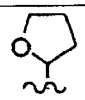
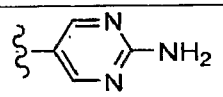
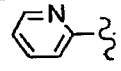
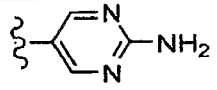
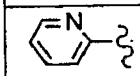
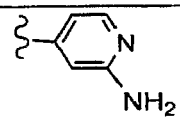
R^1-X-	Z	R^3	R^2
	$-CH_2-$	H	
	$-CH_2-$	H	
	$-CH_2-$	H	
	$-CH_2-$	H	
	$-CH_2-$	H	
	$-CH_2-$	H	
	$-CH_2-$	H	
	$-CH_2-$	H	
	$-CH_2-$	H	
	$-CH_2-$	H	

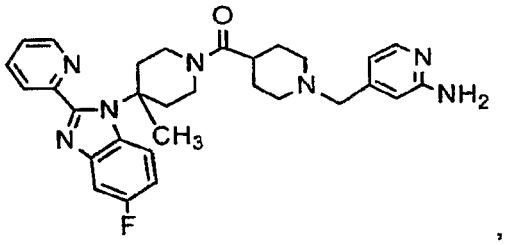
R^1-X-	Z	R^3	R^2
	-CH_2-	H	
	-CH_2-	H	
	-CH_2-	H	
	-CH_2-	H	
	-CH_2-	H	
	-CH_2-	H	
	-CH_2-	H	
	-CH_2-	H	
	-$(CH_2)_3$-	H	
	-CH_2-	H	
	-CH_2-	F	

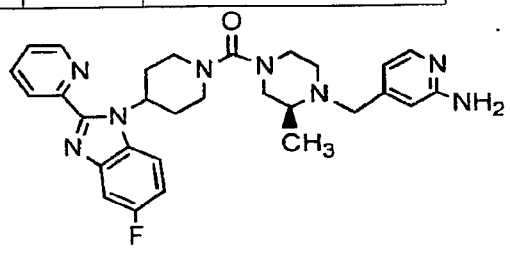
compounds of the following general formula:

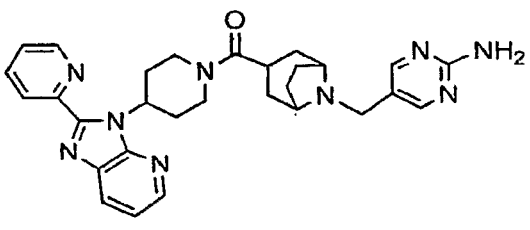


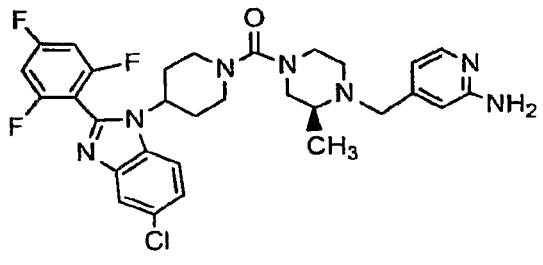
wherein R, M^1, Y, and R^2 are defined as shown in the following Table:

R	M^1	Y	R^2
	CH	$-CH_2-$	
	N	-NH-	
	N	-NH-	
	N	-NH-	
	N	-NH-	
	N	-NH-	

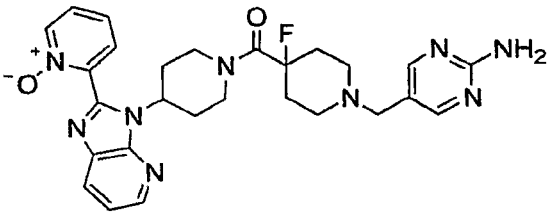


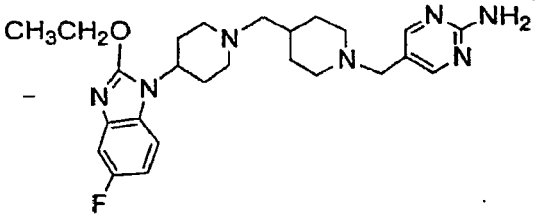


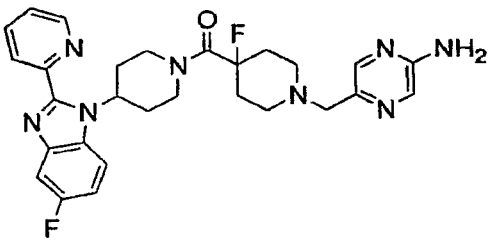


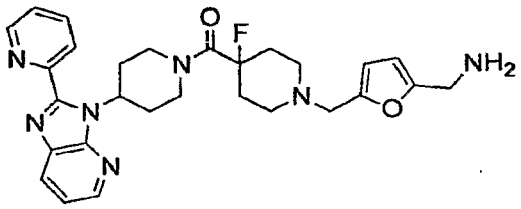


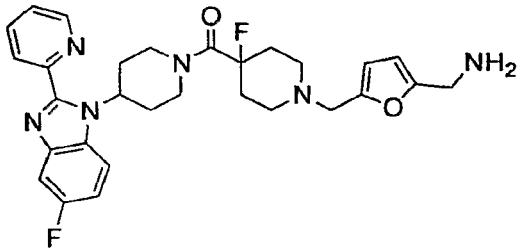
5

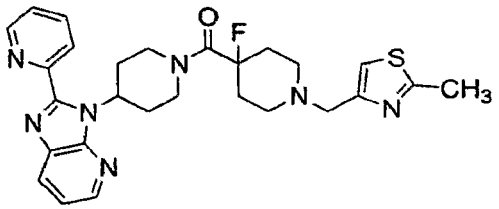


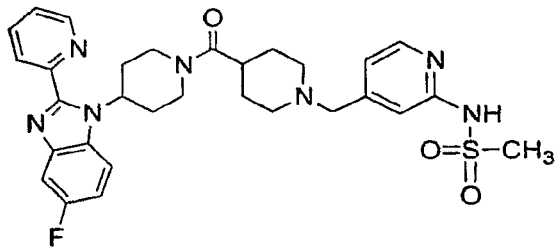


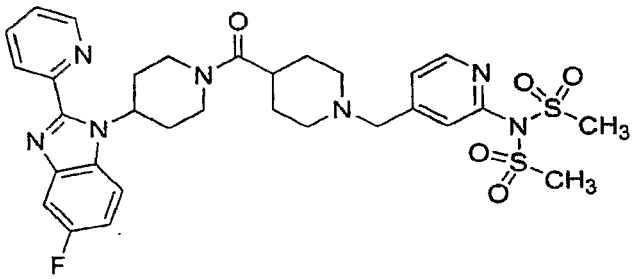


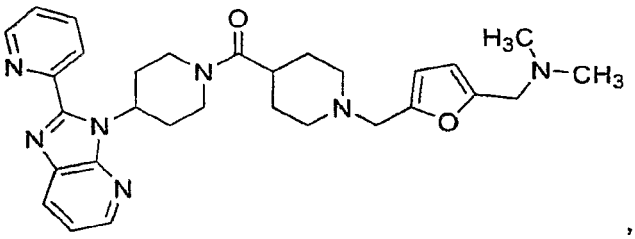


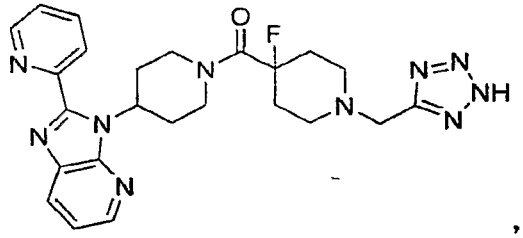


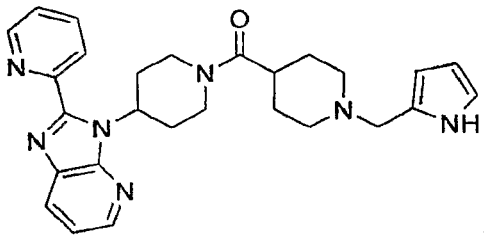


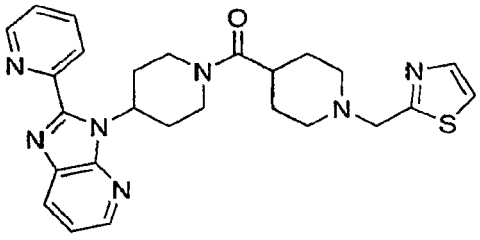


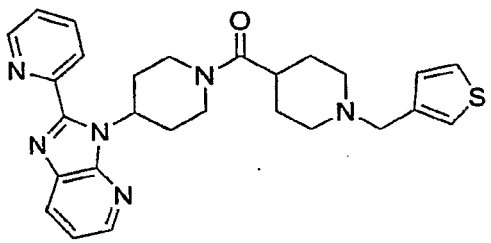
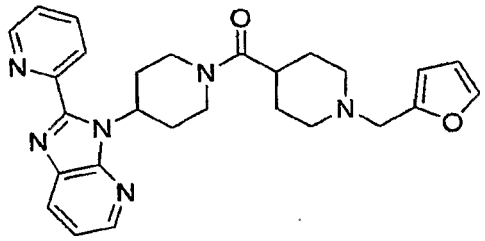
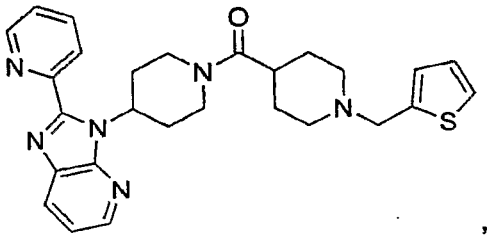
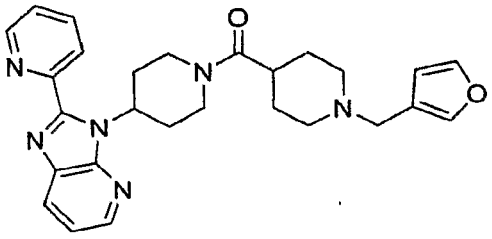
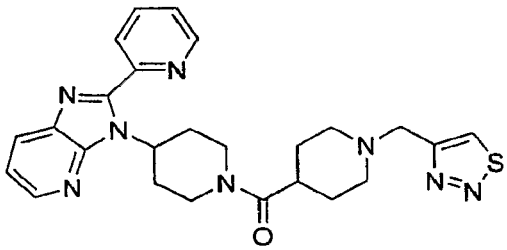
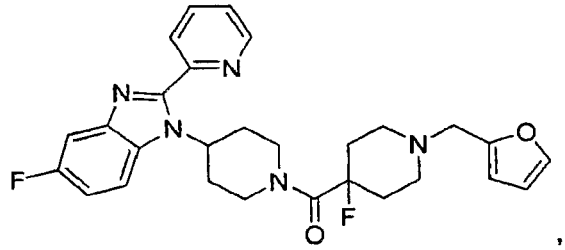
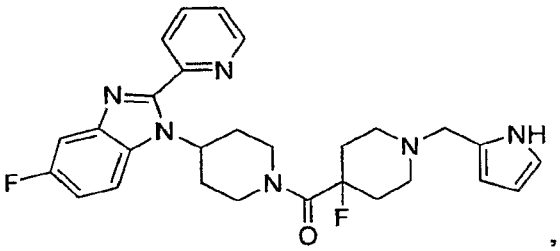
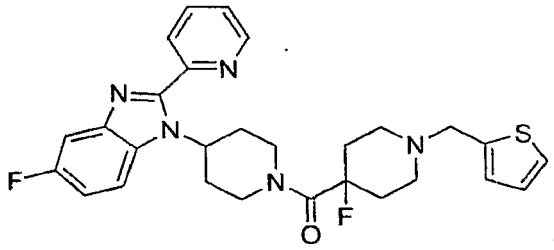
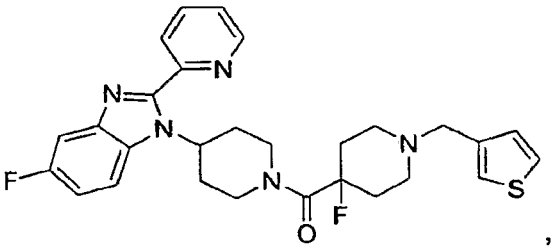
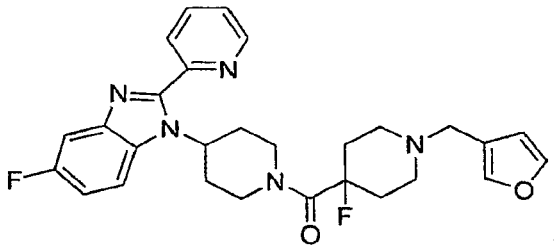
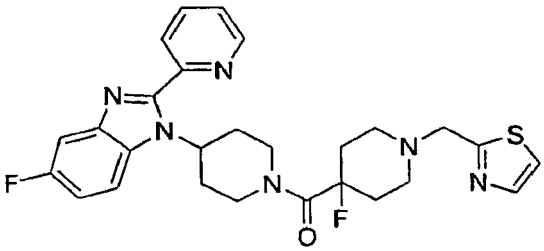
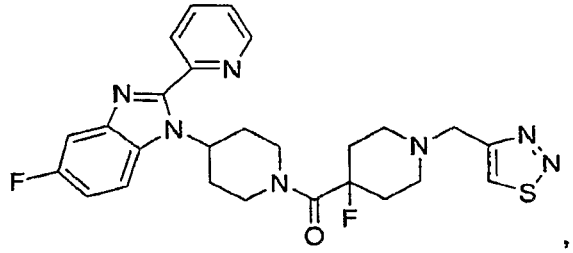


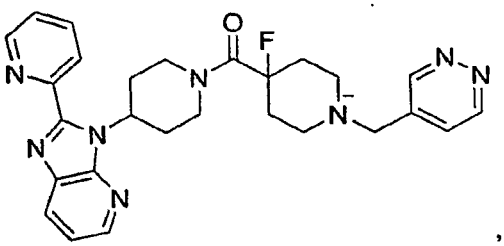


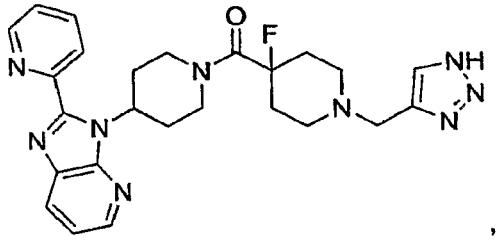


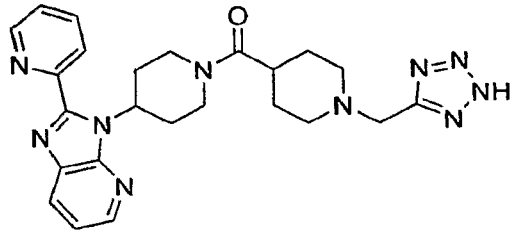


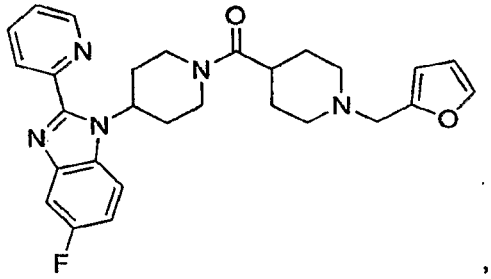


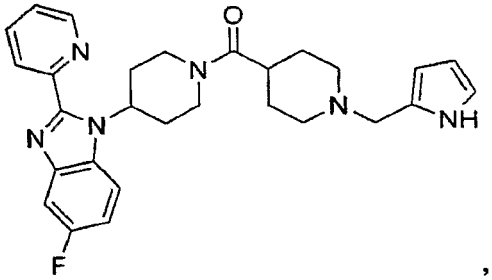

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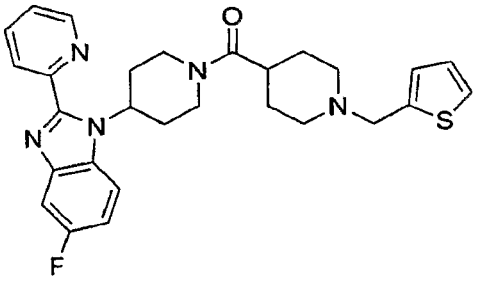


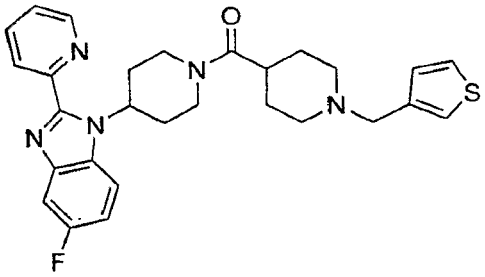


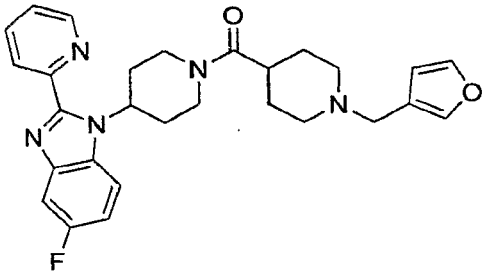


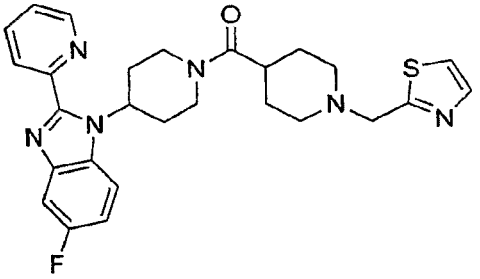


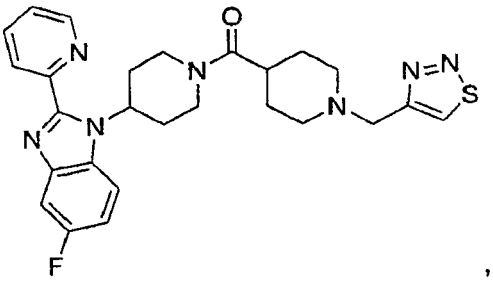




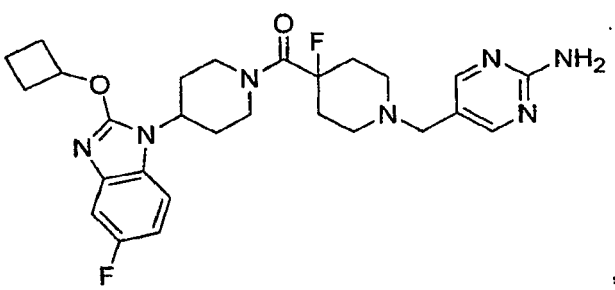




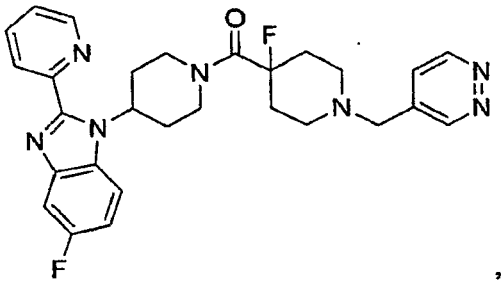




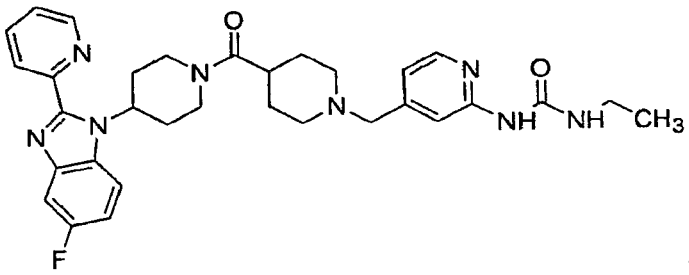
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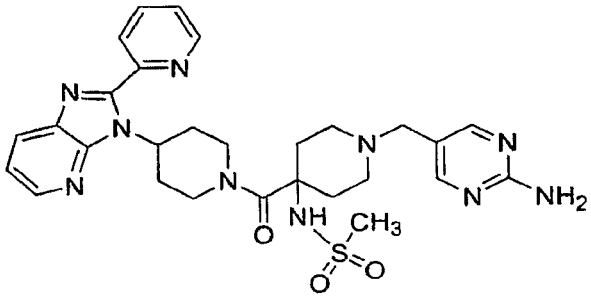
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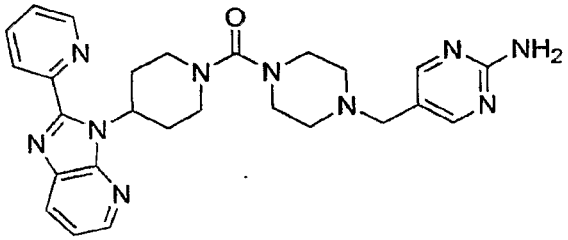
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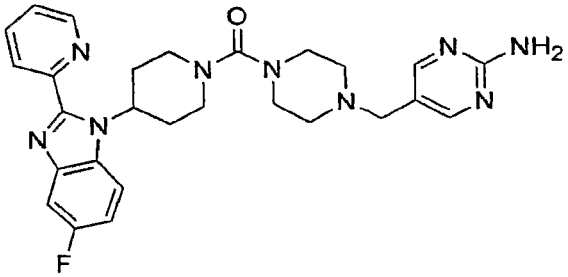
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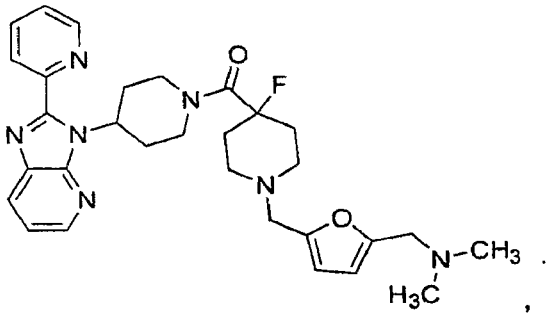
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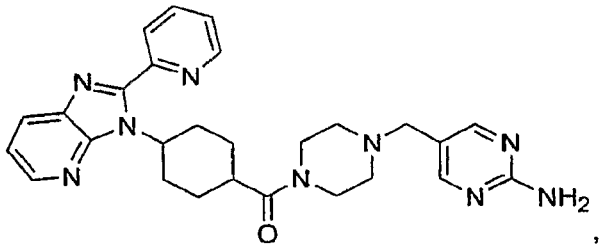
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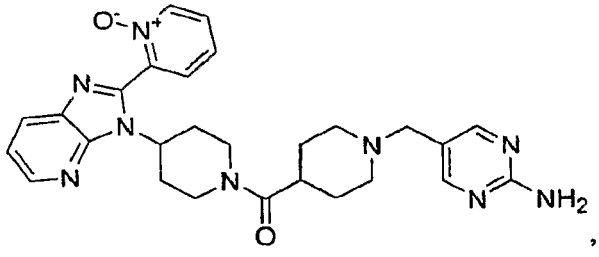
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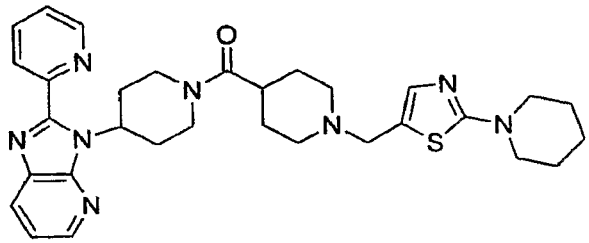
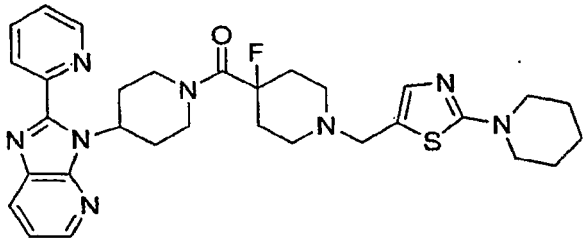
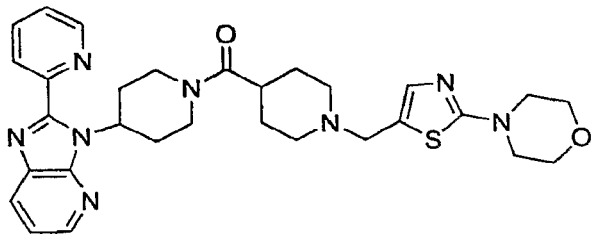
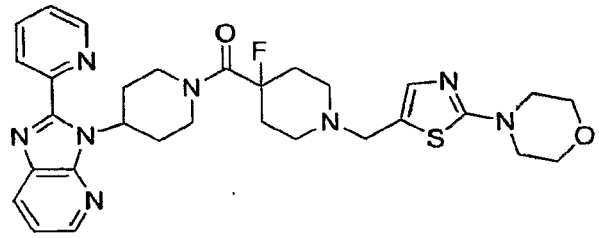
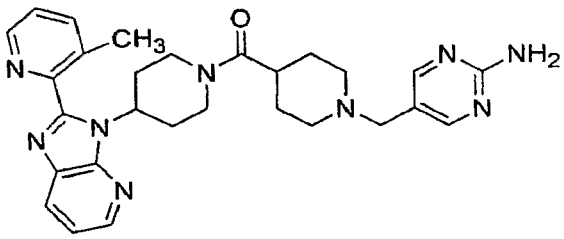
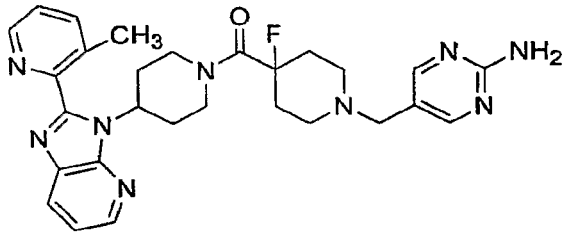
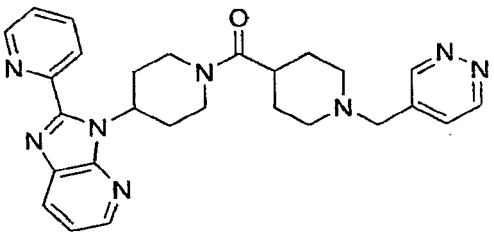
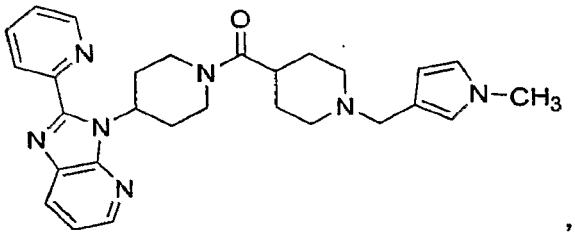
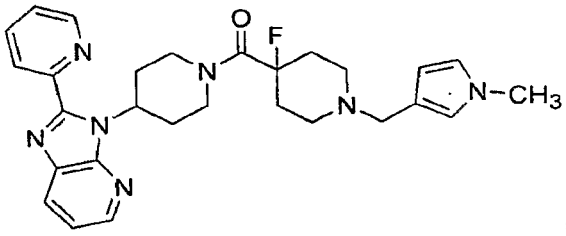
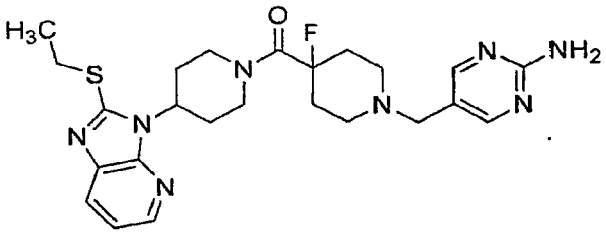
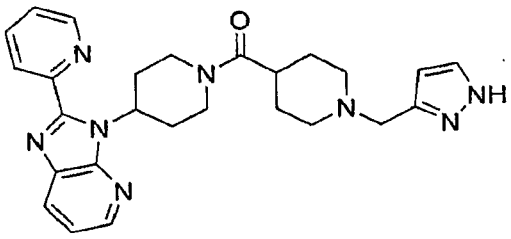
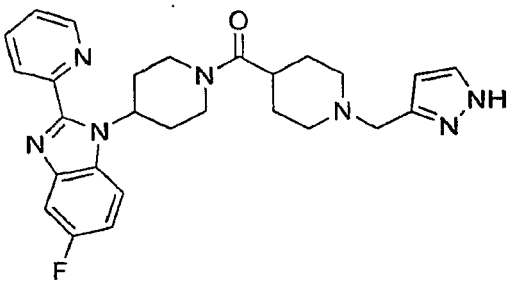


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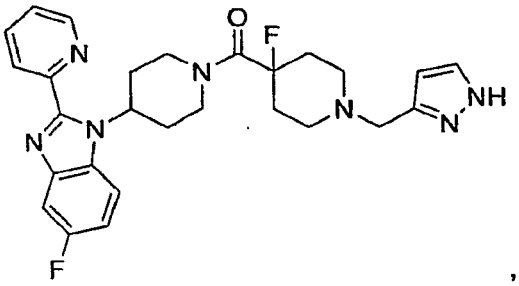


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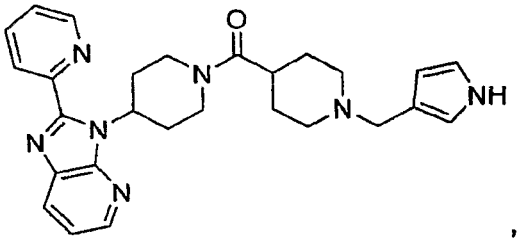
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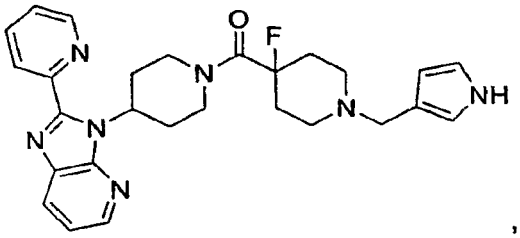
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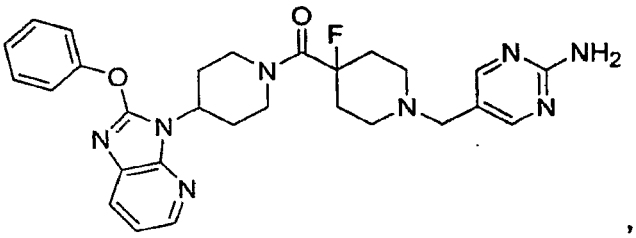
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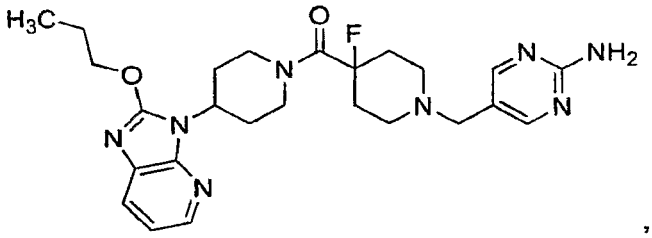
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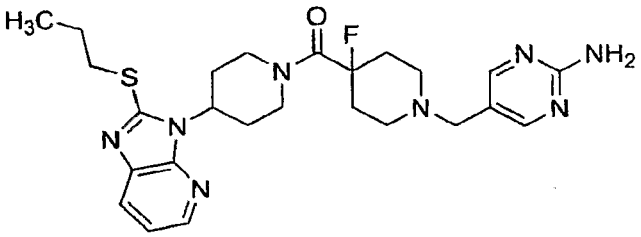
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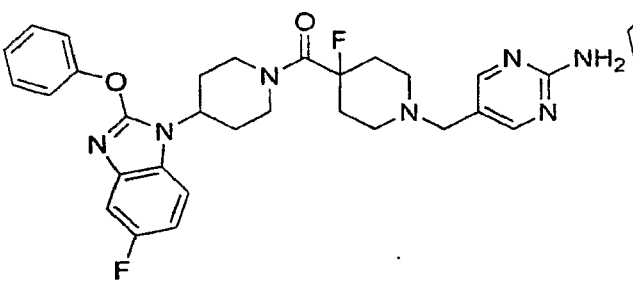
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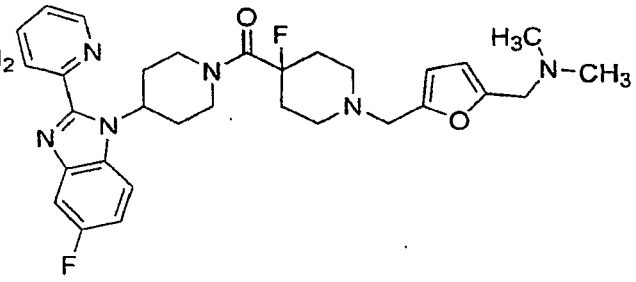


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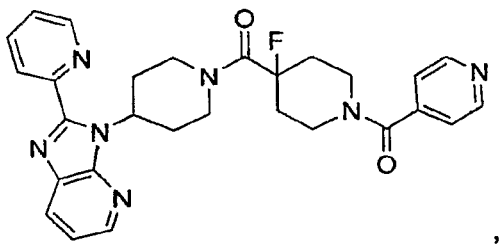


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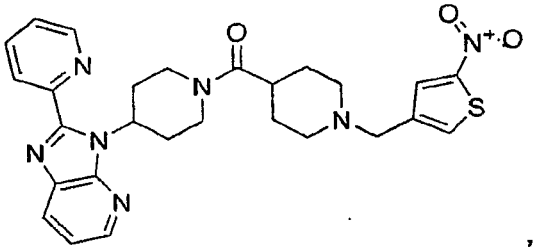




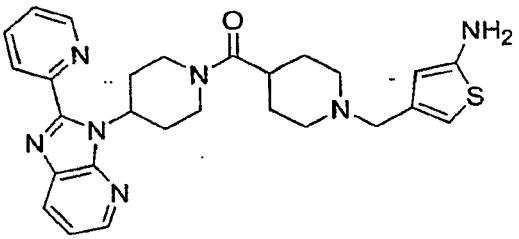
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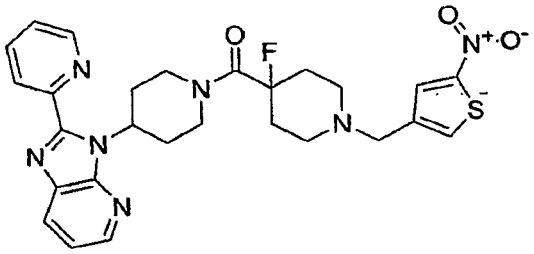


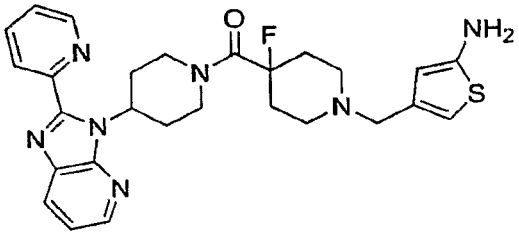
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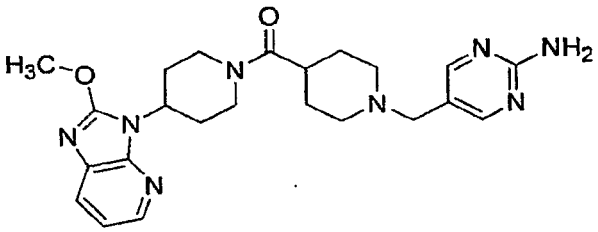


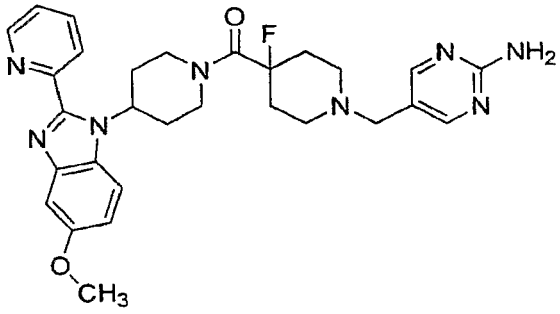
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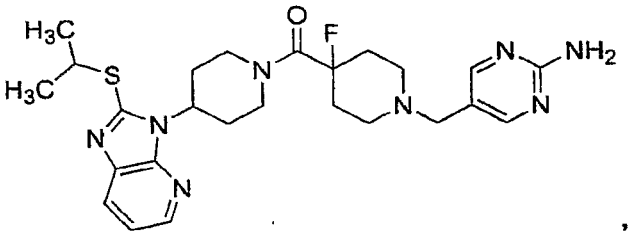


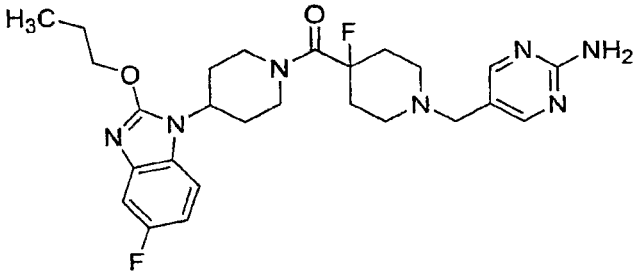


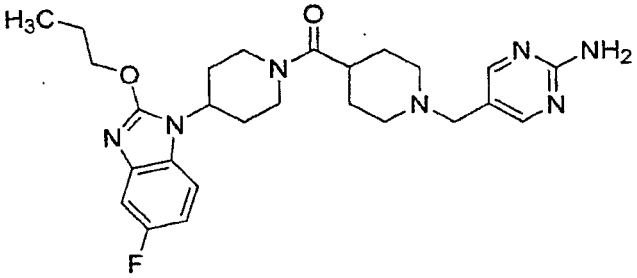


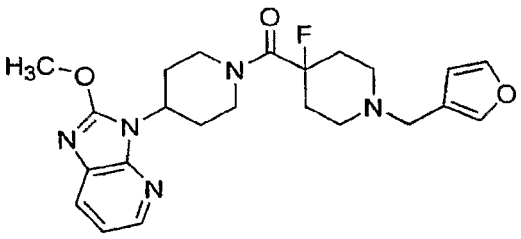


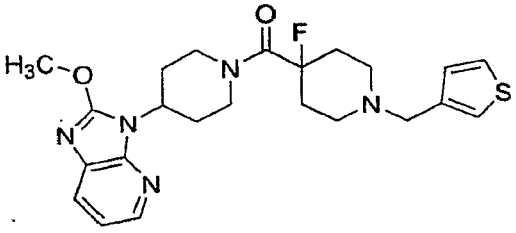


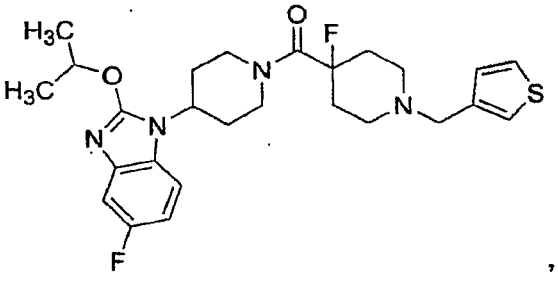


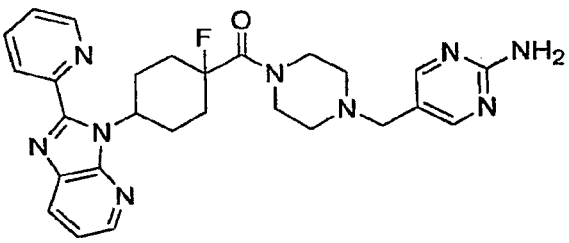


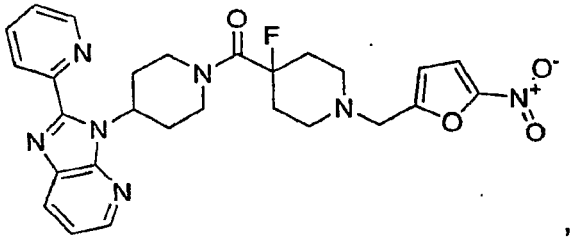


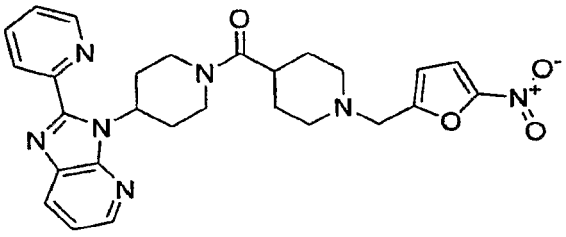


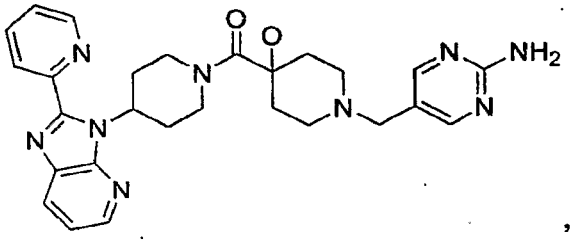


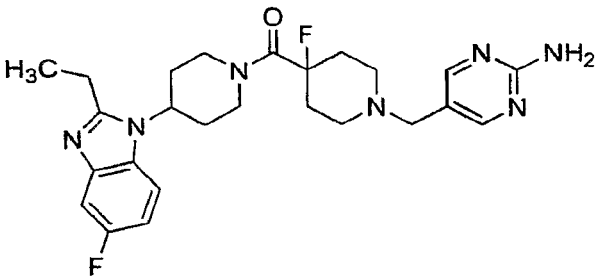


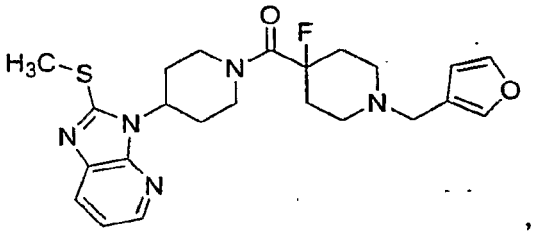


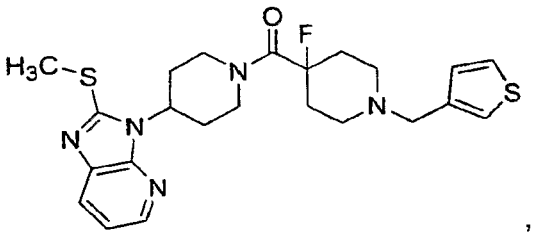


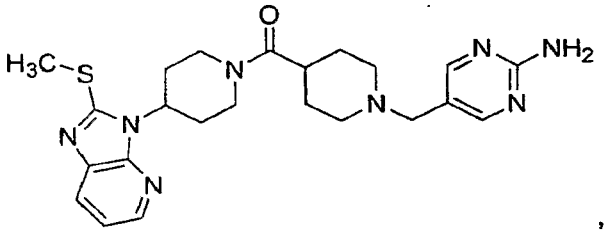


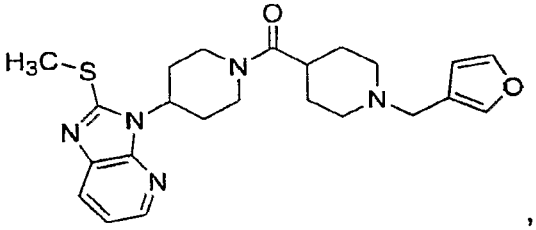


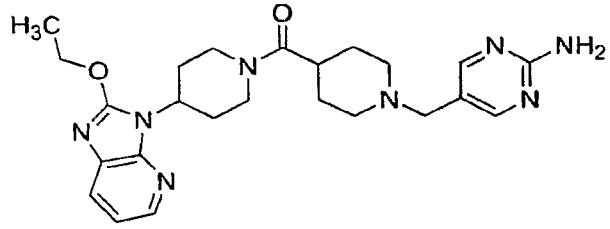


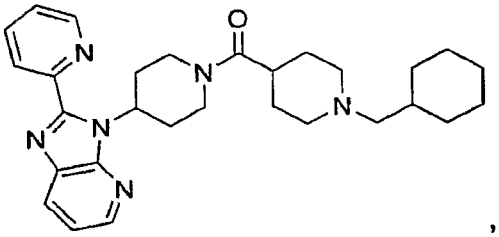


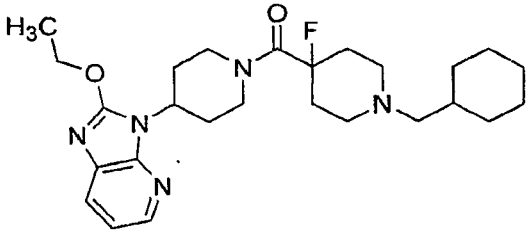


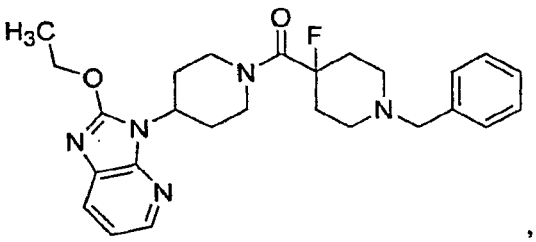


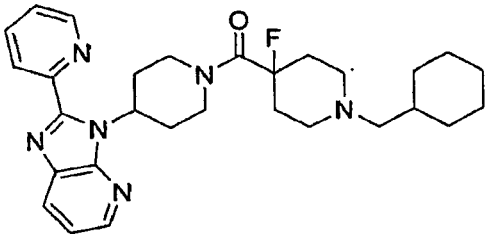


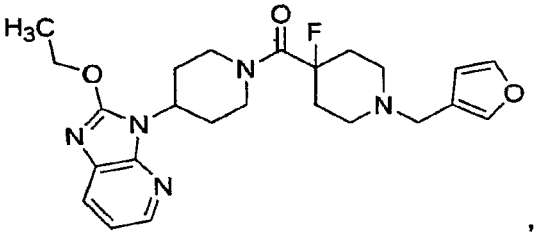


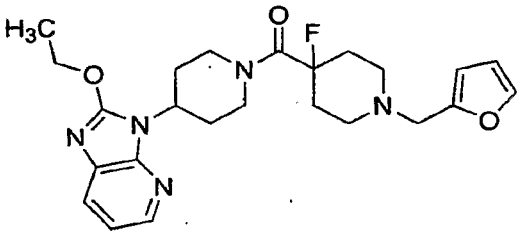


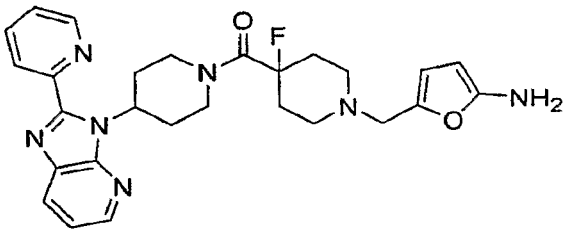


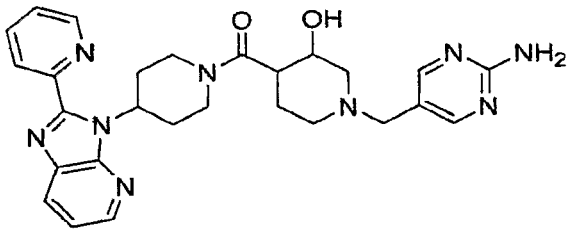


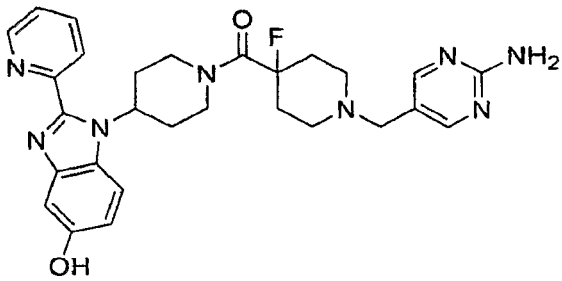


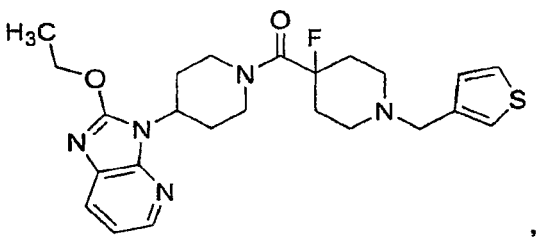


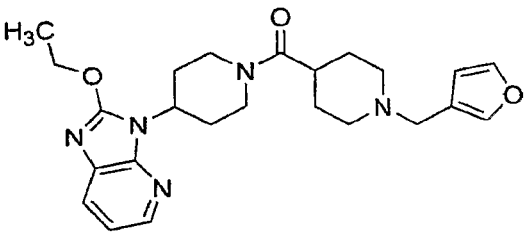


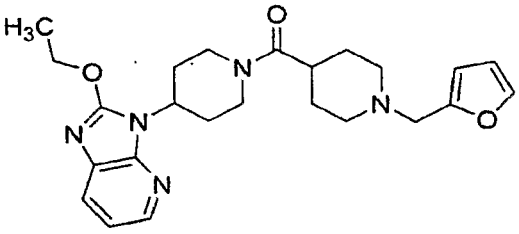


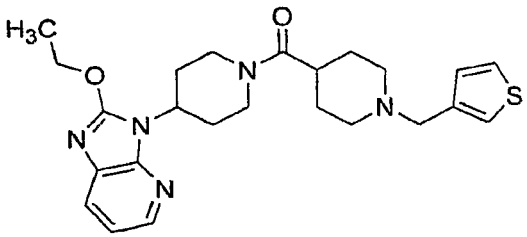


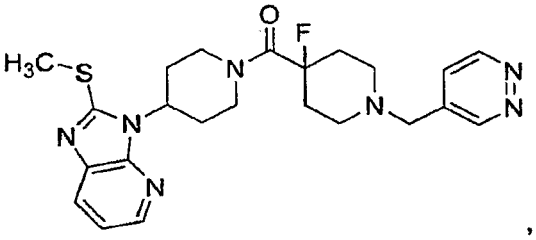


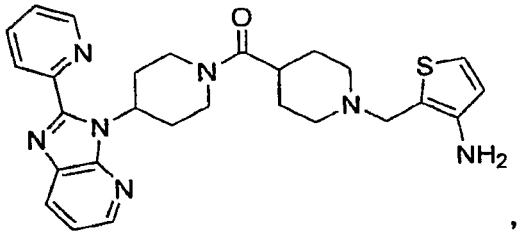
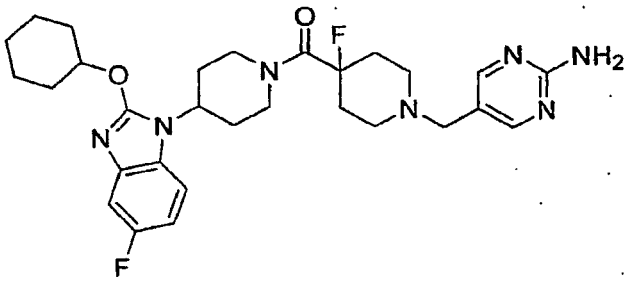
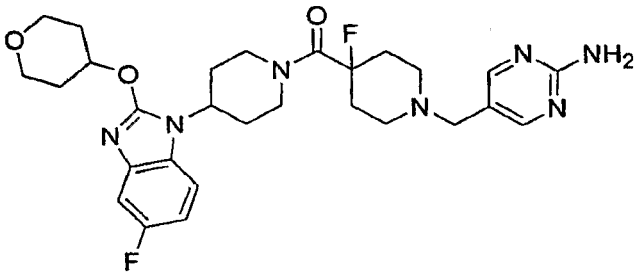
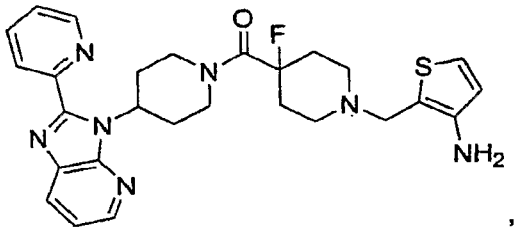
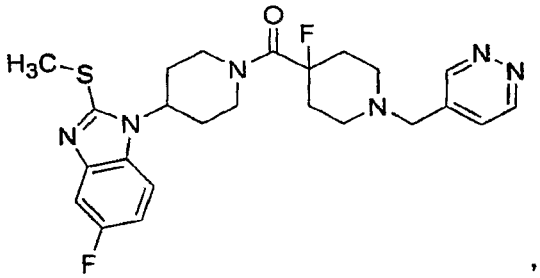
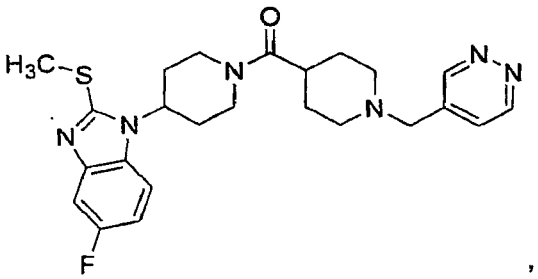
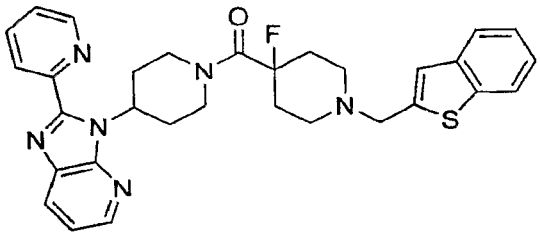
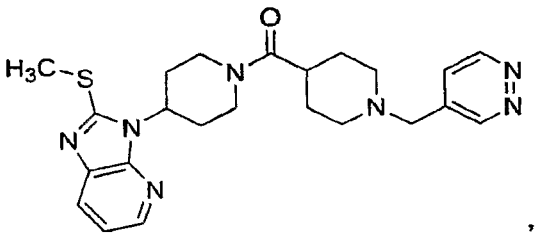
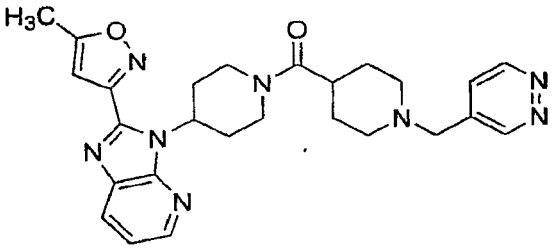
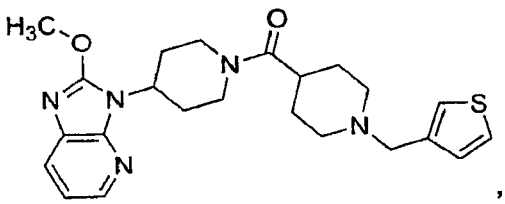
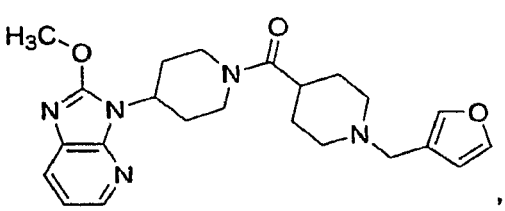
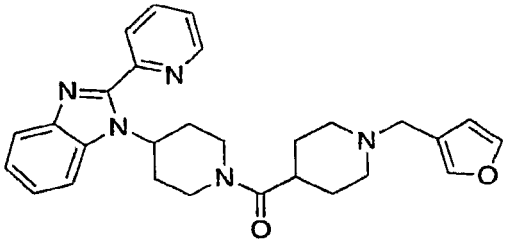




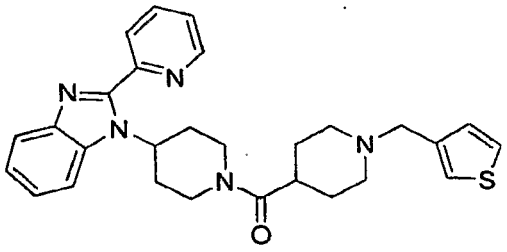


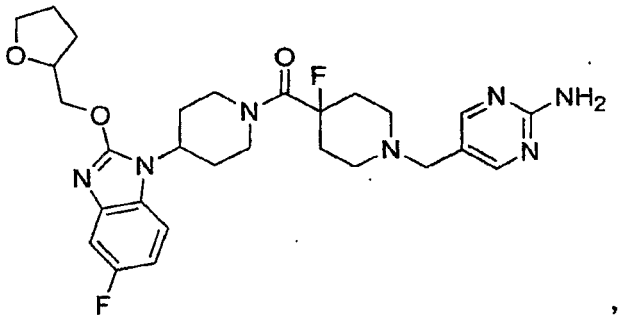


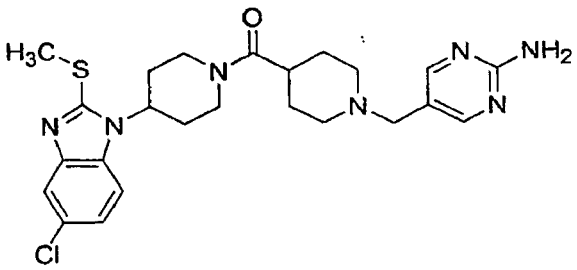


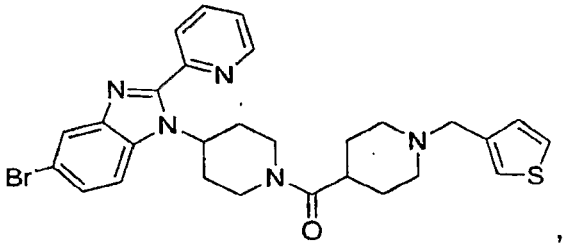

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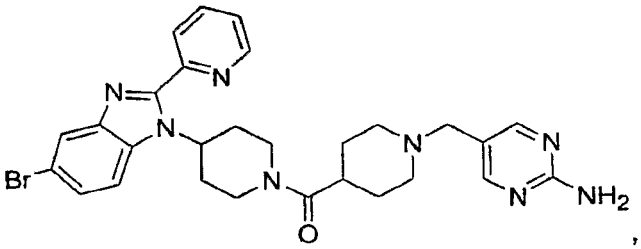
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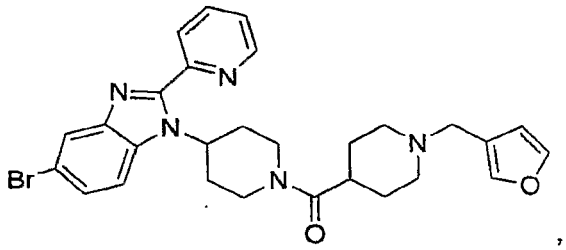


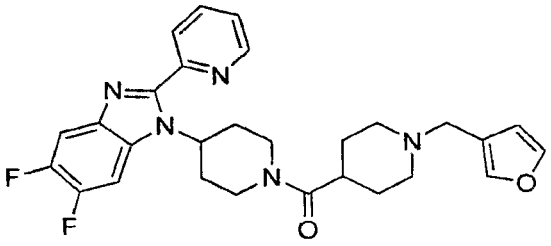


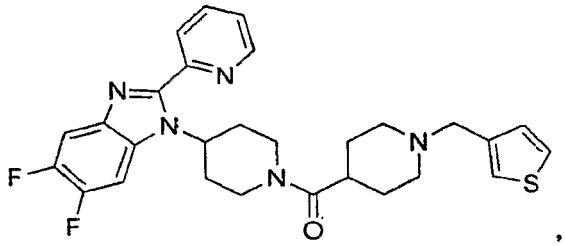


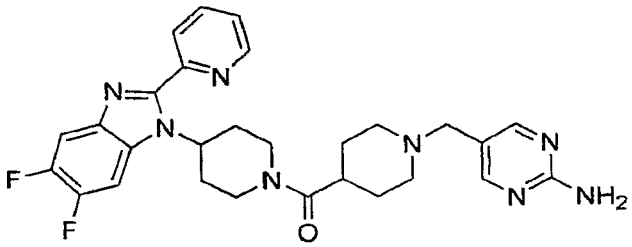


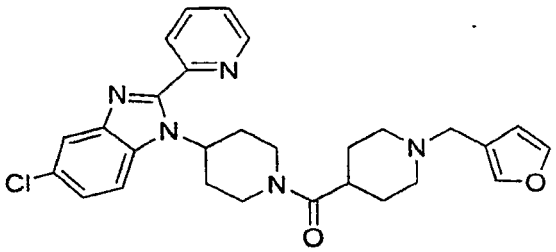


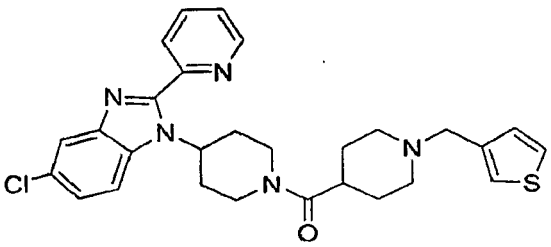


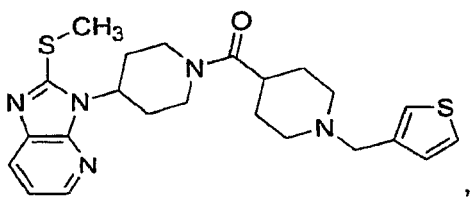


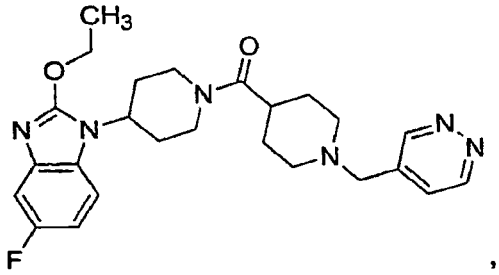
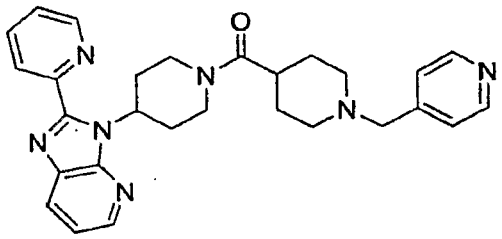
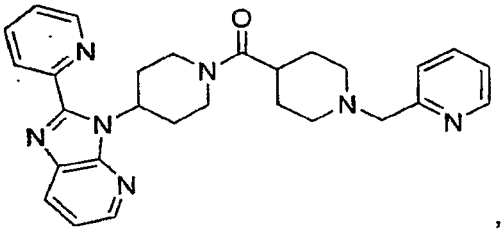
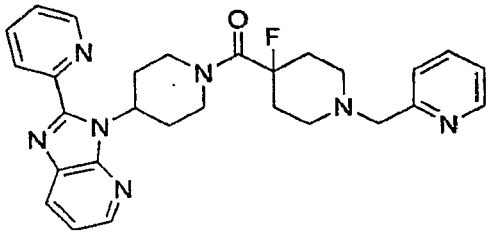
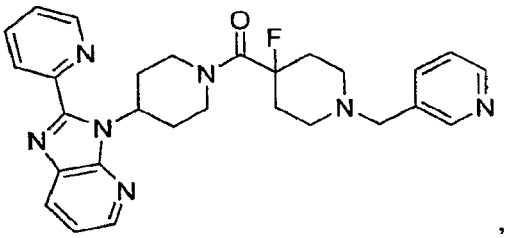
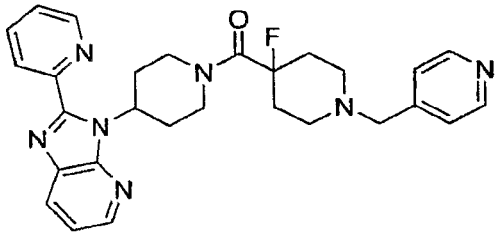
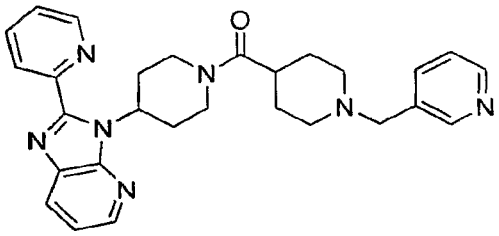
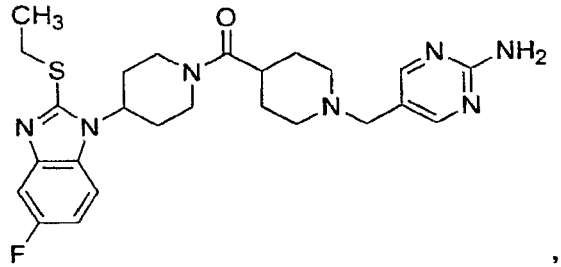
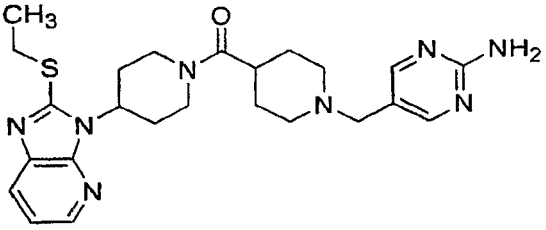
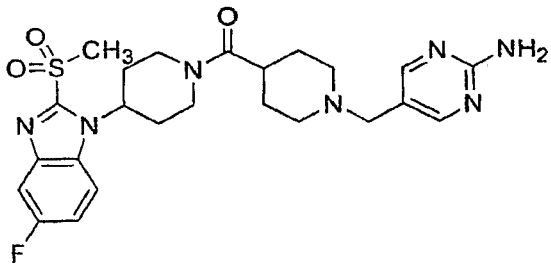
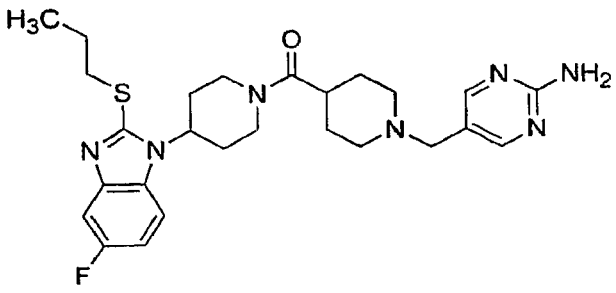
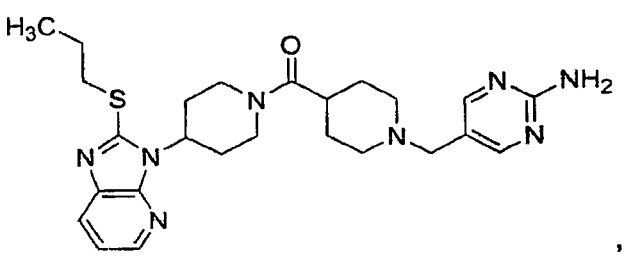


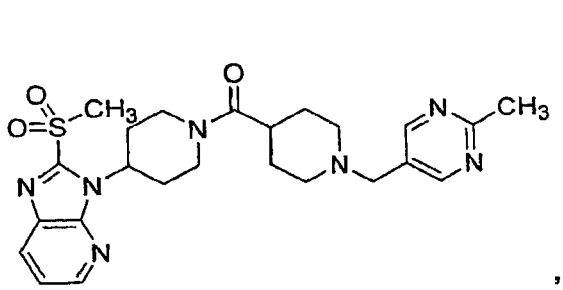


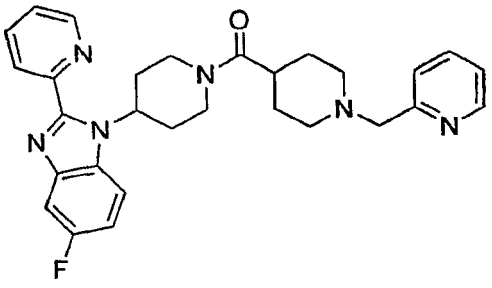


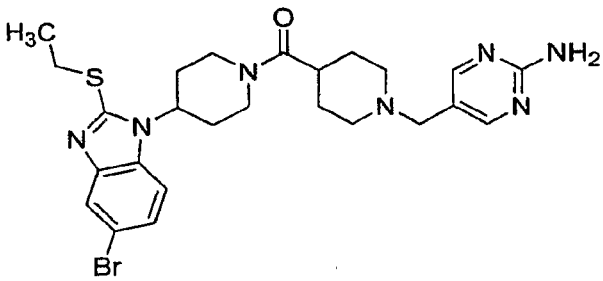


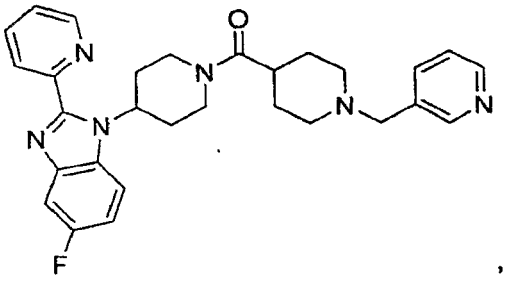


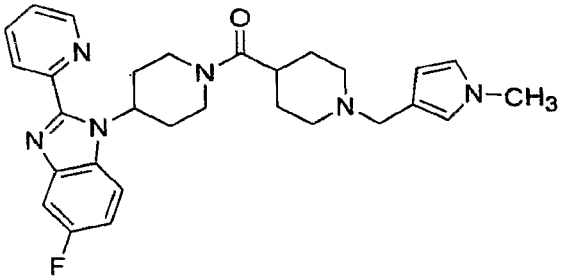

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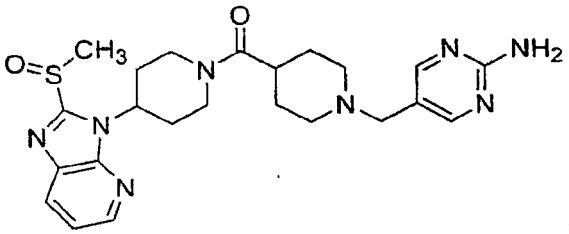


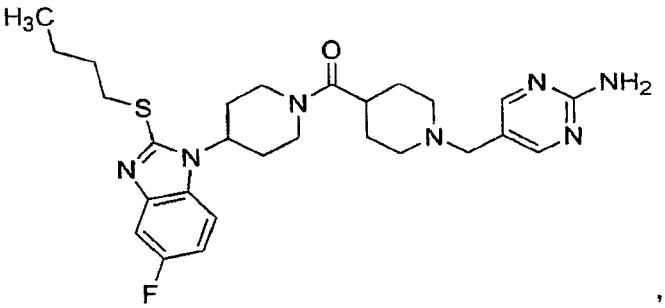


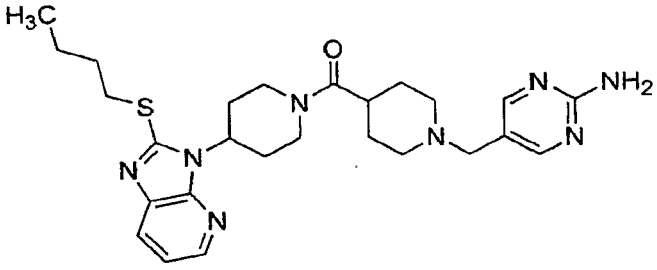


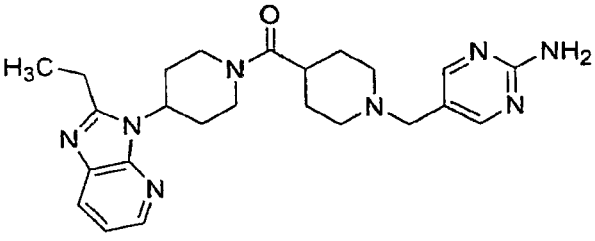


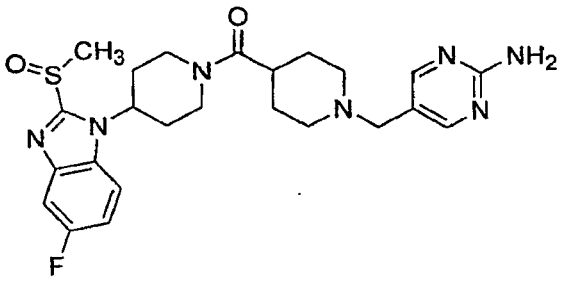




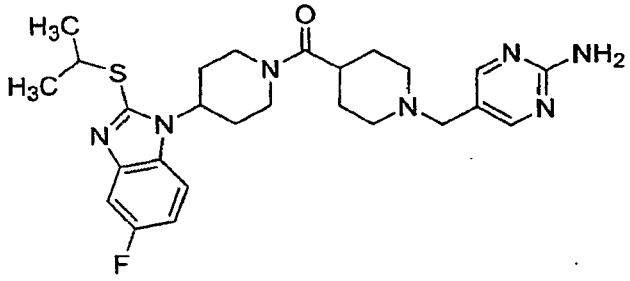




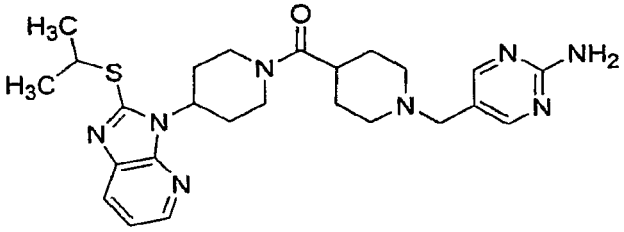




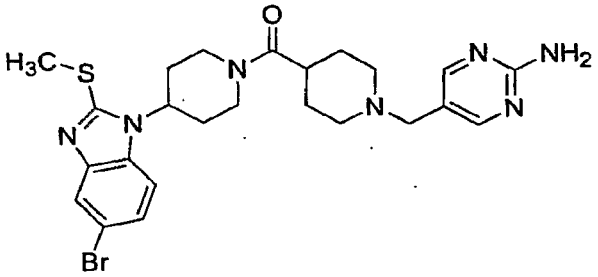
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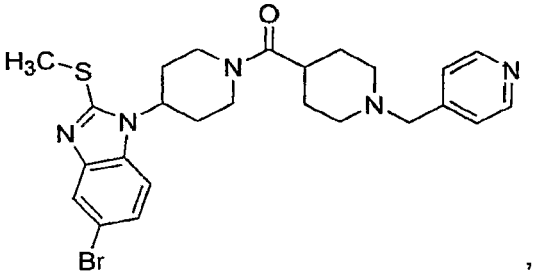
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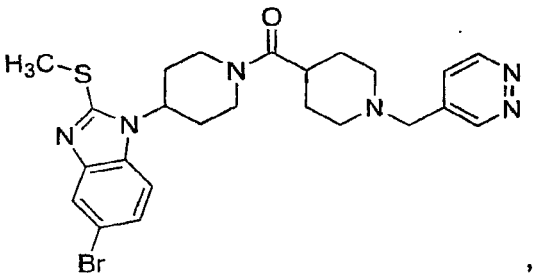
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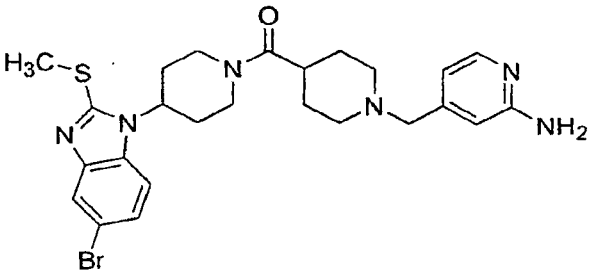
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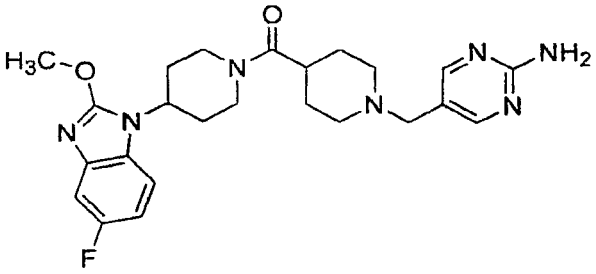
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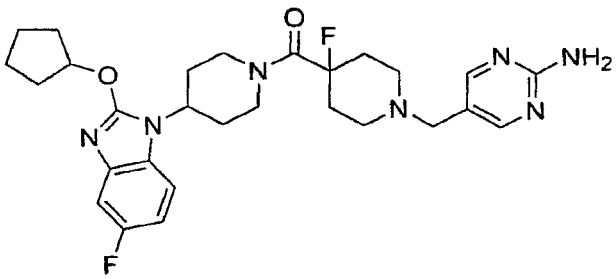
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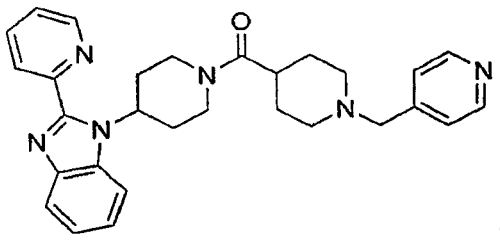
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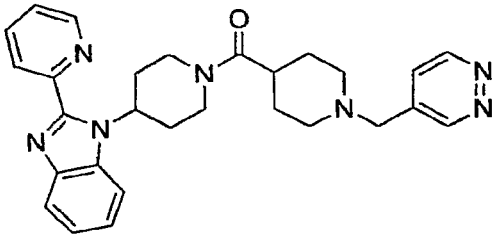


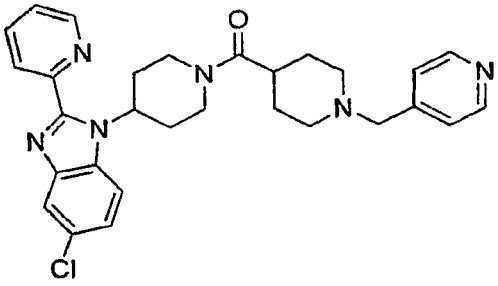
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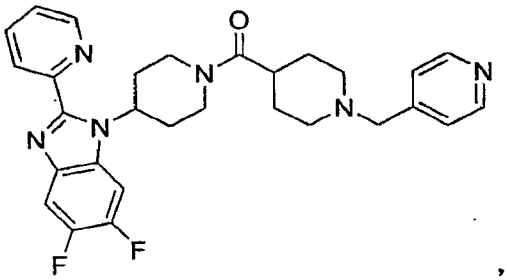


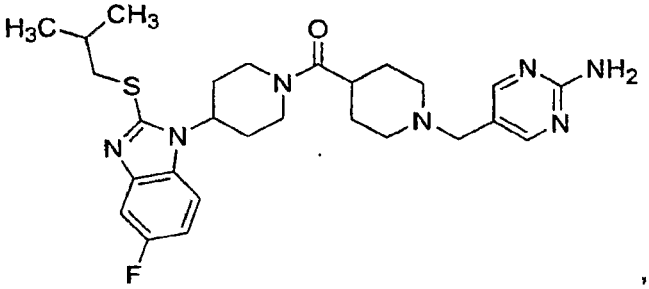
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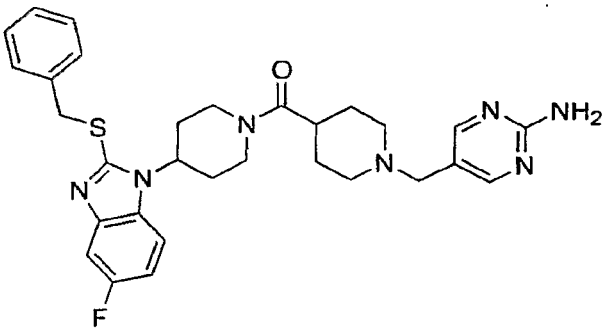
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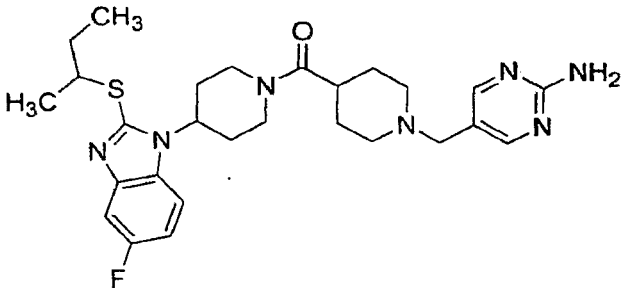


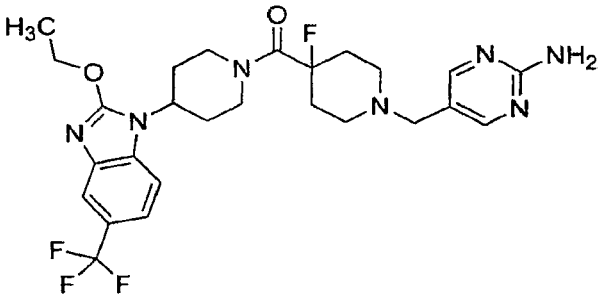


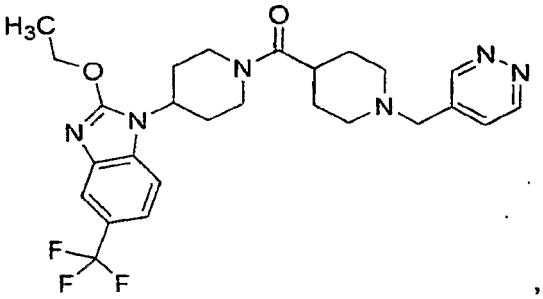


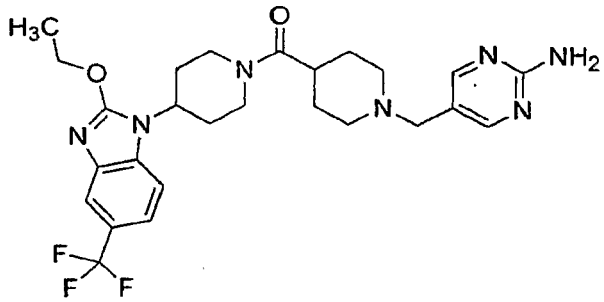


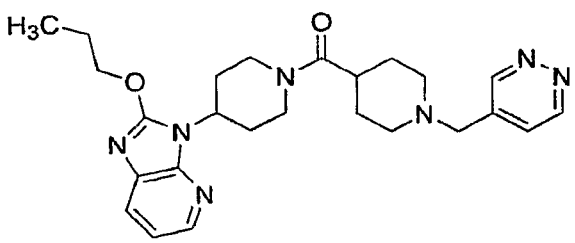


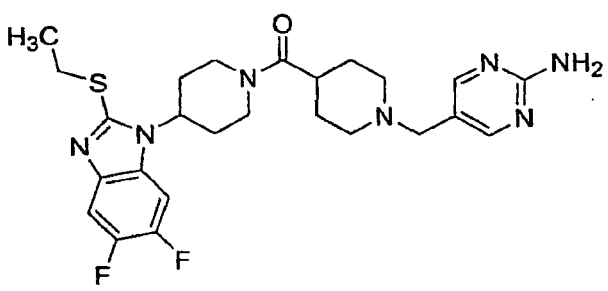


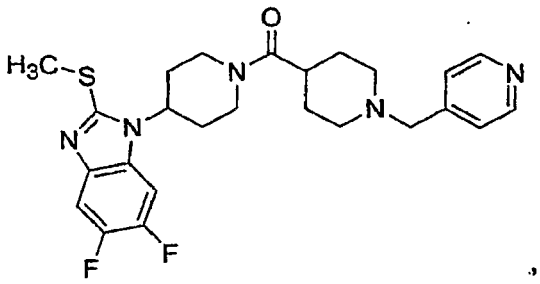


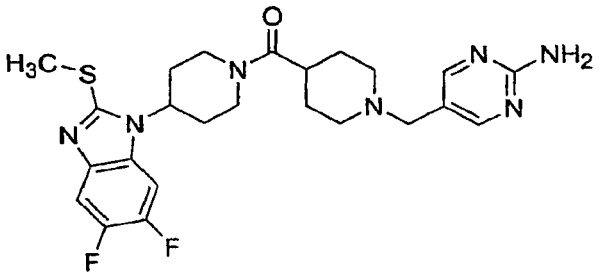


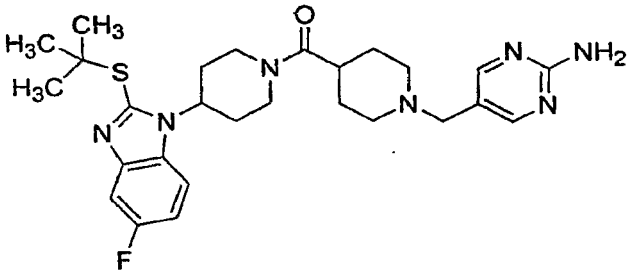


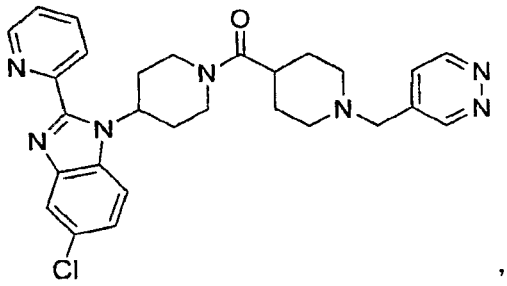


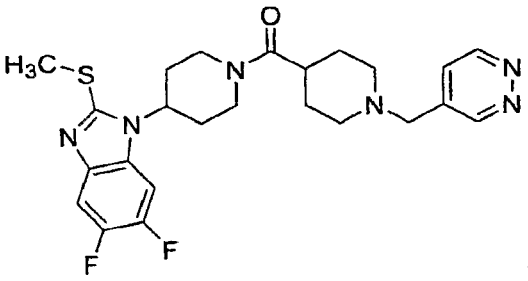


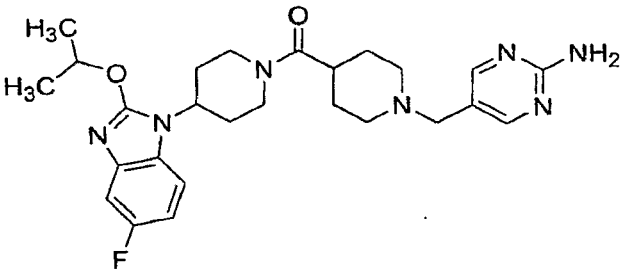


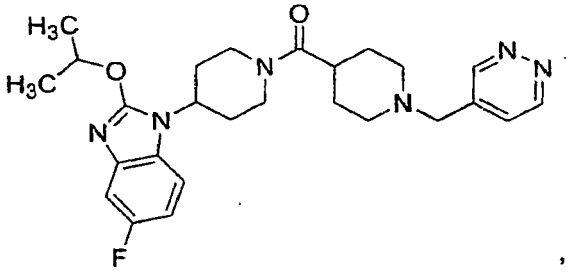


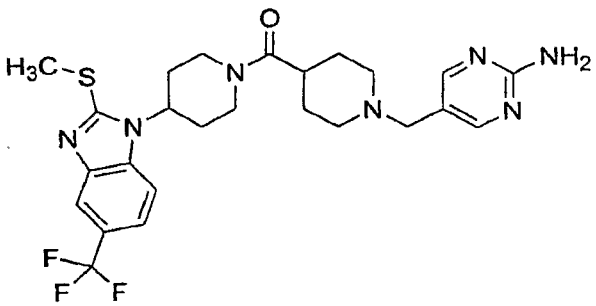


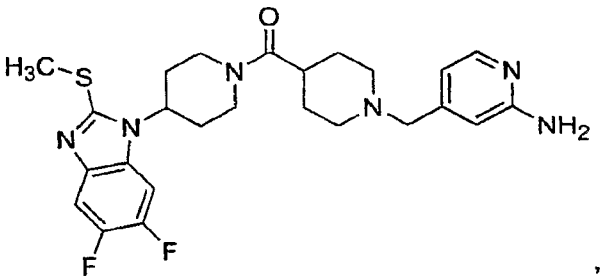


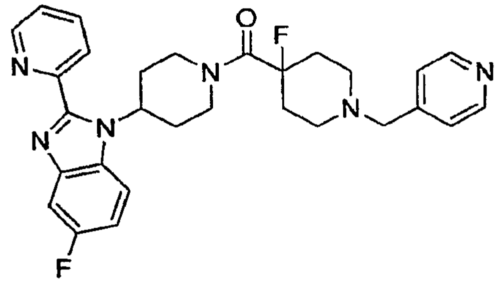
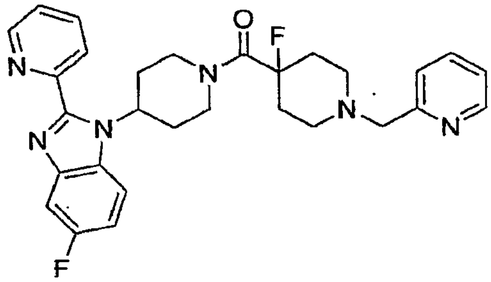


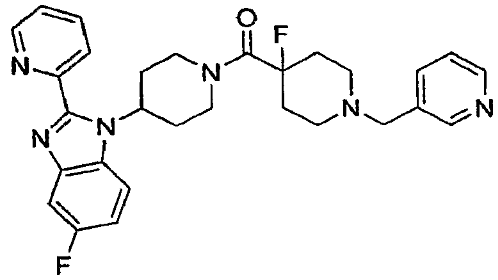
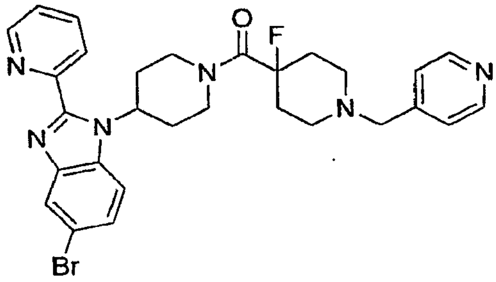


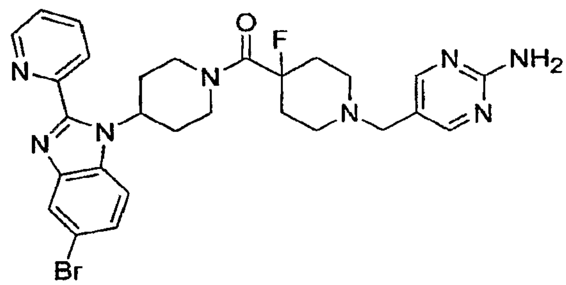
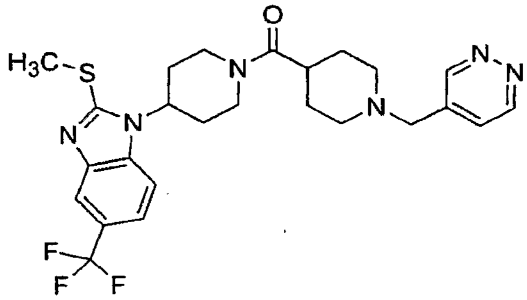


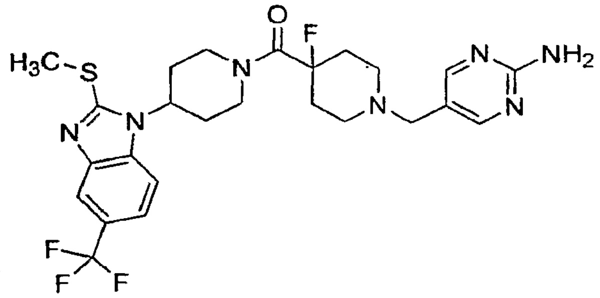
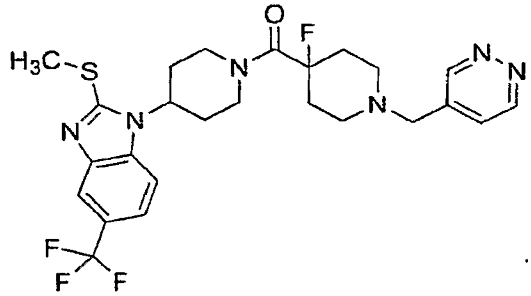


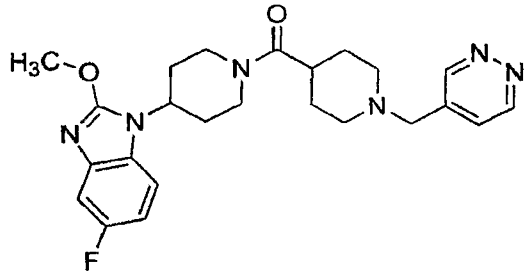
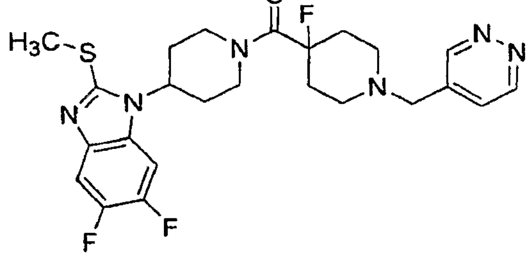


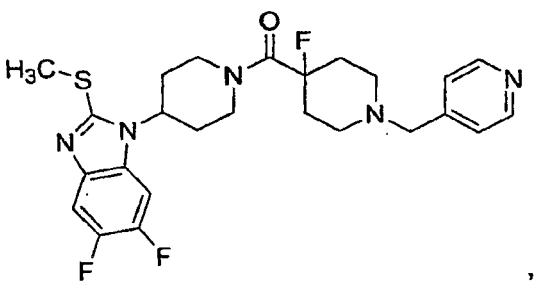
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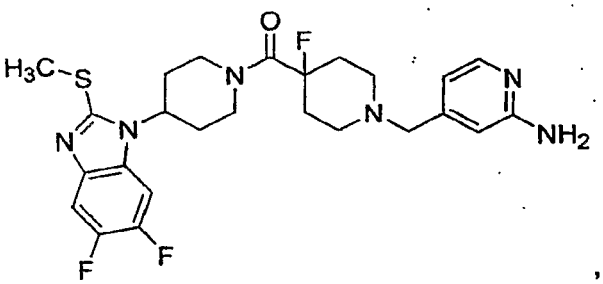
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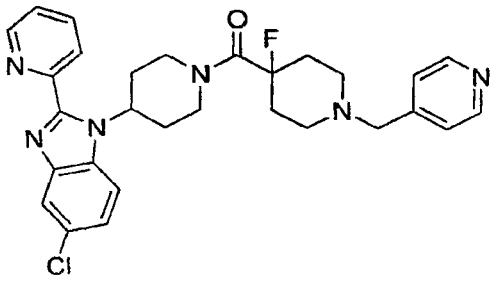
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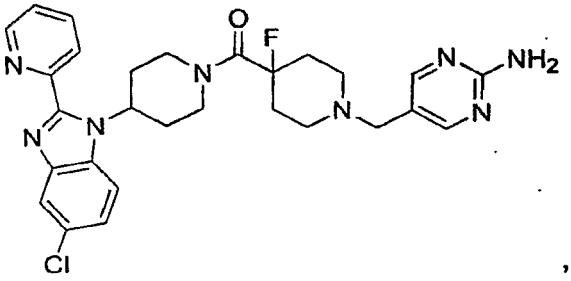
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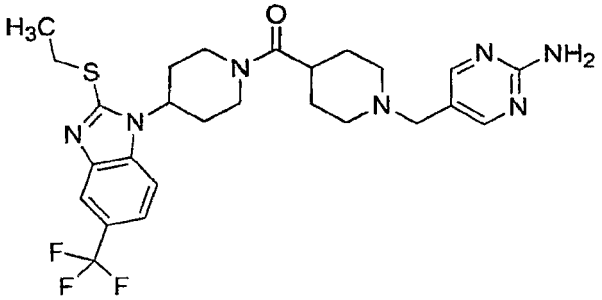
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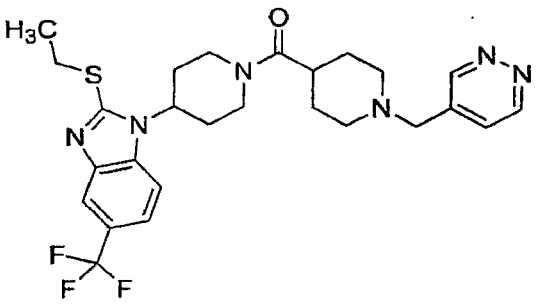
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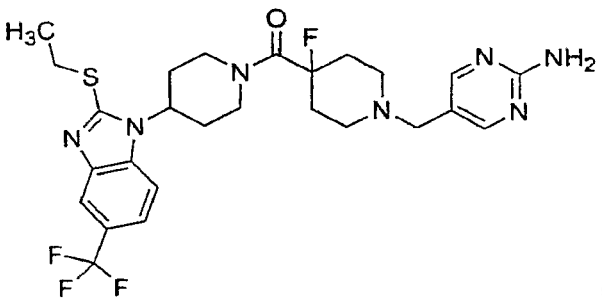
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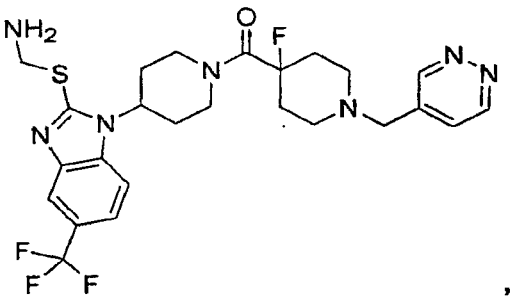
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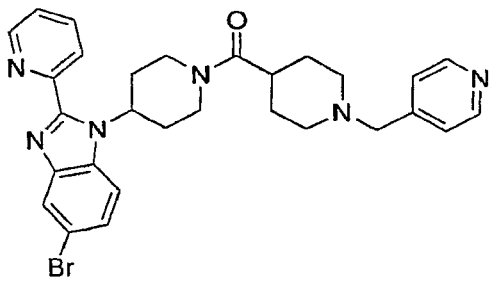
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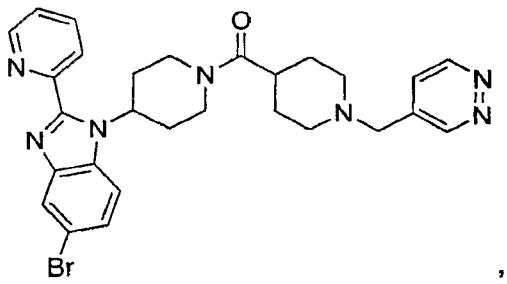
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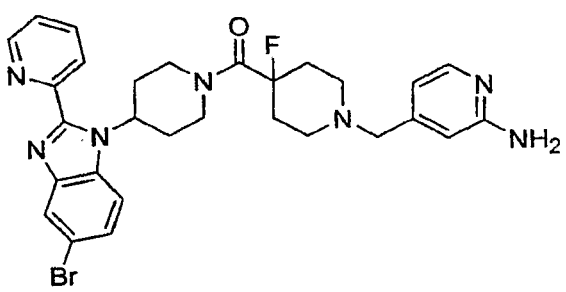


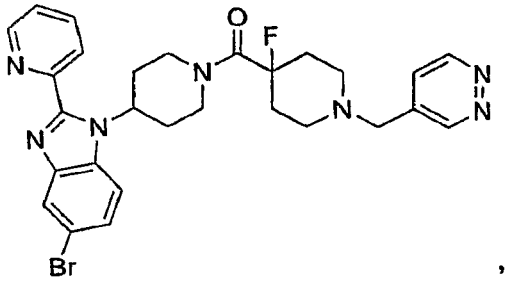
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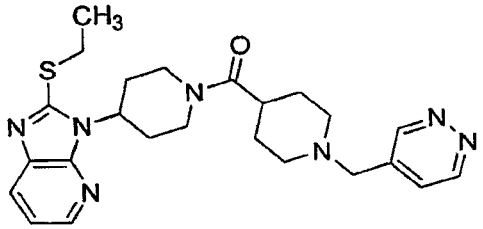


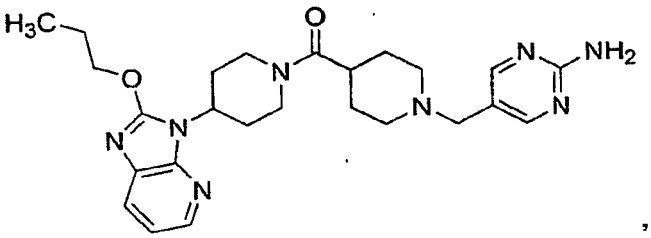
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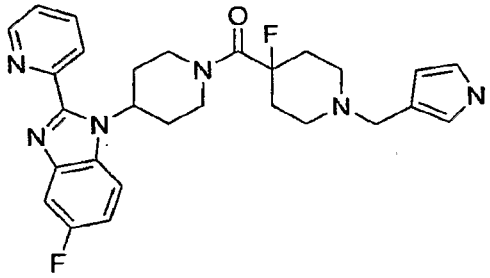
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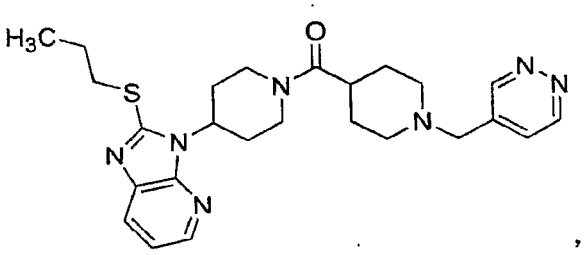


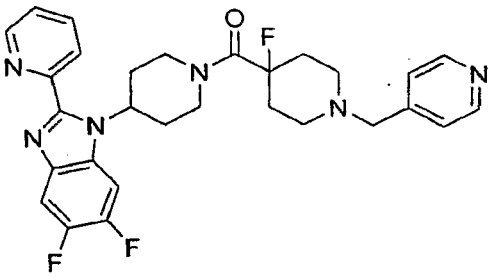


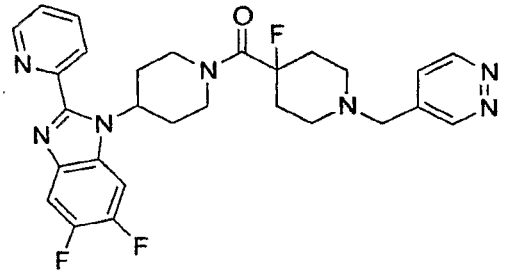


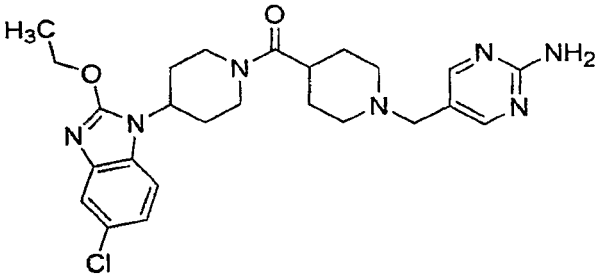


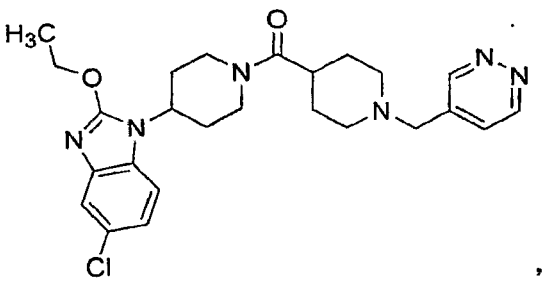




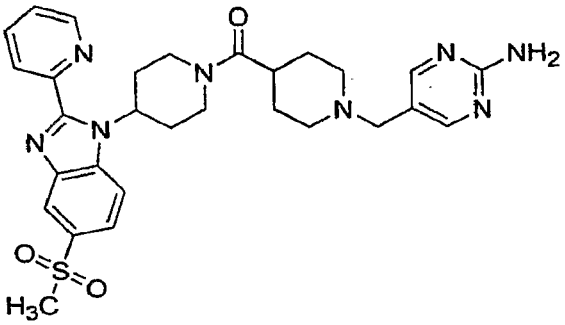


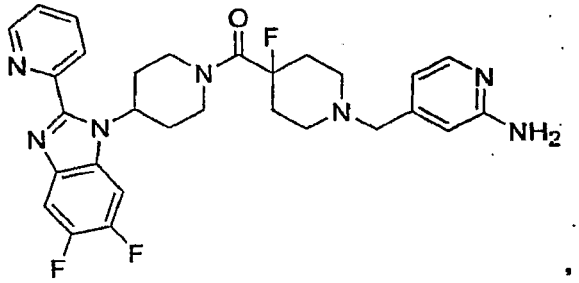


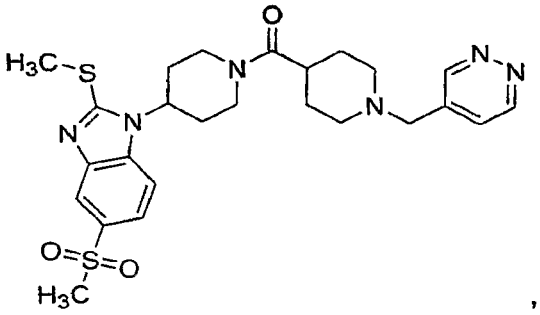


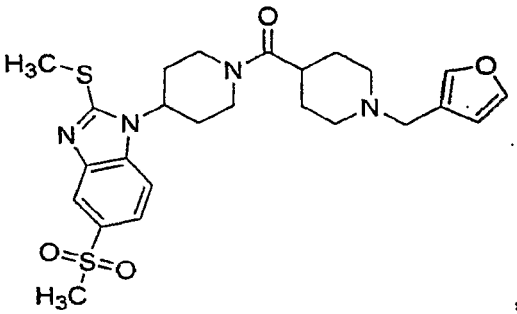


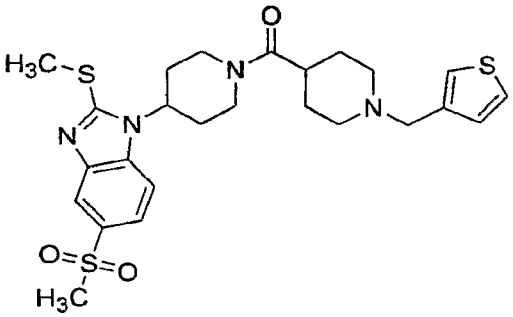
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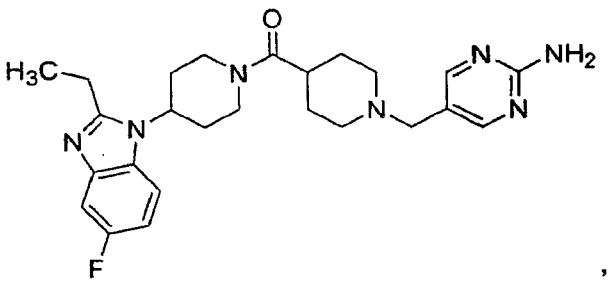


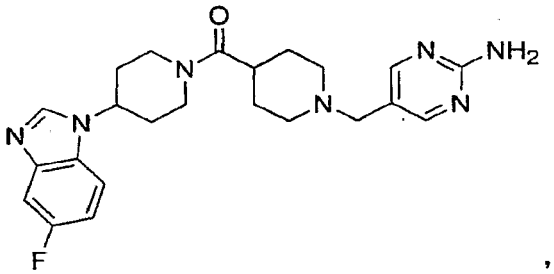


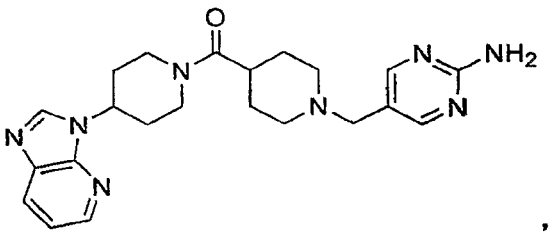


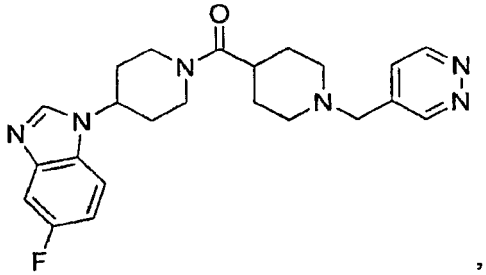


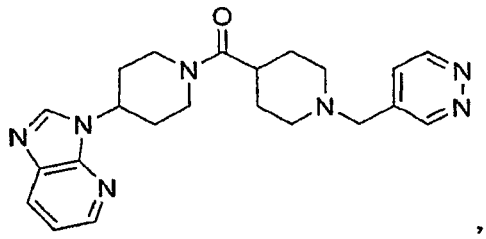


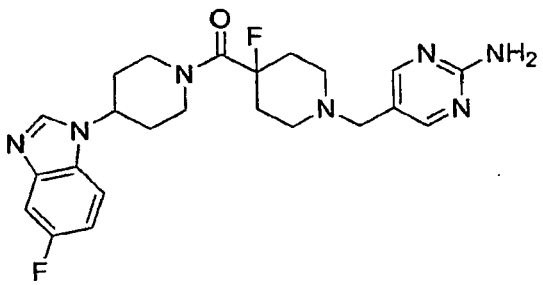


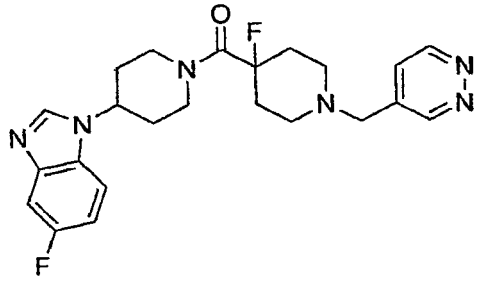


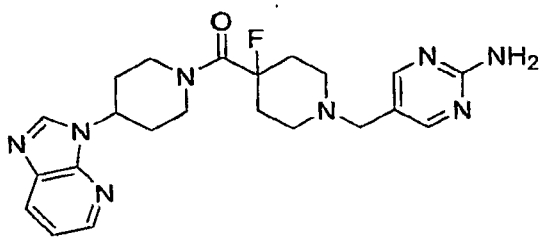


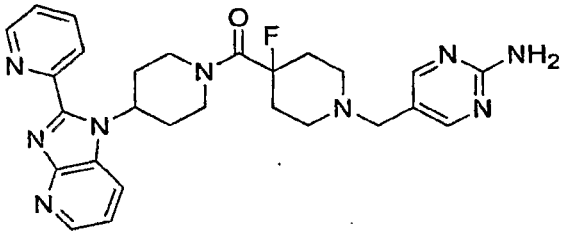


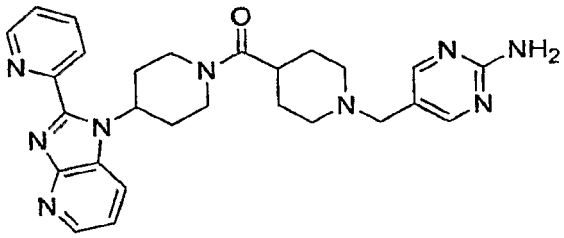


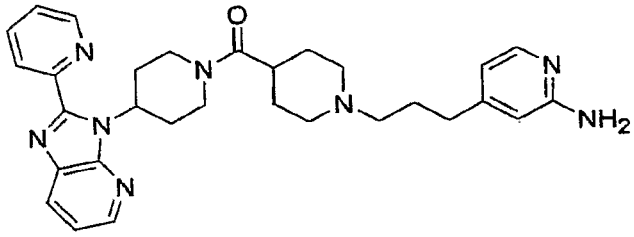


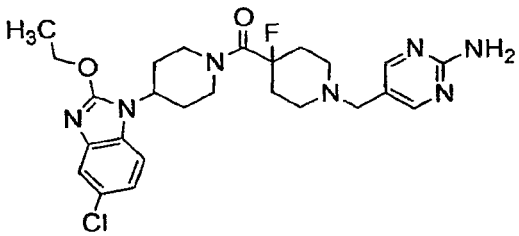


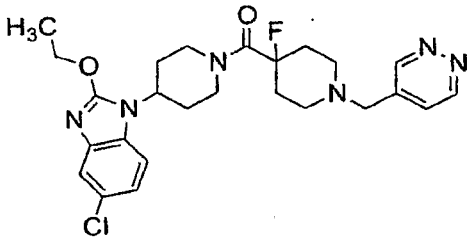


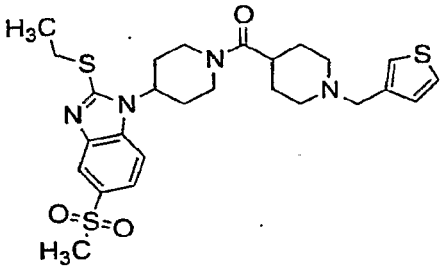


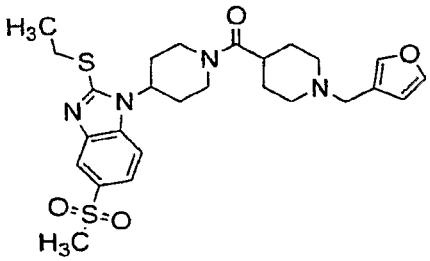


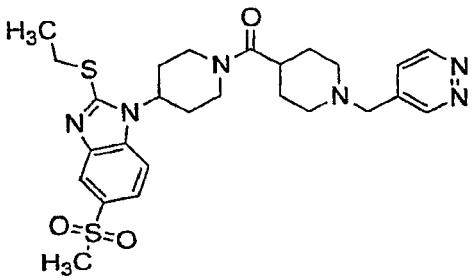


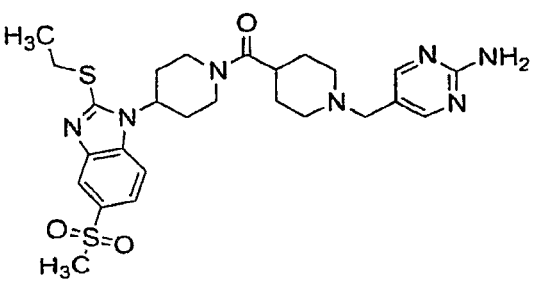


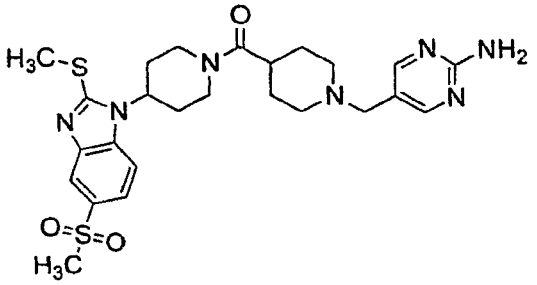


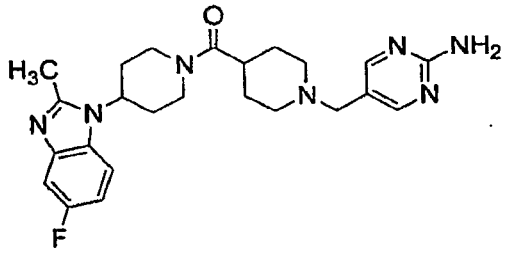


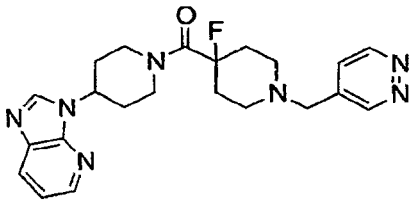


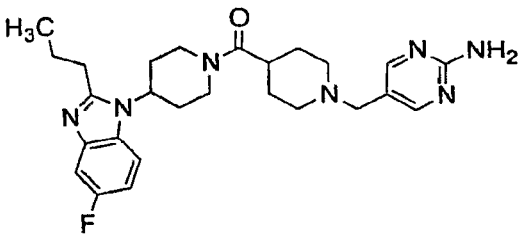


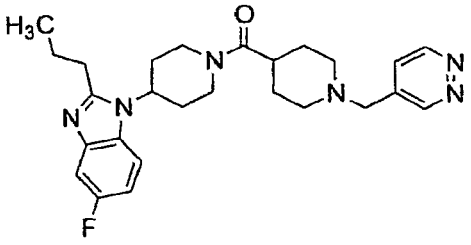


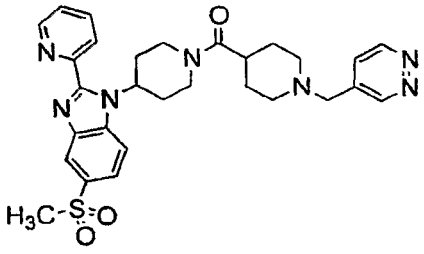


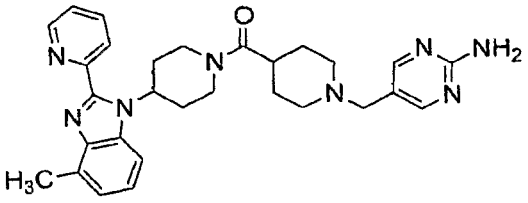


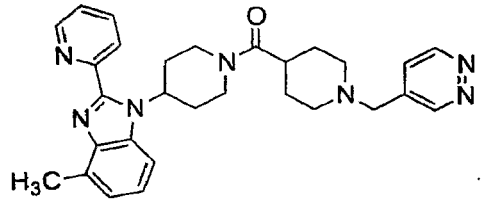


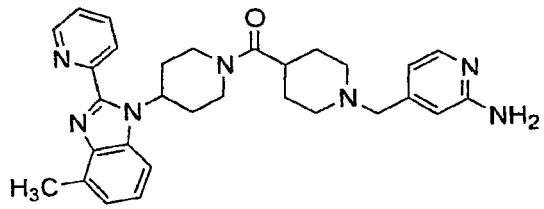


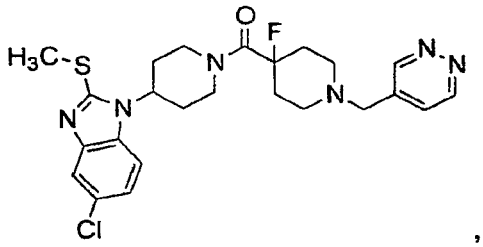


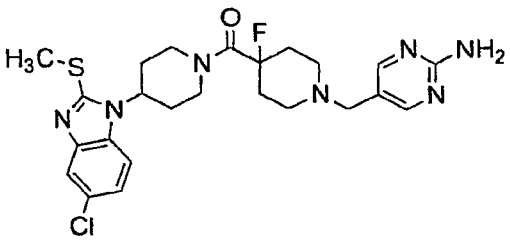


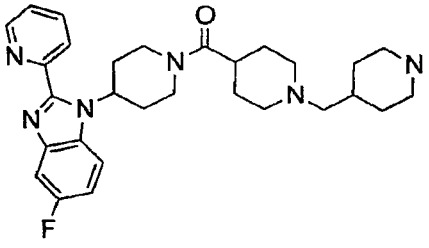


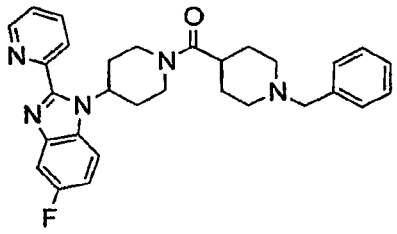


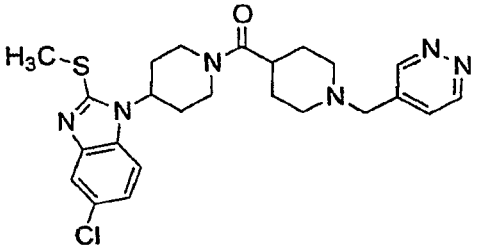


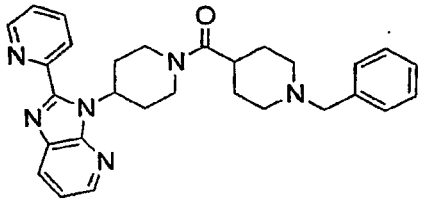


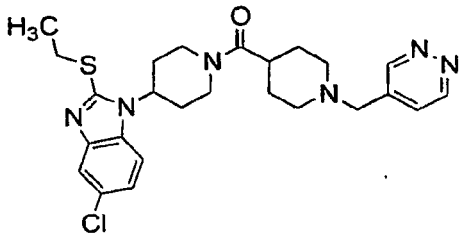


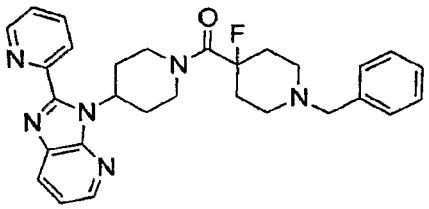


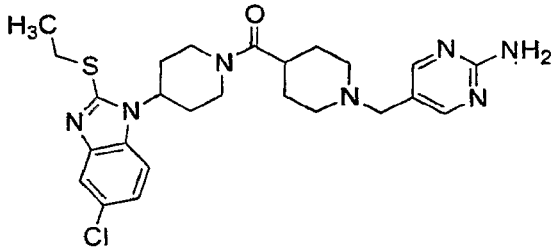


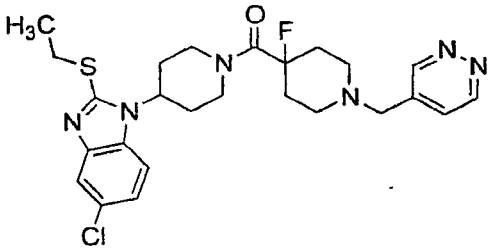


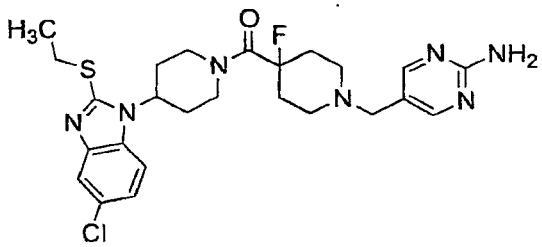


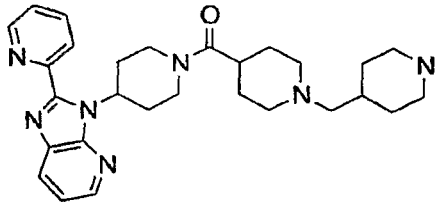


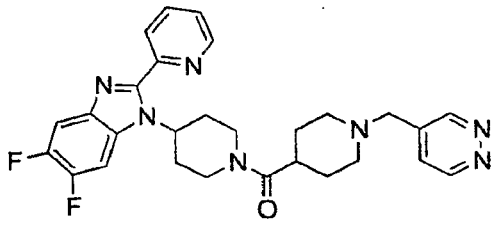


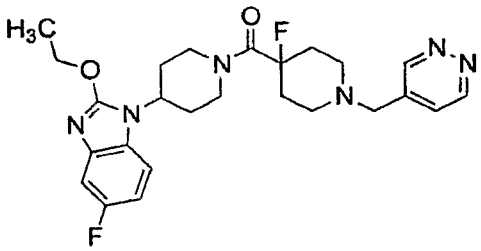


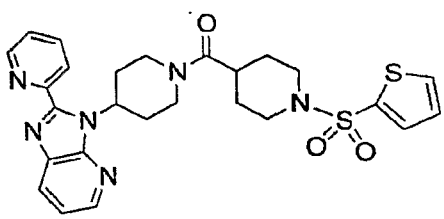


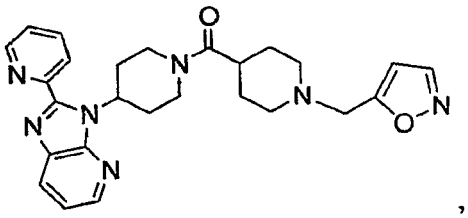


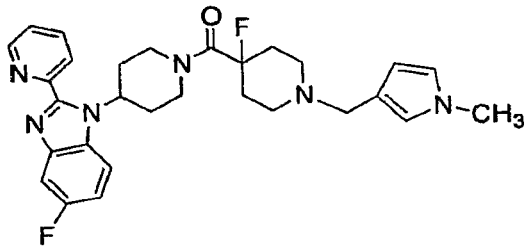


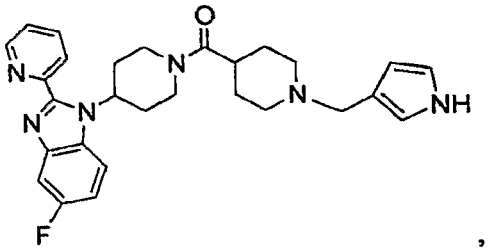


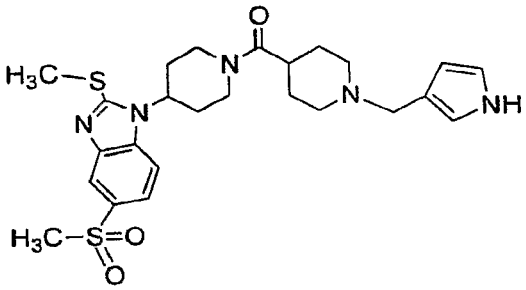


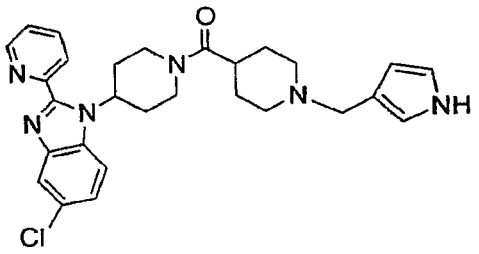


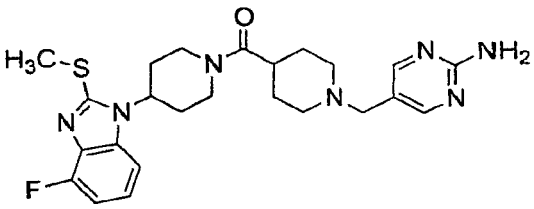


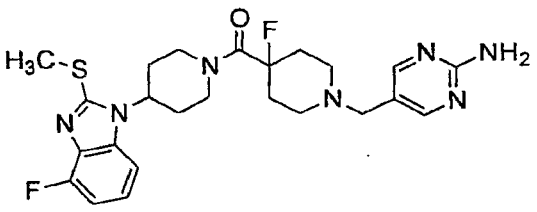


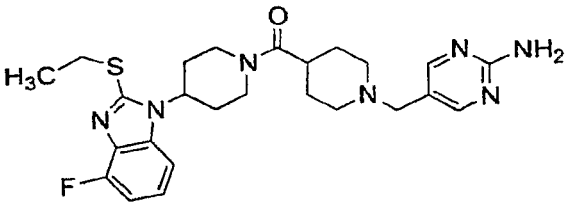


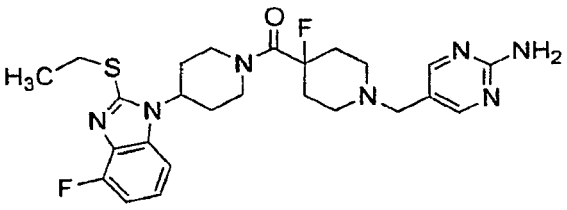


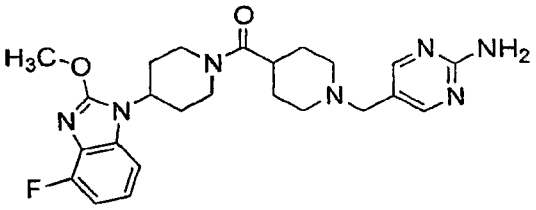


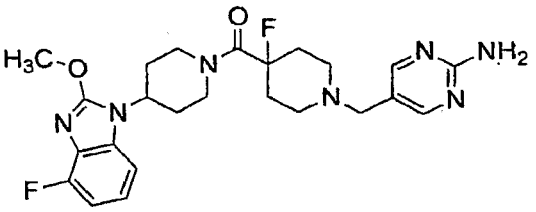


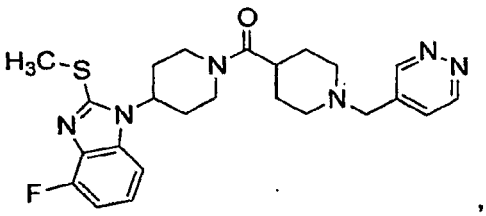
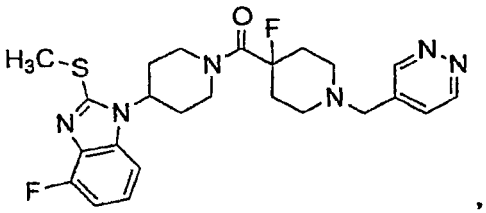
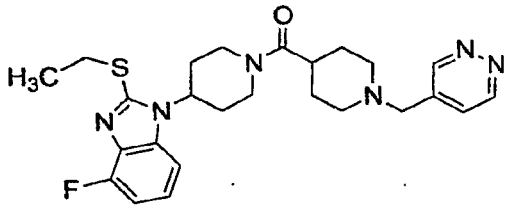
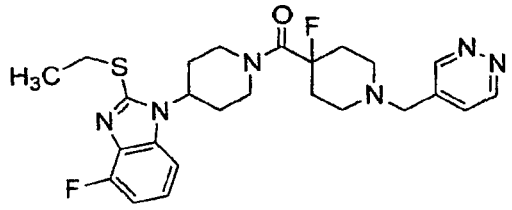
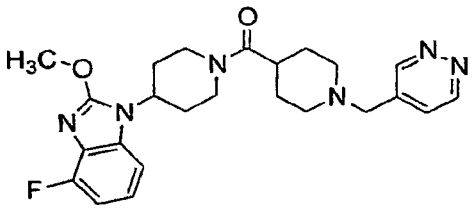
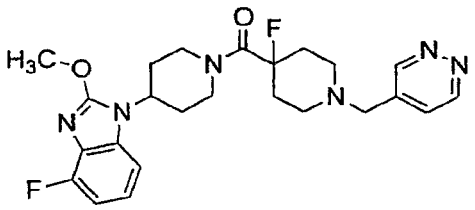
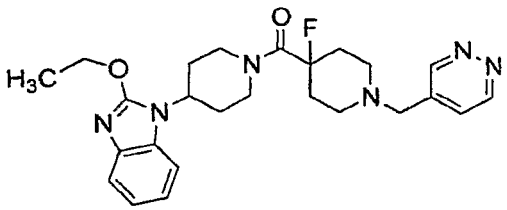
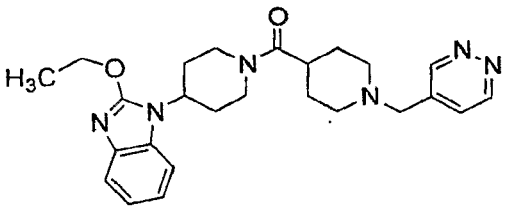
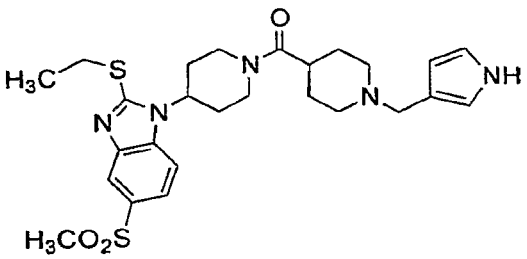
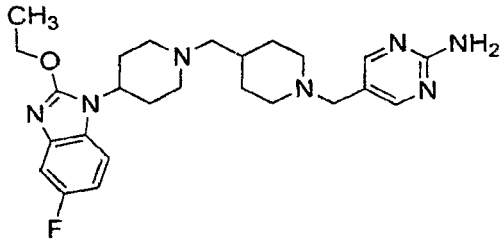
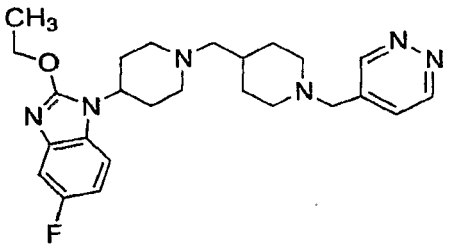
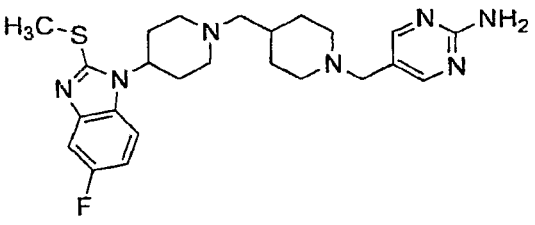


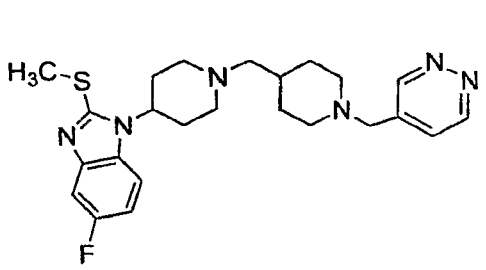
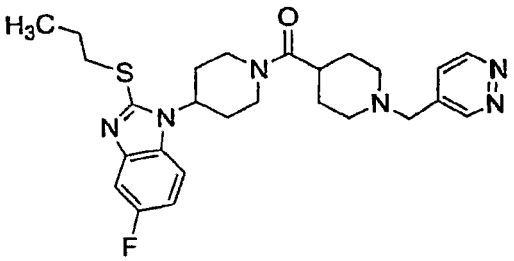
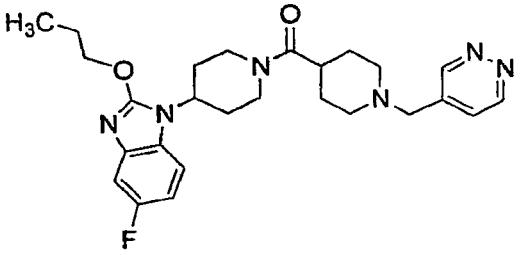
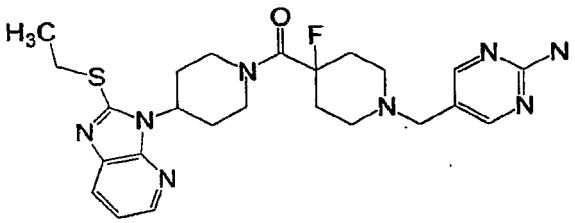




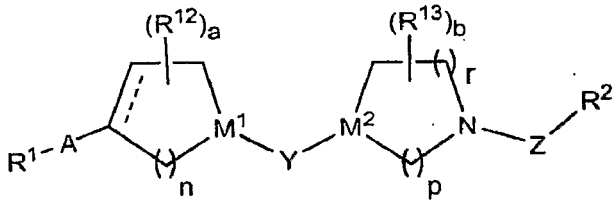




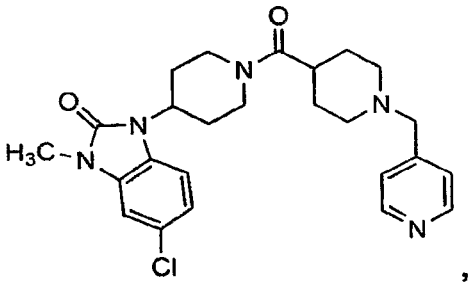
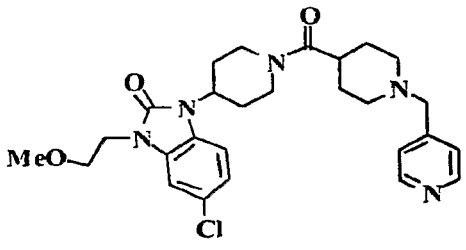
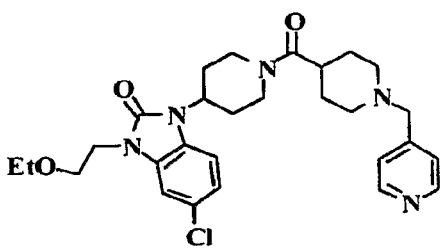
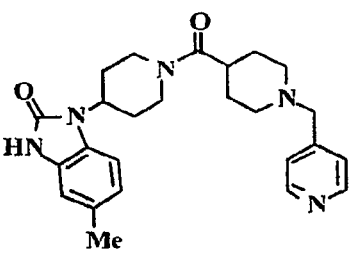
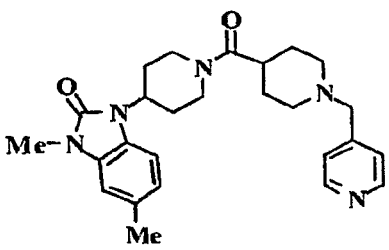

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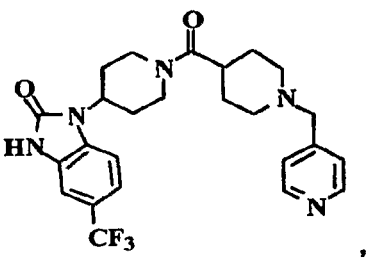
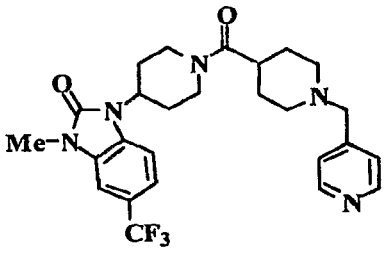
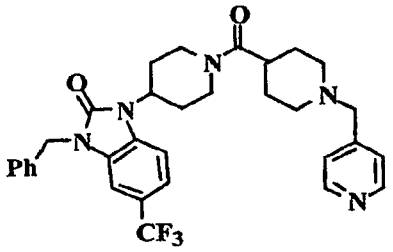
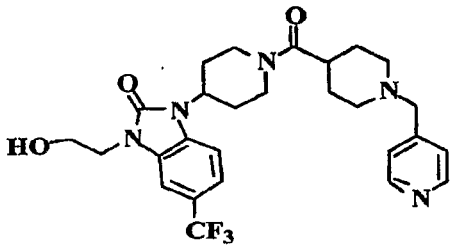
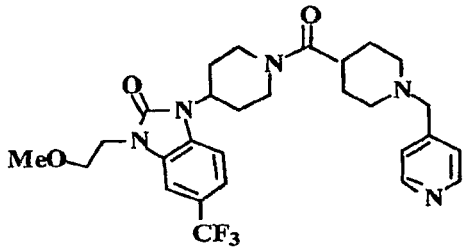
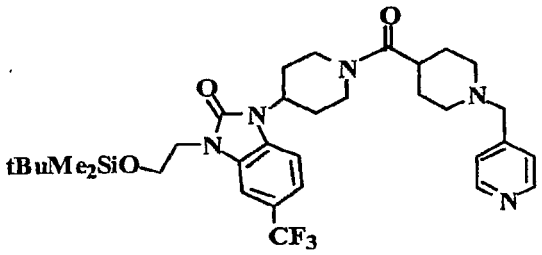
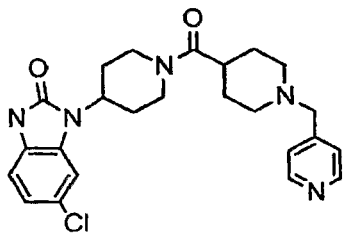
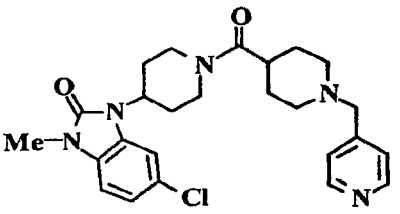
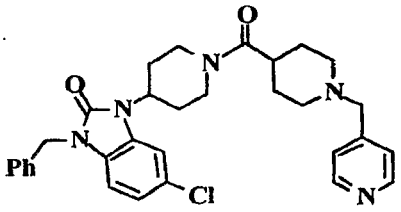
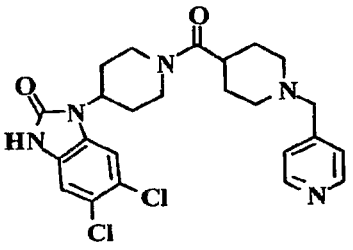
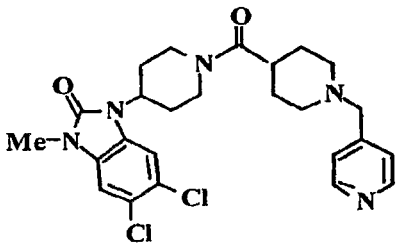
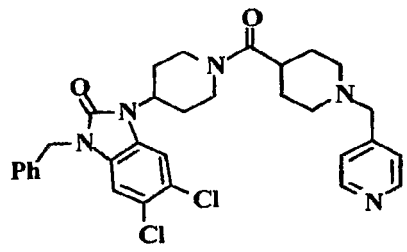
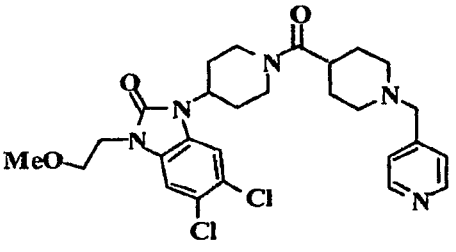
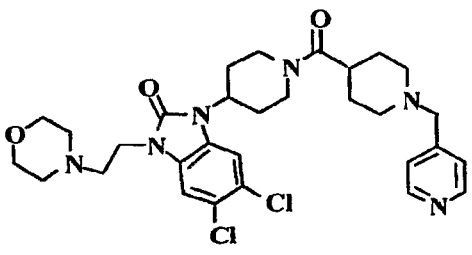

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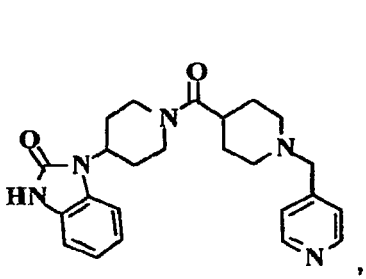
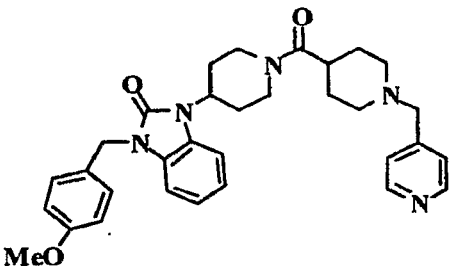
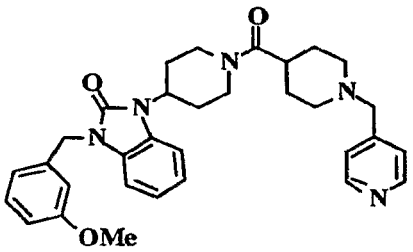
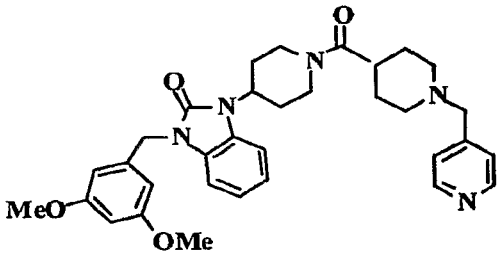
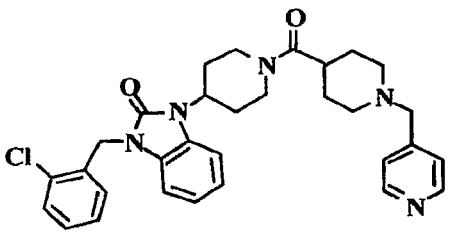
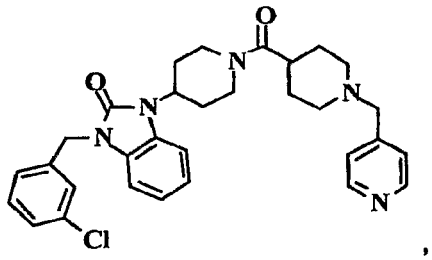
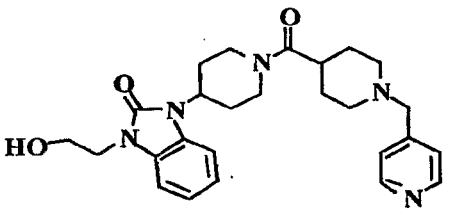
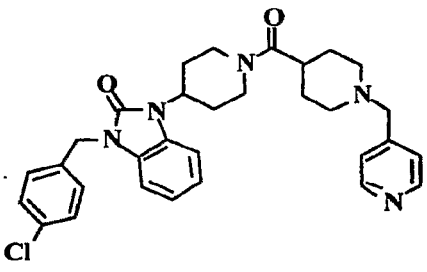
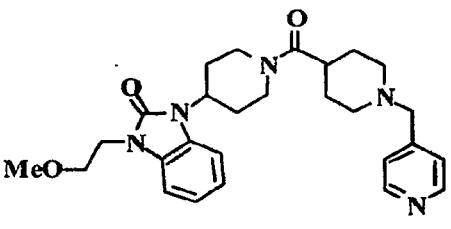
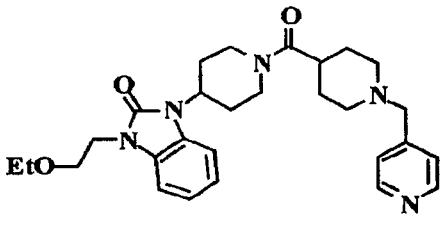
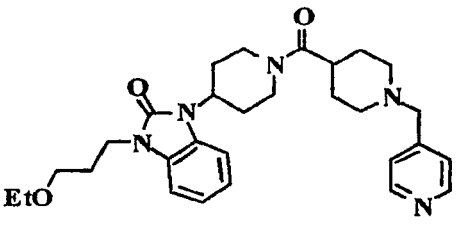
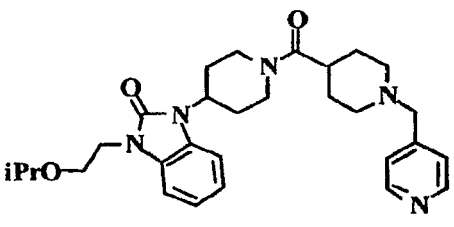
In one embodiment, the H_3 antagonists/inverse agonists of the present invention can have a structure according to Formula (IV):


(IV)

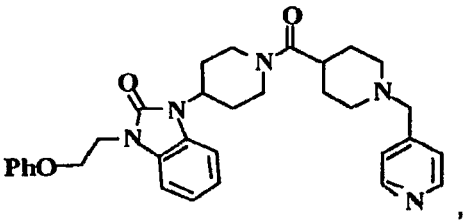
as described in U.S. 2004/0048843, which is herein incorporated by reference in its entirety. Non-limiting examples of compounds of Formula (IV) include:

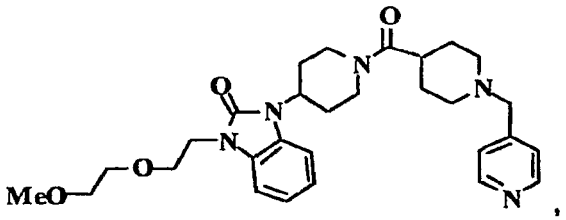

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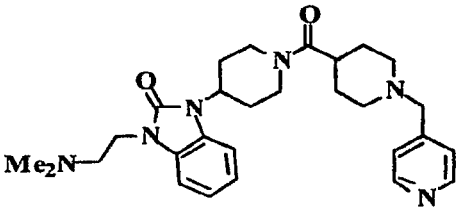

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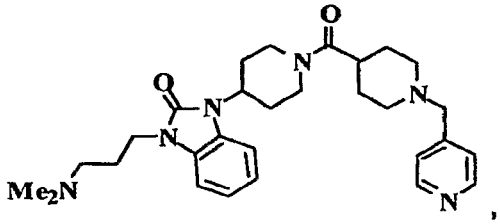













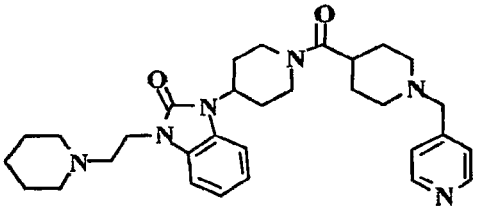
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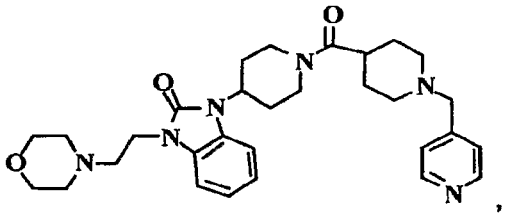

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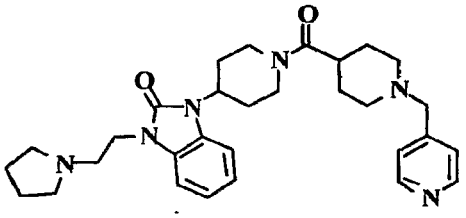

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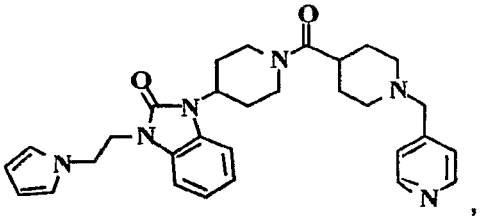

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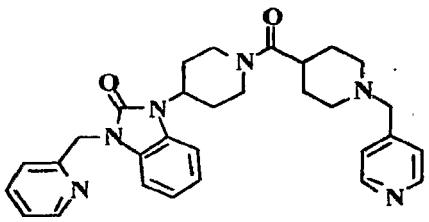

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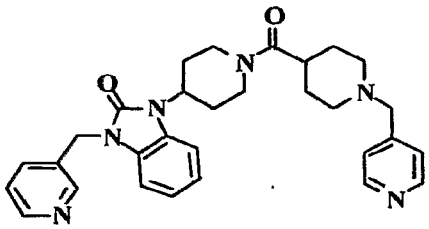


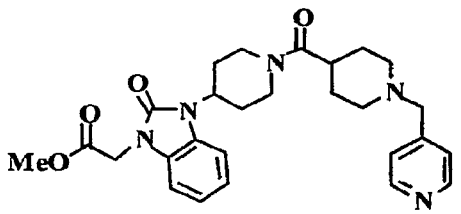


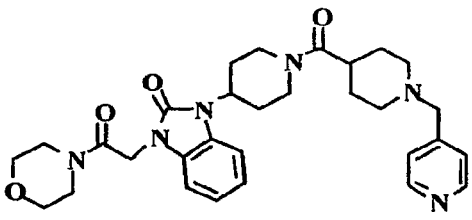


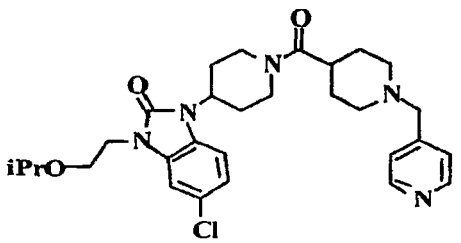


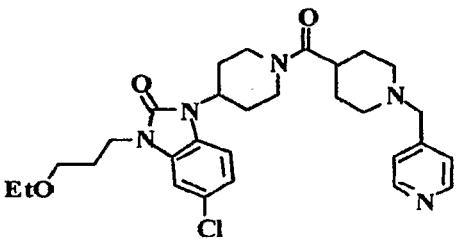


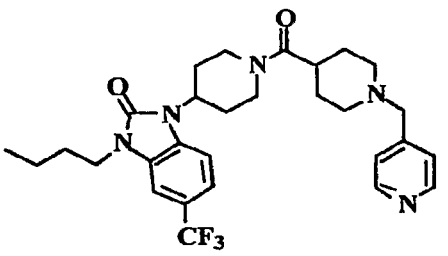
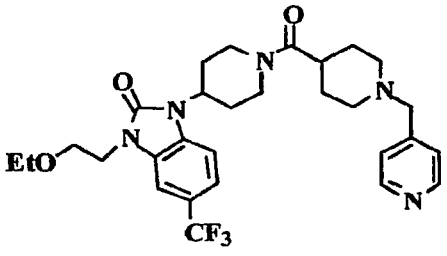
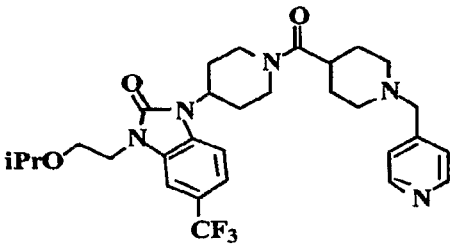
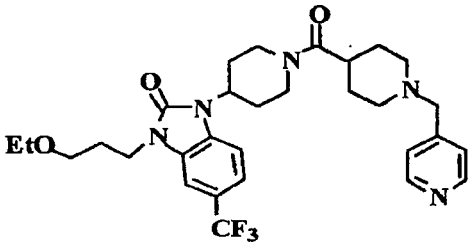
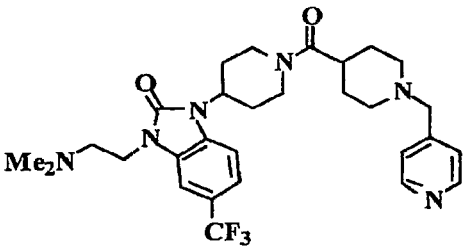
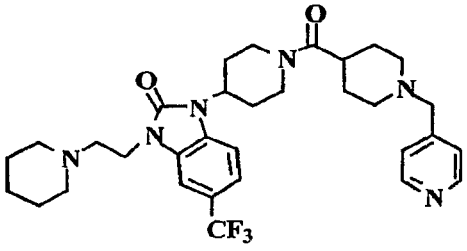
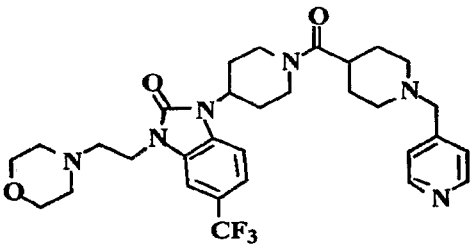
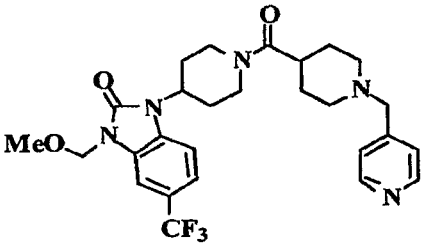
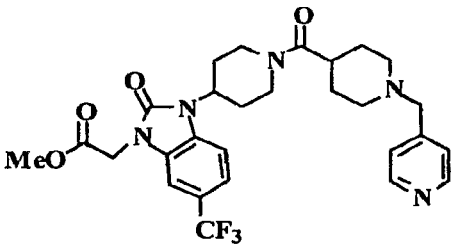
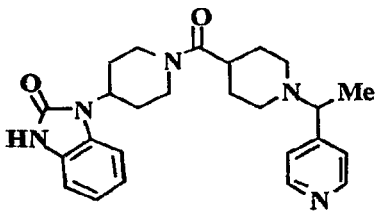
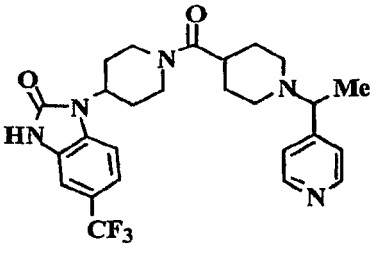
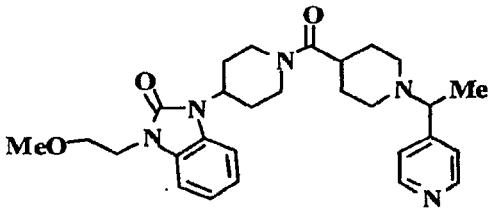
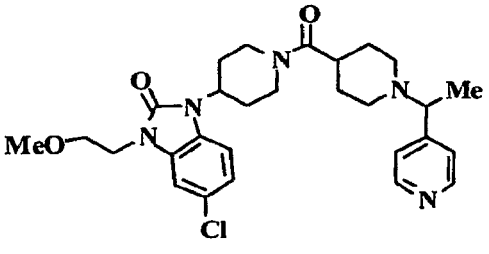



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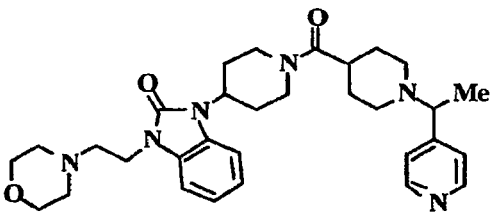
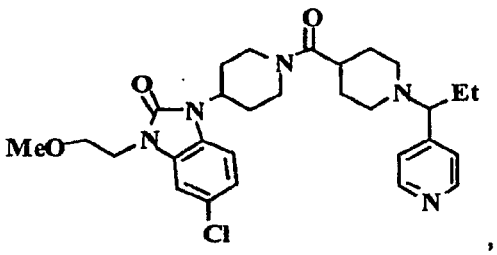
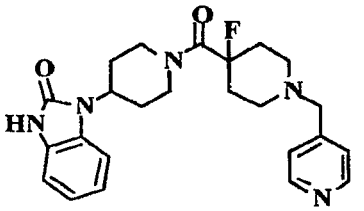
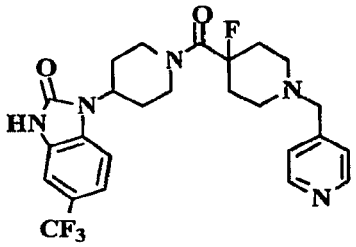
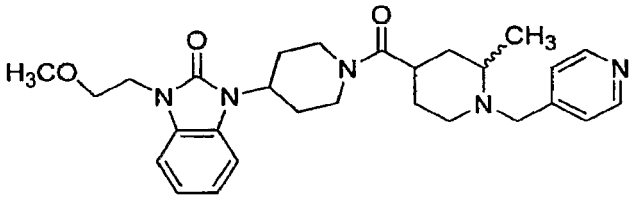
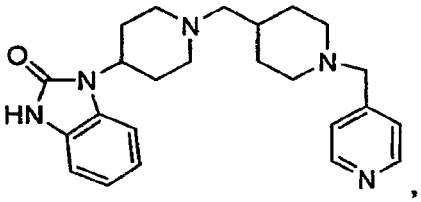
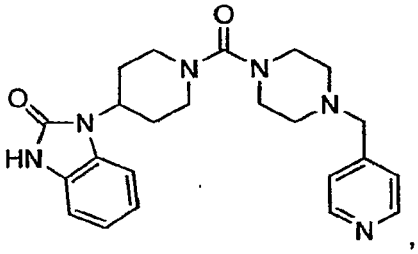
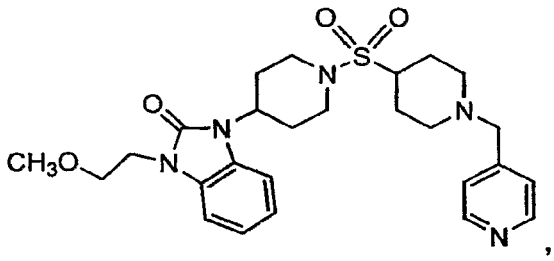
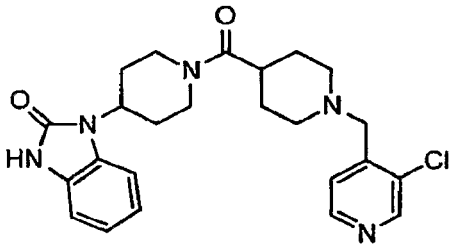
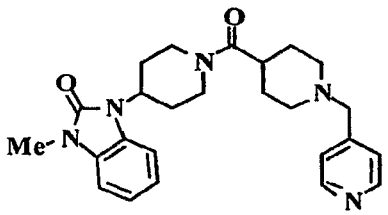
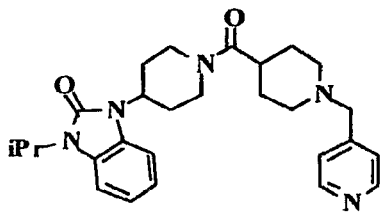
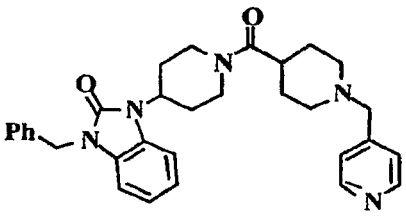
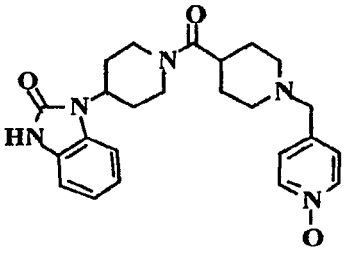



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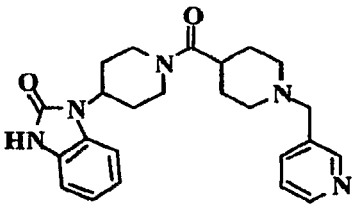
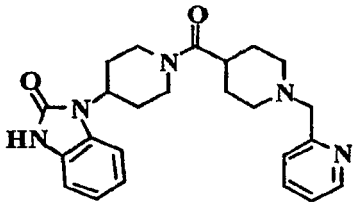
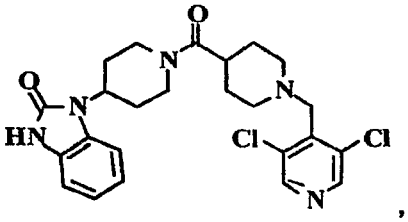
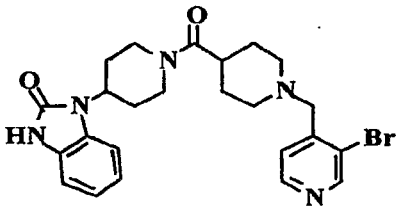
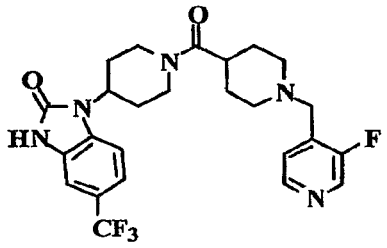
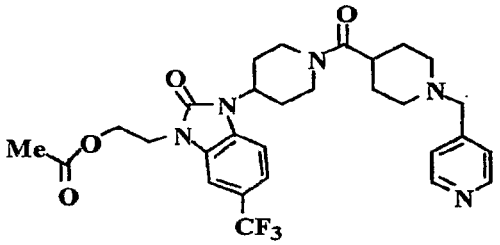
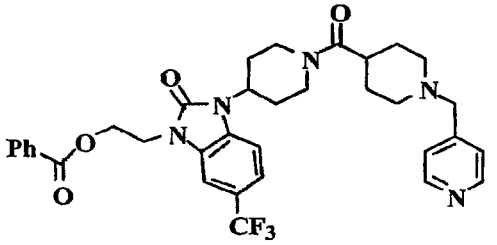
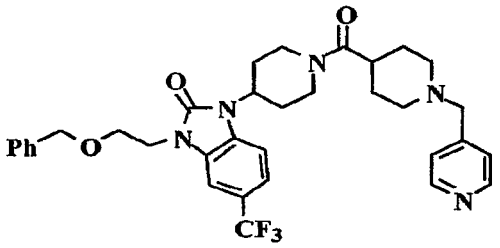
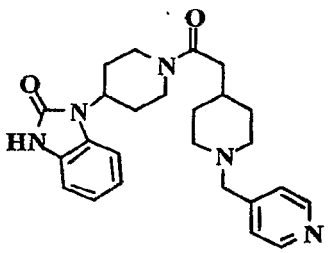
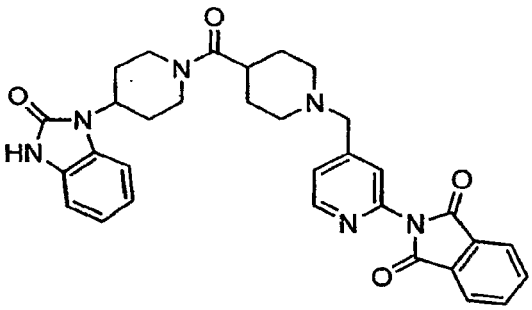
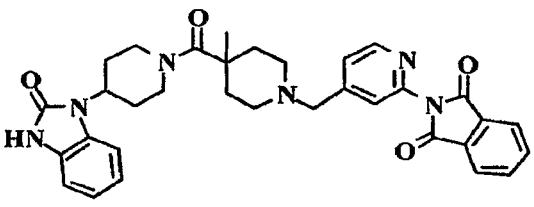
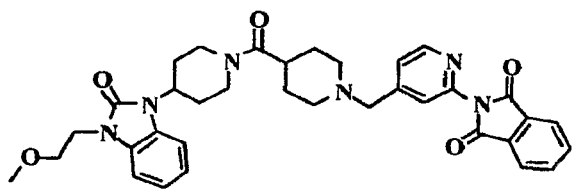
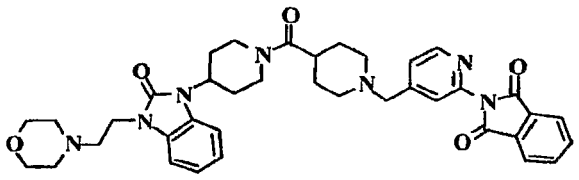

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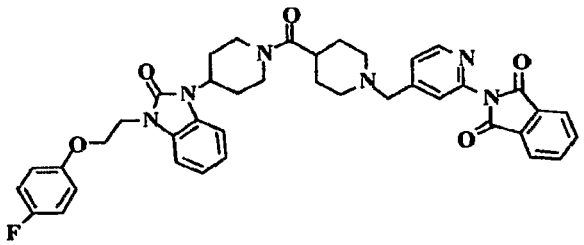
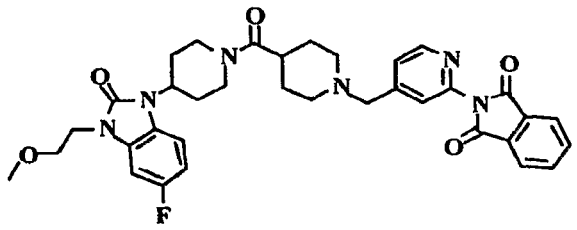
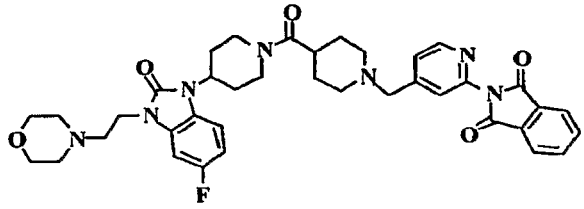
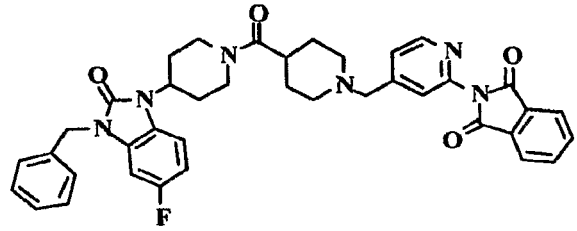
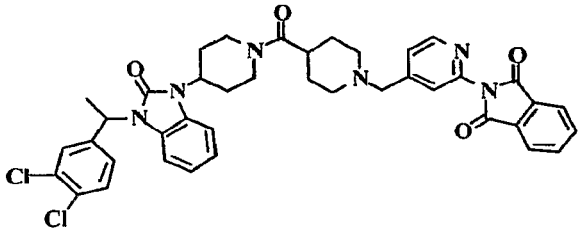
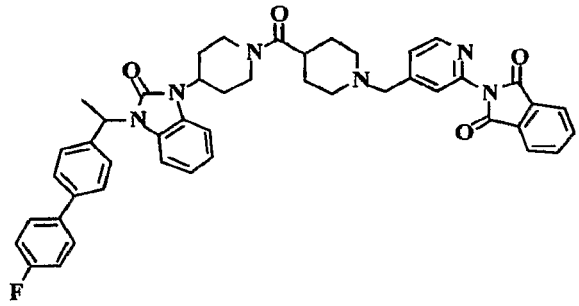
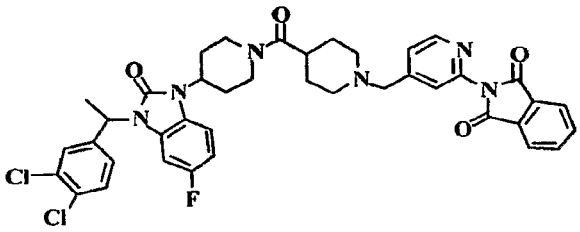
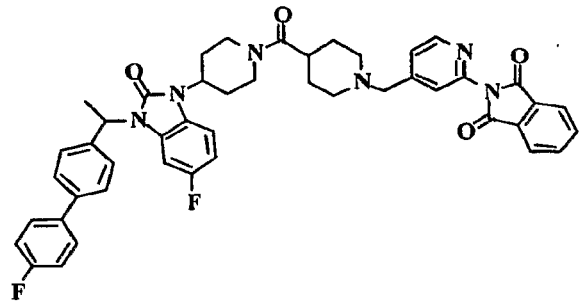
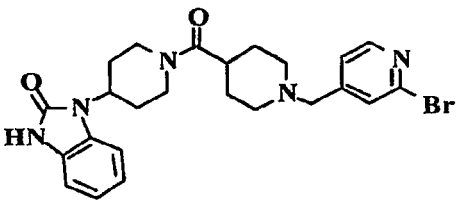
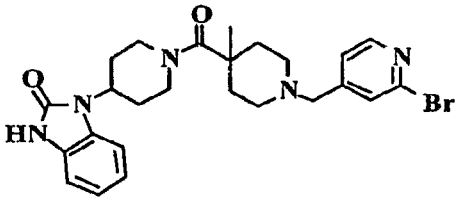
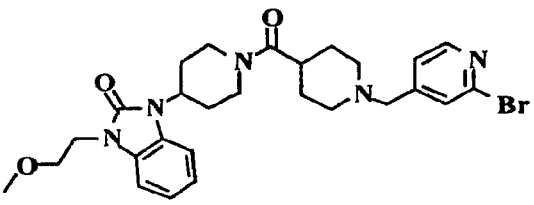
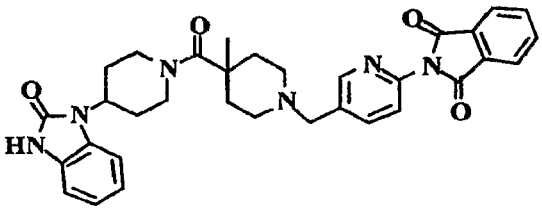
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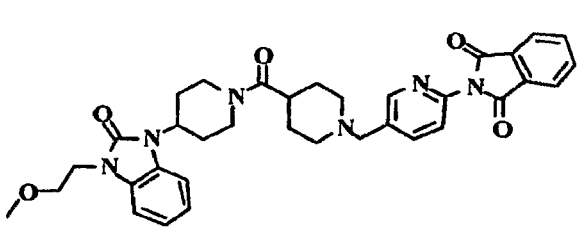

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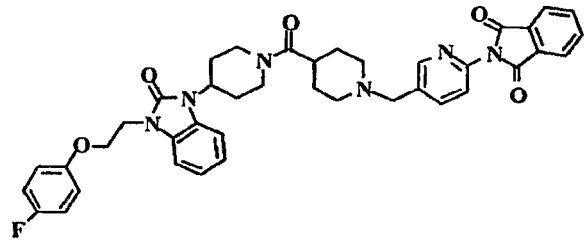
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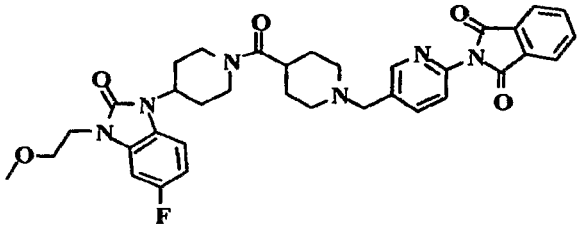

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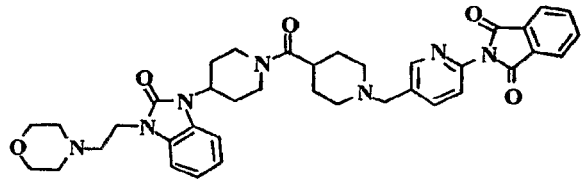
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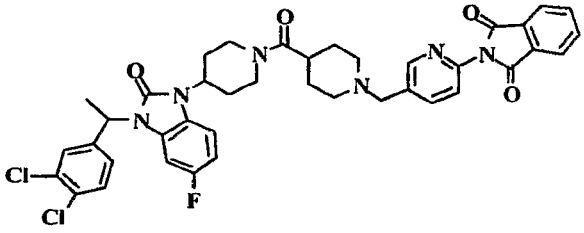

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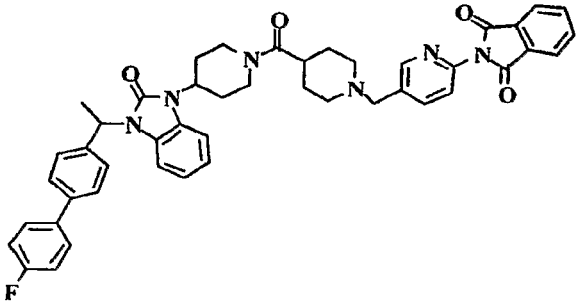


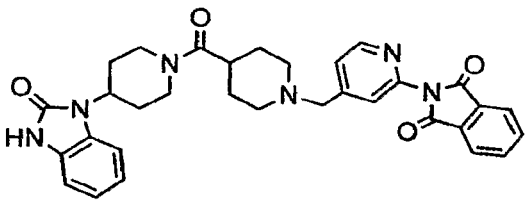


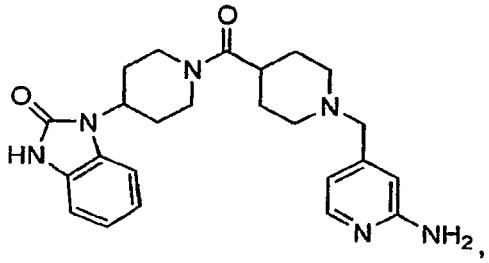


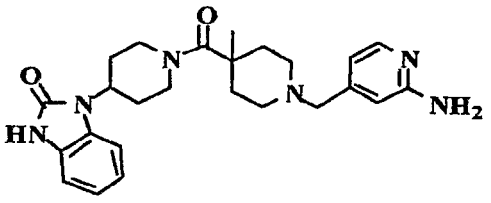


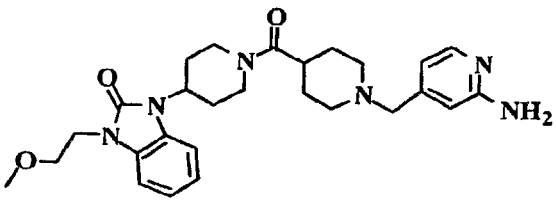


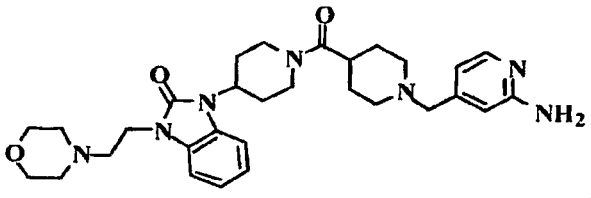


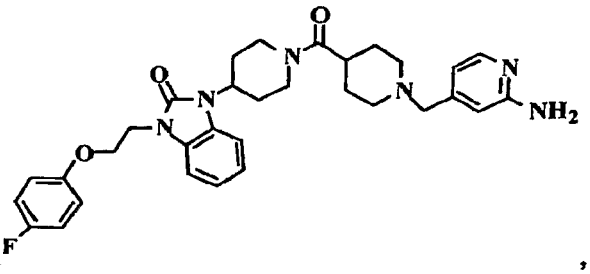


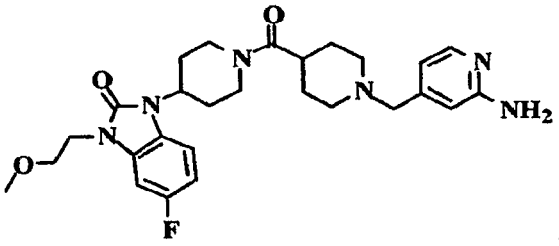
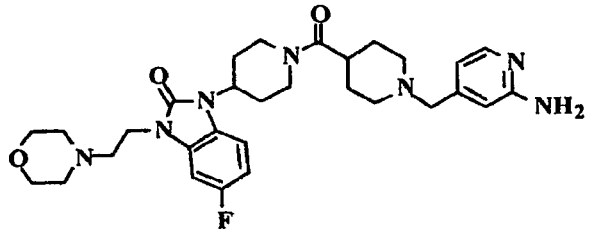
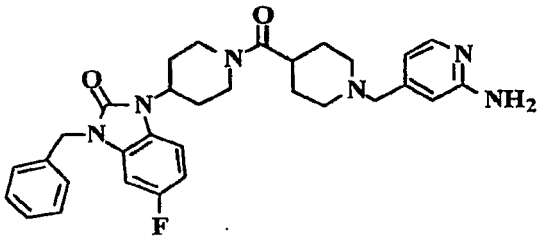
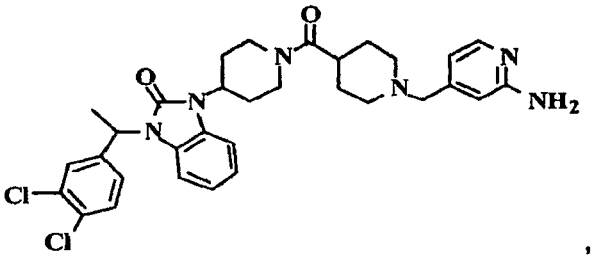
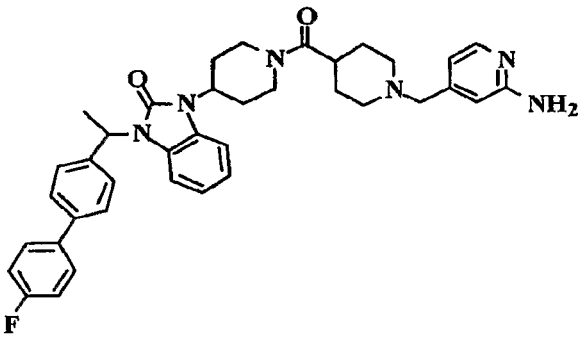
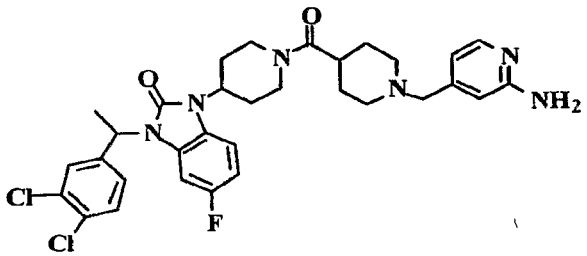
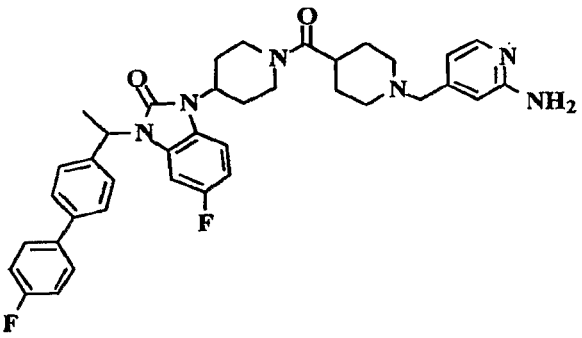
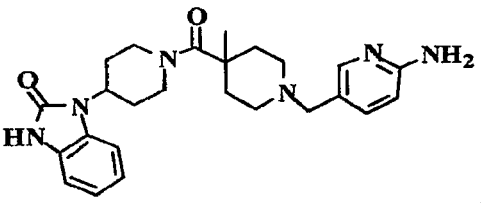
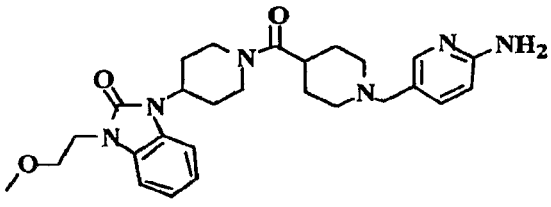
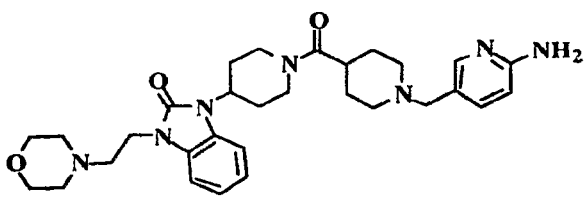




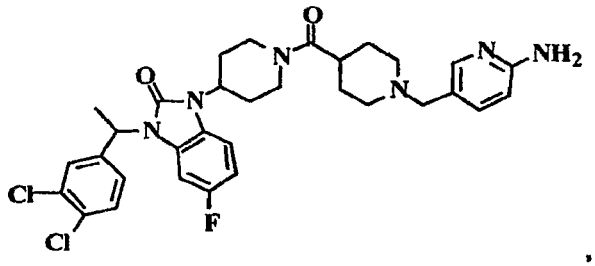


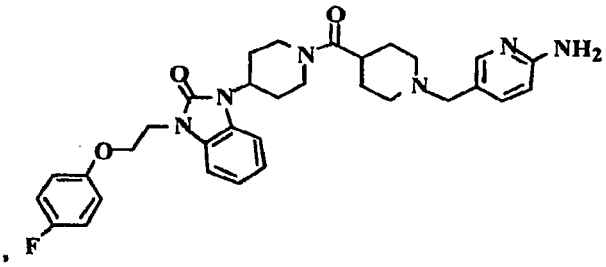


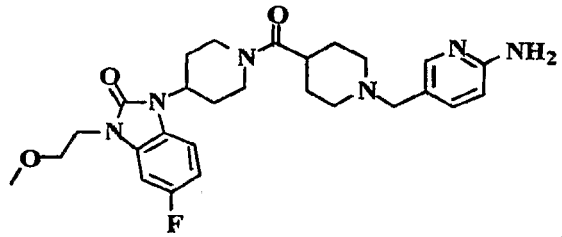


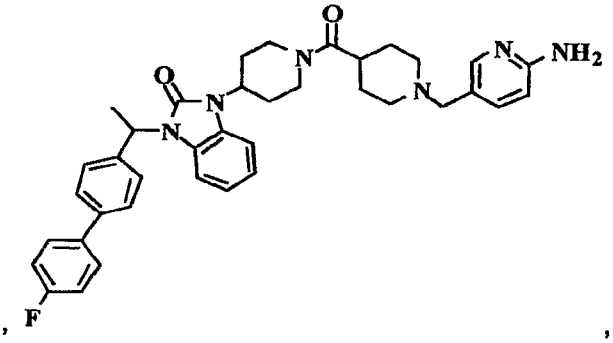

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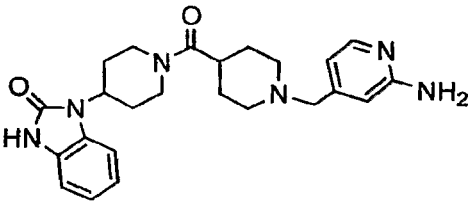
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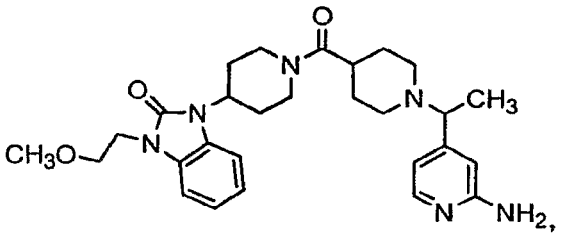


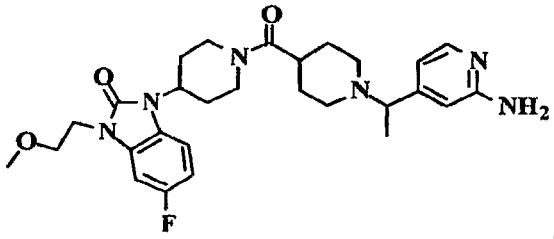


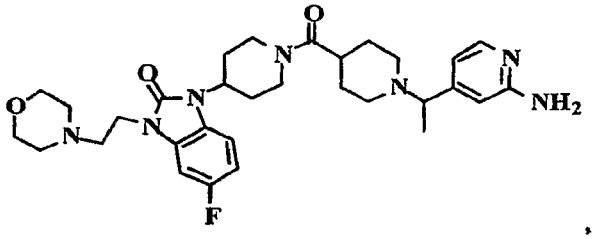


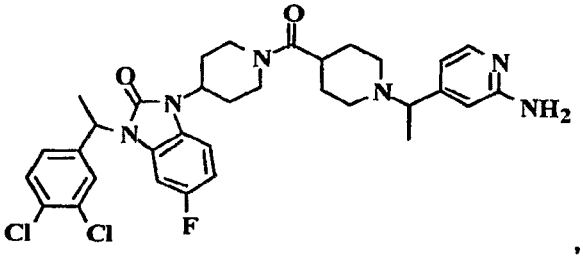


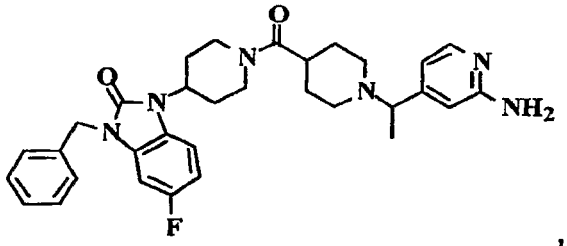


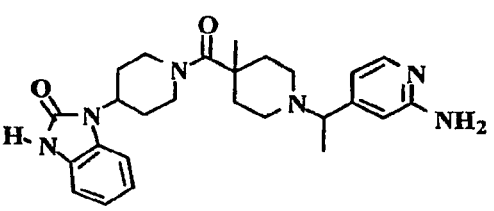


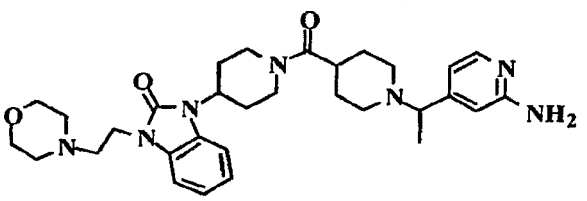


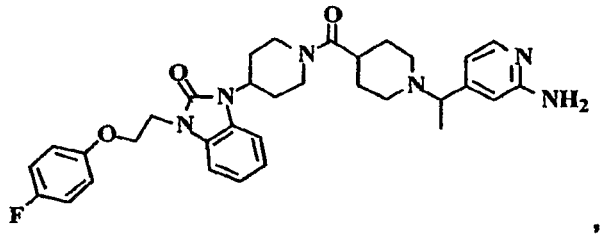
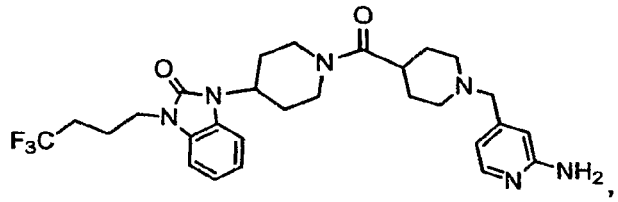
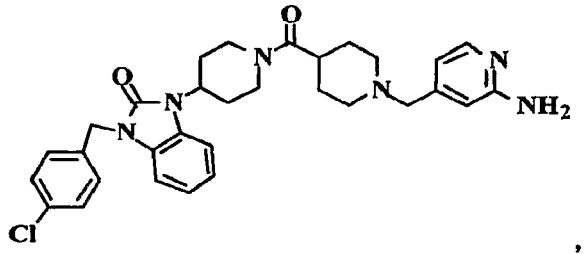
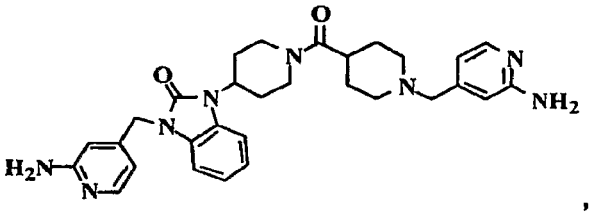
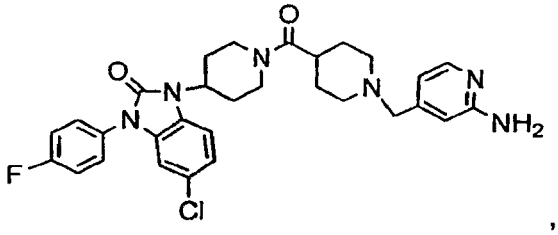
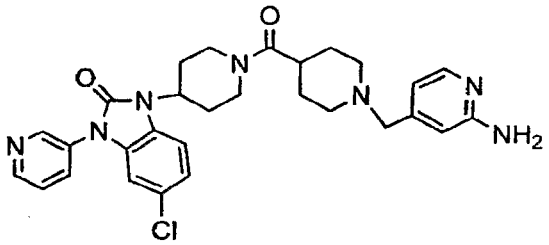
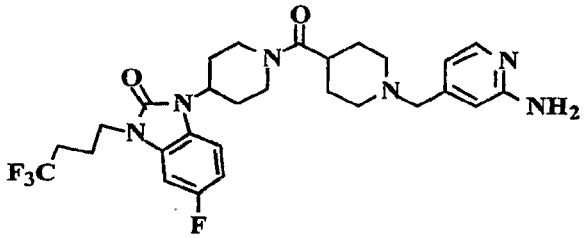
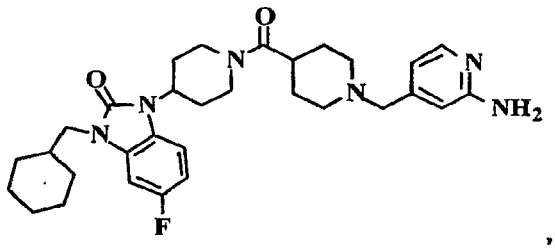
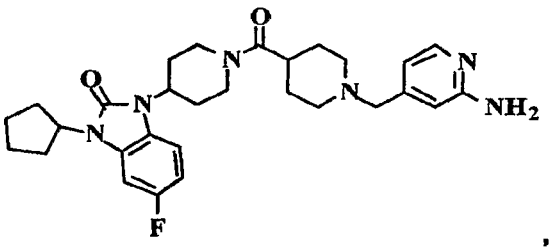
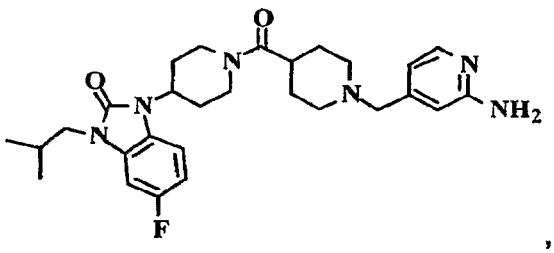




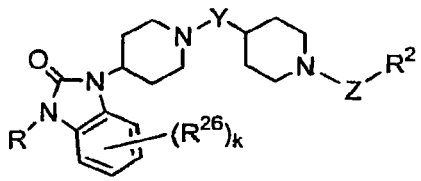






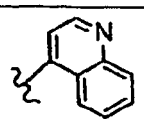
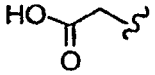
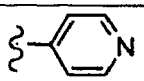
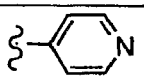
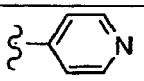
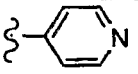
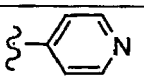
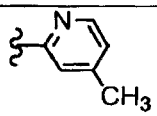
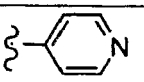
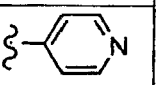
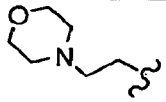
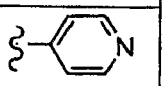
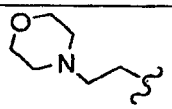
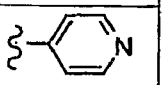
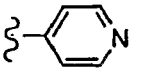
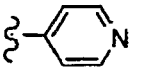
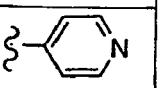
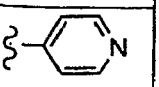
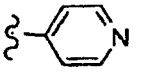











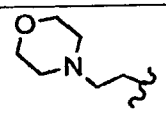
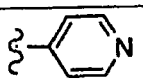
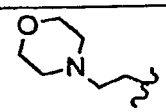
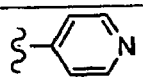
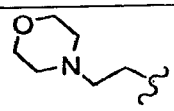
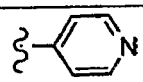
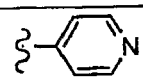
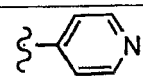
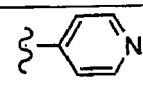
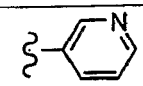
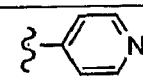
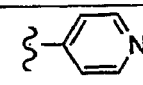
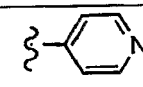
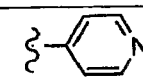
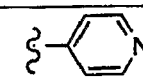
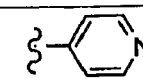
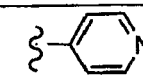
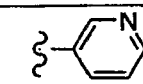
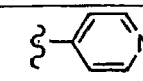
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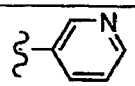
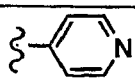
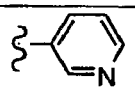
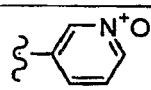
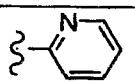
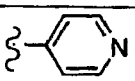
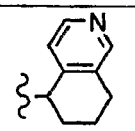
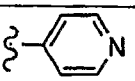
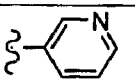
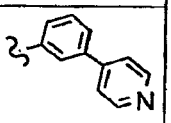
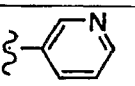
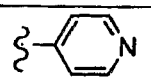
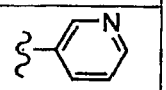
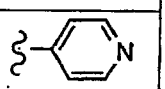
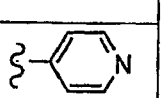


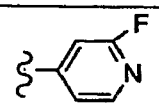
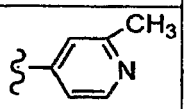
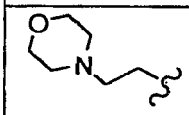
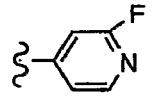
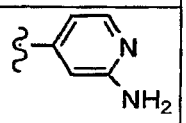
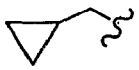
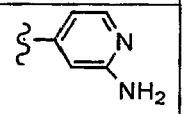
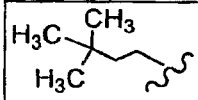
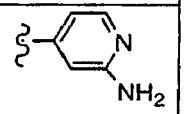
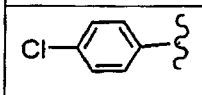
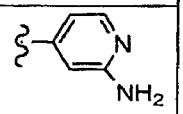
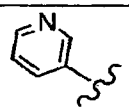
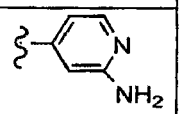
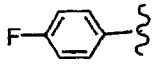
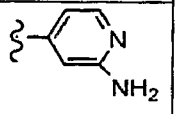
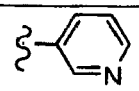
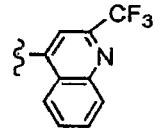
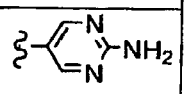
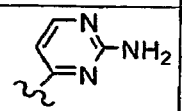
wherein R, $(R^{26})_k$, Y, Z, and R^2 are as defined in the following Table:

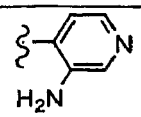
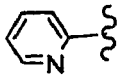
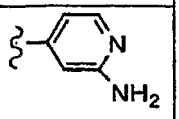
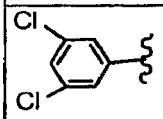
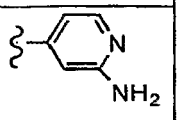
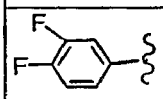
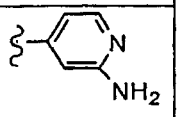
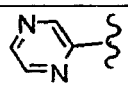
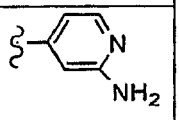
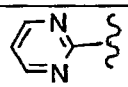
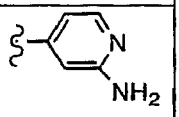
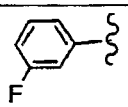
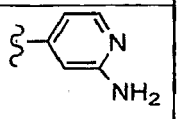
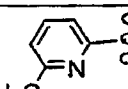
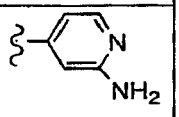
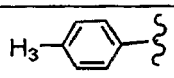
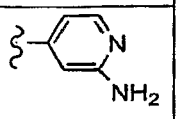
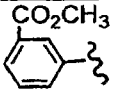
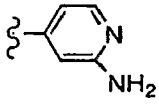
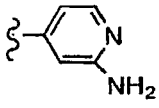
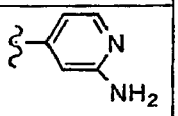
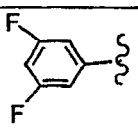
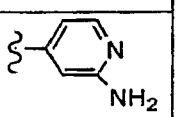
R	$(R^{26})_k$	Y	Z	R^2

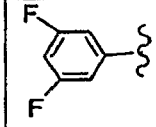
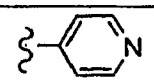
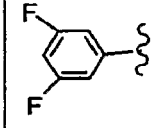
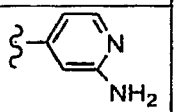
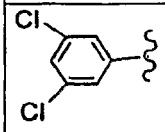
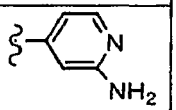
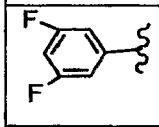
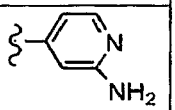
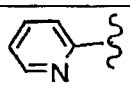
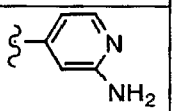
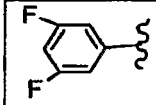
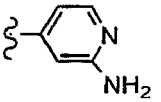
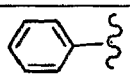
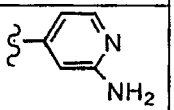
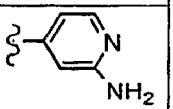
R	$(R^{26})_k$	Y	Z	R^2
H	H	-C(O)-	$-CH_2-$	
	H	-C(O)-	$-CH_2-$	
$CH_3(CH_2)_3-$	H	-C(O)-	$-CH(CH_3)-$	
$CH_3(CH_2)_3-$	H	-C(O)-	$-CH(CH_3)-$	
$CH_3O(CH_2)_2-$	H	-C(O)-	-CH(CN)-	
$CH_3O(CH_2)_2-$	H	-C(O)-	$-C(CH_3)_2-$	
H	H	-C(O)-	bond	
$CH_3O(CH_2)_2-$	5-F	-C(O)-	$-CH_2-$	
$CH_3O(CH_2)_2-$	5-F	-C(O)-	$-CH(CH_3)-$	
	5-F	-C(O)-	$-CH_2-$	
	5-F	-C(O)-	$-CH(CH_3)-$	
H	5-F	-C(O)-	$-CH_2-$	
H	5-F	-C(O)-	$-CH(CH_3)-$	
H	5-Cl	-C(O)-	$-CH_2-$	
CH_3-	5-F	-C(O)-	$-CH_2-$	
$C_6H_5-CH_2-$	5-Cl	-C(O)-	$-CH_2-$	

R	$(R^{26})_k$	Y	Z	R^2
	5-Cl	-C(O)-	$-CH_2-$	
	5-Cl	-C(O)-	$-CH(CH_3)-$	
	5-Cl	-C(O)-	$-CH(CH_3)-$	
H	$5-CF_3-$	-C(O)-	$-CH_2-$	
H	H	$C(O)CH_2-$	$-CH_2-$	
$CH_3O(CH_2)_2-$	H	$C(O)CH_2-$	bond	
$CH_3O(CH_2)_2-$	H	$C(O)CH_2-$	bond	
H	$5-CF_3$	-C(O)NH-	$-CH_2-$	
H	$5-CF_3$	$-SO_2-$	$-CH_2-$	
H	$5-CF_3$	C(=N-CN)-NH-	$-CH_2-$	
H	H	-C(O)-	bond	
H	H	-C(O)-	-C(O)-	
H	H	-C(O)-	$-(CH_2)_2-$	
H	H	-C(O)-	$-C(O)CH_2-$	
H	$5-CF_3$	-C(O)-	bond	
$CH_3O(CH_2)_2-$	H	-C(O)-	-C(=NH)-	

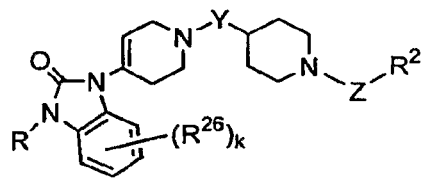
R	$(R^{26})_k$	Y	Z	R^2
$CH_3O(CH_2)_2$-	H	-C(O)-	-C(O)-	
H	5-CF_3	-C(O)-	-C(O)-	
$CH_3O(CH_2)_2$-	H	-C(O)-	-C(O)NH-	
$CH_3O(CH_2)_2$-	H	-C(O)-	-C(O)-	
H	5-CF_3	-C(O)-	-NH-C(O)-	
H	5-CF_3	-C(O)-	-NH-C(O)-	
$CH_3O(CH_2)_2$-	H	-C(O)-	bond	
$CH_3O(CH_2)_2$-	H	-C(O)-	-CH_2-C(=O)-NH-	
$CH_3O(CH_2)_2$-	H	-C(O)-	-C(=O)-NH-CH_2-	
$CH_3O(CH_2)_2$-	H	-C(O)-	bond	
$CH_3O(CH_2)_2$-	H	-C(O)-	N(CN)=C-NH-CH_2-	
$CH_3O(CH_2)_2$-	5-CF_3	-C(O)-	-$(CH_2)_3$-	
$CH_3O(CH_2)_2$-	5-CF_3	-C(O)-	-$(CH_2)_3$-	
$CH_3O(CH_2)_2$-	5-CF_3	-C(O)-	-C(O)-$(CH_2)_2$-	
$CH_3O(CH_2)_2$-	5-CF_3	-C(O)-	-$(CH_2)_4$-	

R	$(R^{26})_k$	Y	Z	R^2
$CH_3O(CH_2)_2$-	H	-C(O)-	$-CH_2$-	
H	5-CF_3	-C(O)-	$-(CH_2)_4$-	
	H	-C(O)-	$-CH_2$-	
H	H	-C(O)-	$-CH(CH_3)$-	
	5-F	-C(O)-	$-CH_2$-	
	5-F	-C(O)-	$-CH_2$-	
	H	-C(O)-	$-CH_2$-	
	5-Cl	-C(O)-	$-CH_2$-	
	5-Cl	-C(O)-	$-CH_2$-	
H	5-CF_3-	-C(O)-	-NH-C(O)-	
$CH_3O(CH_2)_2$-	5-CF_3-	-C(O)-	bond	
$CH_3O(CH_2)_2$-	H	-C(O)-	$-CH_2$-	
$CH_3O(CH_2)_2$-	H	-C(O)-	$-CH_2$-	

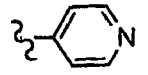
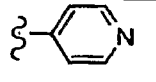
R	$(R^{26})_k$	Y	Z	R^2
$CH_3O(CH_2)_2$-	H	-C(O)-	$-CH_2$-	
	5-F	-C(O)-	$-CH_2$-	
	5-F	-C(O)-	$-CH_2$-	
	5-F	-C(O)-	$-CH_2$-	
	5-F	-C(O)-	$-CH_2$-	
	5-F	-C(O)-	$-CH_2$-	
	5-F	-C(O)-	$-CH_2$-	
	5-F	-C(O)-	$-CH_2$-	
	5-F	-C(O)-	$-CH_2$-	
	5-F	-C(O)-	$-CH_2$-	
	5-F	-C(O)-	$-CH_2$-	
H	5-F	-C(O)-	$-CH_2$-	
CF_3CH_2-	5-F	-C(O)-	$-CH_2$-	
	5-F	-C(O)-	$-CH_2$-	

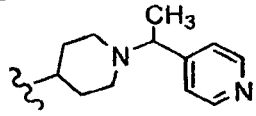
R	$(R^{26})_k$	Y	Z	R^2
	5-Cl	-C(O)-	$-CH_2-$	
	5-Cl	-C(O)-	$-CH_2-$	
	5-Cl	-C(O)-	$-CH_2-$	
	5-Cl	-C(O)-	$-CH(CH_3)-$	
	5-CF_3-	-C(O)-	$-CH_2-$	
	5-CF_3-	-C(O)-	$-CH_2-$	
	5-CF_3-	-C(O)-	$-CH_2-$	
H	5-CF_3-	-C(O)-	$-CH_2-$	

compounds of the following general formula:

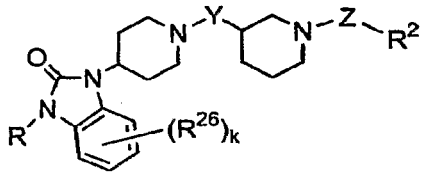


wherein R, $(R^{26})_k$, Y, Z, and R^2 are as defined in the following Table:

R	$(R^{26})_k$	Y	Z	R^2
H	H	-C(O)-	$-CH_2-$	
$N(CH_3)_2$-$(CH_2)_2$-	H	-C(O)-	$-CH_2-$	

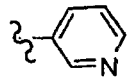
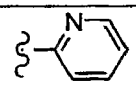
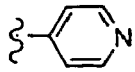
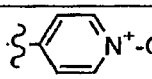
R	$(R^{26})_k$	Y	Z	R^2
H	H	-C(O)-	-C(O)-	

compounds of the following general formula:

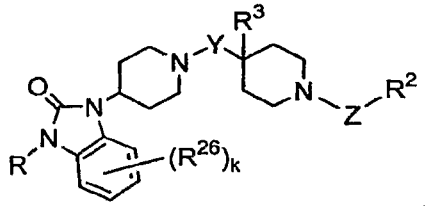


,

wherein R, $(R^{26})_k$, Y, Z, and R^2 are as defined in the following Table:

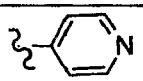
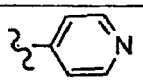
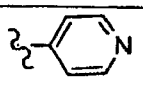
R	$(R^{26})_k$	Y	Z	R^2
H	5-CF_3-	-C(O)-	-CH_2-	
H	5-CF_3-	-C(O)-	-CH_2-	
H	5-CF_3-	-C(O)-	-C(O)-	
H	5-CF_3-	-C(O)-	-CH_2-	

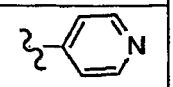
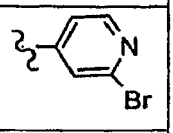
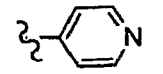
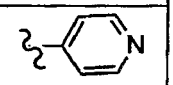
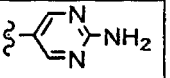
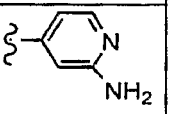
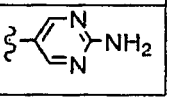
compounds of the following general formula:



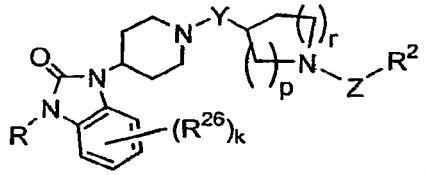
,

wherein R, $(R^{26})_k$, Y, Z, R^3, and R^2 are as defined in the following Table:

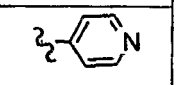
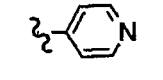
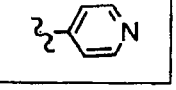
R	$(R^{26})_k$	Y	R^3	Z	R^2
H	H	-C(O)-	-CH_3	-$CH(CH_3)$-	
H	5-CF_3-	-C(O)-	-CH_3	-CH_2-	
H	5-CF_3-	-C(O)-	-OH	-CH_2-	

R	$(R^{26})_k$	Y	R^3	Z	R^2
$CH_3O(CH_2)_2$-	H	-C(O)-	F	-CH(CH_3)-	
H	H	-C(O)-	-CH_3	-CH_2-	
$CH_3O(CH_2)_2$-	5-Cl	-C(O)-	F	-CH(CH_3)-	
$CH_3C(O)(CH_2)_2$-	5-CF_3-	-C(O)-	-CH_3	-CH_2-	
$CH_3O(CH_2)_2$-	H	-C(O)-	F	-CH_2-	
$CH_3O(CH_2)_2$-	H	-C(O)-	F	-CH_2-	
H	5-F	-C(O)-	F	-CH_2-	

compounds of the following general formula:

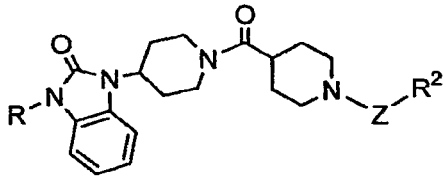


wherein R, $(R^{26})_k$, Y, r, p, Z, and R^2 are defined as in the following Table:

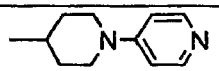
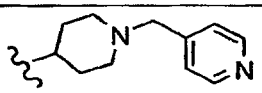
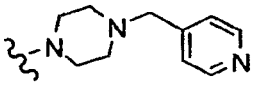
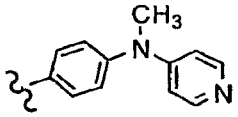
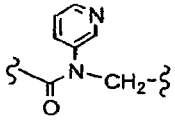
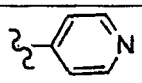
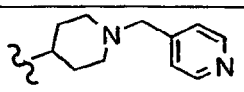
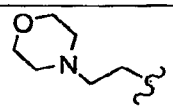
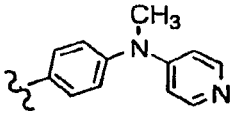
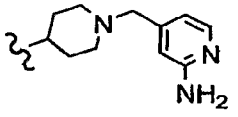
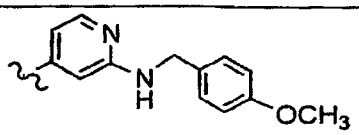
R	$(R^{26})_k$	Y	r	p	Z	R^2
$CH_3O(CH_2)_2$-	H	-C(O)-	0	1	-CH_2-	
$CH_3O(CH_2)_2$-	H	-C(O)-	1	1	-CH_2-	
$CH_3O(CH_2)_2$-	H	-C(O)-	1	3	-CH_2-	

5

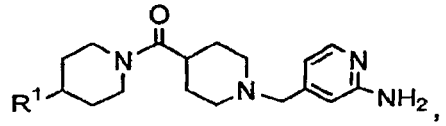
compounds of the following general formula:



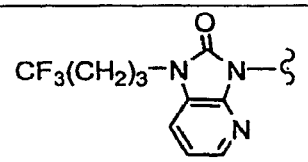
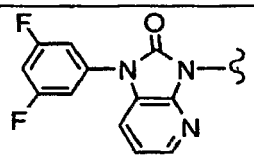
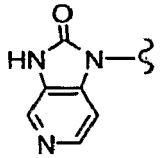
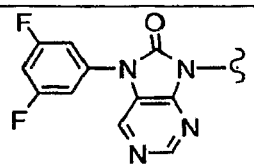
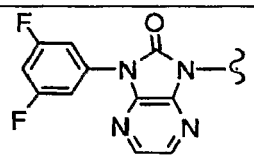
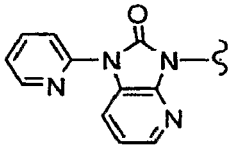
wherein R, Z, and R^2 are defined as in the following Table:

R	Z	R^2
$CH_3O(CH_2)_2$-	-C(O)-	
$CH_3O(CH_2)_2$-	-C(O)-	
$CH_3O(CH_2)_2$-	-C(O)-	
$CH_3O(CH_2)_2$-	-C(O)-	
$CH_3O(CH_2)_2$-		
$CH_3O(CH_2)_2$-	-C(O)-NH-	
	-C(O)-	
$CH_3O(CH_2)_2$-	-C(O)-	
H	$-CH_2-$	

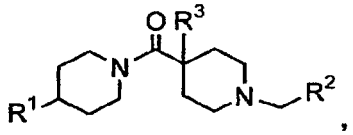
compounds of the following general formula:



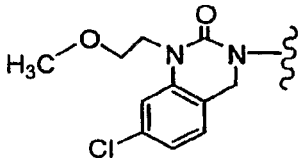
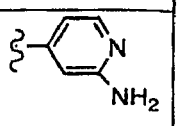
wherein R^1 is defined as shown in the following Table:

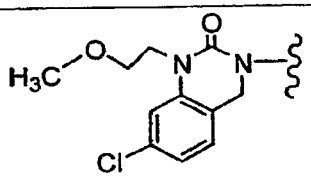
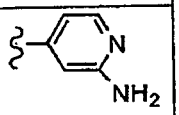
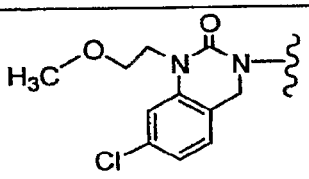
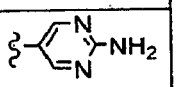
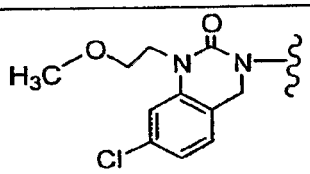
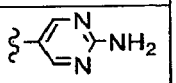
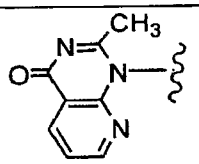
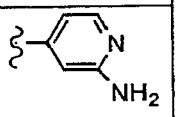
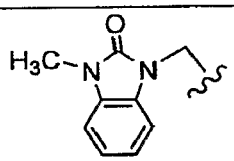
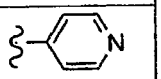
R^1







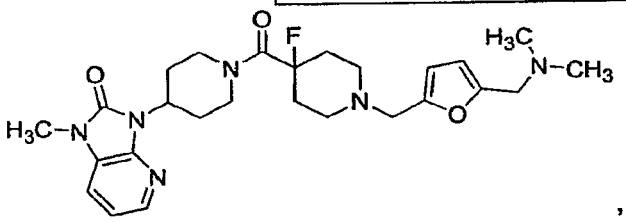
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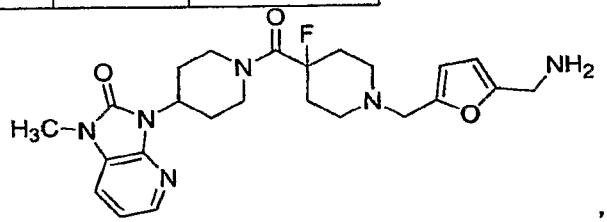


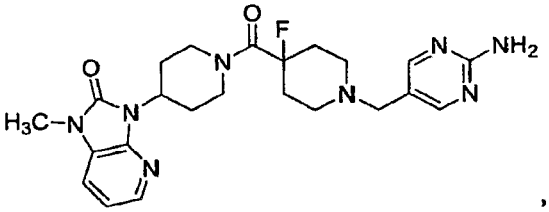
wherein R^1, R^3, and R^2 are defined as shown in the following Table:

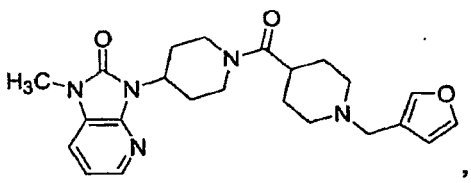
R^1	R^3	R^2
	F	

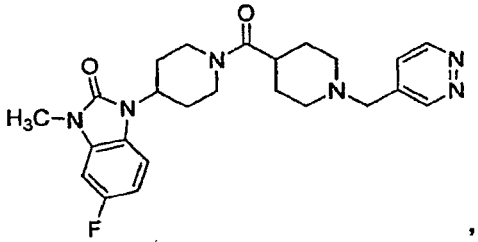
R^1	R^3	R^2
	H	
	H	
	F	
	H	
	H	

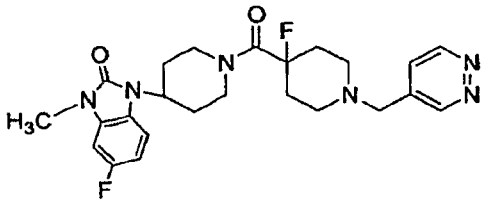


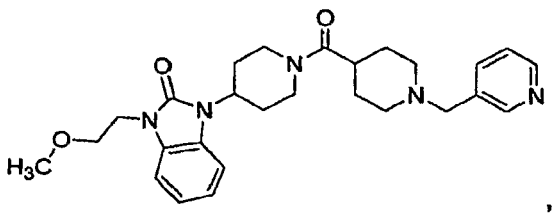


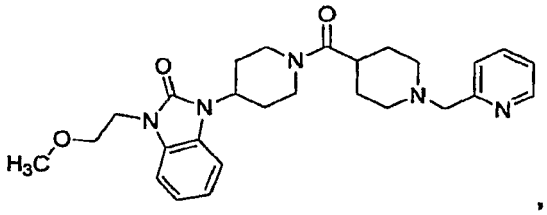


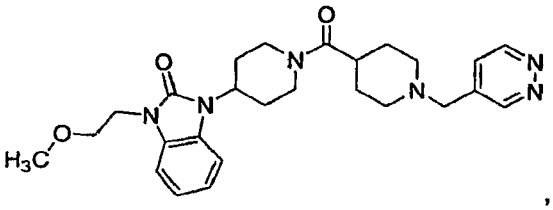


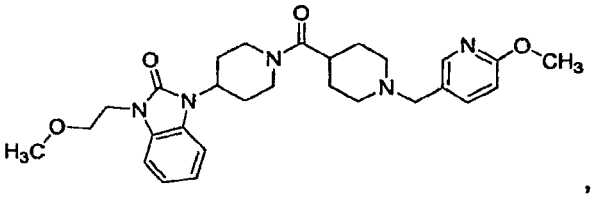


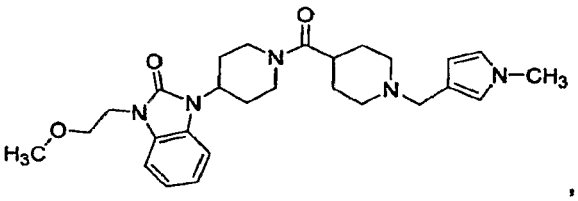


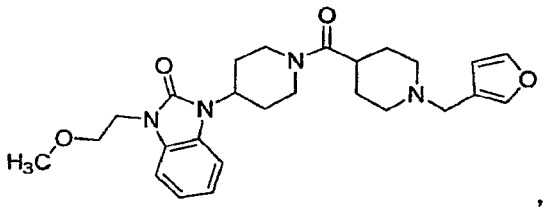


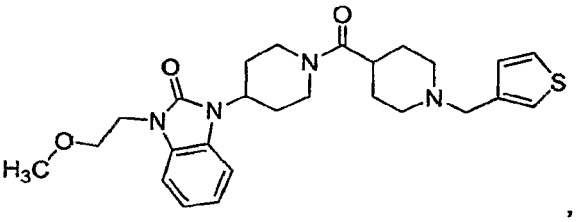


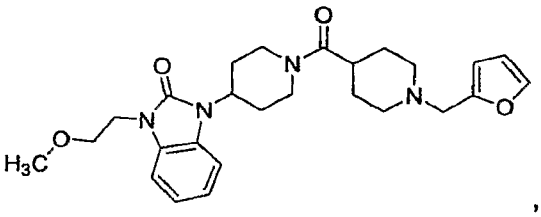


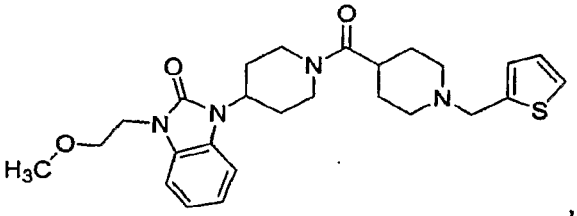


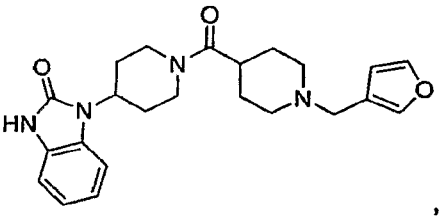




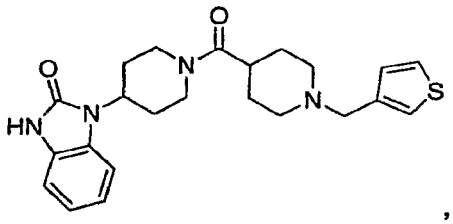


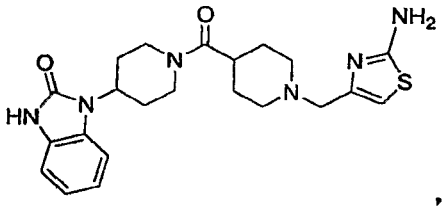


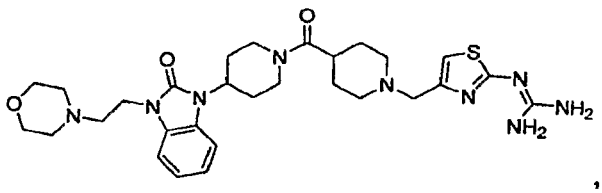


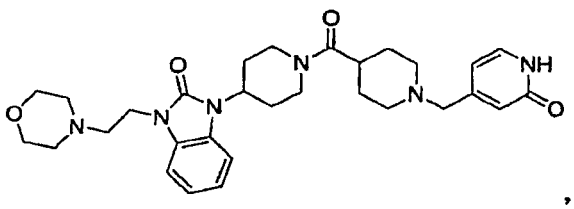


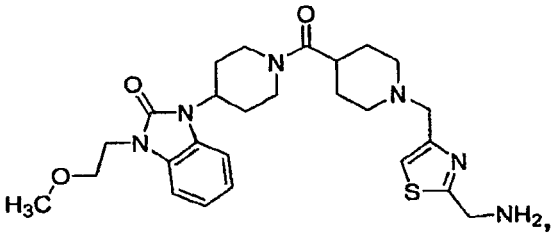
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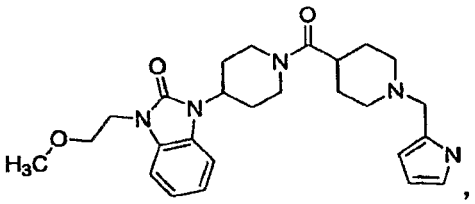


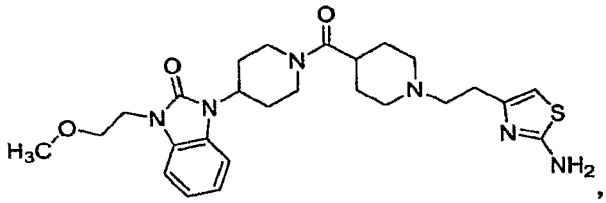


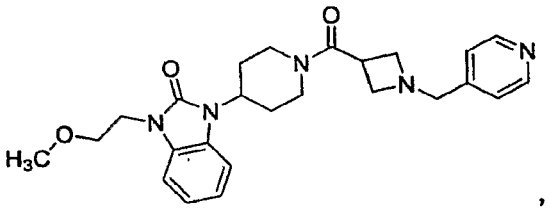


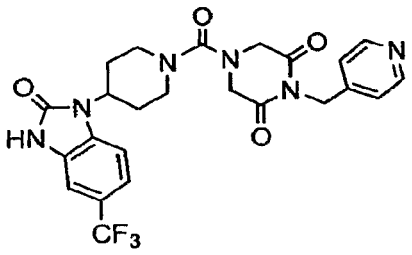


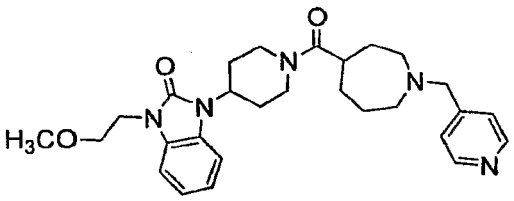


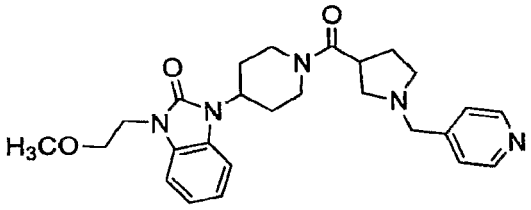




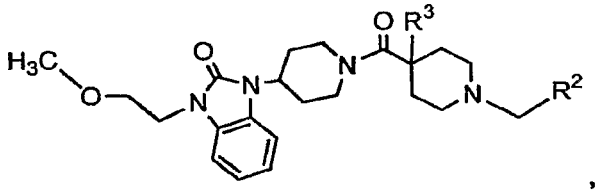




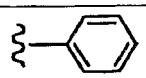
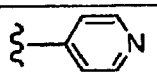


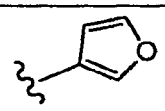
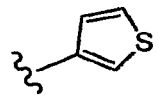
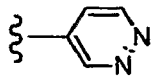
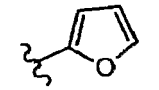
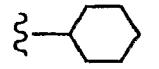
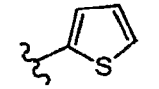
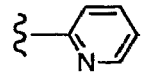


compounds of the following general formula:

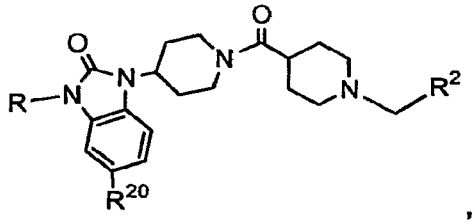


wherein R^3 and R^2 are defined as shown in the following Table:

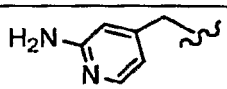
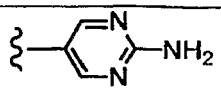
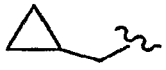
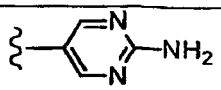
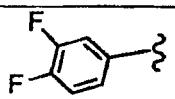
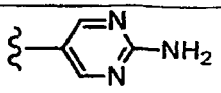
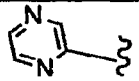
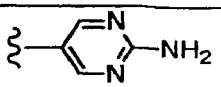
R^3	R^2
H	
F	
F	

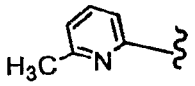
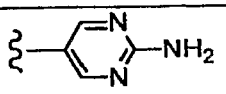
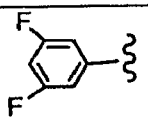
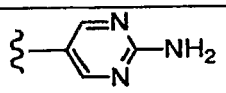
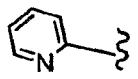
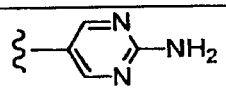
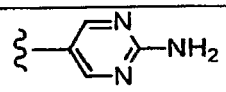
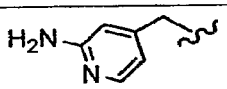
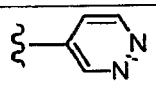
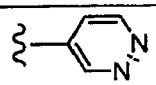
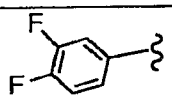
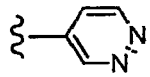
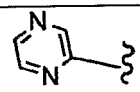
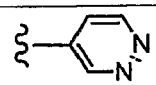
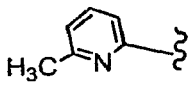
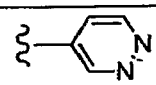
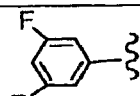
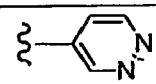
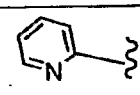
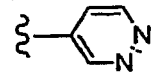
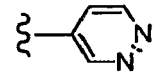
R^3	R^2
F	
F	
F	
F	
F	
F	
F	

compounds of the following general formula:

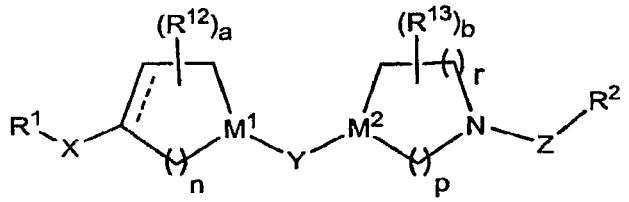


wherein R, R^{20}, and R^2 are defined as shown in the following Table:

R	R^{20}	R^2
	H	
	F	
	F	
	F	

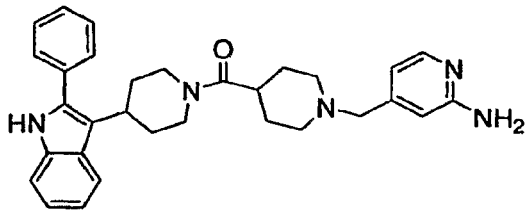
R	R^{20}	R^2
	F	
	F	
	-CF_3	
$CF_3(CH_2)_3$-	F	
	H	
	F	
	F	
	F	
	F	
	F	
	-CF_3	
$CF_3(CH_2)_3$-	F	

In one embodiment, the H_3 antagonists/inverse agonists of the present invention can have a structure according to Formula (V):



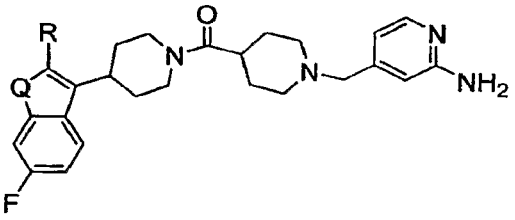
(V)

as described in U.S. 2004/0019099, which is herein incorporated by reference in its entirety. Non-limiting examples of compounds of Formula (V) include:

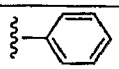


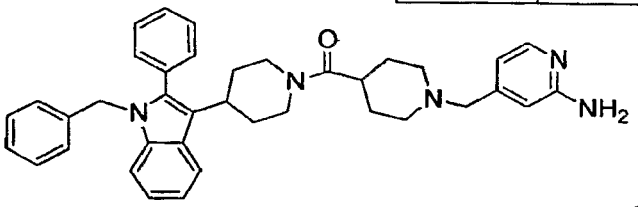
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compounds of the following general formula:

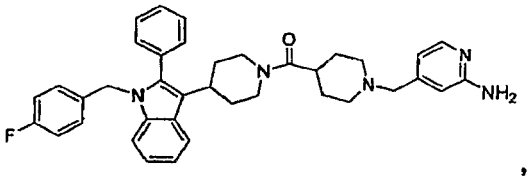


wherein Q and R are as defined in the following Table:

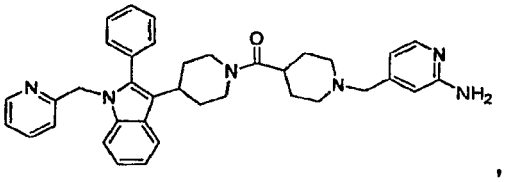
Q	R
O	
O	-CH_3
S	-CH_3
S	-C(O)-O-CH_2CH_3
O	H



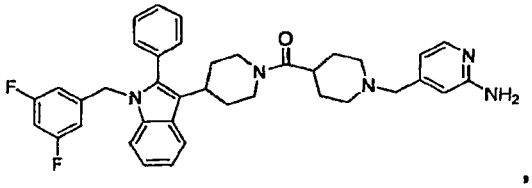
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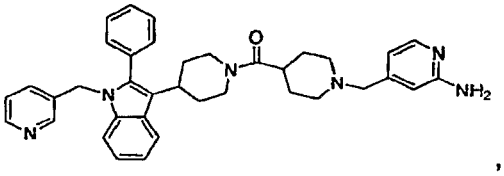
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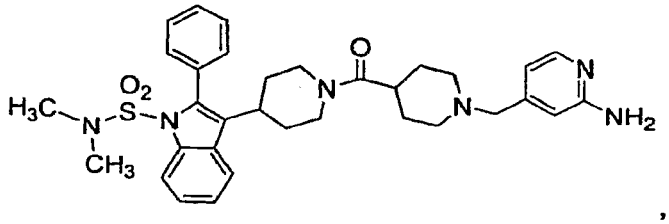
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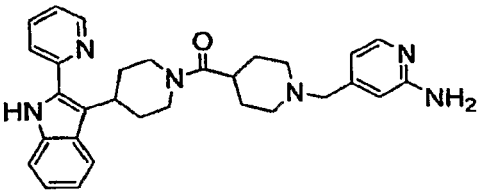
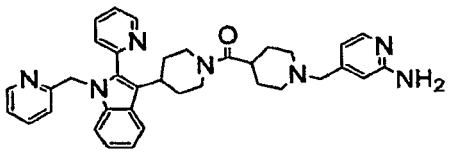
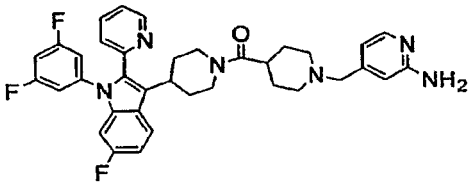
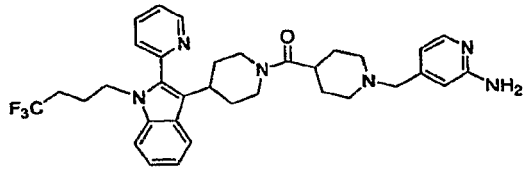
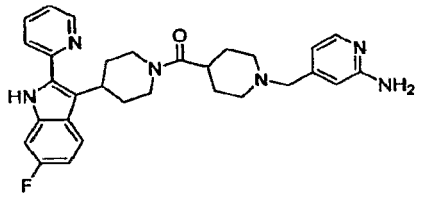
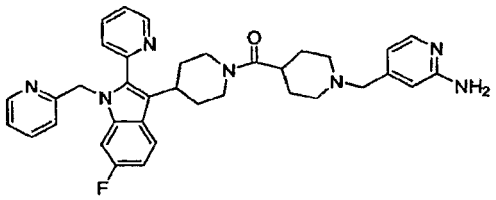
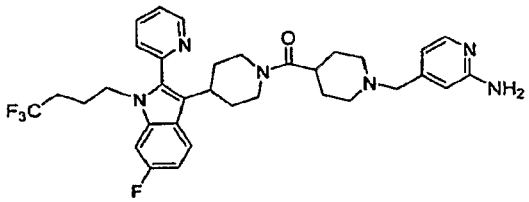
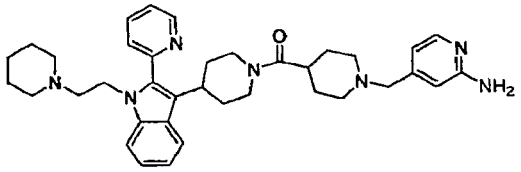
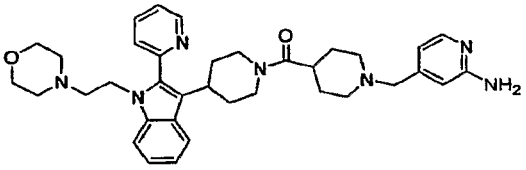
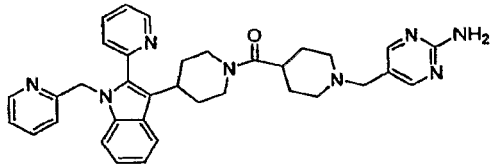
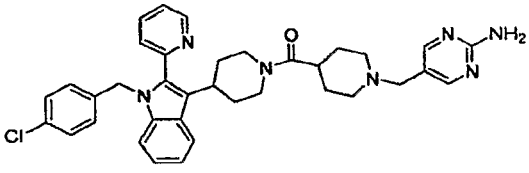
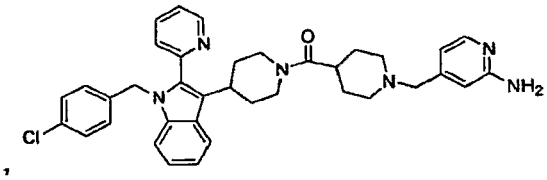
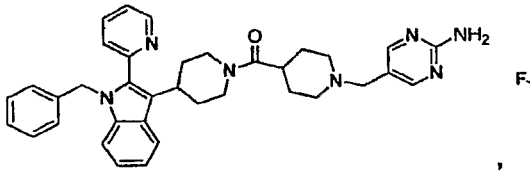
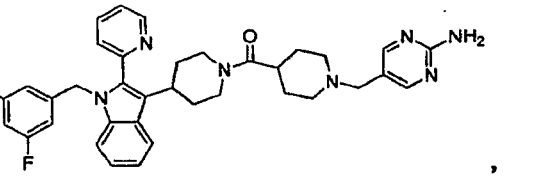
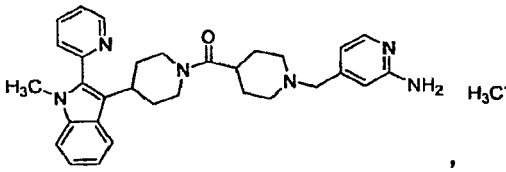
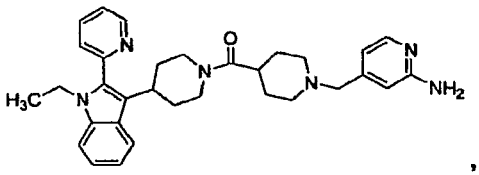
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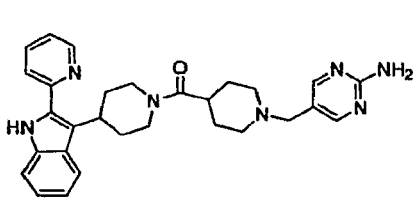
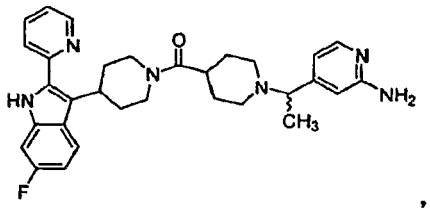
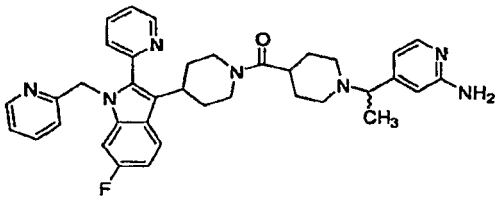
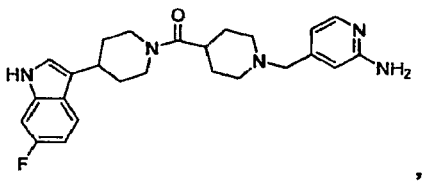
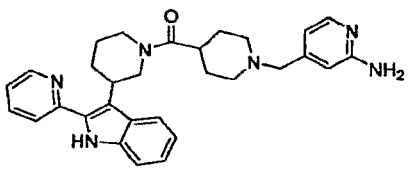
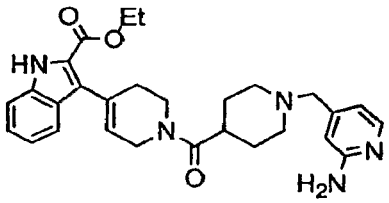
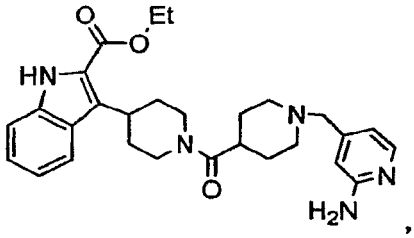
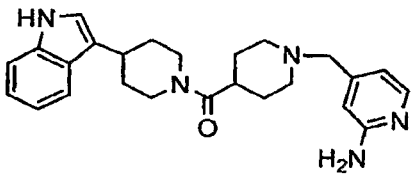
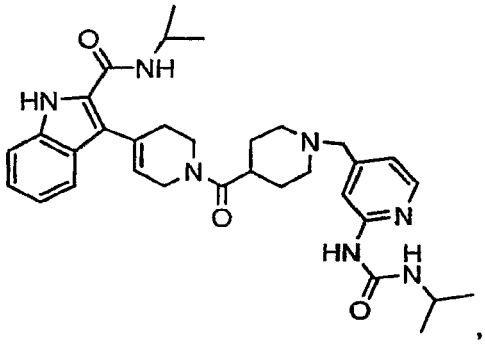
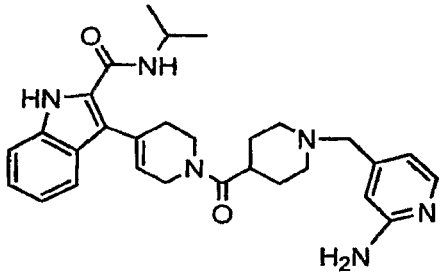
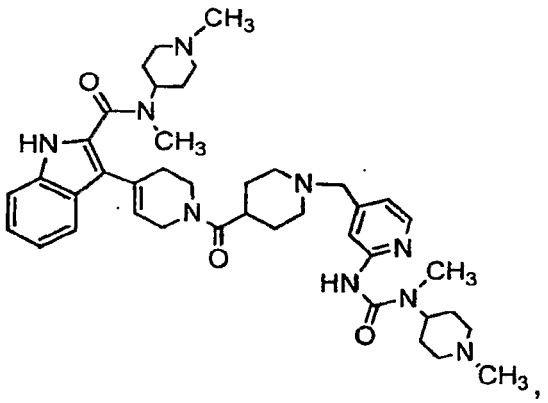


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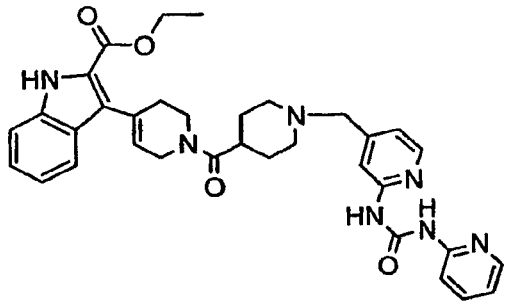
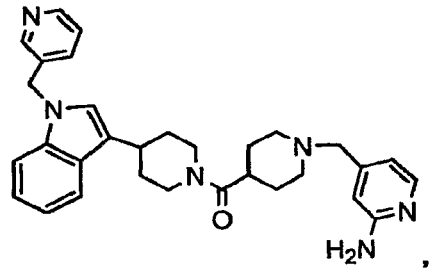
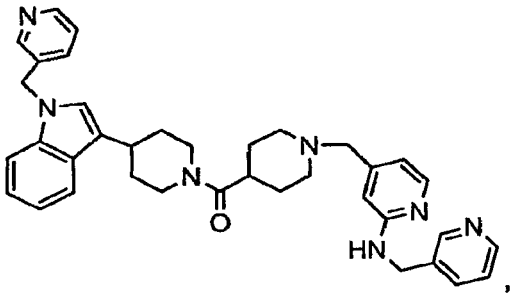
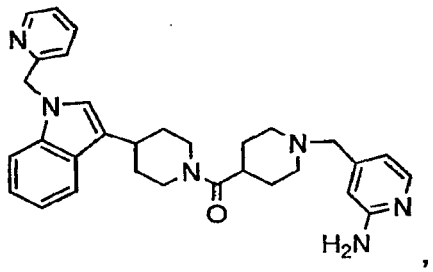
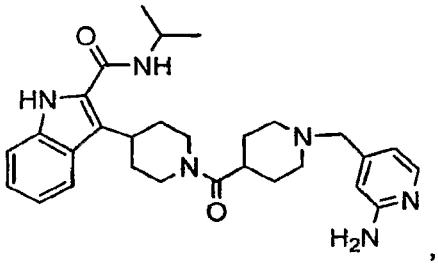
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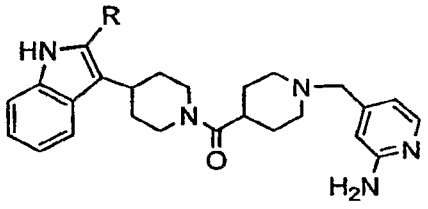

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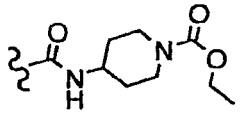
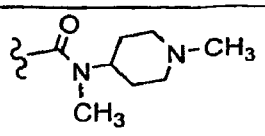
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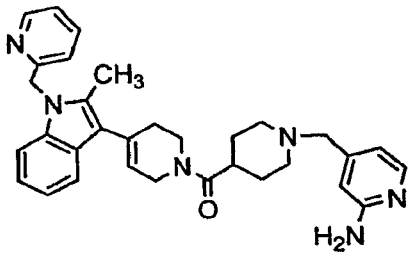

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compounds of the following general formula:

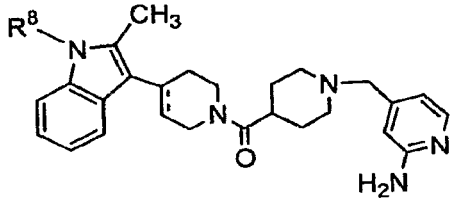


wherein R is as defined in the following Table:

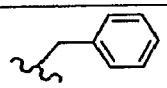
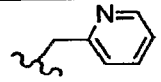
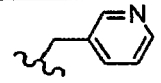
R
-C(O)-NH-CH_3
-C(O)-NH-CH_2CH_3



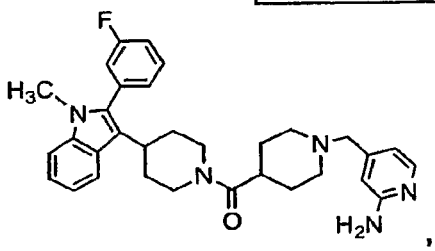


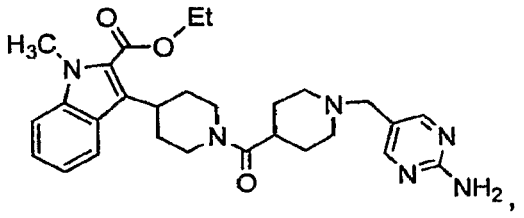
compounds of the following general formula:

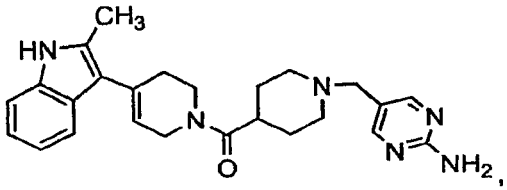


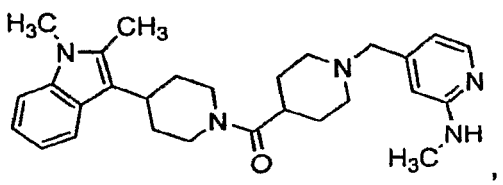
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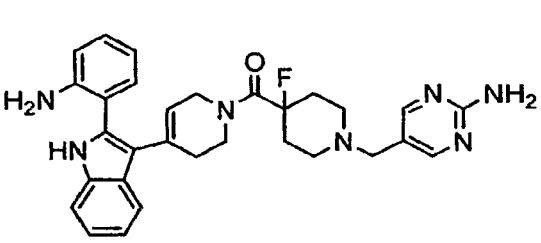
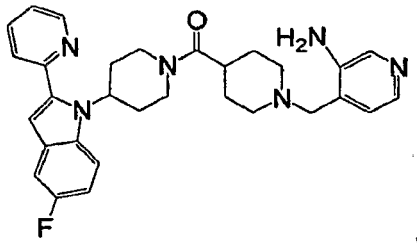
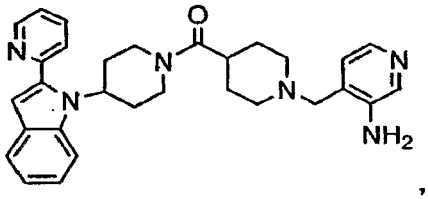
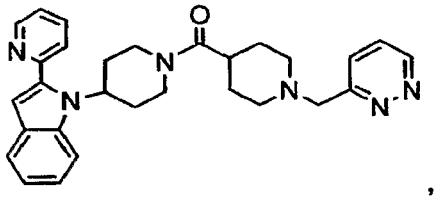
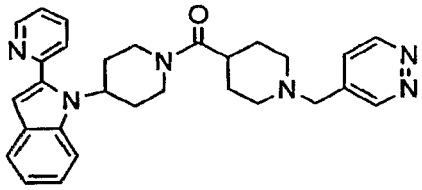
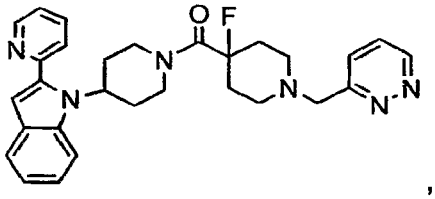
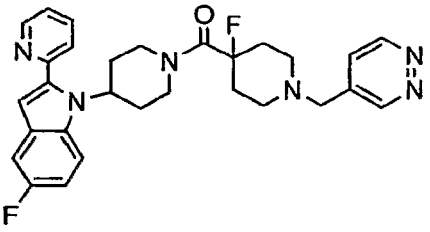
R^8	Optional Double Bond
	present
CF_3-$(CH_2)_3$-	present
CH_3-CH_2-	present
	absent
H	absent
	absent



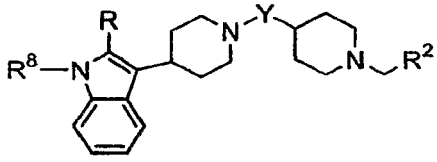




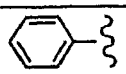
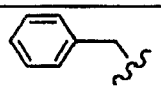
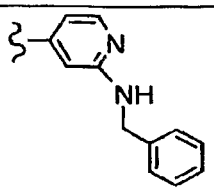
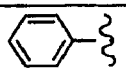
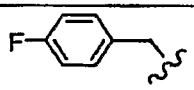
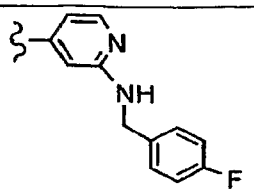


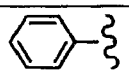
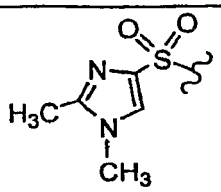
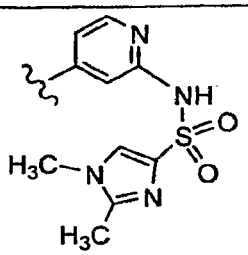
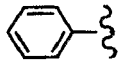
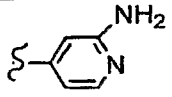
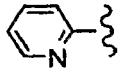
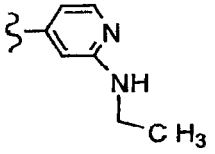
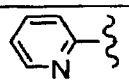
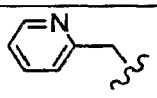
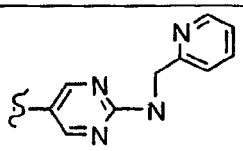
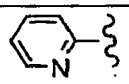
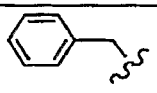
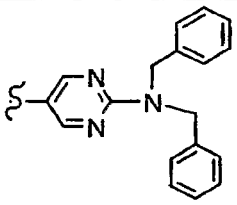
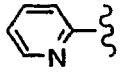
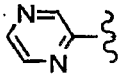
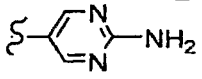
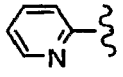
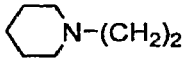
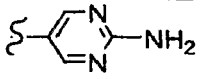
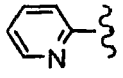
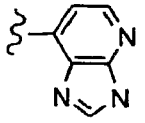

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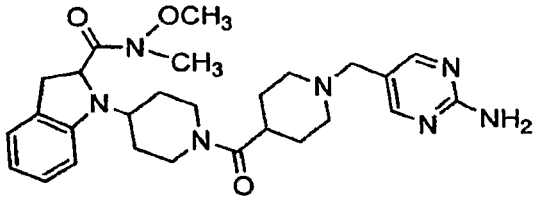
compounds of the following general formula:

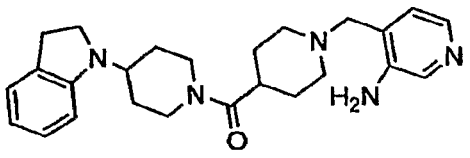


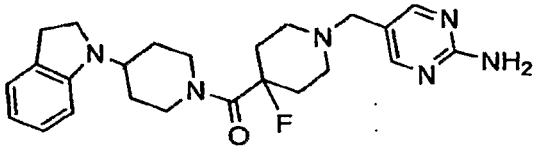
wherein R, R^8 and R^2 are as defined in the following Table:

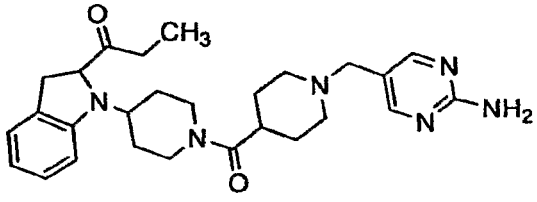
R	R^8	Y	R^2
		- C(O)-	
		- C(O)-	

R	R^8	Y	R^2
		- C(O)-	
	H	bond	
	CH_3CH_2-	- C(O)-	
		- C(O)-	
		- C(O)-	
		- C(O)-	
		- C(O)-	
	H	- C(O)-	

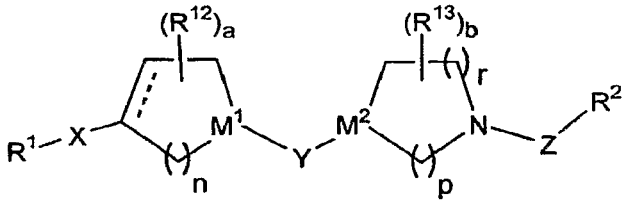

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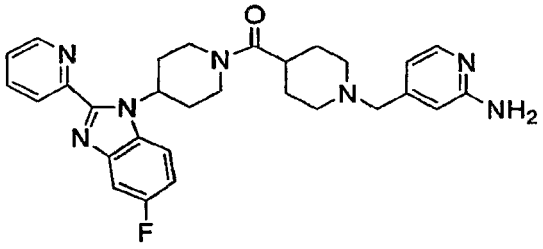

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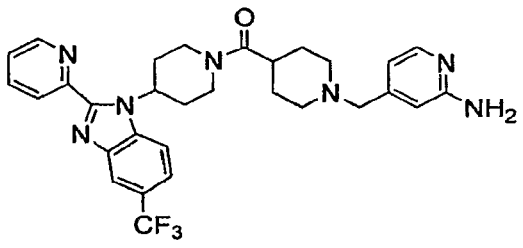
In one embodiment, the H_3 antagonists/inverse agonists of the present invention can have a structure according to Formula (VI):

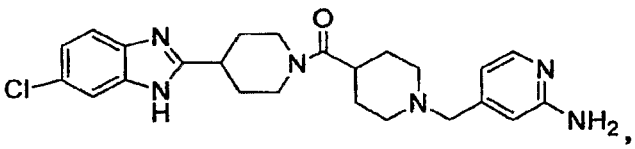


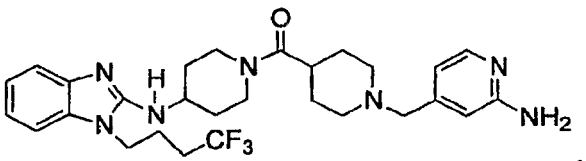
(VI)

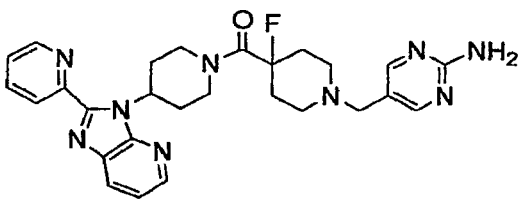
as described in U.S. 2004/0097483, which is herein incorporated by reference in its entirety. Non-limiting examples of compounds of Formula (VI) include:

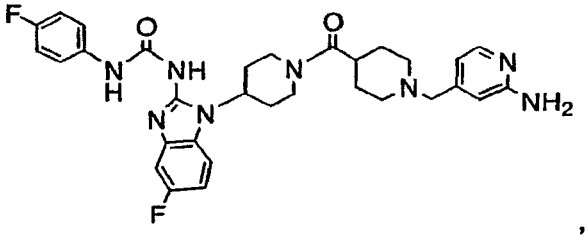

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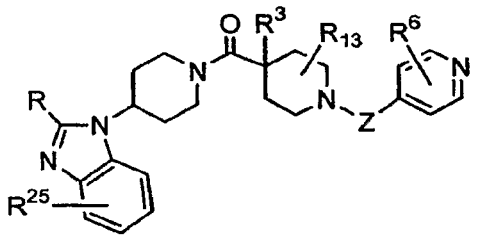

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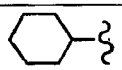
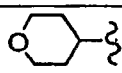
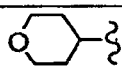
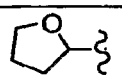
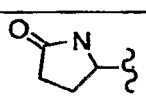
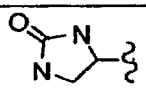

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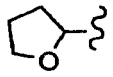
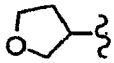
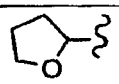
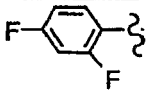
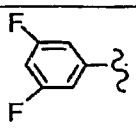
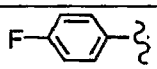
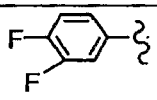
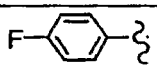
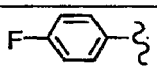
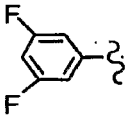
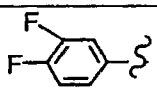
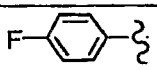
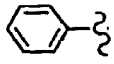
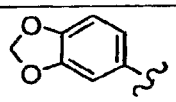
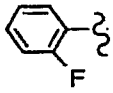

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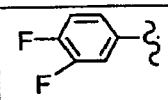
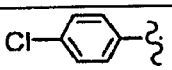
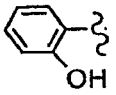
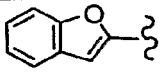
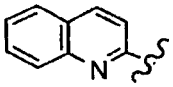
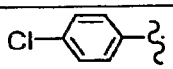
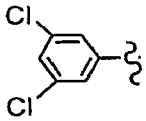
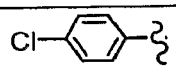
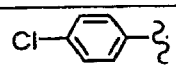
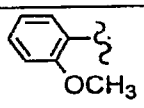
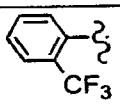
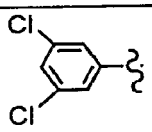
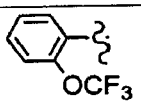
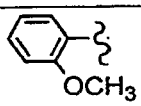
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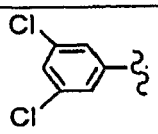
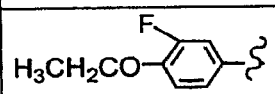
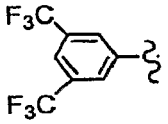
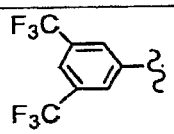
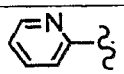
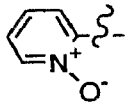
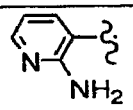
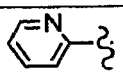
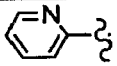
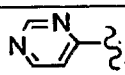
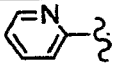
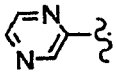
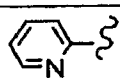
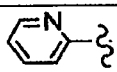


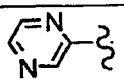
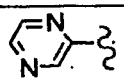
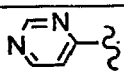
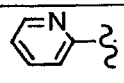
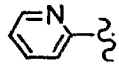
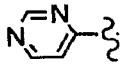
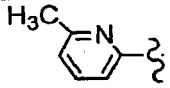
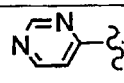
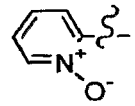
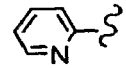
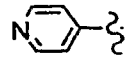
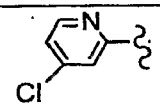
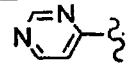
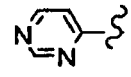
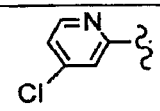
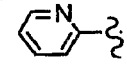
wherein R, R^{25}, R^3, R^{13}, Z and R^6 are as shown in the following table:

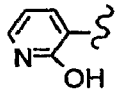
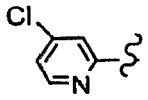
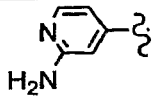
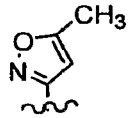
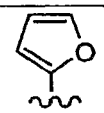
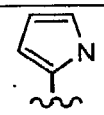
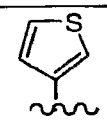
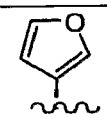
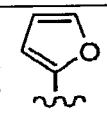
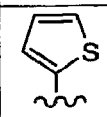
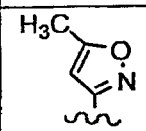
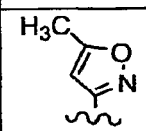
No.	R	R^{25}	R^3	R^{13}	Z	R^6	Physical Data MS (MH^+)
7	$-CH_3$	5-OCH_3	H	H	$-CH_2-$	2-NH_2	463
8	$-CH_3$	6-Cl	H	H	$-CH_2-$	2-NH_2	467
9	$-CH_3$	5-Cl	H	H	$-CH_2-$	2-NH_2	467
10	$-CH_3$	5-Br	H	H	$-CH_2-$	2-NH_2	512
11		5-Cl	H	H	$-CH_2-$	2-NH_2	535
12	benzyl	5-F	H	H	$-CH_2-$	2-NH_2	527
13	$-CH(CH_3)_2$	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
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24		5-F	H	H	$-CH_2-$	2-NH_2	521

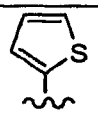
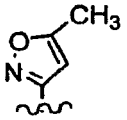
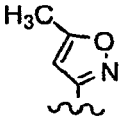
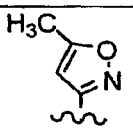
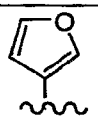
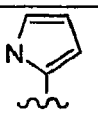
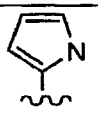
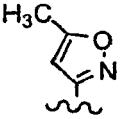
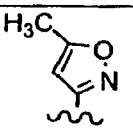
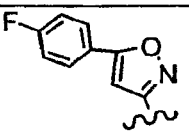
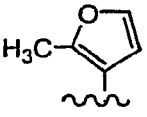
No.	R	R^{25}	R^3	R^{13}	Z	R^6	Physical Data MS (MH^+)
25		5-Br	H	H	$-CH_2-$	$2-NH_2$	568
26		5-F	H	H	$-CH_2-$	$2-NH_2$	507
27		5-F	H	H	$-CH_2-$	$2-NH_2$	507
28		H	H	H	$-CH_2-$	$2-NH_2$	531
29		5-F	H	H	$-CH_2-$	$2-NH_2$	549
30		6-F	H	H	$-CH_2-$	$2-NH_2$	531
31		6,7-di-F	H	H	$-CH_2-$	$2-NH_2$	567
32		6-Cl	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

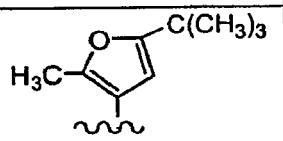
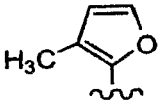
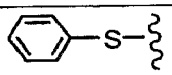
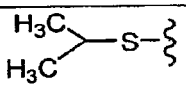
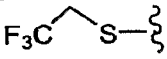
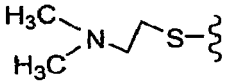
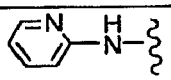
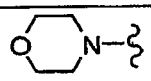
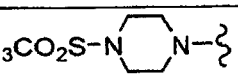
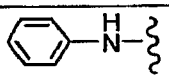
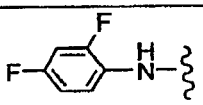
No.	R	R^{25}	R^3	R^{13}	Z	R^6	Physical Data MS (MH^+)
40		5-Br	H	H	$-CH_2-$	$2-NH_2$	610
41		5-F	H	H	$-CH_2-$	$2-NH_2$	547
42		5-F	H	H	$-CH_2-$	$2-NH_2$	529
43		6-F	H	H	$-CH_2-$	$2-NH_2$	553
44		6-F	H	H	$-CH_2-$	$2-NH_2$	564
45		H	H	H	$-CH_2-$	$2-NH_2$	529
46		5-F	H	H	$-CH_2-$	$2-NH_2$	581
47		5-Cl	H	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

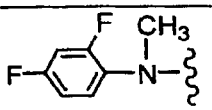
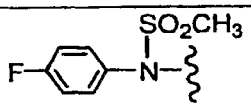
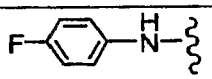
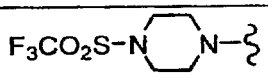
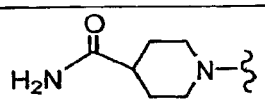
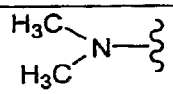
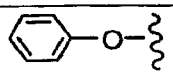
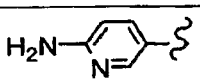
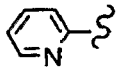
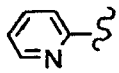
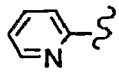
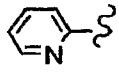
No.	R	R^{25}	R^3	R^{13}	Z	R^6	Physical Data MS (MH^+)
54		6-Cl	H	H	$-CH_2-$	2-NH_2	597
55		5-CH_3	H	H	$-CH_2-$	2-NH_2	571
56		5-Cl	H	H	$-CH_2-$	2-NH_2	665
57		5-Br	H	H	$-CH_2-$	2-NH_2	710
58		6-ethoxy	H	H	$-CH_2-$	2-NH_2	540
59		5-Cl	H	H	$-CH_2-$	2-NH_2	546
60		H	H	H	$-CH_2-$	2-NH_2	511
61		5-F	H	H	$-CH_2-$	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

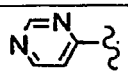
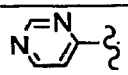
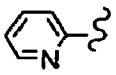
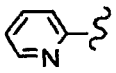
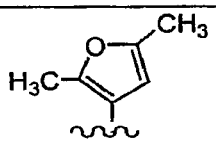
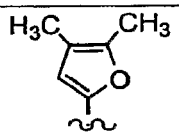
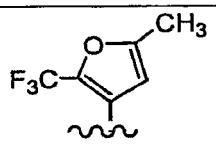
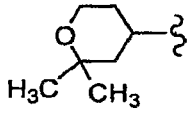
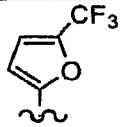
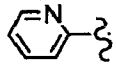
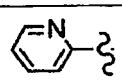
No.	R	R^{25}	R^3	R^{13}	Z	R^6	Physical Data MS (MH^+)
68		5-F	H	H	$-CH_2-$	$2-NH_2$	515
69		5-Cl	H	H	$-CH_2-$	$2-NH_2$	531
70		5-Cl	H	H	$-CH_2-$	$2-NH_2$	531
71		5,6-di-F	H	H	$-CH_2-$	$2-NH_2$	532
72		5-Br	H	H	$-CH_2-$	$2-NH_2$	575
73		6-ethoxy	H	H	$-CH_2-$	$2-NH_2$	541
74		5-F	H	H	$-CH_2-$	$2-NH_2$	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

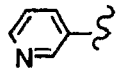
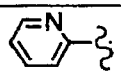
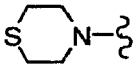
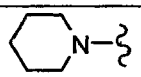
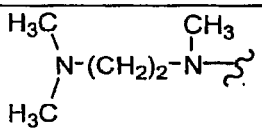
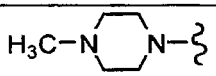
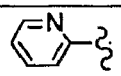
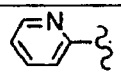
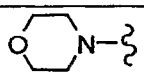
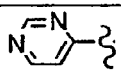
No.	R	R^{25}	R^3	R^{13}	Z	R^6	Physical Data MS (MH^+)
84		5-F	H	H	$-CH_2-$	$2-NH_2$	530
85		$5-CF_3$,7-F	H	H	$-CH_2-$	$2-NH_2$	617
86		5-F	H	H	$-CH_2-$	$2-NH_2$	529
87		H	H	H	$-CH_2-$	$2-NH_2$	500
88		H	H	H	$-CH_2-$	$2-NH_2$	485
89		H	H	H	$-CH_2-$	$2-NH_2$	489
90		6-F	H	H	$-CH_2-$	$2-NH_2$	514
91		6-F	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

No.	R	R^{25}	R^3	R^{13}	Z	R^6	Physical Data MS (MH^+)
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

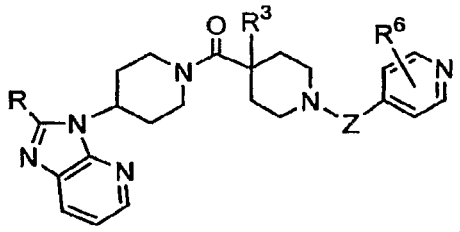
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107		5-F	H	H	$-CH_2-$	$2-NH_2$	573
108		5-F	H	H	$-CH_2-$	$2-NH_2$	517
109	CH_3-S-	5-F	H	H	$-CH_2-$	$2-NH_2$	483
110	CH_3-CH_2-S-	5-F	H	H	$-CH_2-$	$2-NH_2$	497
111	CH_3-SO_2-	5-F	H	H	$-CH_2-$	$2-NH_2$	515
112		5-F	H	H	$-CH_2-$	$2-NH_2$	545
113		5-F	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

No.	R	R^{25}	R^3	R^{13}	Z	R^6	Physical Data MS (MH^+)
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	$-CH(CH_3)-$	$2-NH_2$	528
140		5-F	F	H	$-CH_2-$	$2-NH_2$	532
141		5-F	OH	H	$-CH_2-$	$2-NH_2$	530

No.	R	R^{25}	R^3	R^{13}	Z	R^6	Physical Data MS (MH^+)
142		5-F	H	H	$-CH(CH_3)-$	$2-NH_2$	529
143		5-F	H	H	$-CH(CH_3)-$	$2-NH_2$	529
144		5-F	$-CH_3$	H	$-CH_2-$	$2-NH_2$	528
145		6-F	H	H	$-CH(CH_3)-$	$2-NH_2$	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	$-CH(CH_3)-$	$2-NH_2$	497
155		5-F	H	2-CH_3	$-CH_2-$	$2-NH_2$	528

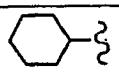
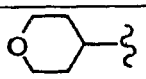
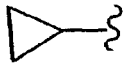
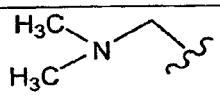
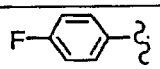
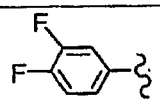
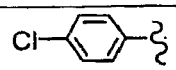
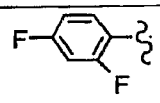
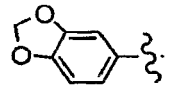
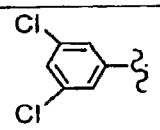
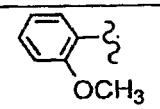
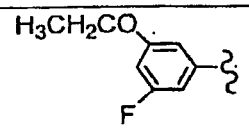
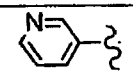
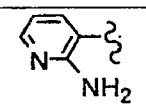
No.	R	R^{25}	R^3	R^{13}	Z	R^6	Physical Data MS (MH^+)
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157		5-F	H	H	$-CH_2-$	$3-NH_2$	514
158		5-F	H	H	$-CH_2-$	$2-NH_2$	589
159		5-F	H	H	$-CH_2-$	$2-NH_2$	520
160	CH_3CH_2O-	5-F	F	H	$-CH_2-$	$2-NH_2$	499
161		5-F	H	H	$-CH_2-$	$2-NH_2$	537
162		5-F	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

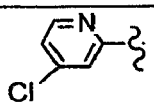
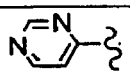
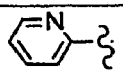
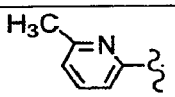
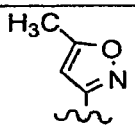
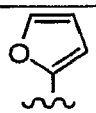
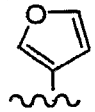
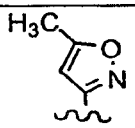
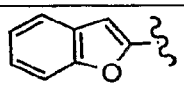
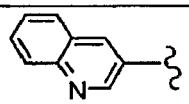
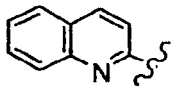
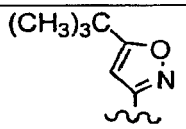
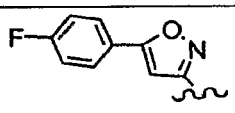
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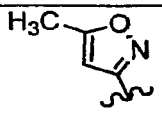
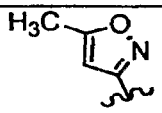
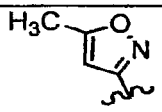
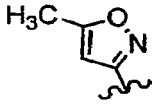
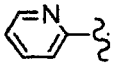
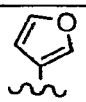
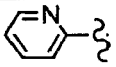
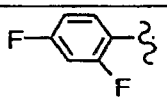
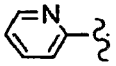
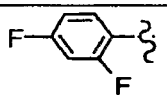


wherein R, R^3, Z and R^6 are as shown in the following table:

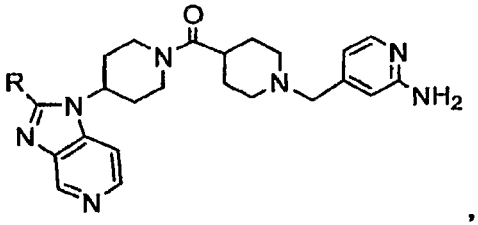
No.	R	R^3	Z	R^6	Physical Data MS (MH^+)

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

No.	R	R^3	Z	R^6	Physical Data MS (MH^+)
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

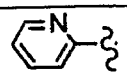
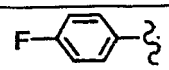
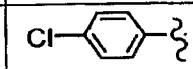
No.	R	R^3	Z	R^6	Physical Data MS (MH^+)
196		F	$-CH_2-$	2-NH_2	519
197		H	$-\overset{CH_3}{\underset{}{CH}}-$	2-NH_2	515
198		OH	$-CH_2-$	2-NH_2	517
199			$-CH_2-$	2-NH_2	577
200		F	$-CH_2-$	2-NH_2	515
201		F	$-CH_2-$	2-NH_2	504
202		H	$-CH_2-$	3-NH_2	497
203		H	$-CH_2-$	3-NH_2	532
204		F	$-CH_2-$	3-NH_2	515
205		F	$-CH_2-$	3-NH_2	550

compounds of the following formula:

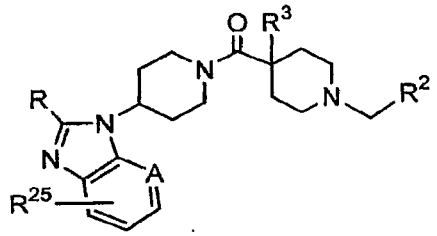


wherein R is as shown in the following table:

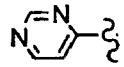
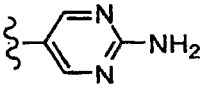
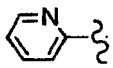
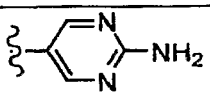
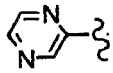
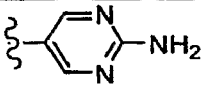
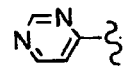
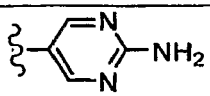
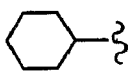
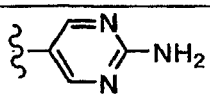
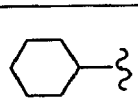
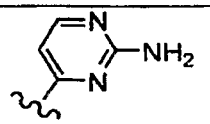
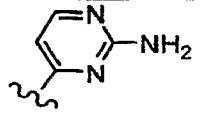
No.	R	Physical Data MS (MH^+)

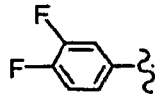
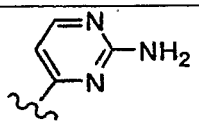
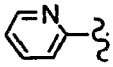
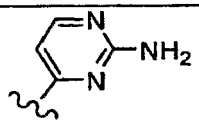
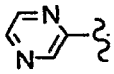
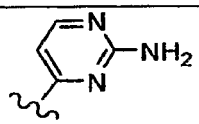
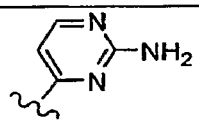
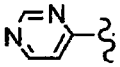
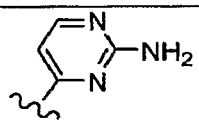
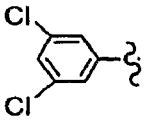
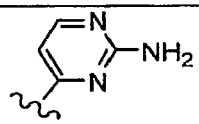
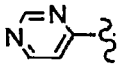
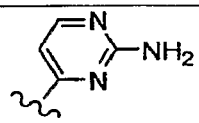
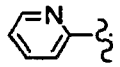
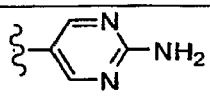
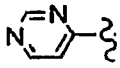
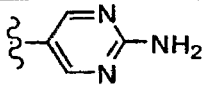
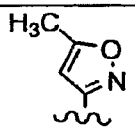
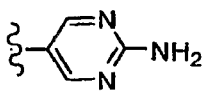
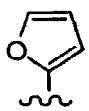
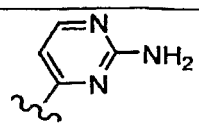
No.	R	Physical Data MS (MH^+)
206	$-CH_3$	434
207		497
208		514
209		530

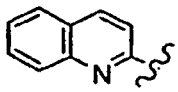
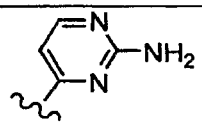
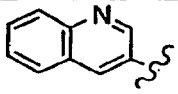
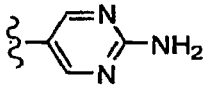
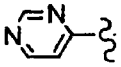
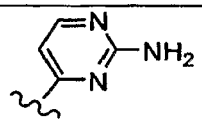
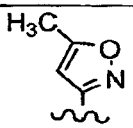
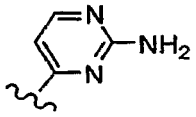
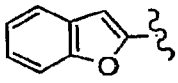
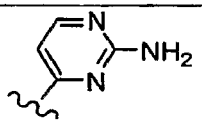
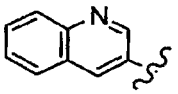
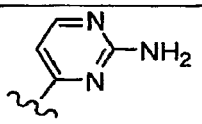
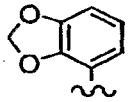
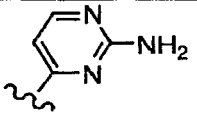
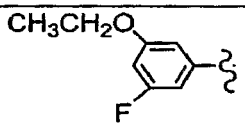
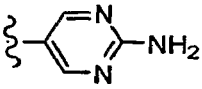
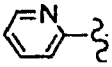
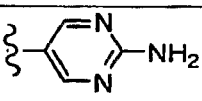
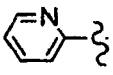
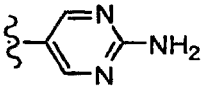
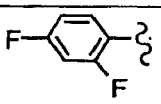
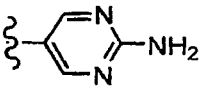
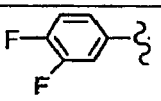
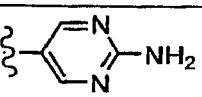
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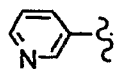
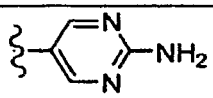
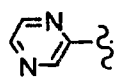
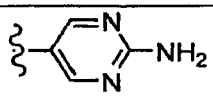
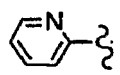
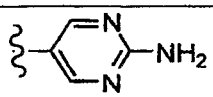
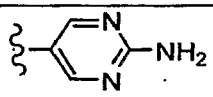
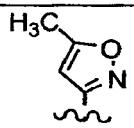
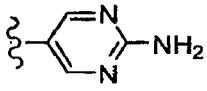
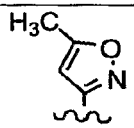
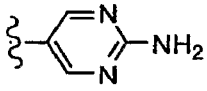
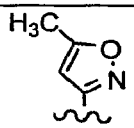
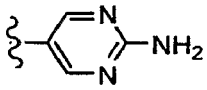
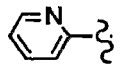
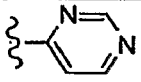
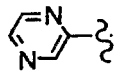
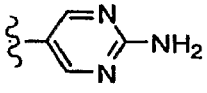
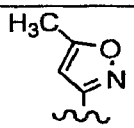
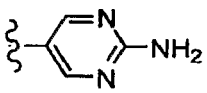
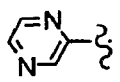
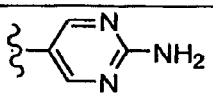
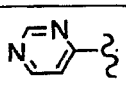
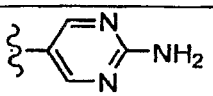
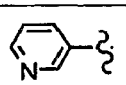
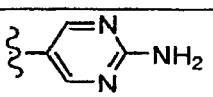


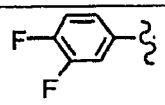
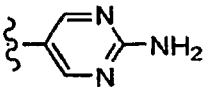
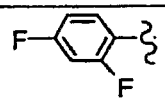
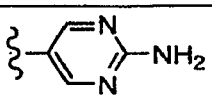
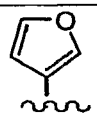
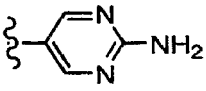
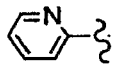
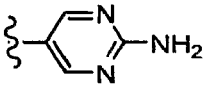
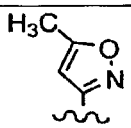
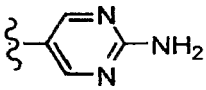
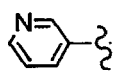
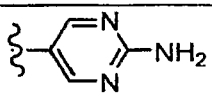
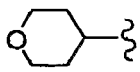
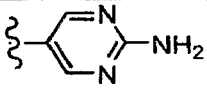
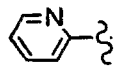
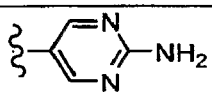
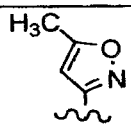
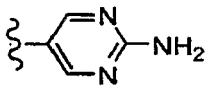
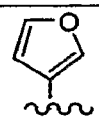
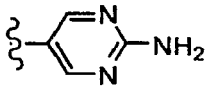
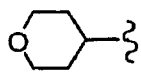
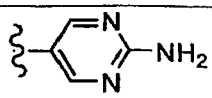
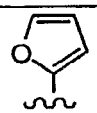
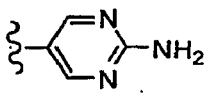
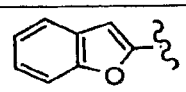
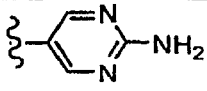
wherein R, R^{25}, A, R^3, and R^2 are as shown in the following table:

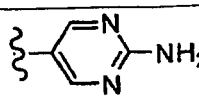
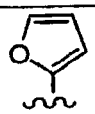
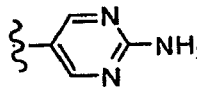
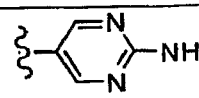
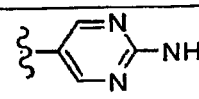
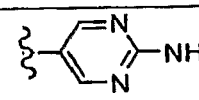
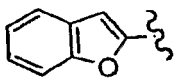
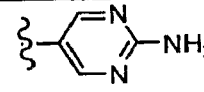
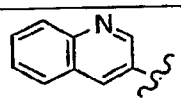
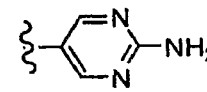
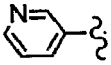
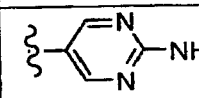
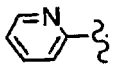
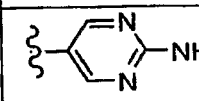
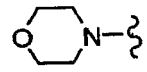
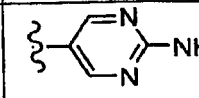
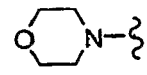
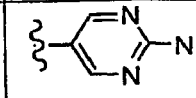
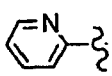
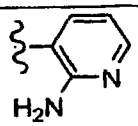
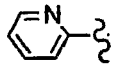
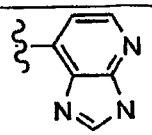
No.	R	R^{25}	A	R^3	R^2	Physical Data MS (MH^+)
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211		5-F	C	H		515
212		5-Cl	C	H		532
213		5-F	C	H		516
214		H	N	H		503
215		H	N	H		503
216	$(CH_3)_2CH-$	H	N	H		463

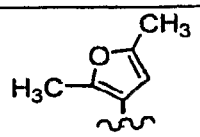
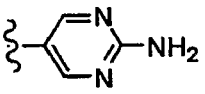
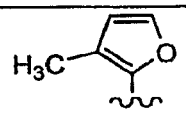
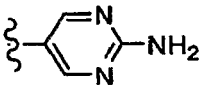
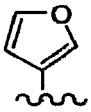
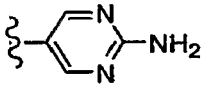
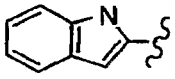
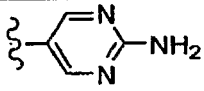
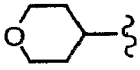
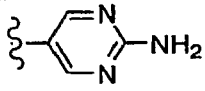
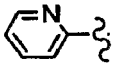
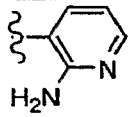
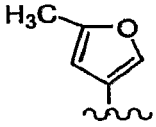
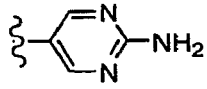
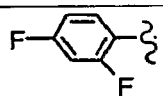
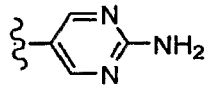
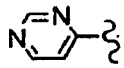
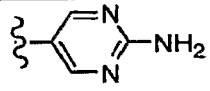
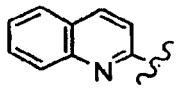
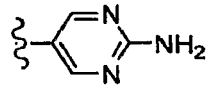
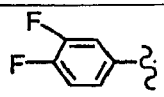
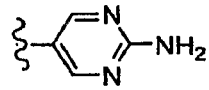
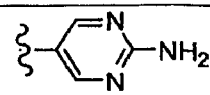
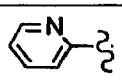
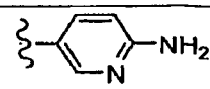
No.	R	R^{25}	A	R^3	R^2	Physical Data MS (MH^+)
217		5-F	C	H		550
218		5-F	C	H		515
219		5-Cl	C	H		532
220		6-Cl	C	H		548
221		5-F	C	H		516
222		6-Cl	C	H		600
223		5-Cl	C	H		532
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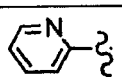
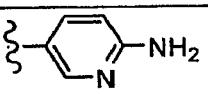
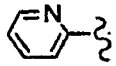
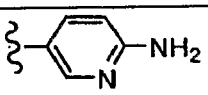
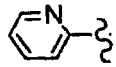
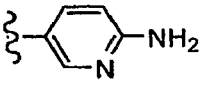
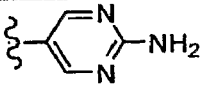
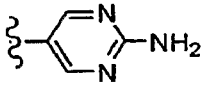
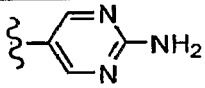
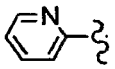
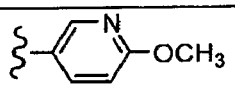
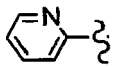
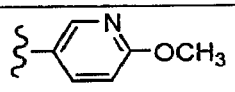
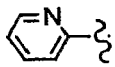
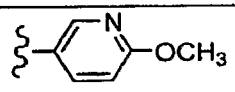
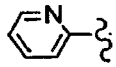
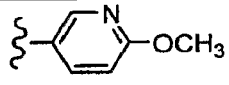
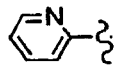
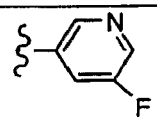
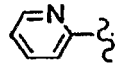
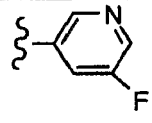
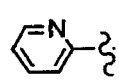
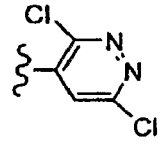
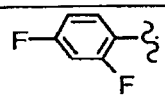
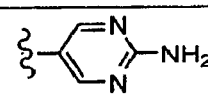
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229		H	N	H		548
230		H	N	H		499
231		H	N	H		502
232		H	N	H		537
233		H	N	H		548
234		H	N	H		541
235		H	N	H		559
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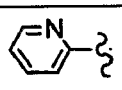
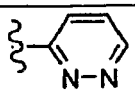
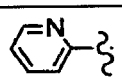
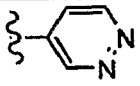
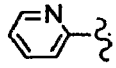
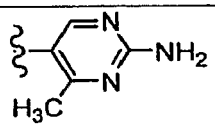
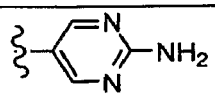
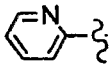
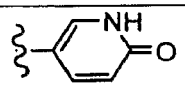
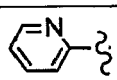
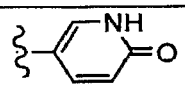
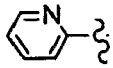
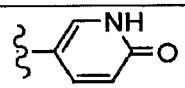
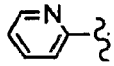
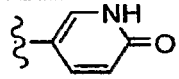
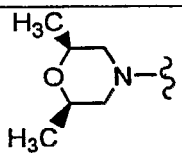
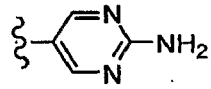
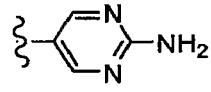
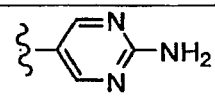
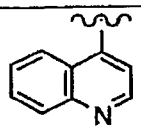
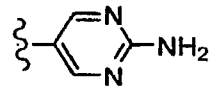
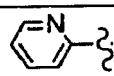
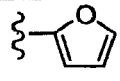
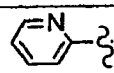
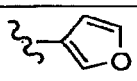
No.	R	R^{25}	A	R^3	R^2	Physical Data MS (MH^+)
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241		5-F	C	H		516
242		H	C	H		497
243	$(CH_3)_2N\text{-}CH_2\text{-}$	H	N	H		478
244		5-F	C	H		519
245		H	C	H		501
246		5,6-di-F	C	H		537
247		5-F	C	H		500
248		5,6-di-F	C	H		534
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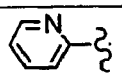
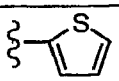
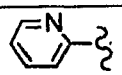
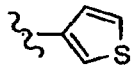
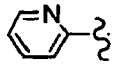
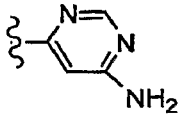
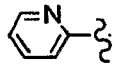
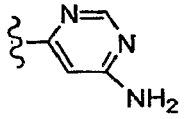
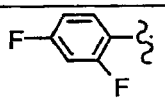
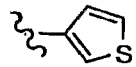
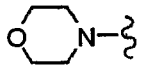
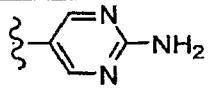
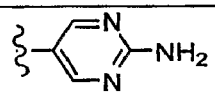
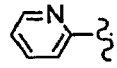
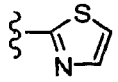
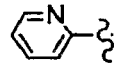
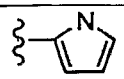
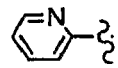
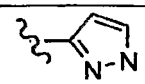
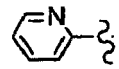
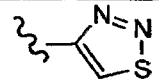
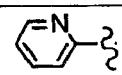
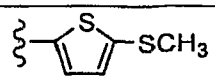
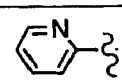
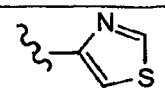
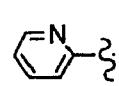
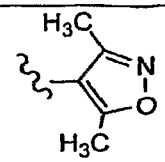
No.	R	R^{25}	A	R^3	R^2	Physical Data MS (MH^+)
253		5-F	C	F		568
254		5-F	C	F		568
255		H	N	H		487
256		H	C	F		515
257		H	C	F		519
258		H	N	F		516
259		H	N	H		505
260		H	N	F		516
261		H	N	F		520
262		5-F	C	H		504
263		5-F	C	H		522
264		5-F	C	H		504
265		H	N	H		537

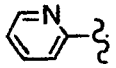
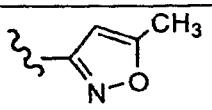
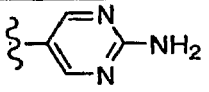
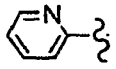
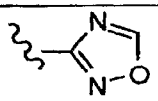
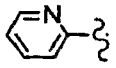
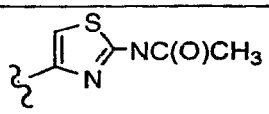
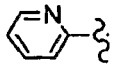
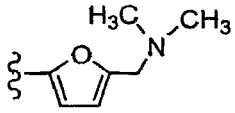
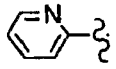
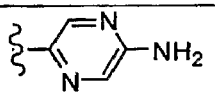
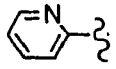
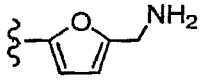
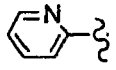
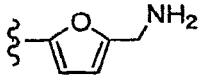
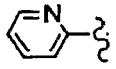
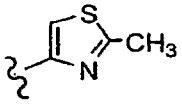
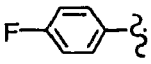
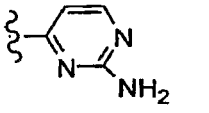
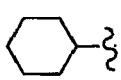
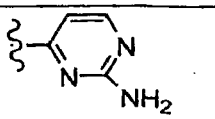
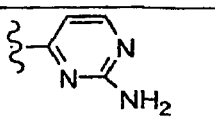
No.	R	R^{25}	A	R^3	R^2	Physical Data MS (MH^+)
266	$(CH_3)_2N\text{-}CH_2\text{-}$	H	N	F		496
267		H	N	F		505
268	$CH_3CH_2\text{-}O\text{-}$	5-F	C	H		482
269	$CH_3\text{-}S\text{-}$	5-F	C	H		484
270	$CH_3CH_2\text{-}O\text{-}$	5-F	C	F		500
271		H	N	F		555
272		H	N	F		566
273		H	N	H		498
274		5,6-di-F	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

No.	R	R^{25}	A	R^3	R^2	Physical Data MS (MH^+)
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

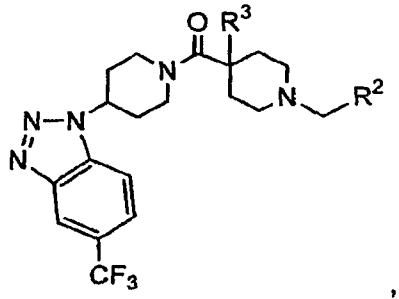
No.	R	R^{25}	A	R^3	R^2	Physical Data MS (MH^+)
292		5-F	C	F		532
293		5-F	C	H		514
294		H	N	H		497
295	$(CH_3)_2N$-	5-F	C	F		499
296	CH_3CH_2-S-	5-F	C	F		516
297	CH_3-O-	5-F	C	F		486
298		H	N	H		512
299		H	N	F		530
300		5-F	C	F		547
301		5-F	C	H		529
302		5-F	C	H		517
303		5-F	C	F		535
304		H	N	H		551
305		H	N	F		551

No.	R	R^{25}	A	R^3	R^2	Physical Data MS (MH^+)
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

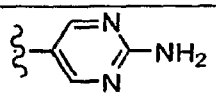
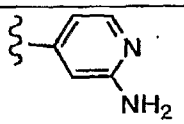
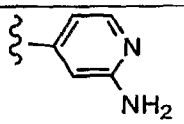
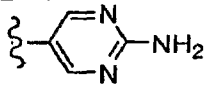
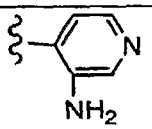
No.	R	R^{25}	A	R^3	R^2	Physical Data MS (MH^+)
320		H	N	F		505
321		H	N	F		505
322		5-F	C	F		533
323		H	N	F		516
325		H	N	F		540
325		H	N	F		524
326	$(CH_3)_2CH$-O-	5-F	C	F		514
327		H	N	F		506
328		H	N	F		488
329		H	N	F		489
330		H	N	F		507
331		H	N	F		551
332		H	N	F		506
333		H	N	F		518

No.	R	R^{25}	A	R^3	R^2	Physical Data MS (MH^+)
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

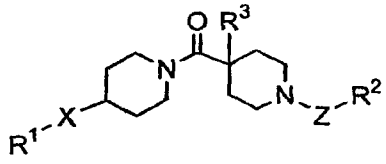
compounds of the following formula:



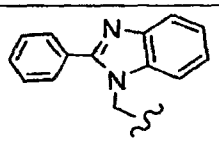
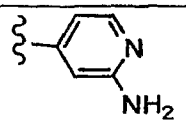
wherein R^3 and R^2 are as shown in the following table:

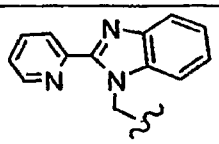
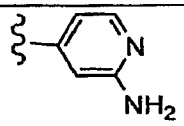
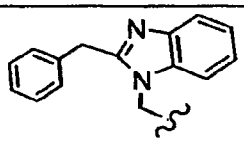
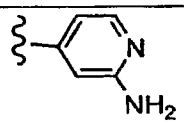
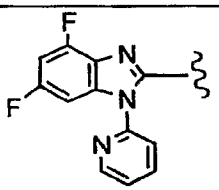
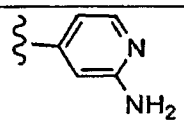
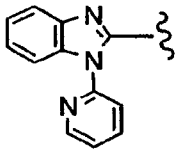
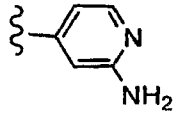
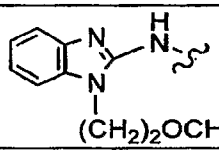
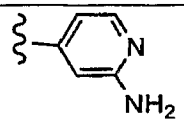
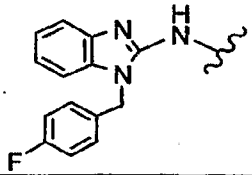
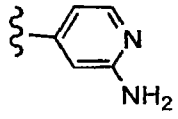
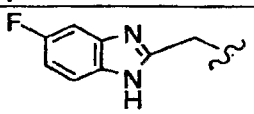
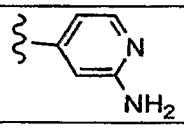
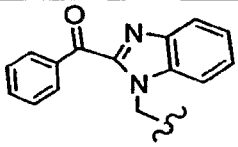
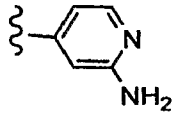
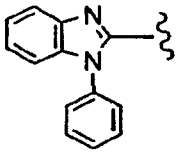
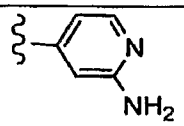
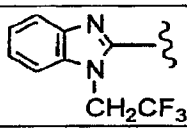
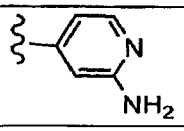
No.	R^3	R^2	Physical Data MS (MH^+)
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348	F		506
349	F		488
350	F		507
351	F		506

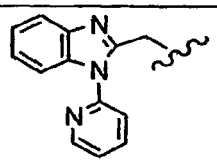
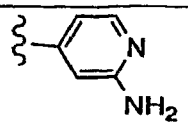
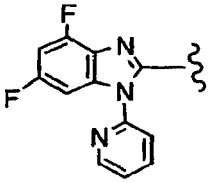
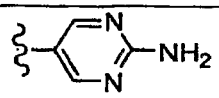
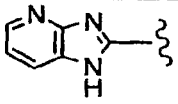
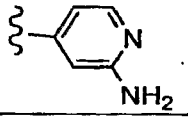
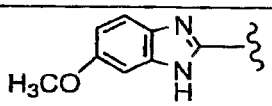
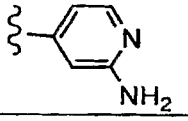
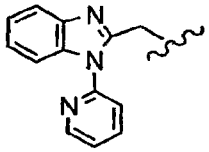
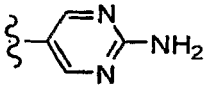
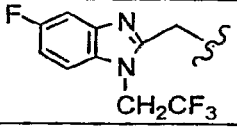
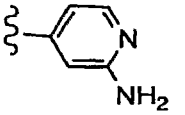
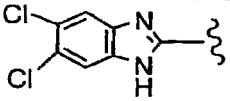
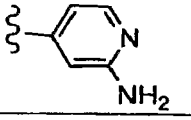
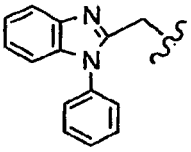
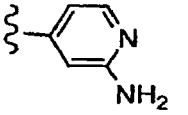
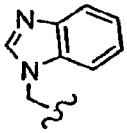
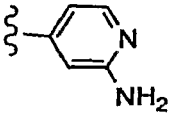
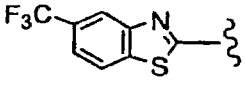
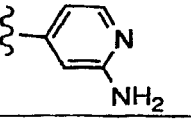
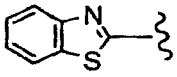
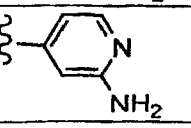
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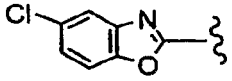
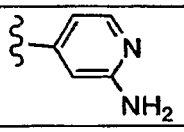
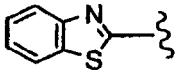
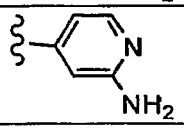
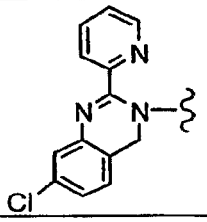
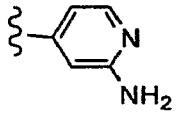
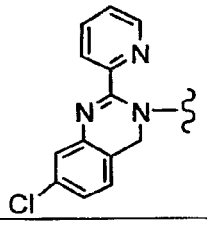
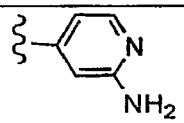


wherein R^1-X-, Z, R^3, and R^2 are as shown in the following table:

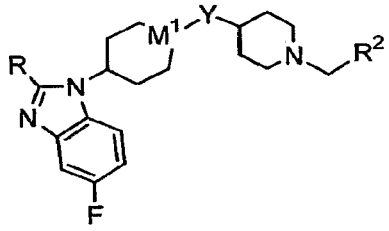
No.	R^1-X-	Z	R^3	R^2	Physical Data MS (MH^+)
352		$-CH_2-$	H		509

No.	R^1-X-	Z	R^3	R^2	Physical Data MS (MH^+)
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
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360		$-CH_2-$	H		537
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362		$-CH_2-$	H		501

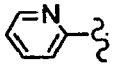
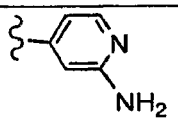
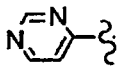
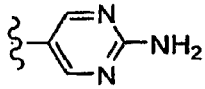
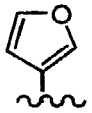
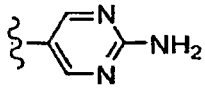
No.	R^1-X-	Z	R^3	R^2	Physical Data MS (MH^+)
363		$-CH_2-$	H		510
364		$-CH_2-$	H		533
365		$-CH_2-$	H		420
366		$-CH_2-$	H		449
367		$-CH_2-$	H		497
368		$-CH_2-$	H		533
369		$-CH_2-$	H		487
370		$-CH_2-$	H		509
371		$-CH_2-$	H		433
372		$-CH_2-$	H		504
373		$-CH_2-$	H		436

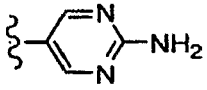
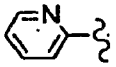
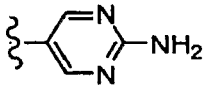
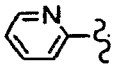
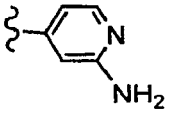
No.	R^1-X-	Z	R^3	R^2	Physical Data MS (MH^+)
374		$-CH_2-$	H		472
375		$-(CH_2)_3-$	H		464
376		$-CH_2-$	H		544
377		$-CH_2-$	F		562

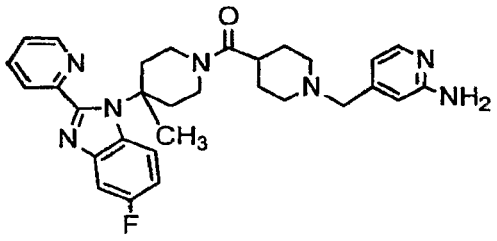
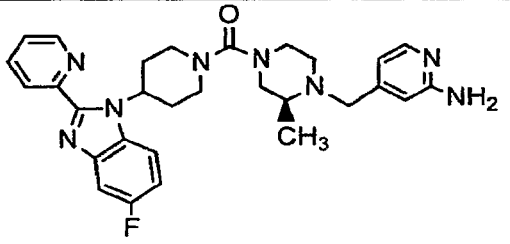
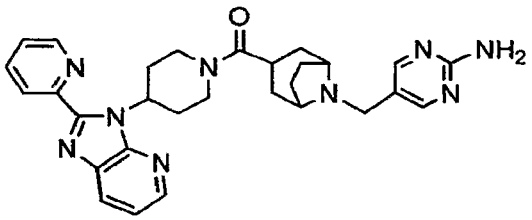
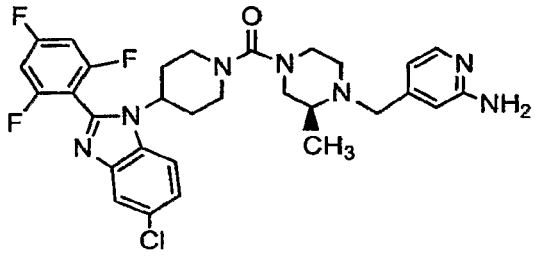
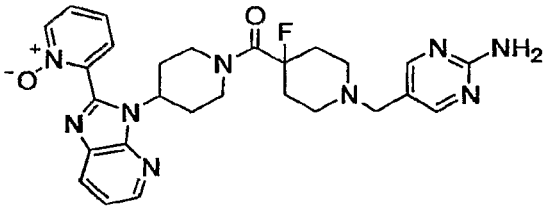
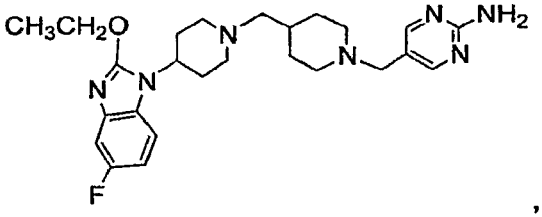
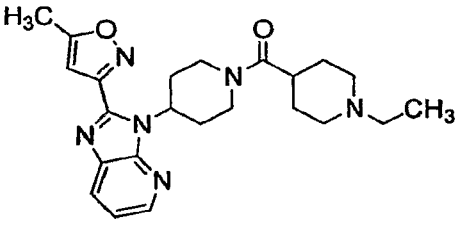
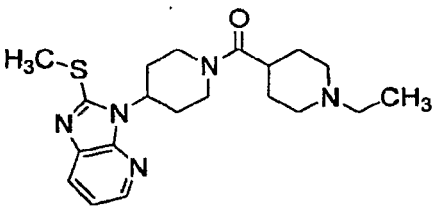
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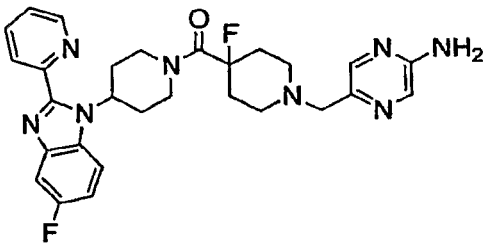
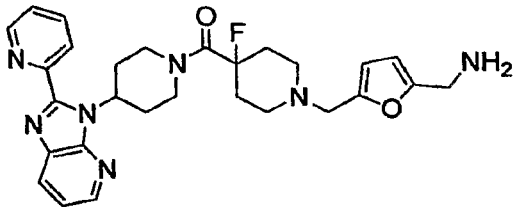
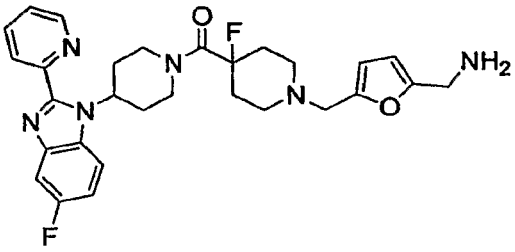
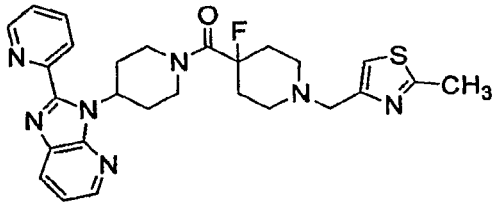
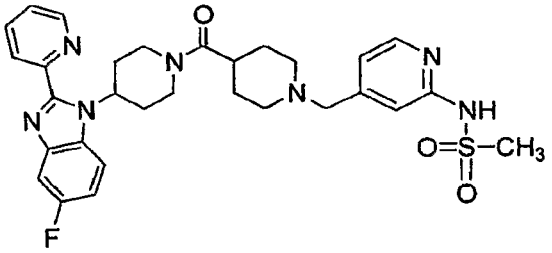
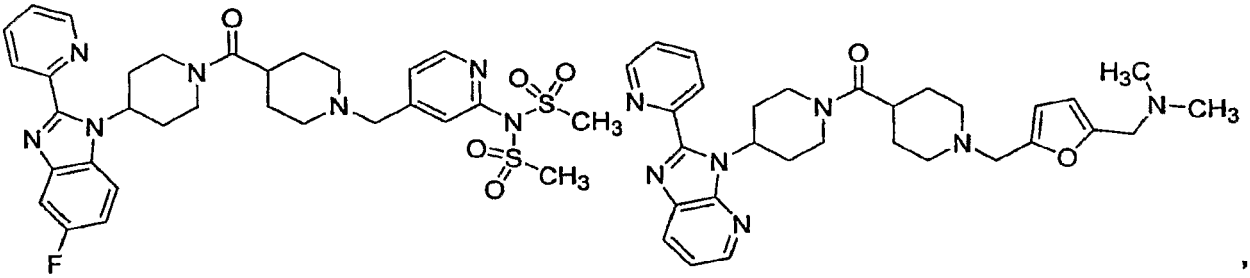
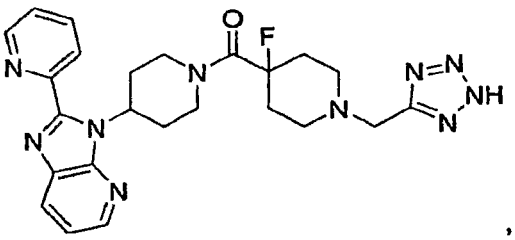
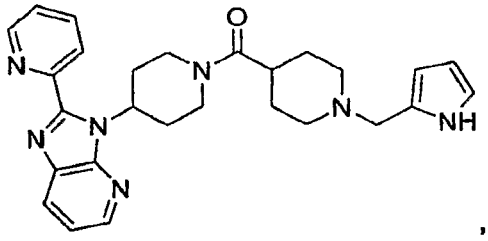
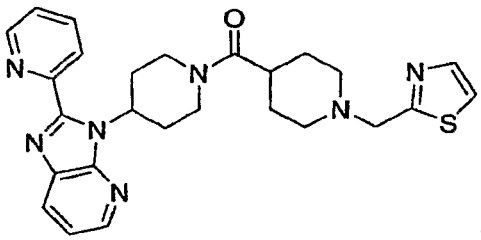
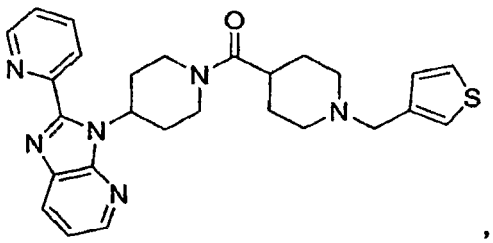


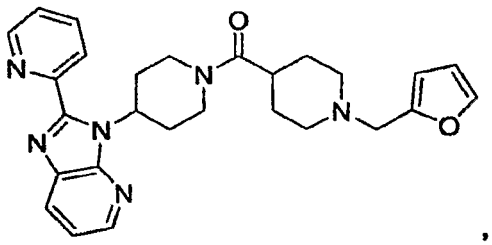
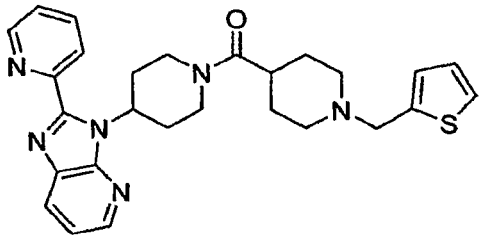
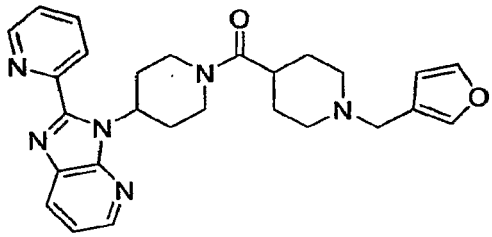
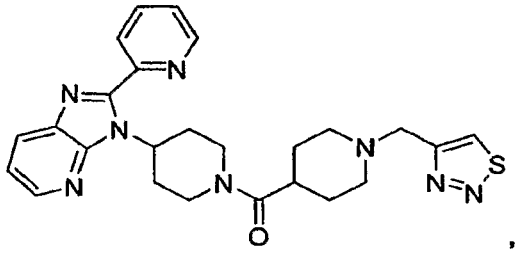
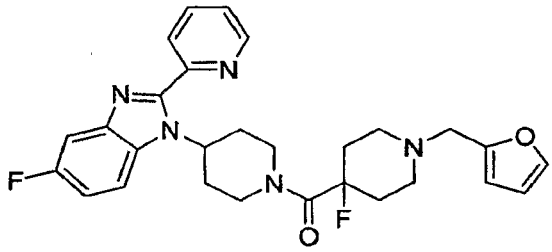
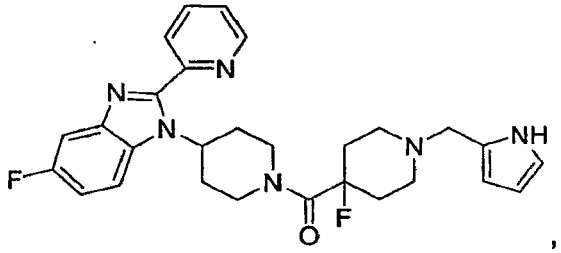
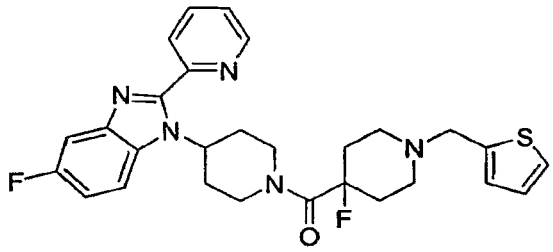
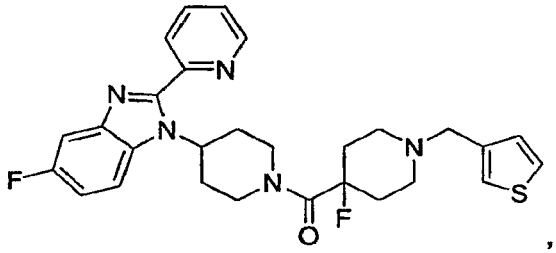
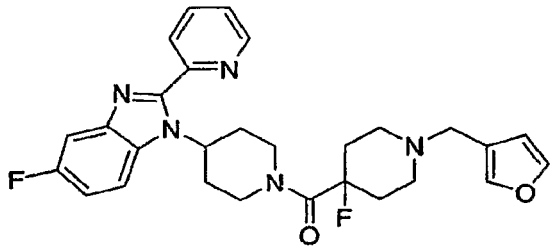
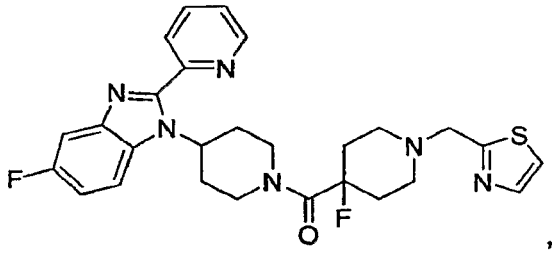
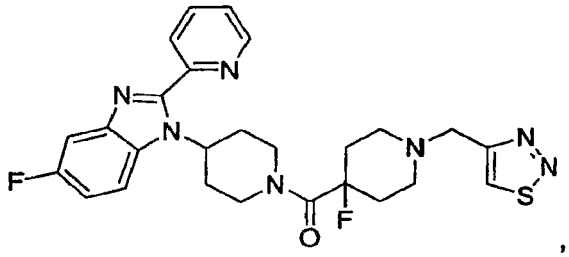
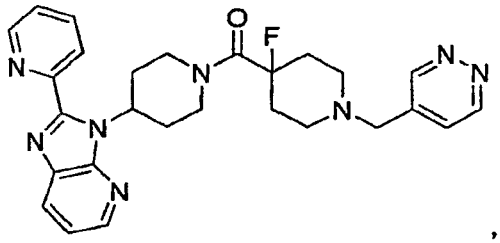
wherein R, M^1, Y, and R^2 are as shown in the following table:

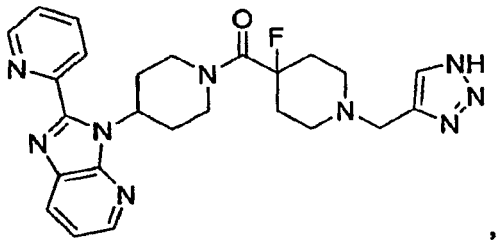
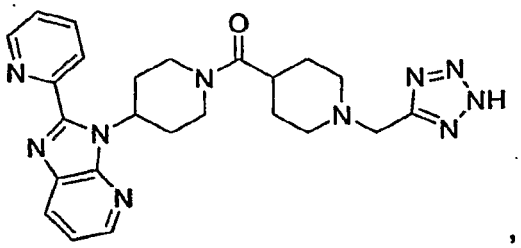
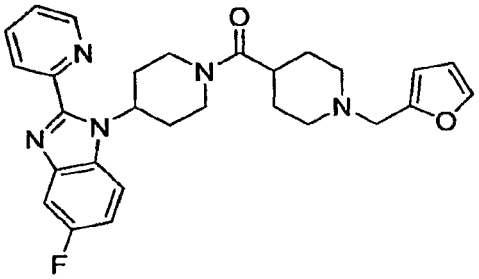
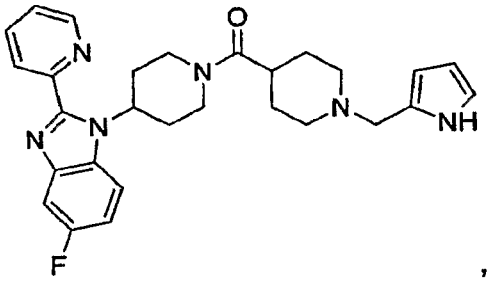
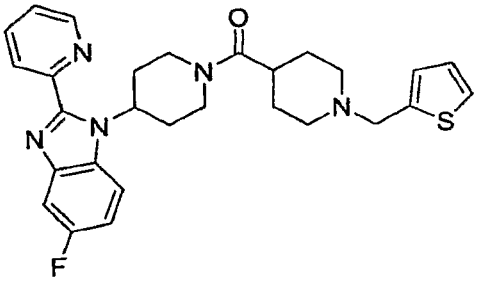
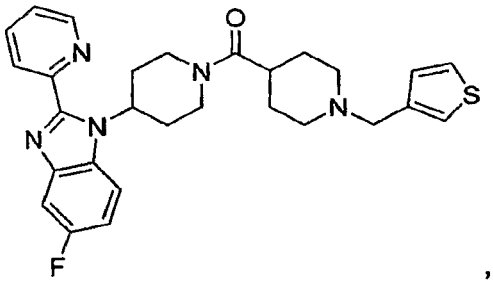
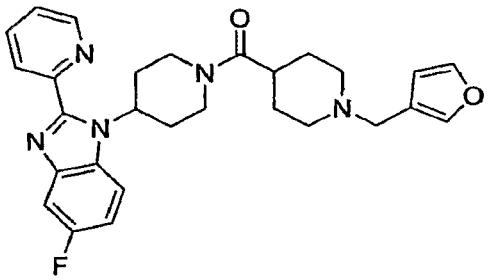
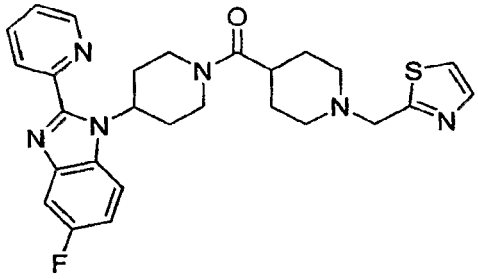
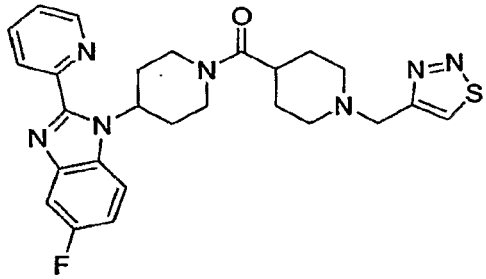
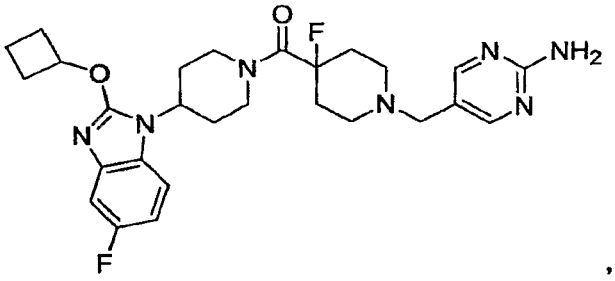
No.	R	M^1	Y	R^2	Physical Data MS (MH^+)
378		CH	$-CH_2-$		500
379		N	-NH-		502
380		N	-NH-		490

No.	R	M^1	Y	R^2	Physical Data MS (MH^+)
381		N	-NH-		494
382		N	-NH-		501
383		N	-NH-		500

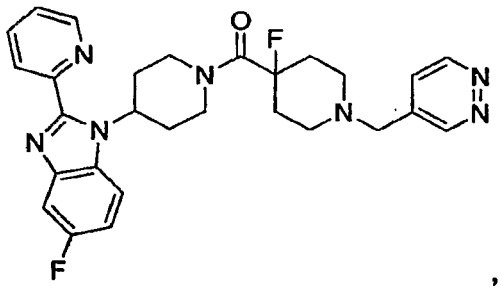
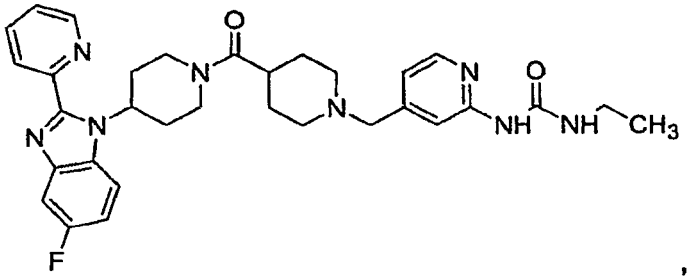
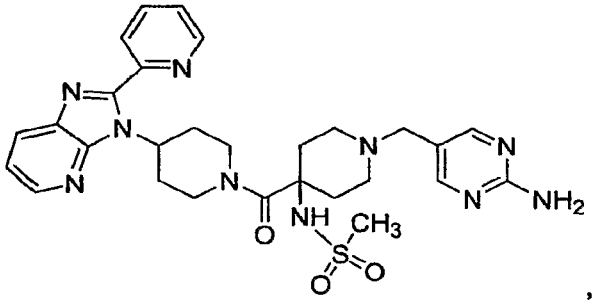
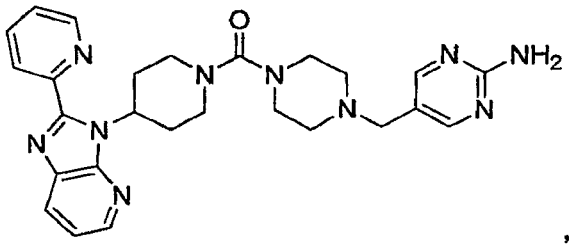
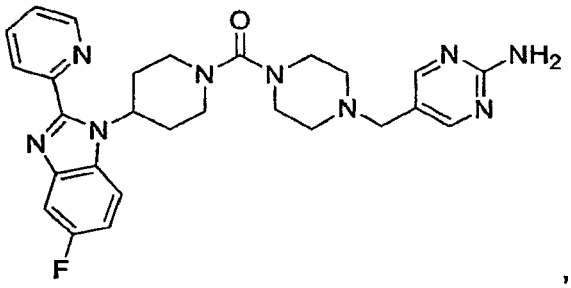
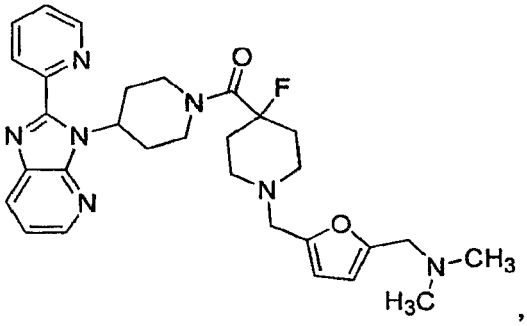
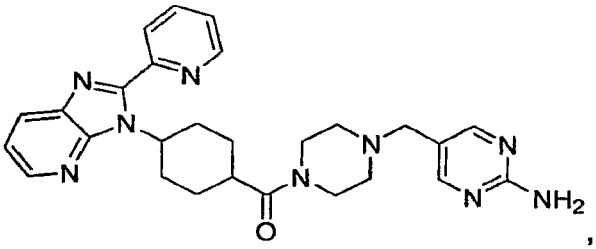
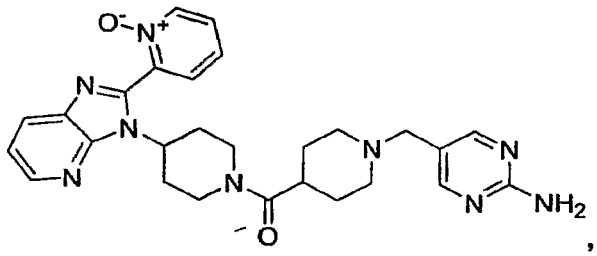
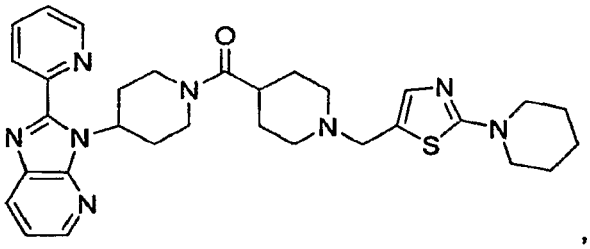
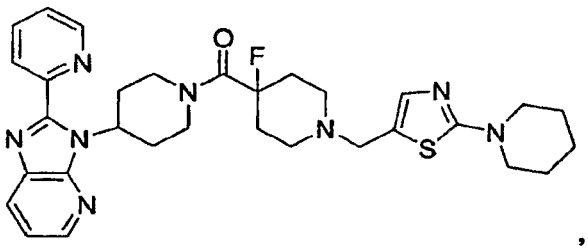
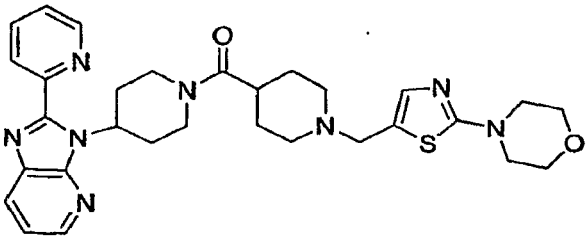
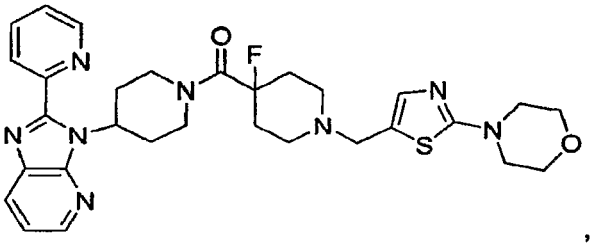
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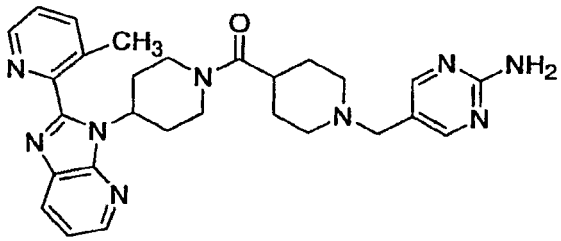
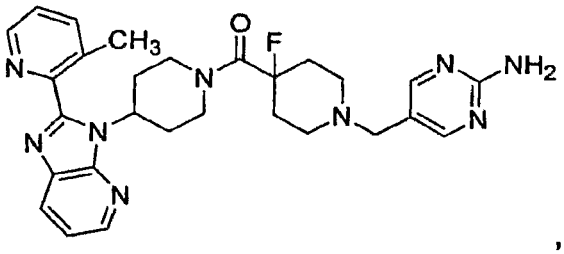
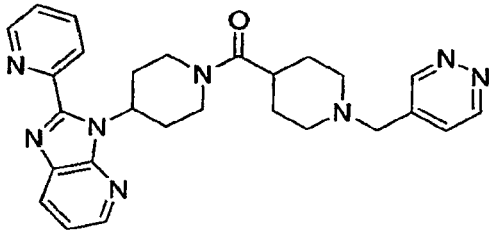
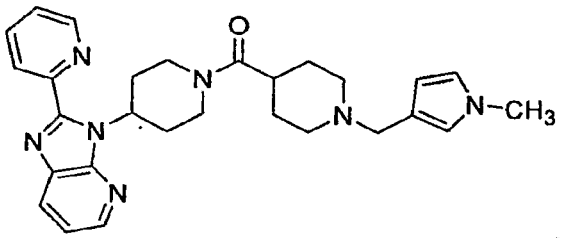
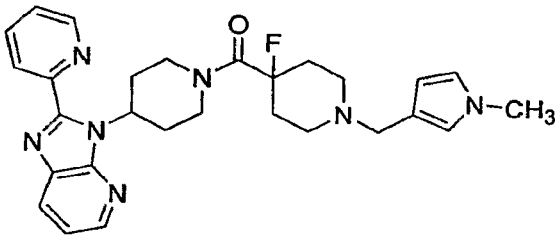
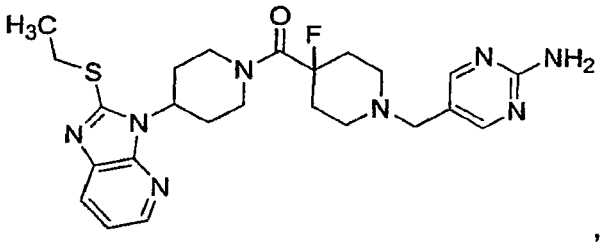
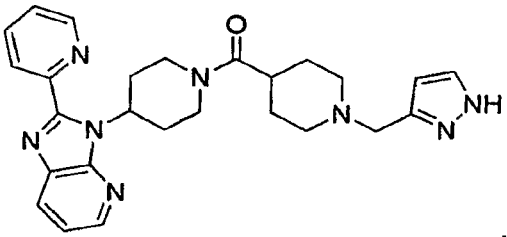
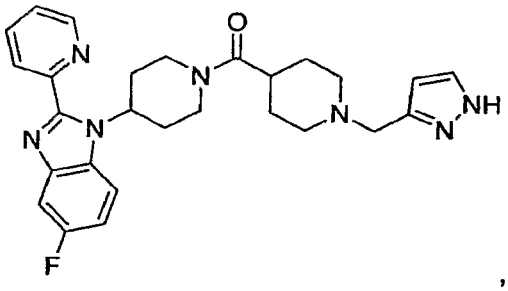
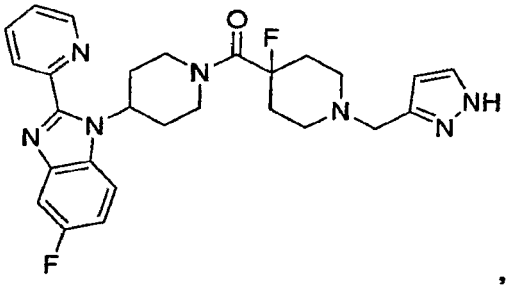
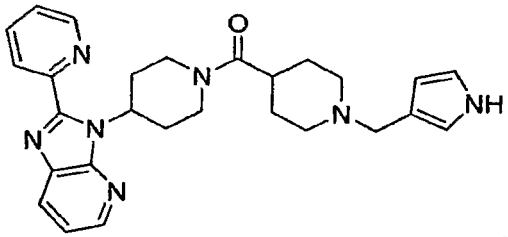
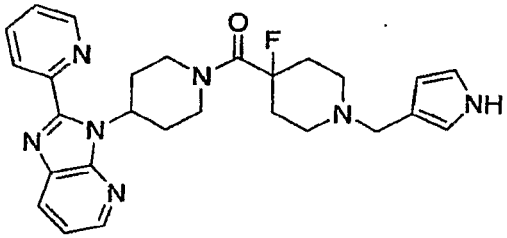
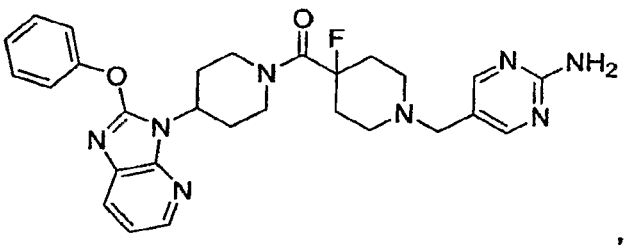

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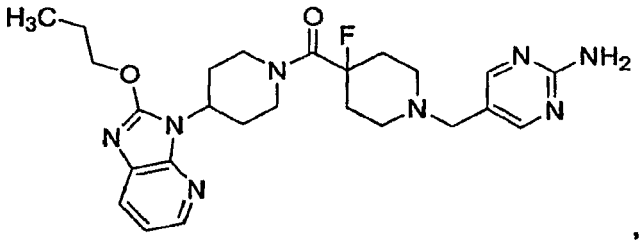

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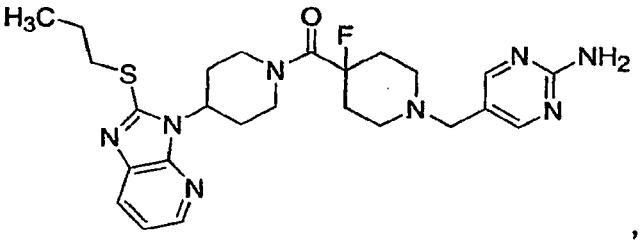
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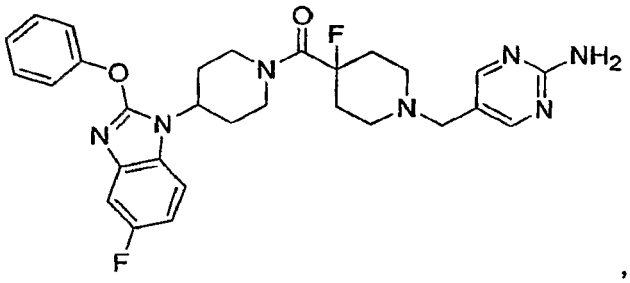

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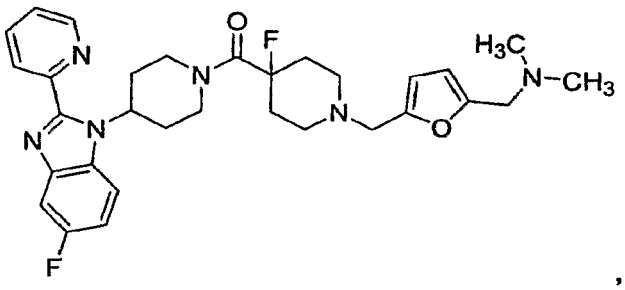

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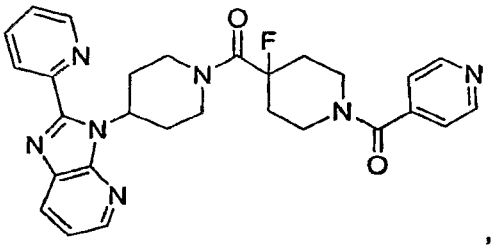
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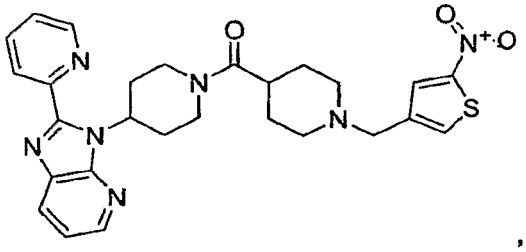


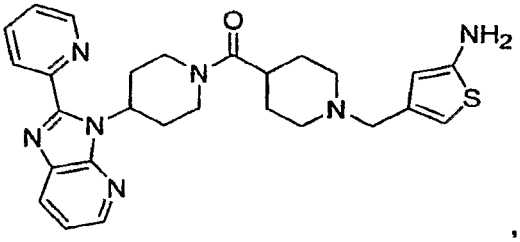


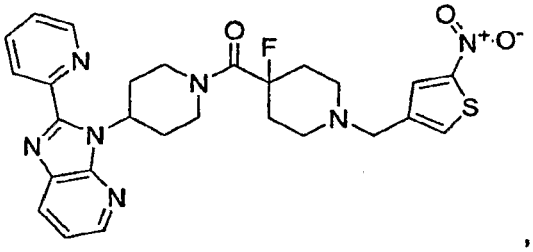


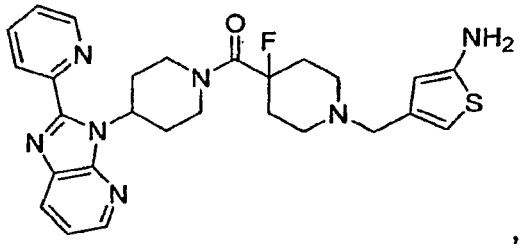


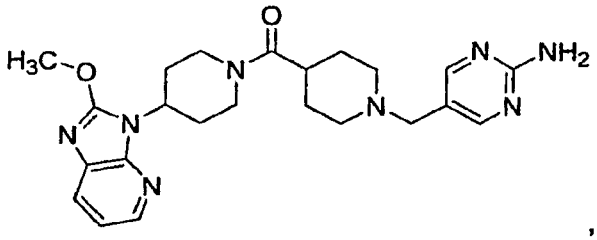


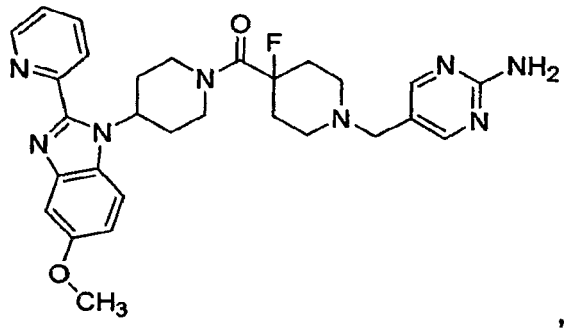


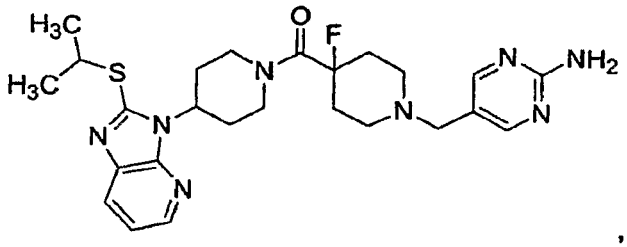


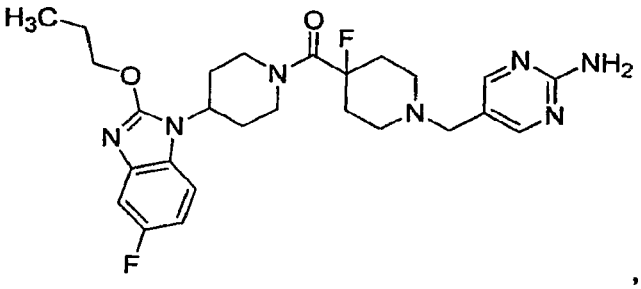


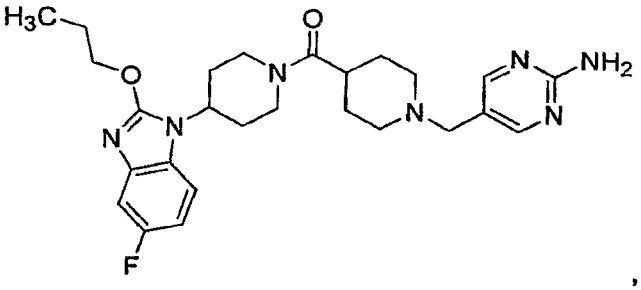


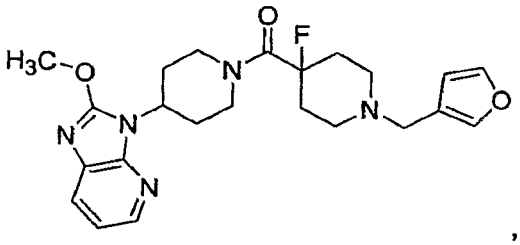


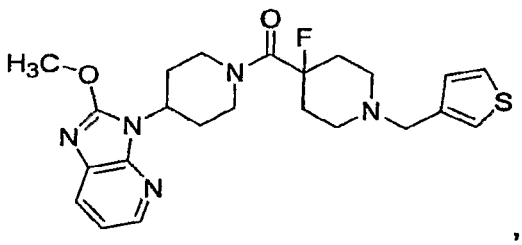


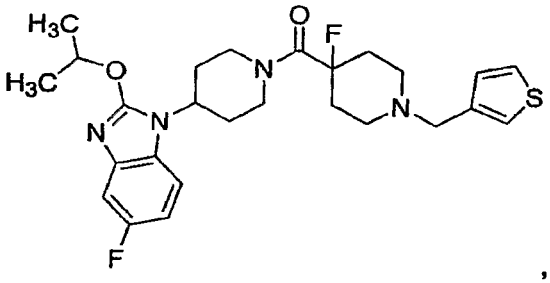


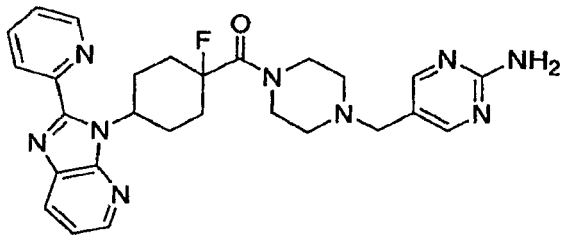


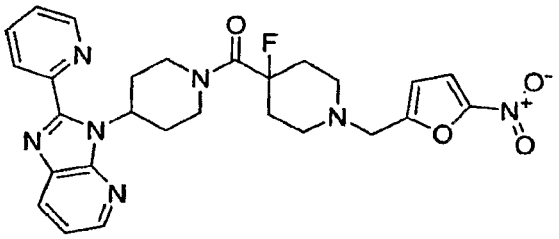


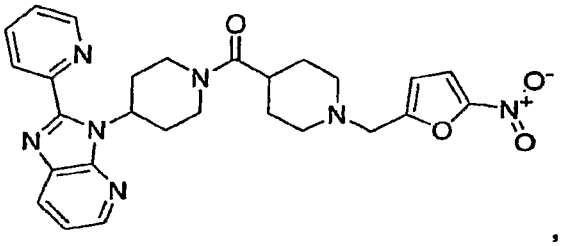


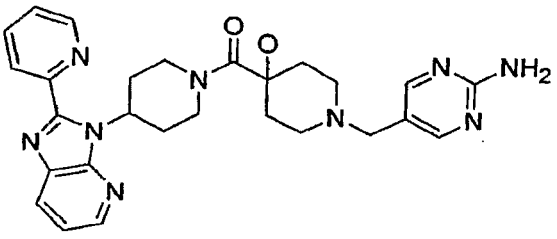


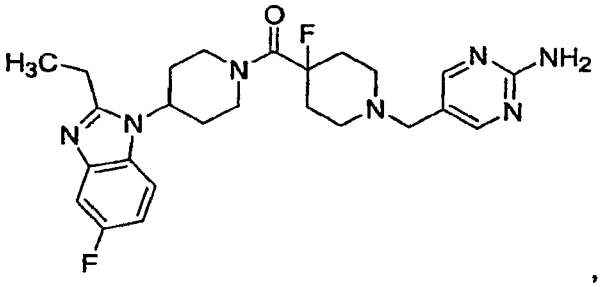
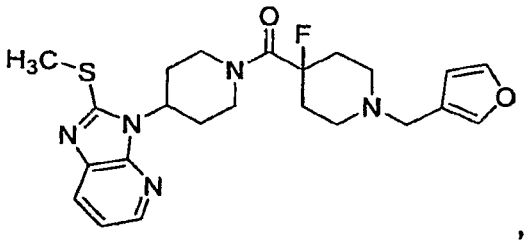
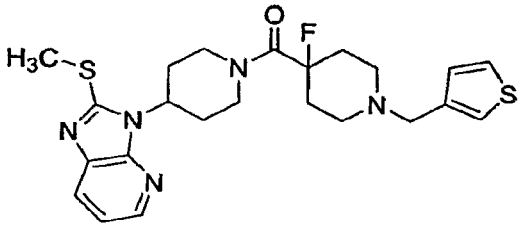
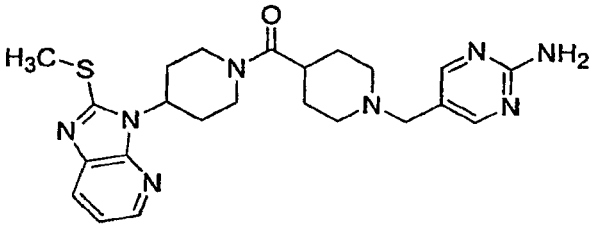
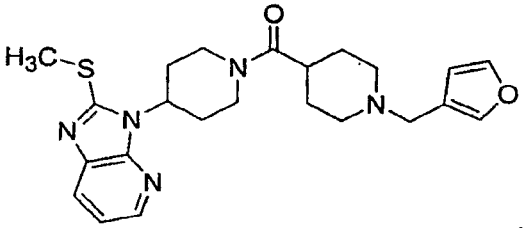
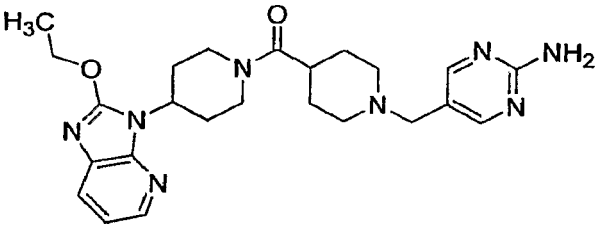
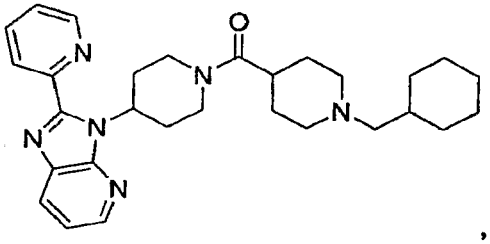
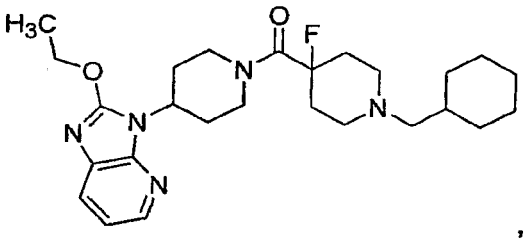
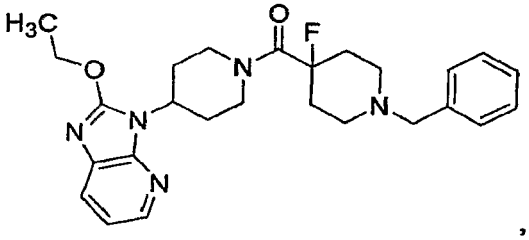
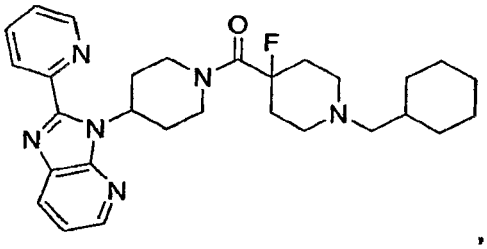
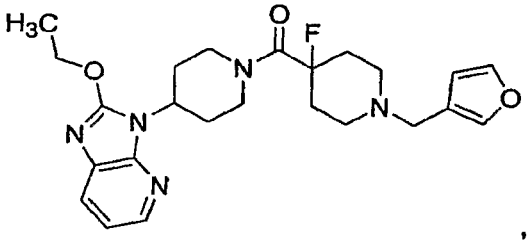
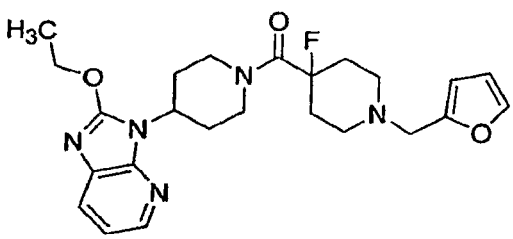




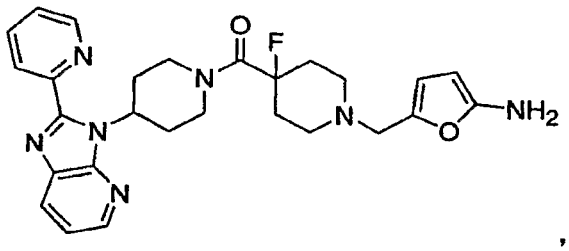
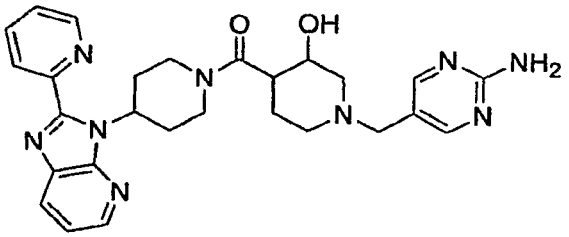
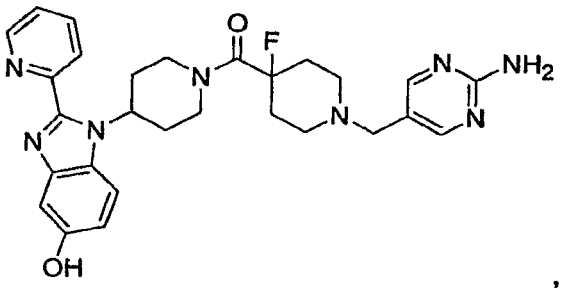
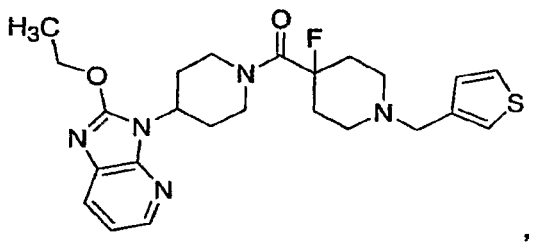
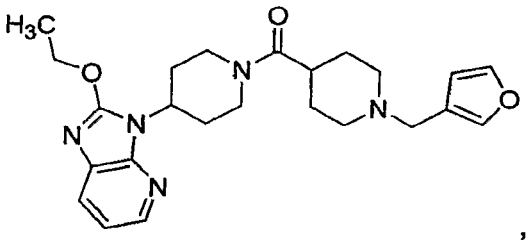
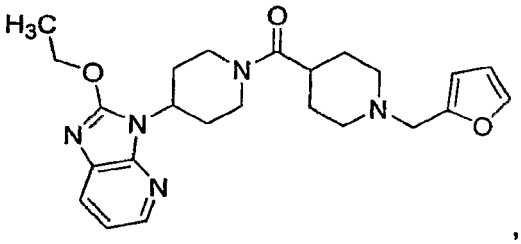
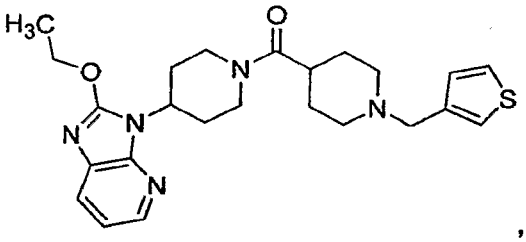
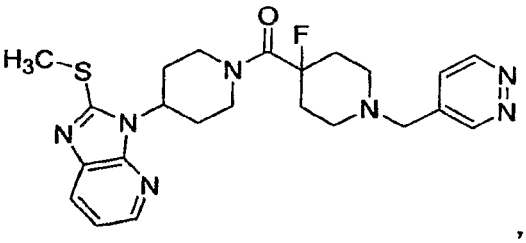
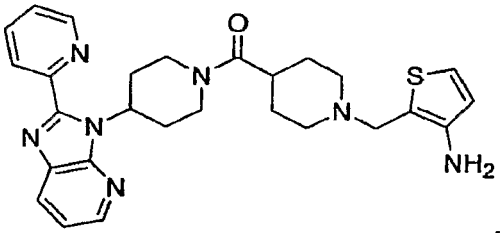
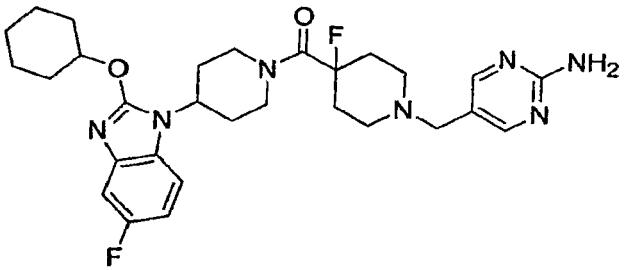
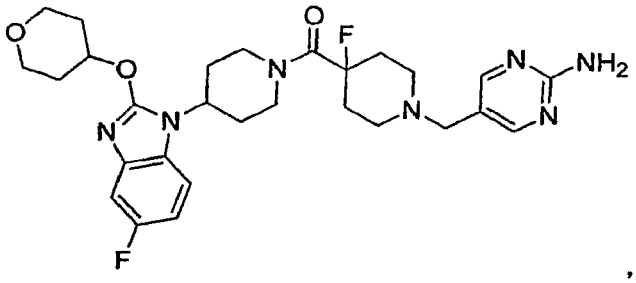
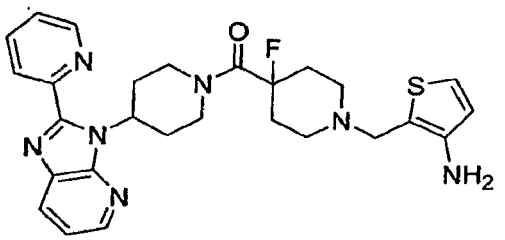







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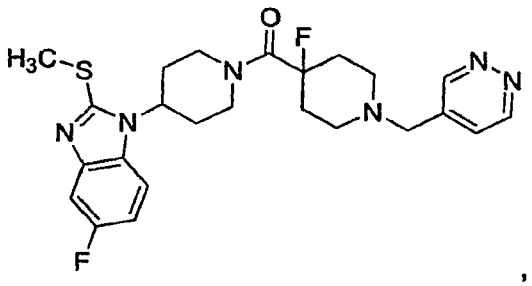
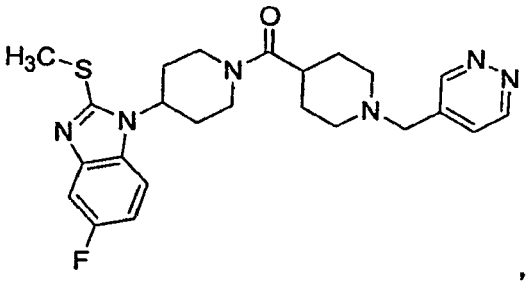
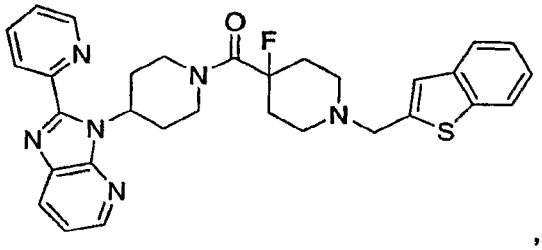
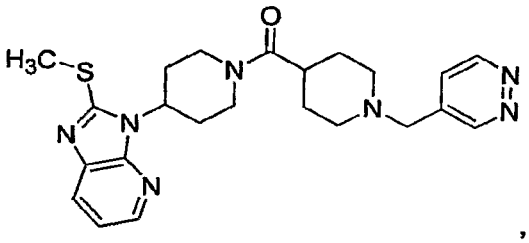
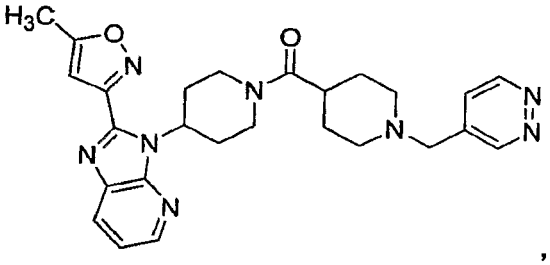
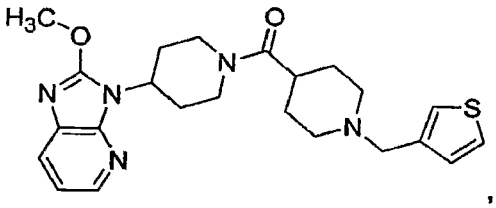
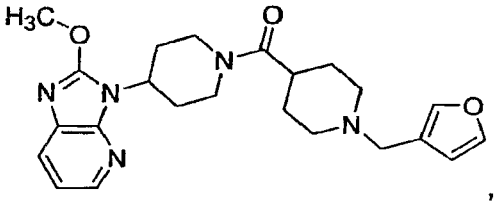
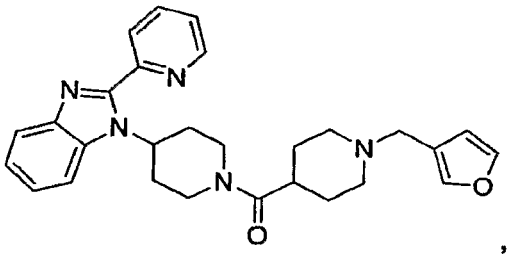
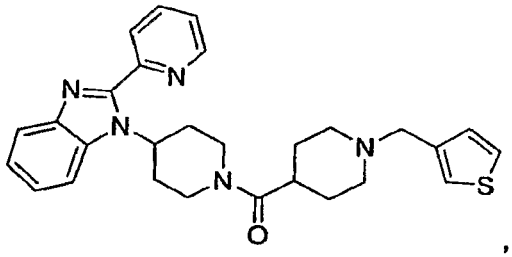
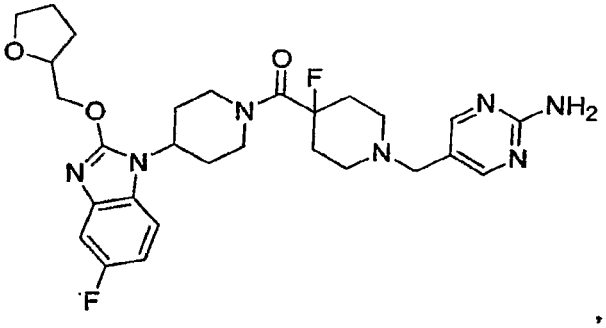
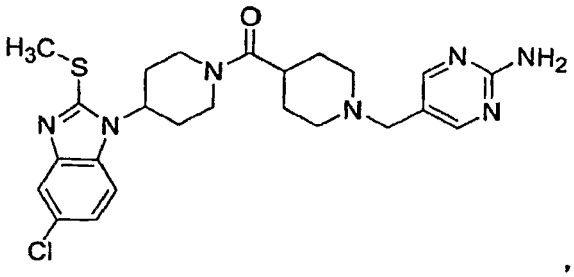
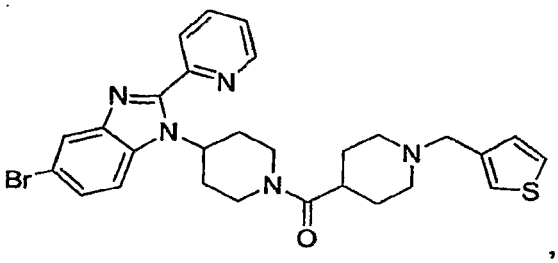
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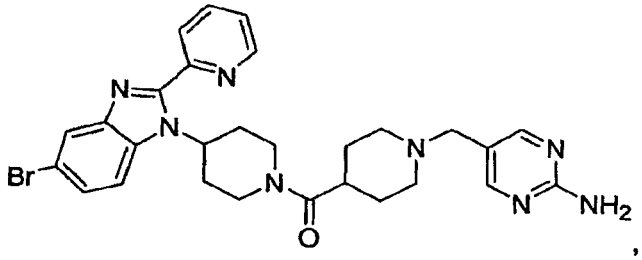
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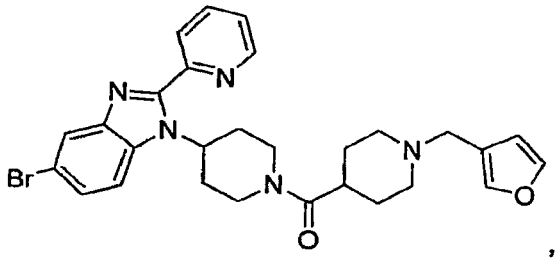
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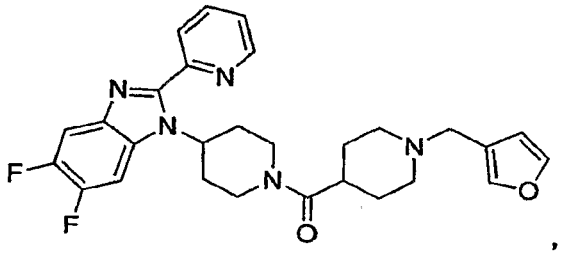
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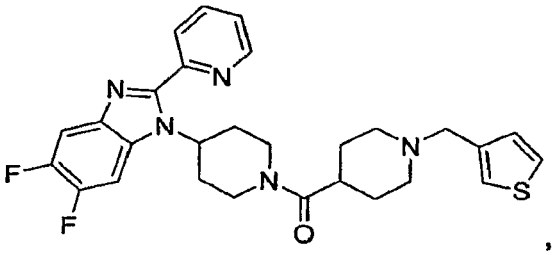

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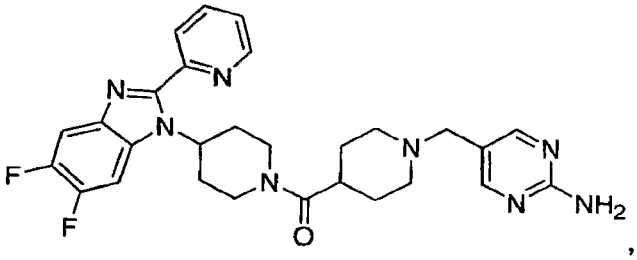
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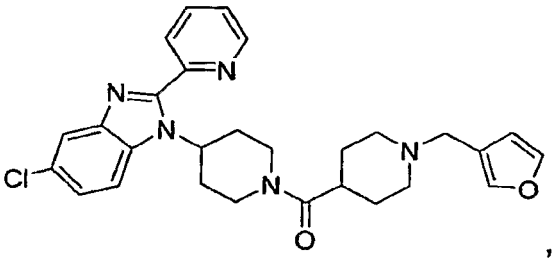


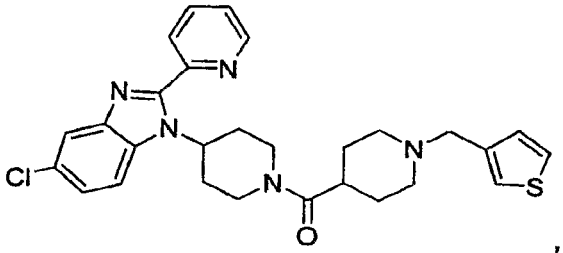


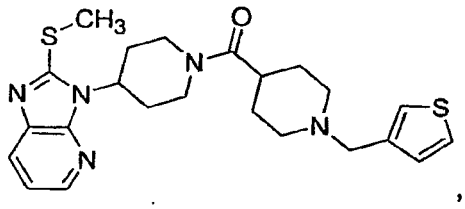


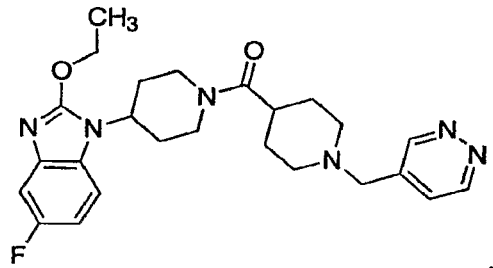


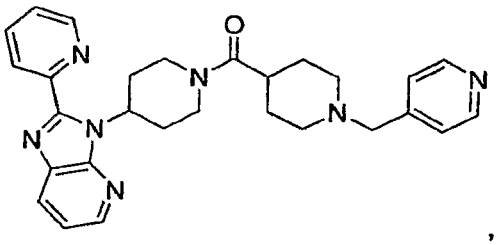


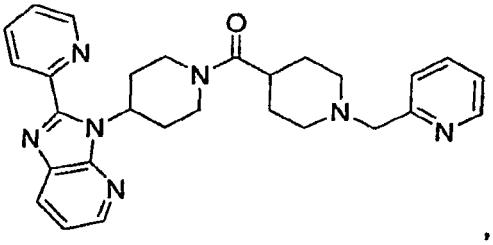


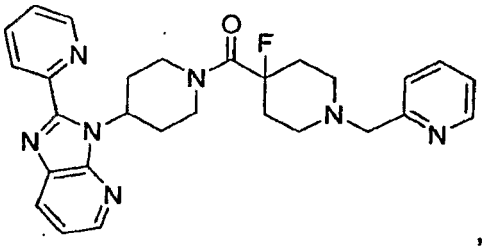


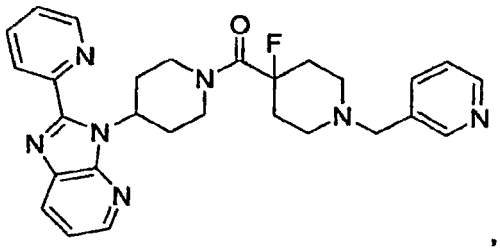
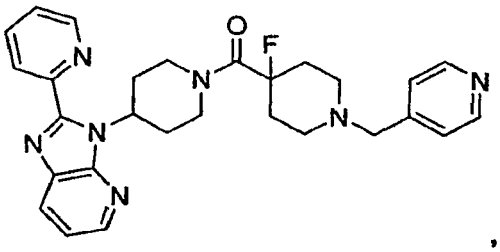
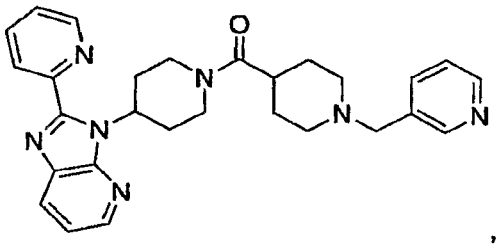
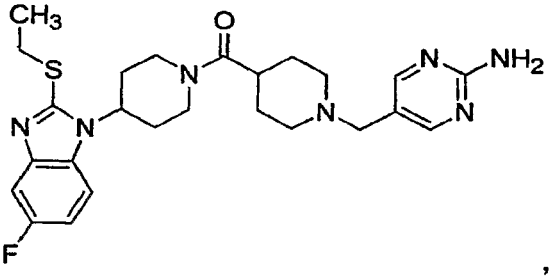
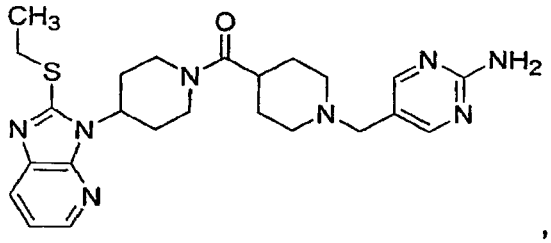
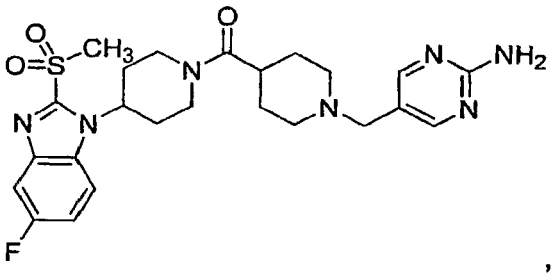
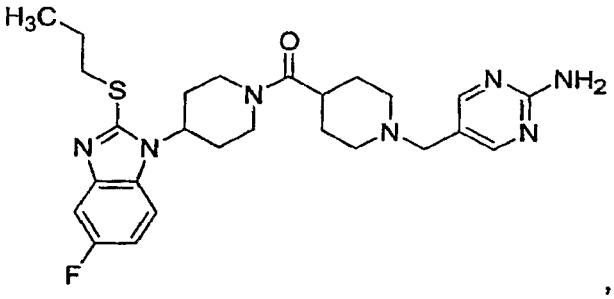
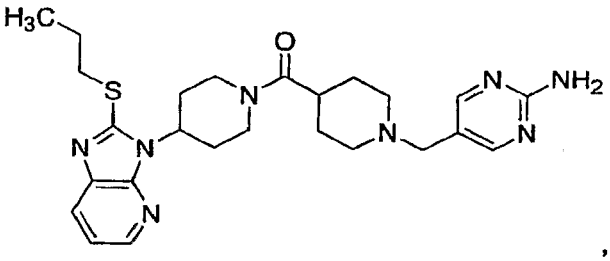
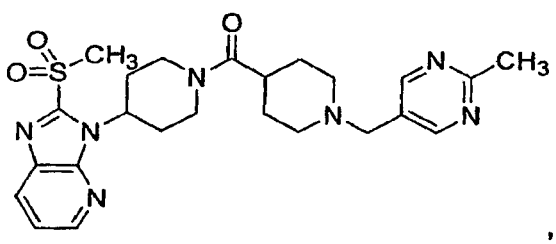
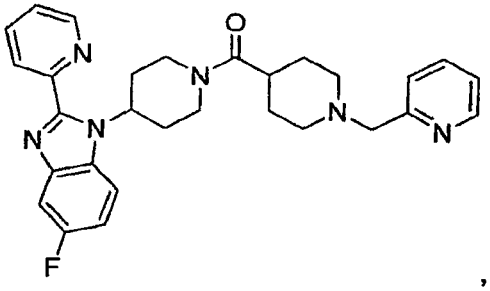
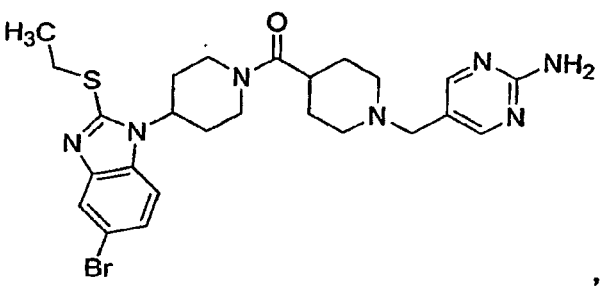
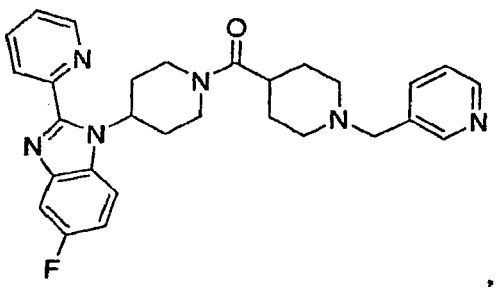




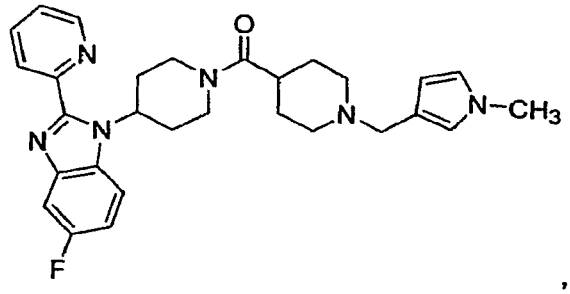




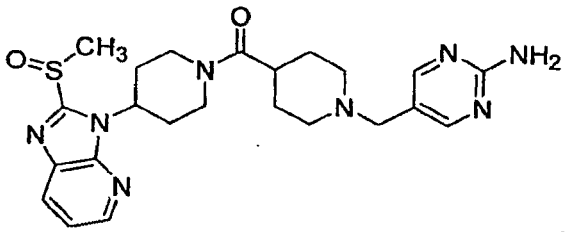



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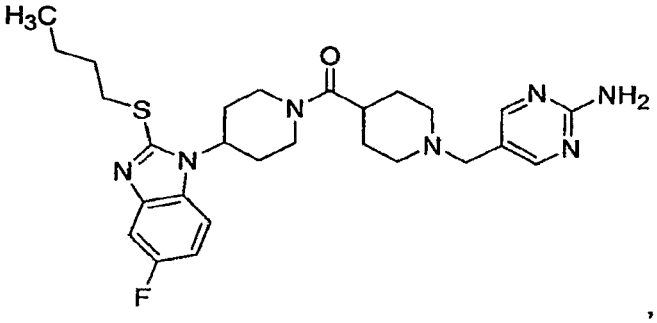
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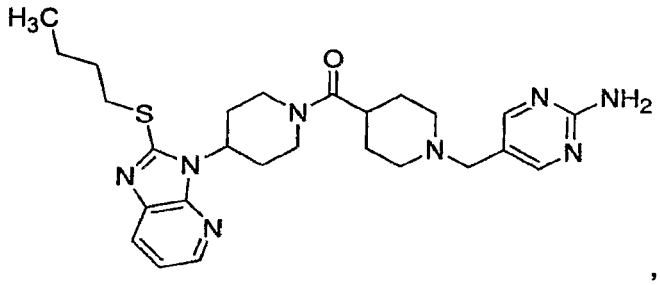
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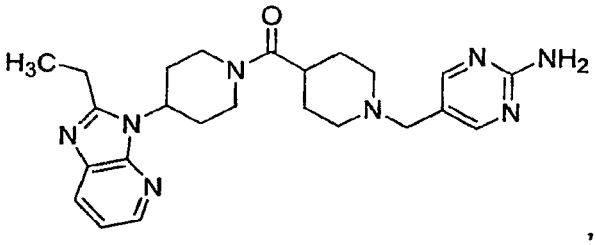
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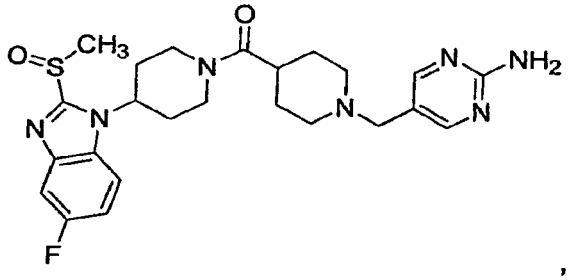
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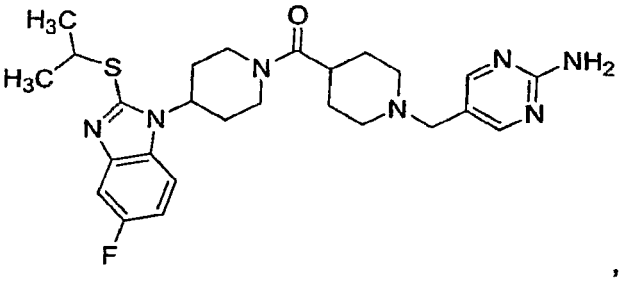
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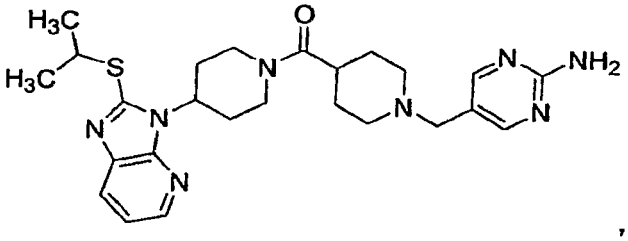
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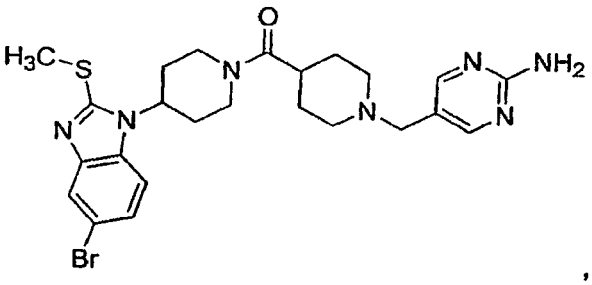
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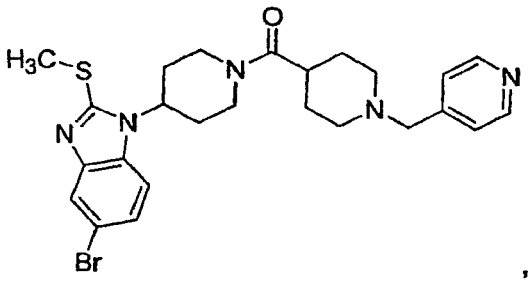


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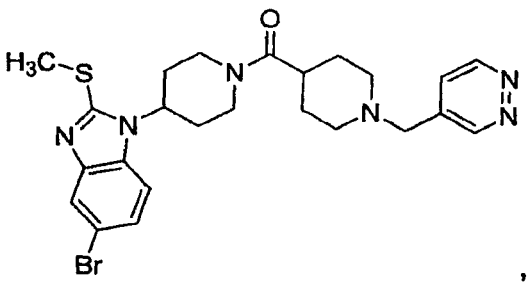


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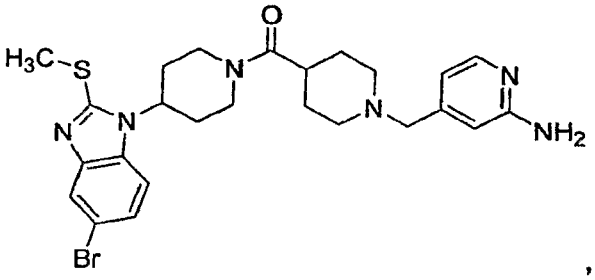
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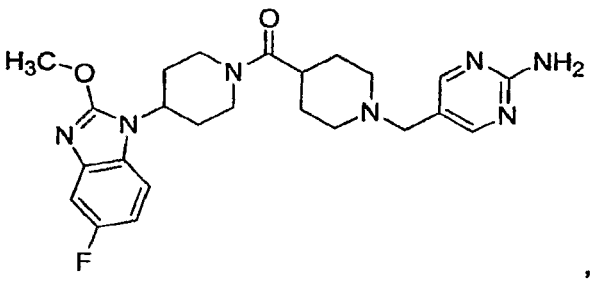
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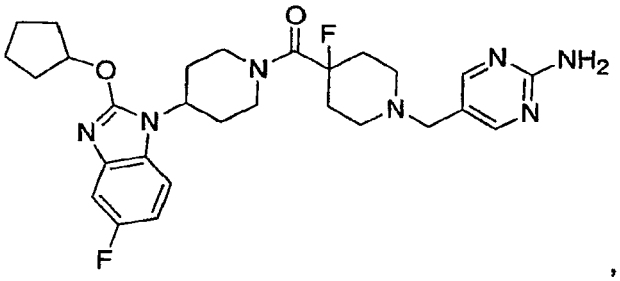
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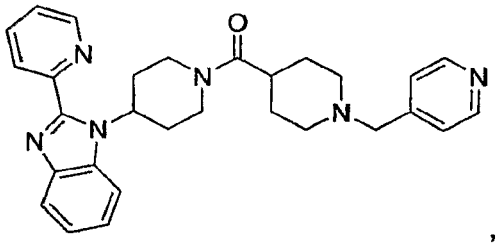
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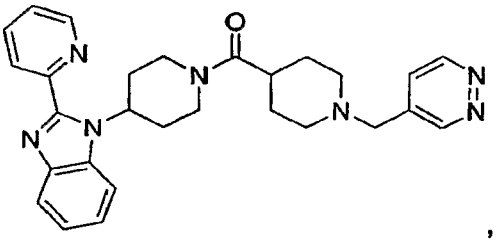
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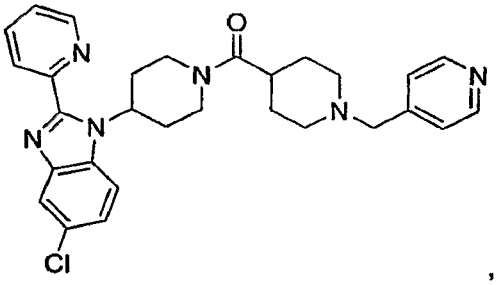
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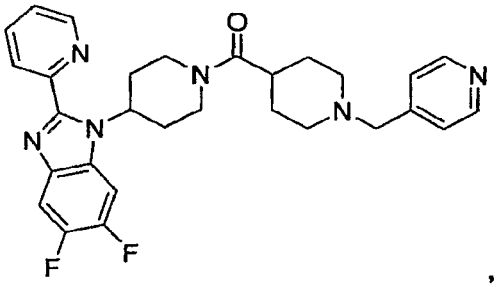
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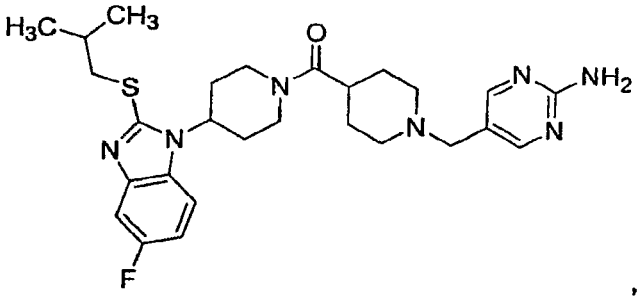
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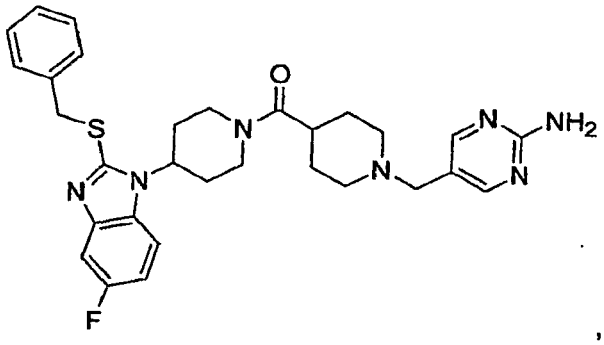


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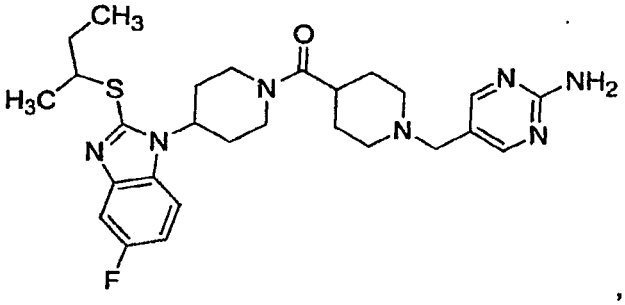


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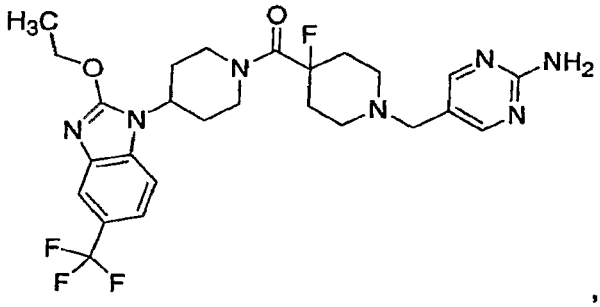
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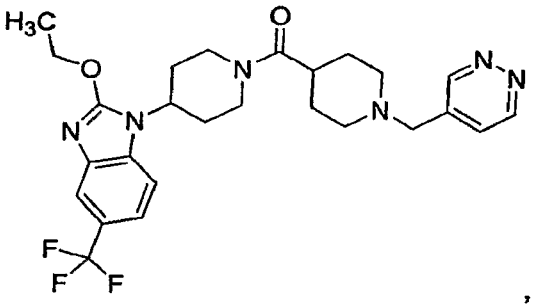
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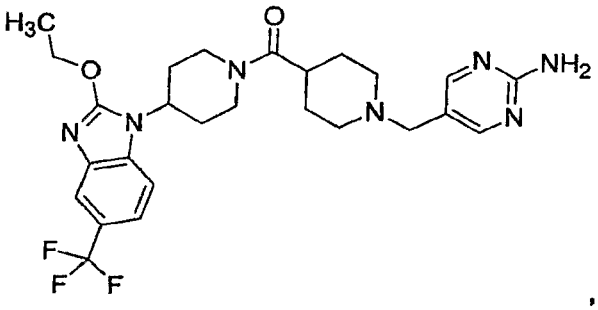
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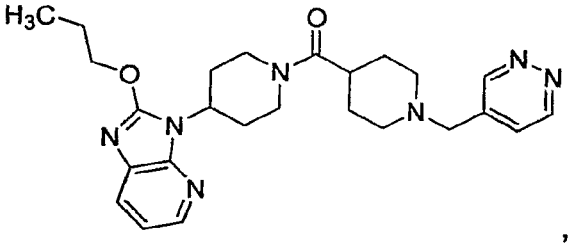
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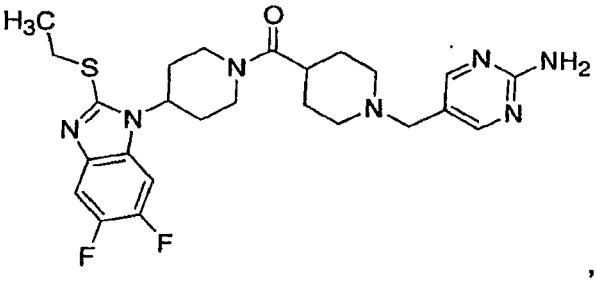
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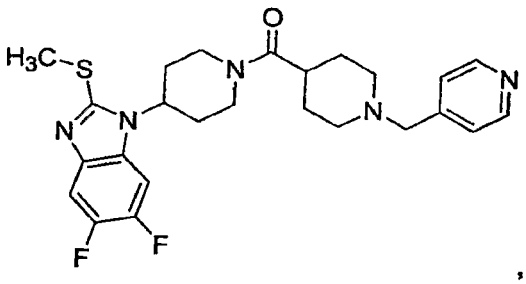
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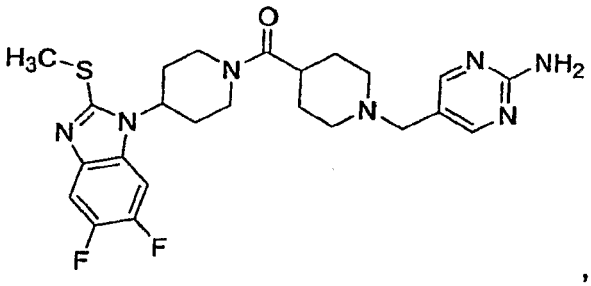
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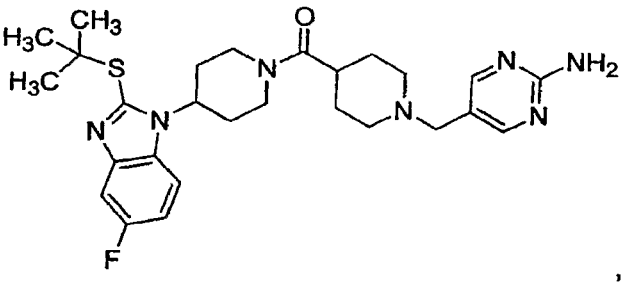
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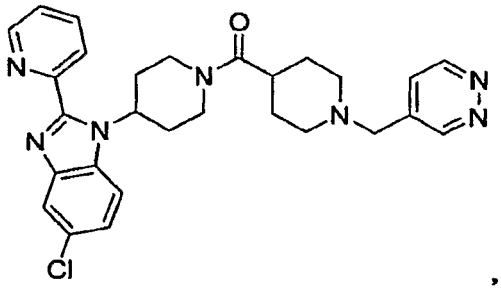
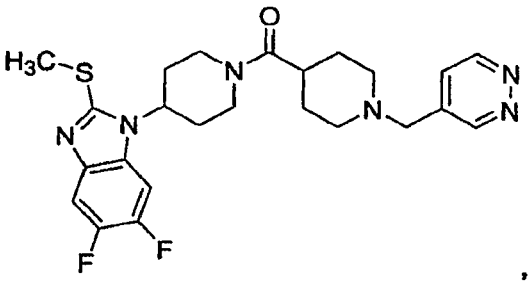
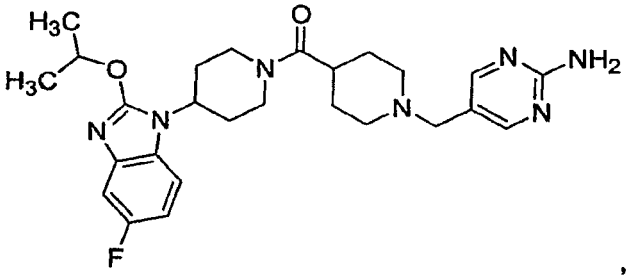
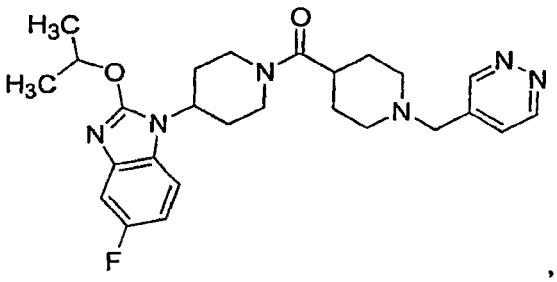
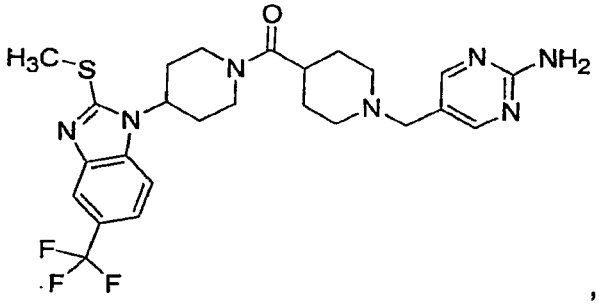
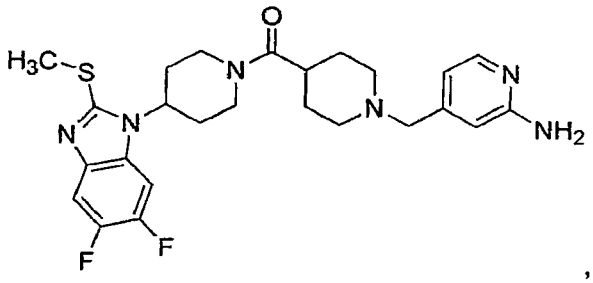
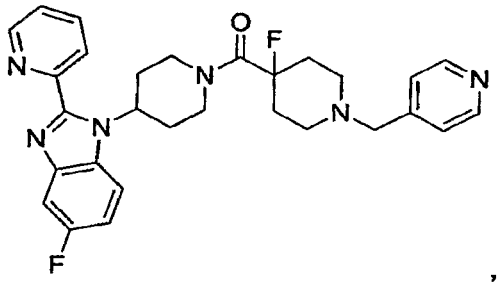
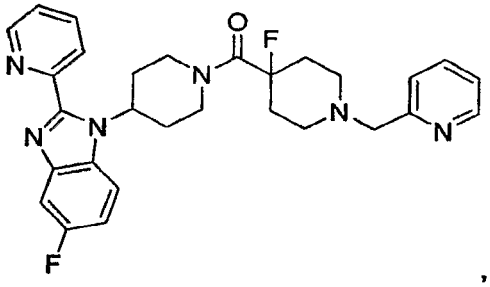
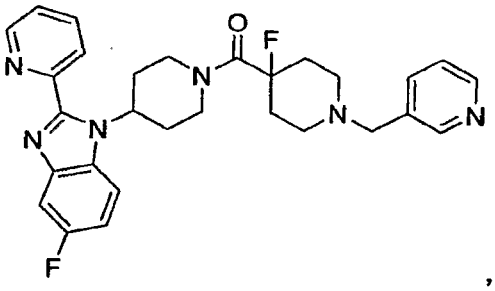
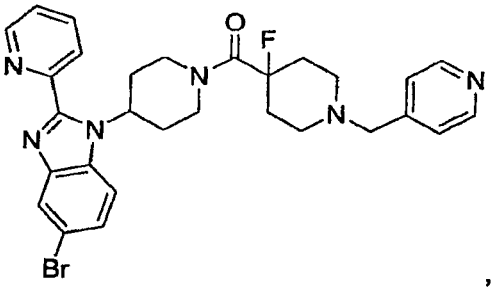


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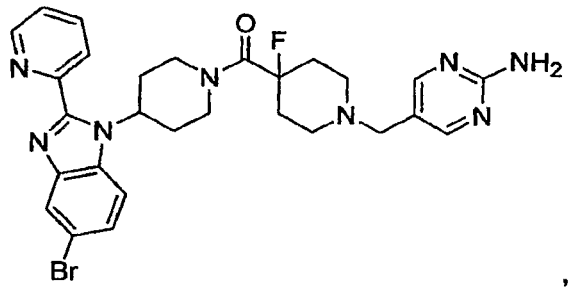
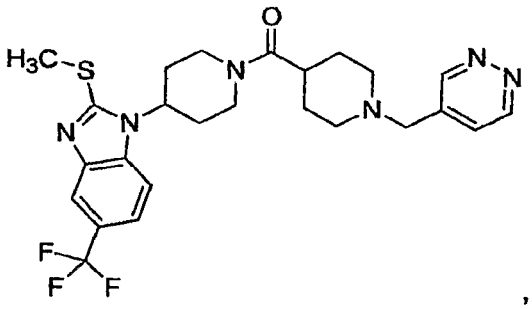
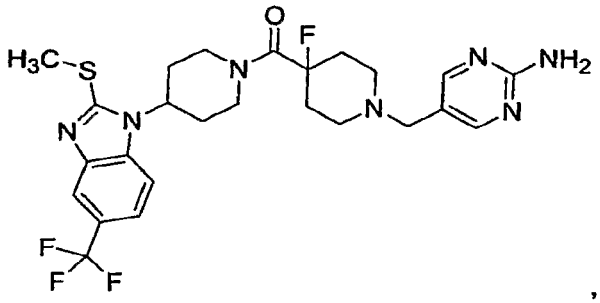
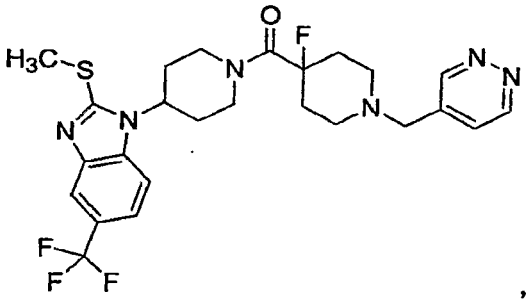
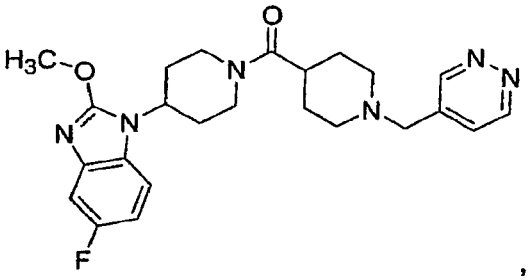
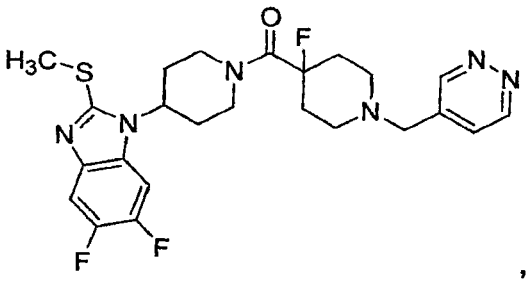
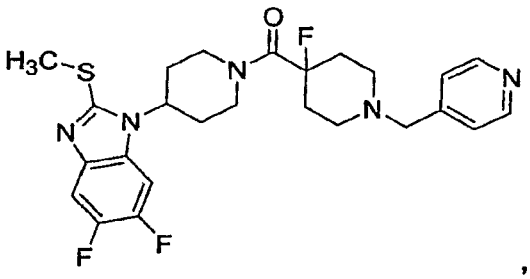
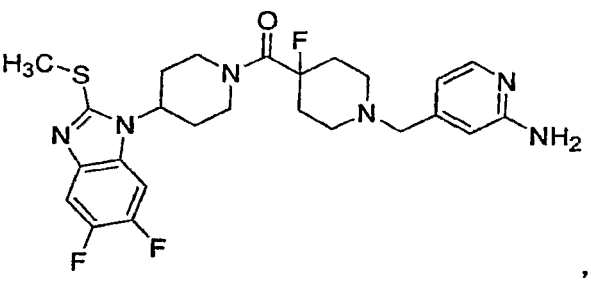
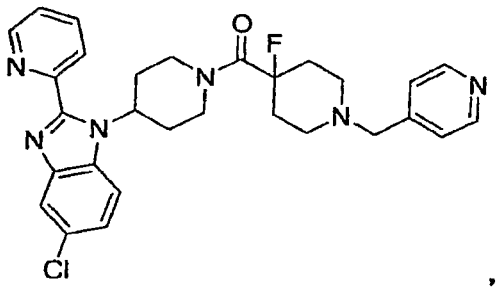
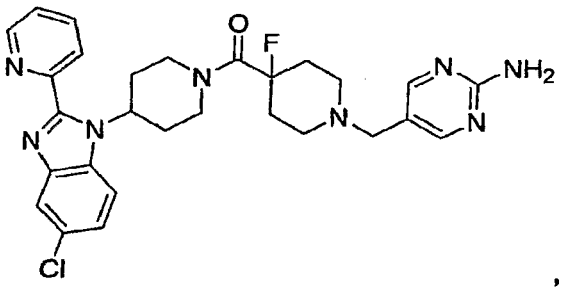


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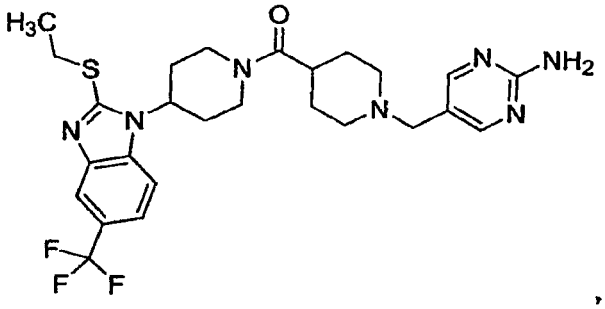
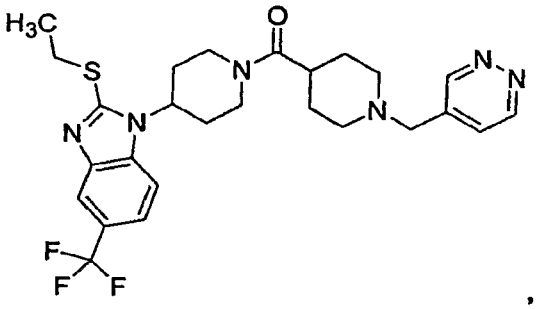
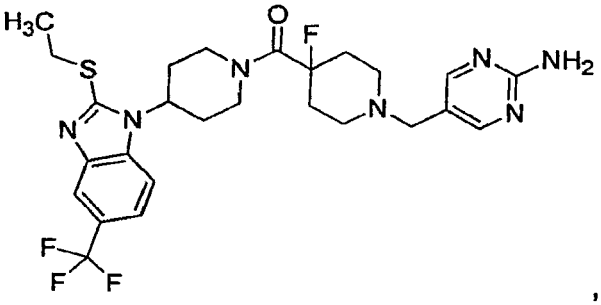
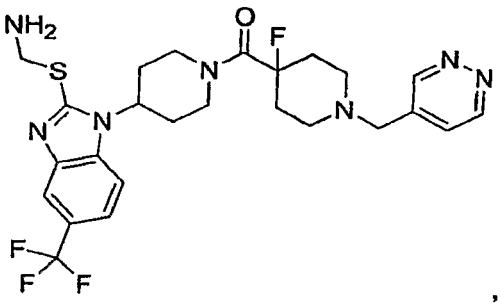
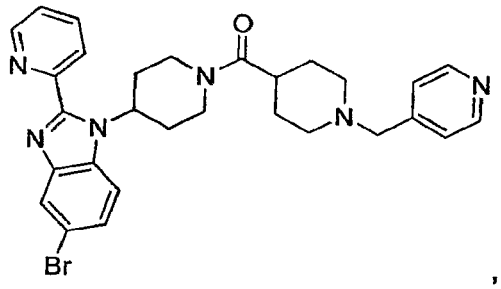
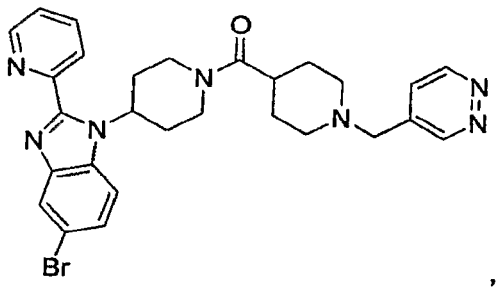
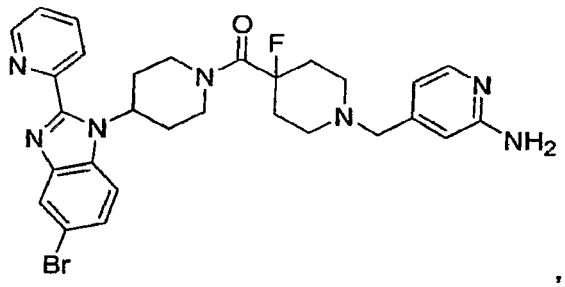
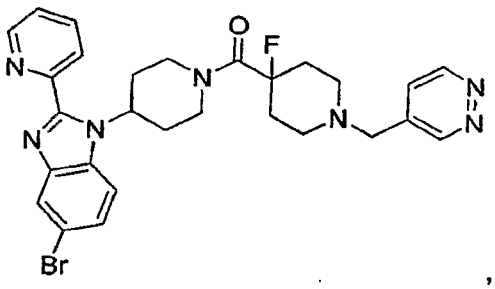
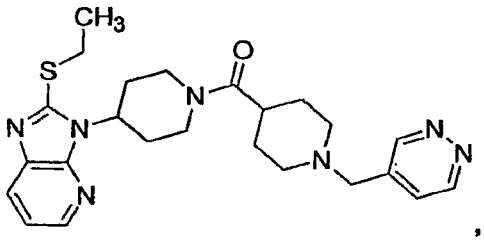
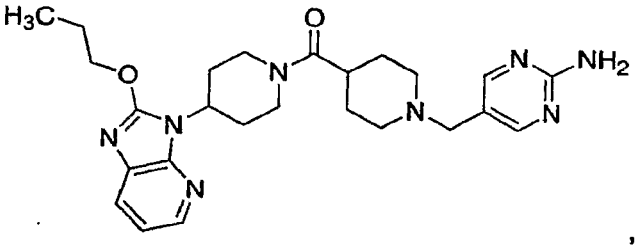
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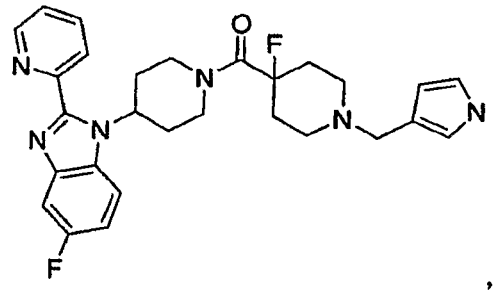
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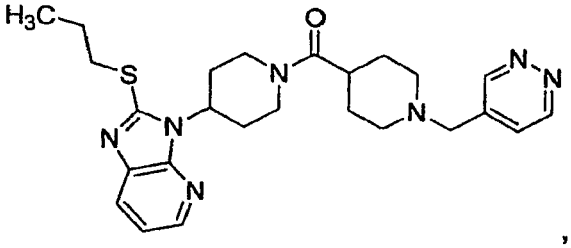
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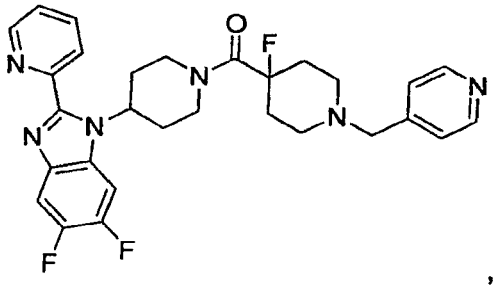
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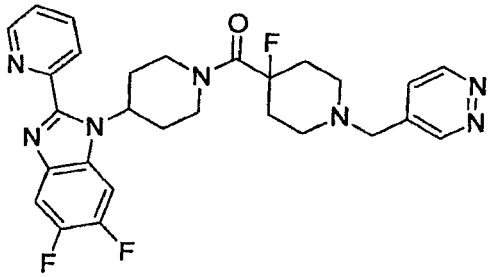
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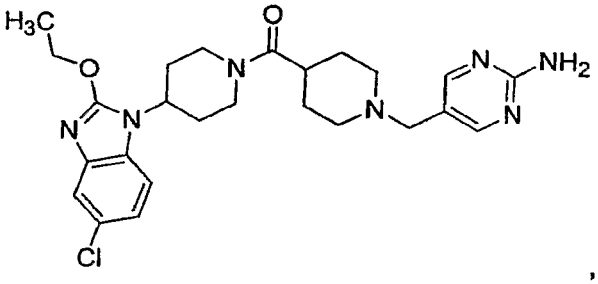
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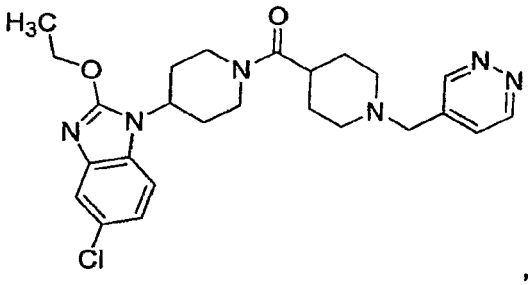
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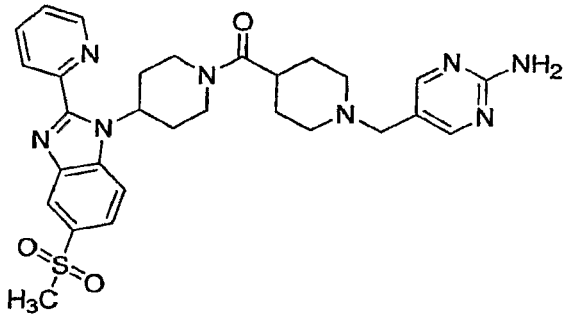
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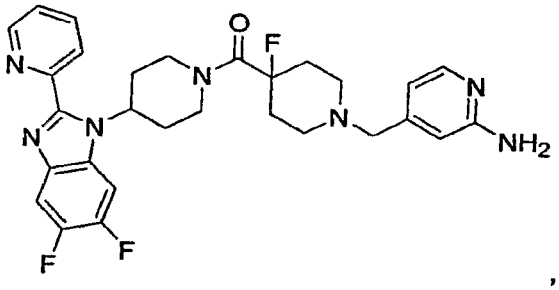
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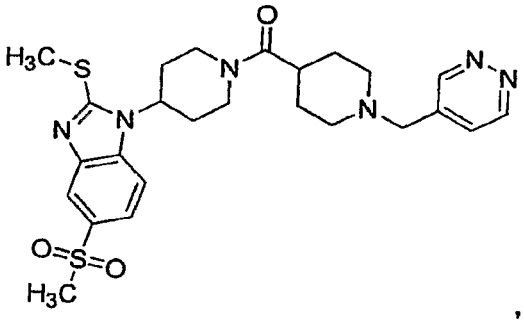
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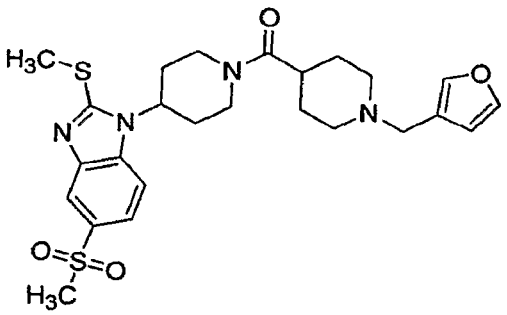
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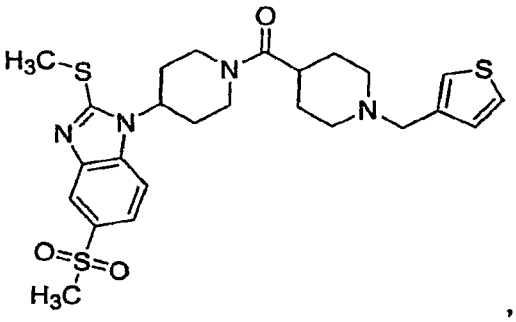


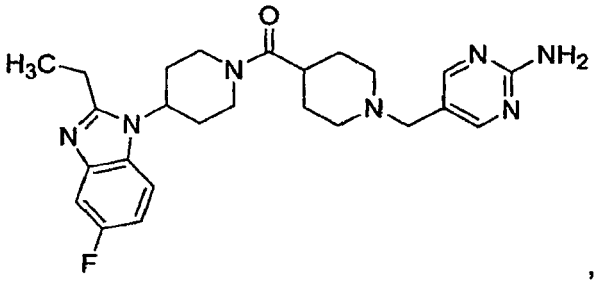
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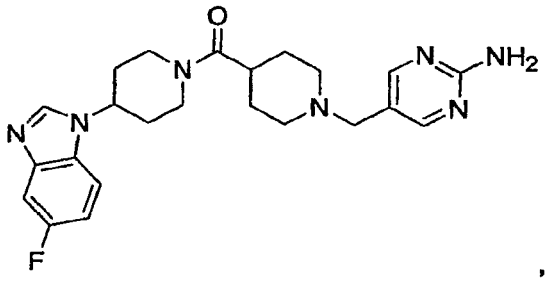


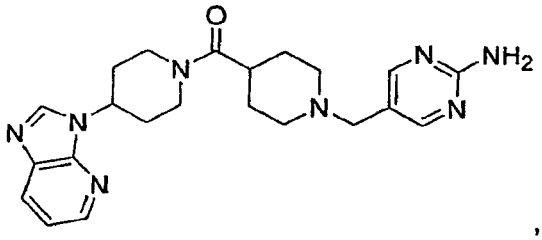
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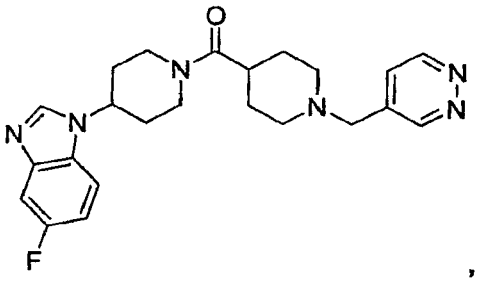
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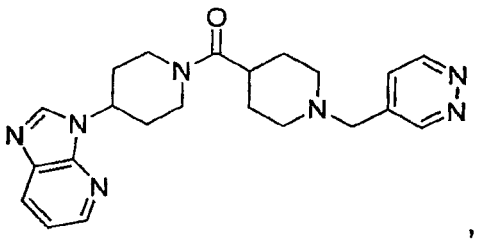


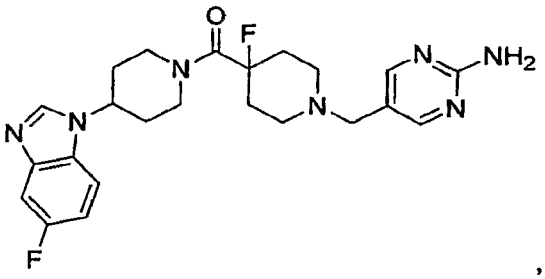


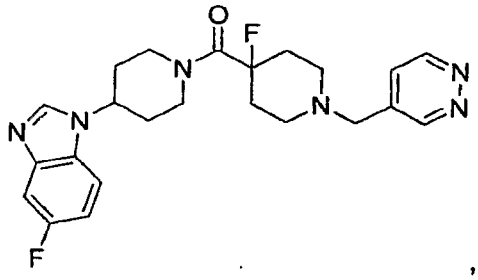


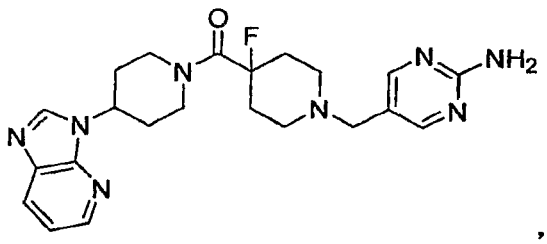


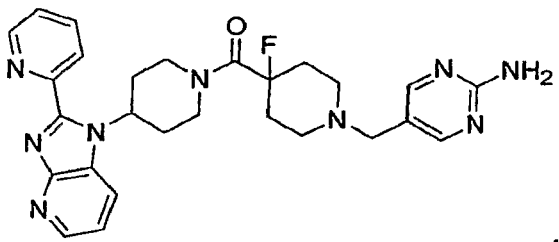


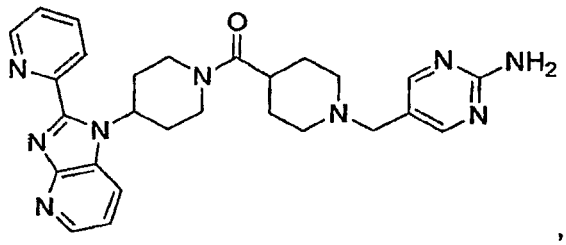


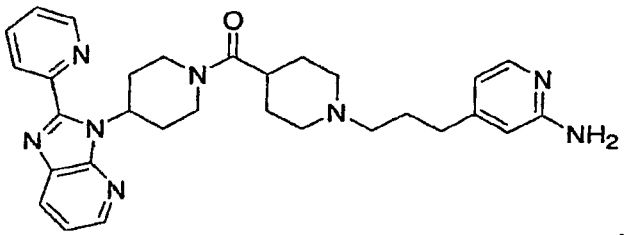


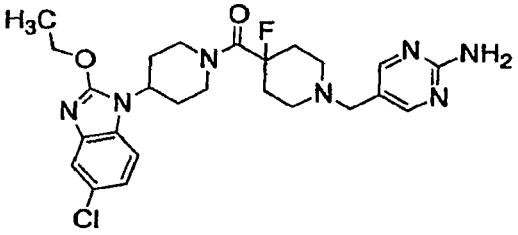
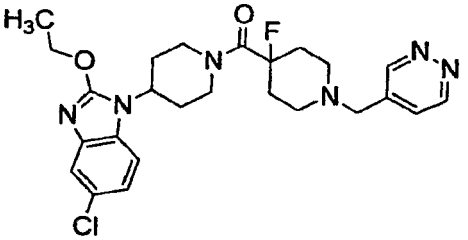
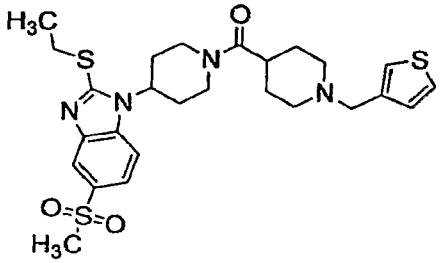
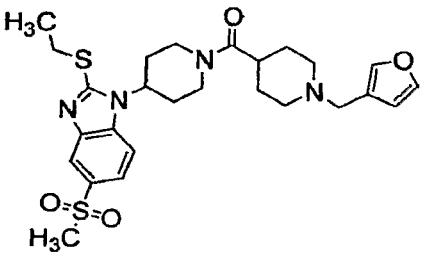
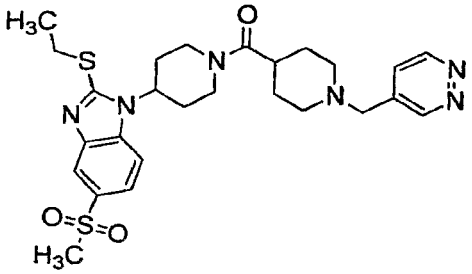
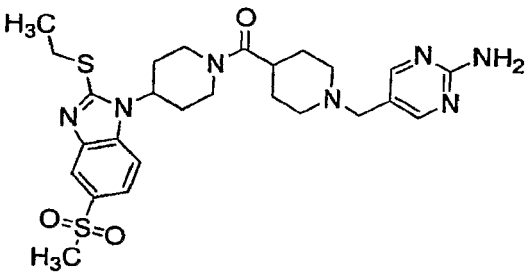
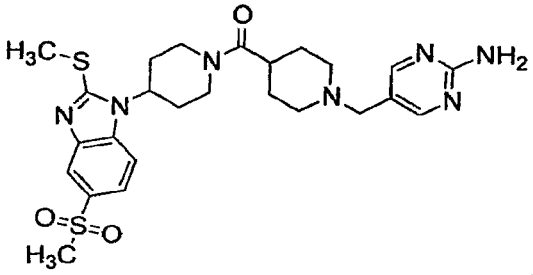
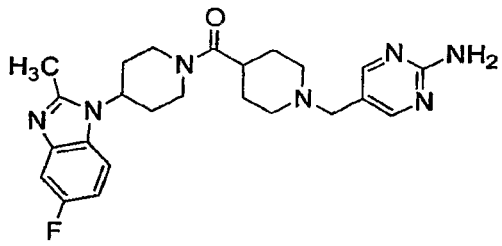
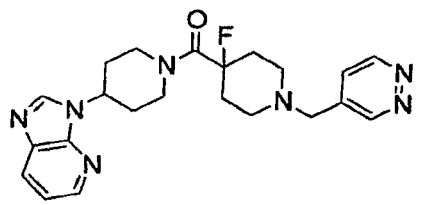
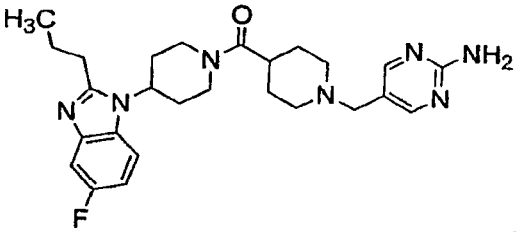
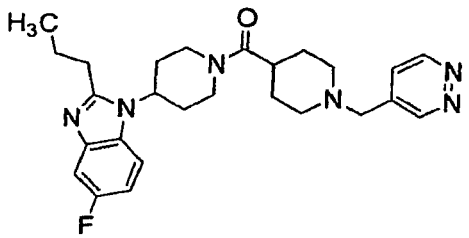
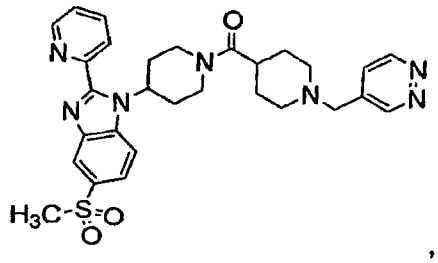




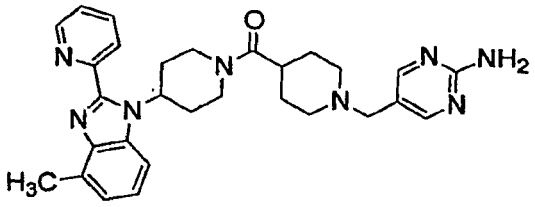
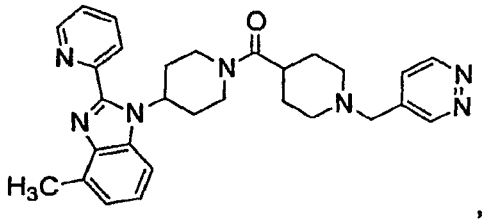
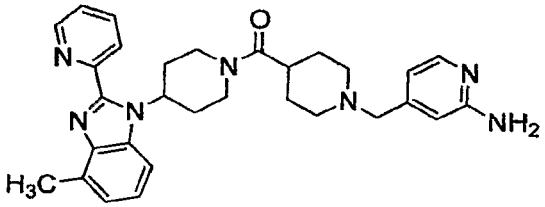
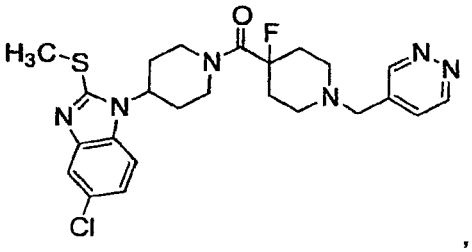
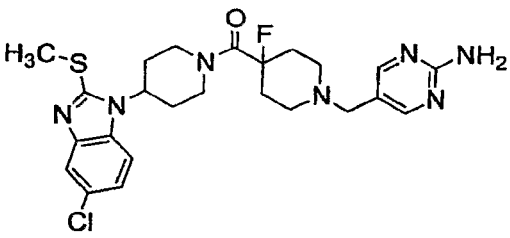
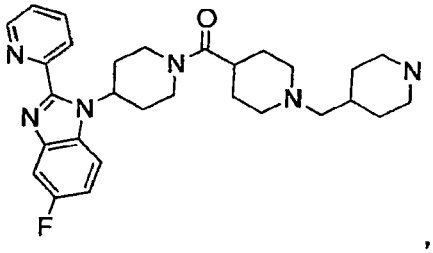
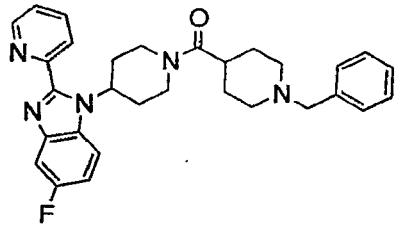
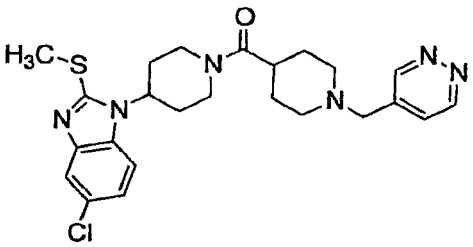
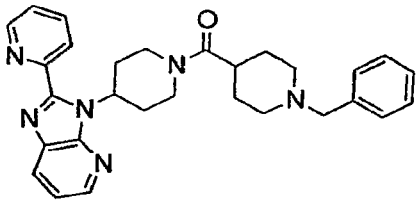
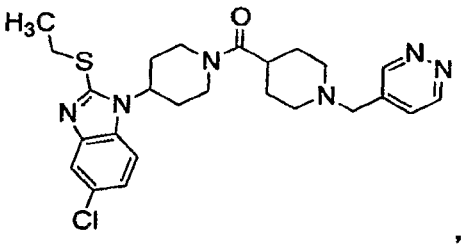
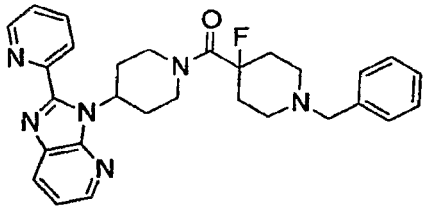
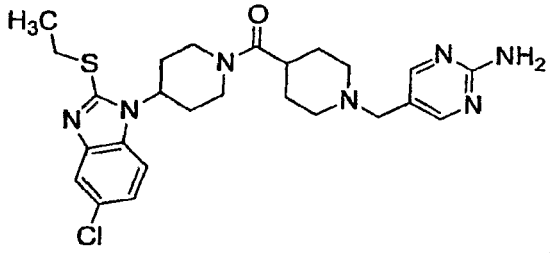




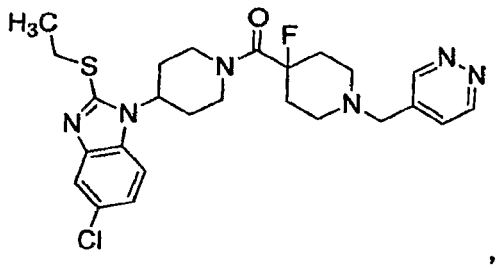
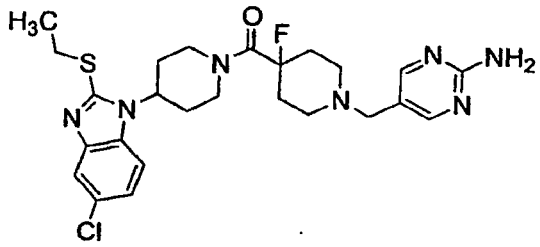
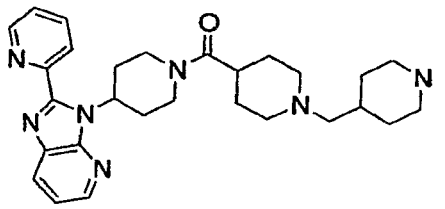
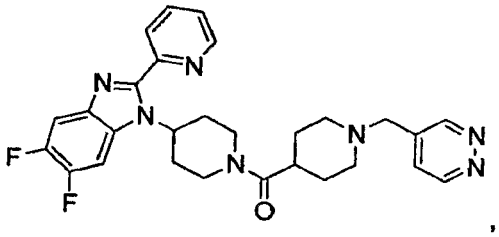
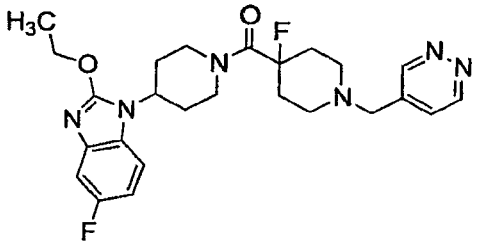
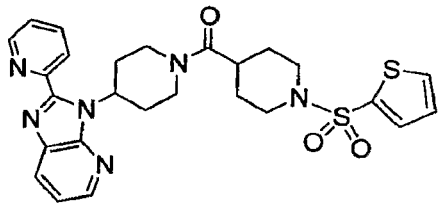
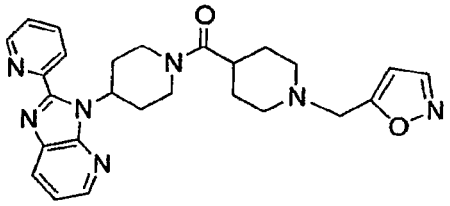
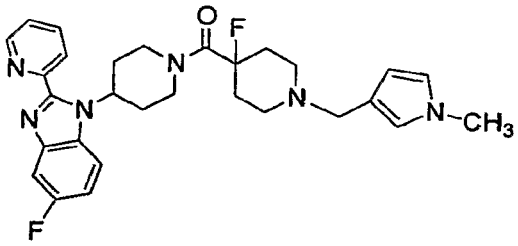
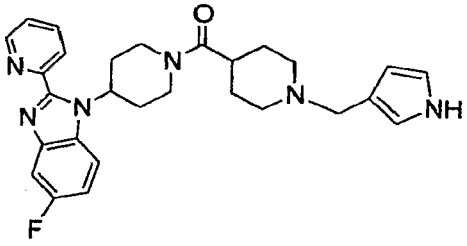
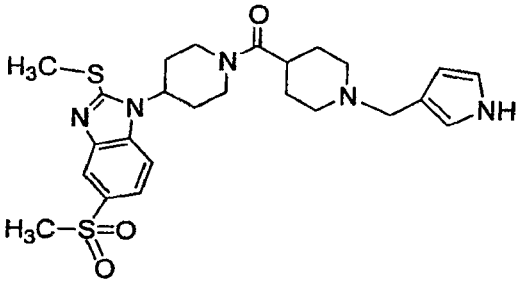
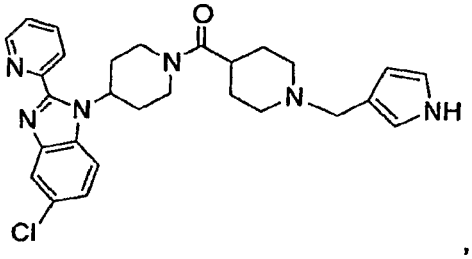
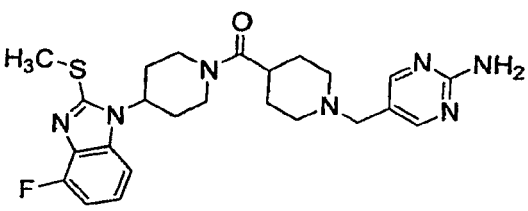



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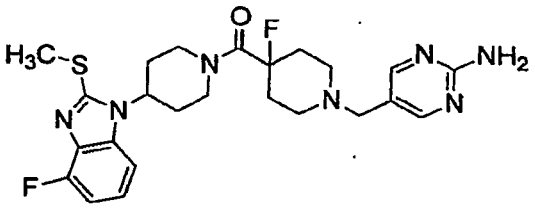
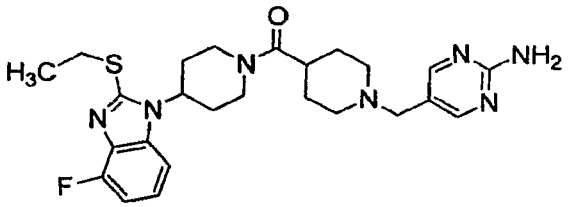
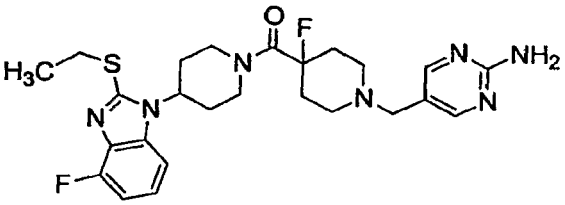
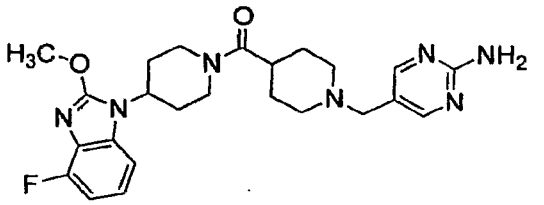
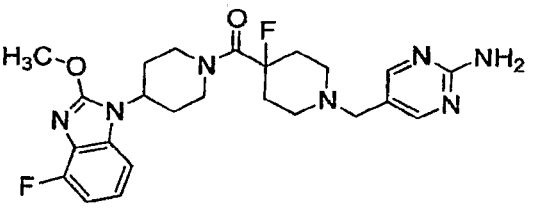
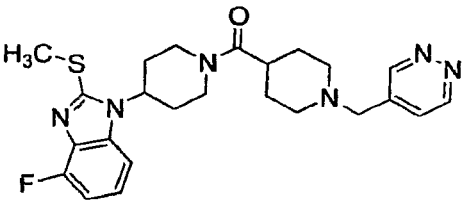
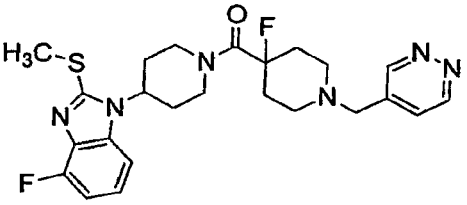
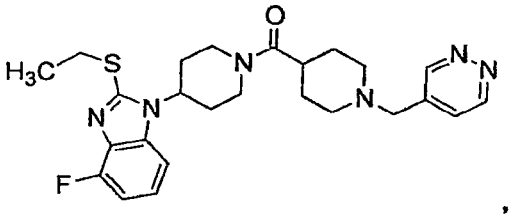
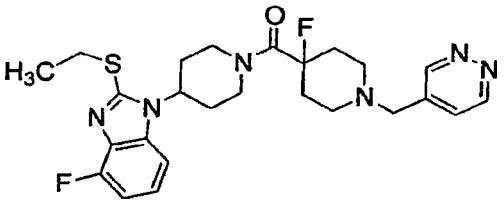
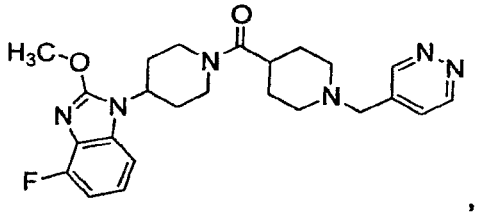
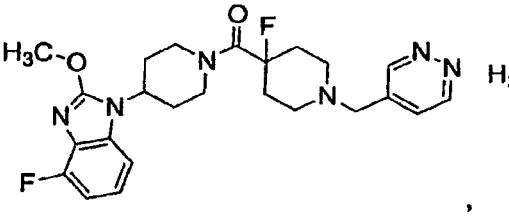
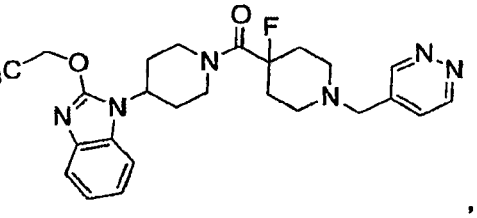
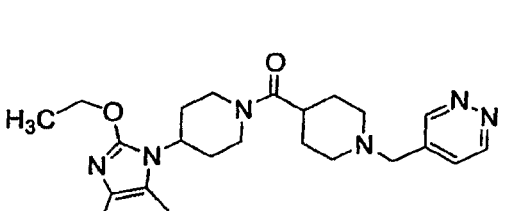
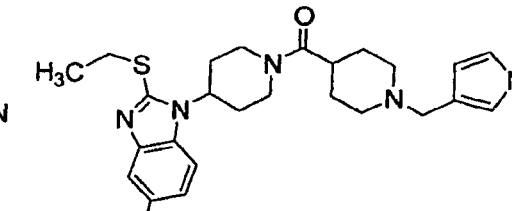
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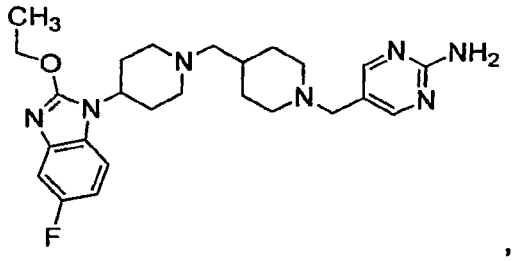
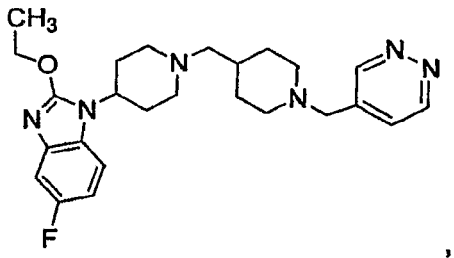
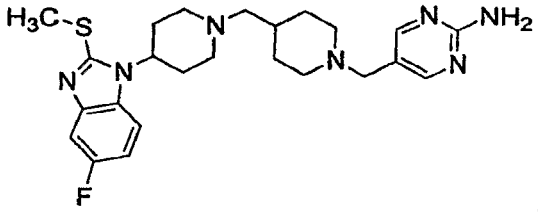
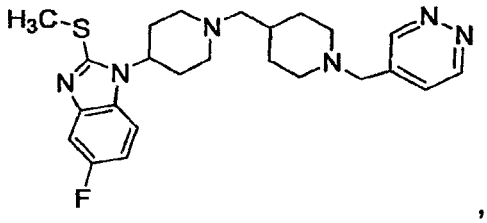
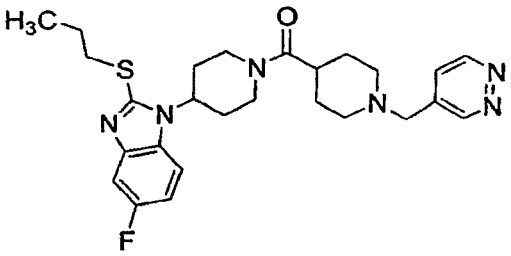
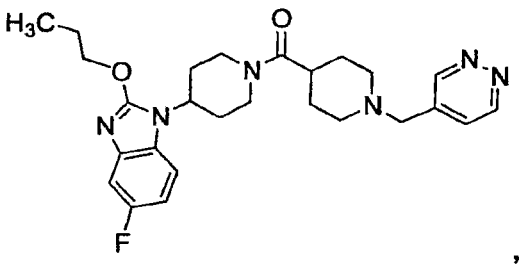
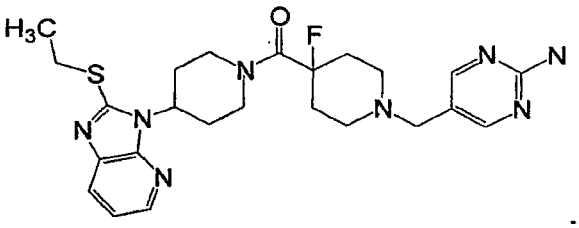

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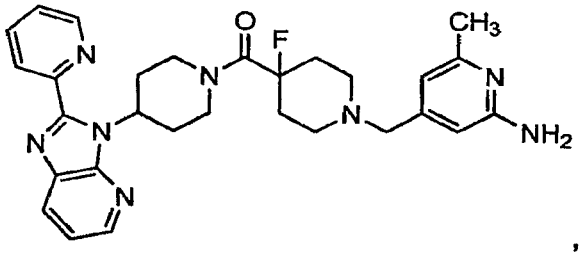

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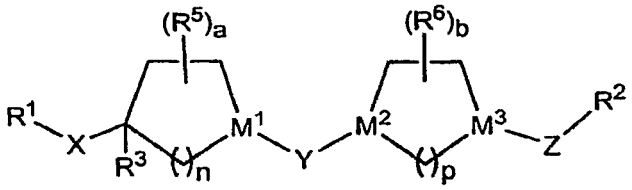

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In another embodiment, the H_3 antagonists/inverse agonists of the present invention can have the following structure:


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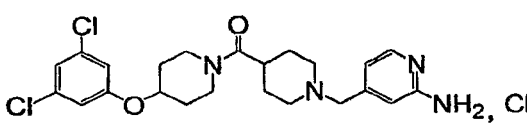
as described in U.S. Provisional Application No. 60/718,673, filed September 20, 2005, and which is herein incorporated by reference in its entirety.

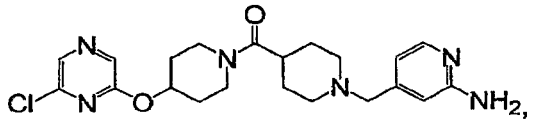
In another embodiment, t he H_3 antagonists/inverse agonists of the present invention can have the following Formula (VII):

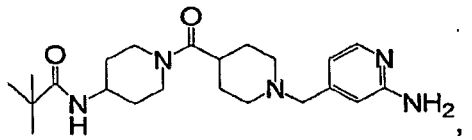


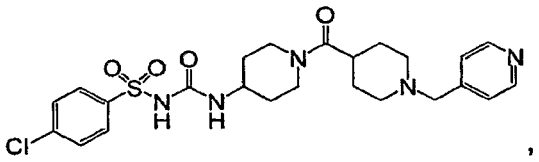
(VII)

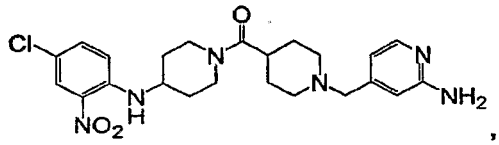
as described in U.S. Provisional Application No. 60/692,110, filed June 20, 2005, and which is herein incorporated by reference in its entirety. Non-limiting examples of compounds of Formula (VII) include:

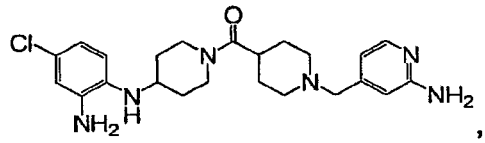


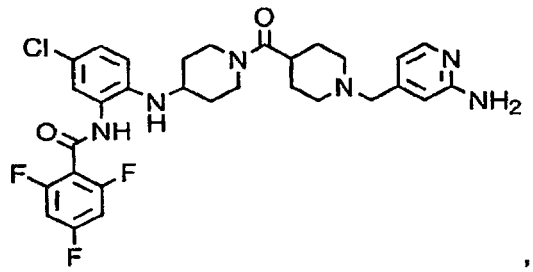


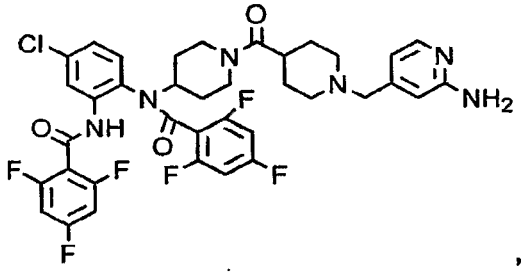


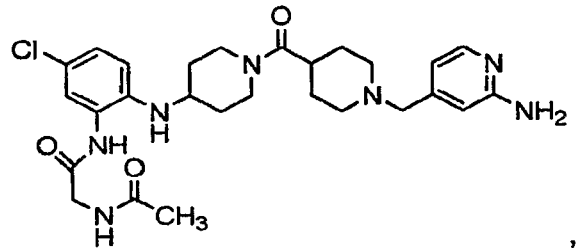


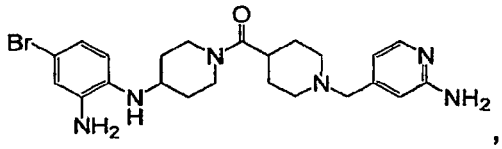


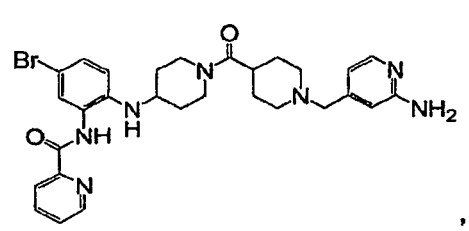


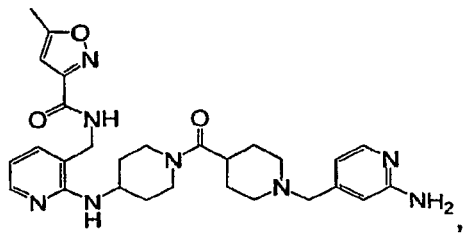


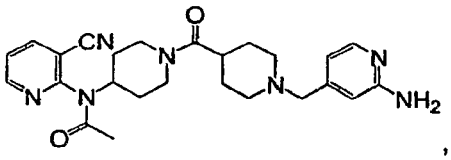
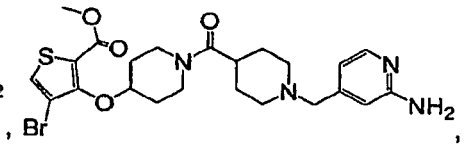
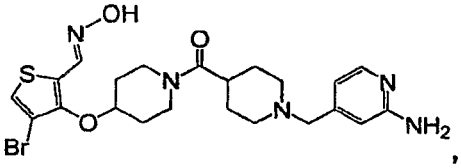
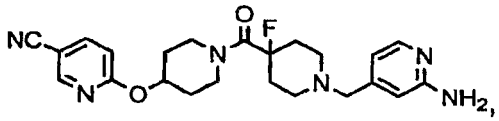
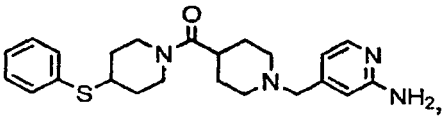
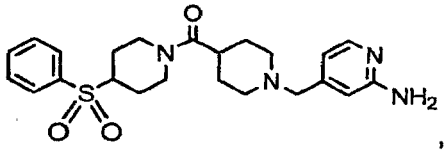
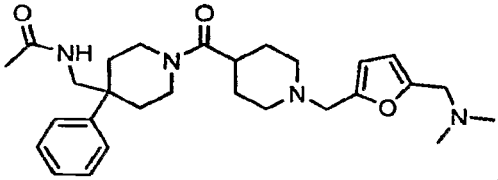
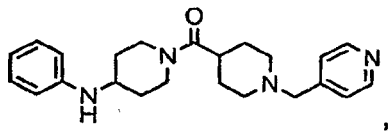
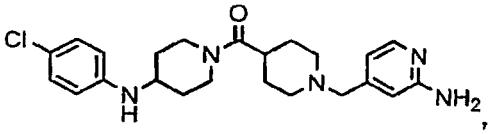
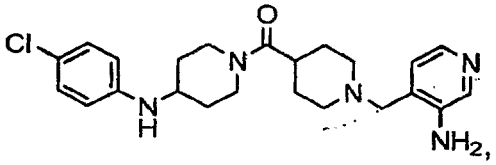
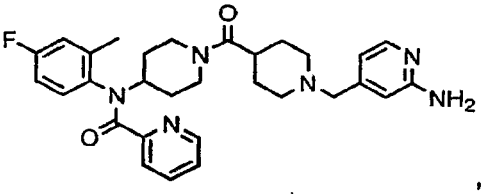
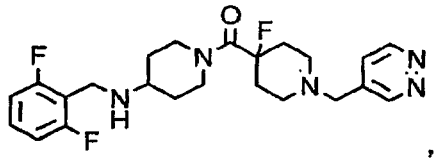
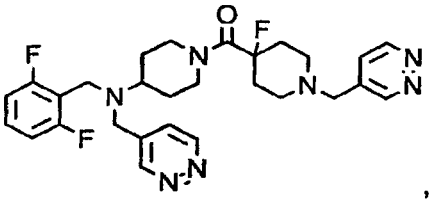
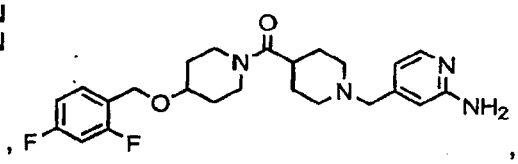
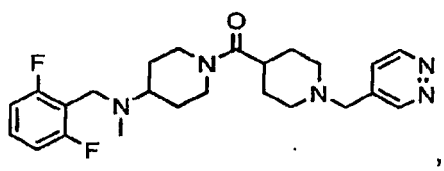
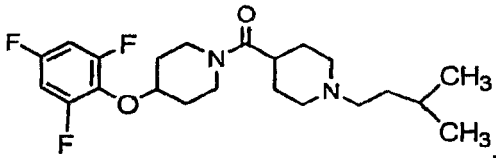
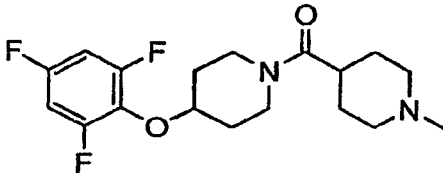
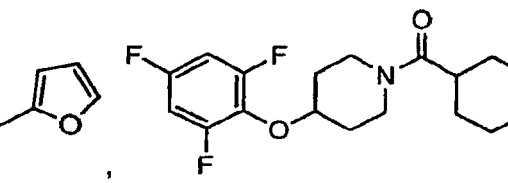


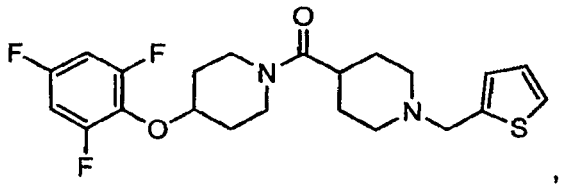
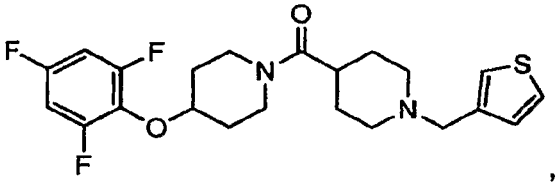
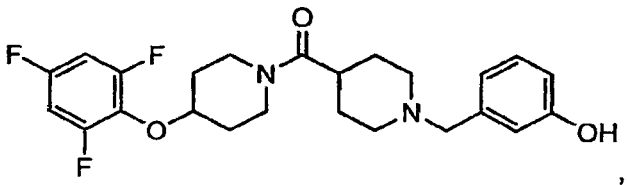
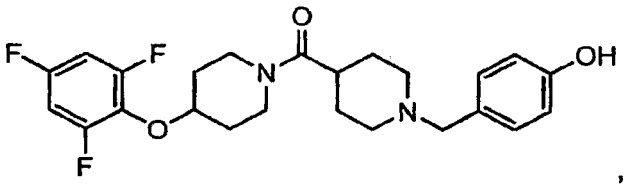
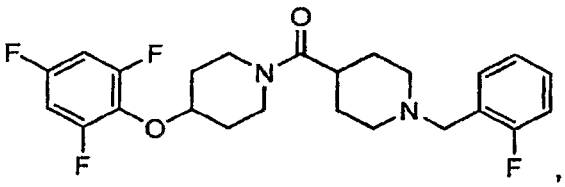
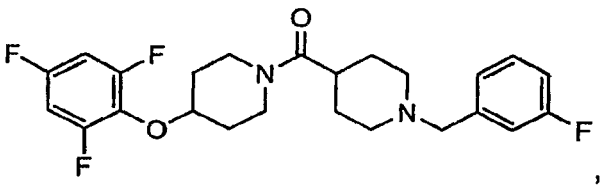
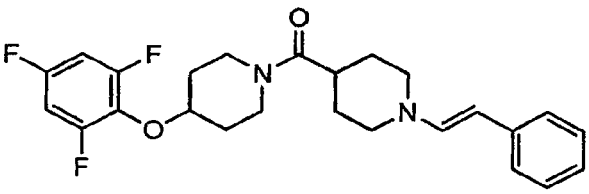
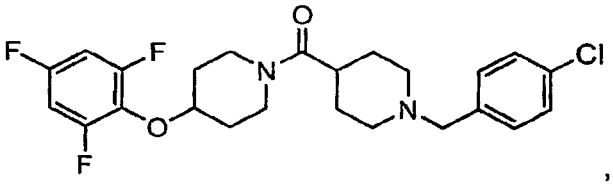
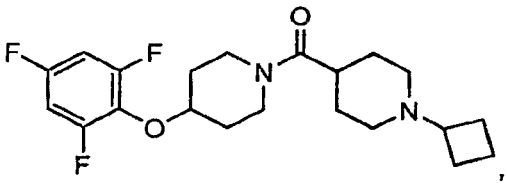
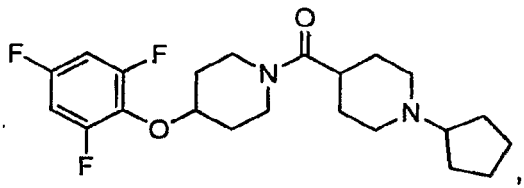
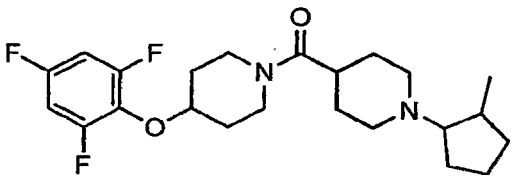
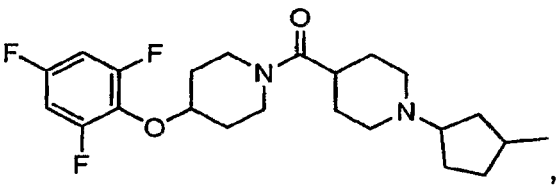
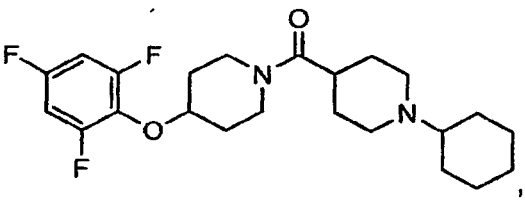
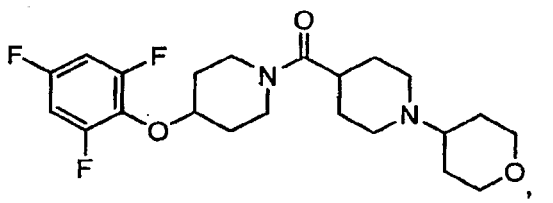
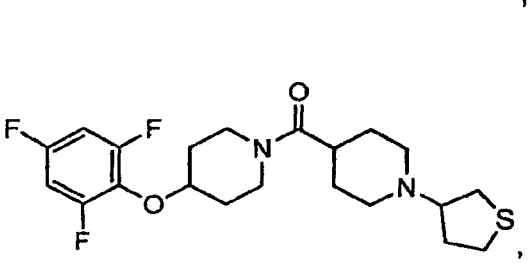
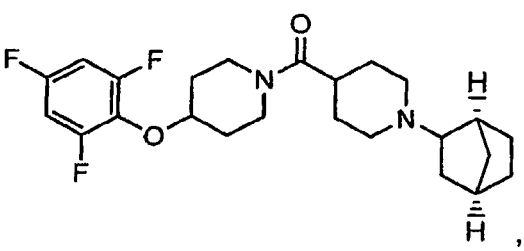


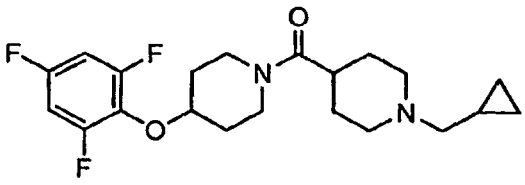
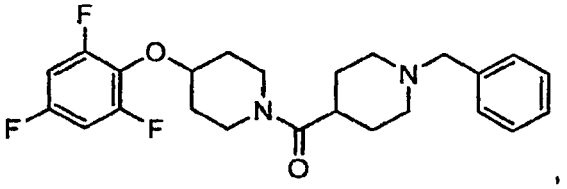
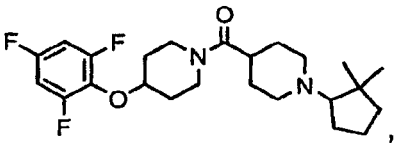
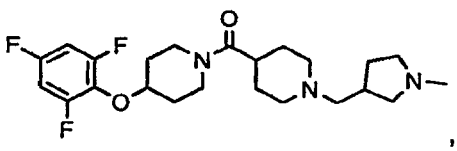
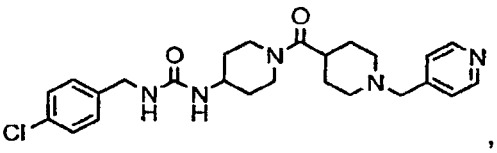
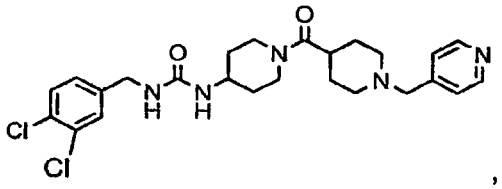
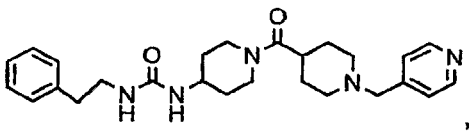
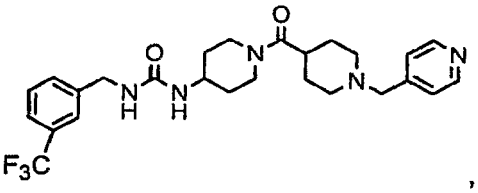
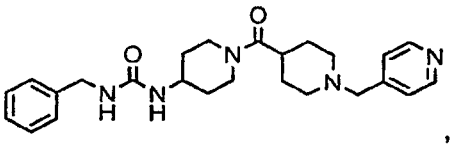
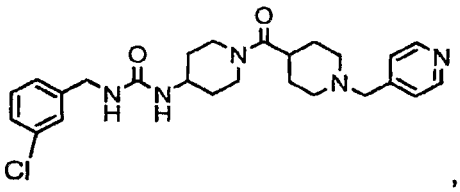
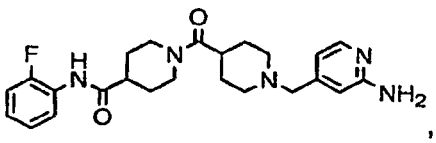
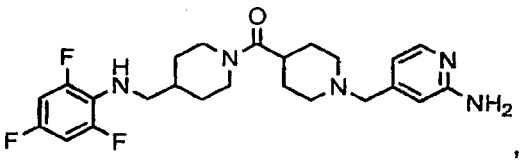
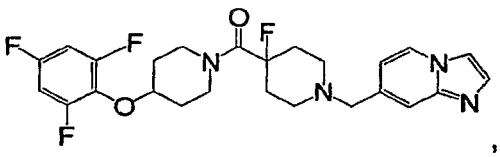
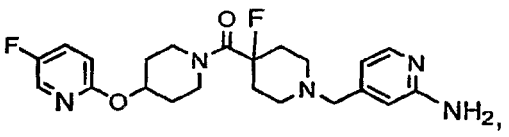
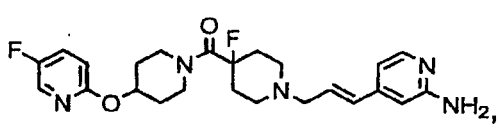
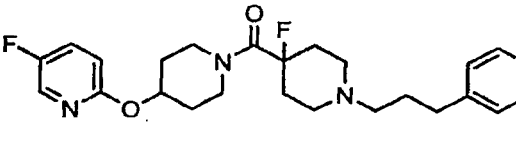
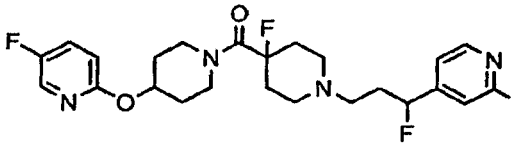
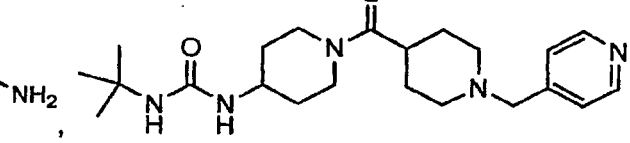






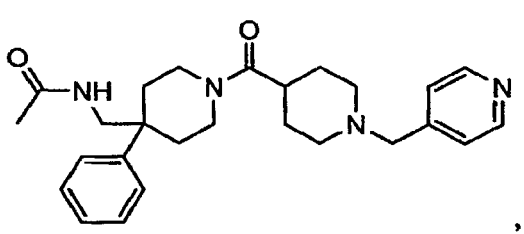
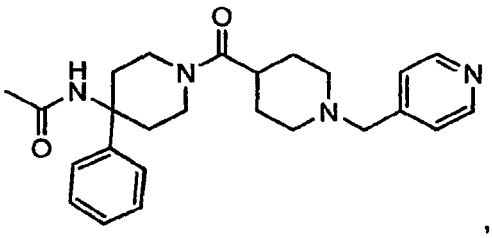
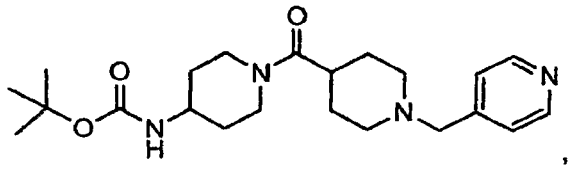
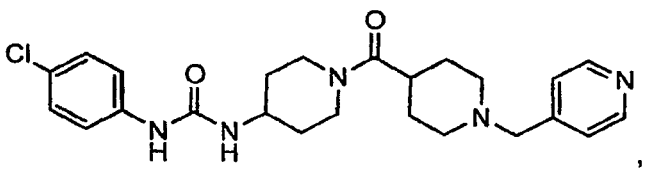
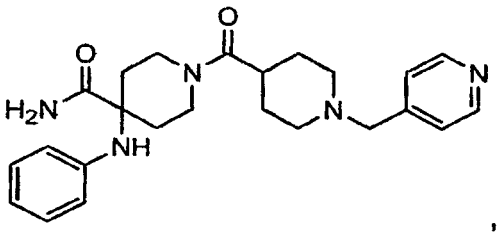
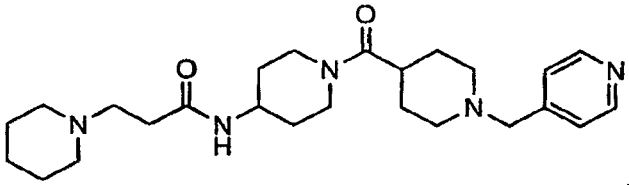
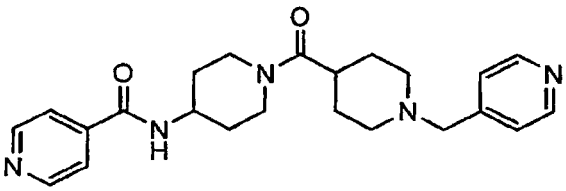
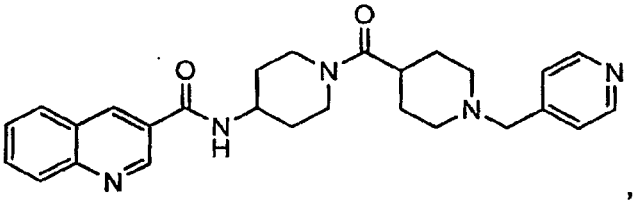
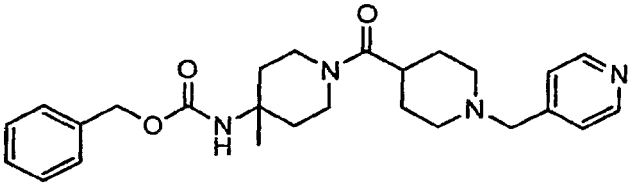
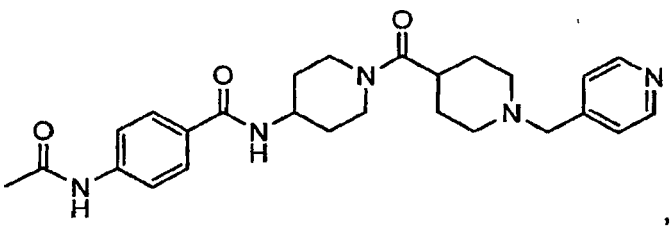
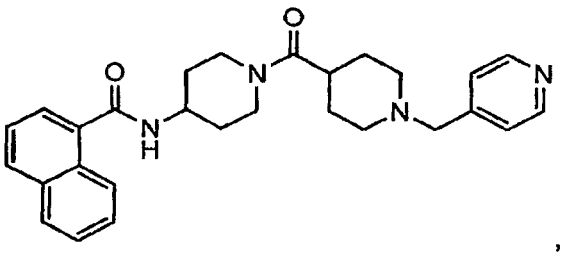
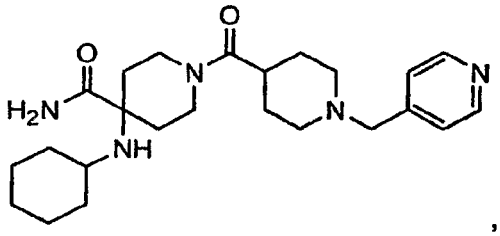
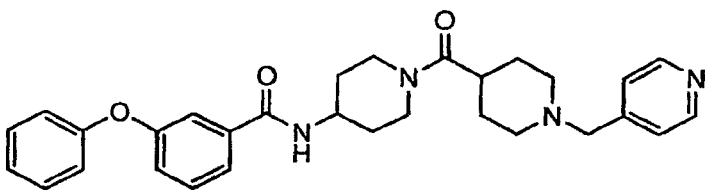

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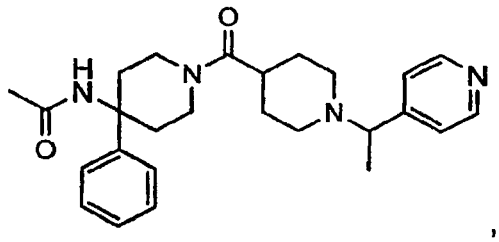
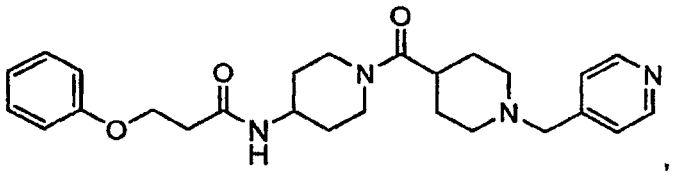
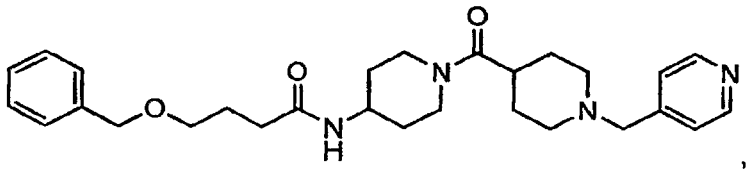
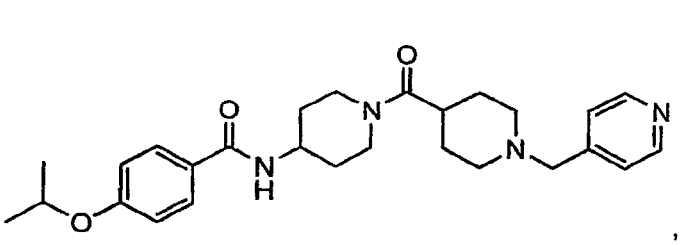
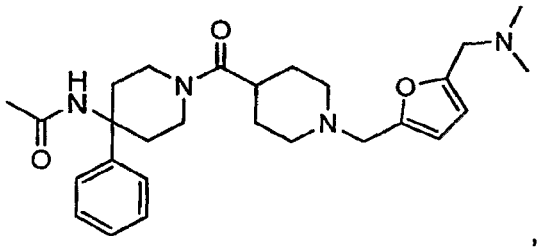
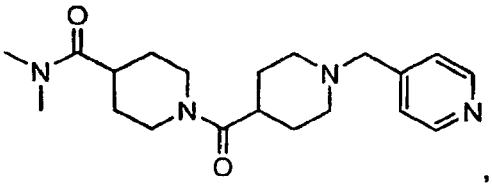
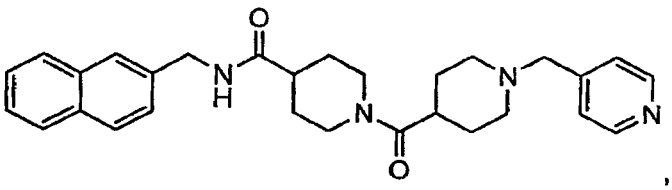
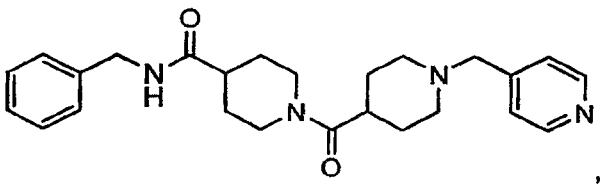
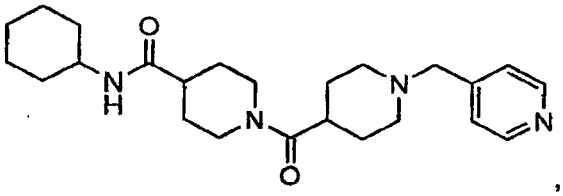
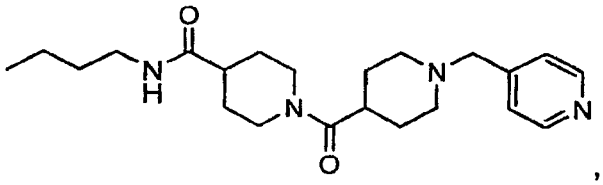
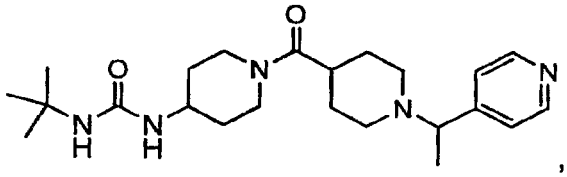
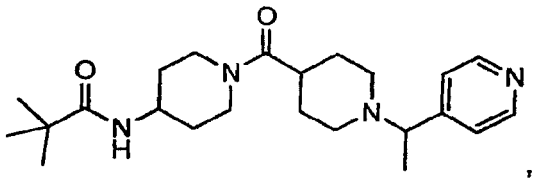
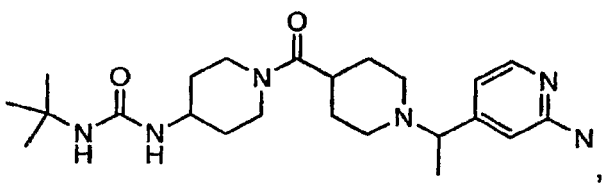
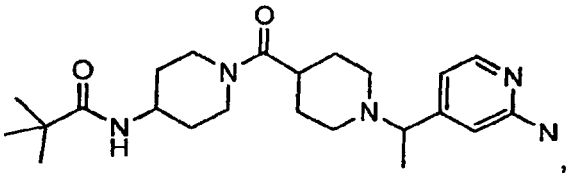
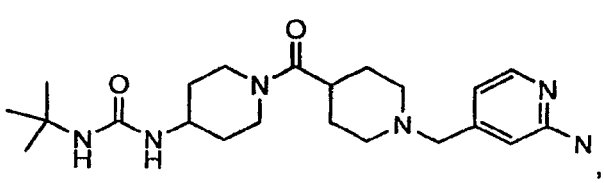

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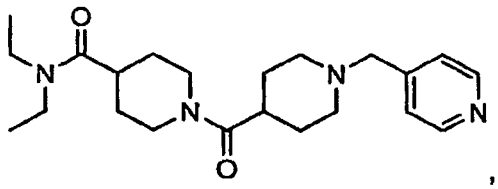
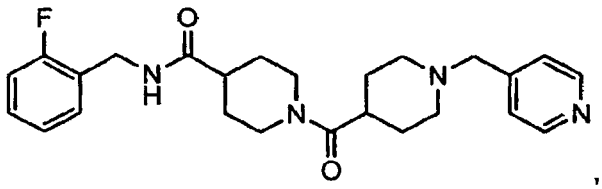
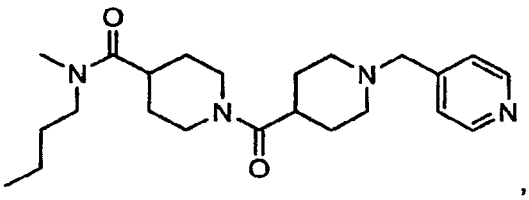
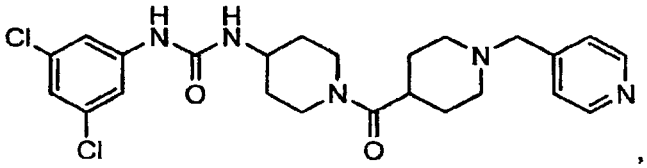
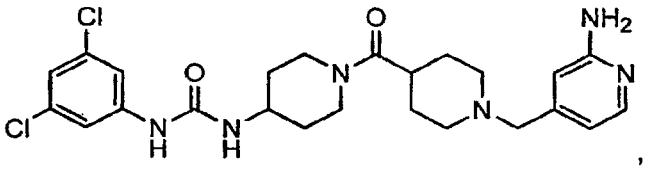
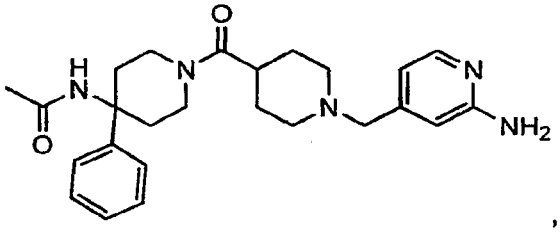
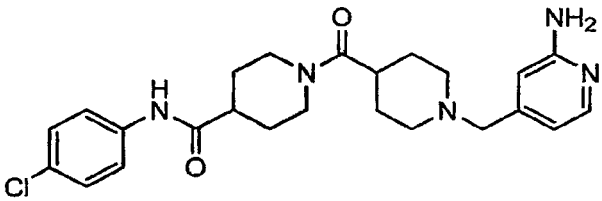
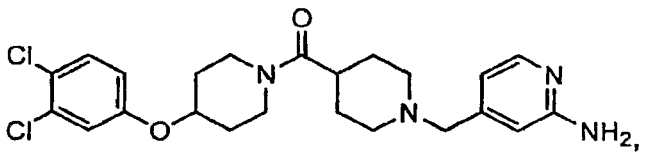
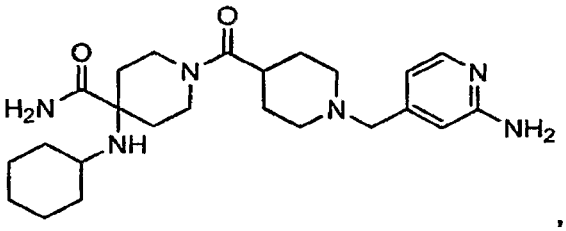
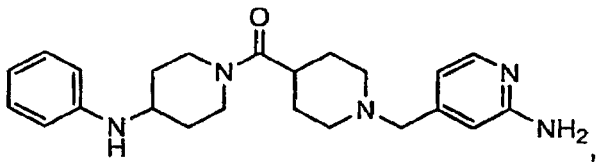
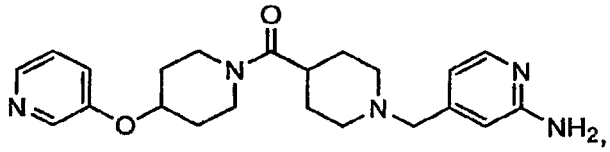
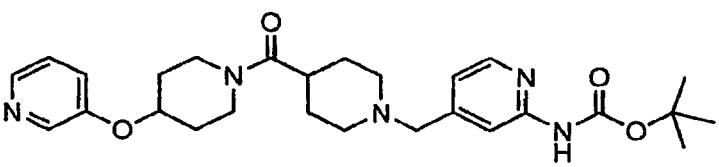
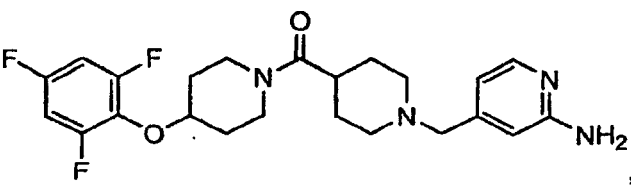
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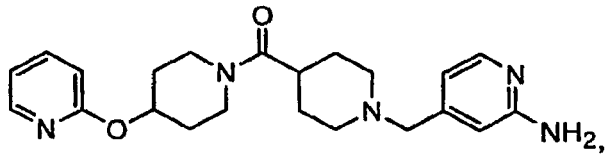
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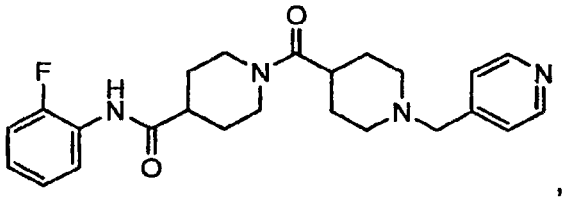

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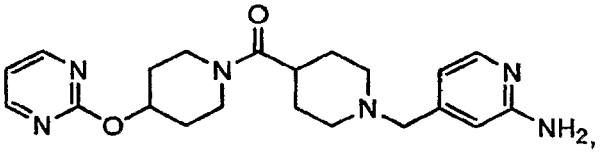

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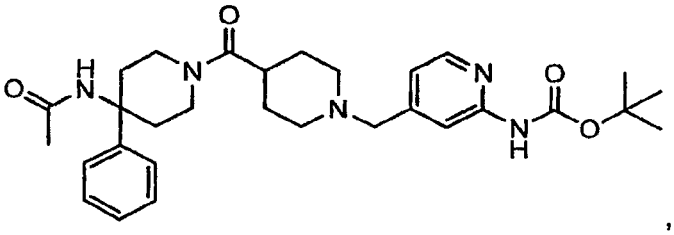

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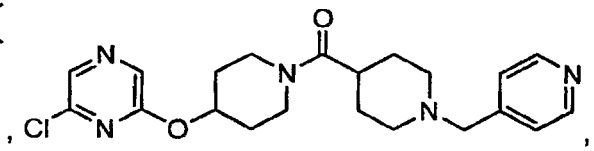
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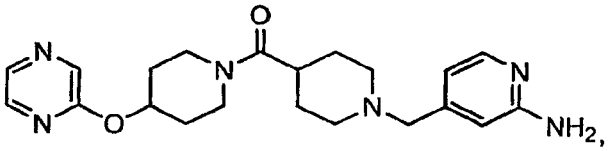


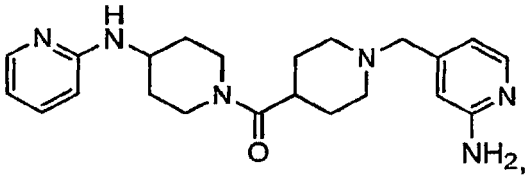


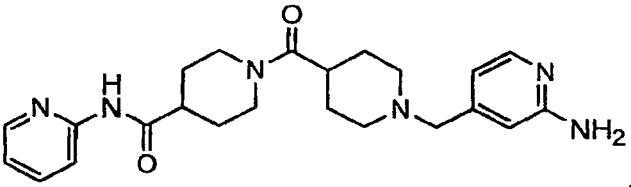


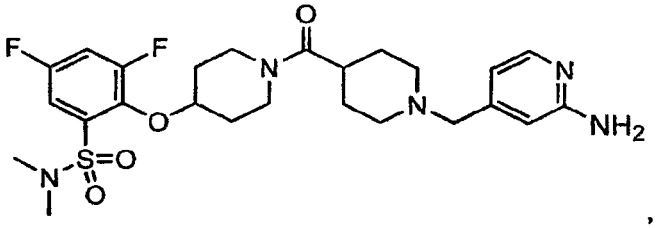


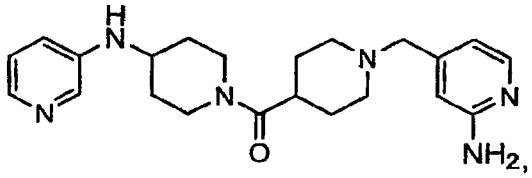


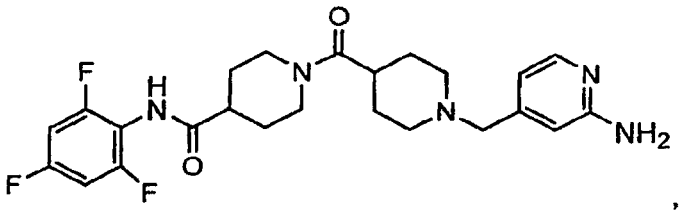


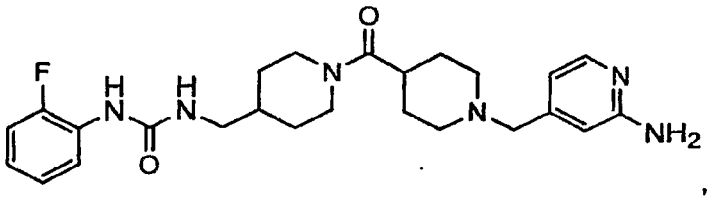


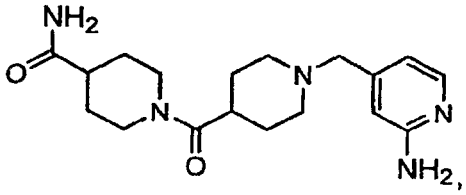


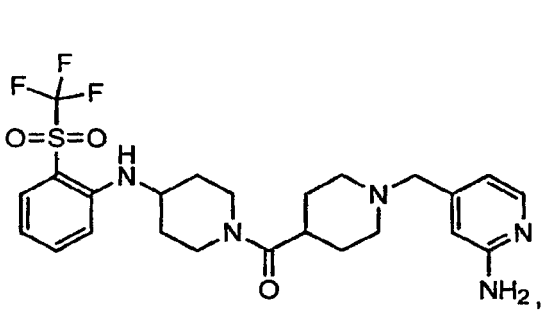


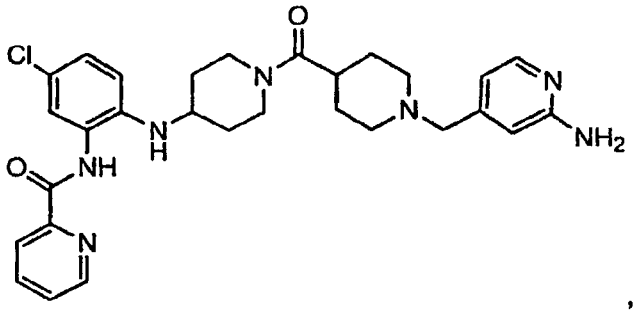


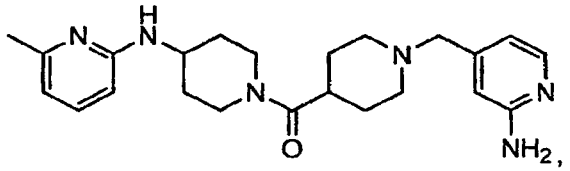


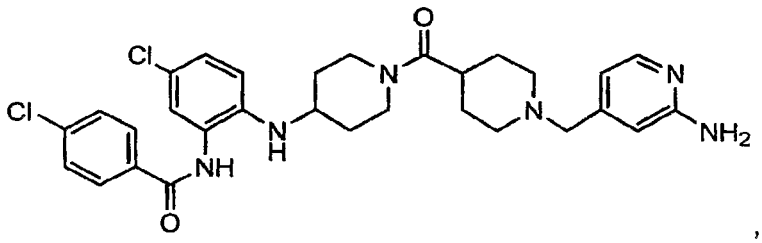


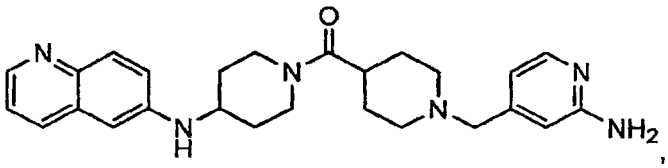


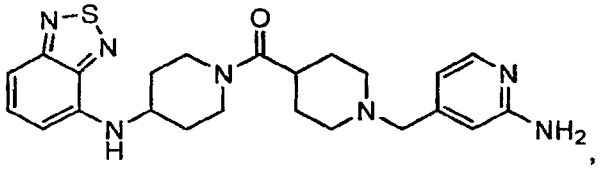


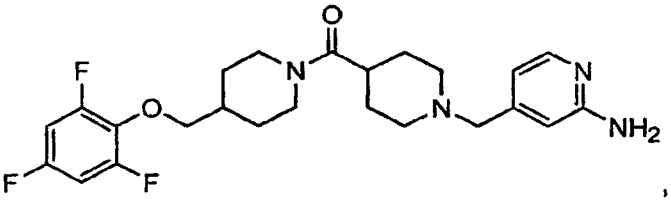


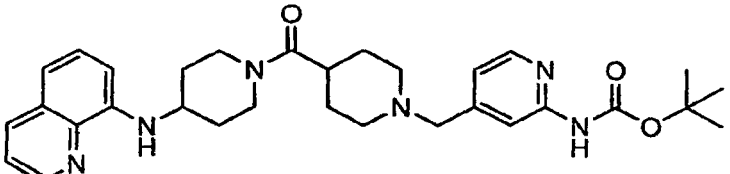


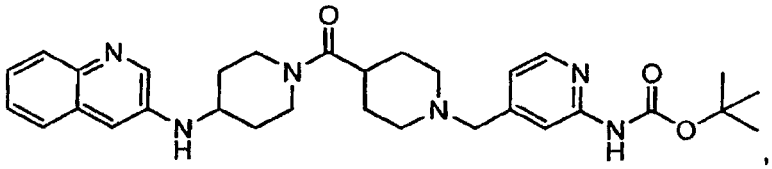


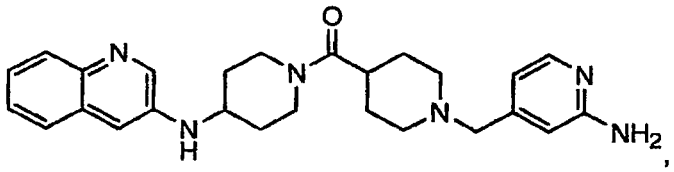


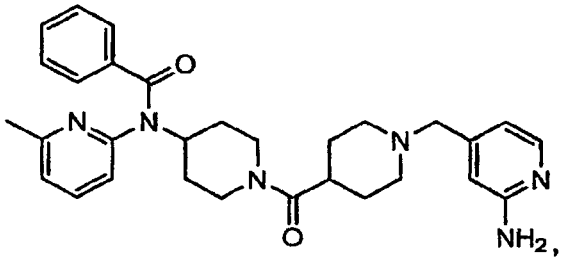


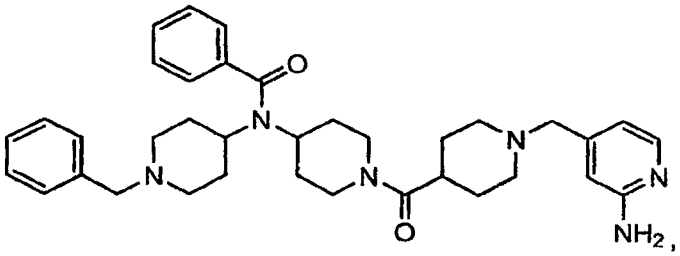


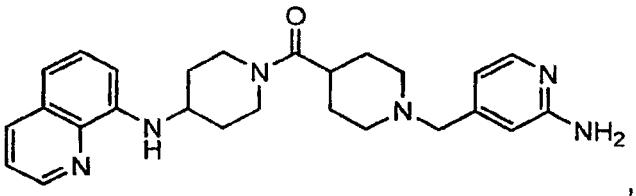


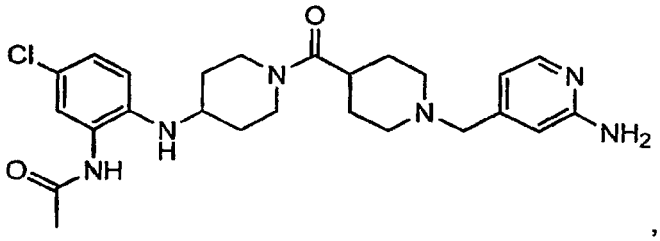


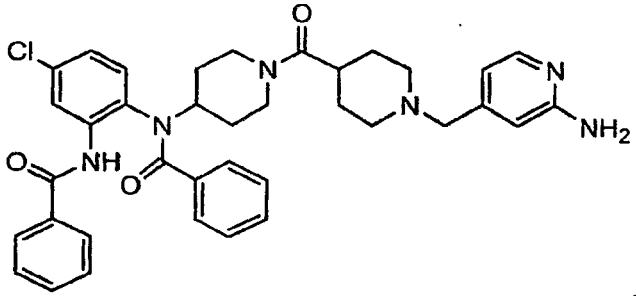

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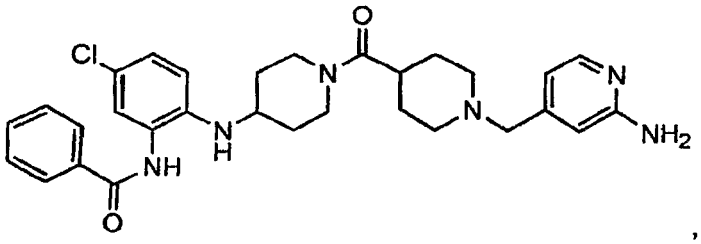

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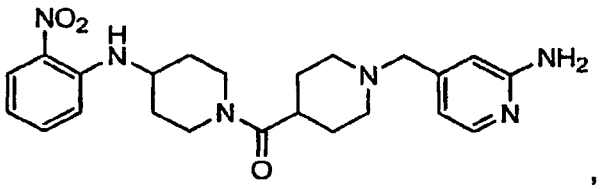
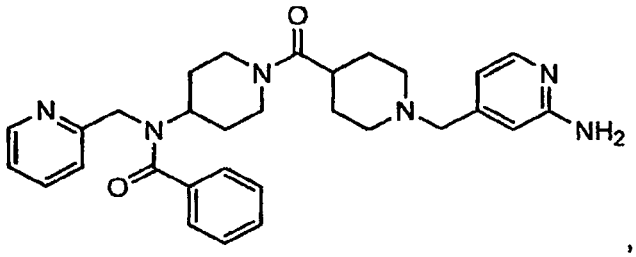
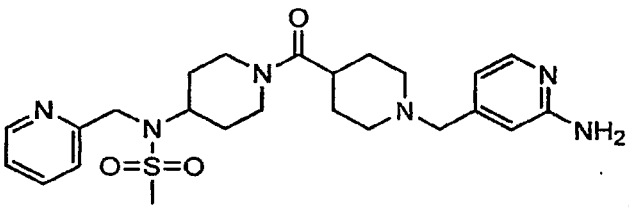
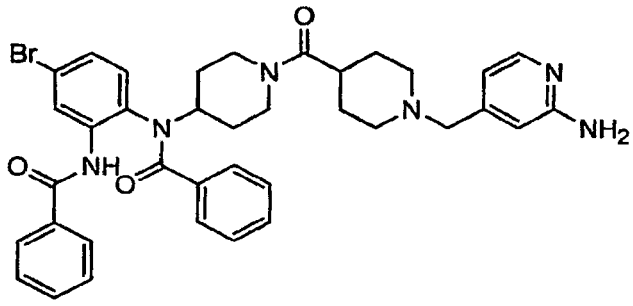
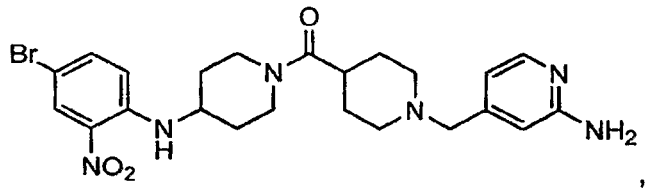
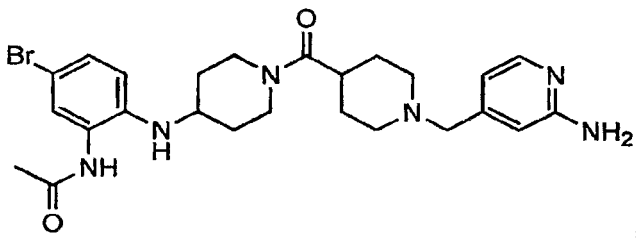
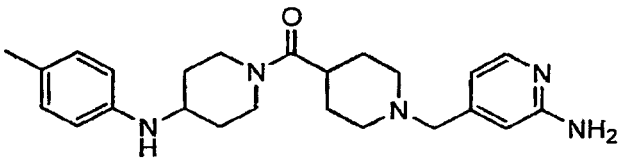
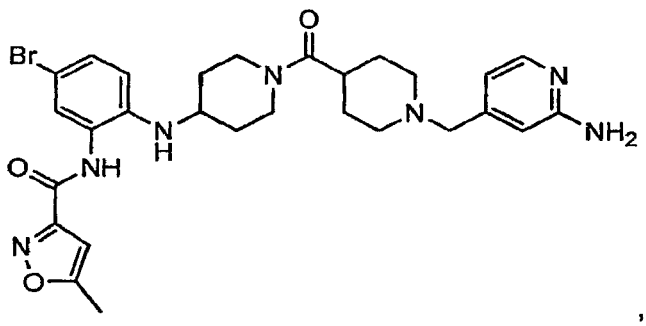
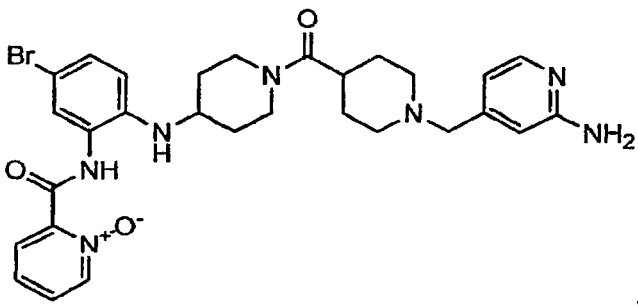

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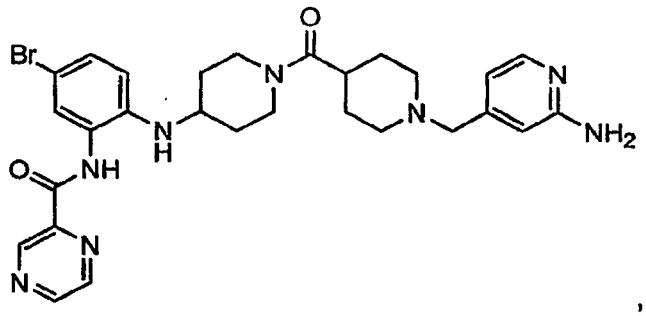

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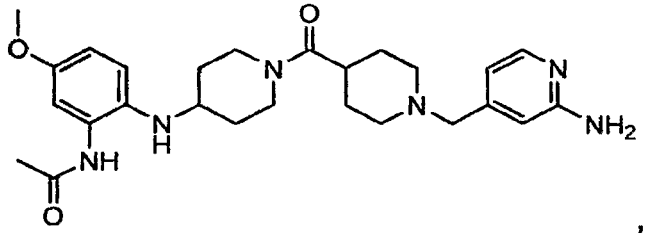

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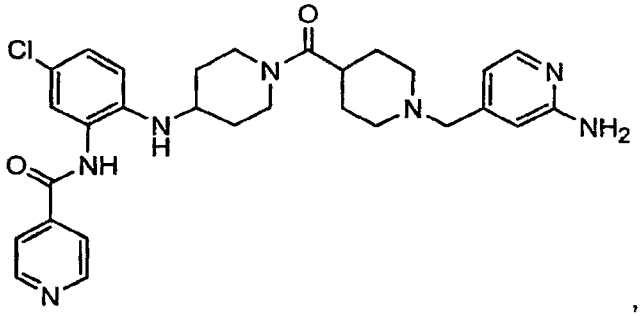

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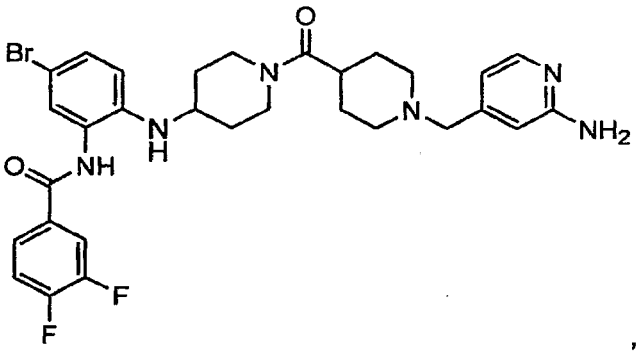
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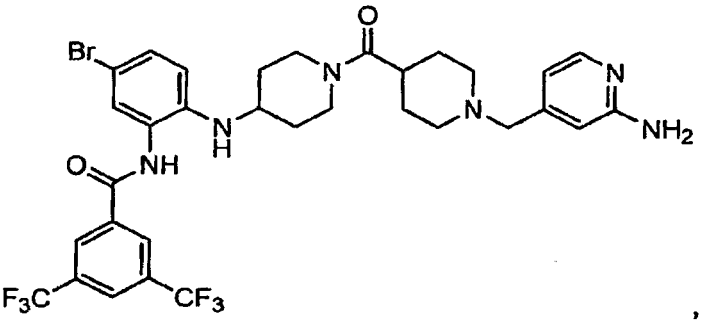
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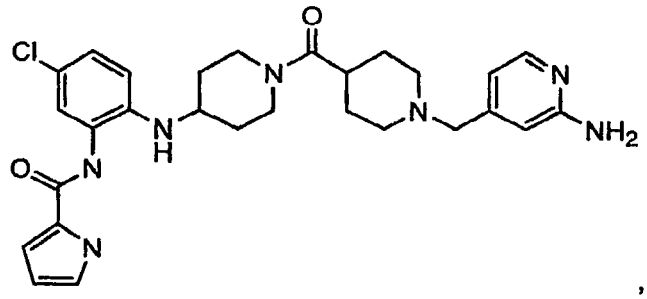
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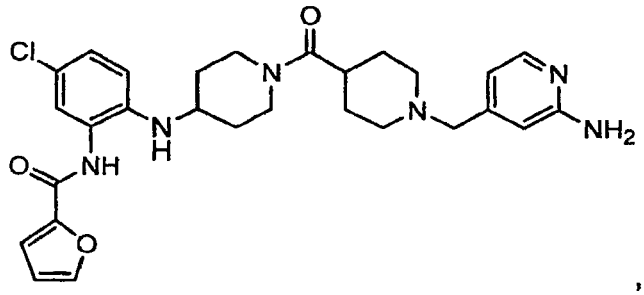
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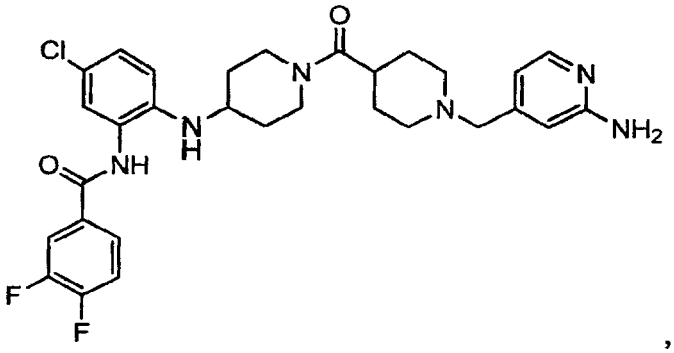
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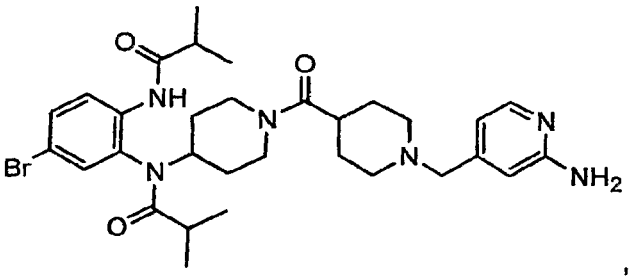
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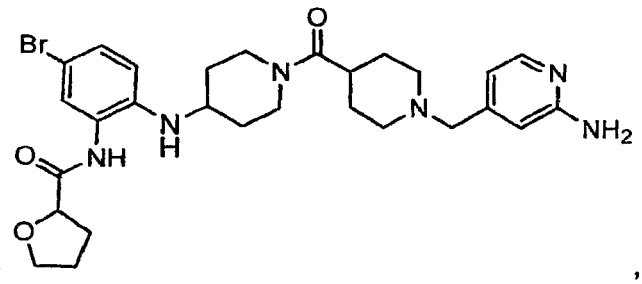
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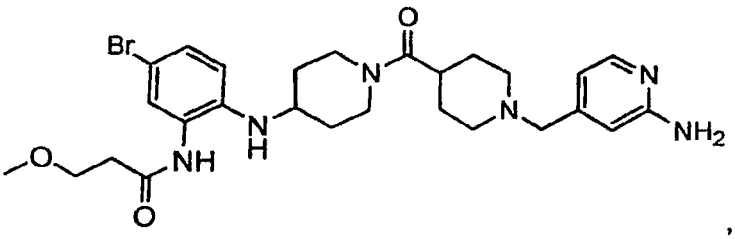
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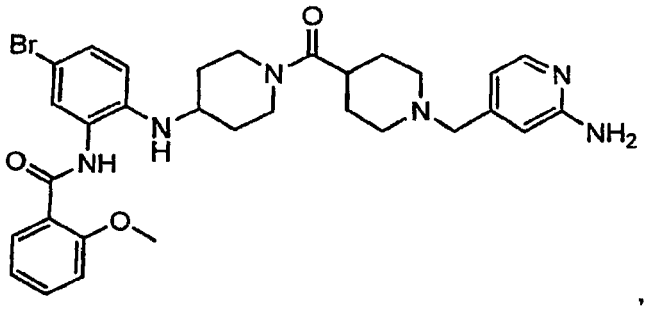
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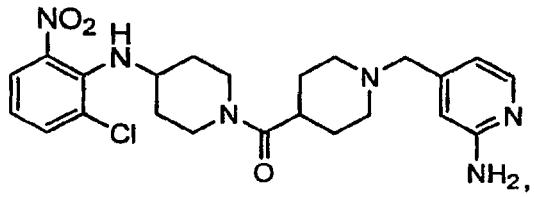


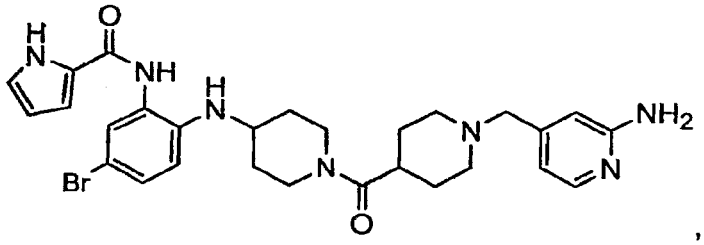
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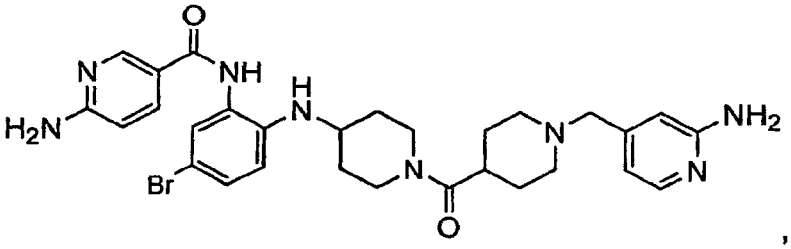


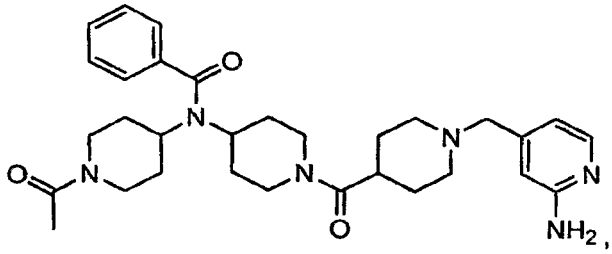
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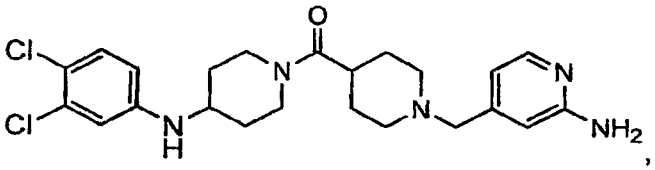


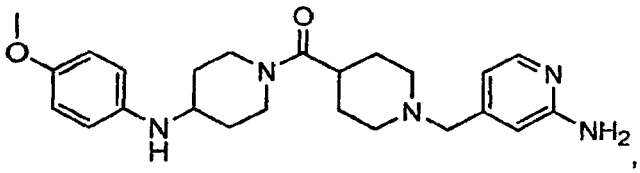


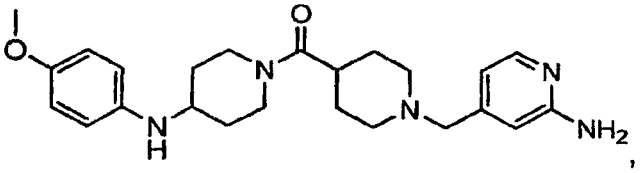


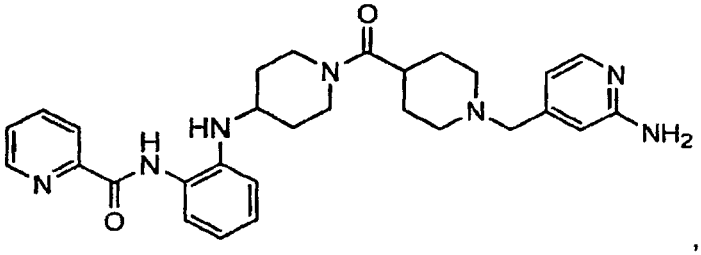


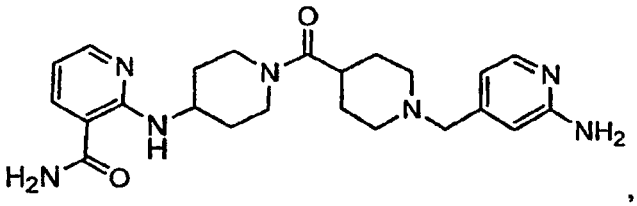
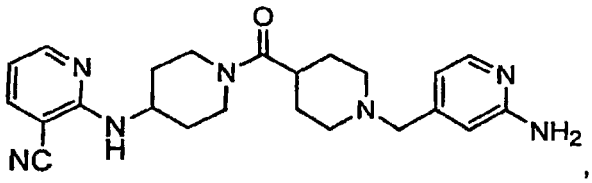
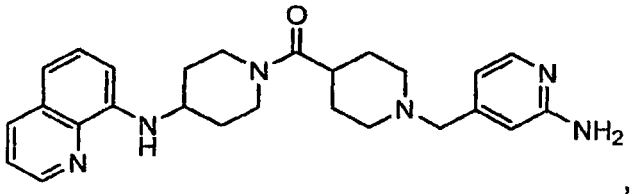
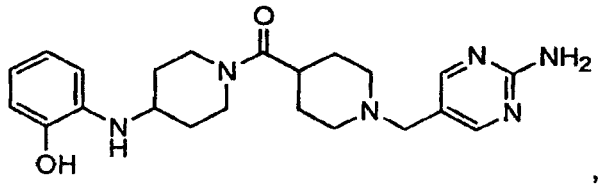
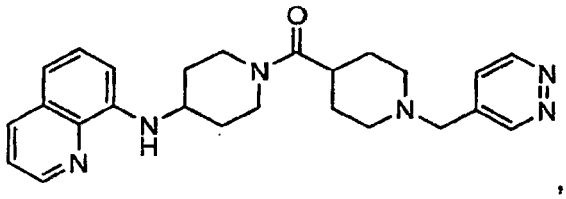
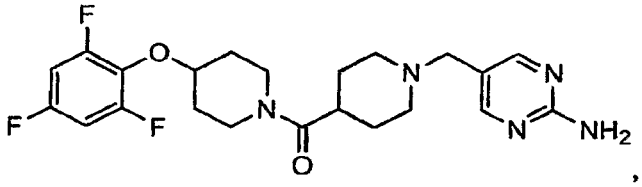
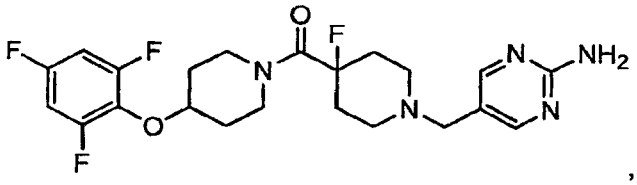
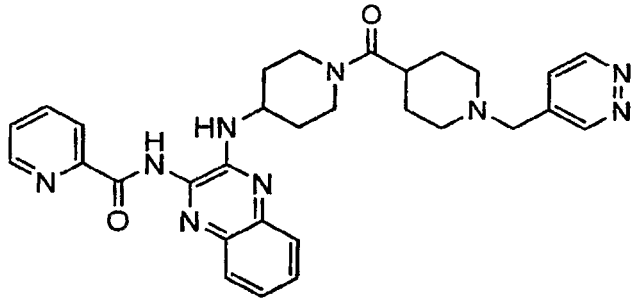
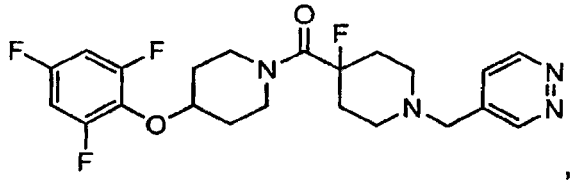
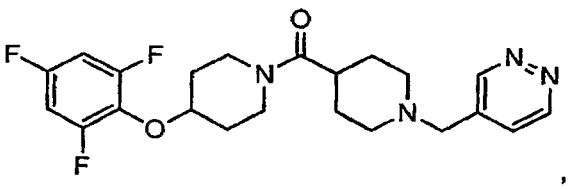
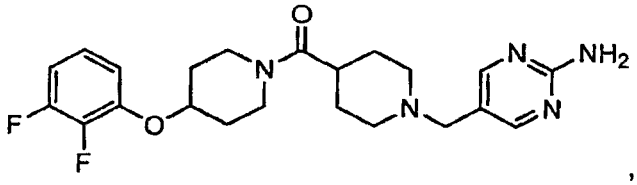
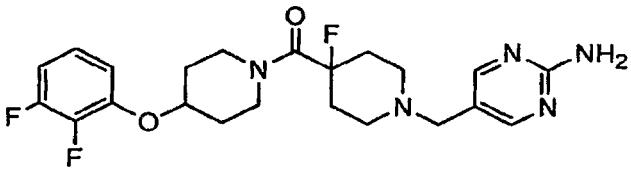
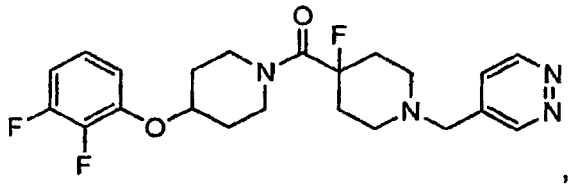
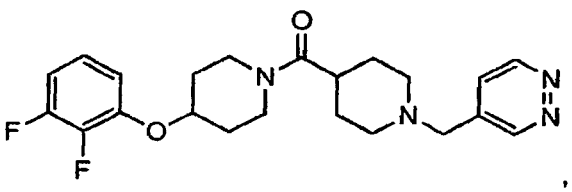
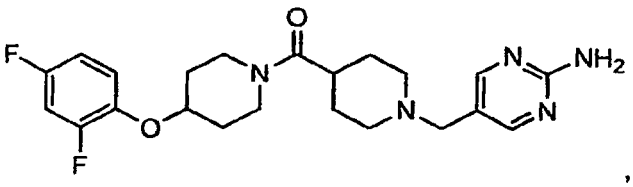
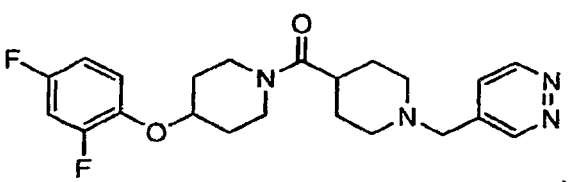


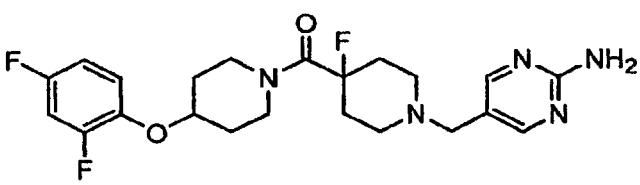
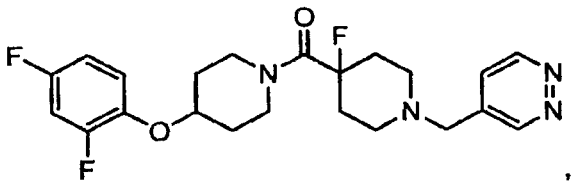
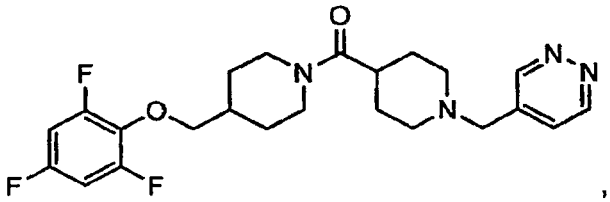
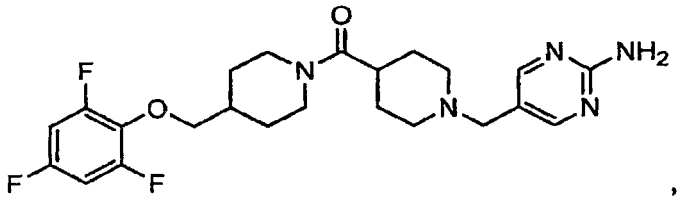
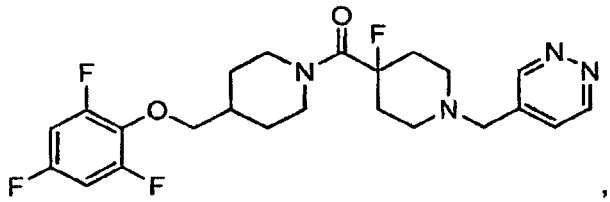
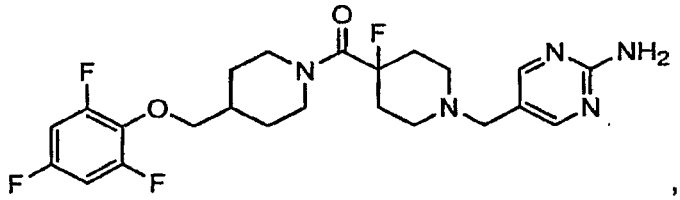
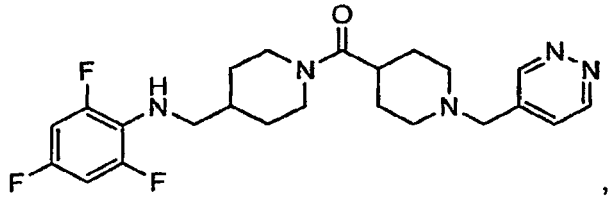
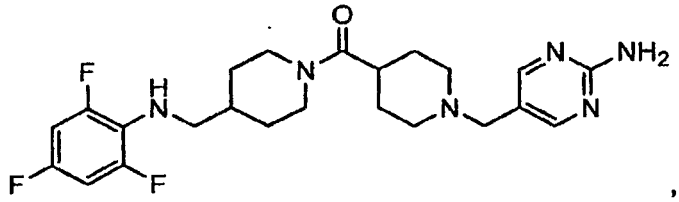
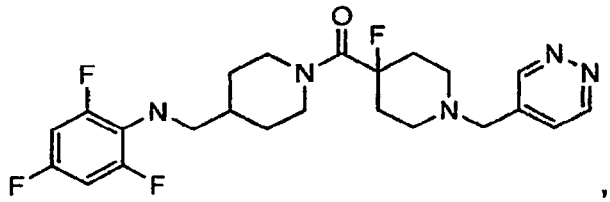


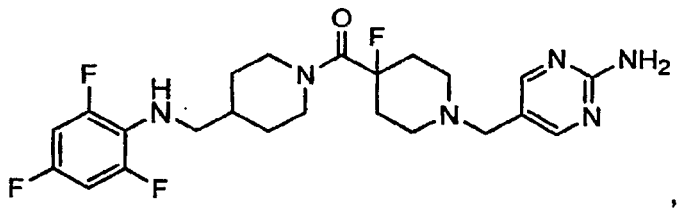


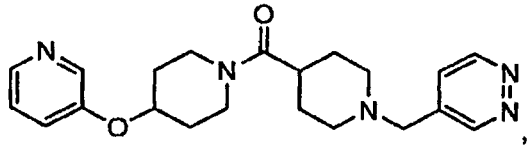


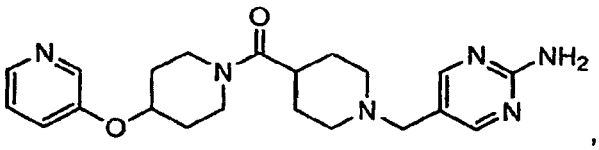


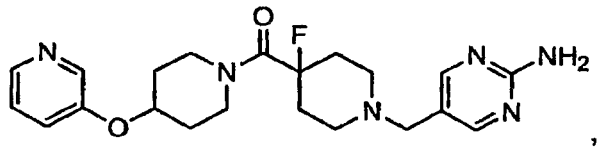

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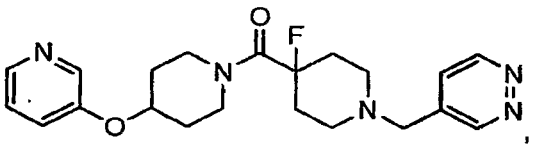

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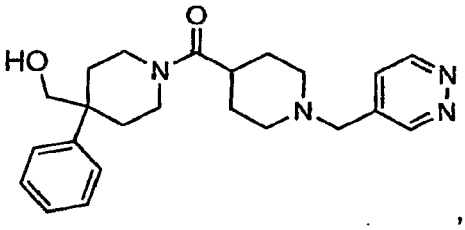


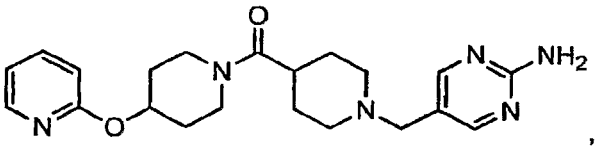


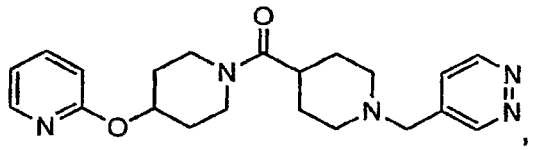


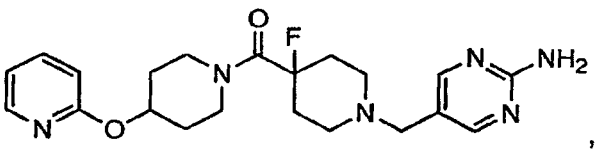


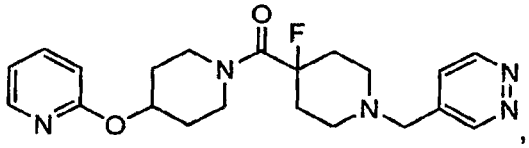


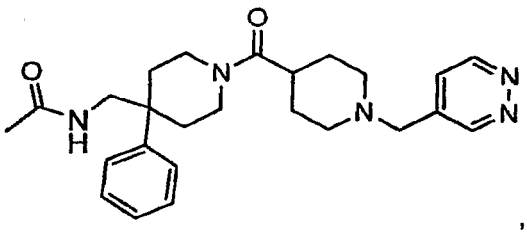


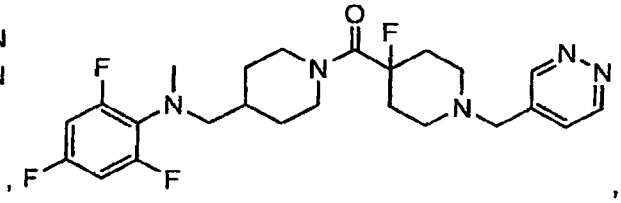


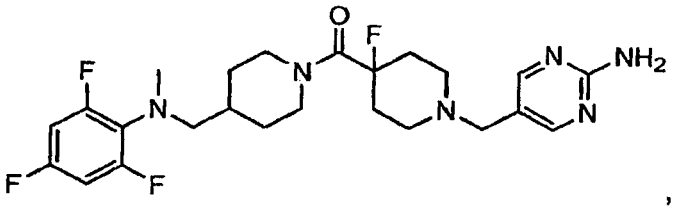


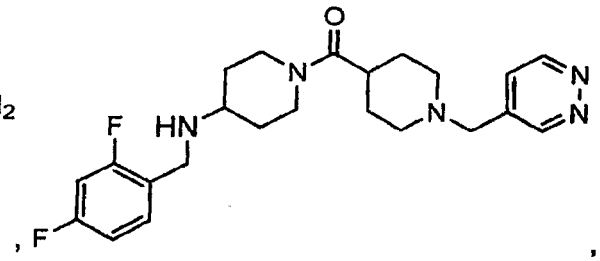


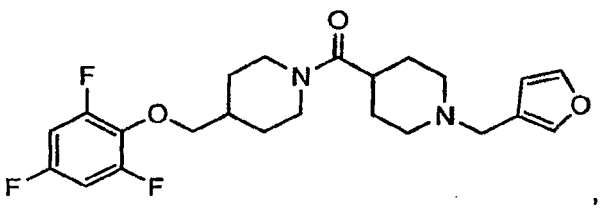


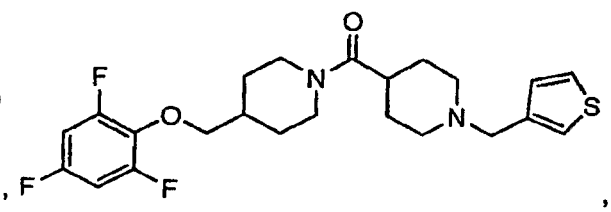


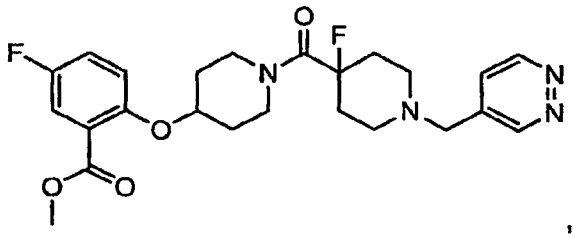
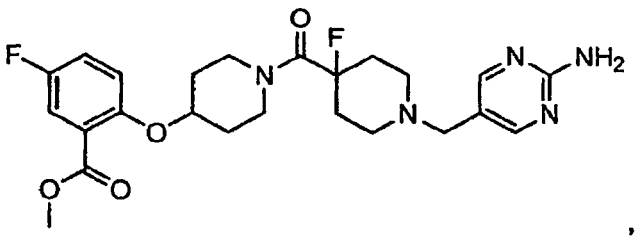
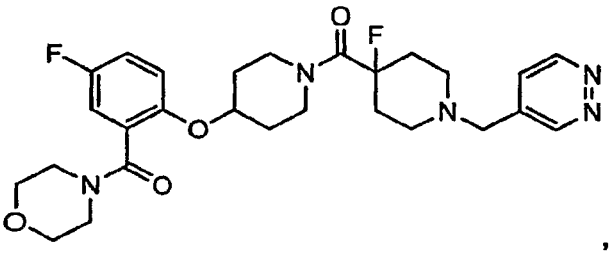
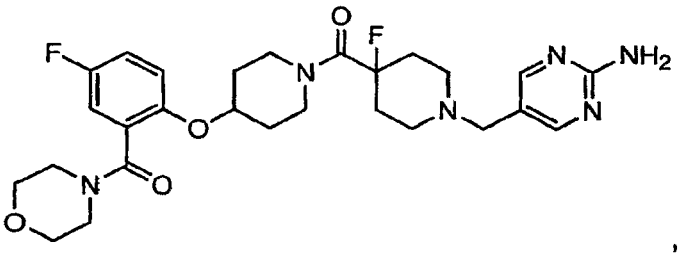
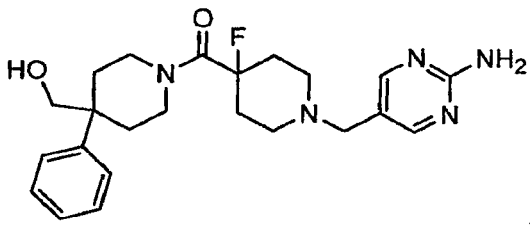
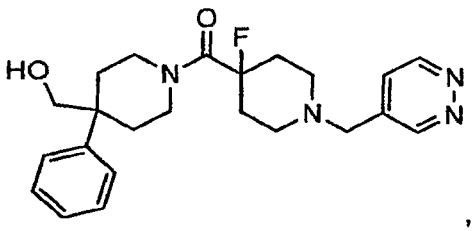
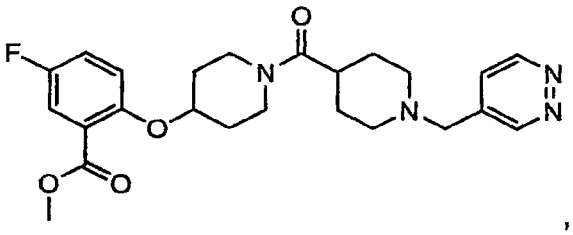
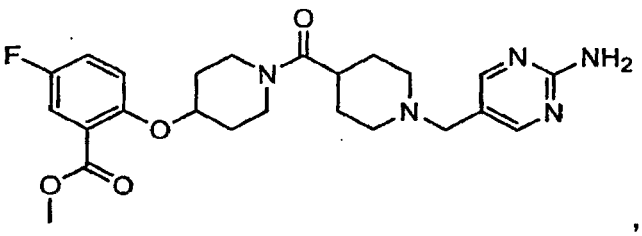
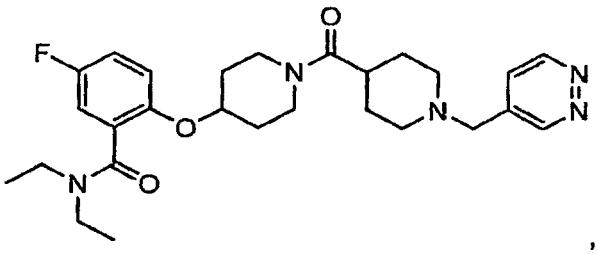
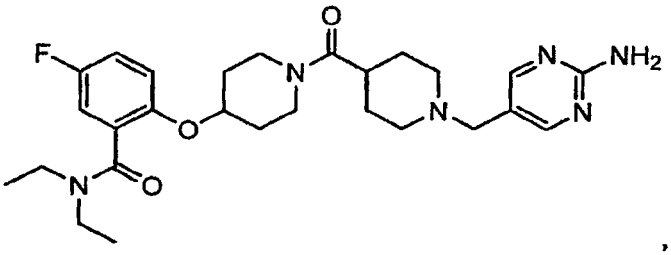
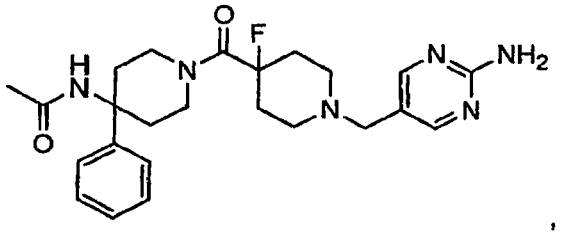


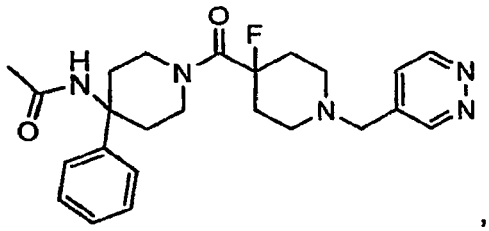
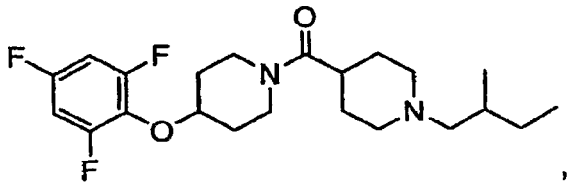
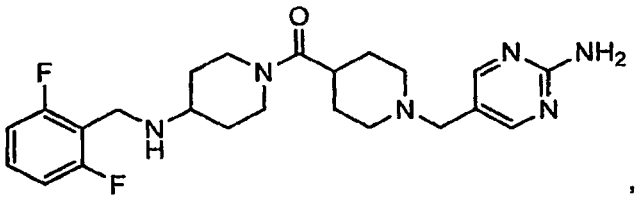
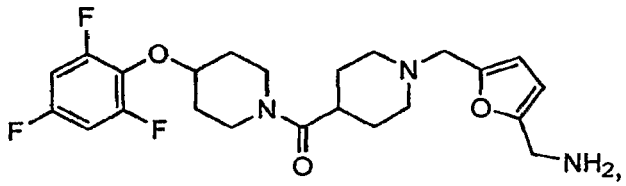
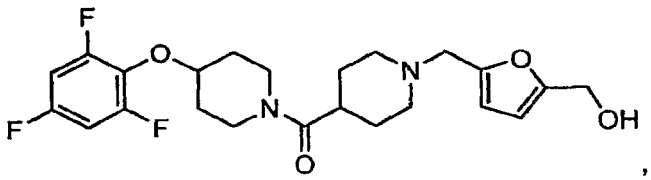
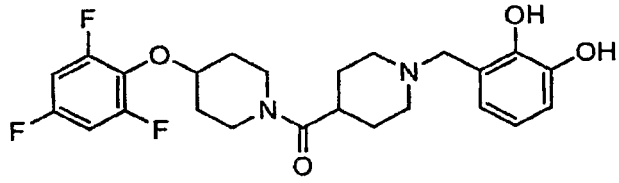
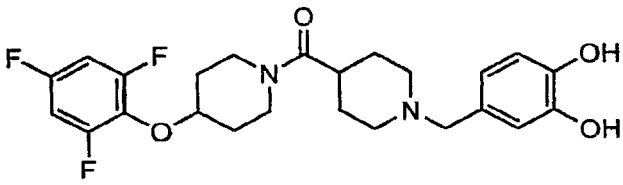
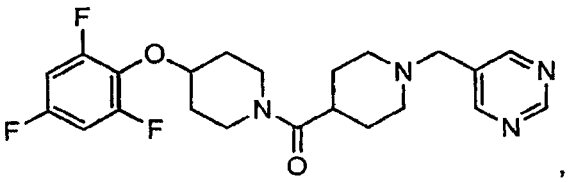
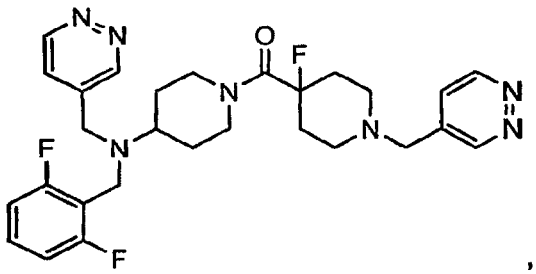
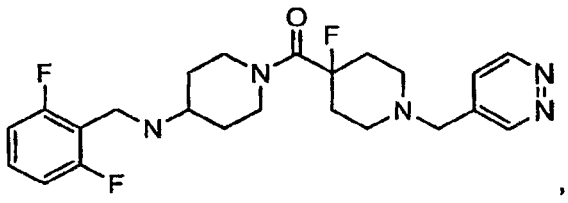
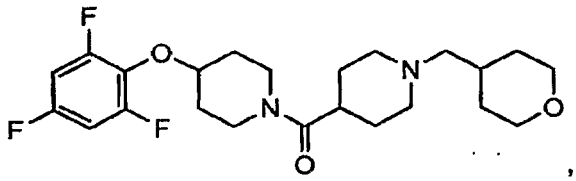
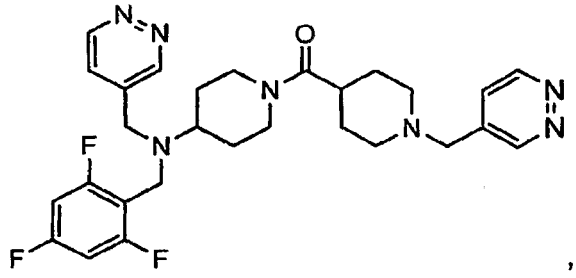
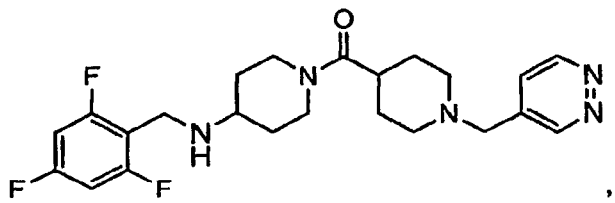
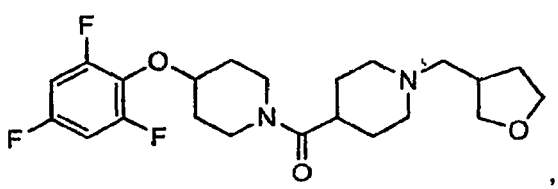




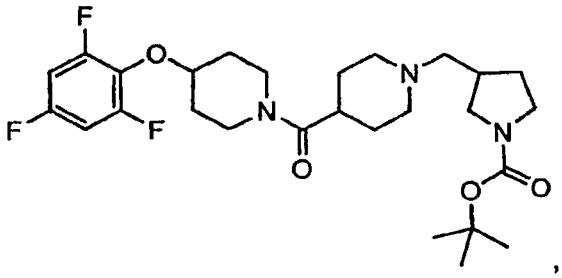


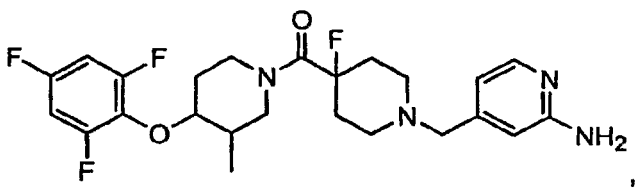


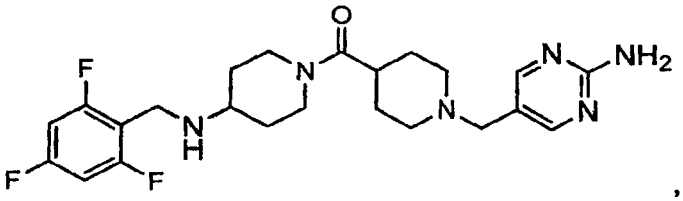

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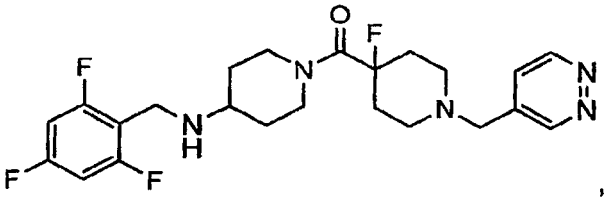

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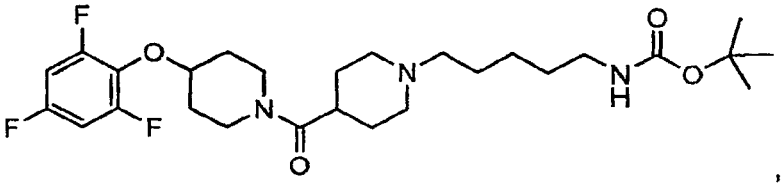
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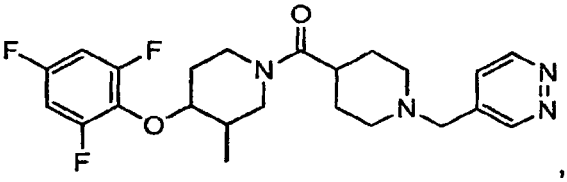


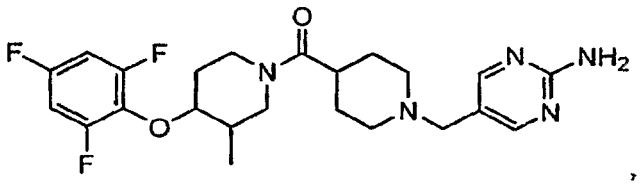


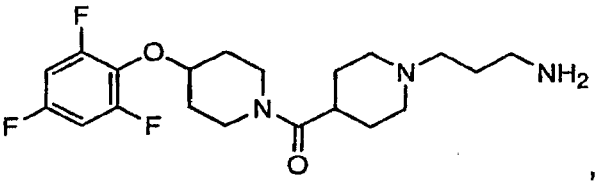


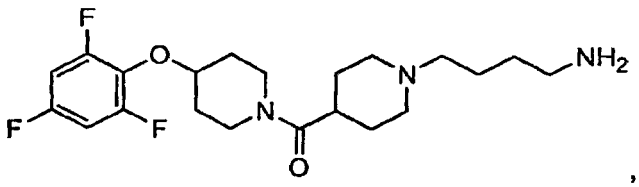


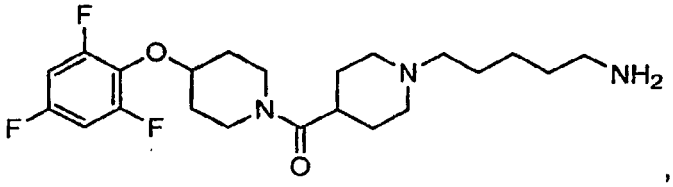


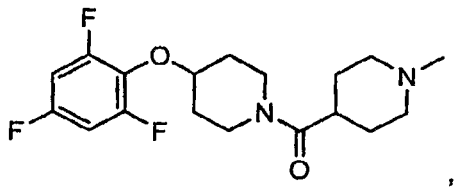


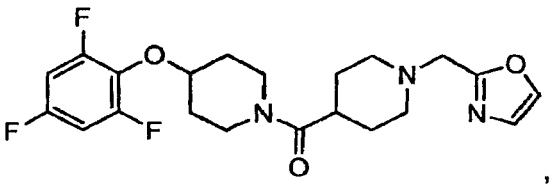


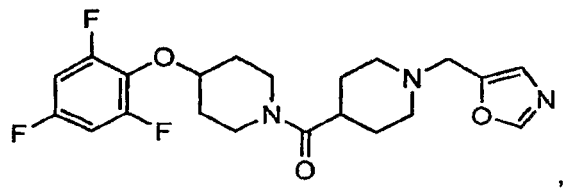


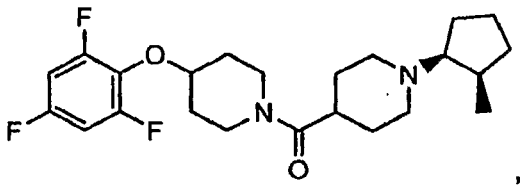
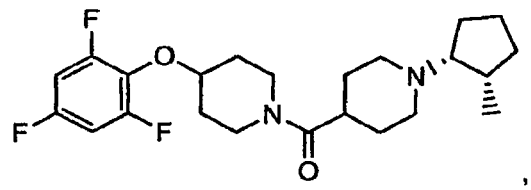
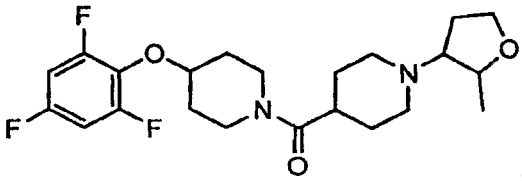
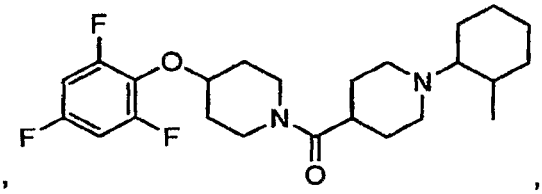
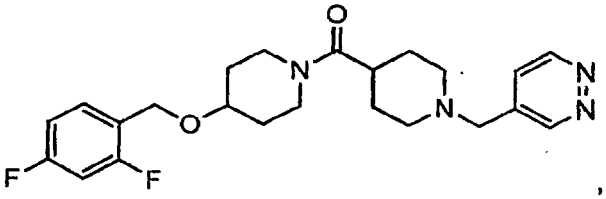
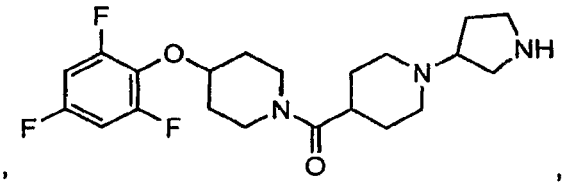
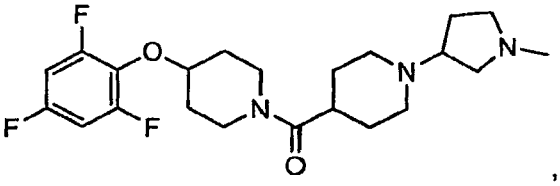
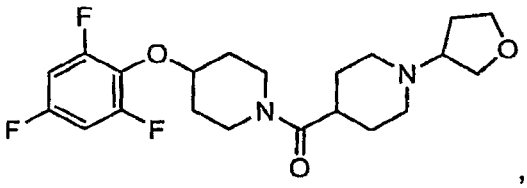
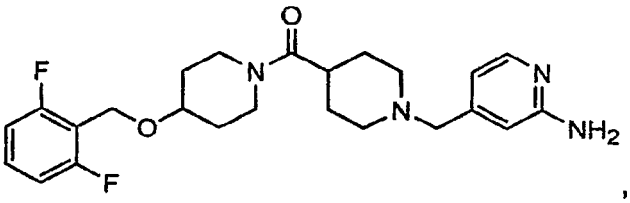
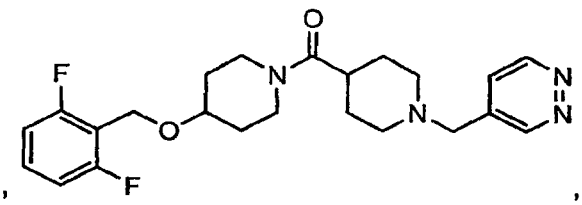
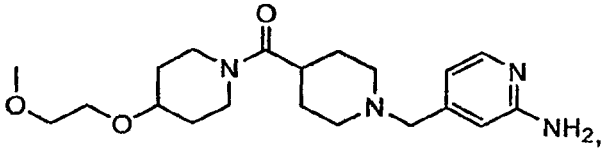
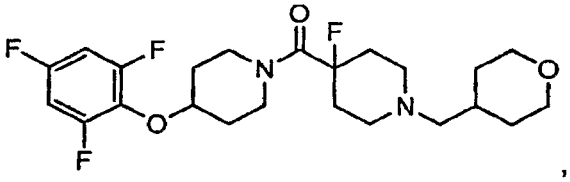
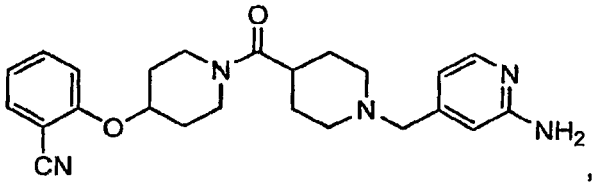
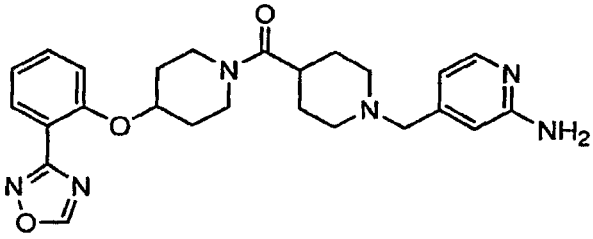
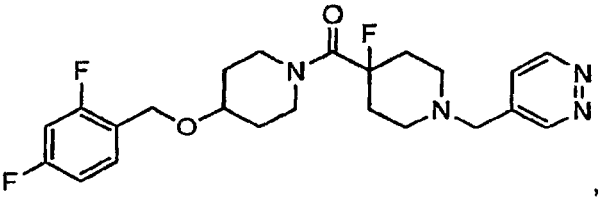
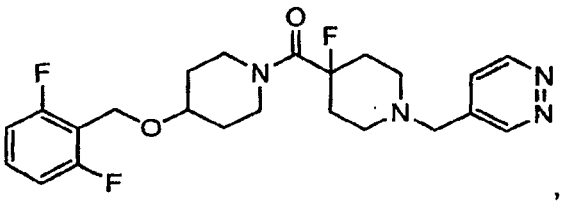


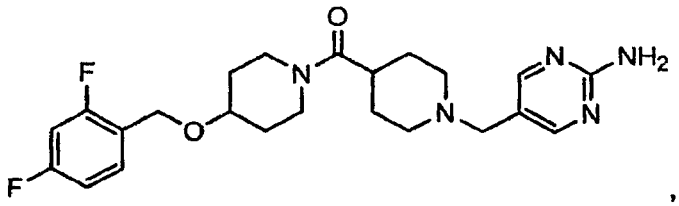


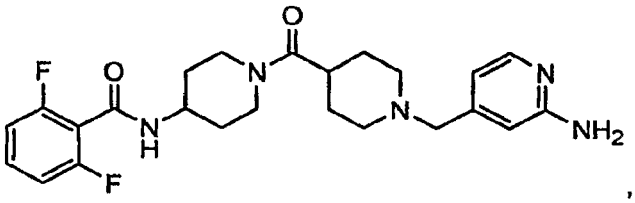


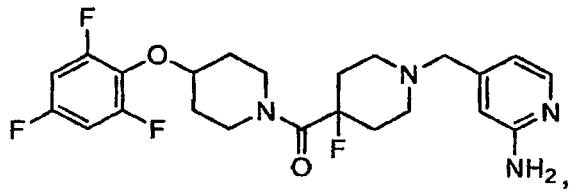


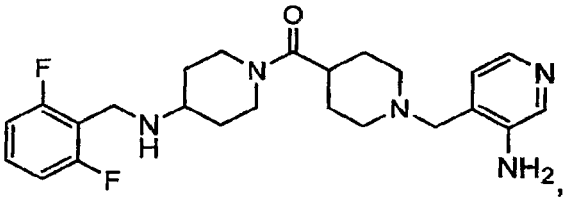


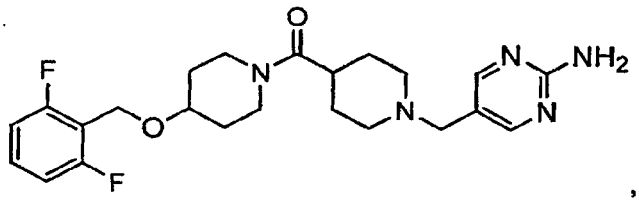

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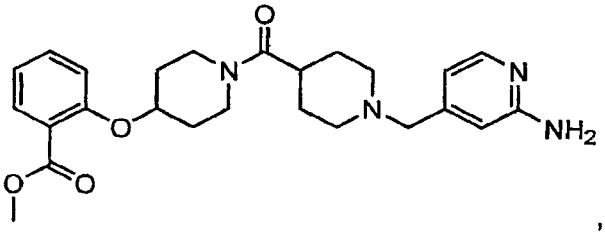


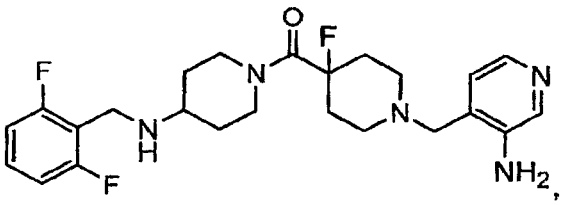


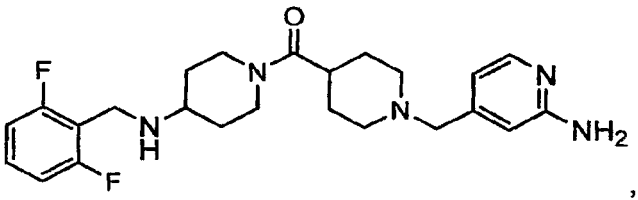


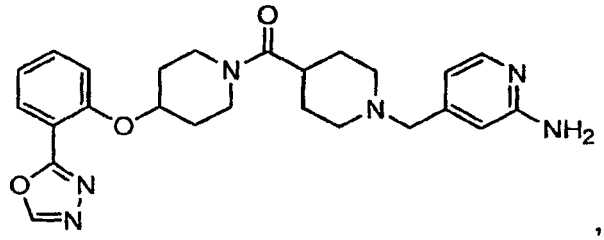


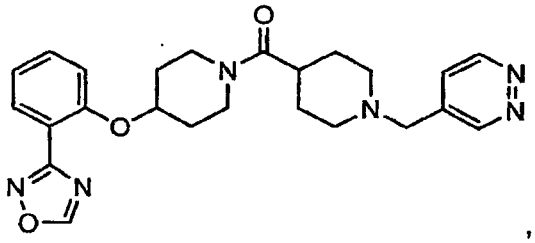


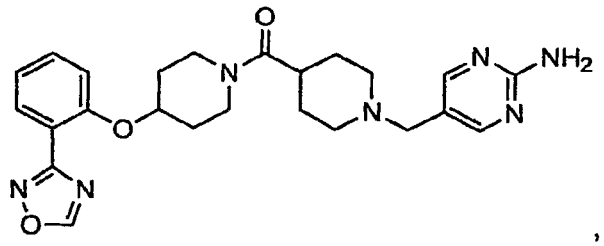


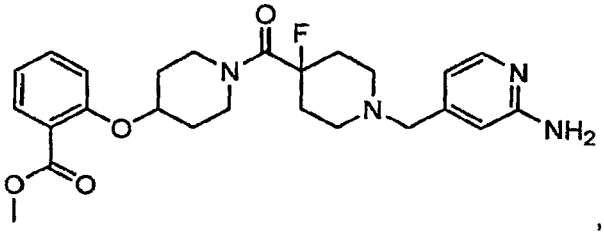


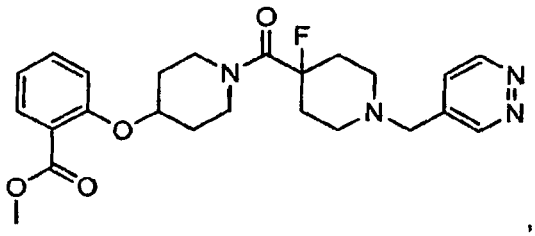


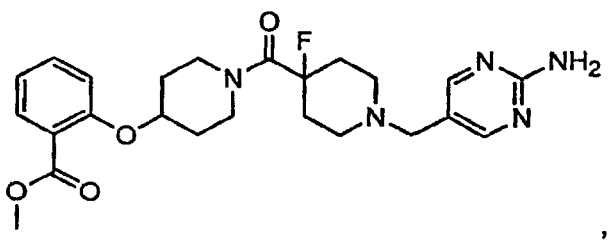
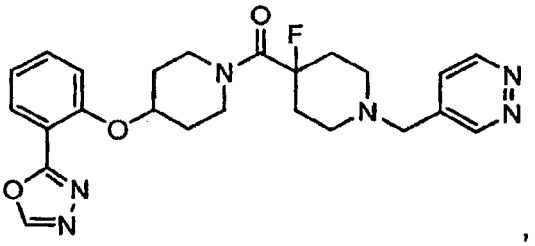
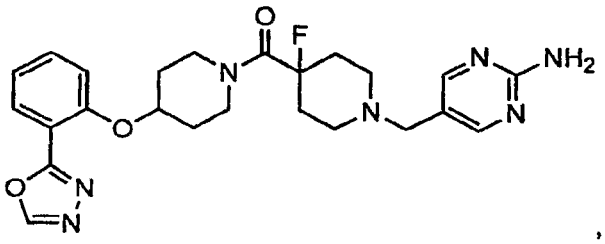
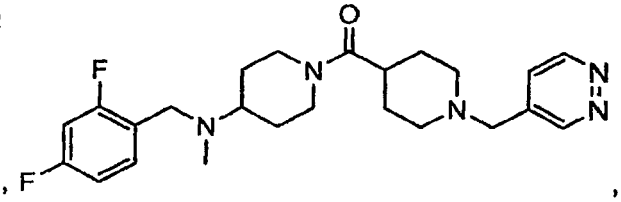
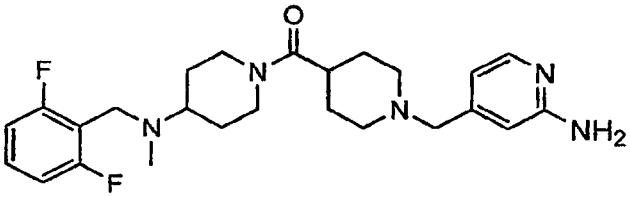
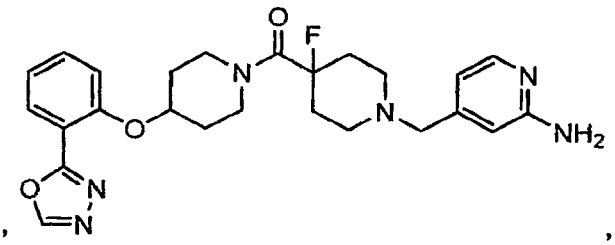
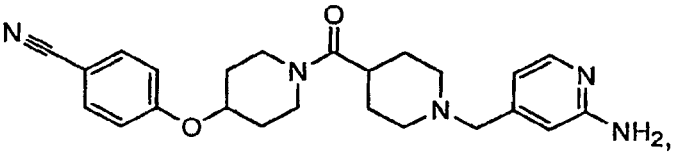
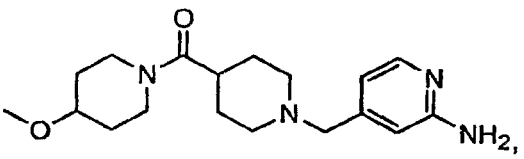
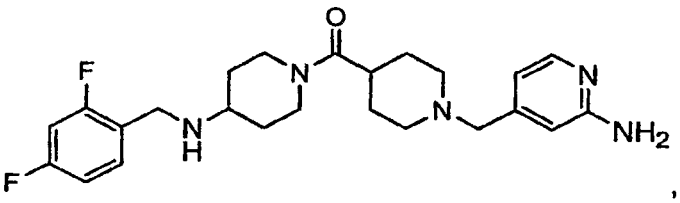
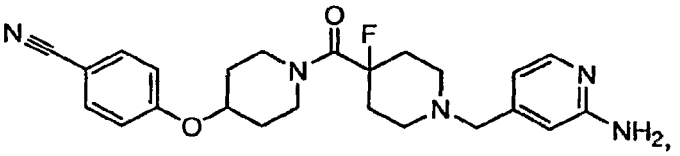
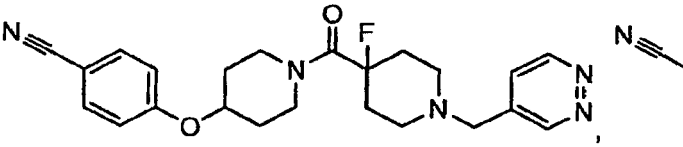
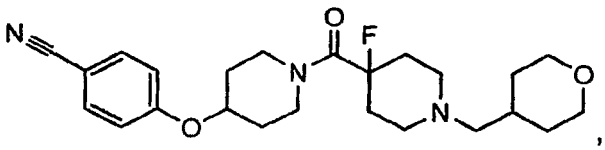
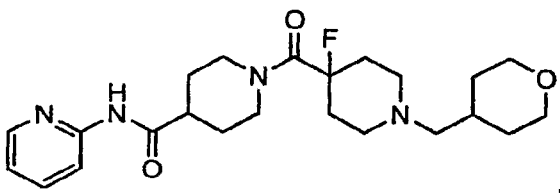
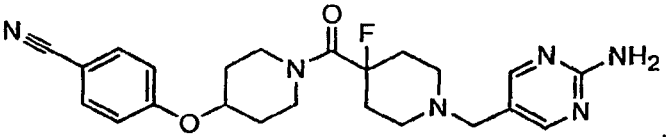


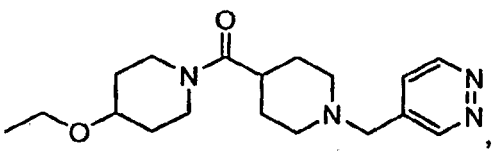


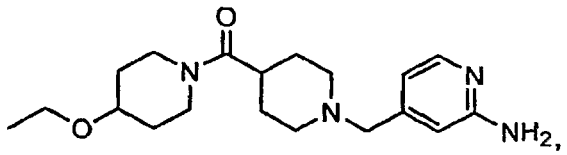


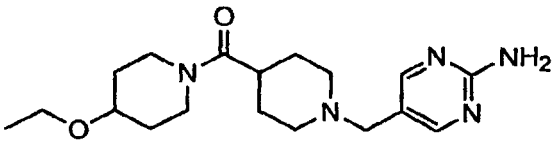


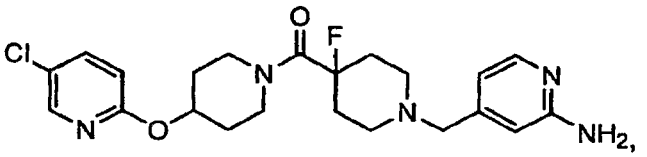


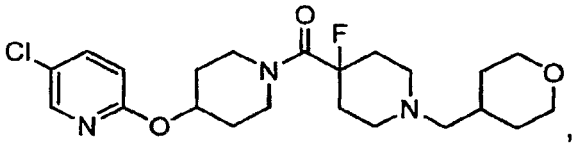

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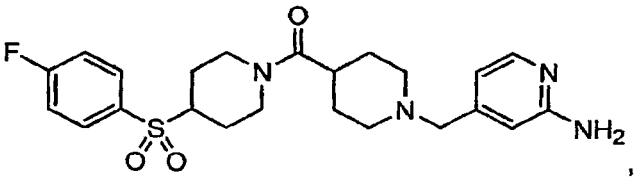


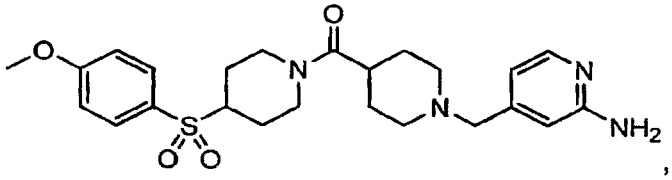


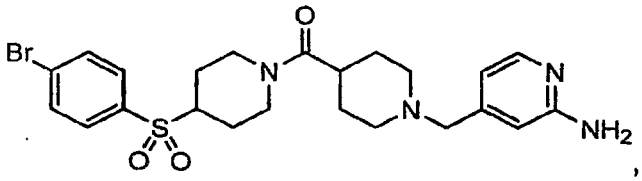


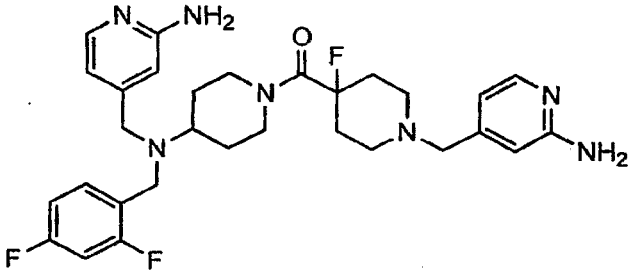


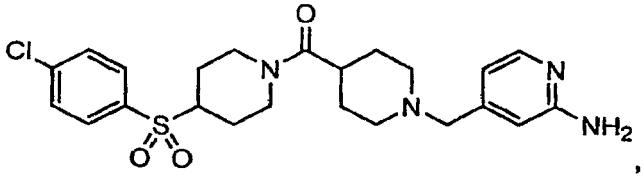


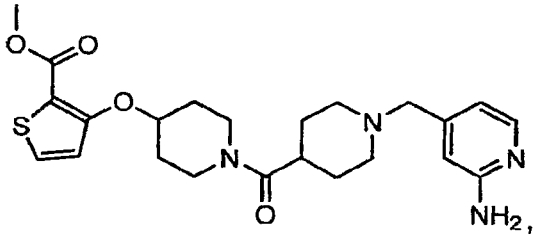


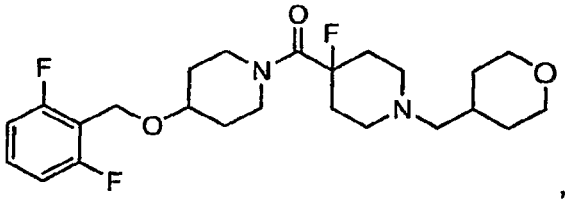


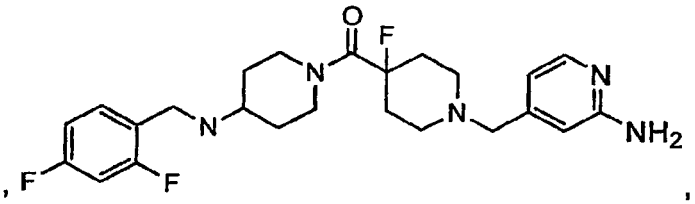


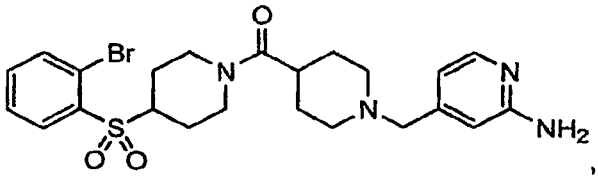


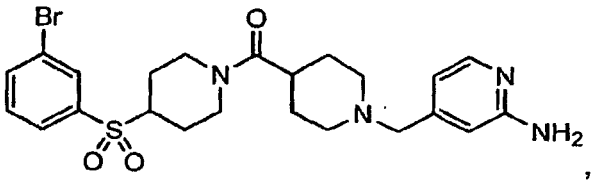


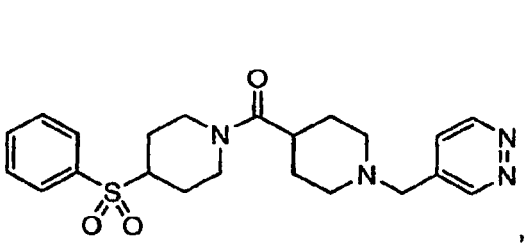


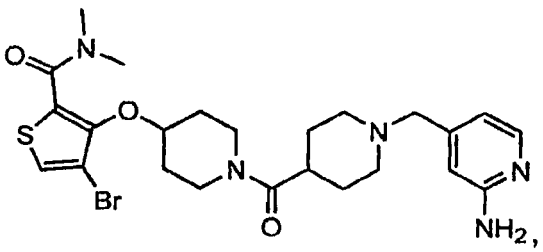


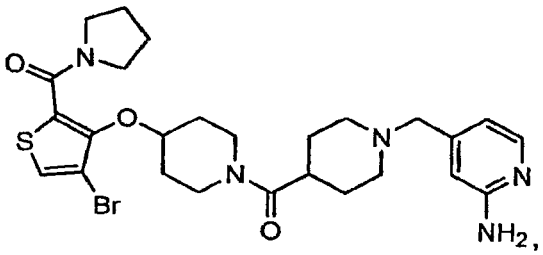


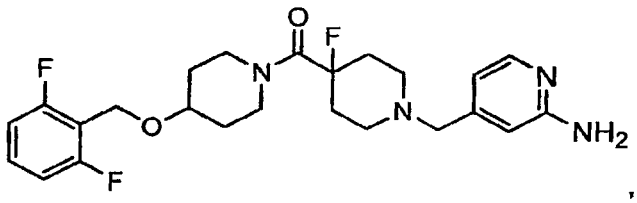


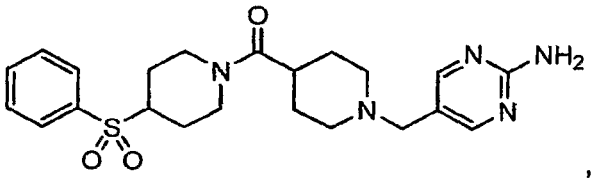


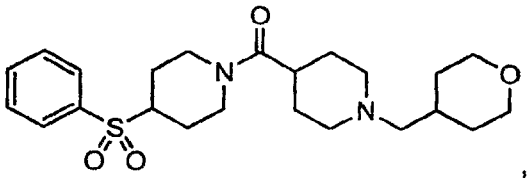


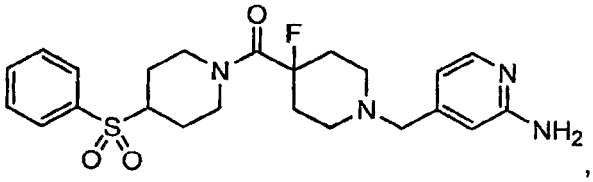


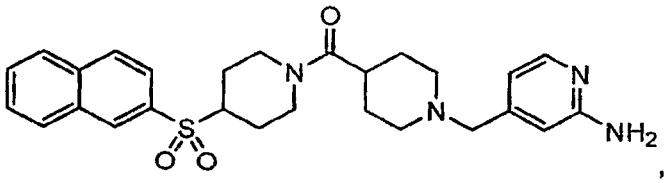


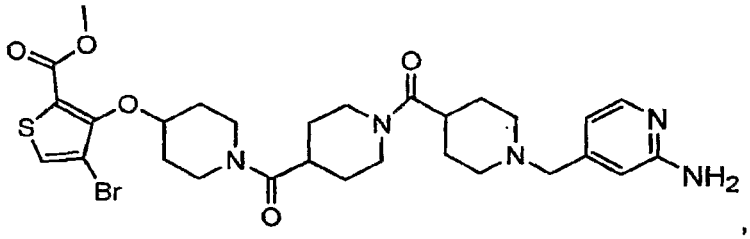




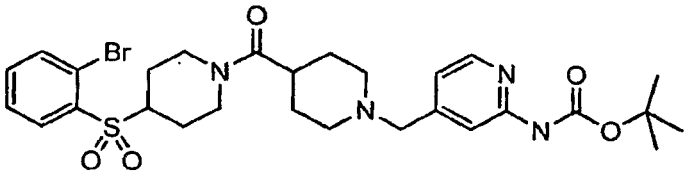


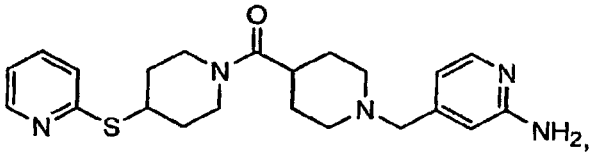


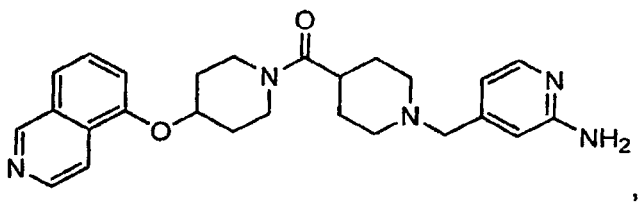


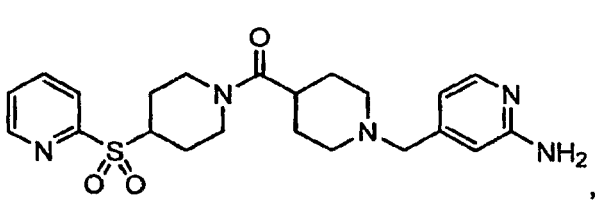
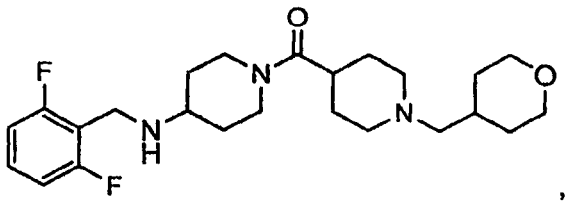
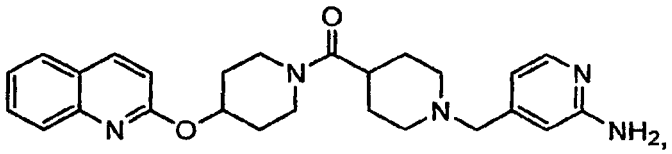
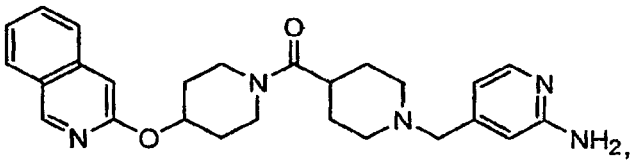
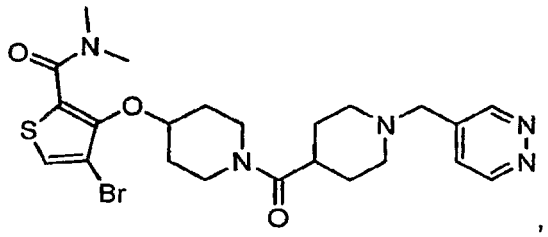
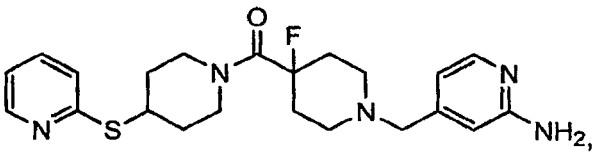
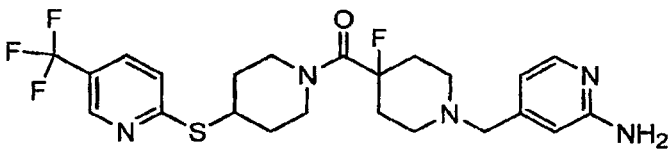
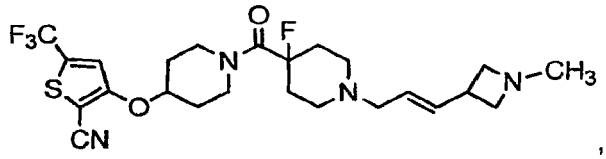
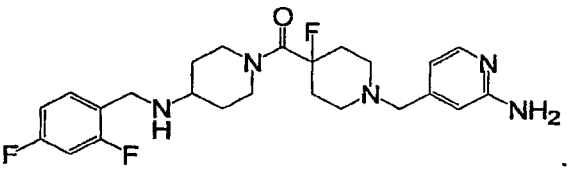


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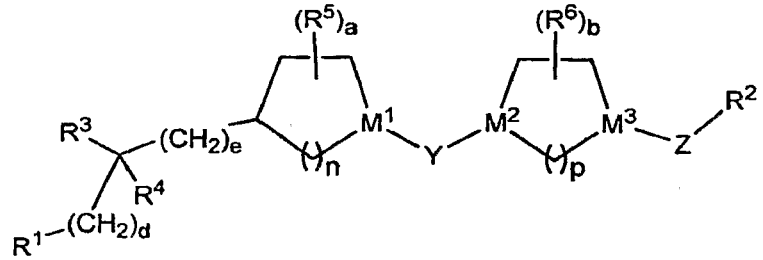






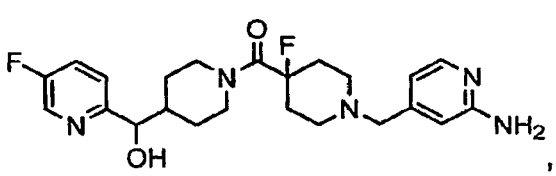
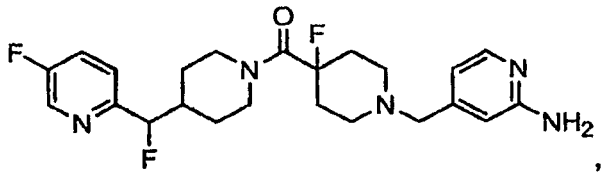
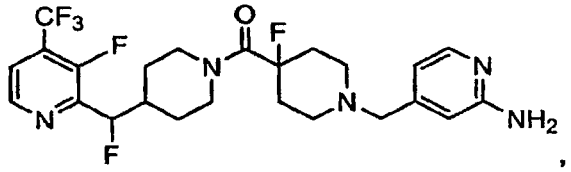
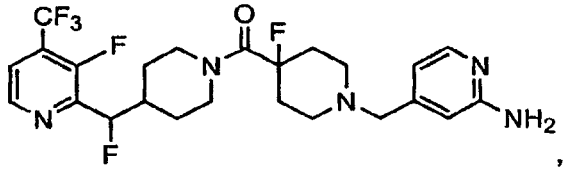
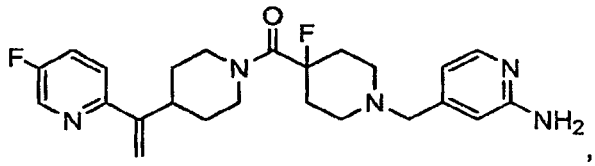
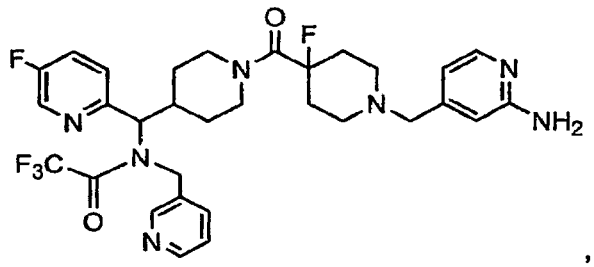
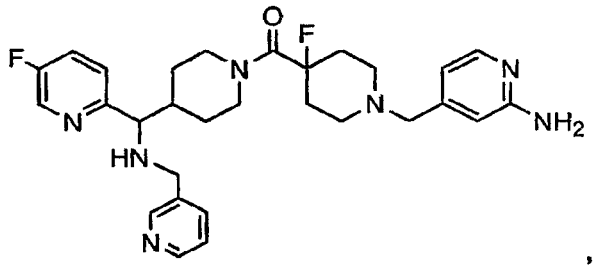
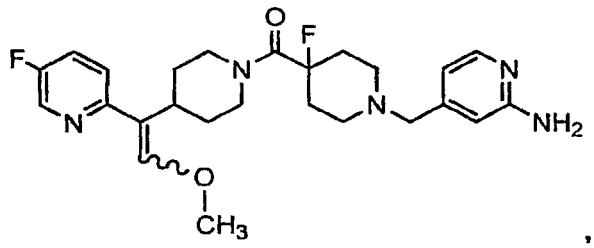
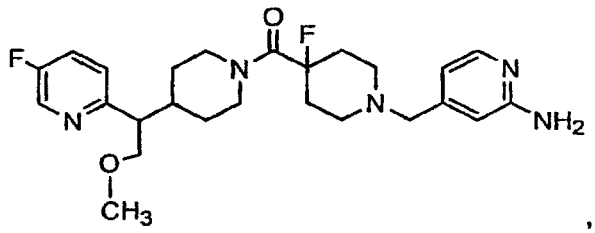
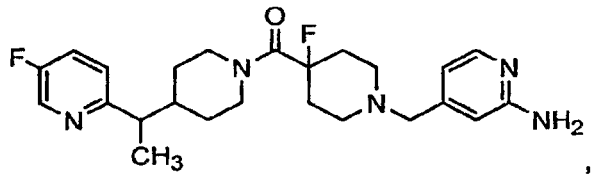
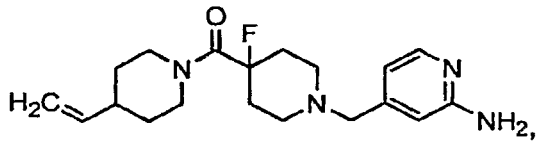
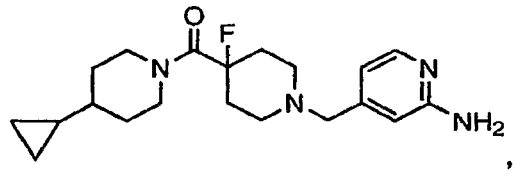
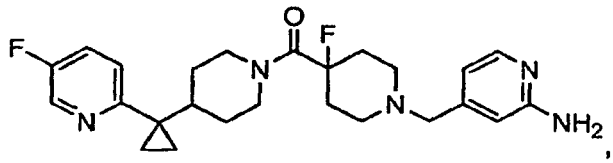
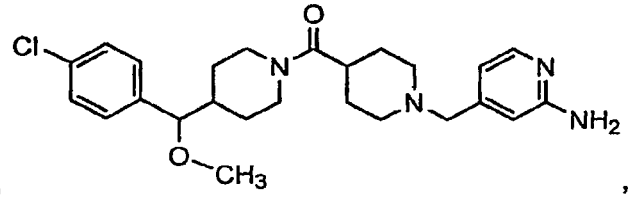

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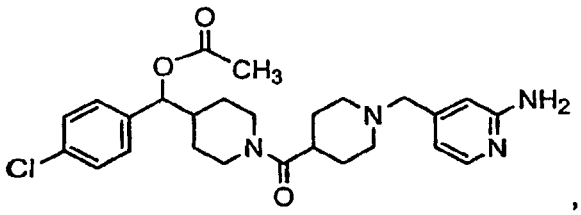
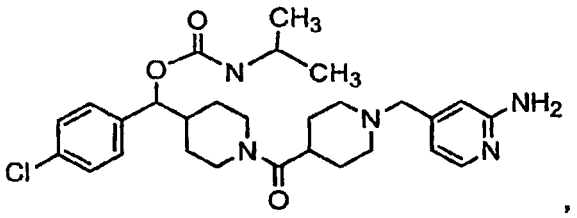
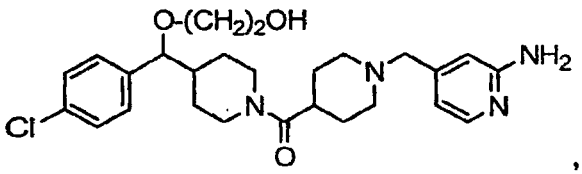
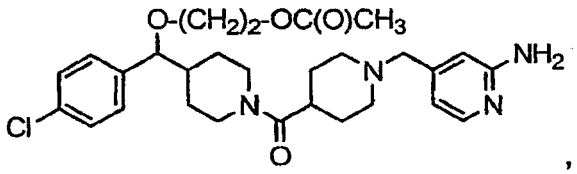
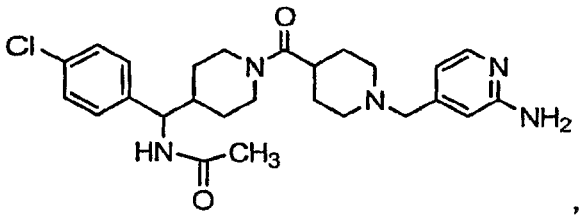
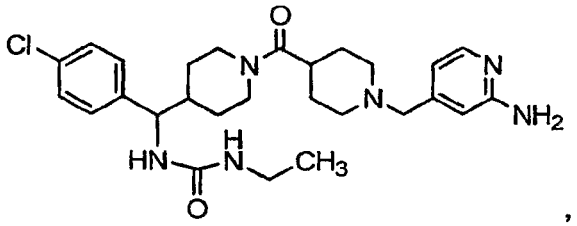
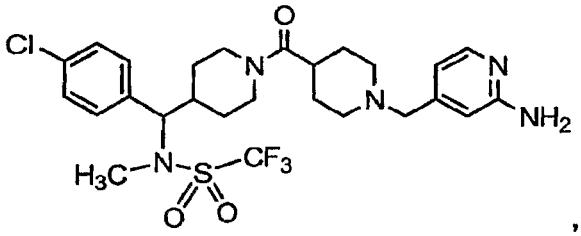
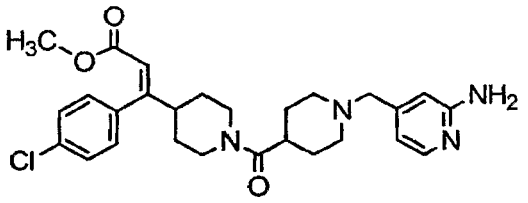
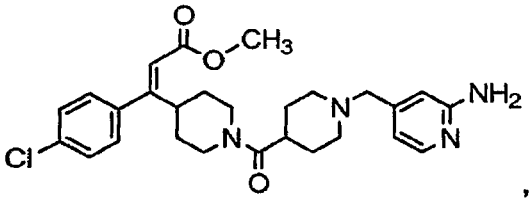
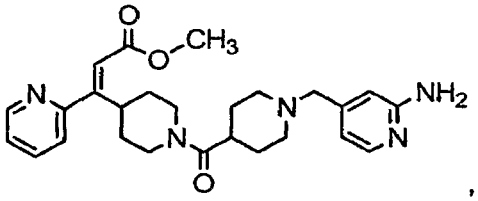
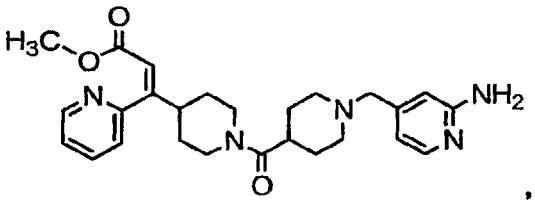
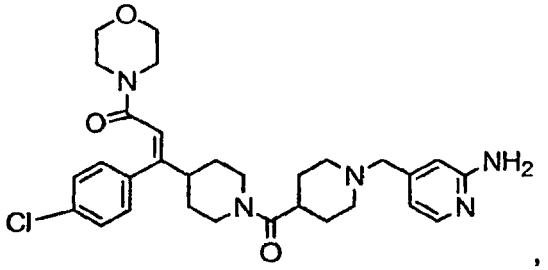
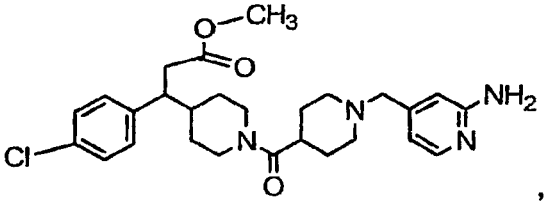
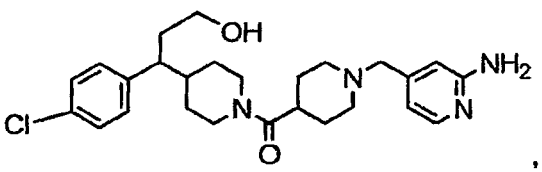
In another embodiment, the H_3 antagonists/inverse agonists of the present invention can have the following Formula (VIII):



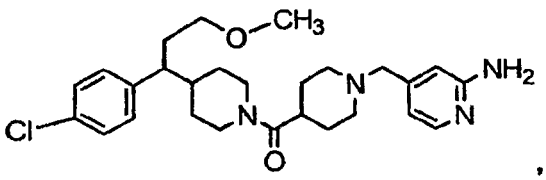
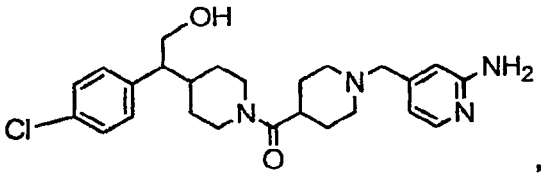
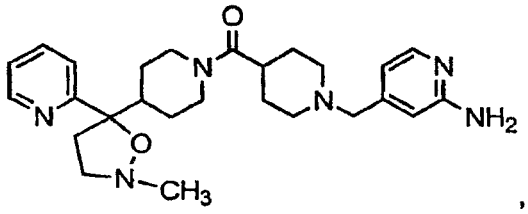
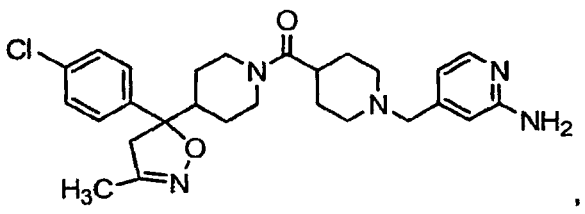
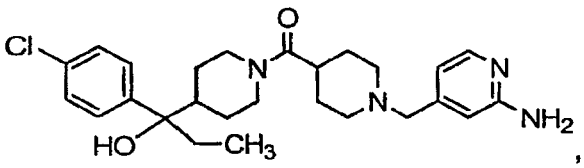
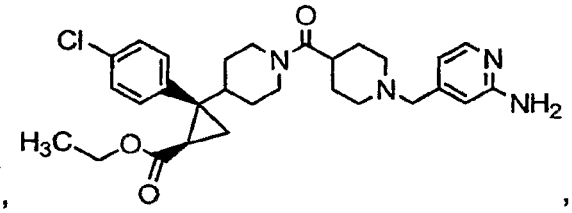
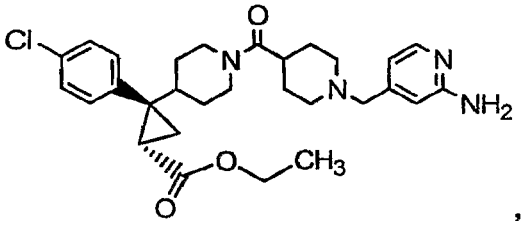
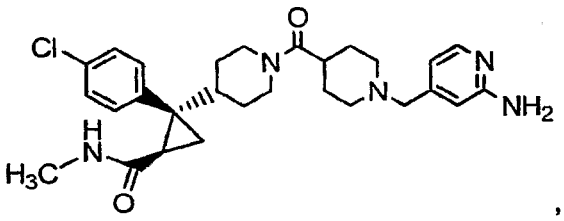
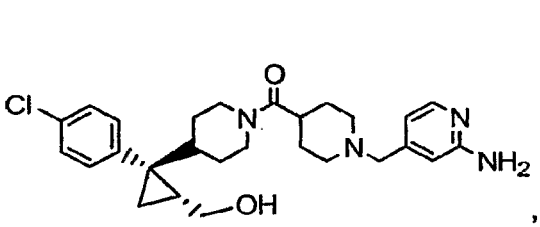
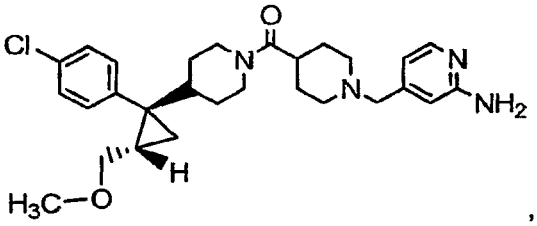
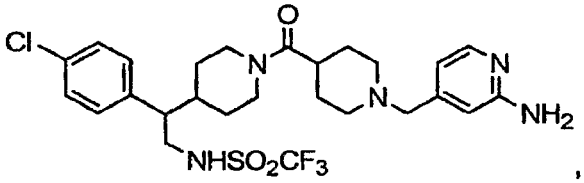
(VIII)

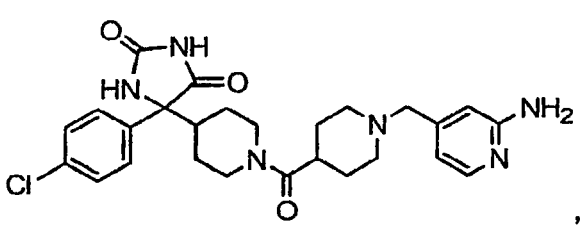
as described in U.S. Provisional Application No. 60/692,175, filed June 20, 2005, and which is herein incorporated by reference in its entirety. Non-limiting examples of compounds of Formula (VIII) include:


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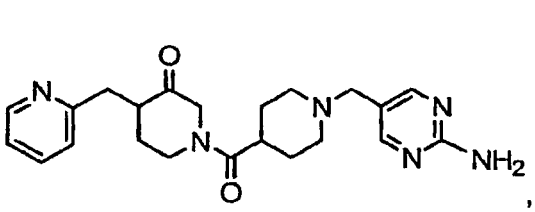
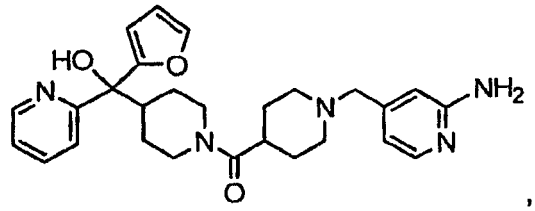
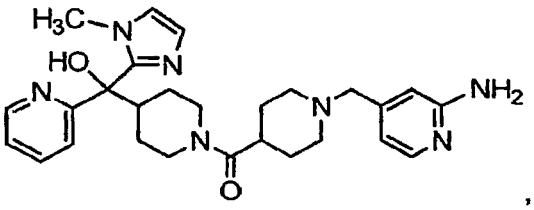
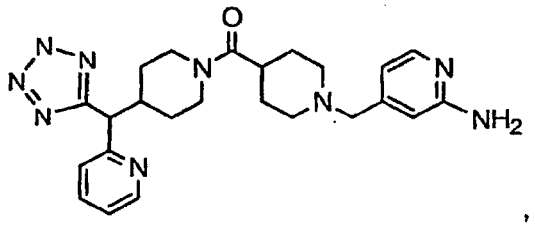
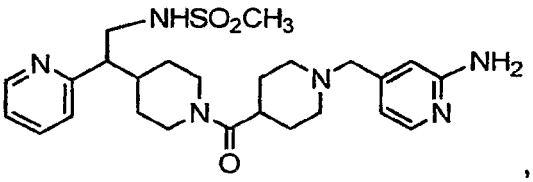
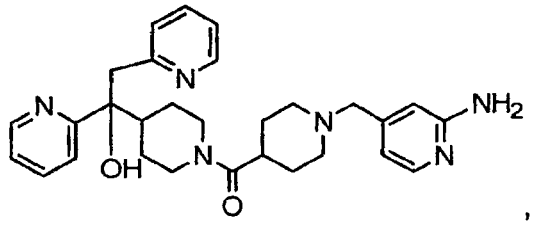
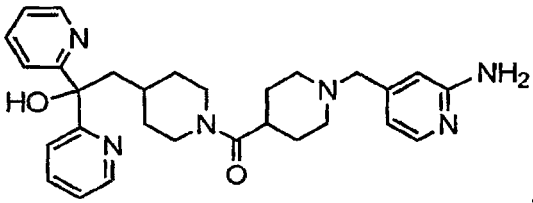
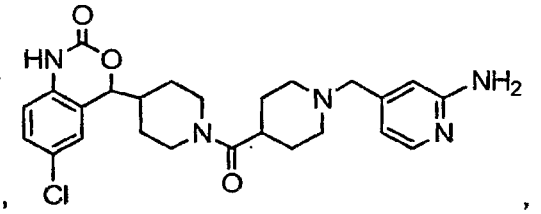
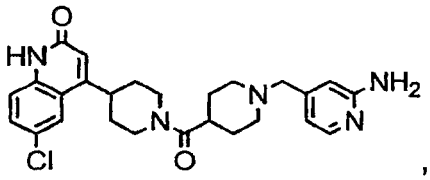
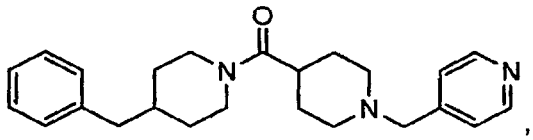
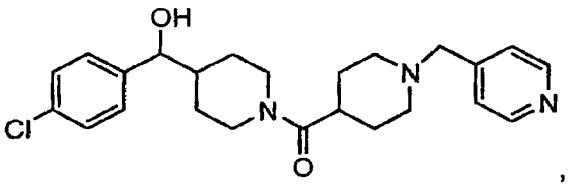
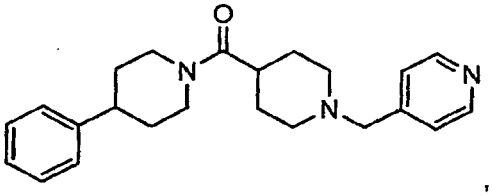
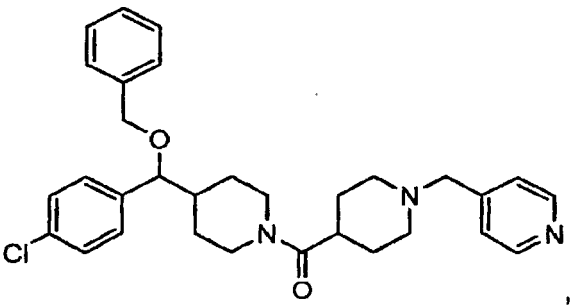
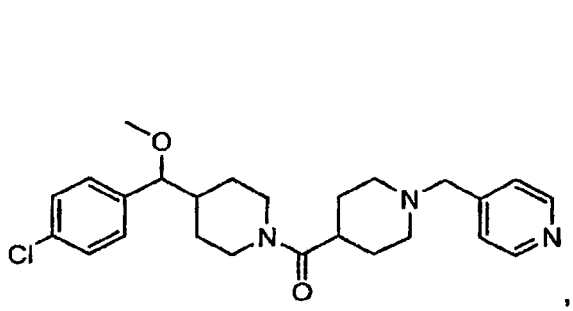

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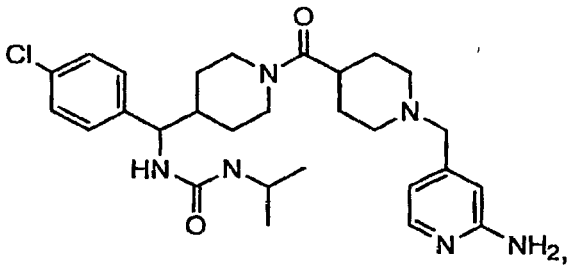
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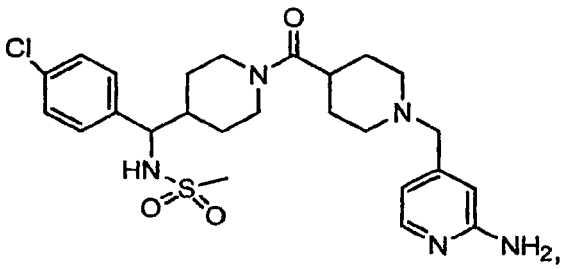
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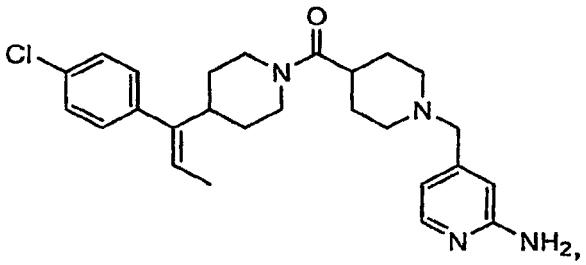
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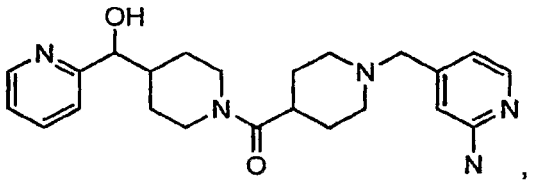

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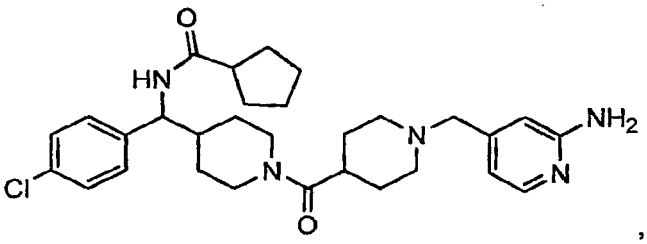
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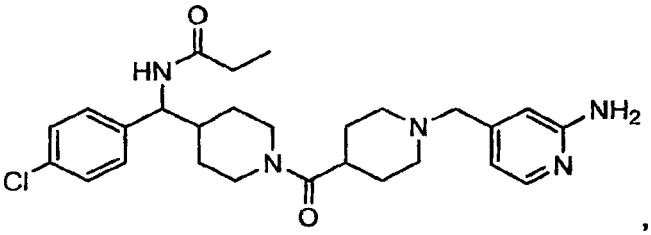


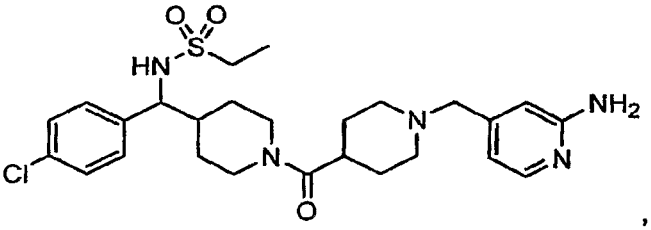


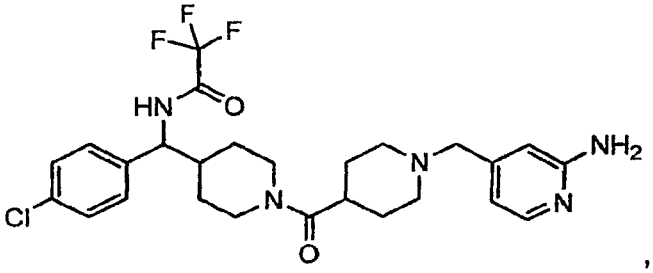


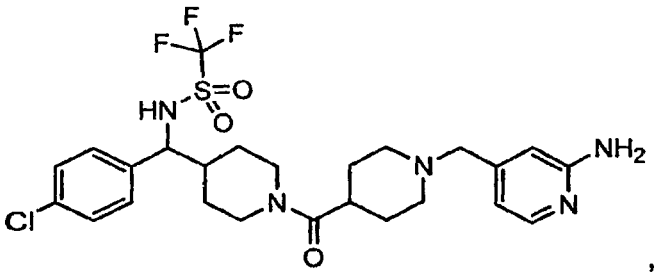




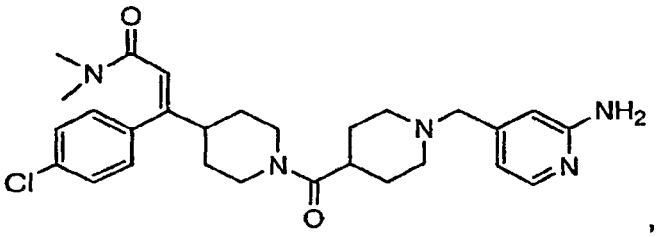




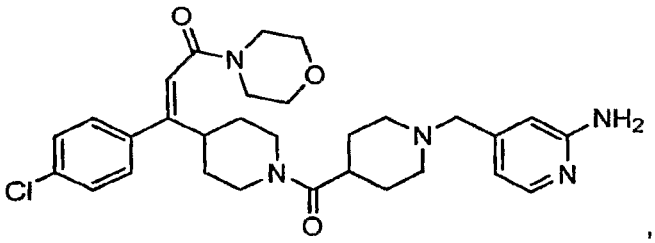




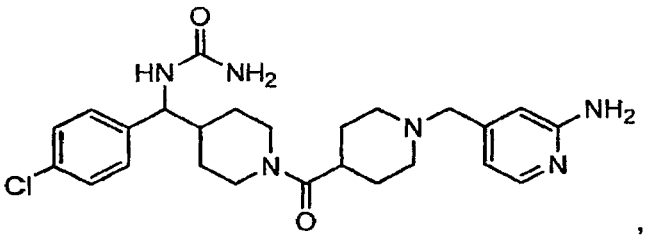
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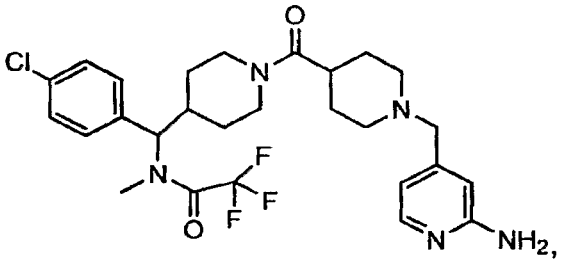
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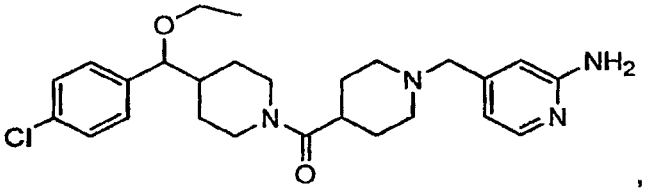
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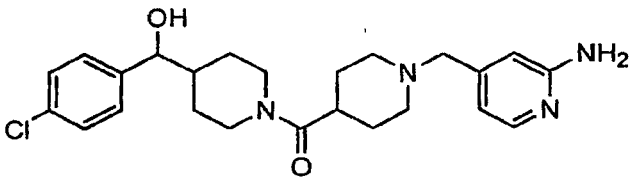
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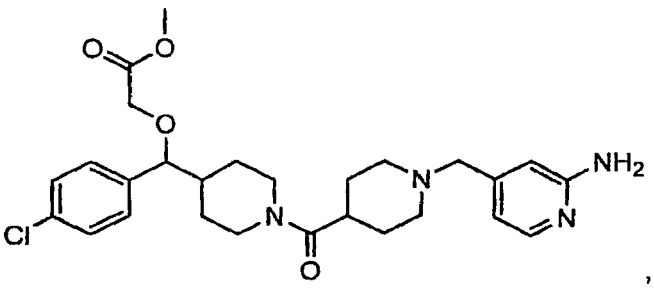
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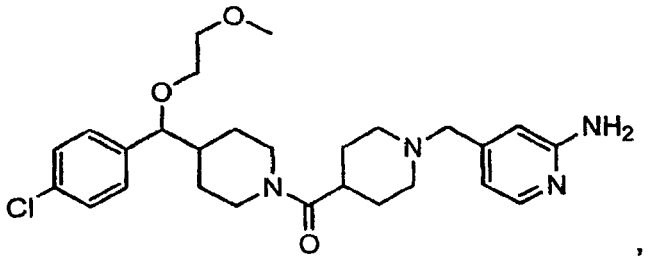
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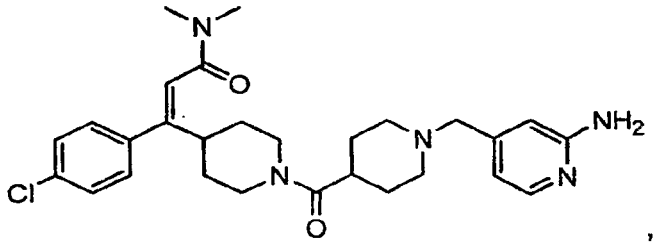
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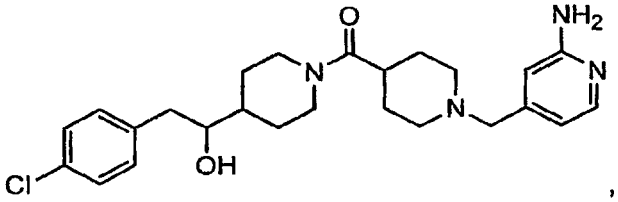
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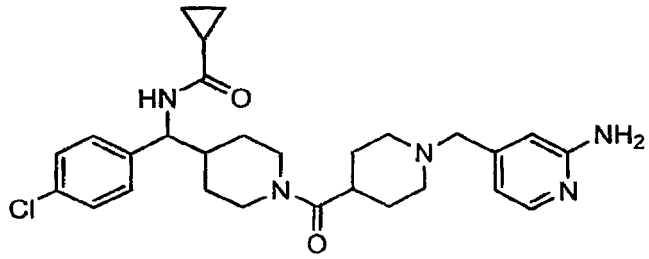
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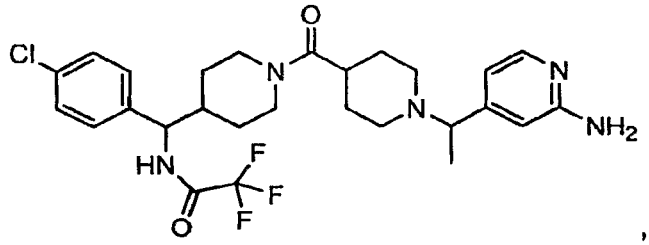
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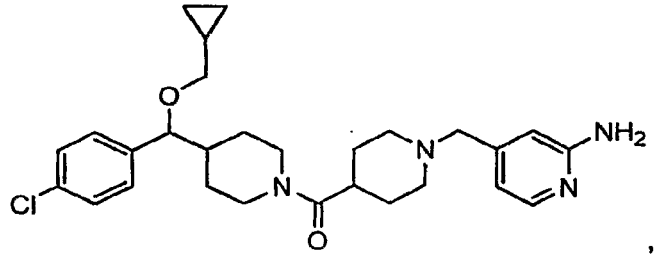
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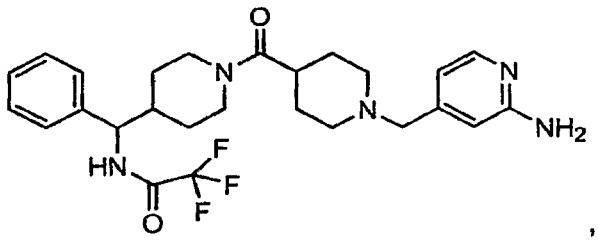
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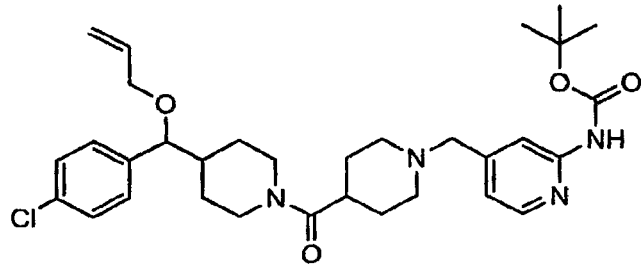
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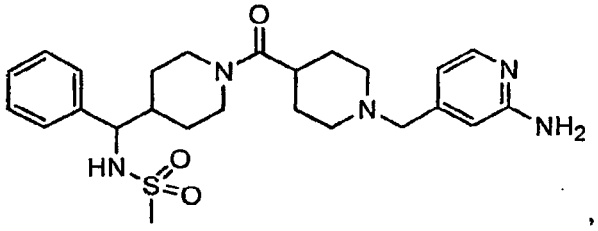
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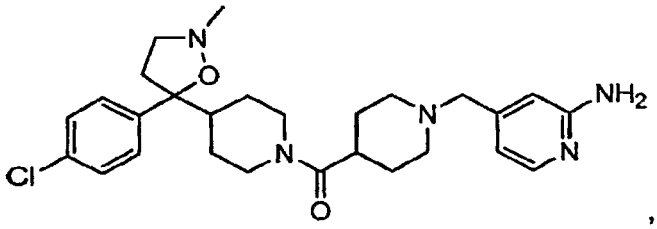
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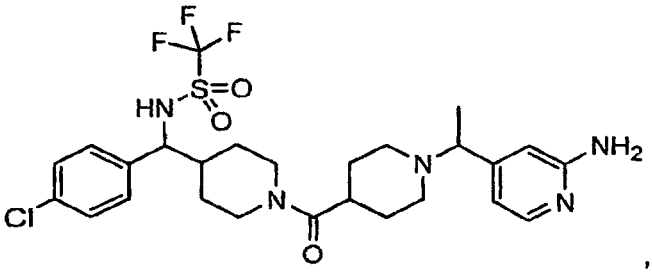
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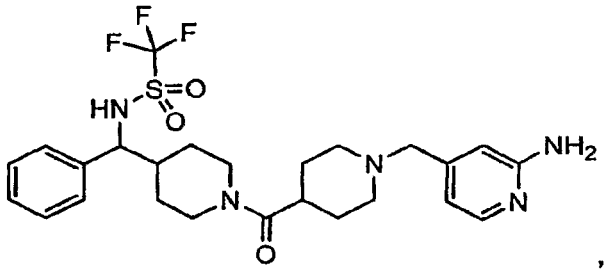
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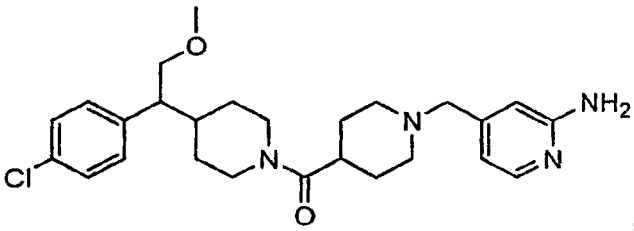
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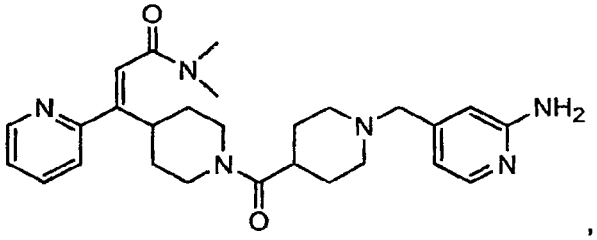
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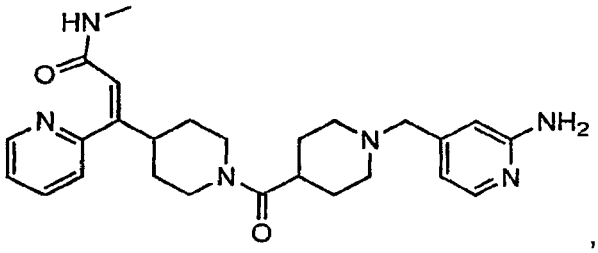
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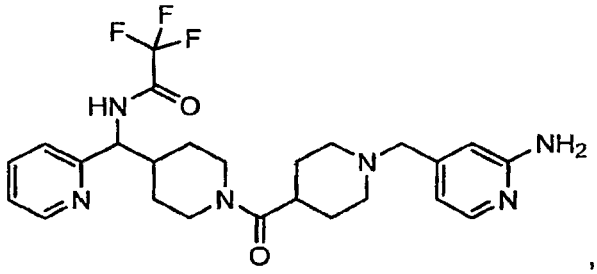
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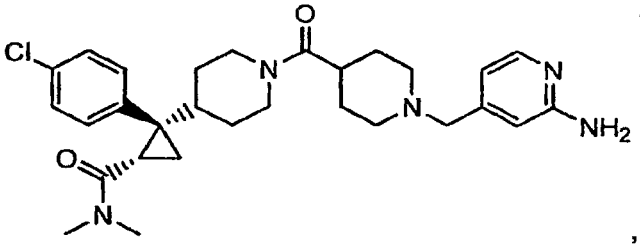
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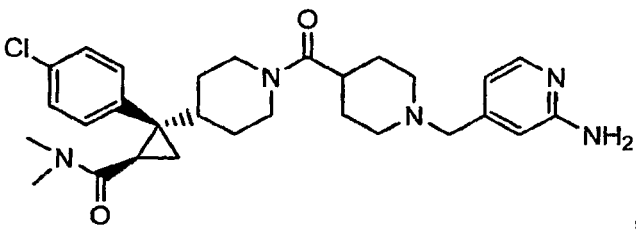
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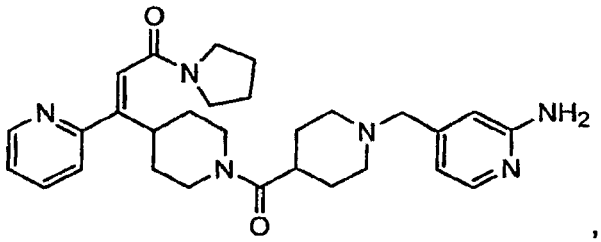
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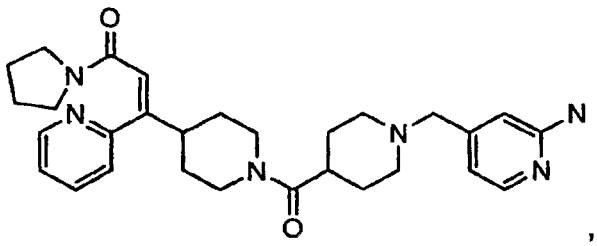
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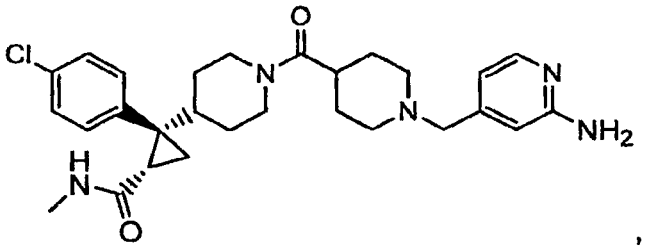
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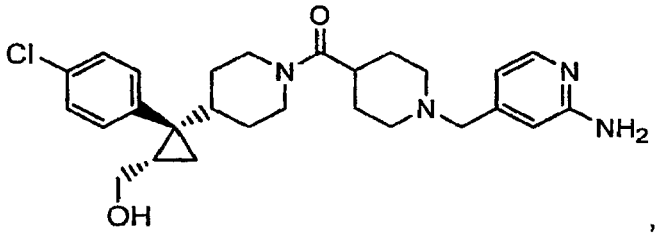
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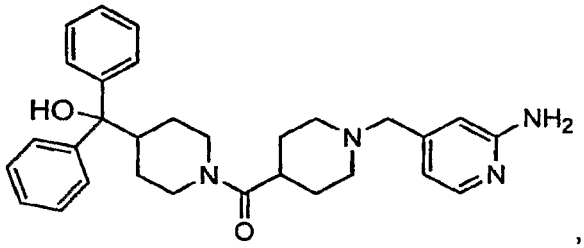
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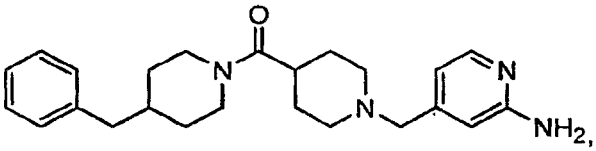
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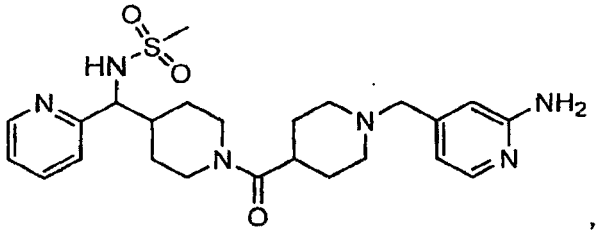
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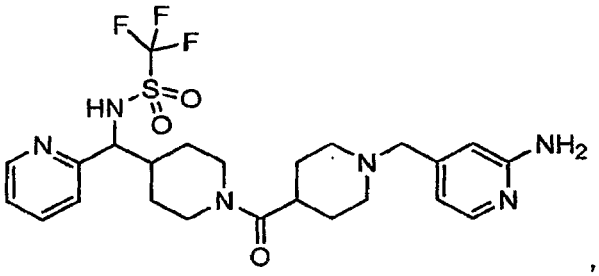
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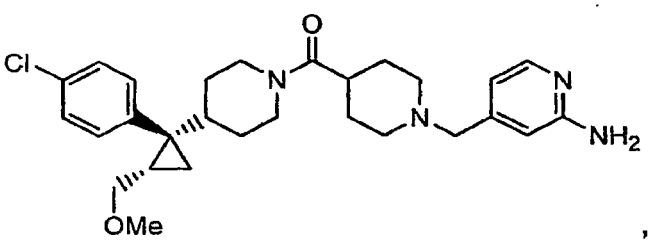
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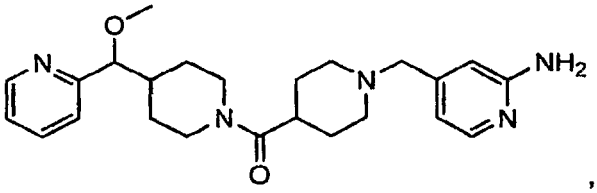
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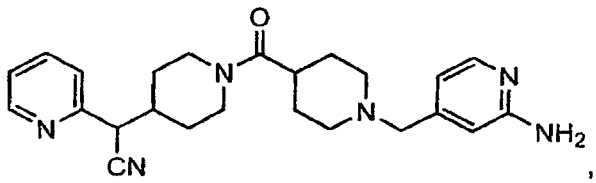
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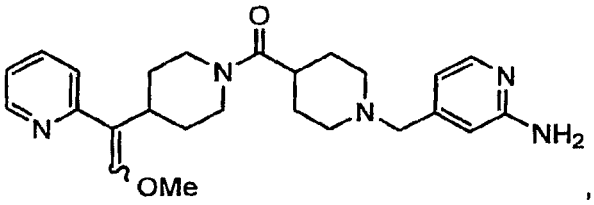
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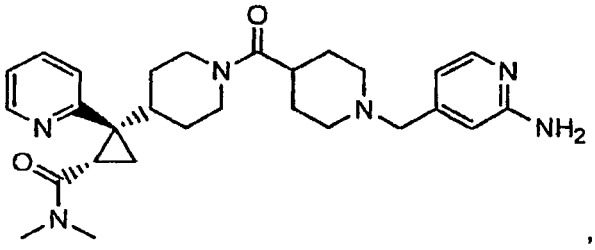
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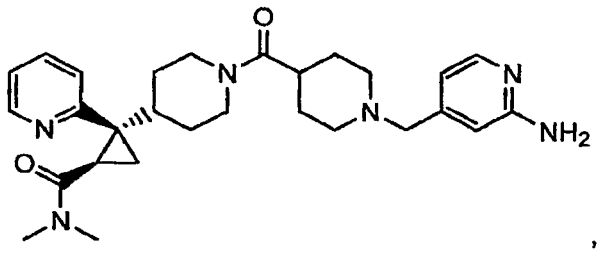
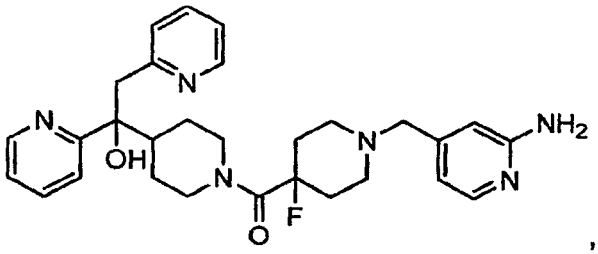
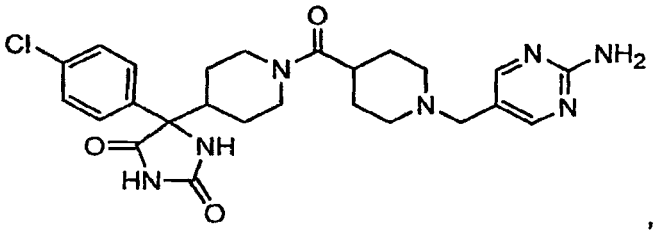
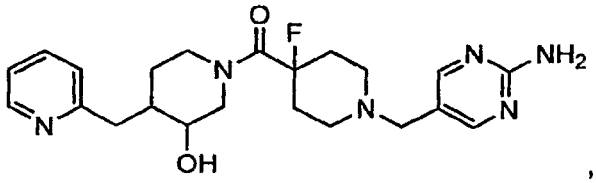
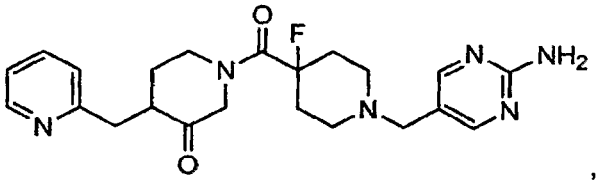
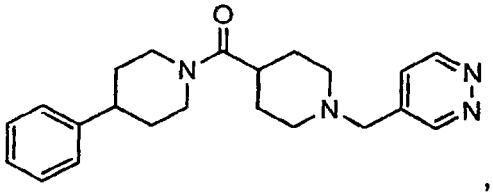
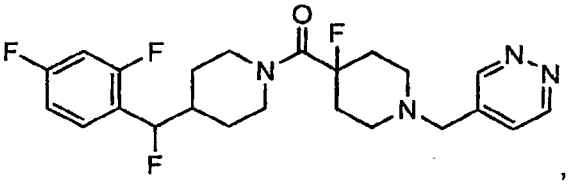
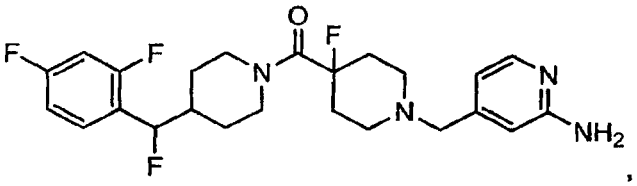
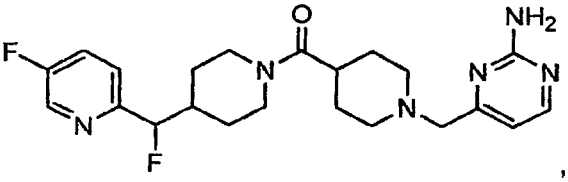
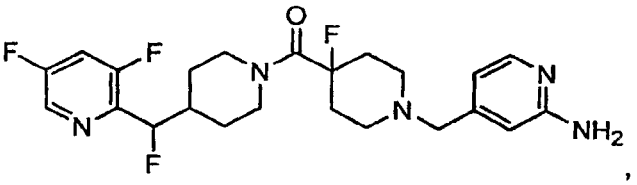
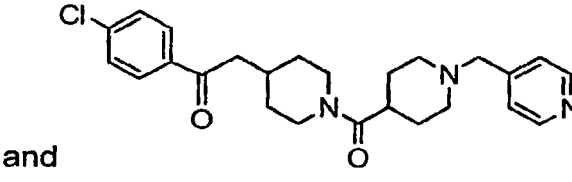
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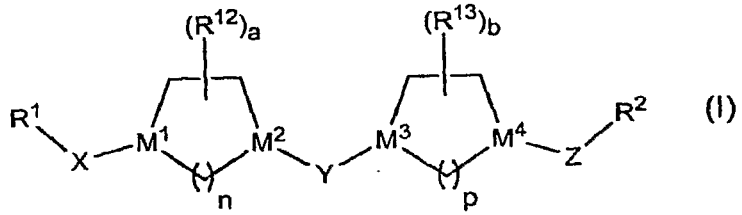
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and .

WE CLAIM:

1. A composition comprising one or more appetite suppressants and one or more metabolic rate enhancers, wherein the appetite suppressant is selected from the group consisting of a CB_1 antagonist, phentermine, sibutramine, and topiramate; and wherein the one or more metabolic rate enhancers are selected from:

(i) a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

(1) R^1 is selected from:

(a) aryl;

(b) heteroaryl;

(c) heterocycloalkyl

(d) alkyl;

(e) cycloalkyl; or

(f) alkylaryl;

wherein the R^1 groups are optionally substituted with 1 to 4 substituents independently selected from:

(1) halogen;

(2) hydroxyl;

(3) lower alkoxy;

(4) $-CF_3$;

(5) CF_3O-;

(6) $-NR^4R^5$;

(7) phenyl;

(8) $-NO_2$,

(9) $-CO_2R^4$;

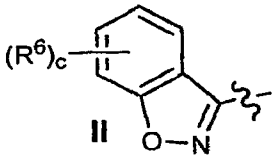
(10) $-CON(R^4)_2$ wherein each R^4 is the same or different;

(11) $-S(O)_mN(R^{20})_2$ wherein each R^{20} is the same or different H or alkyl group;

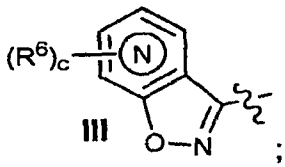
(12) -CN; or

(13) alkyl; or

(2) R^1 and X taken together form a group selected from:

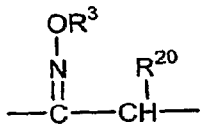


or

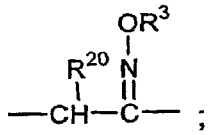


;

(3) X is selected from: =C(O), $=C(NOR^3)$, $=C(NNR^4R^5)$,



or



;

(4) M^1 is carbon;

(5) M^2 is selected from C or N;

(6) M^3 and M^4 are independently selected from C or N;

(7) Y is selected from: is $-CH_2-$, $=C(O)$, $=C(NOR^{20})$ (wherein R^{20} is as defined above), or =C(S);

(8) Z is a $C_1 - C_6$ alkyl group;

(9) R^2 is a five or six-membered heteroaryl ring, said six-membered heteroaryl ring comprising 1 or 2 nitrogen atoms with the remaining ring atoms being carbon, and said five-membered heteroaryl ring containing 1 or 2 heteroatoms selected from: nitrogen, oxygen, or sulfur with the remaining ring atoms being carbon; said five or six membered heteroaryl rings being optionally substituted with 1 to 3 substituents independently selected from: halogen, hydroxyl, lower alkyl, lower alkoxy, $-CF_3$, CF_3O-, $-NR^4R^5$, phenyl, $-NO_2$, $-CO_2R^4$, $-CON(R^4)_2$ wherein each R^4 is the same or different, $-CH_2NR^4R^5$, $-(N)C(NR^4R^5)_2$, or -CN;

(10) R^3 is selected from:

(a) hydrogen;

(b) $C_1 - C_6$ alkyl;

(c) aryl;

(d) heteroaryl;

(e) heterocycloalkyl;

(f) arylalkyl;

(g) $-(CH_2)_e-C(O)N(R^4)_2$ wherein each R^4 is the same or different,

(h) $-(CH_2)_e-C(O)OR^4$;

(i) $-(CH_2)_e-C(O)R^{30}$ wherein R^{30} is a heterocycloalkyl group;

(j) $-CF_3$; or

(k) $-CH_2CF_3$;

wherein the aryl, heteroaryl, heterocycloalkyl, and the aryl portion of said arylalkyl are optionally substituted with 1 to 3 substituents selected from: halogen, -OH, $-OCF_3$, $-CF_3$, -CN, $-N(R^{45})_2$, $-CO_2R^{45}$, or $-C(O)N(R^{45})_2$, wherein each R^{45} is independently selected from: H, alkyl, alkylaryl, or alkylaryl wherein the aryl moiety is substituted with 1 to 3 substituents independently selected from $-CF_3$, -OH, halogen, alkyl, $-NO_2$, or -CN;

(11) R^4 is selected from: hydrogen, $C_1 - C_6$ alkyl, aryl, alkylaryl, said aryl and alkylaryl groups being optionally substituted with 1 to 3 substituents selected from: halogen, $-CF_3$, $-OCF_3$, -OH, $-N(R^{45})_2$, $-CO_2R^{45}$, $-C(O)N(R^{45})_2$, or –CN; wherein R^{45} is as defined above;

(12) R^5 is selected from: hydrogen, $C_1 - C_6$ alkyl, $-C(O)R^4$, $-C(O)_2R^4$, or $-C(O)N(R^4)_2$ wherein each R^4 is independently selected, and R^4 is as defined above;

(13) or R^4 and R^5 taken together with the nitrogen atom to which they are bound forms a five or six membered heterocycloalkyl ring;

(14) R^6 is selected from: alkyl, aryl, alkylaryl, halogen, hydroxyl, lower alkoxy, $-CF_3$, CF_3O-, $-NR^4R^5$, phenyl, $-NO_2$, $-CO_2R^4$, $-CON(R^4)_2$ wherein each R^4 is the same or different, or -CN;

(15) R^{12} is selected from: alkyl, hydroxyl, alkoxy, or fluoro;

(16) R^{13} is selected from: alkyl, hydroxyl, alkoxy, or fluoro;

(17) a is 0 to 2;

(18) b is 0 to 2;

(19) c is 0 to 2;

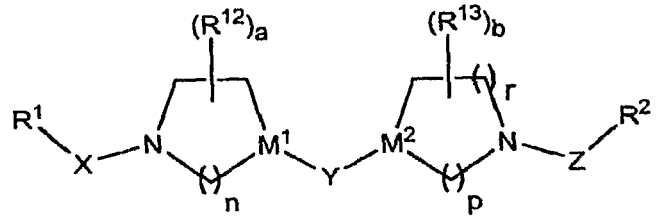
(20) e is 0 to 5;

(21) m is 1 or 2;

(22) n is 1, 2 or 3; and

(23) p is 1, 2 or 3, with the proviso that when M^3 and M^4 are both nitrogen, then p is 2 or 3; or

(ii) a compound of Formula (II):



(II)

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

(A) R^1 is selected from:

(1) aryl;

(2) heteroaryl;

(3) heterocycloalkyl

(4) alkyl;

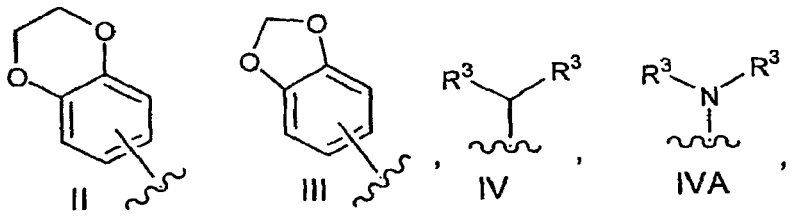
(5) $-C(O)N(R^{4B})_2$;

(6) cycloalkyl;

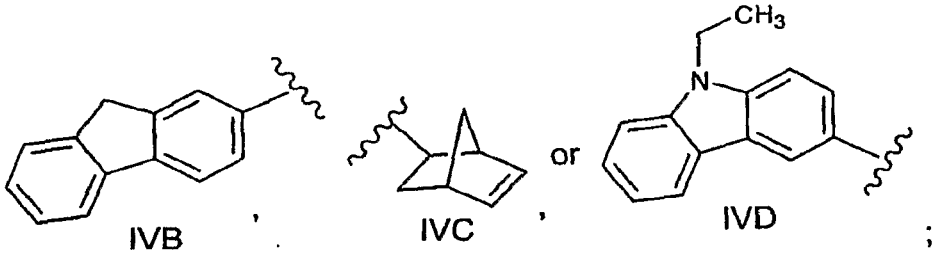
(7) arylalkyl;

(8) heteroarylheteroaryl; or

(9) a group selected from:



II, III, IV, IVA,



IVB, IVC, or IVD;

said aryl, heteroaryl, aryl portion of arylalkyl, phenyl ring of formula II, phenyl ring of formula III, phenyl rings of formula IVB, or phenyl rings of formula IVD are optionally substituted with 1 to 3 substituents independently selected from:

(1) halogen;

(2) hydroxyl;
(3) lower alkoxy;
(4) -Oaryl;
(5) $-SR^{22}$;
(6) $-CF_3$;
(7) $-OCF_3$;
(8) $-OCHF_2$;
(9) $-NR^4R^5$;
(10) phenyl;
(11) NO_2,
(12) $-CO_2R^4$;
(13) $-CON(R^4)_2$ wherein each R^4 is the same or different;
(14) $-S(O)_2R^{22}$;
(15) $-S(O)_2N(R^{20})_2$ wherein each R^{20} is the same or different;
(16) $-N(R^{24})S(O)_2R^{22}$;
(17) -CN;
(18) $-CH_2OH$;
(19) $-OCH_2CH_2OR^{22}$;
(20) alkyl;
(21) substituted phenyl wherein the phenyl has 1 to 3 substituents independently selected from alkyl, halogen, -CN, $-NO_2$, $-OCHF_2$, -Oalkyl;
(22) -Oalkylaryl wherein the aryl group is optionally substituted with 1 to 3 independently selected halogens; or
(23) phenyl;

(C) X is selected from alkyl or $-S(O)_2-$;

(D) Y represents
(1) a single bond; or
(2) Y is selected from $-C(O)-$, $-C(S)-$, $-(CH_2)_q-$, or $-NR^4C(O)-$; with the provisos that:
(a) when M^1 is N, then Y is not $-NR^4C(O)-$; and
(b) when Y is a bond, then M^1 and M^2 are both carbon;

(E) M^1 and M^2 are independently selected from C or N;

(F) Z is selected from: C_1-C_6 alkyl, -SO_2-, -C(O)- or –C(O)NR^4-;

(G) R^2 is selected from:

(1) a six-membered heteroaryl ring having 1 or 2 heteroatoms independently selected from N or N-O, with the remaining ring atoms being carbon;

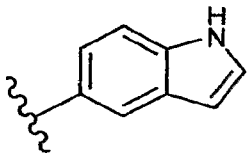
(2) a five-membered heteroaryl ring having 1 to 3 heteroatoms selected from nitrogen, oxygen, or sulfur with the remaining ring atoms being carbon; or

(3) an alkyl group;

(4) an aryl group wherein the substituted phenyl is substituted with 1 to 3 substituents independently selected from: halogen, -Oalkyl, -OCF_3, -CF_3, -CN, -NO_2, -$NHC(O)CH_3$, or -$O(CH_2)_qN(R^{10A})_2$;

(5) -$N(R^{11A})_2$ wherein each R^{11A} is independently selected from: H, alkyl or aryl;

(6) a group of the formula:



; or

(7) a heteroarylheteroaryl group;

said five membered heteroaryl ring ((G)(2) above) or six-membered heteroaryl ring ((G)(1) above) is optionally substituted with 1 to 3 substituents selected from:

(a) halogen;

(b) hydroxyl;

(c) lower alkyl;

(d) lower alkoxy;

(e) -CF_3;

(f) -NR^4R^5;

(g) phenyl;

(h) -NO_2;

(i) $-C(O)N(R^4)_2$ (wherein each R^4 is the same or different);

(j) $-C(O)_2R^4$; or

(k) phenyl substituted with 1 to 3 substituents independently selected from: halogen, -Oalkyl, $-OCF_3$, $-CF_3$, -CN, $-NO_2$ or $-O(CH_2)_qN(R^{10A})_2$;

(H) R^3 is selected from:

(1) aryl;

(2) heteroaryl;

(3) heterocycloalkyl

(4) alkyl; or

(5) cycloalkyl;

wherein the aryl or heteroaryl R^3 groups is optionally substituted with 1 to 3 substituents independently selected from:

(a) halogen;

(b) hydroxyl;

(c) lower alkoxy;

(d) -Oaryl;

(e) $-SR^{22}$;

(f) $-CF_3$;

(g) $-OCF_3$;

(h) $-OCHF_2$;

(i) $-NR^4R^5$;

(j) phenyl;

(k) $-NO_2$,

(l) $-CO_2R^4$;

(m) $-CON(R^4)_2$ wherein each R^4 is the same or different;

(n) $-S(O)_2R^{22}$;

(o) $-S(O)_2N(R^{20})_2$ wherein each R^{20} is the same or different;

(p) $-N(R^{24})S(O)_2R^{22}$;

(q) -CN;

(r) $-CH_2OH$;

(s) $-OCH_2CH_2OR^{22}$; or

(t) alkyl;

(l) R^4 is selected from:

(1) hydrogen;
(2) C_1-C_6 alkyl;
(3) cycloalkyl;
(4) cycloalkylalkyl;
(5) heterocycloalkylalky;
(6) bridged bicyclic cycloalkyl ring;
(7) aryl having a fused heterocycloalkyl ring bound to said aryl ring;
(8) aryl;
(9) arylalkyl;
(10) alkylaryl;
(11) $-(CH_2)_dCH(R^{12A})_2$ wherein d is 1 to 3, and each R^{12A} is independently selected from phenyl or substituted phenyl, said substituted phenyl being substituted with 1 to 3 substituents independently selected from: halogen, -Oalkyl, $-OCF_3$, $-CF_3$, -CN, or $-NO_2$;
(12) heterocycloalkylheteroaryl; or
(13) -(C_1 to C_6)alkylene-O-R^{22};

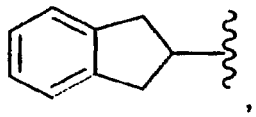
wherein the aryl R^4 group, the aryl portion of the arylalkyl R^4 group, or the aryl portion of the alkylaryl R^4 group is optionally substituted with 1 to 3 substituents independently selected from:

(a) halogen;
(b) hydroxyl;
(c) lower alkyl;
(d) lower alkoxy;
(e) $-CF_3$;
(f) $-N(R^{20})(R^{24})$,
(g) phenyl;
(h) $-NO_2$;
(i) $-C(O)N(R^{20})_2$ (wherein each R^{20} is the same or different),
(j) $-C(O)R^{22}$;
(i) $-(CH_2)_k$-cycloalkyl;

(j) $-(CH_2)_q$-aryl; or

(k) $-(CH_2)_m-OR^{22}$;

(J) each R^{4B} is independently selected from: H, heteroaryl, alkyl, alkenyl, a group of the formula



arylalkyl, or arylalkyl wherein the aryl moiety is substitued with 1-3 substituents independently selected from: halogen;

(K) R^5 is selected from: hydrogen, C_1-C_6 alkyl, $-C(O)R^{20}$, $-C(O)_2R^{20}$, $-C(O)N(R^{20})_2$ (wherein each R^{20} is the same or different);

(L) each R^{10A} is independently selected from H or C_1 to C_6 alkyl, or each R^{10A}, taken together with the nitrogen atom to which they are bound, forms a 4 to 7 membered heterocycloalkyl ring;

(M) R^{12} is

(1) selected from alkyl, hydroxyl, 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

(2) R^{12} forms an alkyl bridge from one ring carbon to another ring carbon;

(N) R^{13} is

(1) selected from alkyl, hydroxyl, 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

(2) R^{13} forms an alkyl bridge from one ring carbon to another ring carbon;

(O) R^{20} is selected from hydrogen, alkyl, or aryl, wherein the 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 form a five or six membered heterocyclic ring;

(P) R^{22} is selected from: heterocycloalkyl, alkyl or aryl, wherein the aryl group is optionally substituted with 1 to 3 groups independently selected from halogen, $-CF_3$, $-OCF_3$, hydroxyl, or methoxy;

(Q) R^{24} is selected from: hydrogen, alkyl, $-SO_2R^{22}$, or aryl, wherein the aryl group is optionally substituted with 1 to 3 groups independently selected from halogen, $-CF_3$, $-OCF_3$, hydroxyl, or methoxy;

(R) a is 0 to 2;

(S) b is 0 to 2;

(T) k is 1 to 5;

(U) m is 2 to 5;

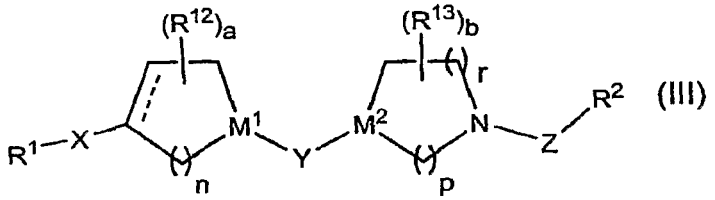
(V) n is 1, 2 or 3 with the proviso that when M^1 is N, then n is not 1;

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

(X) q is 1 to 5; and

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

(iii) a compound of Formula (III):



(III)

or a pharmaceutically acceptable salt, solvate, ester or prodrug 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;

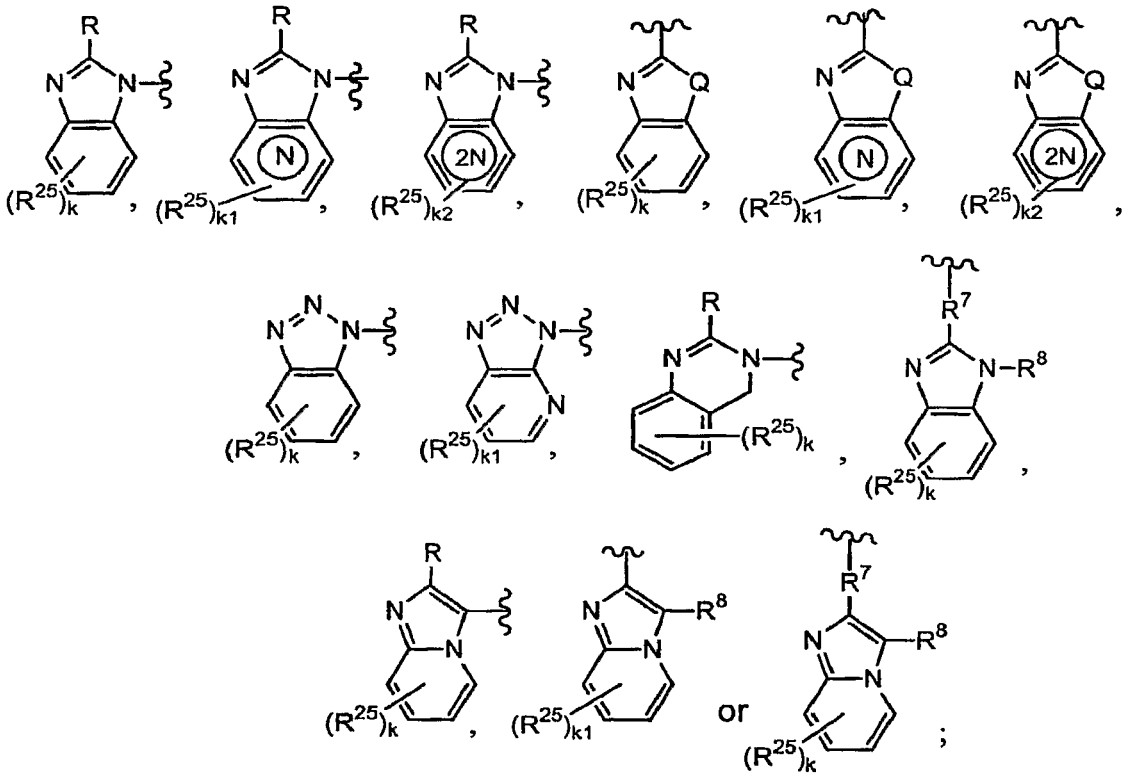
X is a bond or C_1-C_6 alkylene;

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;

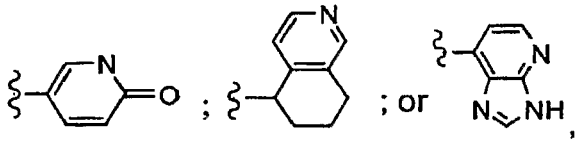
k2 is 0, 1 or 2;

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

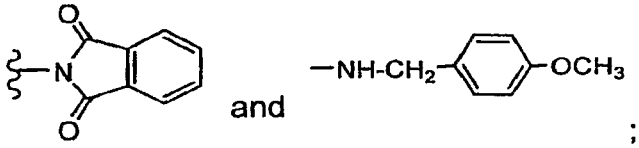
R^3 is H, halogen, C_1-C_6 alkyl, -OH, (C_1-C_6)alkoxy or -$NHSO_2$-(C_1-C_6)alkyl;

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 the 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, -$OCHF_2$, -N$R^{39}R^{40}$, 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 –$O(CH_2)_2O$- 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;

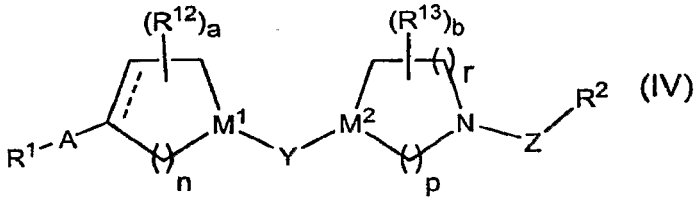
R^{38} is H, C_1-C_6 alkyl, R^{35}-aryl, R^{35}-aryl(C_1-C_6)alkyl-, (C_1-C_6)alkyl-SO_2 or halo(C_1-C_6)alkyl-SO_2-;

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; or

(iv) a compound of Formula (IV):



or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

the dotted line represents an optional double bond;

a is 0 to 3;

b is 0 to 3;

n is 1, 2 or 3;

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

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

A is a bond or C_1-C_6 alkylene;

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

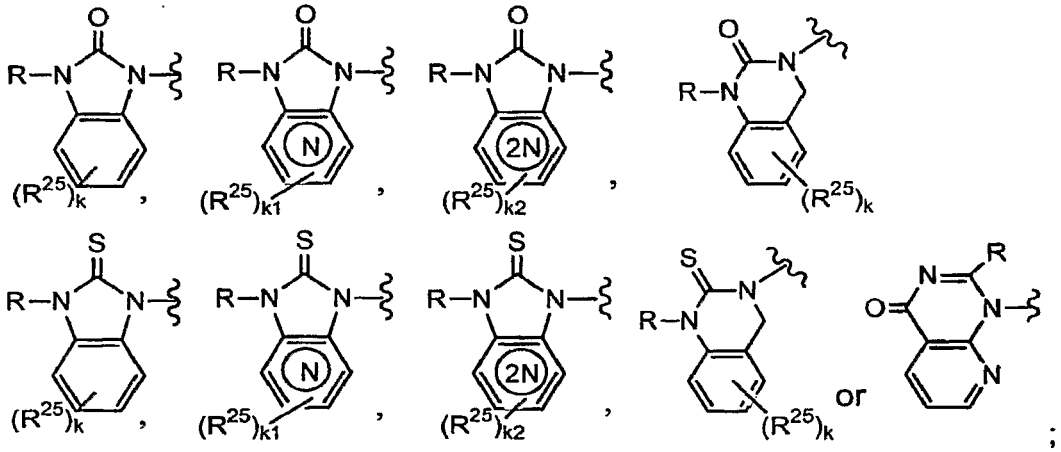
M^2 is $C(R^3)$ or N;

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

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

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

R^1 is



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

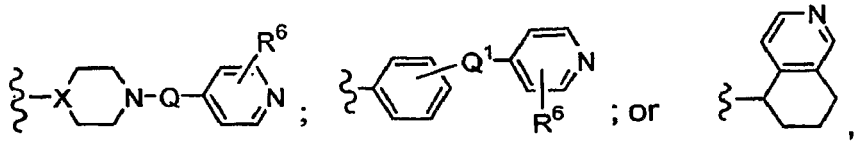
k1 is 0, 1, 2 or 3;

k2 is 0, 1 or 2;

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

R^2 is a six-membered heteroaryl ring having 1 or 2 heteroatoms independently selected from N or N-O, with the remaining ring atoms being carbon; a five-membered heteroaryl ring having 1, 2, 3 or 4 heteroatoms independently selected from N, O or S,

with the remaining ring atoms being carbon; R^{32}-quinolyl; R^{32}-aryl; heterocycloalkyl; (C_3-C_6)cycloalkyl; (C_1-C_6)alkyl; hydrogen;



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

X is CH or N;

Q is a bond or C_1-C_6 alkylene;

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

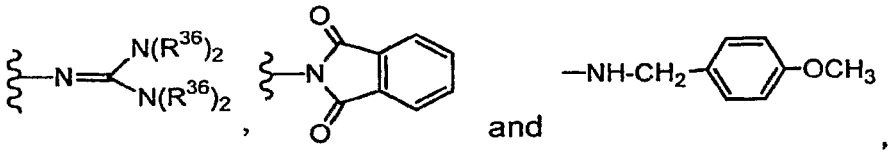
R^3 is H, halogen, C_1-C_6 alkyl, -OH or (C_1-C_6)alkoxy;

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

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

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

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



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

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

R^{13} is independently selected from the group consisting of C_1-C_6 alkyl, hydroxy, C_1-C_6 alkoxy, or fluoro, provided that when R^{13} is hydroxy or fluoro then R^{13} is not

bound to a carbon adjacent to a nitrogen; or two R^{13} substituents together form a C_1 to C_2 alkyl bridge from one ring carbon to another non-adjacent ring carbon; or R^{13} is =O;

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

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

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

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

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

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

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

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

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

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

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

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

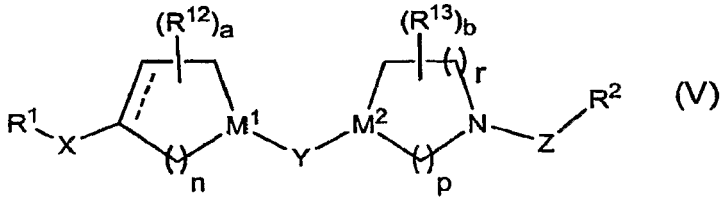
R^{36} is independently selected form the group consisting of H and C_1-C_6 alkyl;

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

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

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

(v) a compound of Formula (V):



(V)

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

a is 0 to 3;

b is 0 to 3;

n is 1, 2 or 3;

p is 1, 2 or 3;

r is 0, 1, 2, or 3;

X is a bond or C_1-C_6 alkylene;

M^1 is CH or N;

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

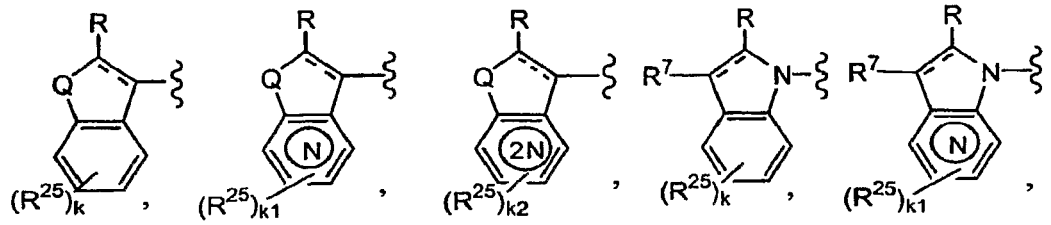
with the provisos that when M^2 is N, p is not 1; and that when r is 0, M^2 is $C(R^3)$; and that the sum of p and r is 1 to 4;

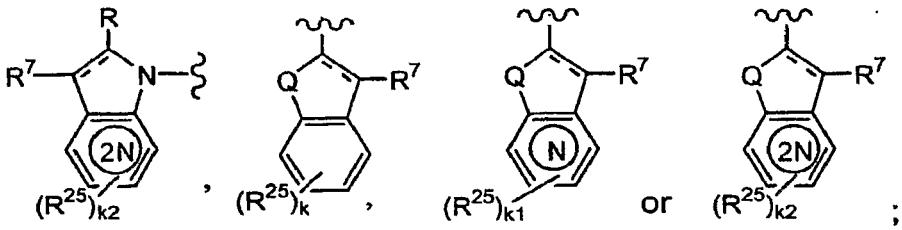
Y is –C(=O)-, -C(=S)-, -$(CH_2)_q$ -, –$NR^4C(=O)$-, -$C(=O)NR^4$-, -$C(=O)CH_2$-, -$SO_{1\text{-}2}$-, –C(=N-CN)-NH- or –NH-C(=N-CN)-; with the provisos that when M^1 is N, Y is not –$NR^4C(=O)$- or –NH-C(=N-CN)-; and when M^2 is N, Y is not -$C(=O)NR^4$- or –C(=N-CN)-NH-;

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

Z is a bond, C_1-C_6 alkylene, C_2-C_6 alkenylene, -C(=O)-, -CH(CN)- 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;

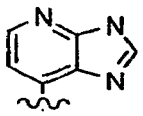
k2 is 0, 1 or 2;

the dotted line represents an optional double bond;

R and R^7 are independently selected from the group consisting of 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}-heterocyclo-alkyl, 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^{22}-$S(O)_{0-2}$-, halo(C_1-C_6)alkyl-$S(O)_{0-2}$-, N(R^{30})(R^{31})-(C_1-C_6)alkyl-$S(O)_{0-2}$-, benzoyl, (C_1-C_6)alkoxy-carbonyl, R^{37}-heterocycloalkyl-N(R^{29})-C(O)-, (C_1-C_6)alkyl-N(R^{29})-C(O)-, (C_1-C_6)alkyl-N(C_1-C_6 alkoxy)-C(O)-, –C(=NOR^{36})R^{36} and –NHC(O)R^{29}; and when the optional double bond is not present, R^7 can be OH;

R^8 is H, C_1-C_6 alkyl, halo(C_1-C_6)alkyl-, (C_1-C_6)alkoxy-(C_2-C_6)alkyl-, R^{32}-aryl(C_1-C_6)alkyl-, R^{32}-aryl, R^{32}-heteroaryl, R^{32}-heteroaryl(C_1-C_6)alkyl-, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl-(C_1-C_6)alkyl, R^{37}-heterocycloalkyl, R^{37}-heterocycloalkyl(C_1-C_6)alkyl, N(R^{30})(R^{31})-(C_2-C_6)alkyl-, R^{22}-$S(O)_2$-, halo(C_1-C_6)alkyl-$S(O)_2$-, R^{22}-$S(O)_{0-1}$-(C_2-C_6)alkyl-, halo(C_1-C_6)alkyl-$S(O)_{0-1}$-(C_2-C_6)alkyl-, (C_1-C_6)alkyl-N(R^{29})-SO_2-, or R^{32}-heteroaryl-SO_2;

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;



or heterocycloalkyl; wherein the 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 or (C_1-C_6)alkoxy;

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

R^5 is hydrogen, C_1-C_6 alkyl, -C(O)R^{20}, -C(O)$_2R^{20}$, –C(O)N(R^{20})$_2$, R^{33}-aryl(C_1-C_6)alkyl or (C_1-C_6)alkyl-SO_2-;

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, -CF_3, -NR^4R^5, -(C_1-C_6)alkyl-NR^4R^5, phenyl, R^{33}-phenyl, NO_2, -CO_2R^4, -CON(R^4)$_2$, -NHC(O)N(R^4)$_2$, R^{32}-heteroaryl-SO_2-NH-, R^{32}-aryl-(C_1-C_6)alkyl-NH-, R^{32}-heteroaryl-(C_1-C_6)alkyl-NH-, R^{32}-heteroaryl-NH-C(O)-NH-, R^{37}-heterocycloalkyl-N(R^{29})-C(O)- and R^{37}-heterocycloalkyl-N(R^{29})-C(O)-NH-;

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 R^{12} forms a C_1 to C_2 alkyl bridge from one ring carbon to another ring carbon;

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 forms a C_1 to C_2 alkyl bridge from one ring carbon to another 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 the 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, –CF_3, -OH, C_1-C_6 alkoxy, (C_1-C_6)alkyl-C(O)-, aryl-C(O)-, N(R^4)(R^5)-C(O)-, N(R^4)(R^5)-S(O)$_{1-2}$-, halo-(C_1-C_6)alkyl- or halo-(C_1-C_6)alkoxy-(C_1-C_6)alkyl-;

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

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

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

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

R^{32} is 1 to 3 substituents independently selected from the group consisting of H, -OH, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, R^{35}-aryl-O-, -SR^{22}, -CF_3, -OCF_3, -$OCHF_2$, -NR^4R^5, phenyl, R^{33}-phenyl, -NO_2, -CO_2R^4, -$CON(R^4)_2$, -$S(O)_2R^{22}$, -$S(O)_2N(R^{20})_2$, -$N(R^{24})S(O)_2R^{22}$, -CN, hydroxy-(C_1-C_6)alkyl-, -$OCH_2CH_2OR^{22}$, and R^{35}-aryl(C_1-C_6)-alkyl-O-, wherein the aryl group is optionally substituted with 1 to 3 independently selected halogens;

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

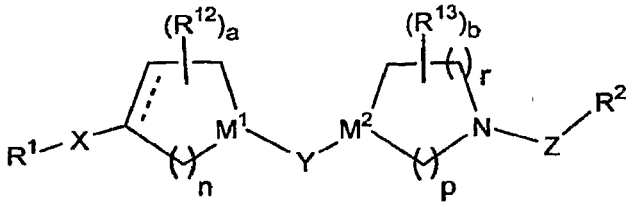
R^{34} is 1 to 3 substituents independently selected from the group consisting of H, halogen, -CF_3, -OCF_3, -OH and –OCH_3;

R^{35} is 1 to 3 substituents independently selected from the group consisting of 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 from the group consisting of H and C_1-C_6 alkyl; and

R^{37} is independently selected from the group consisting of H, C_1-C_6 alkyl and (C_1-C_6)alkoxycarbonyl; or

(vi) a compound of Formula (VI):



(VI)

or a pharmaceutically acceptable salt, solvate, ester or prodrug 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;

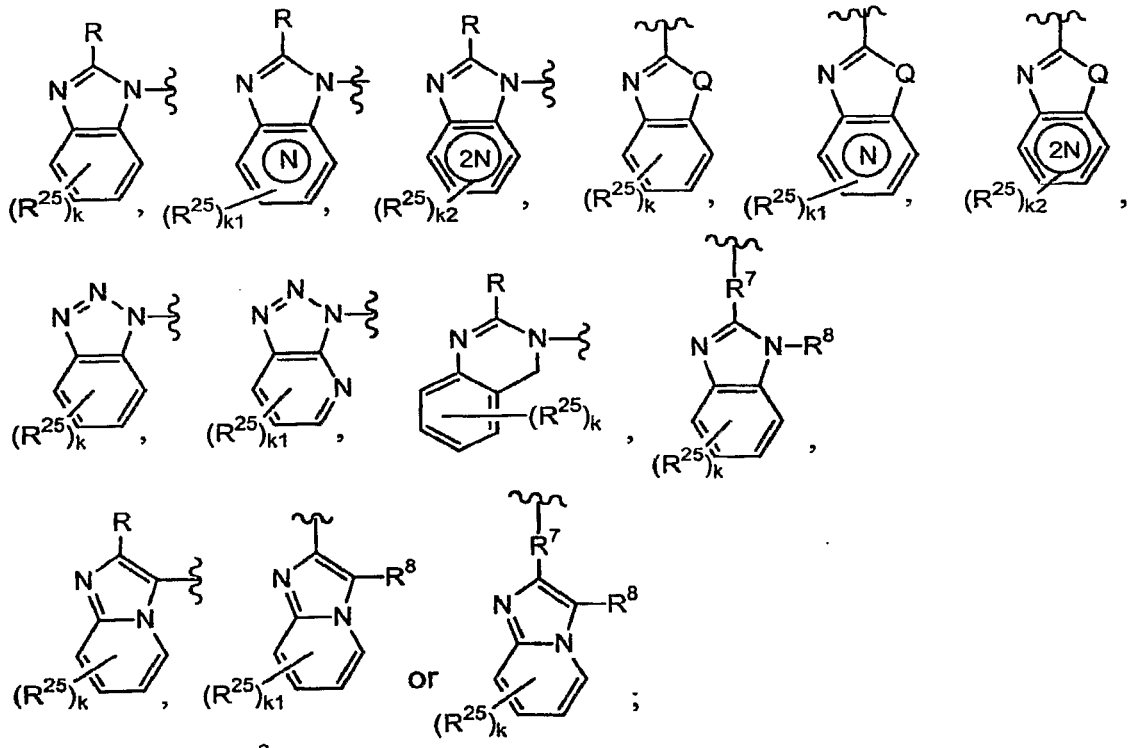
X is a bond or C_1-C_6 alkylene;

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;

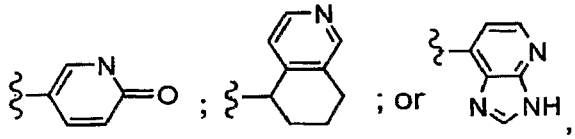
k1 is 0, 1, 2 or 3;

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

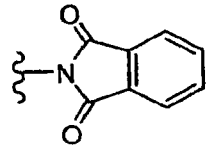
R^3 is H, halogen, C_1-C_6 alkyl, -OH, (C_1-C_6)alkoxy or –$NHSO_2$-(C_1-C_6)alkyl;

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;

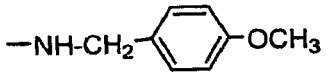
R^5 is hydrogen, C_1-C_6 alkyl, -C(O)R^{20}, -$C(O)_2R^{20}$, –C(O)N(R^{20})$_2$, (C_1-C_6)alkyl-SO_2-, or (C_1-C_6)alkyl-SO_2-NH-;

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, $-CO_2R^4$, $-CON(R^4)_2$,



and



;

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 the 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;

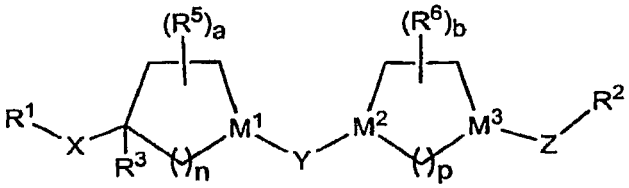
R^{38} is H, C_1-C_6 alkyl, R^{35}-aryl, R^{35}-aryl(C_1-C_6)alkyl-, (C_1-C_6)alkyl-SO_2 or halo(C_1-C_6)alkyl-SO_2-;

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; or

(vii) a compound of Formula (VII):



(VII)

or a pharmaceutically acceptable salt, solvate, prodrug or ester thereof, wherein:

a is 0, 1 or 2;

b is 0, 1 or 2;

n is 1, 2 or 3;

p is 1, 2 or 3;

M^1 is CH or N;

M^2 is CH, CF or N;

M^3 is CH or N

with the proviso that when M^2 and M^3 are each N, p is 2 or 3;

Y is $-C(=O)-$, $-C(=S)-$, $-(CH_2)_q-$, $-C(=NOR^7)-$ or $-SO_{1-2}-$;

q is 1, 2, 3, 4 or 5, provided that when M^1 and M^2 are both N, q is 2, 3, 4 or 5;

X is $-N(R^4)-$, $-N(R^4)-CH(R^{19})-$, $-CH(R^{19})-N(R^4)-$, $-(CH_2)_r-C(O)-N(R^4)-$, $-O-(CH_2)_2-C(O)-N(R^4)-$, $-CH_2-O-(CH_2)_3-C(O)-N(R^4)-$, $-(CH_2)_t-N(R^4)-C(O)-$, $-C(O)-N(R^4)-CH_2-$, $-(CH_2)_r-N(R^{19})C(O)N(R^{19})-$, $-N(R^{19})C(O)N(R^{19})-(CH_2)_r-$, $-(CH_2)_t-OC(O)N(R^{19})-$, $-N(R^{19})C(O)O-$, $-O-$, $-OCH_2-$,$-CH_2O-$, $-OC(O)-$, $-C(O)O-$, $-S-$, $-S(O)-$ or $-SO_2-$;

r is 0, 1, 2 or 3;

t is 0 or 1;

Z is a bond, R^8-alkylene, $-CH(R^{20})-CH(R^{20})-O-$, $-CH(R^{20})-CH(R^{20})-N-$, $-CH(R^{20})-(R^{23}-C_1-C_5$ alkylene), $-CH(R^{20})-C(R^{20})=C(R^{20})-$, $-CH(R^{20})-C(R^{20})=C(R^{20})-(R^{23}-C_1-C_3$ alkylene) or R^8-alkylene interrupted by a cycloalkylene or heterocycloalkylene group, provided that when M^3 is N and Z is R^8-alkylene interrupted by a heterocycloalkylene group bonded through a ring nitrogen, the alkylene portion of the Z group has 2-4 carbon atoms between M^3 and said nitrogen;

R^1 is H, R^{10}-alkyl, R^{10}-cycloalkyl, R^{10}-aryl, R^{10}-heteroaryl or R^{10}-heterocycloalkyl;

R^2 is R^{16}-alkyl, R^{16}-alkenyl, R^{16}-aryl, R^{16}-heteroaryl, R^{16}-cycloalkyl or R^{16}-heterocycloalkyl;

R^3 is H, alkyl, R^{21}-aryl, R^{22}-cycloalkyl, R^{22}-heterocycloalkyl, R^{21}-heteroaryl or $-C(O)NH_2$;

R^4 is H, alkyl, haloalkyl, R^{18}-aryl, R^{18}-heteroaryl, R^{18}-arylalkyl, $-C(O)R^{12}$ or $-SO_2R^{13}$;

R^5 and R^6 are each independently selected from the group consisting of halo, alkyl, -OH, alkoxy, $-CF_3$ and –CN; or two R^5 substituents on the same carbon atom or two R^6 substituents on the same carbon atom form =O;

R^7 is H, alkyl, haloalkyl, aryl or heteroaryl;

R^8 is 1, 2 or 3 substituents independently selected from the group consisting of H, cycloalkyl, heterocycloalkyl, aryl, heteroaryl and $-CF_3$;

each R^9 is independently selected from the group consisting of H and alkyl;

R^{10} is 1, 2, 3 or 4 substituents independently selected from the group consisting of H, halo, alkyl, -OH, alkoxy, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, $-CF_3$, $-OCF_3$, $-NO_2$, -C(O)-alkyl, -C(O)-heterocycloalkyl, $-CO_2R^{11}$, $-N(R^{11})_2$, $-CON(R^{11})_2$, $-NHC(O)R^{11}$, -NHC(O)-alkoxyalkyl-, $-NHC(O)-CH_2-NHC(O)CH_3$, $-NHSO_2R^{11}$, $-CH(=NOR^{19})$, $-SO_2N(R^{11})_2$, $-SO_2CF_3$ and –CN;

each R^{11} is independently selected from the group consisting of H, alkyl, haloalkyl, R^{18}-aryl, R^{18}-heteroaryl, R^{18}-arylalkyl, cycloalkyl and heterocycloalkyl;

R^{12} is alkyl, cycloalkyl, aryl, heteroaryl or heterocycloalkyl;

R^{13} is alkyl, aryl or alkylsulfonylalkyl;

R^{16} is 1, 2 or 3 substituents independently selected from the group consisting of H, halo, alkyl, -OH, alkoxy, hydroxyalkyl, aryl, aryloxy, $-CF_3$, $-OCF_3$, $-NO_2$, $-CO_2R^{17}$, $-N(R^{17})_2$, -alkylene-$N(R^{17})_2$, $-CON(R^{17})_2$, $-NHC(O)R^{17}$, $-NHC(O)OR^{17}$, $-NHSO_2R^{17}$, $-SO_2N(R^{17})_2$ and –CN;

each R^{17} is independently selected from the group consisting of H, alkyl, haloalkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl;

R^{18} is 1, 2 or 3 substituents independently selected from the group consisting of H, alkyl, halo, alkoxy, $-CF_3$ and -alkylene-$N(R^{17})_2$;

R^{19} is independently selected from the group consisting of H and alkyl;

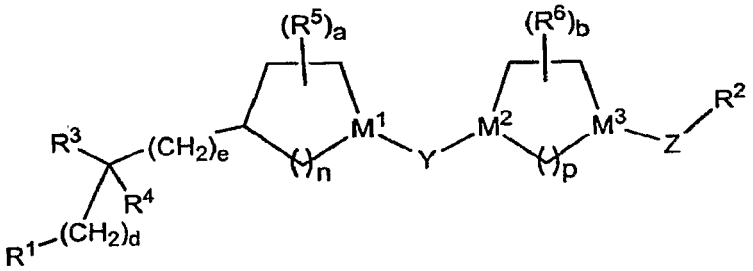
R^{20} is independently selected from the group consisting of H and alkyl;

R^{21} is 1, 2, 3 or 4 substituents independently selected from the group consisting of H, halo, alkyl, -OH, alkoxy, $-CF_3$, $-CHF_2$, $-OCF_3$, $-NO_2$, -CN, $-C(O)N(R^{19})_2$ and $-N(R^{19})_2$;

R^{22} is 1, 2 or 3 substituents independently selected from the group consisting of halo, alkyl, -OH, alkoxy, $-CF_3$ and –CN; and

R^{23} is 1, 2 or 3 substituents independently selected from the group consisting of H, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-CF_3$, halo, -CN, -OH, alkoxy, $-OCF_3$, $-NO_2$, and $-N(R^9)_2$; or

(viii) a compound of Formula (VIII):



(VIII)

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

a is 0, 1 or 2;

b is 0, 1 or 2;

d is 0 or 1;

e is 0 or 1

n is 1, 2 or 3;

p is 1, 2 or 3;

M^1 is CH or N;

M^2 is CH, CF or N;

M^3 is CH or N

with the proviso that when M^2 and M^3 are each N, p is 2 or 3;

Y is $-C(=O)-$, $-C(=S)-$, $-(CH_2)_q-$, $-C(=NOR^7)-$ or $-SO_{1-2}-$;

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

Z is a bond, R^8-alkylene, $-CH(R^{20})-CH(R^{20})-O-$, $-CH(R^{20})-CH(R^{20})-N-$, $-CH(R^{20})-(R^{23}-C_1-C_5$ alkylene), $-CH(R^{20})-C(R^{20})=C(R^{20})-$, $-CH(R^{20})-C(R^{20})=C(R^{20})-(R^{23}-C_1-C_3$ alkylene) or R^8-alkylene interrupted by a cycloalkylene or heterocycloalkylene group, provided that when M^3 is N and Z is R^8-alkylene interrupted by a heterocycloalkylene group bonded through a ring nitrogen, the alkylene portion of the Z group has 2-4 carbon atoms between M^3 and said nitrogen;

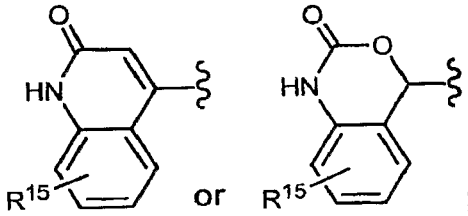
R^1 is H, alkyl, alkenyl, R^{10}-cycloalkyl, R^{10}-aryl, R^{10}-pyridyl, R^{10}-quinolyl or R^{10}-heterocycloalkyl;

R^3 and R^4 are independently selected from the group consisting of H, halo, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, hydroxyalkoxy, alkoxyalkoxy, aryl, arylalkyl, cycloalkyl, heterocycloalkyl, heteroaryl, heteroarylalkyl, $-OR^{12}$, -CN, $-(CH_2)_f-N(R^{12})_2$, $-(CH_2)_f-N(R^{19})-SO_2R^{12}$, $-(CH_2)_f-N(R^{19})-C(O)R^{12}$, $-(CH_2)_f-NHC(O)NHR^{12}$, $-(CH_2)_f-NHC(O)OR^{12}$, $-O-C(O)NHR^{12}$, $-(CH_2)_f-C(O)OR^{12}$ and $-O-(CH_2)_f-C(O)OR^{12}$, provided that when one of R^3 and R^4 is a heteroatom-linked substituent, the other is H;

f is 0, 1 or 2;

or R^3 and R^4, together with the carbon to which they are attached, form $-C(=C(R^{15})(R^{18})-$, a 3-7 membered cycloalkyl ring substituted by R^{13}, a 3-7-membered heterocycloalkyl ring substituted by R^{13}, a R^{13}-phenyl ring, or a 5-6-membered heteroaryl ring substituted by R^{13}; or when d is 1, or e is 1, or both d and e are 1, R^3 and R^4, together with the carbon to which they are attached, form –C(O)-;

or $R^1-(CH_2)_d-C(R^3)(R^4)-(CH_2)_e-$ forms



;

R^2 is R^{16}-alkyl, R^{16}-alkenyl, R^{16}-aryl, R^{16}-heteroaryl, R^{16}-cycloalkyl or R^{16}-heterocycloalkyl;

R^5 and R^6 are each independently selected from the group consisting of halo, alkyl, -OH, alkoxy, $-CF_3$ and –CN; or two R^5 substituents on the same carbon atom form =O;

R^7 is H, alkyl, haloalkyl, aryl or heteroaryl;

R^8 is 1, 2 or 3 substituents independently selected from the group consisting of H, cycloalkyl, heterocycloalkyl, aryl, heteroaryl and $-CF_3$;

each R^9 is independently selected from the group consisting of H and alkyl;

R^{10} is 1 to 4 substituents independently selected from the group consisting of H, halo, alkyl, -OH, alkoxy, aryl, heteroaryl, aryloxy, $-CF_3$, $-CHF_2$, $-OCF_3$, $-NO_2$, $-CO_2R^{11}$, $-N(R^{11})_2$, $-CON(R^{11})_2$, $-NHC(O)R^{11}$, $-NHC(O)OR^{11}$, $-NHSO_2R^{11}$, $-SO_2N(R^{11})_2$ and –CN;

each R^{11} is independently selected from the group consisting of H, alkyl, haloalkyl, aryl, heteroaryl, arylalkyl, cycloalkyl and heterocycloalkyl;

each R^{12} is independently selected from the group consisting of H, alkyl, alkenyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl and heterocycloalkyl;

R^{13} is 1 to 4 substituents independently selected form the group consisting of H, halo, alkyl, -OH, alkoxy, hydroxyalkyl, alkoxyalkyl, $-CO_2R^{14}$, $-C(O)N(R^{14})_2$, $-CF_3$, and –CN; or two R^{13} substituents on the same carbon atom form =O;

each R^{14} is independently selected from the group consisting of H and alkyl;

R^{15} is H, alkyl, halo, aryl or $–CF_3$;

R^{16} is 1 to 3 substituents independently selected from the group consisting of H, halo, alkyl, -OH, alkoxy, aryl, aryloxy, $-CF_3$, $-OCF_3$, $-NO_2$, $-CO_2R^{17}$, $-N(R^{17})_2$, $-CON(R^{17})_2$, $-NHC(O)R^{17}$, $-NHC(O)OR^{17}$, $-NHSO_2R^{17}$, $-SO_2N(R^{17})_2$ and –CN;

each R^{17} is independently selected from the group consisting of H, alkyl, haloalkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl;

R^{18} is H, alkyl, halo, aryl, $–CF_3$, alkoxy, heteroaryl, $-O-C(O)R^{12}$, $-C(O)N(R^{12})_2$, $-C(O)OR^{12}$ or –C(O)-heterocycloalkyl;

R^{19} is H alkyl or pyridylmethyl;

R^{20} is independently selected from the group consisting of H and alkyl; and

R^{21} is 1, 2 or 3 substituents independently selected from the group consisting of H, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-CF_3$, halo, -CN, -OH, alkoxy, $-OCF_3$, $-NO_2$, and $–N(R^9)_2$.

2. The composition of Claim 1, wherein the CB_1 antagonist is rimonabant.

3. The composition of Claim 1, wherein the H_3 antagonist/inverse agonist is a compound of Formula (I).

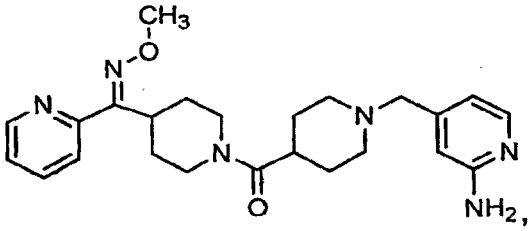
4. The composition of Claim 1, wherein the H_3 antagonist/inverse agonist is a compound of Formula (II).

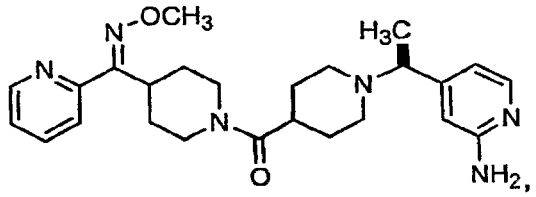
5. The composition of Claim 1, wherein the H_3 antagonist/inverse agonist is a compound of Formula (III).

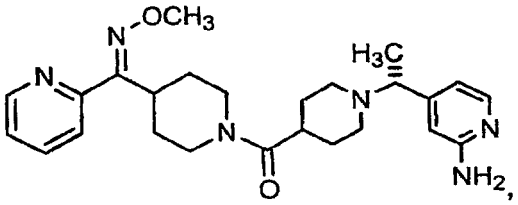
6. The composition of Claim 1, wherein the H_3 antagonist/inverse agonist is a compound of Formula (IV).

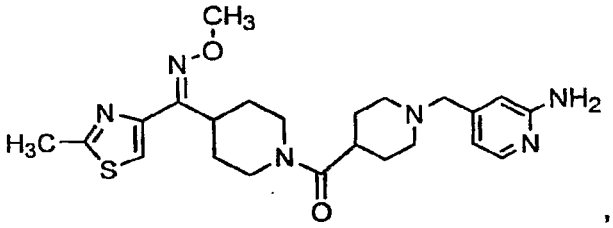
7. The composition of Claim 1, wherein the H_3 antagonist/inverse agonist is a compound of Formula (V).

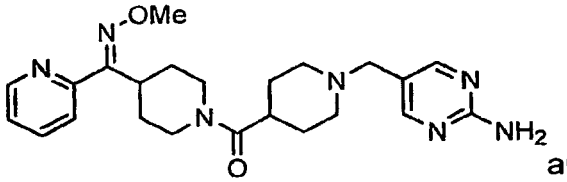
8. The composition of Claim 3, wherein the H_3 antagonist/inverse agonist is a compound selected from the group consisting of:



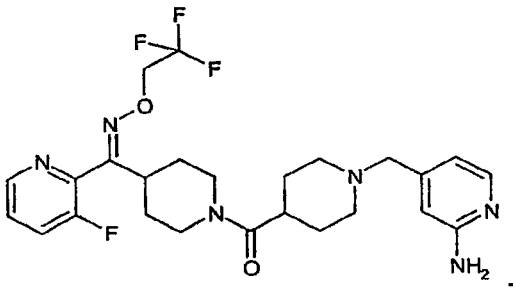




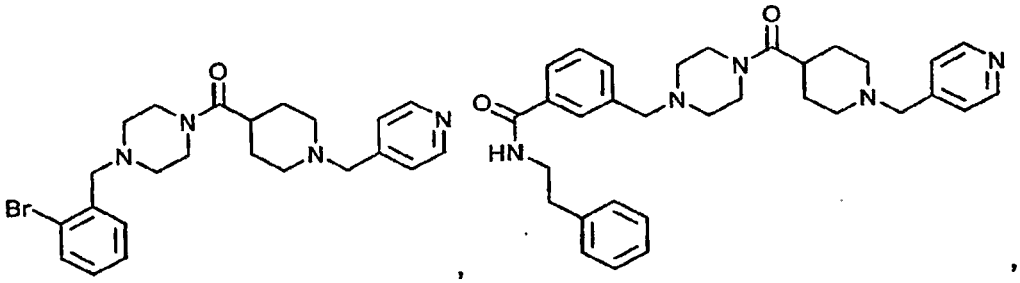




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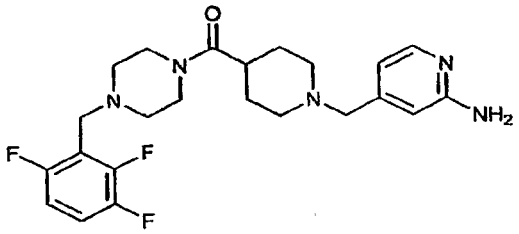


9. The composition of Claim 4, wherein the H_3 antagonist/inverse agonist is a compound selected from the group consisting of:

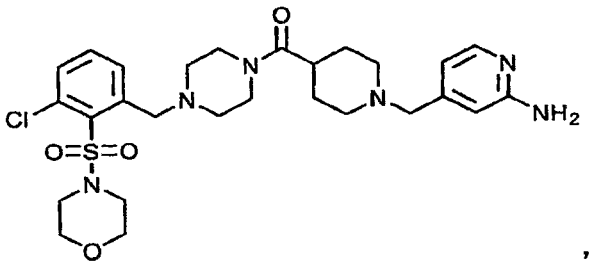


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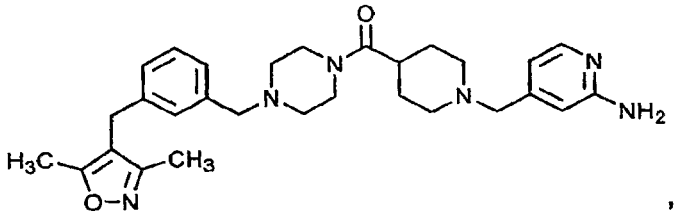
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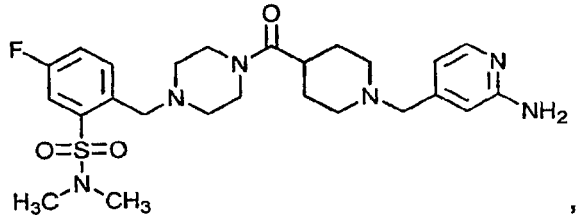
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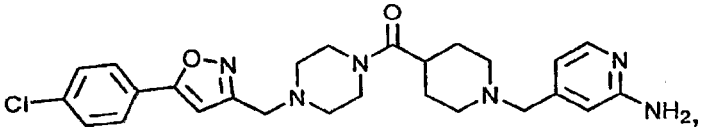
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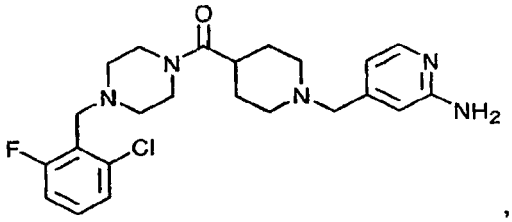
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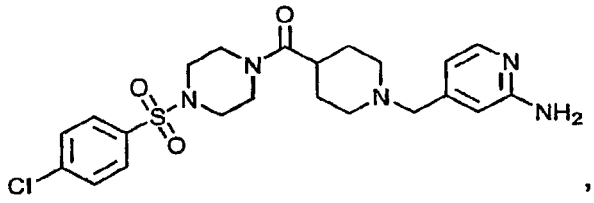
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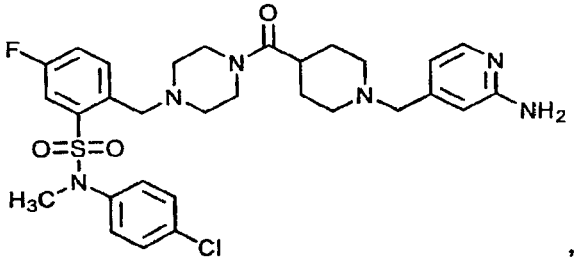
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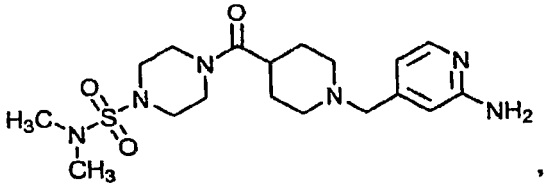
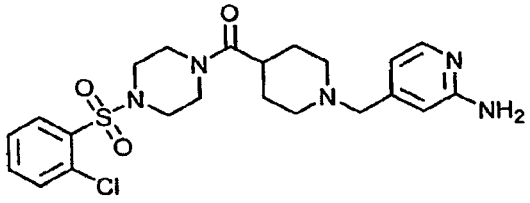


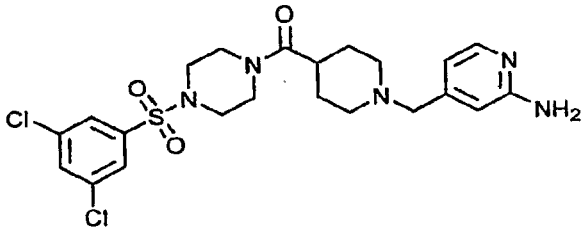
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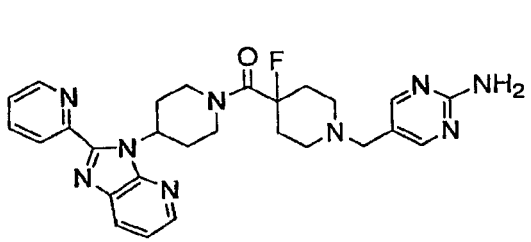
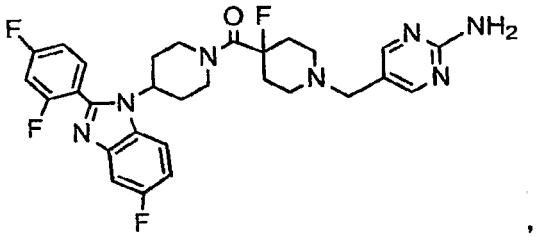
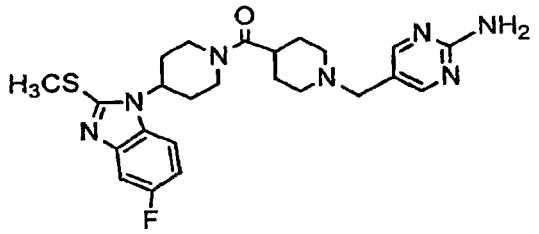
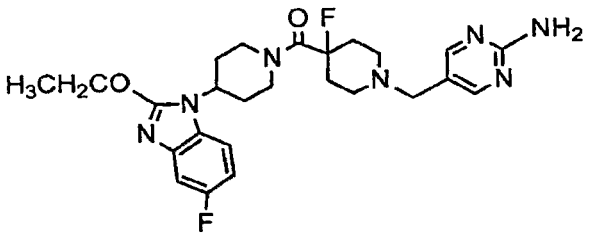
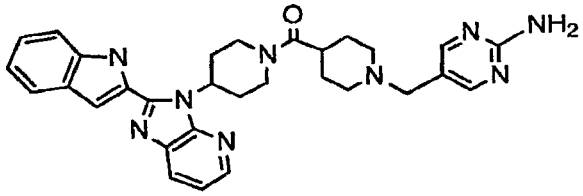
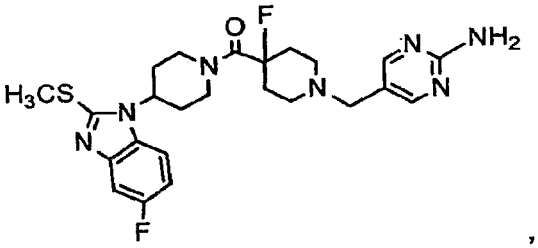
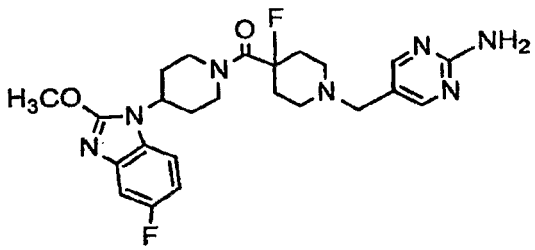
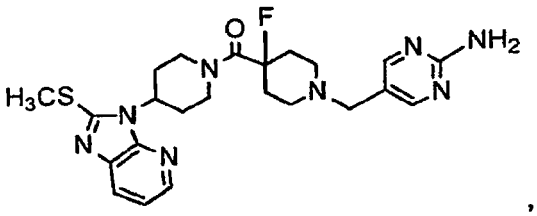
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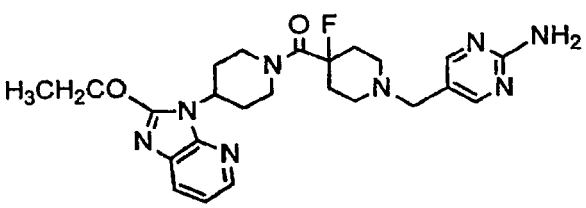
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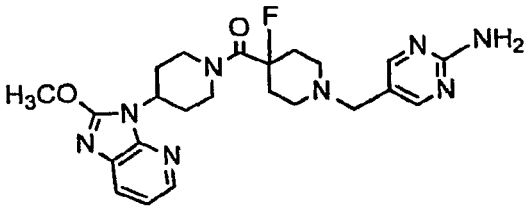

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10. The composition of Claim 5, wherein the H_3 antagonist/inverse agonist is a compound selected from the group consisting of:

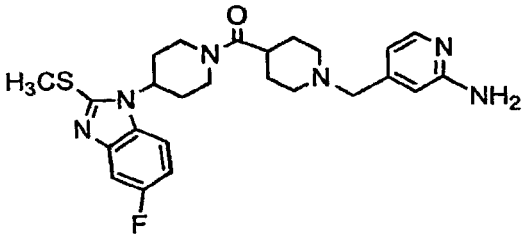

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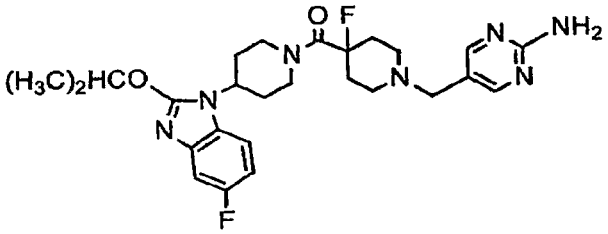
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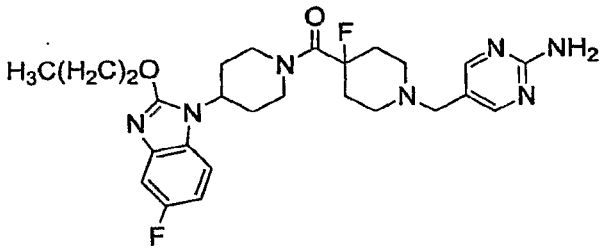
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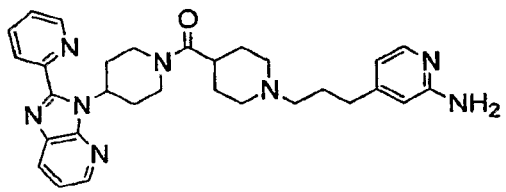
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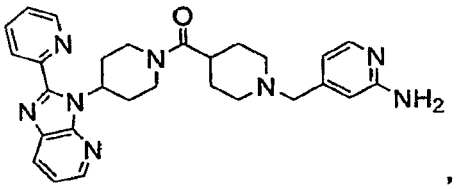
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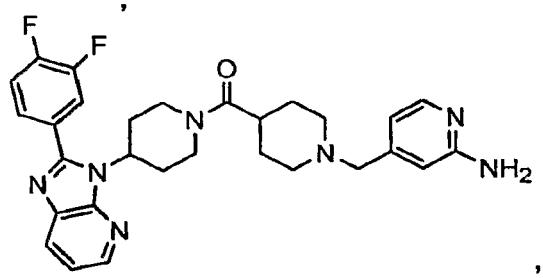
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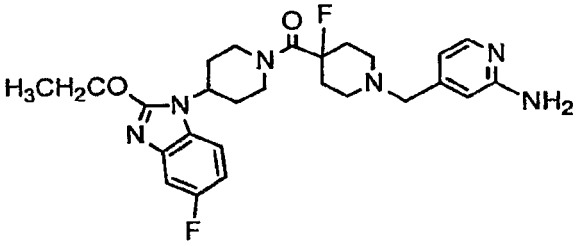


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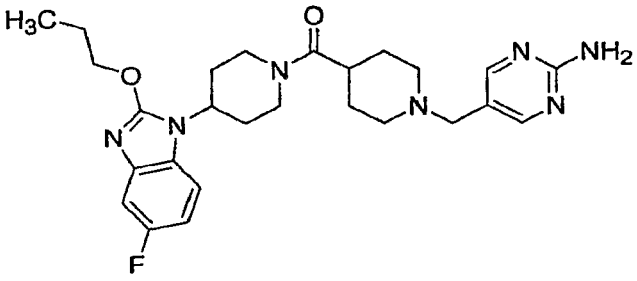


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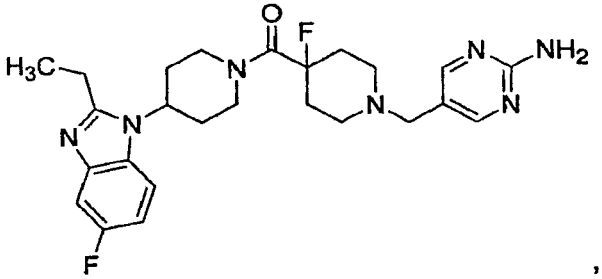
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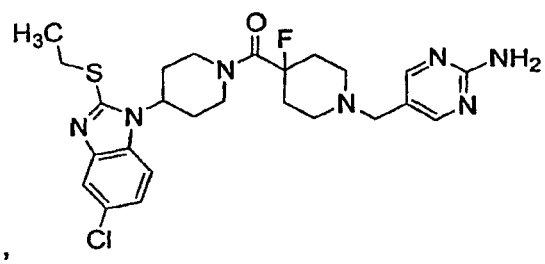
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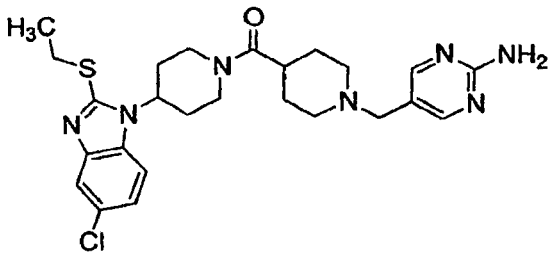
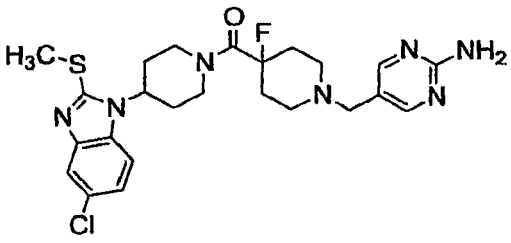
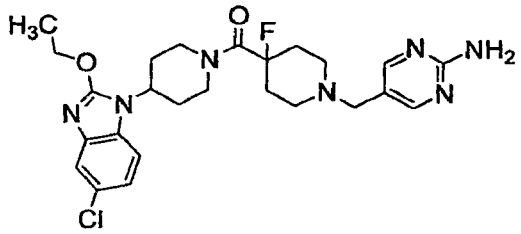
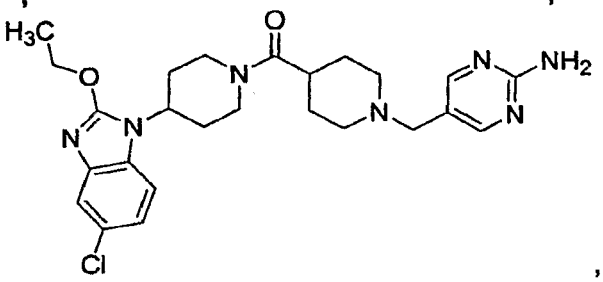
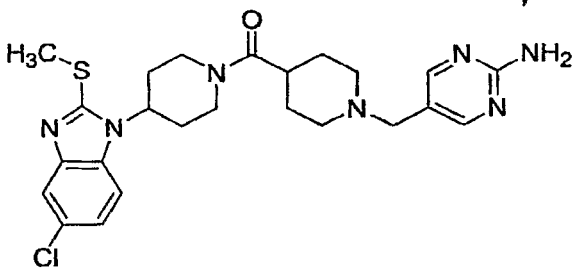
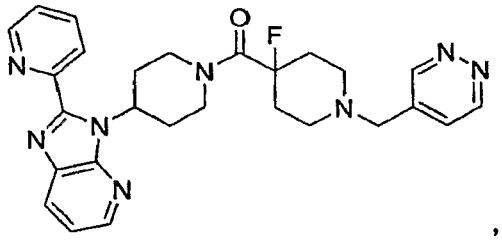
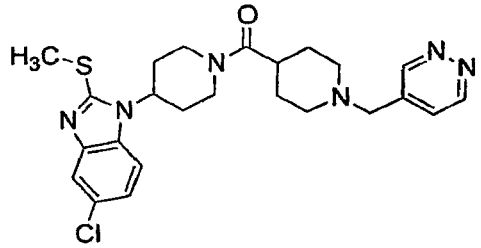
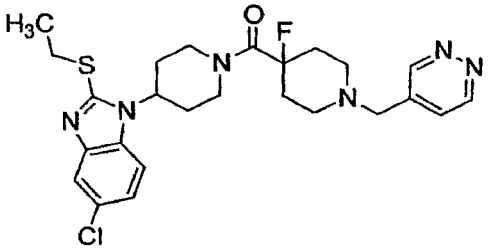
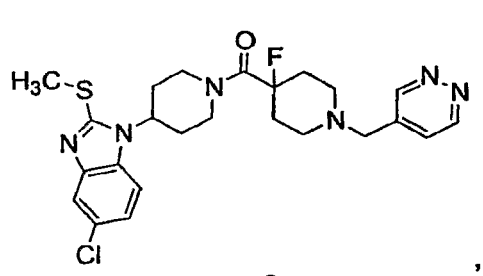
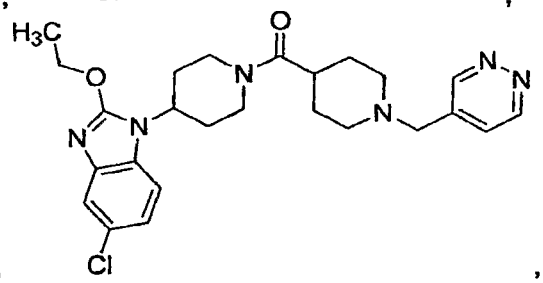
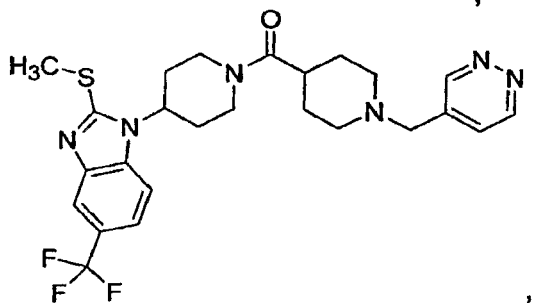
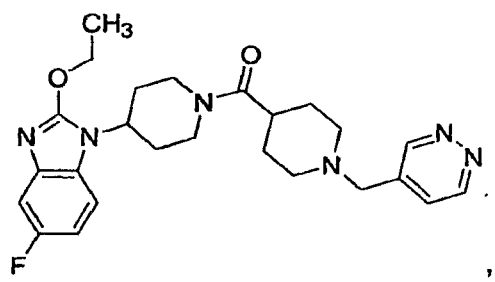
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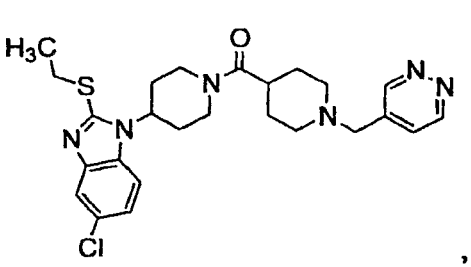
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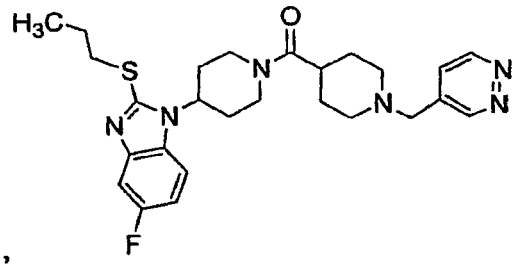
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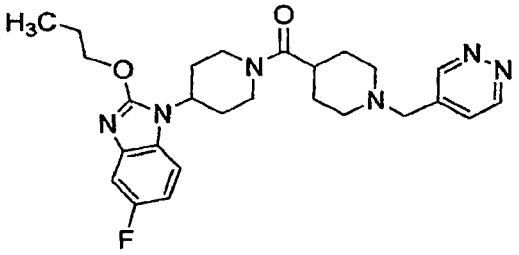

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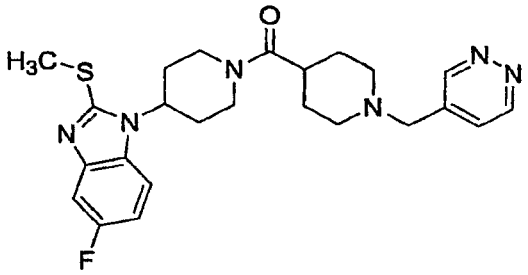


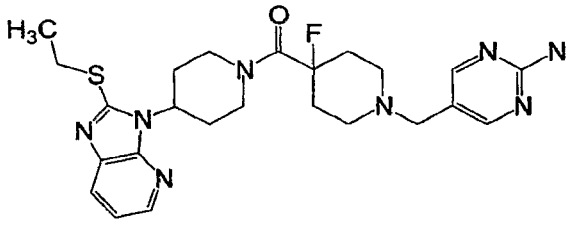
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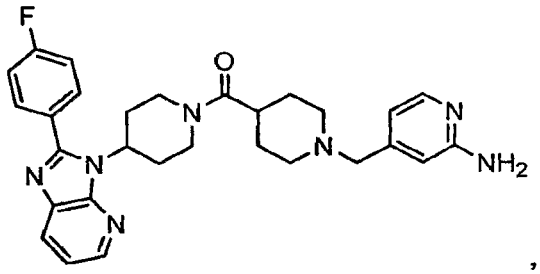


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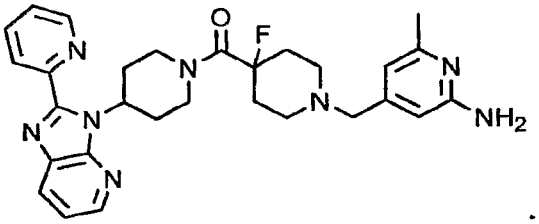




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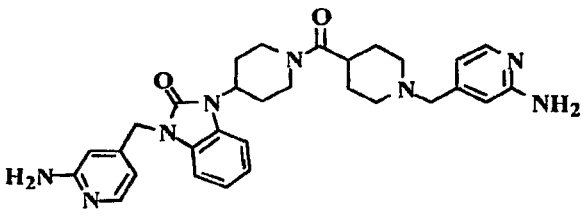
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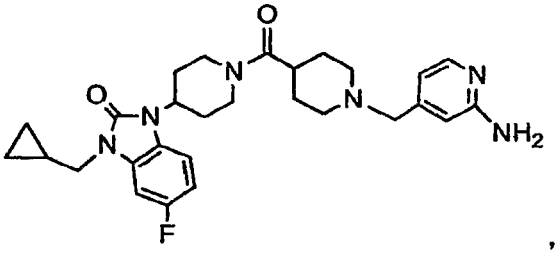
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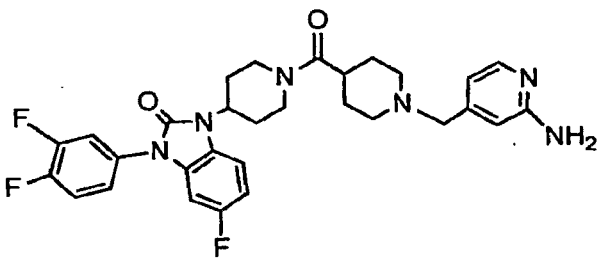
11. The composition of Claim 6, wherein the H_3 antagonist/inverse agonist is a compound selected from the group consisting of:



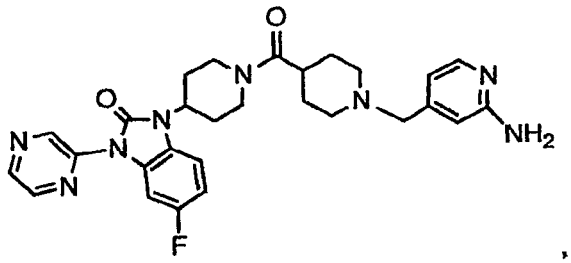
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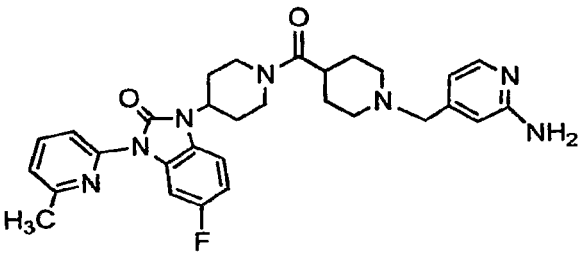
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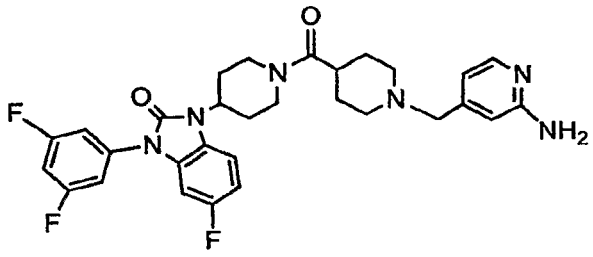
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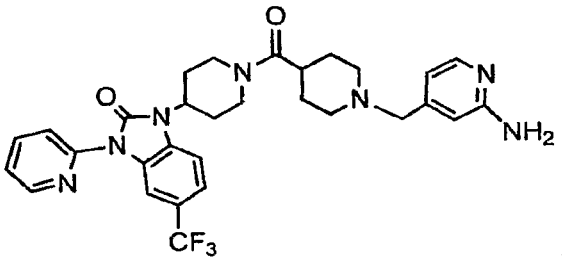
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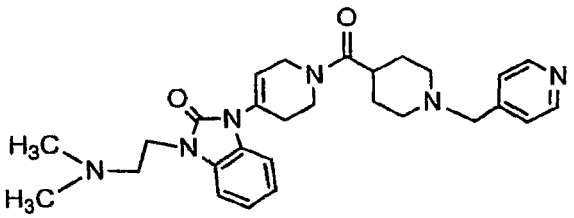
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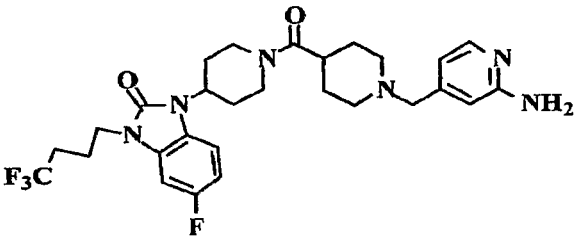
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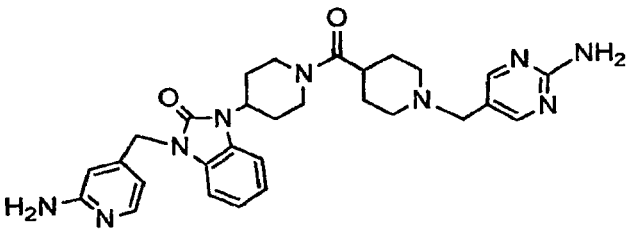
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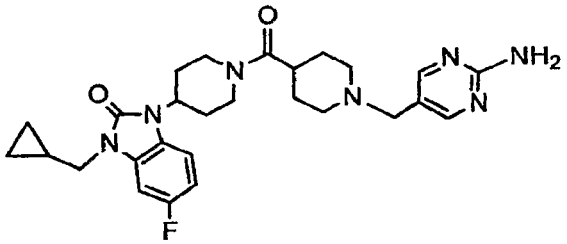
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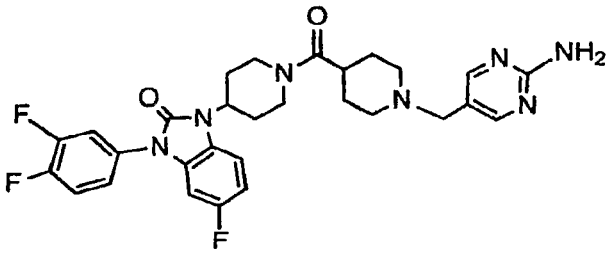
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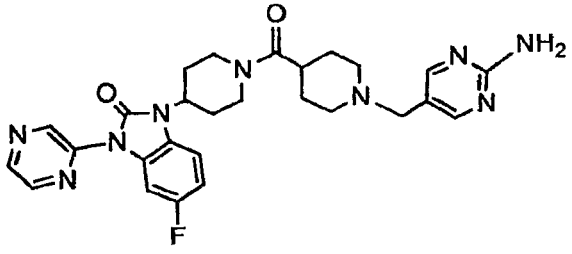
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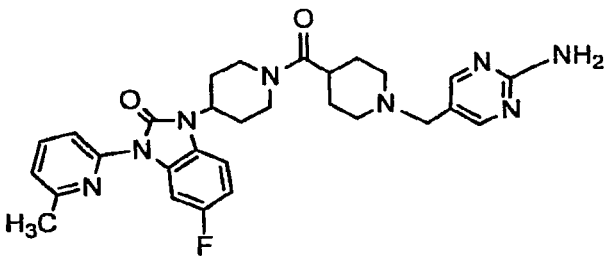
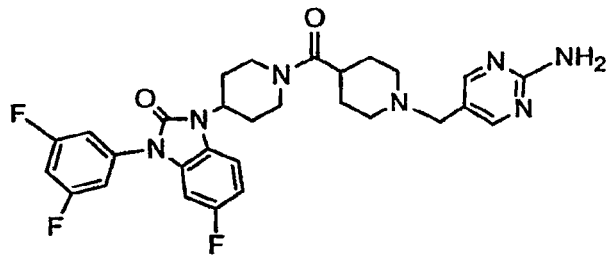
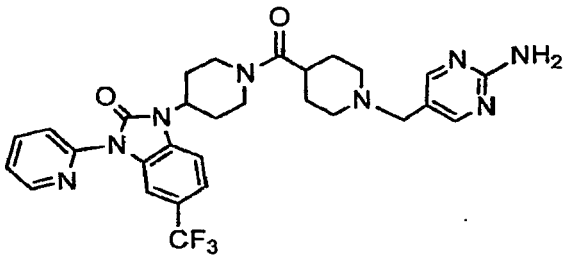
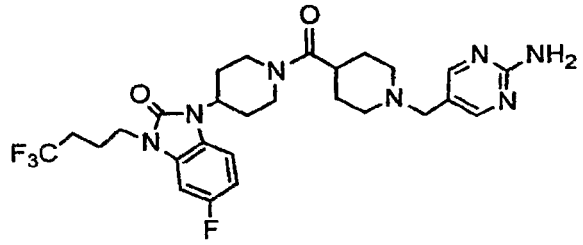
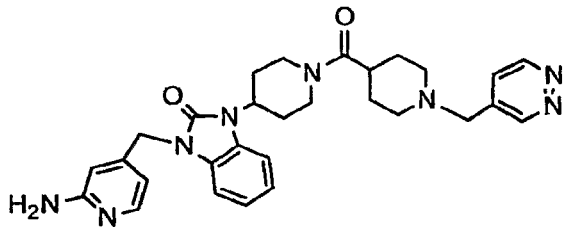
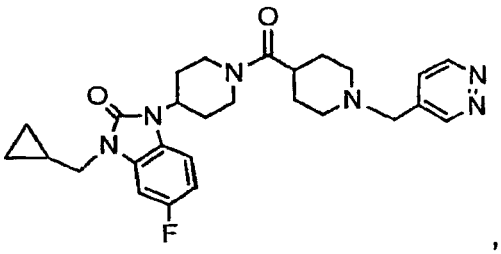
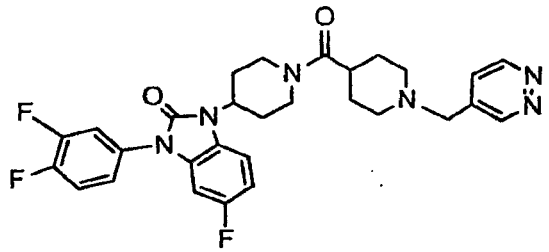
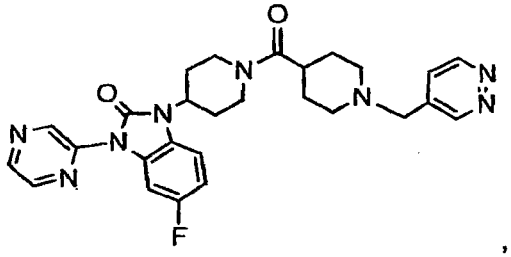
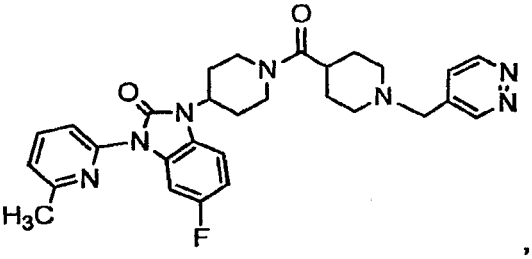
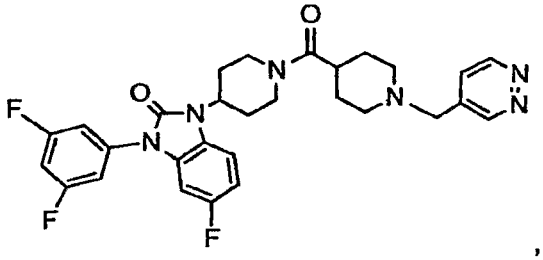
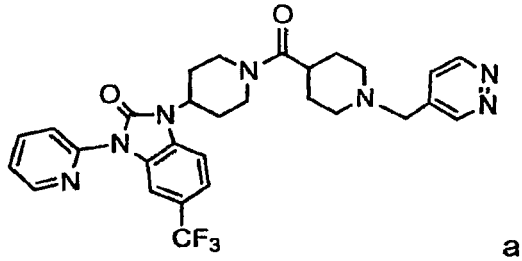
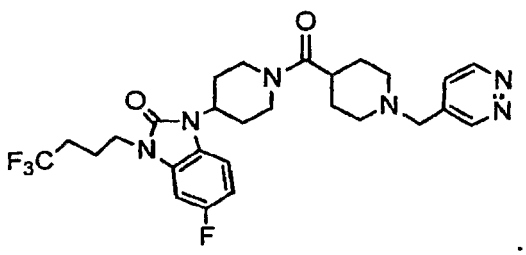
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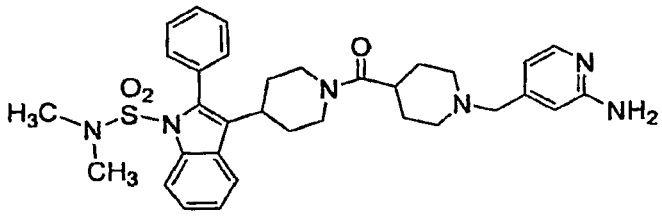
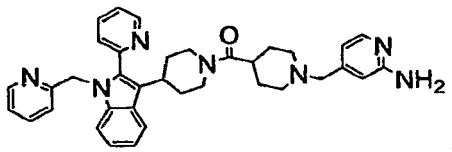
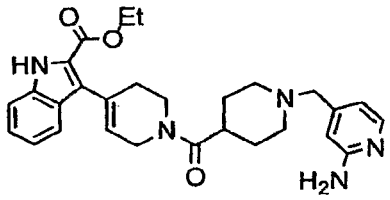
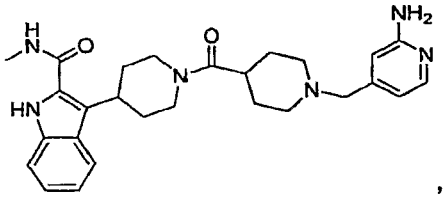
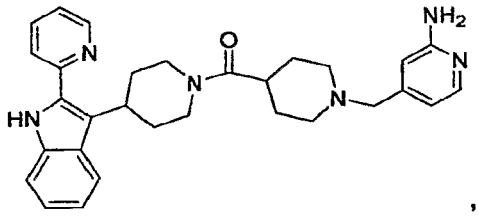
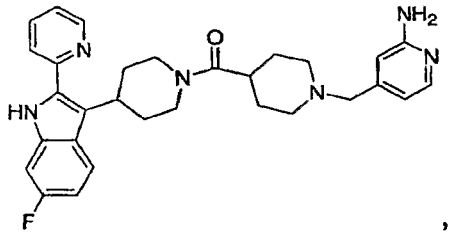
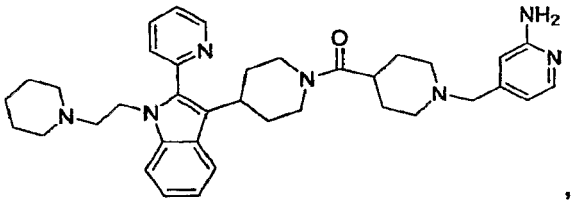
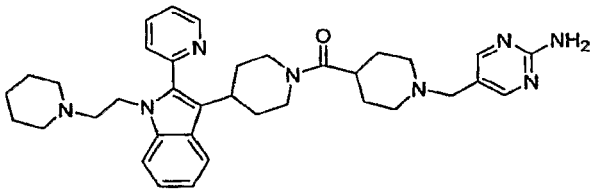
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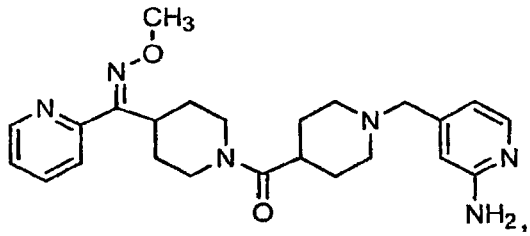
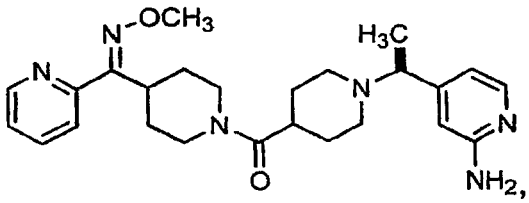
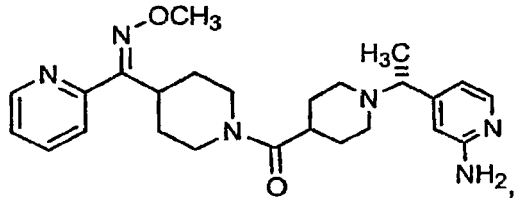
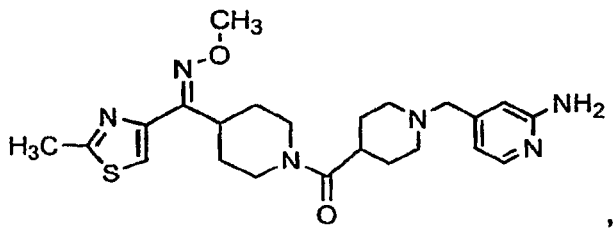
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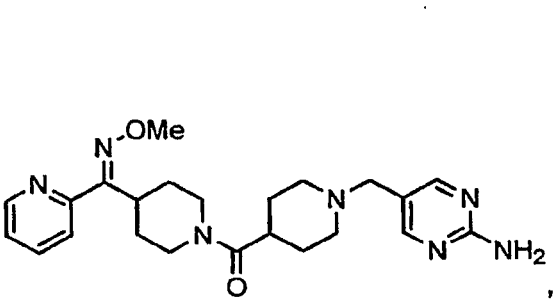

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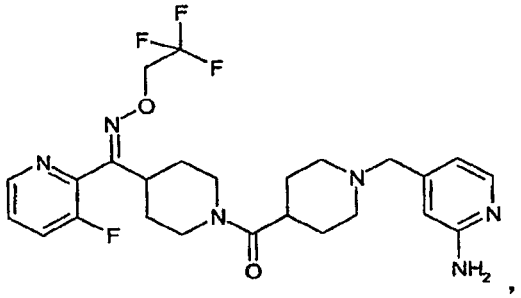
12. The composition of Claim 7, wherein the H_3 antagonist/inverse agonist is a compound selected from the group consisting of:

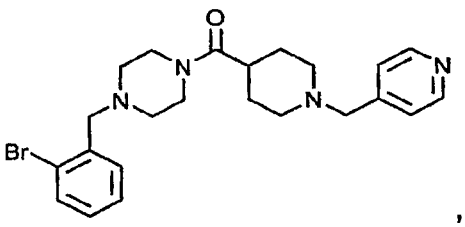

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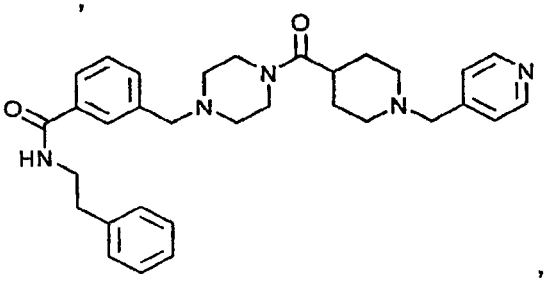
13. The composition of Claim 1, wherein the H_3 antagonist/inverse agonist is a compound selected from the group consisting of:

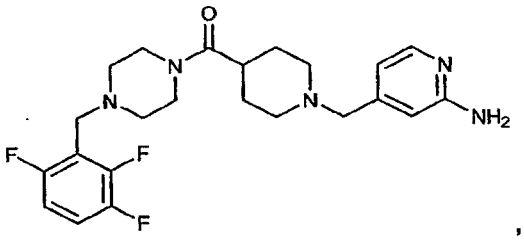

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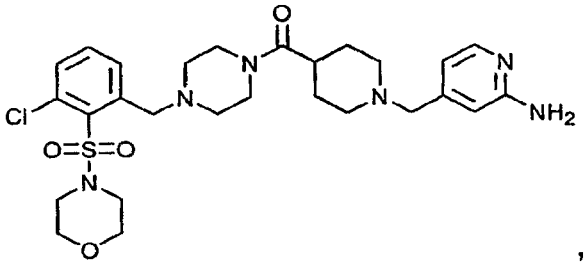


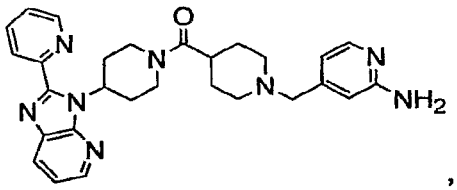


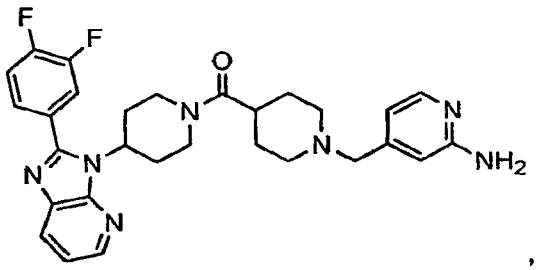


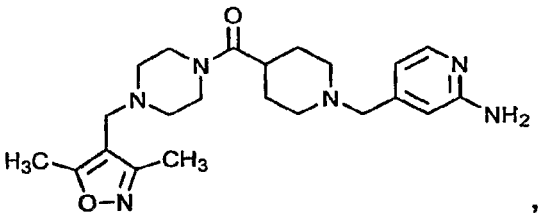


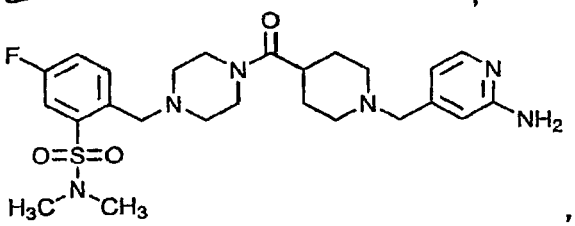


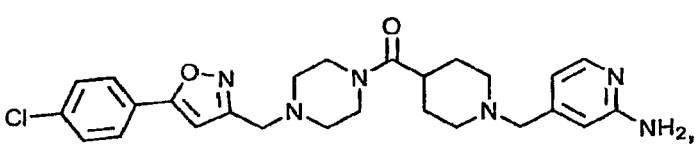


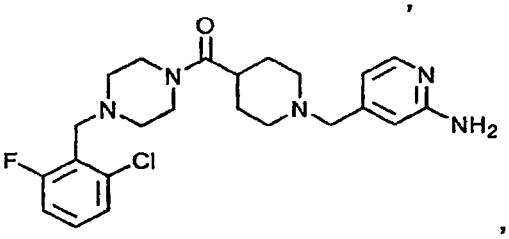


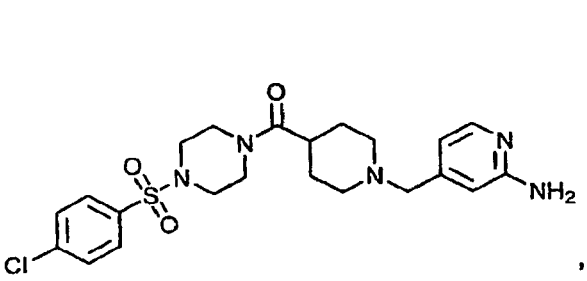
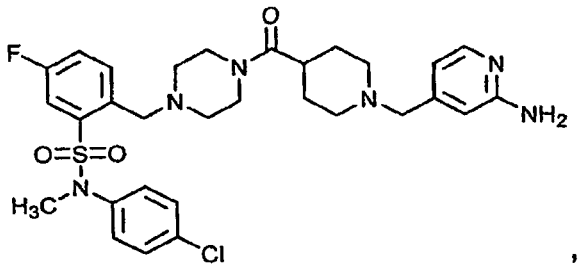
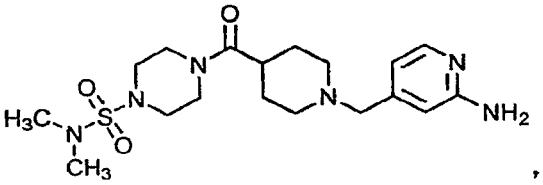
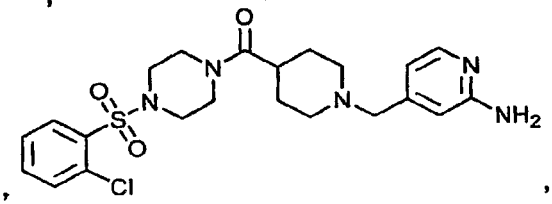
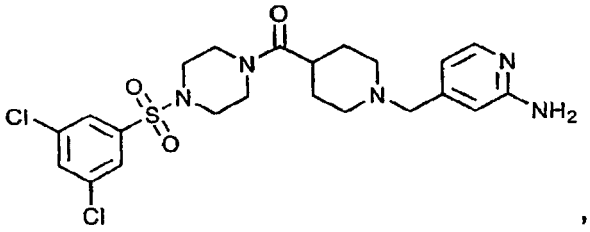
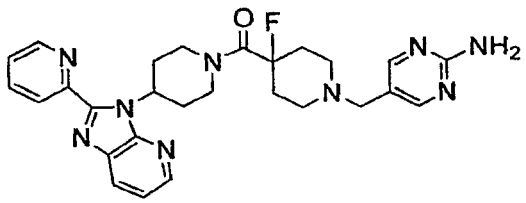
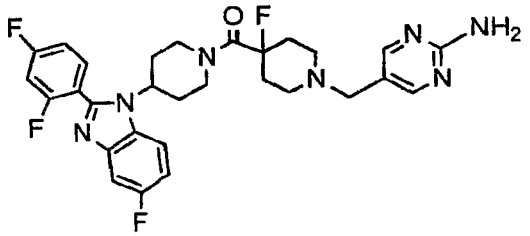
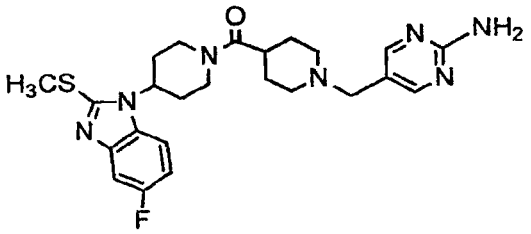
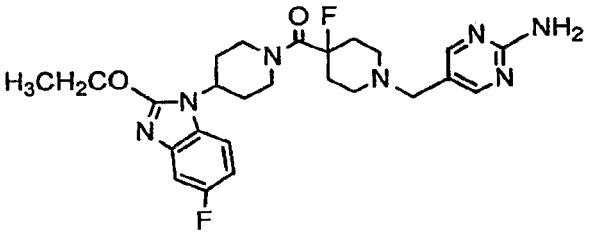
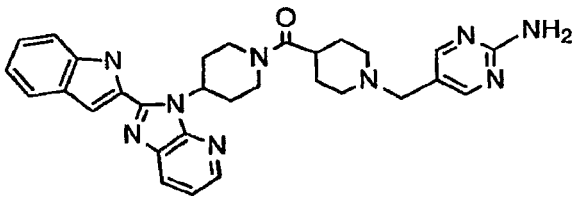
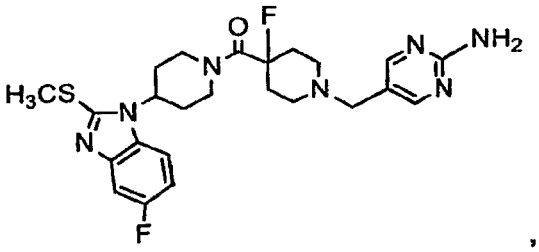
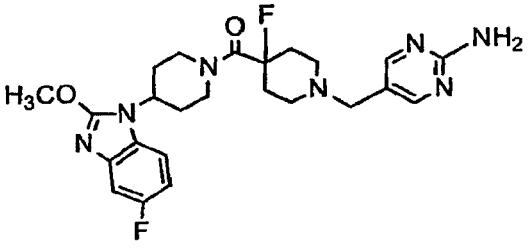
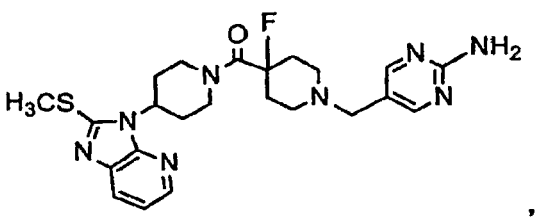




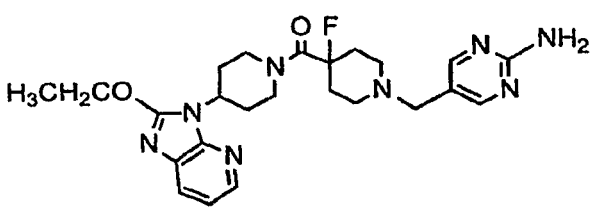
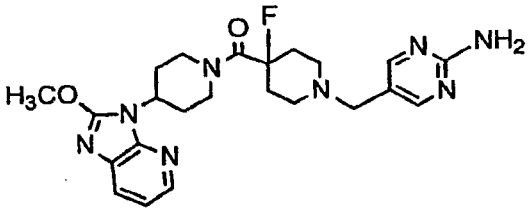
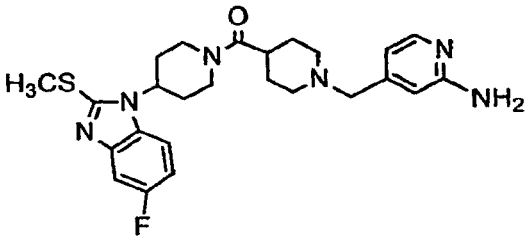
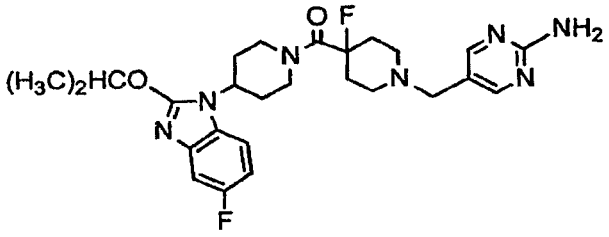
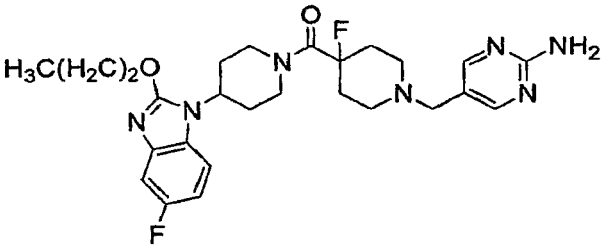
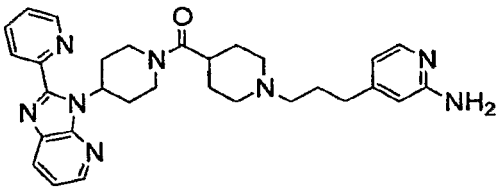
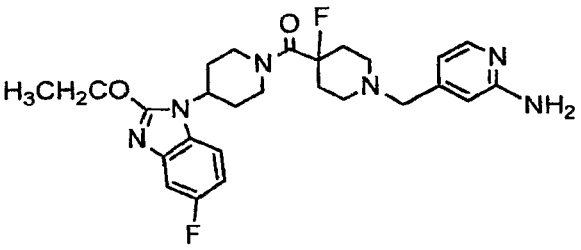
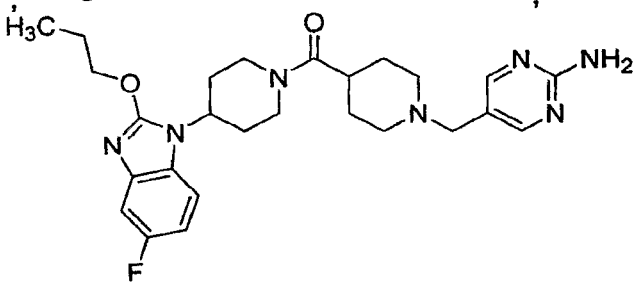
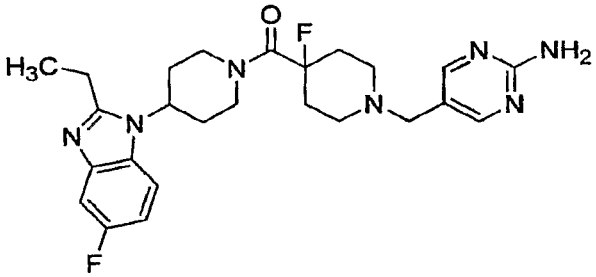
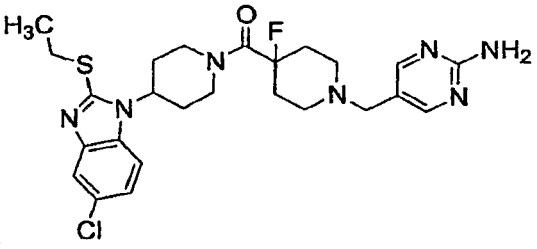
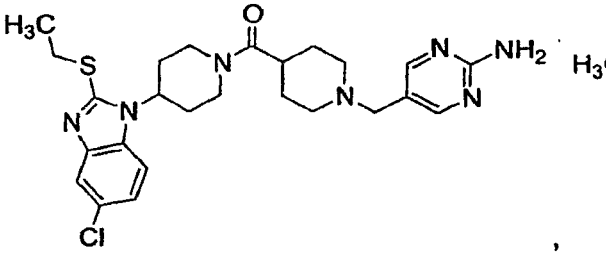
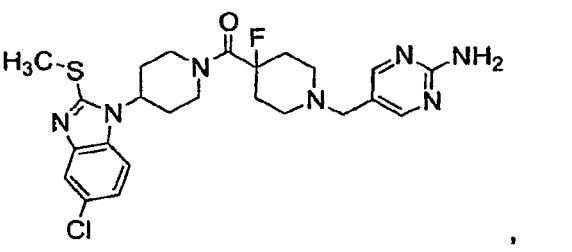






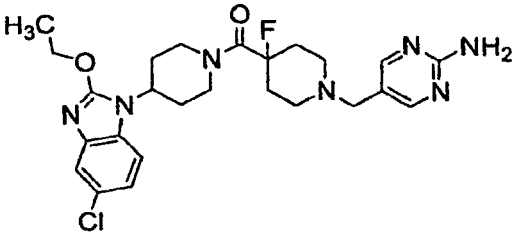
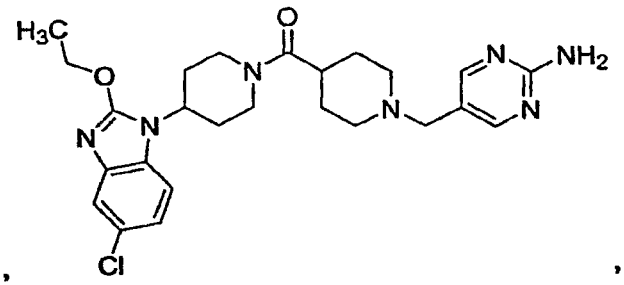
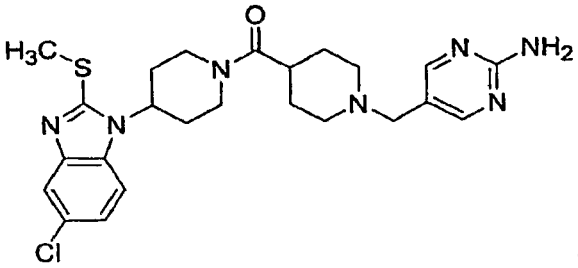
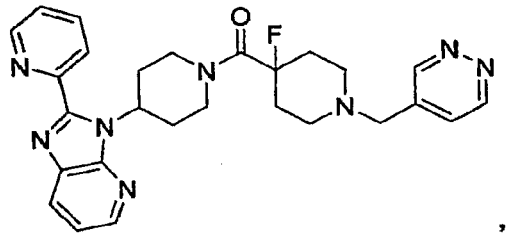
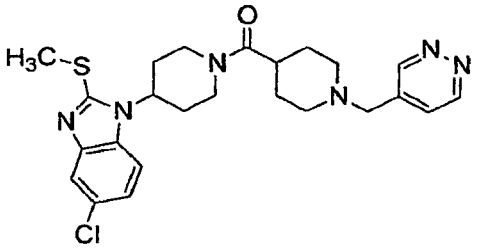
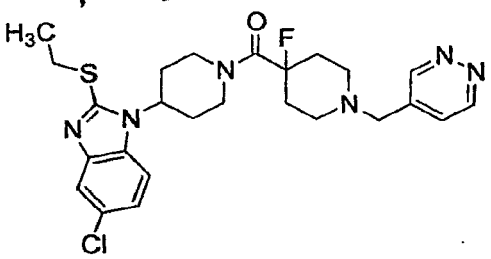
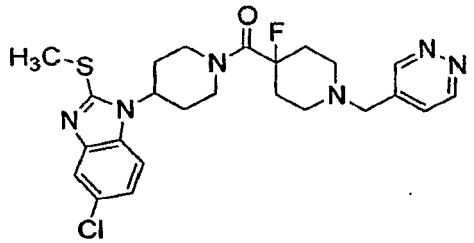
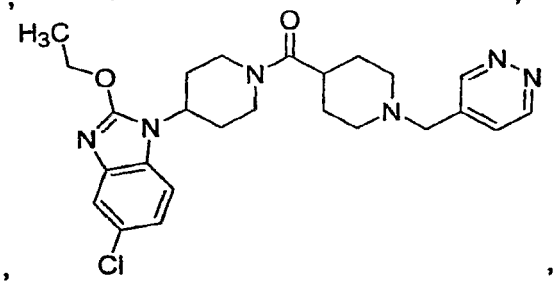
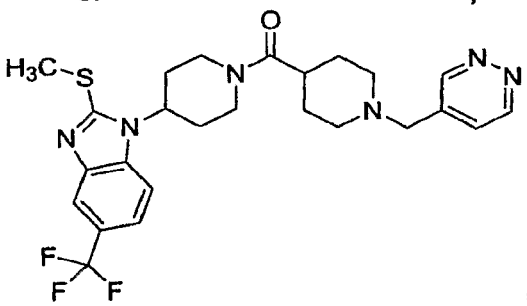
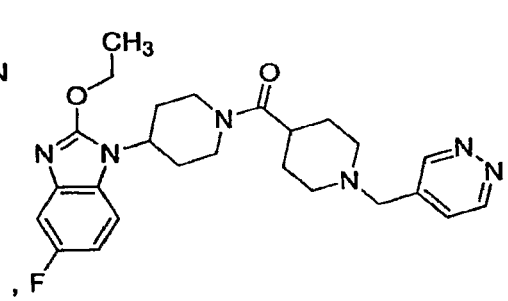

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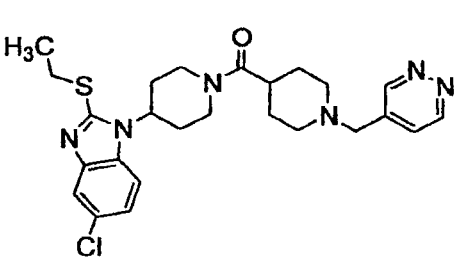
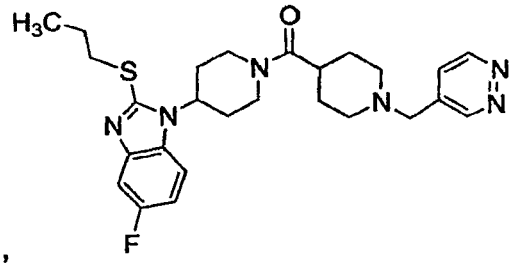
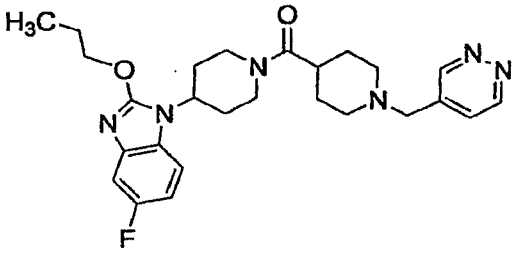
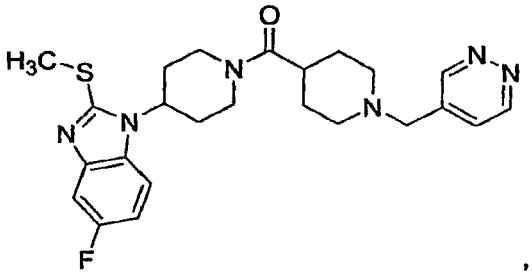
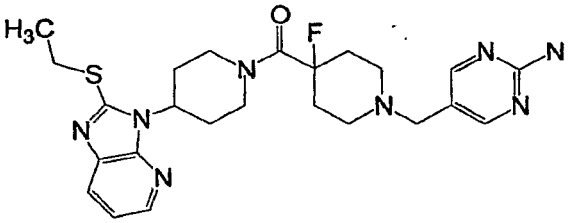
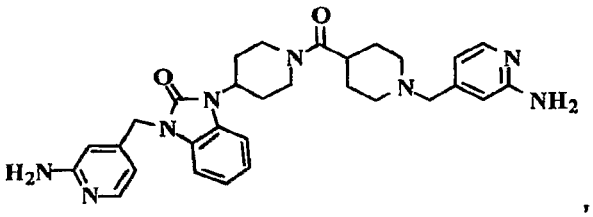
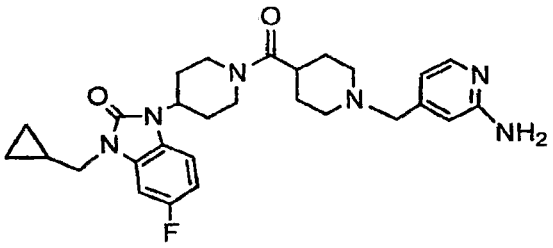
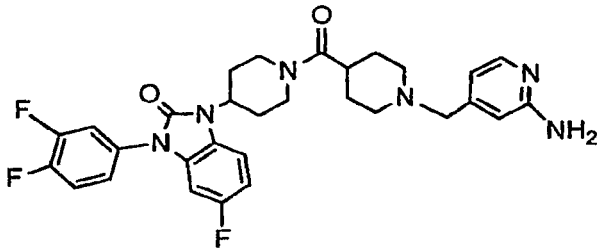
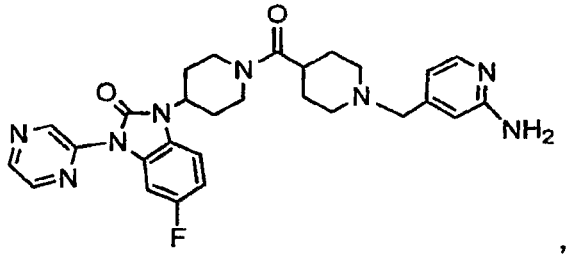
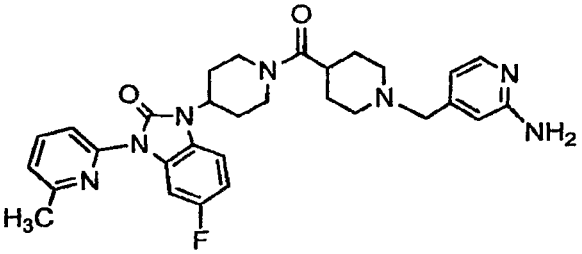
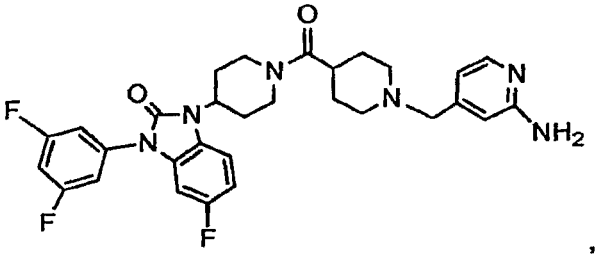
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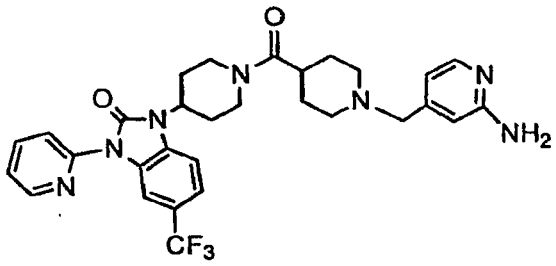
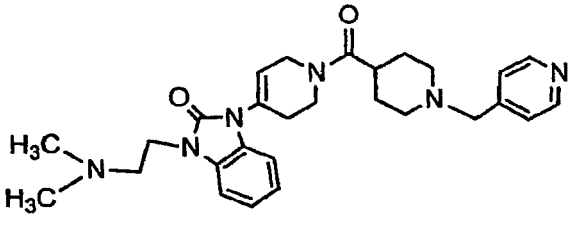
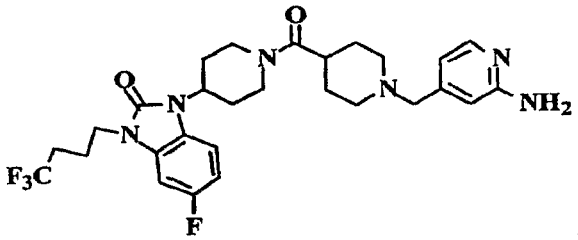
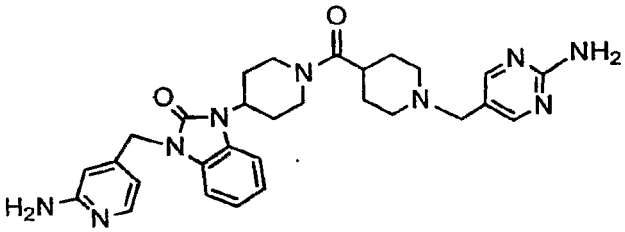
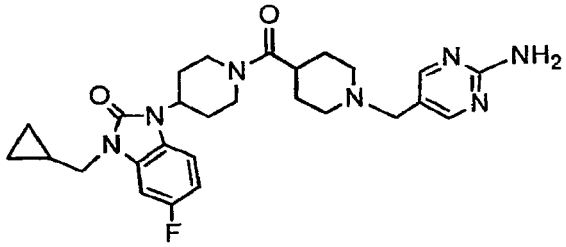
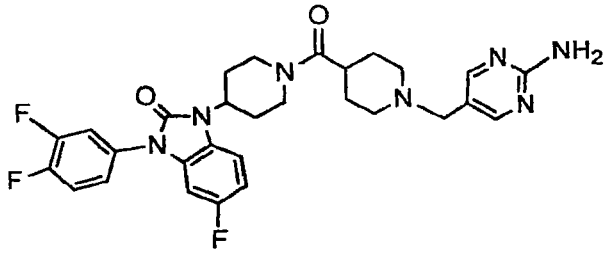
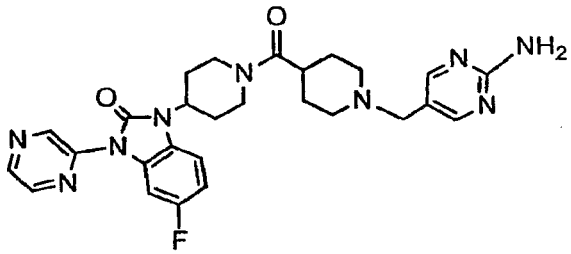
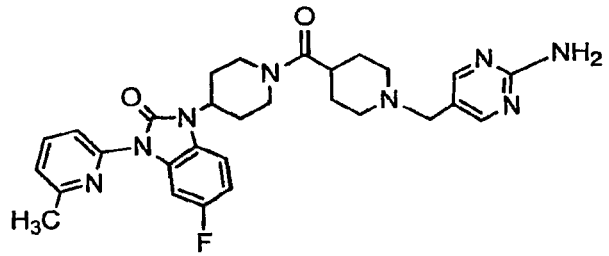
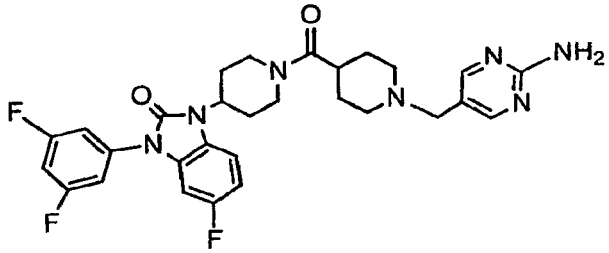
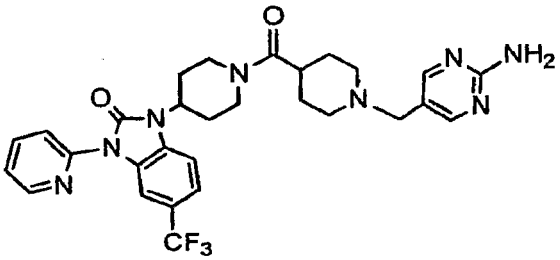
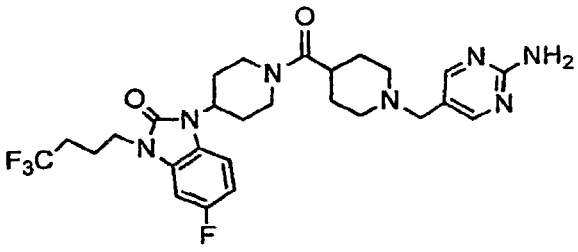

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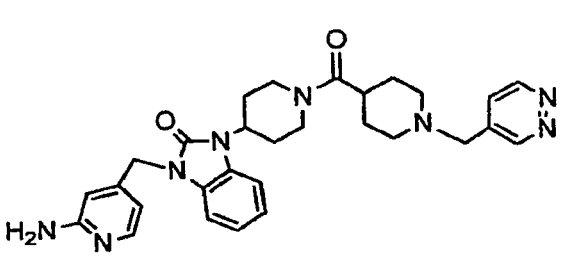
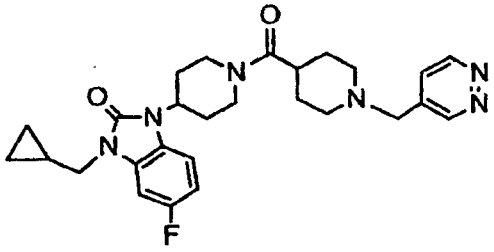
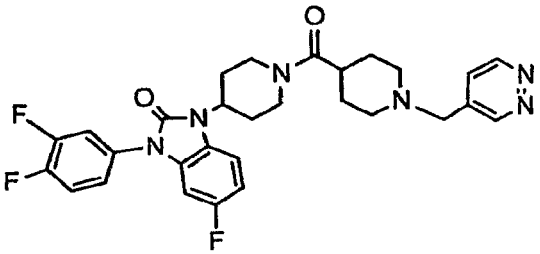
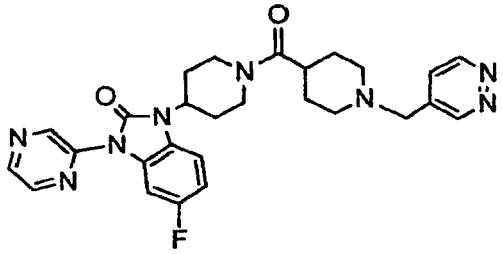
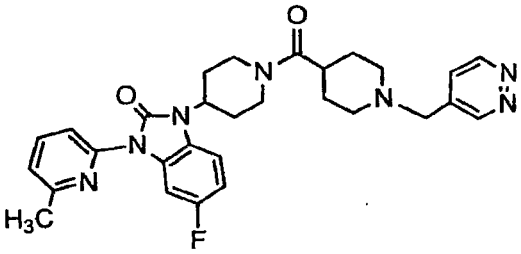
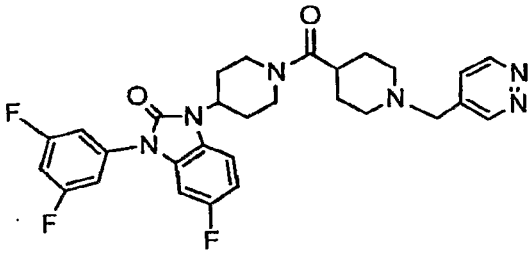
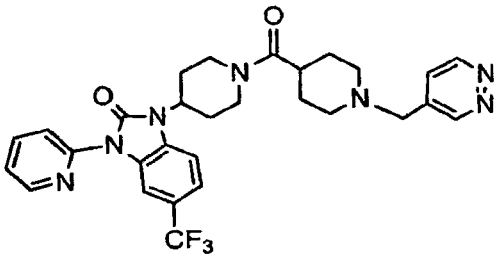
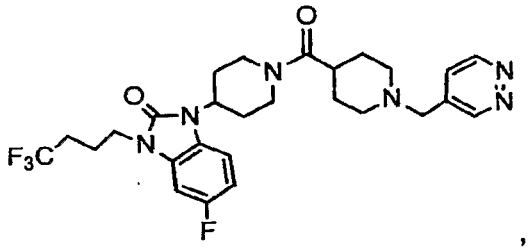
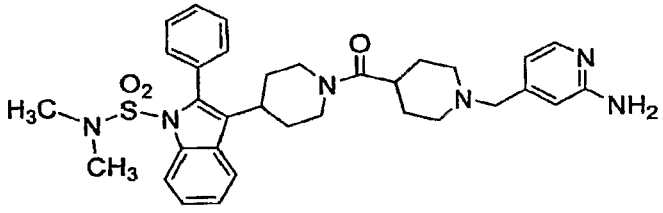
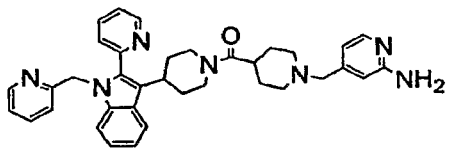
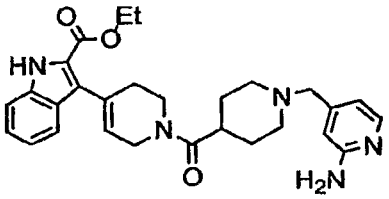
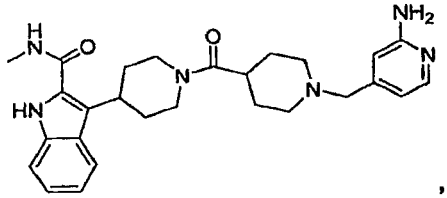
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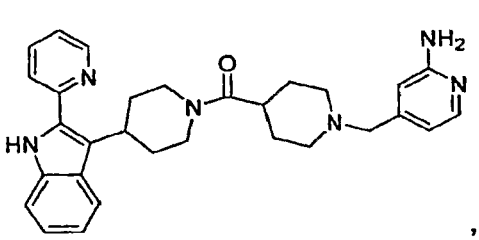
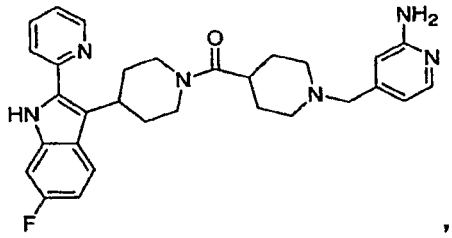
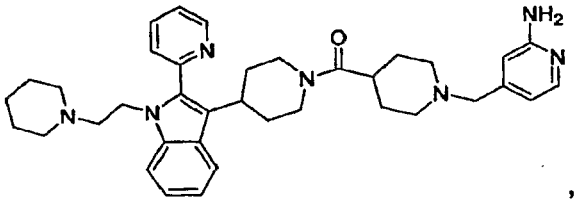
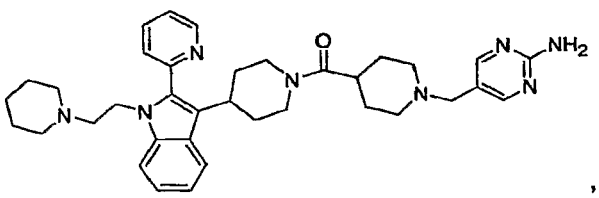
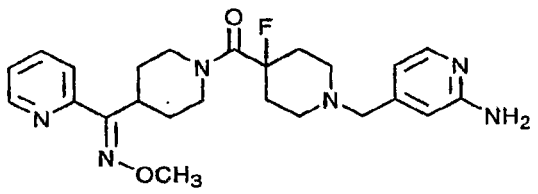
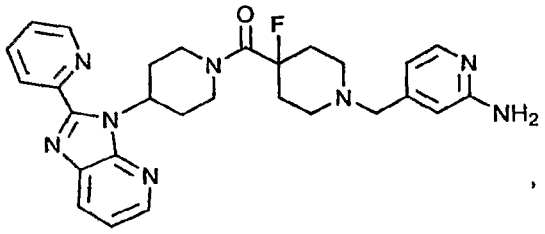
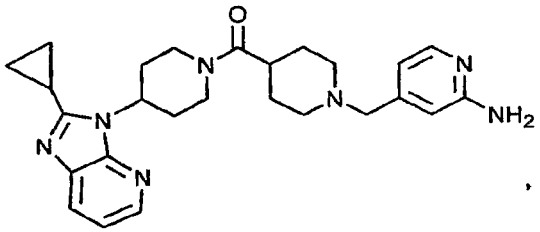
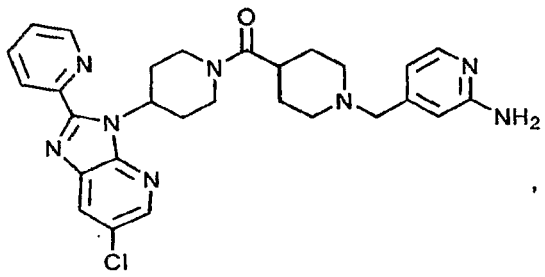
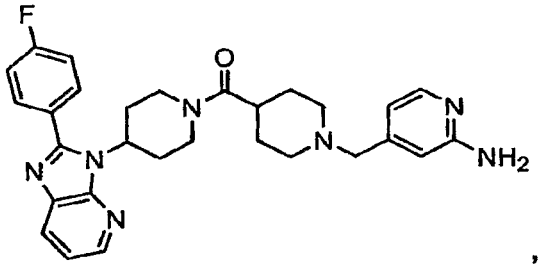
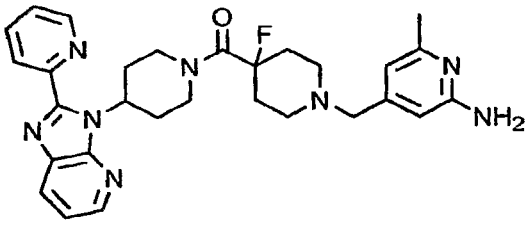
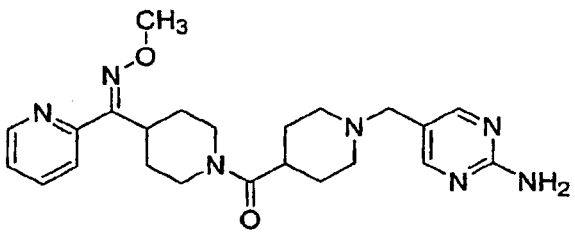
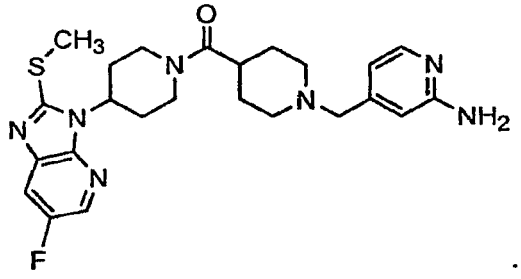

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and

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14. The composition of Claim 13, wherein the appetite suppressant is rimonabant.

15. The composition of Claim 13, wherein the appetite suppressant is phentermine.

16. The composition of Claim 13, wherein the appetite suppressant is sibutramine.

17. The composition of Claim 13, wherein the appetite suppressant is topiramate.

18. The composition of Claim 1, further comprising an HMG-CoA reductase inhibitor.

19. The composition of Claim 18, wherein the HMG-CoA reductase inhibitor is pravastatin, lovastatin, simvastatin, fluvastatin, atorvastatin, and rosuvastatin.

20. The composition of Claim 19, wherein the HMG-CoA reductase inhibitor is simvastatin.

21. The composition of Claim 13, further comprising an HMG-CoA reductase inhibitor.

22. The composition of Claim 21, wherein the HMG-CoA reductase inhibitor is pravastatin, lovastatin, simvastatin, fluvastatin, atorvastatin, or rosuvastatin.

23. The composition of Claim 22, wherein the HMG-CoA reductase inhibitor is simvastatin.

24. The composition of Claim 22, wherein the appetite suppressant is rimonabant.

25. The composition of Claim 22, wherein the appetite suppressant is phentermine.

26. The composition of Claim 22, wherein the appetite suppressant is sibutramine.

27. The composition of Claim 22, wherein the appetite suppressant is topiramate.

28. The composition of Claim 1, further comprising an anti-diabetic agent.

29. The composition of Claim 13, further comprising an anti-diabetic agent.

30. The composition of Claim 22, further comprising an anti-diabetic agent.

31. The composition of claim 28, wherein the anti-diabetic agent is a sulfonylurea, an insulin sensitizer, an α-glucosidase inhibitor, an insulin secretagogue, an anti-obesity agent, a meglitinide, insulin or an insulin-containing composition.

32. The composition of claim 31, wherein the anti-diabetic agent is an insulin sensitizer or a sulfonylurea.

33. The composition of claim 32, wherein the insulin sensitizer is a PPAR activator.

34. The composition of claim 33, wherein the PPAR activator is a thiazolidinedione.

35. The composition of claim 29, wherein the anti-diabetic agent is a sulfonylurea, an insulin sensitizer, an α-glucosidase inhibitor, an insulin secretagogue, an anti-obesity agent, a meglitinide, insulin or an insulin-containing composition.

36. The composition of claim 35, wherein the anti-diabetic agent is an insulin sensitizer or a sulfonylurea.

37. The composition of claim 36, wherein the insulin sensitizer is a PPAR activator.

38. The composition of claim 37, wherein the PPAR activator is a thiazolidinedione.

39. The composition of claim 30, wherein the anti-diabetic agent is a sulfonylurea, an insulin sensitizer, an α-glucosidase inhibitor, an insulin secretagogue, an anti-obesity agent, a meglitinide, insulin or an insulin-containing composition.

40. The composition of claim 39, wherein the anti-diabetic agent is an insulin sensitizer or a sulfonylurea.

41. The composition of claim 40, wherein the insulin sensitizer is a PPAR activator.

42. The composition of claim 41, wherein the PPAR activator is a thiazolidinedione.

43. A method of treating obesity or an obesity-related disorder in a patient comprising administering a therapeutically effective amount of the composition of Claim 1 to a patient in need thereof.

44. A method of treating obesity or an obesity-related disorder in a patient comprising administering a therapeutically effective amount of the composition of Claim 13 to a patient in need thereof.

45. A method of treating obesity or an obesity-related disorder in a patient comprising administering a therapeutically effective amount of the composition of Claim 22 to a patient in need thereof.

46. A method of treating obesity or an obesity-related disorder in a patient comprising administering a therapeutically effective amount of the composition of Claim 28 to a patient in need thereof.

47. A method of treating obesity or an obesity-related disorder in a patient comprising administering a therapeutically effective amount of the composition of Claim 29 to a patient in need thereof.

48. A method of treating obesity or an obesity-related disorder in a patient comprising administering a therapeutically effective amount of the composition of Claim 30 to a patient in need thereof.

49. A method of treating diabetes in a patient comprising administering a therapeutically effective amount of the composition of Claim 1 to a patient in need thereof.

50. A method of treating diabetes in a patient comprising administering a therapeutically effective amount of the composition of Claim 13 to a patient in need thereof.

51. A method of treating diabetes in a patient comprising administering a therapeutically effective amount of the composition of Claim 22 to a patient in need thereof.

52. A method of treating obesity or an obesity-related disorder in a patient comprising administering a therapeutically effective amount of the composition of Claim 30 to a patient in need thereof.

53. A method of treating diabetes in a patient comprising administering a therapeutically effective amount of the composition of Claim 28 to a patient in need thereof.

54. A method of treating diabetes in a patient comprising administering a therapeutically effective amount of the composition of Claim 29 to a patient in need thereof.

55. A method of treating diabetes in a patient comprising administering a therapeutically effective amount of the composition of Claim 30 to a patient in need thereof.