PHENYL-PIPERAZINE DERIVATIVES AS MODULATORS OF MUSCARINIC RECEPTORS

TECHNICAL FIELD OF THE INVENTION

[001] The present invention relates to modulators of muscarinic receptors. The present invention also provides compositions comprising such modulators, and methods therewith for treating muscarinic receptor mediated diseases.

BACKGROUND OF THE INVENTION

[002] The neurotransmitter acetylcholine binds to two types of cholinergic receptors: the ionotropic family of nicotinic receptors and the metabotropic family of muscarinic receptors. Muscarinic receptors belong to the large superfamily of plasma membrane-bound G protein coupled receptors (GPCRs). To date, five subtypes of muscarinic receptors (M_1-M_5) have been cloned and sequenced from a variety of species, and show a remarkably high degree of homology across species and receptor subtype. These M_1-M_5 muscarinic receptors are predominantly expressed within the parasympathetic nervous system which exerts excitatory and inhibitory control over the central and peripheral tissues and participate in a number of physiologic functions, including heart rate, arousal, cognition, sensory processing, and motor control.

[003] Muscarinic agonists such as muscarine and pilocarpine, and antagonists, such as atropine have been known for over a century, but little progress has been made in the discovery of receptor subtype-selective compounds, thereby making it difficult to assign specific functions to the individual receptors. See, e.g., DeLapp, N. *et al.*, "Therapeutic Opportunities for Muscarinic Receptors in the Central Nervous System," *J. Med. Chem.*, **43(23)**, pp. 4333-4353 (2000); Hulme, E. C. *et al.*, "Muscarinic Receptor Subtypes,"

Ann. Rev. Pharmacol. Toxicol., **30**, pp. 633-673 (1990); Caulfield, M. P. *et al.*, "Muscarinic Receptors-Characterization, Coupling, and Function," *Pharmacol. Ther.*, 58, pp. 319-379 (1993); Caulfield, M. P. *et al.*, International Union of Pharmacology. XVII. Classification of Muscarinic Acetylcholine Receptors," *Pharmacol. Rev.*, 50, pp. 279-290 (1998), the disclosures of which are incorporated herein by reference.

[004] The Muscarinic family of receptors is the target of a large number of pharmacological agents used for various diseases, including leading drugs for COPD, asthma, urinary incontinence, glaucoma, Alzheimer's (AchE inhibitors), and Pain.

[005] Pain can be roughly divided into three different types: acute, inflammatory, and neuropathic. Acute pain serves an important protective function in keeping the organism safe from stimuli that may produce tissue damage. Severe thermal, mechanical, or chemical inputs have the potential to cause severe damage to the organism if unheeded. Acute pain serves to quickly remove the individual from the damaging environment. Acute pain by its very nature generally is short lasting and intense. Inflammatory pain on the other had may last for much longer periods of time and it's intensity is more graded. Inflammation may occur for many reasons including tissue damage, autoimmune response, and pathogen invasion. Inflammatory pain is mediated by an "inflammatory soup" that consists of substance P, histamines, acid, prostaglandin, bradykinin, CGRP, cytokines, ATP, and neurotransmitter release. The third class of pain is neuropathic and involves nerve damage that results in reorganization of neuronal proteins and circuits yielding a pathologic "sensitized" state that can produce chronic pain lasting for years. This type of pain provides no adaptive benefit and is particularly difficult to treat with existing therapies.

[006] Pain, particularly neuropathic and intractable pain is a large unmet medical need. Millions of individuals suffer

from severe pain that is not well controlled by current therapeutics. The current drugs used to treat pain include NSAIDS, COX2 inhibitors, opioids, tricyclic antidepressants, and anticonvulsants. Neuropathic pain has been particularly difficult to treat as it does not respond well to opiods until high doses are reached. Gabapentin is currently the favored therapeutic for the treatment of neuropathic pain although it works in only 60% of patients where it shows modest efficacy. The drug is however very safe and side effects are generally tolerable although sedation is an issue at higher doses.

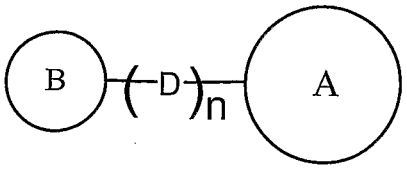
[007] Despite the large therapeutic value of this family, cholinergic drugs are limited by the lack of selectivity of these agents, with significant activation of the parasympathetic autonomous system and elevated incidence of adverse effects. The molecular cloning of the muscarinic receptors and the identification of the physiological role of specific isoforms using knock-out mice, has recently delineated novel opportunities for selective muscarinic ligands, and has helped to define the selectivity profile that is required for enhanced efficacy and reduced side effects.

[008] There is a need for modulators of muscarinic receptors M_1-M_5. There is also a need for methods for treating muscarinic receptor-mediated diseases.

[009] There is also a need for modulators of muscarinic receptors that are selective as to subtypes M_1-M_5.

SUMMARY OF THE INVENTION

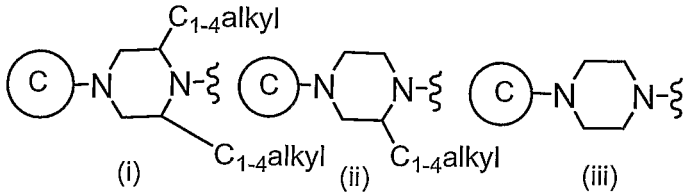
[010] The present invention provides a method of modulating activity of a muscarinic receptor, comprising the step of contacting said receptor with a compound having the formula:



(I);

wherein:

B is selected from



;

D is CF_2, CH_2, or CHR^9;

Ring C is phenyl optionally substituted with 1 to 4 of R^1, R^2, R^3, R^4, or R^5;

Ring A is a 3-8 membered monocyclic carbocyclic ring, a 7-14 membered bicylic carbocyclic ring, a 7-14 tricyclic carbocyclic ring, a 3-8 membered monocyclic heterocyclic ring, a 7-14 membered bicylic heterocyclic ring, or a 7-14 tricyclic heterocyclic ring, in which the heterocyclic rings contain 1-5 atoms selected from O, S, and N;

wherein ring A contains up to 5 substituents independently selected from R^1, R^2, R^3, R^4, or R^5;

Each R^1 is independently oxo or $((C1\text{-}C4)aliphatic)_m\text{-}Q^1$;

Each Q^1 is independently halo, CN, NO_2, CF_3, OCF_3, OH, SR^6, $S(O)R^6$, SO_2R^6, $N(R^6)_2$, NR^6R^8, COOH, $COOR^6$ or OR^6;

Each R^2 is independently aliphatic optionally substituted with 1-3 substituents independently selected from R^1, R^4, or R^5;

Each R^3 is independently a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring, wherein each of the cycloaliphatic, aryl, heterocyclic, or heteroaryl are optionally substituted with 1-3 substituents independently selected from R^1, R^2, R^4, or R^5;

Each R^4 is independently OR^5, OR^6, $OC(O)R^6$, $OC(O)R^5$, $OC(O)OR^6$, $OC(O)OR^5$, $OC(O)N(R^6)_2$, $OC(O)N(R^5)_2$, $OC(O)N(R^6R^5)$, $S(O)_iR^6$, $S(O)_iR^5$, $SO_2N(R^6)_2$, $SO_2N(R^5)_2$, $SO_2NR^5R^6$, $C(O)R^5$, $C(O)OR^5$, $C(O)R^6$, $C(O)OR^6$, $C(O)N(R^6)_2$, $C(O)N(R^5)_2$, $C(O)N(R^5R^6)$, $C(O)N(OR^6)R^6$, $C(O)N(OR^5)R^6$, $C(O)N(OR^6)R^5$, $C(O)N(OR^5)R^5$, $C(NOR^6)R^6$, $C(NOR^6)R^5$, $C(NOR^5)R^6$, $C(NOR^5)R^5$, $N(R^6)_2$, $N(R^5)_2$, $N(R^5R^6)$, $NR^5C(O)R^5$, $NR^6C(O)R^6$, $NR^6C(O)R^5$, $NR^6C(O)OR^6$, $NR^5C(O)OR^6$, $NR^6C(O)OR^5$, $NR^5C(O)OR^5$, $NR^6C(O)N(R^6)_2$, $NR^6C(O)NR^5R^6$, $NR^6C(O)N(R^5)_2$, $NR^5C(O)N(R^6)_2$, $NR^5C(O)NR^5R^6$, $NR^5C(O)N(R^5)_2$, $NR^6SO_2R^6$, $NR^6SO_2R^5$, $NR^5SO_2R^5$, $NR^6SO_2N(R^6)_2$, $NR^6SO_2NR^5R^6$, $NR^6SO_2N(R^5)_2$, $NR^5SO_2NR^5R^6$, $NR^5SO_2N(R^5)_2$, $N(OR^6)R^6$, $N(OR^6)R^5$, $N(OR^5)R^5$, or $N(OR^5)R^6$;

Each R^5 is independently a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring, wherein each of the cycloaliphatic, aryl, heterocyclic, or heteroaryl are optionally substituted with 1 to 3 of R^1;

Each R^6 is independently H or aliphatic optionally substituted with R^7;

Each R^7 is independently a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring, wherein each of the cycloaliphatic, aryl, heterocyclic, or heteroaryl are optionally substituted with 1 to 2 of (C_1-C_6)-straight or branched alkyl, (C_2-C_6) straight or branched alkenyl or alkynyl, 1,2-methylenedioxy, 1,2-ethylenedioxy, or $(CH_2)_n-Q^2$;

Each Q^2 is independently selected from halo, CN, NO_2, CF_3, OCF_3, OH, S-aliphatic, S(O)-aliphatic, SO_2-aliphatic, COOH, C(O)O-aliphatic, or O-aliphatic;

Each R^8 is independently an amino protecting group;

Each R^9 is independently R^2, R^3, or R^6;

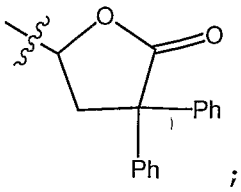
Each i is independently 0, 1, 2, or 3;

Each m is independently 0 or 1; and

Each n is independently 0 or 1;

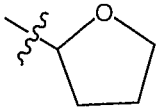
further provided that

(i) when n is 1, D is CH_2, C is phenyl, and B is piperazine

then ring A is not 

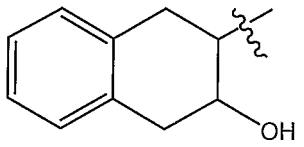
;

(ii) when n is 1, D is CH_2, C is phenyl, and B is piperazine

then ring A is not 

;

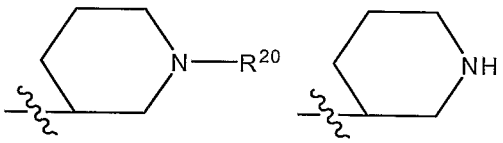
(iii) when n is 0, C is phenyl, and B is piperazine then

ring A is not 

;

(iv) when n is 1, D is CH_2, ring A is 1,2,3,4 tetrahydroquinoline optionally substituted with R^4, and B is piperazine, then C is not phenyl substituted with halo, phenyl substituted with $-OCH_3$, or phenyl substituted with halo and $-OCH_3$;

(v) when n is 1, D is CH_2, ring A is



in which R^{20} is $-C(O)R5$, $-C(O)R6$, $-C(O)OR5$, $C(O)OR6$, and B is piperazine, then C is not phenyl optionally substituted with halo or $-OCH_3$.

[011] The present invention also provides compounds of formula (I), compositions comprising compounds of formula (I), and methods of treating muscarinic receptor mediated diseases using compounds of formula (I).

[012] Advantageously, the compounds of the invention unexpectedly modulate muscarinic receptors.

DETAILED DESCRIPTION OF THE INVENTION

[013] As used herein, the following definitions shall apply unless otherwise indicated.

[014] The term "muscarinic receptor," without a prefix specifying the receptor subtype, refers to one or more of the five receptor subtypes M_1-M_5.

[015] The term "modulating" as used herein means increasing or decreasing, e.g. activity, by a measurable amount. Compounds that modulate muscarinic activity by increasing the activity of the muscarinic receptors are called agonists. Compounds that modulate muscarinic activity by decreasing the activity of the muscarinic receptors are called antagonists. An agonist interacts with a muscarinic receptor to increase the ability of the receptor to transduce an intracellular signal in response to endogenous ligand binding. An antagonist interacts with a muscarinic receptor and competes with the endogenous ligand(s) or substrate(s) for binding site(s) on the receptor to decrease the ability of the receptor to transduce an intracellular signal in response to endogenous ligand binding.

[016] The phrase "treating or reducing the severity of a muscarinic receptor mediated disease" refers both to treatments for diseases that are directly caused by muscarinic activities and alleviation of symptoms of diseases not directly caused by muscarinic activities. Examples of diseases whose symptoms may be affected by muscarinic activity include, but are not limited to, CNS derived pathologies including cognitive disorders, Attention Deficit Hyperactivity Disorder (ADHD), obesity, Alzheimer's disease, various dementias such as vascular dementia, psychosis including schizophrenia, mania, bipolar disorders,pain conditions including acute and chronic syndromes, Huntington's Chorea, Friederich's ataxia, Gilles de la Tourette's Syndrome, Downs Syndrome, Pick disease, clinical depression, Parkinson's disease, peripheral disorders such as `reduction of intra ocular pressure in Glaucoma and treatment of dry eyes and dry mouth including Sjögren's Syndrome,

bradhycardia, gastric acid secretion, asthma, GI disturbances and wound healing.

[017] The phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted."

[018] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated (alkyl) or is unsaturated (alkenyl or alkynyl). Unless otherwise specified, an aliphatic group has 1 to 12 carbon atoms, preferably, 1-6 carbon atoms, and more preferably, 1-4 carbon atoms. Up to three, and preferably two, $-CH_2-$ in said aliphatic may be replaced with O, S, or $-NR^6$.

[019] The term "cycloaliphatic" means a saturated or partially unsaturated monocyclic or bicyclic hydrocarbon ring that has a single point of attachment to the rest of the molecule. Unless otherwise specified, preferred cycloaliphatic rings are 3-8 membered monocyclic rings, more preferably 3-6, and even more preferably, 3, 5, or 6. Also preferred, unless otherwise specified, are 8-12 membered bicyclic hydrocarbon rings, more preferably 10 membered bicyclic hydrocarbon rings.

[020] The term "heteroatom," unless otherwise specified, means nitrogen, oxygen, or sulfur and includes any oxidized form of nitrogen and sulfur, and the quaternized form of any basic nitrogen. Also the term "nitrogen" includes a substitutable nitrogen of a heterocyclic ring. As an example, in a saturated or partially unsaturated ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or as in N-substituted pyrrolidinyl.

[021] The term "unsaturated", as used herein, means a double bond or a triple bond. Each such bond constitutes one unit of unsaturation.

[022] The term "aryl" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", refers to

monocyclic, bicyclic and tricyclic aromatic carbocyclic ring systems. Unless otherwise specified, preferred aryl rings have a total of five to fourteen ring members, wherein at least one ring, if bicyclic or tricyclic, in the system is aromatic and wherein each ring in the system contains up to 6 ring members. The term "aryl" may be used interchangeably with the term "aryl ring". Phenyl is an example of aryl.

[023] The term "heterocycle", "heterocyclyl", or "heterocyclic" as used herein means non-aromatic, monocyclic, bicyclic or tricyclic ring systems wherein one or more ring members is a heteroatom. Unless otherwise specified, each ring in the system preferably contains contains 3 to 7 ring members with preferably 1-3 heteroatoms.

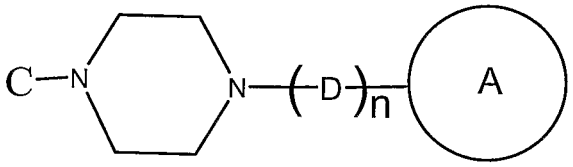
[024] The term "heteroaryl", used alone or as part of a larger moiety as in "heteroaralkyl" or "heteroarylalkoxy", refers to monocyclic, bicyclic and tricyclic ring systems, wherein at least one ring in the system is aromatic, and at least one ring in the system contains one or more heteroatoms. Unless otherwise specified, such ring systems preferably have a total of 5 to 15 ring members, wherein each ring in the system preferably contains 3 to 7 ring members, with preferably 1-3 heteroatoms. The term "heteroaryl" may be used interchangeably with the term "heteroaryl ring" or the term "heteroaromatic".

[025] The term "amino protecting group" refers to a suitable chemical group that may be attached to a nitrogen atom. The term "protected" refers to when the designated functional group is attached to a suitable chemical group (protecting group). Examples of suitable amino protecting groups and protecting groups are described in T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); L. Paquette, ed. Encyclopedia of Reagents for Organic Synthesis,

John Wiley and Sons (1995) and are exemplified in certain of the specific compounds used in this invention.

[026] A combination of substituents or variables is permissible only if such a combination results in a stable or chemically feasible compound. A stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40°C or less, in the absence of moisture, light, or other chemically reactive conditions, for at least a week.

[027] According to one embodiment, the present invention provides a method of modulating activity of a muscarinic receptor, comprising the step of contacting said receptor with a compound having the formula (IA):



(IA);

wherein:

D is CF_2, CH_2, or CHR^9, S(O), $S(O)_2$, C(O);

Ring A is a 3-8 membered monocyclic or 7-14 membered bicylic aryl, a 3-8 membered monocyclic or 7-14 membered bicylic heteroaryl, a 3-8 membered monocyclic or 7-14 membered bicylic or tricyclic carbocyclic ring, or a 3-8 membered monocyclic or 7-14 membered bicylic or tricyclic heterocyclic ring containing 1-5 atoms selected from O, S, and N;

in which ring A contains up to 5 substituents independently selected from R^1, R^2, R^3, R^4, or R^5; and

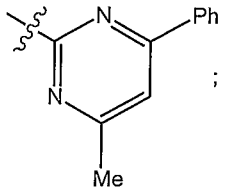
Each of C, R1, R2, R3, R4, R5, R6, R7, R8, R9, and n are defined above as in formula I.

[028] Embodiments of this aspect of the invention include one or more of the following.

[029] D is CF_2, CH_2, CHR^9, or C(O). D is D is CF_2, CH_2, CHR^9. D is CH_2 or C(O), or D is CH_2 or CF_2. D is CH_2. D is C(O). n is 0. n is 1.

[030] The methods of the present invention employ compounds of formula (IA) provided that in formula (IA) one or more of the following:

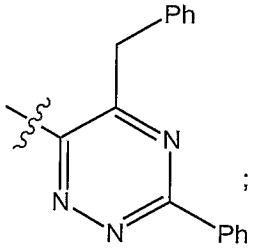
(i) when n is 0 and C is phenyl, then ring A is



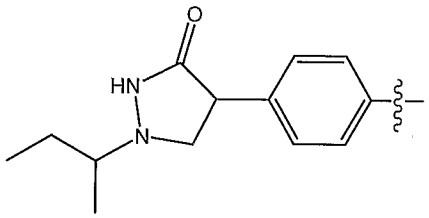
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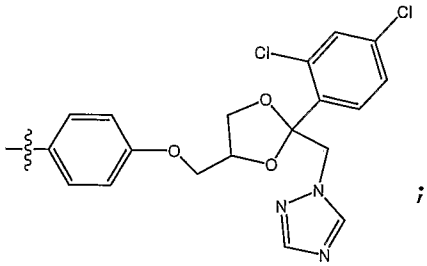
not

(ii) when n is 0 and C is 3-chlorophenyl, then ring A is not



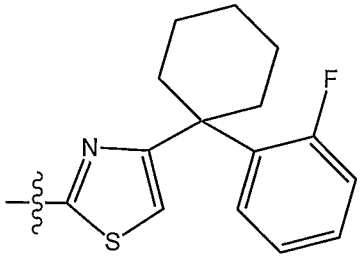
;

(iii) when n is 0 and C is 

, then ring A is not 

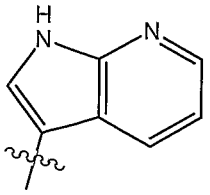
; and

(iv) when n is 0 and C is 2-methoxyphenyl, then ring A is not



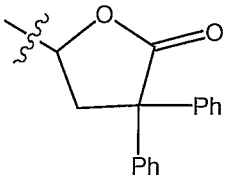
;

(v) when n is 1, D is CH_2, and C is 4-chlorophenyl, then ring A



is not ;

(vi) when n is 1, D is CH_2, and C is phenyl, then ring A is not



;

(viii) when n is 1, D is CHR^9 wherein R^9 is methyl, and C is 2-methoxyphenyl, phenyl, or 4-nitrophenyl, then ring A is not 4-benzenesulfonyl-phenyl, or 4-(4'-tolyl)-phenyl.

[031] A is an optionally substituted monocyclic C3-C8 cycloaliphatic ring, such as an optionally substituted cyclopropyl, cyclopentyl, cyclohexyl, or cycloheptyl. A is an optionally substituted C7-C14 cycloaliphatic ring, such as a bicylic, bridged bicyclic or bridged tricyclic. In particular, A is an optionally substituted 1-adamantyl, 2-adamantyl, 1-norbornyl, or 1-bicyclo[2.2.1]hept-5-en-2-yl. A is an optionally substituted C6-C10 aryl ring. In particular, A is an optionally substituted phenyl or naphthyl. A is an optionally substituted C5-C12 heteroaryl ring. For instance, A is selected from an optionally substituted triazinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyridinyl, thiadiazolyl, triazolyl, oxadiazolyl, isothiazolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, pyrrolyl, thienyl, furanyl, indolizinyl, indolyl, isoindolyl, benzofuranyl, benzo[b]thienyl, 1H-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, acridinyl, phenazinyl, phenothiazinyl, or phenoxazinyl. A is an optionally substituted monocyclic, bicylic, bridged bicyclic or bridged

tricyclic C3-C12 heterocyclic ring. A is selected from an optionally substituted aziridine, oxirane, thiirane, pyrrolidyl, tetrahydrofuranyl, tetrahydrothienyl, dioxolanyl, pyrrolinyl, pyranyl, pyrazolinyl, pyrazolidinyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, piperazinyl, 3H-indolyl, or indolinyl.

[032] In other embodiments of compounds of formulae I and IA, A is a monocyclic, bicylic, bridged bicyclic or bridged tricyclic C3-C12 heterocyclic ring, each optionally substituted with 1-5 substituents independently selected from R^1, R^2, R^3, R^4, or R^5. For instance, A is selected from optionally substituted oxirane, thiirane, pyrrolidyl, tetrahydrofuranyl, tetrahydrothienyl, dioxolanyl, pyrrolinyl, pyranyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, or indolinyl. As described below in certain embodiments, ring A together with any substituents on ring A do not include any basic nitrogen atoms.

[033] Two R^1 groups form 1,2-methylenedioxy, or 1,2-ethylenedioxy. Two R^1 groups form -CH=CH-CH=CH-, -CH=N-CH=CH-, -CH=CH-NH-. R^1 is R^6, wherein R^6 is straight chain or branched (C1-C6)alkyl or (C2-C6 alkenyl) or alkynyl, optionally substituted with R^7. R^1 is $(CH_2)_m$-Y, wherein m is 0, 1, or 2, and Y is halo, CN, NO_2, CF_3, OCF_3, OH, SR^6, $S(O)R^6$, SO_2R^6, NH_2, NHR^6, $N(R^6)_2$, NR^6R^8, COOH, $COOR^6$ or OR^6. R^1 is selected from halo, CF_3, NH_2, NH(C1-C4 alkyl), $NHC(O)CH_3$, OH, O(C1-C4 alkyl), OPh, O-benzyl, S-(C1-C4 alkyl), C1-C4 aliphatic, NO_2, CN, methylenedioxy, ethylenedixoy, SO_2NH(C1-C4 alkyl), or SO_2N(C1-C4 alkyl)$_2$. R^1 is selected from methyl, n-propyl, i-propyl, t-butyl, halo, CF_3, NH_2, $NH(CH_3)$, $NHC(O)CH_3$, OH, OCH_3, OPh, O-benzyl, S-(C_2H_5), S-CH_3, NO_2, CN, methylenedioxy, SO_2NH(n-propyl), or SO_2N(n-propyl)$_2$.

[034] R^2 is a straight chain or branched (C1-C6)alkyl or (C2-C6) alkenyl or alkynyl, optionally substituted with R^1, R^4,

or R^5. R^2 is a straight chain or branched (C1-C4)alkyl or (C2-C4) alkenyl or alkynyl, optionally substituted with R^1, R^4, or R^5.

[035] R^3 is an optionally substituted phenyl, napthyl, C5-C10 heteroaryl or C3-C7 heterocyclyl. R^3 is an optionally substituted phenyl, C5-C6 heteroaryl, or C3-C6 heterocyclyl.

[036] R^4 is selected from OR^5, OR^6, SR^5, SR^6, NR^5COR^5, NR^5COR^6, NR^6COR^5, or NR^6COR^6.

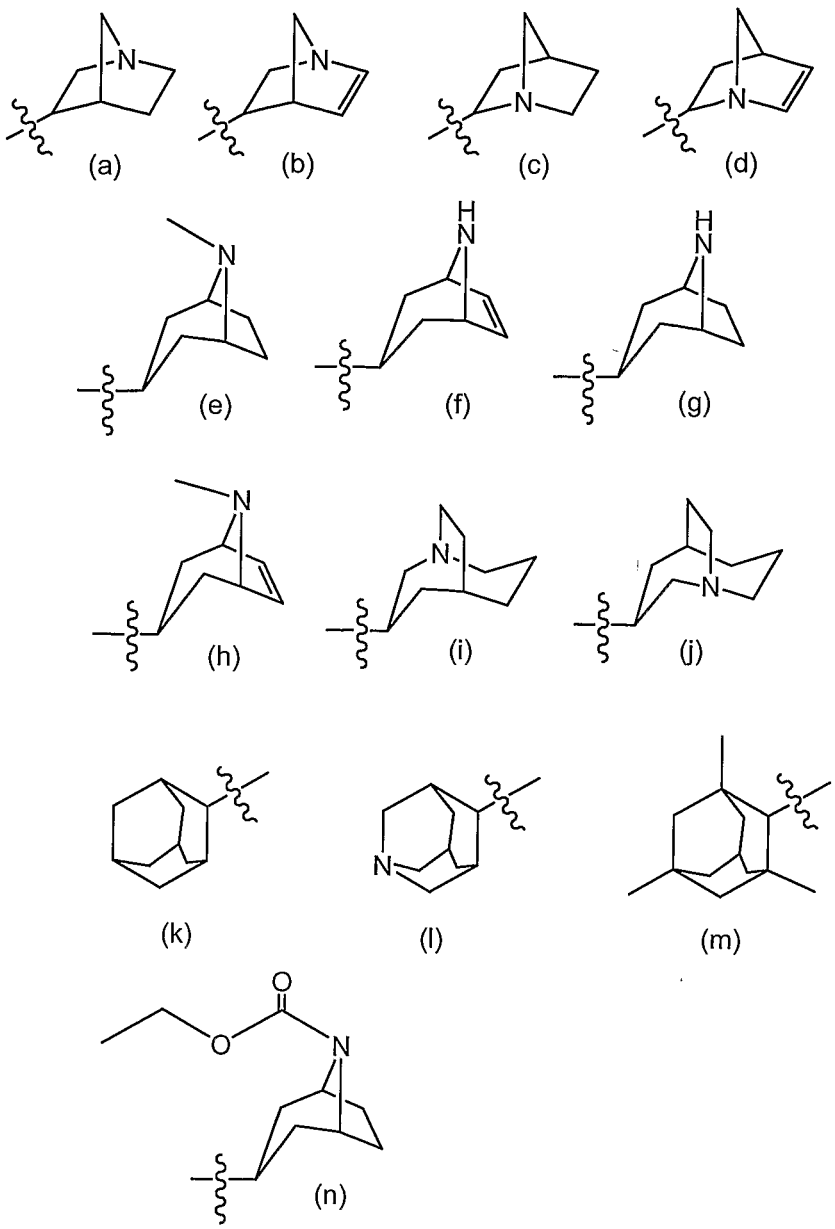
[037] R^5 is C5-C6 cycloalkyl, C6 or C10 aryl, C5-C10 heteroaryl or C3-C7 heterocyclyl, optionally substituted with up to 2 R^1. R^5 is an optionally substituted cyclohexyl, phenyl, C5-C6 heteroaryl, or C3-C6 heterocyclyl.

[038] R^6 is H. R^6 is a straight chain or branched (C1-C6)alkyl or (C2-C6 alkenyl) or alkynyl, optionally substituted with R^7. R^6 is a straight chain or branched (C1-C6)alkyl or (C2-C6 alkenyl) or alkynyl.

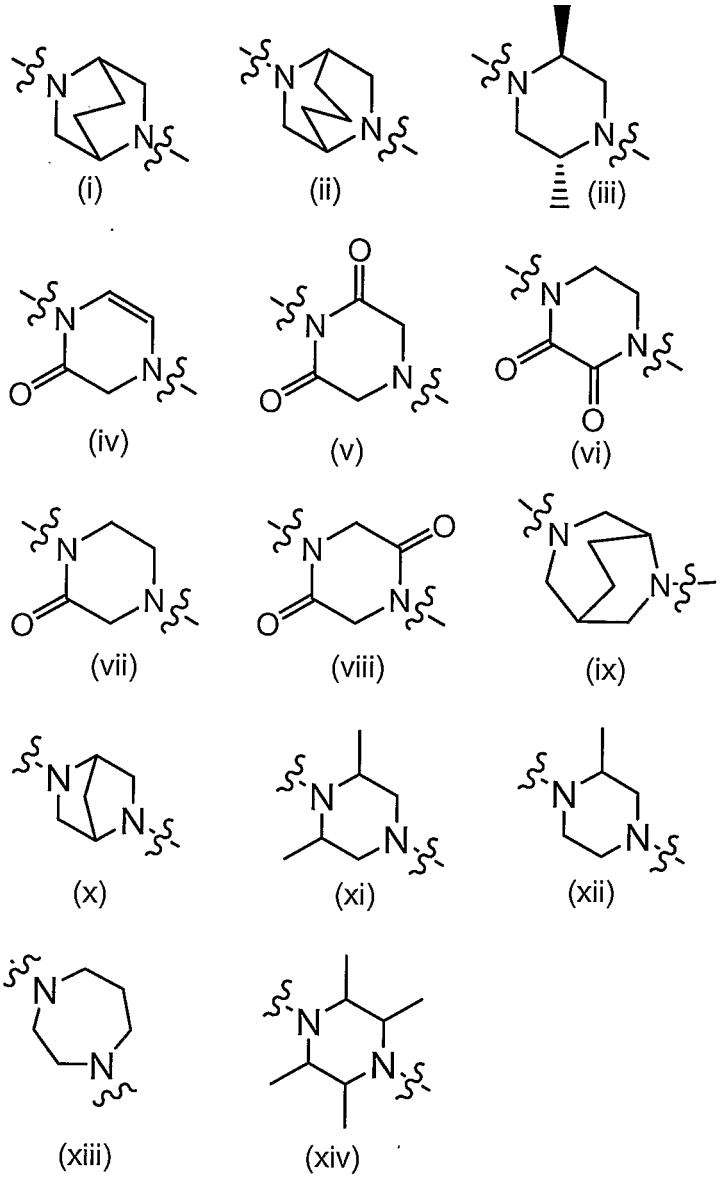
[039] R^7 is C5-C6 cycloalkyl, phenyl, naphthyl, C5-C10 heteroaryl or C3-C7 heterocyclyl, optionally substituted with straight chain or branched (C1-C6)alkyl or (C2-C6 alkenyl) or alkynyl. R^7 is C5-C6 cycloalkyl, phenyl, naphthyl, C5-C10 heteroaryl or C3-C7 heterocyclyl, optionally substituted with 1-2-methylenedioxy, 1,2-ethylenedioxy, or $(CH_2)_n$-Q^2. In still other embodiments R^7 is an optionally substituted cyclohexyl, phenyl, C5-C6 heteroaryl, or C3-C6 heterocyclyl.

[040] R^8 is acetyl, arylsulfonyl or alkylsulfonyl.

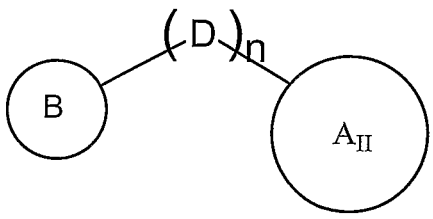
[041] Ring A is selected from (a)-(n) as shown below:



[042] The invention also features compounds of formula I in which the piperazine ring may be replaced by any one of the following (i)-(xiv).



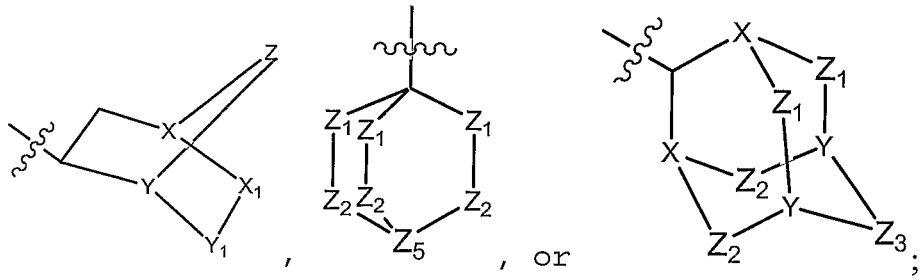
[043] According to another aspect, the present invention provides a compound having formula (II):



(II);

wherein:

ring A_{II} is selected from:



, , or ;

X, Y, and Z_5 are each independently CR' or N;

X_1 and Y_1 are independently selected from a bond, CH_2, CHR^9, O, S, NH, NR', C(O), S(O), or SO_2 provided that both X_1 and Y_1 are not simultaneously a bond;

Z is $C(R')_2$, $C(R')_2$-$C(R')_2$, $C(R')_2$-Q, or Q, wherein Q is O, NR', S(O), SO_2, or C(O);

Each of Z_1, Z_2, Z_3, and Z_4 is independently selected from CH_2, CHR', O, S, NH, NR', C(O), S(O), SO_2;

Each R' is independently selected from (C1-C4)aliphatic)$_m$-Q^1, $S(O)_iR^6$, $S(O)_iR^5$, $SO_2N(R^6)_2$, $SO_2N(R^5)_2$, $SO_2NR^5R^6$, $C(O)R^5$, $C(O)OR^5$, $C(O)R^6$, $C(O)OR^6$, $C(O)N(R^6)_2$, $C(O)N(R^5)_2$, $C(O)N(R^5R^6)$, $C(O)N(OR^6)R^6$, $C(O)N(OR^5)R^6$, $C(O)N(OR^6)R^5$, $C(O)N(OR^5)R^5$, $C(NOR^6)R^6$, $C(NOR^6)R^5$, $C(NOR^5)R^6$, $C(NOR^5)R^5$, R^2, or R_6, provided that when any of X_1, Y_1, Z, Z_1, Z_2, Z_3, and Z_4 are NR', then R' is $S(O)_iR^6$, $S(O)_iR^5$, $SO_2N(R^6)_2$, $SO_2N(R^5)_2$, $SO_2NR^5R^6$, $C(O)R^5$, $C(O)OR^5$, $C(O)R^6$, $C(O)OR^6$, $C(O)N(R^6)_2$, $C(O)N(R^5)_2$, $C(O)N(R^5R^6)$, $C(O)N(OR^6)R^6$, $C(O)N(OR^5)R^6$, $C(O)N(OR^6)R^5$, $C(O)N(OR^5)R^5$, $C(NOR^6)R^6$, $C(NOR^6)R^5$, $C(NOR^5)R^6$, $C(NOR^5)R^5$;

Each of B, D, Q^1, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, and n are defined above as in formula I; and

further provided one or more of the following:

(i) when C is dimethyl-fluoro-phenyl, n is 1, D is CH_2, Z is $C(CH_3)_2$, X and Y are both CH, and B is piperazine, then X_1 and Y_1 are not both CH_2; and

(ii) when C is 2-methylphenyl, n is 1, D is C(O), Z is $C(alkyl)_2$, X_1 and Y_1 both are simultaneously CH or CH_2, and B is piperazine, then X and Y are not simultaneously CH;

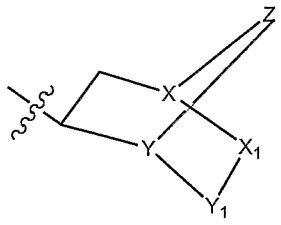
(iii) when C is phenyl substituted with R2, D is C(O) or CH_2, n is 1, and B is piperazine, then ring A_{II} is not adamantanyl; and

(iv) the compound is not 1-phenyl-4-4(tricycle[3.3.1.13,7] dec-1ylmethyl-piperazine.

[044] Embodiments of the compounds of formula II include one or more of the following.

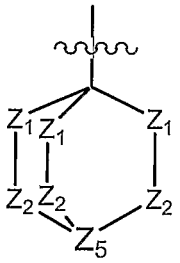
[045] The radical R' in the compounds of formula (II) is $(C1\text{-}C4)aliphatic)_m\text{-}Q^1$. The radical R' is R^2. The radical R' is R_6.

[046] The ring A_{II} in formula (II) has the structure



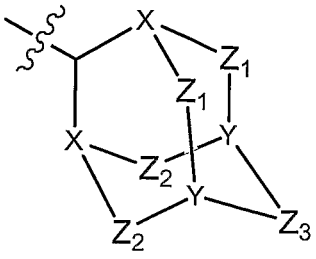
, wherein X, Y, Z, X_1 and Y_1 are as described above. X and Y are CH. One of X and Y is CH and the other of X and Y is N. X_1 and Y_1 are both CH_2. X_1 and Y_1 are both NR. One of X_1 and Y_1 is CH_2 and the other of X_1 and Y_1 is NR, such as NH. Z is O, CH_2 or NR, such as NH. Z is C(O), $-CH_2\text{-}C(O)\text{-}$, or $-C(O)\text{-}CH_2\text{-}$.

[047] The ring A_1 in formula (II) has the structure



, wherein Z_1, Z_2, and Z_5 are as described above. Each of Z_1 and Z_2 is CH_2, CHR, NH, or C(O). Each of Z_1 and Z_2 is CH_2 or NH. Z_5 is CH. Z_5 is N.

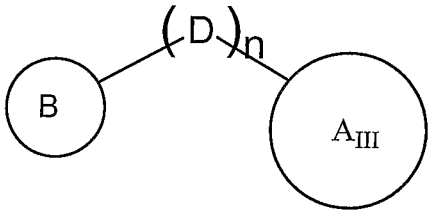
[048] The ring A_1 in formula (II) has the structure



, wherein Z_1, Z_3, X and Y are as defined above. Z_1 and Z_3 are each independently CH_2 or NH. Z_1 and Z_3 are each CH_2. Preferably, each of X and Y is CH. Or, each of X and Y is N. Or, one of two X is N. Or, one of two Y is N.

[049] In other embodiments of compounds of formula II, the variables X, Y, and Z_5 are each independently CR'; X_1 and Y_1 are independently selected from a bond, CH_2, CHR^9, O, S, NR', C(O), S(O), SO_2, or together form -CH=CH-, provided that both X_1 and Y_1 are not simultaneously a bond; Z is $C(R')_2$, $C(R')_2$-$C(R')_2$, $C(R')_2$-Q, or Q, wherein Q is O, NR', S(O), SO_2, or C(O); Each of Z_1, Z_2, Z_3, and Z_4 is independently selected from CH_2, CHR', O, S, NR', C(O), S(O), SO_2; and R' is selected from (C1-C4)aliphatic)$_m$-Q^1, R^2, or R_6, provided that when any of X_1, Y_1, Z, Z_1, Z_2, Z_3, and Z_4 are NR', then R' is not hydrogen.

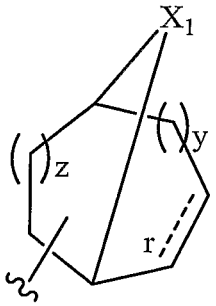
[050] According to another aspect, the present invention provides a compound having formula (III):



(III);

wherein:

ring A_{III} is



optionally substituted with 1-3 of R';

X_1 is independently selected from a bond, CH_2, CHR^9, O, S, NH, NR', C(O), S(O), SO_2;

Each R' is independently selected from $(C1\text{-}C4)aliphatic)_m\text{-}Q^1$, $S(O)_iR^6$, $S(O)_iR^5$, $SO_2N(R^6)_2$, $SO_2N(R^5)_2$, $SO_2NR^5R^6$, $C(O)R^5$, $C(O)OR^5$, $C(O)R^6$, $C(O)OR^6$, $C(O)N(R^6)_2$, $C(O)N(R^5)_2$, $C(O)N(R^5R^6)$, $C(O)N(OR^6)R^6$, $C(O)N(OR^5)R^6$, $C(O)N(OR^6)R^5$, $C(O)N(OR^5)R^5$, $C(NOR^6)R^6$, $C(NOR^6)R^5$, $C(NOR^5)R^6$, $C(NOR^5)R^5$, R^2, or R_6, provided that when any of X_1, Y_1, Z, Z_1, Z_2, Z_3, and Z_4 are NR', then R' is $S(O)_iR^6$, $S(O)_iR^5$, $SO_2N(R^6)_2$, $SO_2N(R^5)_2$, $SO_2NR^5R^6$, $C(O)R^5$, $C(O)OR^5$, $C(O)R^6$, $C(O)OR^6$, $C(O)N(R^6)_2$, $C(O)N(R^5)_2$, $C(O)N(R^5R^6)$, $C(O)N(OR^6)R^6$, $C(O)N(OR^5)R^6$, $C(O)N(OR^6)R^5$, $C(O)N(OR^5)R^5$, $C(NOR^6)R^6$, $C(NOR^6)R^5$, $C(NOR^5)R^6$, $C(NOR^5)R^5$;

Each y is 0, 1 or 2;

Each z is 0, 1, or 2, provided that y + z is 1, 2, or 3;

Bond r is a single or double bond; and

Each of B, D, Q1, R1, R2, R3, R4, R5, R6, R7, R8, R9, and n are defined above as in formula I;

provided that when D is CH_2, y is 1 and z is 2, that X1 is other than C(O) or -CH(OH)-.

[051] Embodiments of this aspect include one or more of the following. X_1 is NR'. X_1 is $-N(C(O)OR_5)-$. X_1 is independently selected from a bond, CH_2, CHR^9, O, S, NR', C(O), S(O), SO_2; and R' is selected from $(C1\text{-}C4)aliphatic)_m\text{-}Q^1$, R^2, or R_6, provided that R_6 is not hydrogen.

[052] In some embodiments, the compounds of formulae I, IA, II, and III include only a single basic nitrogen atom in any of B, D, or A and any of the substituents attached to B, D, and

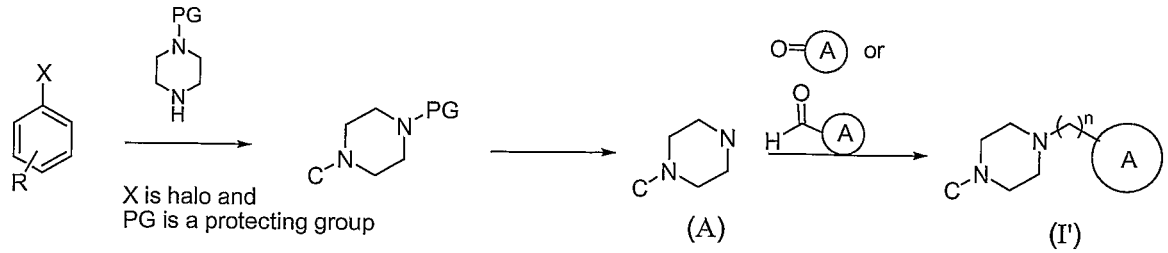
A, wherein a basic nitrogen atom is defined as any nitrogen whose conjugate acid pka is greater than 7.1. For instance, the nitrogen atom at the 4 position relative to C is a basic nitrogen atom. In other embodiments, A and substituents attached to A do not include any basic nitrogen atoms, but B and D along with substituents attached to B and D may include one or more basic nitrogen atoms. Alternatively, ring A does not include any basic nitrogen atoms that form ring A, such as the nitrogen in piperidine, but B, D, and substituents attached to B,D, and A may include one or more basic nitrogen atoms.

[053] In still other aspects, the invention features compounds of formulae I, IA, II, and III that include combinations of the different aspects and embodiments described above. For instance, embodiments of compounds of formula III may include one or more of the embodiments described above for compounds of formula I.

[054] Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools or probes in biological assays.

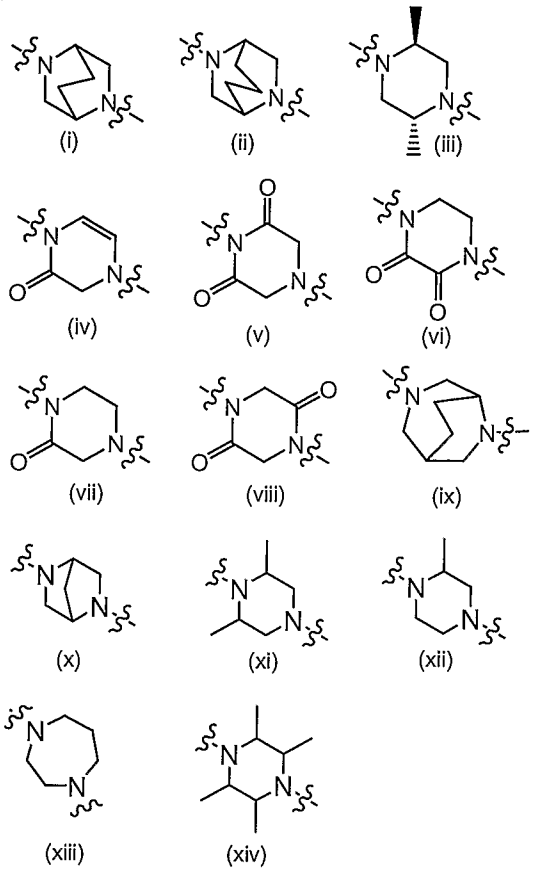
[055] The compounds of formulae (I, IA, II, and III) may be readily synthesized using methods known in the art. An exemplary synthetic route to produce compounds of formula (I, IA II, and III), when ring B is piperazine, is provided below in Scheme 1.

Scheme 1:

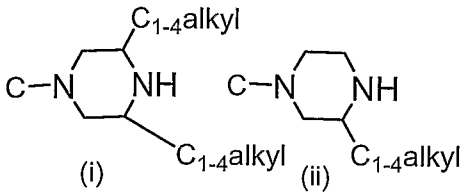


[056] Referring to Scheme 1, the reaction of a ketone or aldehyde with an amine of formula (A) in the presence of a suitable reducing agent, e.g., sodium triacetoxyborohydride, produces compounds of formula I'. One of skill in the art will recognize that the above synthetic route depicted above are generic and can be readily adapted for other embodiments of compound formula (I) using methods known to those skilled in the art.

[057] Compounds of formula (A) may be purchased commercially or synthesized from an optionally protected piperazine and aryl halide using methods known to those skilled in the art. Additionally, compounds of formulae I, IA, II, and III in which the piperazine ring is replaced by



may be produced using the methods described herein and other methodologies known to those skilled in the art. For instance, the other piperazine rings may be replaced to provide the following amines



[058] The present invention includes within its scope pharmaceutically acceptable prodrugs of the compounds of the present invention. A "pharmaceutically acceptable prodrug" means any pharmaceutically acceptable salt, ester, salt of an ester, or other derivative of a compound of the present invention which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention or an active metabolite or residue thereof. Preferred prodrugs are those that increase the bioavailability of the

compounds of this invention when such compounds are administered to a mammal or which enhance delivery of the parent compound to a biological compartment relative to the parent species.

[059] The term "pharmaceutically acceptable carrier, adjuvant, or vehicle" refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[060] Pharmaceutically acceptable salts of the compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acid salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate and undecanoate. Other

acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

[061] Salts derived from appropriate bases include alkali metal (e.g., sodium and potassium), alkaline earth metal (e.g., calcium or magnesium), ammonium and $N^+(C_{1-4}$ alkyl$)_4$ salts or salts of lysine and arginine. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization. Other salts can be found in "Practical Process, Research, & Development," Anderson, Neal G., Academic Press, 2000, the contents of which are incorporated herein by reference.

[062] The compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, intermuscularly, subcutaneously, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

[063] For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[064] The pharmaceutically acceptable compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

[065] Alternatively, the pharmaceutically acceptable compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the

drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

[066] The pharmaceutically acceptable compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

[067] Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

[068] For topical applications, the pharmaceutically acceptable compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutically acceptable compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[069] For ophthalmic use, the pharmaceutically acceptable compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutically

acceptable compositions may be formulated in an ointment such as petrolatum.

[070] The pharmaceutically acceptable compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[071] Most preferably, the pharmaceutically acceptable compositions of this invention are formulated for oral administration.

[072] The amount of the compounds of the present invention that may be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the host treated, the particular mode of administration. Preferably, the compositions should be formulated so that a dosage of between 0.01-100 mg/kg body weight/day of the modulator can be administered to a patient receiving these compositions.

[073] It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound of the present invention in the composition will also depend upon the particular compound in the composition.

[074] Depending upon the particular condition, or disease, to be treated or prevented, additional therapeutic agents, which are normally administered to treat or prevent that condition,

may also be present in the compositions of this invention. As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated."

[075] According to a preferred embodiment, the compounds of formulae (I, IA, II, and III) are selective modulators of M_1, M_2 and M_4. More preferably, the compounds of formula (I, IA, II, and III) are selective modulators of M_1 and M_4. Or, the compounds of formula (I, IA, II, and III) are selective modulators of M_2 and M_4. Yet more preferably, the compounds of formula (I, IA, II, and III) are selective modulators of one of M_1, M_2, and M_4. The compounds of formula (I, IA, II, and III) are selective modulators of M_4. The compounds of formula (I, IA, II, and III) are selective modulators of M_1.

[076] Applicants believe that the ability of the compounds of the present invention to modulate the activity of muscarinic receptors is derived from the affinity of these compounds to the muscarinic receptors. Such affinity, applicants believe, activates a muscarinic receptor (i.e, an agonist) or inhibits the activity of a muscarinic receptor.

[077] According to another embodiment, the compounds of formula (I, IA, II, and III) are selective activators of all of M_1, M_2, and M_4. In other embodiments, the compounds of formula (I, IA, II, and III) are selective activators of one of M_1, M_2, and M_4 and selective inhibitors of the other two of M_1, M_2, and M_4. In another embodiment, the compounds of formula (I, IA, II, and III) are selective activators of up to two of M_1, M_2, and M_4 and selective inhibitors of the other of M_1, M_2, and M_4. In still another embodiment, the compounds of formula (I, IA, II, and III) are selective inhibitors of all of M_1, M_2, and M_4.

[078] According to another embodiment, the compounds of compounds of formula (I, IA, II, and III) are selective inhibitors of one or more of M_1, M_2, or M_4. In one embodiment, preferably, the compounds of formula (I, IA, II, and III) are selective inhibitors of M_4. In another embodiment, the compounds of formulae (I, IA, II, and III) are selective inhibitors of M_1. In yet another embodiment, the compounds of formulae (I, IA, II,

and III) are selective inhibitors of M_1 and M_4. In still another embodiment, the compounds of formulae (I, IA, II, and III) are selective inhibitors of M_1 and M_2 or M_4 and M_2.

[079] The term "selective" as used herein means a measurably greater ability to modulate one muscarinic receptor subtype when compared to the other muscarinic receptor subtypes. E.g., the term "selective M_4 agonist" means a compound that has a measurably greater ability to act as an M_4 agonist when compared to that compound's agonist activity with the other muscarinic receptor subtype(s).

[080] According to an alternative embodiment, the present invention provides a method of treating a muscarinic receptor mediated disease in a mammal, comprising the step of administering to said mammal a composition comprising a compound of formulae (I, IA, II, and III), or a preferred embodiment thereof as set forth above.

[081] According to a preferred embodiment, the present invention provides a method of treating a disease mediated by one or more of M_1, M_2, or M_4, comprising the step of administering to said mammal a composition comprising a compound of formula (I, IA, II, and III), or a preferred embodiment thereof as set forth above. Or in another embodiment the disease is mediated by M_2. Or, said disease is mediated by M_1. Yet more preferably, said disease is mediated by M_4. In still further embodiments, the disease is mediate by all of M_1, M_2, and M_4. In another embodiment, the disease is mediate by two of M_1, M_2, and M_4.

[082] According to a preferred embodiment, the present invention provides a method of treating or reducing the severity of a disease in a patient, wherein said disease is selected from CNS derived pathologies including cognitive disorders, Attention Deficit Hyperactivity Disorder (ADHD), obesity, Alzheimer's disease, various dementias such as vascular dementia, psychosis associated with CNS disorders including schizophrenia, mania, bipolar disorders, pain conditions including acute and chronic

syndromes, Huntington's Chorea, Friederich's ataxia, Gilles de la Tourette's Syndrome, Downs Syndrome, Pick disease, clinical depression, Parkinson's disease, peripheral disorders such as reduction of intra ocular pressure in Glaucoma and treatment of dry eyes and dry mouth including Sjögren's Syndrome, and wound healing, wherein said method comprises the step of contacting said patient with a compound according to the present invention.

[083] In one embodiment, the present invention provides a method for the treatment or lessening the severity of acute, chronic, neuropathic, or inflammatory pain, arthritis, migrane, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, incontinence, visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head or neck pain, severe or intractable pain, nociceptive pain, breakthrough pain, postsurgical pain, or cancer pain is provided comprising administering an effective amount of a compound, or a pharmaceutically acceptable composition comprising a compound to a subject in need thereof. In certain embodiments, a method for the treatment or lessening the severity of acute, chronic, neuropathic, or inflammatory pain is provided comprising administering an effective amount of a compound or a pharmaceutically acceptable composition to a subject in need thereof. In certain other embodiments, a method for the treatment or lessening the severity of radicular pain, sciatica, back pain, head pain, or neck pain is provided comprising administering an effective amount of a compound or a pharmaceutically acceptable composition to a subject in need thereof. In still other embodiments, a method for the treatment or lessening the severity of severe or intractable pain, acute

pain, post-surgical pain, back pain, or cancer pain is provided comprising administering an effective amount of a compound or a pharmaceutically acceptable composition to a subject in need thereof.

[084] According to an alternative embodiment, the present invention provides a method of treating or reducing the severity of a disease in a patient, wherein said disease is selected from pain, psychosis (including schizophrenia, hallucinations, and delusions), Alzheimer's disease, Parkinson's disease, glaucoma, bradhycardia, gastric acid secretion, asthma, GI disturbances or wound healing.

[085] According to a preferred embodiment, the present invention is useful for treating or reducing the severity of psychosis, Alzheimer's disease, pain, or Parkinson's disease.

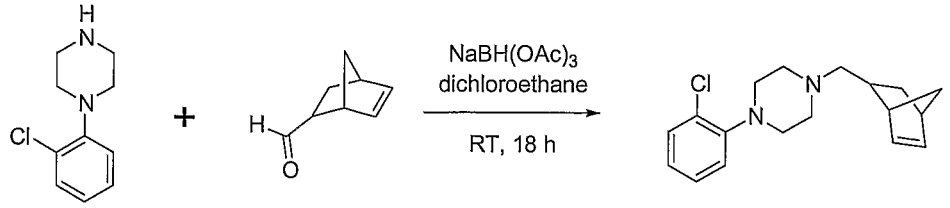
[086] In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

[087] All references cited above are incorporated herein by reference.

[088] Other embodiments of the compounds of formulae (I, IA, II, and III) are shown below. The following examples are illustrative of the compounds of formula (I, IA, II, and III) and are not meant to be limiting.

EXAMPLES

Example 1: Synthesis of 1-Bicyclo[2.2.1]hept-5-en-2-ylmethyl-4-(2-chloro-phenyl)-piperazine.

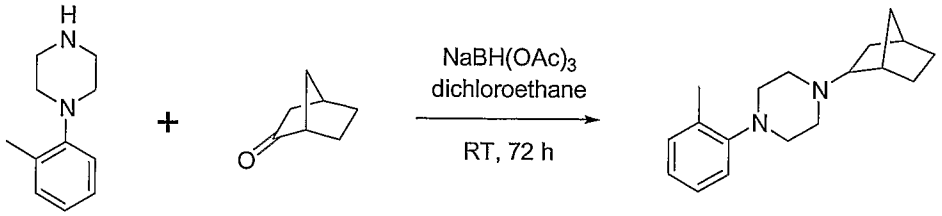


[089] 1-(2-Chloro-phenyl)-piperazine (4.0 g, 20.34 mmol) was dissolved in 80 mL anhydrous 1,2-dichloroethane (DCE) in a 250 mL flask, followed by the addition of 2.48 g (20.34 mmol) of 5-norbornene-2-carboxaldehyde and 6.05 g (28.47 mmol, 1.4 eq) of sodium triacetoxyborohydride [NaBH(OAc)3]. The flask was flushed with nitrogen and allowed to stir for 18 h. The reaction was diluted with 0.1 N NaOH and the product extracted into dichloromethane (3 × 100 mL). The dichloromethane was washed with 10% saturated sodium bicarbonate, brine, dried over Na_2SO_4, and concentrated to form a colorless oil. The residue was brought up in 30 mL anhydrous diethyl ether and the product precipitated as the HCl salt with the addition of 10.2 mL HCl in ether (2.0 M solution in ether, 20.4 mmol). The white precipitate was filtered, washed with ether, and then recrystallized from ethyl acetate/methanol to yield the product as white crystals.

[090] ^{1}H NMR (400 mHz, DMSO-d_6) δ 10.34 (bs, 1H), 7.45 (dd, J = 7.9 Hz, 1.4 Hz, 1H), 7.35 (dt, J = 7.9 Hz, 1.4 Hz, 1H), 7.21 (dd, J = 8.1 Hz, 1.4 Hz, 1H), 7.11 (dt, J = 7.8 Hz, 1.4 Hz, 1H), 6.24 (m, 0.8H), 6.14 (m, 0.4H), 6.07 (m, 0.8H), 3.59 (m, 2H), 3.38 (m, 2H), 3.11-3.30 (m, 4.5H), 2.90-3.05 (m, 1.5H), 2.75-2.90 (m, 2H), 2.54 (m, 0.8H, obscured by DMSO), 2.00 (m, 0.8H), 1.80 (m, 0.2H), 1.2-1.37 (m, 2.5H), 0.71 (m, 0.8H);

[091] LC/MS retention time (10-99% CH_3CN/0.085% TFA gradient over 5 min): 2.39 min; Theoretical $(M+H)^+$ m/z = 303.2; Found 303.2.

Example 2: Synthesis of 1-Bicyclo[2.2.1]hept-2-yl-4-o-tolyl-piperazine.

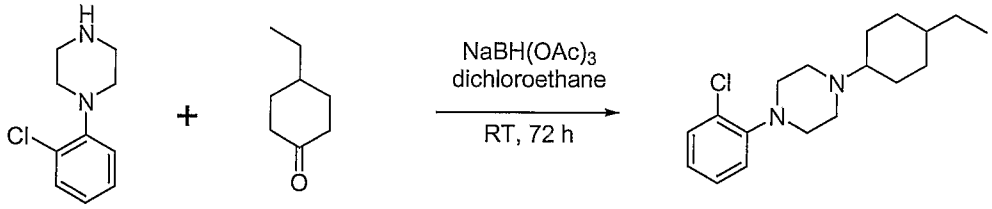


[092] 1-(2-Methyl-phenyl)-piperazine (1.76 g, 10.0 mmol) was dissolved in 20 mL anhydrous 1,2-dichloroethane (DCE) in a 100 mL flask, followed by the addition of 1.10 g (10.0 mmol) of norcamphor, 1.15 mL glacial acetic acid (20 mmol), and 2.97 g (14.0 mmol) of sodium triacetoxyborohydride [$NaBH(OAc)_3$]. The flask was flushed with nitrogen and allowed to stir for 72 h at room temperature. The reaction was diluted with 20% saturated sodium bicarbonate and the product extracted into dichloromethane (3 × 100 mL). The dichloromethane was washed brine, dried over Na_2SO_4, and concentrated to form a colorless oil. The residue was brought up in 30 mL anhydrous diethyl ether and clarified with 1 mL anhydrous ethanol. The product was precipitated as the HCl salt with the addition of 4.9 mL HCl in ether (2.0 M solution in ether, 9.8 mmol). The white precipitate was filtered, washed with ether, and dried to yield the product as a white powder.

[093] ^1H NMR (400 mHz, DMSO-d_6) δ 10.50 (bs, 1H), 7.17-7.21 (m, 2H), 6.99-7.04 (m, 2H), 3.40-3.50 (m, 4H), 3.18-3.32 (m, 2H), 3.05-3.16 (m, 3H), 2.58 (m, 1H), 2.27 (m, 1H), 2.25 (m, 3H), 1.90-1.96 (m, 2H), 1.49-1.60 (m, 3H), 1.29-1.45 (m, 3H);

[094] LC/MS retention time (10-99% CH_3CN/0.085% TFA gradient over 5 min): 2.10 min; Theoretical $(M+H)^+$ m/z = 271.4; Found 271.4.

Example 3: Synthesis of 1-(2-Chloro-phenyl)-4-(4-ethyl-cyclohexyl)-piperazine



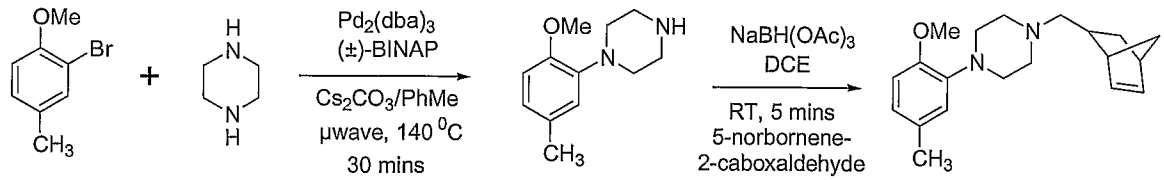
[095] 2-chlorophenylpiperazine (140 mg, 0.713 mmol) and 4-ethylcyclohexanone (100 mg, 0.792 mmol) were mixed in 1,2-dichloroethane (4 mL) and then treated with sodium

triacetoxyborohydride (218 mg, 1.03 mmol) and glacial acetic acid (43 mg, 0.713 mmol). The mixture was stirred under N_2 at room temperature for 18 h. The reaction was quenched through the addition of 1.0 N NaOH (10 mL), and the product extracted in to methylene chloride (2 × 100 mL). The methylene chloride was washed with brine (25 mL), dried over Na_2SO_4, and filtered. The solvent was evaporated to give the crude free base as a colorless oil. The product was dissolved in anhydrous diethyl ether and treated with ethereal HCl (1 eq) to give the HCl salt. Recrystallization from ethyl acetate/methanol provided the product as white crystals.

[096] ^{1}H NMR (HCl salt, d_6-DMSO) δ 10.35 (bs, 1H), 7.46 (dd, 1H), 7.35 (dt, 1H), 7.21 (dd, 1H), 7.11 (dt, 1H), 3.60 (d, 2H), 3.43 (d, 2H), 3.11-3.24 (m, 5H), 1.35-2.0 (m, 11H), 0.86 (t, 3H);

[097] LC/MS retention time (10-99% CH_3CN/0.05% TFA gradient over 5 min): 2.75 min. Theoretical $(M+H)^+$ m/z = 307.2; Found 307.2.

Example 4: Synthesis of 1-Bicyclo[2.2.1]hept-5-en-2-ylmethyl-4-(2-methoxy-5-methyl-phenyl)-piperazine.



[098] 15 mg (0.016 mmol, 0.027 eq) Tris(dibenzylidene-acetone)dipalladium (0) (Pd_2dba_3), 27 mg (0.043 mmol, 0.072 eq) racemic-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl [(±)-BINAP] and 450 mg (1.38 mmol, 2.3 eq) cesium carbonate were combined in a microwave vial. 1.5 mL anhydrous toluene was added, followed by 121 mg (0.60 mmol, 1.0 eq) 2-bromo-4-methylanisole and 207 mg (2.40 mmol, 4.0 eq) piperazine. The vial was flushed with

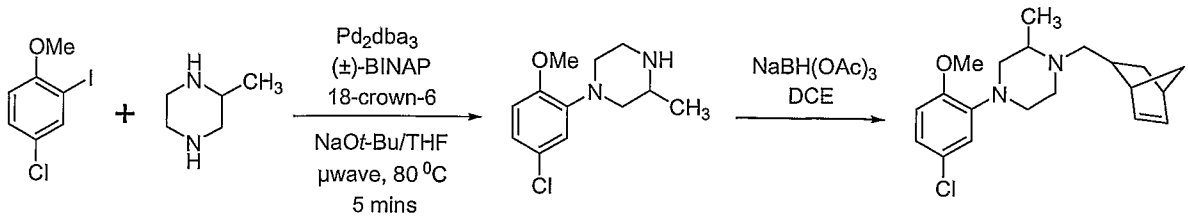
nitrogen prior to being microwaved at 140 ^{0}C for 30 minutes. The reaction mixture was diluted with 3.0 mL DMSO:methanol (1:1), filtered and purified by reverse-phase HPLC (2-99% CH_3CN in 0.085% TFA (aq), 50 mL/min, 3 x 1.5 mL injected). Yield = 83 mg (43%) of 1-(2-Methoxy-5-methyl-phenyl)-piperazine as a pale yellow oil (isolated as the mono-TFA salt);

[099] ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.97 (br s, 2H), 6.85 (d, J = 8.2 Hz, 1H), 6.80 (dd, J = 8.2 Hz, 1.3 Hz, 1H), 6.74 (d, J = 1.7 Hz, 1H), 3.75 (s, 3H), 3.23 (br m, 4H), 3.14 (br m, 4H), 2.22 (s, 3H); LC/MS retention time (10-99% CH_3CN/0.05% TFA gradient over 5 min): 1.58 min; Theoretical $(M+H)^+$ m/z = 207.1; Found 207.2.

[0100] 32 mg (0.10 mmol, 1.0 eq) of 1-(2-Methoxy-5-methyl-phenyl)-piperazine (as the mono-TFA salt) was suspended in 1.0 mL anhydrous 1,2-dichloroethane (DCE) and treated with 1.0 eq (10 mg) triethylamine. 1.0 eq (12 mg) 5-norbornene-2-carboxaldehyde was added, followed by 1.4 eq (30 mg) sodium triacetoxyborohydride [$NaBH(OAc)_3$]. The reaction was stirred at room temperature for 5 minutes, then quenched with 1.0 mL DMSO:methanol (1:1). The reaction mixture was filtered and purified by reverse-phase HPLC (2-99% CH_3CN in 0.085% TFA (aq), 50 mL/min, 2.0 mL injected). Yield = 30 mg (70%) (isolated as the mono-TFA salt);

[0101] ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.73 (br s, 1H), 6.86 (d, J = 8.2 Hz, 1H), 6.81 (dd, J = 8.2 Hz, 1.2 Hz, 1H), 6.73 (d, J = 1.7 Hz, 1H), 6.25 (m, 0.8H), 6.15 (m, 0.2H), 6.04 (m, 0.8H), 5.92 (m, 0.2H), 3.75 (s, 3H), 3.58 (m, 2H), 3.48 (m, 2H), 3.18 (br m, 2H), 2.95 (br m, 4H), 2.80 (m, 2H), 2.23 (s, 3H), 2.00 (m, 0.8H), 1.78 (m, 0.4H), 1.35 (m, 1.4H), 1.27 (m, 1.6H), 0.67 (m, 0.8H); LC/MS retention time (10-99% CH_3CN/0.05% TFA gradient over 5 min): 2.16 min; Theoretical $(M+H)^+$ m/z = 313.2; Found 313.2.

Example 5: Synthesis of 1-Bicyclo[2.2.1]hept-5-en-2-ylmethyl-4-(5-chloro-2-methoxy-phenyl)-2-methyl-piperazine.



[0102] 10 mg (0.010 eq) $Pd_2dba_3 \cdot CHCl_3$, 9.0 mg (0.015 eq) racemic BINAP, 135 mg (1.4 eq) NaOt-Bu, 370 mg (1.4 eq) 18-crown-6 ether and 1.0 mL anhydrous tetrahydrofuran were combined in a microwave vial. 268 mg (1.0 eq, 1.0 mmol) 4-Chloro-2-iodoanisole was added, followed by 120 mg (1.2 eq) racemic 2-methylpiperazine. The vial was flushed with nitrogen prior to being microwaved at 80°C for 5 minutes. The reaction mixture was diluted with 1.0 mL DMSO:methanol (1:1) and centrifuged (4,000 rpm, RT, 8 min). The supernatant was filtered and purified by reverse-phase HPLC (2-99% CH_3CN in 0.085% TFA (aq), 50 mL/min, 2.0 mL injected). Yield = 50 mg (14%) of a light brown oil (isolated as the mono-TFA salt);

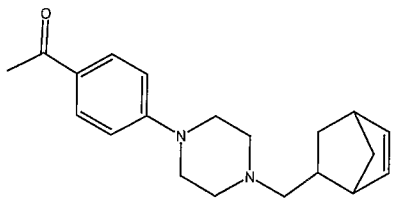
[0103] ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.14 (br d, J = 8.6 Hz, 1H), 8.71 (br d, J = 7.8 Hz, 1H), 7.10 (dd, J = 8.7 Hz, 2.4 Hz, 1H), 6.99 (d, J = 8.8 Hz, 1H), 6.94 (d, J = 2.5 Hz, 1H), 3.80 (s, 3H), 3.42 (br m, 4H), 3.17 (m, 1H), 2.85 (m, 1H), 2.72 (m, 1H), 1.25 (d, J = 6.4 Hz, 3H); LC/MS retention time (10-99% CH_3CN/0.05% TFA gradient over 5 min): 1.82 min; Theoretical $(M+H)^+$ m/z = 241.1; Found 241.2.

[0104] 48 mg (0.2 mmol) of 1-(5-Chloro-2-methoxy-phenyl)-3-methyl-piperazine was dissolved in 1.5 mL anhydrous 1,2-dichloroethane. 5-Norbornene-2-carboxaldehyde (25 mg, 0.2 mmol) was added, followed by followed by 63 mg (0.3 mmol) sodium triacetoxyborohydride [$NaBH(OAc)_3$]. The reaction was stirred overnight, then quenched with 1.0 mL DMSO:methanol (1:1). The

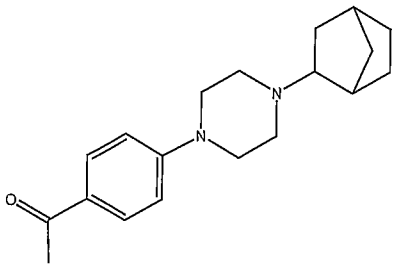
reaction mixture was filtered and purified by reverse-phase HPLC (2-99% CH_3CN in 0.085% TFA (aq), 50 mL/min, 2.0 mL injected), and the product 1-bicyclo[2.2.1]hept-5-en-2-ylmethyl-4-(5-chloro-2-methoxy-phenyl)-2-methyl-piperazine isolated as the mono-TFA salt. Theoretical $(M+H)^+$ m/z = 347.9; Found 348.0.

Example 6:

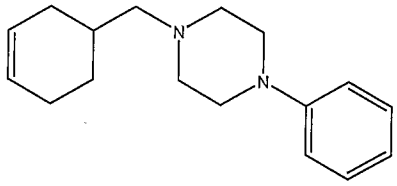
[0105] Specific Compounds of Formulae I, IA, II, and III (I-1 through I-188) may be produced by methods described above using modifications know to those skilled in the art.



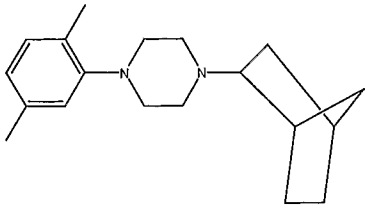
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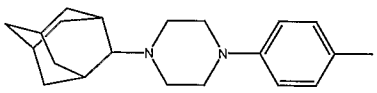
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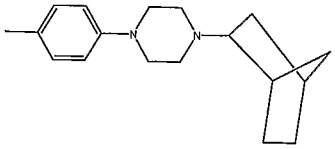
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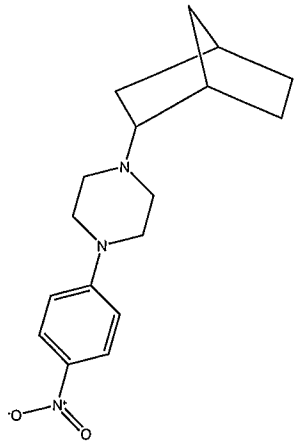
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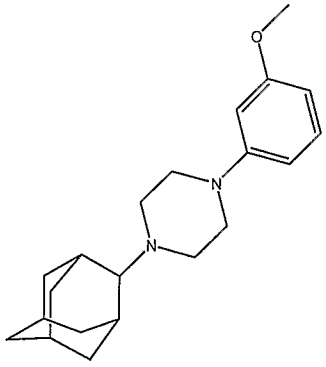
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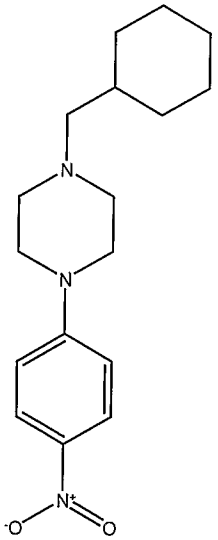
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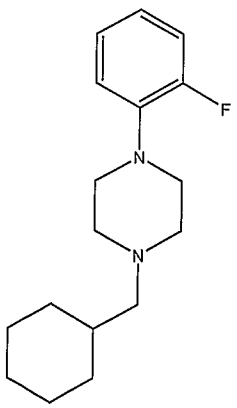
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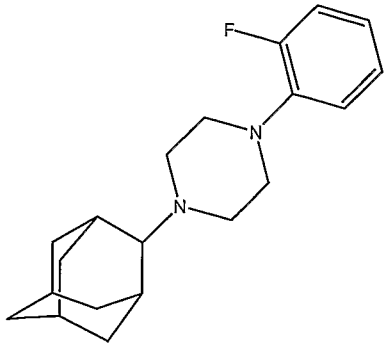
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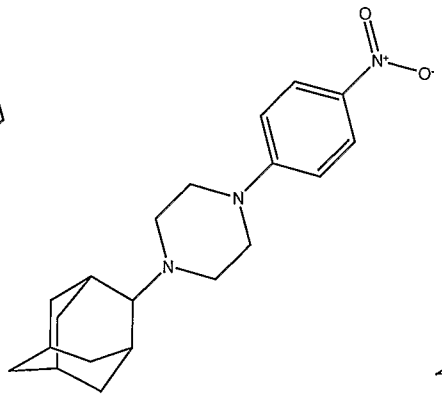
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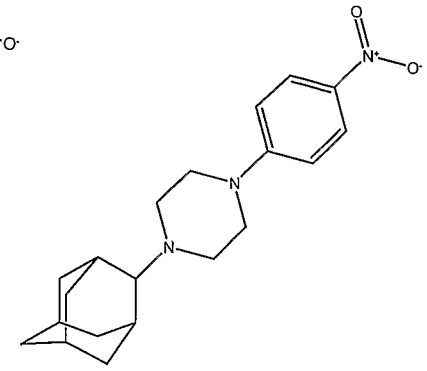
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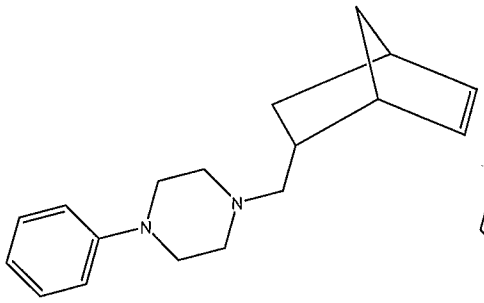
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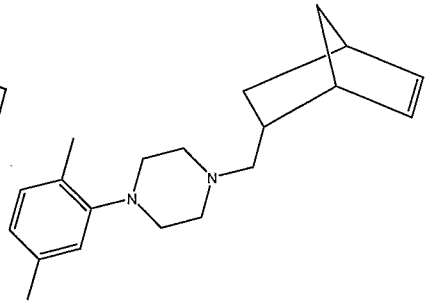
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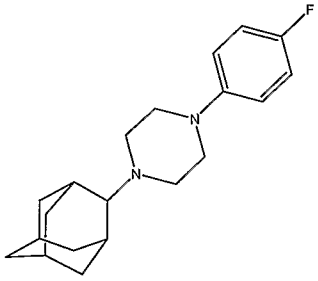
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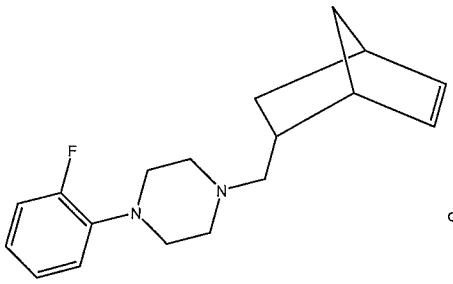
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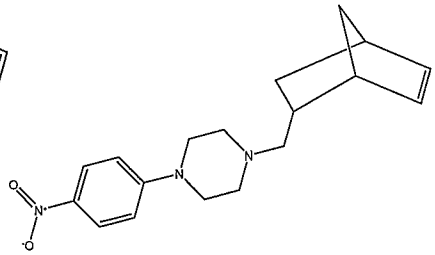
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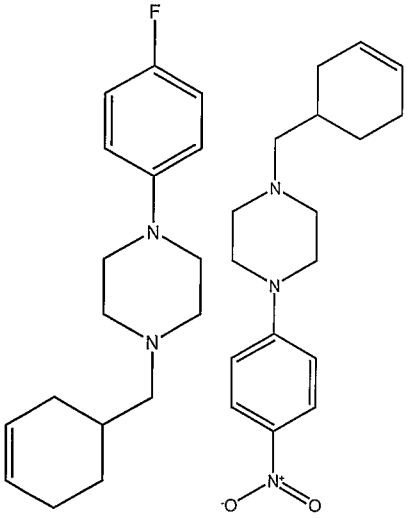
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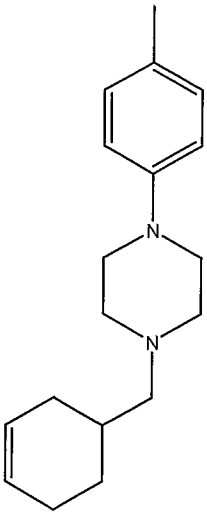


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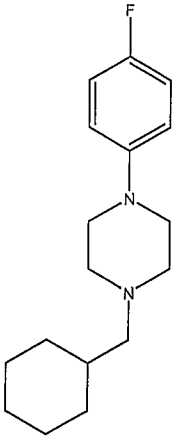


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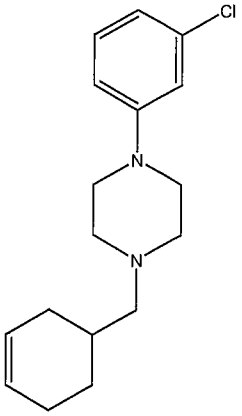
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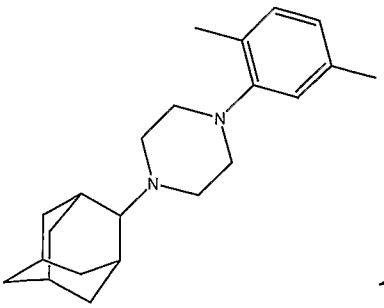
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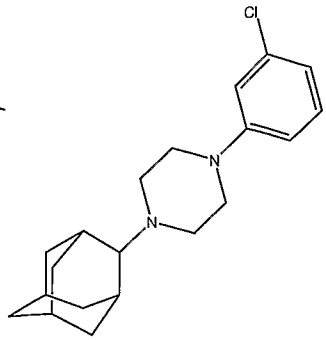
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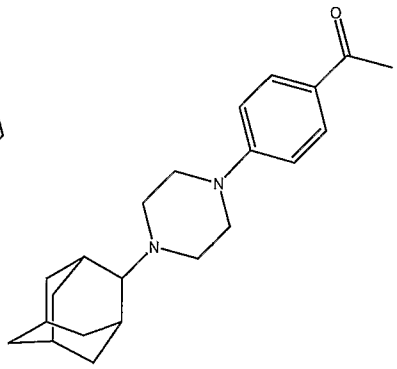
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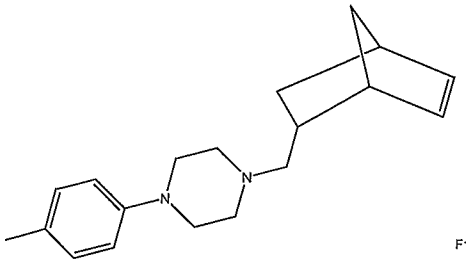
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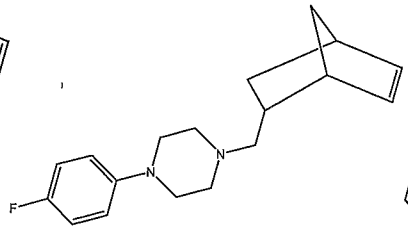
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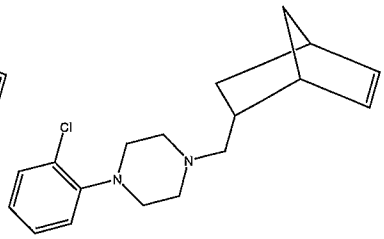
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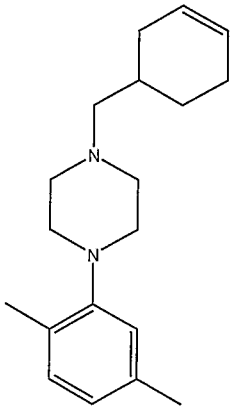
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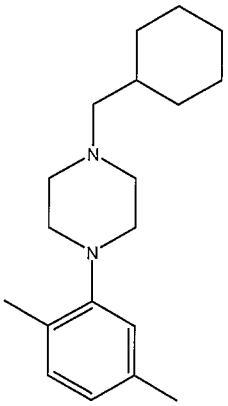
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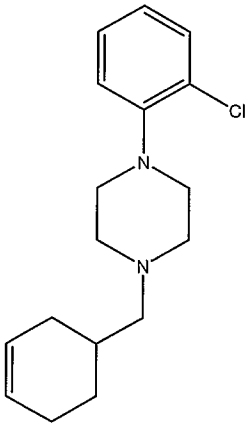
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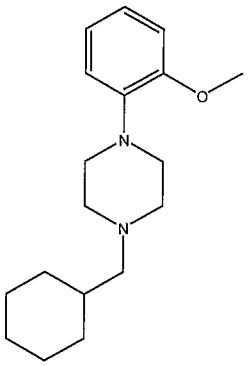
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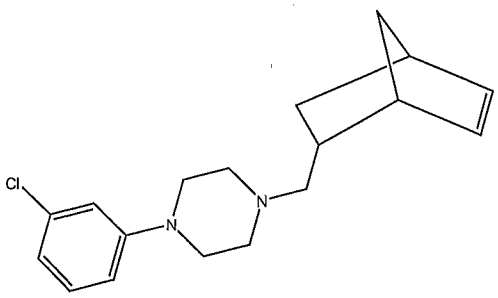
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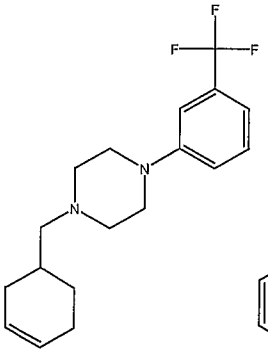
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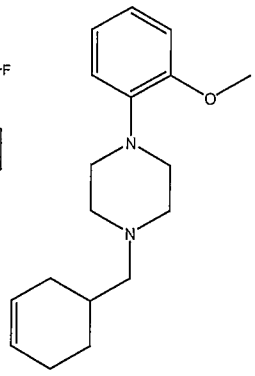
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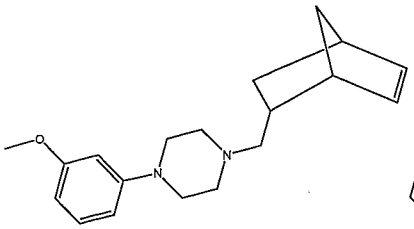
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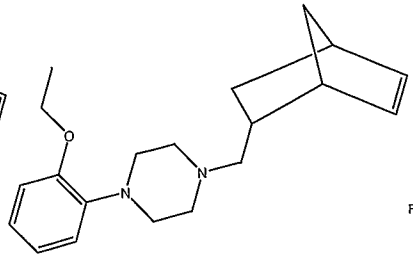
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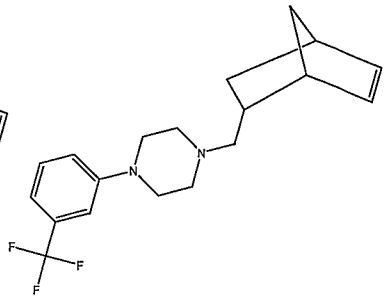
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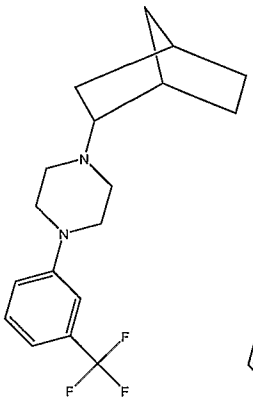
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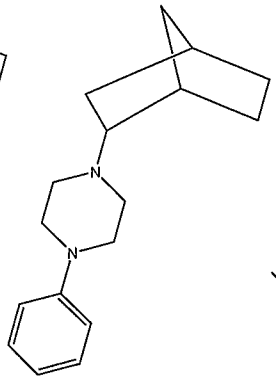
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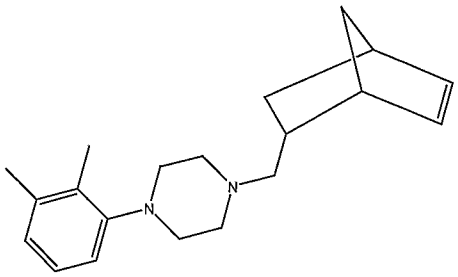
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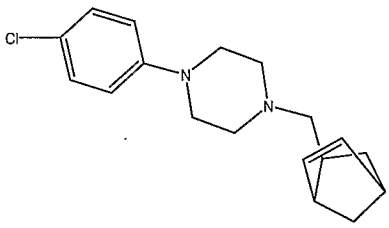
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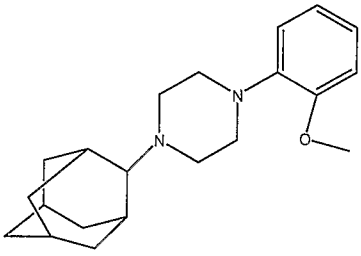
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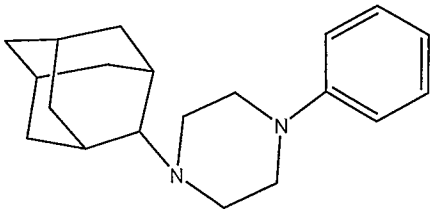
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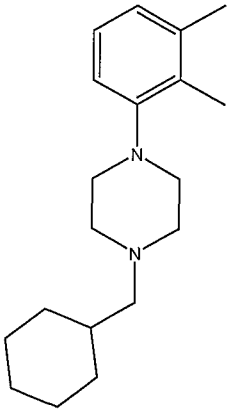
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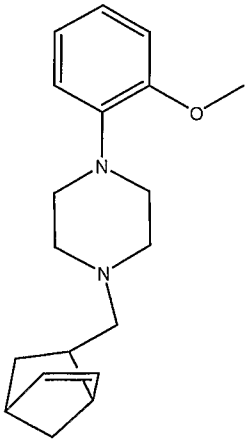
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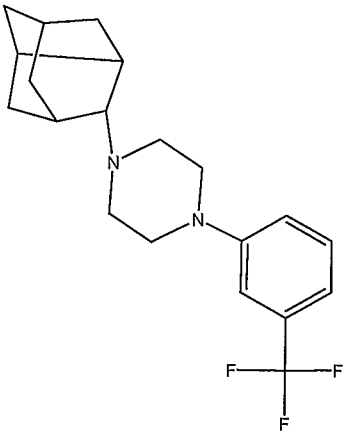
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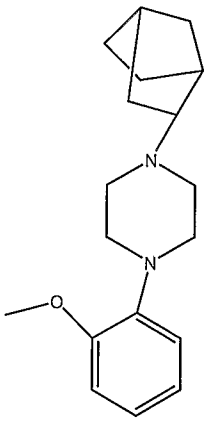
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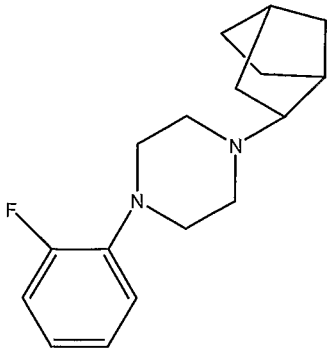
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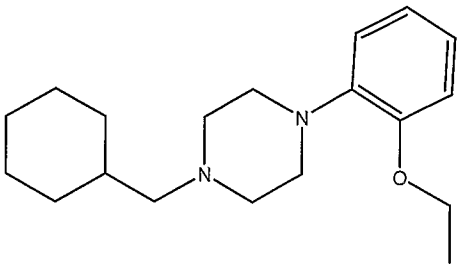
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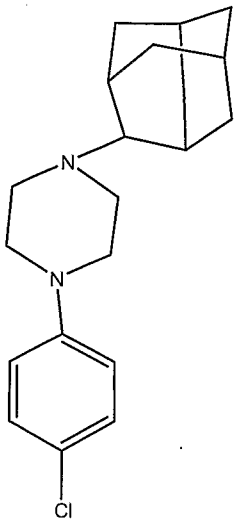
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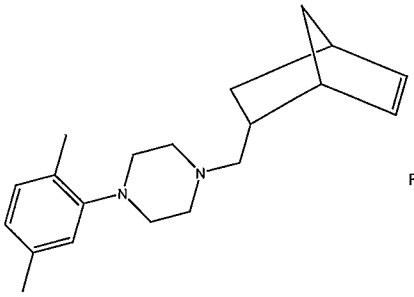
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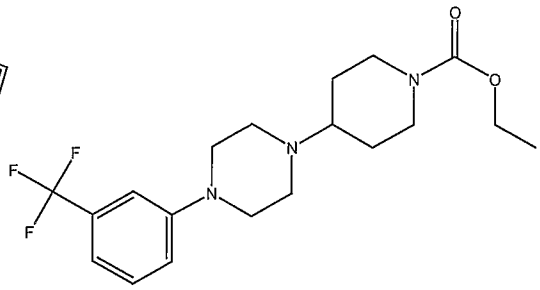
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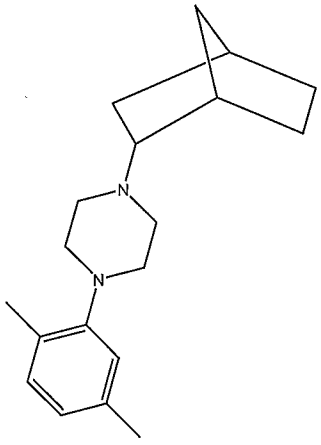
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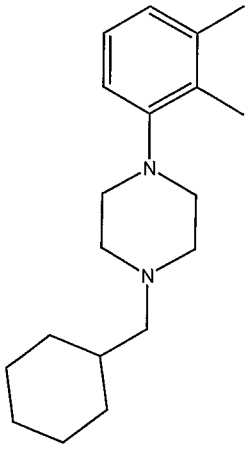
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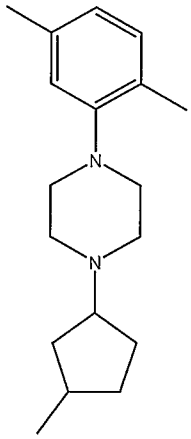
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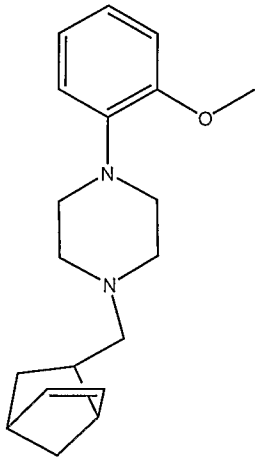
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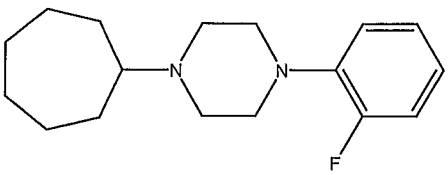
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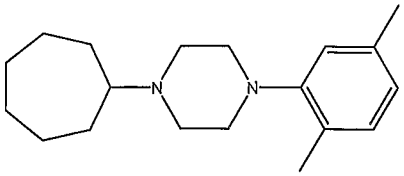
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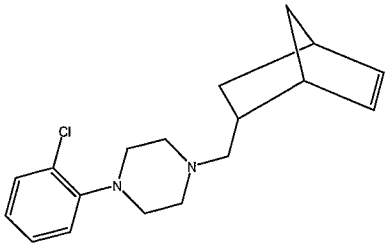
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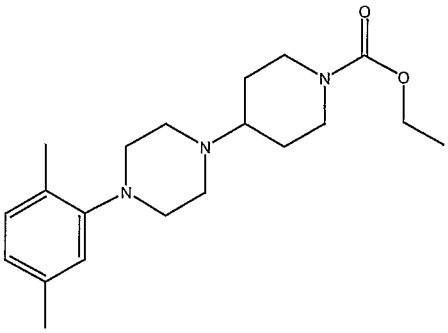
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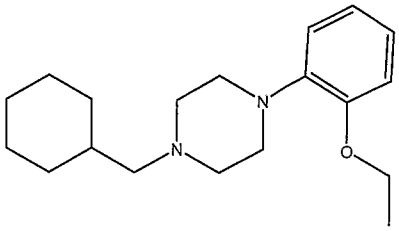
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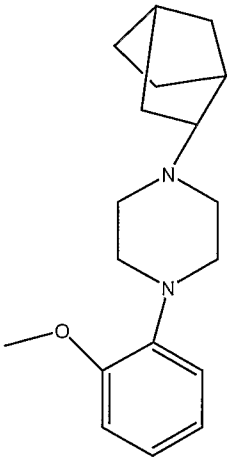
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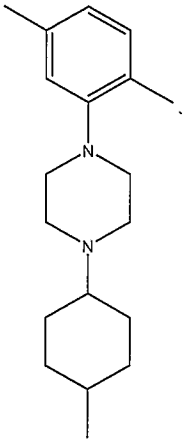
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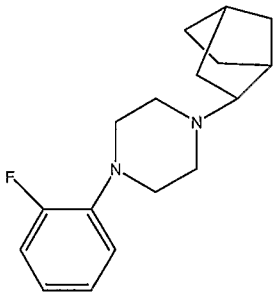
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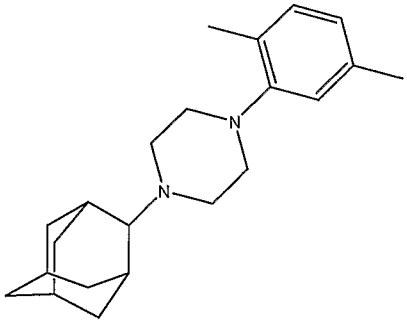
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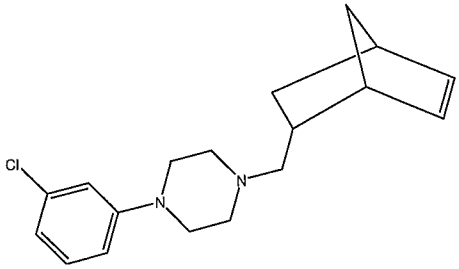
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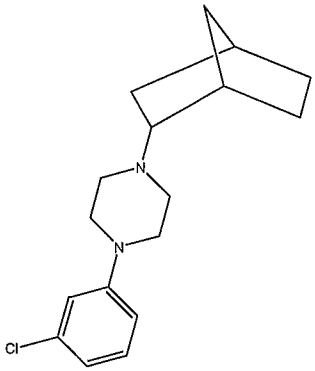
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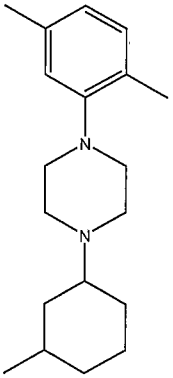
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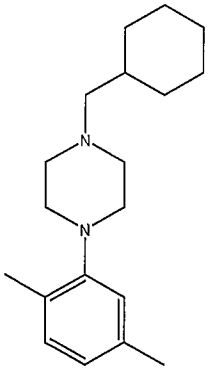
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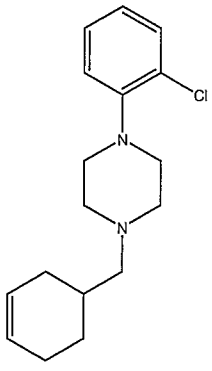
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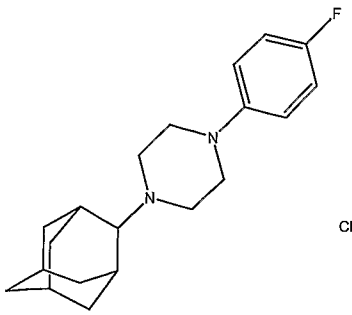
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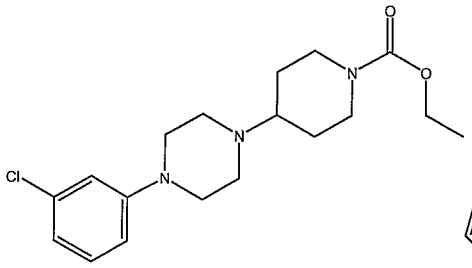
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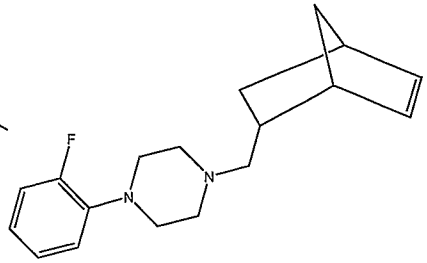
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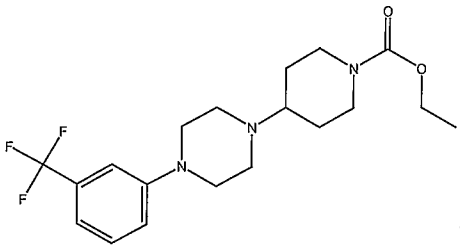
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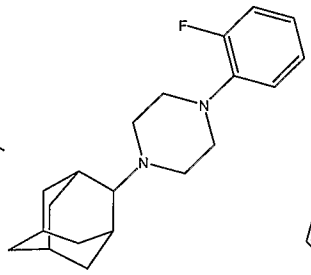
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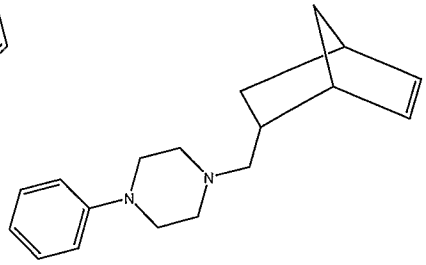
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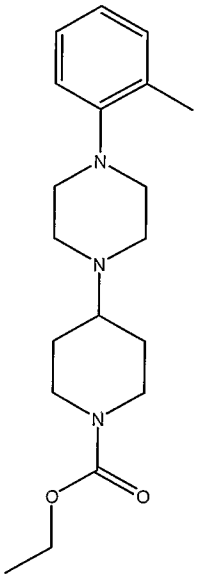
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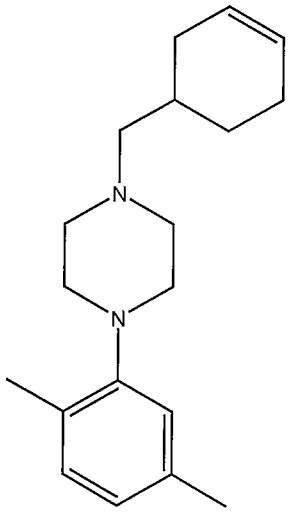
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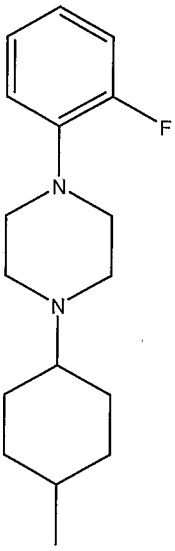
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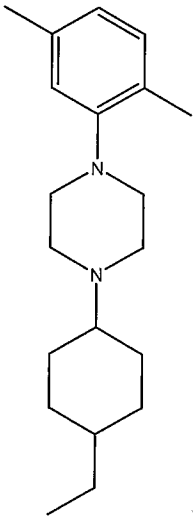
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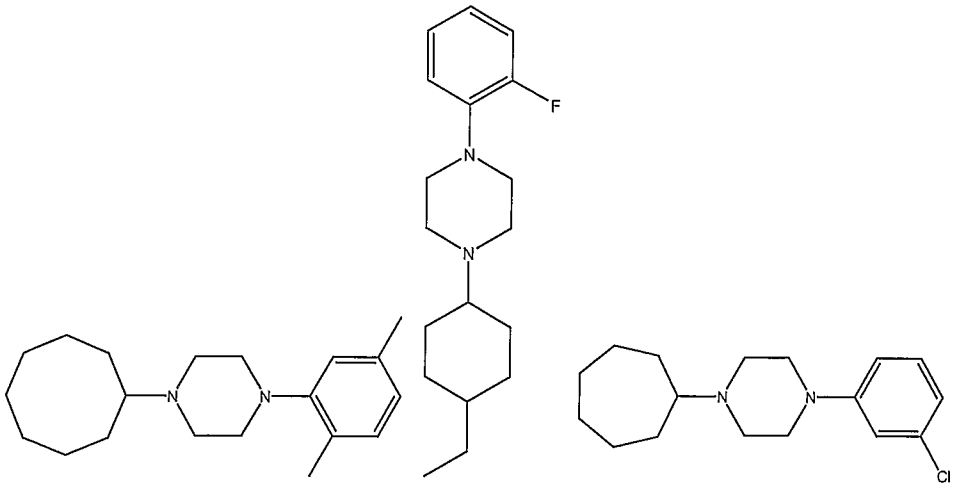
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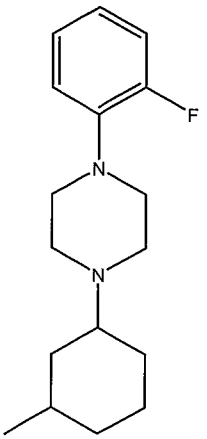
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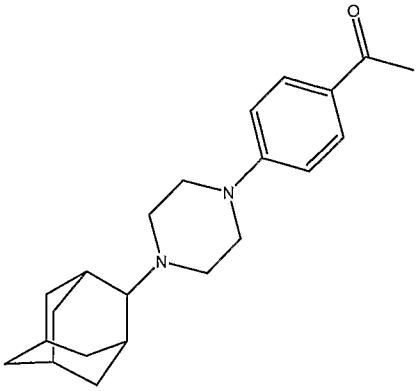
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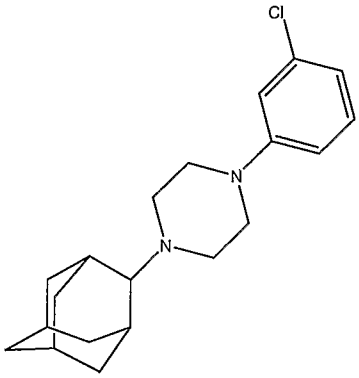
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86



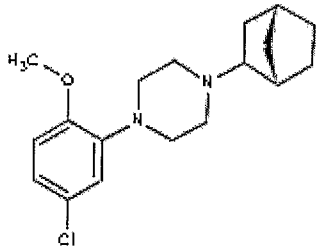
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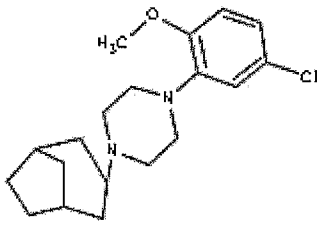
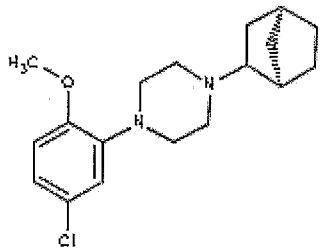


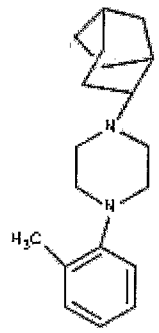
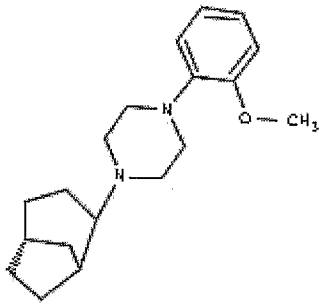
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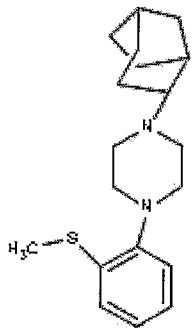
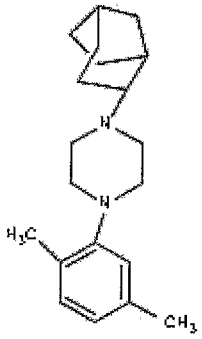
Example 7

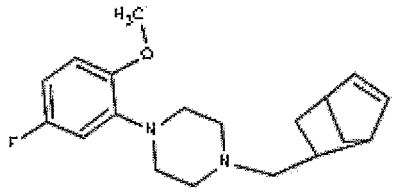
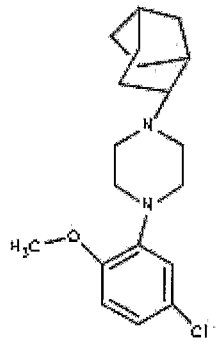
[0106] Additional Compounds of formulae I, IA, II, and III (89 - I-294) were produced by methods described above using modifications know to those skilled in the art.

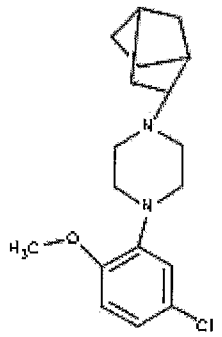
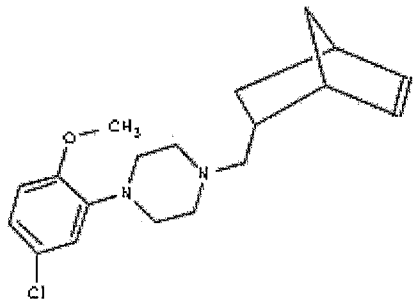
Compound	Cmpd #	LC/MS m/z	LC-RT (min)
	89	321.30	2.27

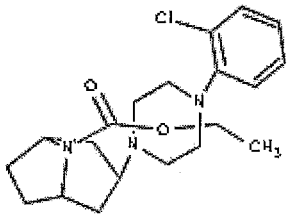
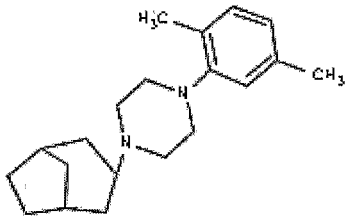
Compound	Cmpd #	LC/MS m/z	LC-RT (min)
	90	335.40	2.25
	91	321.10	2.28

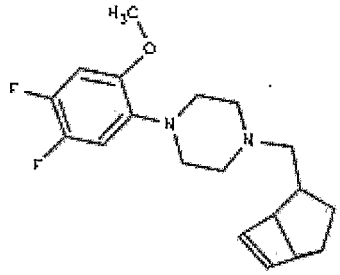
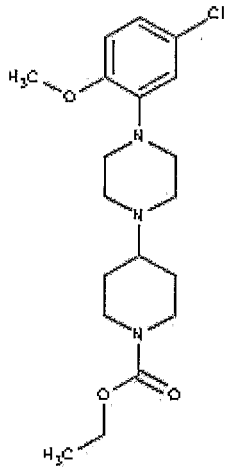
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	92	285.20	2.17
	93	301.20	1.97

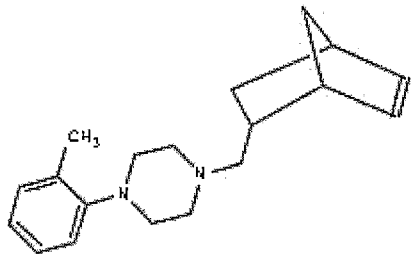
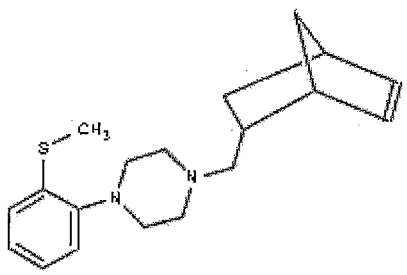
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	94	317.20	2.24
	95	299.20	2.36

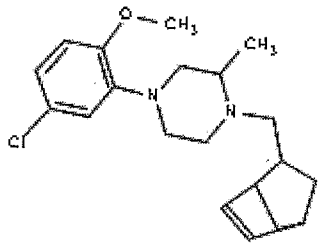
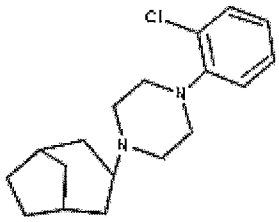
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	96	317.00	2.09
	97	335.40	2.22

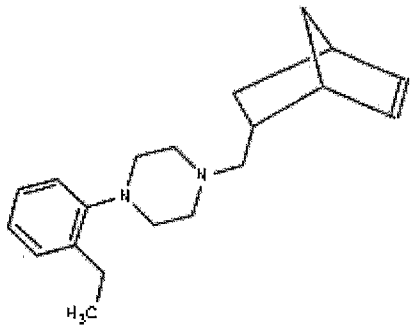
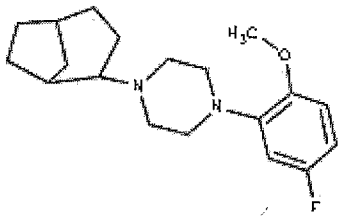
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	98	321.10	2.40
	99	333.30	2.55

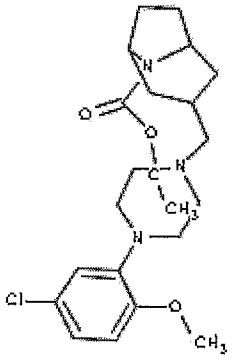
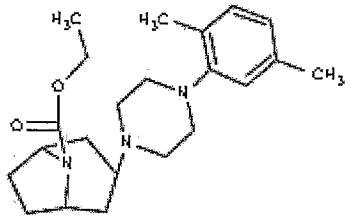
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	100	378.20	2.12
	101	299.20	2.42

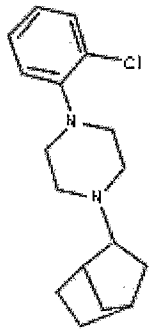
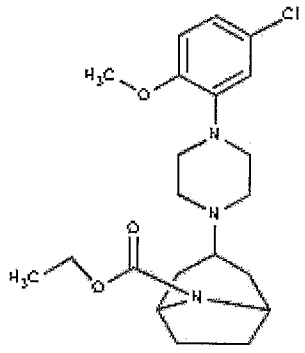
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	103	382.00	2.05

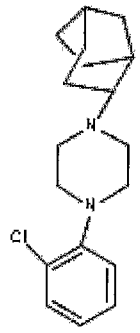
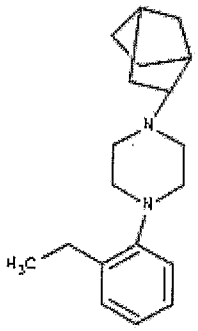
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	104	283.10	2.57
	105	315.20	2.26

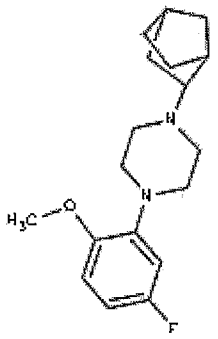
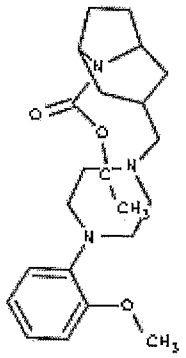
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	106	347.20	2.36
	107	305.20	2.30

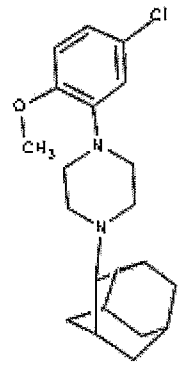
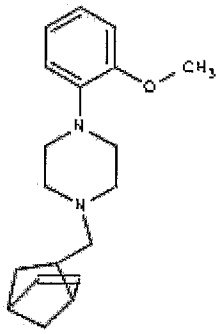
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	109	319.20	2.15

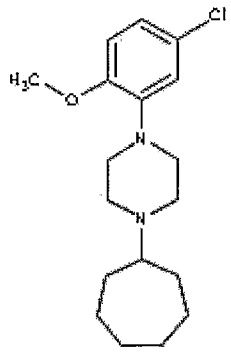
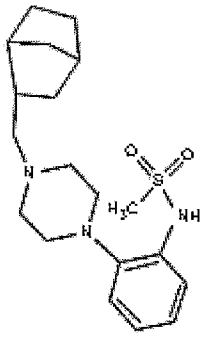
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	110	421.21	2.07
	111	372.20	2.26

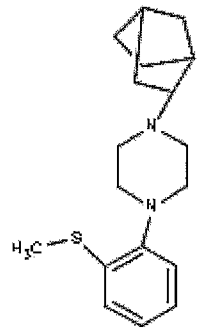
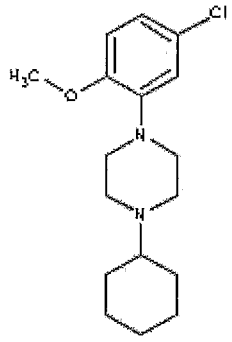
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	112	290.83	2.04
	113	408.50	2.15

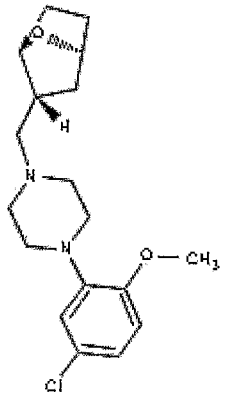
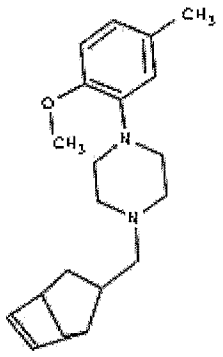
Compound	Cmpd #	LC/MS m/z	LC-RT (min)
	114	305.20	2.19
	115	285.10	2.50

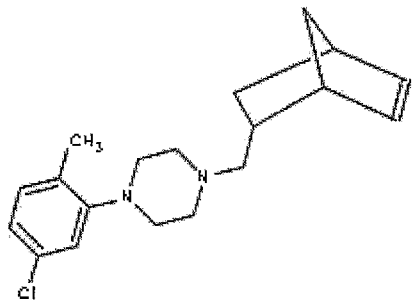
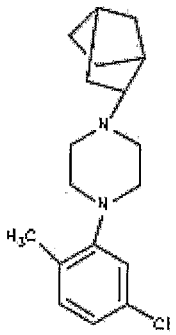
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	117	387.25	1.76

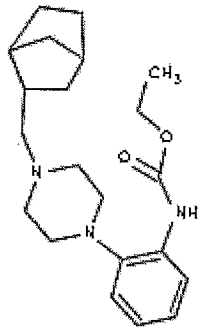
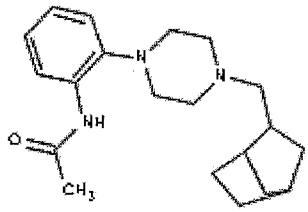
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	118	361.20	2.39
	119	299.20	2.05

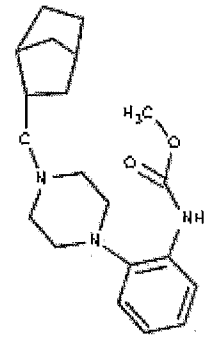
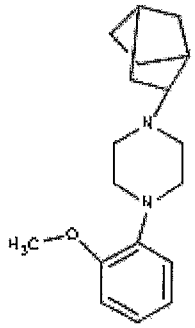
Compound	Cmpd #	LC/MS m/z	LC-RT (min)
	120	323.50	3.12
	121	364.40	2.08

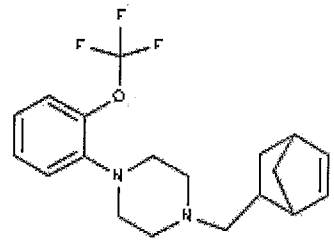
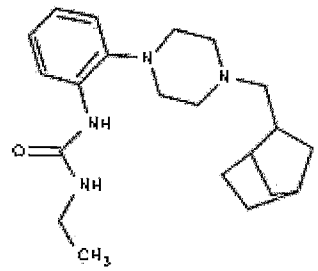
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	122	303.20	2.12
	123	309.30	3.06

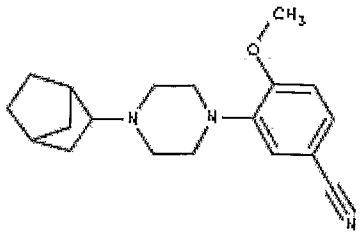
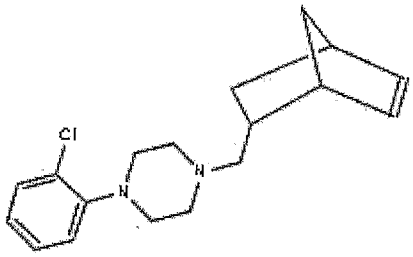
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	124	336.16	1.79
	125	313.20	2.16

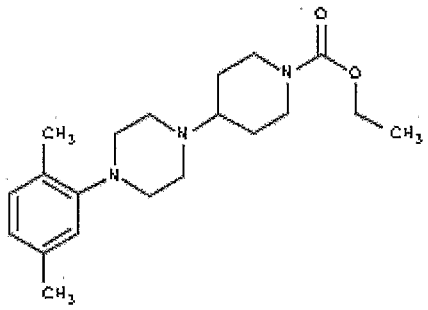
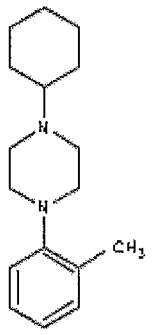
Compound	Cmpd #	LC/MS m/z	LC-RT (min)
	126	317.00	2.45
	127	305.32	2.30

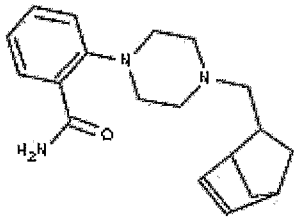
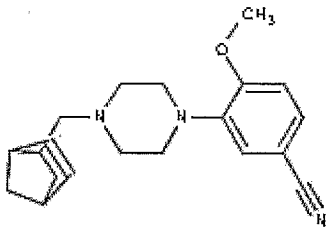
Compound	Cmpd #	LC/MS m/z	LC-RT (min)
	128	358.20	2.35
	129	328.20	1.85

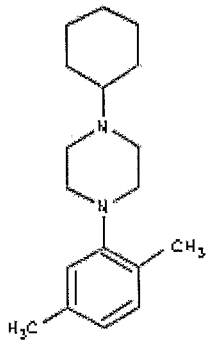
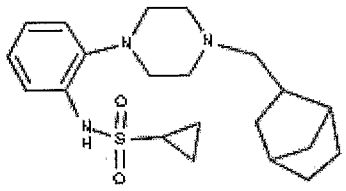
Compound	Cmpd #	LC/MS m/z	LC-RT (min)
	130	344.20	2.15
	131	287.00	2.20

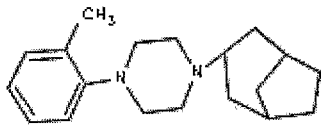
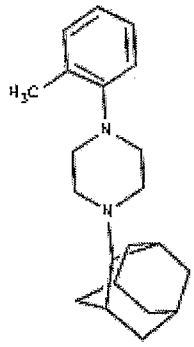
Compound	Cmpd #	LC/MS m/z	LC-RT (min)
	132	353.20	2.50
	134	357.20	2.02

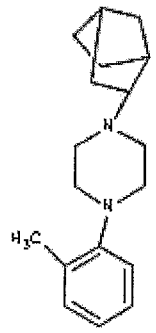
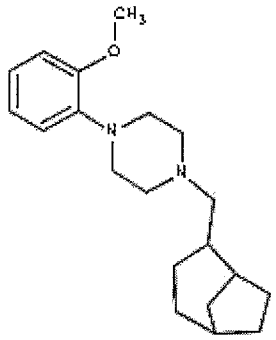
Compound	Cmpd #	LC/MS m/z	LC-RT (min)
	135	312.20	1.86
	136	303.50	2.35

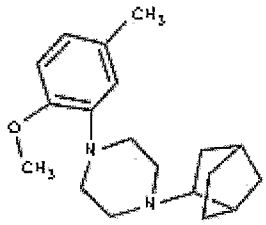
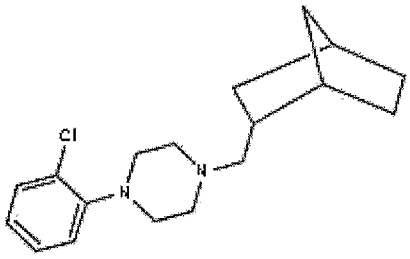
Compound	Cmpd #	LC/MS m/z	LC-RT (min)
	137		
	138	259.20	2.06

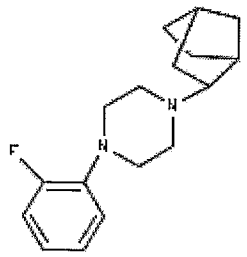
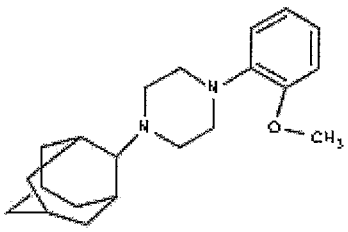
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	139	312.20	1.55
	140	324.20	2.03

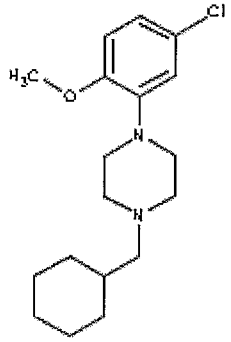
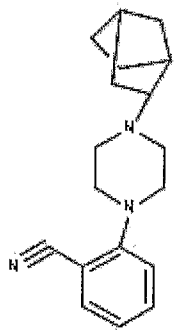
Compound	Cmpd #	LC/MS m/z	LC-RT (min)
	141	273.20	2.23
	142	390.40	2.30

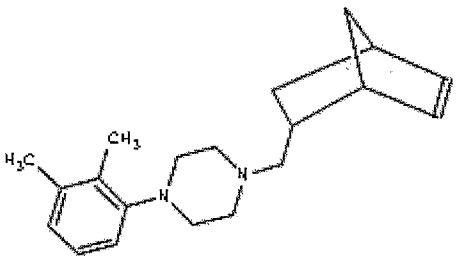
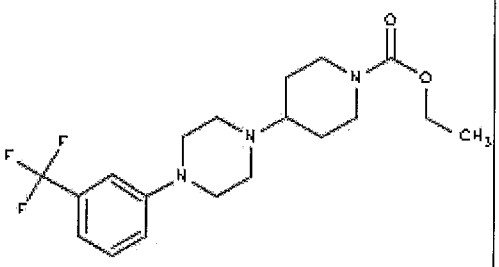
Compound	Cmpd #	LC/MS m/z	LC-RT (min)
	143	285.20	2.22
	144	311.20	2.37

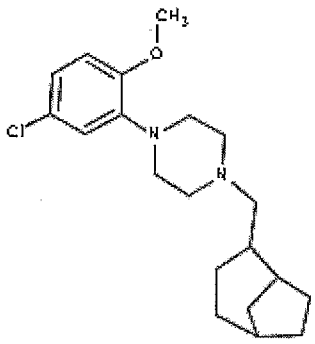
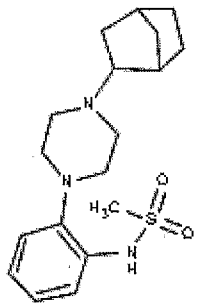
Compound	Cmpd #	LC/MS m/z	LC-RT (min)
	145	272.10	2.35,2.10
	146	314.20	2.11

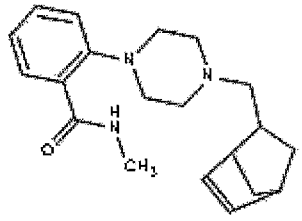
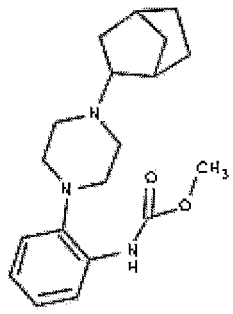
Compound	Cmpd #	LC/MS m/z	LC-RT (min)
	147	301.20	2.01
	148	305.30	2.58

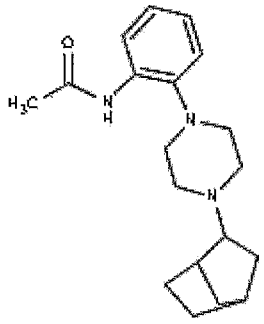
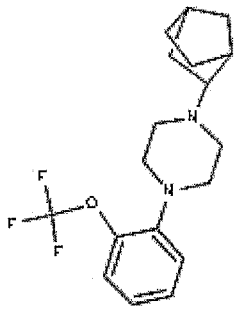
Compound	Cmpd #	LC/MS m/z	LC-RT (min)
	149		
	151	327.20	2.14

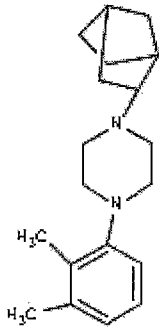
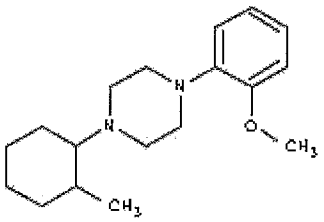
Compound	Cmpd #	LC/MS m/z	LC-RT (min)
	152	323.30	3.09
	153	282.30	2.09

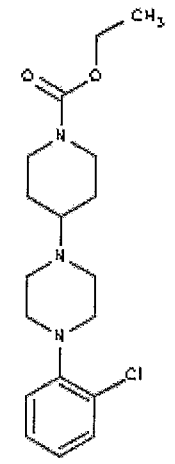
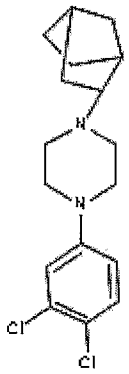
Compound	Cmpd #	LC/MS m/z	LC-RT (min)
	155	297.40	2.41
	156		

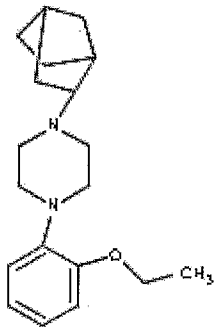
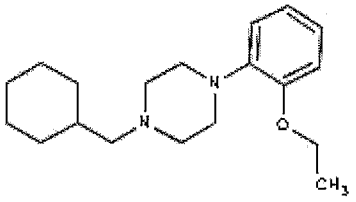
Compound	Cmpd #	LC/MS m/z	LC-RT (min)
	157	348.20	2.66
	158	350.20	1.82

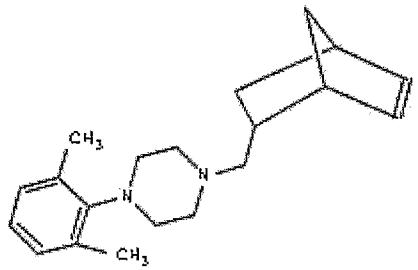
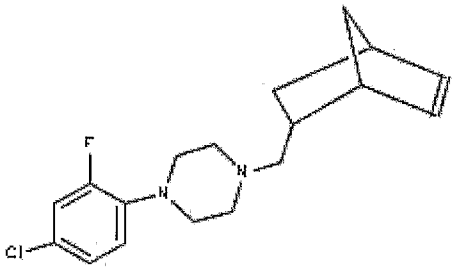
Compound	Cmpd #	LC/MS m/z	LC-RT (min)
	160	326.20	1.64
	161	330.40	1.92

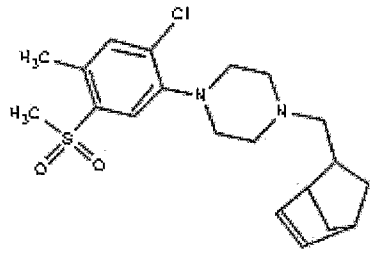
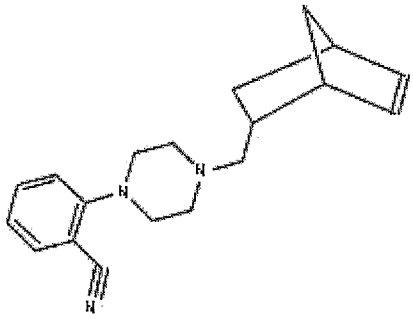
Compound	Cmpd #	LC/MS m/z	LC-RT (min)
	162	314.20	1.52
	163	341.00	2.72

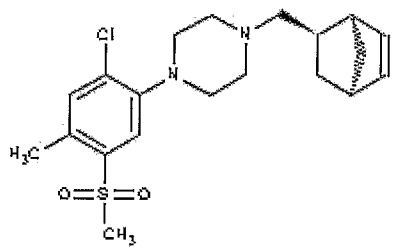
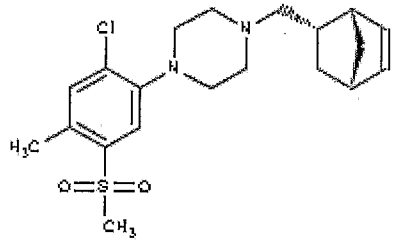
Compound	Cmpd #	LC/MS m/z	LC-RT (min)
	166	285.20	2.26
	167	289.00	1.93

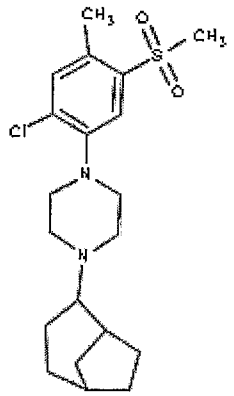
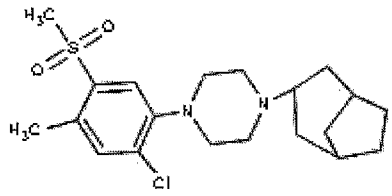
Compound	Cmpd #	LC/MS m/z	LC-RT (min)
	168	352.20	1.99
	169	325.20	2.29

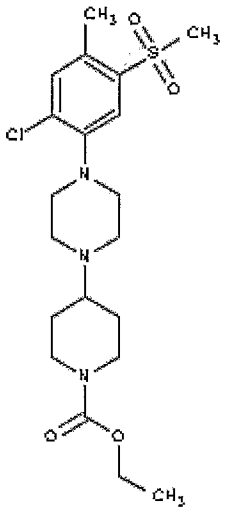
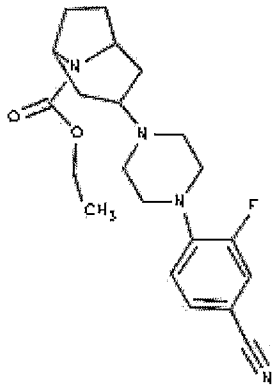
Compound	Cmpd #	LC/MS m/z	LC-RT (min)
	170	301.10	2.25
	172		

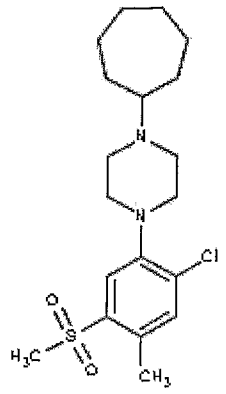
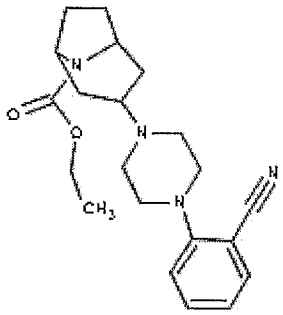
Compound	Cmpd #	LC/MS m/z	LC-RT (min)
	175	297.10	2.64
	176	321.00	2.34

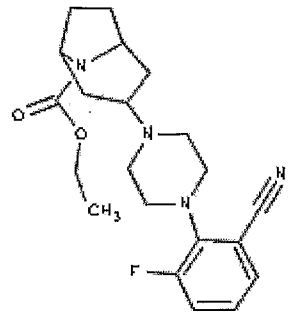
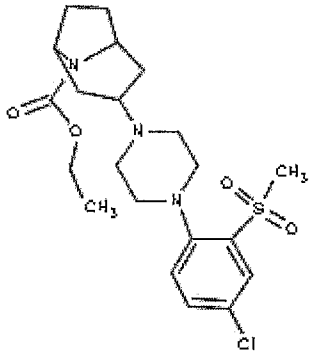
Compound	Cmpd #	LC/MS m/z	LC-RT (min)
	177	395.00	2.35
	178	294.30	2.35

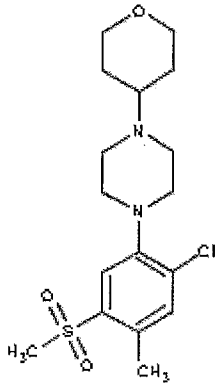
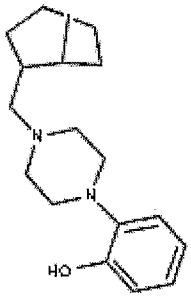
Compound	Cmpd #	LC/MS m/z	LC-RT (min)
	179	395.00	2.36
	180	395.00	2.36

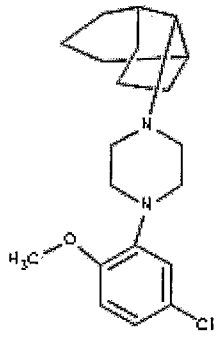
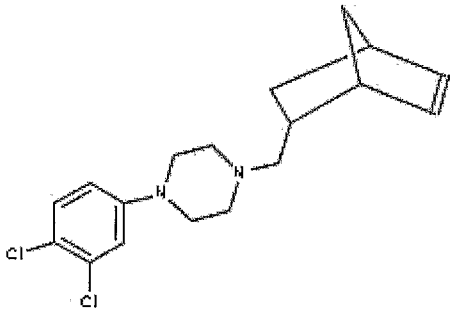
Compound	Cmpd #	LC/MS m/z	LC-RT (min)
	181	397.20	2.29
	182	397.00	2.34

Compound	Cmpd #	LC/MS m/z	LC-RT (min)
	183	444.20	2.14
	184	387.00	2.02

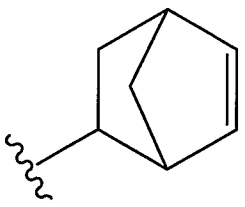
Compound	Cmpd #	LC/MS m/z	LC-RT (min)
	185	385.00	2.35
	186	369.00	2.16

Compound	Cmpd #	LC/MS m/z	LC-RT (min)
	187	387.20	2.14
	188	456.20	2.24

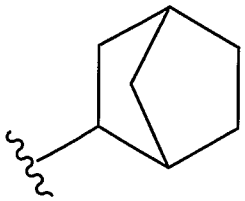
Compound	Cmpd #	LC/MS m/z	LC-RT (min)
	189	373.00	1.83
	190	287.20	1.82

Compound	Cmpd #	LC/MS m/z	LC-RT (min)
	191	349.20	2.30
	192	337.40	2.45

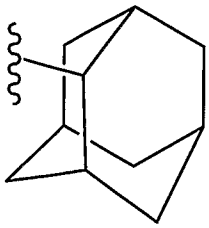
[0107] The A-ring in examples 96, 102, 106, 125, 129, 139, 140, 150, 160, and 177 may also be illustrated as



[0108] The A ring in examples 112, 134, 162, and 190 may also be illustrated as



[0109] The A ring in example 118 may also be illustrated as



Example 8

Functional mobilization of intracellular calcium to determine muscarinic receptor activity

[0110] CHO cells expressing muscarinic receptors (M1 to M5) are grown as monolayers in tissue culture flasks at 37°C in a humidified atmosphere containing 5% CO_2 and passaged every 3-5 days. The growth media is Dulbecco's modified eagles medium (DMEM, Gibco Cat# 12430-054), containing 25 mM Hepes and supplemented with Fetal Bovine Serum (Hyclone, cat# SH30071.03), 0.1 mM of MEM non-essential amino acids (GIBCO, Cat# 11140-050), 1 mM MEM Sodium Pyruvate (GIBCO Cat# 11360-070) and 100 units/ml of Penicillin G and 100 µg/ml of Streptomycin (GIBCO Cat# 15140-122). The recombinant muscarinic receptor cell lines are grown under antibiotic pressure with media containing 25 µg/ml zeocin and 500 µg/ml G418 (M1-CHO), 4 µg/ml puromycin, 50 µg/ml zeocin and 2.5 µg/ml blasticidin (M2 and M4-CHO) or 50 µg/ml zeocin and 4 µg/ml puromycin (M3 and M5-CHO).

[0111] Cells are harvested at 80-90% confluence using Versene (GIBCO Cat# 15040-066), collected by centrifugation and seeded 18-24 hrs prior to running the calcium assay at a density of 5,000-10,000 cells/well in back-walled, clear-bottomed 384-well plates (BD Biocoat, poly-D-lysine, Cat#356663). The day of the experiment, the cells are washed with a plate washer

(Bioteck Instruments, ELX 405) using bath1 buffer (140-mM NaCl, 4.5-mM KCl, 2-mM $CaCl_2$, 1-mM $MgCl_2$, 10-mM Hepes-Na, 10-mM Glucose, pH 7.4, with NaOH) containing 1 mM Probenecid. Next, the calcium dye Fluo-3 (25 µl/well of Fluo-3 AM at 4 µM, Molecular Probes F-1241, in Bath 1 buffer containing 1 mM Probenecid) is added to the 25 µl of Bath 1 remaining in each well after the plate wash and the dye is loaded at 37°C in the tissue culture incubator for 60-90 min. The fluorescent dye is removed using the plate washer with Bath 1 containing 1 mM Probenecid, leaving 25 µl/well of this solution after the wash. Alternatively, cells can be loaded with the calcium indicator from Molecular Devices (Calcium 3 Assay Reagents, Cat # R7181) adding 5 µl of a 5X solution dye in Bath 1 containing 1 mM Probenecid (10 ml per dye flask cat# R7182 to generate a solution 20X) to 20 µl of the same buffer. After loading for 60 min, the experiment can be run without having to remove the dye.

[0112] Compounds are prepared at a 2x fold concentration in a 96-well plate (round bottom, Costar Corning cat# 3656), by reconstituting the pre-spotted compounds in bath 1 containing 1 mM probenecid. The final concentration DMSO is 0.5 %, and the amount of DMSO is normalized across the assay plate. To determine an agonist action of the compounds on muscarinic receptors, the reconstituted compounds are added (25 µl compound/well) to the cell assay plate (containing 25 µl/well) using the multi-channel robotic system of the FLIPR 3 Instrument (Molecular Devices, Sunnyvale, CA). To determine a functional inhibitory action of the compounds on muscarinic receptors, the reconstituted compounds are added (25 µl compound/well) to the assay plate and pre-incubated for 15 min prior to adding 25 µl of Carbachol at 3X the EC80 for each muscarinic subtype. Alternatively, the compounds can be co-applied simultaneously with the agonist. In both assay modes, the fluorescence is recorded for 60 sec (excitation wavelength is 488 nM and emission wavelength 540 nm) using the FLIPR 3 instrument.

[0113] The potency, efficacy and selectivity of the muscarinic compounds were evaluated by screening the compound activity across the whole family (M1 to M5 cells).

[0114] The compounds of the present invention were found to selectively modulate the muscarinic receptors selectively over the other receptor types.

EXAMPLE 9:

β-Lactamase Assay to determine muscarinic receptor activity

[0115] CHO cells expressing muscarinic receptors (M1 to M5) and containing a gene reporter system (β-Lactamase) with transcriptional control mediated by calcium release (NFAT activation). See Zlokarnik, G; Negulescu, P.A.; Knapp, T.E.; Mere, L; Burres, N; Feng, L; Whitney, M; Roemer, K; Tsien, R.Y. Quantitation of transcription and clonal selection of single living cells with β-lactamase as reporter. Science, 1998 Jan 2, 279(5347):84-8. The cells are grown as monolayers in tissue culture flasks at 37°C in a humidified atmosphere containing 5% CO_2 and passaged every 3-5 days. The growth media is Dulbecco's modified eagles medium (DMEM, Gibco Cat# 12430-054), containing 25 mM Hepes and supplemented with 10% Fetal Bovine Serum (Hyclone, cat# SH30071.03), 0.1 mM of MEM non-essential amino acids (GIBCO, Cat# 11140-050), 1 mM MEM Sodium Pyruvate (GIBCO Cat# 11360-070) and 100 units/ml of Penicillin G and 100 µg/ml of Streptomycin (GIBCO Cat# 15140-122). The recombinant muscarinic receptor cell lines are grown under antibiotic pressure with media containing 25 µg/ml zeocin and 500 µg/ml G418 (M1-CHO), 4 µg/ml puromycin, 50 µg/ml zeocin and 2.5 µg/ml blasticidin (M2 and M4-CHO) or 50 µg/ml zeocin and 4 µg/ml puromycin (M3 and M5-CHO).

[0116] Cells are harvested at 80-90% confluence using Accutase (Innovative Cell Technologies, Inc. Cat# AT104),

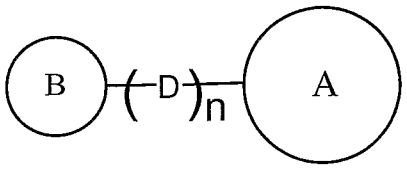
collected by centrifugation and seeded for 2-6 hours at a density of 15,000-20,000 cells/well in black-walled, clear-bottomed 384-well plates (BD Biocoat, poly-D-lysine, Cat#356663). Media is replaced with DMEM + 1% Fetal Bovine Serum and incubated for another 12-18 hrs prior to running the β-Lactamase assay. The day of the experiment, compounds are prepared at a 1x fold concentration in a 96-well plate (round bottom, Costar Corning cat# 3656), by reconstituting the pre-spotted compounds in DMEM + 1% FBS. The final concentration of DMSO is 0.5 %, and the amount of DMSO is normalized across the assay plate. To determine an agonist action of the compounds on muscarinic receptors, the reconstituted compounds are added (25 µl compound/well) to the cell assay plate (where the media has been removed) using the multi-channel robotic system, Multimek 96 (Beckman). The compounds are incubated with the cells for 3 hours at 37°C, 5% CO_2. to allow for expression of the reporter gene β-Lactamase.

[0117] After 3 hours, 5 µl of 6X fold concentrated CCF2/AM dye are added to the assay plates and incubated at room temperature for 1 hour. Fluorescent emission at two wavelengths (460 nm and 530 nm) is determined using the CytoFluor Series 4000 (PerSeptive Biosystems) and the calculations for reporter gene expression determined as specified in prior publications {Zlokarnik, G; Negulescu, P.A.; Knapp, T.E.; Mere, L; Burres, N; Feng, L; Whitney, M; Roemer, K; Tsien, R.Y. Quantitation of transcription and clonal selection of single living cells with β-lactamase as reporter. Science, 1998 Jan 2, 279(5347):84-8.}

[0118] The compounds of the present invention were found to modulate the muscarinic receptor activity using the β-Lactamase Assay.

Claims

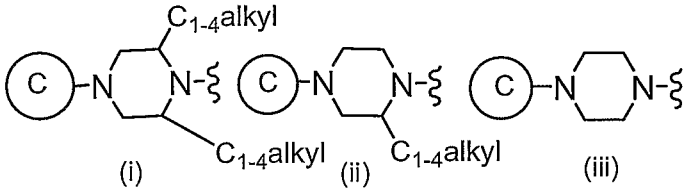
1. A method of modulating activity of a muscarinic receptor, comprising the step of contacting said receptor with a compound having the formula:



(I);

wherein:

B is selected from



;

D is CF_2, CH_2, or CHR^9;

Ring C is phenyl optionally substituted with 1 to 4 of R^1, R^2, R^3, R^4, or R^5;

Ring A is a 3-8 membered monocyclic carbocyclic ring, a 7-14 membered bicylic carbocyclic ring, a 7-14 tricyclic carbocyclic ring, a 3-8 membered monocyclic heterocyclic ring, a 7-14 membered bicylic heterocyclic ring, or a 7-14 tricyclic heterocyclic ring, in which the heterocyclic rings contain 1-5 atoms selected from O, S, and N;

wherein ring A contains up to 5 substituents independently selected from R^1, R^2, R^3, R^4, or R^5;

Each R^1 is independently oxo or $((C1\text{-}C4)aliphatic)_m\text{-}Q^1$;

Each Q^1 is independently halo, CN, NO_2, CF_3, OCF_3, OH, SR^6, $S(O)R^6$, SO_2R^6, $N(R^6)_2$, NR^6R^8, COOH, $COOR^6$ or OR^6;

Each R^2 is independently aliphatic optionally substituted with 1-3 substituents independently selected from R^1, R^4, or R^5;

Each R^3 is independently a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring, wherein each of the cycloaliphatic, aryl, heterocyclic, or heteroaryl are optionally substituted with 1-3 substituents independently selected from R^1, R^2, R^4, or R^5;

Each R^4 is independently OR^5, OR^6, $OC(O)R^6$, $OC(O)R^5$, $OC(O)OR^6$, $OC(O)OR^5$, $OC(O)N(R^6)_2$, $OC(O)N(R^5)_2$, $OC(O)N(R^6R^5)$, $S(O)_iR^6$, $S(O)_iR^5$, $SO_2N(R^6)_2$, $SO_2N(R^5)_2$, $SO_2NR^5R^6$, $C(O)R^5$, $C(O)OR^5$, $C(O)R^6$, $C(O)OR^6$, $C(O)N(R^6)_2$, $C(O)N(R^5)_2$, $C(O)N(R^5R^6)$, $C(O)N(OR^6)R^6$, $C(O)N(OR^5)R^6$, $C(O)N(OR^6)R^5$, $C(O)N(OR^5)R^5$, $C(NOR^6)R^6$, $C(NOR^6)R^5$, $C(NOR^5)R^6$, $C(NOR^5)R^5$, $N(R^6)_2$, $N(R^5)_2$, $N(R^5R^6)$, $NR^5C(O)R^5$, $NR^6C(O)R^6$, $NR^6C(O)R^5$, $NR^6C(O)OR^6$, $NR^5C(O)OR^6$, $NR^6C(O)OR^5$, $NR^5C(O)OR^5$, $NR^6C(O)N(R^6)_2$, $NR^6C(O)NR^5R^6$, $NR^6C(O)N(R^5)_2$, $NR^5C(O)N(R^6)_2$, $NR^5C(O)NR^5R^6$, $NR^5C(O)N(R^5)_2$, $NR^6SO_2R^6$, $NR^6SO_2R^5$, $NR^5SO_2R^5$, $NR^6SO_2N(R^6)_2$, $NR^6SO_2NR^5R^6$, $NR^6SO_2N(R^5)_2$, $NR^5SO_2NR^5R^6$, $NR^5SO_2N(R^5)_2$, $N(OR^6)R^6$, $N(OR^6)R^5$, $N(OR^5)R^5$, or $N(OR^5)R^6$;

Each R^5 is independently a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring, wherein each of the cycloaliphatic, aryl, heterocyclic, or heteroaryl are optionally substituted with 1 to 3 of R^1;

Each R^6 is independently H or aliphatic optionally substituted with R^7;

Each R^7 is independently a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring, wherein each of the cycloaliphatic, aryl, heterocyclic, or heteroaryl are optionally substituted with 1 to 2 of (C_1-C_6)-straight or branched alkyl, (C_2-C_6) straight or branched alkenyl or alkynyl, 1,2-methylenedioxy, 1,2-ethylenedioxy, or $(CH_2)_n-Q^2$;

Each Q^2 is independently selected from halo, CN, NO_2, CF_3, OCF_3, OH, S-aliphatic, S(O)-aliphatic, SO_2-aliphatic, COOH, C(O)O-aliphatic, or O-aliphatic;

Each R^8 is independently an amino protecting group;

Each R^9 is independently R^2, R^3, or R^6;

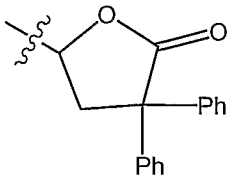
Each i is independently 0, 1, 2, or 3;

Each m is independently 0 or 1; and

Each n is independently 0 or 1;

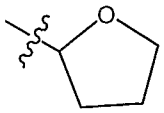
further provided that

(i) when n is 1, D is CH_2, C is phenyl, and B is piperazine

then ring A is not 

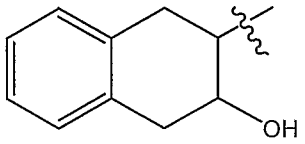
;

(ii) when n is 1, D is CH_2, C is phenyl, and B is piperazine

then ring A is not 

;

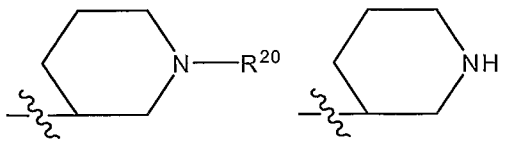
(iii) when n is 0, C is phenyl, and B is piperazine then

ring A is not 

;

(iv) when n is 1, D is CH_2, ring A is 1,2,3,4 tetrahydroquinoline optionally substituted with R^4, and B is piperazine, then C is not phenyl substituted with halo, phenyl substituted with $-OCH_3$, or phenyl substituted with halo and $-OCH_3$;

(v) when n is 1, D is CH_2, ring A is



in which R^{20} is -C(O)R5, -C(O)R6, -C(O)OR5, C(O)OR6, and B is piperazine, then C is not phenyl optionally substituted with halo or $-OCH_3$.

2. The method according to claim 1, wherein D is CH_2 or CHR^9.

3. The method according to claims 1, wherein D is CH_2 or CF_2.

4. The method according to claim 3, wherein D is CH_2.

5. The method according to claim 2, wherein D is CHR^9.

6. The method according to any one of claims 1-4, wherein n is 0.

7. The method according to any one of claims 1-4, wherein n is 1.

8. The method according to any one of claims 1-7, wherein A is an monocyclic C3-C8 cycloaliphatic ring optionally substituted with 1-5 substituents independently selected from R^1, R^2, R^3, R^4, or R^5.

9. The method according to claim 8, wherein A is a cyclopropyl, cyclopentyl, cyclohexyl, or cycloheptyl, each optionally substituted with 1-5 substituents independently selected from R^1, R^2, R^3, R^4, or R^5.

10. The method according to any one of claims 1-9, wherein A is a bicylic, bridged bicyclic or bridged tricyclic C7-C14 cycloaliphatic ring, each optionally substituted with 1-5 substituents independently selected from R^1, R^2, R^3, R^4, or R^5.

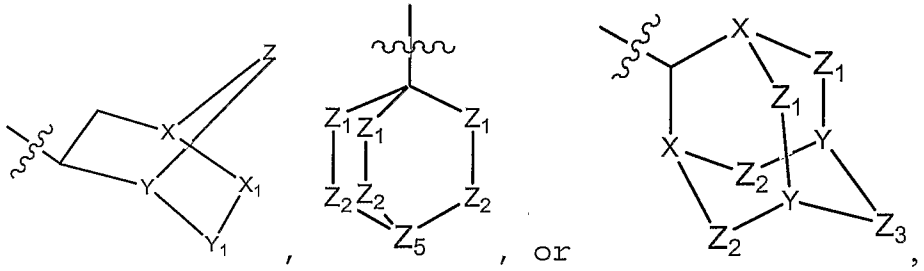
11. The method according to claim 11, wherein A is 1-adamantyl, 2-adamantyl, 1-norbornyl, or 1-bicyclo[2.2.1]hept-5-en-2-yl.

12. The method according to any one of claims 1-8, wherein A is a monocyclic, bicylic, bridged bicyclic or bridged

tricyclic C3-C12 heterocyclic ring, each optionally substituted with 1-5 substituents independently selected from R^1, R^2, R^3, R^4, or R^5, provided that ring A together with any substituent of ring A does not include a basic nitrogen atom.

13. The method according to claim 12, wherein A is selected from optionally substituted pyrrolidyl, tetrahydrofuranyl, tetrahydrothienyl, dioxolanyl, pyrrolinyl, pyranyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, or indolinyl, provided that ring A together with any substituent of ring A does not include a basic nitrogen atom.

14. The method according to claim 1, wherein A is



in which

X, Y, and Z_5 are each independently CR';

X_1 and Y_1 are independently selected from a bond, CH_2, CHR^9, O, S, NR', C(O), S(O), or SO_2 provided that both X_1 and Y_1 are not simultaneously a bond;

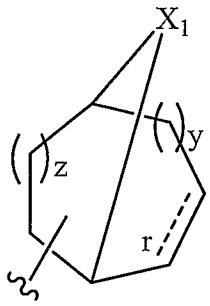
Z is $C(R')_2$, $C(R')_2$-$C(R')_2$, $C(R')_2$-Q, or Q, wherein Q is O, NR', S(O), SO_2, or C(O);

Each of Z_1, Z_2, Z_3, and Z_4 is independently selected from CH_2, CHR', O, S, NR', C(O), S(O), SO_2;

R' is selected from $(C1\text{-}C4)aliphatic)_m$-$Q^1$, $S(O)_iR^6$, $S(O)_iR^5$, $SO_2N(R^6)_2$, $SO_2N(R^5)_2$, $SO_2NR^5R^6$, $C(O)R^5$, $C(O)OR^5$, $C(O)R^6$, $C(O)OR^6$, $C(O)N(R^6)_2$, $C(O)N(R^5)_2$, $C(O)N(R^5R^6)$, $C(O)N(OR^6)R^6$, $C(O)N(OR^5)R^6$, $C(O)N(OR^6)R^5$, $C(O)N(OR^5)R^5$, $C(NOR^6)R^6$, $C(NOR^6)R^5$, $C(NOR^5)R^6$, $C(NOR^5)R^5$, R^2, or R_6, provided that when any of X_1, Y_1, Z, Z_1, Z_2,

Z_3, and Z_4 are NR', then R' is $S(O)_iR^6$, $S(O)_iR^5$, $SO_2N(R^6)_2$, $SO_2N(R^5)_2$, $SO_2NR^5R^6$, $C(O)R^5$, $C(O)OR^5$, $C(O)R^6$, $C(O)OR^6$, $C(O)N(R^6)_2$, $C(O)N(R^5)_2$, $C(O)N(R^5R^6)$, $C(O)N(OR^6)R^6$, $C(O)N(OR^5)R^6$, $C(O)N(OR^6)R^5$, $C(O)N(OR^5)R^5$, $C(NOR^6)R^6$, $C(NOR^6)R^5$, $C(NOR^5)R^6$, $C(NOR^5)R^5$.

15. The method according to claim 1, wherein A is



optionally substituted with 1-3 of R'; in which

X_1 is independently selected from a bond, CH_2, CHR^9, O, S, NR', C(O), S(O), SO_2;

R' is selected from (C1-C4)aliphatic)$_m$-Q^1, $S(O)_iR^6$, $S(O)_iR^5$, $SO_2N(R^6)_2$, $SO_2N(R^5)_2$, $SO_2NR^5R^6$, $C(O)R^5$, $C(O)OR^5$, $C(O)R^6$, $C(O)OR^6$, $C(O)N(R^6)_2$, $C(O)N(R^5)_2$, $C(O)N(R^5R^6)$, $C(O)N(OR^6)R^6$, $C(O)N(OR^5)R^6$, $C(O)N(OR^6)R^5$, $C(O)N(OR^5)R^5$, $C(NOR^6)R^6$, $C(NOR^6)R^5$, $C(NOR^5)R^6$, $C(NOR^5)R^5$, R^2, or R_6, provided that when any of X_1, Y_1, Z, Z_1, Z_2, Z_3, and Z_4 are NR', then R' is $S(O)_iR^6$, $S(O)_iR^5$, $SO_2N(R^6)_2$, $SO_2N(R^5)_2$, $SO_2NR^5R^6$, $C(O)R^5$, $C(O)OR^5$, $C(O)R^6$, $C(O)OR^6$, $C(O)N(R^6)_2$, $C(O)N(R^5)_2$, $C(O)N(R^5R^6)$, $C(O)N(OR^6)R^6$, $C(O)N(OR^5)R^6$, $C(O)N(OR^6)R^5$, $C(O)N(OR^5)R^5$, $C(NOR^6)R^6$, $C(NOR^6)R^5$, $C(NOR^5)R^6$, $C(NOR^5)R^5$;

y is 0, 1, or 2;

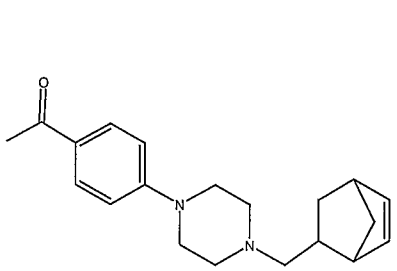
z is 0, 1, or 2; and

bond r is optionally a single or double bond;

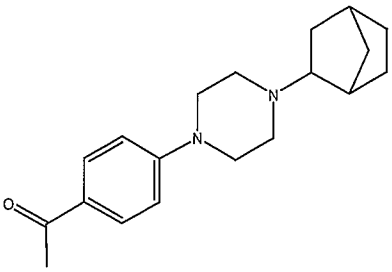
provided that when D is CH_2, y is 1 and z is 2, that X1 is other than C(O) or -CH(OH)-.

16. The method according to claim 1, wherein B is piperazine.

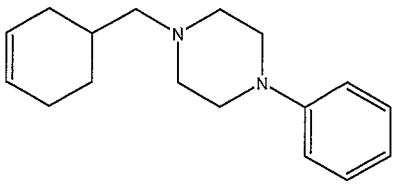
17. The method according to claim 1, wherein said compound of formula (I) is selected from any one of compounds



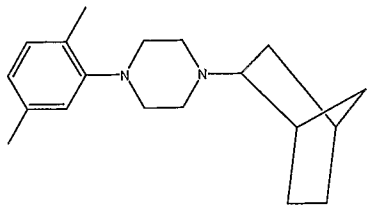
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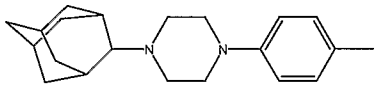
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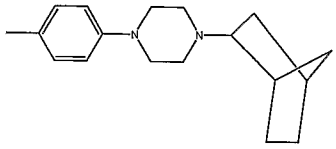
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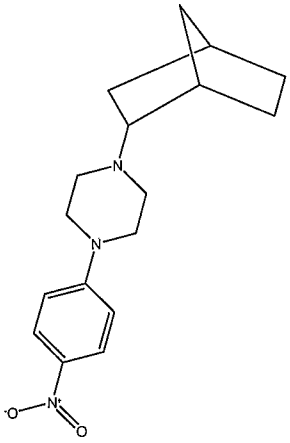
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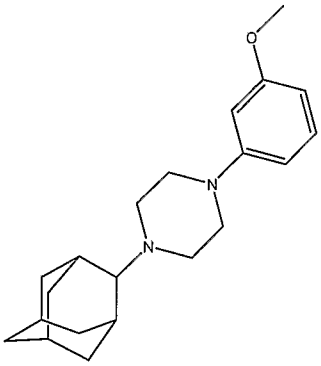
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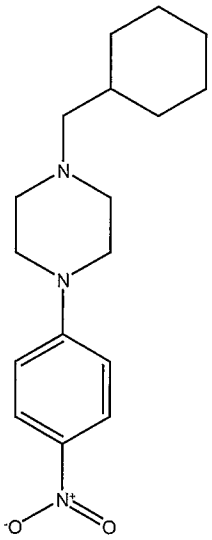
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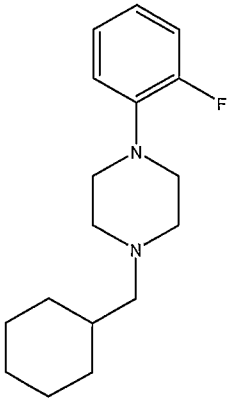
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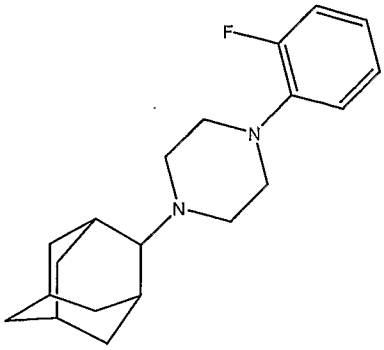
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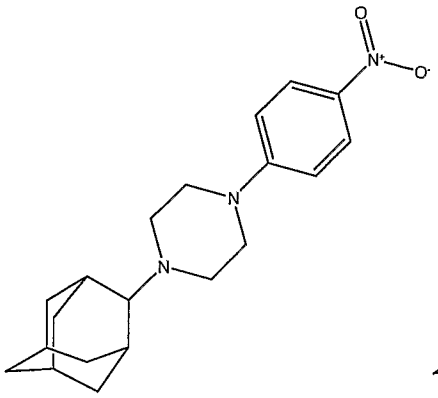
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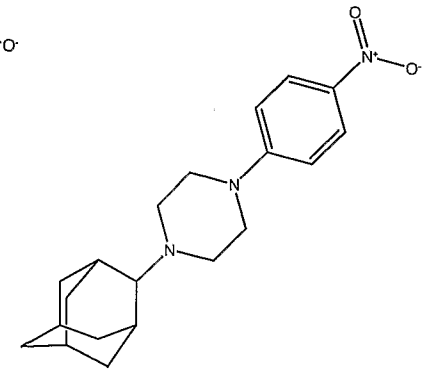
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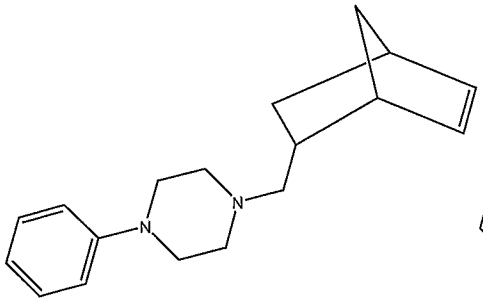
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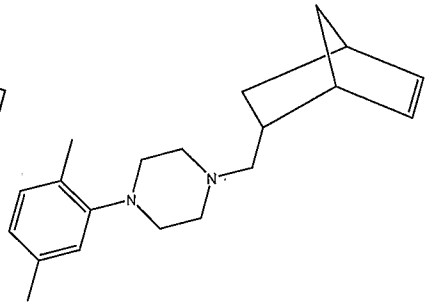
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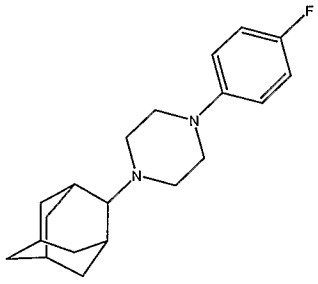
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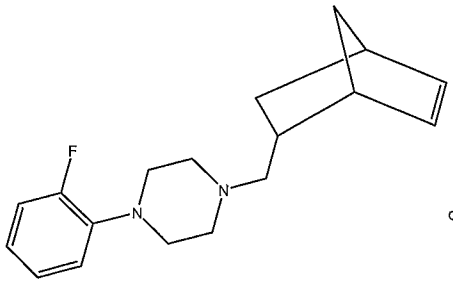
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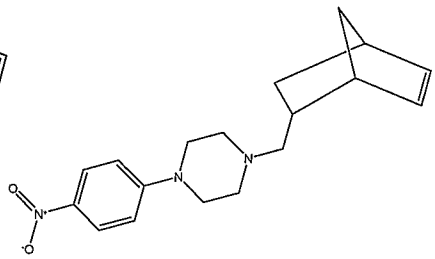
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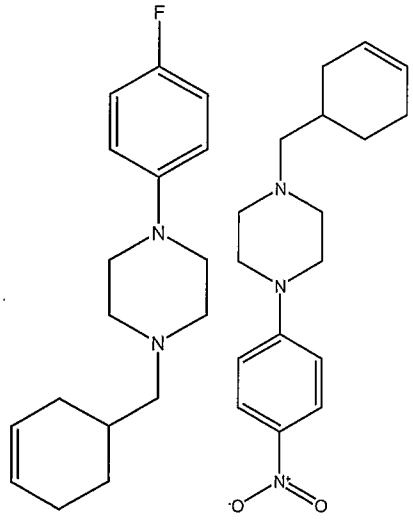
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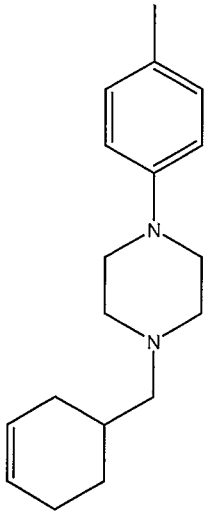


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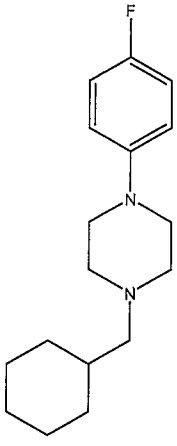


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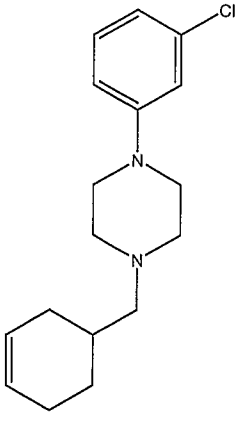
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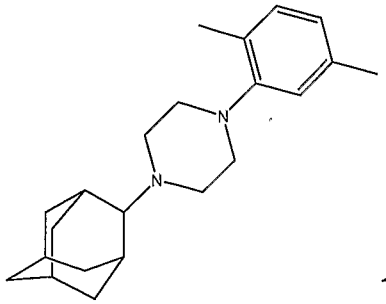
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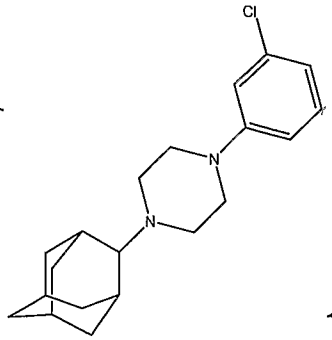
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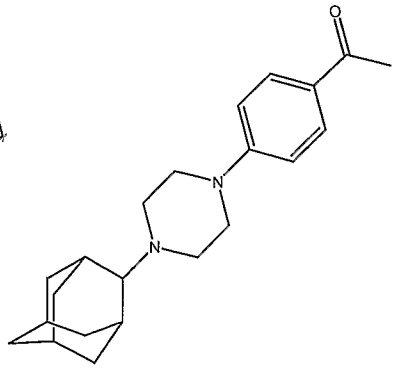
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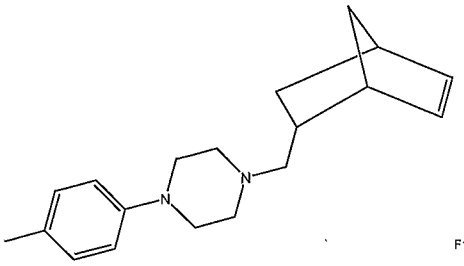
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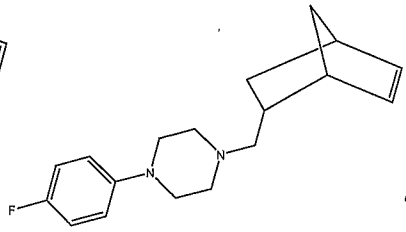
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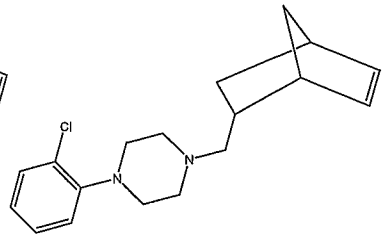
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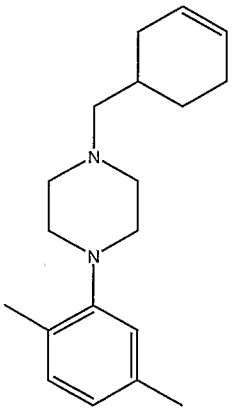
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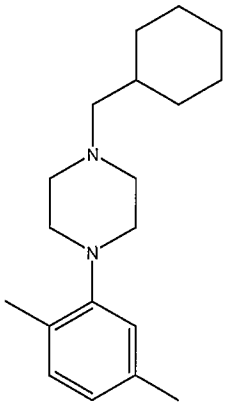
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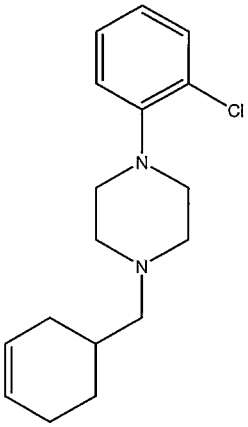
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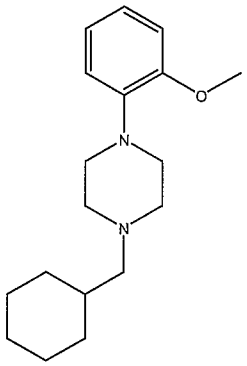
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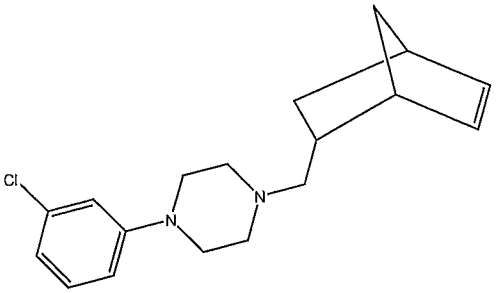
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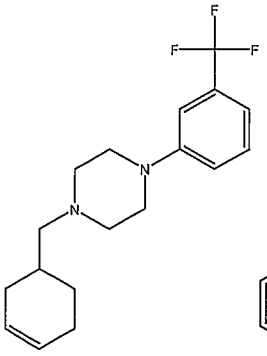
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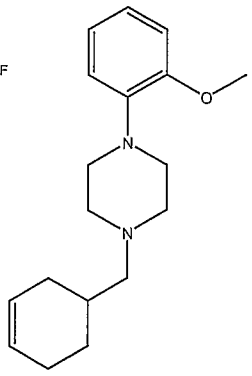
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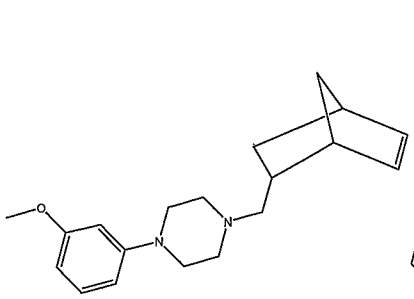
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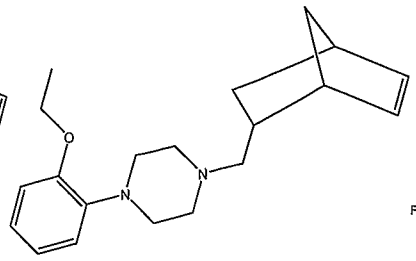
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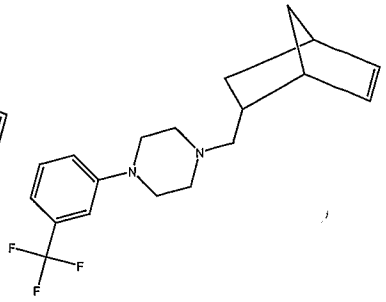
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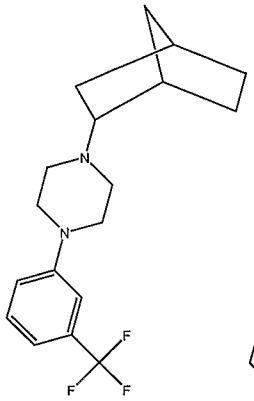
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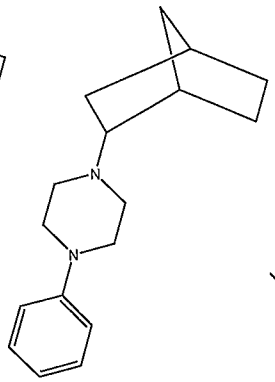
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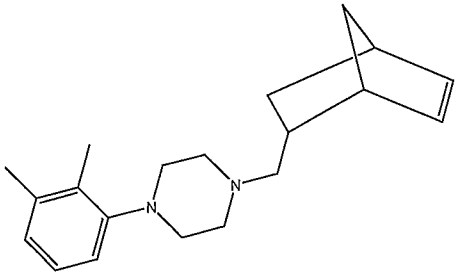
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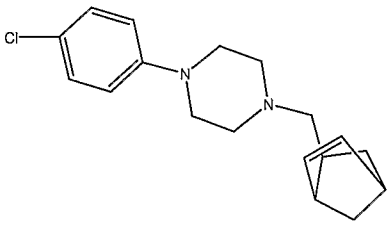
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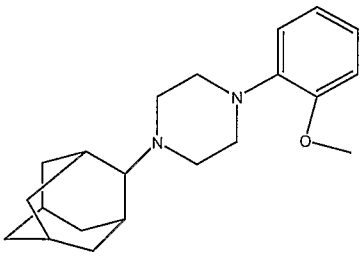
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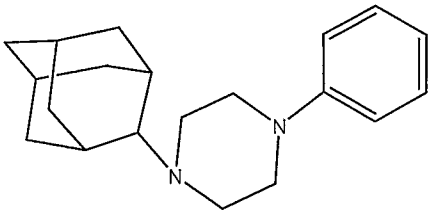
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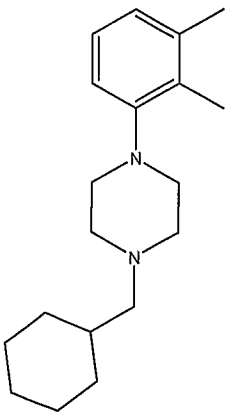
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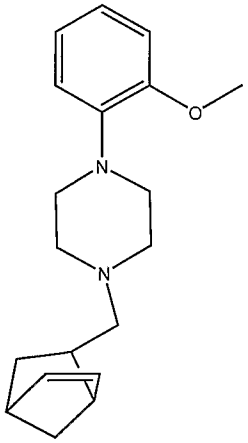
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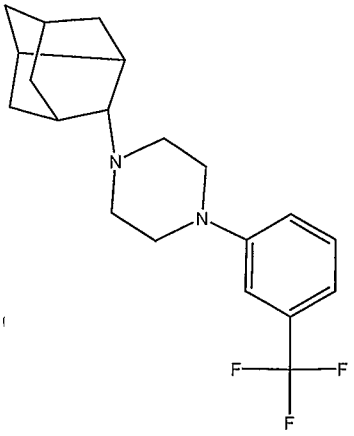
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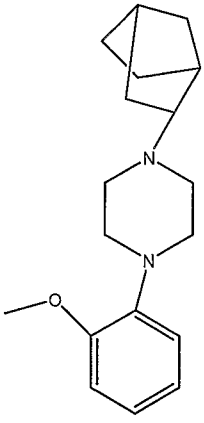
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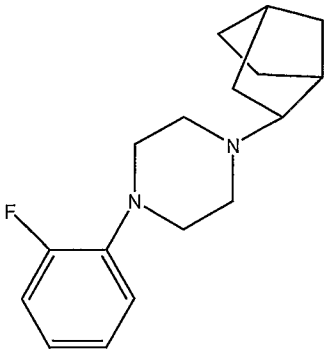
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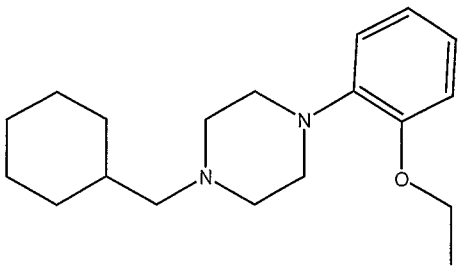
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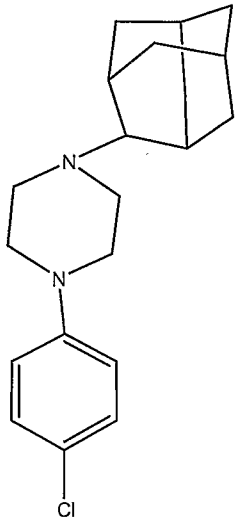
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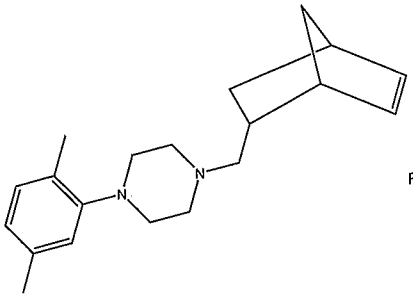
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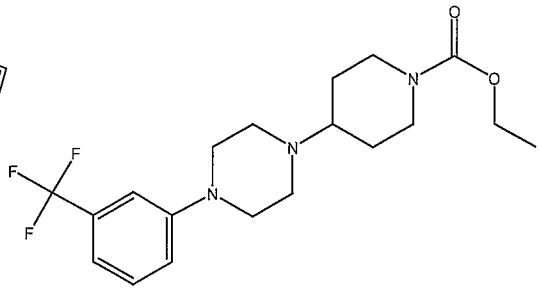
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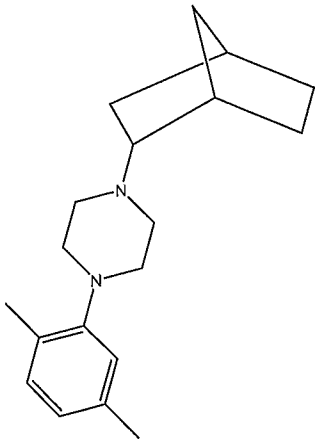
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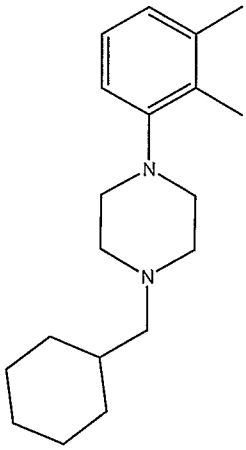
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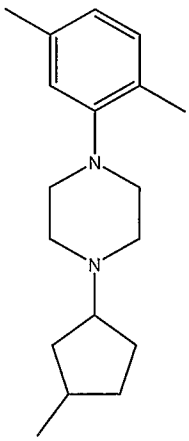
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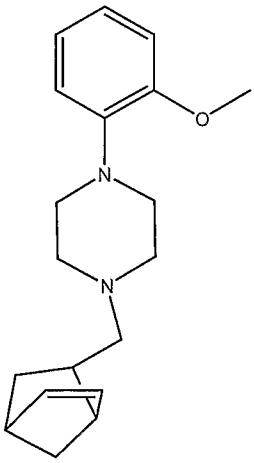
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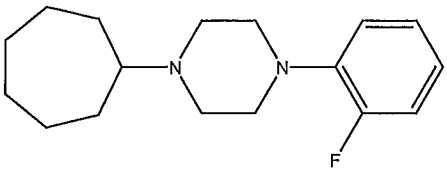
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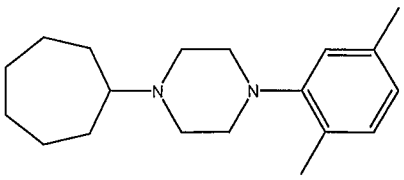
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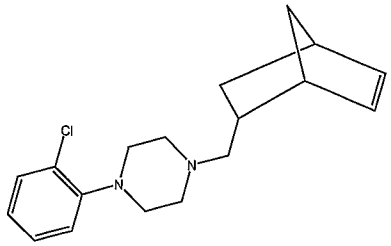
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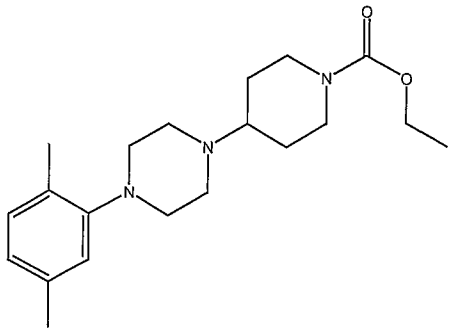
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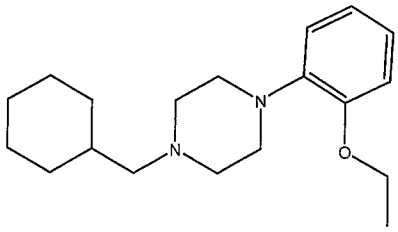
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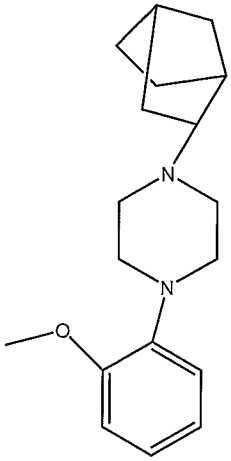
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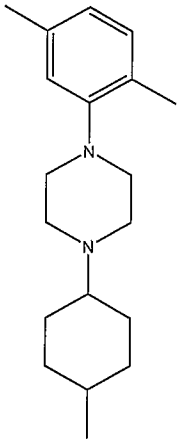
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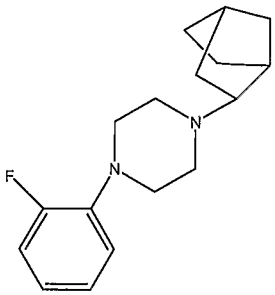
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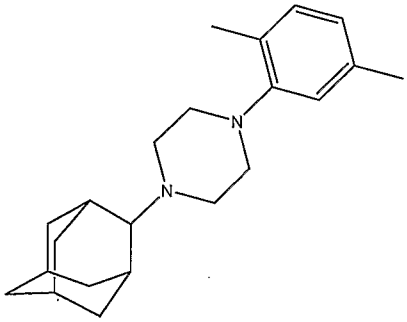
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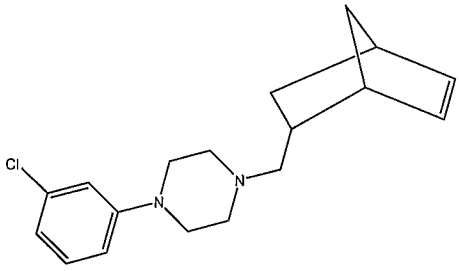
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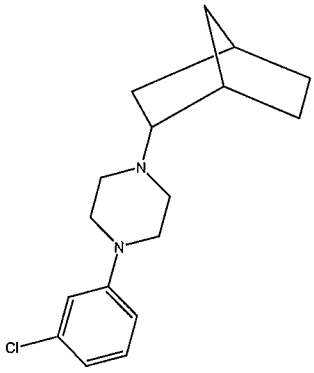
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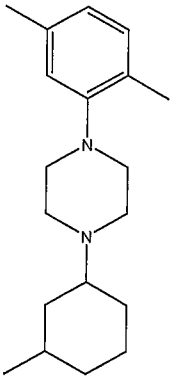
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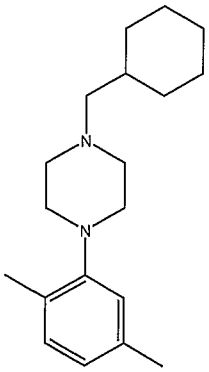
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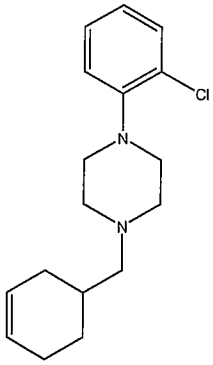
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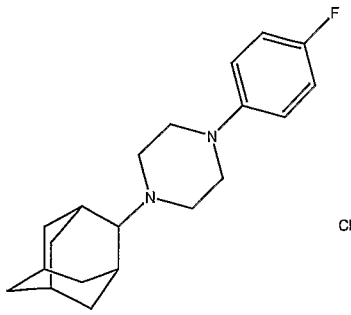
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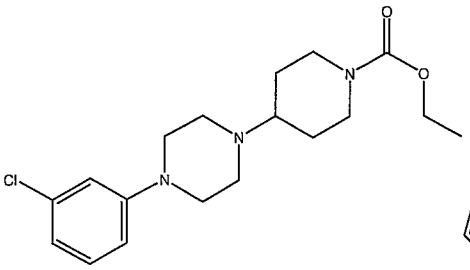
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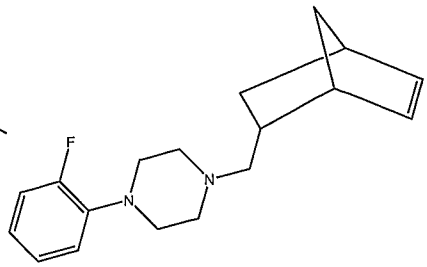
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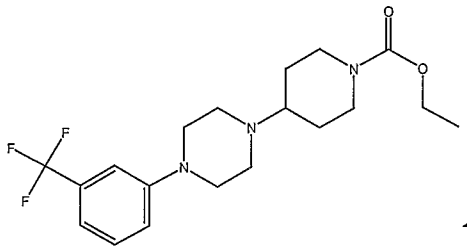
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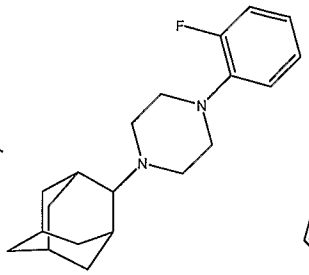
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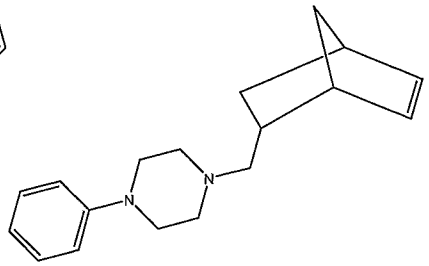
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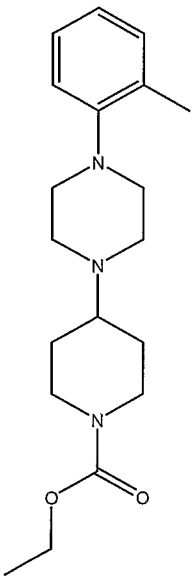
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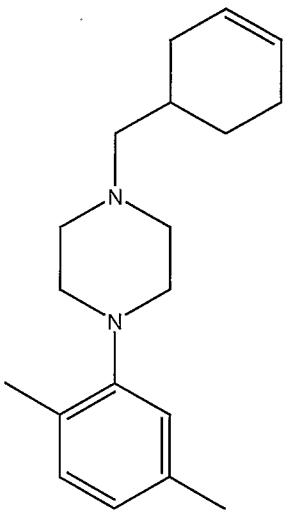
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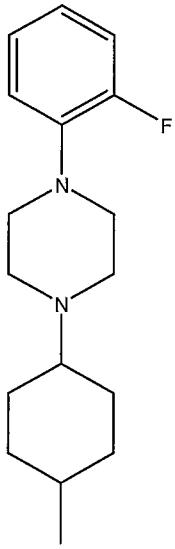
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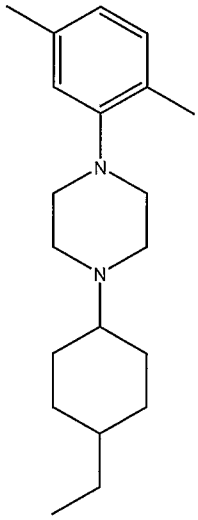
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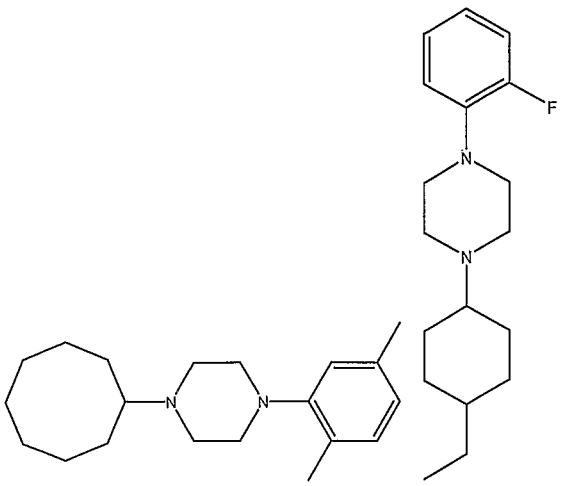
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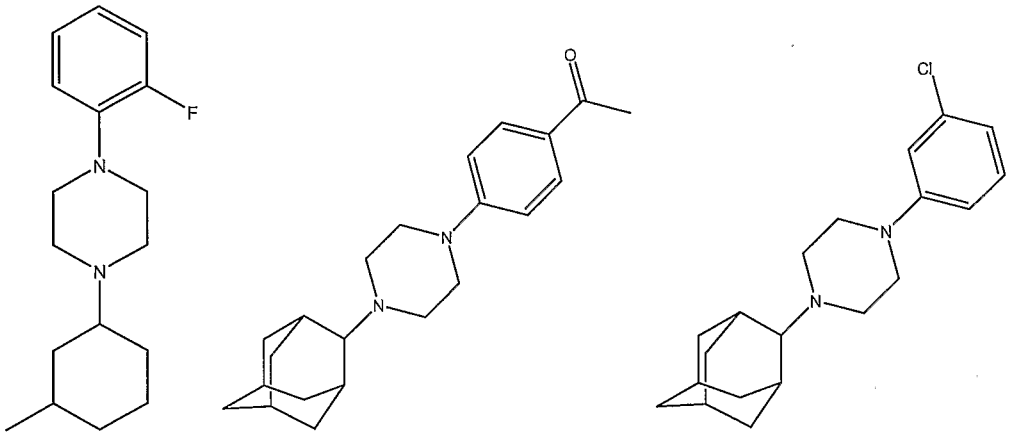
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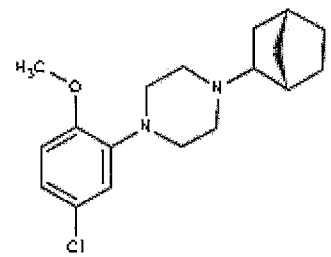
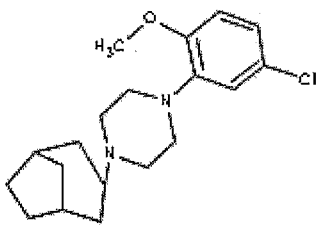


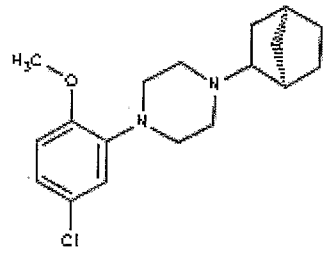
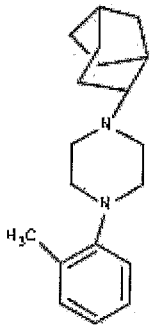
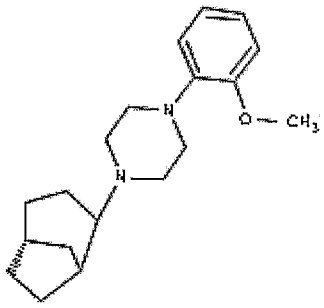
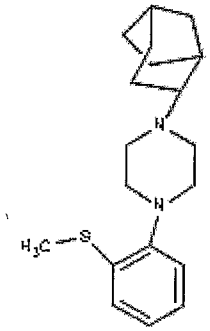
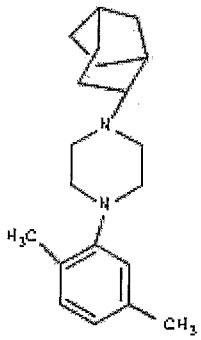
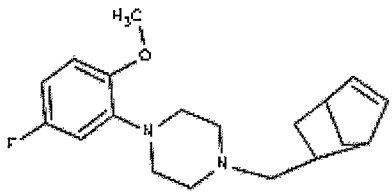
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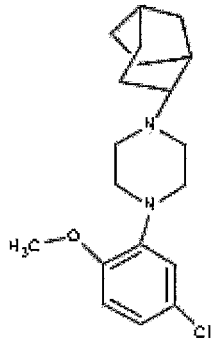
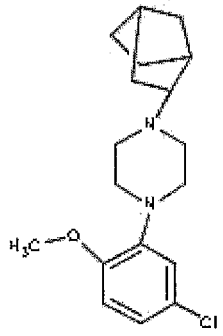
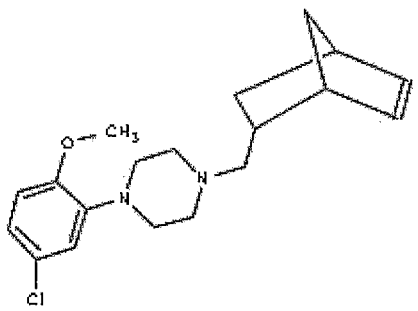
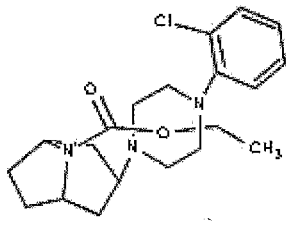
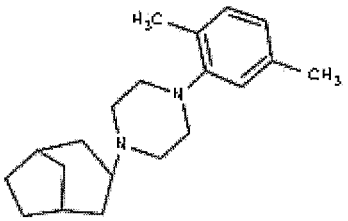
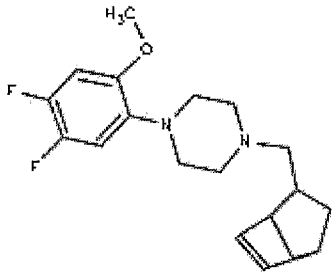


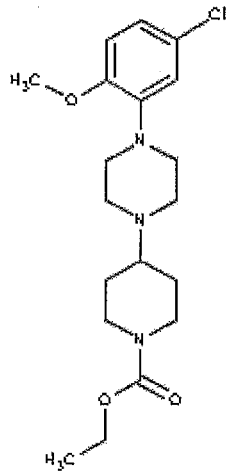
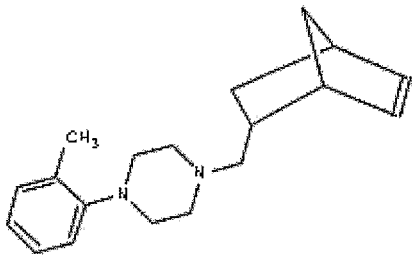
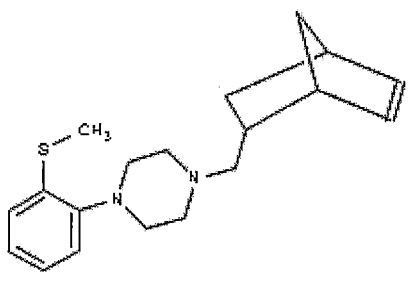
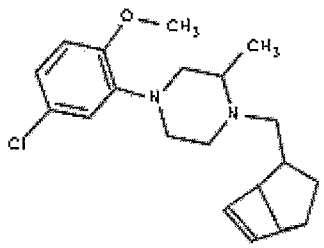
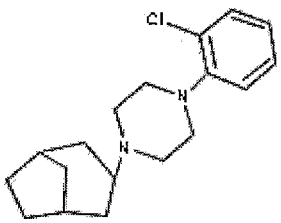
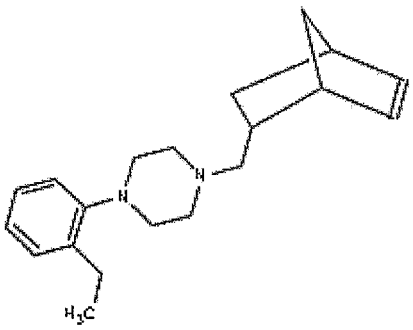
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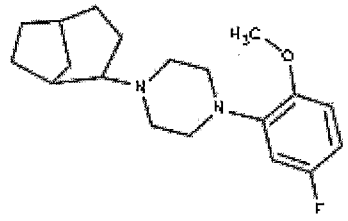
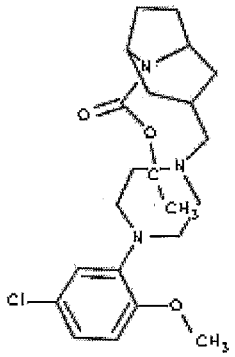
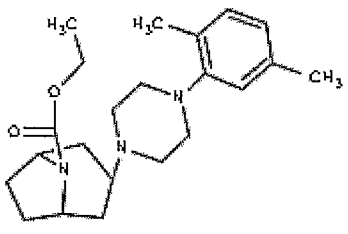
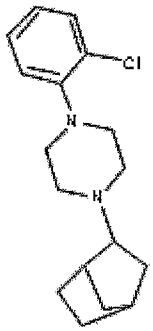
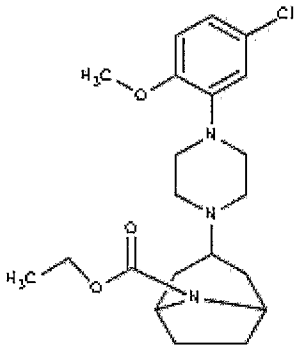
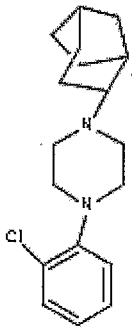
18. The method according to claim 1, wherein said compound of formula (I) is selected from any one of compounds

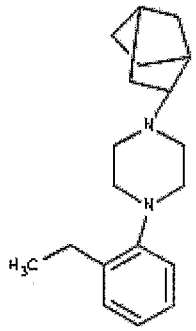
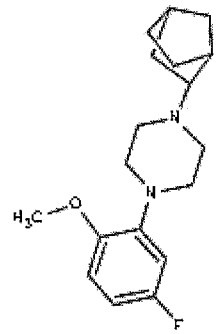
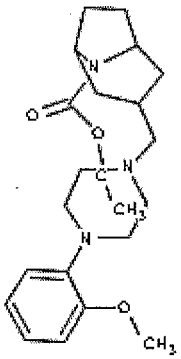
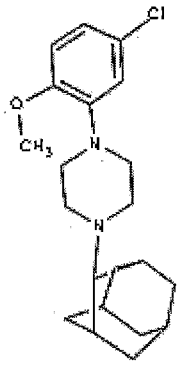
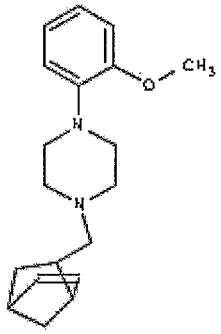
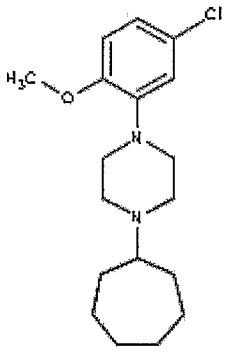
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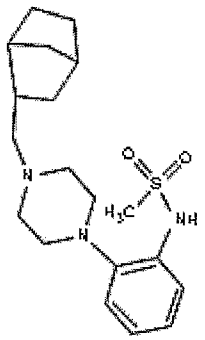
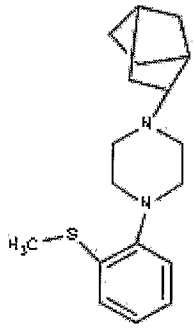
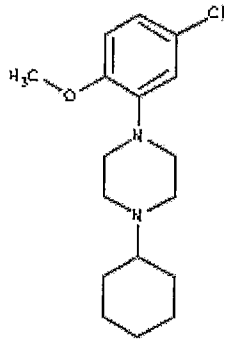
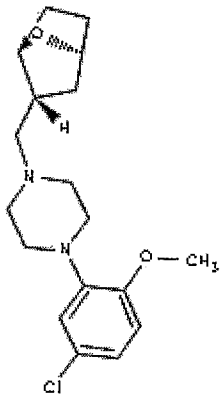
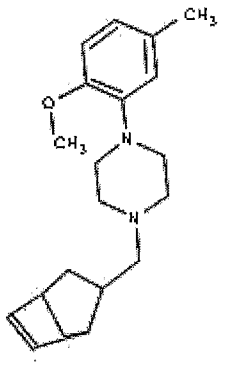
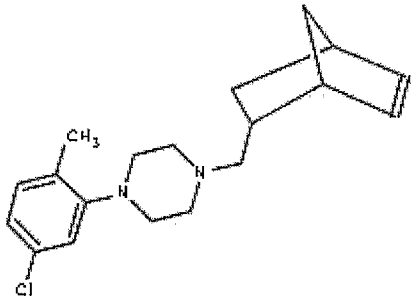
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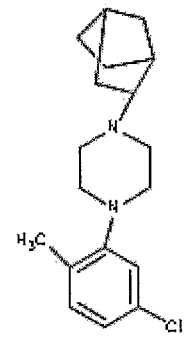
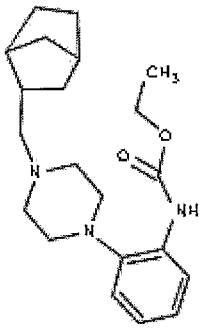
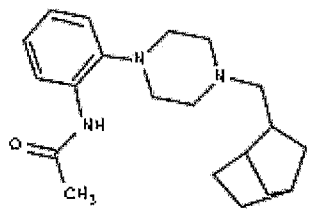
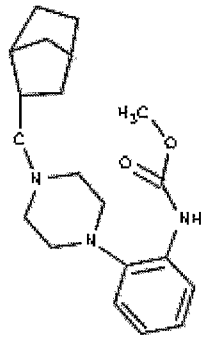
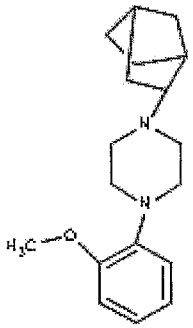
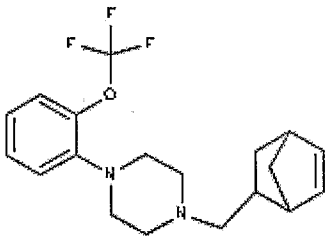
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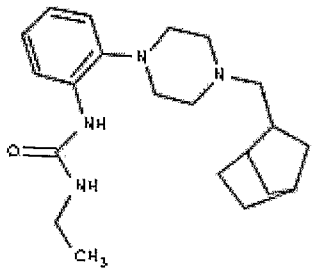
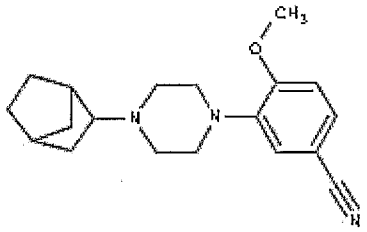
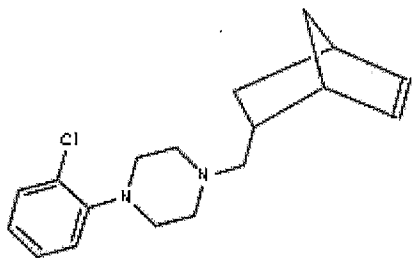
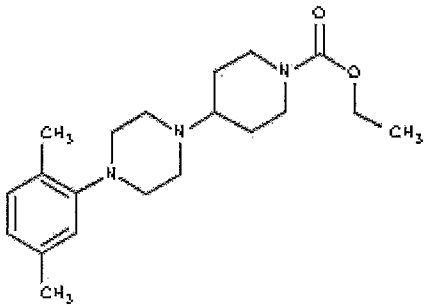
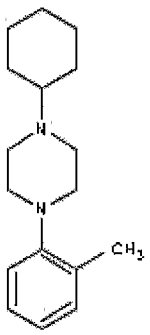
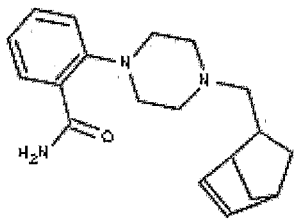
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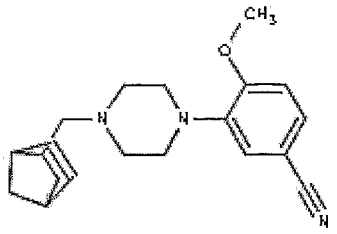
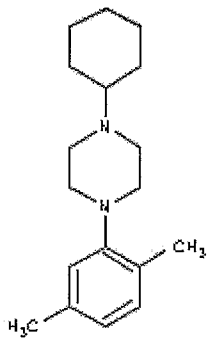
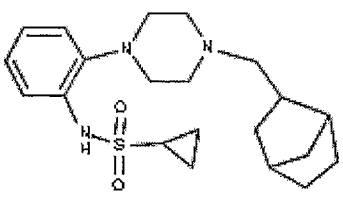
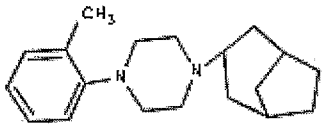
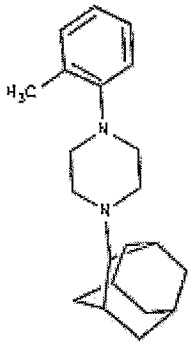
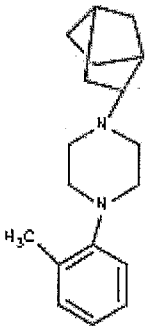
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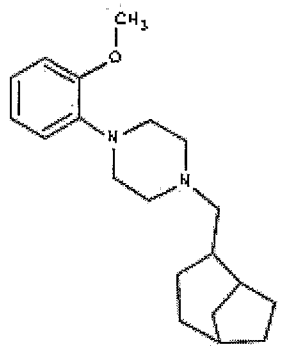
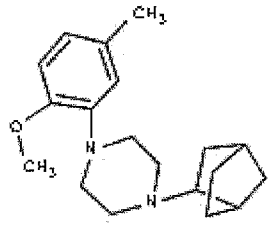
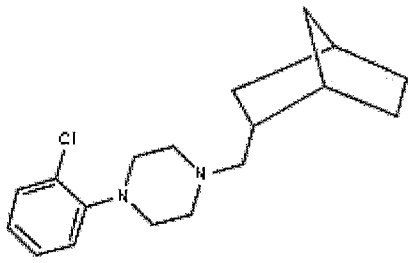
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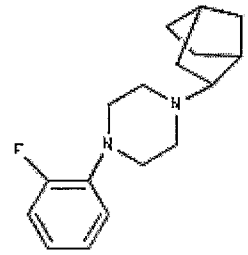
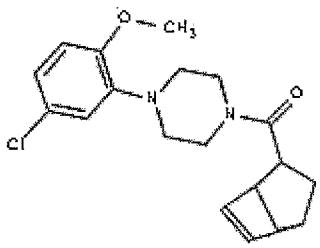
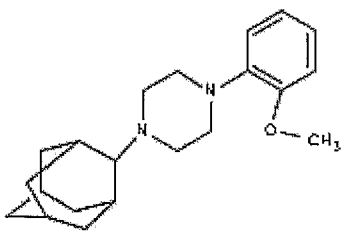
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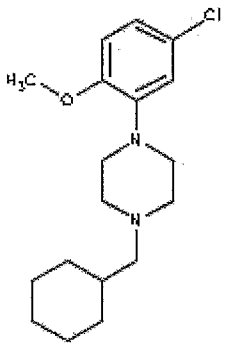
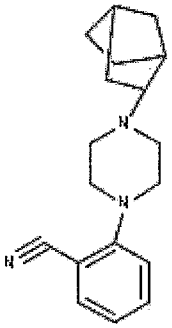
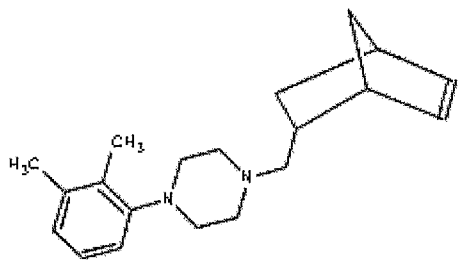
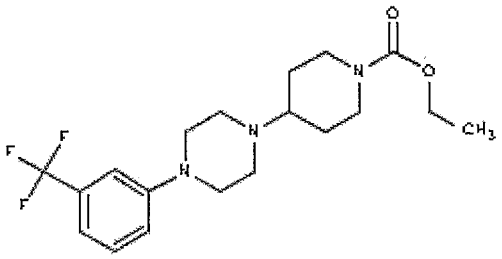
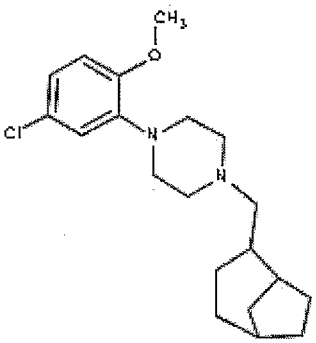
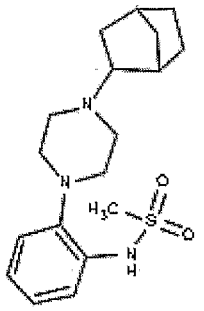
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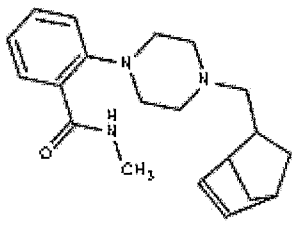
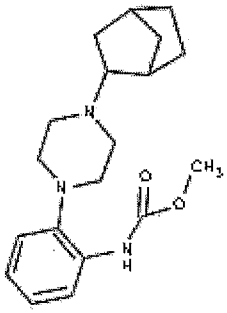
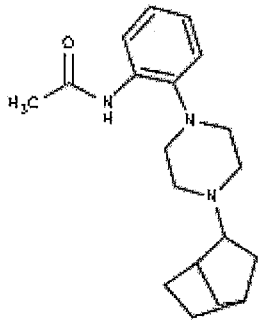
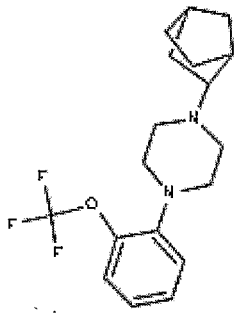
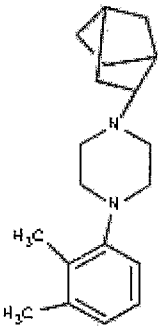
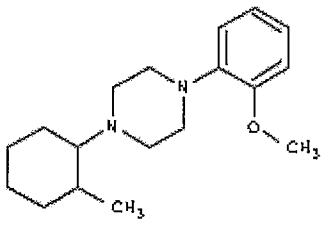
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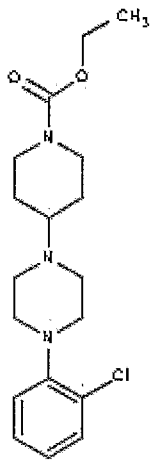
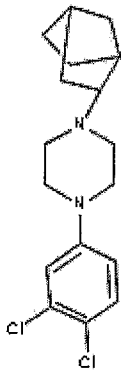
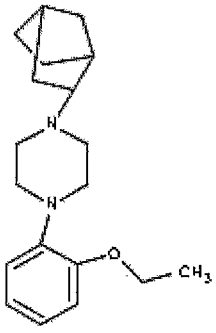
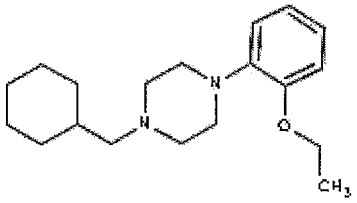
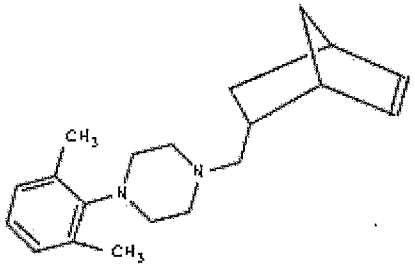
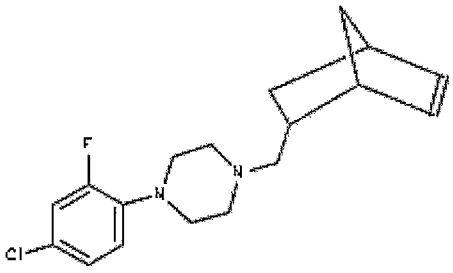
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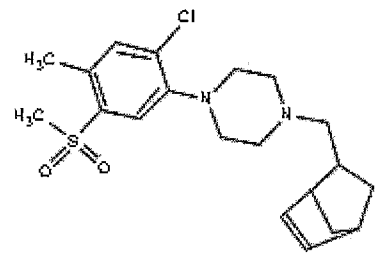
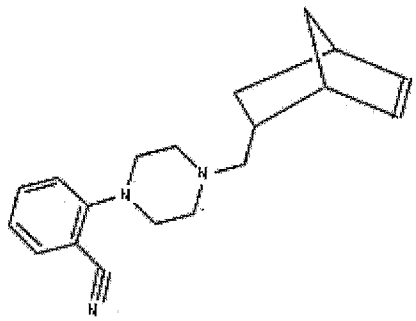
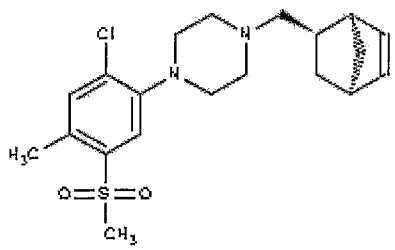
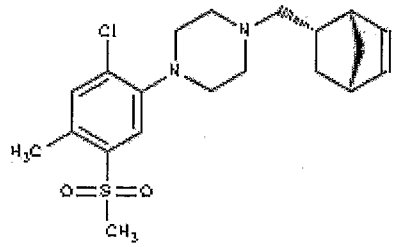
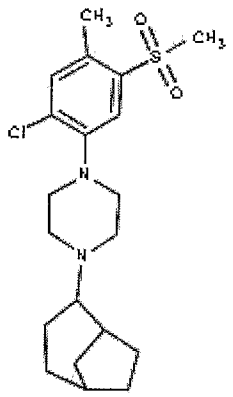
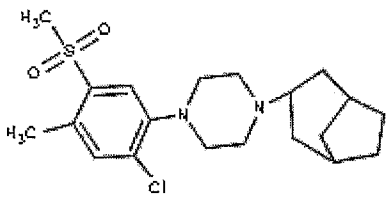
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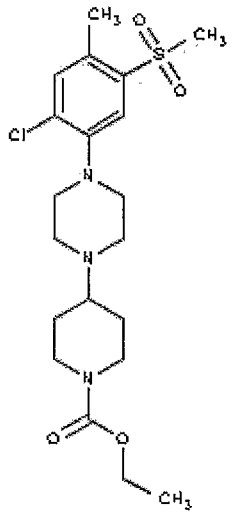
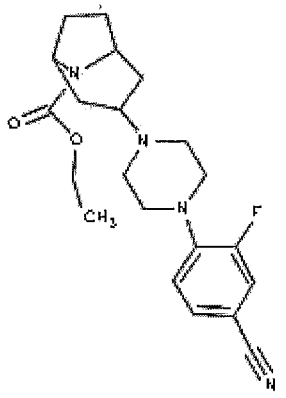
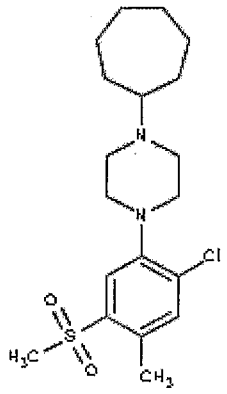
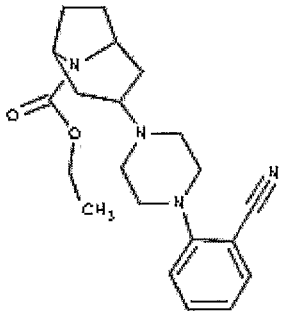
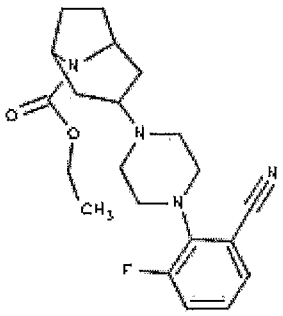
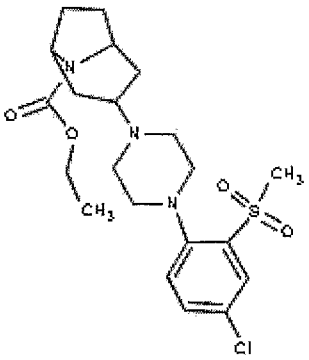
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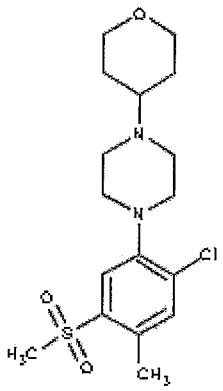
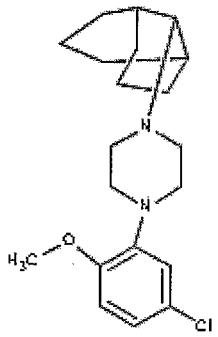
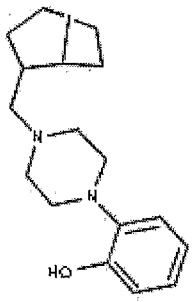
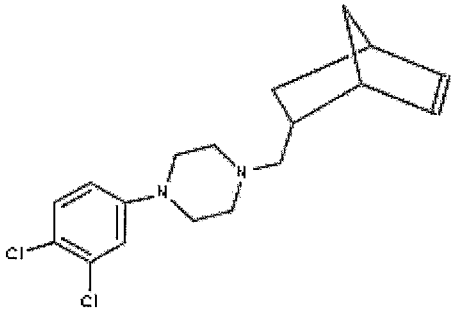
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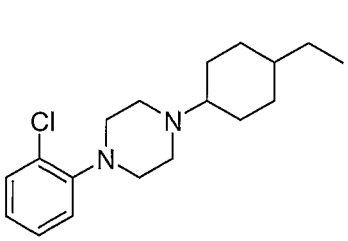
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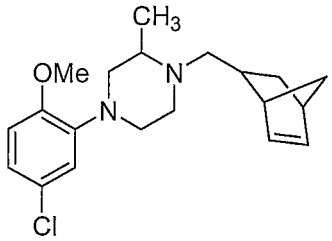
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or 

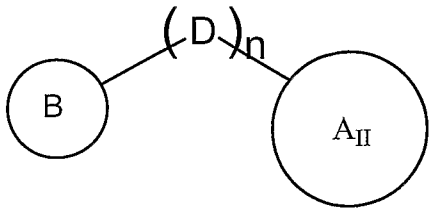
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19. The method according to any one of claims 1-18, wherein said method is selective for at least one of M_1 and M_4.

20. The method according to claim 19, wherein said method is selective for M_4.

21. The method according to any one of claims 1-20, wherein the modulation is activation.

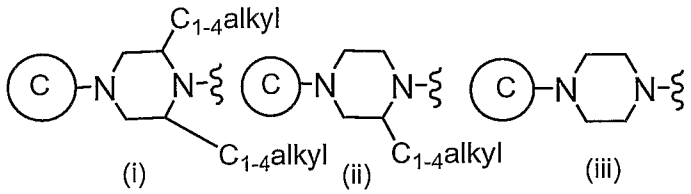
22. A compound having formula (II):



(II);

wherein:

B is selected from

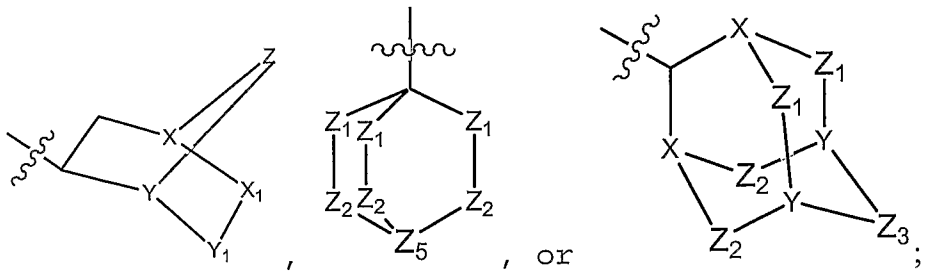


;

D is CF_2, CH_2, or CHR^9;

Ring C is phenyl optionally substituted with 1 to 4 of R^1, R^2, R^3, R^4, or R^5;

ring A_{II} is selected from:



, , or ;

X, Y, and Z_5 are each independently CR';

X_1 and Y_1 are independently selected from a bond, CH_2, CHR^9, O, S, NR', C(O), S(O), SO_2, or X_1 and Y_1 are together -CH=CH-, provided that both X_1 and Y_1 are not simultaneously a bond;

Each Z is independently $C(R')_2$, $C(R')_2$-$C(R')_2$, $C(R')_2$-Q, or Q, wherein Q is O, NR', S(O), SO_2, or C(O);

Each of Z_1, Z_2, Z_3, and Z_4 is independently selected from CHR', O, S, NR', C(O), S(O), SO_2;

Each R' is independently selected from $(C1\text{-}C4)aliphatic)_m$-$Q^1$, $S(O)_iR^6$, $S(O)_iR^5$, $SO_2N(R^6)_2$, $SO_2N(R^5)_2$, $SO_2NR^5R^6$, $C(O)R^5$, $C(O)OR^5$, $C(O)R^6$, $C(O)OR^6$, $C(O)N(R^6)_2$, $C(O)N(R^5)_2$, $C(O)N(R^5R^6)$, $C(O)N(OR^6)R^6$, $C(O)N(OR^5)R^6$, $C(O)N(OR^6)R^5$, $C(O)N(OR^5)R^5$, $C(NOR^6)R^6$, $C(NOR^6)R^5$, $C(NOR^5)R^6$, $C(NOR^5)R^5$, R^2, or R_6, provided that when any of X_1, Y_1, Z, Z_1, Z_2, Z_3, and Z_4 are NR', then R' is $S(O)_iR^6$, $S(O)_iR^5$, $SO_2N(R^6)_2$, $SO_2N(R^5)_2$, $SO_2NR^5R^6$, $C(O)R^5$, $C(O)OR^5$, $C(O)R^6$, $C(O)OR^6$, $C(O)N(R^6)_2$, $C(O)N(R^5)_2$, $C(O)N(R^5R^6)$, $C(O)N(OR^6)R^6$, $C(O)N(OR^5)R^6$, $C(O)N(OR^6)R^5$, $C(O)N(OR^5)R^5$, $C(NOR^6)R^6$, $C(NOR^6)R^5$, $C(NOR^5)R^6$, $C(NOR^5)R^5$;

Each R^1 is independently oxo or $((C1\text{-}C4)aliphatic)_m$-$Q^1$;

Each Q^1 is independently halo, CN, NO_2, CF_3, OCF_3, OH, SR^6, $S(O)R^6$, SO_2R^6, $N(R^6)_2$, NR^6R^8, COOH, $COOR^6$ or OR^6;

Each R^2 is independently aliphatic optionally substituted with 1-3 substituents independently selected from R^1, R^4, or R^5;

Each R^3 is independently a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring, wherein each of the cycloaliphatic, aryl, heterocyclic, or heteroaryl are optionally substituted with 1-3 substituents independently selected from R^1, R^2, R^4, or R^5;

Each R^4 is independently OR^5, OR^6, $OC(O)R^6$, $OC(O)R^5$, $OC(O)OR^6$, $OC(O)OR^5$, $OC(O)N(R^6)_2$, $OC(O)N(R^5)_2$, $OC(O)N(R^6R^5)$, $S(O)_iR^6$, $S(O)_iR^5$, $SO_2N(R^6)_2$, $SO_2N(R^5)_2$, $SO_2NR^5R^6$, $C(O)R^5$, $C(O)OR^5$, $C(O)R^6$, $C(O)OR^6$, $C(O)N(R^6)_2$, $C(O)N(R^5)_2$, $C(O)N(R^5R^6)$,

$C(O)N(OR^6)R^6$, $C(O)N(OR^5)R^6$, $C(O)N(OR^6)R^5$, $C(O)N(OR^5)R^5$, $C(NOR^6)R^6$, $C(NOR^6)R^5$, $C(NOR^5)R^6$, $C(NOR^5)R^5$, $N(R^6)_2$, $N(R^5)_2$, $N(R^5R^6)$, $NR^5C(O)R^5$, $NR^6C(O)R^6$, $NR^6C(O)R^5$, $NR^6C(O)OR^6$, $NR^5C(O)OR^6$, $NR^6C(O)OR^5$, $NR^5C(O)OR^5$, $NR^6C(O)N(R^6)_2$, $NR^6C(O)NR^5R^6$, $NR^6C(O)N(R^5)_2$, $NR^5C(O)N(R^6)_2$, $NR^5C(O)NR^5R^6$, $NR^5C(O)N(R^5)_2$, $NR^6SO_2R^6$, $NR^6SO_2R^5$, $NR^5SO_2R^5$, $NR^6SO_2N(R^6)_2$, $NR^6SO_2NR^5R^6$, $NR^6SO_2N(R^5)_2$, $NR^5SO_2NR^5R^6$, $NR^5SO_2N(R^5)_2$, $N(OR^6)R^6$, $N(OR^6)R^5$, $N(OR^5)R^5$, or $N(OR^5)R^6$;

Each R^5 is independently a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring, wherein each of the cycloaliphatic, aryl, heterocyclic, or heteroaryl are optionally substituted with 1 to 3 of R^1;

Each R^6 is independently H or aliphatic optionally substituted with R^7;

Each R^7 is independently a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring, wherein each of the cycloaliphatic, aryl, heterocyclic, or heteroaryl are optionally substituted with 1 to 2 of (C_1-C_6)-straight or branched alkyl, (C_2-C_6) straight or branched alkenyl or alkynyl, 1,2-methylenedioxy, 1,2-ethylenedioxy, or $(CH_2)_n-Q^2$;

Each Q^2 is independently selected from halo, CN, NO_2, CF_3, OCF_3, OH, S-aliphatic, S(O)-aliphatic, SO_2-aliphatic, COOH, C(O)O-aliphatic, or O-aliphatic;

Each R^8 is independently an amino protecting group;

Each R^9 is independently R^2, R^3, or R^6;

Each i is 0, 1, 2, or 3;

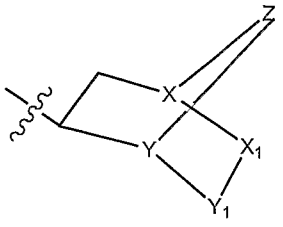
Each m is 0 or 1;

Each n is 0 or 1; and

Further provided that:

(i) when C is dimethyl-fluoro-phenyl, n is 1, D is CH_2, Z is $C(CH_3)_2$, X and Y are both CH, and B is piperazine, then X_1 and Y_1 are not both CH_2; and

(ii) when C is phenyl substituted with R2, D is CH_2, n is 1, and B is piperazine, then ring A_{II} is not adamantanyl; and (iii) the compound is not 1-phenyl-4-4(tricycle[3.3.1.13,7] dec-1ylmethyl-piperazine.

23. The compound according to claim 22, wherein ring A_{II} is 

.

24. The compound according to claim 23, wherein X and Y are CH.

25. The compound according to claim 23, wherein each R' in X and Y are different.

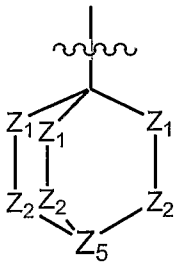
26. The compound according to claim 23, wherein X_1 and Y_1 are both CH_2.

27. The compound according to claim 23, wherein X_1 and Y_1 together for -CH=CH-.

28. The compound according to claim 23, wherein one of X_1 and Y_1 is CH_2 and the other of X_1 and Y_1 is NR'.

29. The compound according to claim 23, wherein Z is O, CH_2 or NR'.

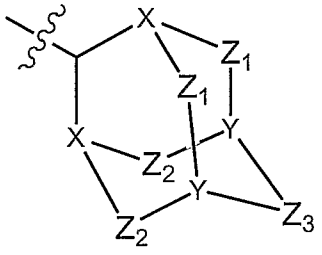
30. The compound according to claim 23, wherein Z is C(O), $-CH_2-C(O)-$, or $-C(O)-CH_2-$.

31. The compound according to claim 22, wherein ring A_{II} is .

32. The compound according to claim 31, wherein each of Z_1 and Z_2 is independently CH_2, CHR', NR', or C(O).

33. The compound according to claim 31, wherein each of Z_1 and Z_2 is independently CH_2 or NR'.

34. The compound according to claim 31, wherein each of Z_1 and Z_2 is CH_2.

35. The compound according to claim 22, wherein ring A_{II} is .

36. The compound according to claim 35, wherein each of Z_1 and Z_3 is independently CH_2 or NR'.

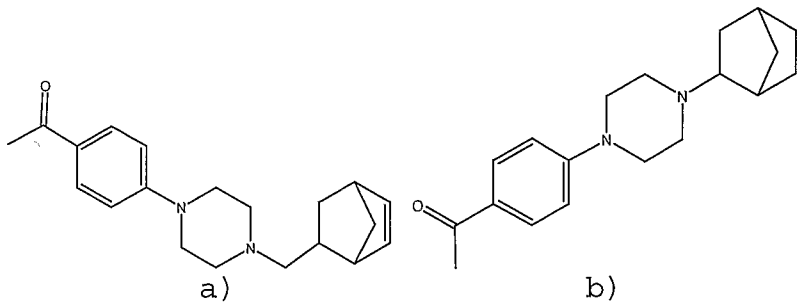
37. The compound according to claim 35, wherein Z_1 and Z_3 are each CH_2.

38. The compound according to claim 35, wherein each of X and Y is CR'.

39. The compound according to claim 35, wherein each of X and Y is CH.

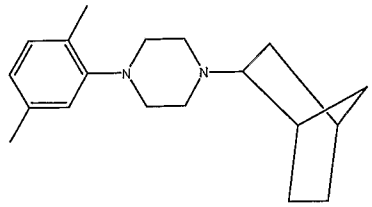
40. The compound according to any of claims 22-39 wherein B is piperazine.

41. The compound according to claim 22 selected from

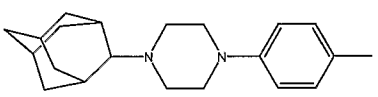


a)

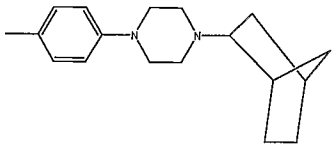
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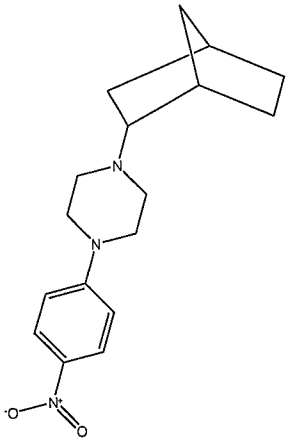
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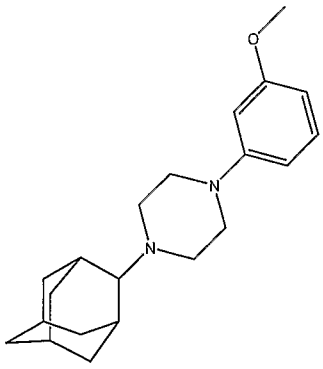
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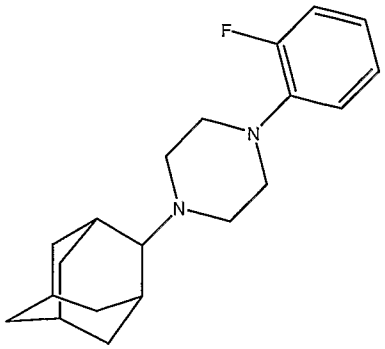
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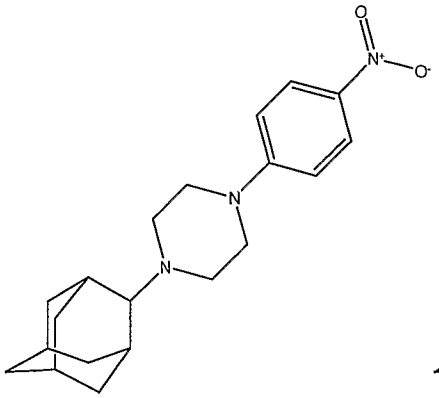
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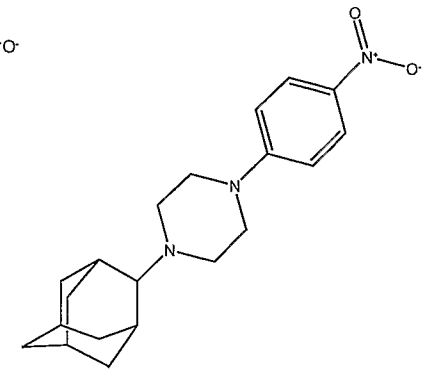
g)



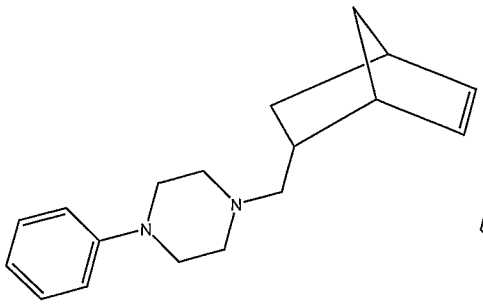
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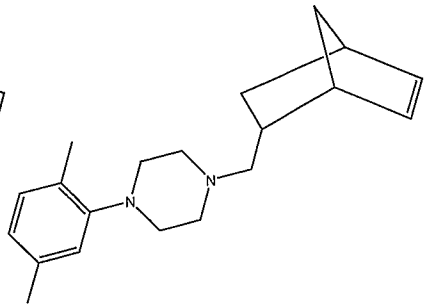
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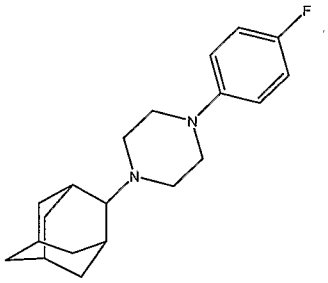
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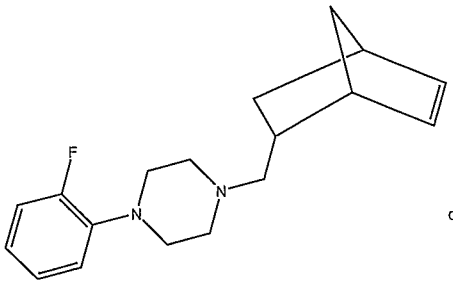
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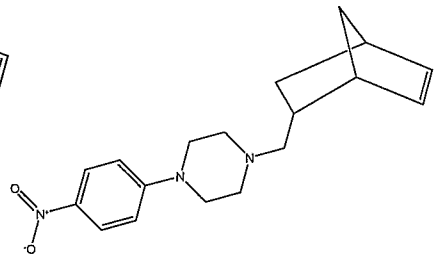
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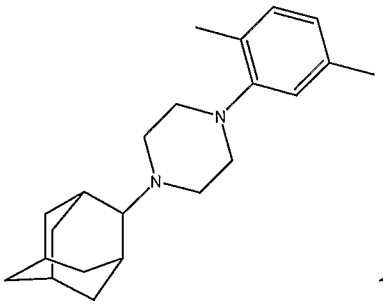
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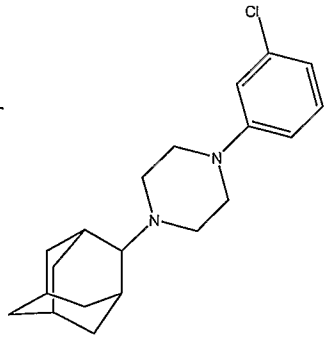
m)



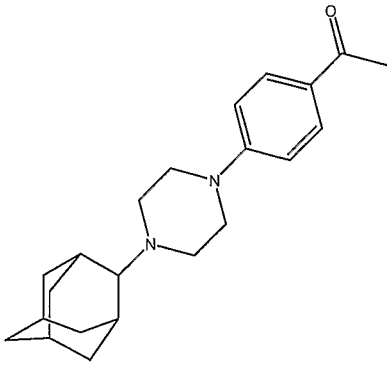
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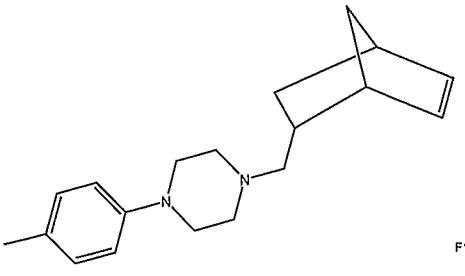
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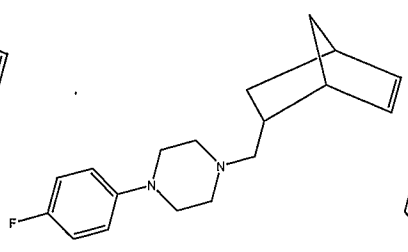


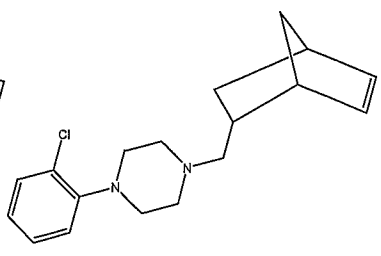
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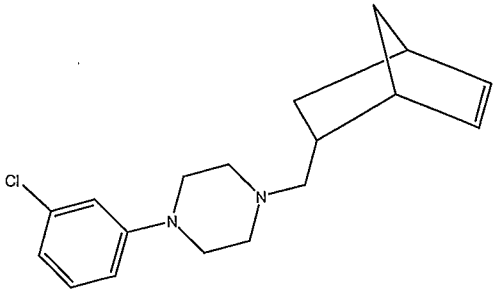
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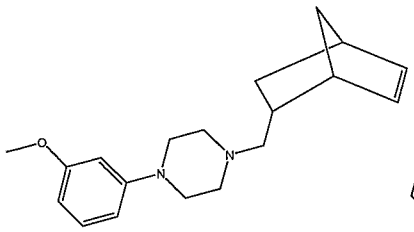




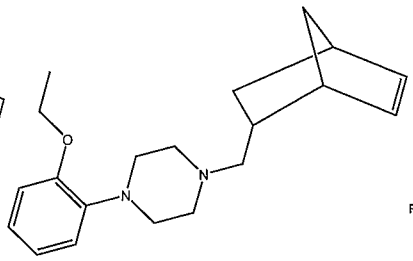
r) s) t)



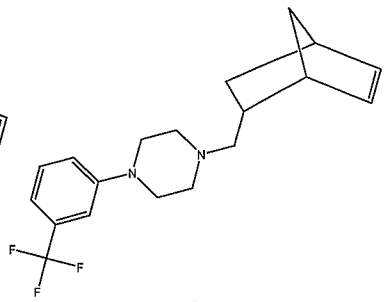
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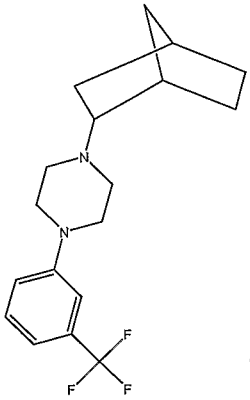
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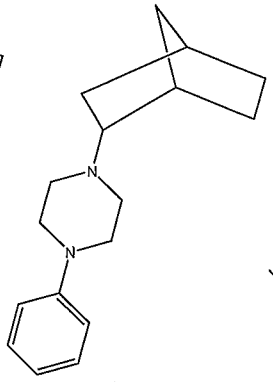
w)



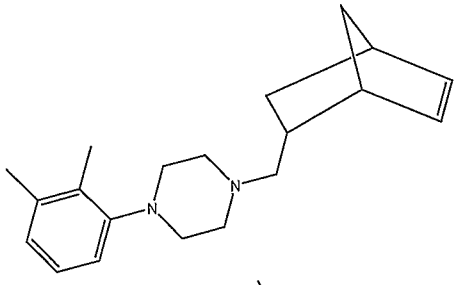
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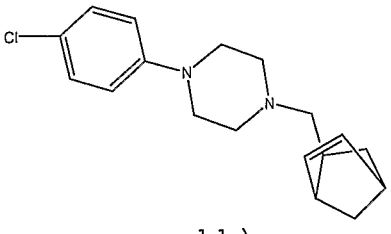
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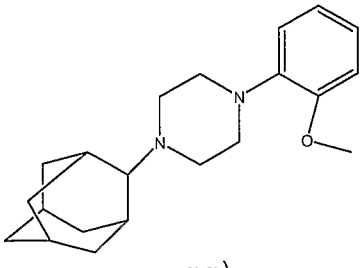
z)



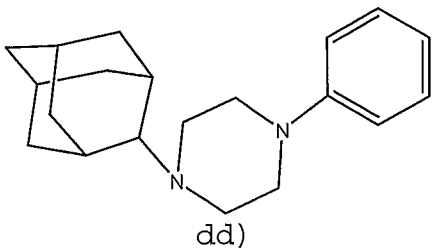
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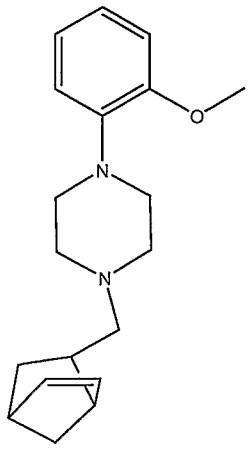
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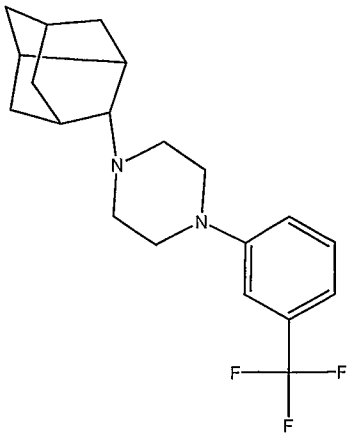
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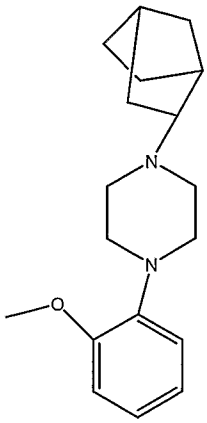
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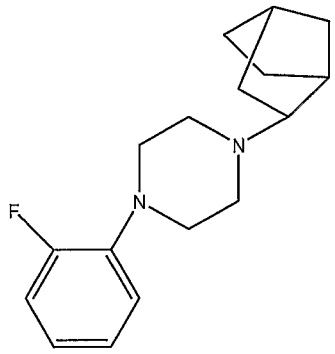
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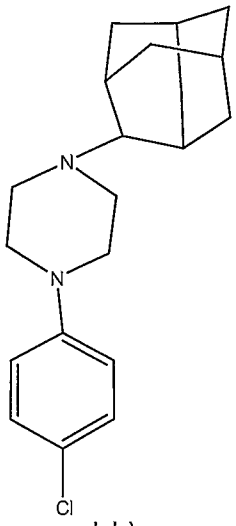
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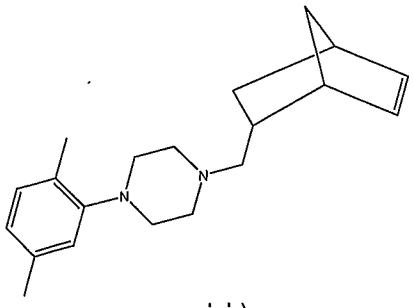
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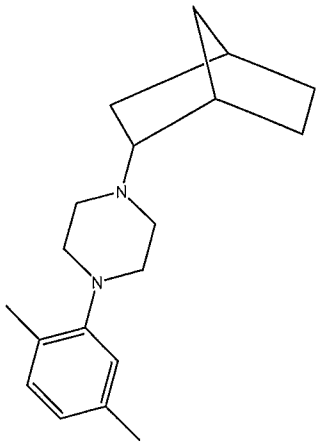
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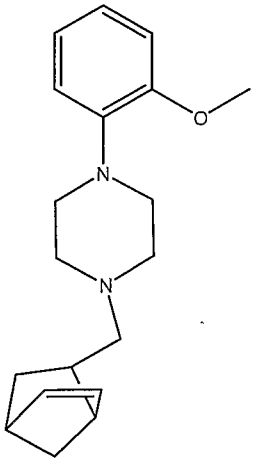
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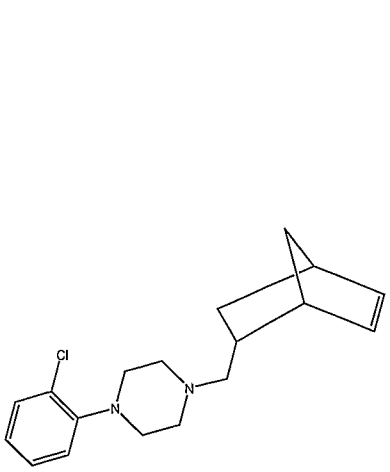
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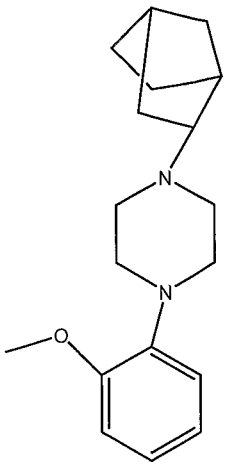
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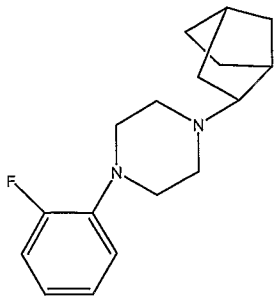
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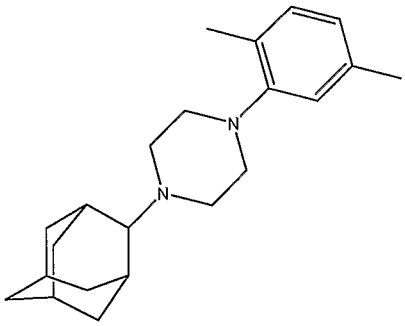
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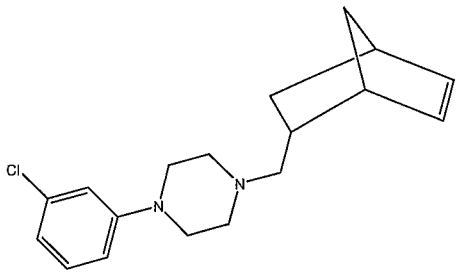
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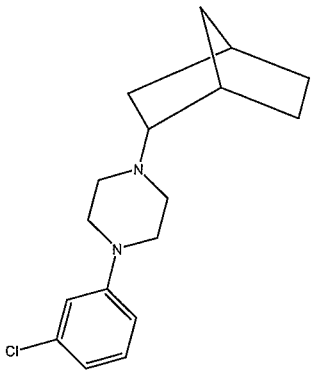
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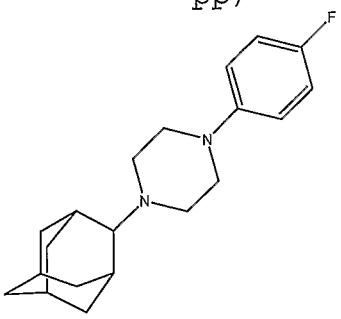
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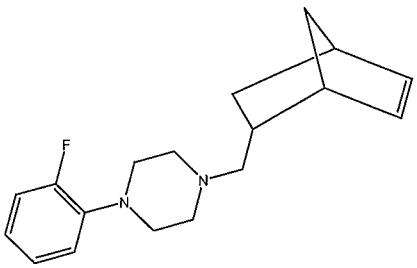
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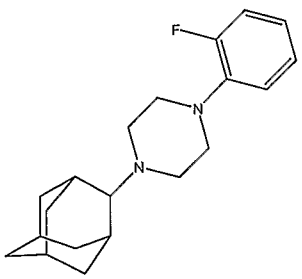
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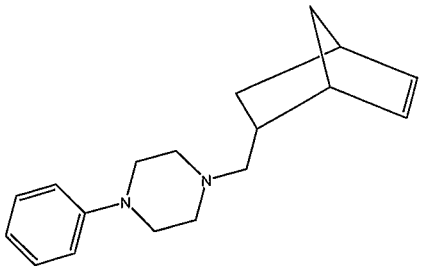
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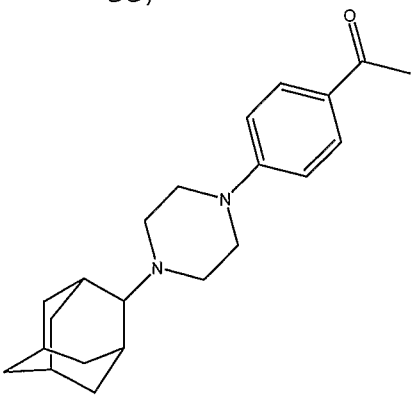
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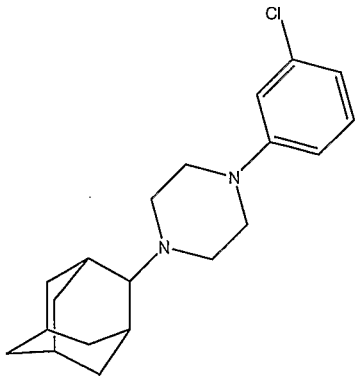
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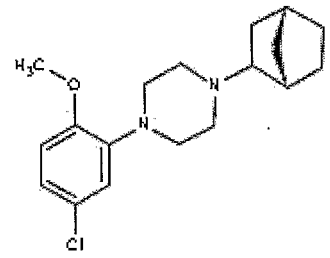
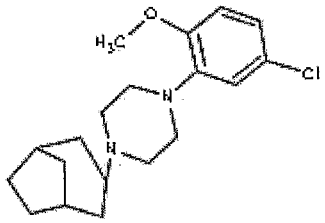
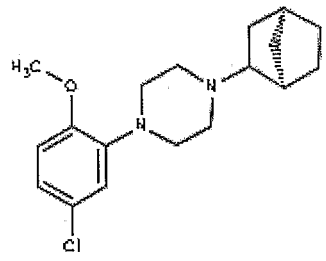
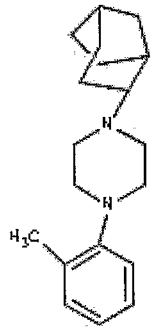
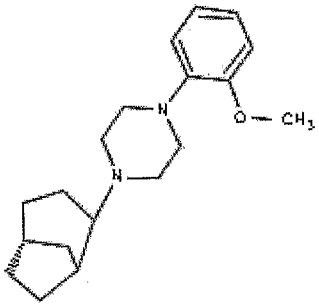
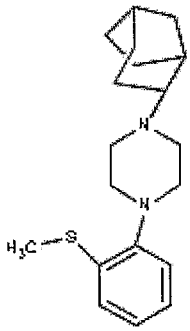


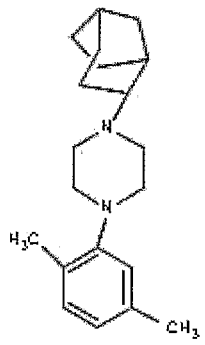
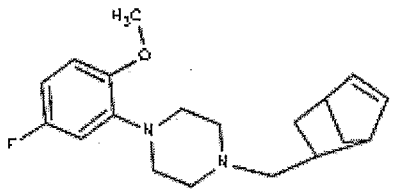
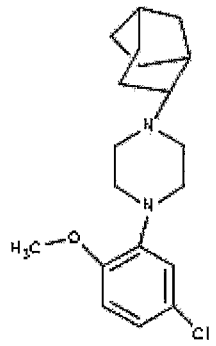
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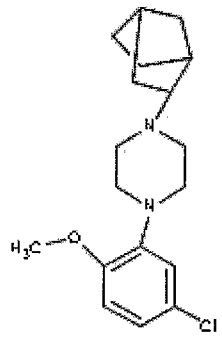
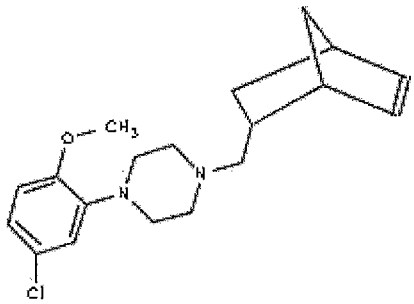
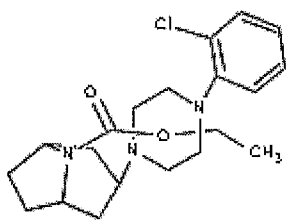


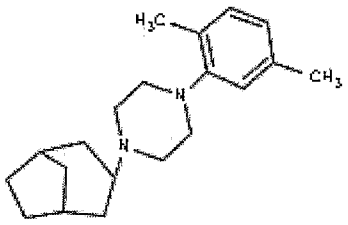
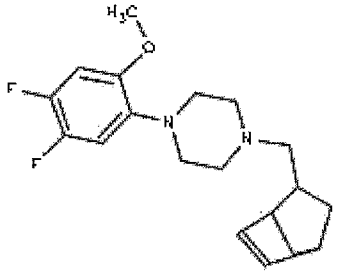
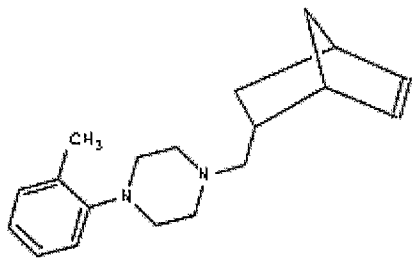
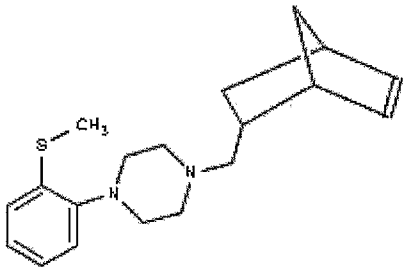
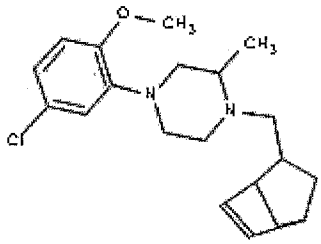
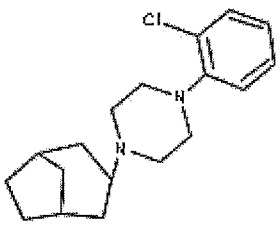
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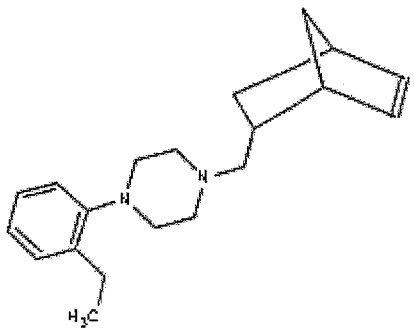
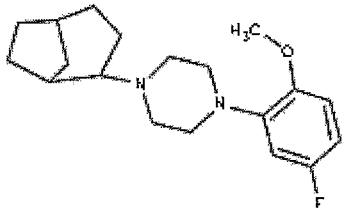
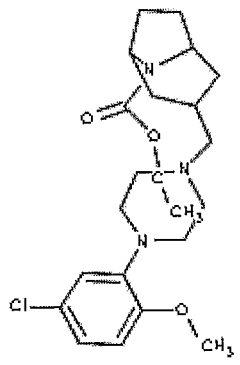
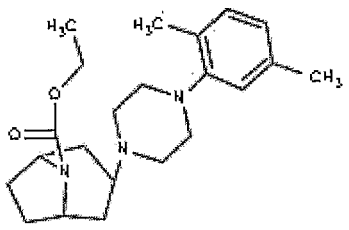
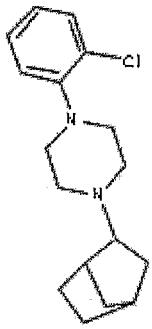
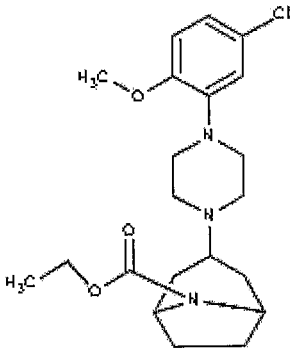
42. The compound according to claim 22

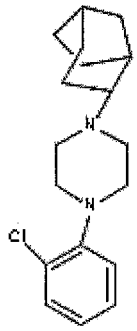
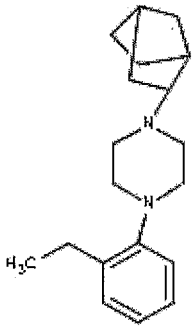
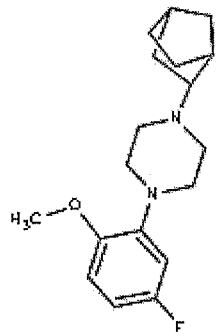
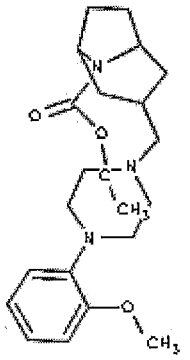
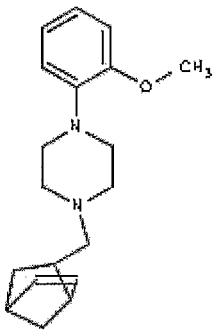
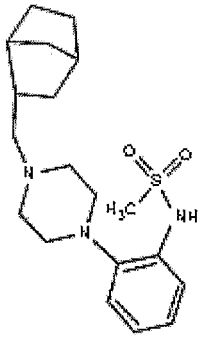
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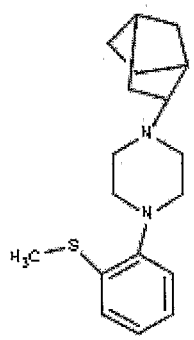
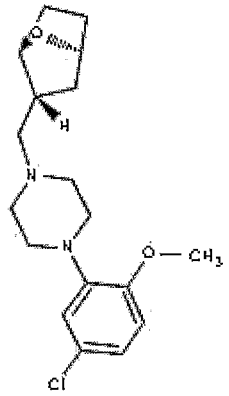
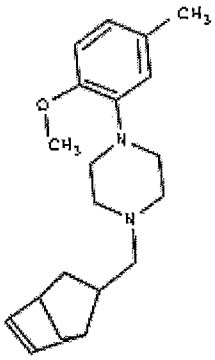
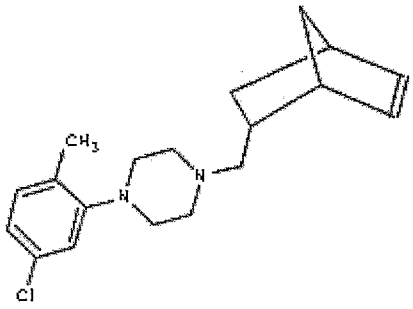
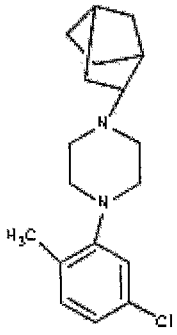
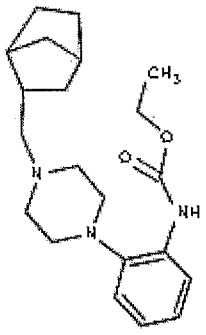
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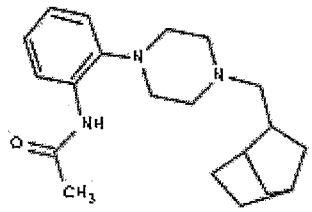
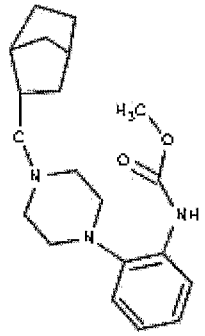
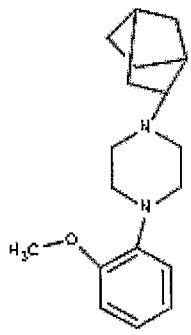
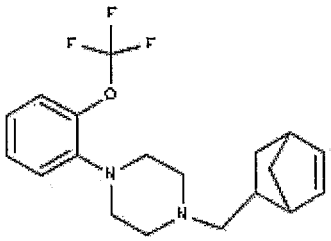
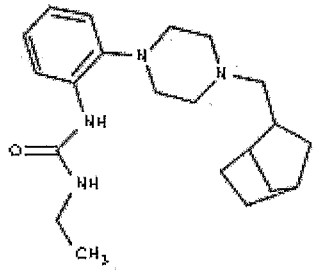
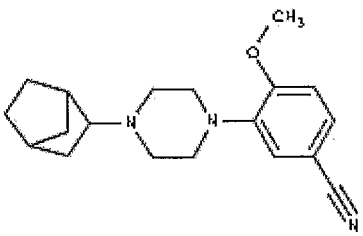
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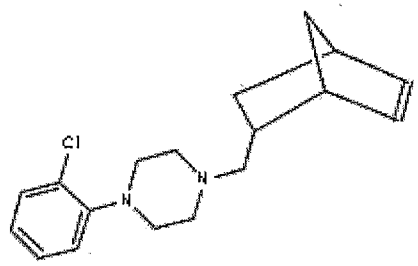
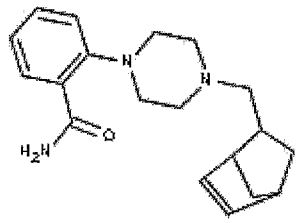
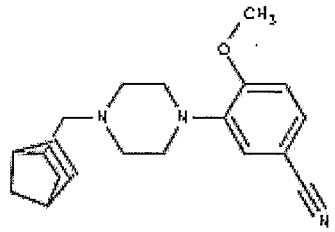
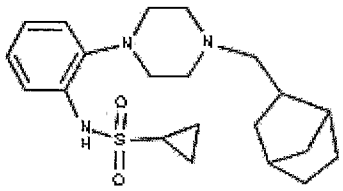
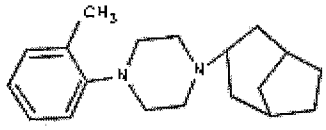
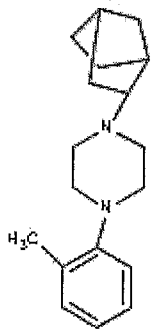
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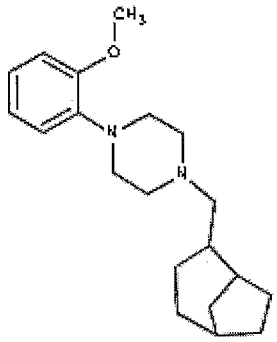
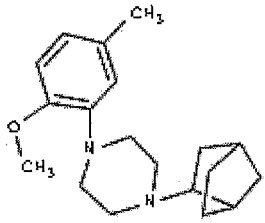
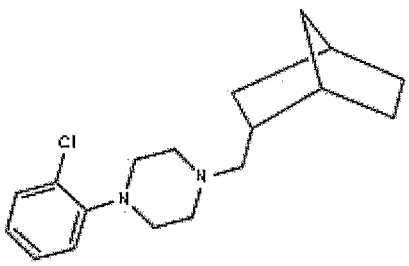
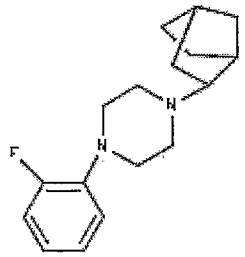
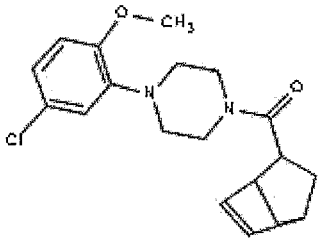
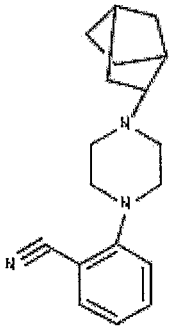
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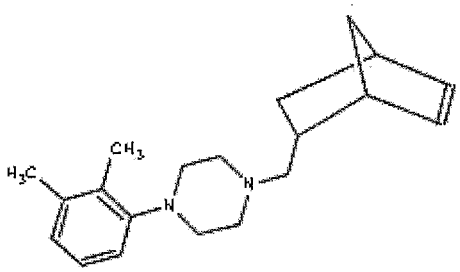
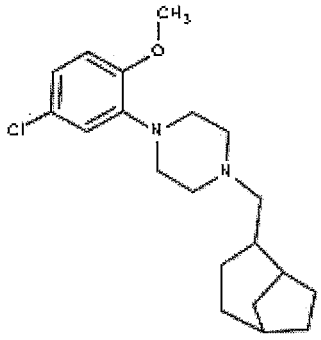
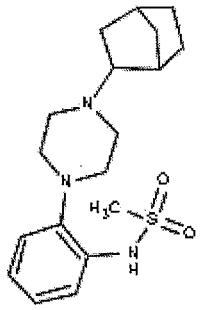
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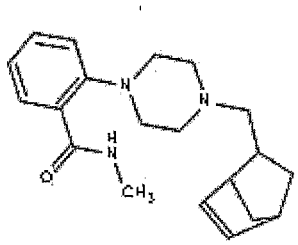
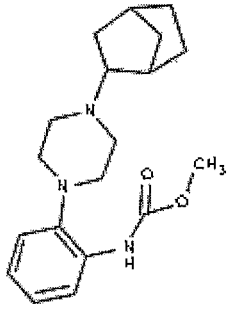
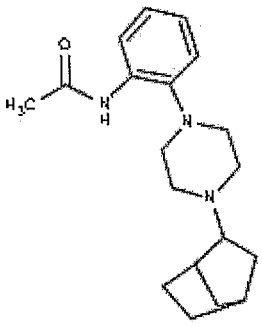
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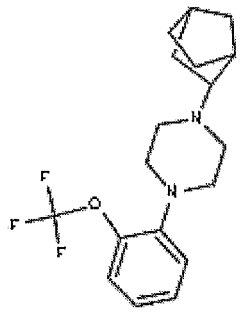
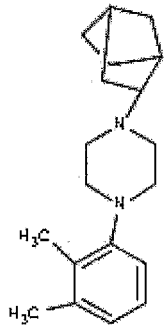
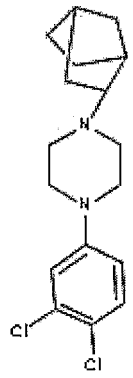
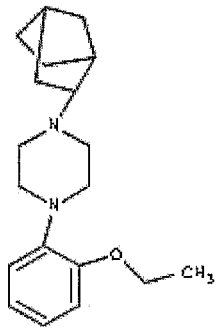
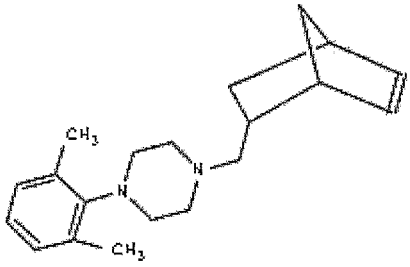
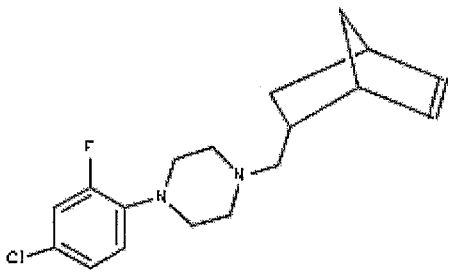
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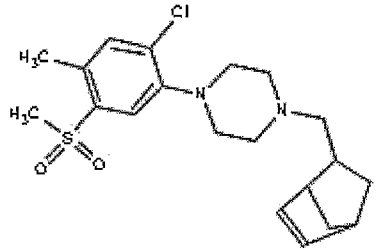
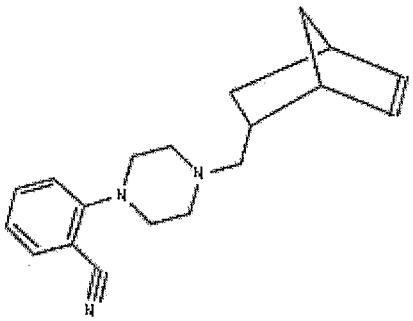
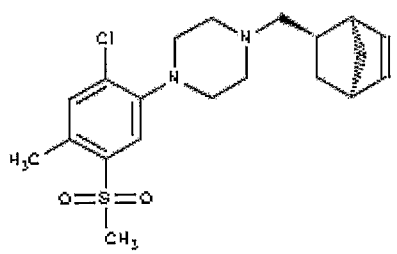
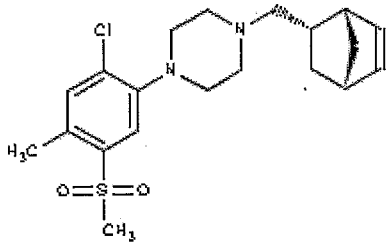
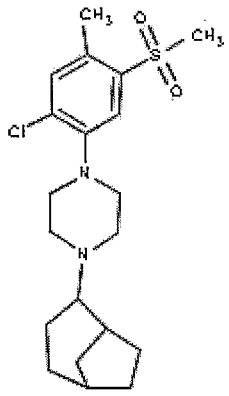
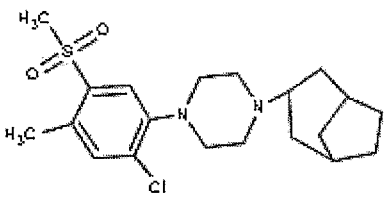
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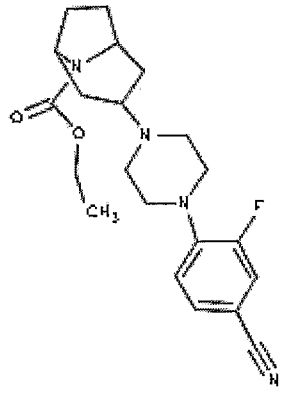
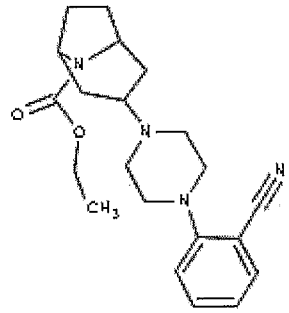
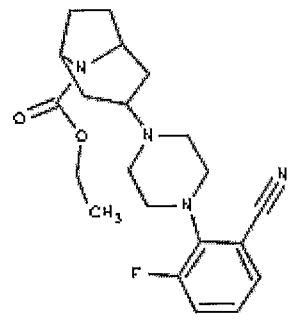
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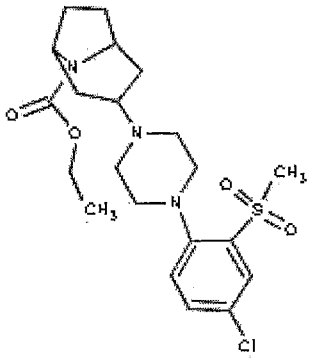
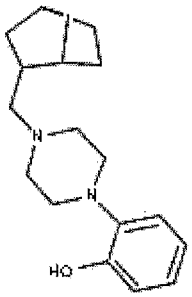
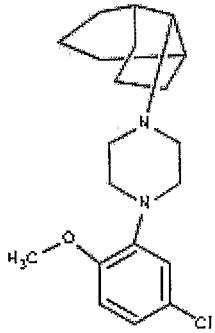
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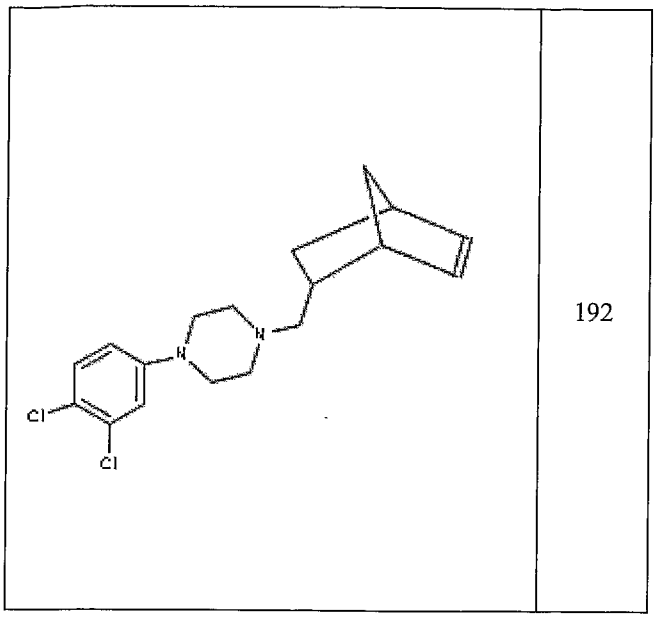
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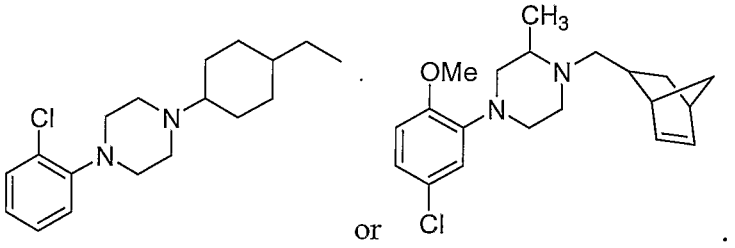
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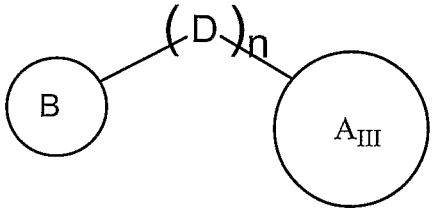


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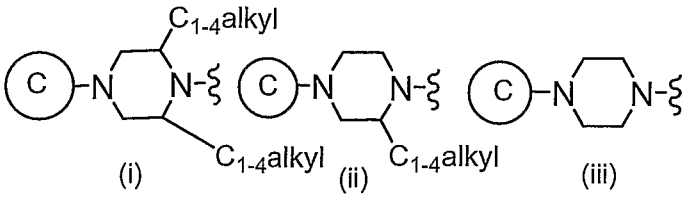
43. A compound of formula III



(III);

wherein:

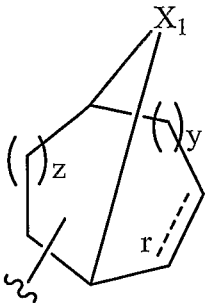
B is selected from



D is CF_2, CH_2, or CHR^9;

Ring C is phenyl optionally substituted with 1 to 4 of R^1, R^2, R^3, R^4, or R^5;

ring A_{III} is



optionally substituted with 1-3 of R';

X_1 is independently selected from a bond, CH_2, CHR^9, O, S, NR', C(O), S(O), SO_2;

Each R' is independently selected from (C1-C4)aliphatic$_m$-Q^1, $S(O)_iR^6$, $S(O)_iR^5$, $SO_2N(R^6)_2$, $SO_2N(R^5)_2$, $SO_2NR^5R^6$, $C(O)R^5$, $C(O)OR^5$, $C(O)R^6$, $C(O)OR^6$, $C(O)N(R^6)_2$, $C(O)N(R^5)_2$, $C(O)N(R^5R^6)$, $C(O)N(OR^6)R^6$, $C(O)N(OR^5)R^6$, $C(O)N(OR^6)R^5$, $C(O)N(OR^5)R^5$, $C(NOR^6)R^6$, $C(NOR^6)R^5$, $C(NOR^5)R^6$, $C(NOR^5)R^5$, R^2, or R_6, provided that when any of X_1, Y_1, Z, Z_1, Z_2, Z_3, and Z_4 are NR', then R' is $S(O)_iR^6$, $S(O)_iR^5$, $SO_2N(R^6)_2$, $SO_2N(R^5)_2$, $SO_2NR^5R^6$, $C(O)R^5$, $C(O)OR^5$, $C(O)R^6$, $C(O)OR^6$, $C(O)N(R^6)_2$, $C(O)N(R^5)_2$, $C(O)N(R^5R^6)$, $C(O)N(OR^6)R^6$, $C(O)N(OR^5)R^6$, $C(O)N(OR^6)R^5$, $C(O)N(OR^5)R^5$, $C(NOR^6)R^6$, $C(NOR^6)R^5$, $C(NOR^5)R^6$, $C(NOR^5)R^5$; R^1 is oxo or ((C1-C4)aliphatic$_m$-Q^1;

Each Q^1 is independently halo, CN, NO_2, CF_3, OCF_3, OH, SR^6, $S(O)R^6$, SO_2R^6, $N(R^6)_2$, NR^6R^8, COOH, $COOR^6$ or OR^6;

Each R^2 independently is aliphatic optionally substituted with 1-3 substituents independently selected from R^1, R^4, or R^5;

Each R^3 is independently a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring, wherein each of the cycloaliphatic, aryl, heterocyclic, or heteroaryl are optionally substituted with 1-3 substituents independently selected from R^1, R^2, R^4, or R^5;

Each R^4 is independently OR^5, OR^6, $OC(O)R^6$, $OC(O)R^5$, $OC(O)OR^6$, $OC(O)OR^5$, $OC(O)N(R^6)_2$, $OC(O)N(R^5)_2$, $OC(O)N(R^6R^5)$, $S(O)_iR^6$, $S(O)_iR^5$, $SO_2N(R^6)_2$, $SO_2N(R^5)_2$, $SO_2NR^5R^6$, $C(O)R^5$, $C(O)OR^5$, $C(O)R^6$, $C(O)OR^6$, $C(O)N(R^6)_2$, $C(O)N(R^5)_2$, $C(O)N(R^5R^6)$, $C(O)N(OR^6)R^6$, $C(O)N(OR^5)R^6$, $C(O)N(OR^6)R^5$, $C(O)N(OR^5)R^5$, $C(NOR^6)R^6$, $C(NOR^6)R^5$, $C(NOR^5)R^6$, $C(NOR^5)R^5$, $N(R^6)_2$, $N(R^5)_2$, $N(R^5R^6)$, $NR^5C(O)R^5$, $NR^6C(O)R^6$, $NR^6C(O)R^5$, $NR^6C(O)OR^6$, $NR^5C(O)OR^6$, $NR^6C(O)OR^5$, $NR^5C(O)OR^5$, $NR^6C(O)N(R^6)_2$, $NR^6C(O)NR^5R^6$, $NR^6C(O)N(R^5)_2$, $NR^5C(O)N(R^6)_2$, $NR^5C(O)NR^5R^6$, $NR^5C(O)N(R^5)_2$, $NR^6SO_2R^6$, $NR^6SO_2R^5$, $NR^5SO_2R^5$, $NR^6SO_2N(R^6)_2$, $NR^6SO_2NR^5R^6$, $NR^6SO_2N(R^5)_2$, $NR^5SO_2NR^5R^6$, $NR^5SO_2N(R^5)_2$, $N(OR^6)R^6$, $N(OR^6)R^5$, $N(OR^5)R^5$, or $N(OR^5)R^6$;

Each R^5 is independently a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring, wherein each of the cycloaliphatic, aryl, heterocyclic, or heteroaryl are optionally substituted with 1 to 3 of R^1;

Each R^6 is independently H or aliphatic optionally substituted with R^7;

Each R^7 is independently a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring, wherein each of the cycloaliphatic, aryl, heterocyclic, or heteroaryl are optionally substituted with 1 to 2 of (C_1-C_6)-straight or branched alkyl, (C_2-C_6) straight or branched alkenyl or alkynyl, 1,2-methylenedioxy, 1,2-ethylenedioxy, or $(CH_2)_n-Q^2$;

Each Q^2 is independently selected from halo, CN, NO_2, CF_3, OCF_3, OH, S-aliphatic, S(O)-aliphatic, SO_2-aliphatic, COOH, C(O)O-aliphatic, or O-aliphatic;

Each R^8 is independently an amino protecting group;

Each R^9 is independently R^2, R^3, or R^6;

Each i is 0, 1, 2, or 3;

Each m is 0 or 1;

Each n is 0 or 1;

Each y is 0, 1 or 2;

Each z is 0, 1, or 2 provided that y + z is 1, 2, or 3; and

Bond r is a single or double bond;

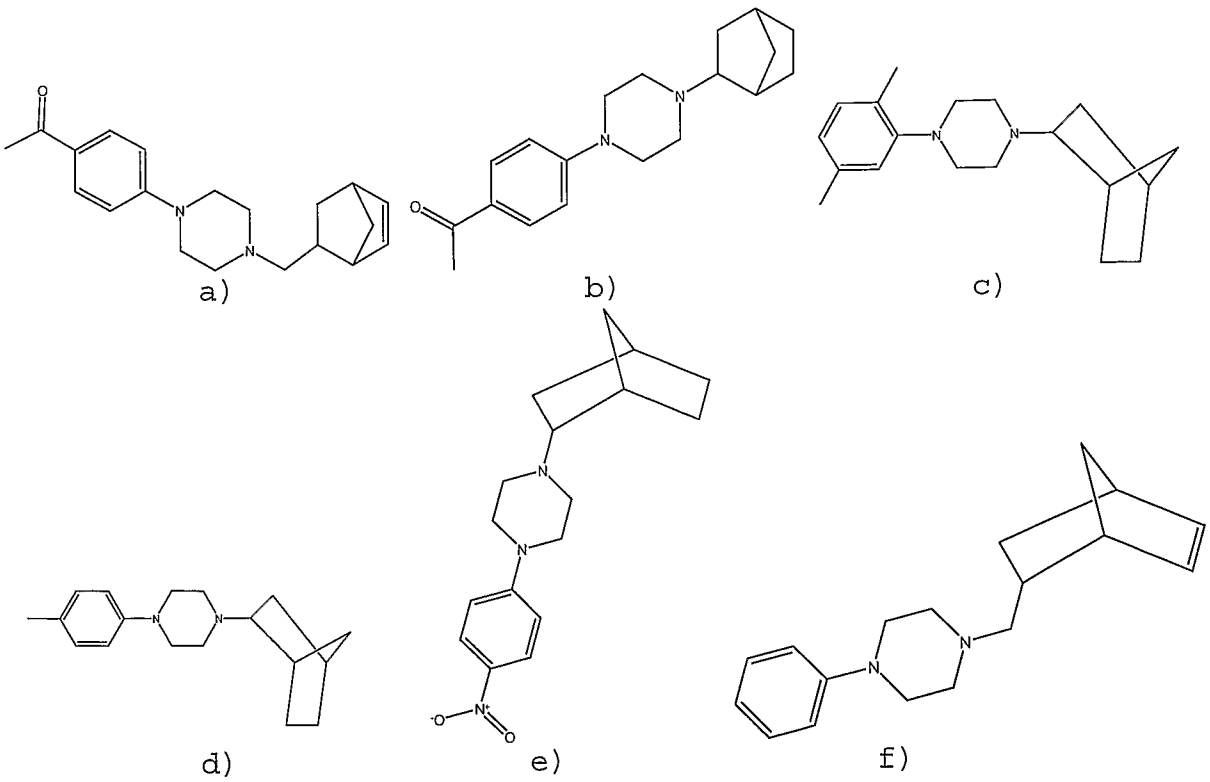
provided that when D is CH_2, y is 1 and z is 2, that X1 is other than C(O) or -CH(OH)-.

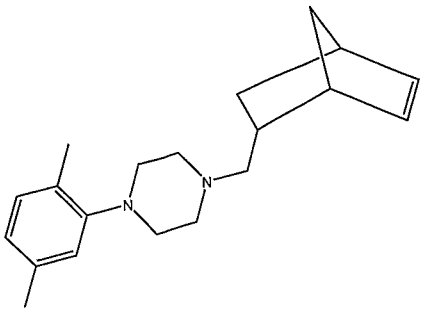
44. The compound according to claim 43, wherein X_1 is NR'.

45. The compound of claim 43, wherein X_1 is $-N(C(O)OR_5)-$.

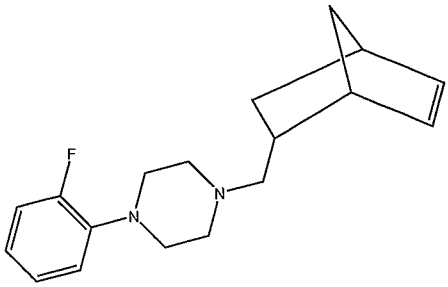
46. The compound according to 43, 44, or 45, wherein B is piperazine.

47. The compound of claim 43 selected from

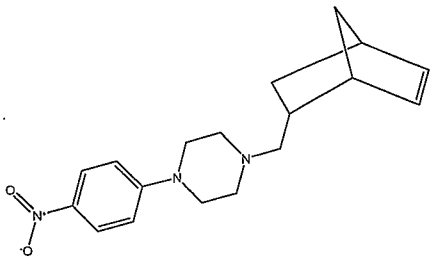




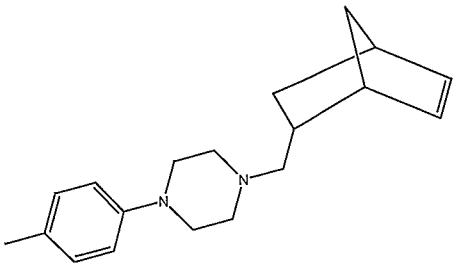
g)



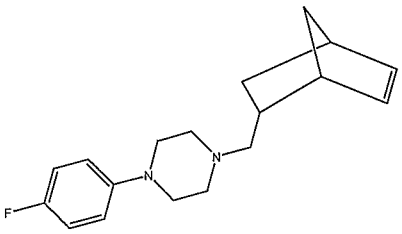
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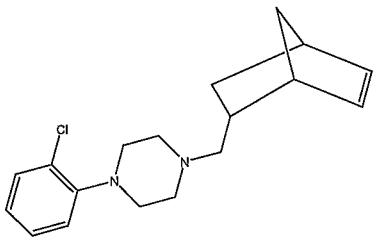
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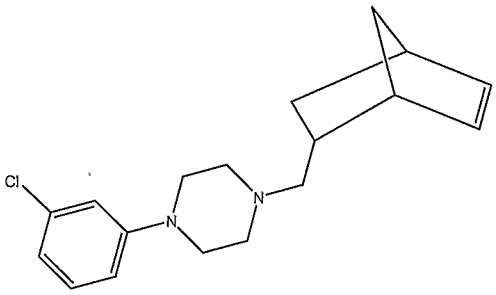
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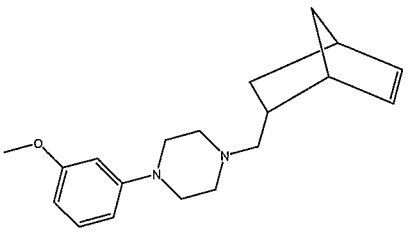
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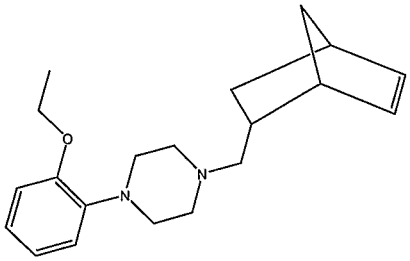
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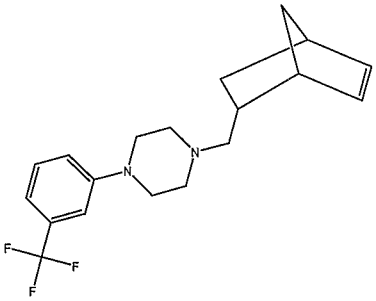
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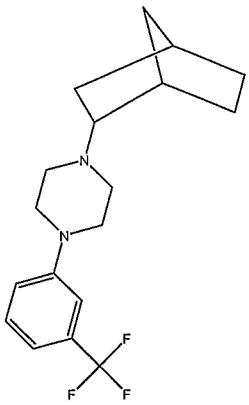
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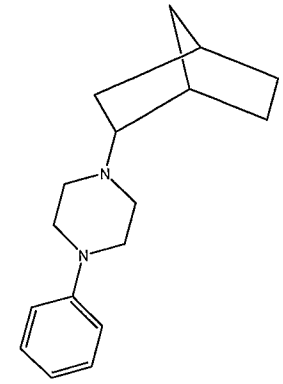
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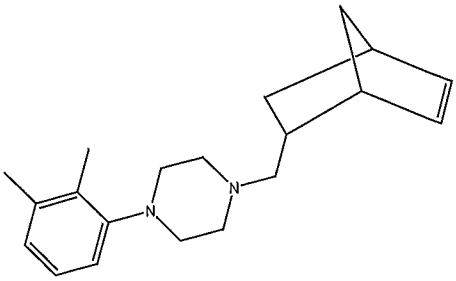
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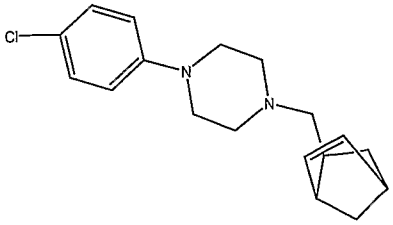
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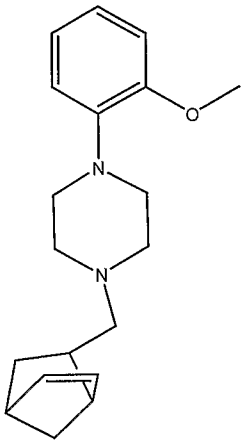
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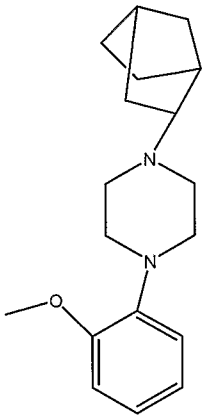
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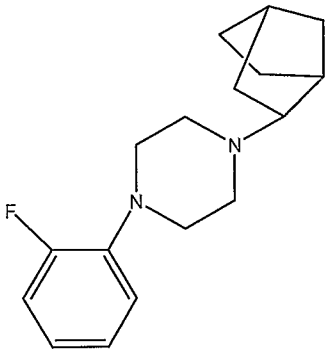
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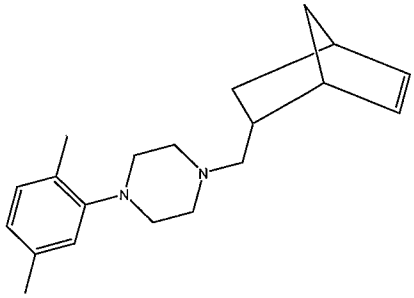
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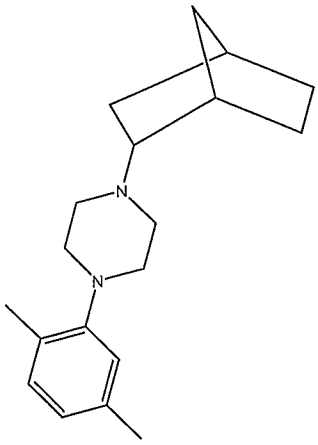
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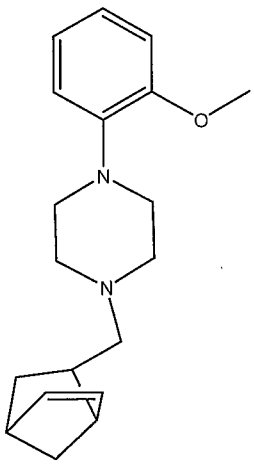
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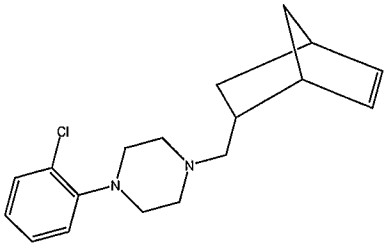
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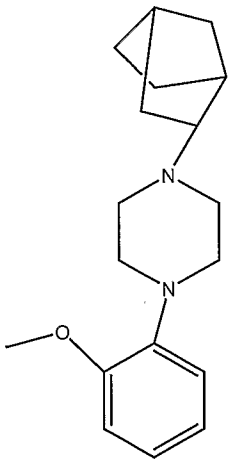
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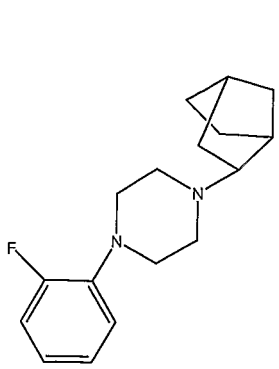
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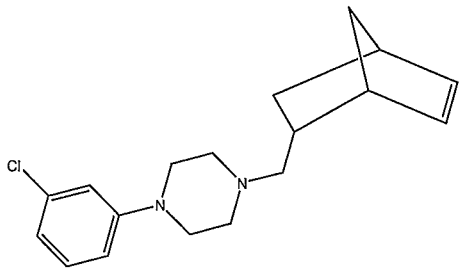
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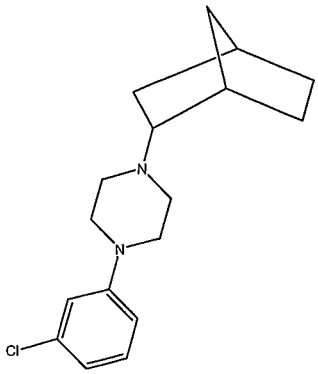
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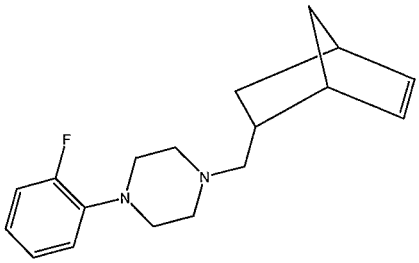
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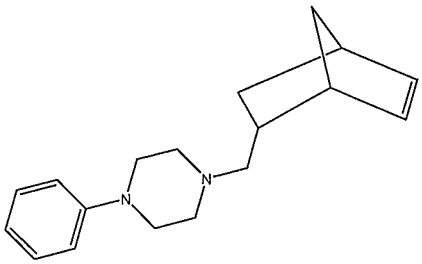
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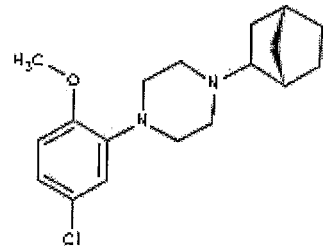
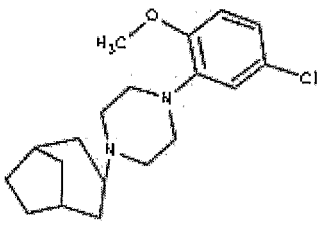


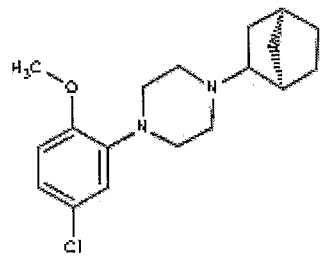
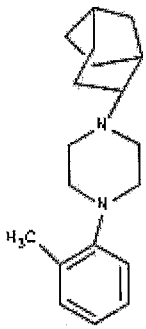
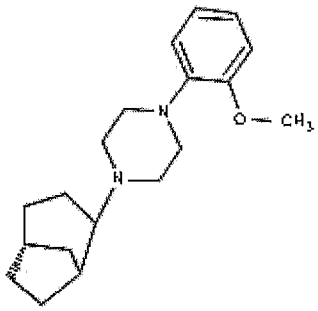
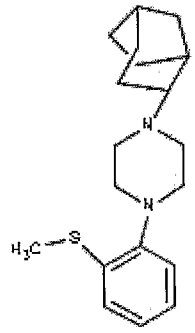
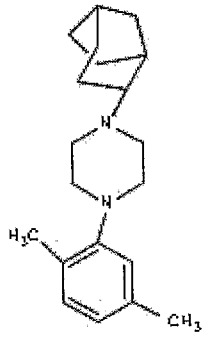
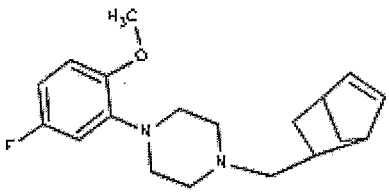
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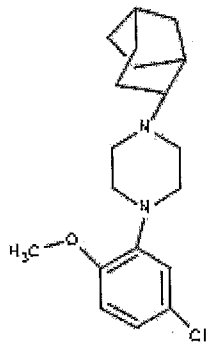
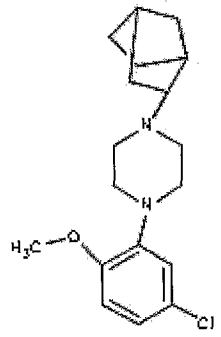
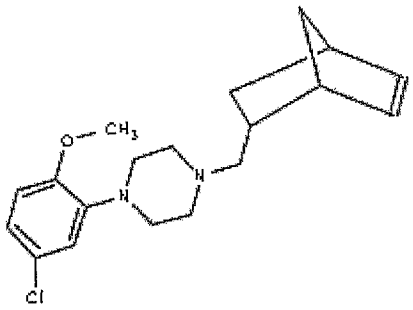
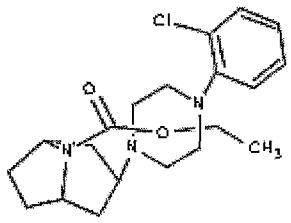
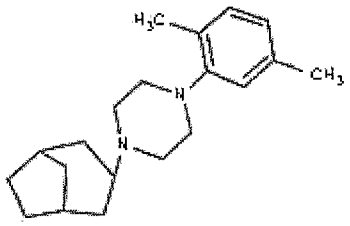
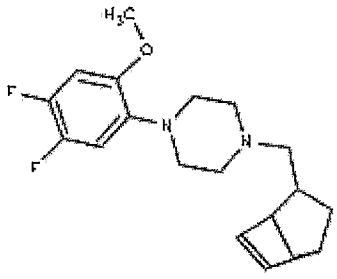


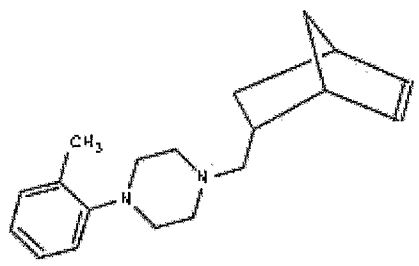
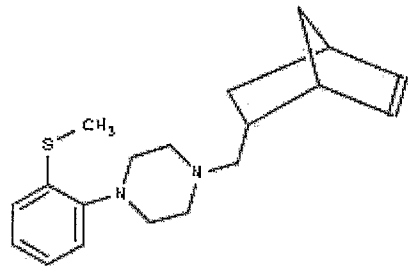
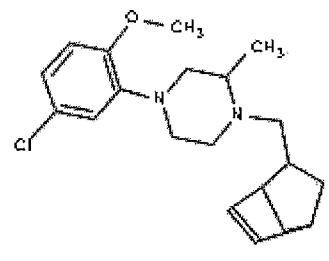
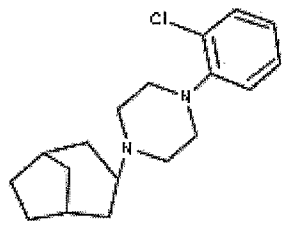
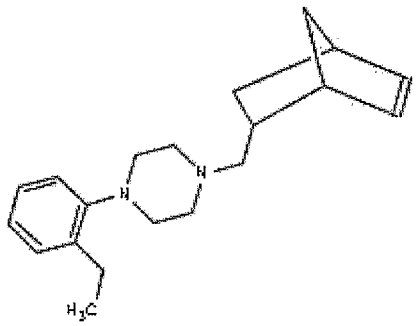
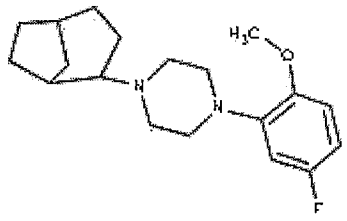
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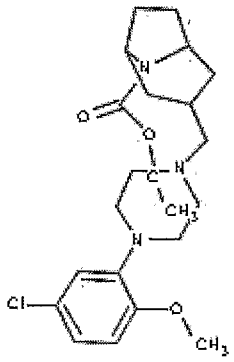
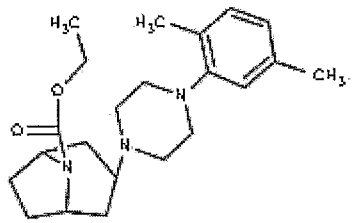
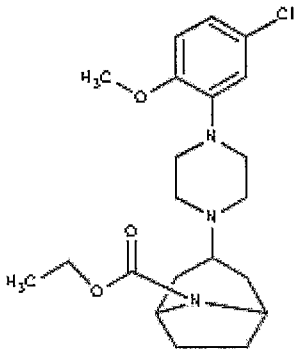
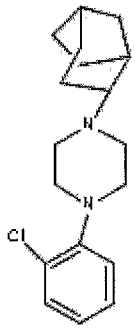
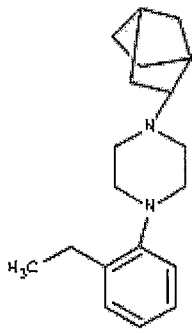
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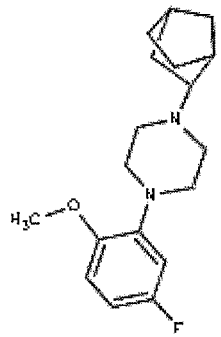
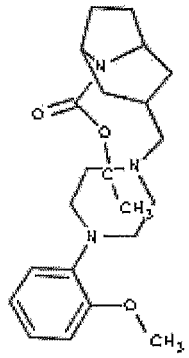
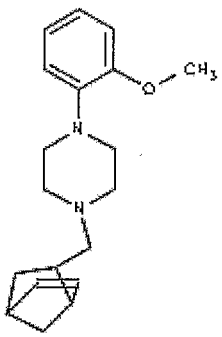
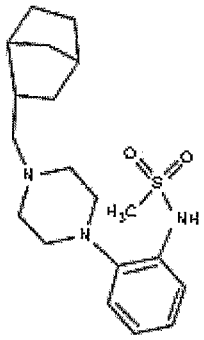
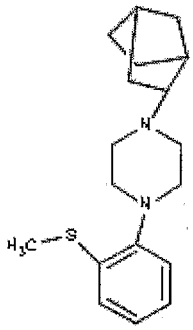
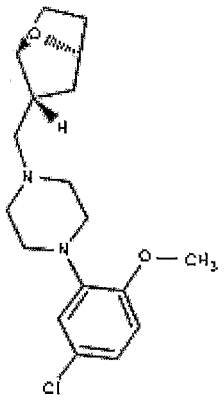
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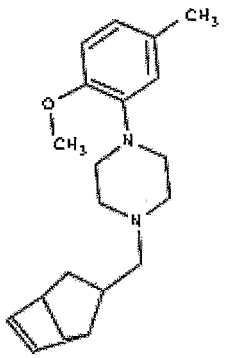
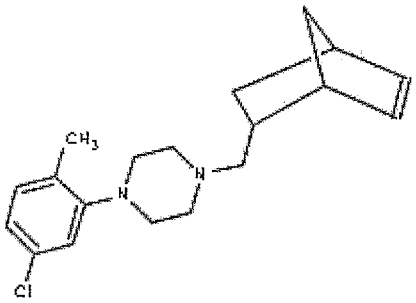
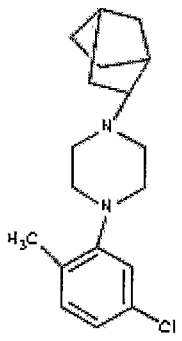
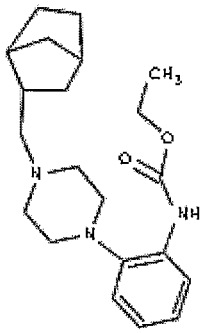
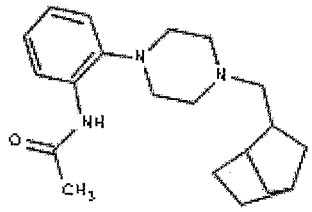
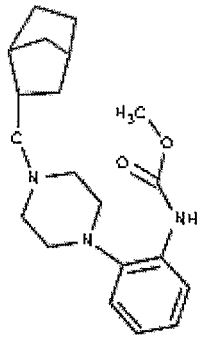
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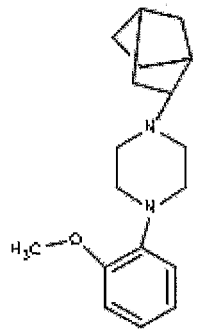
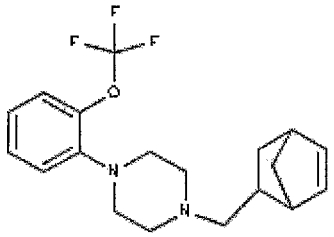
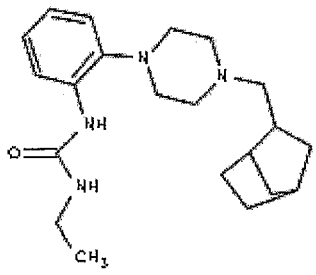
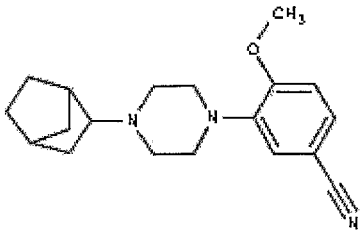
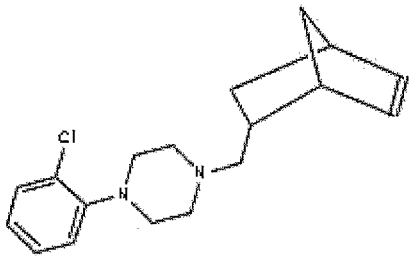
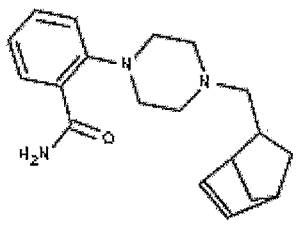
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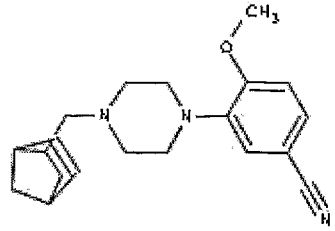
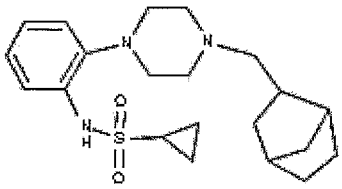
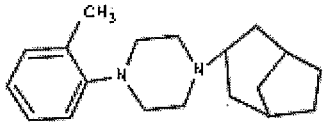
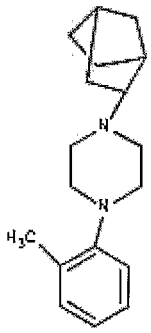
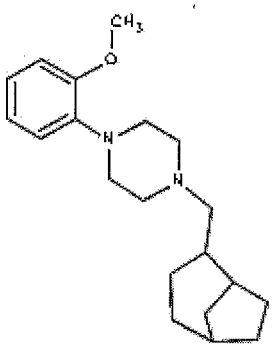
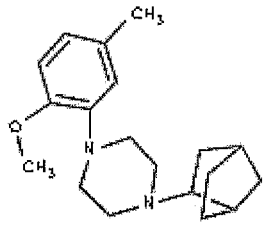
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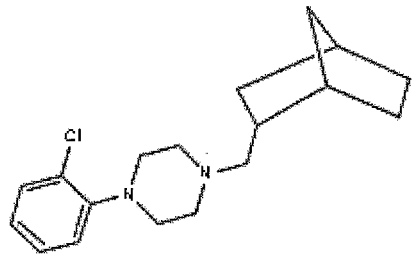
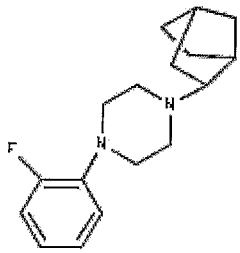
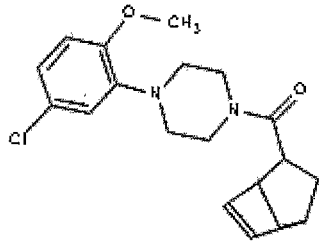
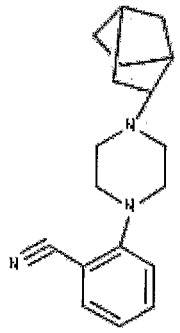
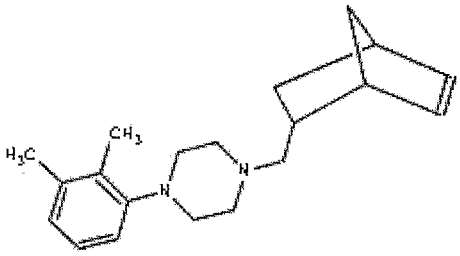
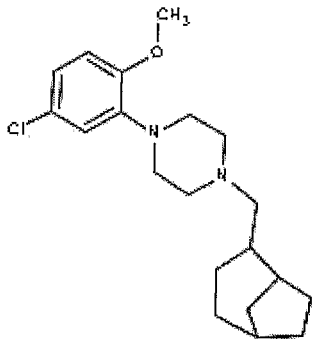
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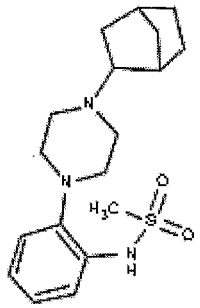
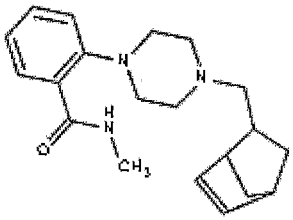
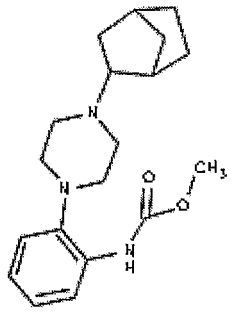
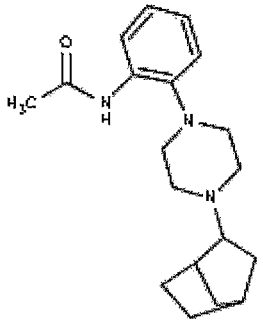
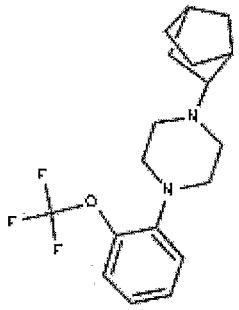
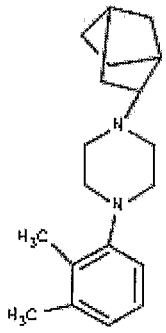
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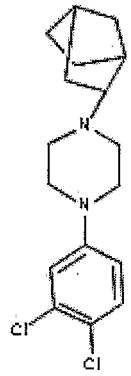
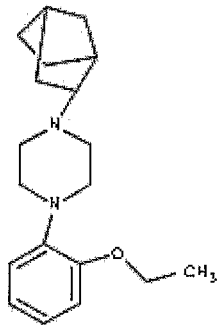
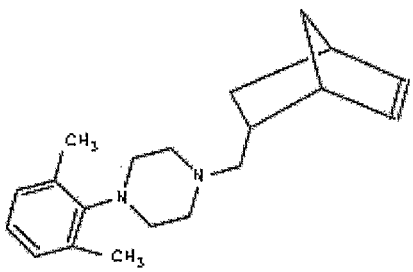
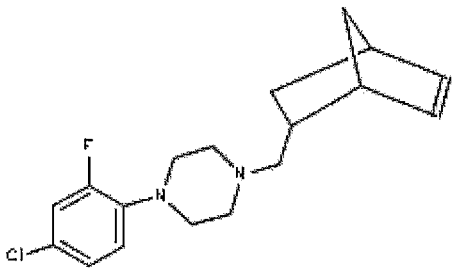
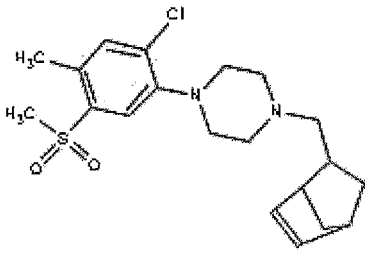
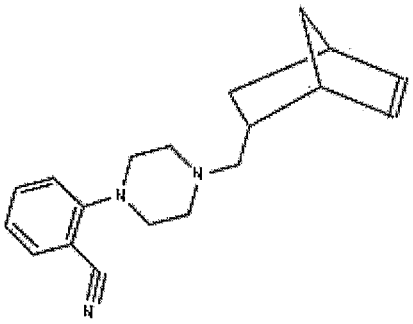
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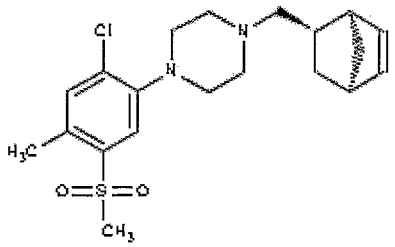
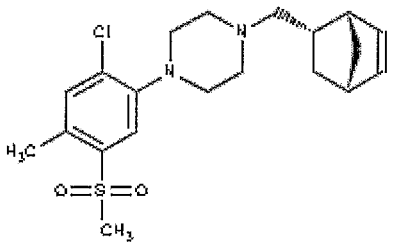
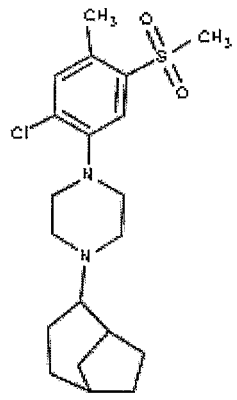
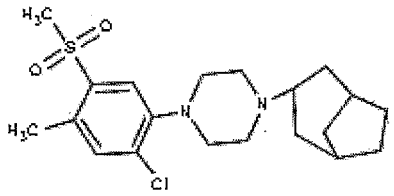
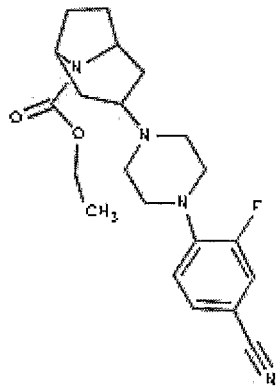
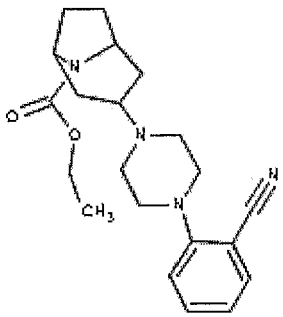
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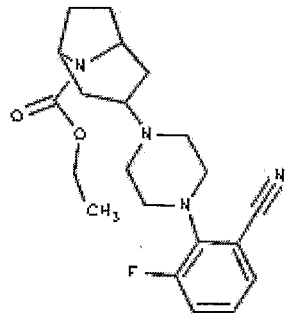
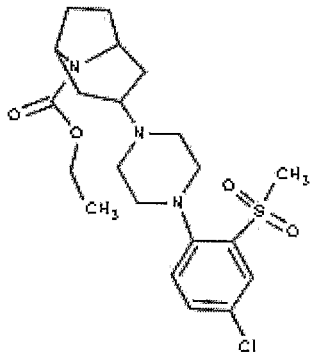
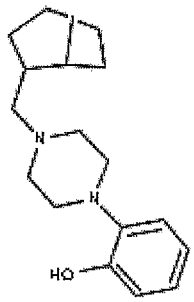
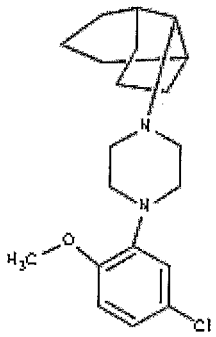
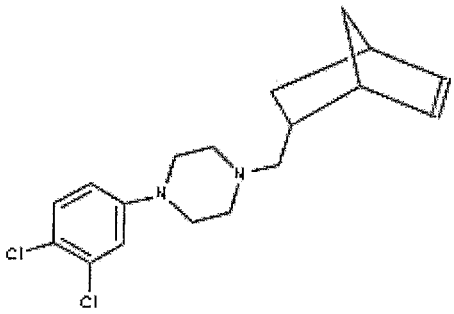
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49. A pharmaceutical composition comprising a compound a compound according to any one of claims 22-48 and a pharmaceutical carrier.

50. A method of treating or reducing the severity of a muscarinic receptor mediated disease in a mammal, comprising the step of administering to said mammal a compound as described in any one of claims 1-48, or a composition according to claim 49.

51. The method according to claim 50, wherein said muscarinic receptor is M_4.

52. The method according to claim 50, wherein said receptor is M_1.

53. A method of treating or reducing the severity of a disease in a patient, wherein said disease is selected from CNS derived pathologies including cognitive disorders, Attention Deficit Hyperactivity Disorder (ADHD), obesity, Alzheimer's disease, various dementias such as vascular dementia, psychosis associated with CNS disorders including schizophrenia, mania, bipolar disorders, pain conditions including acute and chronic syndromes, Huntington's Chorea, Friederich's ataxia, Gilles de la Tourette's Syndrome, Downs Syndrome, Pick disease, clinical depression, Parkinson's disease, peripheral disorders such as reduction of intra ocular pressure in Glaucoma and treatment of dry eyes and dry mouth including Sjögren's Syndrome, bradhycardia, gastric acid secretion, asthma, GI disturbances, and wound healing, wherein said method comprises the step of contacting said patient with a compound as described in any one of claims 1-48 or a composition according to claim 49.