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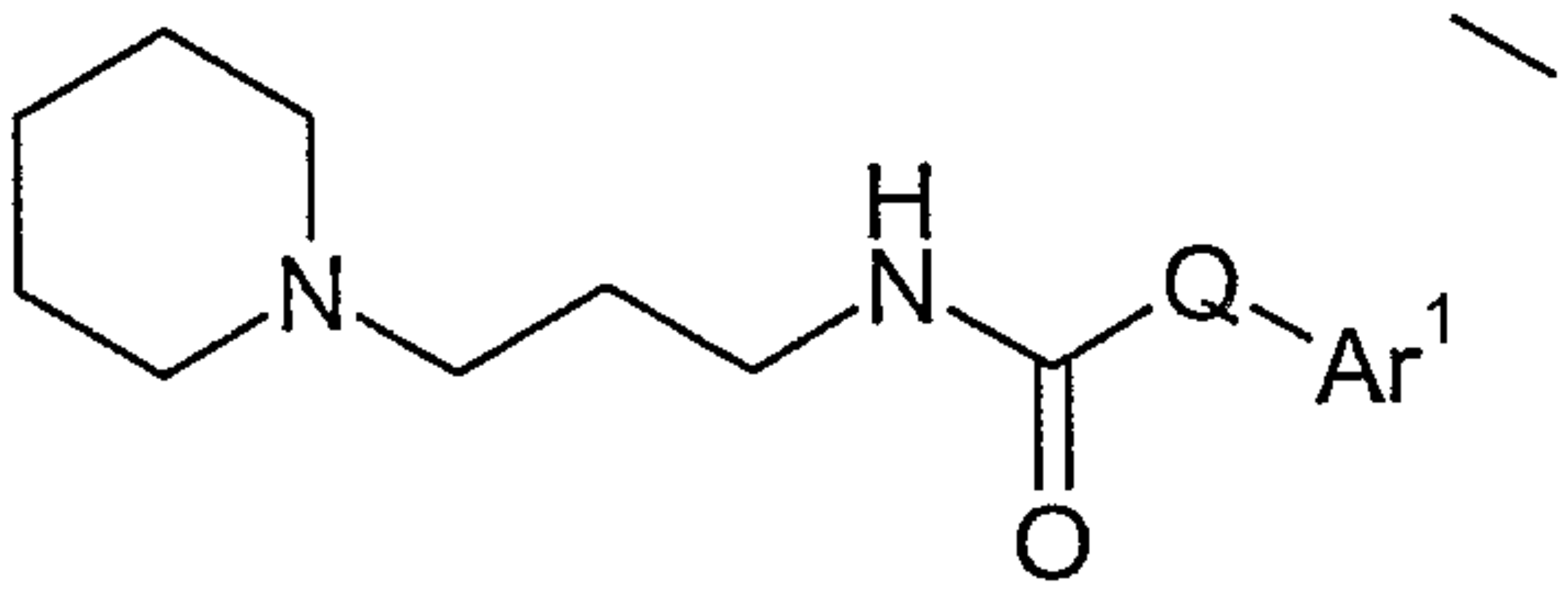
(54) Titre : NOUVEAUX DERIVES DE PIPERIDINE UTILISES EN TANT QUE LIGANDS DU RECEPTEUR H3 D'HISTAMINE POUR LE TRAITEMENT DE LA DEPRESSION

(54) Title: NOVEL PIPERIDINE DERIVATIVES AS HISTAMINE H3 RECEPTOR LIGANDS FOR TREATMENT OF DEPRESSION



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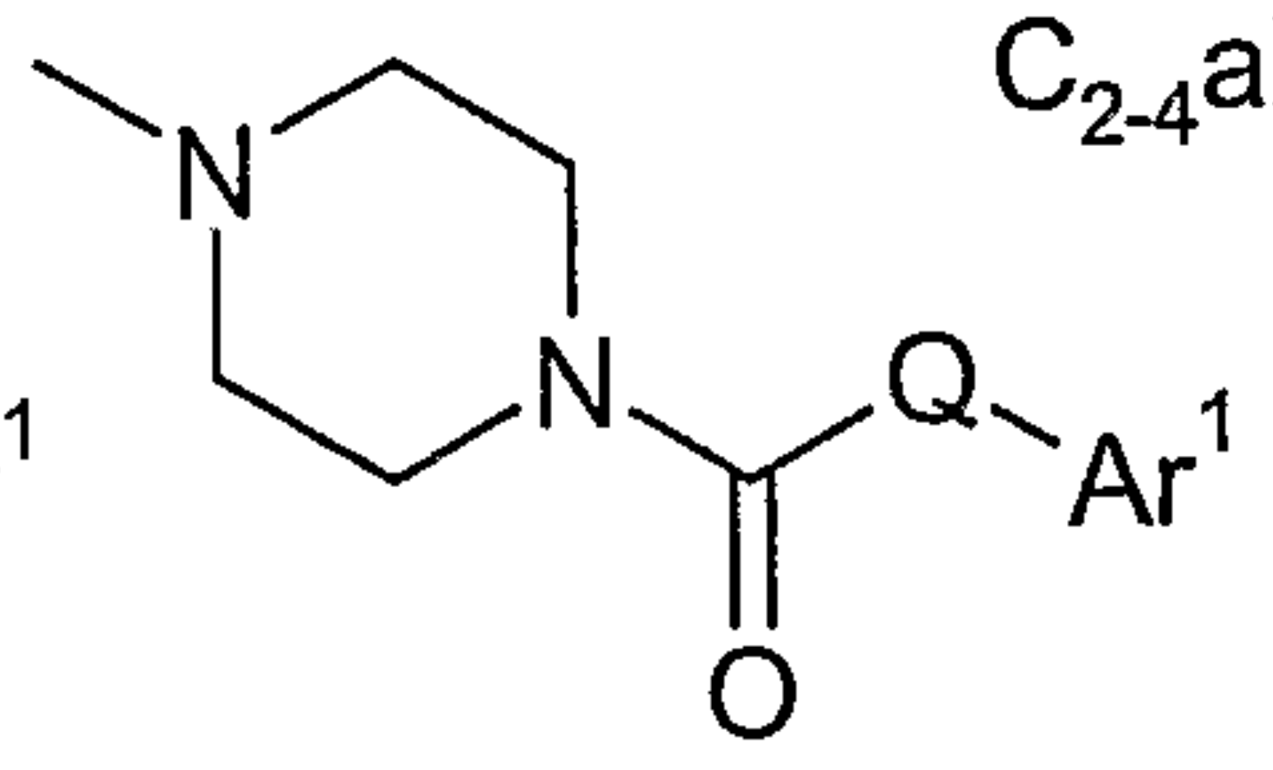

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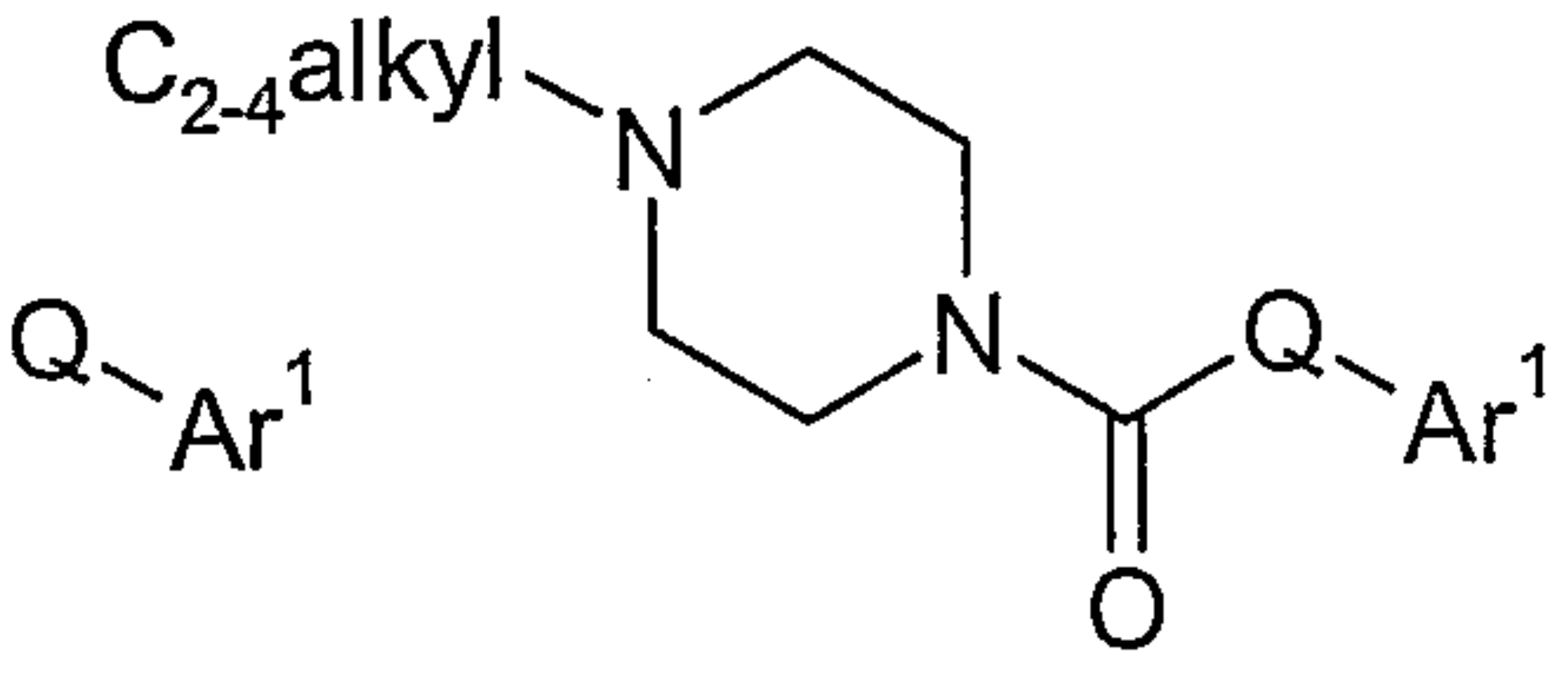

(III)

(57) **Abrégé/Abstract:**
Compounds of formula (I) wherein Ar^1 and Q are as defined in the specification, as well as salts, enantiomers thereof and pharmaceutical compositions including the compounds are prepared. They are useful in therapy, in particular in the treatment of depression.

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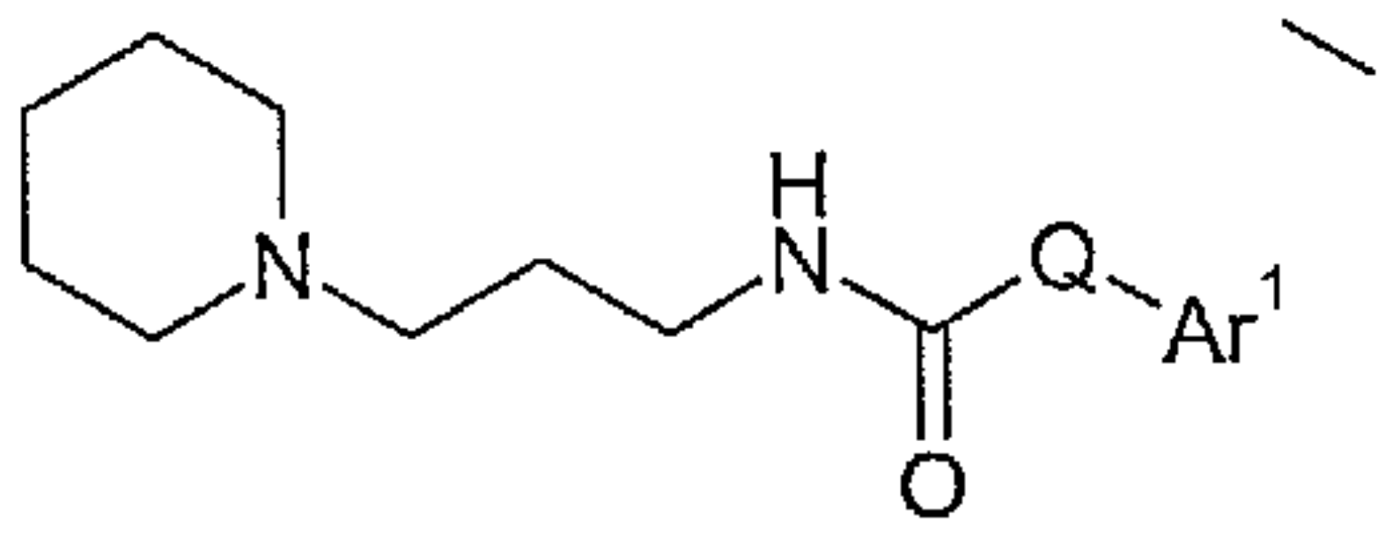
(54) Title: NOVEL PIPERIDINE DERIVATIVES AS HISTAMINE H3 RECEPTOR LIGANDS FOR TREATMENT OF DEPRESSION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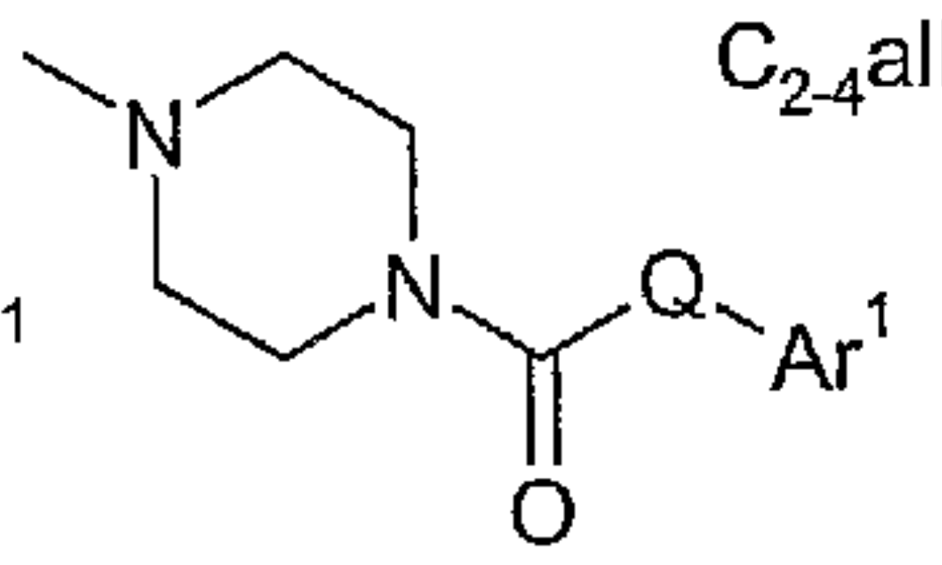
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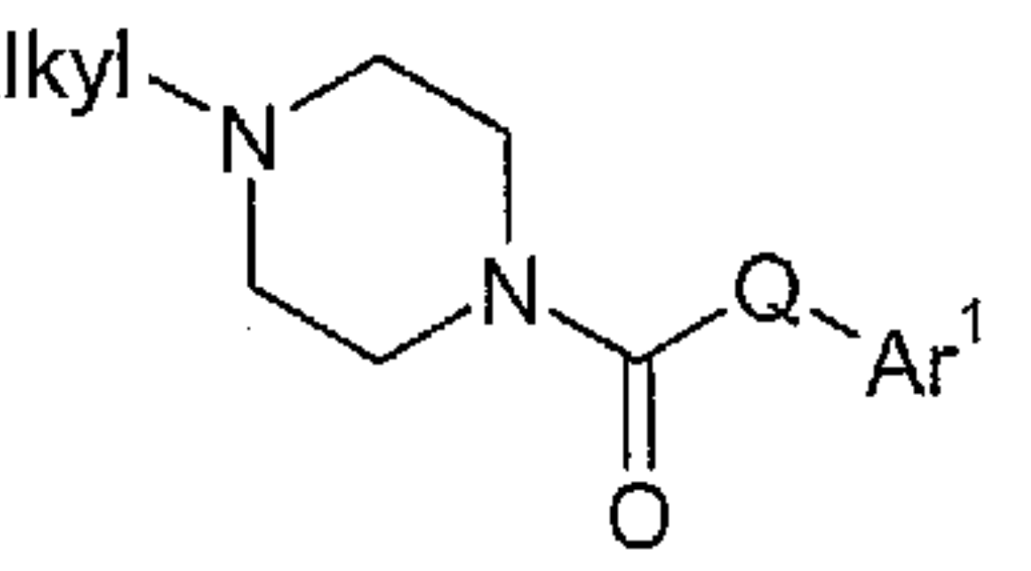
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NOVEL COMPOUNDS

FIELD OF THE INVENTION

This invention relates histamine receptor ligands. More specifically, the invention relates to histamine H3 receptor ligands, preparation thereof and uses thereof.

BACKGROUND OF THE INVENTION

The histamine H3 receptor is of current interest for the development of new medicaments. This receptor is a presynaptic autoreceptor located both in the central and the peripheral nervous system, the skin and in organs such as the lung, the intestine, probably the spleen and the gastrointestinal tract. Recent evidence suggests that the H3 receptor shows intrinsic, constitutive activity, in vitro as well as in vivo (i.e., it is active in the absence of an agonist. Compounds acting as inverse agonists can inhibit this activity. The histamine H3 receptor has been demonstrated to regulate the release of histamine and also of other neurotransmitters such as serotonin and acetylcholine. Some histamine H3 ligands such as histamine H3 receptor antagonists or inverse agonists may increase the release of these neurotransmitters in the brain whereas other histamine H3 ligands such as histamine H3 receptor agonists may lead to an inhibition of the biosynthesis of histamine and an inhibition of the release of histamine and also of other neurotransmitters. This suggests that histamine H3 receptor agonists, inverse agonists and antagonists could be mediators of neuronal activity. Accordingly, the histamine H3 receptor may be a target for new therapeutics.

There are publications that disclose the preparation and use of imidazole derivative histamine H3 ligands. However, there are needs for additional histamine H3 ligands.

DESCRIPTION OF THE INVENTION

Unless specified otherwise within this specification, the nomenclature used in this specification generally follows the examples and rules stated in *Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F, and H*, Pergamon Press, Oxford, 1979, which is incorporated by references herein for its exemplary chemical structure names and rules on naming chemical structures.

The term "C_{m-n}" or "C_{m-n} group" used alone or as a prefix, refers to any group having m to n carbon atoms.

The term “hydrocarbon” used alone or as a suffix or prefix, refers to any structure comprising only carbon and hydrogen atoms up to 14 carbon atoms.

The term “hydrocarbon radical” or "hydrocarbyl" used alone or as a suffix or prefix, refers to any structure as a result of removing one or more hydrogens from a hydrocarbon.

The term “alkyl” used alone or as a suffix or prefix, refers to monovalent straight or branched chain hydrocarbon radicals comprising 1 to about 12 carbon atoms.

The term “alkylene” used alone or as suffix or prefix, refers to divalent straight or branched chain hydrocarbon radicals comprising 1 to about 12 carbon atoms, which serves to links two structures together.

The term “alkenyl” used alone or as suffix or prefix, refers to a monovalent straight or branched chain hydrocarbon radical having at least one carbon-carbon double bond and comprising at least 2 up to about 12 carbon atoms.

The term “alkynyl” used alone or as suffix or prefix, refers to a monovalent straight or branched chain hydrocarbon radical having at least one carbon-carbon triple bond and comprising at least 2 up to about 12 carbon atoms.

The term “cycloalkyl,” used alone or as suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical comprising at least 3 up to about 12 carbon atoms.

The term “cycloalkenyl” used alone or as suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical having at least one carbon-carbon double bond and comprising at least 3 up to about 12 carbon atoms.

The term “cycloalkynyl” used alone or as suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical having at least one carbon-carbon triple bond and comprising about 7 up to about 12 carbon atoms.

The term “aryl” used alone or as suffix or prefix, refers to a monovalent hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, (*e.g.*, 4n + 2 delocalized electrons) and comprising 5 up to about 14 carbon atoms.

The term “arylene” used alone or as suffix or prefix, refers to a divalent hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, (*e.g.*, 4n + 2 delocalized electrons) and comprising 5 up to about 14 carbon atoms, which serves to link two structures together.

The term “heterocycle” used alone or as a suffix or prefix, refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s). Heterocycle may be saturated or unsaturated, containing one or more double bonds, and heterocycle may contain more than one ring. When a heterocycle contains more than one ring, the rings may be fused or unfused. Fused rings generally refer to at least two rings share two atoms therebetween. Heterocycle may have aromatic character or may not have aromatic character.

The term "heteroaromatic" used alone or as a suffix or prefix, refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s), wherein the ring-containing structure or molecule has an aromatic character (*e.g.*, 4n + 2 delocalized electrons).

The term “heterocyclic group,” “heterocyclic moiety,” “heterocyclic,” or “heterocyclo” used alone or as a suffix or prefix, refers to a radical derived from a heterocycle by removing one or more hydrogens therefrom.

The term “heterocyclyl” used alone or as a suffix or prefix, refers a monovalent radical derived from a heterocycle by removing one hydrogen therefrom.

The term “heterocyclylene” used alone or as a suffix or prefix, refers to a divalent radical derived from a heterocycle by removing two hydrogens therefrom, which serves to links two structures together.

The term “heteroaryl” used alone or as a suffix or prefix, refers to a heterocyclyl having aromatic character.

The term “heterocylcoalkyl” used alone or as a suffix or prefix, refers to a heterocyclyl that does not have aromatic character.

The term “heteroarylene” used alone or as a suffix or prefix, refers to a heterocyclylene having aromatic character.

The term “heterocycloalkylene” used alone or as a suffix or prefix, refers to a heterocyclylene that does not have aromatic character.

The term "six-membered" used as prefix refers to a group having a ring that contains six ring atoms.

The term "five-membered" used as prefix refers to a group having a ring that contains five ring atoms.

A five-membered ring heteroaryl is a heteroaryl with a ring having five ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S.

Exemplary five-membered ring heteroaryls are thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4- oxadiazolyl.

A six-membered ring heteroaryl is a heteroaryl with a ring having six ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S.

Exemplary six-membered ring heteroaryls are pyridyl, pyrazinyl, pyrimidinyl, triazinyl and pyridazinyl.

The term "substituted" used as a prefix refers to a structure, molecule or group, wherein one or more hydrogens are replaced with one or more C_{1-6}hydrocarbon groups, or one or more chemical groups containing one or more heteroatoms selected from N, O, S, F, Cl, Br, I, and P. Exemplary chemical groups containing one or more heteroatoms include $-NO_2$, -OR, -Cl, -Br, -I, -F, $-CF_3$, -C(=O)R, -C(=O)OH, $-NH_2$, -SH, -NHR, $-NR_2$, -SR, $-SO_3H$, $-SO_2R$, -S(=O)R, -CN, -OH, -C(=O)OR, $-C(=O)NR_2$, -NRC(=O)R, oxo (=O), imino (=NR), thio (=S), and oximino (=N-OR), wherein each "R" is a C_{1-6}hydrocarbyl. For example, substituted phenyl may refer to nitrophenyl, methoxyphenyl, chlorophenyl, aminophenyl, etc., wherein the nitro, methoxy, chloro, and amino groups may replace any suitable hydrogen on the phenyl ring.

The term "substituted" used as a suffix of a first structure, molecule or group, followed by one or more names of chemical groups refers to a second structure, molecule or group, which is a result of replacing one or more hydrogens of the first structure, molecule or group with the one or more named chemical groups. For example, a "phenyl substituted by nitro" refers to nitrophenyl.

Heterocycle includes, for example, monocyclic heterocycles such as: aziridine, oxirane, thiirane, azetidine, oxetane, thietane, pyrrolidine, pyrroline, imidazolidine, pyrazolidine, pyrazoline, dioxolane, sulfolane 2,3-dihydrofuran, 2,5-dihydrofuran tetrahydrofuran, thiophane, piperidine, 1,2,3,6-tetrahydro-pyridine, piperazine, morpholine, thiomorpholine, pyran, thiopyran, 2,3-dihydropyran, tetrahydropyran, 1,4-dihydropyridine, 1,4-dioxane, 1,3-dioxane, dioxane, homopiperidine, 2,3,4,7-tetrahydro-1*H*-azepine homopiperazine, 1,3-dioxepane, 4,7-dihydro-1,3-dioxepin, and hexamethylene oxide.

In addition, heterocycle includes aromatic heterocycles, for example, pyridine, pyrazine, pyrimidine, pyridazine, thiophene, furan, furazan, pyrrole, imidazole, thiazole, oxazole, pyrazole, isothiazole, isoxazole, 1,2,3-triazole, tetrazole, 1,2,3-thiadiazole, 1,2,3-oxadiazole, 1,2,4-triazole, 1,2,4-thiadiazole, 1,2,4-oxadiazole, 1,3,4-triazole, 1,3,4-thiadiazole, and 1,3,4- oxadiazole.

Additionally, heterocycle encompass polycyclic heterocycles, for example, indole, indoline, isoindoline, quinoline, tetrahydroquinoline, isoquinoline, tetrahydroisoquinoline, 1,4-benzodioxan, coumarin, dihydrocoumarin, benzofuran, 2,3-dihydrobenzofuran, isobenzofuran, chromene, chroman, isochroman, xanthene, phenoxathiin, thianthrene, indolizine, isoindole, indazole, purine, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, phenanthridine, perimidine, phenanthroline, phenazine, phenothiazine, phenoxazine, 1,2-benzisoxazole, benzothiophene, benzoxazole, benzthiazole, benzimidazole, benztriazole, thioxanthine, carbazole, carboline, acridine, pyrolizidine, and quinolizidine.

In addition to the polycyclic heterocycles described above, heterocycle includes polycyclic heterocycles wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms common to both rings. Examples of such bridged heterocycles include quinuclidine, diazabicyclo[2.2.1]heptane and 7-oxabicyclo[2.2.1]heptane.

Heterocyclyl includes, for example, monocyclic heterocyclyls, such as: aziridinyl, oxiranyl, thiiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, dioxolanyl, sulfolanyl, 2,3-dihydrofuranyl, 2,5-dihydrofuranyl, tetrahydrofuranyl, thiophanyl, piperidinyl, 1,2,3,6-tetrahydro-pyridinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, 2,3-dihydropyranyl, tetrahydropyranyl, 1,4-dihydropyridinyl, 1,4-dioxanyl, 1,3-dioxanyl, dioxanyl, homopiperidinyl, 2,3,4,7-tetrahydro-1*H*-azepinyl, homopiperazinyl, 1,3-dioxepanyl, 4,7-dihydro-1,3-dioxepinyl, and hexamethylene oxidyl.

In addition, heterocyclyl includes aromatic heterocyclyls or heteroaryl, for example, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, furyl, furazanyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4 oxadiazolyl.

Additionally, heterocyclyl encompasses polycyclic heterocyclyls (including both aromatic or non-aromatic), for example, indolyl, indolinyl, isoindolinyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, 1,4-benzodioxanyl, coumarinyl, dihydrocoumarinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, isobenzofuranyl, chromenyl, chromanyl, isochromanyl, xanthenyl, phenoxathiinyl, thianthrenyl, indolizinyl, isoindolyl, indazolyl, purinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, phenanthridinyl, perimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxazinyl, 1,2-benzisoxazolyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benzimidazolyl, benztriazolyl, thioxanthinyl, carbazolyl, carbolinyl, acridinyl, pyrolizidinyl, and quinolizidinyl.

In addition to the polycyclic heterocyclyls described above, heterocyclyl includes polycyclic heterocyclyls wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms common to both rings. Examples of such bridged heterocycles include quinuclidinyl, diazabicyclo[2.2.1]heptyl; and 7-oxabicyclo[2.2.1]heptyl.

The term “alkoxy” used alone or as a suffix or prefix, refers to radicals of the general formula –O-R, wherein R is selected from a hydrocarbon radical. Exemplary alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, isobutoxy, cyclopropylmethoxy, allyloxy, and propargyloxy.

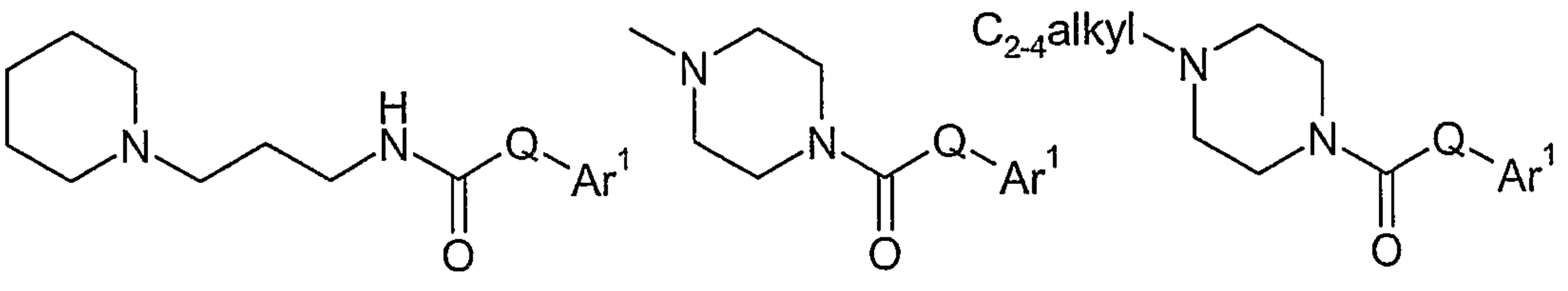
The term “amine” or “amino” used alone or as a suffix or prefix, refers to radicals of the general formula –NRR’, wherein R and R’ are independently selected from hydrogen or a hydrocarbon radical.

Halogen includes fluorine, chlorine, bromine and iodine.

"Halogenated," used as a prefix of a group, means one or more hydrogens on the group is replaced with one or more halogens.

"RT" or "rt" means room temperature.

In one aspect, the invention provides a compound of formula I, II or III, a pharmaceutically acceptable salt thereof, diastereomers thereof, enantiomers thereof, and mixtures thereof:



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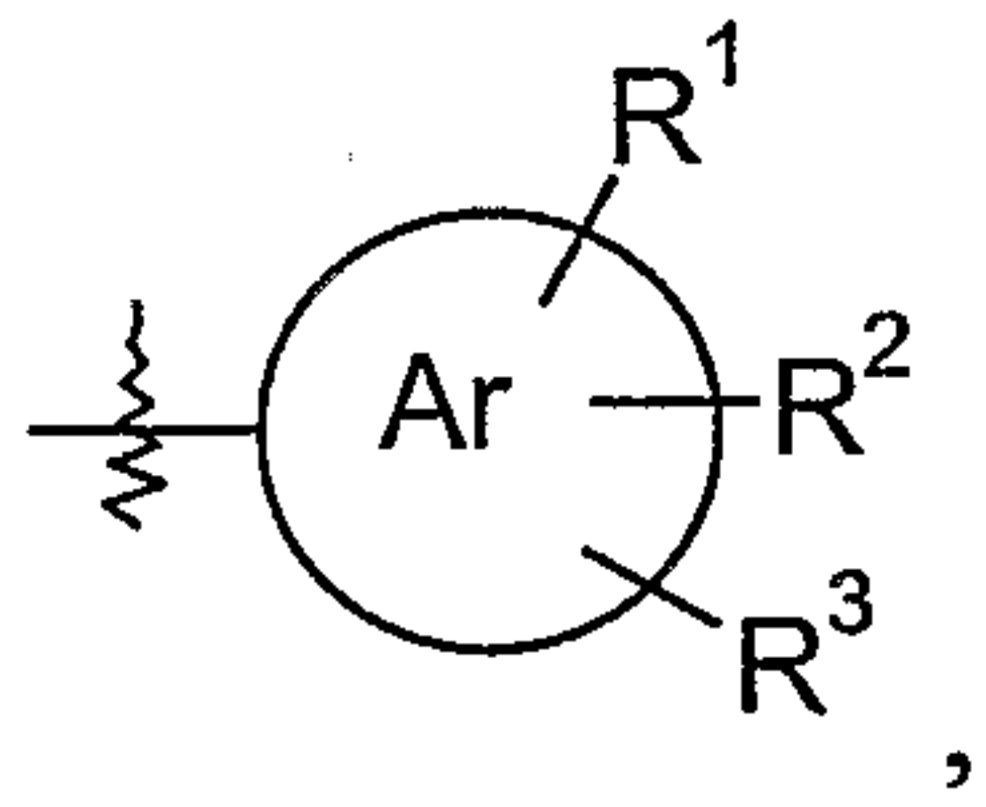
I II III

wherein

Ar^1 is selected from C_{6-10}aryl and C_{2-9}heteroaryl, wherein said C_{6-10}aryl and C_{2-9}heteroaryl are optionally substituted with one or more groups selected from -R, $-NO_2$, -OR, -Cl, -Br, -I, -F, $-CF_3$, $-OCF_3$, -C(=O)R, -C(=O)OH, $-NH_2$, -SH, -NHR, $-NR_2$, -SR, $-SO_3H$, $-SO_2R$, $-SO_2NR$, -S(=O)R, -CN, -OH, -C(=O)OR, $-C(=O)NR_2$, -NRC(=O)R, and -NRC(=O)-OR, wherein R is, independently, a hydrogen, C_{3-6}cycloalkyl, C_{3-6}heterocyclyl, phenyl, benzyl, C_{1-6}alkyl or C_{2-6}alkenyl and wherein said R is further optionally substituted with one or more groups selected from methyl, methoxy, hydroxy and halogen; and

Q is a divalent or trivalent group that connects the carbonyl with Ar^1, wherein said divalent or trivalent group contains at least one nitrogen, said nitrogen is directly connected to the carbonyl group of formula I, II or III to form an amide bond therebetween, and said trivalent group is fused with Ar^1.

In one embodiment, the compound of the present invention may be a compound of formula I, wherein Ar^1 is represented by



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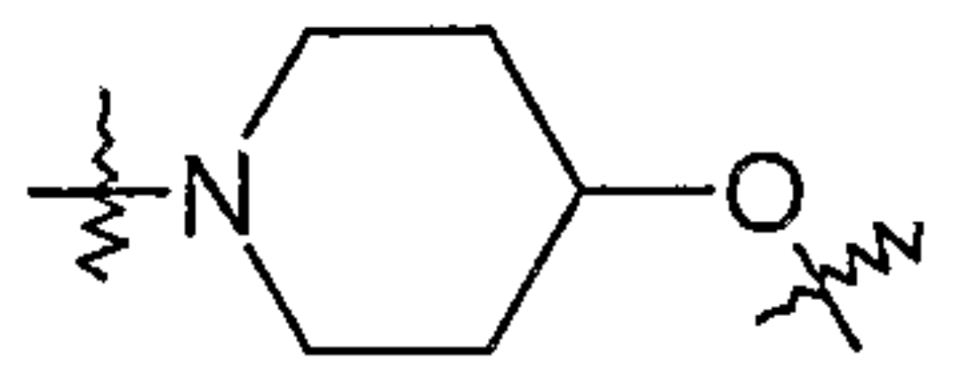
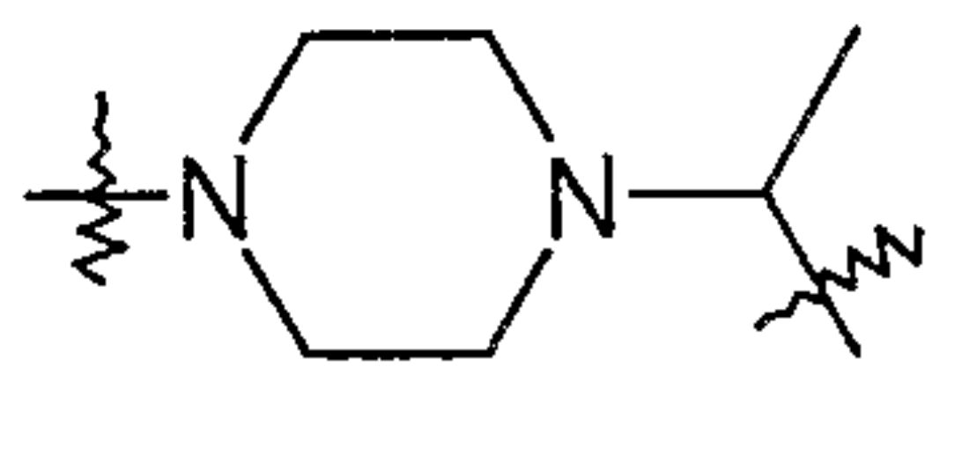
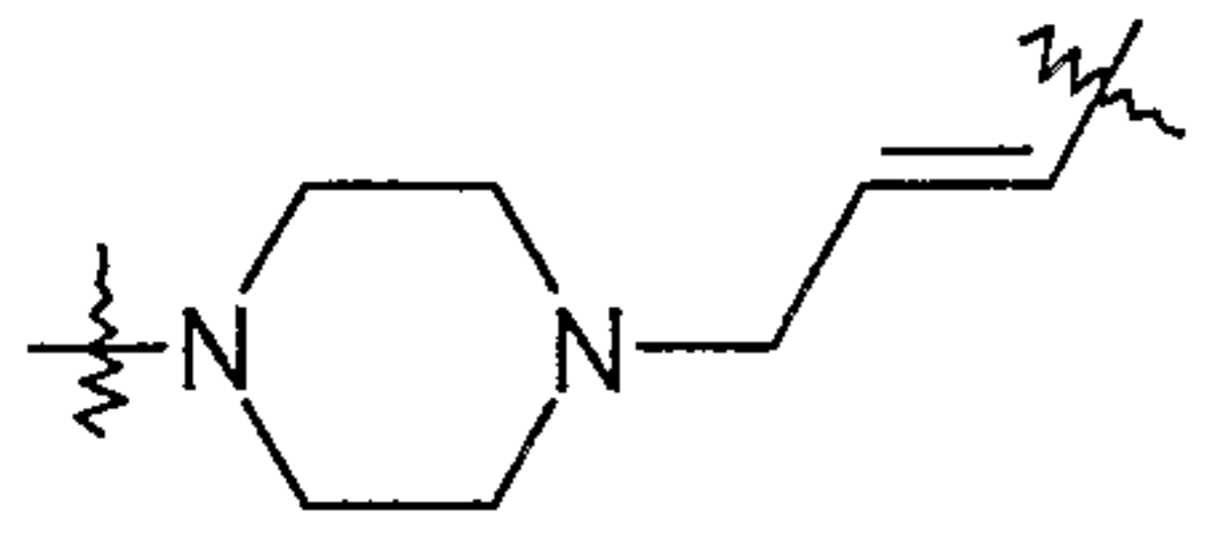
wherein Ar is selected from phenyl, pyridyl, naphthyl, 1,2,3,4-tetrahydro-naphthyl; thienyl, furyl, thiazolyl, benzo[1,3]dioxolyl, 4,5,6,7-tetrahydro-thieno[2,3-c]pyridinyl; 2,3-dihydro-benzo[1,4]dioxinyl; quinolyl; isoquinolyl; indolyl; pyrroyl, benzotriazolyl; benzoimidazolyl, 2,3-dihydro-benzofuranyl; 2,3-dihydro-isoindol-1-on-yl; benzo[1,2,3]thiadiazolyl, benzothiazolyl, and 4H-benzo[1,4]oxazin-3-on-yl;

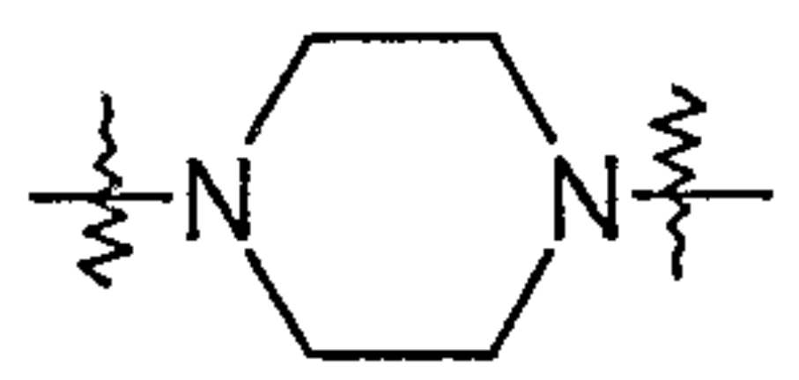
R^1, R^2 and R^3 are independently selected from -R, $-NO_2$, -OR, -Cl, -Br, -I, -F, $-CF_3$, -C(=O)R, -C(=O)OH, $-NH_2$, -SH, -NHR, $-NR_2$, -SR, $-SO_3H$, $-SO_2R$, $-SO_2NR$, -S(=O)R, -CN, -OH, -C(=O)OR, $-C(=O)NR_2$, -NRC(=O)R, and -NRC(=O)-OR, wherein R is, independently, a hydrogen, C_{5-6}cycloalkyl, C_{3-5}heterocyclyl, phenyl, benzyl, C_{1-4}alkyl or C_{2-4}alkenyl, and wherein said R is further optionally substituted with one or more groups selected from methyl, methoxy, hydroxy and halogen;

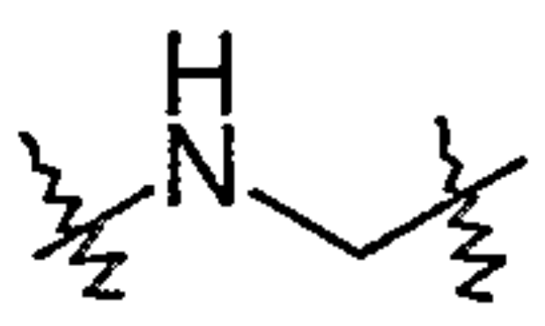
Q is selected from:

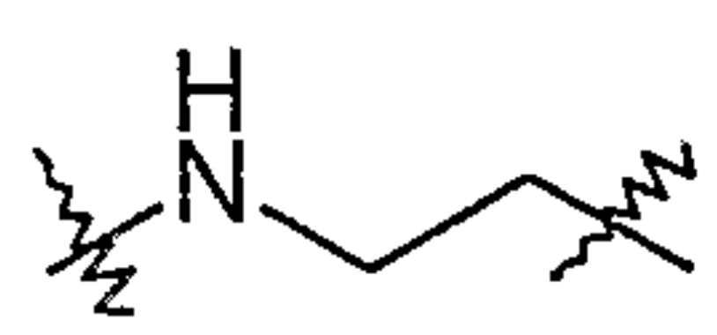


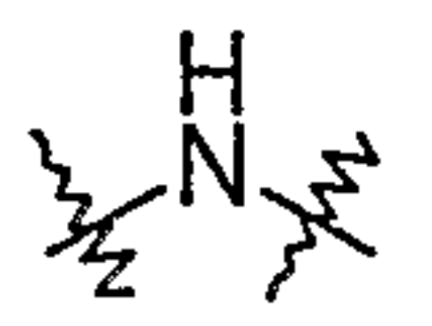


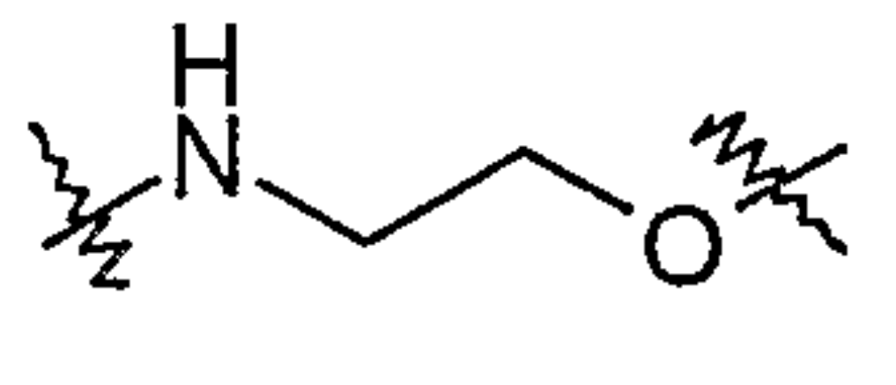


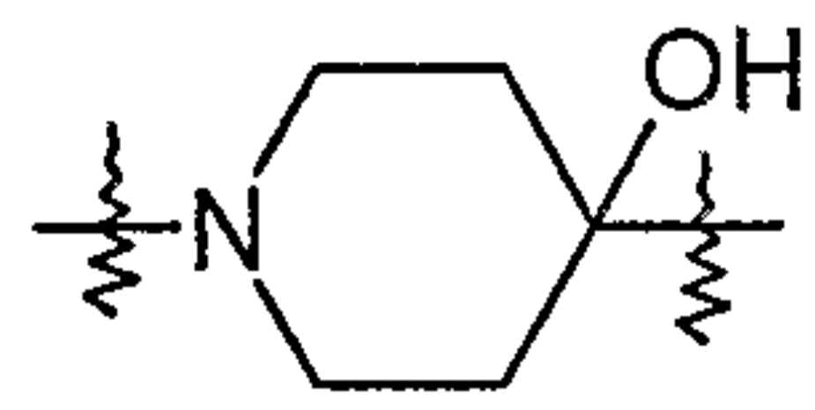


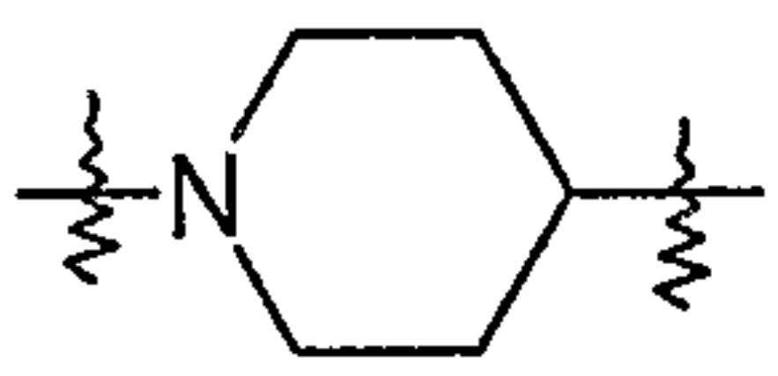


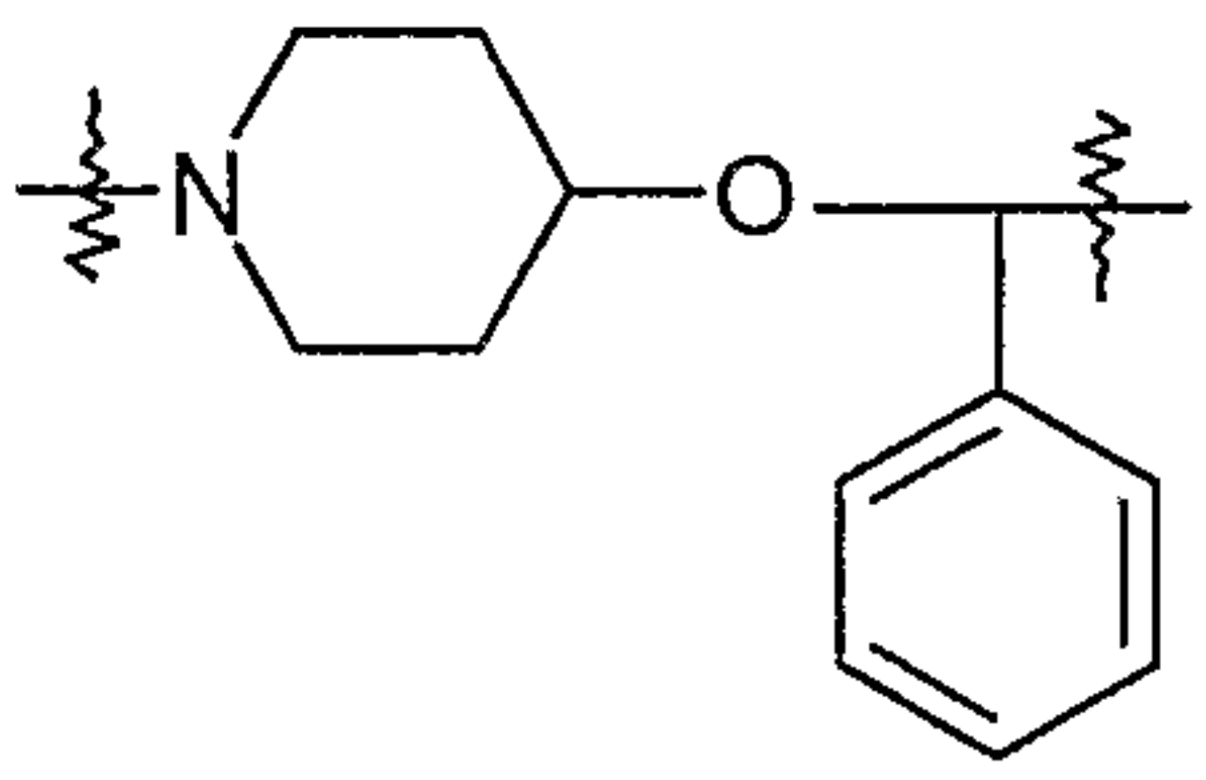


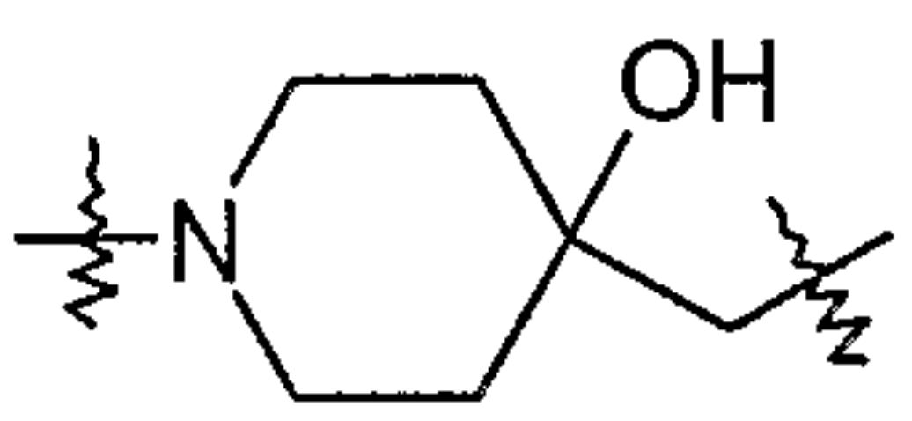


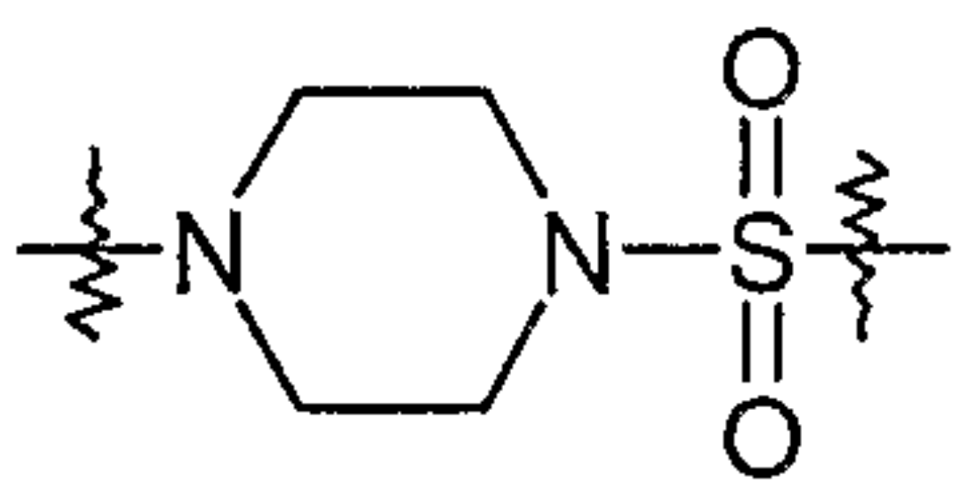


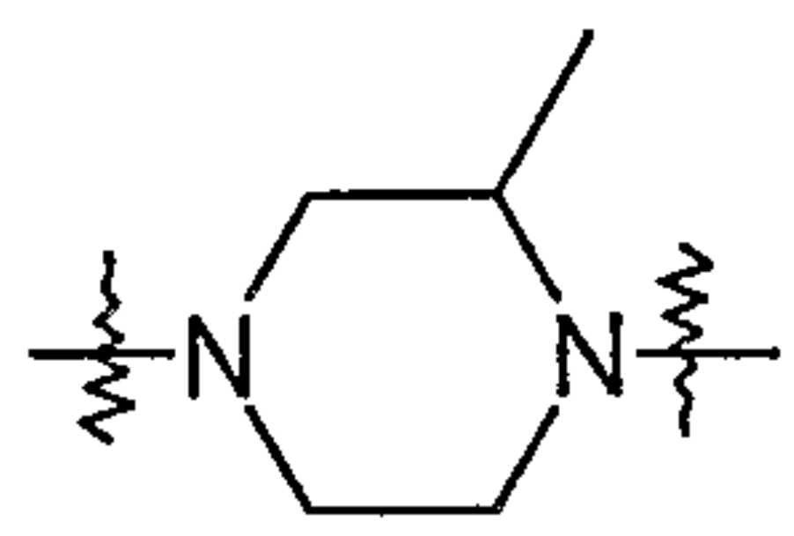


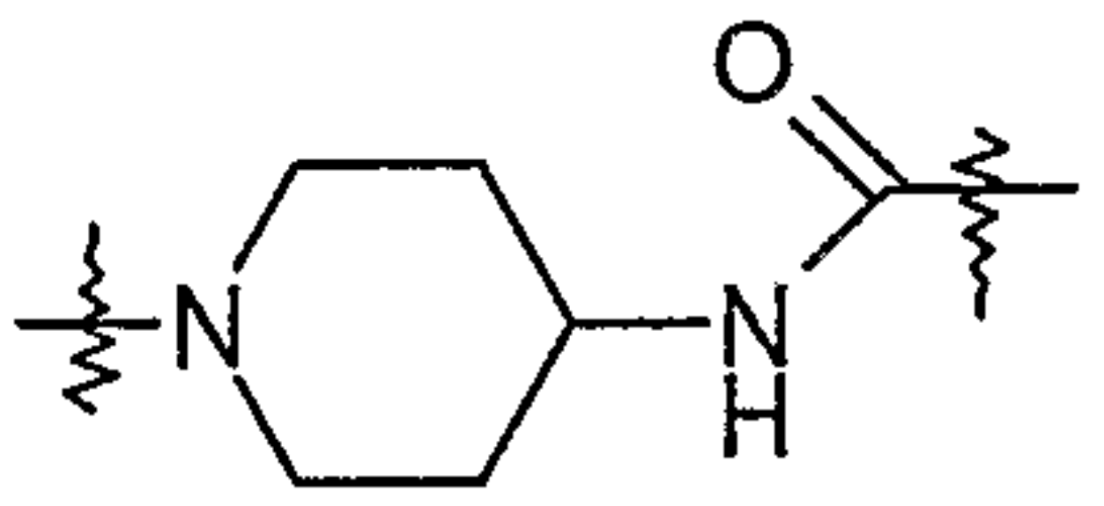


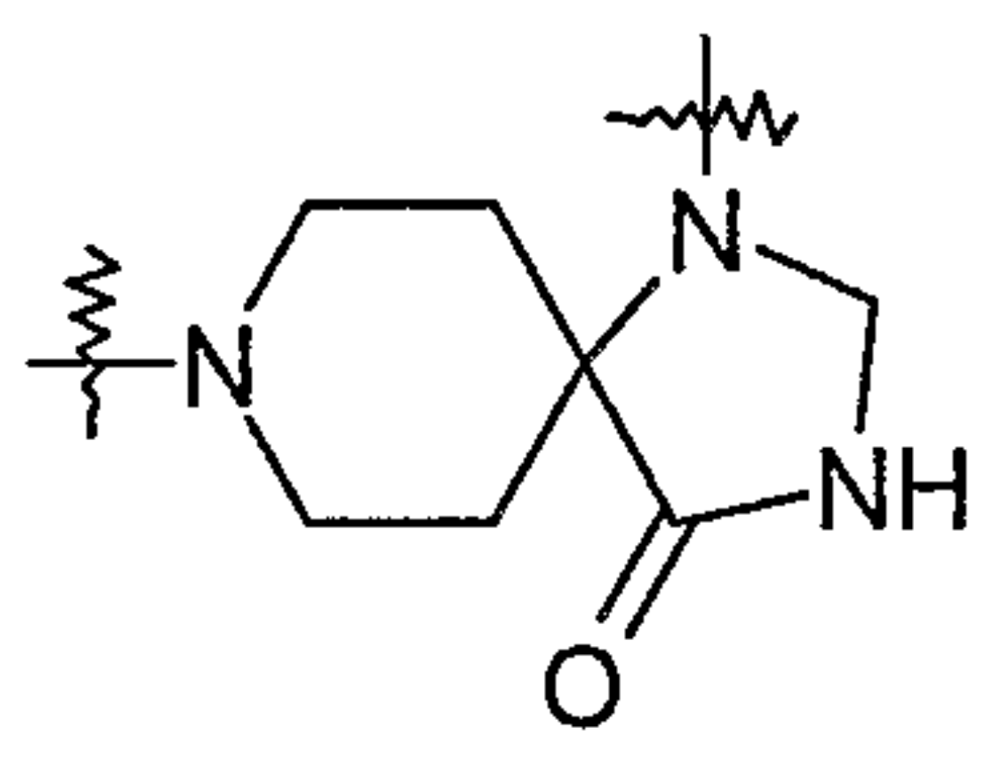


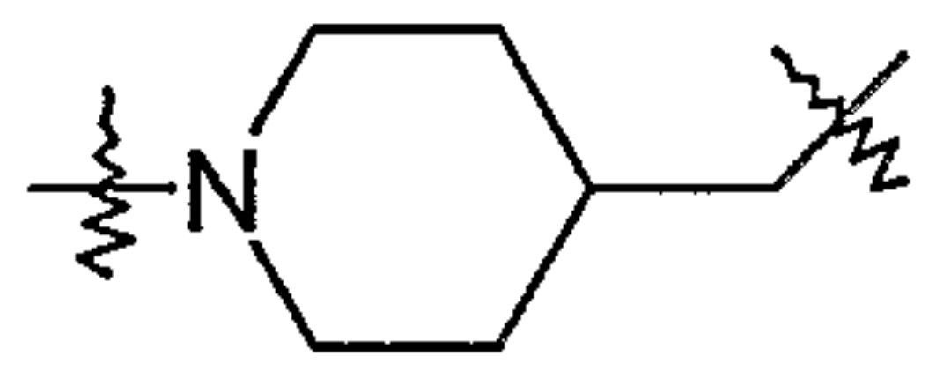


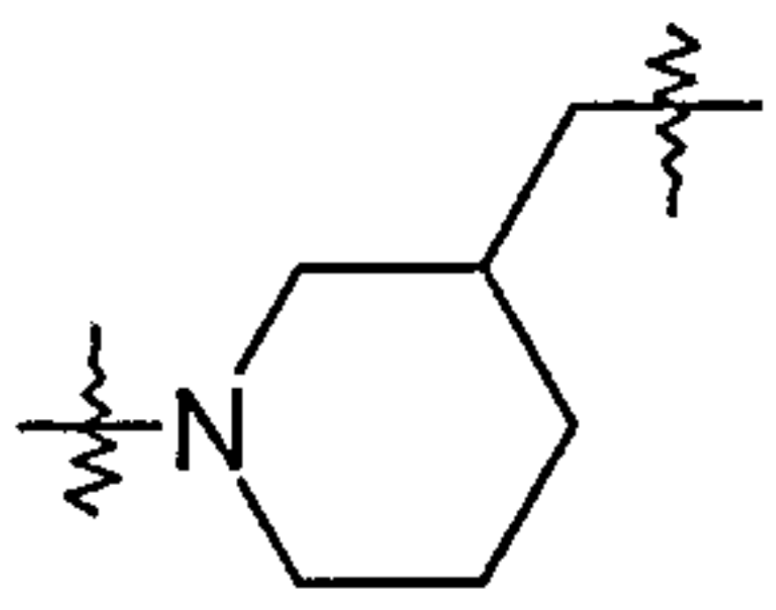


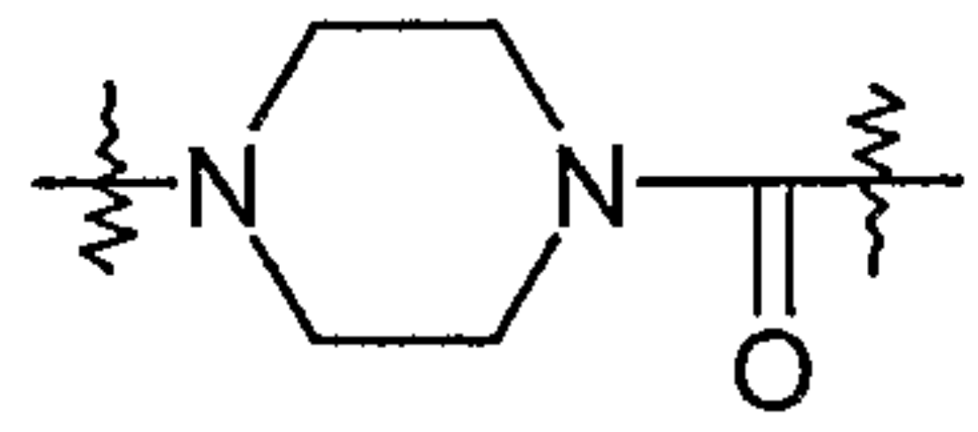


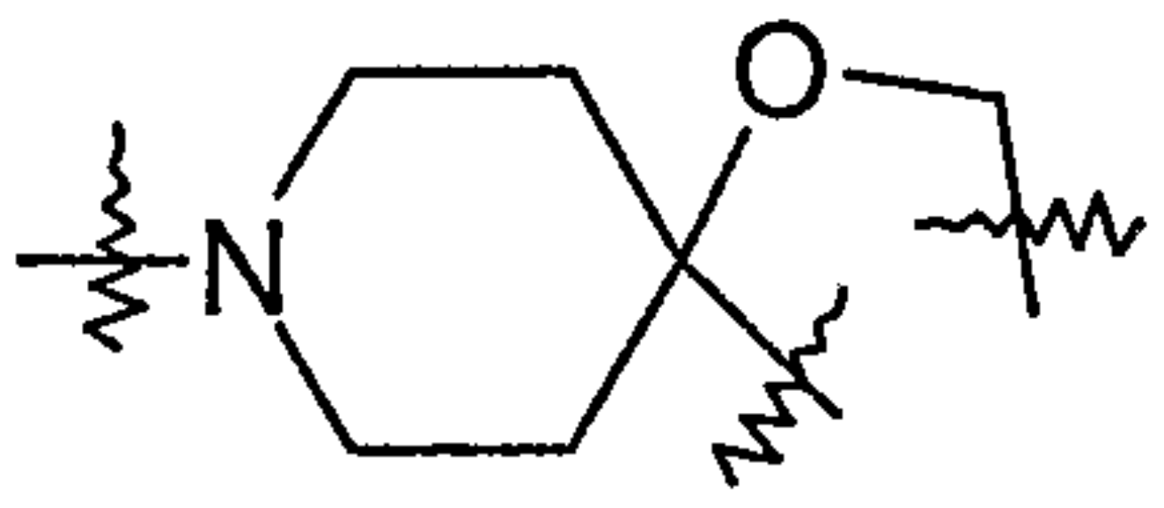








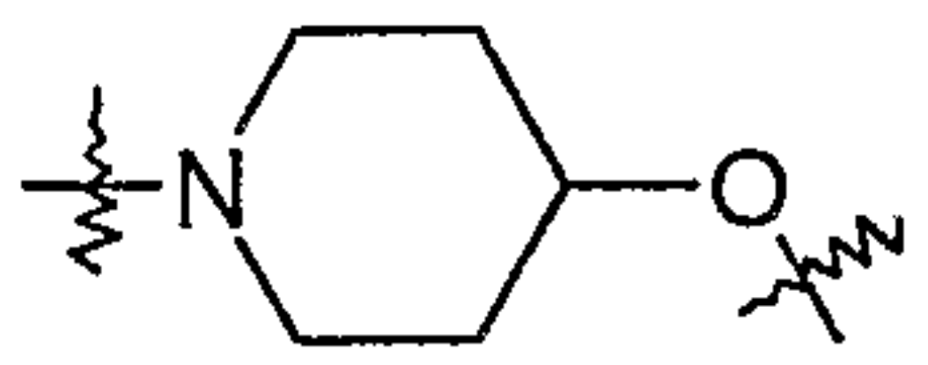
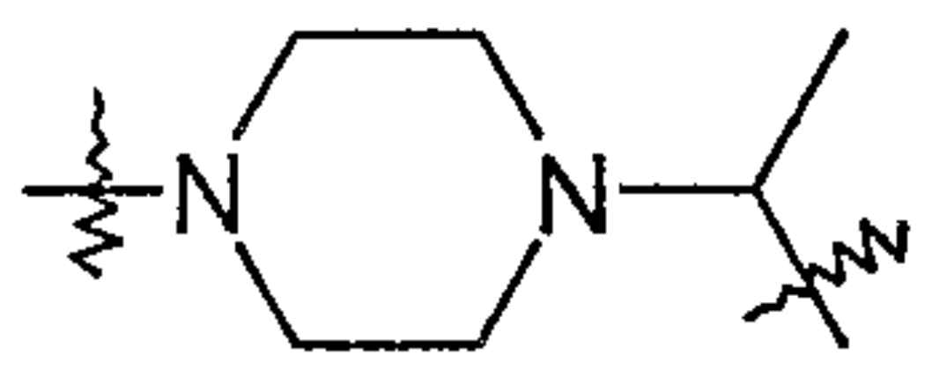
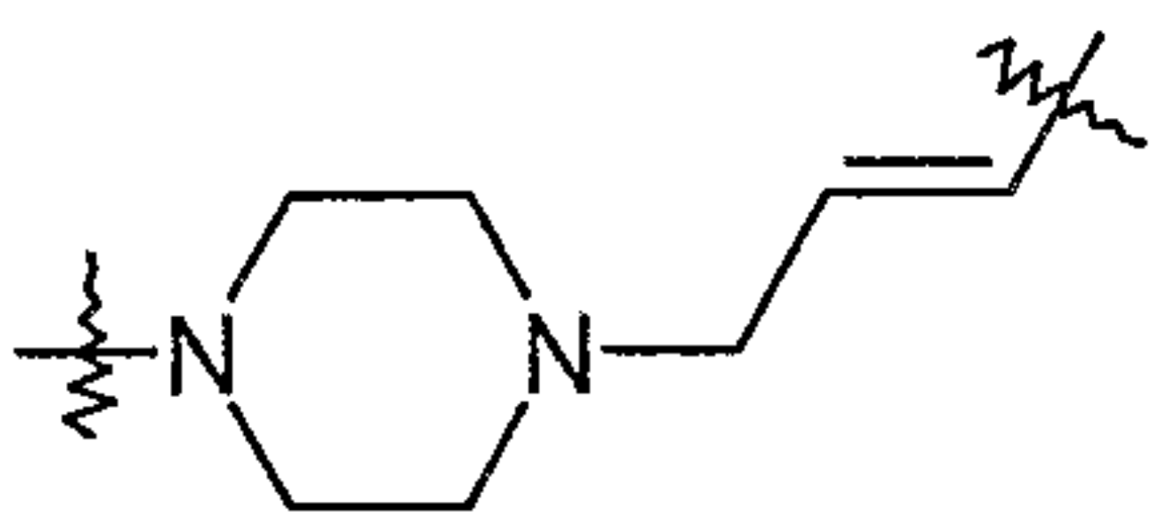
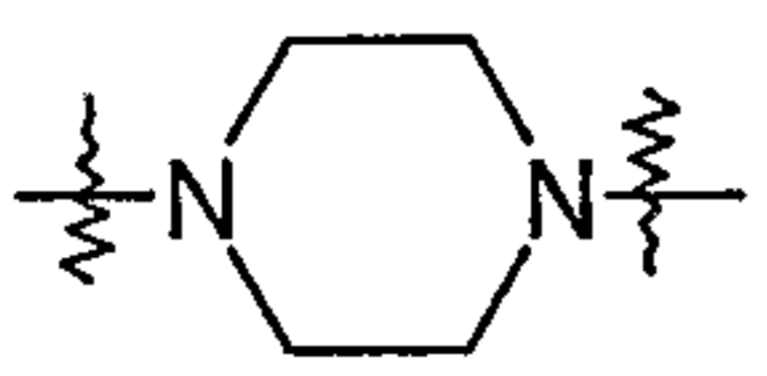
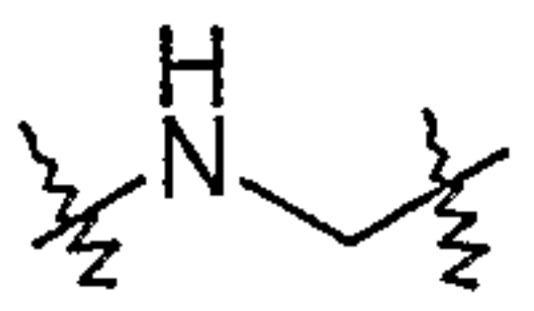
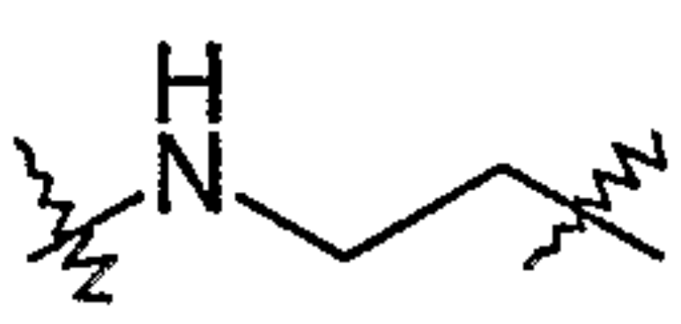
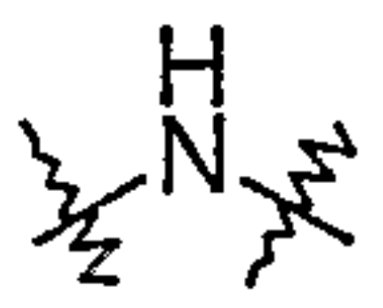
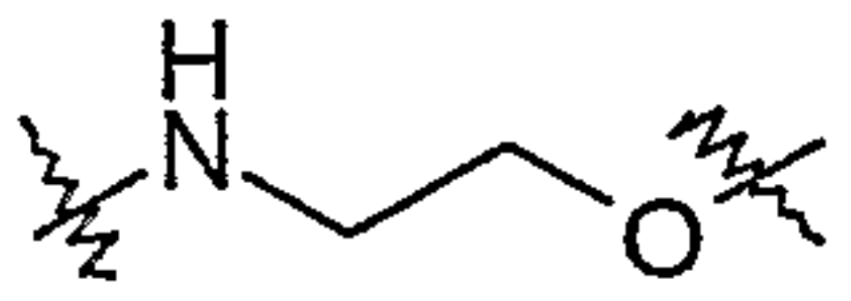
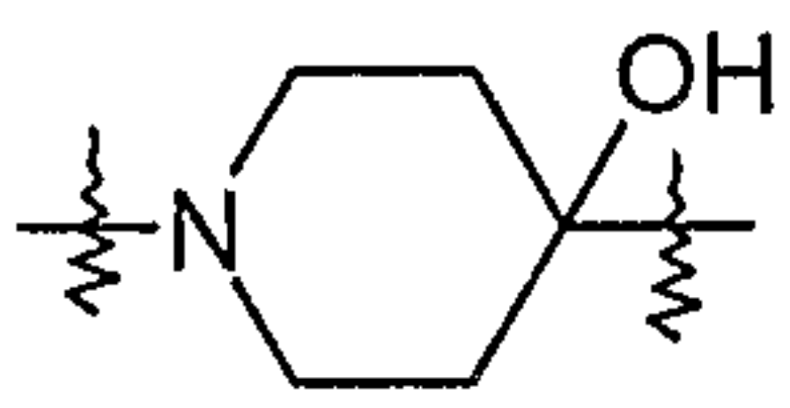
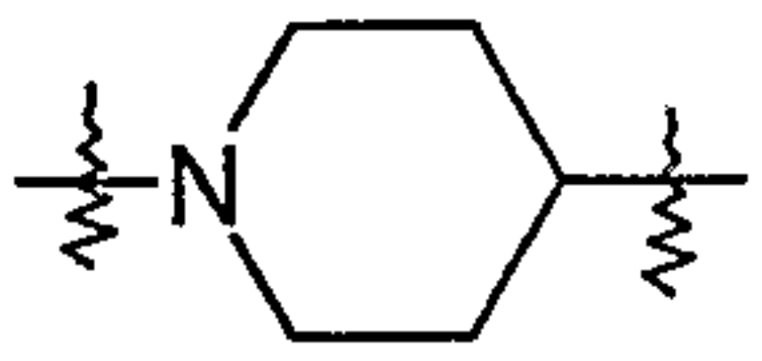
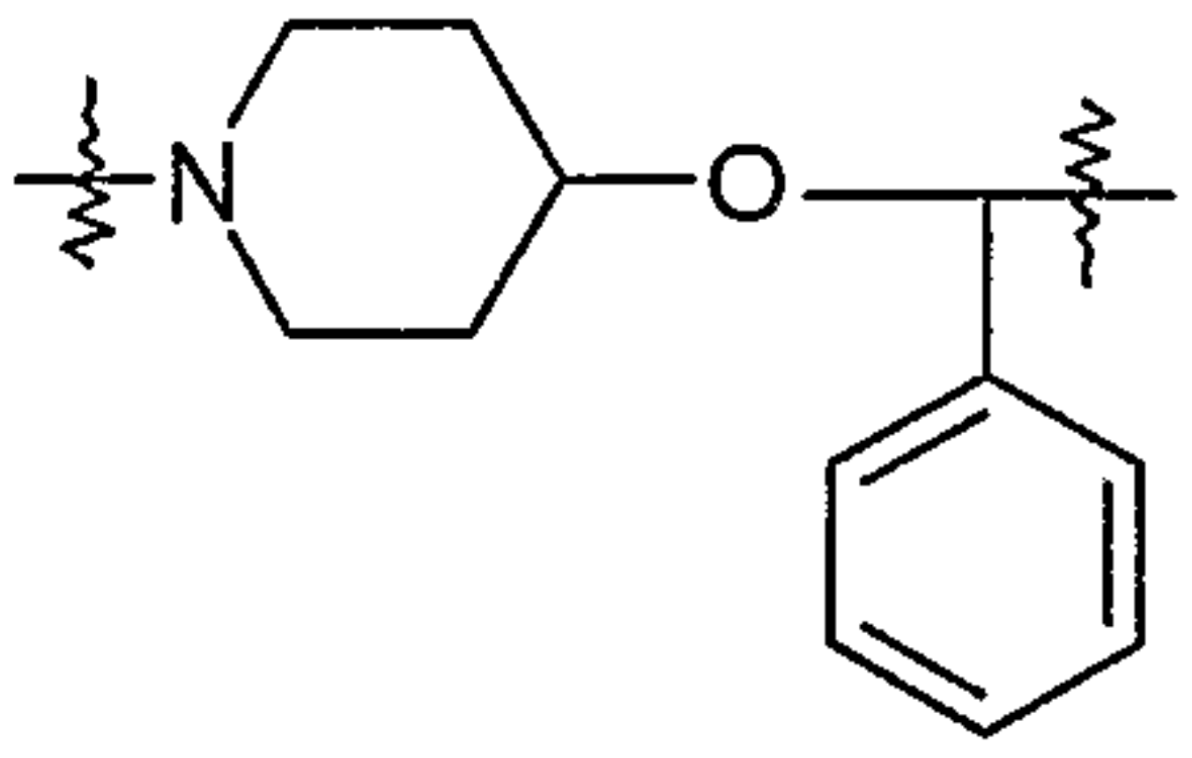
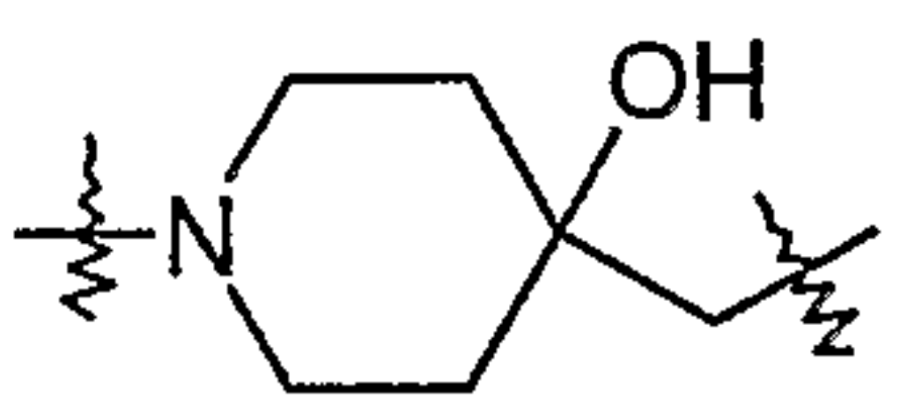
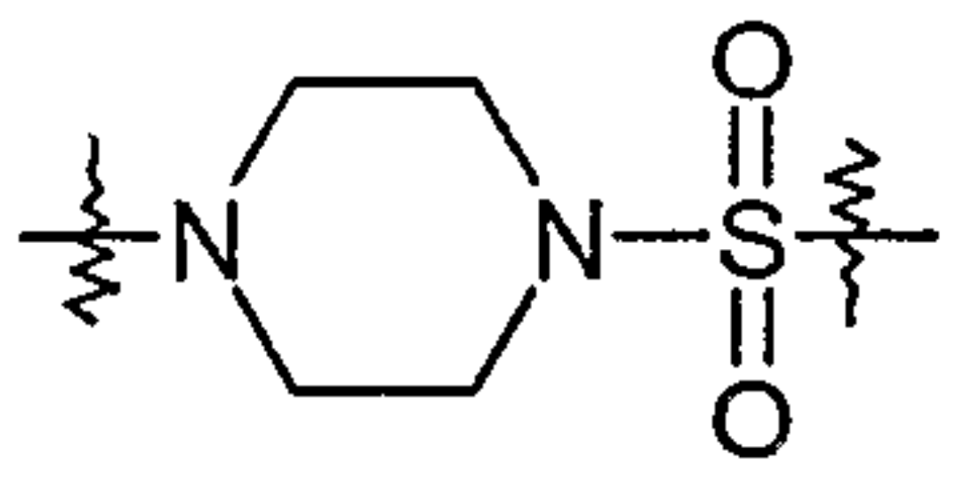
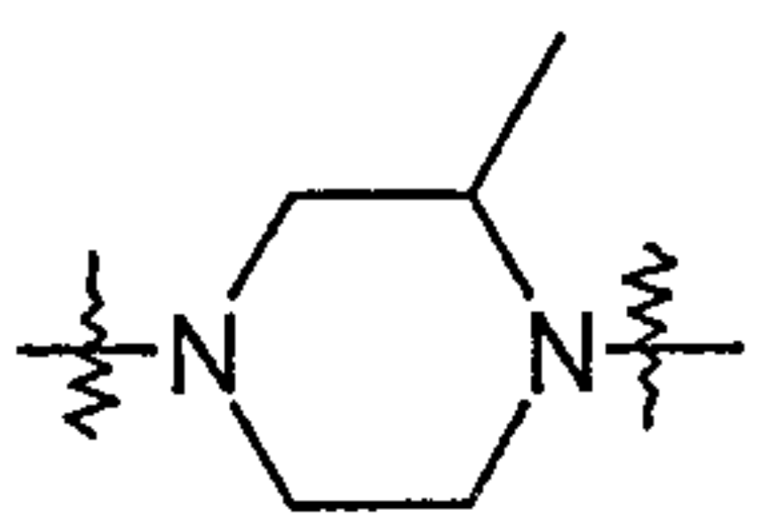
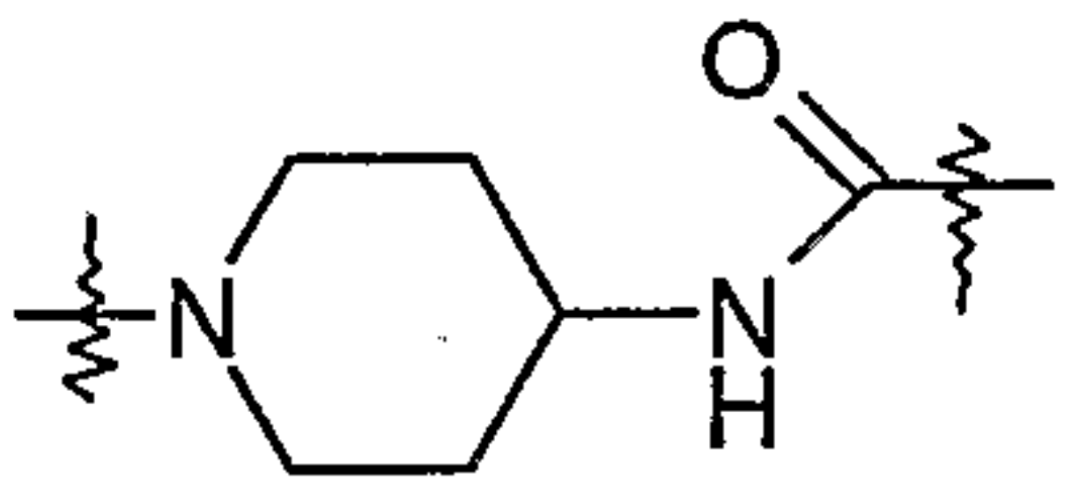
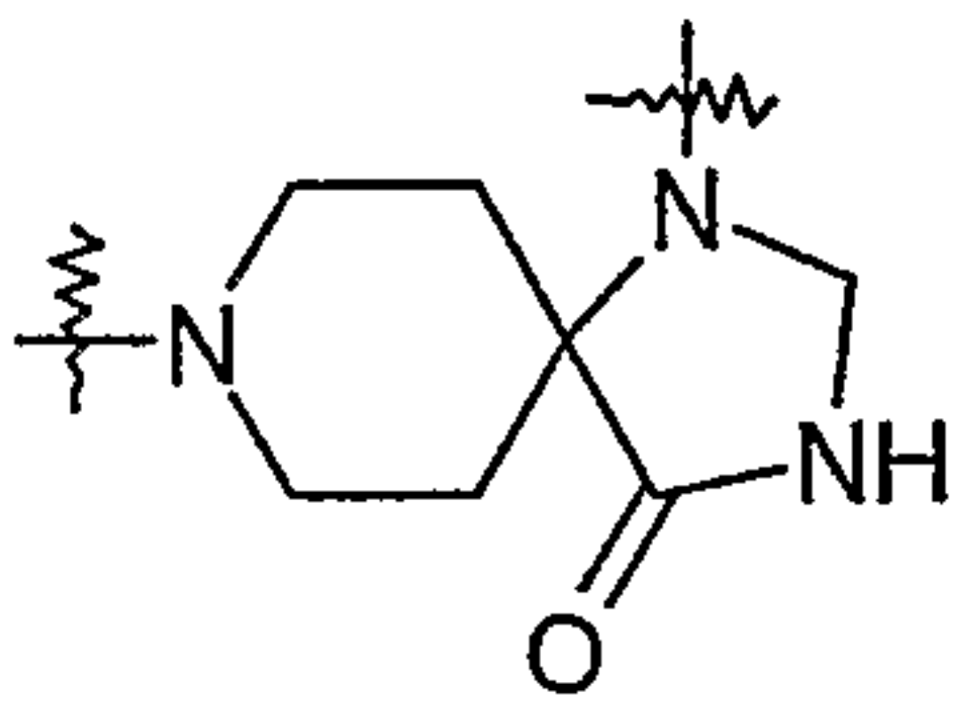
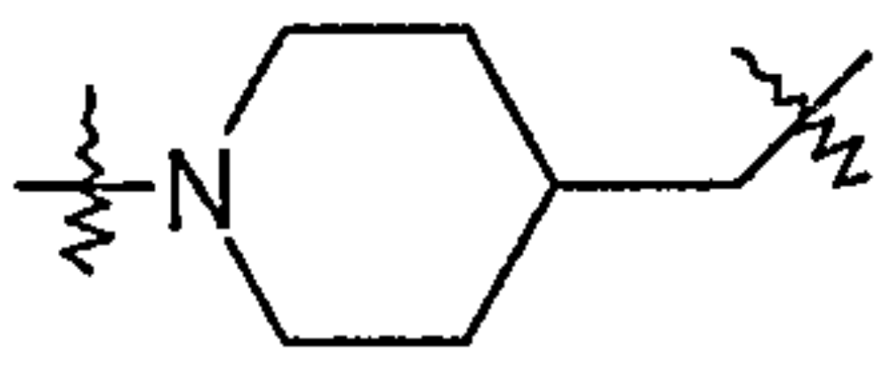
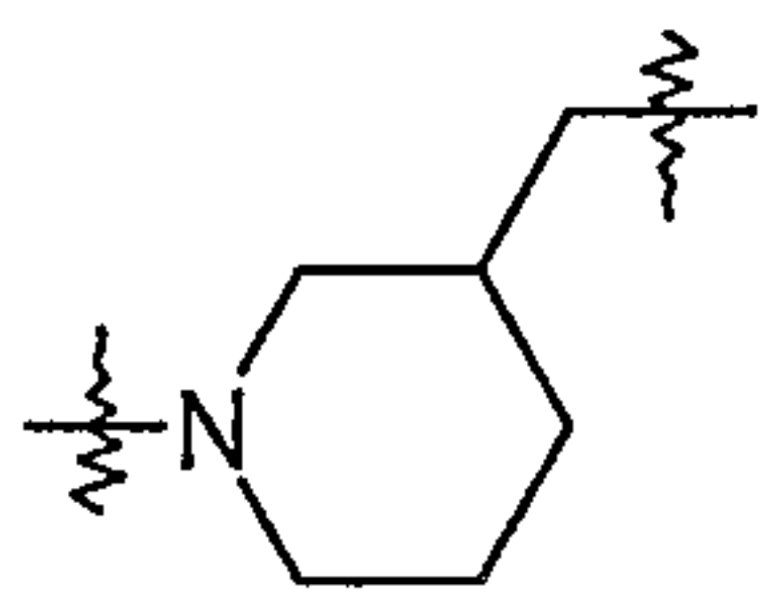
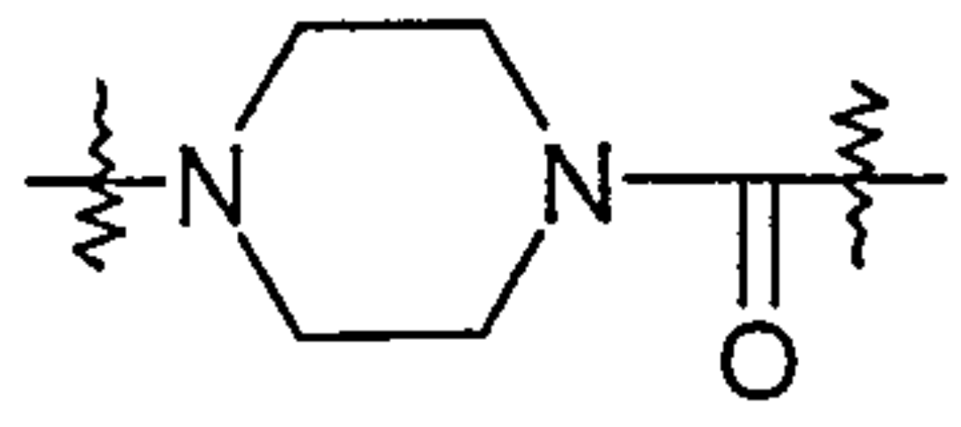


or Q may be a trivalent group such as  , which is fused with Ar^1, wherein Ar^1 is a divalent aromatic group such as 1,2-phenylene.

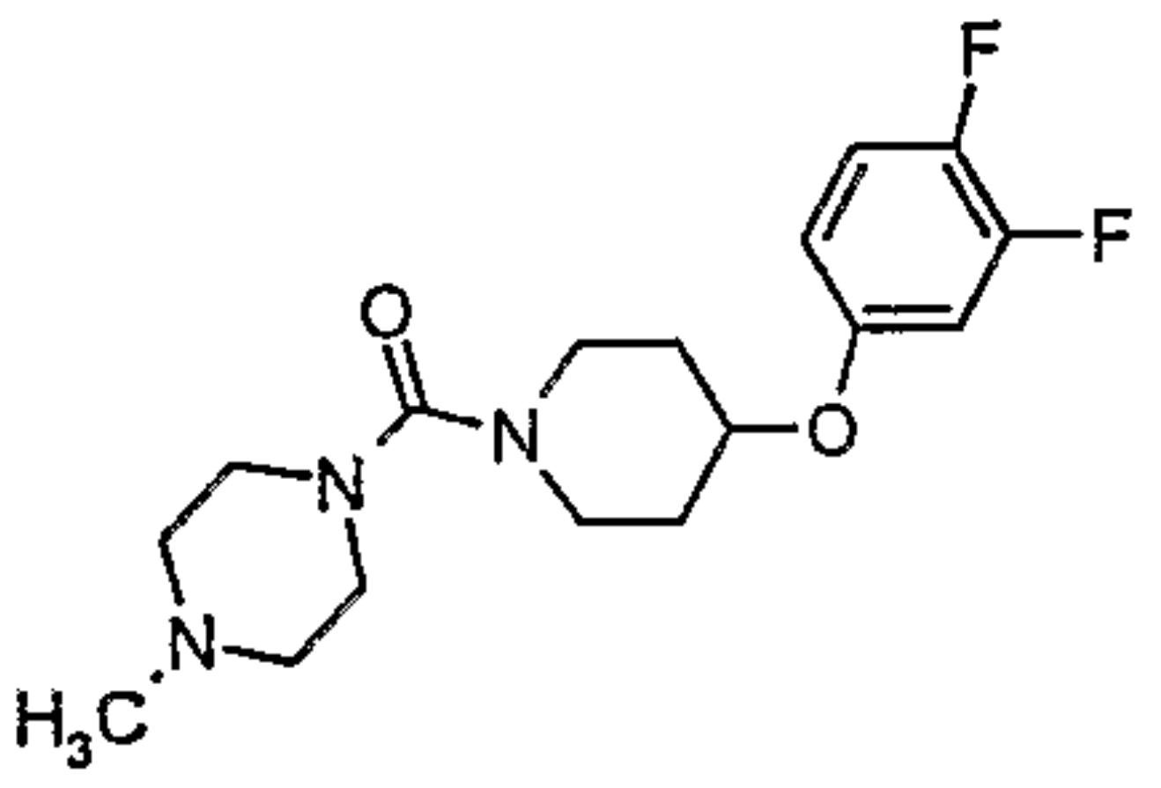
In another embodiment, the compounds of the present invention are represented by formula I, wherein Ar^1 is selected from phenyl, 2-pyridyl, 4-pyridyl; 1-naphthyl, 2-naphthyl, 1,2,3,4-tetrahydro-naphth-1-yl; 1,2,3,4-tetrahydro-naphth-5-yl; 2-thienyl, 3-thienyl, 2-furyl, 2-thiazolyl, benzo[1,3]dioxol-5-yl, 4,5,6,7-tetrahydro-thieno[2,3-c]pyridin-2-yl; 2,3-dihydro-benzo[1,4]dioxin-6-yl; 2,3-dihydro-benzo[1,4]dioxin-2-yl; quinol-2-yl, isoquinol-5-yl; 1H-indol-4-yl, 1H-indol-3-yl, 1H-indol-2-yl, 1H-indol-7-yl, 1-pyrroyl, 1H-benzotriazol-5-yl, 1H-benzoimidazol-5-yl, 2,3-dihydro-benzofuran-5-yl, 2,3-dihydro-isoindol-1-on-2-yl; benzo[1,2,3]thiadiazol-5-yl, benzo[1,2,3]thiadiazol-6-yl, benzothiazol-6-yl, benzothiazol-2-

yl, and 4H-benzo[1,4]oxazin-3-on-7-yl, wherein Ar^1 is further optionally substituted with one or more groups selected from C_{1-4}alkyl, C_{2-4}alkenyl, C_{1-4}alkoxy, C_{1-4}alkenyloxy, phenoxy, 4-methoxyphenoxy, benzyl, acetoamino, methylsulfonyl, methoxycarbonyl, nitro, chloro, fluoro, bromo, iodo, 1-pyrroyl, 2-methyl-pyrro-1-yl, amino, phenylsulfonyl, aceto,1-piperidinyl, [1,2,3]thiadiazol-4-yl, 4-morpholinyl, methoxy, ethoxy, isopropyloxy, methythio, cyano, dimethylamino, hydroxy, methylaminosulfonyl, trifluoromethyl, trifluoromethoxy, phenyl, phenoxy, benzyl, 4-hydroxyl-phenyl, diethylamino, methylsulfonyl, aminosulfonyl, cyclohexyl, 1-pyrrolyl, 1H-pyrazol-3-yl, 5-tetrazolyl, 1-piperidinyl, 1-pyrazolyl, methylsulfonylmethyl, 3,5-dimethyl-pyrazolyl, pyrrolidin-2-on-1-yl; and

Q is selected from

In a further embodiment, the compounds of the present invention are selected from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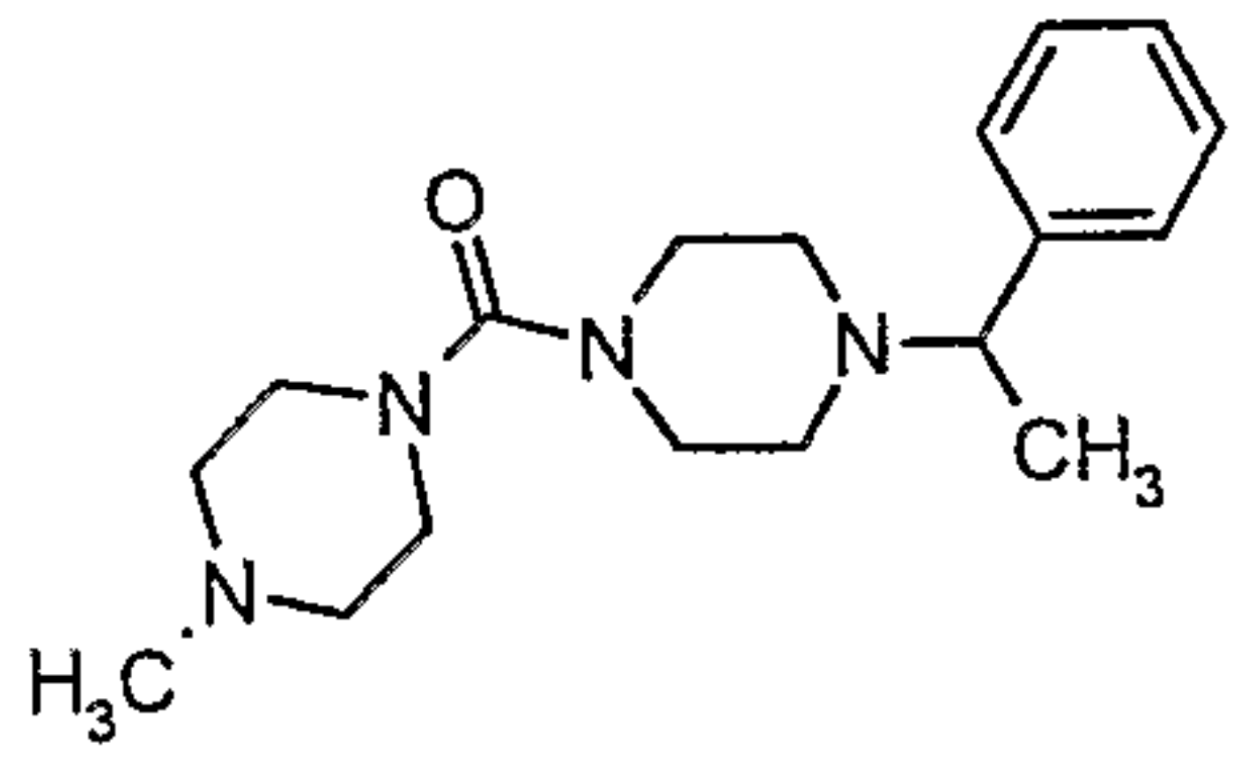
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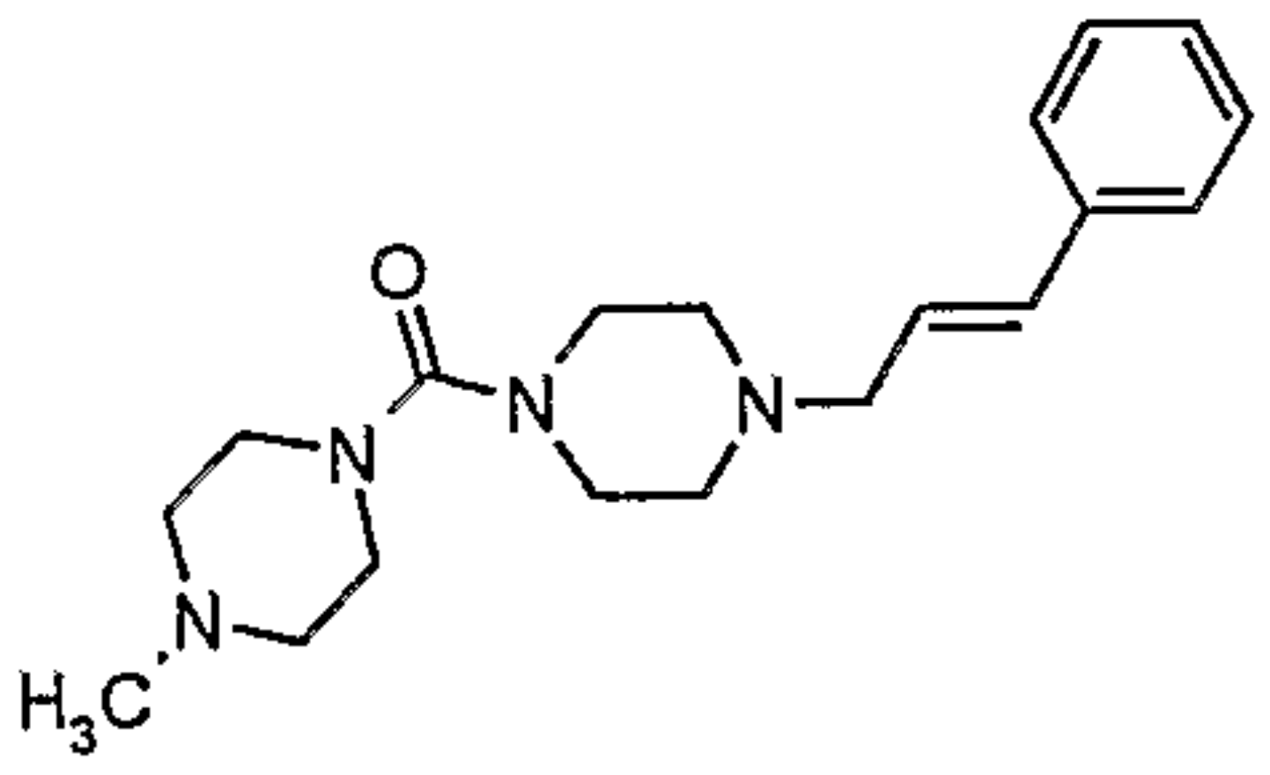
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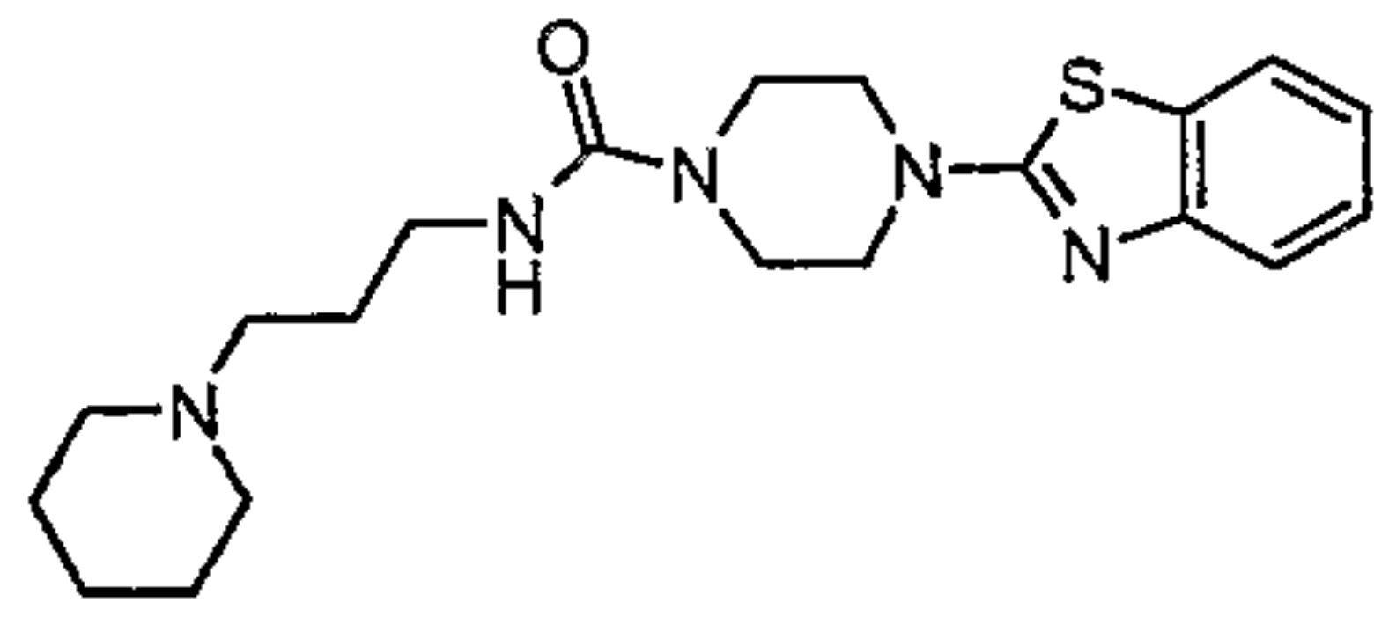
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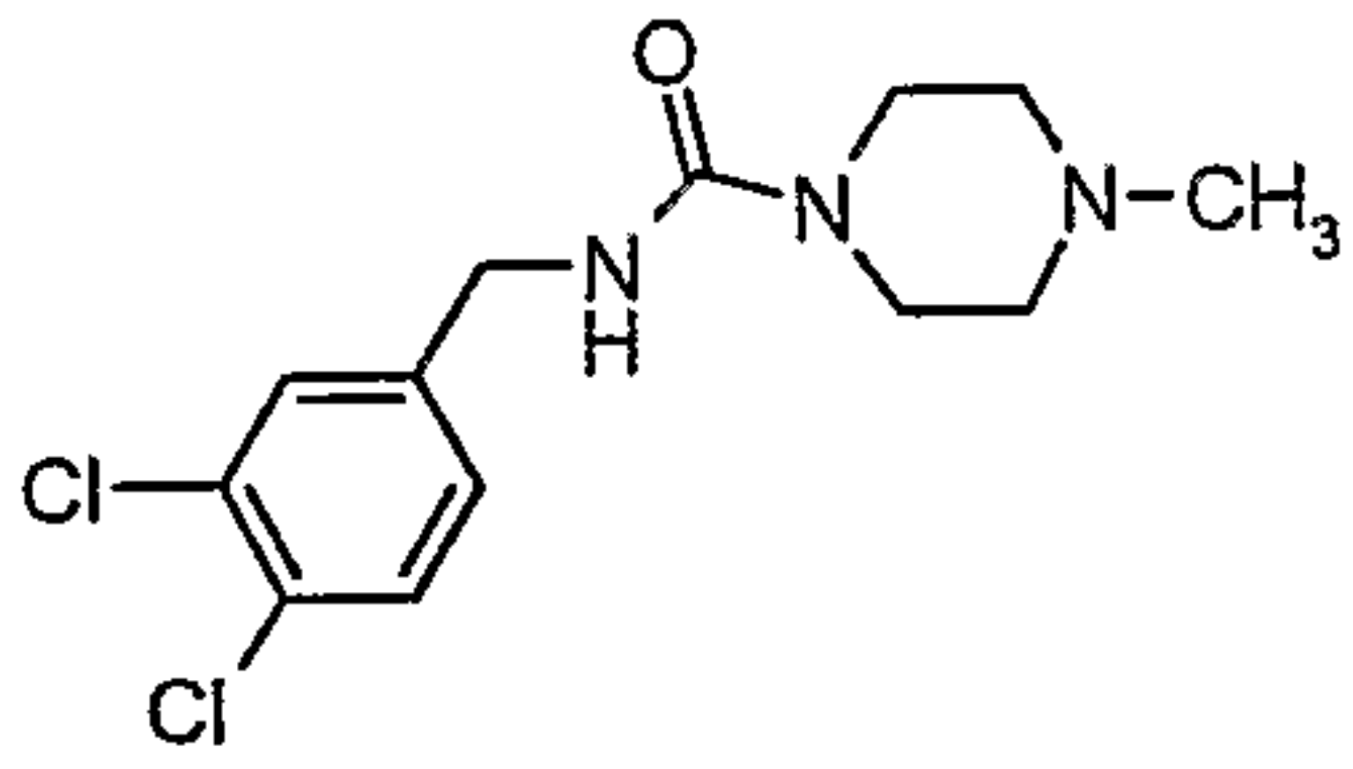
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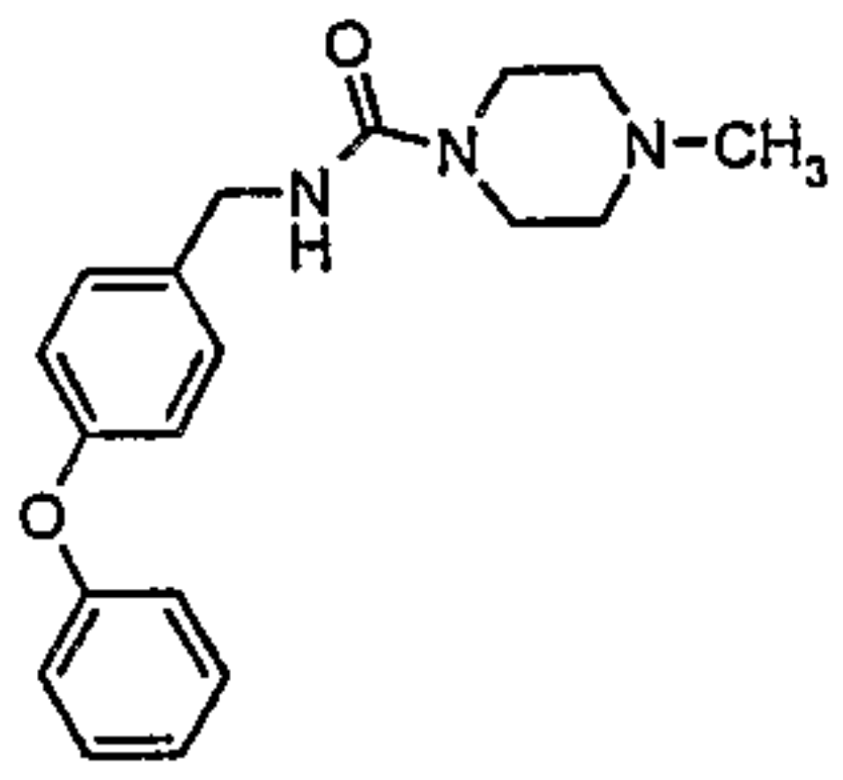
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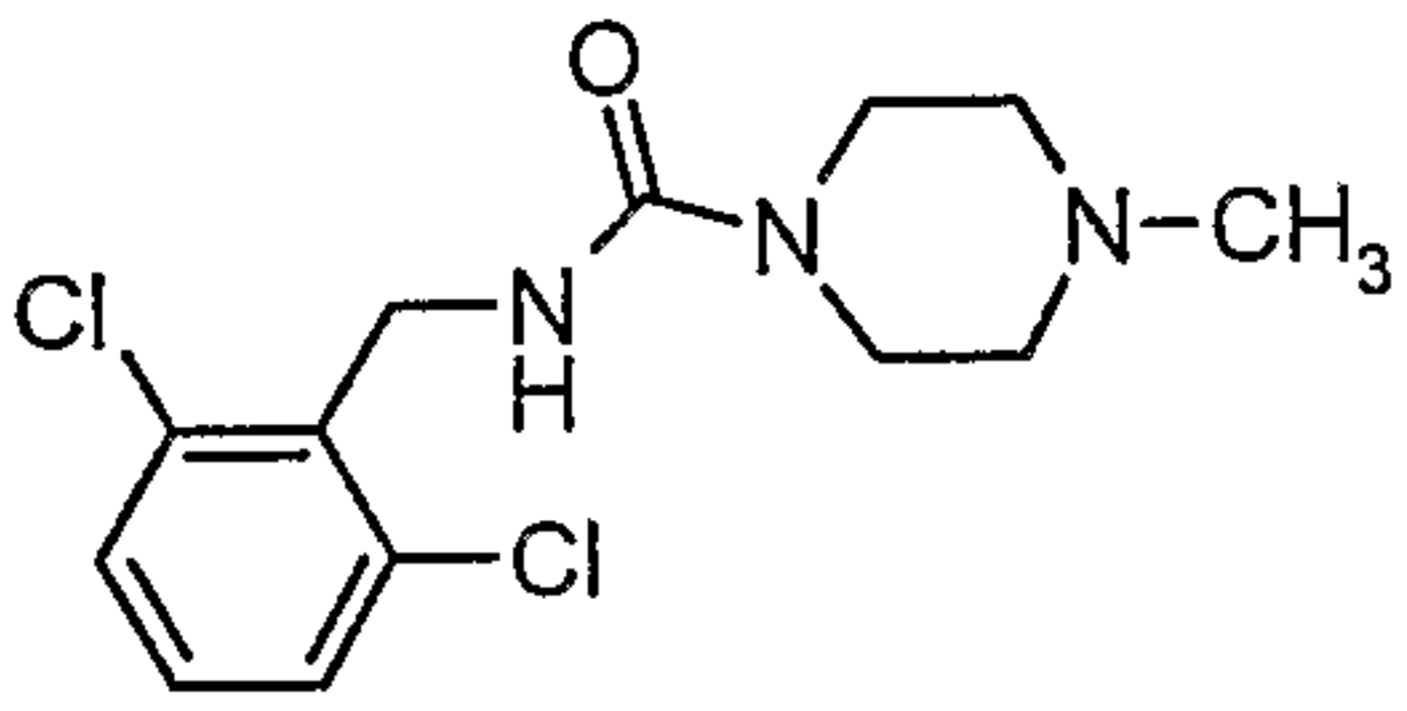
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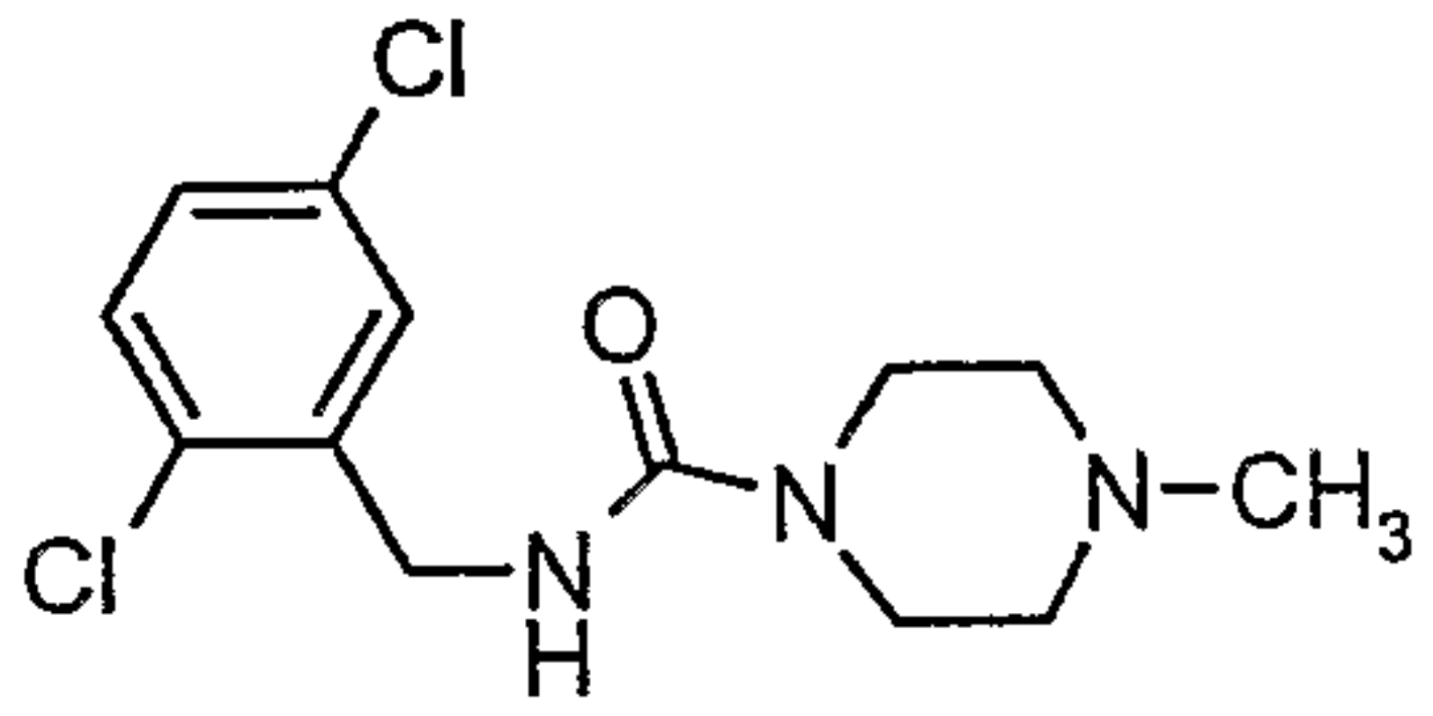
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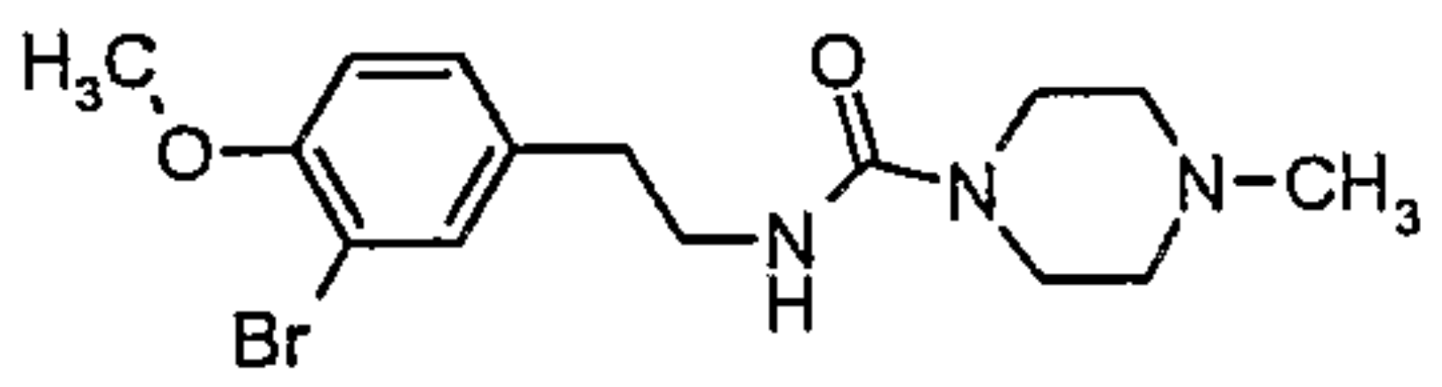
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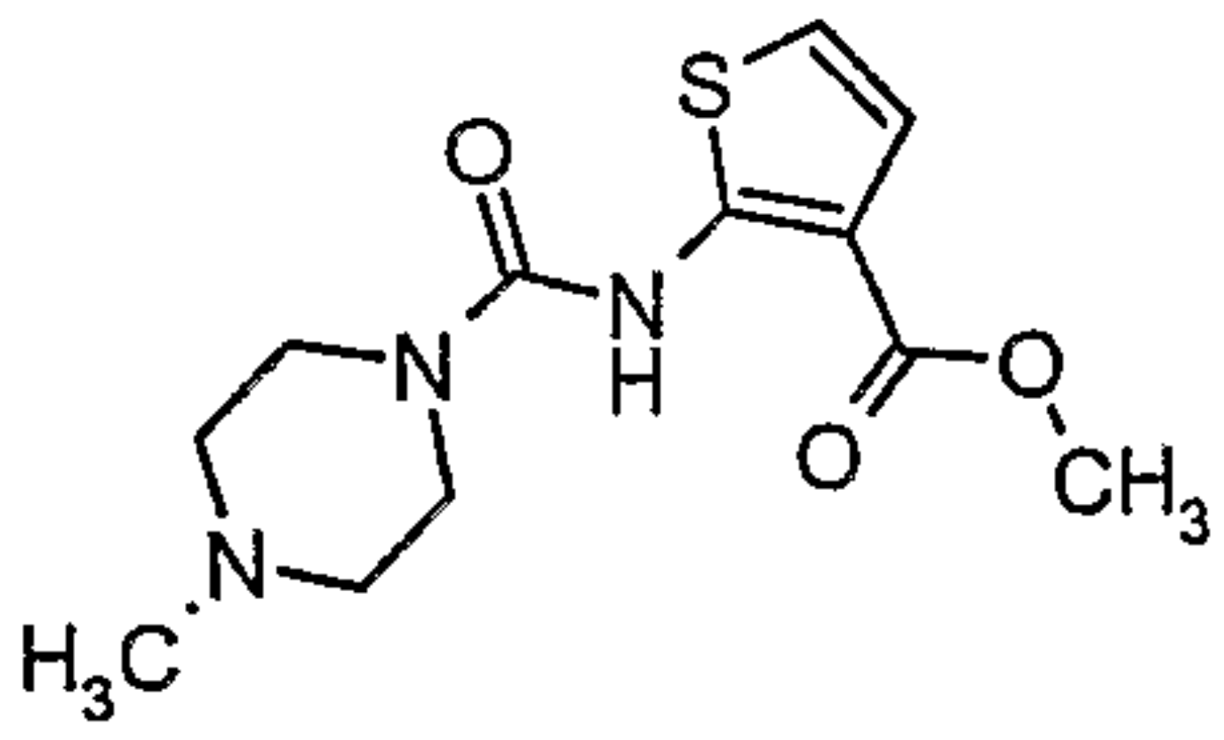
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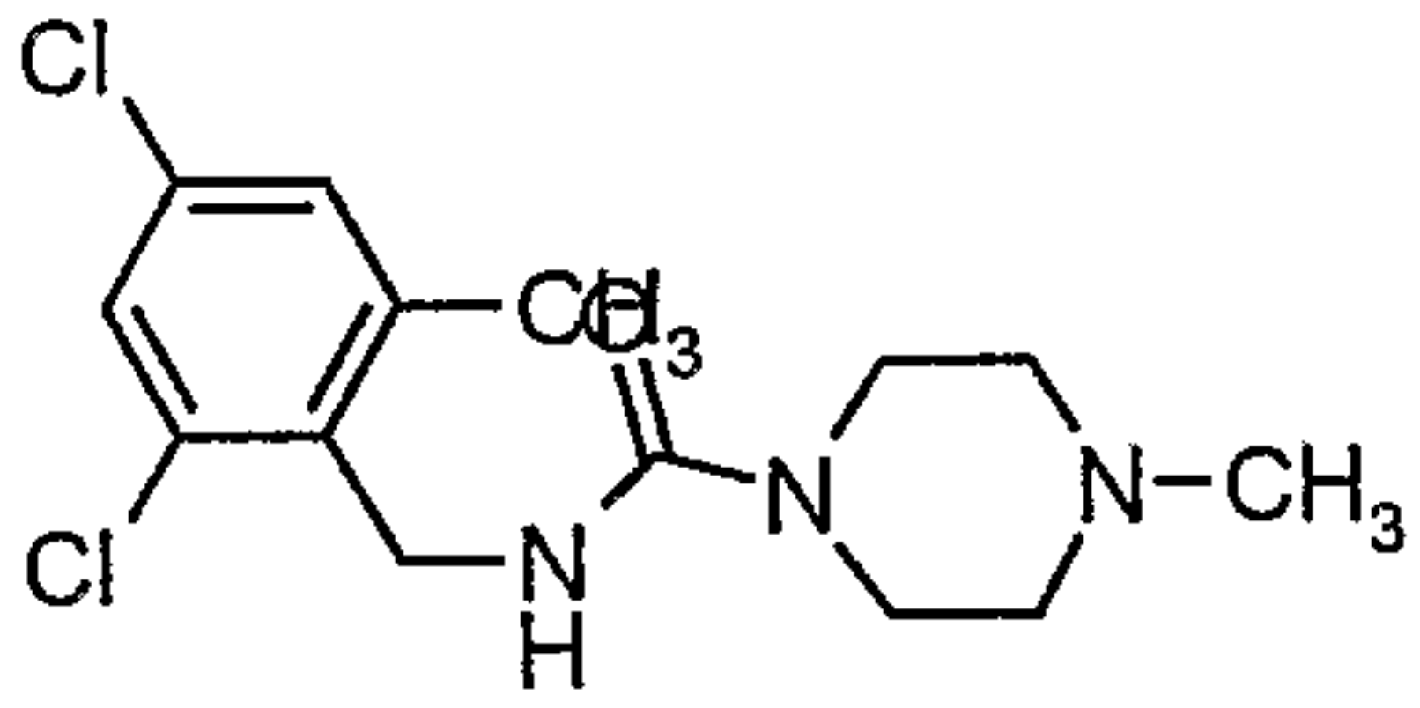
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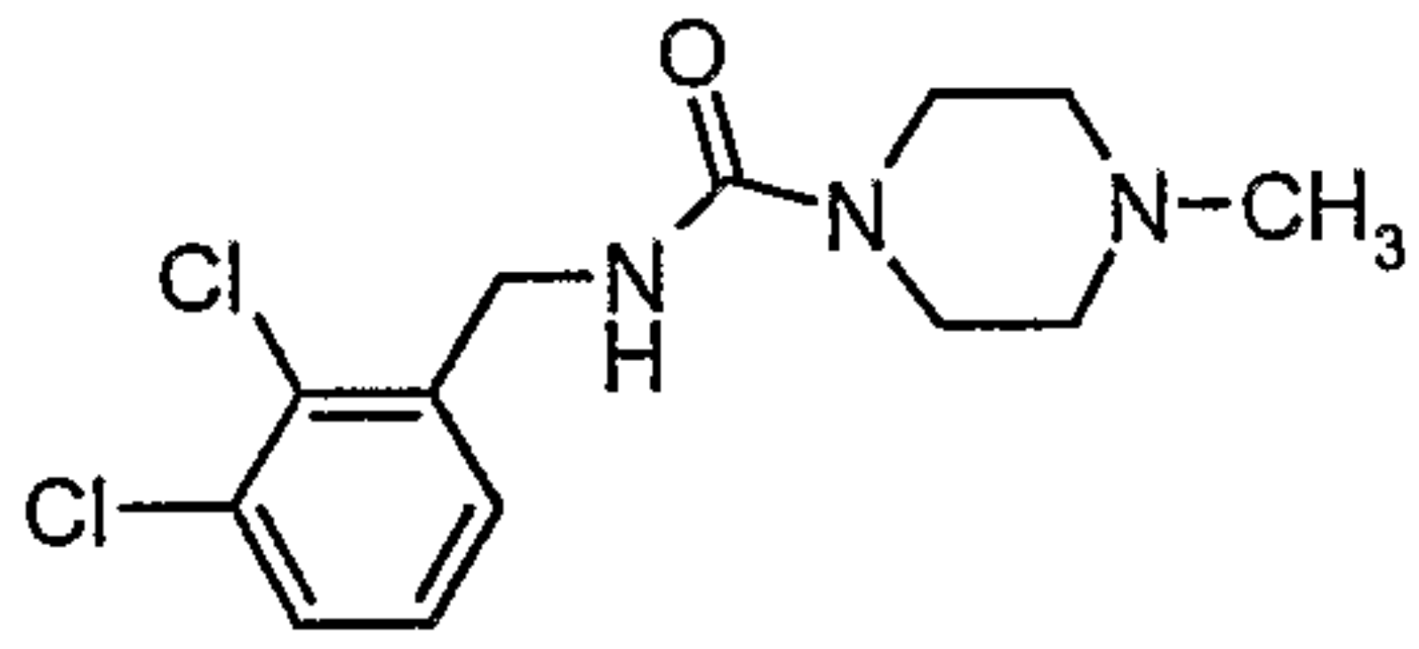
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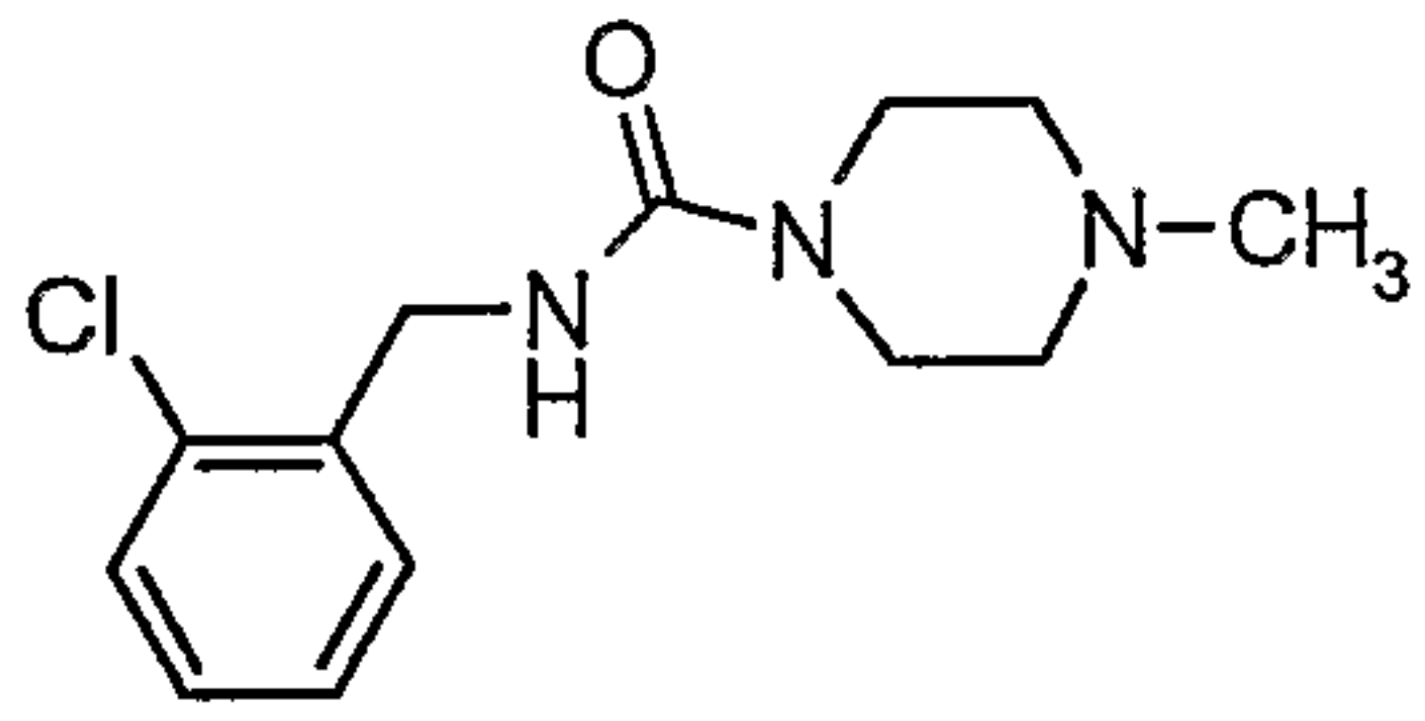
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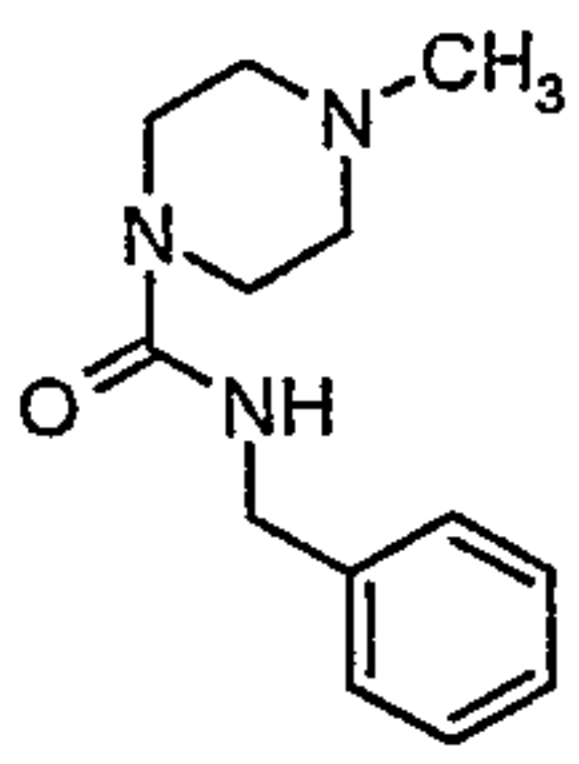
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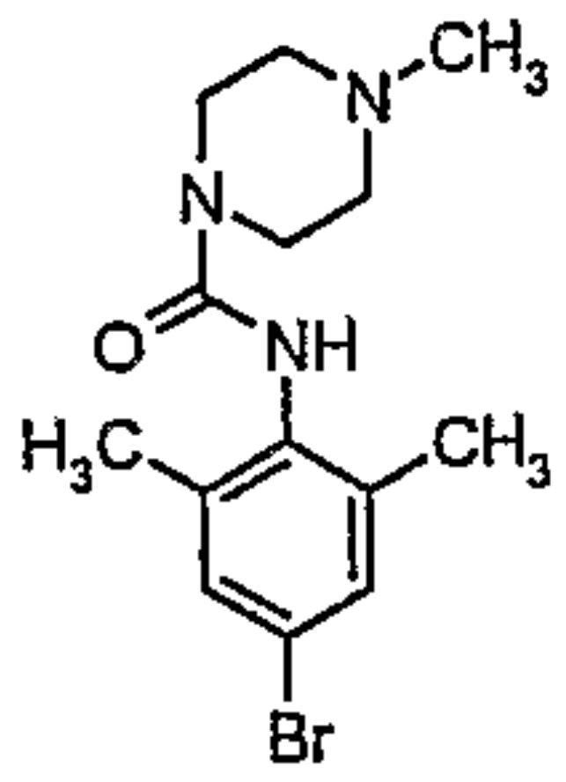
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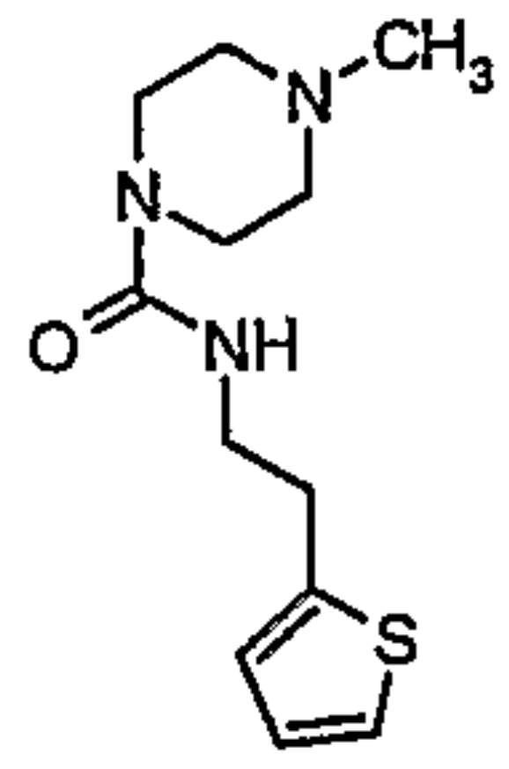
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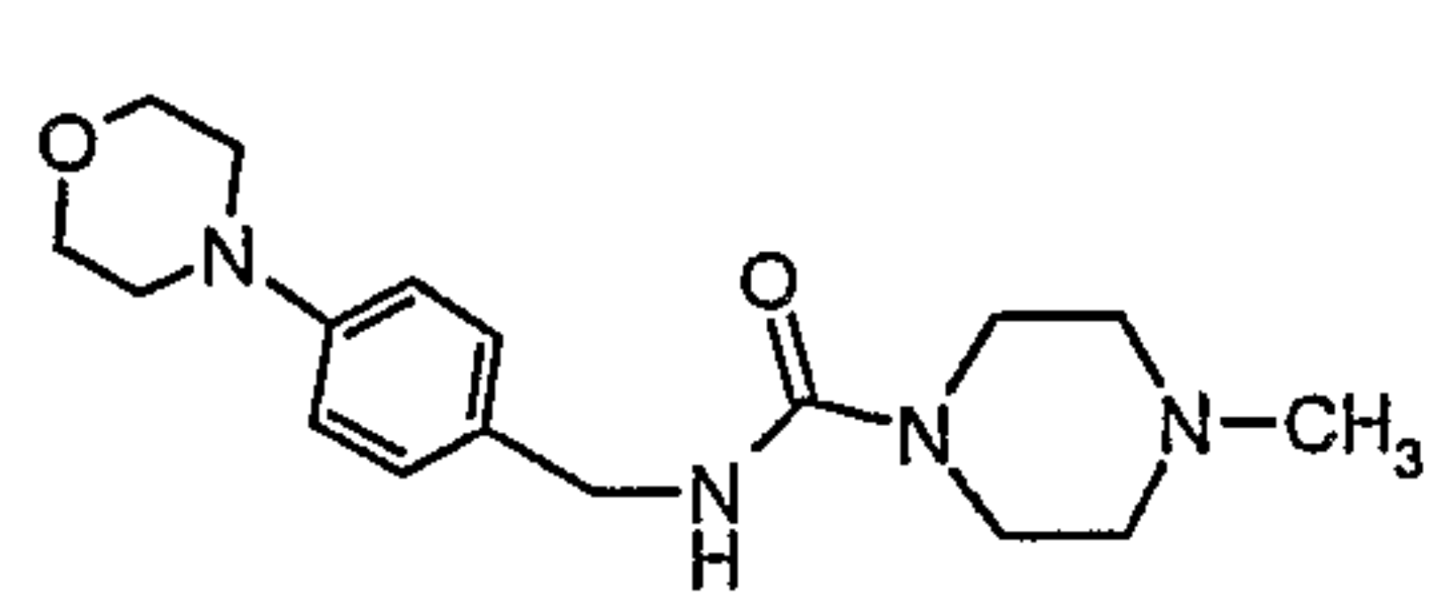
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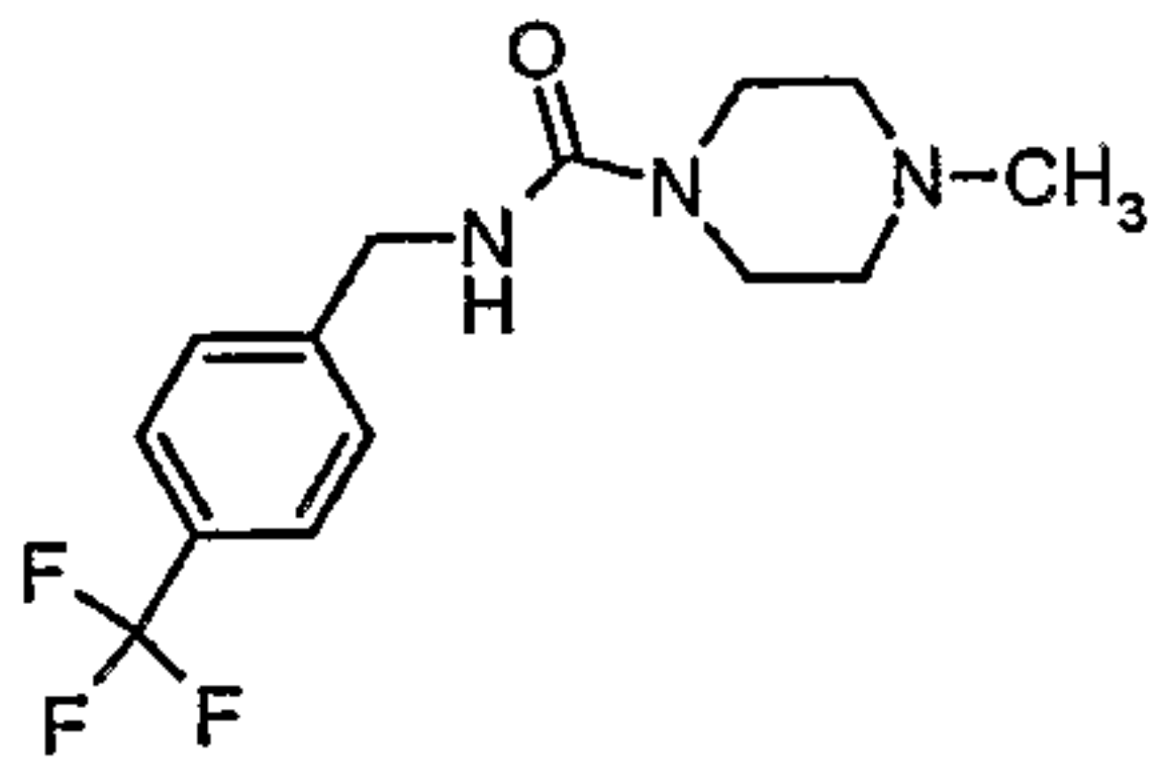
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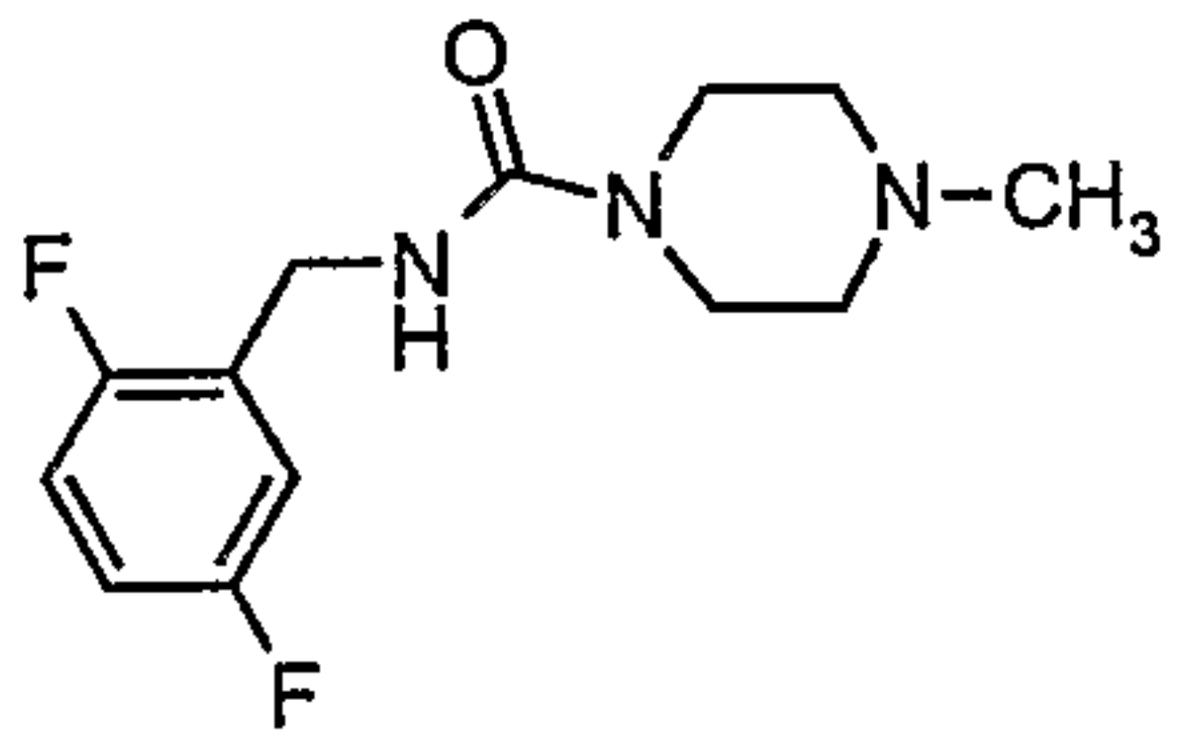
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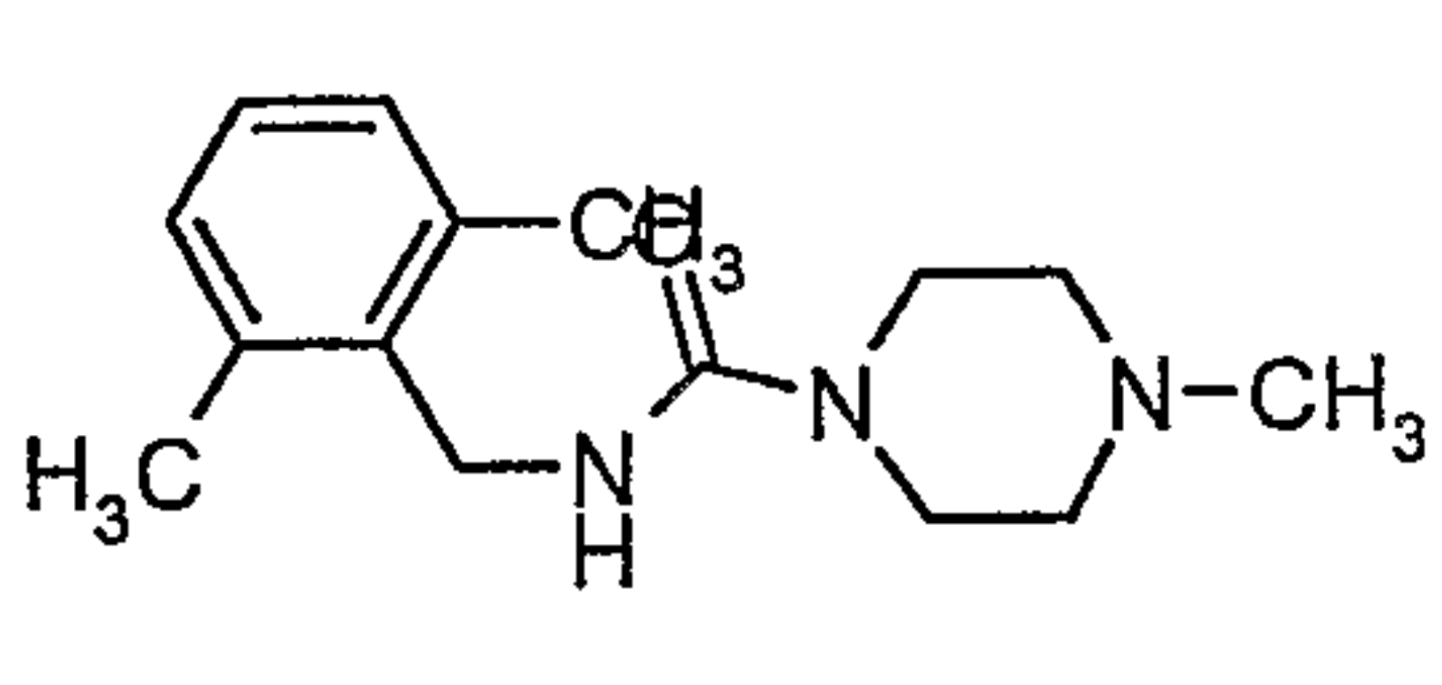
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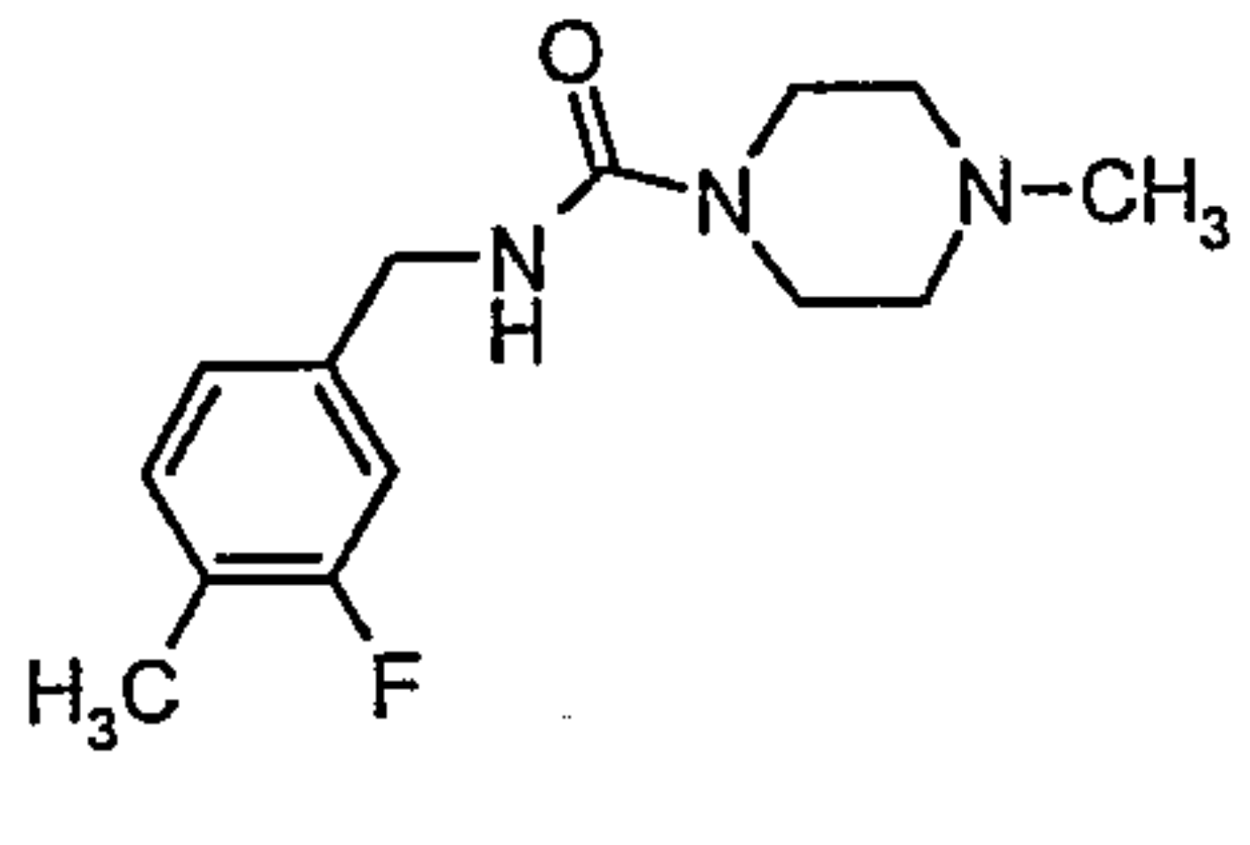
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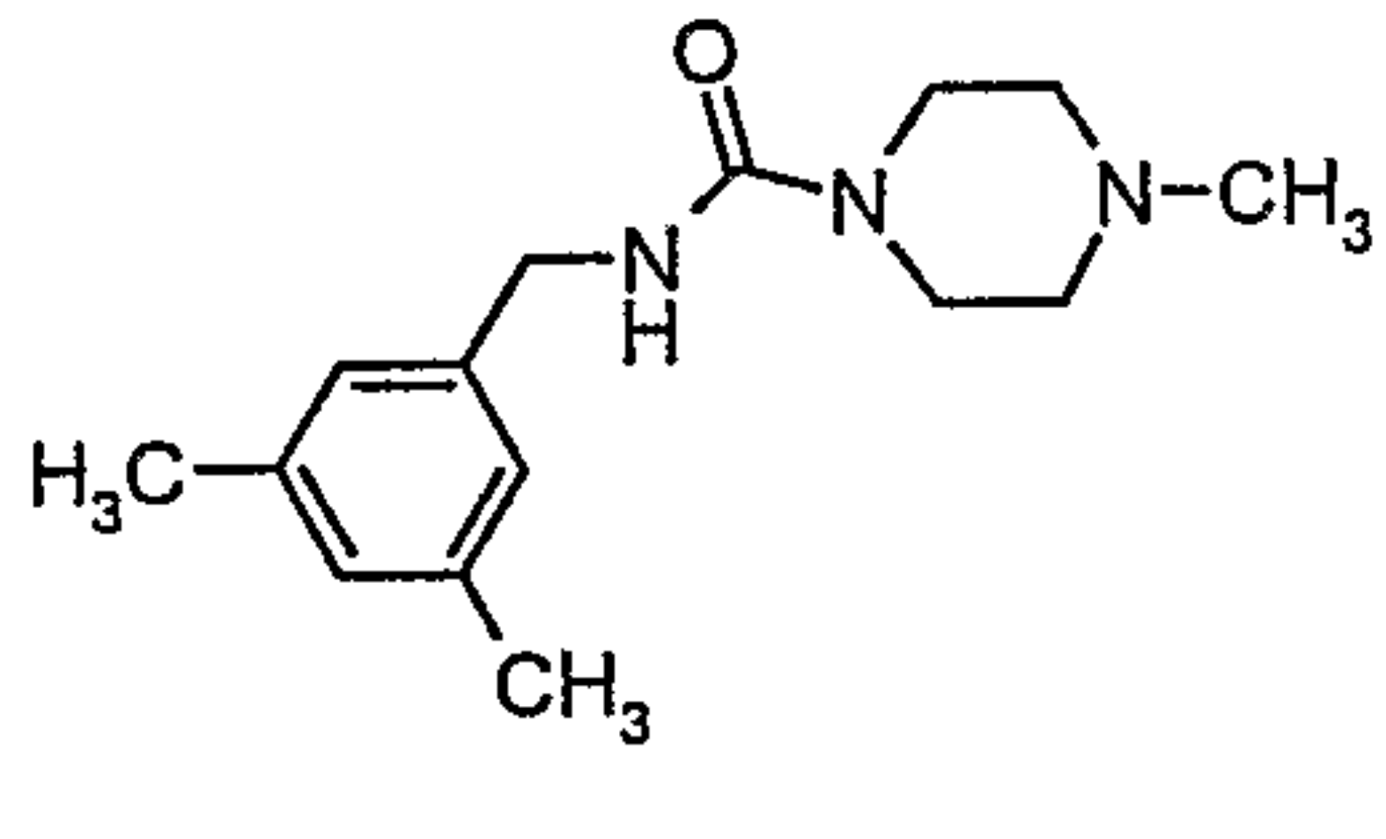
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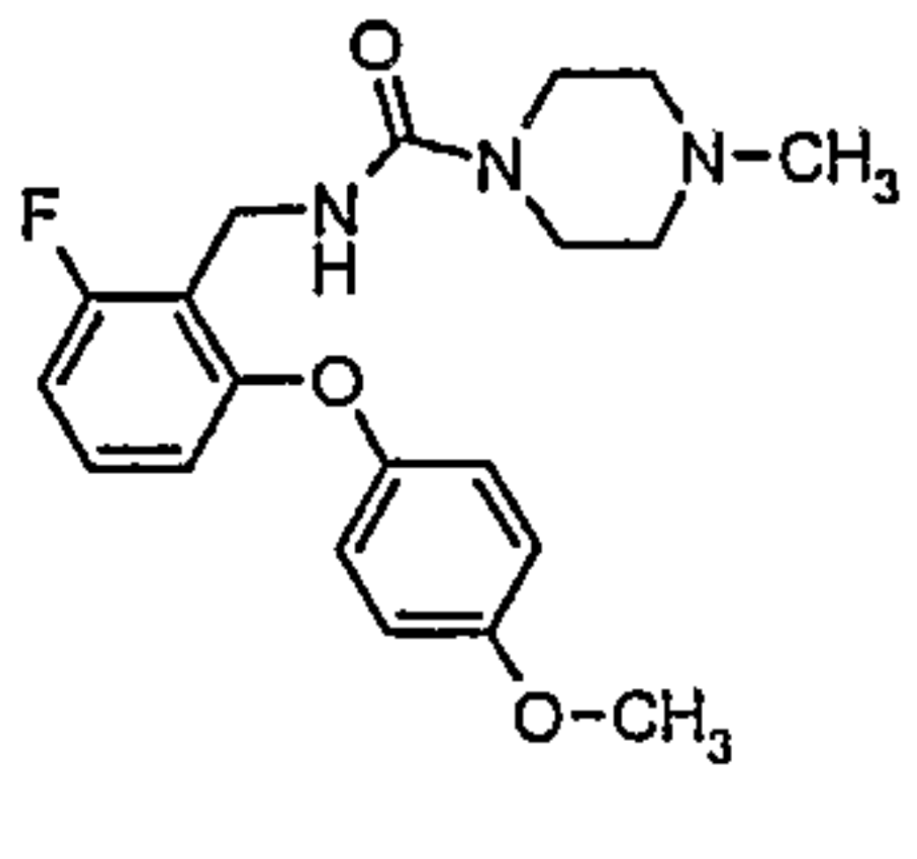
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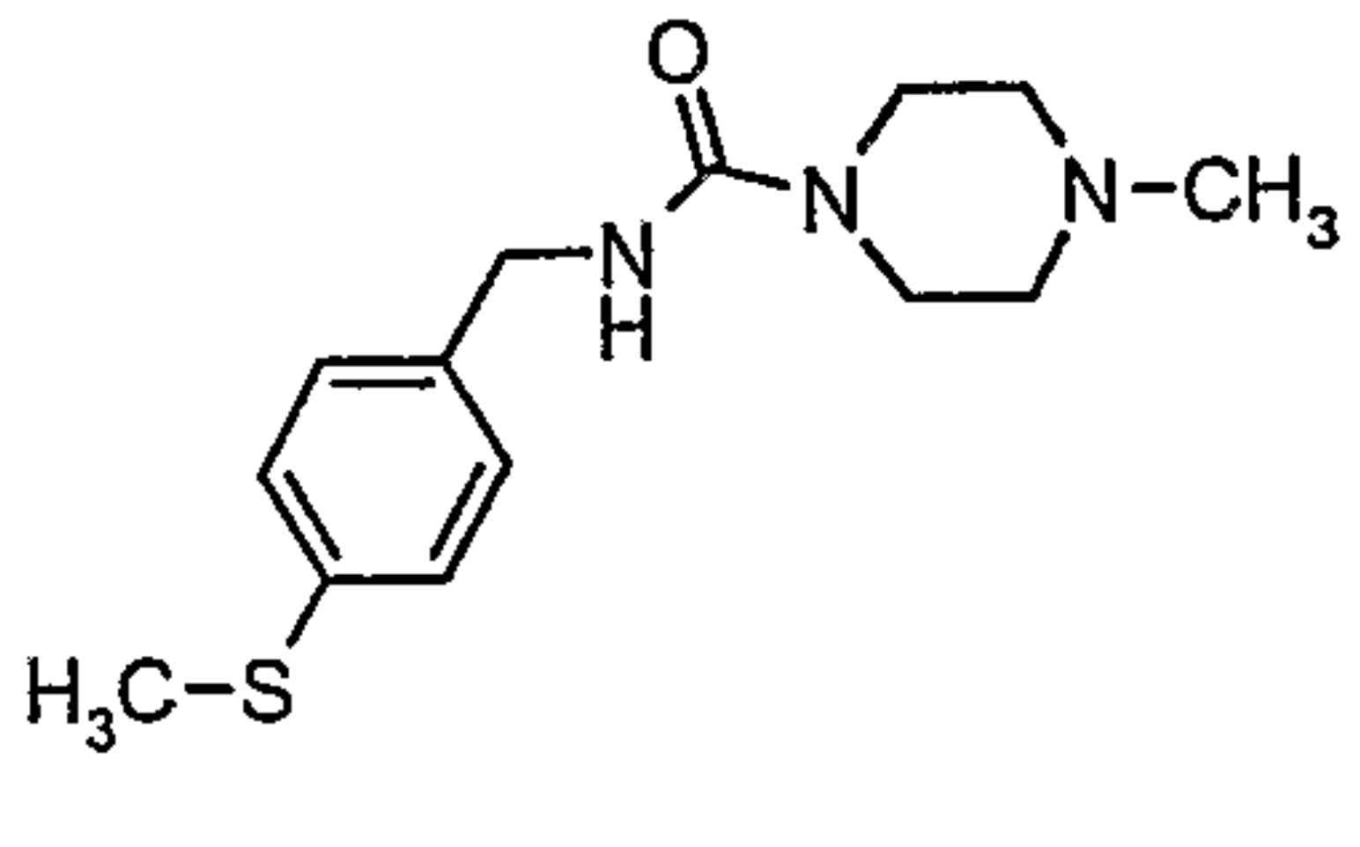
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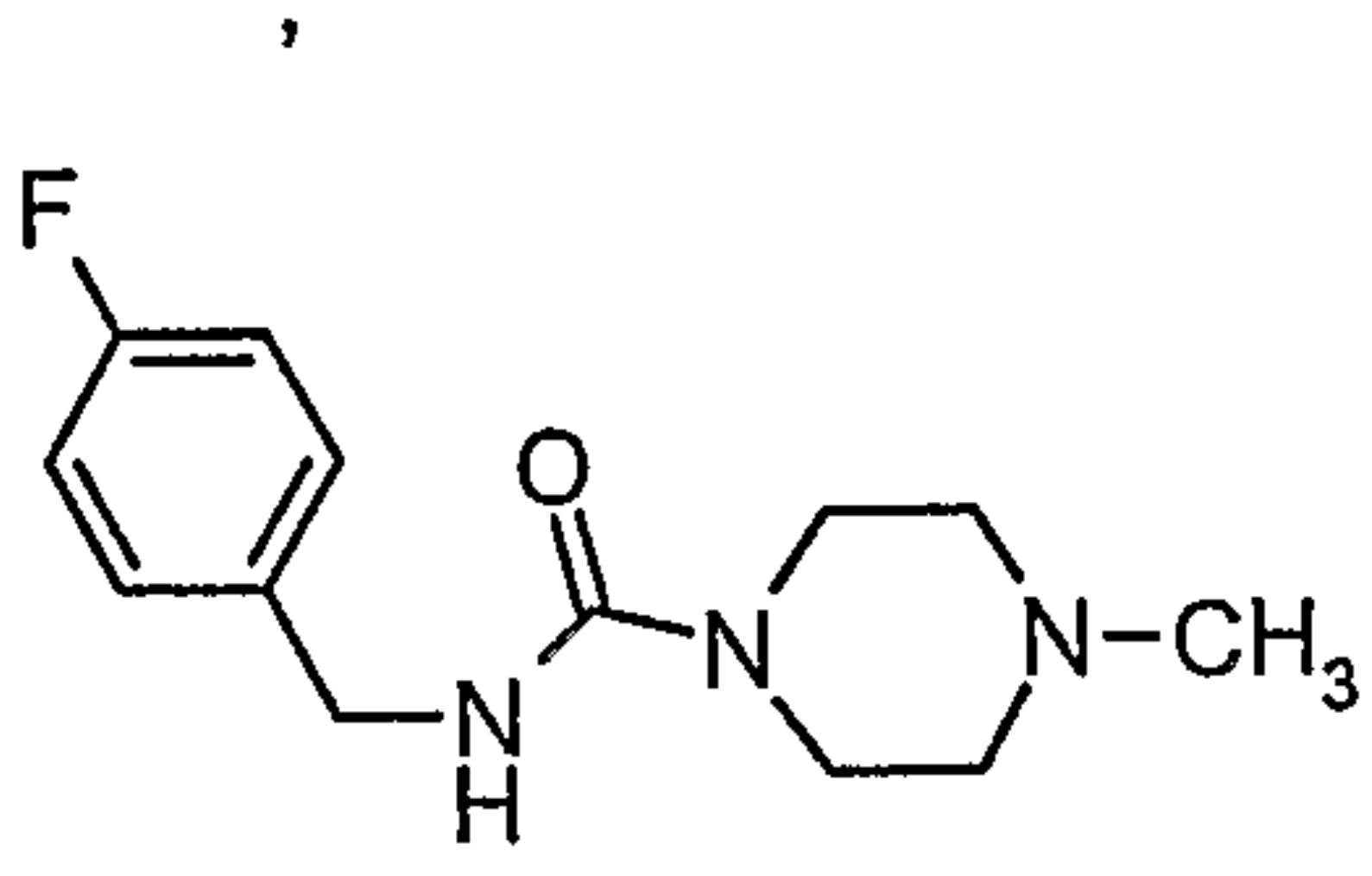
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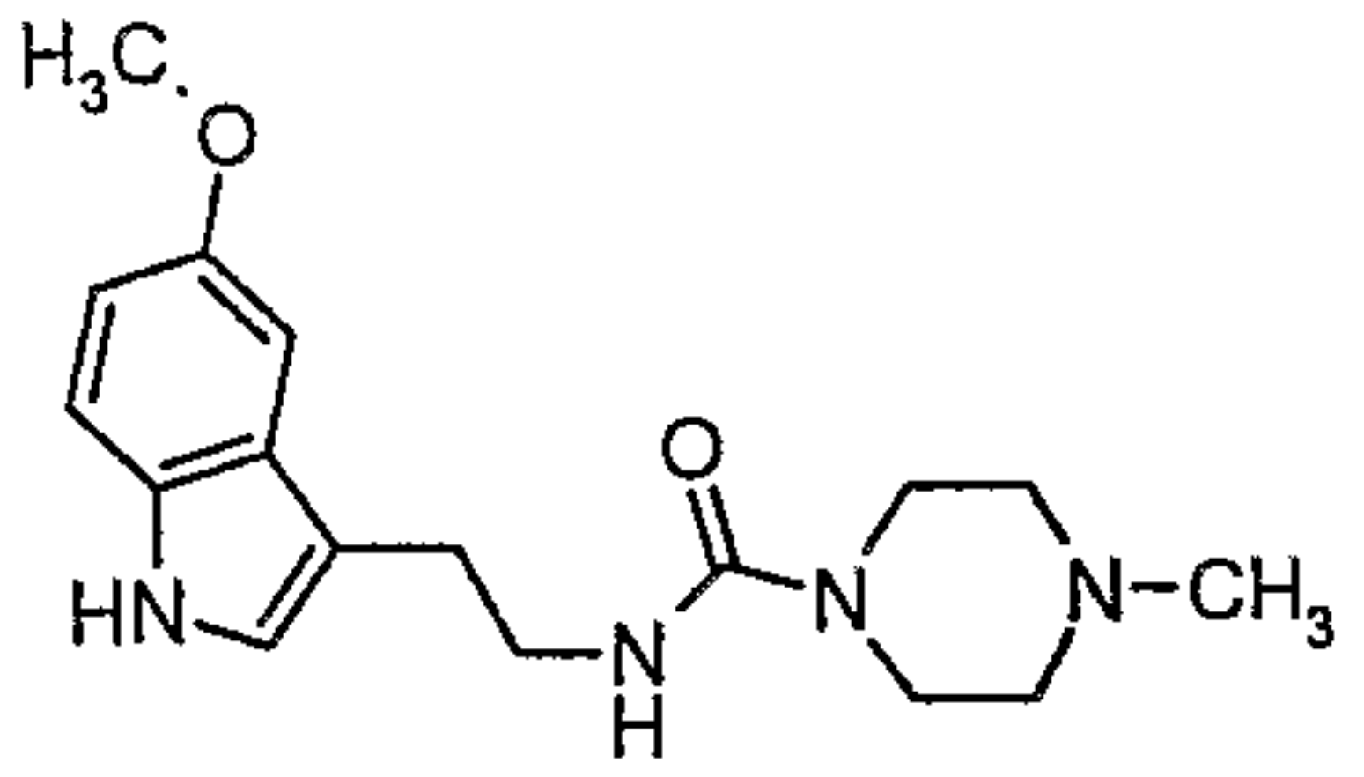
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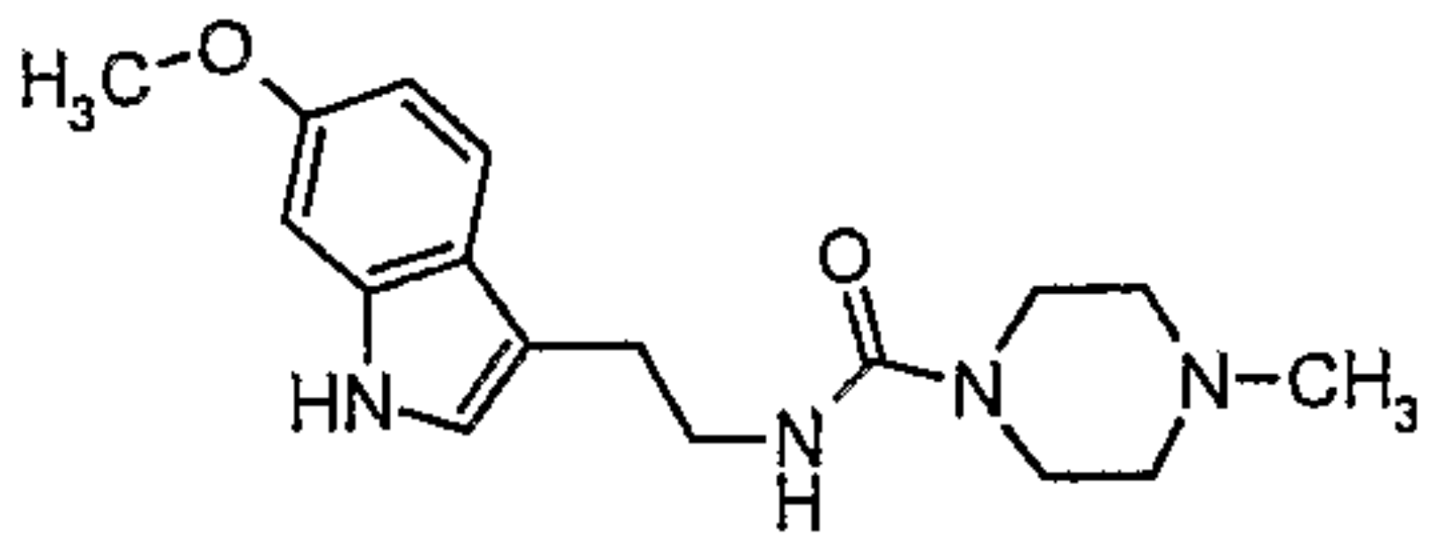
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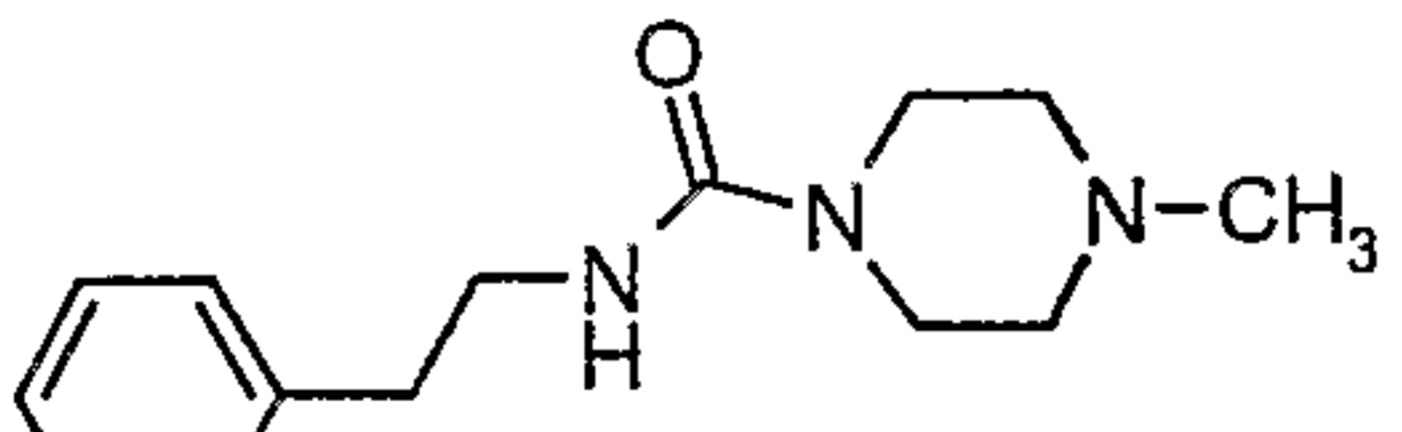
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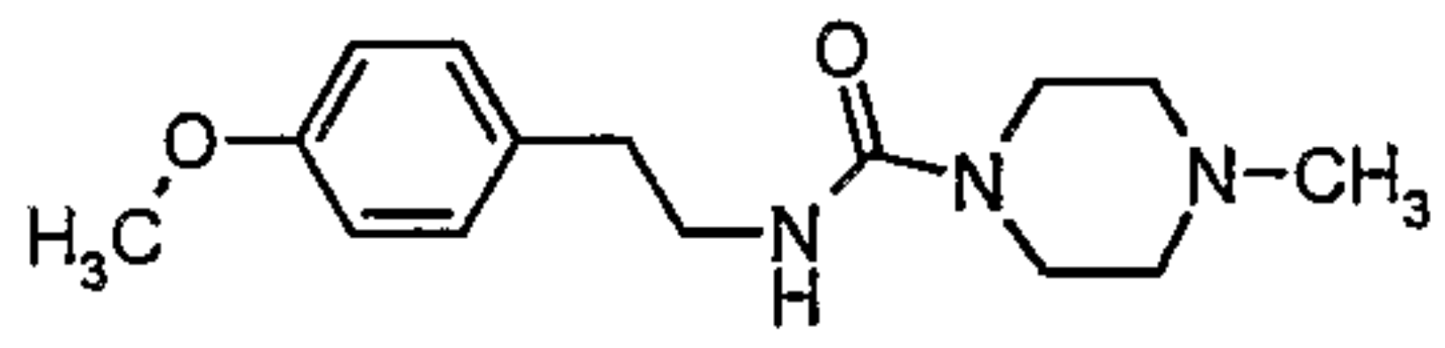
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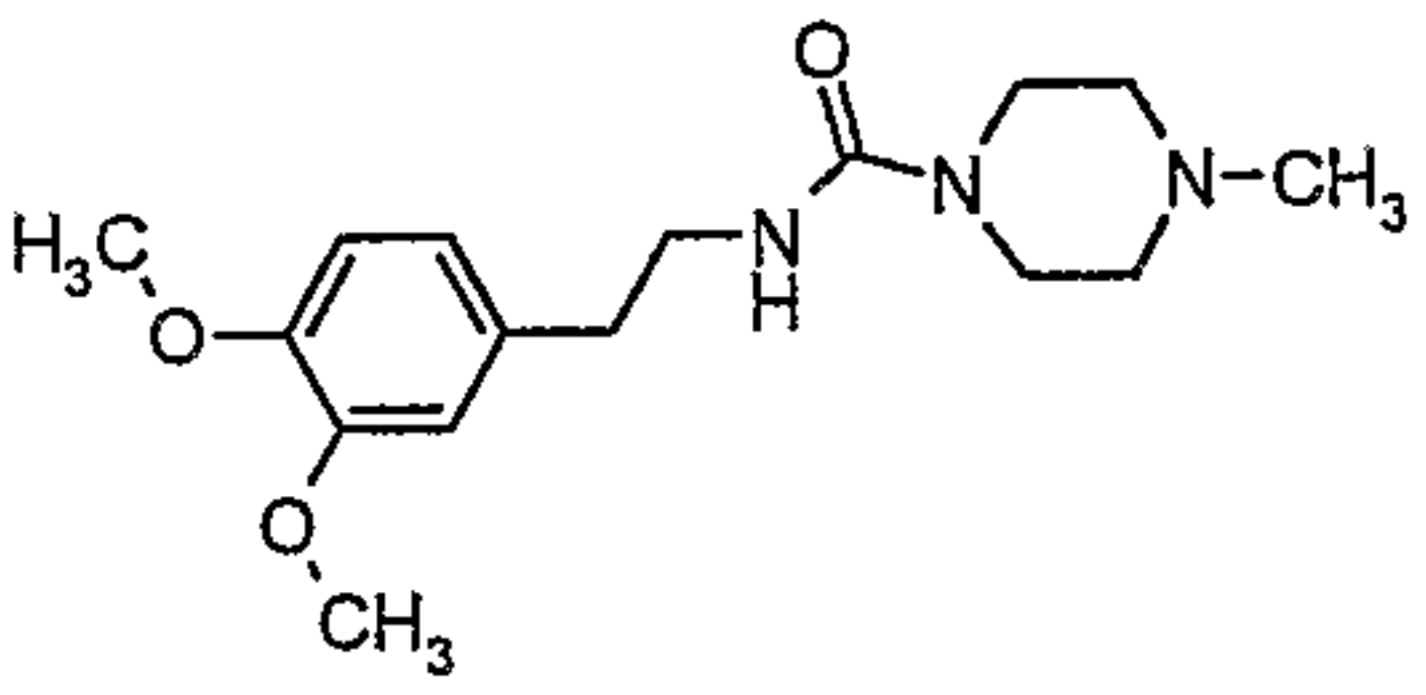
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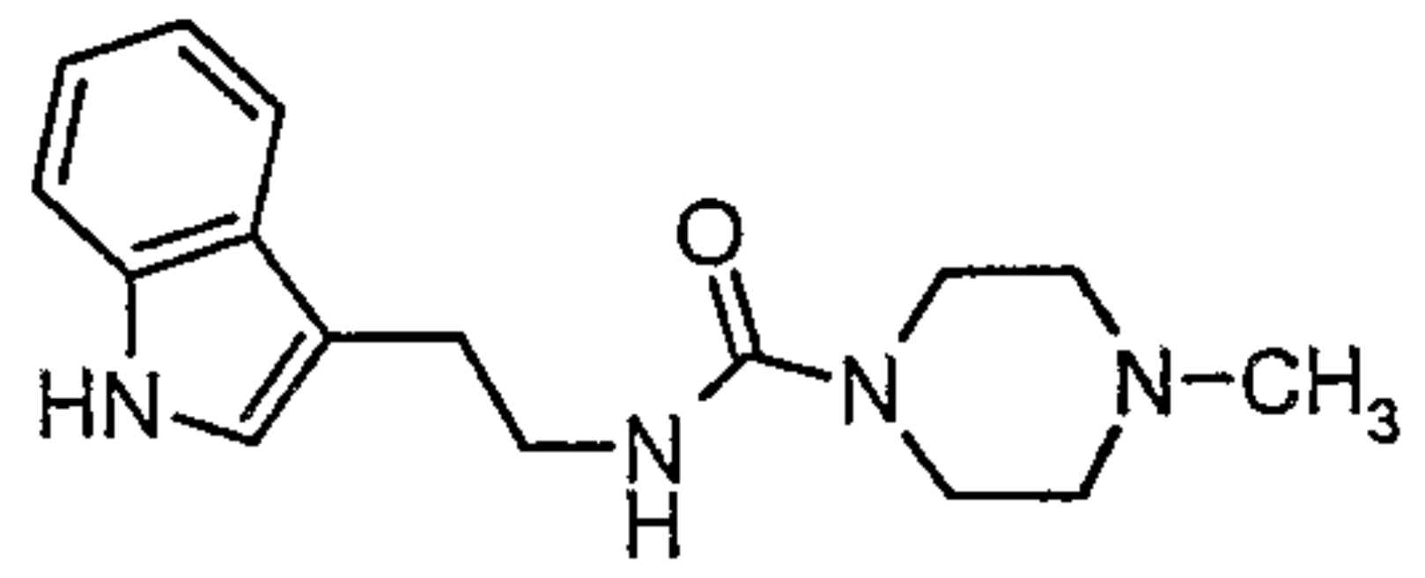
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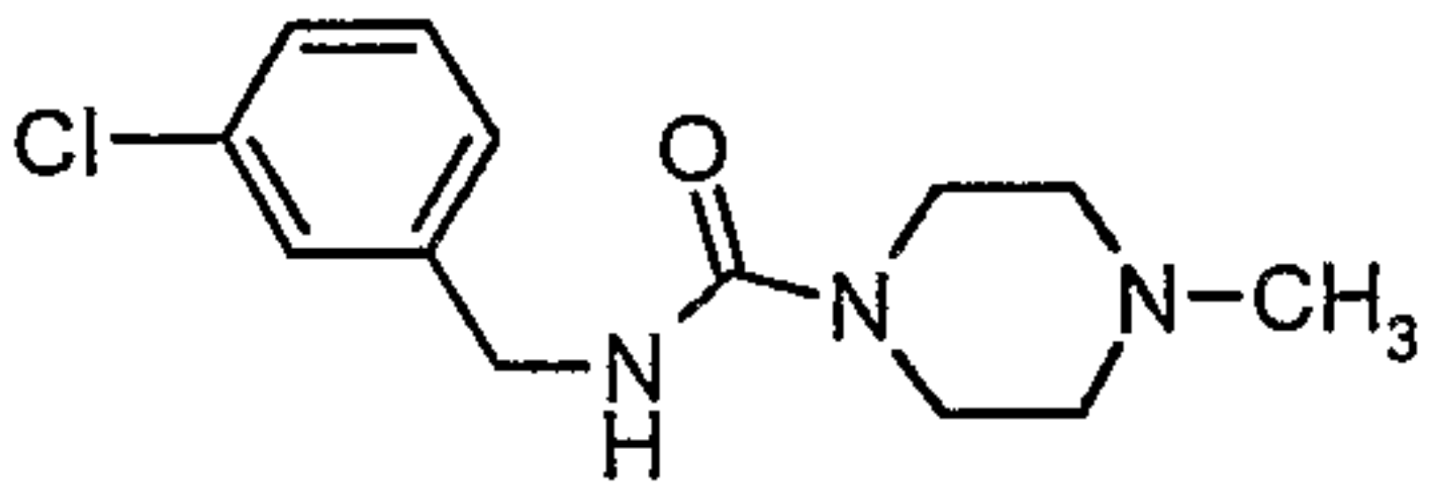
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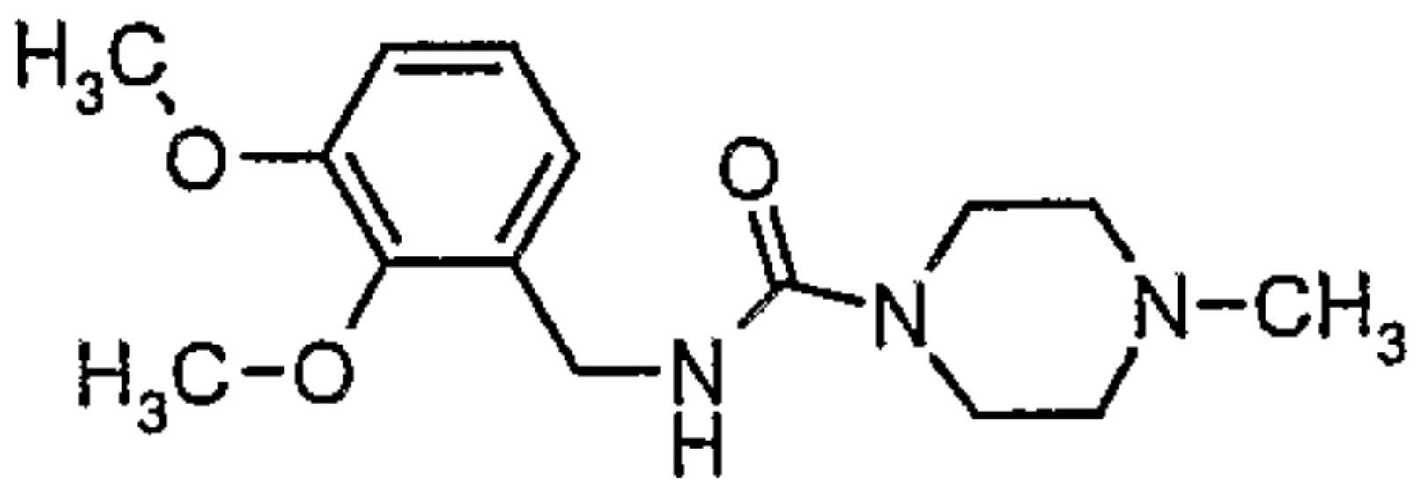
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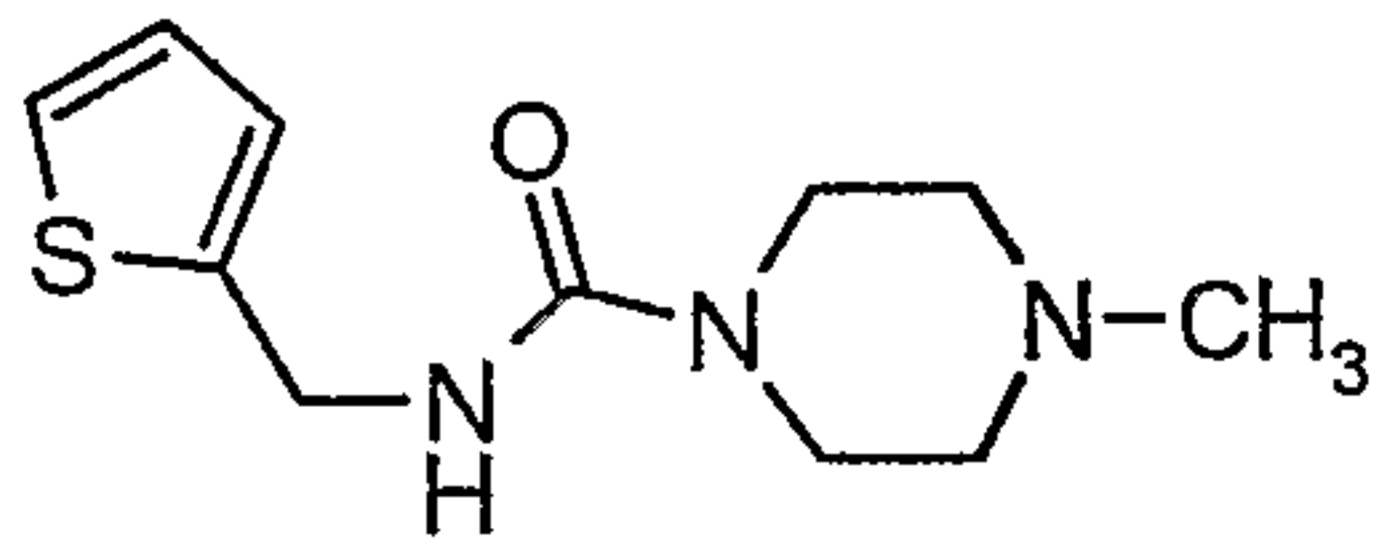
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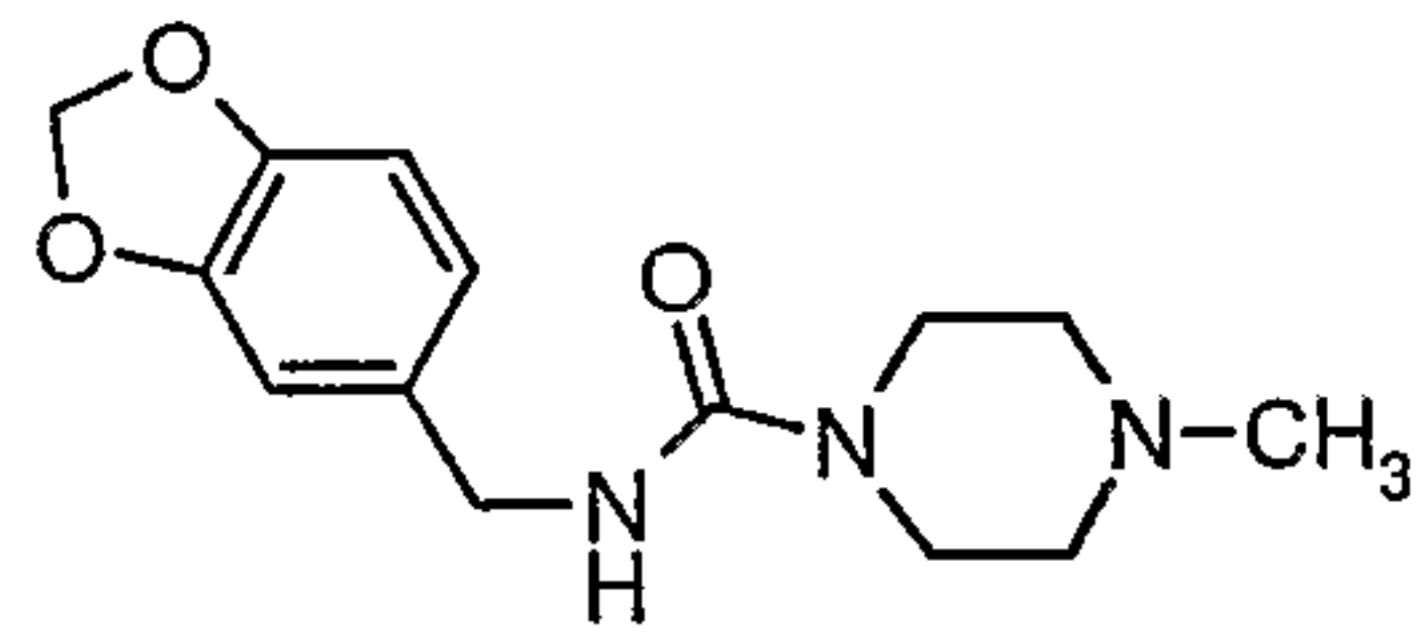
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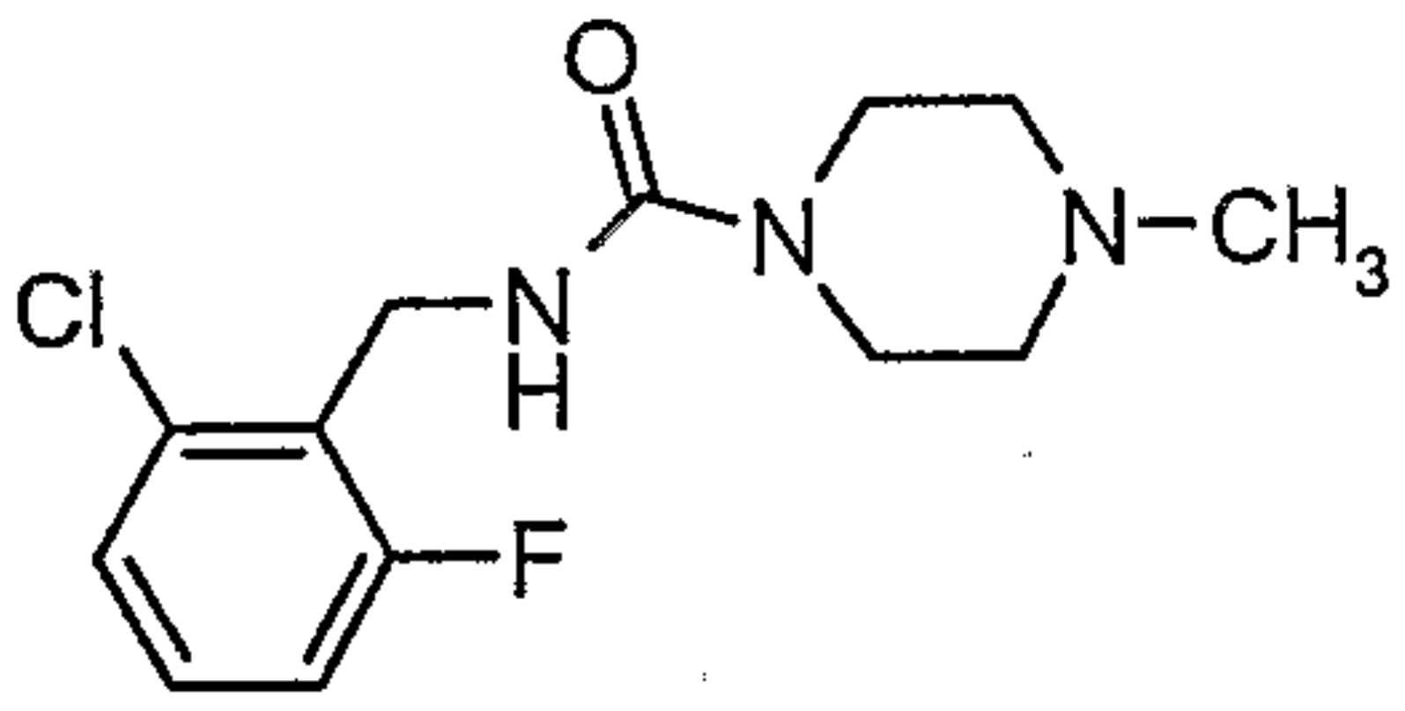
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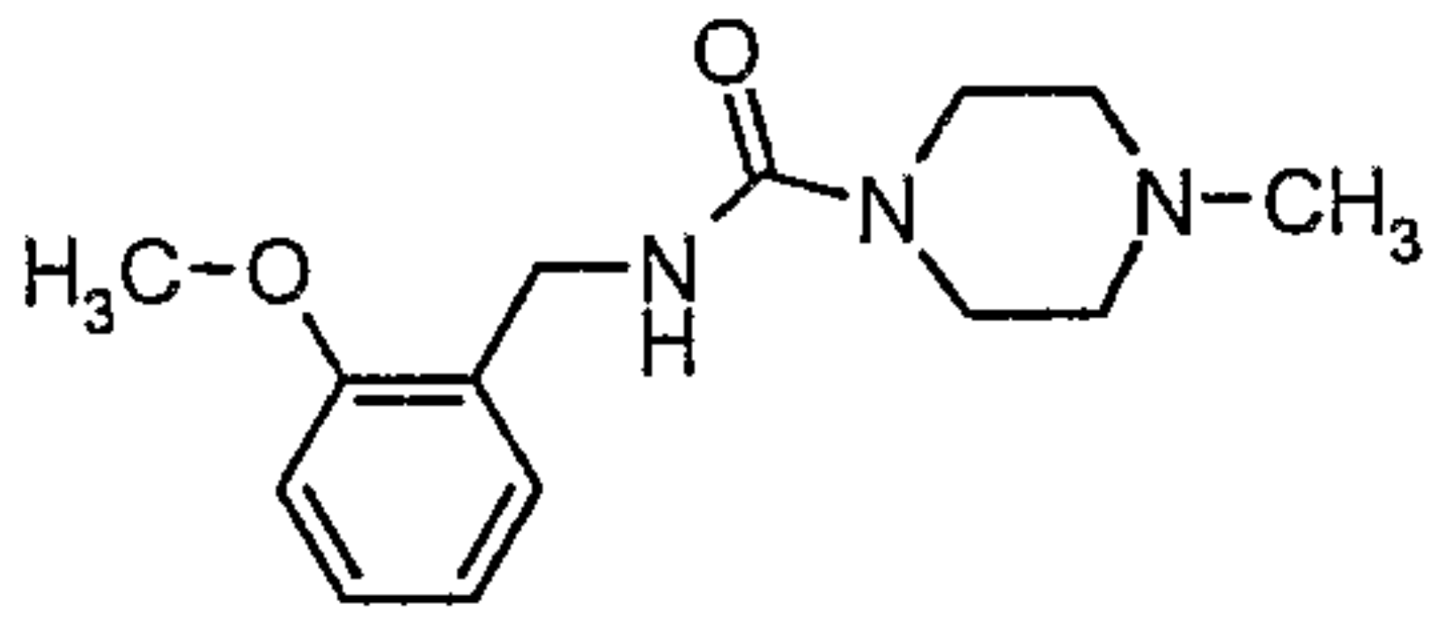
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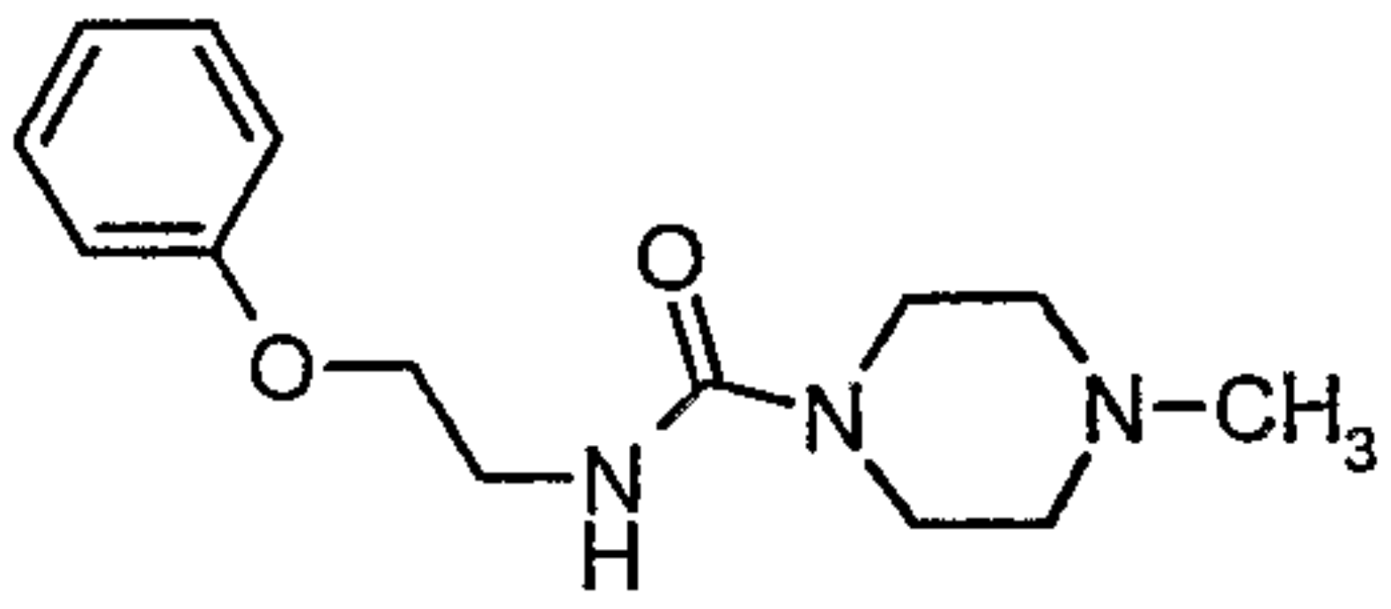
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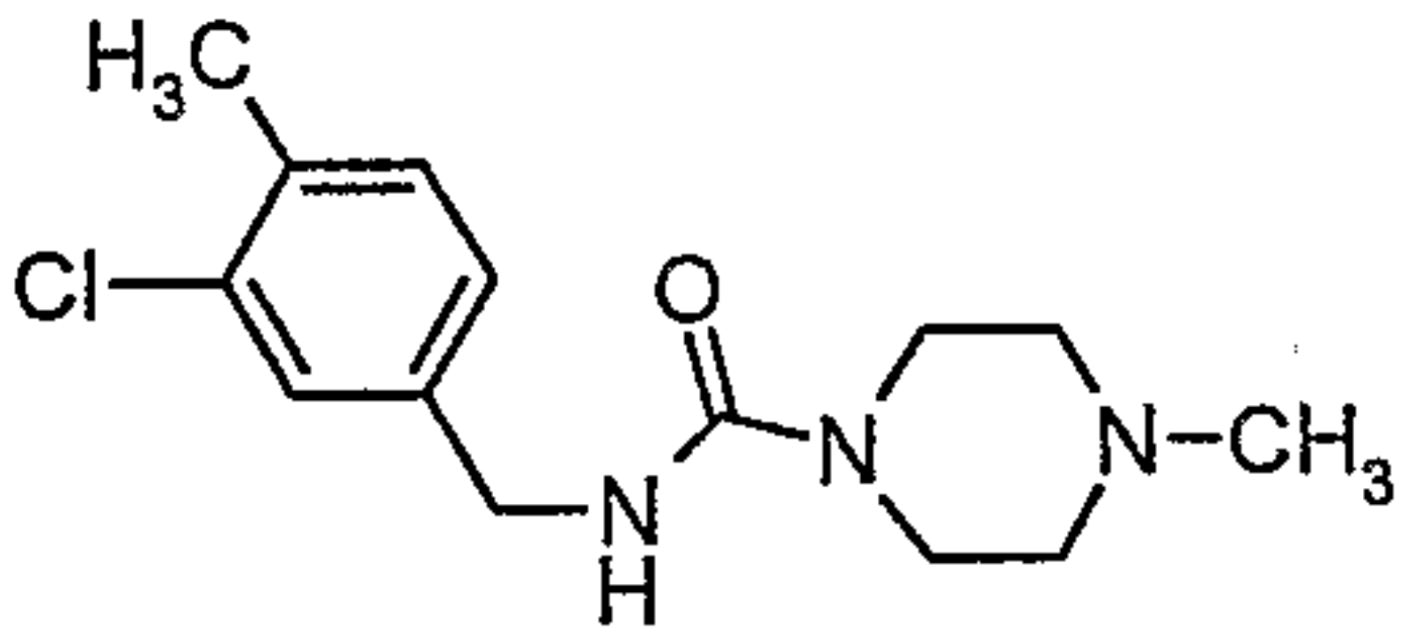
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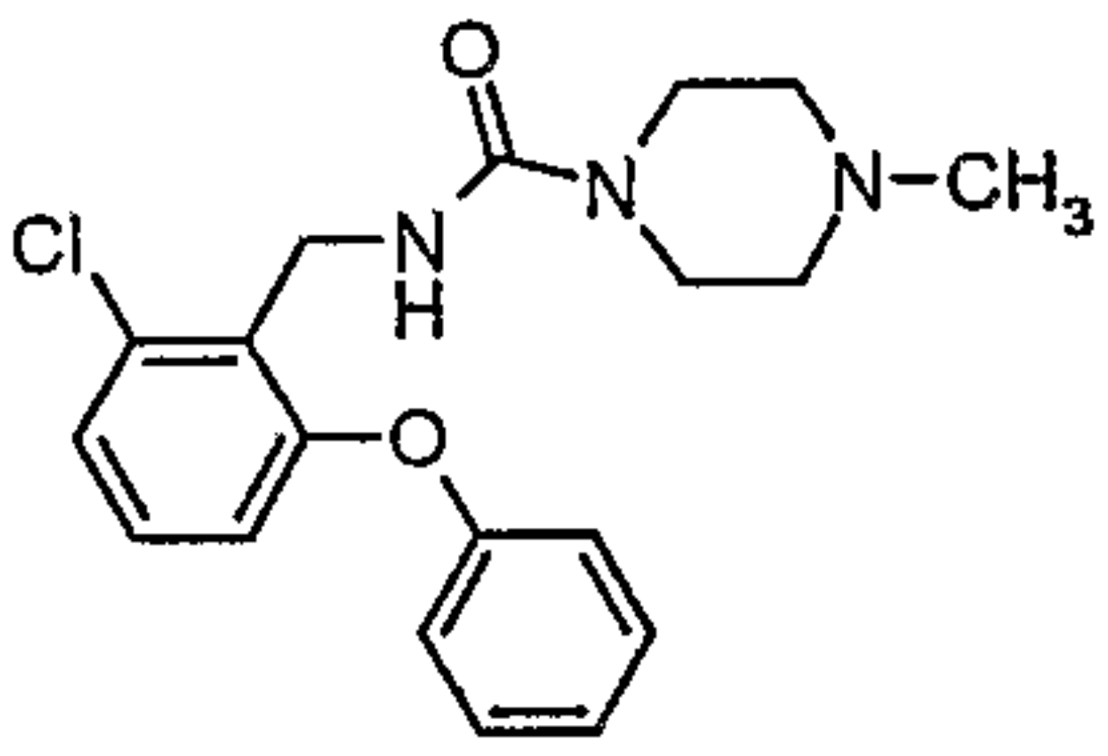
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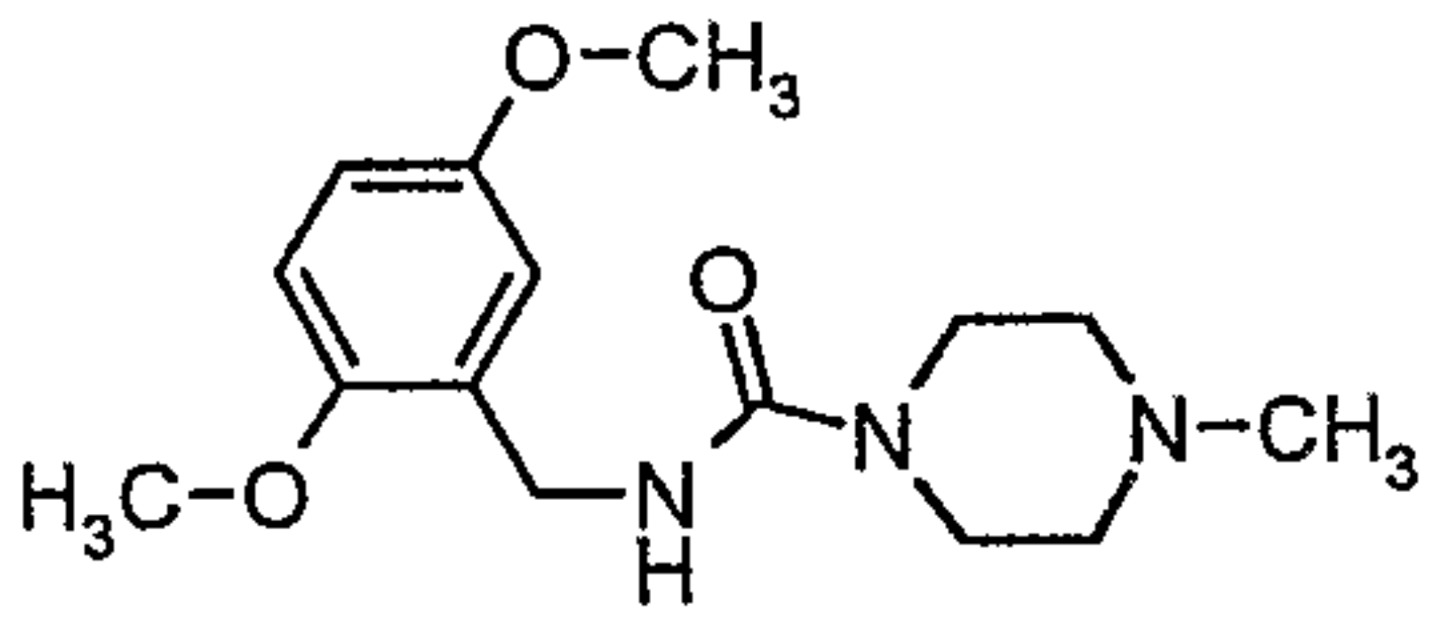
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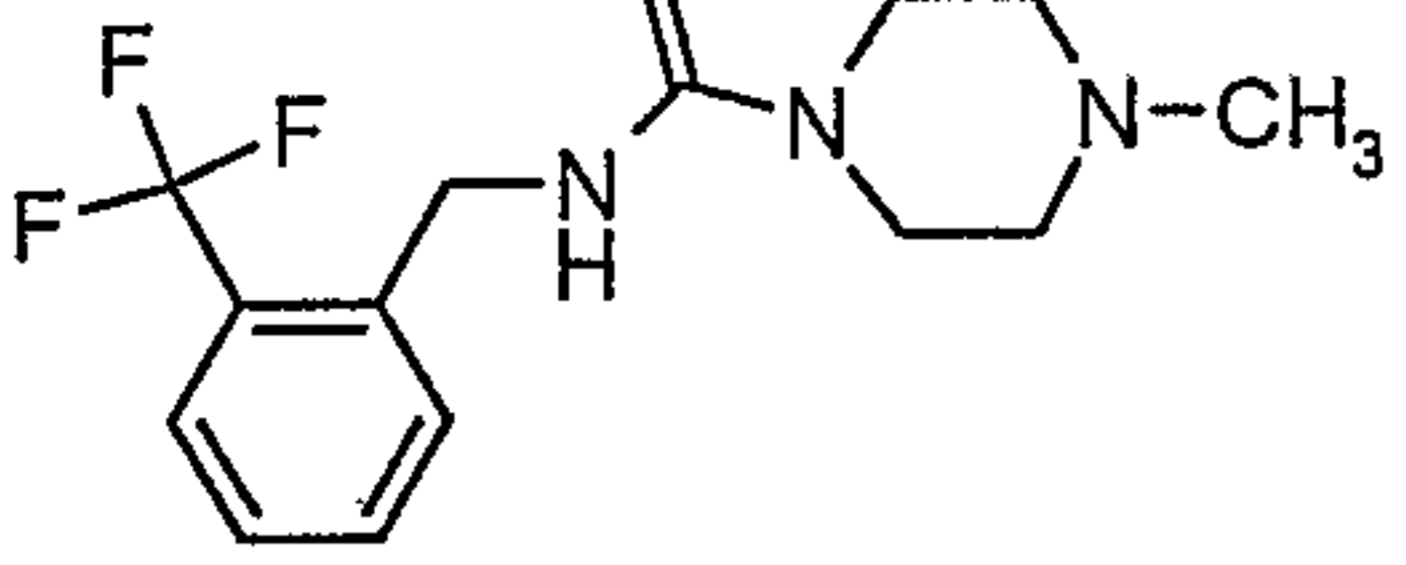
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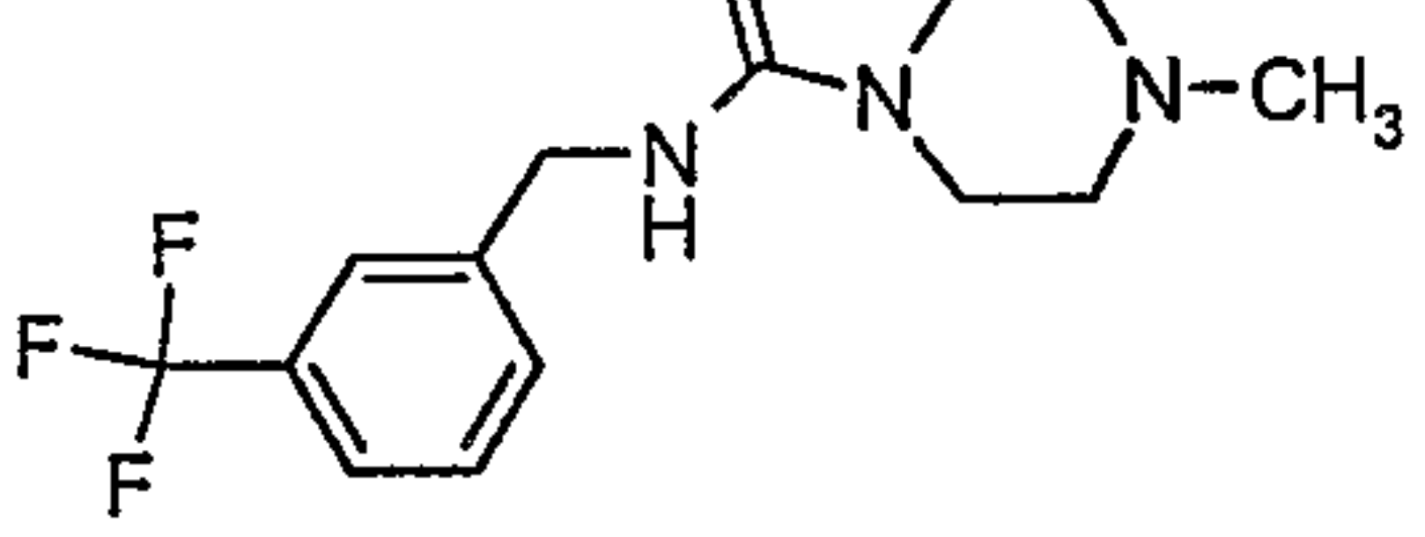
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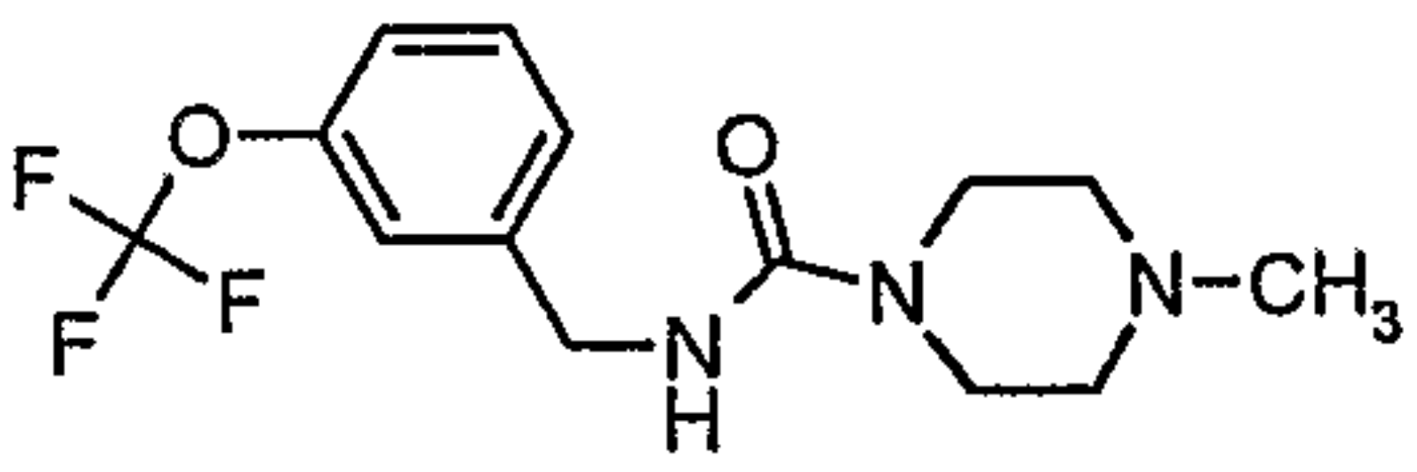
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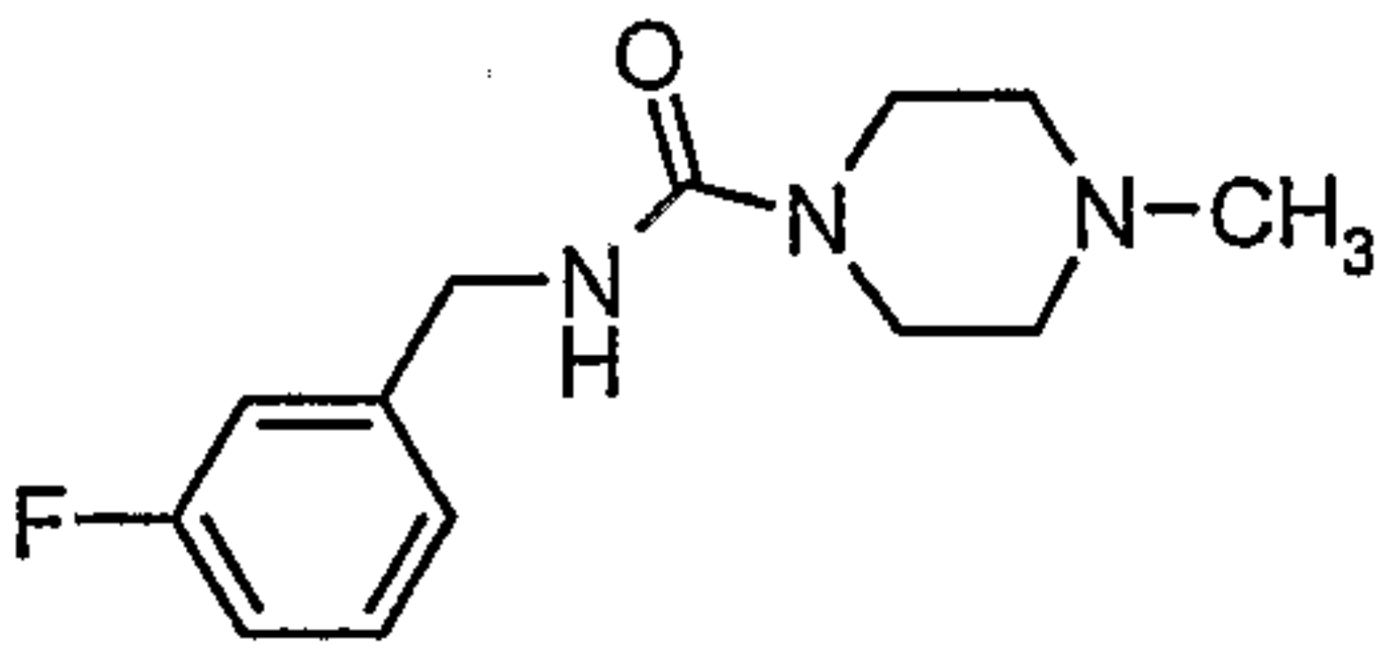
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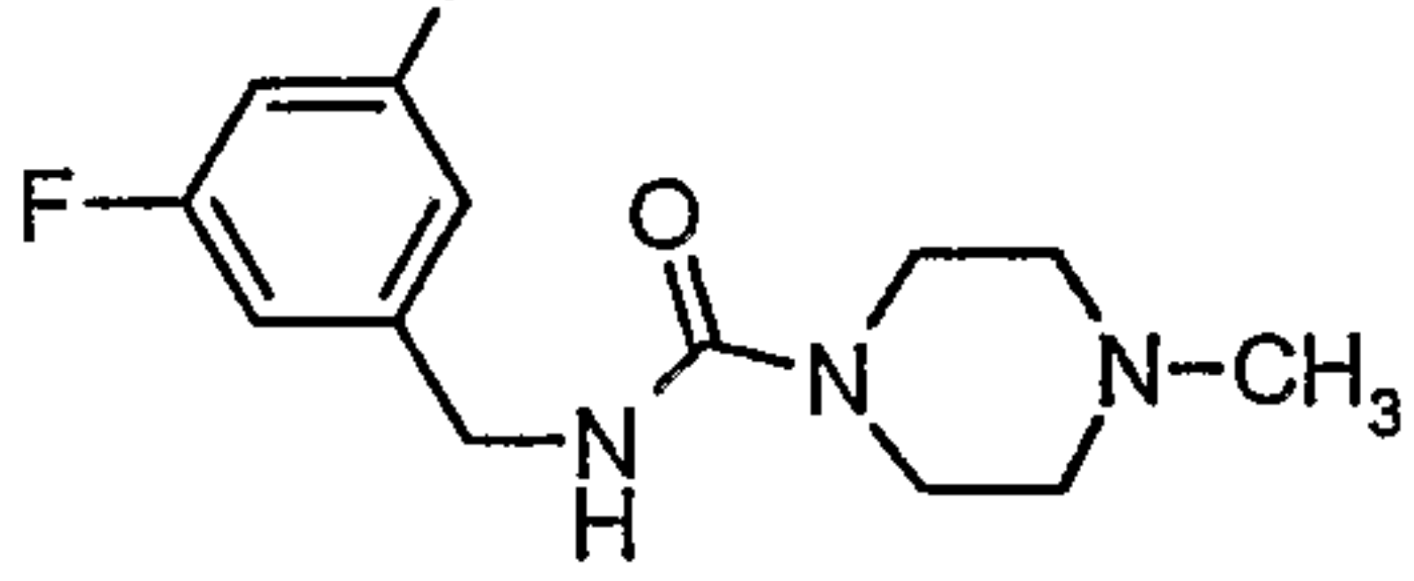
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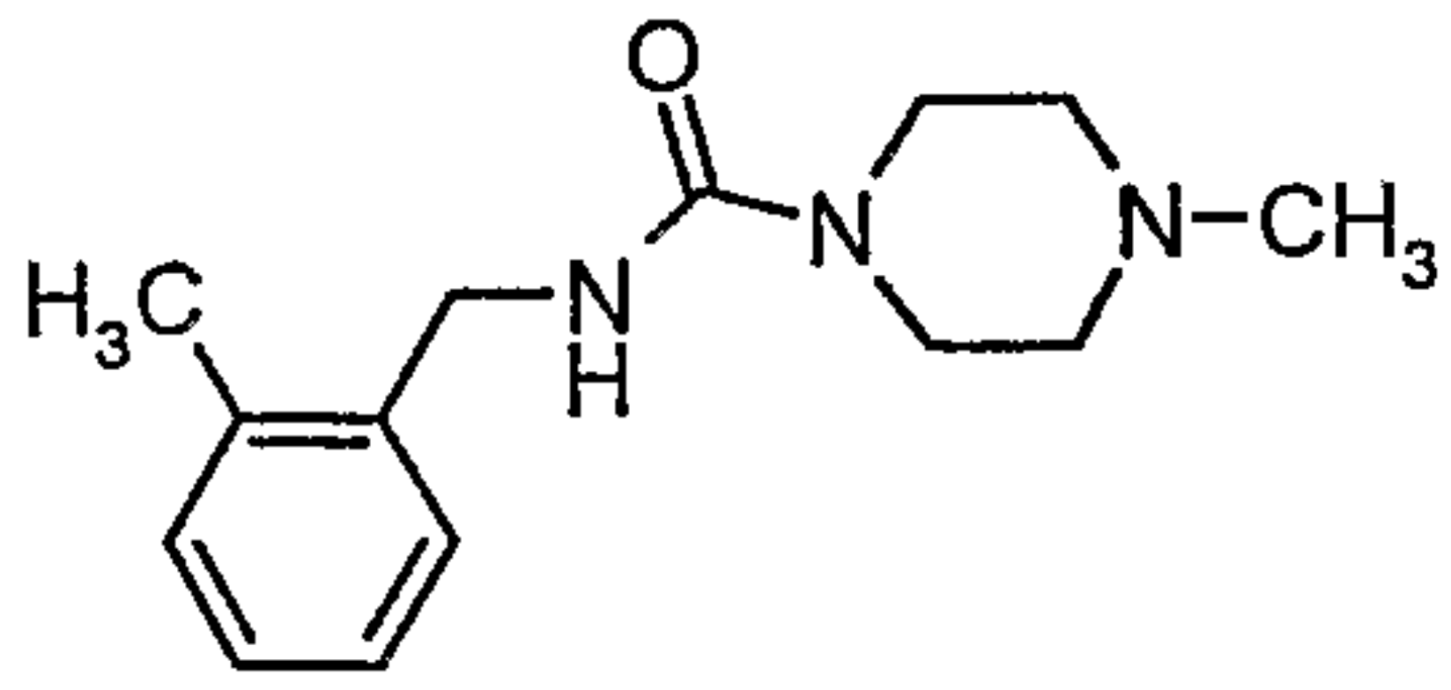
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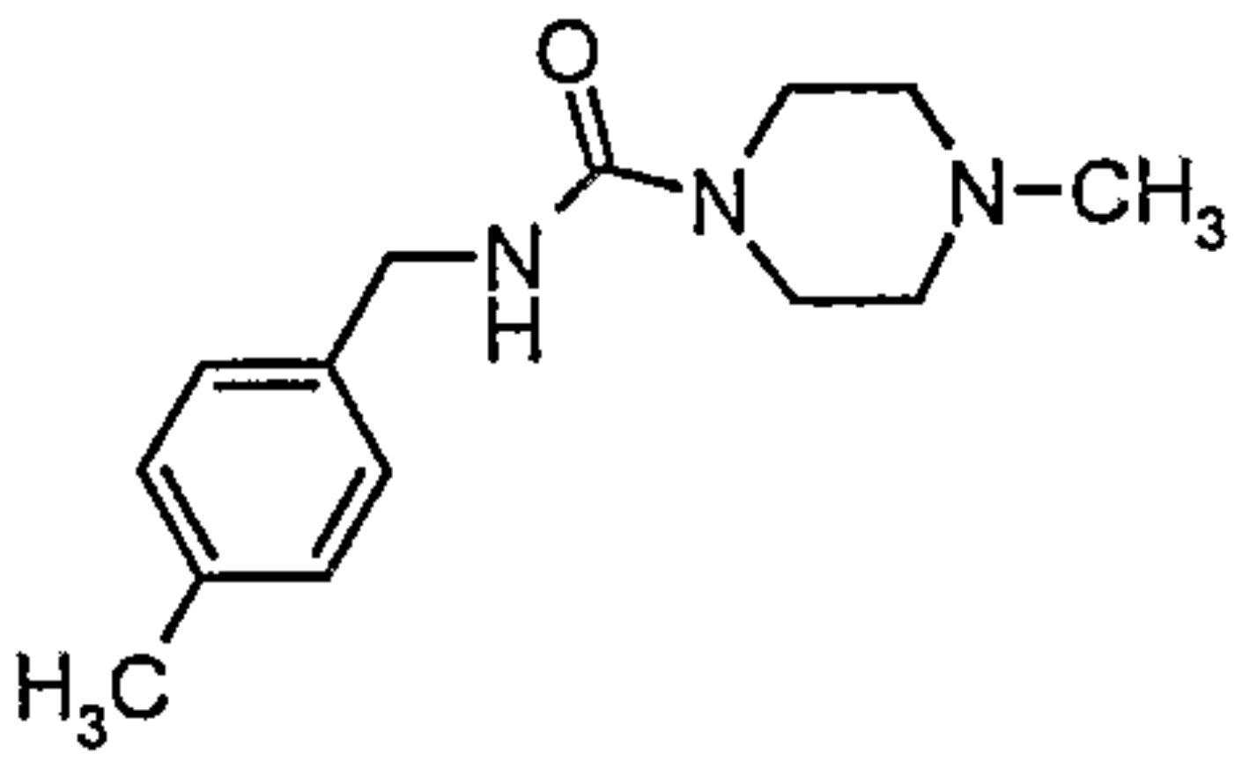
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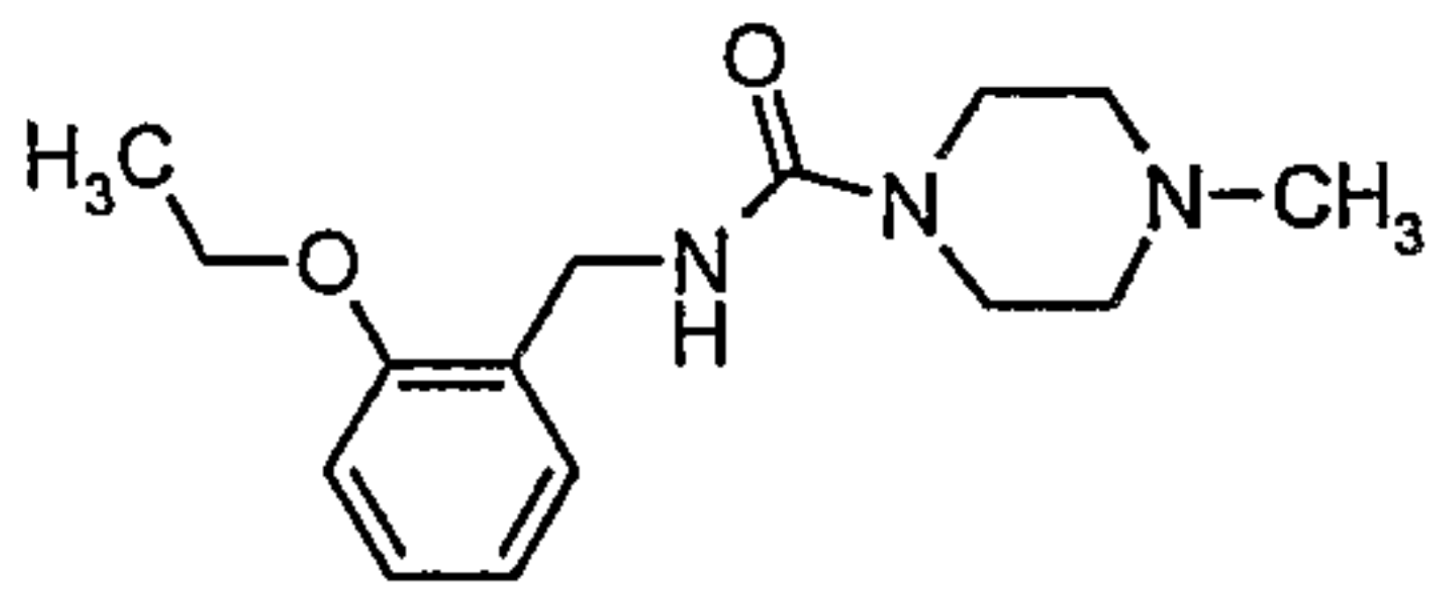
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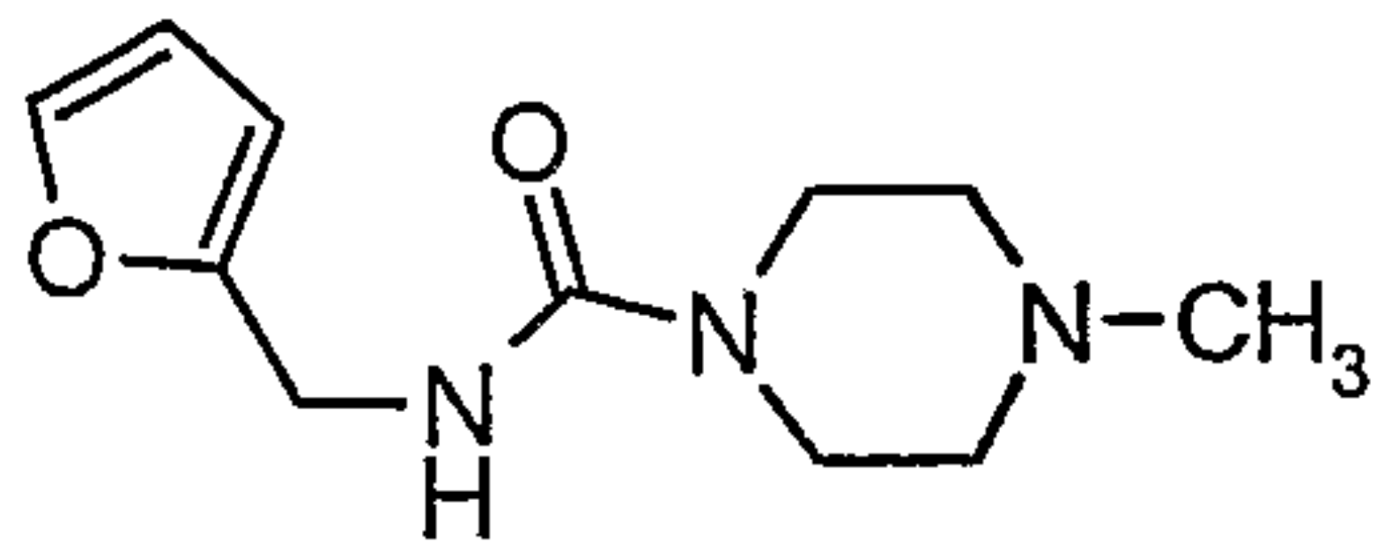
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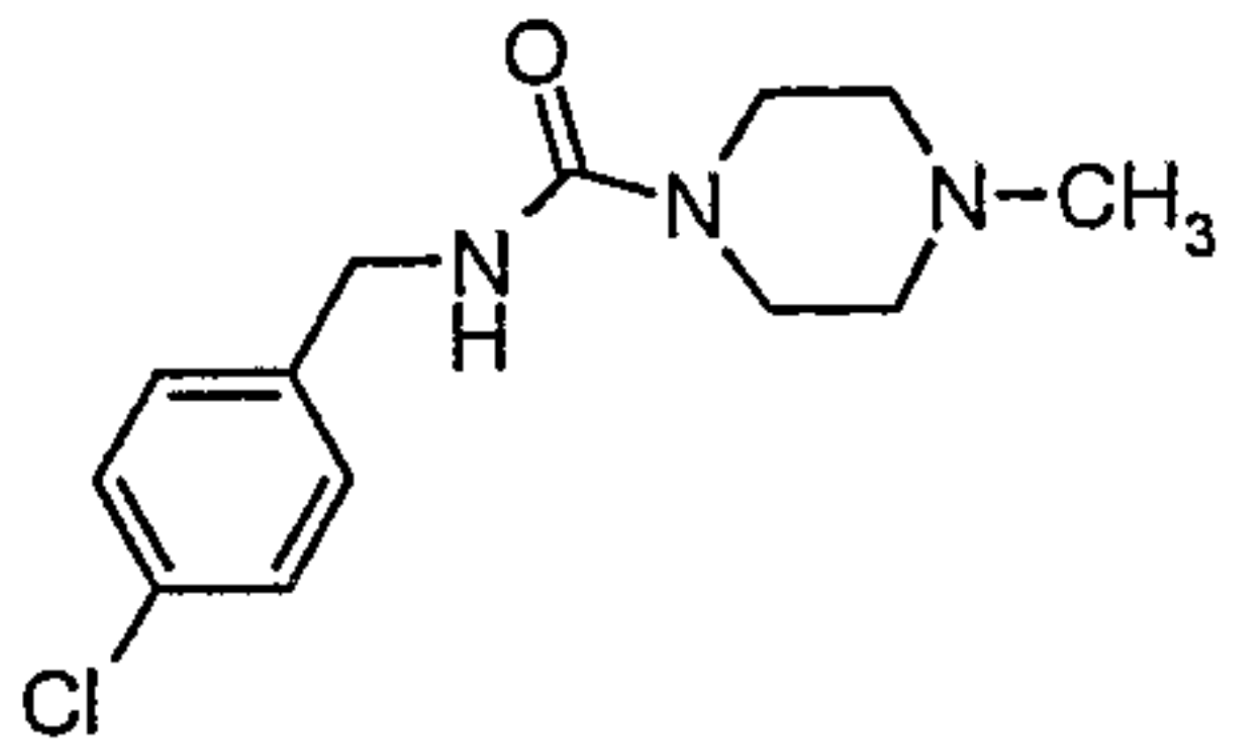
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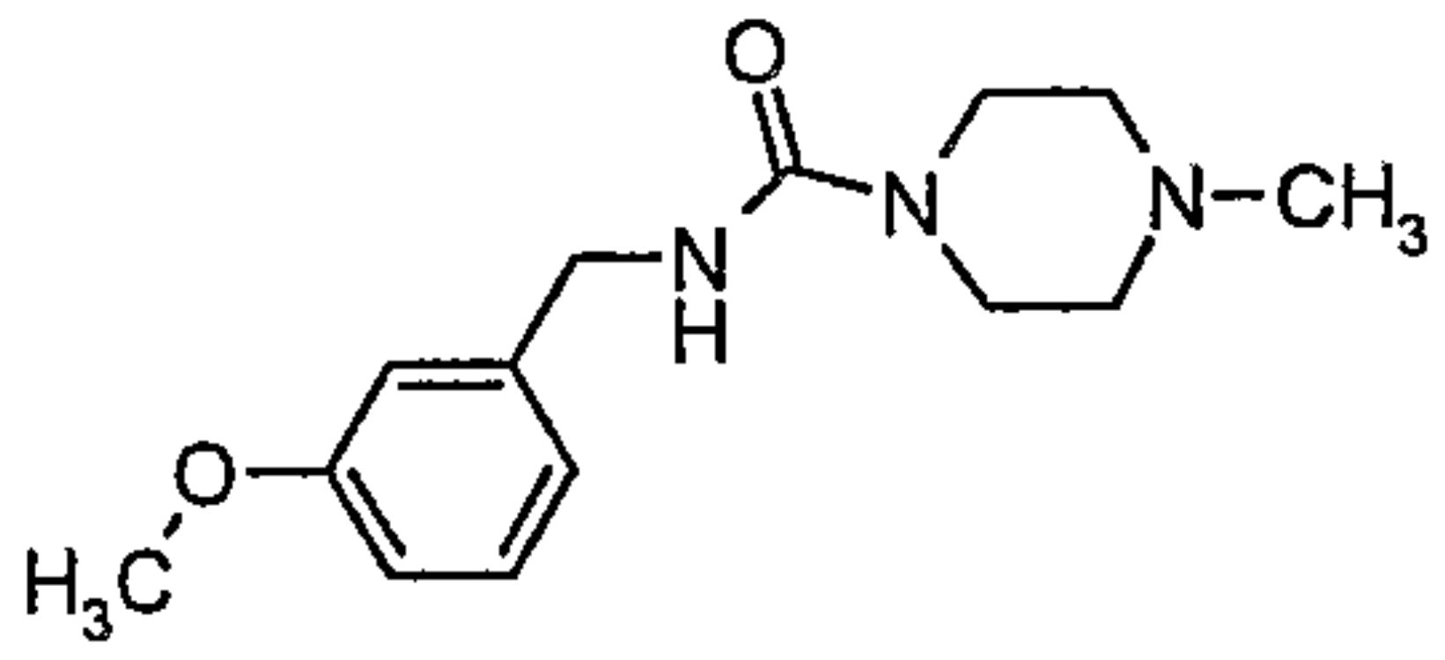
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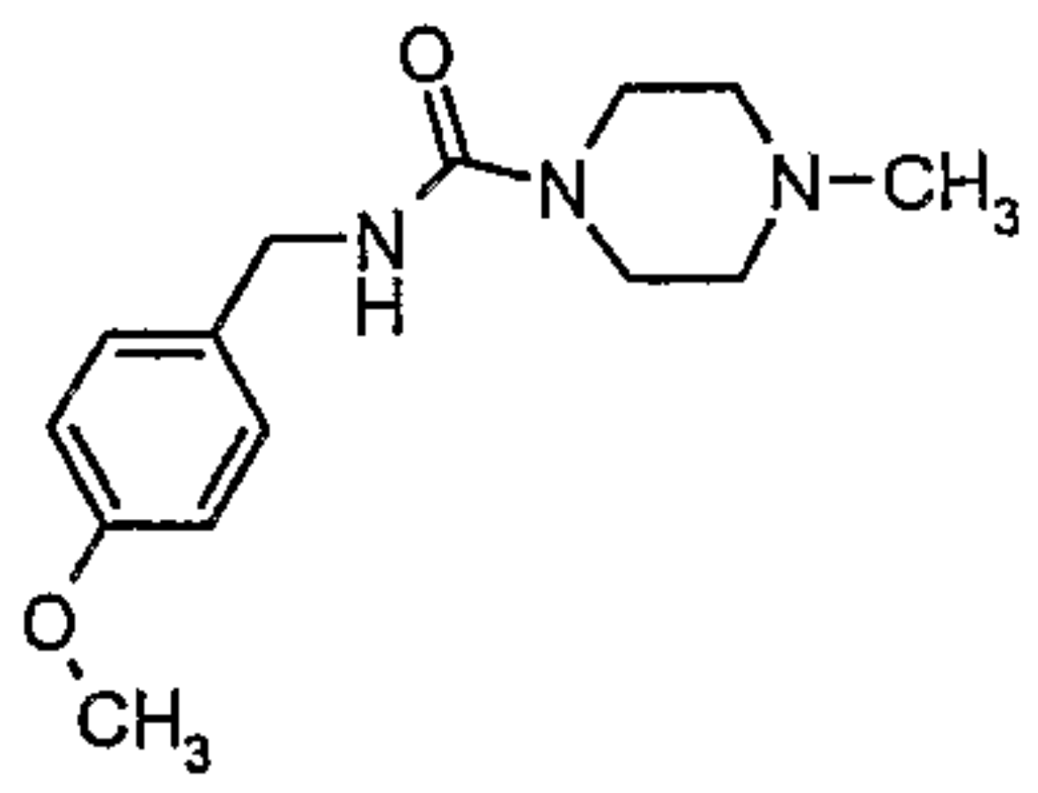
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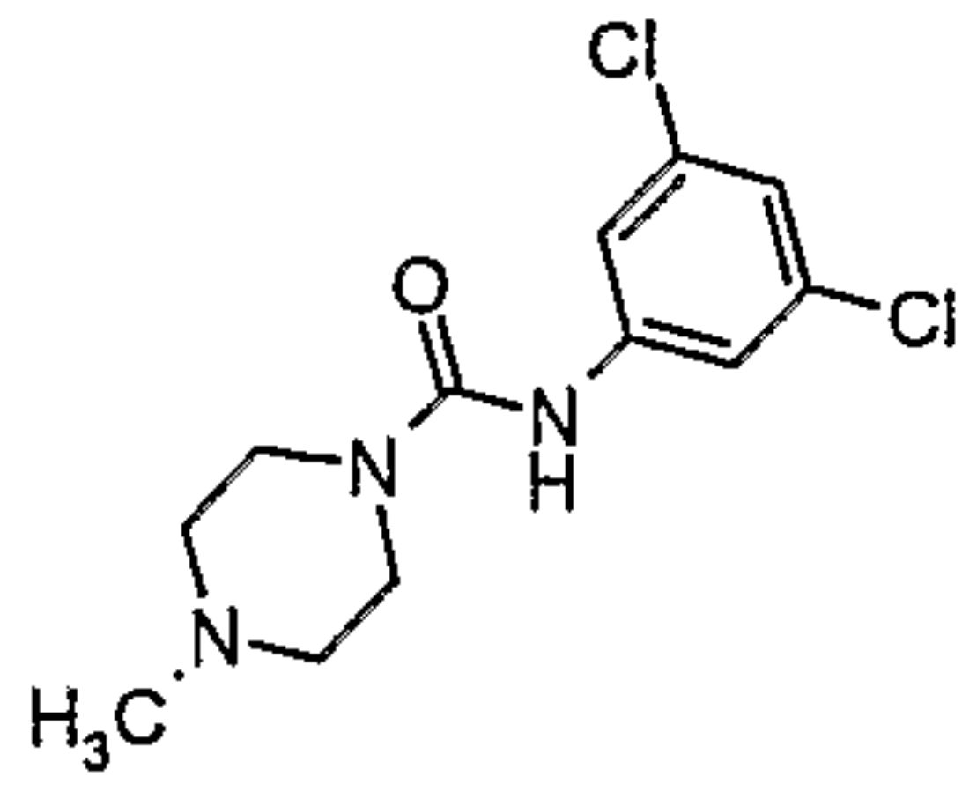
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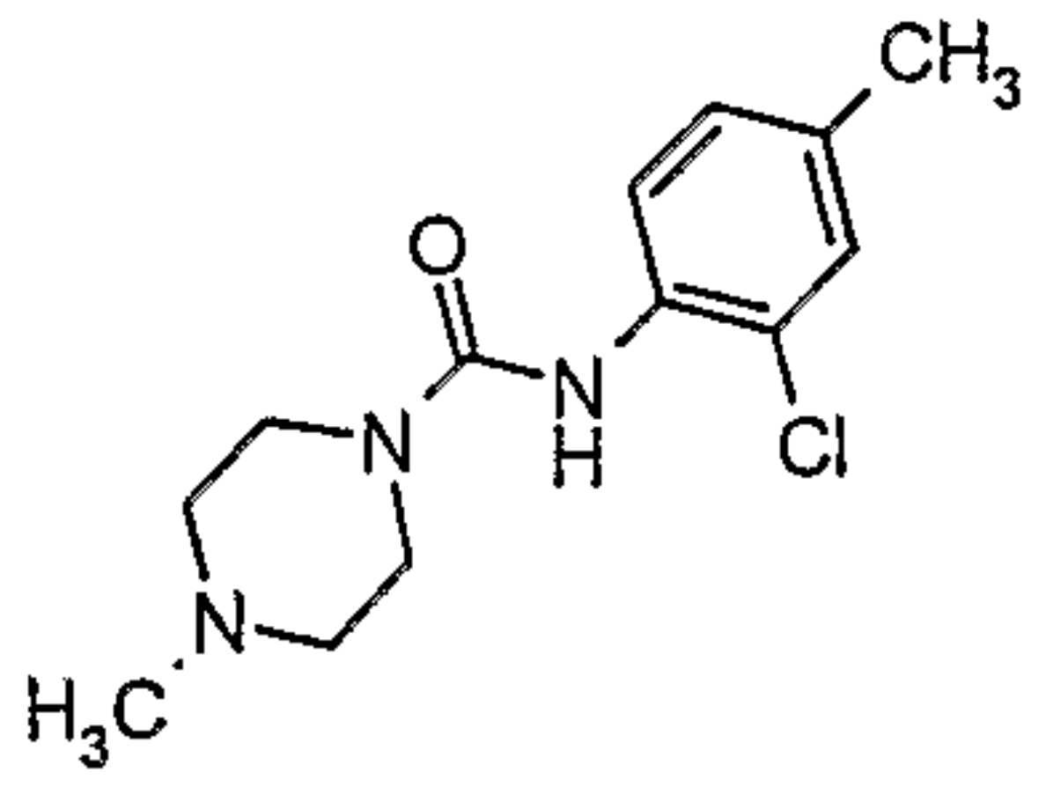
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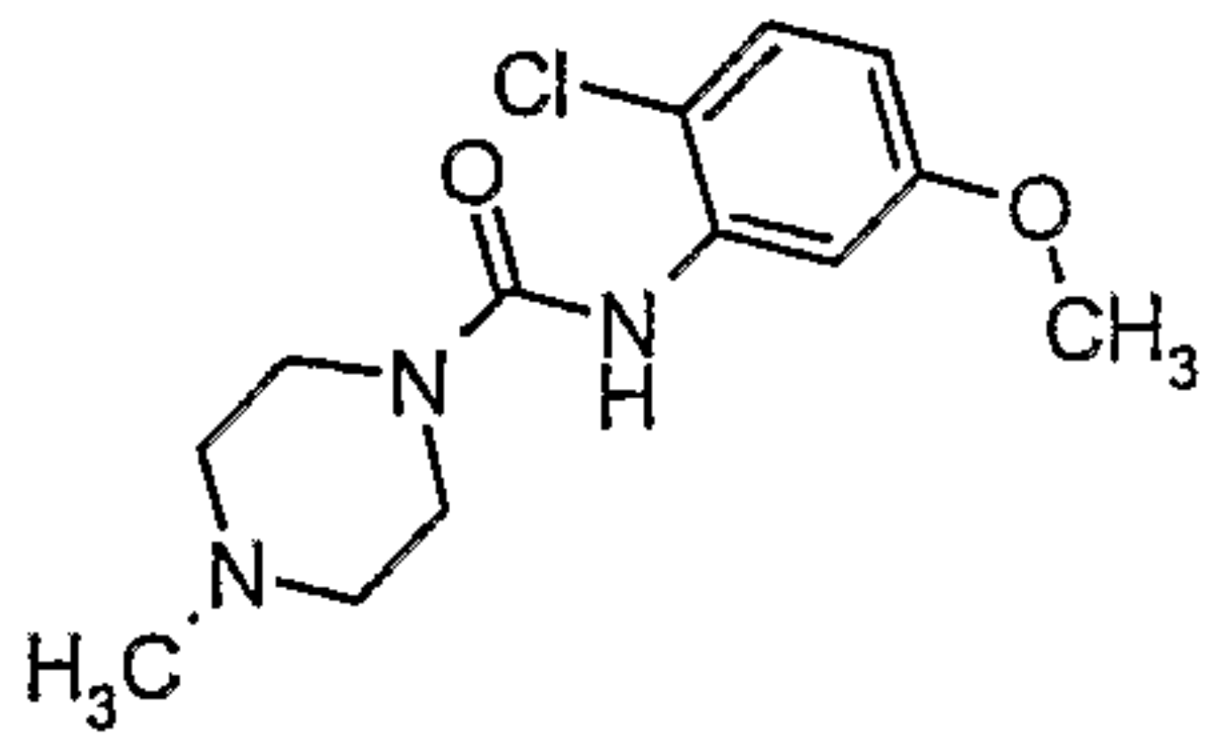
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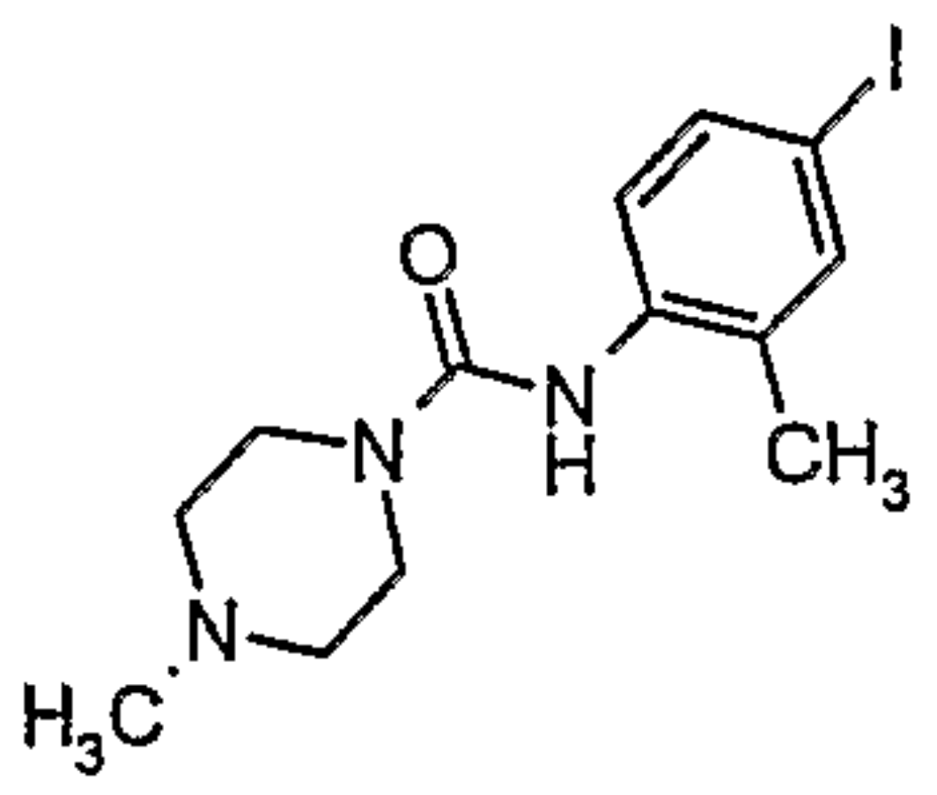
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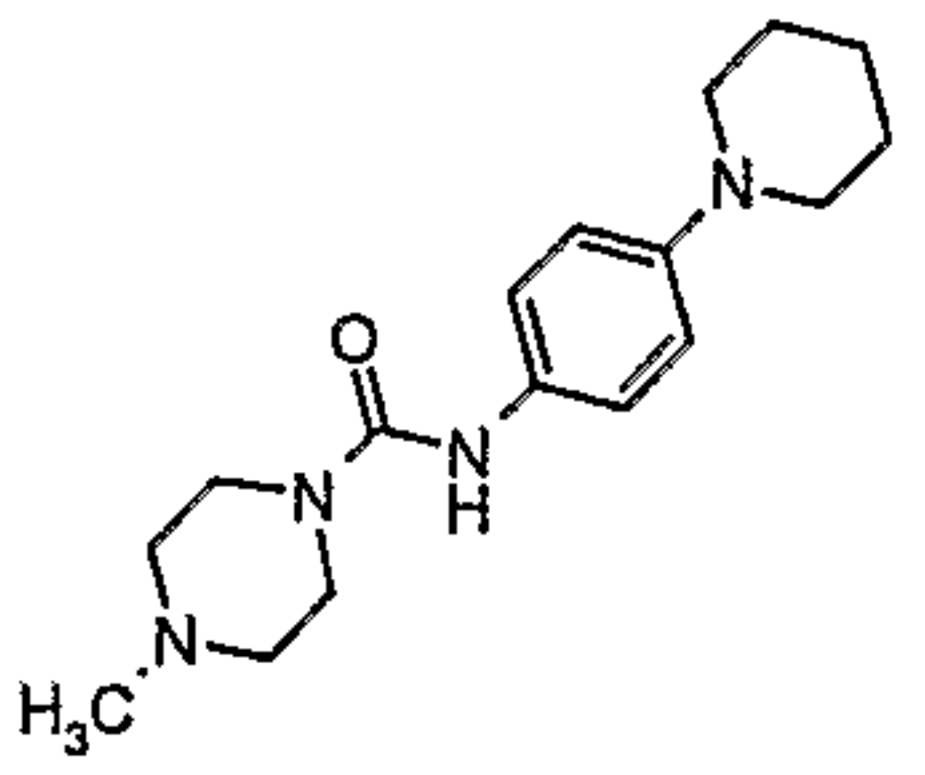
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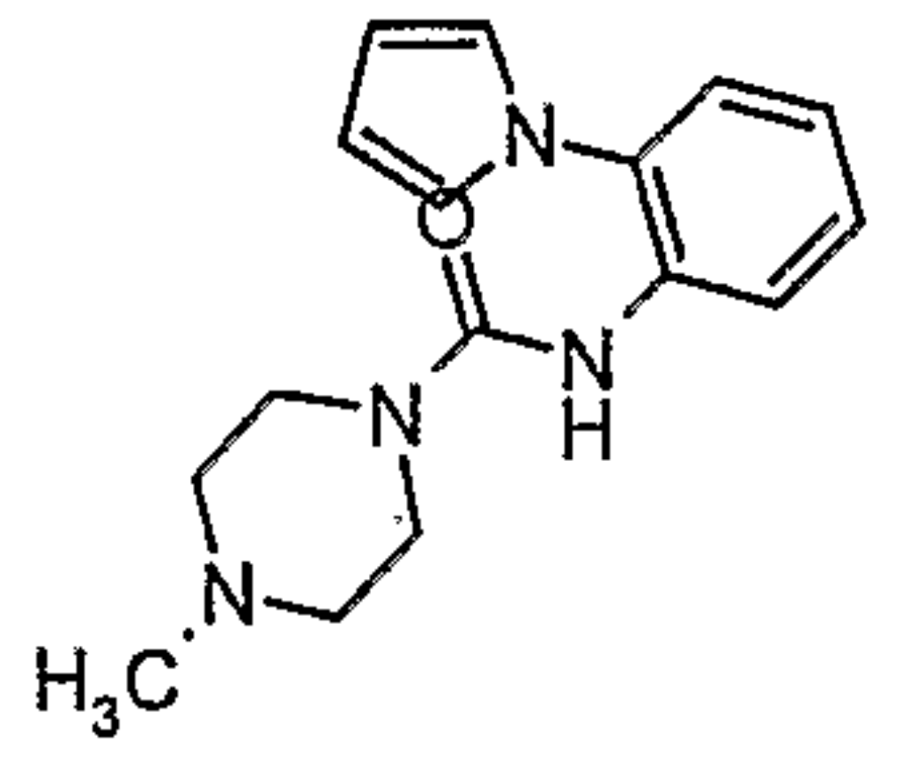
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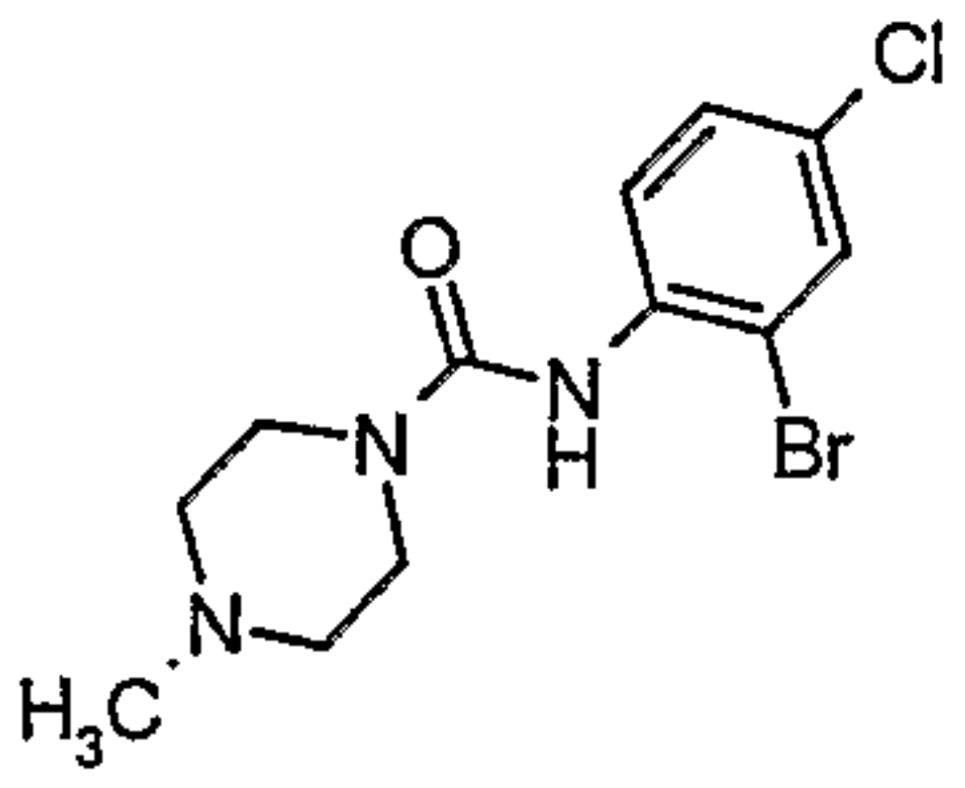
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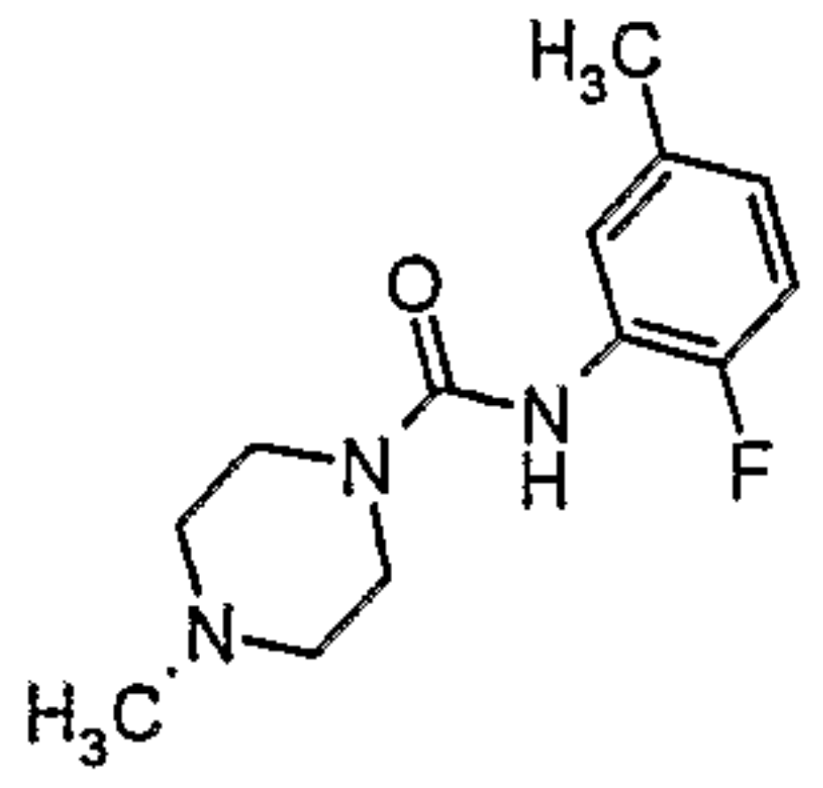
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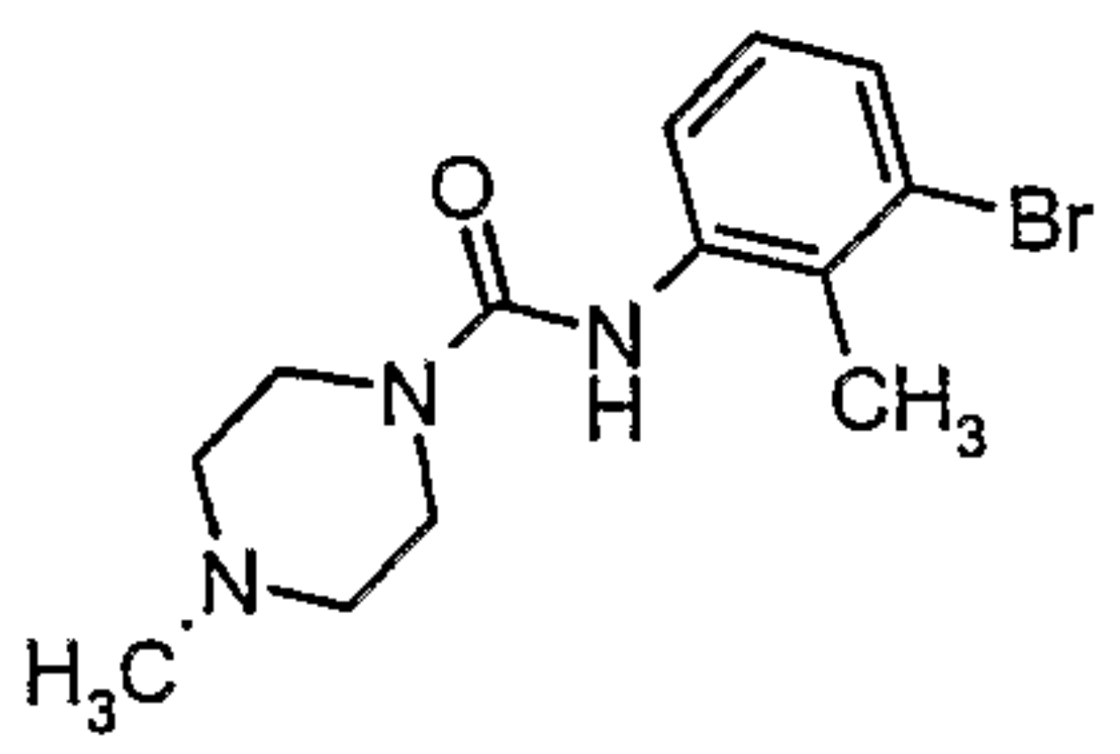
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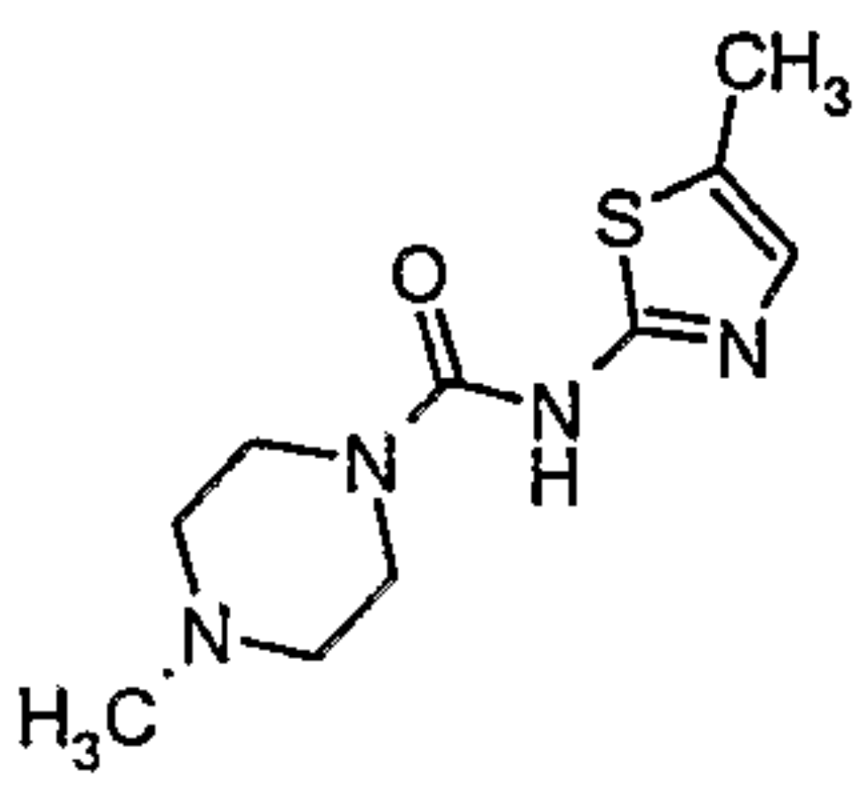
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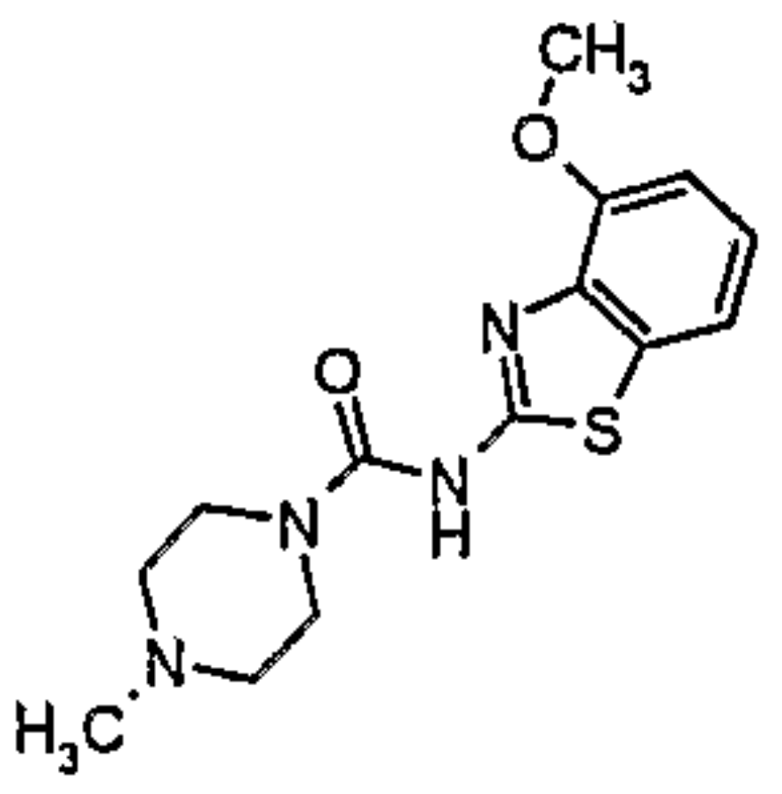
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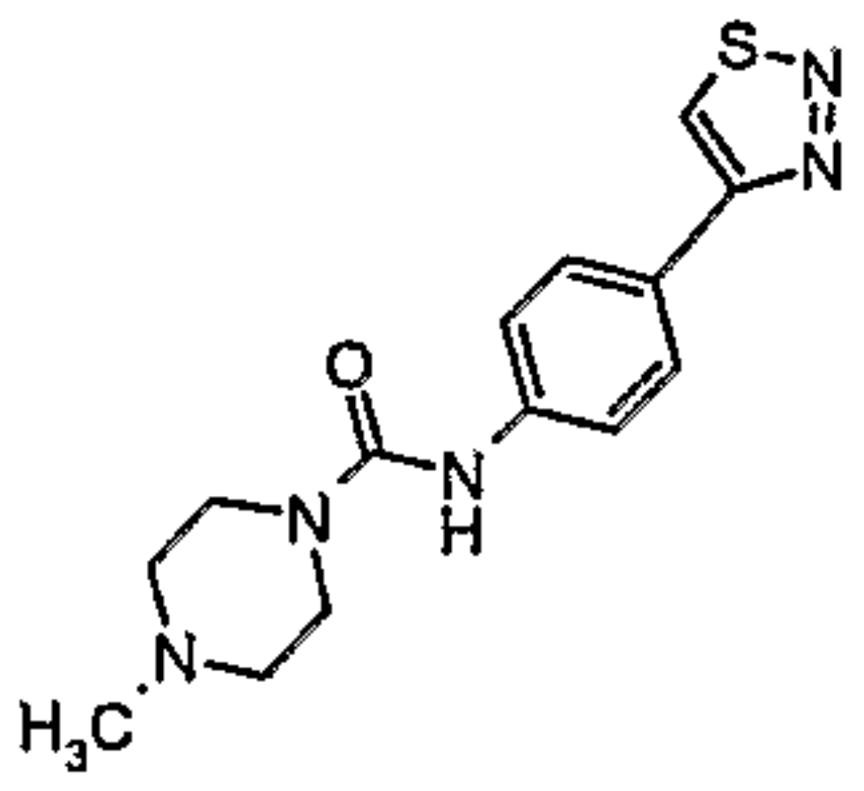
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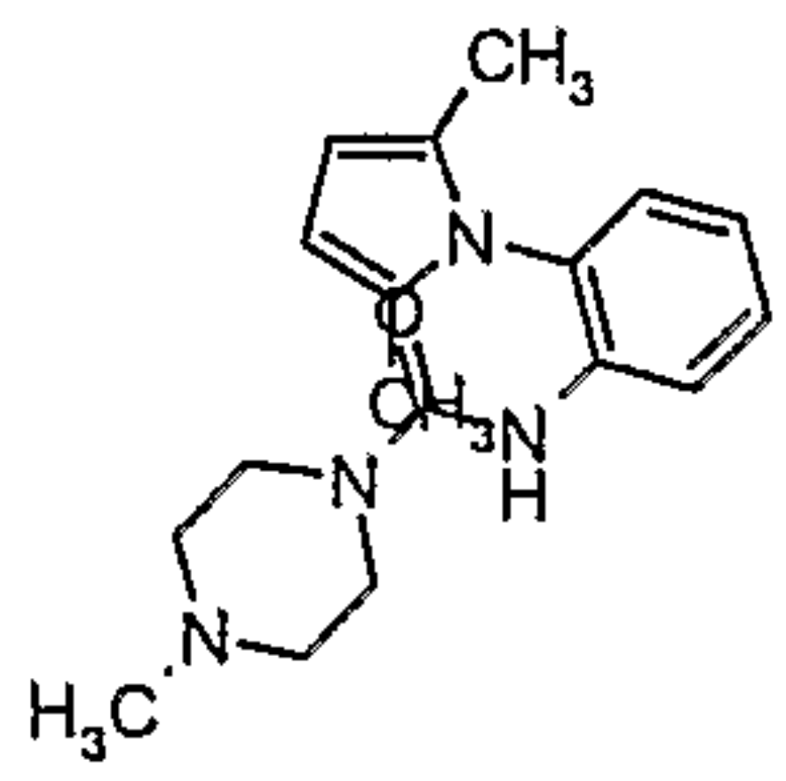
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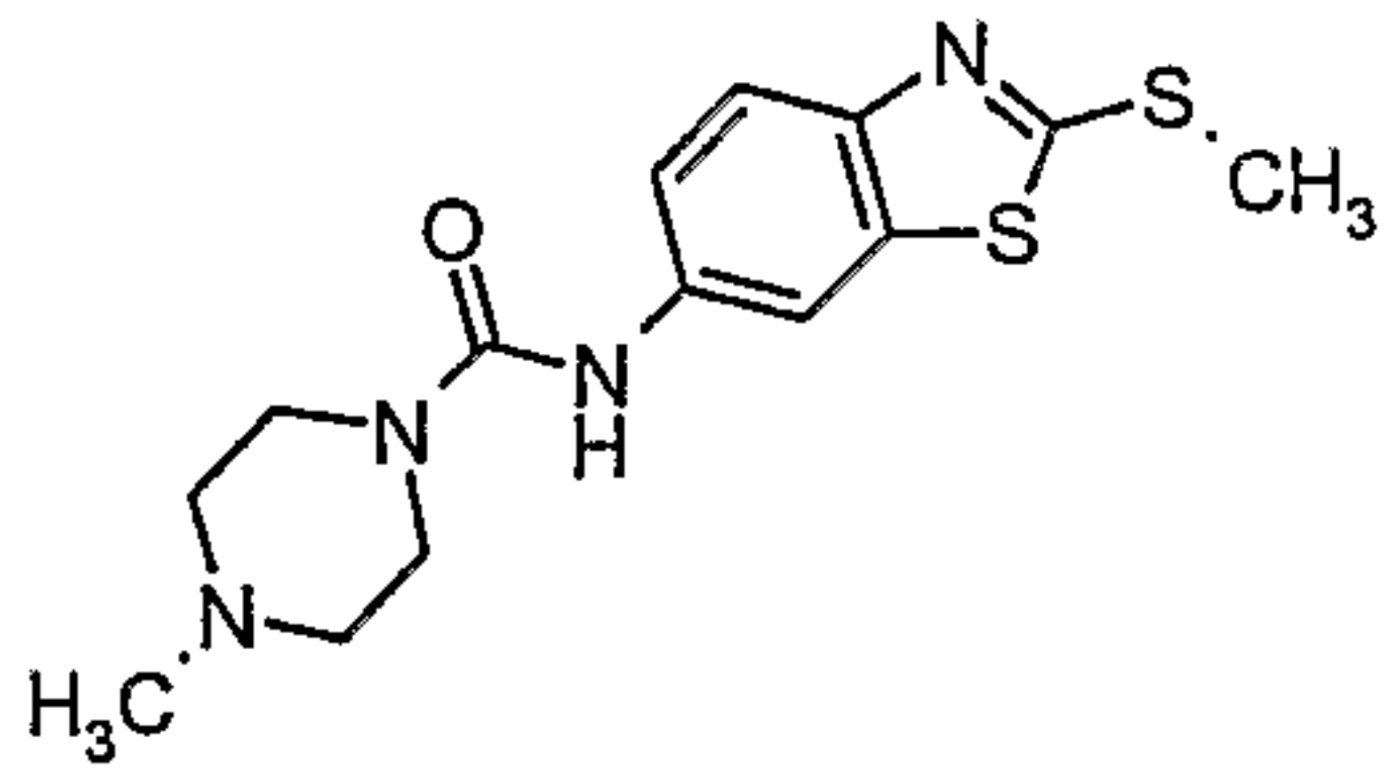
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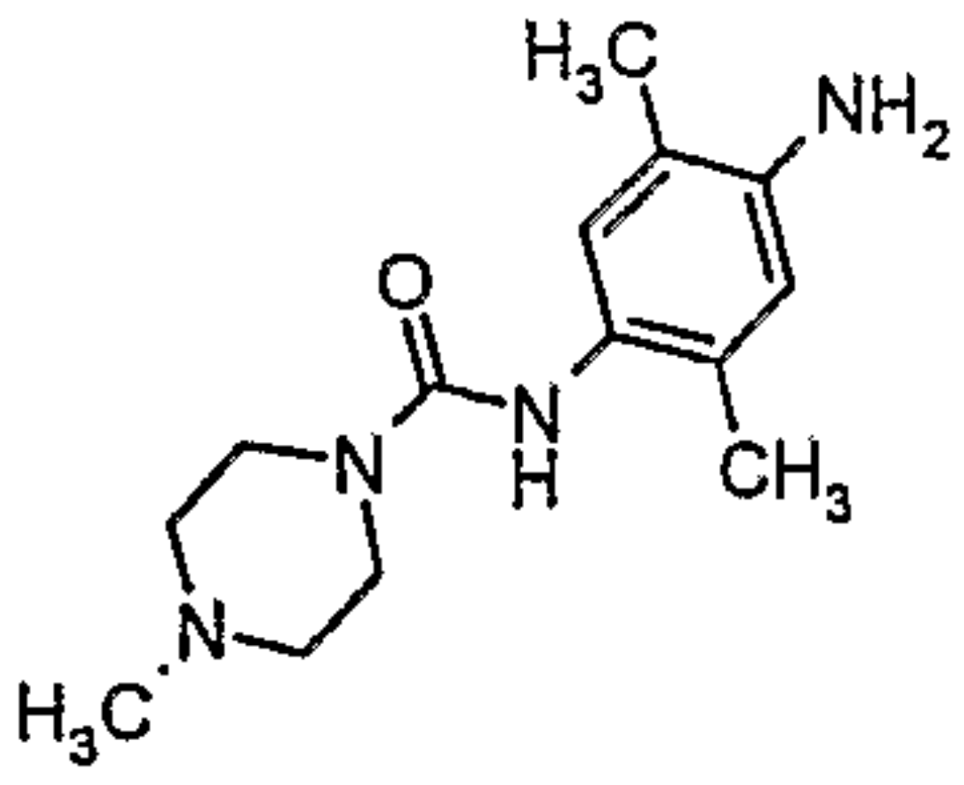
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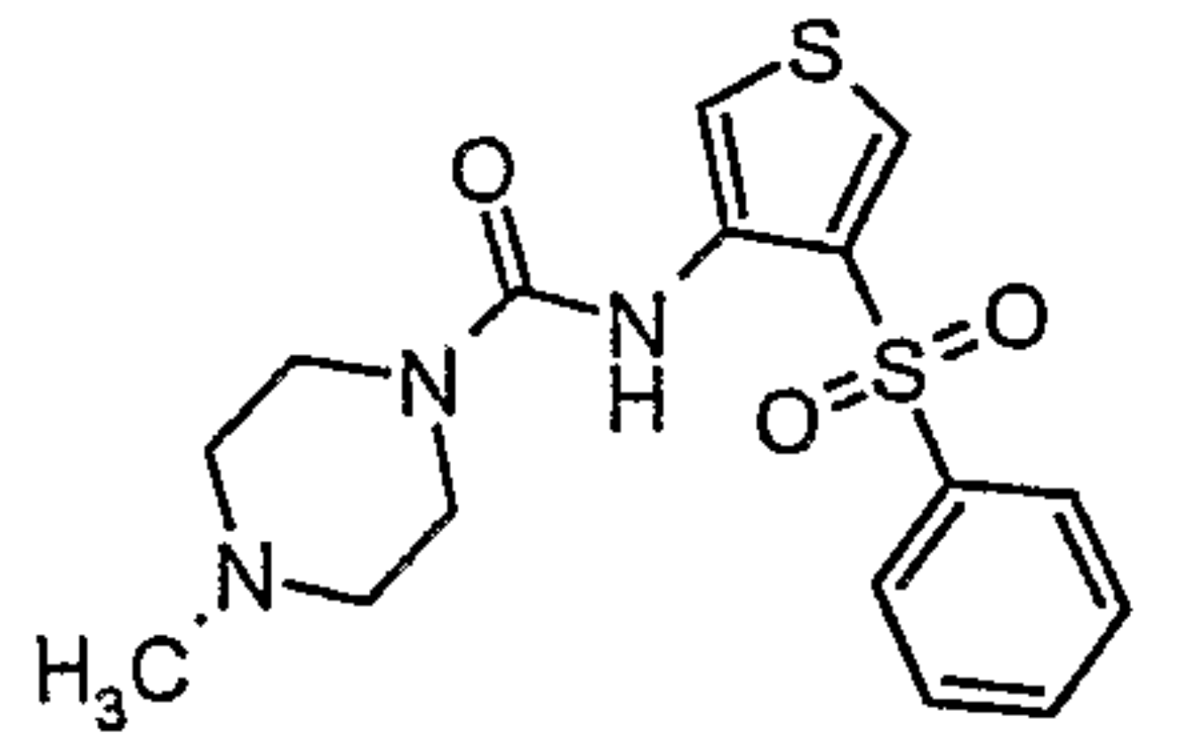
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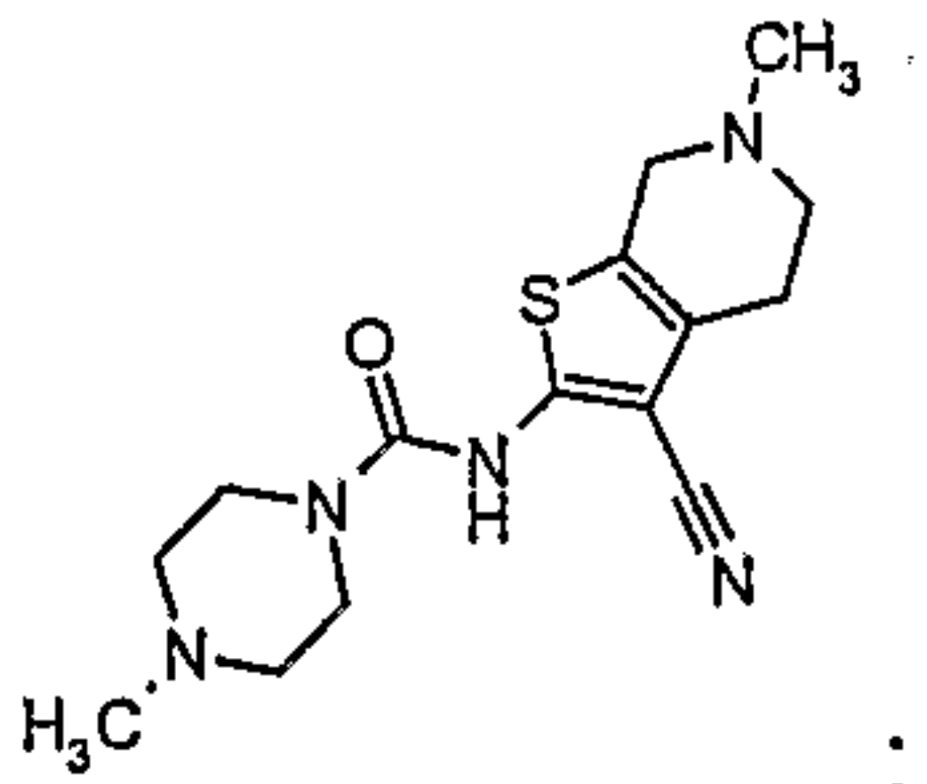
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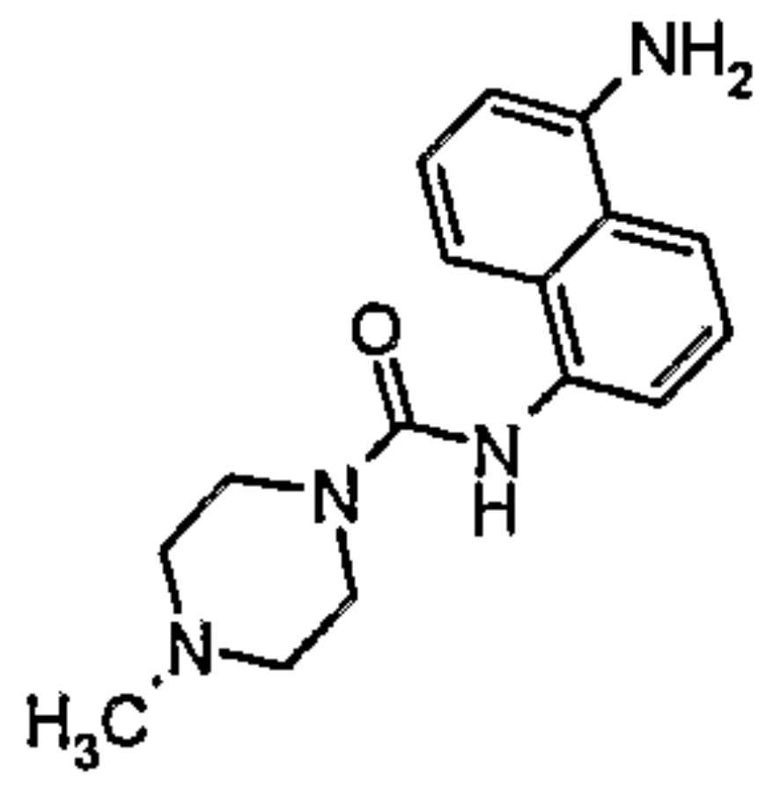
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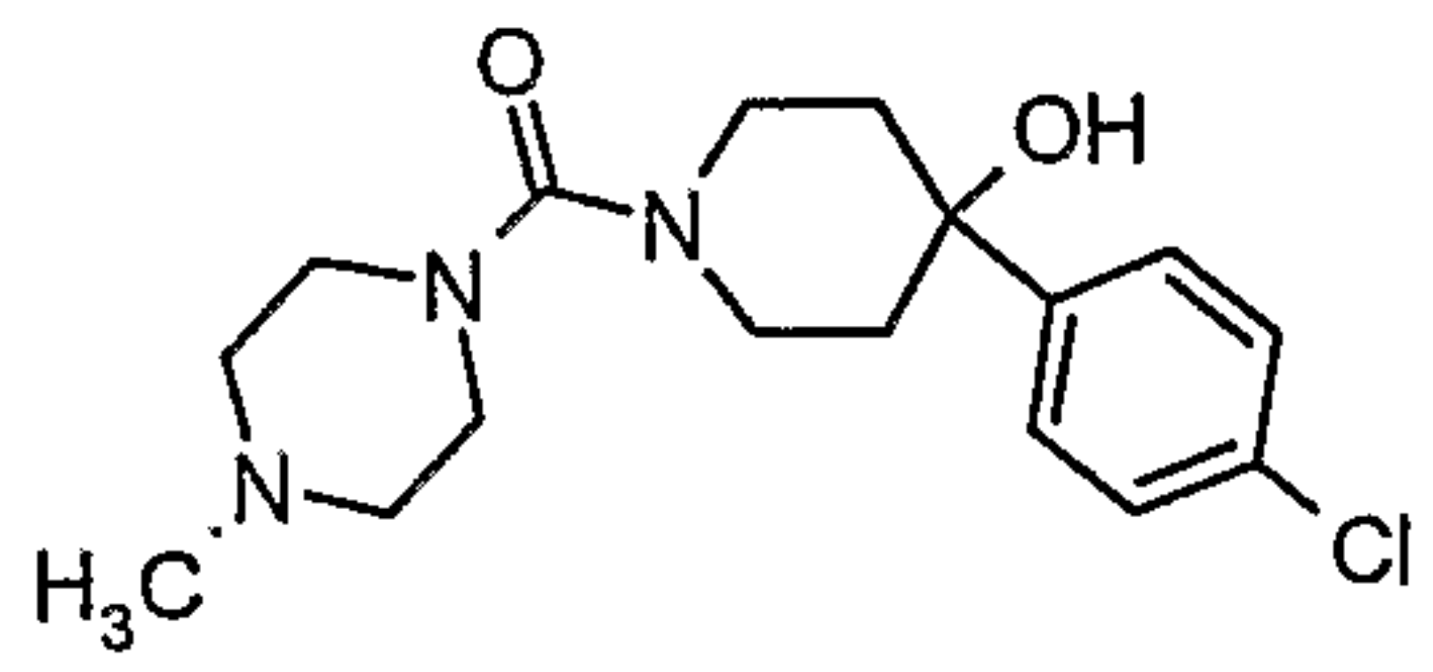
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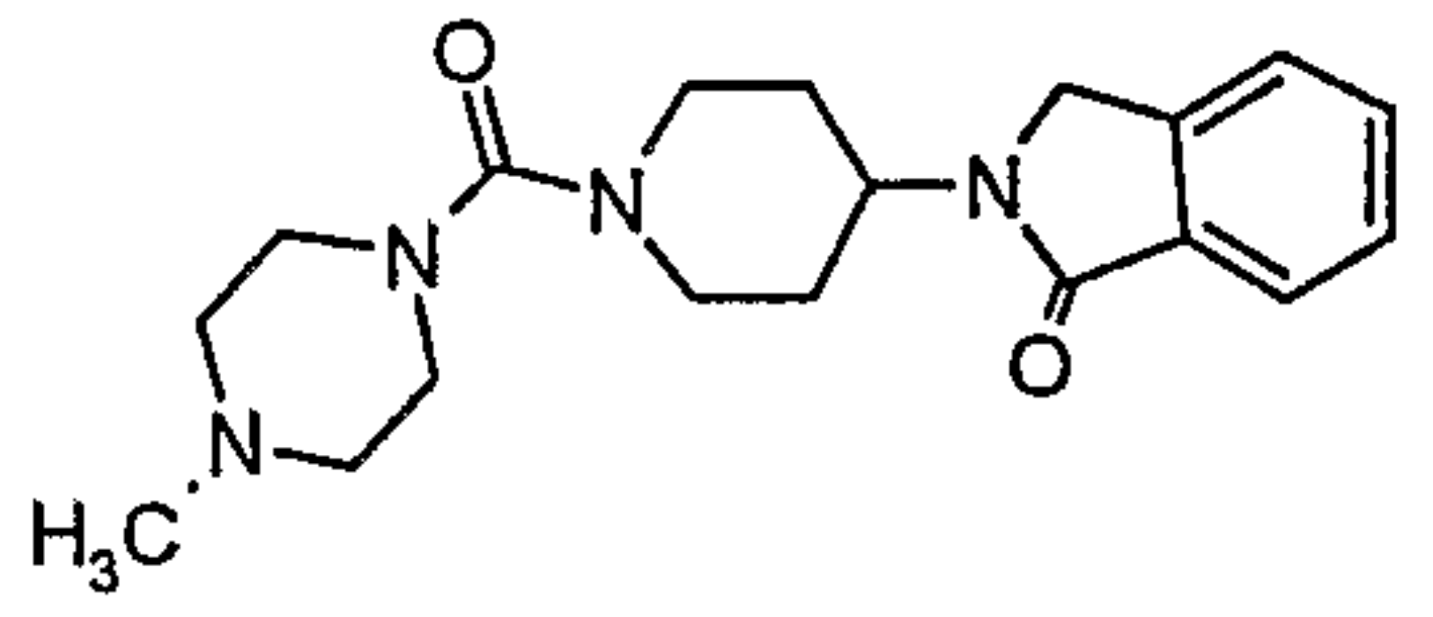
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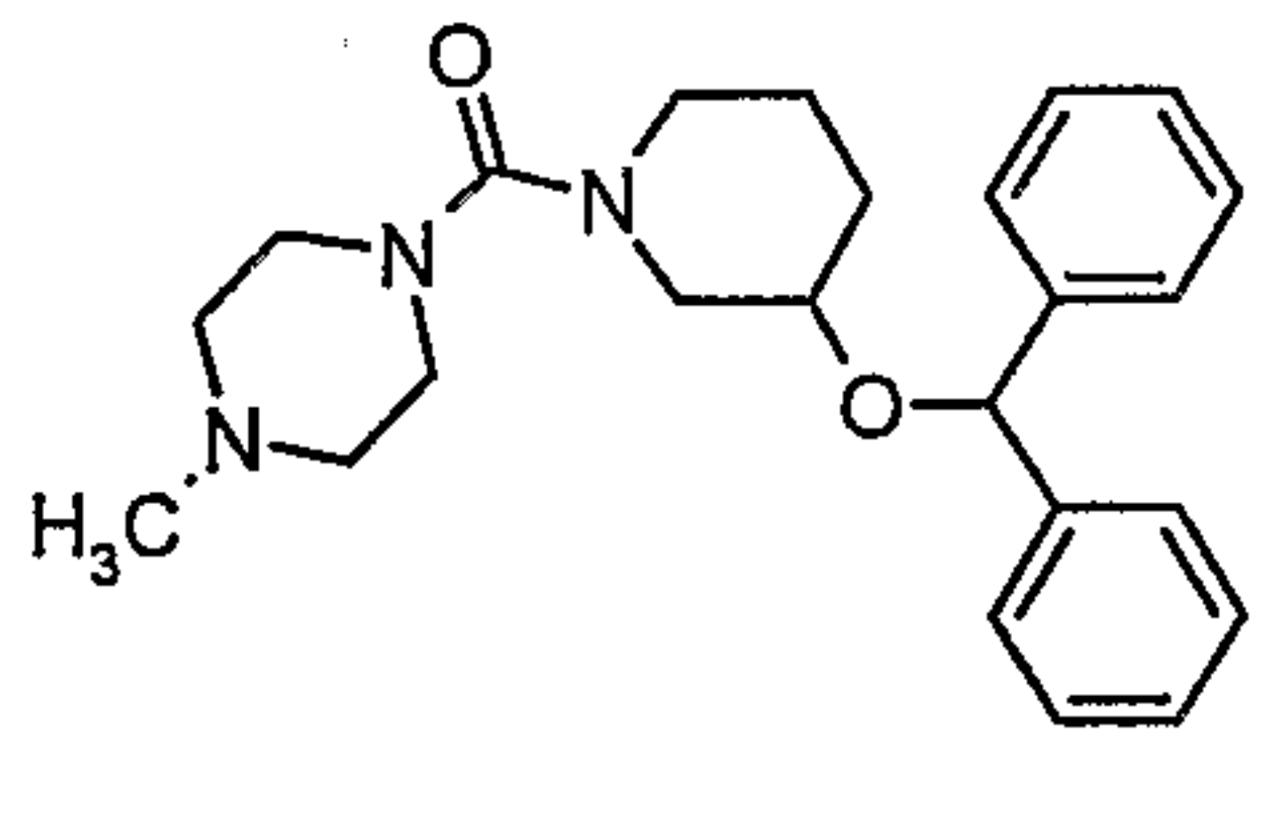
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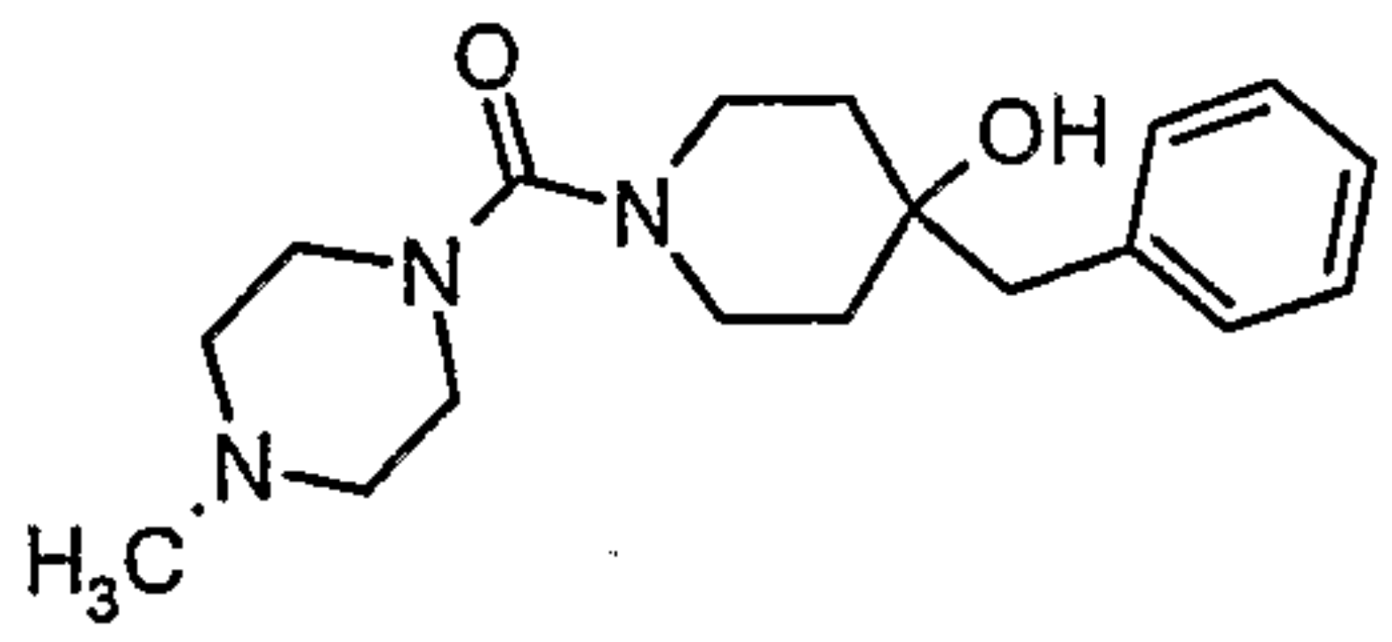
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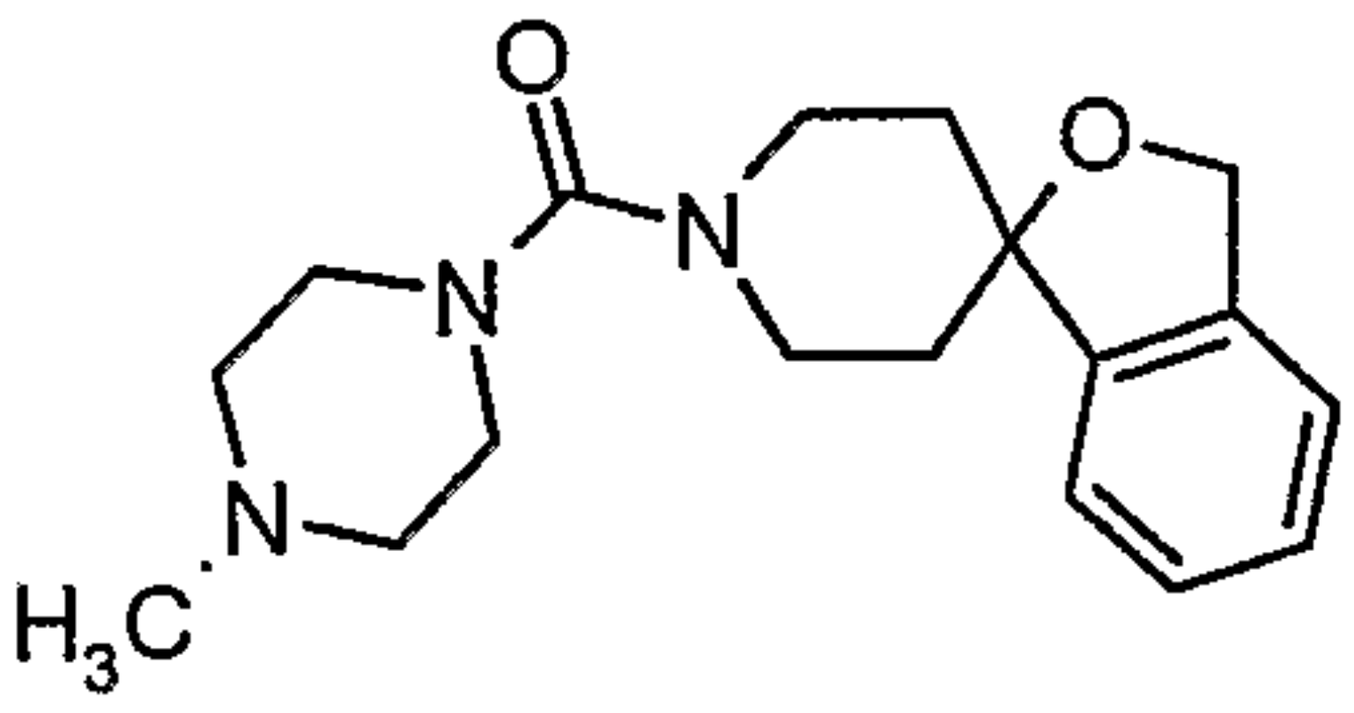
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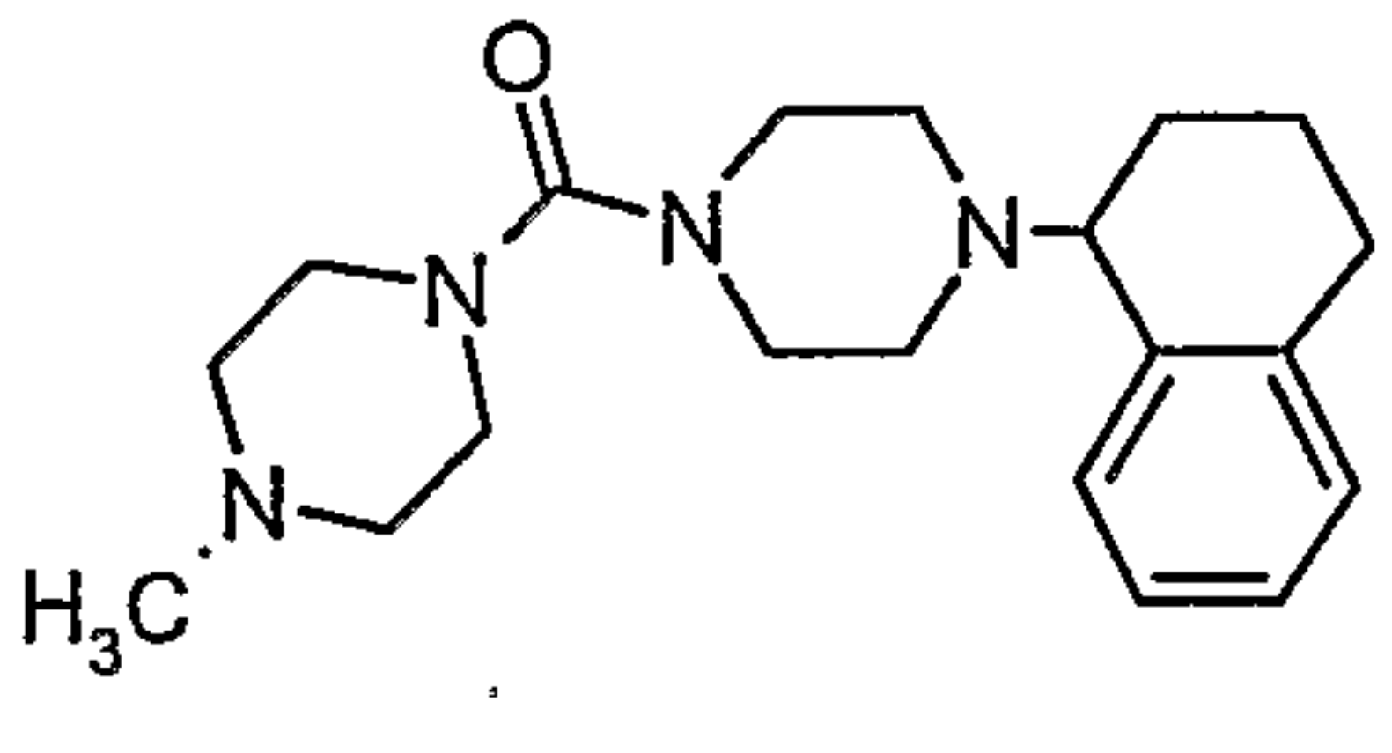
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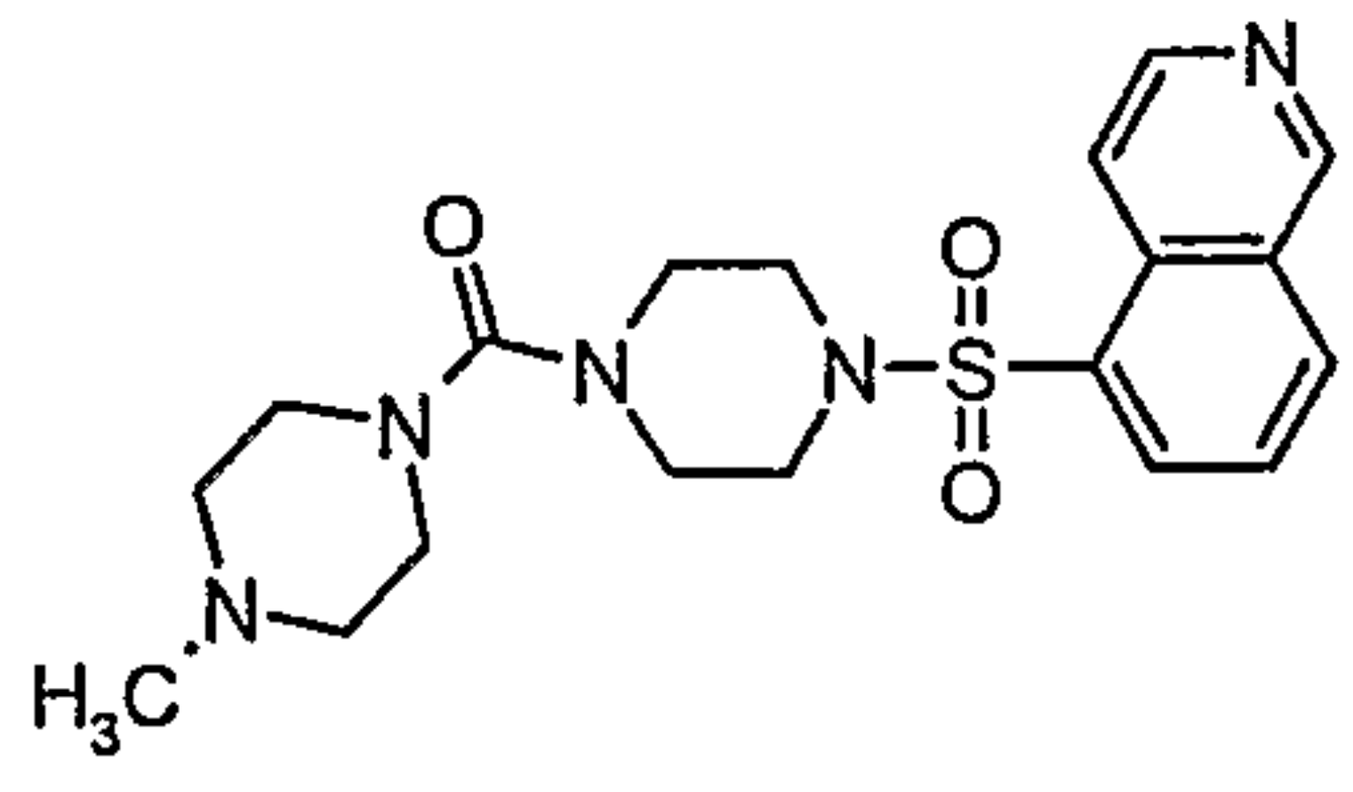
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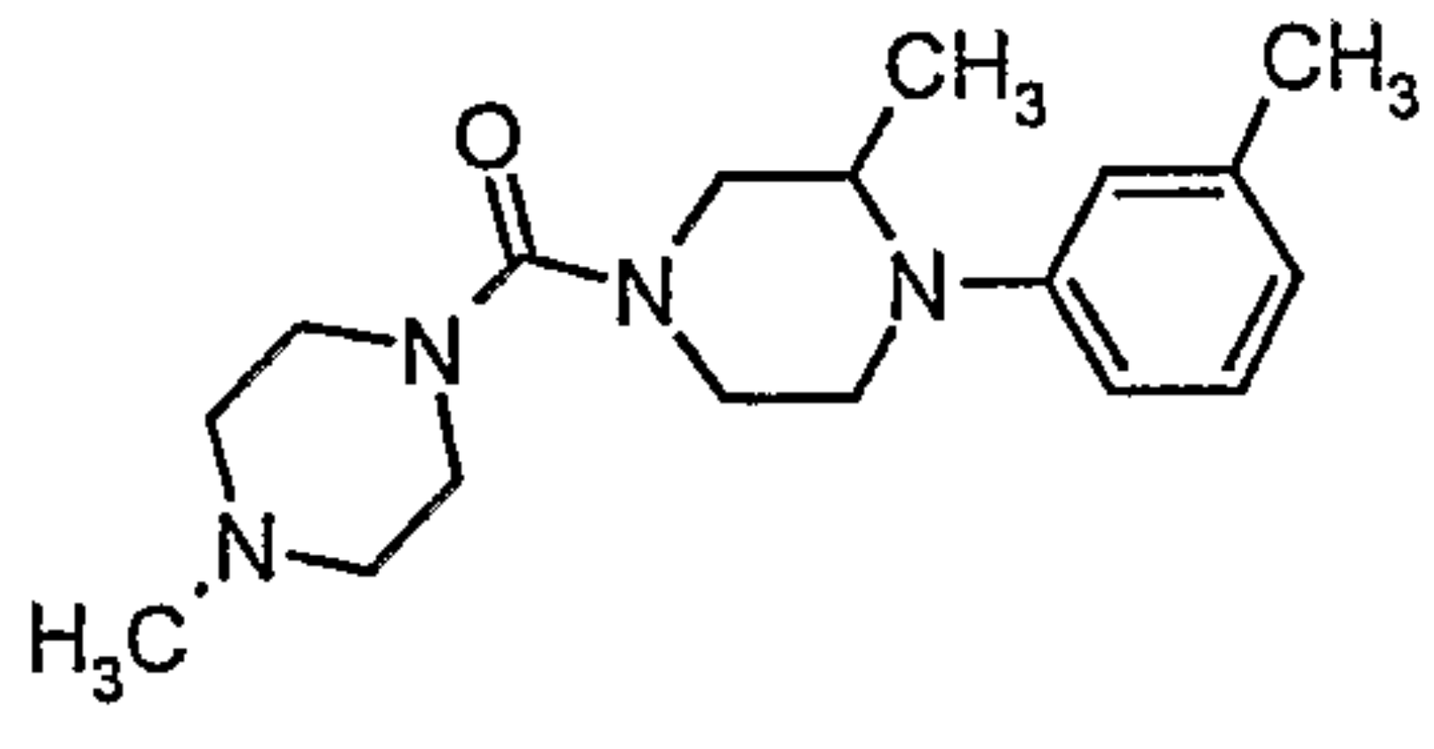
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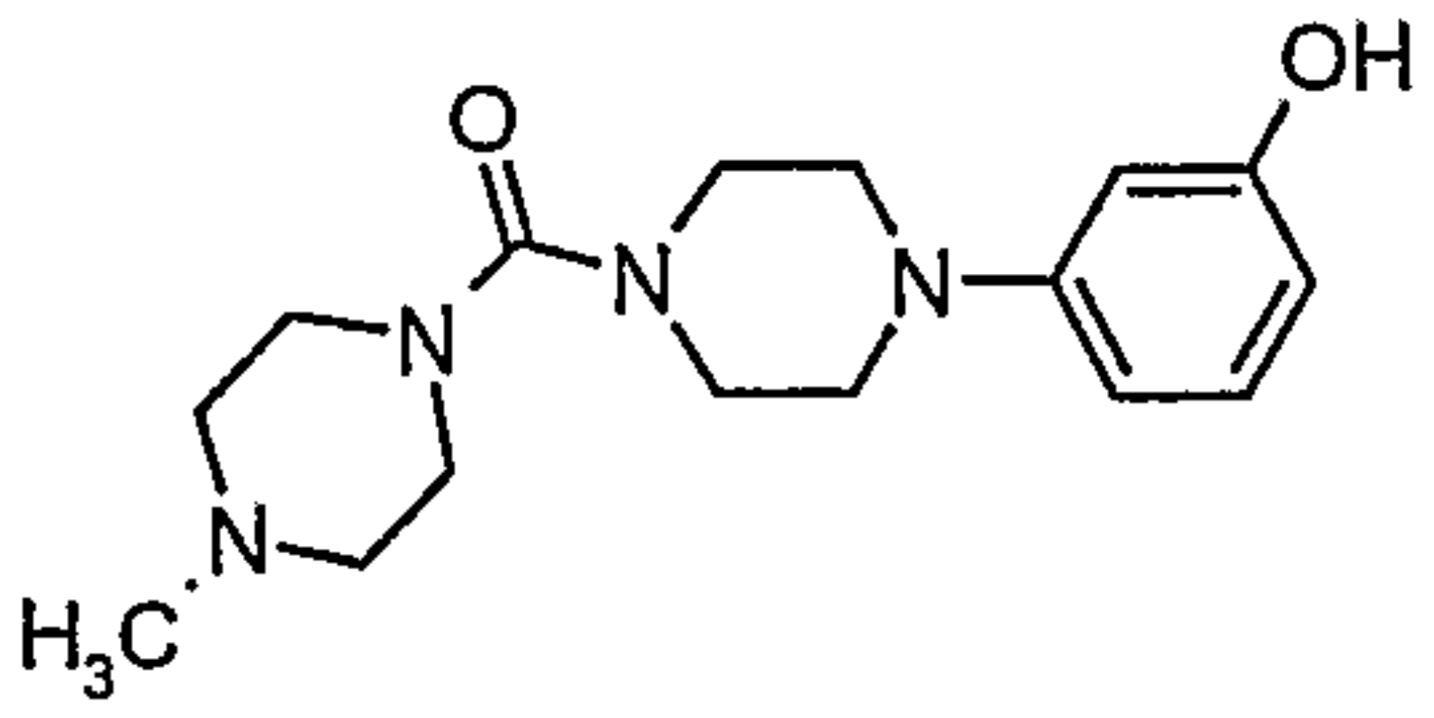
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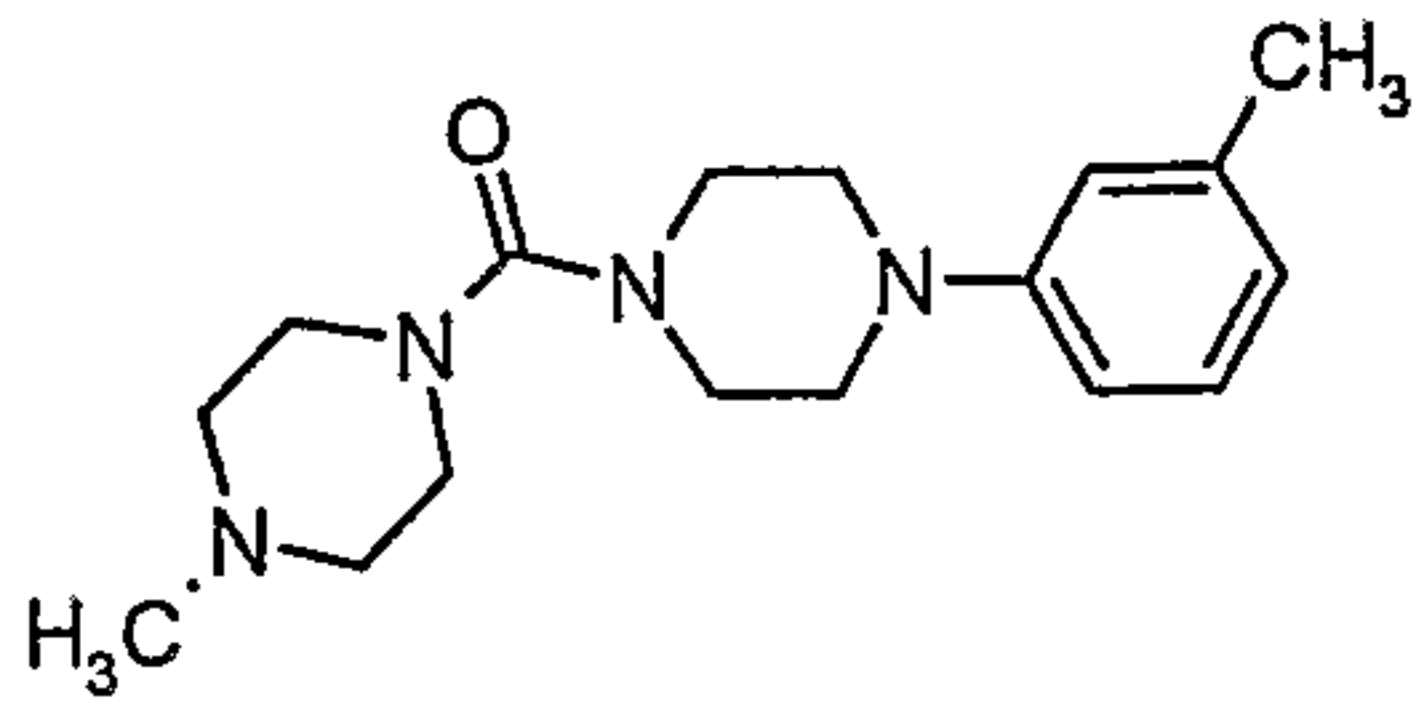
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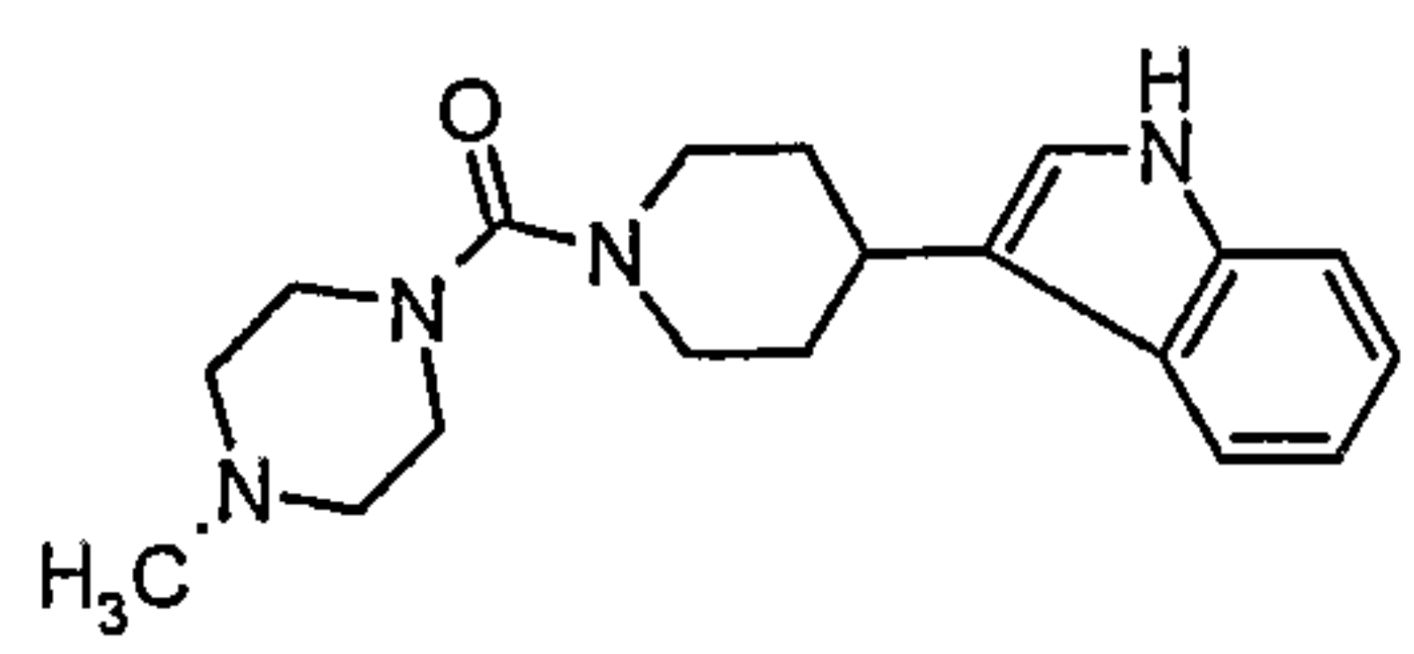
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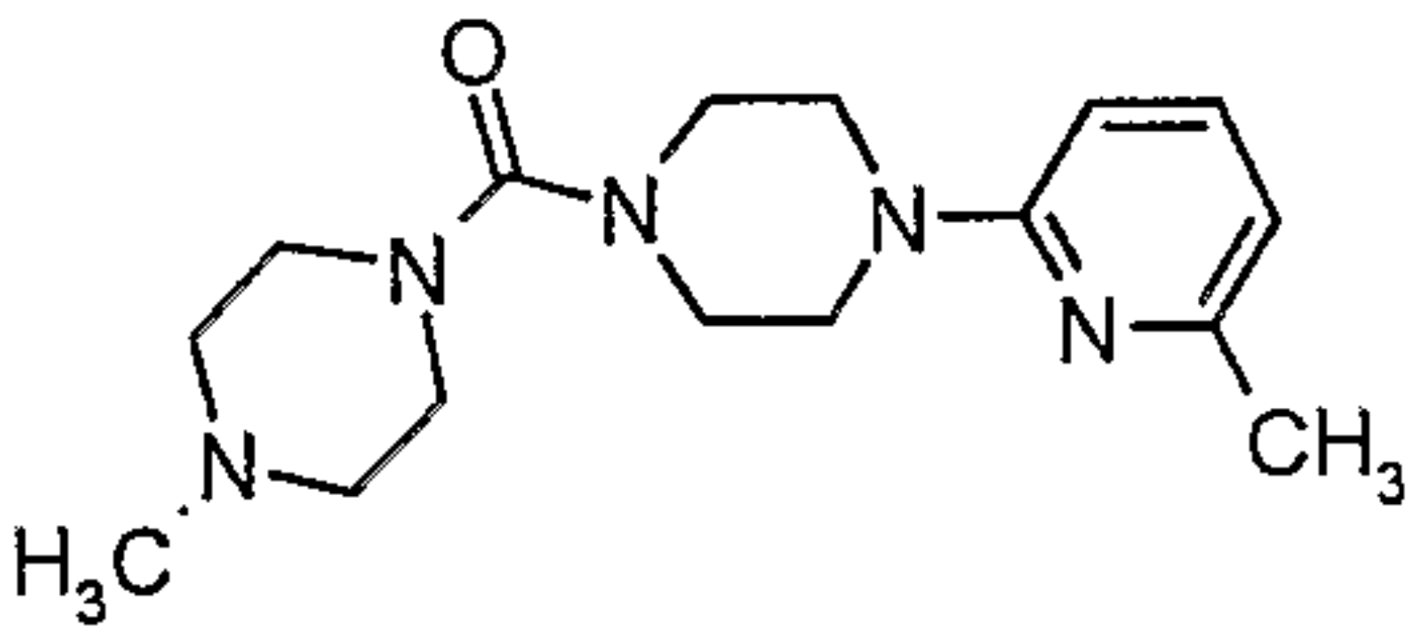
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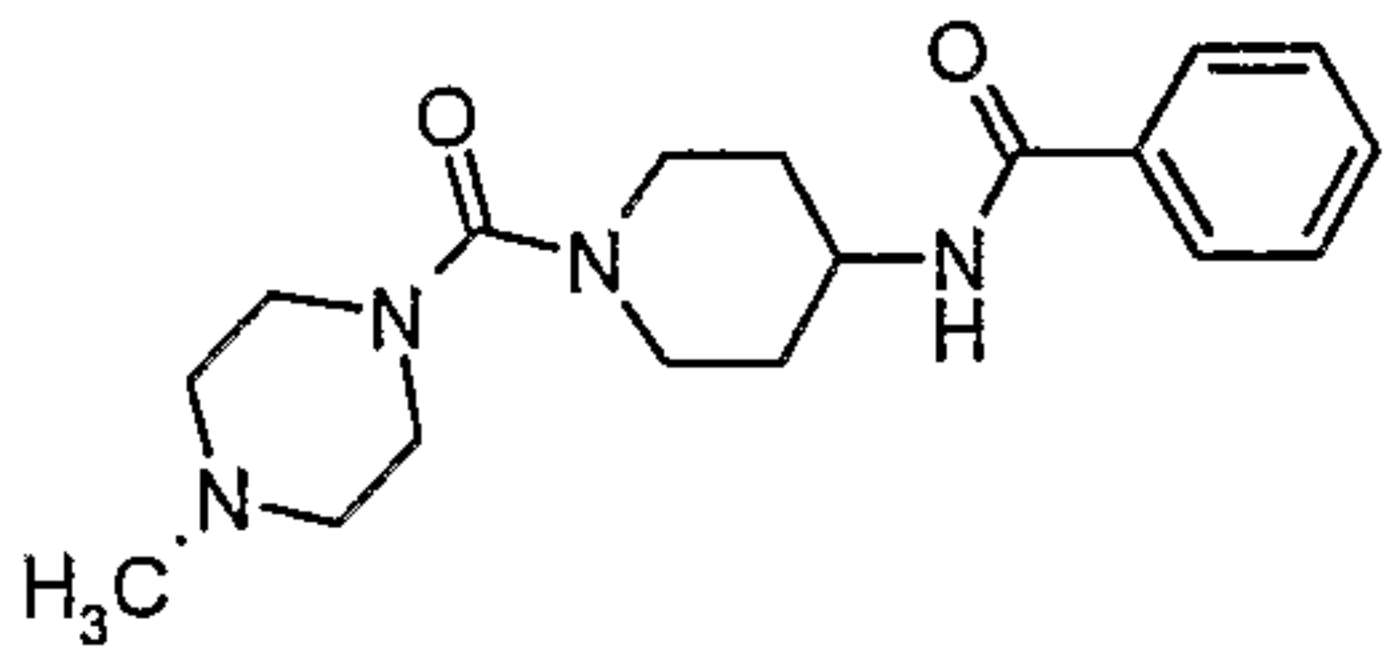
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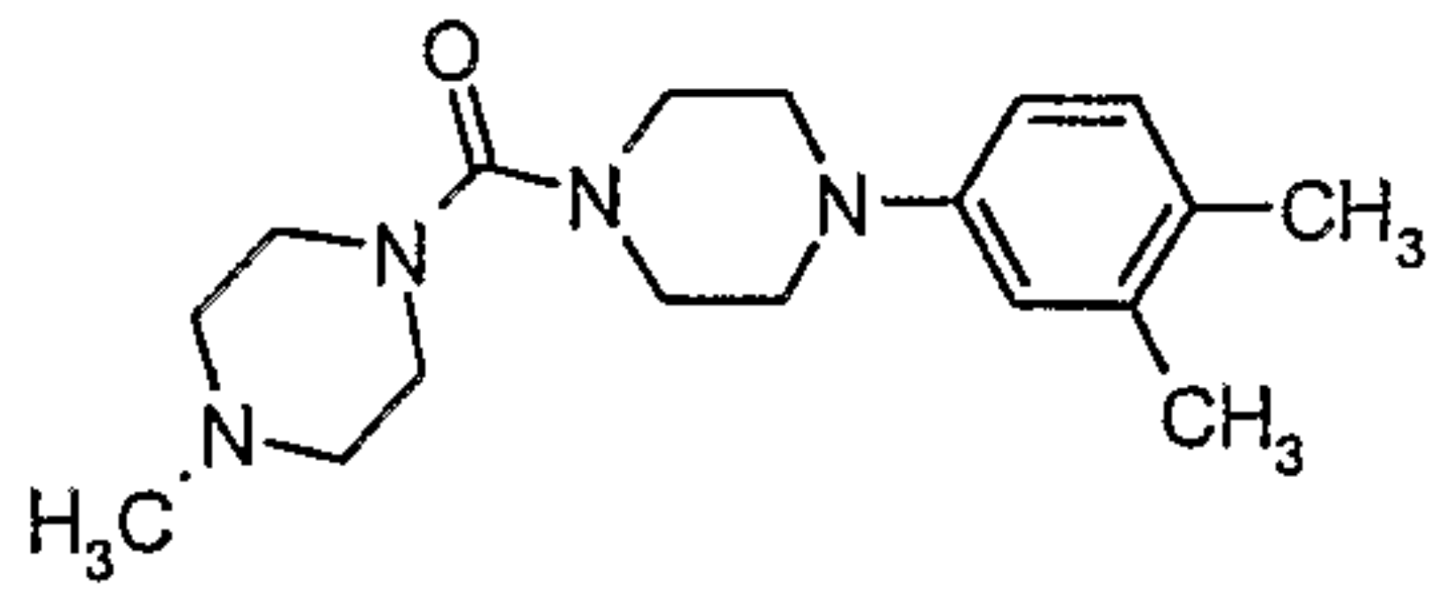
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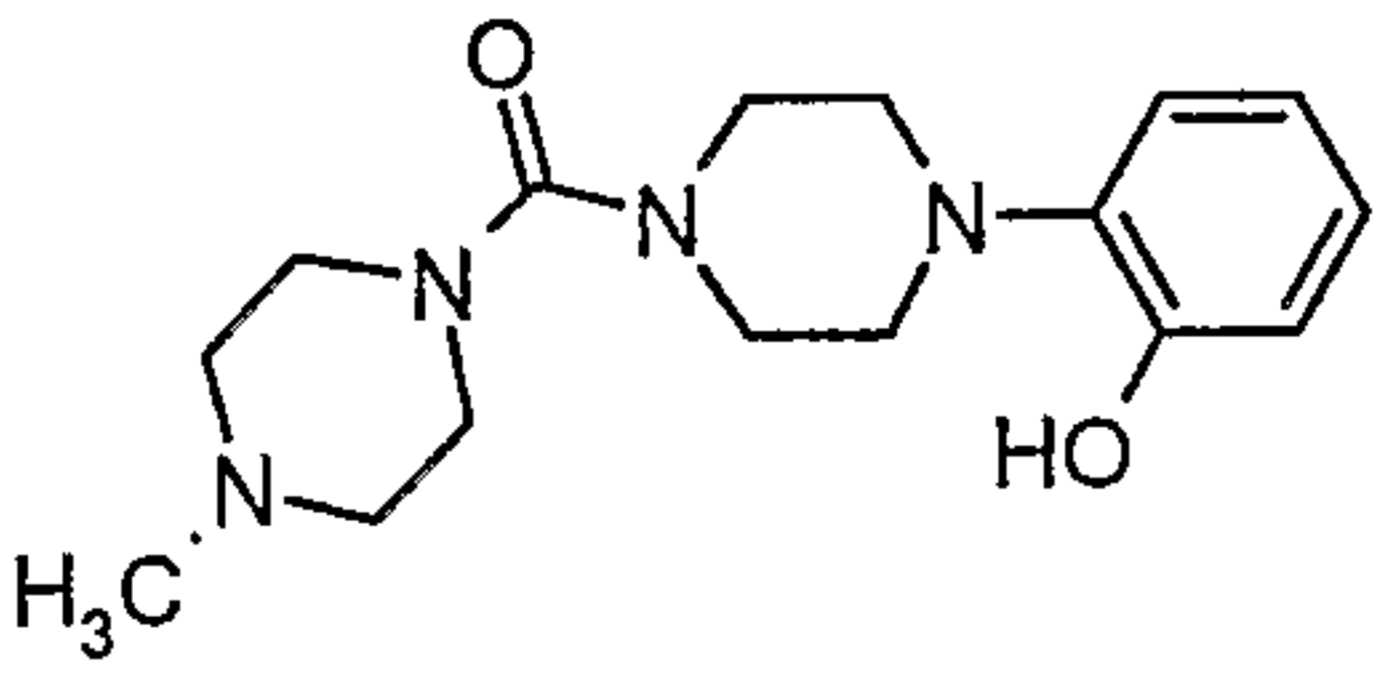
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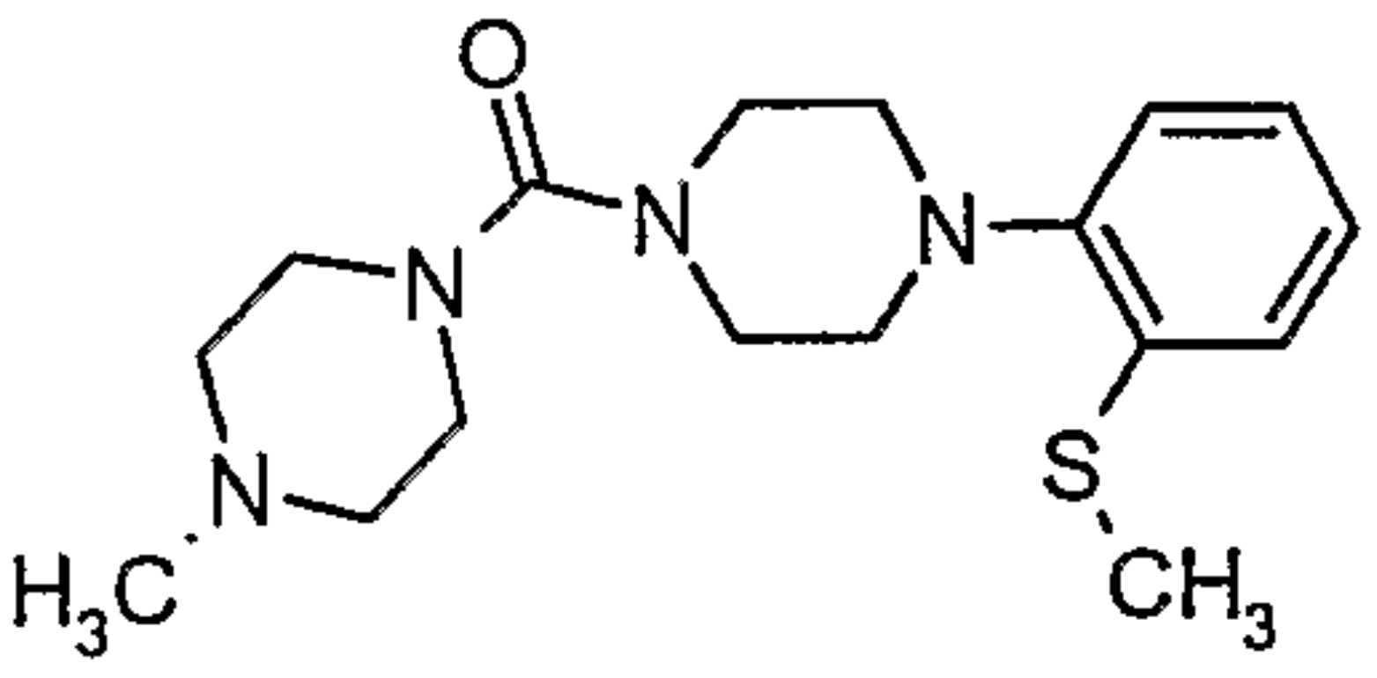
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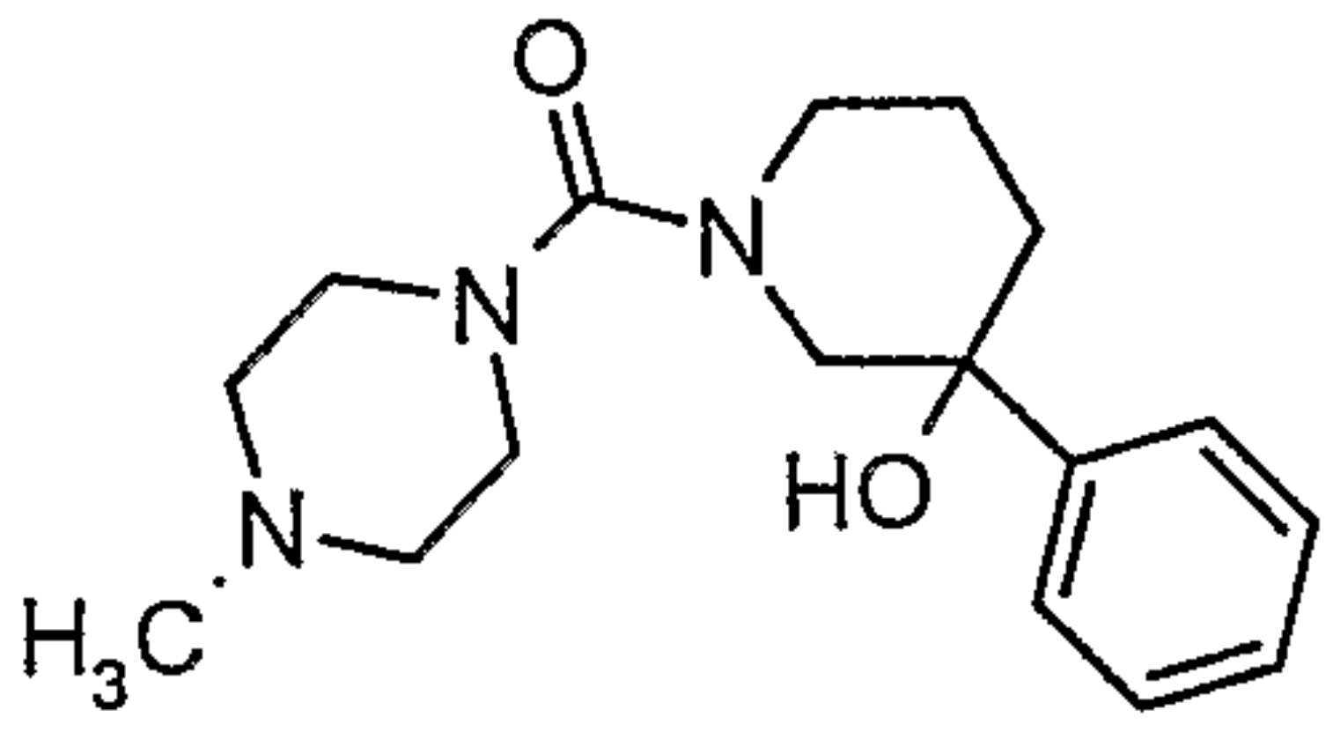
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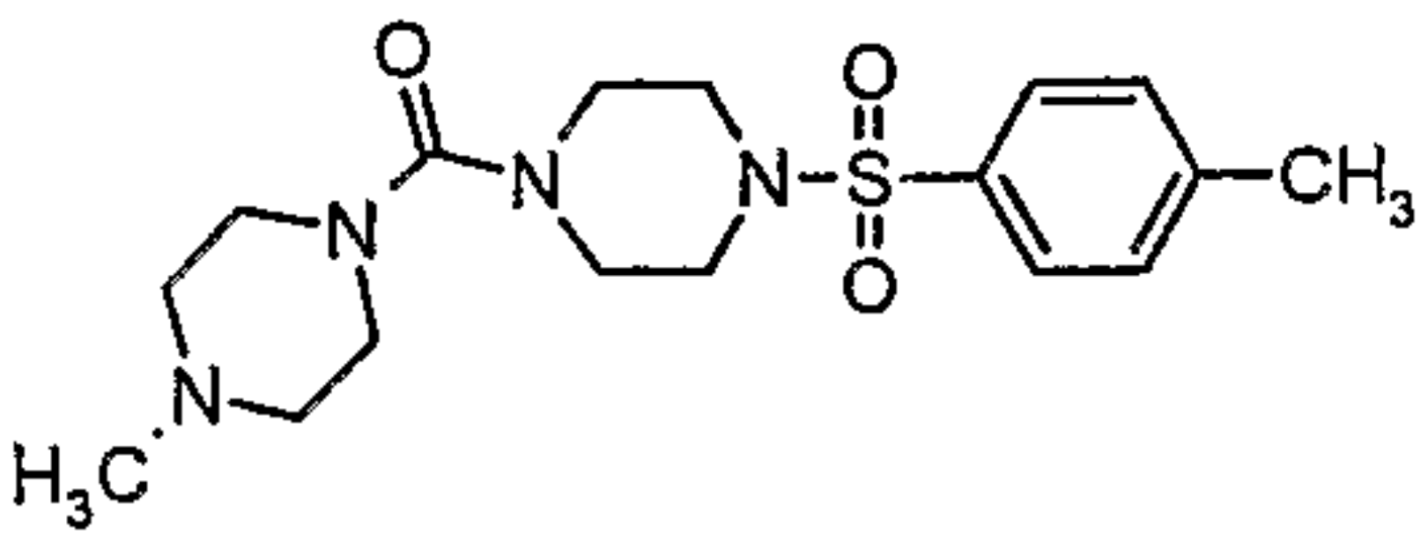
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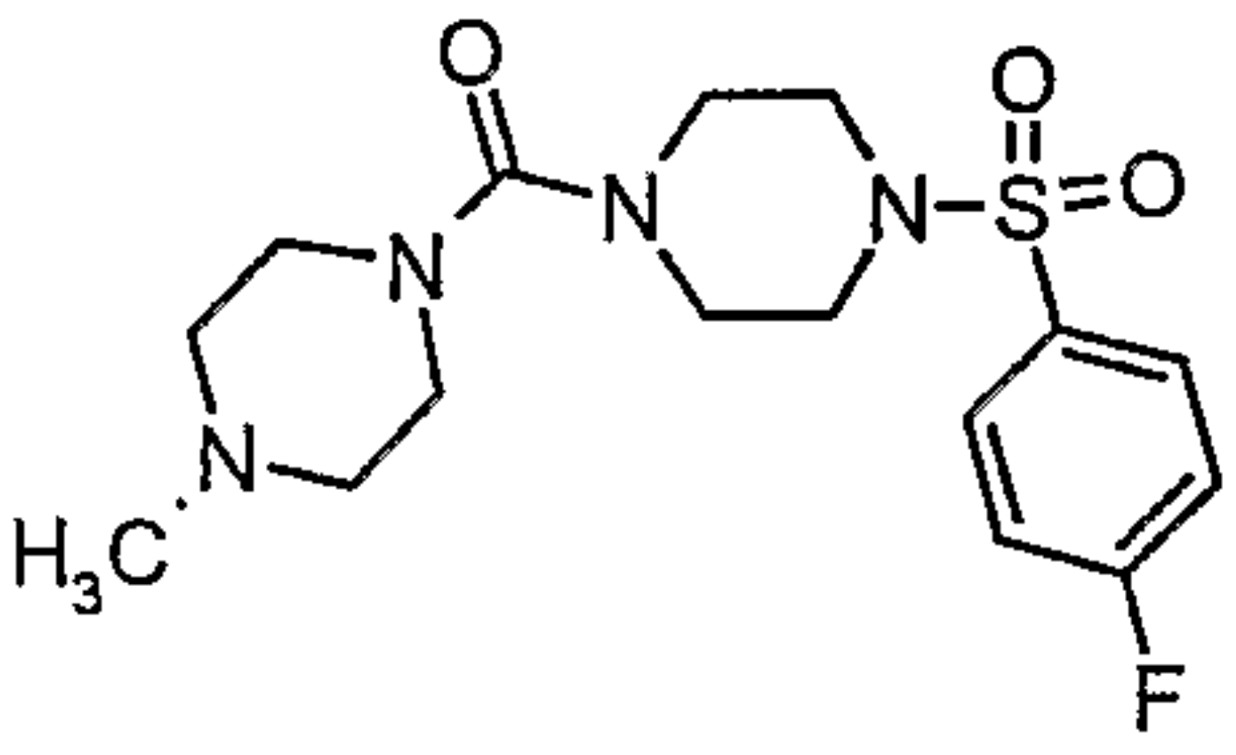
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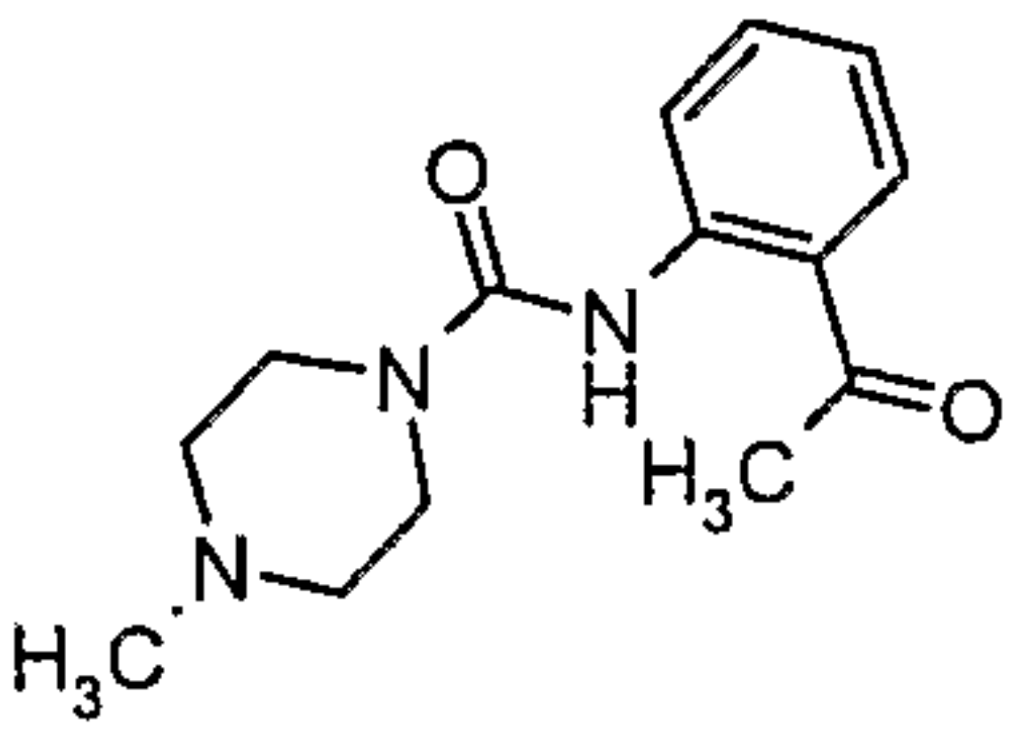
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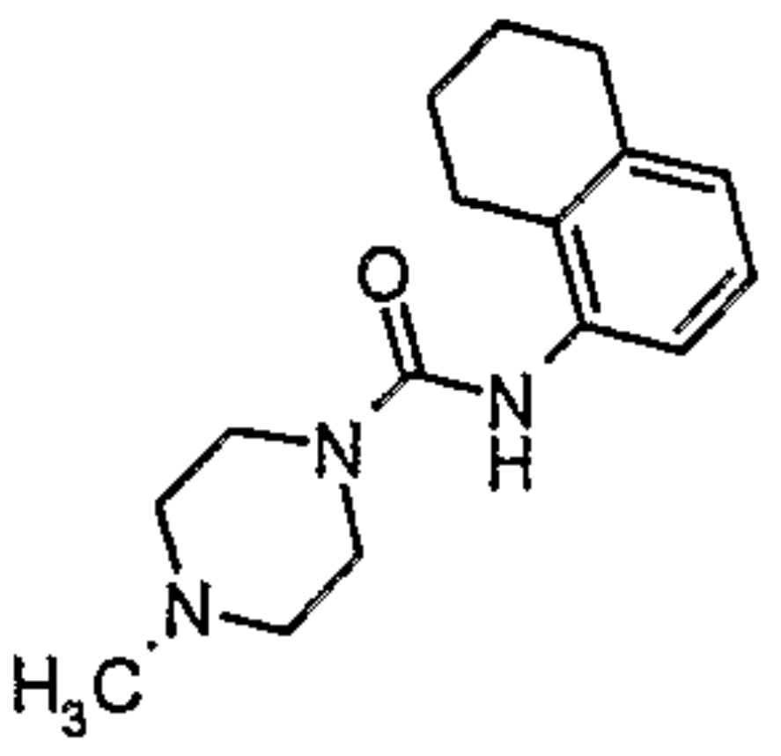
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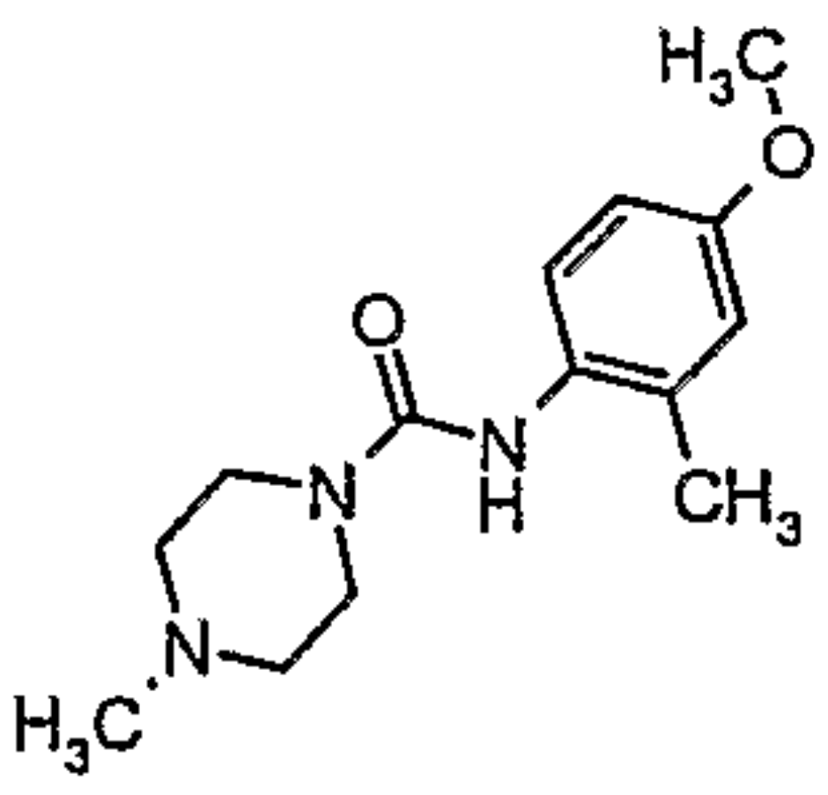
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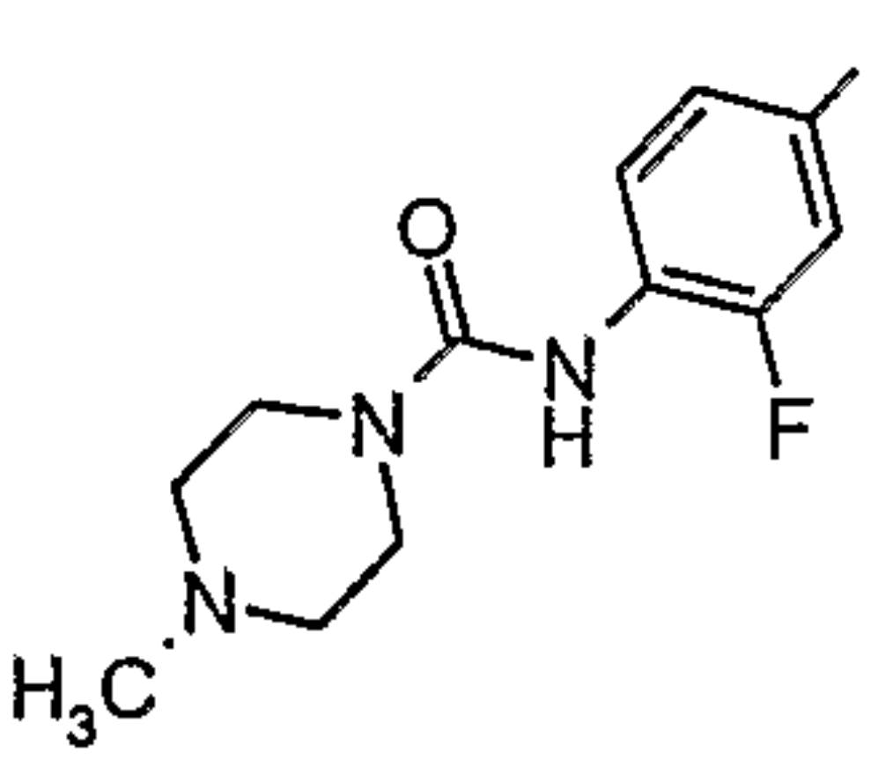
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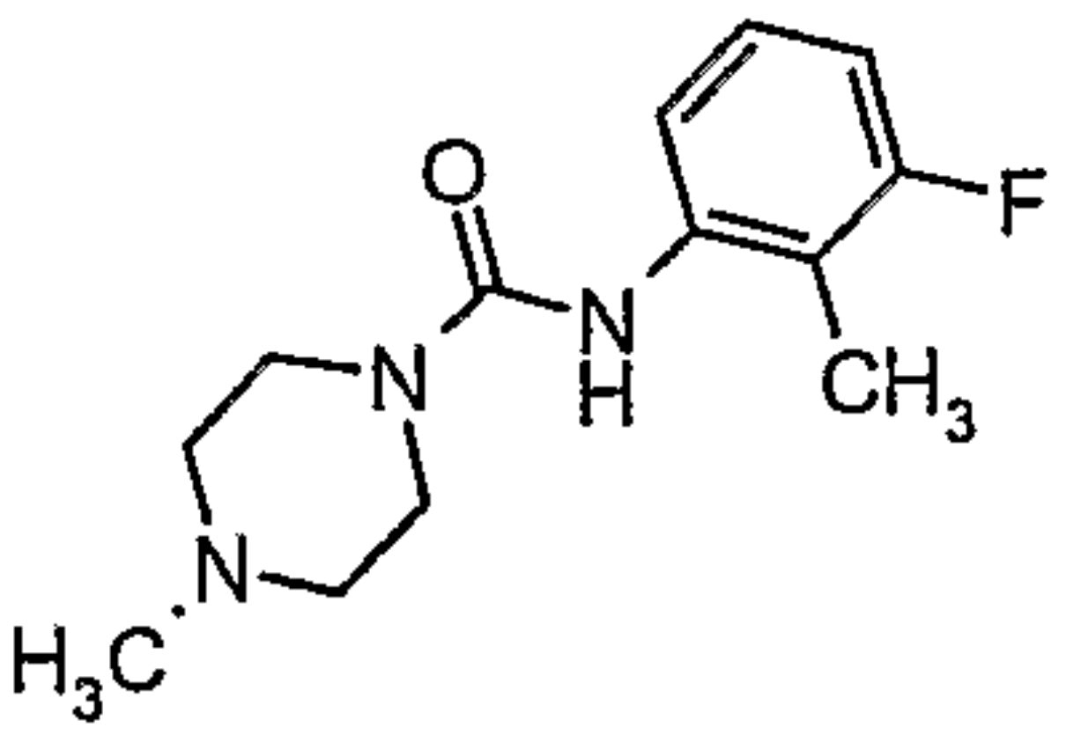
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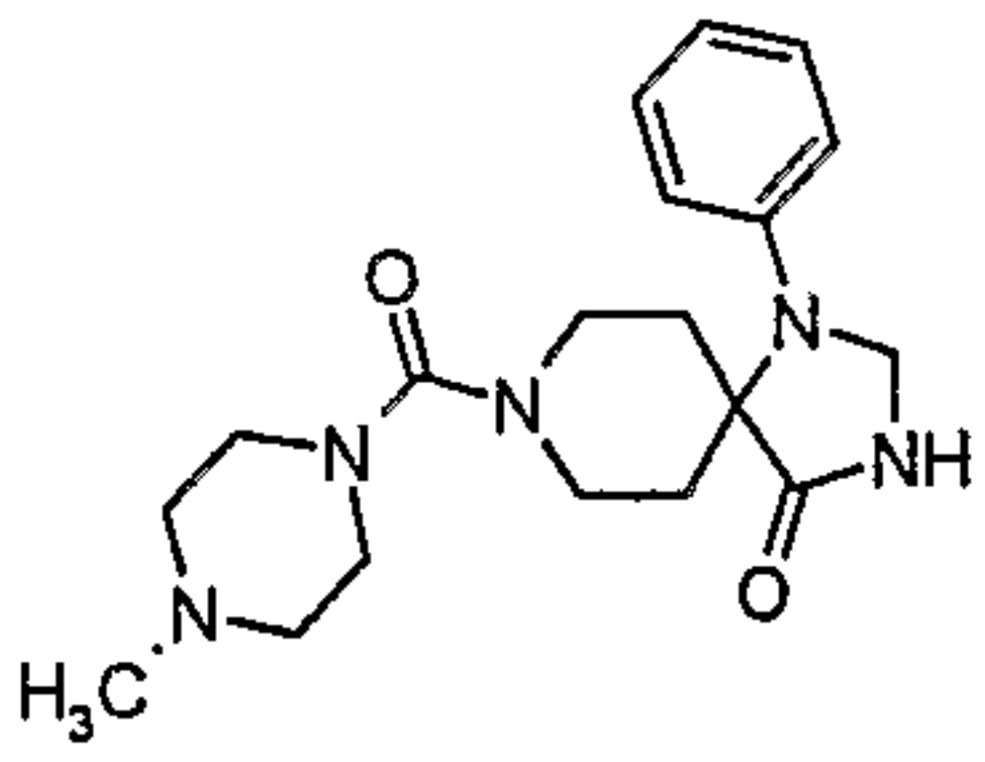
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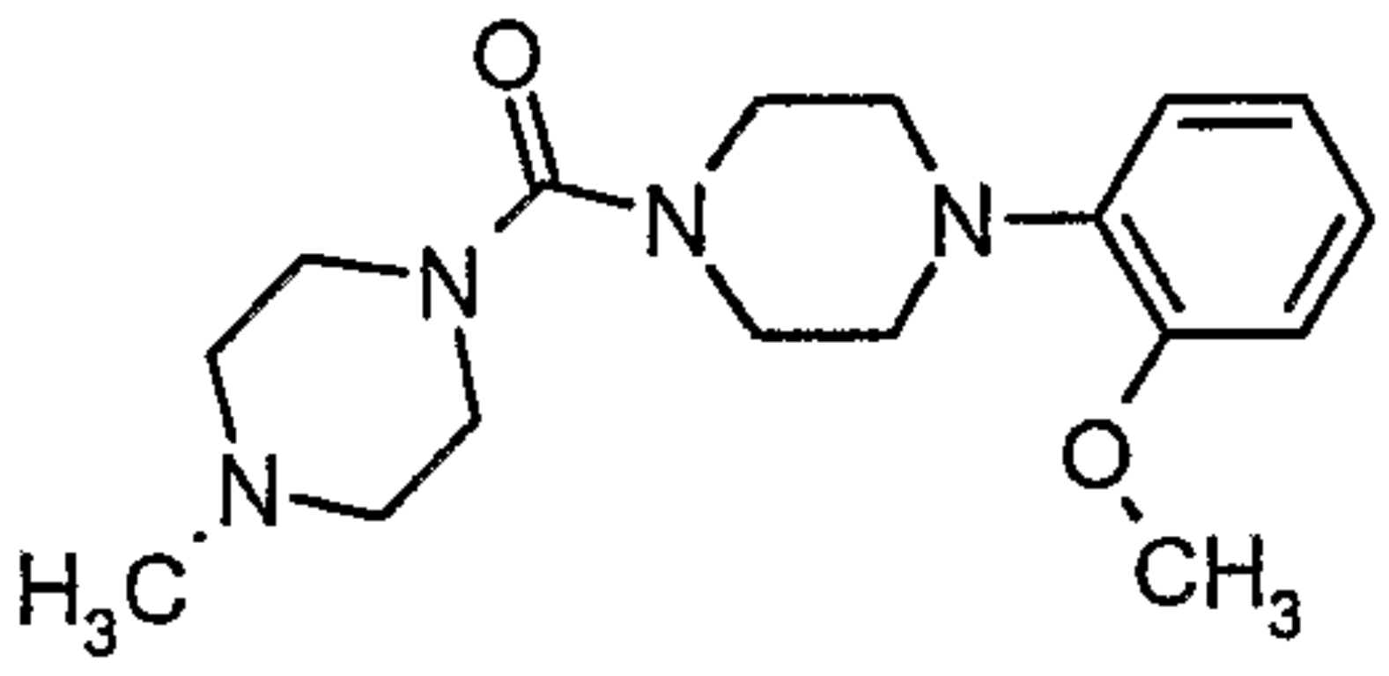
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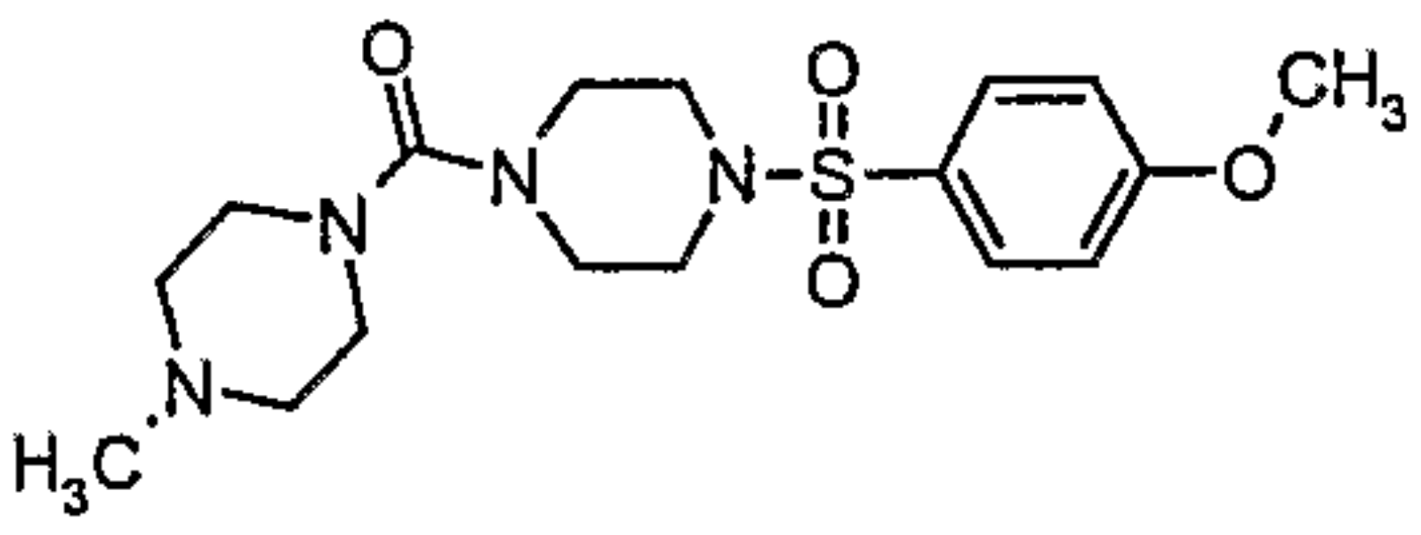
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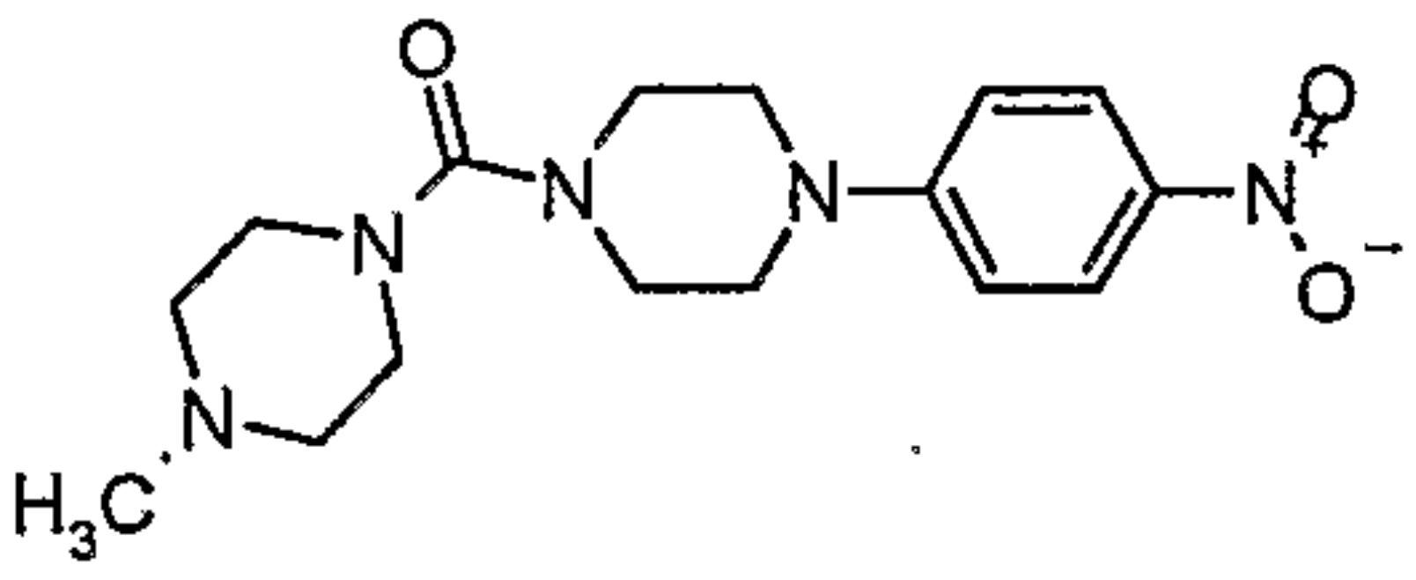
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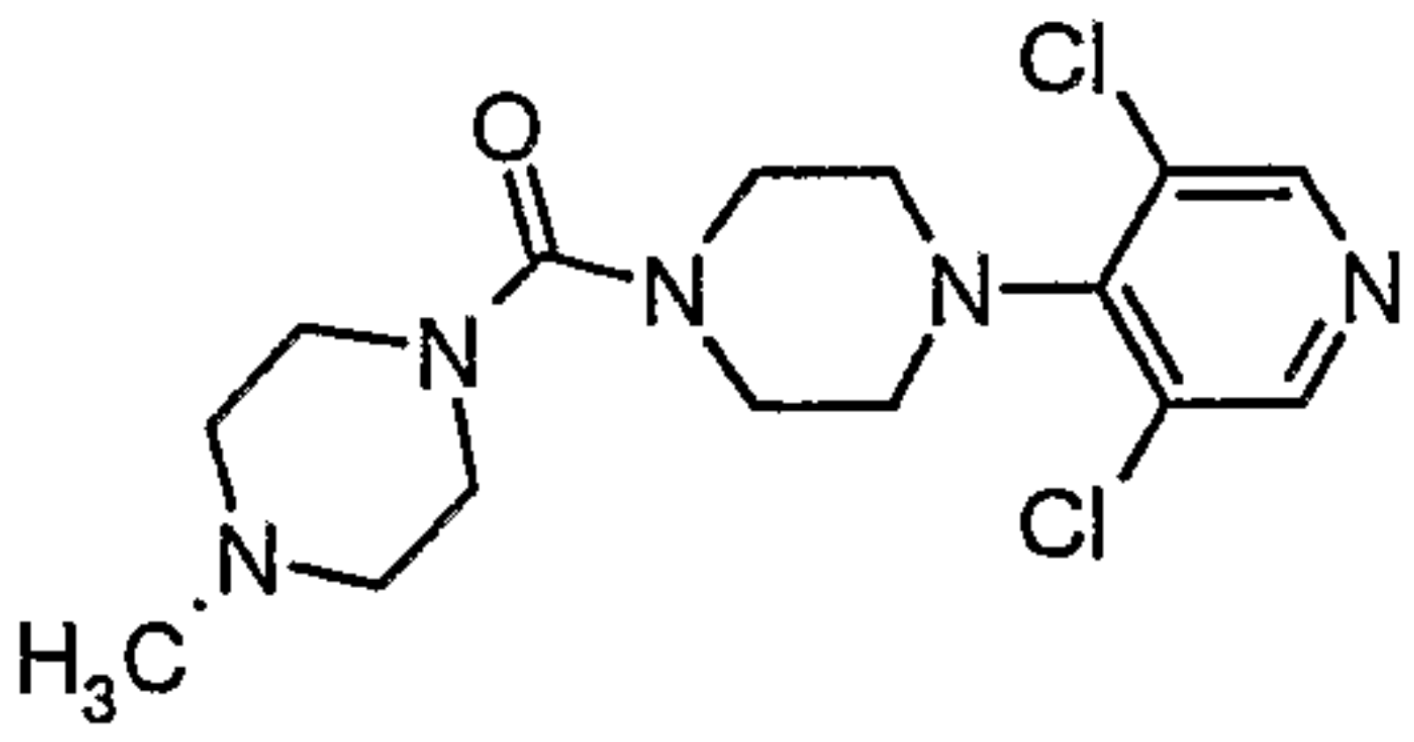
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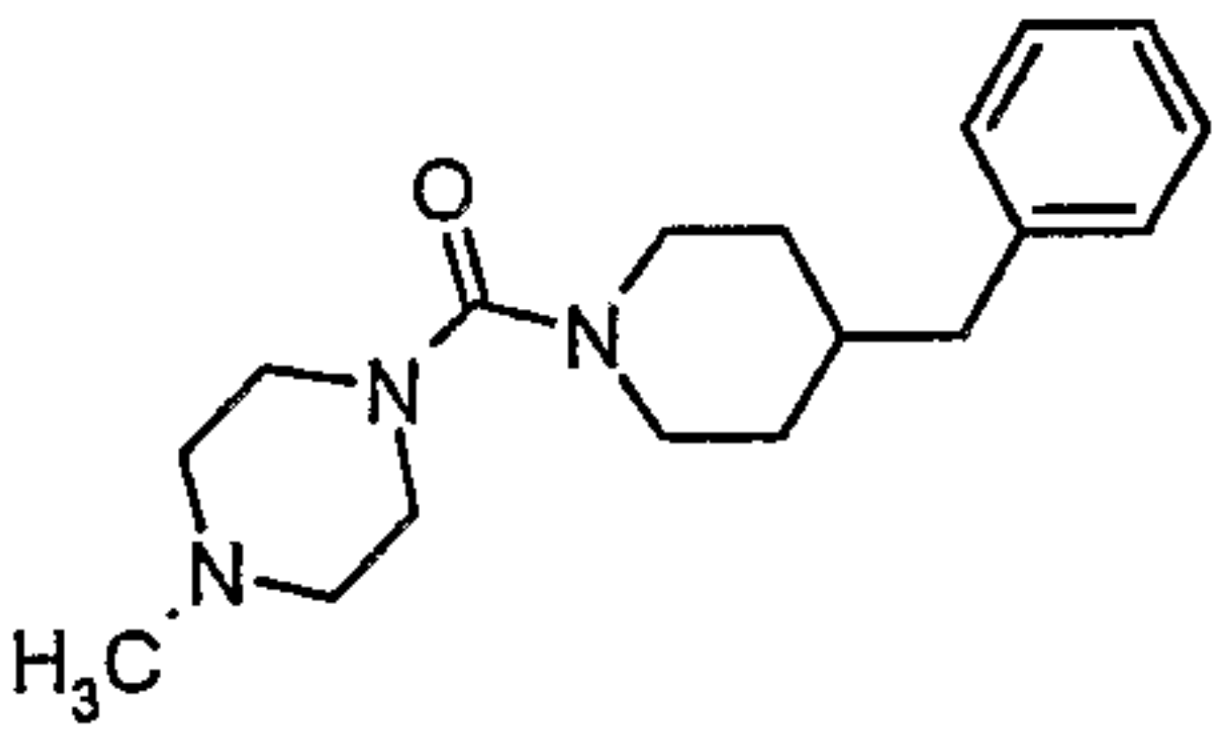
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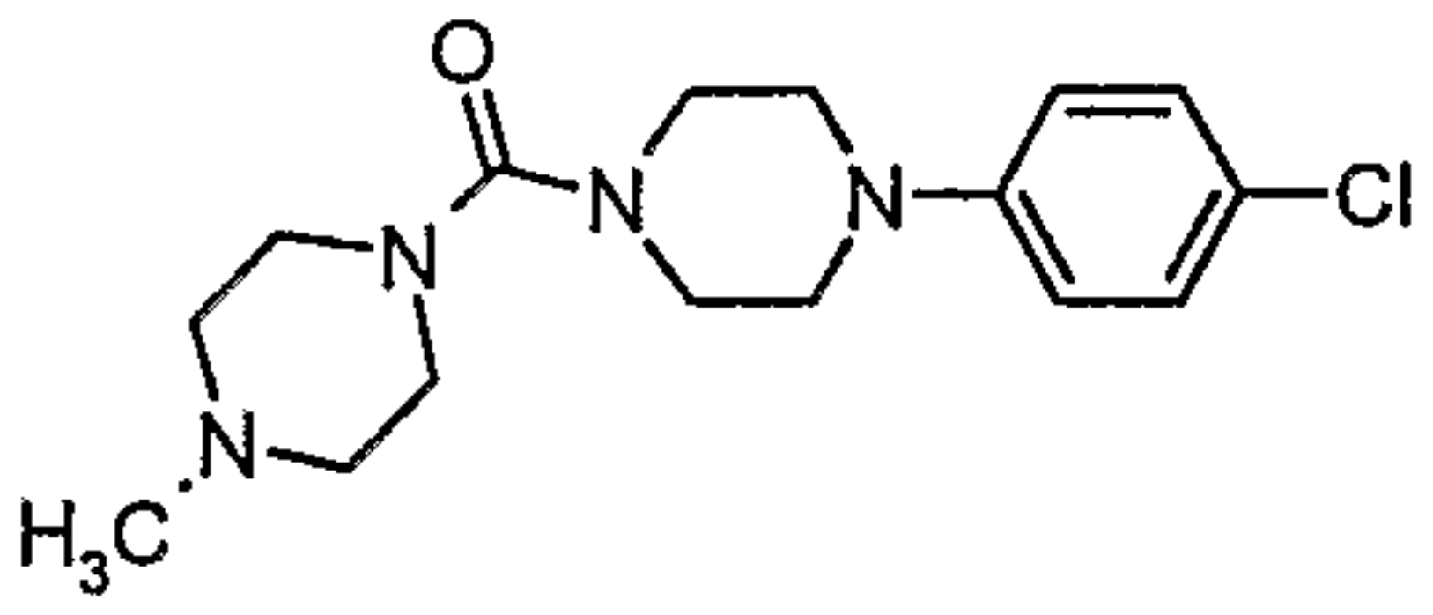
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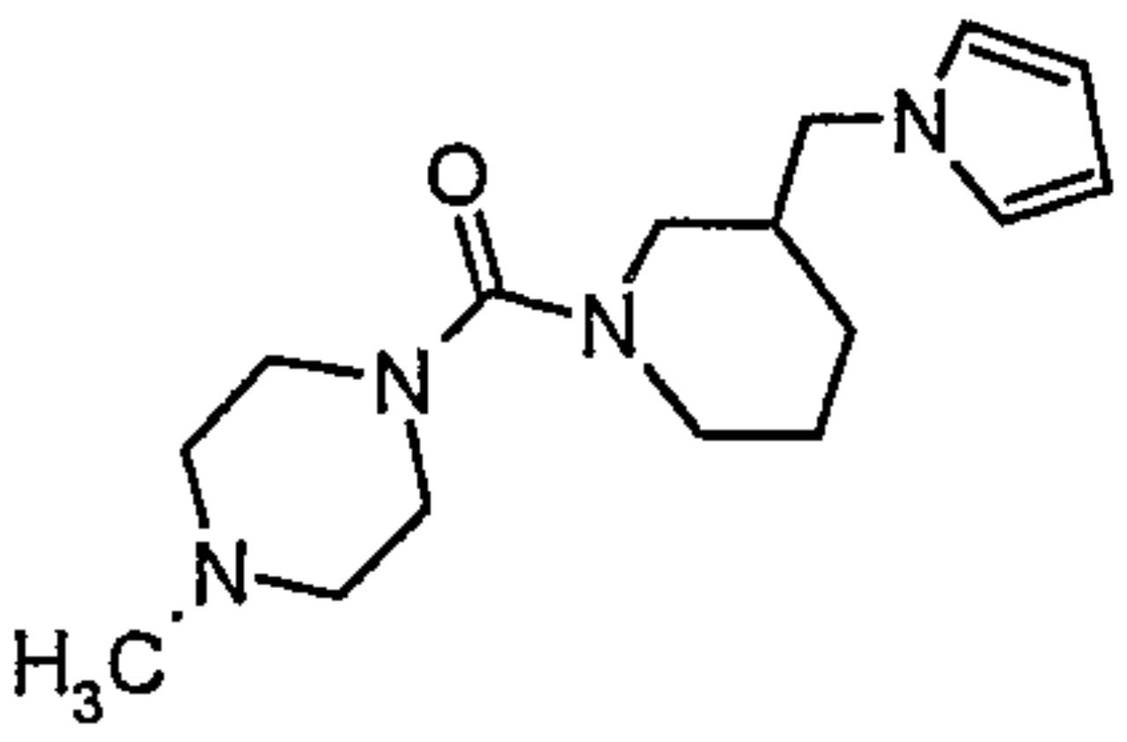
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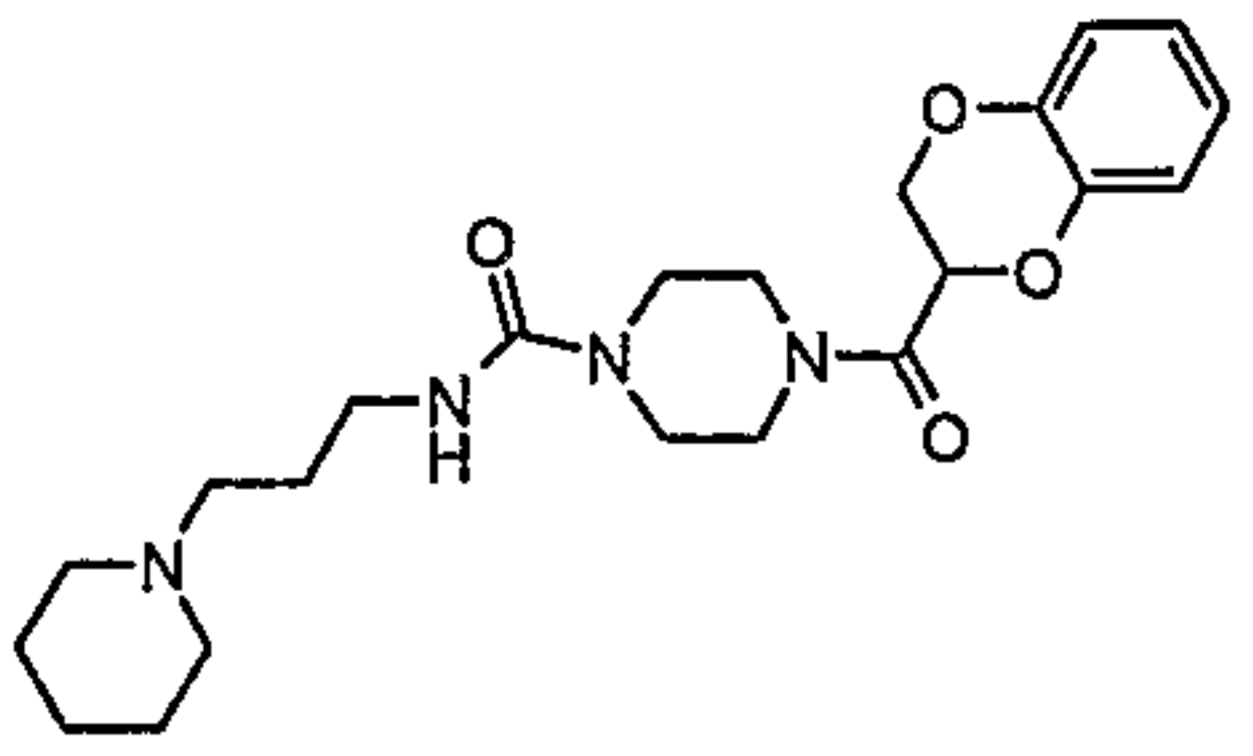
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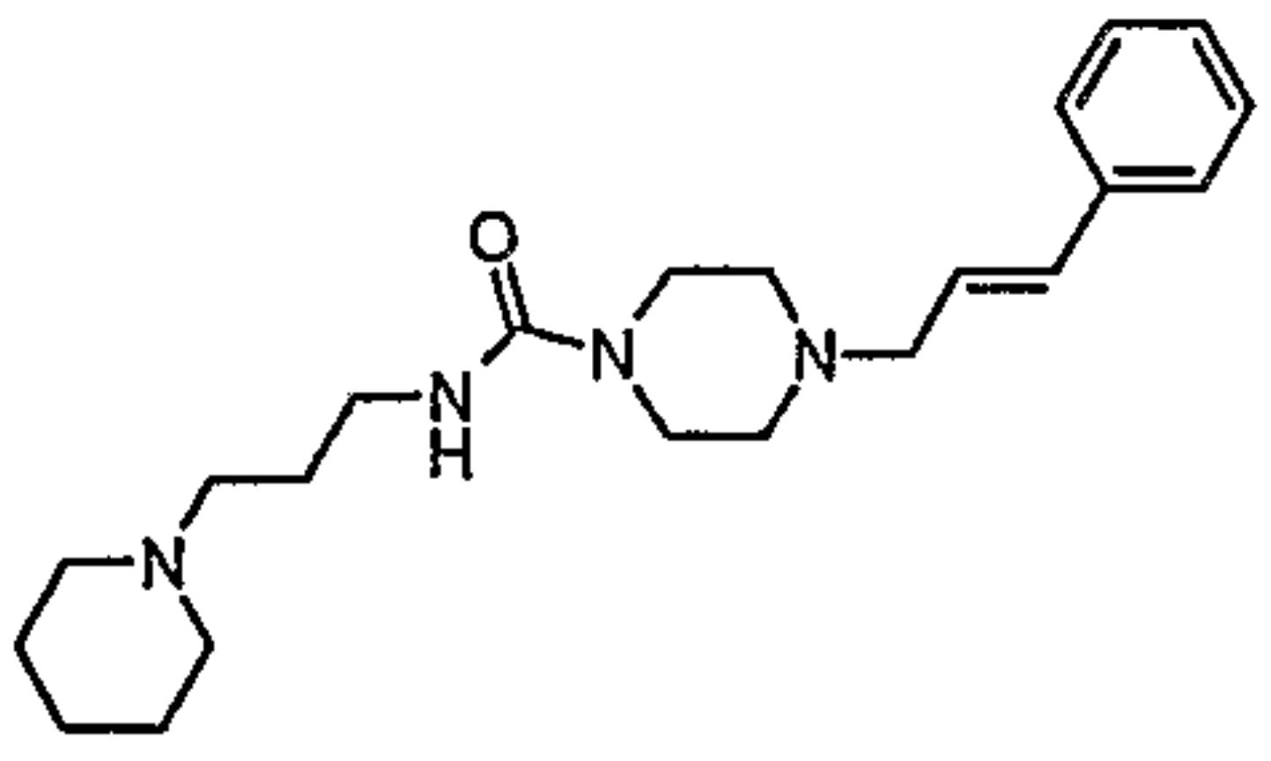
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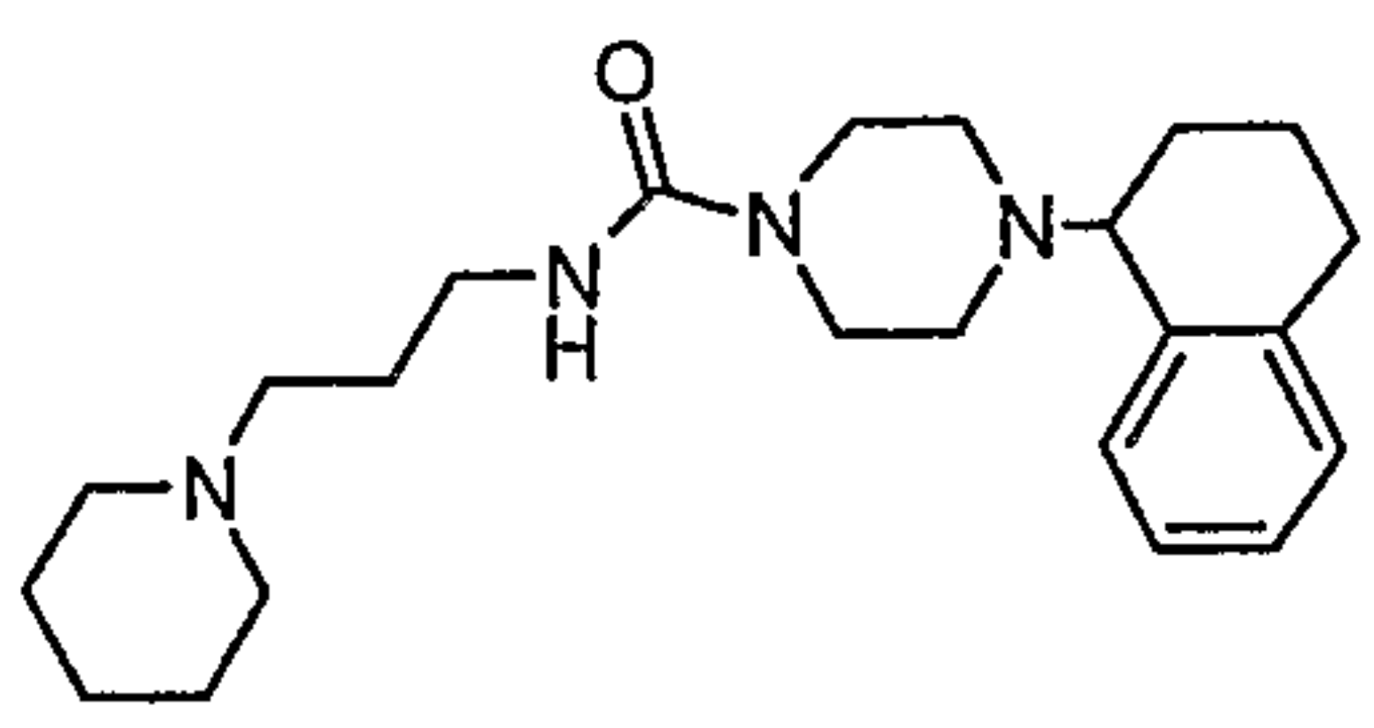
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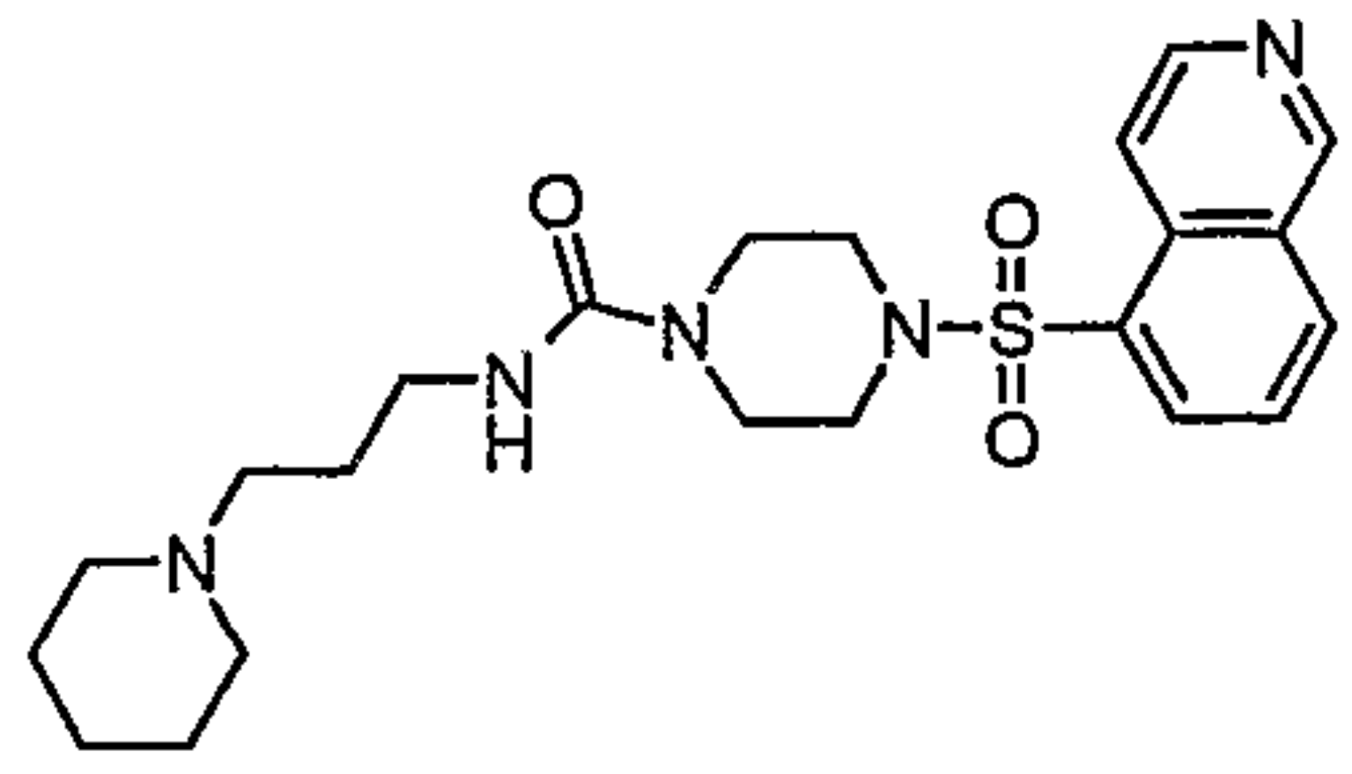
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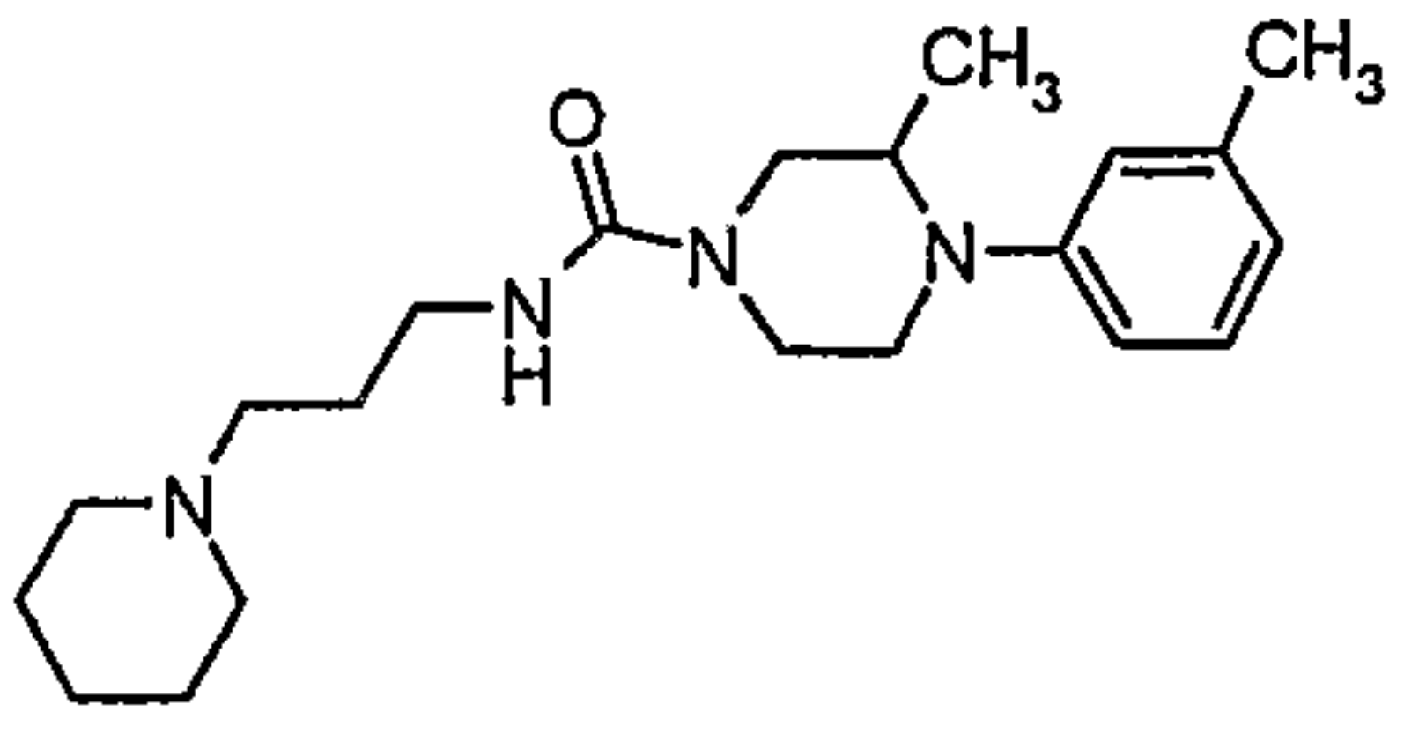
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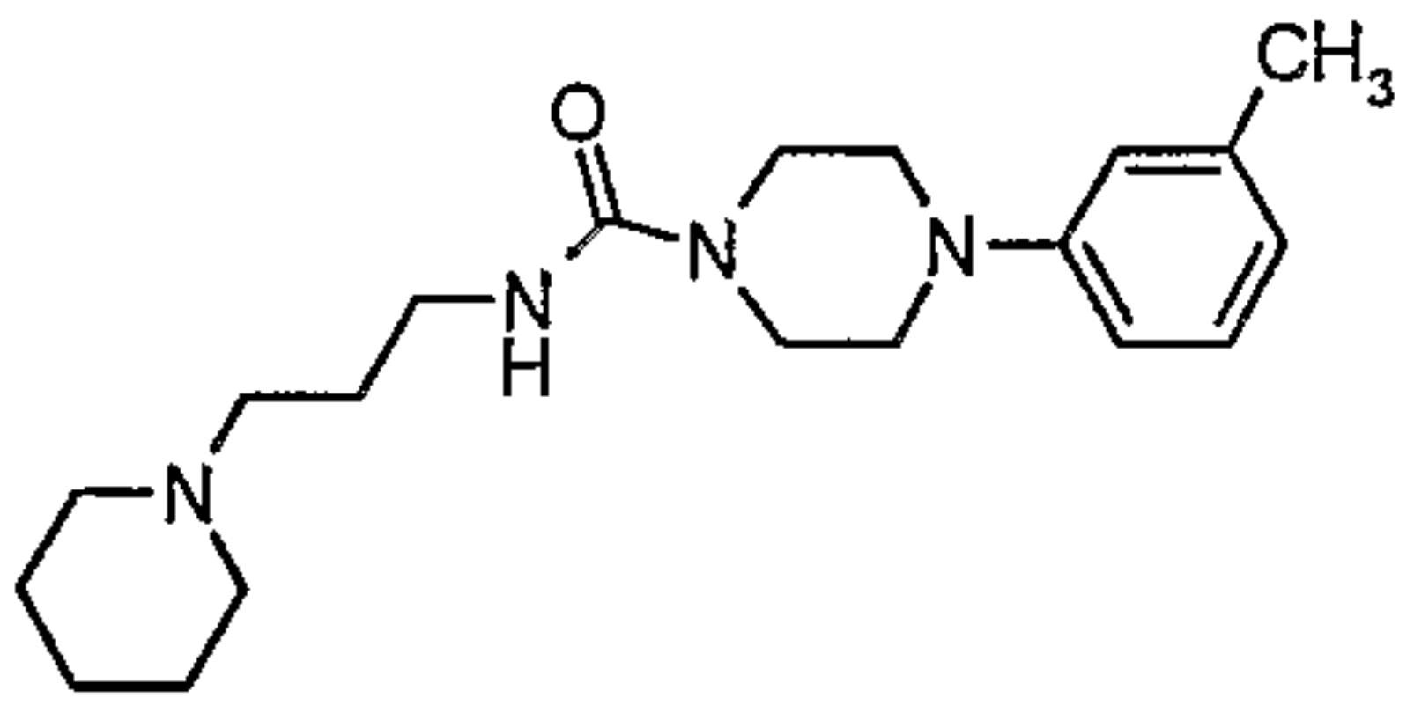
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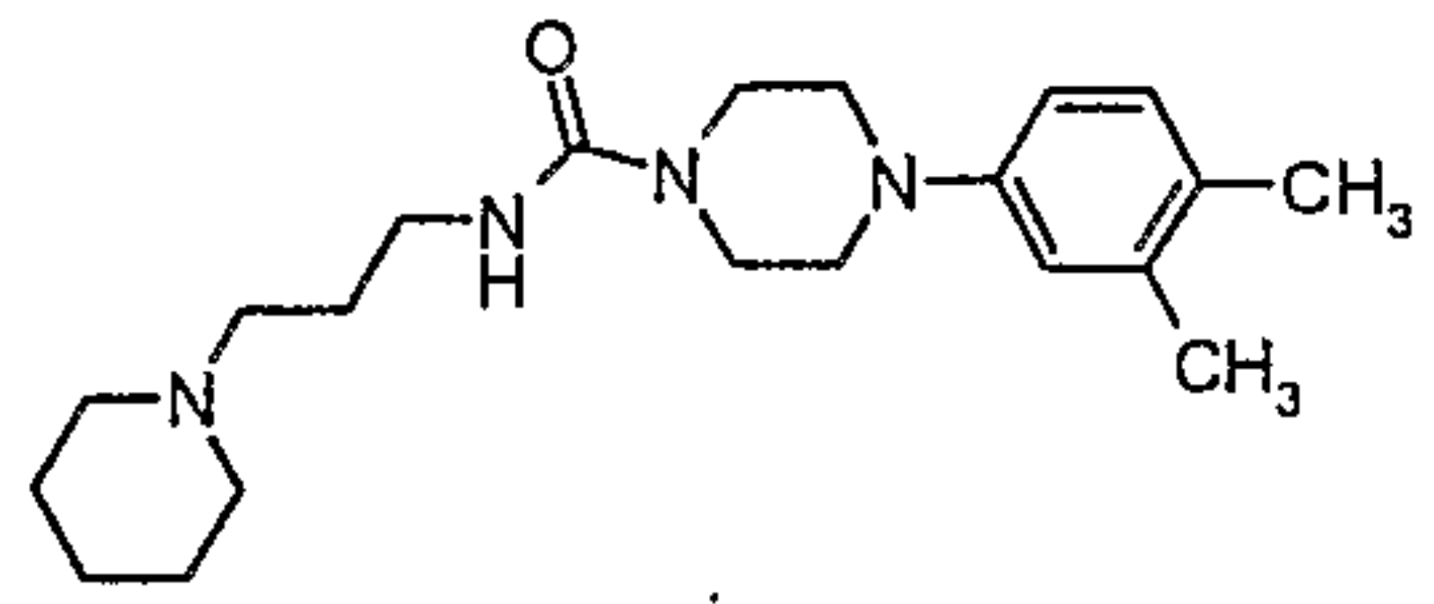
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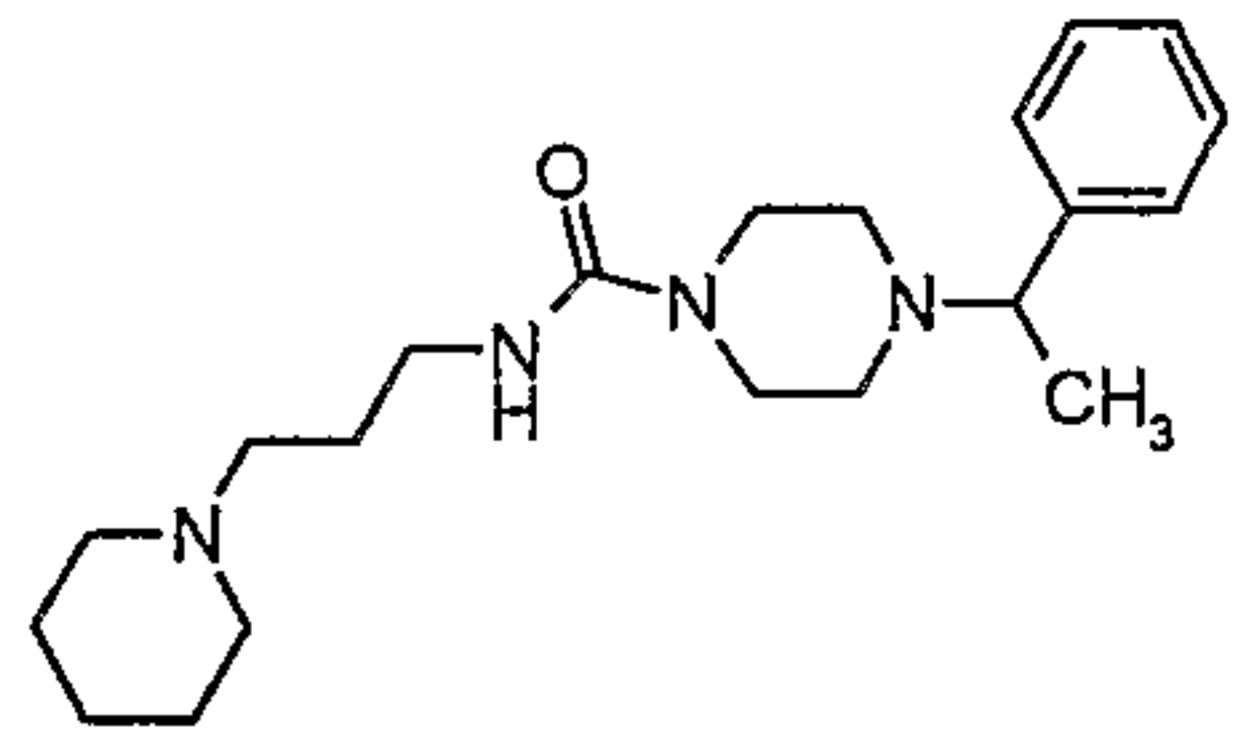
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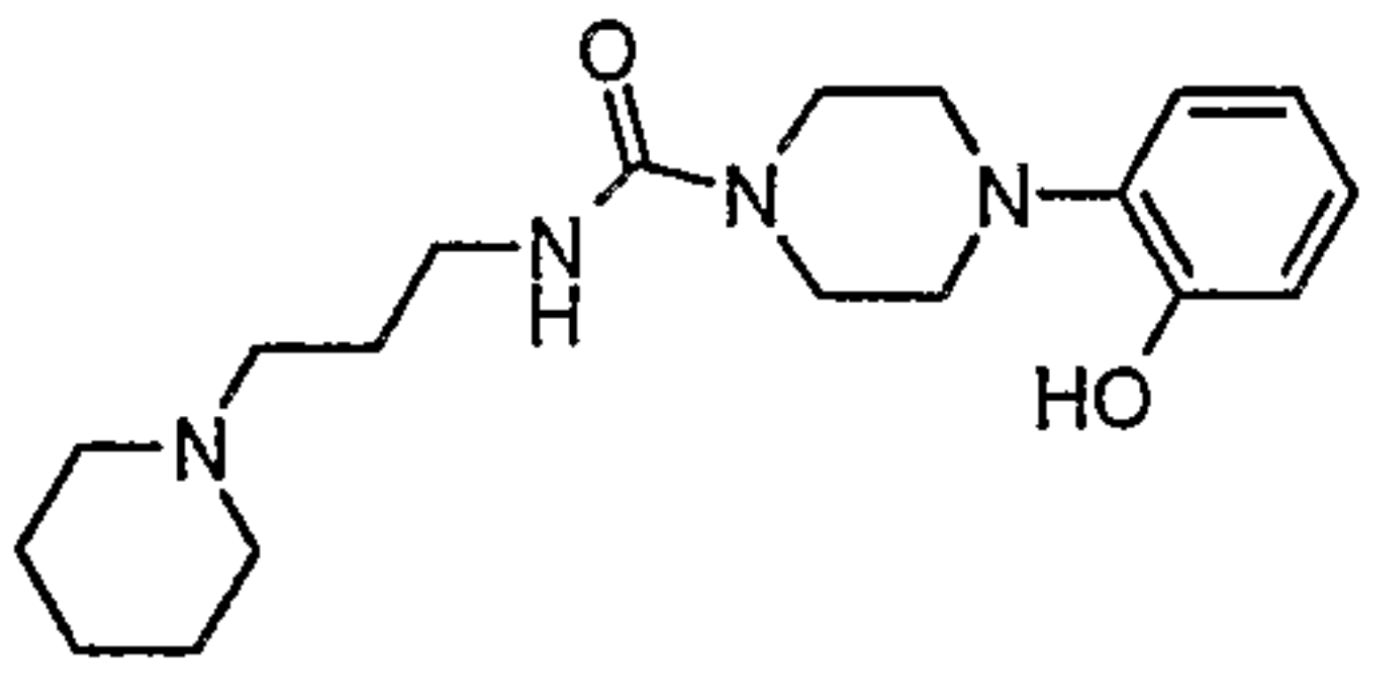
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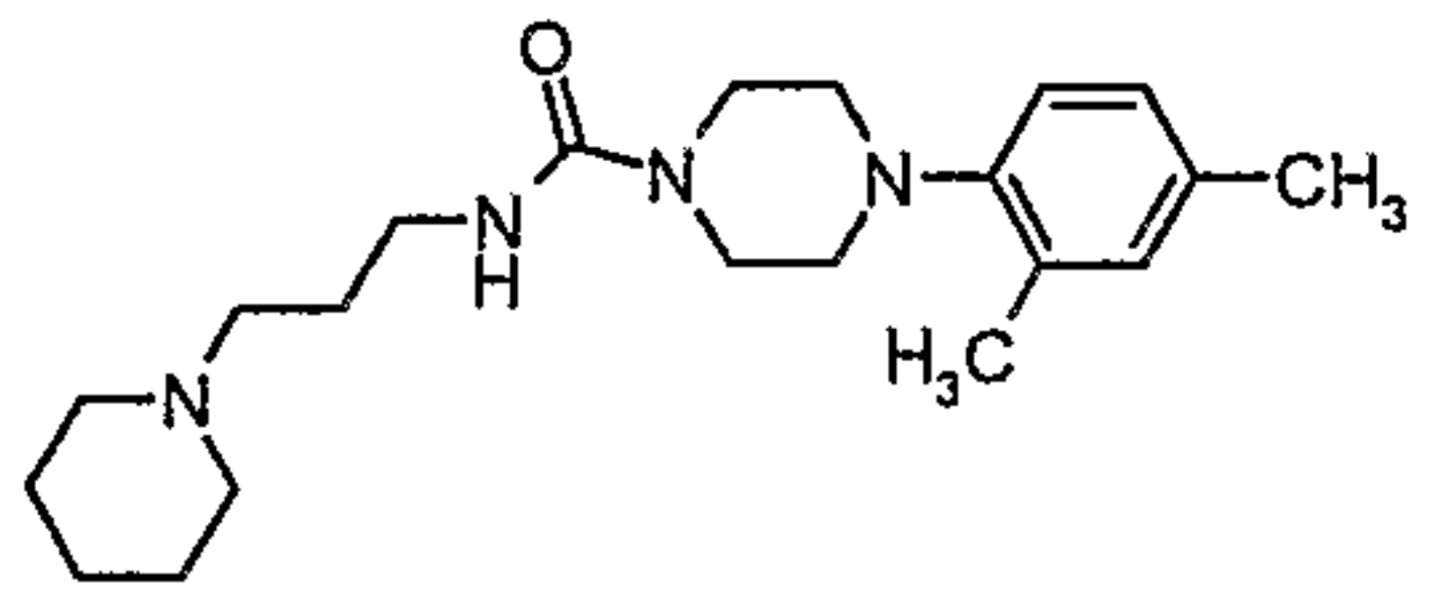
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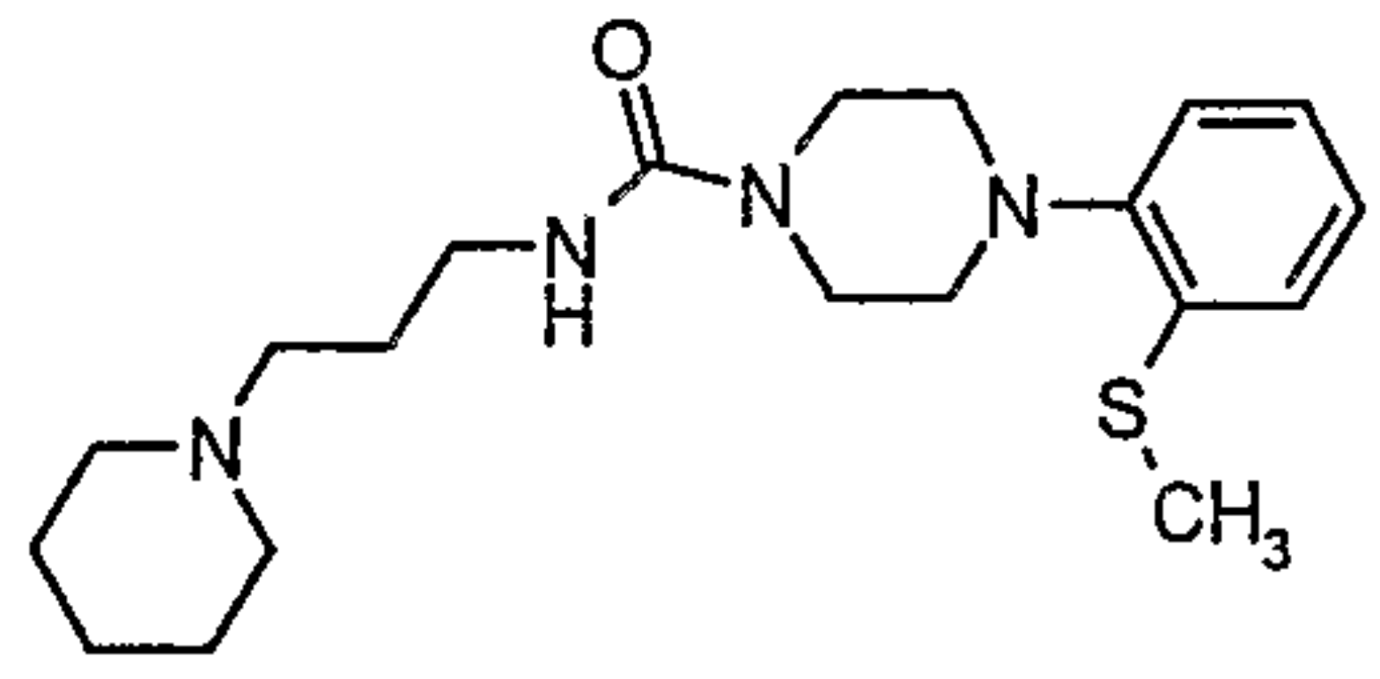
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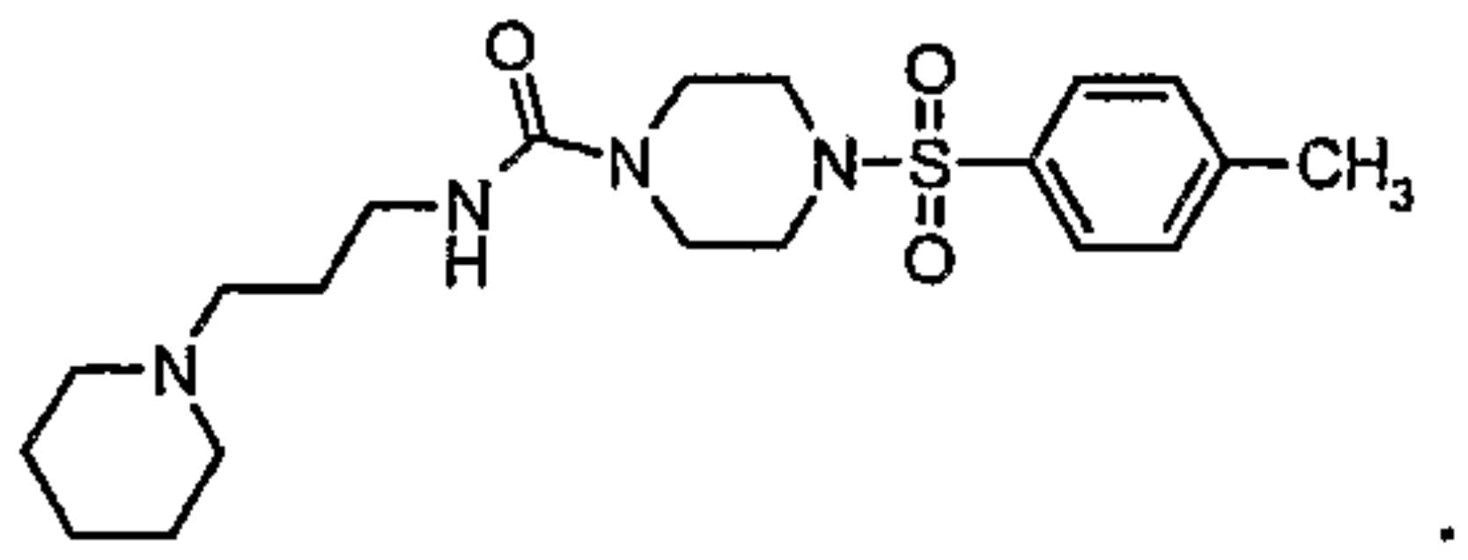
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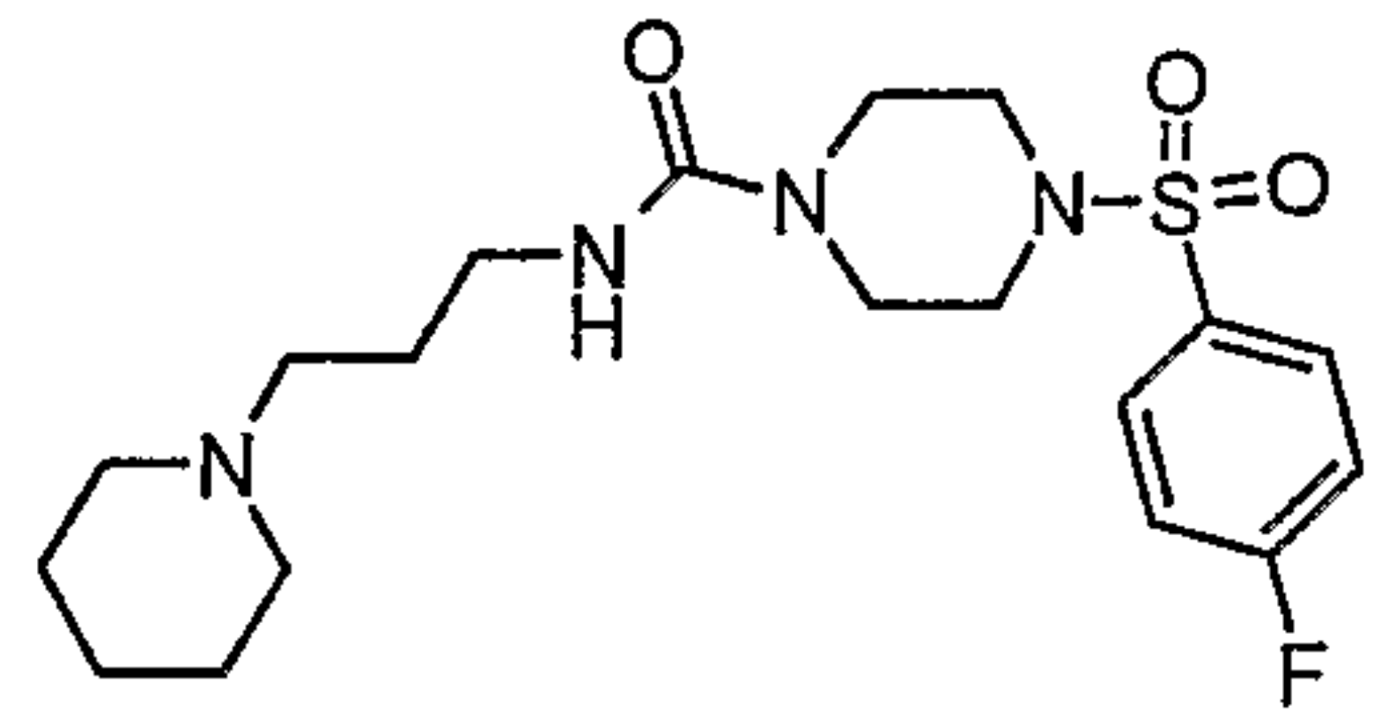
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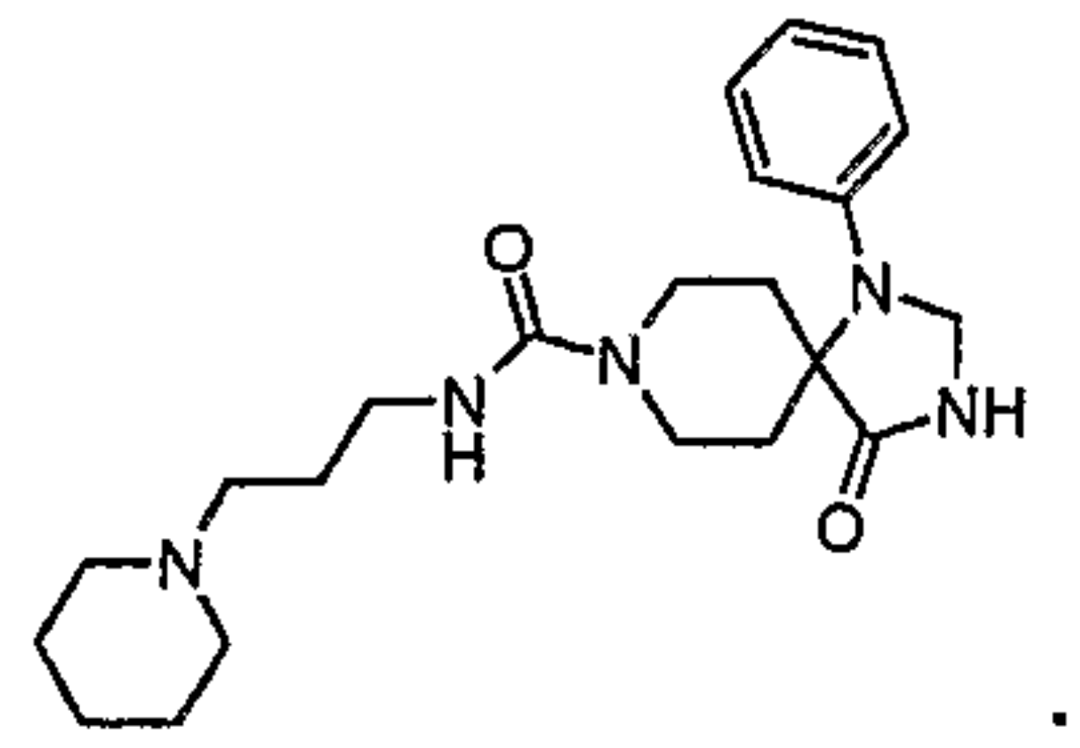
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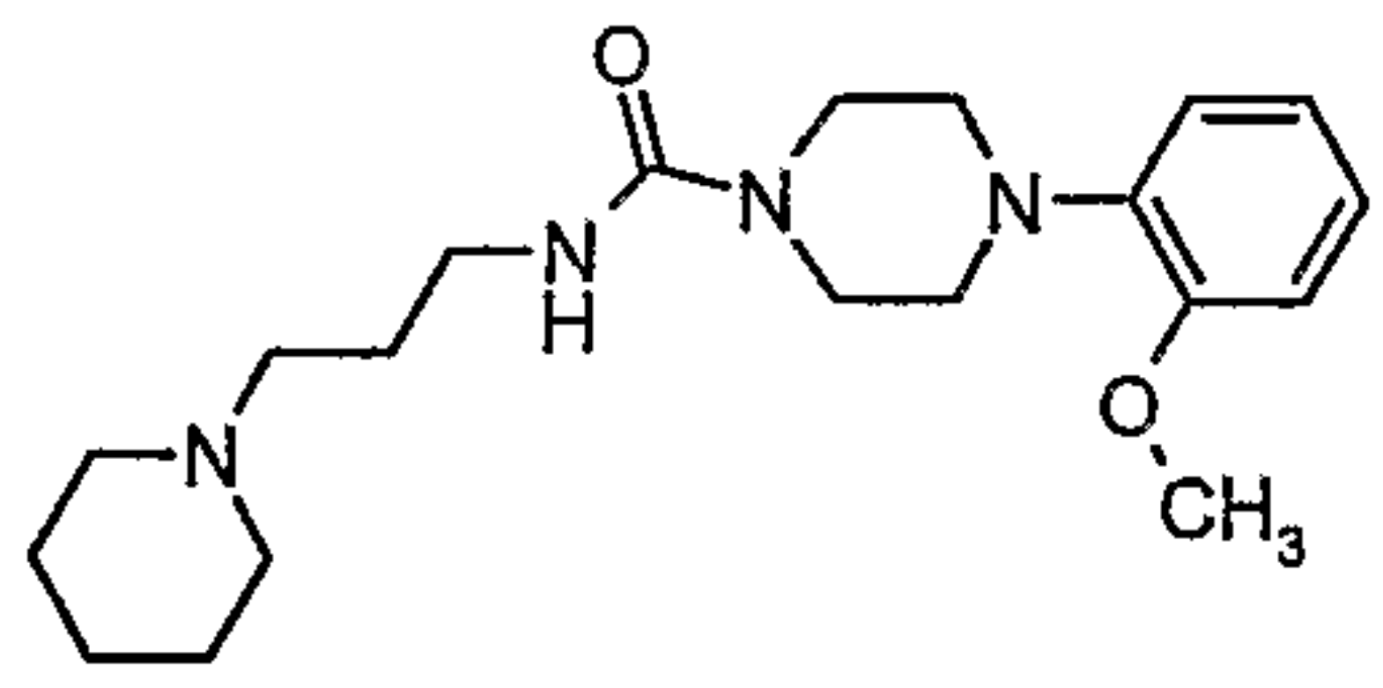
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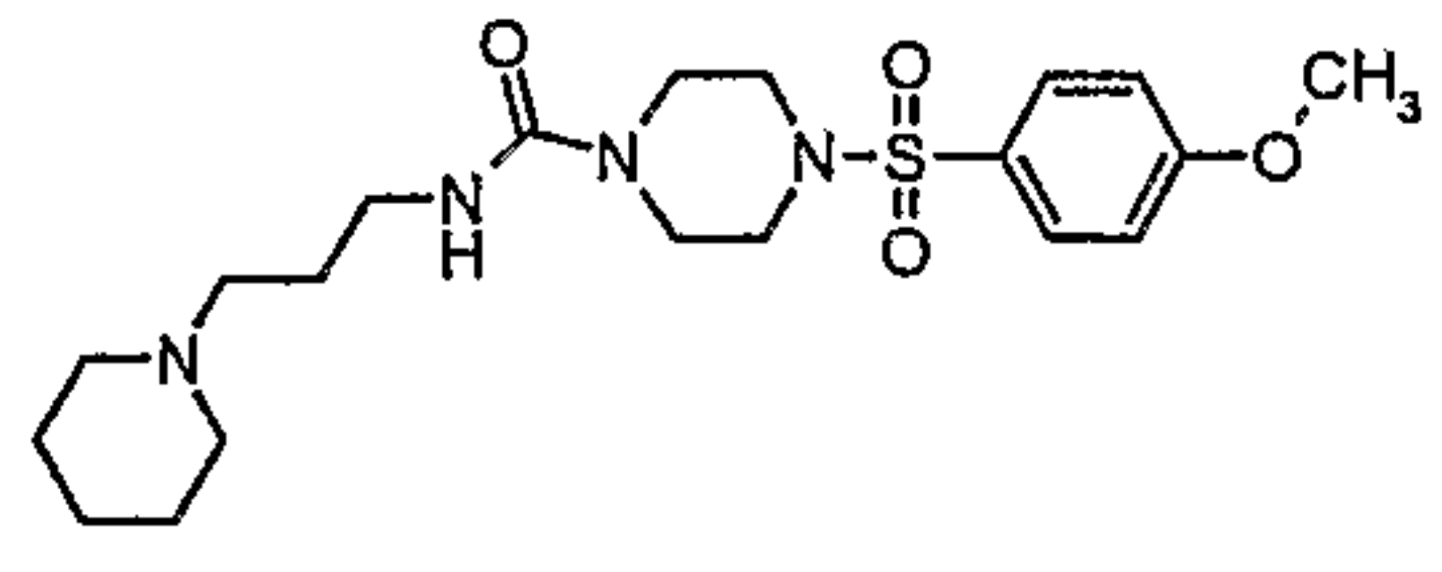
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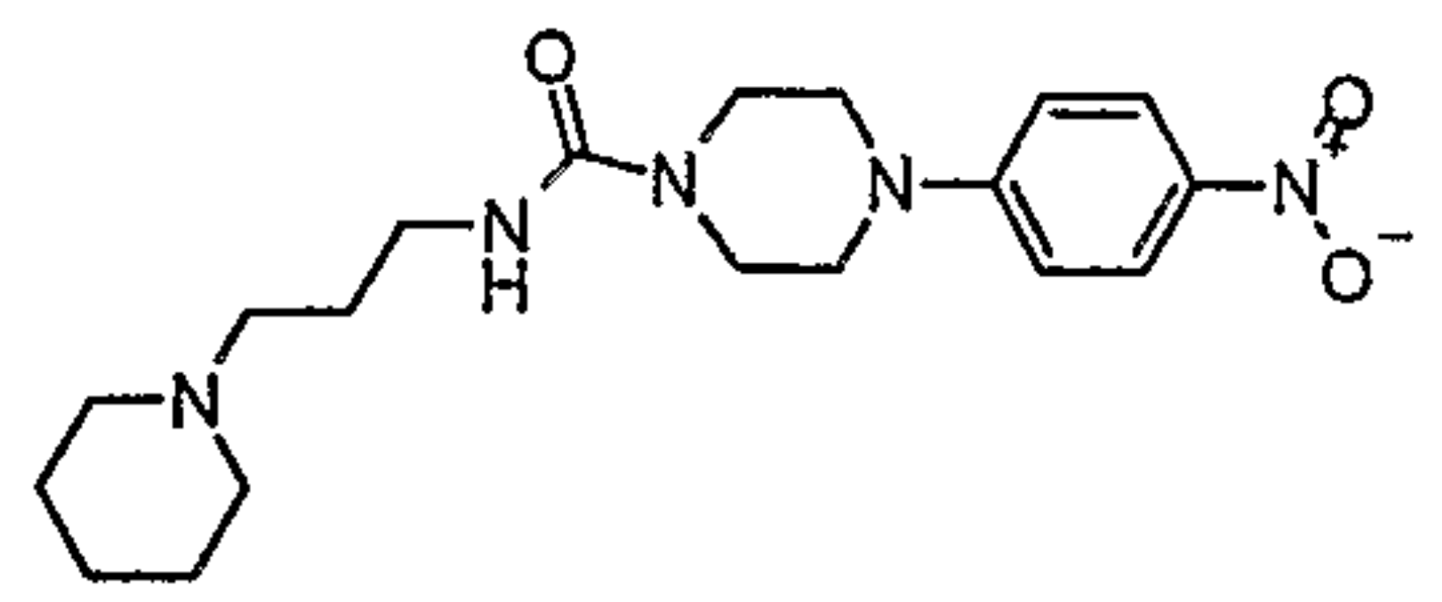
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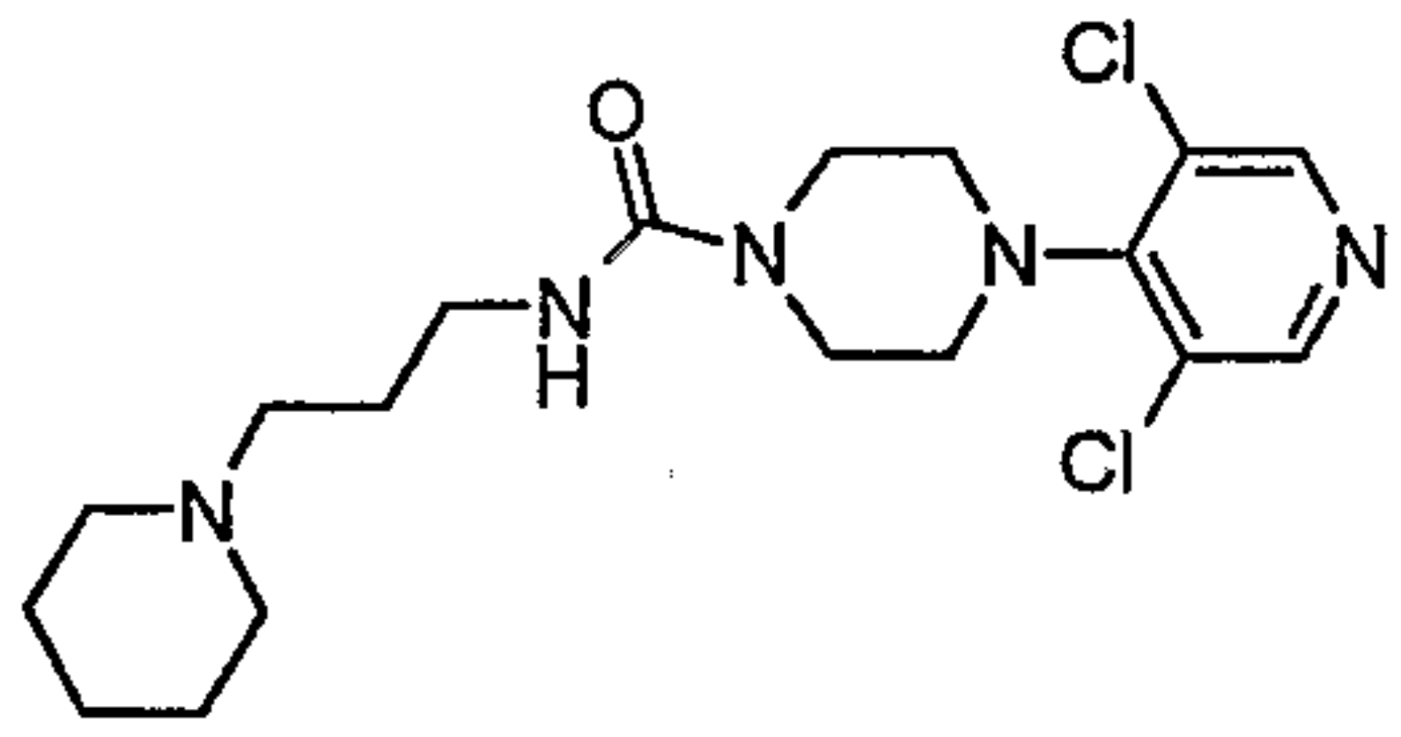
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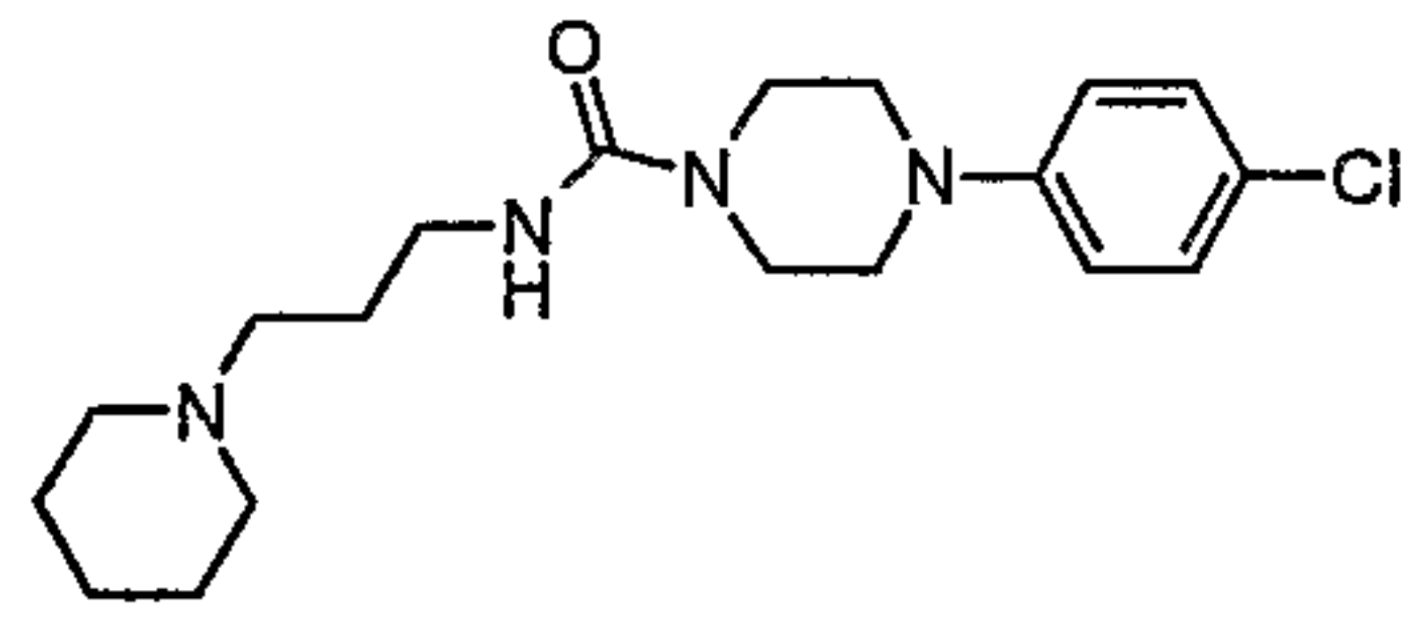
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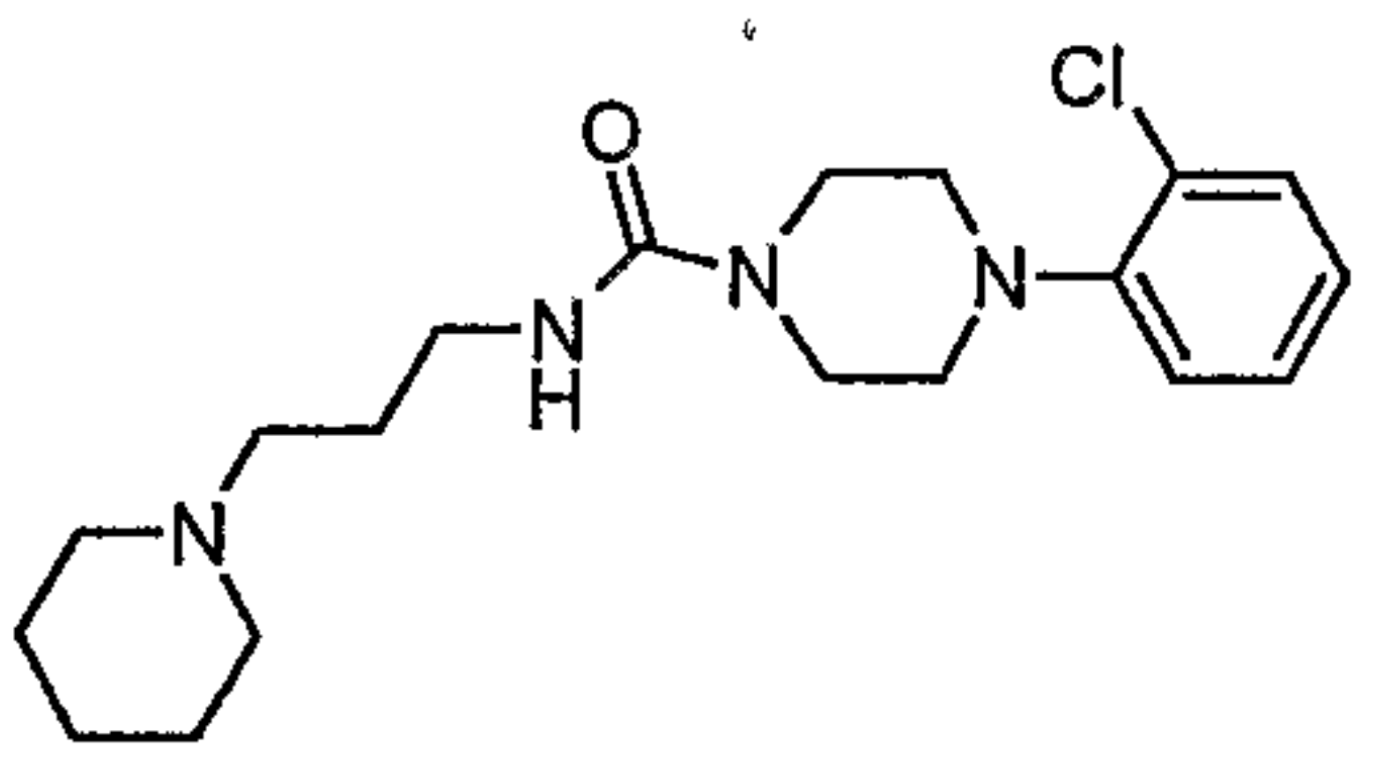

; and pharmaceutically acceptable salts thereof.

It will be understood that when compounds of the present invention contain one or more chiral centers, the compounds of the invention may exist in, and be isolated as, enantiomeric or diastereomeric forms, or as a racemic mixture. The present invention includes any possible enantiomers, diastereomers, racemates or mixtures thereof, of a compound of Formula I or II. The optically active forms of the compound of the invention may be prepared, for example, by chiral chromatographic separation of a racemate, by synthesis from optically active starting materials or by asymmetric synthesis based on the procedures described thereafter.

It will also be appreciated that certain compounds of the present invention may exist as geometrical isomers, for example E and Z isomers of alkenes. The present invention includes any geometrical isomer of a compound of Formula I or II. It will further be understood that the present invention encompasses tautomers of the compounds of the formula I, II or III.

It will also be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It will further be understood that the present invention encompasses all such solvated forms of the compounds of the formula I, II or III.

Within the scope of the invention are also salts of the compounds of the formula I, II or III. Generally, pharmaceutically acceptable salts of compounds of the present invention may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound, for example an alkyl amine with a suitable acid, for example, HCl or acetic acid, to afford a physiologically acceptable anion. It may also be possible to make a corresponding alkali metal (such as sodium, potassium, or lithium) or an alkaline earth metal (such as a calcium) salt by treating a compound of the present invention having a suitably acidic proton, such as a carboxylic acid or a phenol with one equivalent of an alkali metal or alkaline earth metal hydroxide or alkoxide (such as the ethoxide or methoxide), or a suitably basic organic amine (such as choline or meglumine) in an aqueous medium, followed by conventional purification techniques.

In one embodiment, the compound of formula I, II or III above may be converted to a pharmaceutically acceptable salt or solvate thereof, particularly, an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, methanesulphonate or *p*-toluenesulphonate.

The compounds of the present invention are useful in the treatment of a wide range of conditions and disorders in which an interaction with the histamine H3 receptor is beneficial. Thus, the compounds may find use e.g. in the treatment of diseases of the central nervous system, the peripheral nervous system, the cardiovascular system, the pulmonary system, the gastrointestinal system and the endocrinological system.

The compounds of the present invention are useful in therapy, espcially for the treatment of various depression conditions.

Compounds of the invention are useful as immunomodulators, especially for autoimmune diseases, such as arthritis, for skin grafts, organ transplants and similar surgical needs, for collagen diseases, various allergies, for use as anti-tumour agents and anti viral agents.

Compounds of the invention are useful for the treatment of obesity, epilepsy, Alzheimer's disease, dementia, schizophrenia, cognitive defect, rhinitis, cognition disorders, central nervous system disease, neurological disorder, epilepsy, attention deficit hyperactivity disorder, eating disorder, allergic rhinitis, allergy, inflammation, migraine, sleep disorder, narcolepsy, anxiety disorder, psychiatric conditions, depression, multiple sclerosis, anxiety, bipolar disorder, stroke, sleep disorder, mental disorder, cognitive disorder and non-insulin dependent diabetes.

Compounds of the invention are useful as an anti-depression agent. Combinations of agents with different properties may be used to achieve a balance of effects needed to treat depression.

Also within the scope of the invention is the use of any of the compounds according to the formula I, II or III above, for the manufacture of a medicament for the treatment of any of the conditions discussed above.

A further aspect of the invention is a method for the treatment of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the formula I, II or III above, is administered to a patient in need of such treatment.

Thus, the invention provides a compound of formula I, II or III, or pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of formula I, II or III, or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The term "therapeutic" and "therapeutically" should be contrued accordingly. The term "therapy" within the context of the present invention further encompasses to administer an effective amount of a compound of the present invention, to mitigate either a pre-existing disease state, acute or chronic, or a recurring condition. This definition also encompasses prophylactic therapies for prevention of recurring conditions and continued therapy for chronic disorders.

In use for therapy in a warm-blooded animal such as a human, the compound of the invention may be administered in the form of a conventional pharmaceutical composition by any route including orally, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracially, intravenously, epidurally, intrathecally, intracerebroventricularly and by injection into the joints.

In one embodiment of the invention, the route of administration may be orally, intravenously or intramuscularly.

The dosage will depend on the route of administration, the severity of the disease, age and weight of the patient and other factors normally considered by the attending physician, when determining the individual regimen and dosage level at the most appropriate for a particular patient.

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid and liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or table disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided compound of the invention, or the active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture in then poured into convenient sized moulds and allowed to cool and solidify.

Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

The term composition is also intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form compositions include solutions, suspensions, and emulsions. For example, sterile water or water propylene glycol solutions of the active compounds may be liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Depending on the mode of administration, the pharmaceutical composition will preferably include from 0.05% to 99%w (per cent by weight), more preferably from 0.10 to 50%w, of the compound of the invention, all percentages by weight being based on total composition.

A therapeutically effective amount for the practice of the present invention may be determined, by the use of known criteria including the age, weight and response of the individual patient, and interpreted within the context of the disease which is being treated or which is being prevented, by one of ordinary skills in the art.

Within the scope of the invention is the use of any compound of formula I, II or III as defined above for the manufacture of a medicament.

Also within the scope of the invention is the use of any compound of formula I, II or III for the manufacture of a medicament for the therapy of depression.

Additionally provided is the use of any compound according to Formula I or II for the manufacture of a medicament for the therapy of various depression conditions.

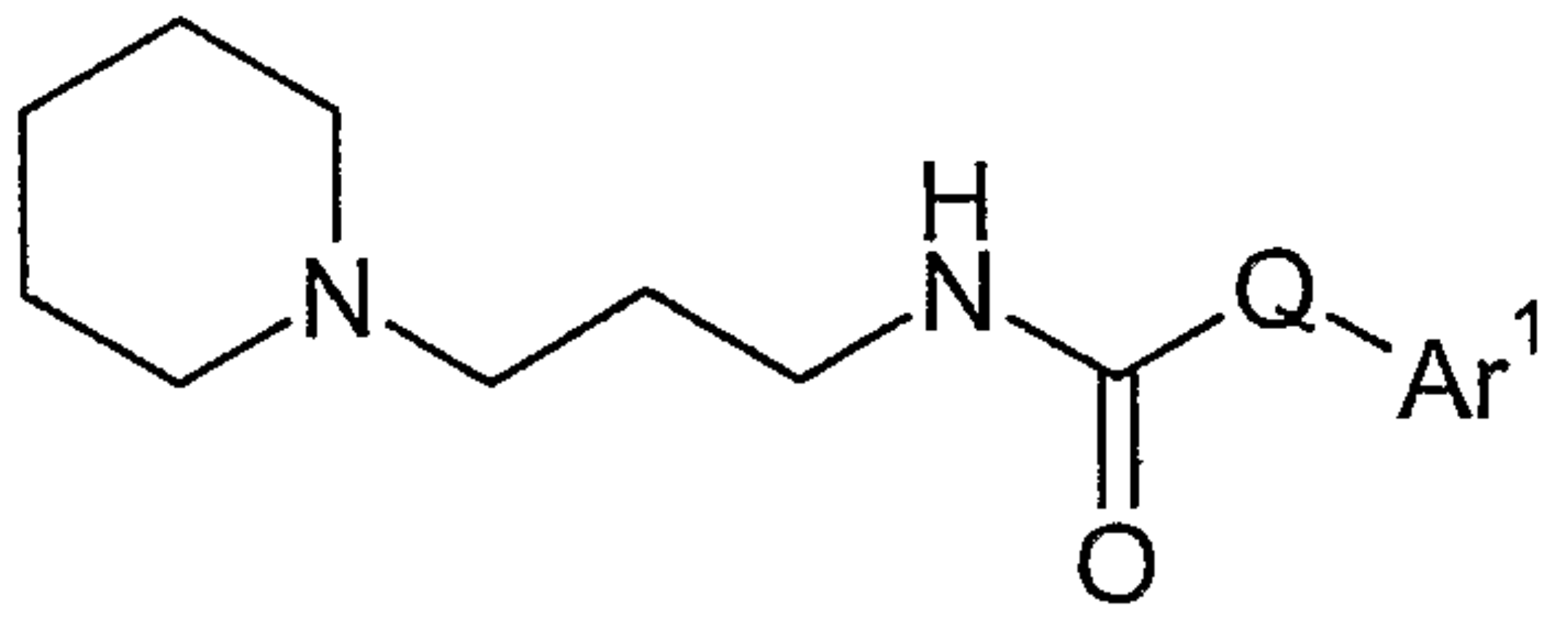
A further aspect of the invention is a method for therapy of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the formula I, II or III above, is administered to a patient in need of such therapy.

Additionally, there is provided a pharmaceutical composition comprising a compound of Formula I or II, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

Particularly, there is provided a pharmaceutical composition comprising a compound of Formula I or II, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier for therapy, more particularly for therapy of depression.

Further, there is provided a pharmaceutical composition comprising a compound of Formula I or II, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier use in any of the conditions discussed above.

In a further aspect, the invention provides a process for preparing a compound of formula I, comprising:



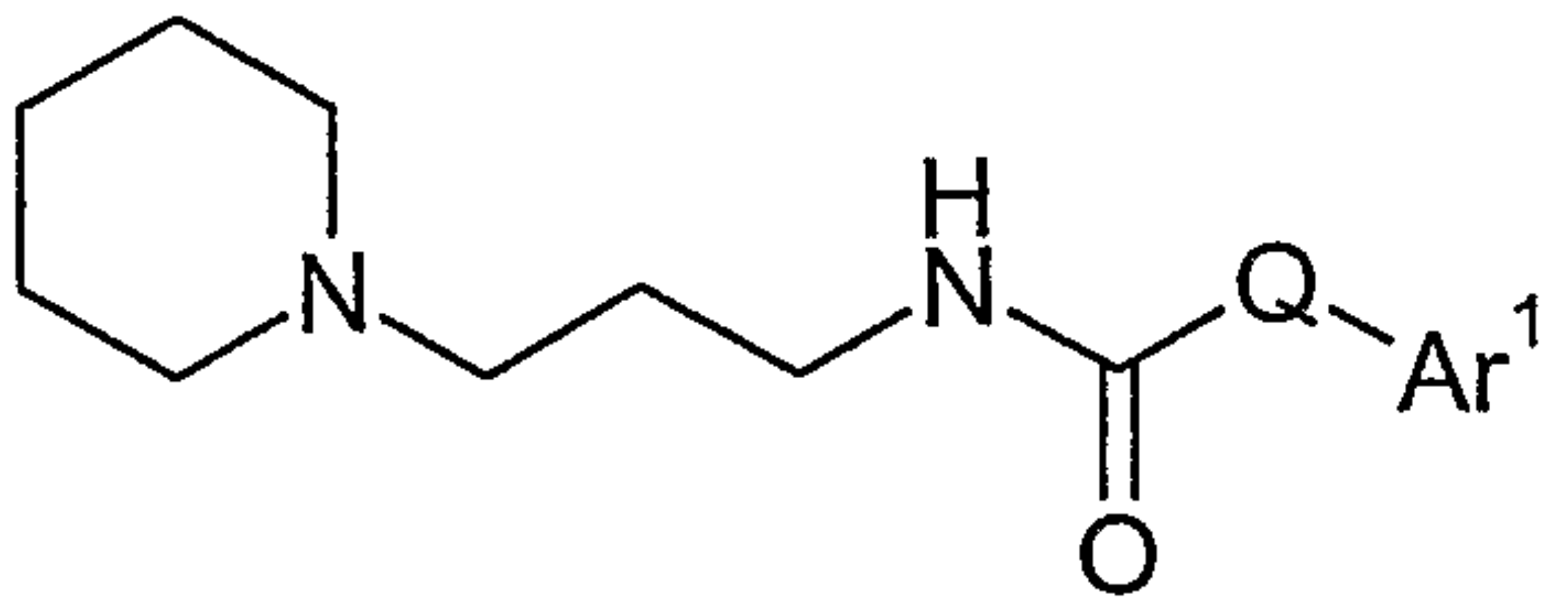
I

reacting Ar^1-Q-H with 3-(1-piperidino)propylamine and a haloformate,

Ar^1 is selected from C_{6-10}aryl and C_{2-9}heteroaryl, wherein said C_{6-10}aryl and C_{2-9}heteroaryl are optionally substituted with one or more groups selected from -R, $-NO_2$, -OR, -Cl, -Br, -I, -F, $-CF_3$, $-OCF_3$, -C(=O)R, -C(=O)OH, $-NH_2$, -SH, -NHR, $-NR_2$, -SR, $-SO_3H$, $-SO_2R$, $-SO_2NR$, -S(=O)R, -CN, -OH, -C(=O)OR, $-C(=O)NR_2$, -NRC(=O)R, and -NRC(=O)-OR, wherein R is, independently, a hydrogen, C_{3-6}cycloalkyl, C_{3-6}heterocyclyl, phenyl, benzyl, C_{1-6}alkyl or C_{2-6}alkenyl and wherein said R is further optionally substituted with one or more groups selected from methyl, methoxy, hydroxy and halogen;

Q is a divalent or trivalent group that connects the carbonyl with Ar^1, wherein said divalent or trivalent group contains at least one nitrogen, wherein said nitrogen of Q is connected to the H in Ar^1-Q-H to form an amino, and said trivalent group is fused with Ar^1; and said Q-H of Ar^1-Q-H forms an amino group.

In one embodiment, the process of preparing a compound of formula I comprising:



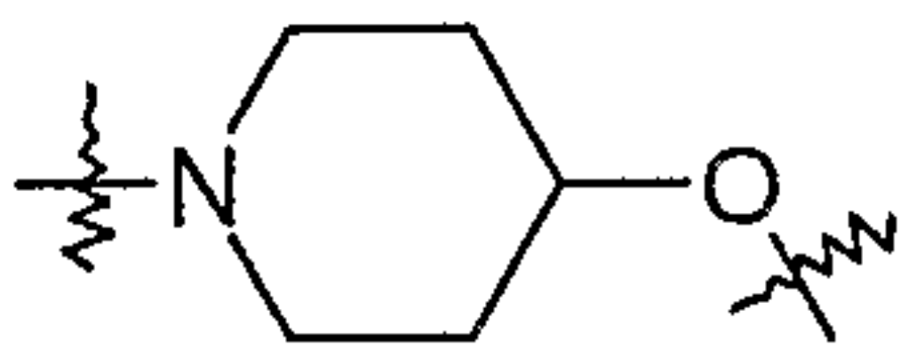
I

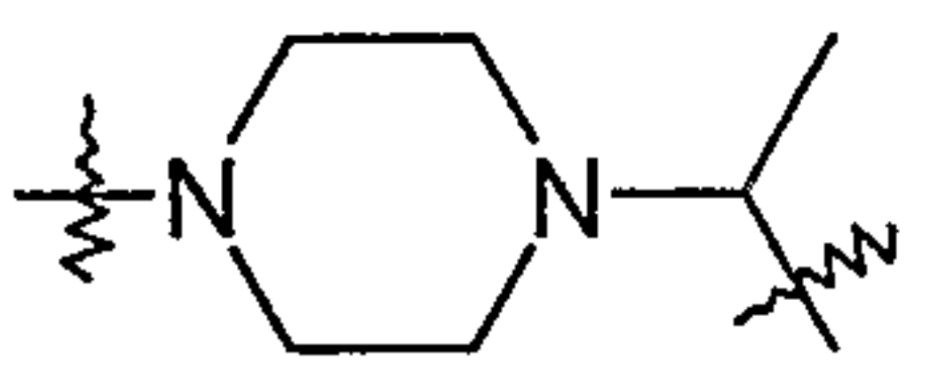
combining Ar^1-Q-H with 3-(1-piperidino)propylamine and a haloformate,

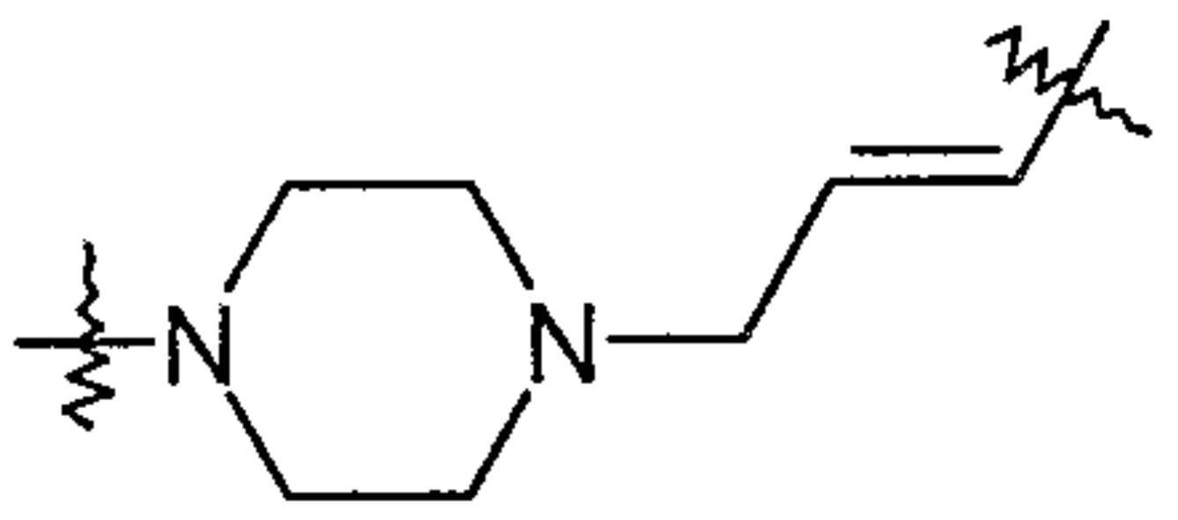
wherein Ar^1 is selected from phenyl, 2-pyridyl, 4-pyridyl; 1-naphthyl, 2-naphthyl, 1,2,3,4-tetrahydro-naphth-1-yl; 1,2,3,4-tetrahydro-naphth-5-yl; 2-thienyl, 3-thienyl, 2-furyl, 2-thiazolyl, benzo[1,3]dioxol-5-yl, 4,5,6,7-tetrahydro-thieno[2,3-c]pyridin-2-yl; 2,3-dihydro-benzo[1,4]dioxin-6-yl; 2,3-dihydro-benzo[1,4]dioxin-2-yl; quinol-2-yl, isoquinol-5-yl; 1H-indol-4-yl, 1H-indol-3-yl, 1H-indol-2-yl, 1H-indol-7-yl, 1-pyrroyl, 1H-benzotriazol-5-yl, 1H-benzoimidazol-5-yl, 2,3-dihydro-benzofuran-5-yl, 2,3-dihydro-isoindol-1-on-2-yl; benzo[1,2,3]thiadiazol-5-yl, benzo[1,2,3]thiadiazol-6-yl, benzothiazol-6-yl, benzothiazol-2-

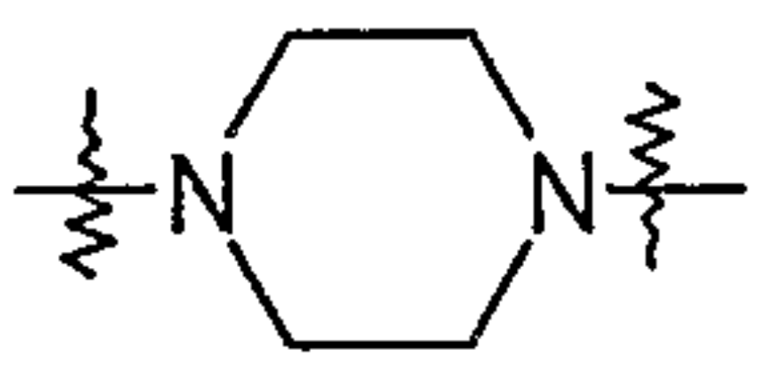
yl, and 4H-benzo[1,4]oxazin-3-on-7-yl, wherein Ar^1 is further optionally substituted with one or more groups selected from C_{1-4}alkyl, C_{2-4}alkenyl, C_{1-4}alkoxy, C_{1-4}alkenyloxy, phenoxy, 4-methoxyphenoxy, benzyl, acetoamino, methylsulfonyl, methoxycarbonyl, nitro, chloro, fluoro, bromo, iodo, 1-pyrroyl, 2-methyl-pyrro-1-yl, amino, phenylsulfonyl, aceto,1-piperidinyl, [1,2,3]thiadiazol-4-yl, 4-morpholinyl, methoxy, ethoxy, isopropyloxy, methythio, cyano, dimethylamino, hydroxy, methylaminosulfonyl, trifluoromethyl, trifluoromethoxy, phenyl, phenoxy, benzyl, 4-hydroxyl-phenyl, diethylamino, methylsulfonyl, aminosulfonyl, cyclohexyl, 1-pyrrolyl, 1H-pyrazol-3-yl, 5-tetrazolyl, 1-piperidinyl, 1-pyrazolyl, methylsulfonylmethyl, 3,5-dimethyl-pyrazolyl, pyrrolidin-2-on-1-yl; and

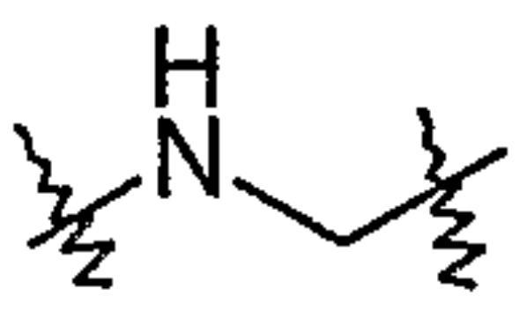
Q is selected from

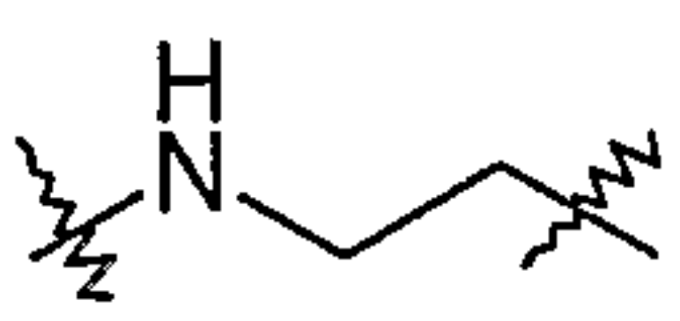


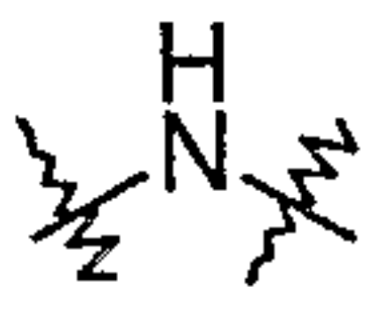


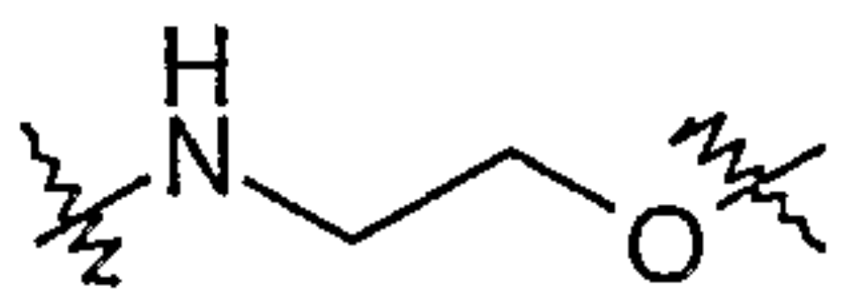


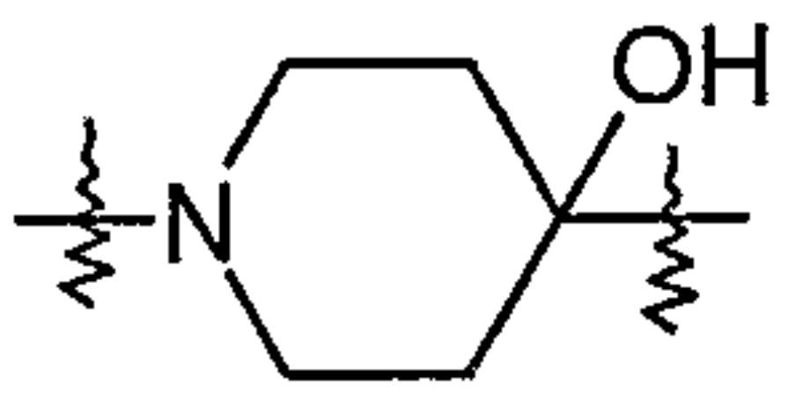


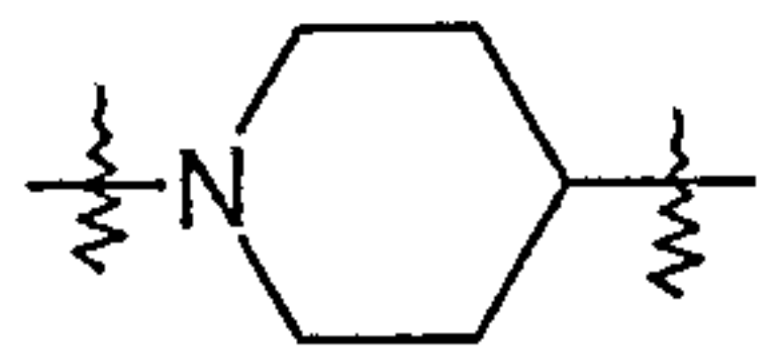


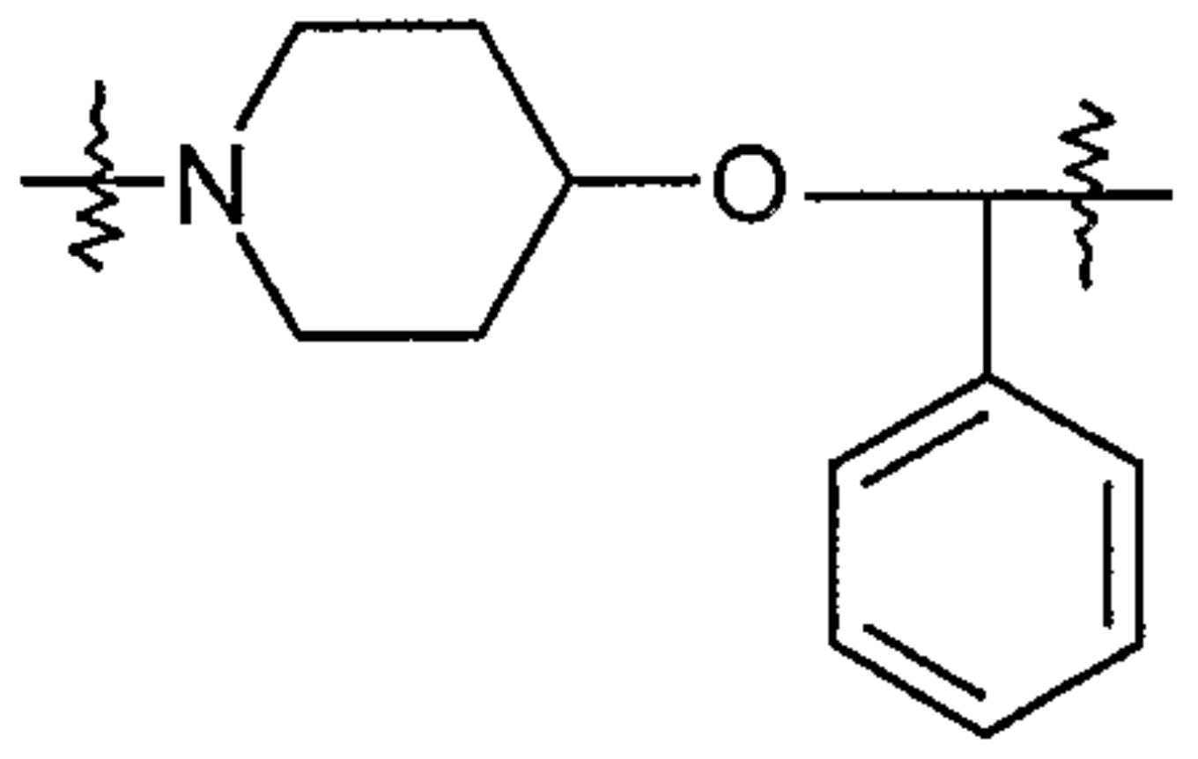


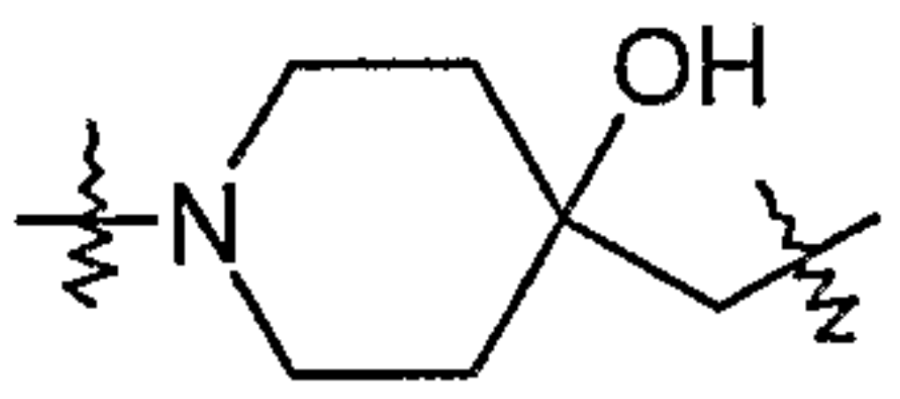


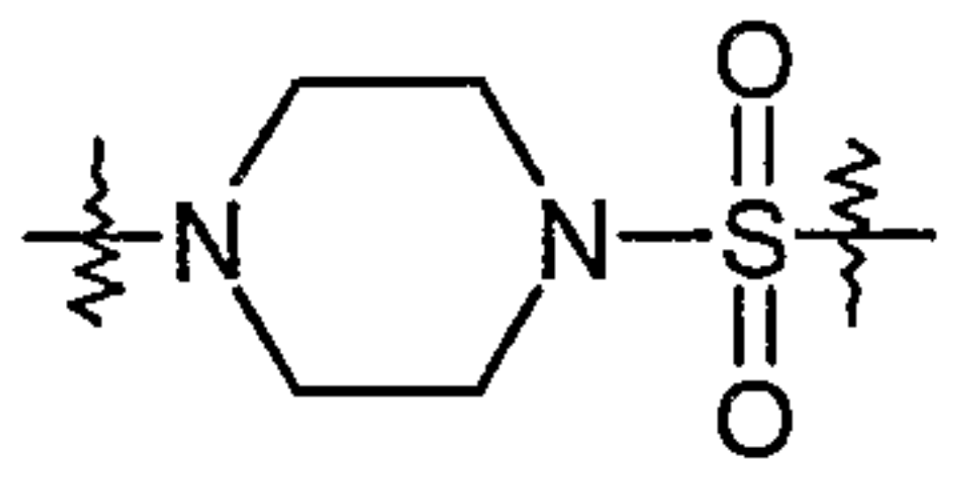


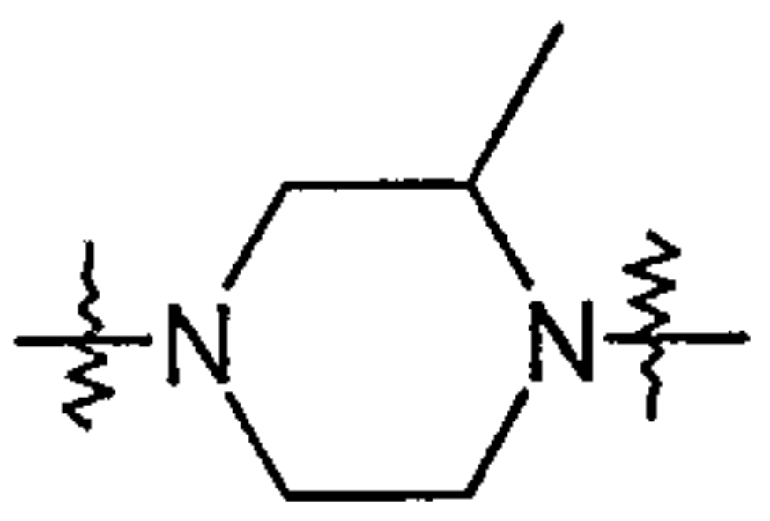


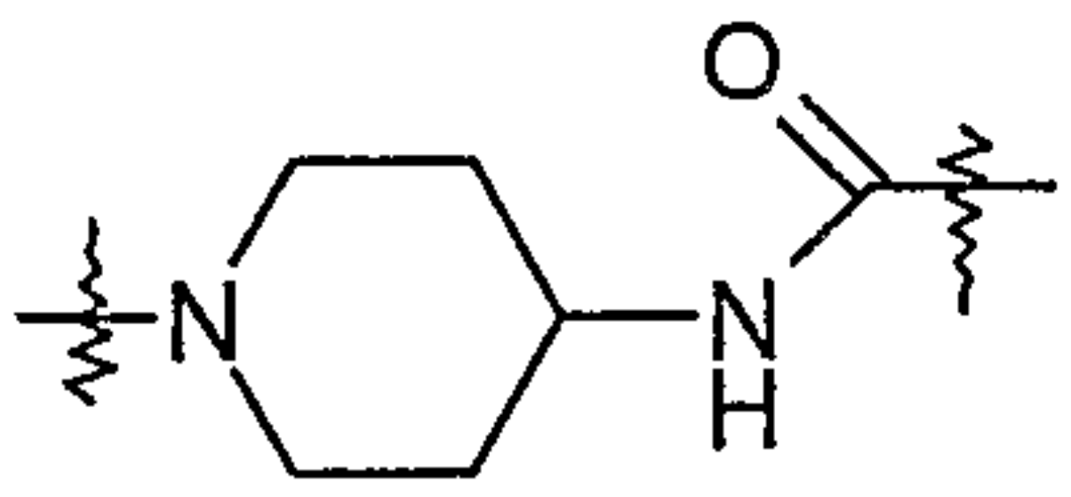


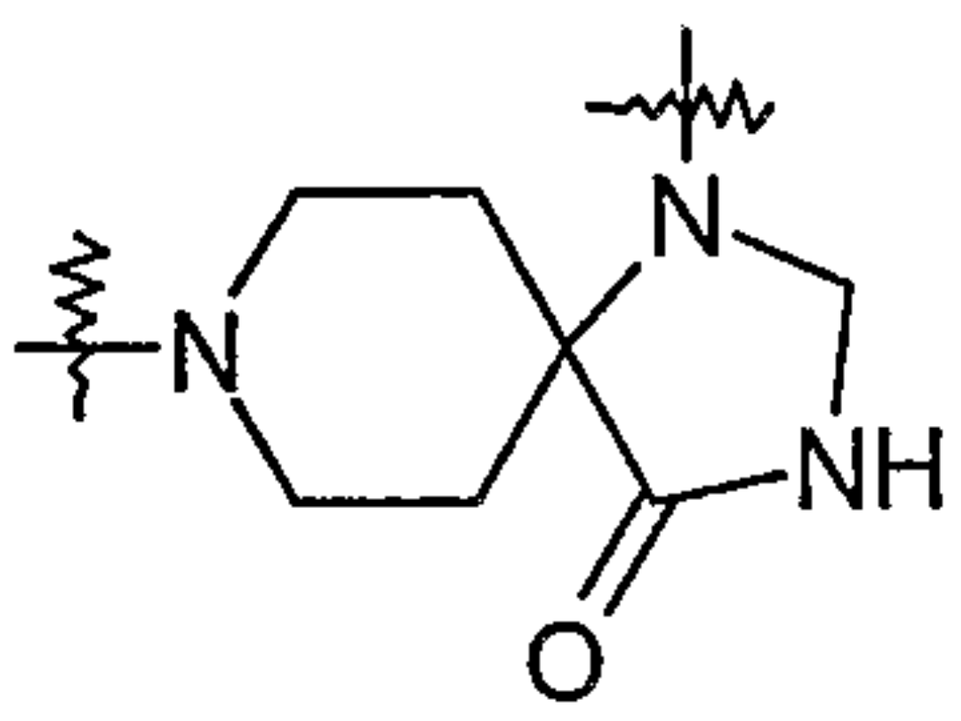


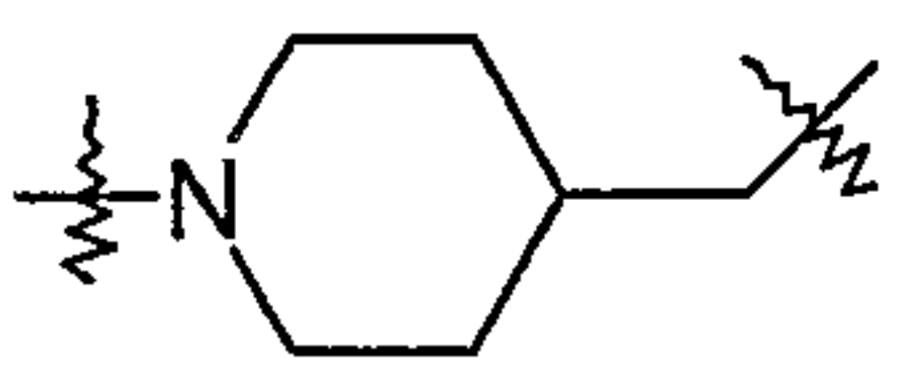


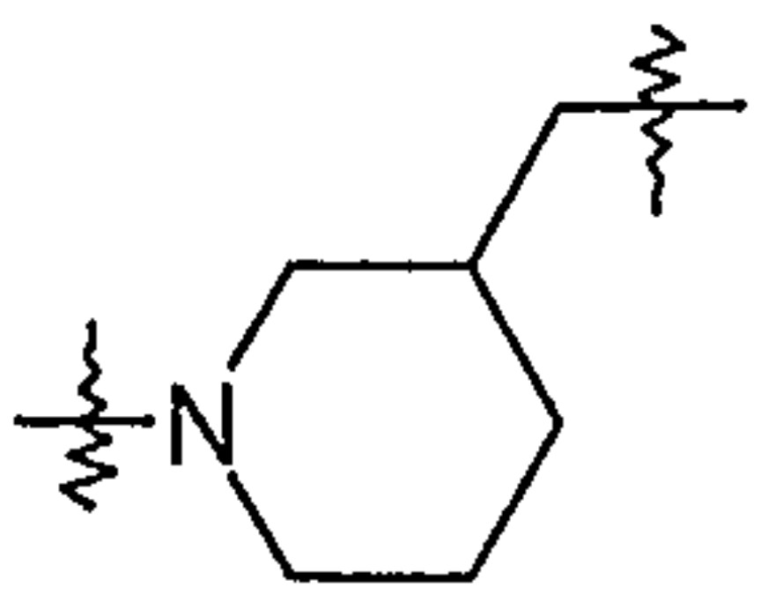


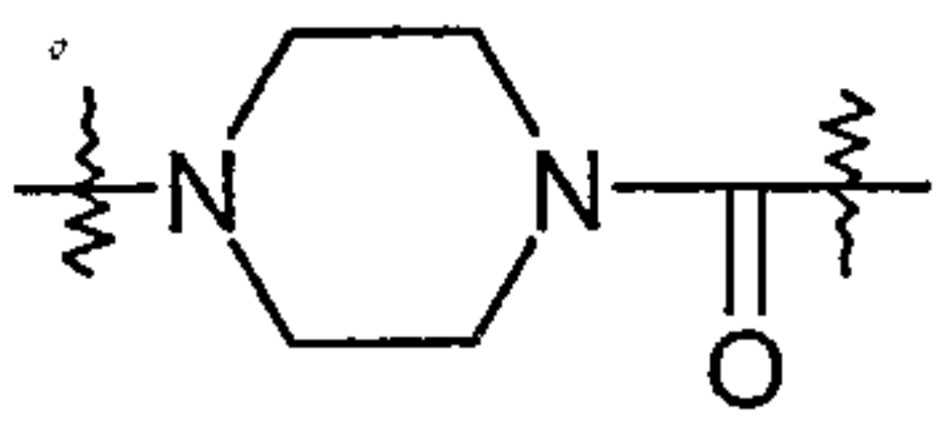












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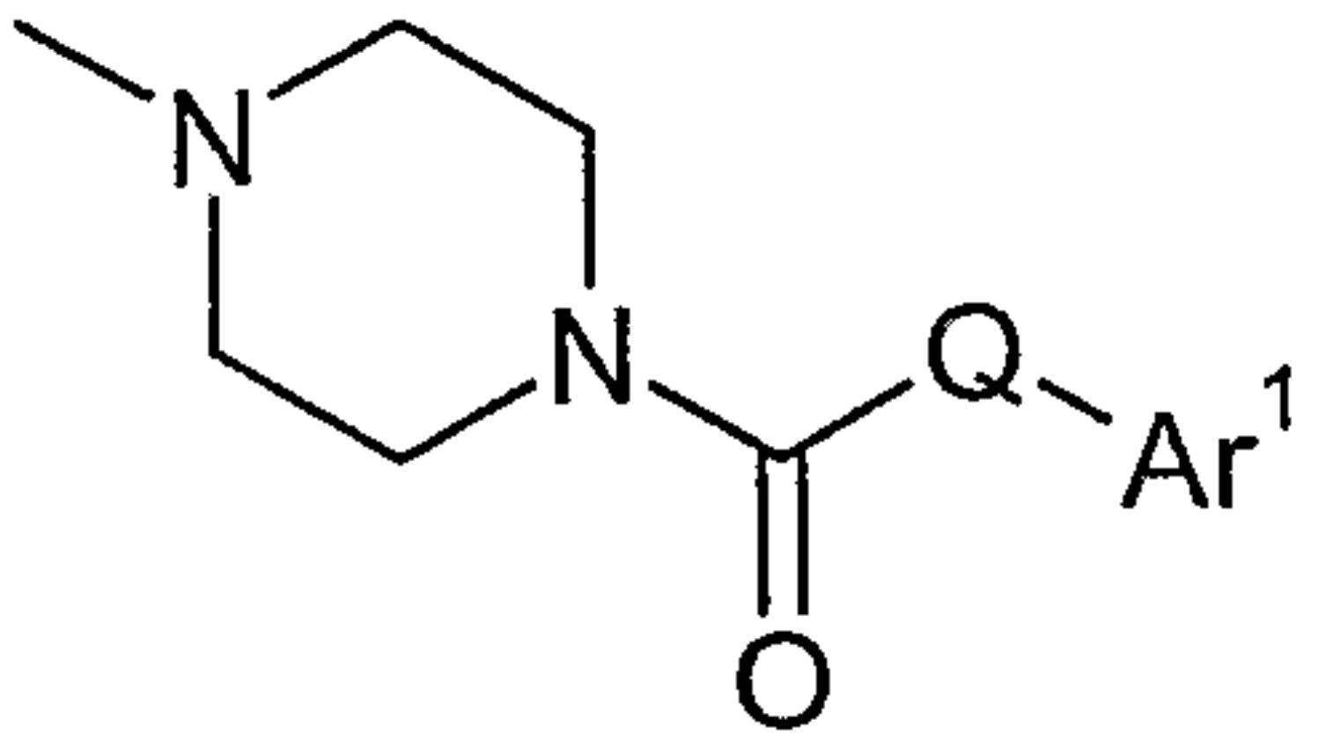
and wherein the left side nitrogen atom in the above-identified structures of Q is connected to the H in Ar^1-Q-H to form an amino group.

In a particular embodiment, the step of combining Ar^1-Q-H with 3-(1-piperidino)propylamine and a haloformate may be carried out at ambient temperature and in the presence of organic base such as diisopropylethylamine. The haloformate may be 4-nitrophenyl chloroformate.

In a further aspect, the invention provides a process for preparing a compound of formula II, comprising:



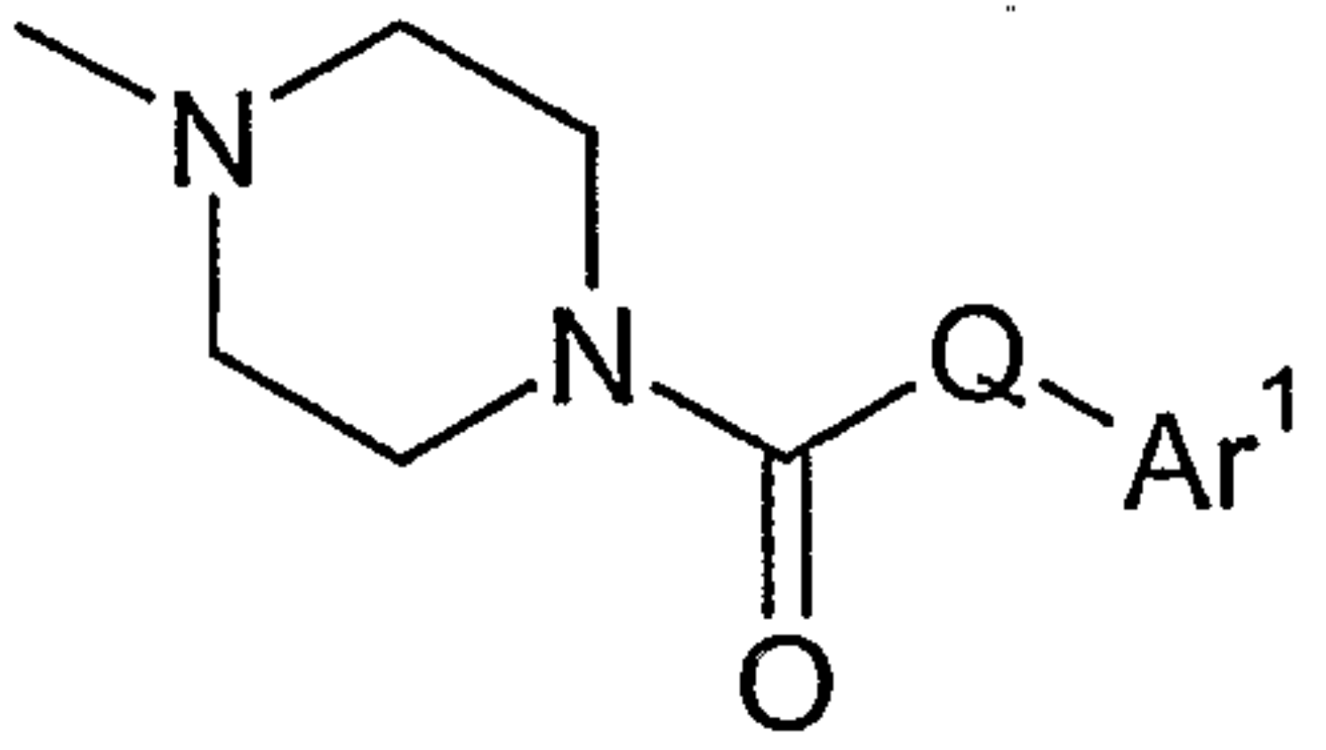
II

reacting Ar^1-Q-H with N-methyl piperazine and a haloformate,

Ar^1 is selected from C_{6-10}aryl and C_{2-9}heteroaryl, wherein said C_{6-10}aryl and C_{2-9}heteroaryl are optionally substituted with one or more groups selected from -R, $-NO_2$, -OR, -Cl, -Br, -I, -F, $-CF_3$, $-OCF_3$, -C(=O)R, -C(=O)OH, $-NH_2$, -SH, -NHR, $-NR_2$, -SR, $-SO_3H$, $-SO_2R$, $-SO_2NR$, -S(=O)R, -CN, -OH, -C(=O)OR, $-C(=O)NR_2$, -NRC(=O)R, and -NRC(=O)-OR, wherein R is, independently, a hydrogen, C_{3-6}cycloalkyl, C_{3-6}heterocyclyl, phenyl, benzyl, C_{1-6}alkyl or C_{2-6}alkenyl and wherein said R is further optionally substituted with one or more groups selected from methyl, methoxy, hydroxy and halogen;

Q is a divalent or trivalent group that connects the carbonyl with Ar^1, wherein said divalent or trivalent group contains at least one nitrogen, wherein said nitrogen of Q is connected to the H in Ar^1-Q-H to form an amino, and said trivalent group is fused with Ar^1; and said Q-H of Ar^1-Q-H forms an amino group.

In one embodiment, the process of preparing a compound of formula II comprising:

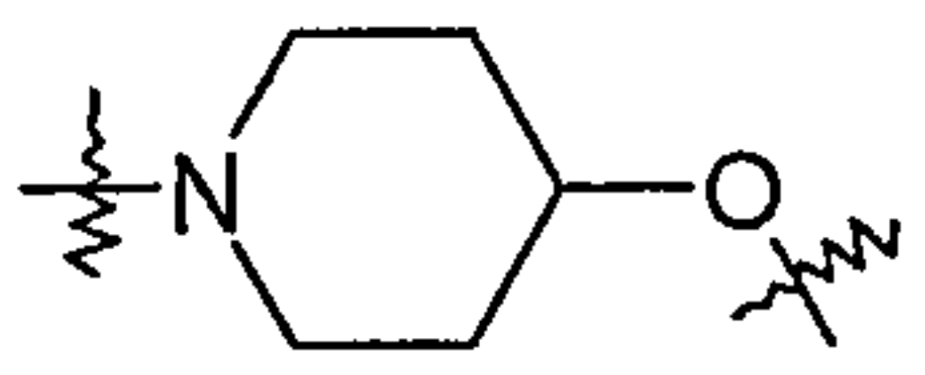
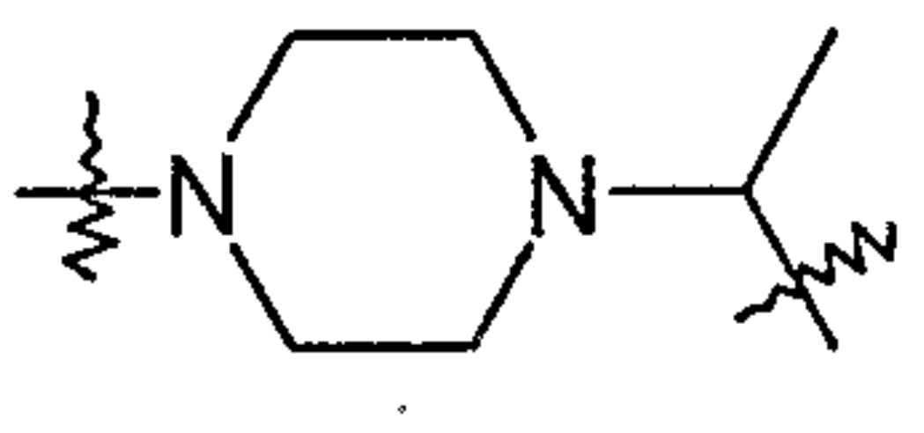
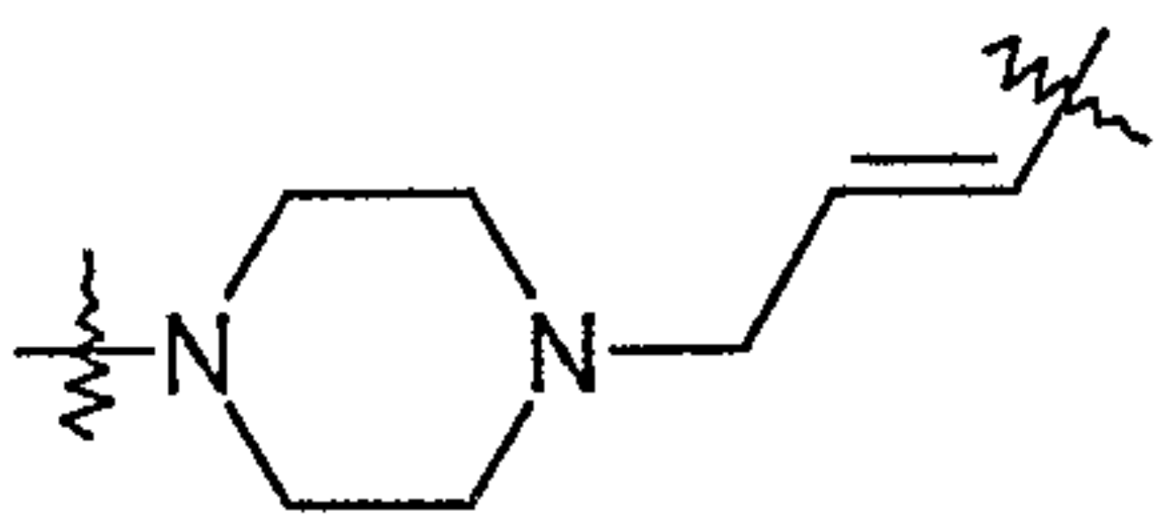


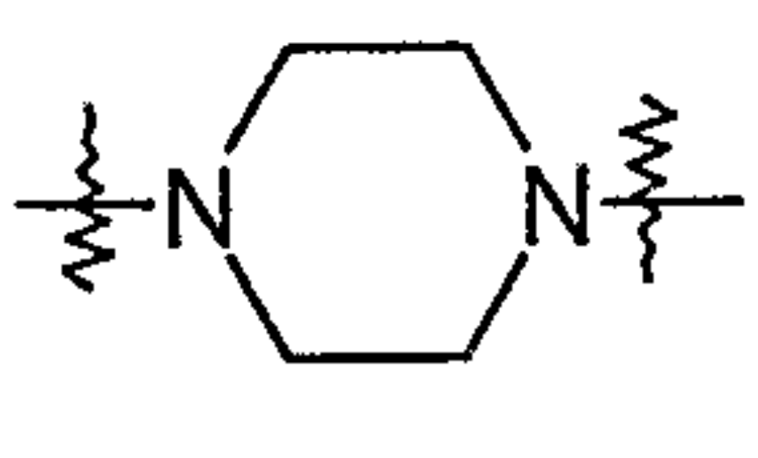
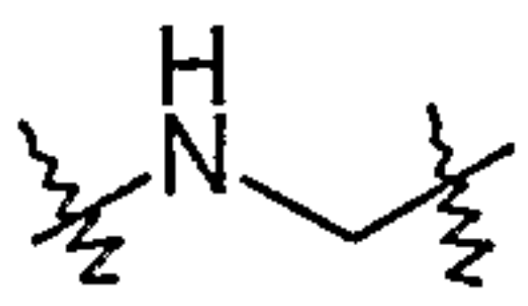
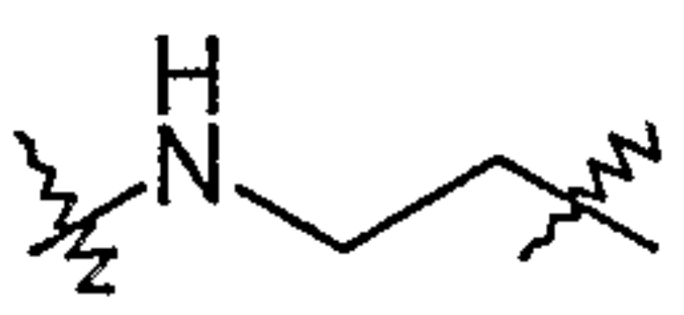
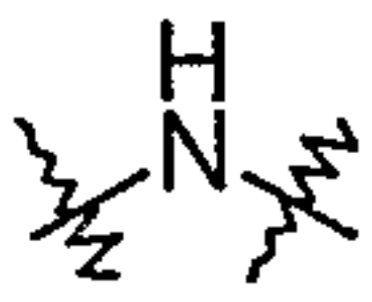
II

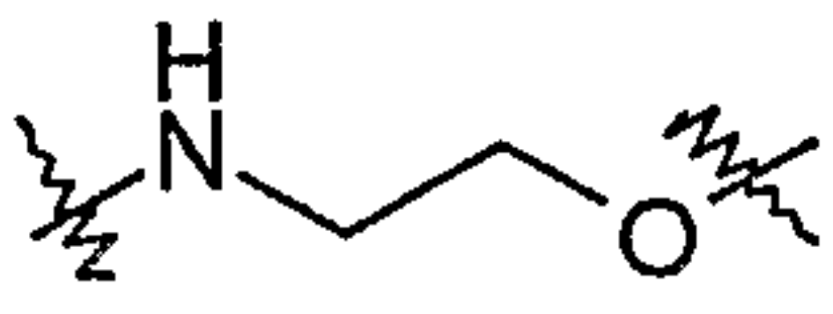
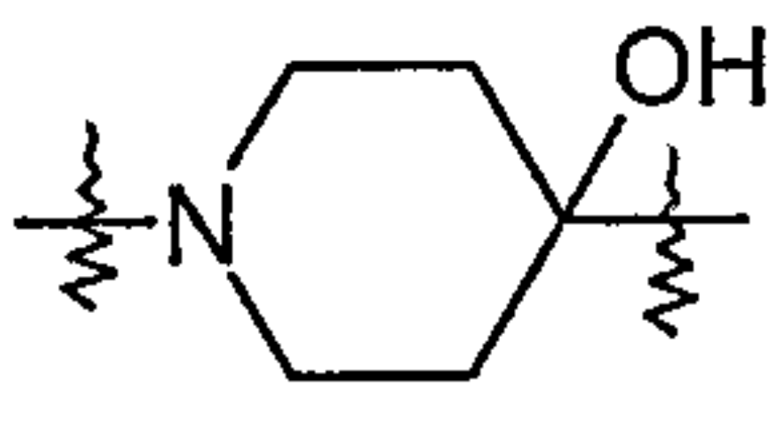
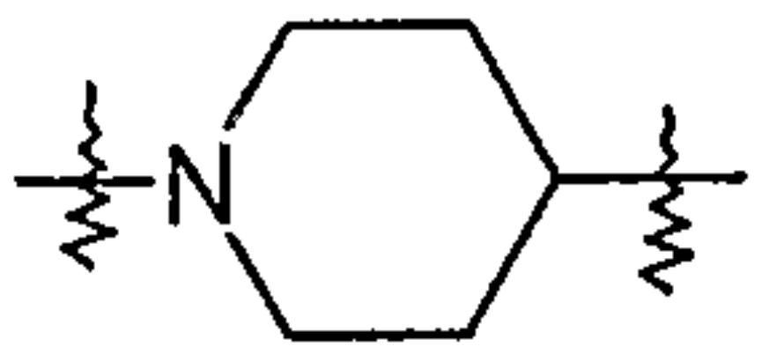
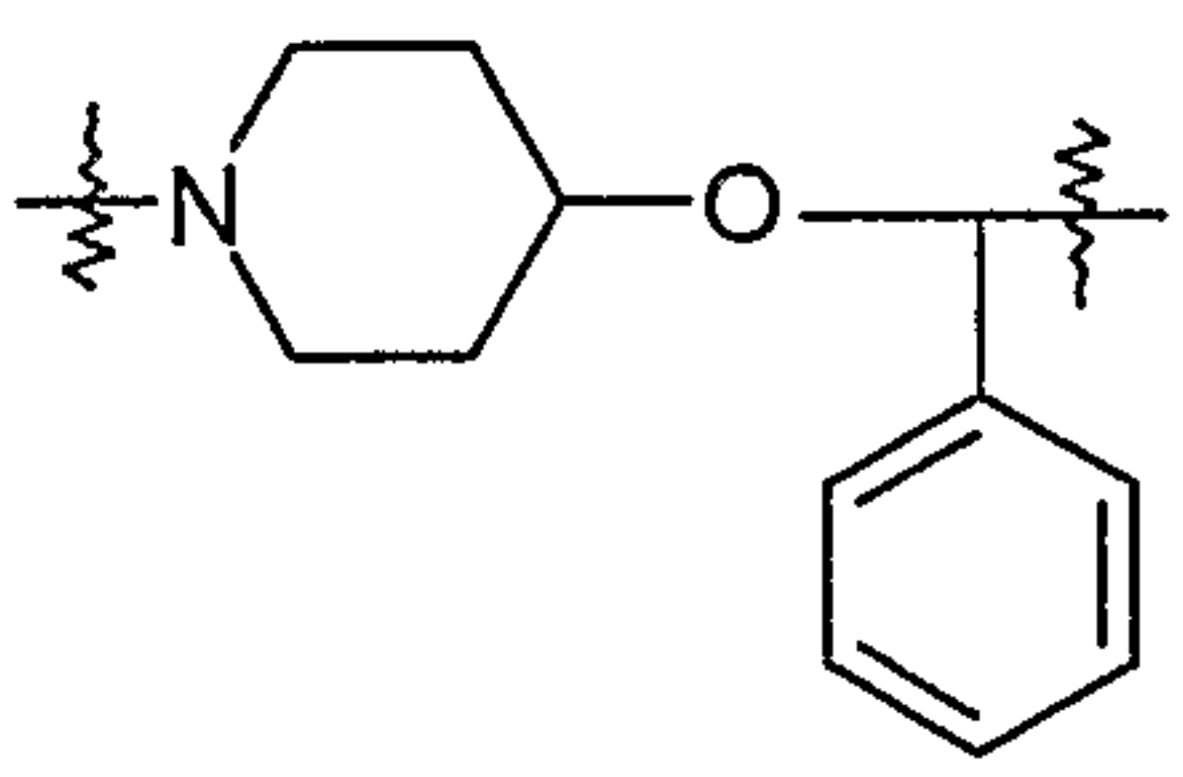
combining Ar^1-Q-H with N-methyl piperazine and a haloformate,

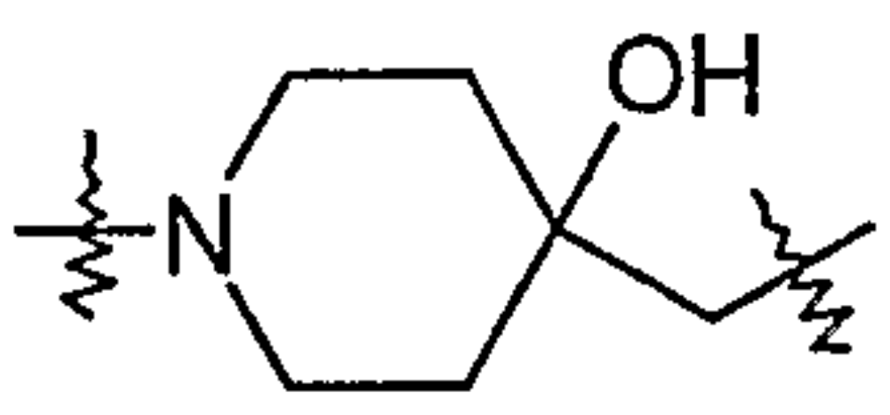
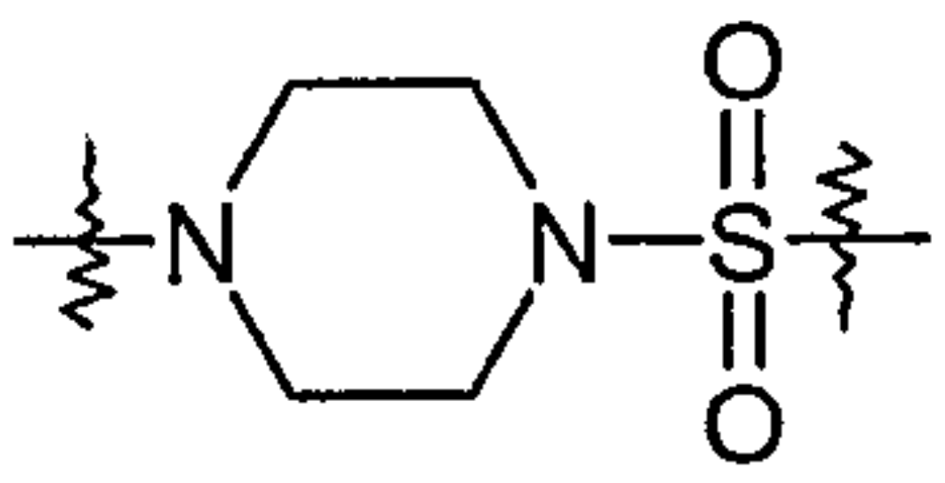
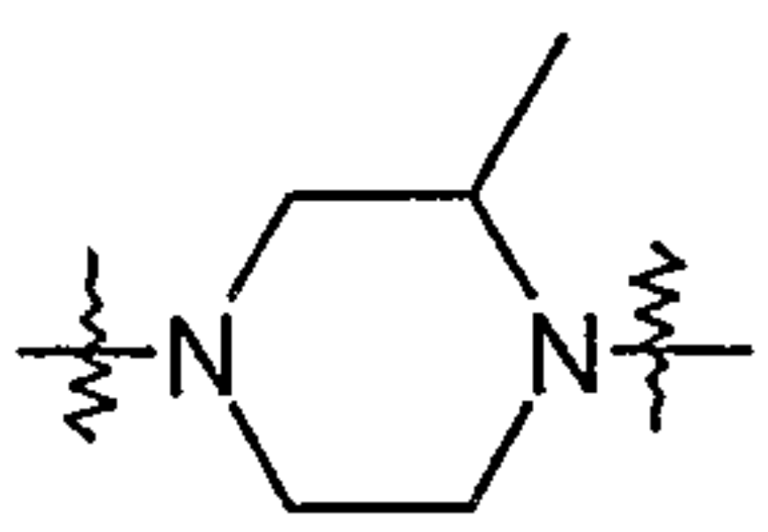
wherein Ar^1 is selected from phenyl, 2-pyridyl, 4-pyridyl; 1-naphthyl, 2-naphthyl, 1,2,3,4-tetrahydro-naphth-1-yl; 1,2,3,4-tetrahydro-naphth-5-yl; 2-thienyl, 3-thienyl, 2-furyl, 2-thiazolyl, benzo[1,3]dioxol-5-yl, 4,5,6,7-tetrahydro-thieno[2,3-c]pyridin-2-yl; 2,3-dihydro-benzo[1,4]dioxin-6-yl; 2,3-dihydro-benzo[1,4]dioxin-2-yl; quinol-2-yl, isoquinol-5-yl; 1H-indol-4-yl, 1H-indol-3-yl, 1H-indol-2-yl, 1H-indol-7-yl, 1-pyrroyl, 1H-benzotriazol-5-yl, 1H-benzoimidazol-5-yl, 2,3-dihydro-benzofuran-5-yl, 2,3-dihydro-isoindol-1-on-2-yl; benzo[1,2,3]thiadiazol-5-yl, benzo[1,2,3]thiadiazol-6-yl, benzothiazol-6-yl, benzothiazol-2-yl, and 4H-benzo[1,4]oxazin-3-on-7-yl, wherein Ar^1 is further optionally substituted with one or more groups selected from C_{1-4}alkyl, C_{2-4}alkenyl, C_{1-4}alkoxy, C_{1-4}alkenyloxy, phenoxy, 4-methoxyphenoxy, benzyl, acetoamino, methylsulfonyl, methoxycarbonyl, nitro, chloro, fluoro, bromo, iodo, 1-pyrroyl, 2-methyl-pyrro-1-yl, amino, phenylsulfonyl, aceto,1-piperidinyl, [1,2,3]thiadiazol-4-yl, 4-morpholinyl, methoxy, ethoxy, isopropyloxy, methythio, cyano, dimethylamino, hydroxy, methylaminosulfonyl, trifluoromethyl, trifluoromethoxy, phenyl, phenoxy, benzyl, 4-hydroxyl-phenyl, diethylamino, methylsulfonyl, aminosulfonyl, cyclohexyl, 1-pyrrolyl, 1H-pyrazol-3-yl, 5-tetrazolyl, 1-piperidinyl, 1-pyrazolyl, methylsulfonylmethyl, 3,5-dimethyl-pyrazolyl, pyrrolidin-2-on-1-yl; and

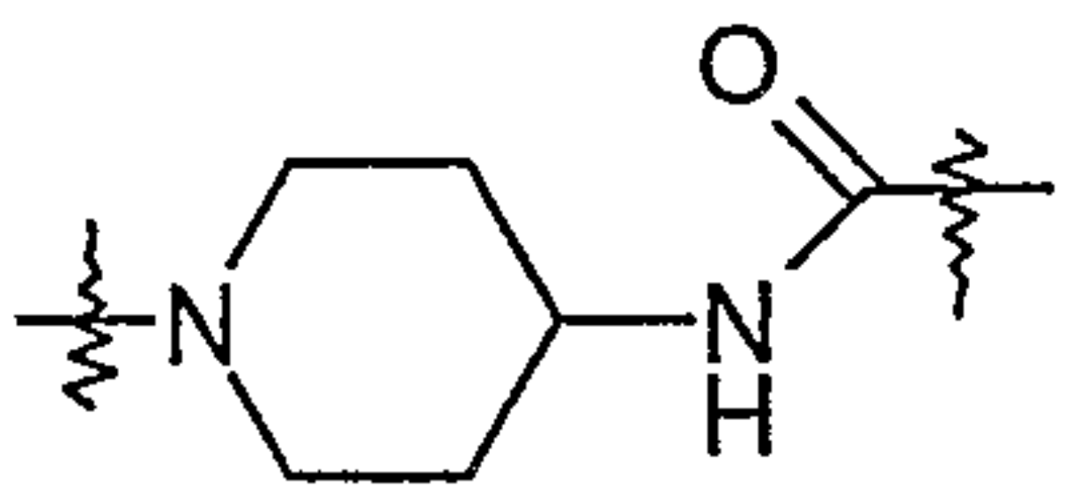
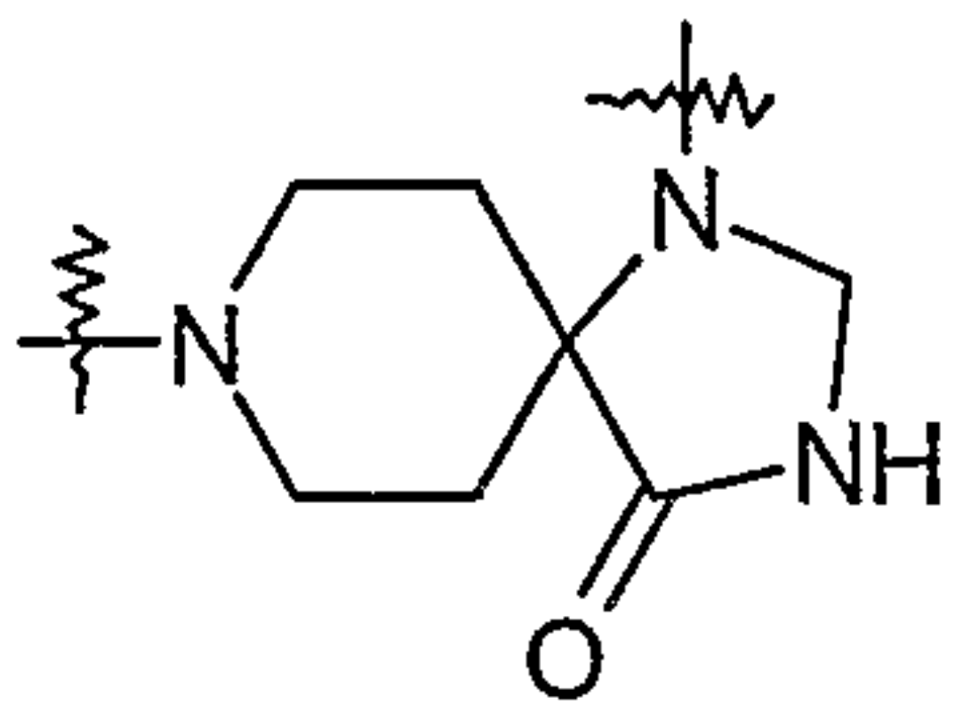
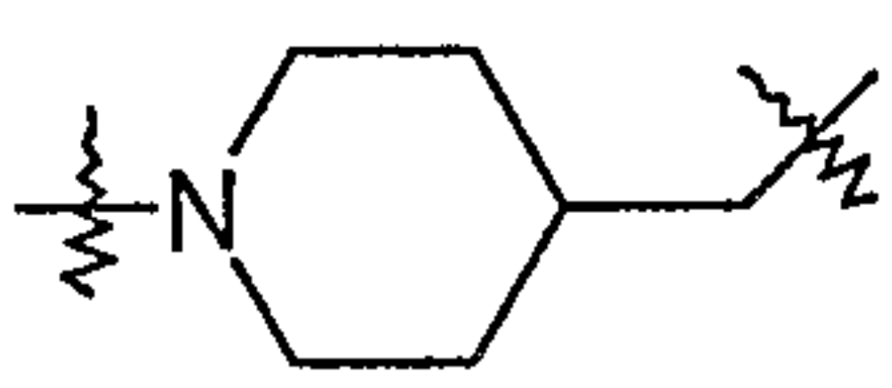
Q is selected from

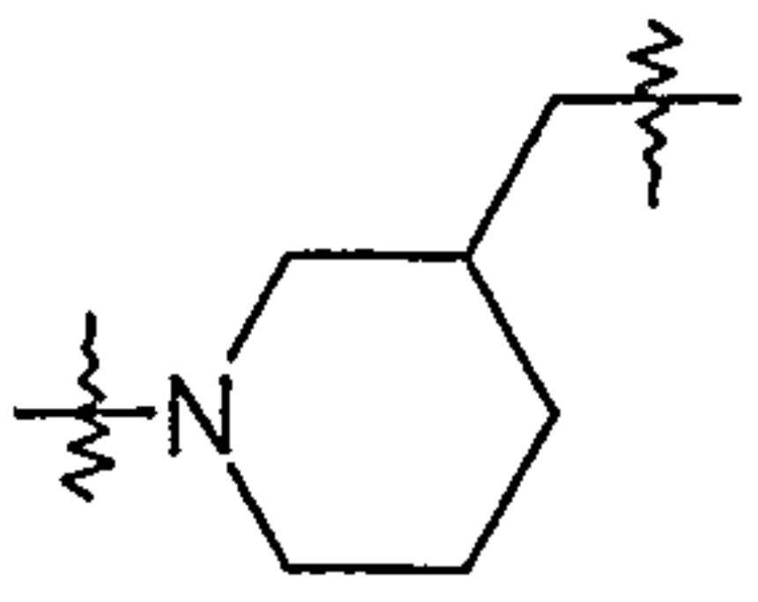
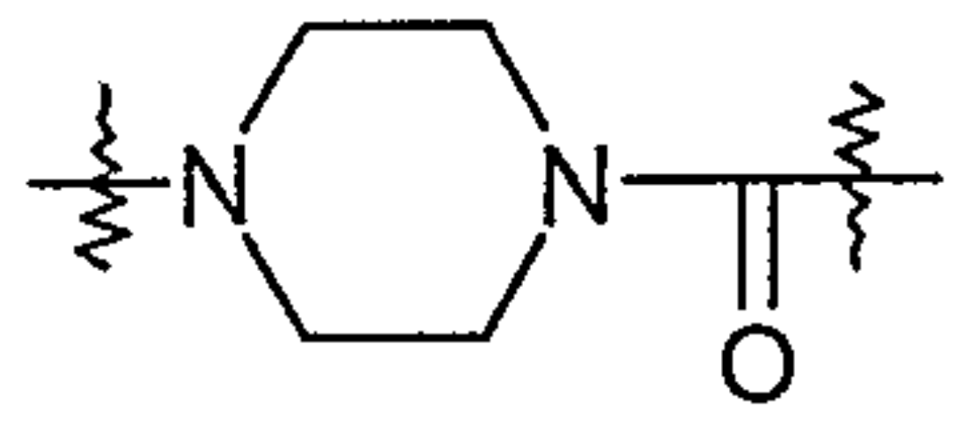




,

and wherein the left side nitrogen atom in the above-identified structures of Q is connected to the H in Ar^1-Q-H to form an amino group.

In a particular embodiment, the step of combining Ar^1-Q-H with 3-(1-piperidino)propylamine and a haloformate may be carried out at ambient temperature and in the presence of organic base such as diisopropylethylamine. The haloformate may be 4-nitrophenyl chloroformate.

BIOLOGICAL EVALUATION

The compounds of the invention are found to be active towards H3 receptors in warm-blooded animal, e.g., human. Particularly the compounds of the invention are found to be effective H3 receptor ligands. *In vitro* assays, *infra*, demonstrate these surprising activities. These activities may be related to in vivo activity and may not be linearly correlated with binding affinity. In these *in vitro* assays, a compound is tested for their activity toward H3 receptors and pIC_{50} is obtained to determine the activity for a particular compound towards H3 receptors.

FLIPR Assay Identification of Antagonists of the Human H3 receptor

Cell culture:

H3 receptor activation in response to histamine mediates intracellular Ca^{2+} mobilization in human H3 receptor transfected CHO-K1 cells. This increase in Ca^{2+} can be measured using the fluorometric imaging plate reader (FLIPR) employing Fluo-3AM loaded H3 receptor transfected cells. CHO-H3-Gα16 transfected cells were cultured in T225 cm^2 tissue culture flasks as monolayers in NUT Hams (with 1% (v/v) Glutamine) supplemented with 10% (v/v) heat inactivated fetal bovine serum and grown under 1 mg/ml. Geneticin antibiotic selection and 1 mg/ml Zeocin selection. Cultures were maintained at 37 °C in a humidified atmosphere of 5% CO_2 and passaged every 3 days.

Assay Buffer:

To 1000 mL of Hanks Balanced Salt solution, add 4.8g of HEPES and 0.714g probenecid (which is dissolved in 5 mL 1 M NaOH and added to the solution). This buffer is pH adjusted to 7.4 with NaOH. Assay Buffer contains 10% DMSO (v/v) was prepared for the compound preparation plates. Usually 200ml (containing 20ml neat DMSO) will be sufficient for 12 x 384 plates.

Loading Buffer:

To 120 mL Assay Buffer 100 mg BSA and 1 vial MDC FLIPR Calcium assay reagent (dissolved in assay buffer) was added immediately prior to loading cells:

Compound Vehicle Control Buffer:

400 µL DMSO was added to 20 mL Assay Buffer to produce 2% (v/v) solution (0.4% (v/v) final)

FLIPR assay

Histamine EC50 determination: Cells were harvested using 1x dissociation solution and plated onto poly-D-lysine coated FLIPR plates at 1.0x10^4 cells per well 18-24 hours prior to experiment. Media was removed from the cells by tipping and the plates gently blotted onto tissue to remove any excess medium. 30 µL loading buffer was added to all wells for 90 min at 37 °C.

96 well histamine EC50 plate was made and then 40 µL was indexed into 4 quadrants in a 384 well plate. 96 well compound vehicle plates were made and indexed into a quadrant of a 384 well plate. Plates were transferred to FLIPR and run using a standard protocol. The results were used to calculate an EC50 for histamine.

Compound testing: Cells were harvested using 1x dissociation solution and plated onto poly-D-lysine coated FLIPR plates at 1.0x10^4 cells per well 18-24 hours prior to experiment. Media was removed from the cells by tipping and the plates gently blotted onto tissue to remove any excess medium. 30 µL loading buffer was added to all wells for 90 min at 37 °C. 96 well histamine plate (x 10 EC50) was made and then 60 µL was indexed into 4 quadrants in a 384 well plate. Each 96 well compound plate was made and indexed into a quadrant of a 384 well plate. An ATP plate was made in a 96 well plate and then 60 µL was indexed into 4 quadrants in a 384 well plate. Plates transferred to FLIPR and run using a standard protocol. 30 µL of cells in loading buffer were placed in the wells of FLIPR 384 plate, 10 µL compound solution was added, values were read for 5min to determine compound effects, 10 µL agonist solution was added, values were read to determine agonist response, 10 µL ATP added to and values were read for 5min to determine ATP response.

Final assay concentrations: Compound concentration range = 10 µM to 0.1 µM; Vehicle 0.4% DMSO; histamine= 2x calculated EC50; ATP = 11µM

Assay for inhibitors of [^{3}H]-Histamine Binding to Human Recombinant H4 Receptor.

pIC_{50} values were determined for compounds of the invention with a binding assay that allows the identification of inhibitors of [^{3}H]-histamine by binding to membranes from CHO cells that over-express human recombinant H4 receptors. Cells suitable for performing this assay are commercially available, for example from Euroscreen as catalogue number 1220; [^{3}H]-histamine suitable for performing this assay is commercially available, for example from Amersham as catalogue number TRK 631.

Compounds were dissolved in 500 µl of DMSO and diluted in DMSO to yield a 1 mM stock based on the formula weight of the compound. Stock solutions were diluted serially in DMSO in half log steps to give compound concentrations of 1000, 300, 100, 30 and 10 µM. Typically 5 point duplicate curves were determined. For 10 point curves single concentrations were typically 1000, 300, 100, 30, 10, 3, 1, 0.3, 0.1 and 0.03 µM. Assay buffer was added to each of the above concentrations to give 10%(v/v) DMSO (1:10 dilution). 5 µl of each diluted compound solution assayed in duplicate at a final compound concentration range of 10, 3, 1, 0.3 and 0.1 µM in 1% (v/v) DMSO. More active compounds were assayed at lower concentrations. Assays were performed in 96 deep well plates containing 0.1-10µM compounds or 20 µM histamine; 0.015 mg protein/well H4 membranes and 3.9 nM of [^{3}H]-histamine in a final volume of 200 µl. Plates were incubated at room temperature for 1.5 hours. The contents of the wells was captured on filters, washed 2x 1 mL with Tris/EDTA wash buffer. The filters were dried for about 2 hrs at 60 °C and the [^{3}H] determined by scintillation counting.

Data was analyzed to construct inhibition curves and pIC_{50} estimated by non-linear regression using a 4 parameter logistic model. The IC_{50} is the concentration of compound giving 50% inhibition relative to the plate controls. Thioperamide was used as the standard compound in this assay.

% Inhibition = 100-((sample reading – NSB reading)/(control reading - NSB reading)x100)

$pIC_{50} = -\log(IC_{50})$

EXAMPLES

The invention will further be described in more detail by the following Examples which describe methods whereby compounds of the present invention may be prepared, purified, analyzed and biologically tested, and which are not to be construed as limiting the invention.

Abbreviation used in the following examples and General Process Conditions:

aq.: aqueous;
atm: atmospheric pressure;
BOC: 1,1-dimethylethoxycarbonyl;
ACN: acetonitrile;
DCM: dichloromethane;
DMR: N,N-dimethylformamide;
DMSO: dimethyl sulfoxide;
EtOH: ethanol;
Et_2O: diethyl ether;
EtOAc: ethyl acetate;
h: hour(s);
HPLC: high performance liquid chromatography;
EDC·HCl: 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride;
HOBT: 1-hydroxybenzotriazole;
MeOH: methanol;
min: minutes;
MS: mass spectrum;
NMR: nuclear magnetic resonance;
psi: pounds per square inch;
RT: room temperature;
sat.: saturated;
TEA: triethylamine;
TFA: trifluoroacetic acid;
THF: tetrahydrofuran.

Temperatures are given in degrees Celsius (°C). Unless otherwise stated, operations were carried out at room or ambient temperature (18-25 °C).

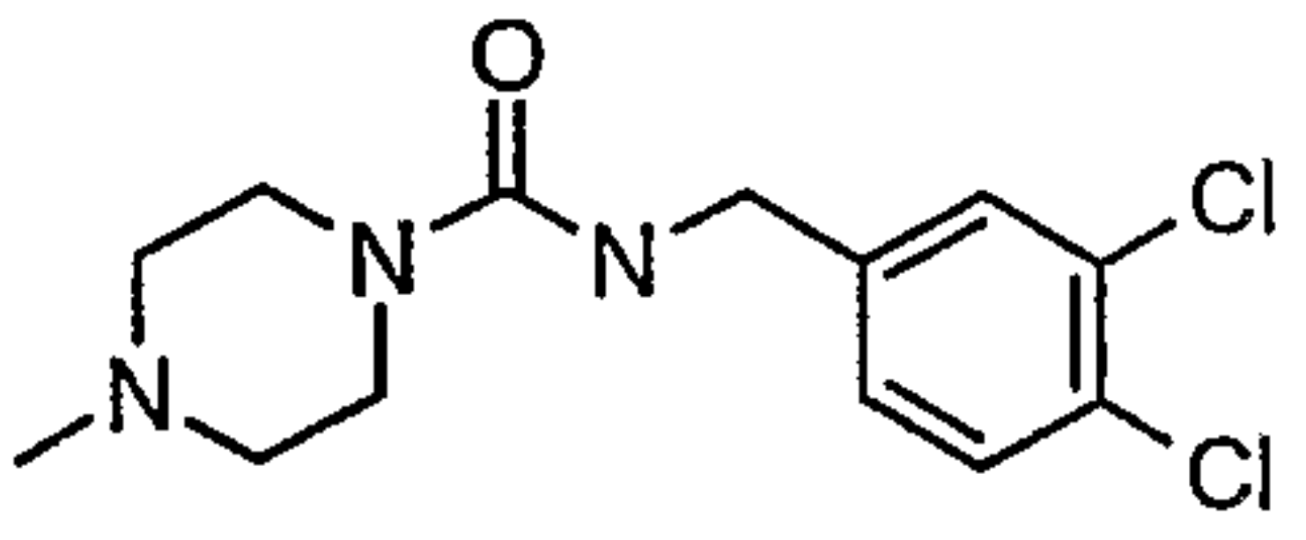
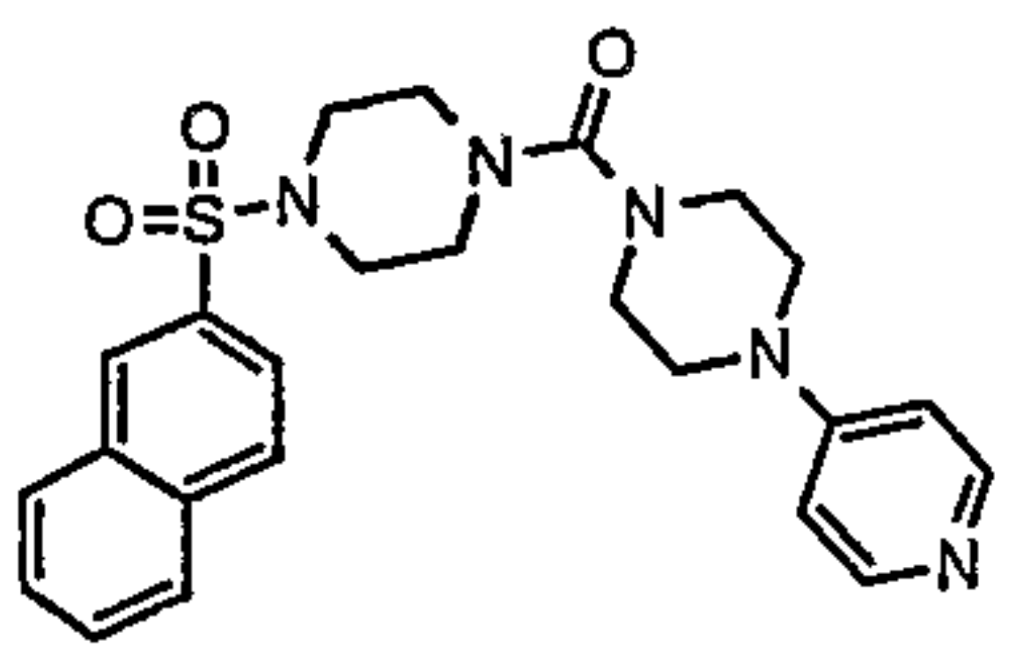
Chromatography means flash column chromatography on silica gel unless otherwise noted. Solvent mixture compositions are given as volume percentages or volume ratios.

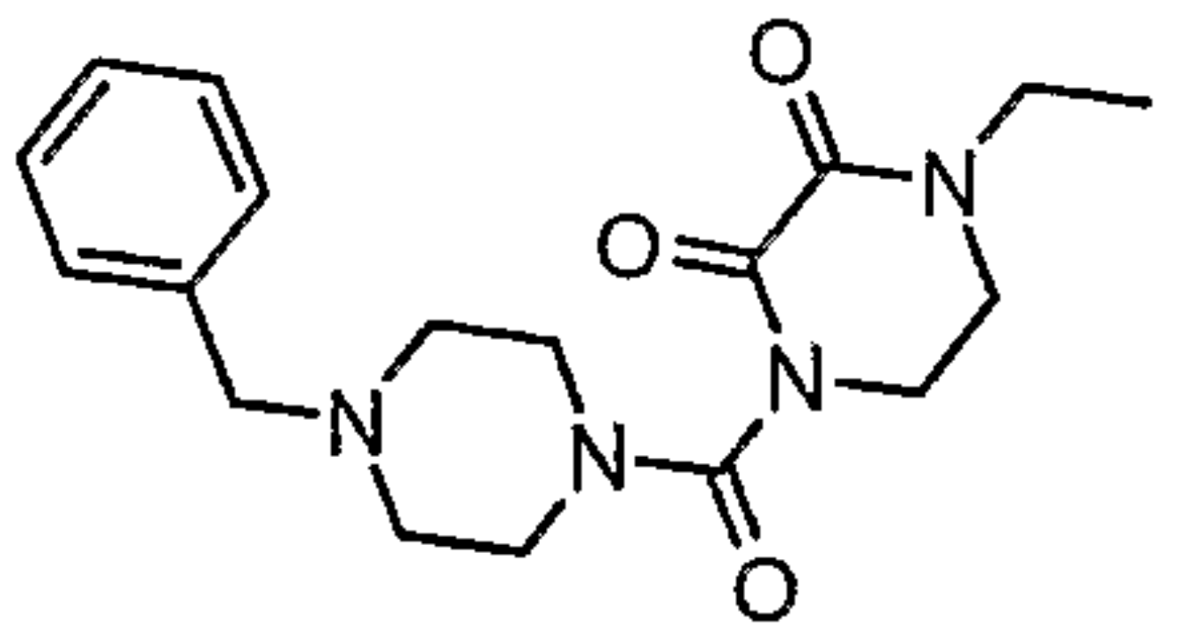
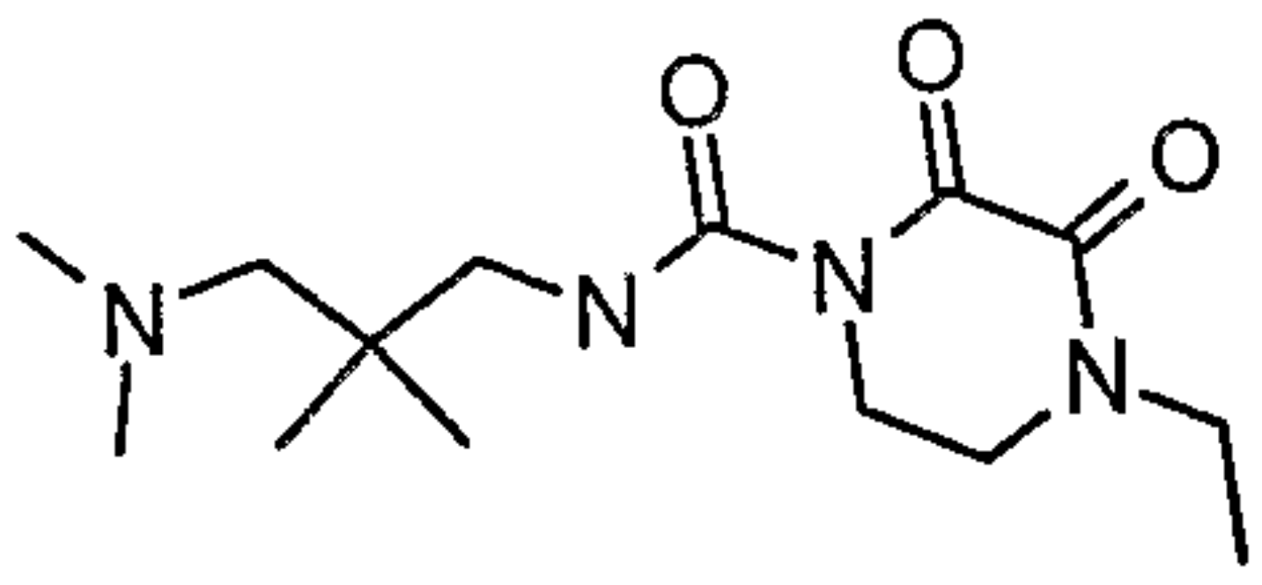
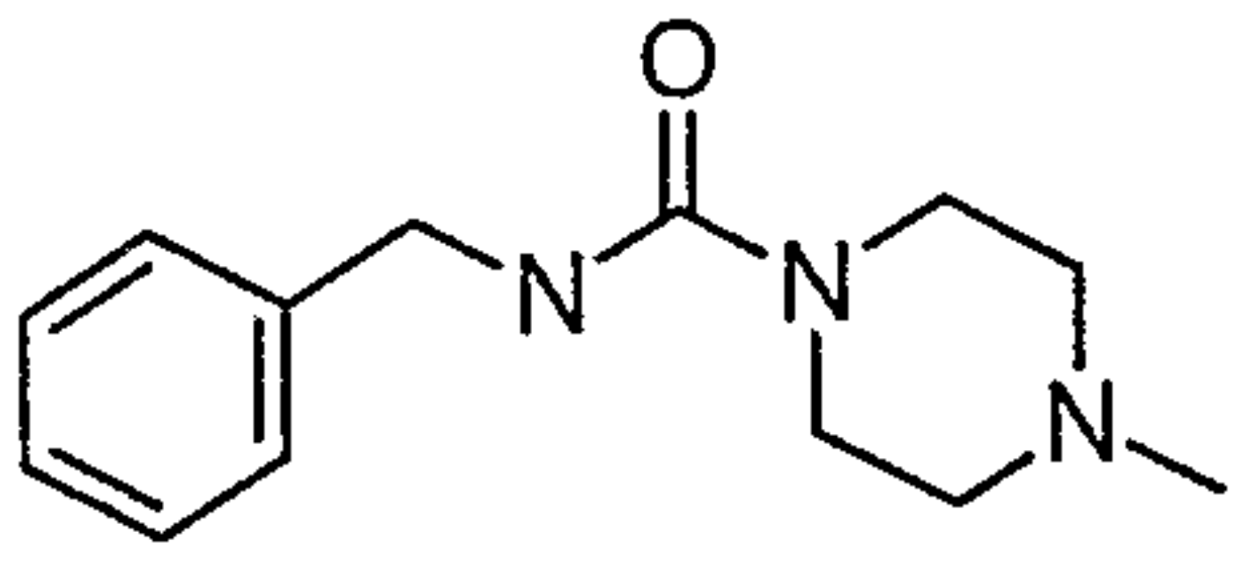
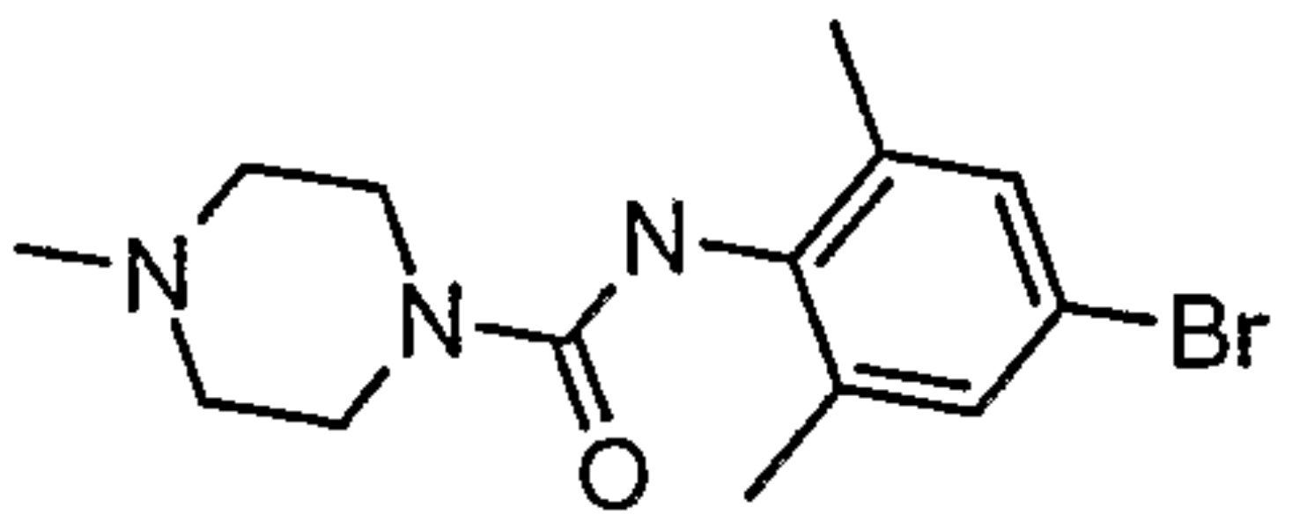
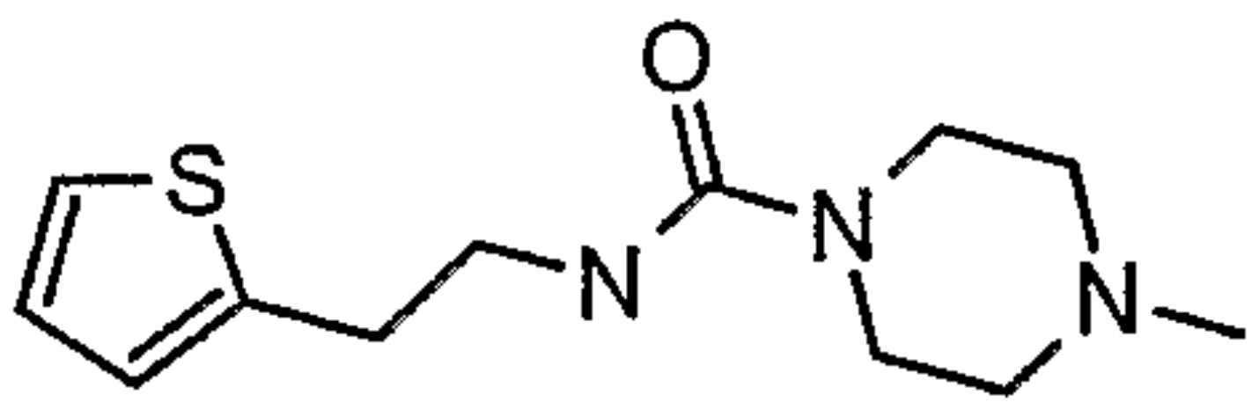
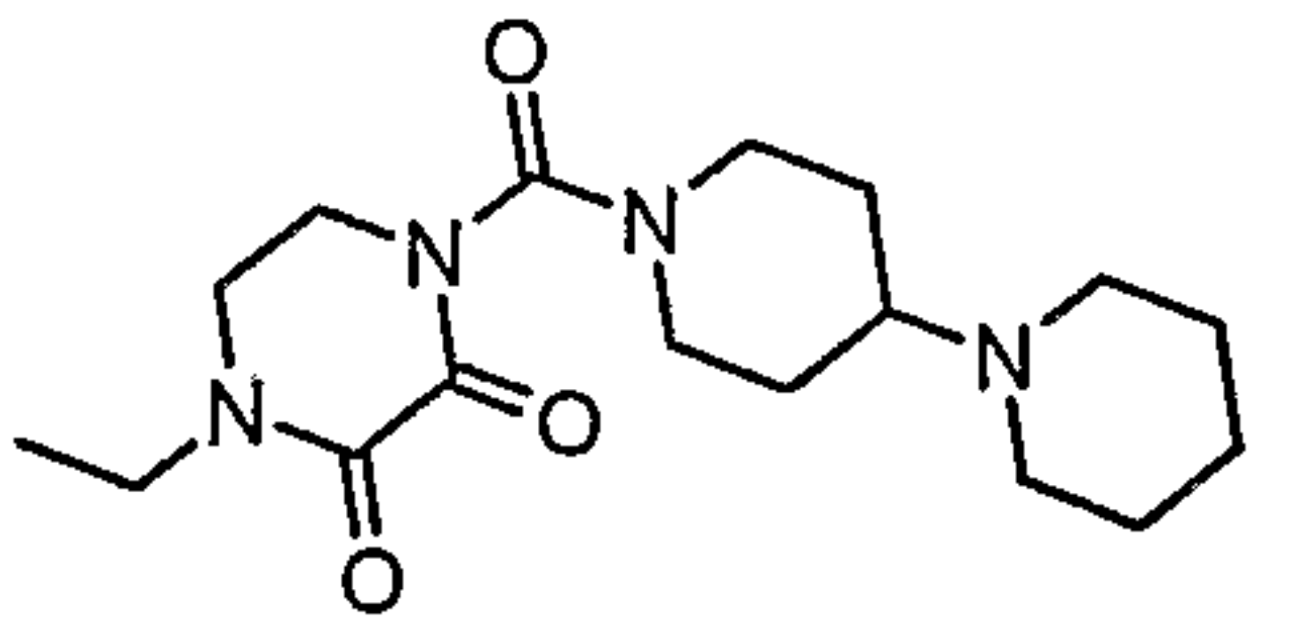
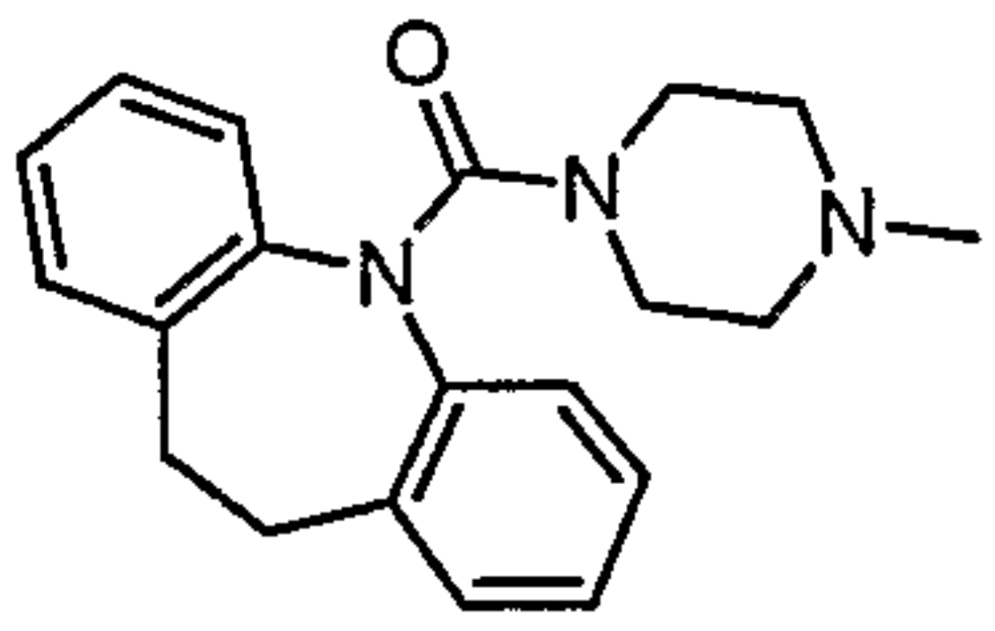
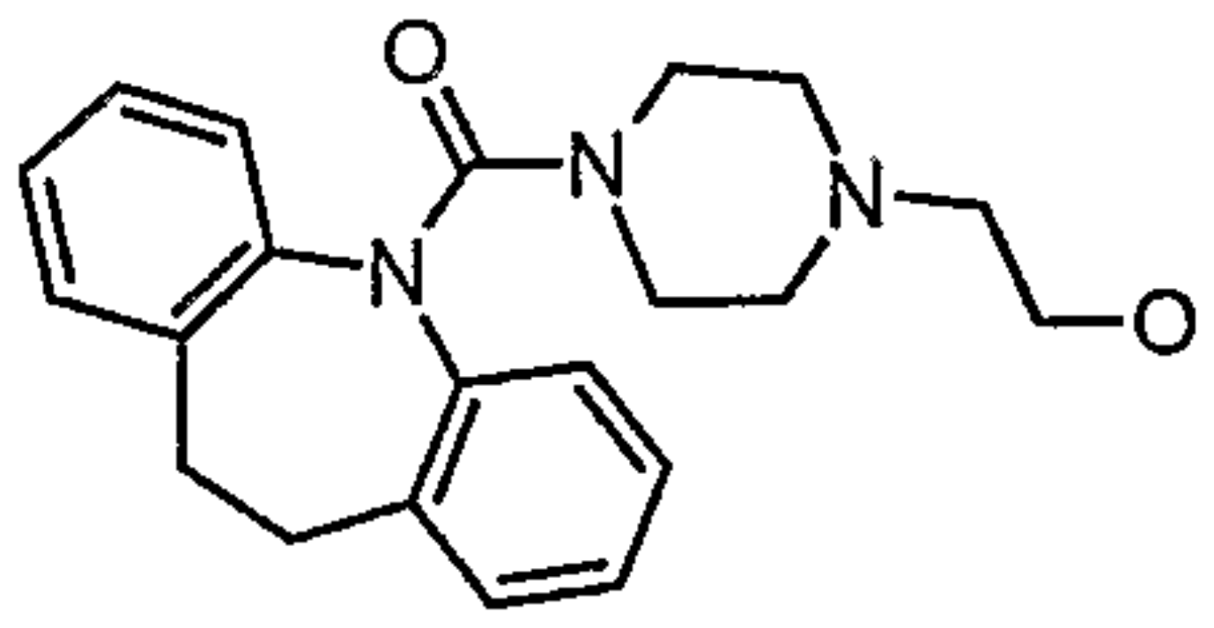
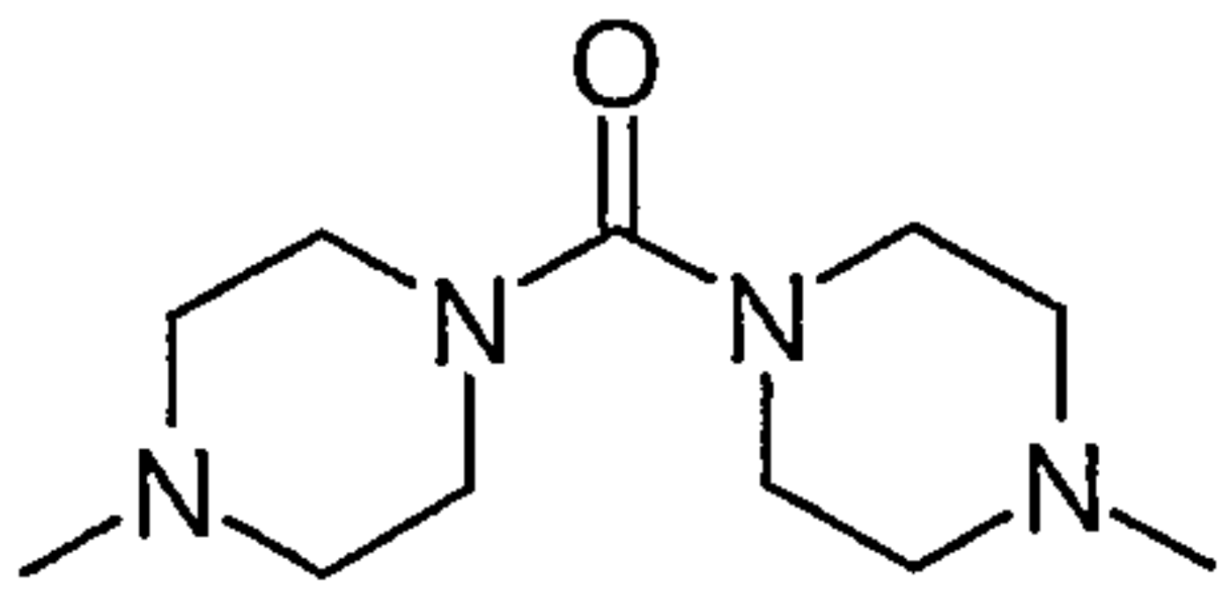
Where noted that a final compound was converted to the citrate salt, the free base was dissolved in MeOH, DCM, or ACN, combined with citric acid (1.0 equivalents) in MeOH, concentrated under reduced pressure and dried under vacuum (25-60 °C). When indicated that the salt was isolated by filtration from Et_2O, the citrate salt of the compound was stirred in Et_2O for 4-18 h, recovered by filtration, washed with Et_2O, and dried under vacuum (25-60 °C).

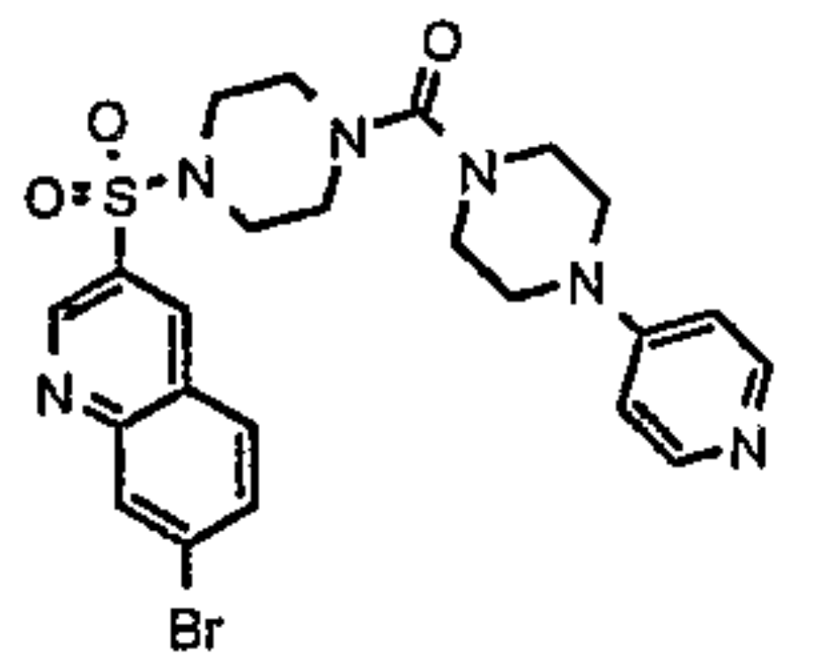
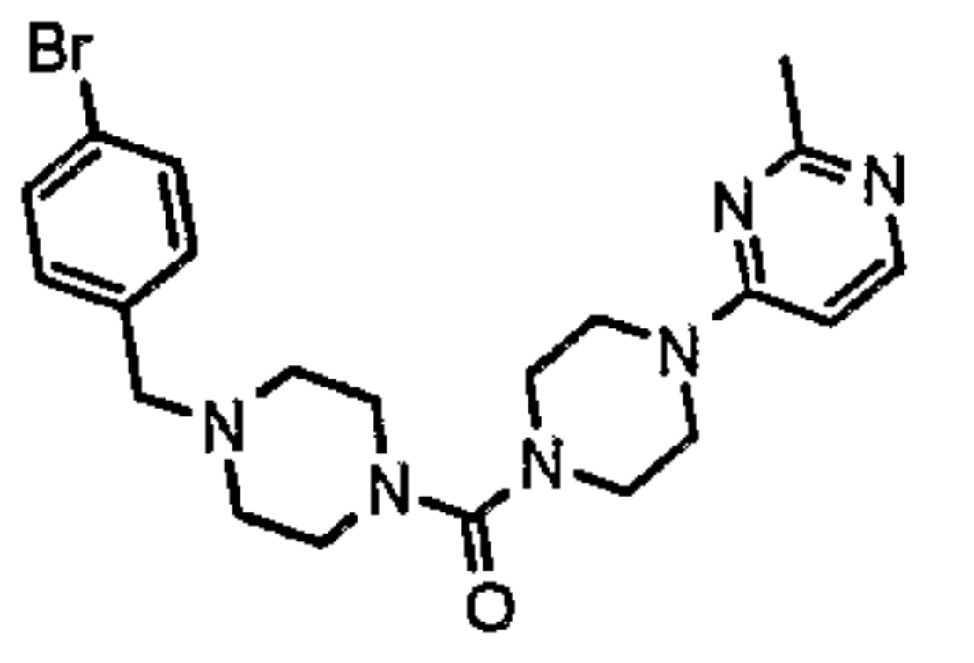
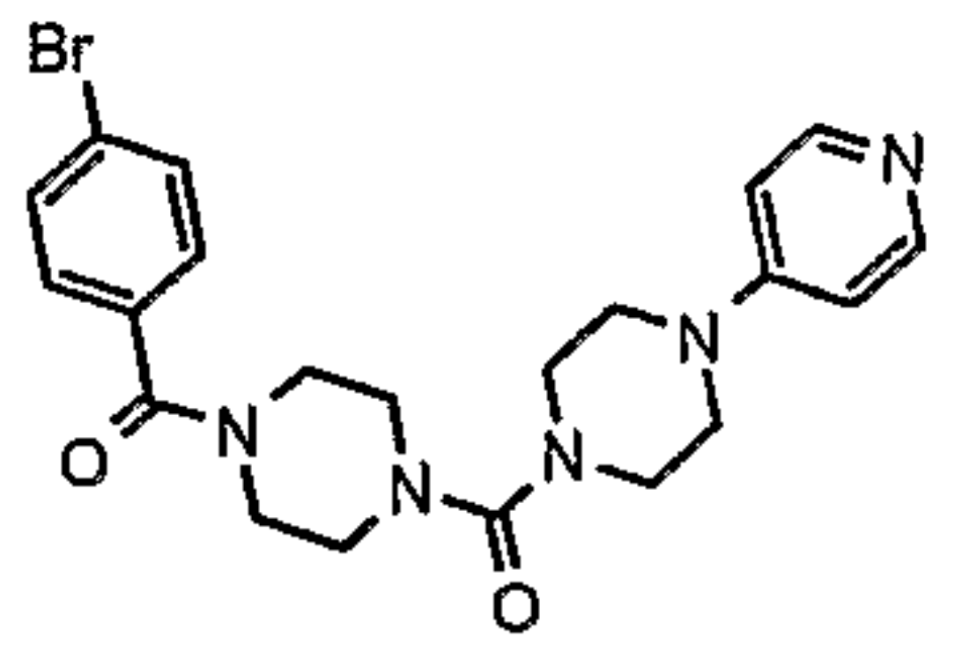
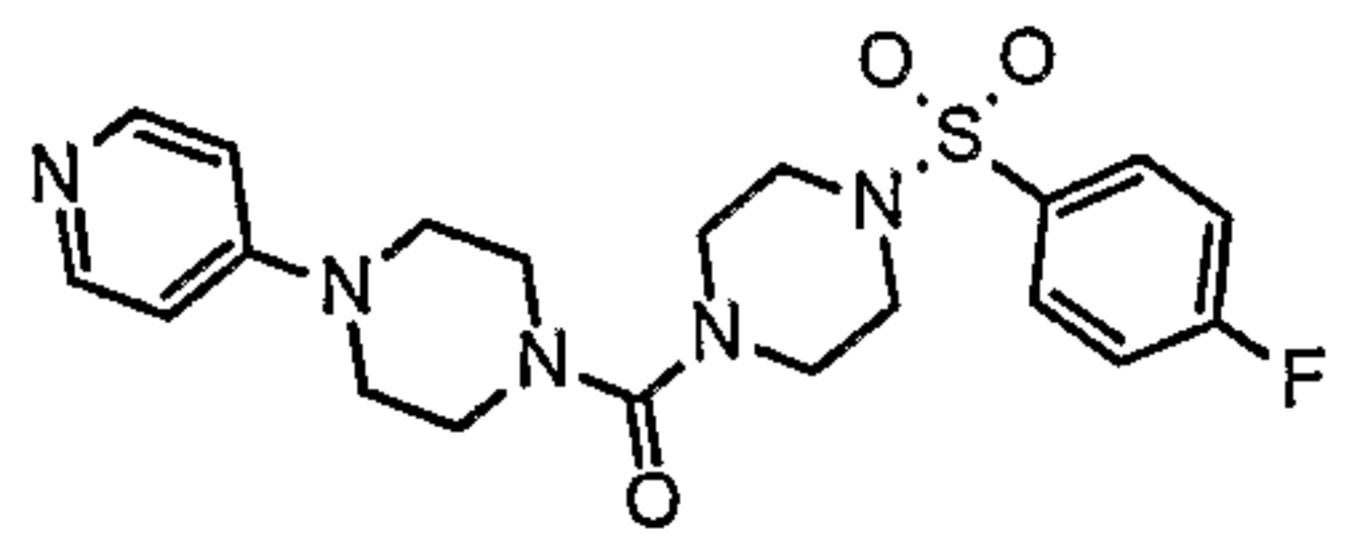
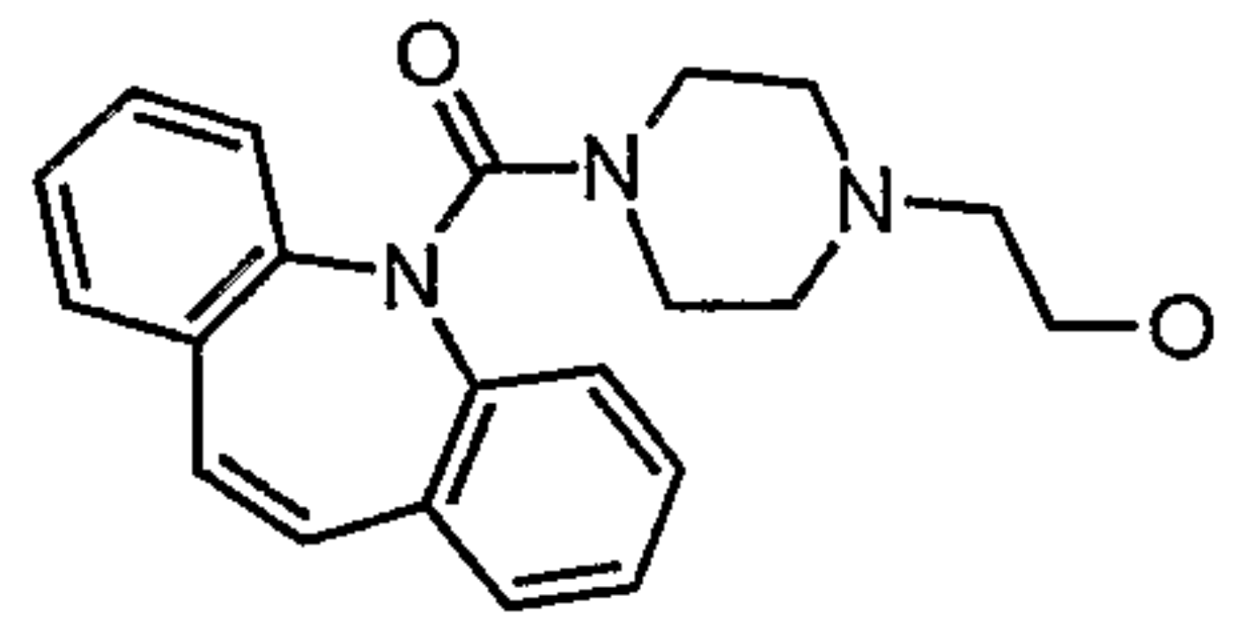
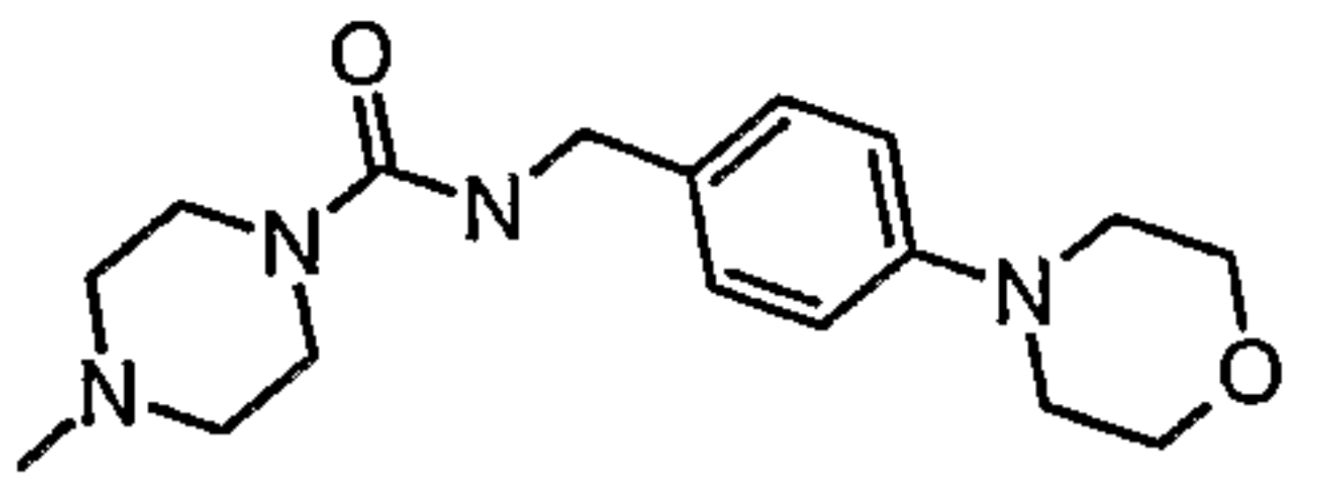
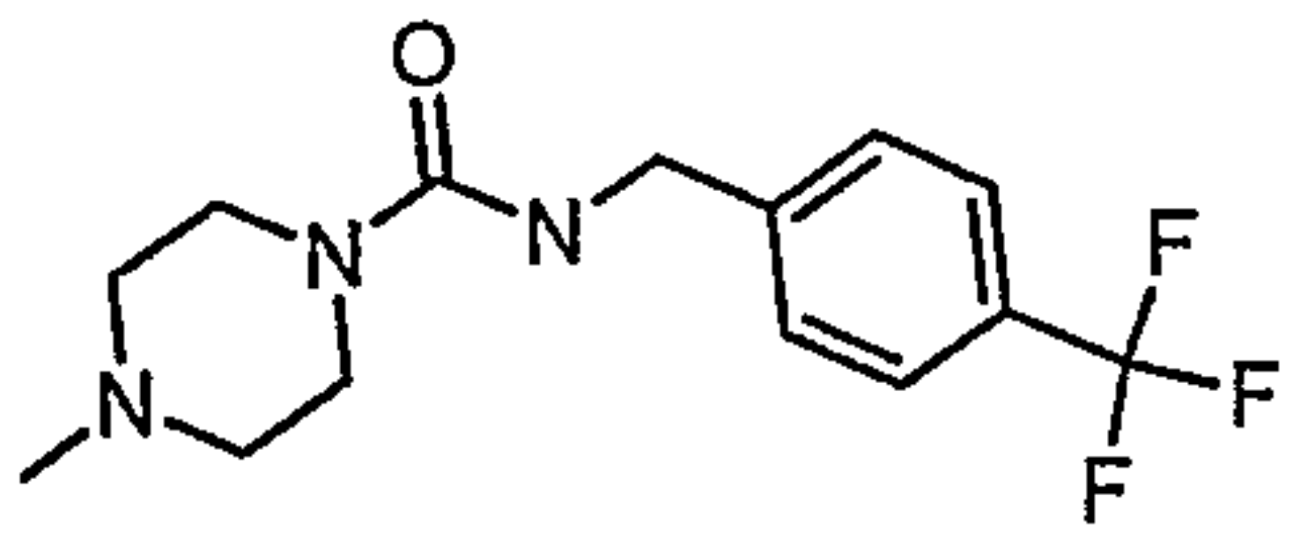
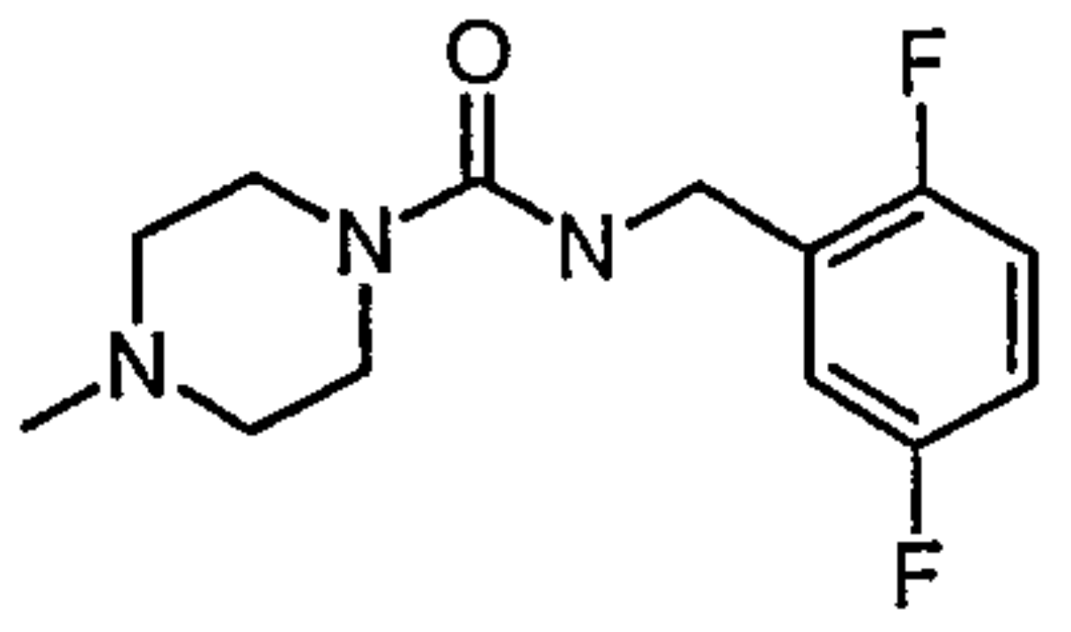
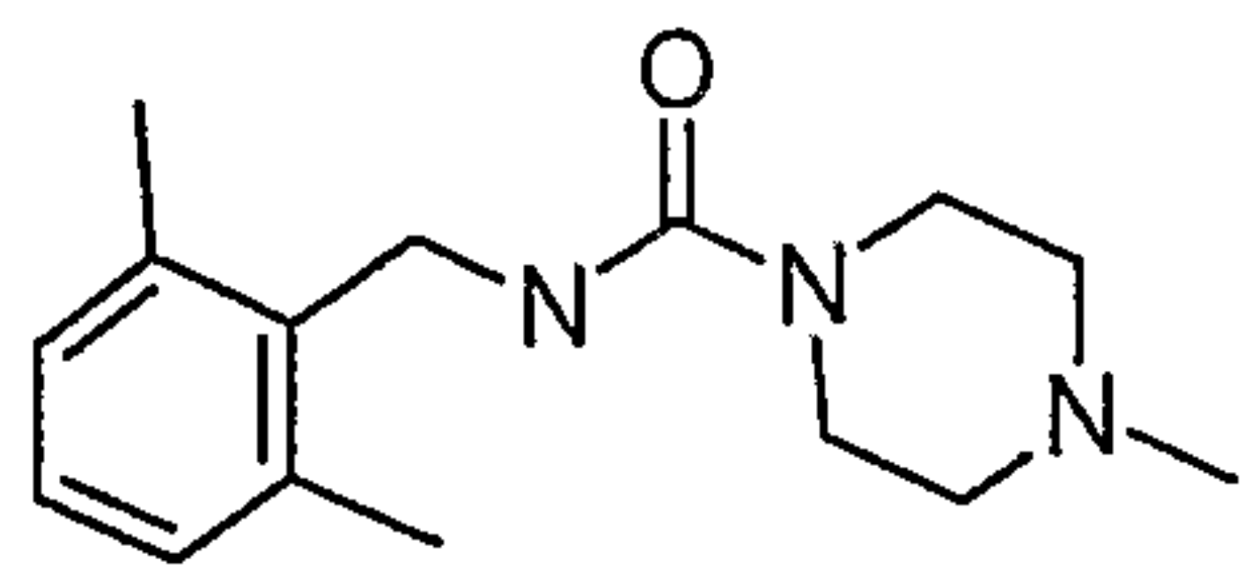
Example 1: N-(3,4-dichlorobenzyl)-4-methylpiperazine-1-carboxamide

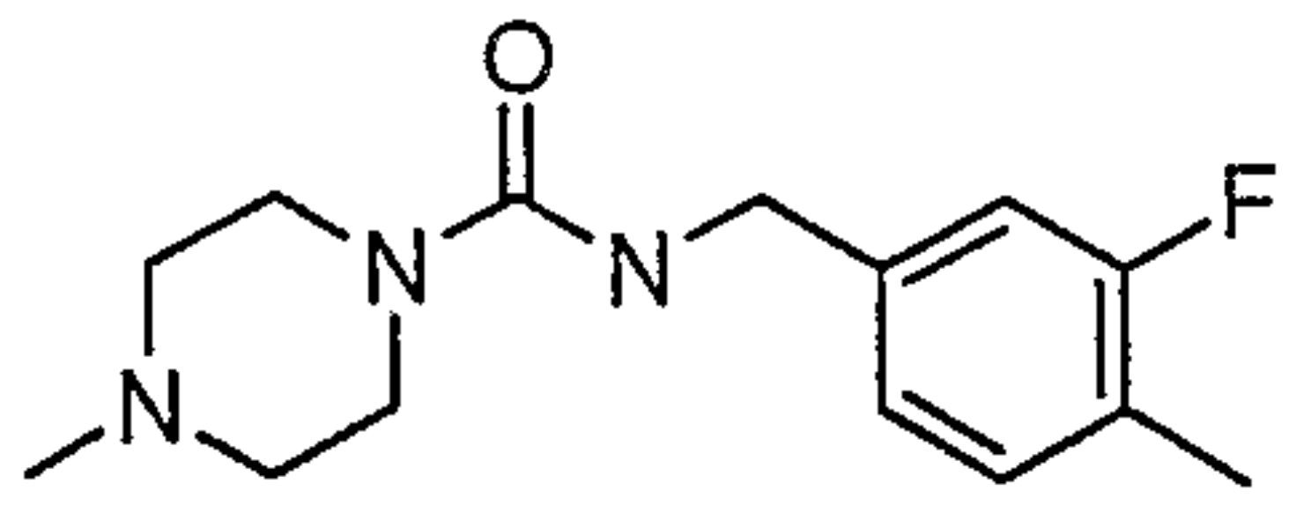
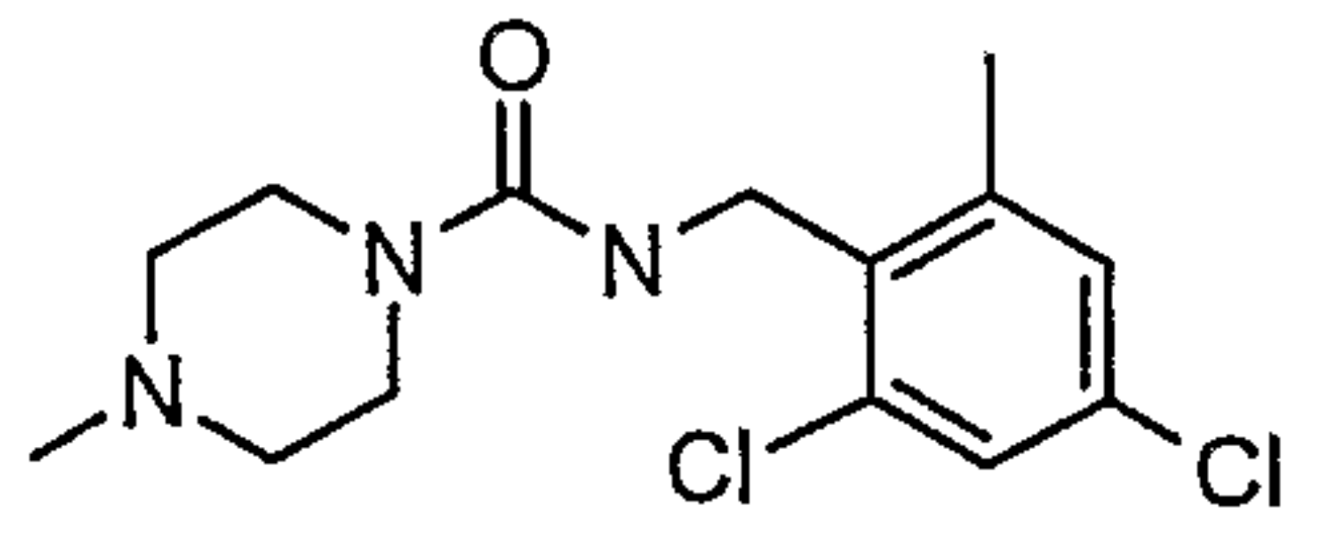
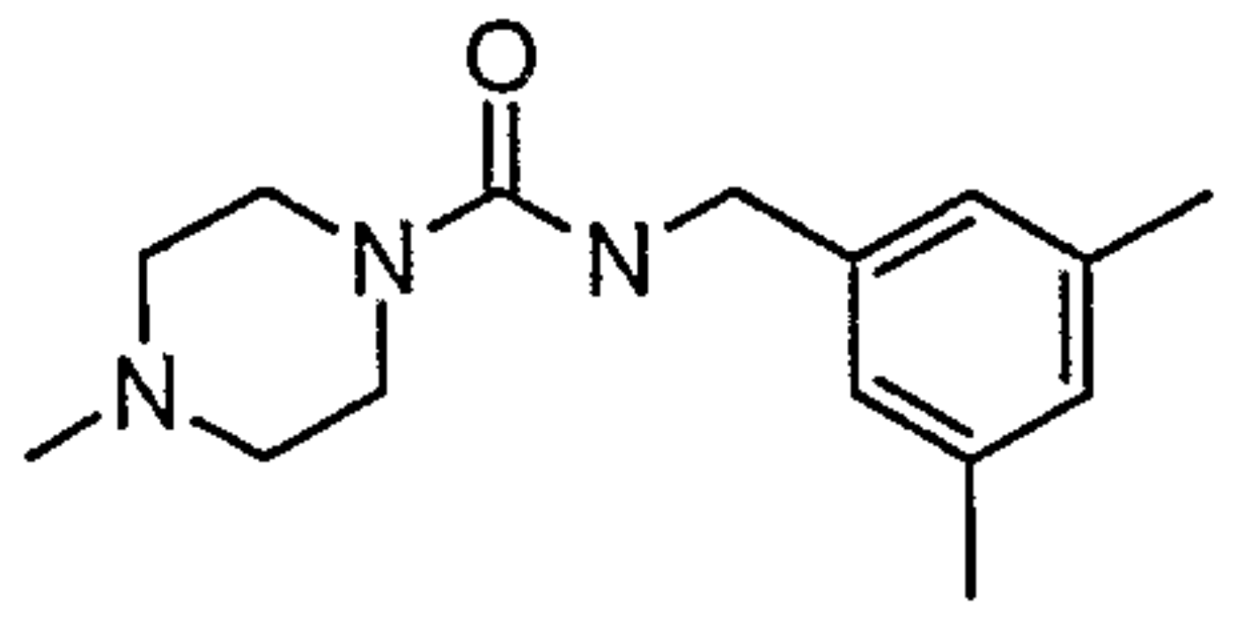
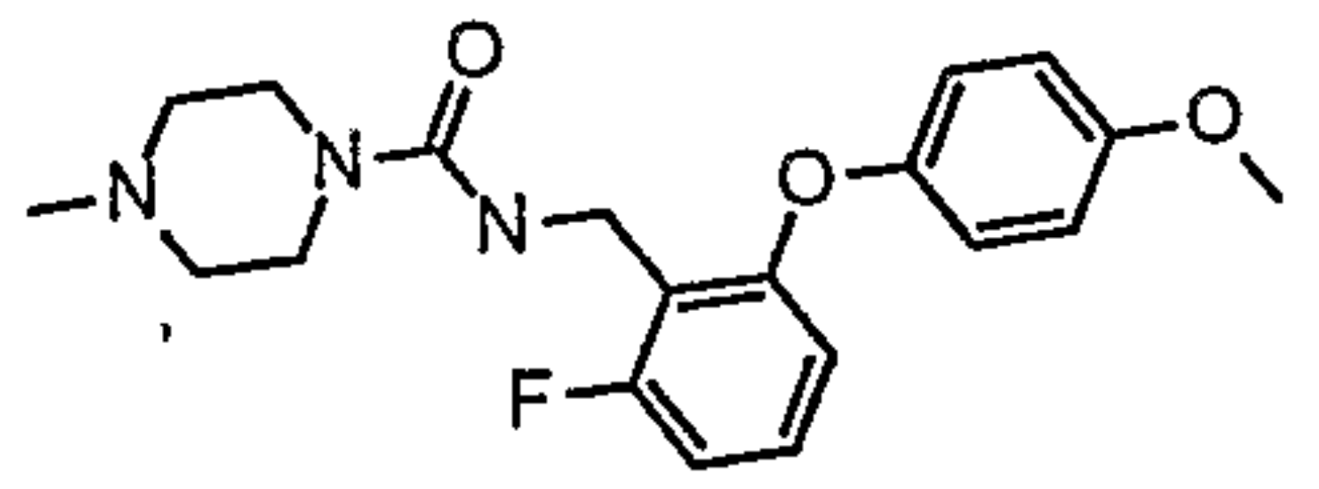
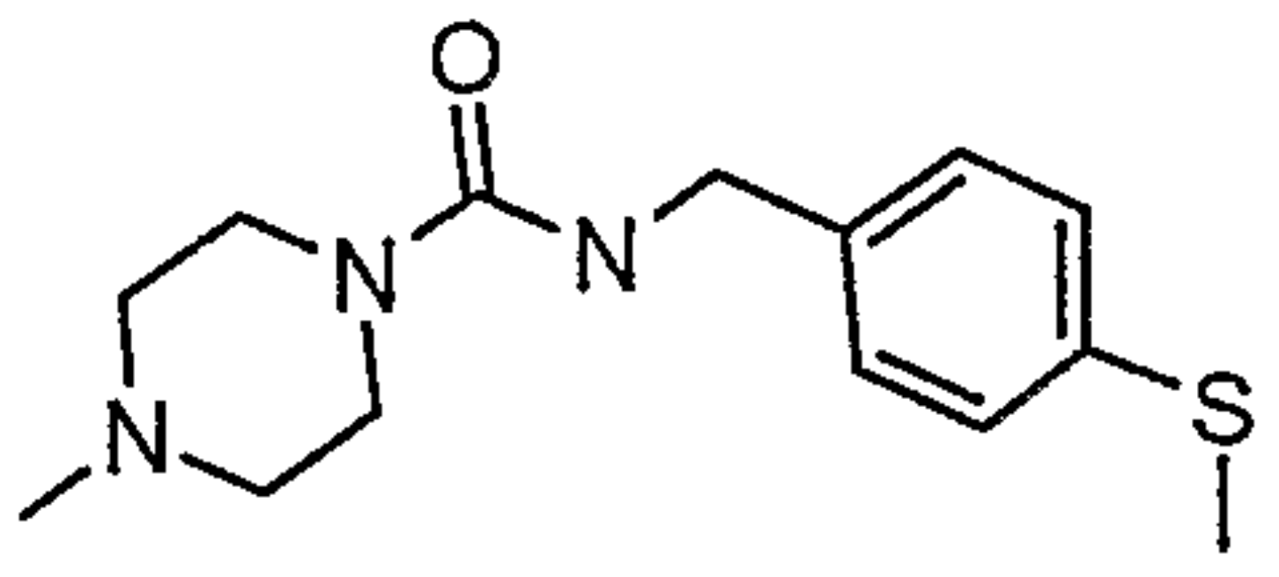
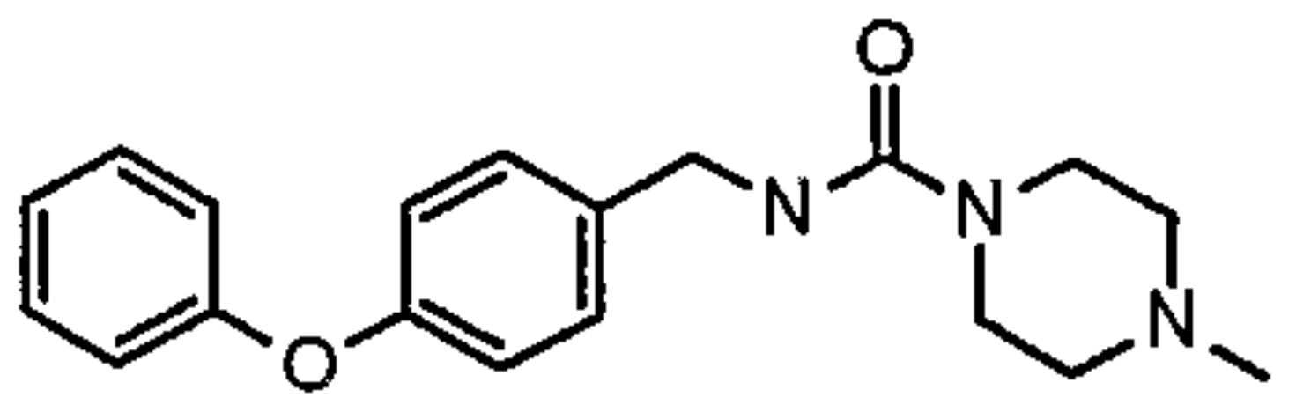
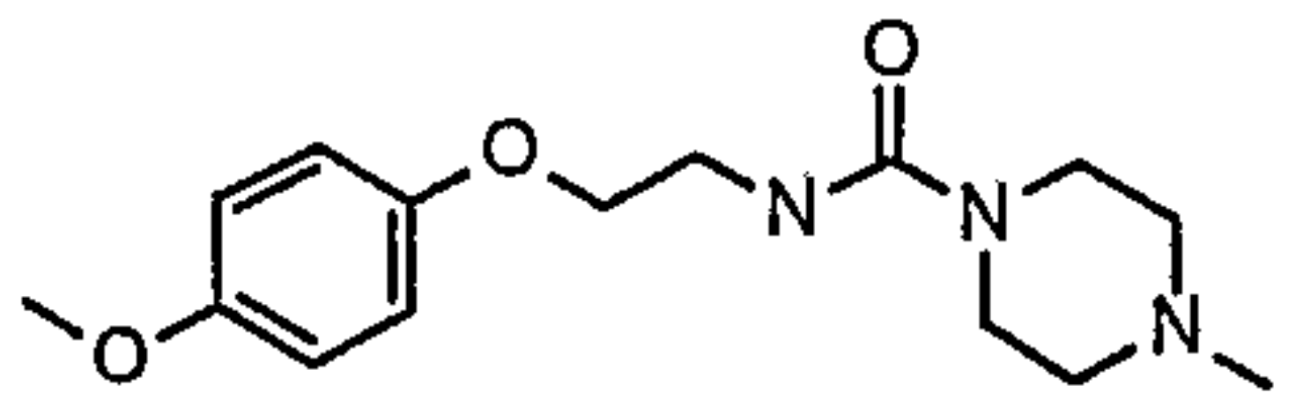
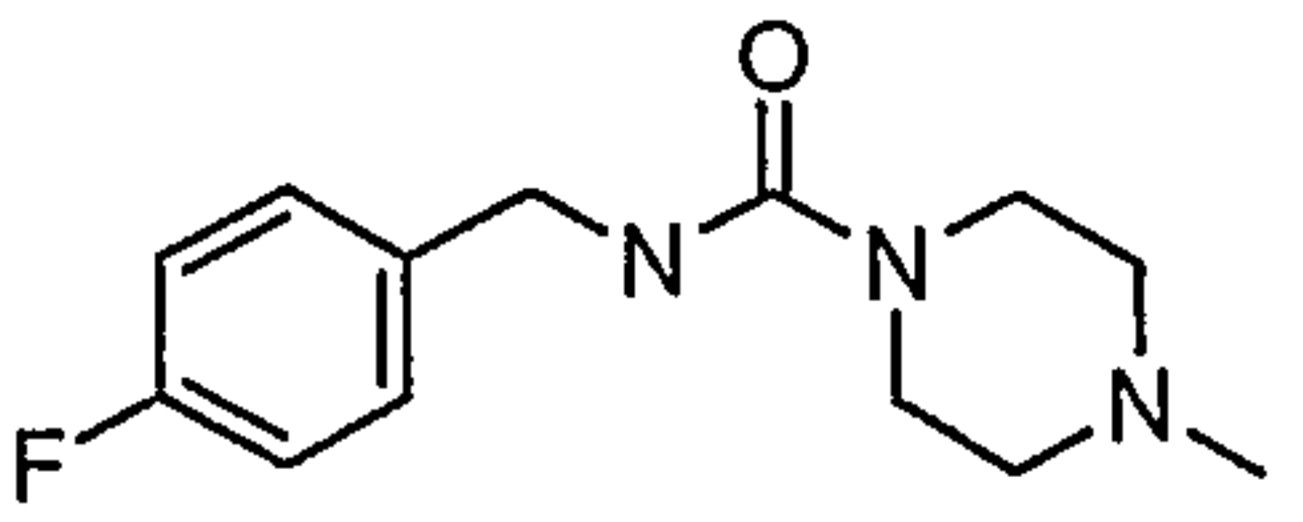
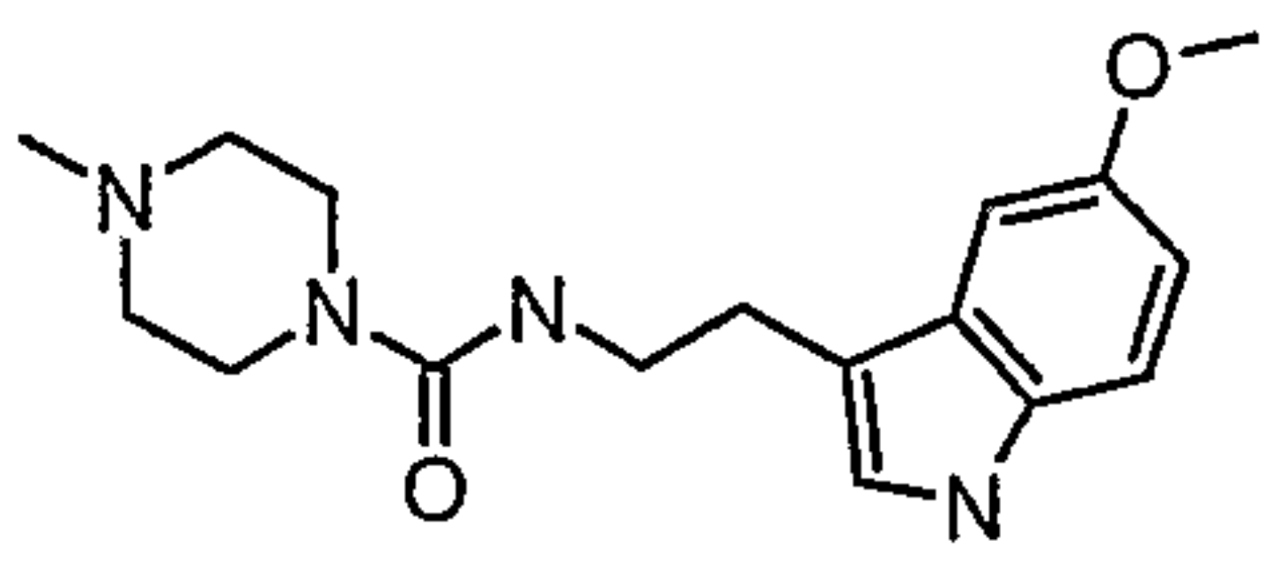
To a solution of 3,4-dichlorobenzylamine (0.195 g, 1.11 mmol) and diisopropylethylamine (0.193 mL, 1.11 mmol) in 4 mL of THF was added a preformed solution of 4-nitrophenyl chloroformate (0.223 g, 1.11 mmol) in 4 mL of THF. The reaction mixture was stirred at RT for 3.5 h. To this solution was added N-methyl piperazine (0.442 g, 4.42 mmol) and the resulting solution was stirred at RT for 16h. The reaction mixture was concentrated under reduced pressure, diluted with EtOAc (50 mL) and the solution was washed with saturated aqueous sodium bicarbonate (2 x 50 mL) and brine (50 mL). The solvent was removed under reduced pressure and the residue was subjected to supercritical fluid chromatography (21 mm x 150 mm diol-bonded SiO_2 (6μm particle size), isocratic method, 25% MeOH (containing 0.5% isopropyl amine) in CO_2) to afford the title compound as a pale yellow solid (0.245 g, 73%). MS m/z 302.2 $(M+H)^+$; ^1H NMR (300.1 MHz, DMSO-d_6) δ 2.17 (s, 3H), 2.22-2.26 (m, 4H), 3.25-3.31 (m, 4H), 4.20 (d, *J*=5.8Hz, 2H), 7.12 (t, *J*=5.8Hz, 1H), 7.23 (dd, *J*=8.2, 2.0Hz, 1H), 7.47 (d, *J*=1.8Hz, 1H), 7.56 (d, *J*=8.2Hz, 1H).

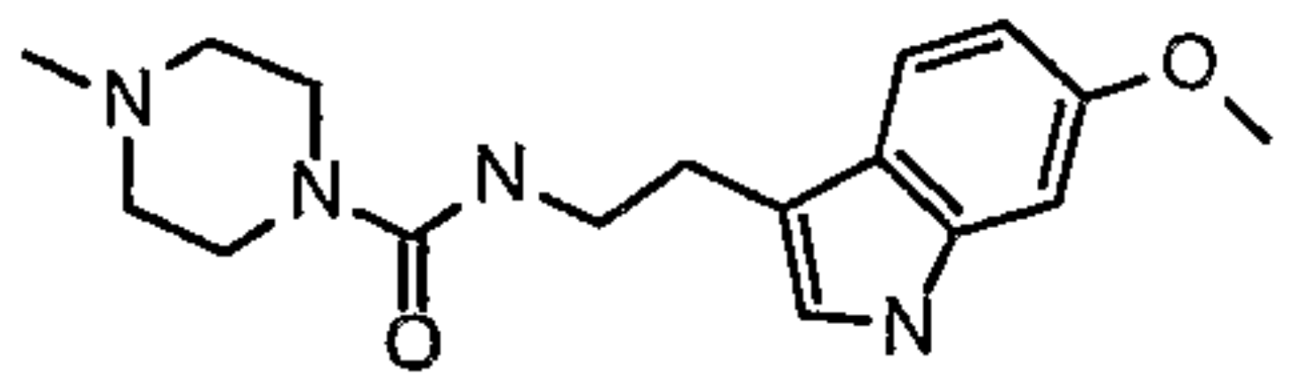
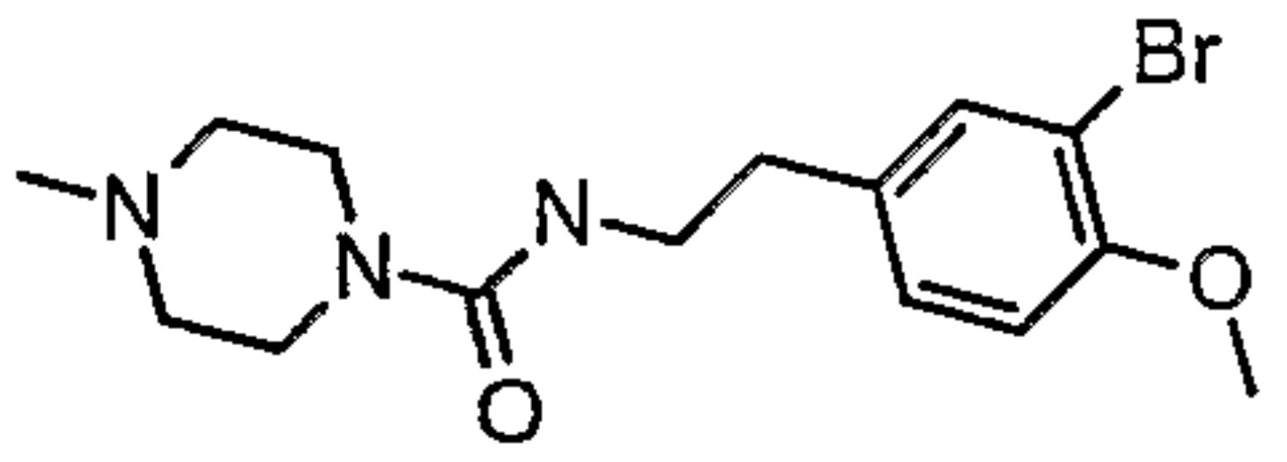
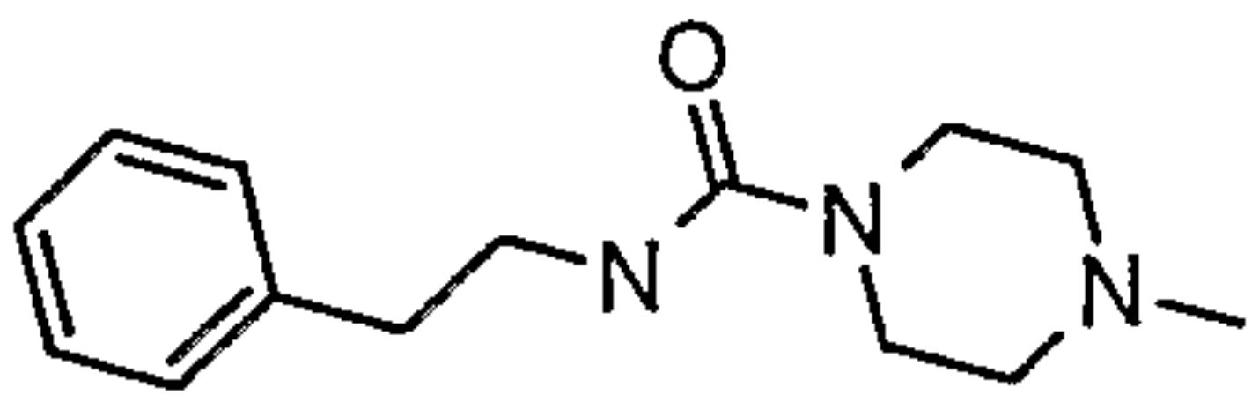
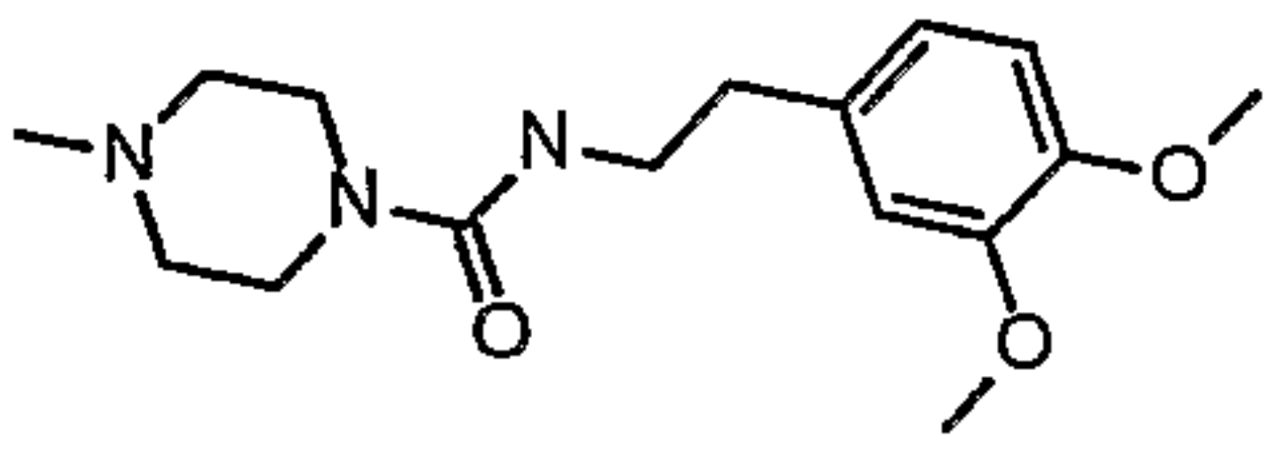
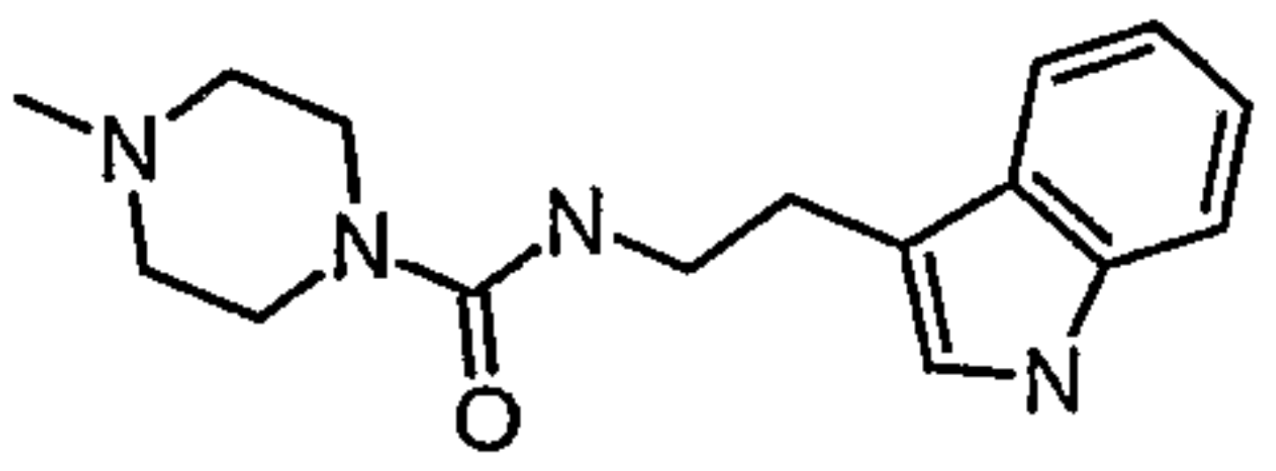
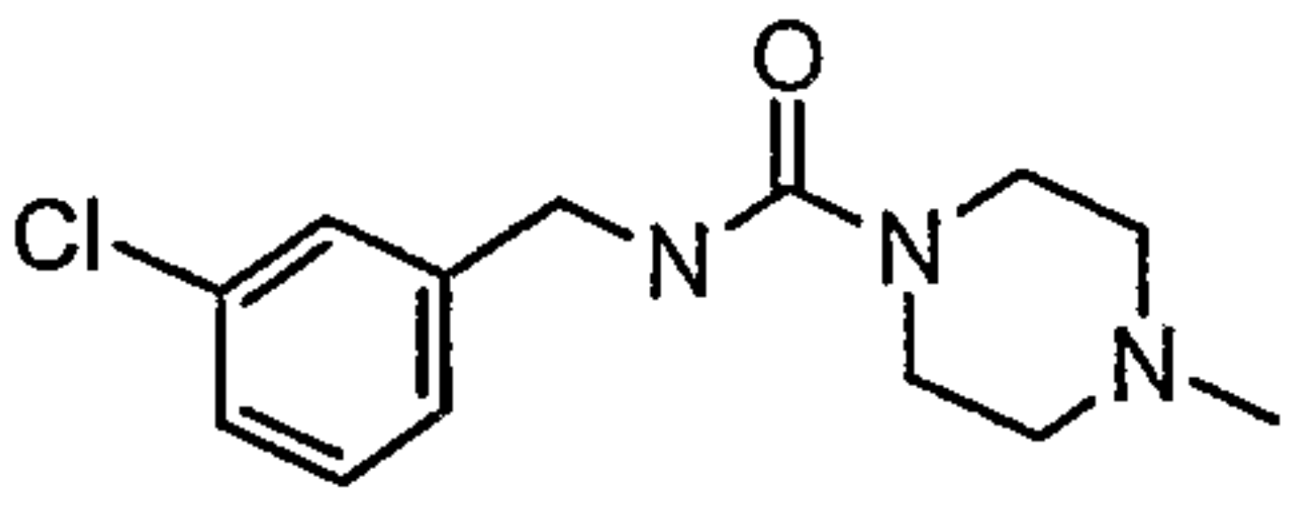
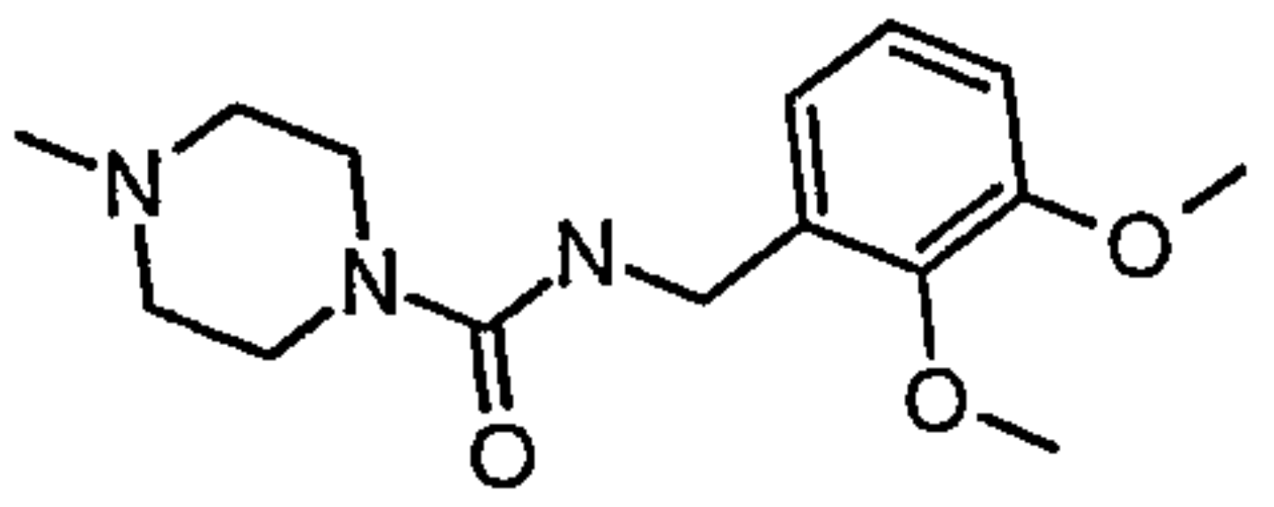
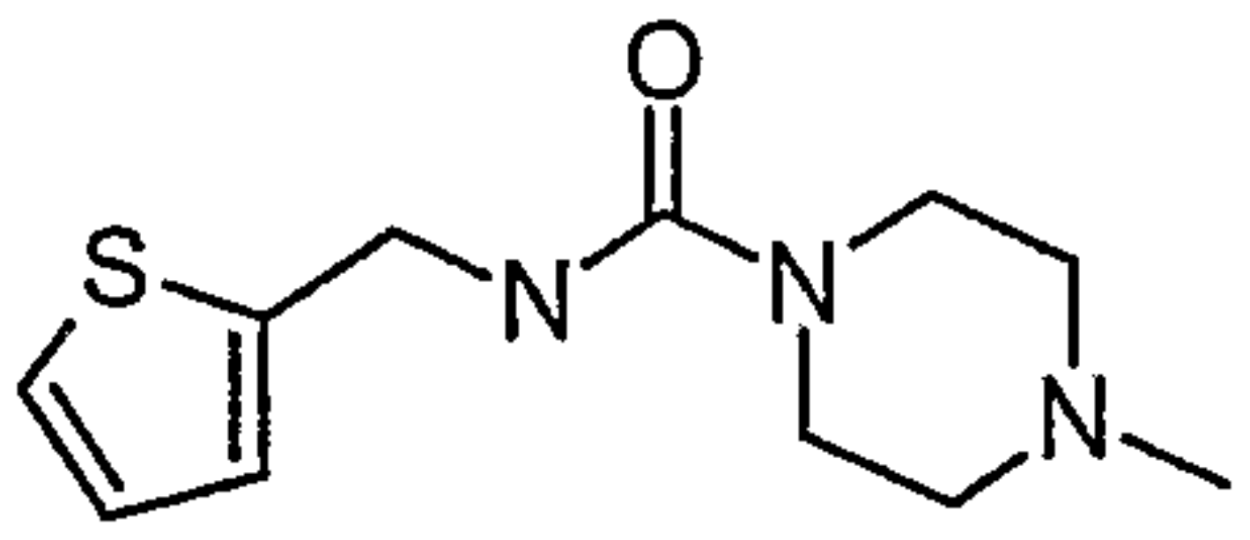
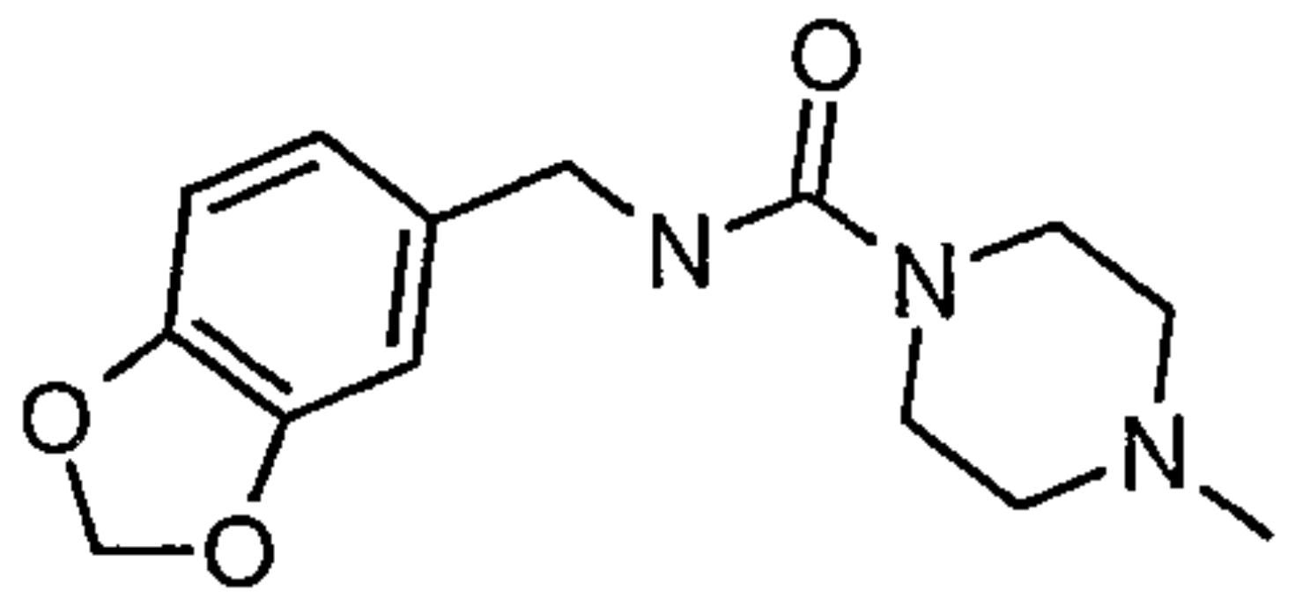
The above procedure may be used to synthesize the following compounds:

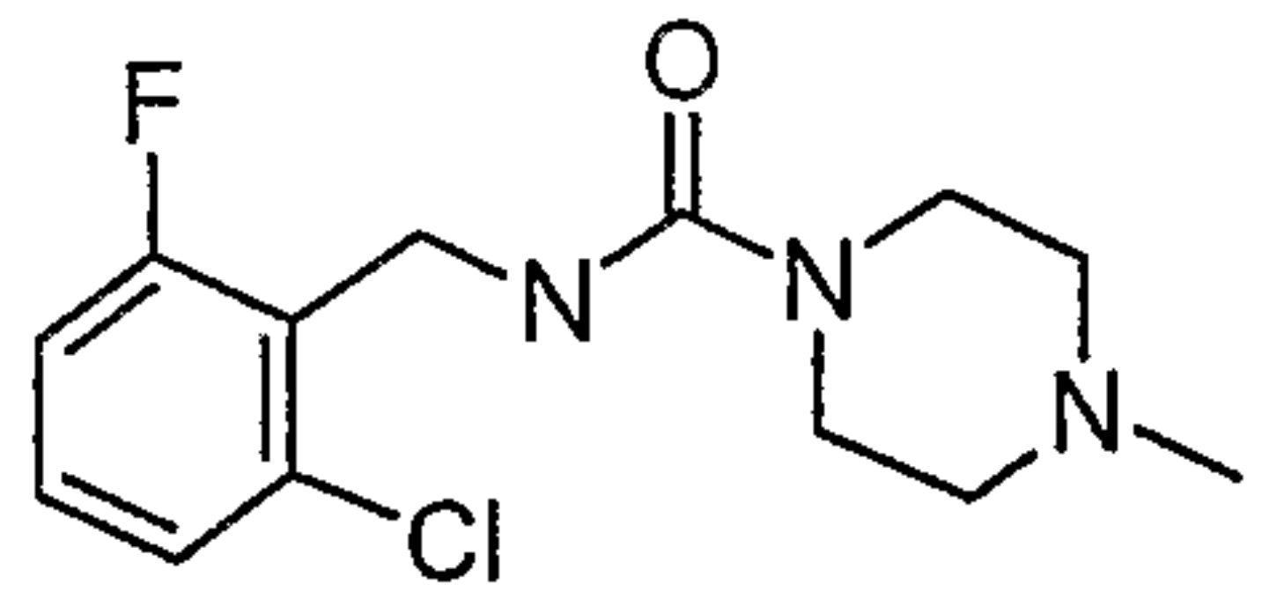
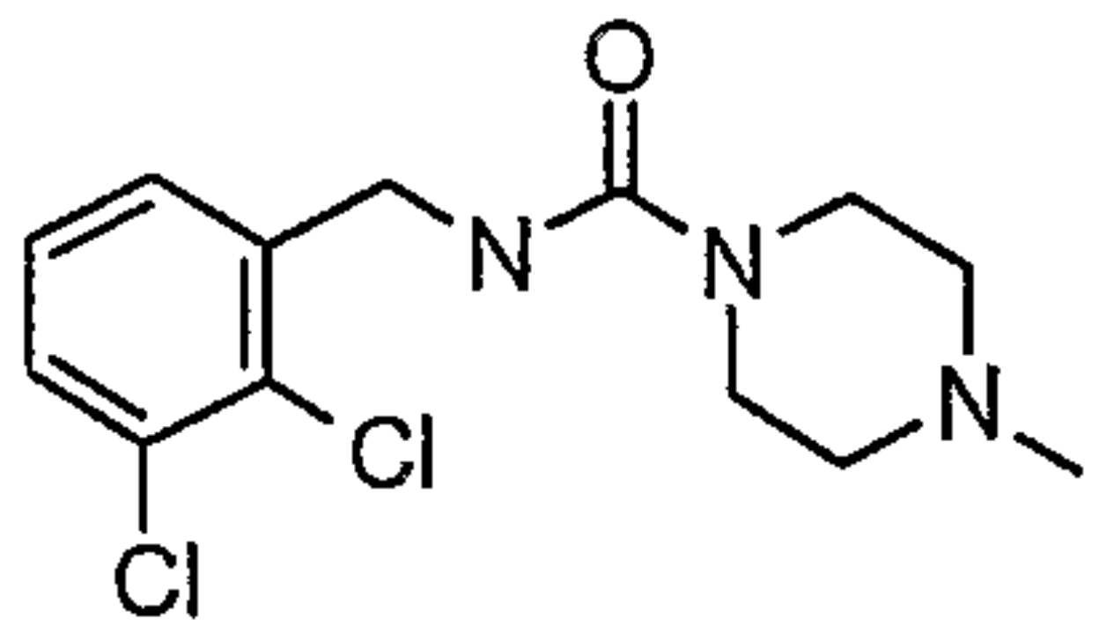
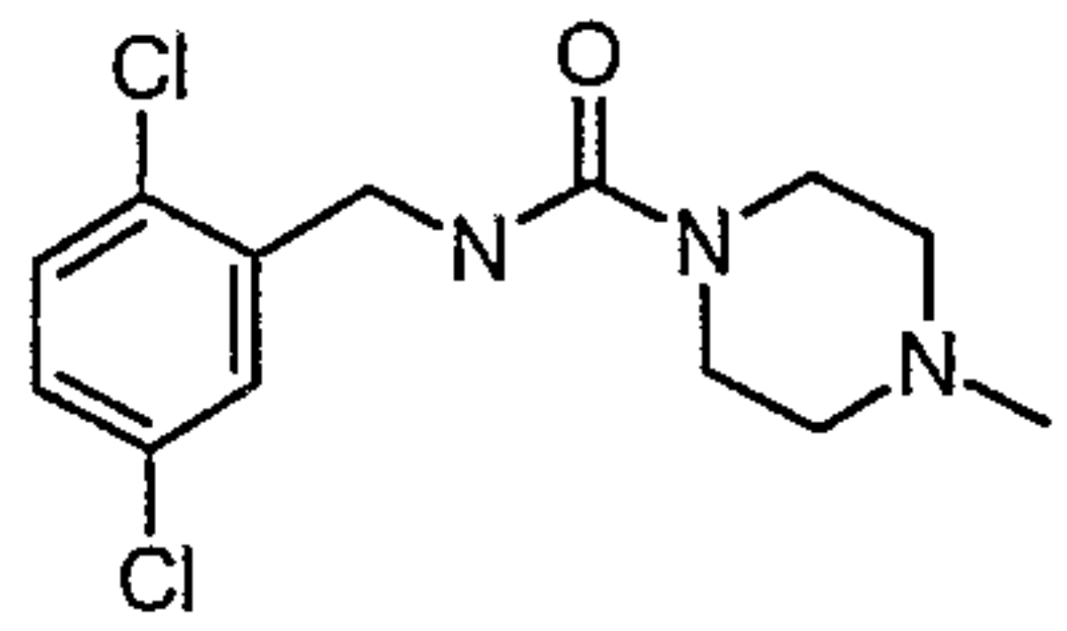
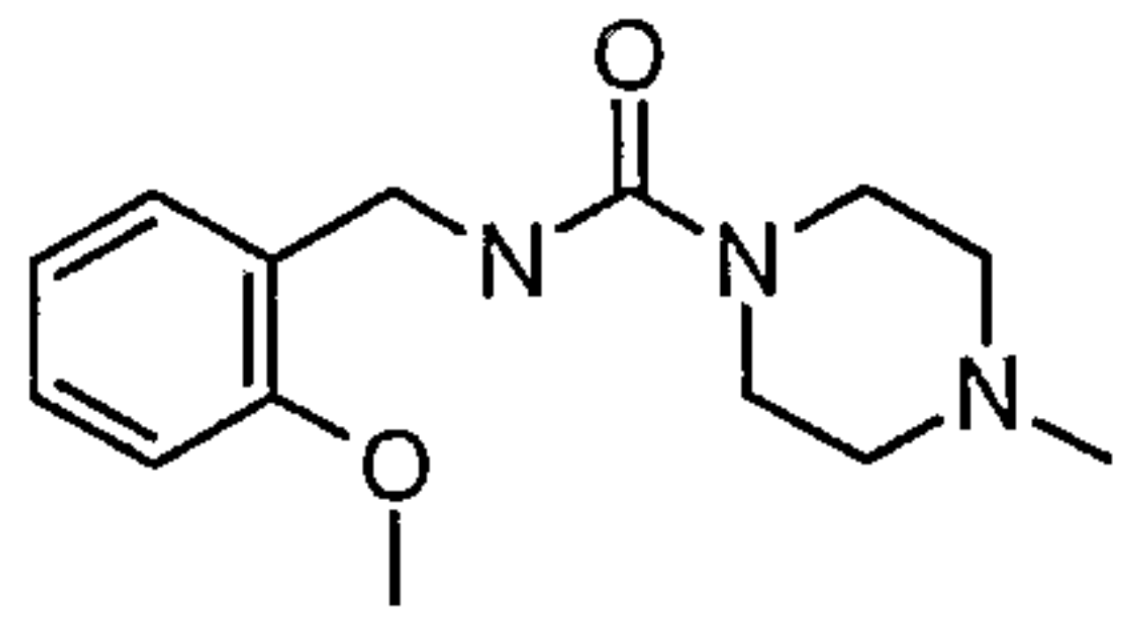
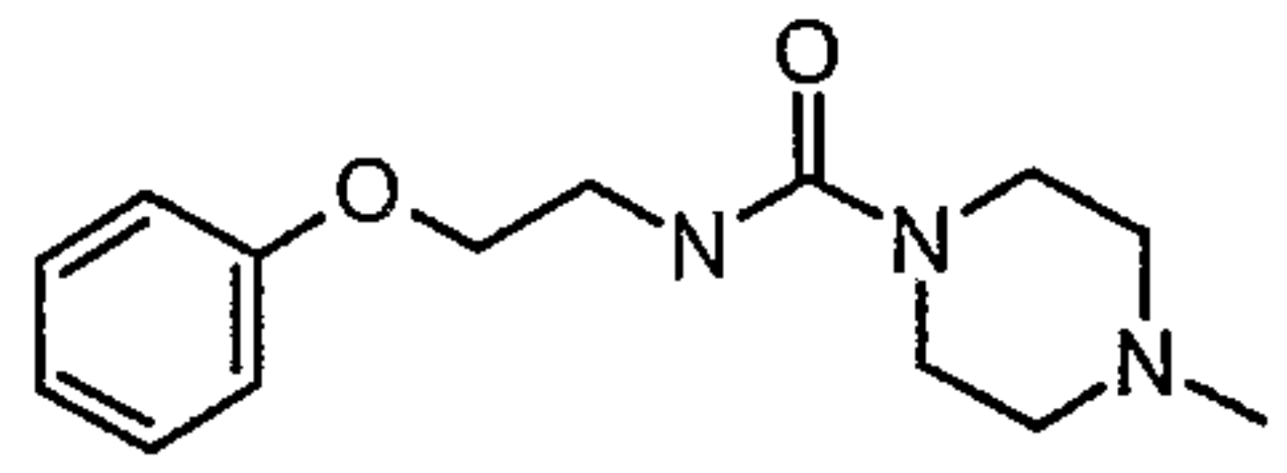
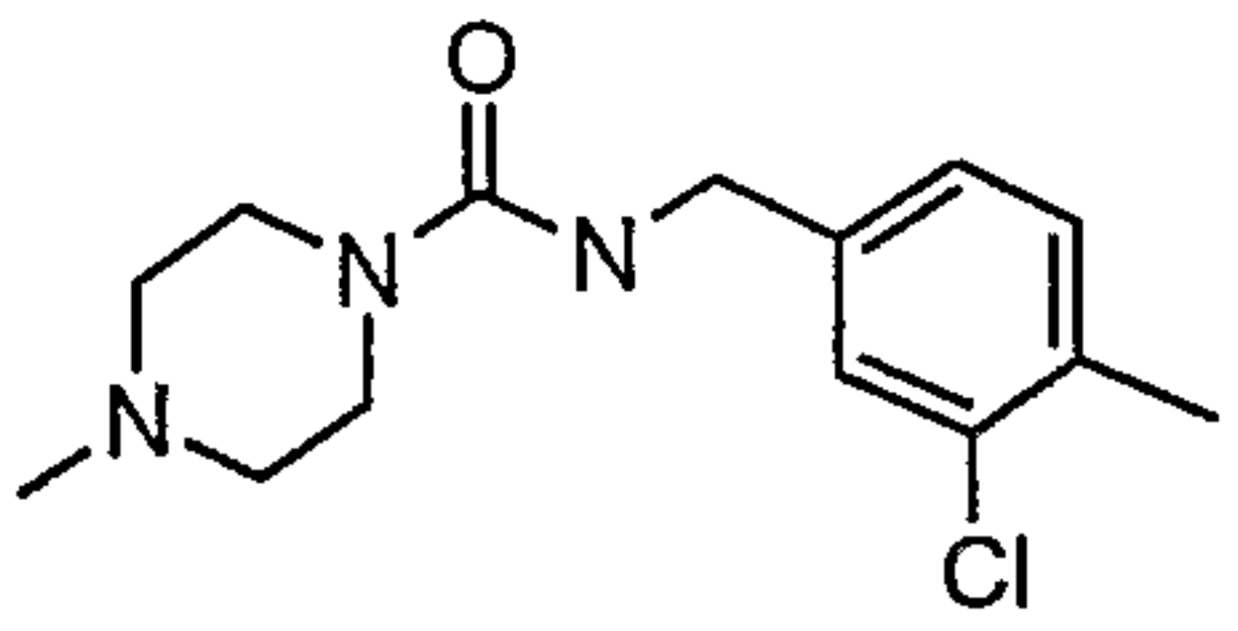
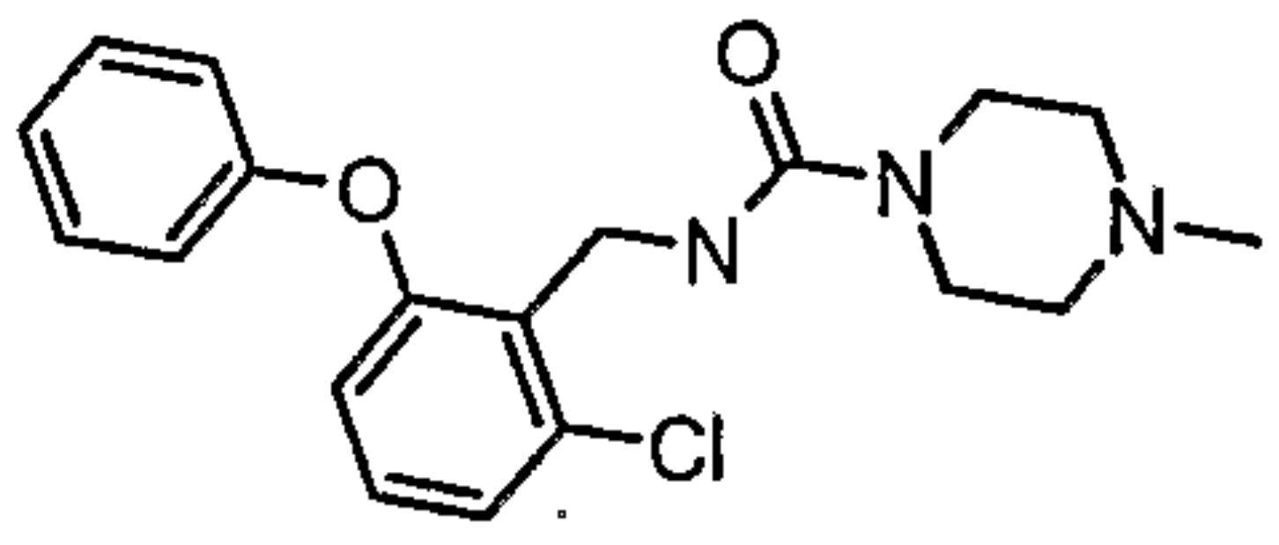
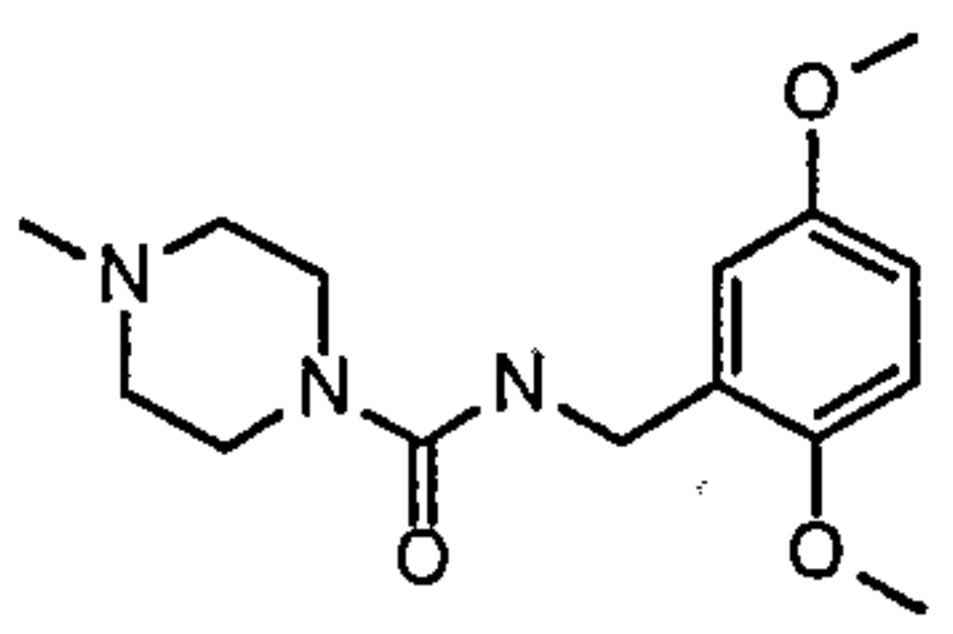
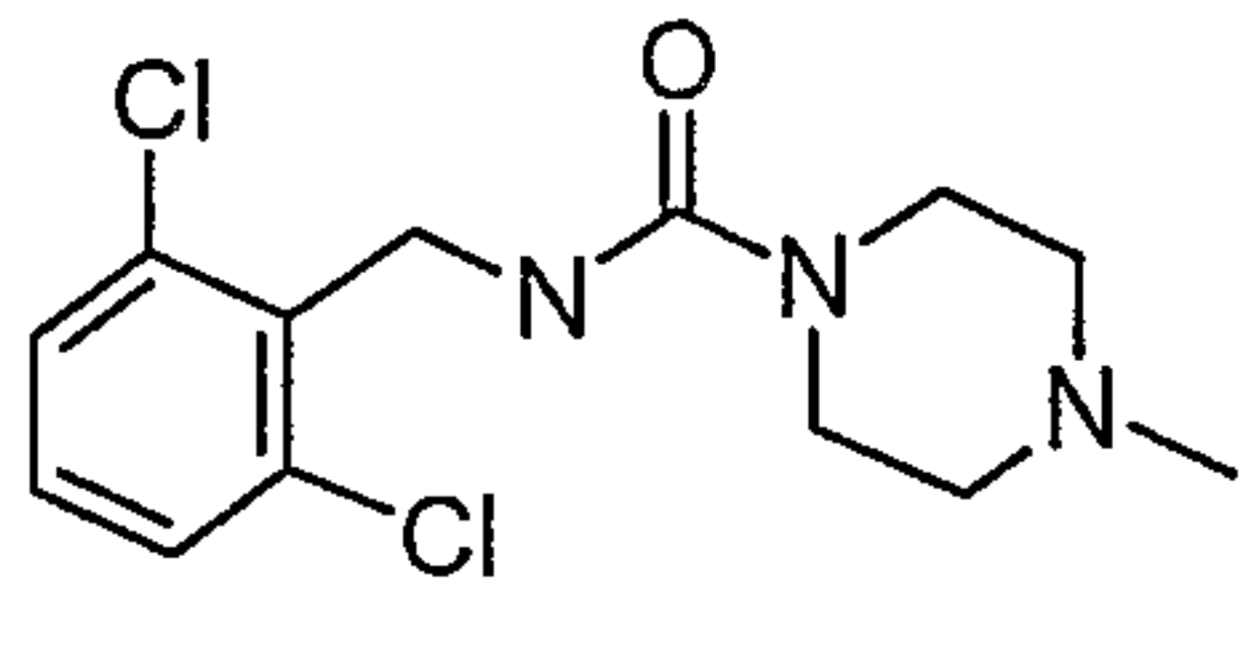
Example No.	STRUCTURE	Name	MW	Exact Mass	MH+
1.		N-(3,4-dichlorobenzyl)-4-methylpiperazine-1-carboxamide	302.2	301.1	302.1
2.		(4-(naphthalen-2-ylsulfonyl)piperazin-1-yl)(4-(pyridin-4-yl)piperazin-1-yl)methanone	465.58	465.2	466.2

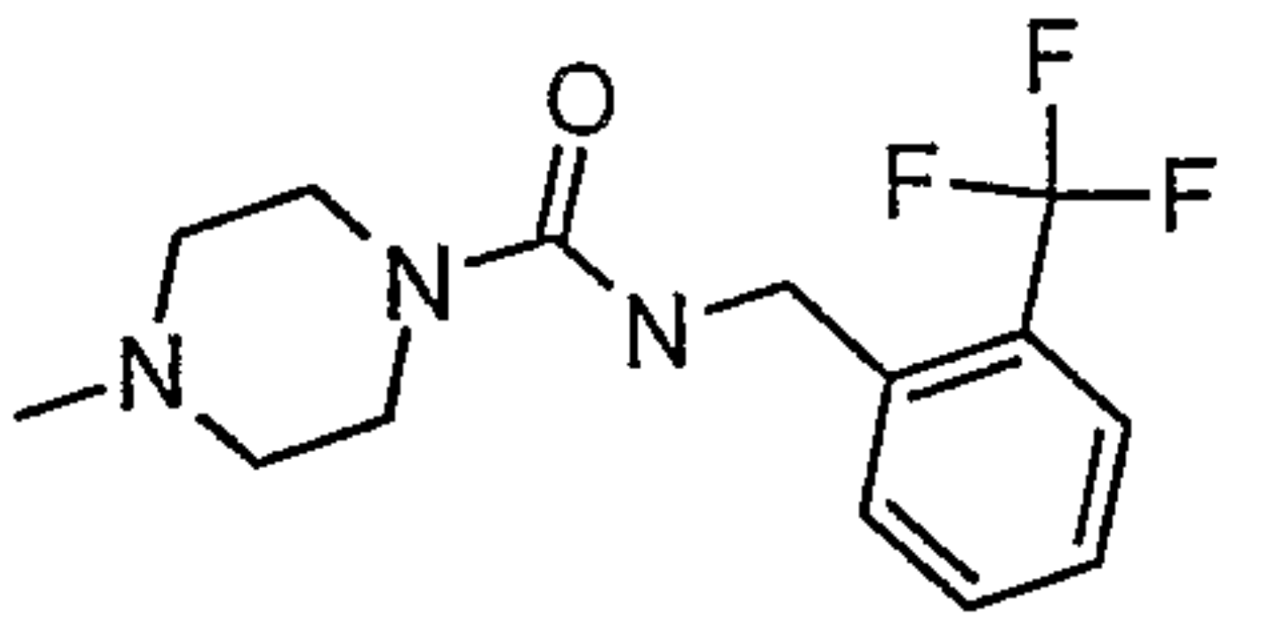
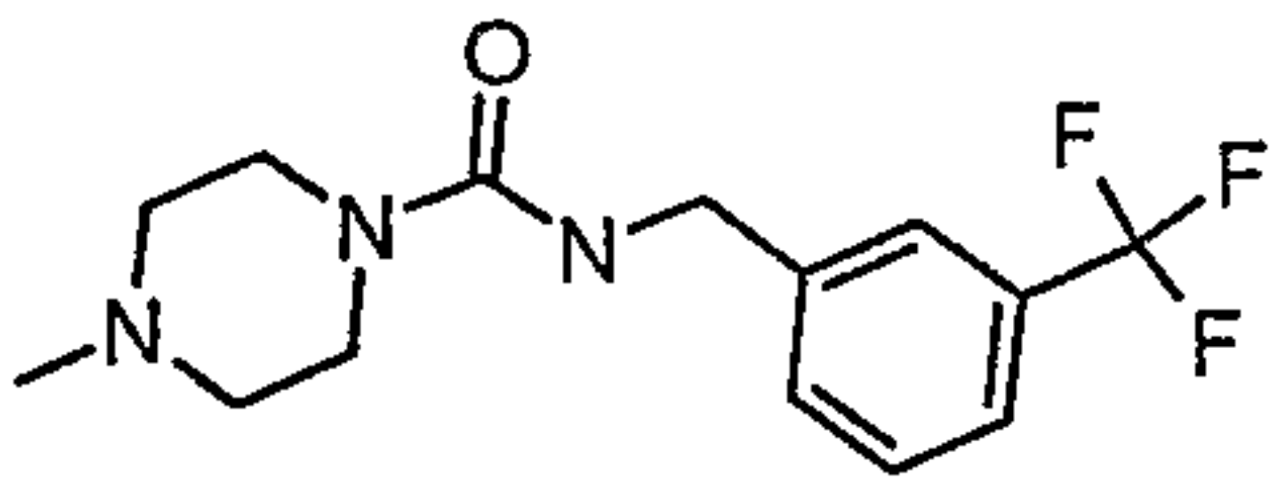
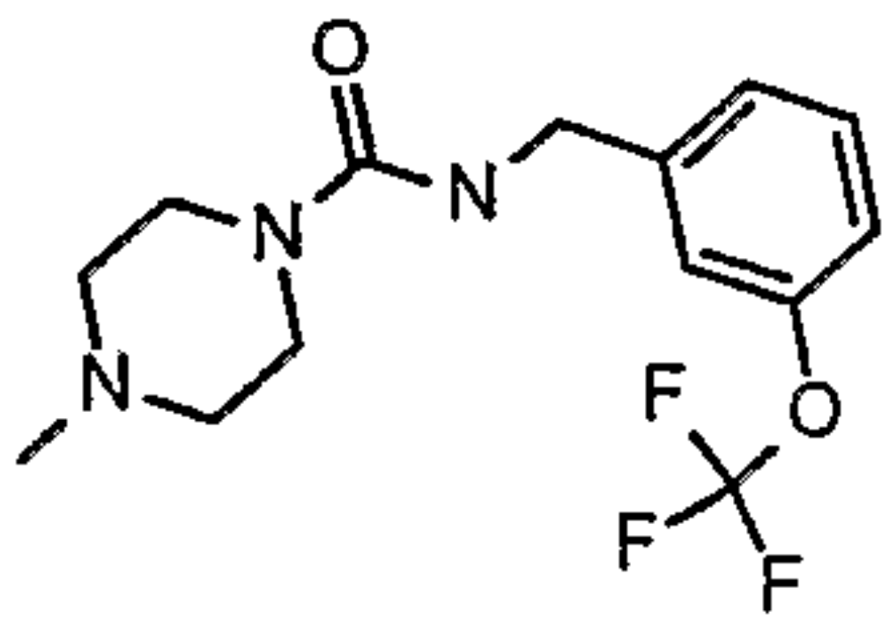
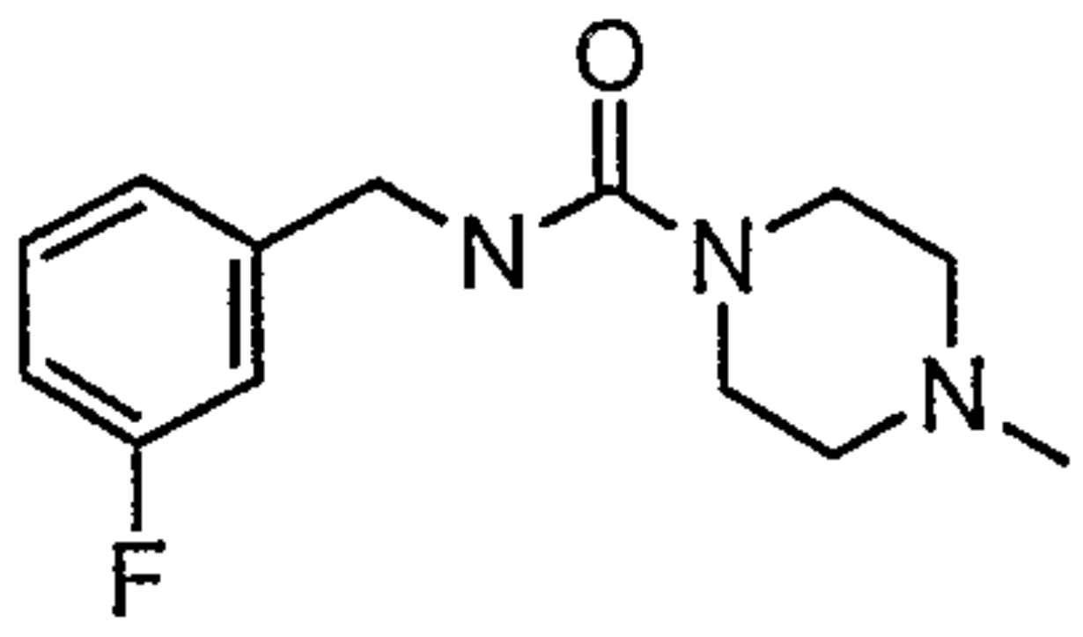
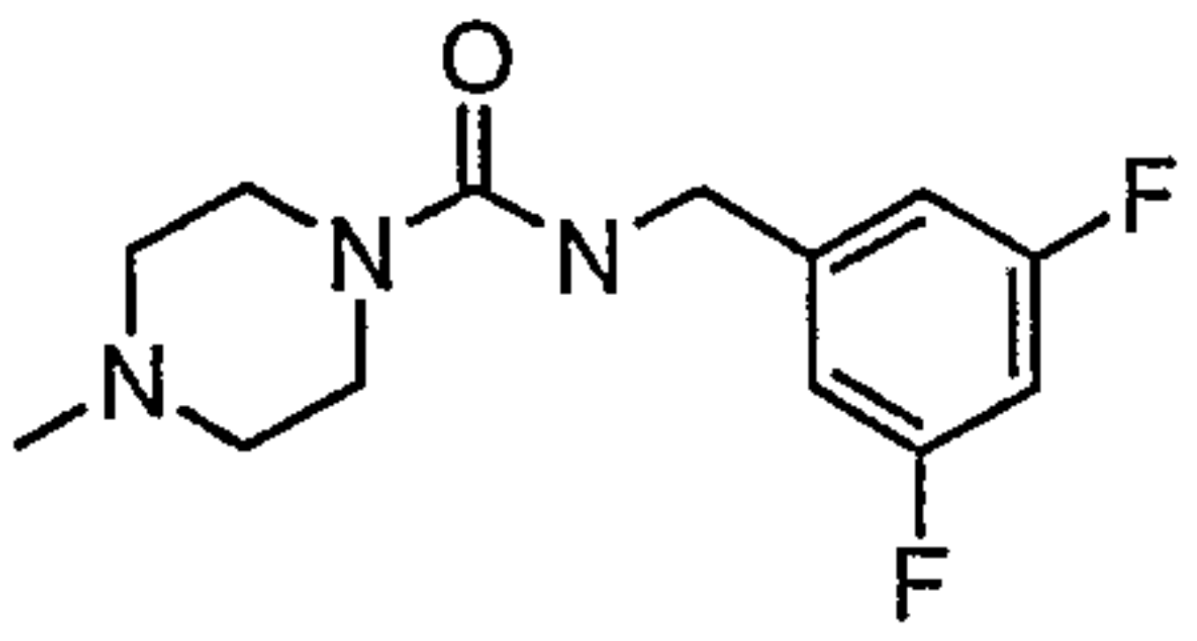
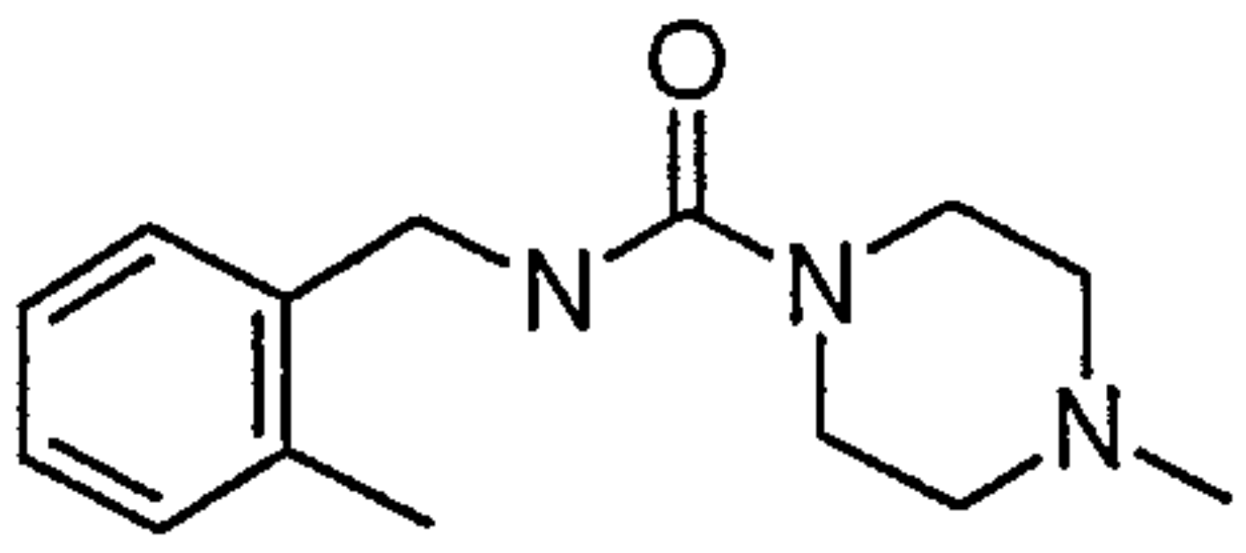
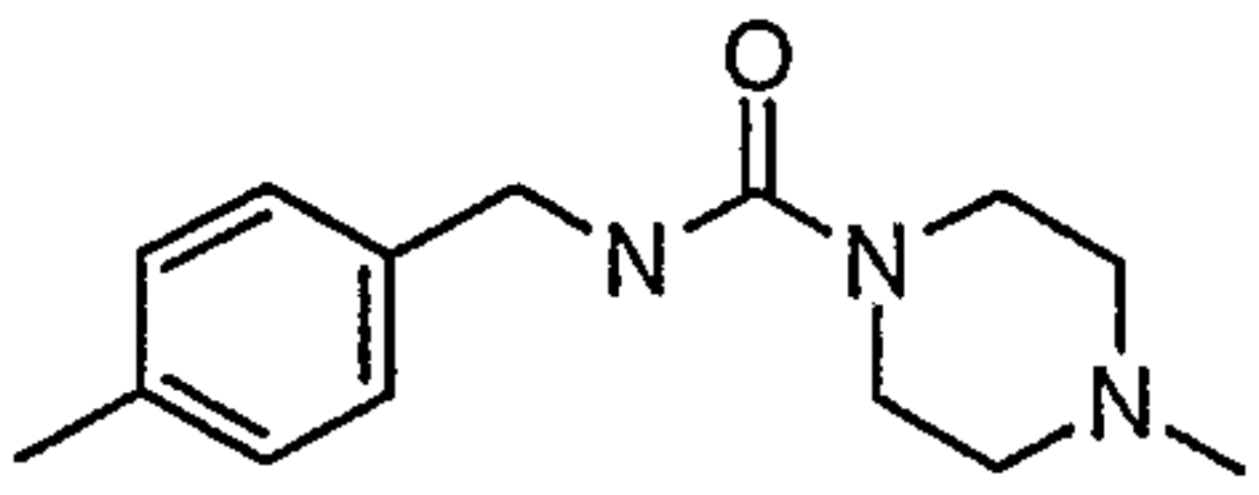
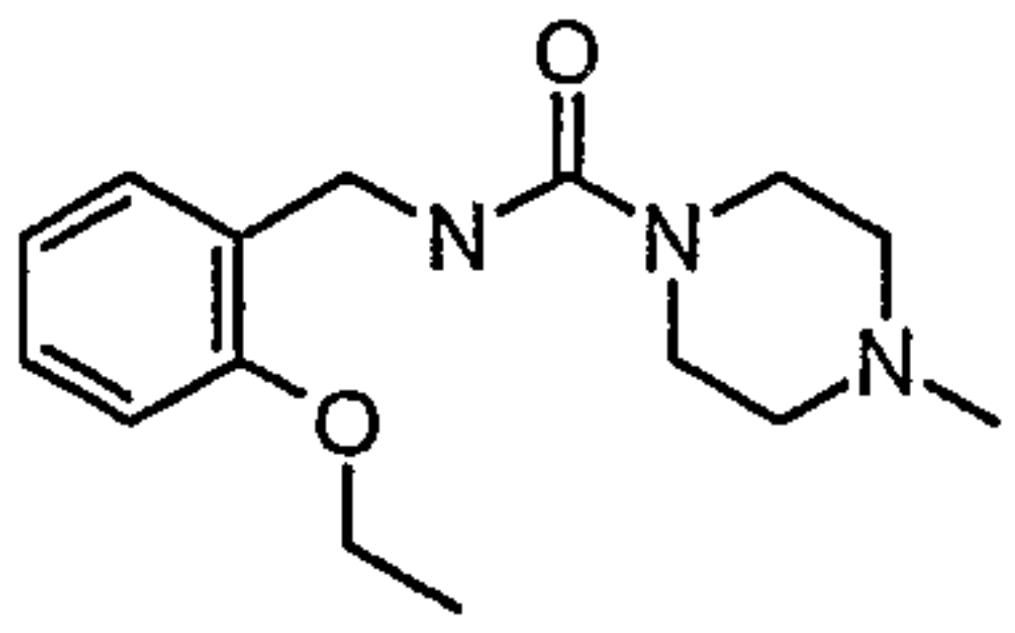
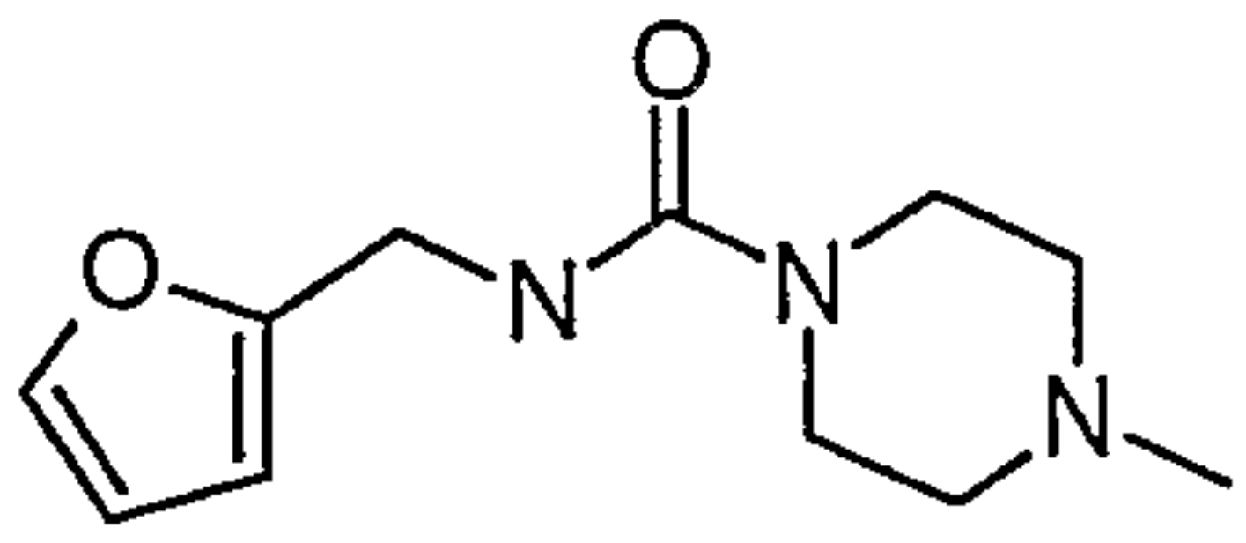
Example No.	STRUCTURE	Name	MW	Exact Mass	MH+
3.		1-(4-benzylpiperazine-1-carbonyl)-4-ethylpiperazine-2,3-dione	344.41	344.2	345.2
4.		N-(3-(dimethylamino)-2,2-dimethylpropyl)-4-ethyl-2,3-dioxopiperazine-1-carboxamide	298.38	298.2	299.2
5.		N-benzyl-4-methylpiperazine-1-carboxamide	233.31	233.2	234.2
6.		N-(4-bromo-2,6-dimethylphenyl)-4-methylpiperazine-1-carboxamide	326.24	325.1	326.1
7.		4-methyl-N-(2-(thiophen-2-yl)ethyl)piperazine-1-carboxamide	253.37	253.1	254.1
8.		1-(1,4'-bipiperidine-1'-carbonyl)-4-ethylpiperazine-2,3-dione	336.43	336.2	337.2
9.		5-[(4-methylpiperazin-1-yl)carbonyl]-10,11-dihydro-5H-dibenzo[b,f]azepine	321.42	321.2	322.2
10.		2-[4-(10,11-dihydro-5H-dibenzo[b,f]azepin-5-ylcarbonyl)piperazin-1-yl]ethanol	351.45	351.2	352.2
11.		bis(4-methylpiperazin-1-yl)methanone	226.32	226.2	227.2

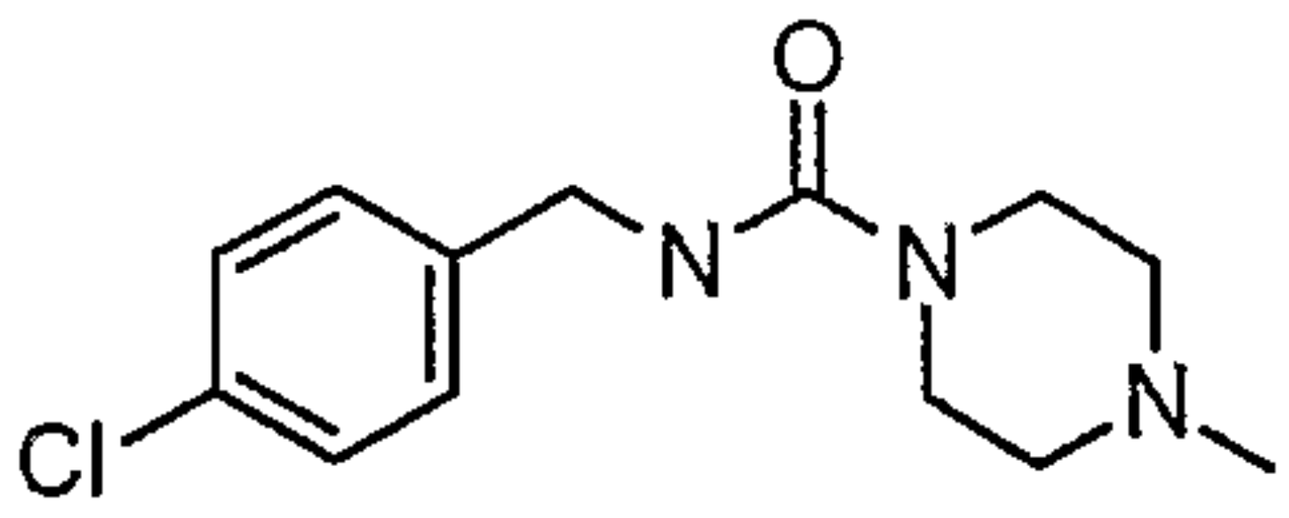
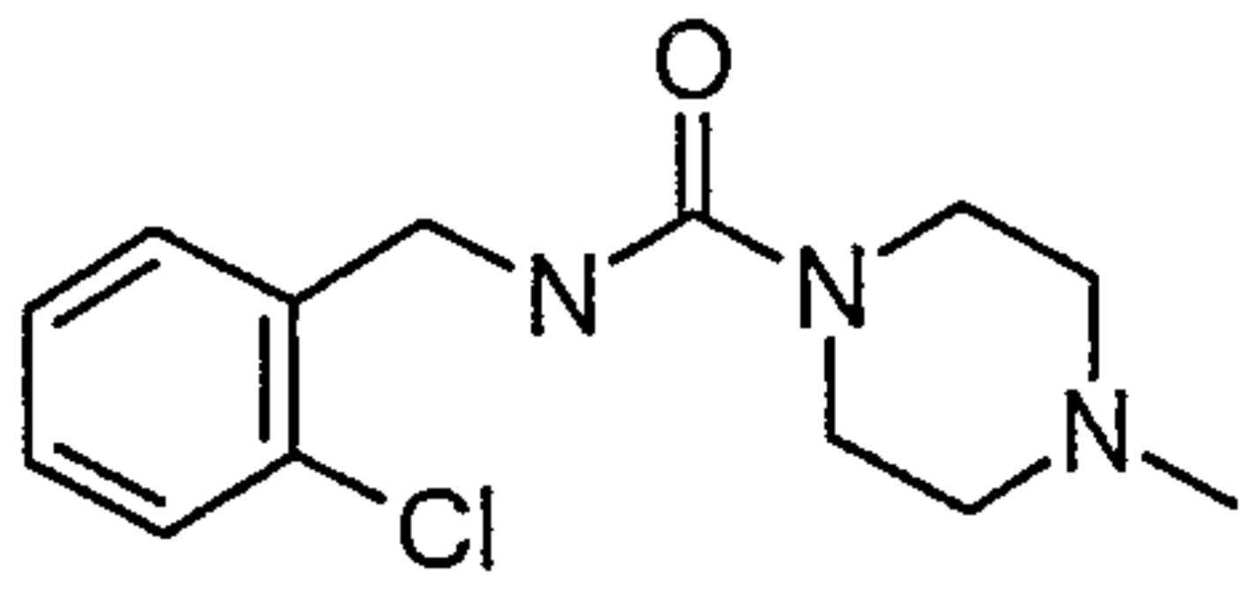
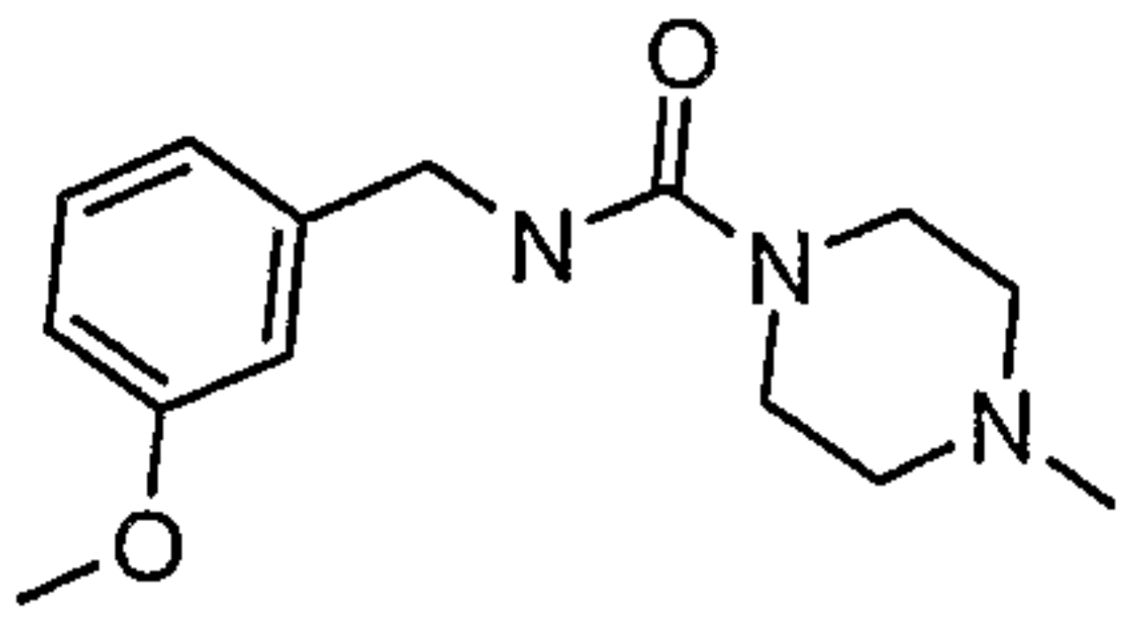
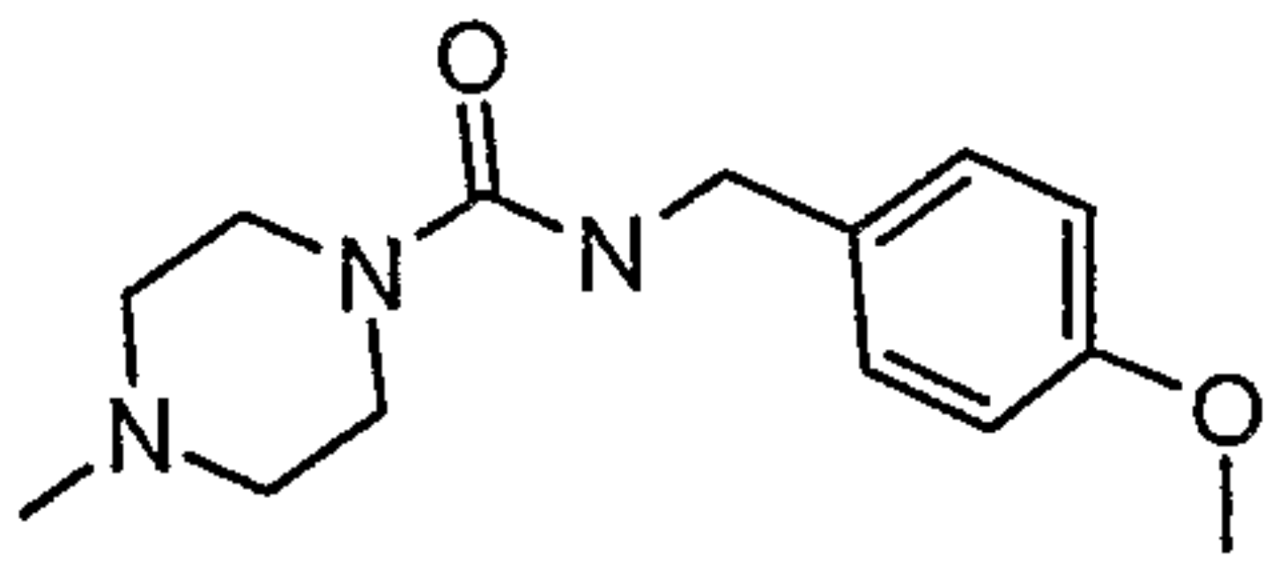
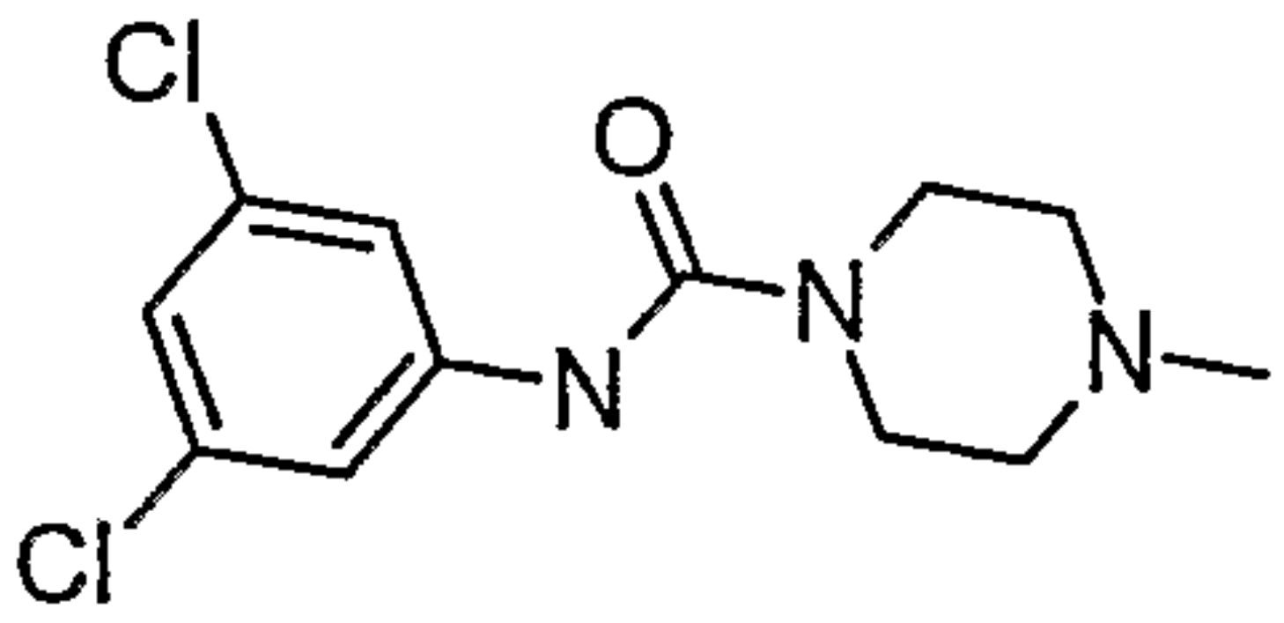
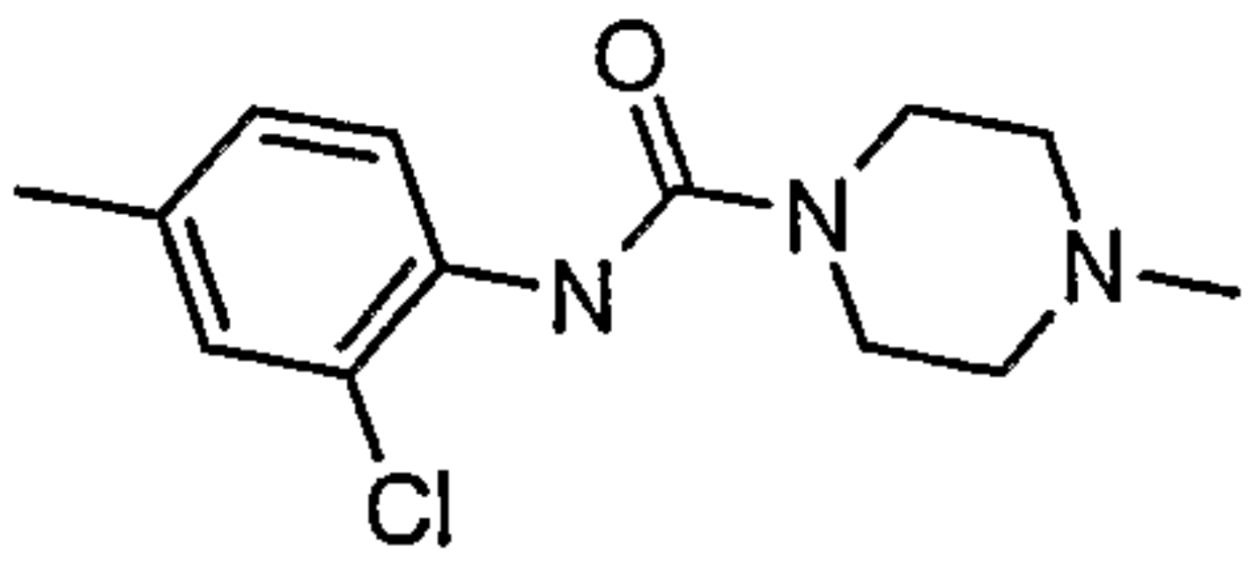
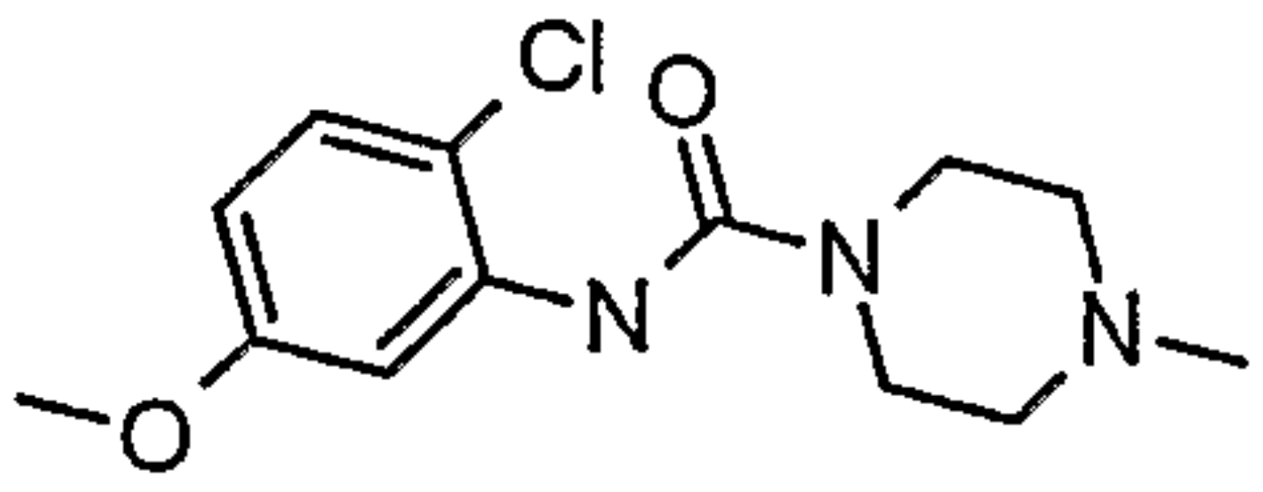
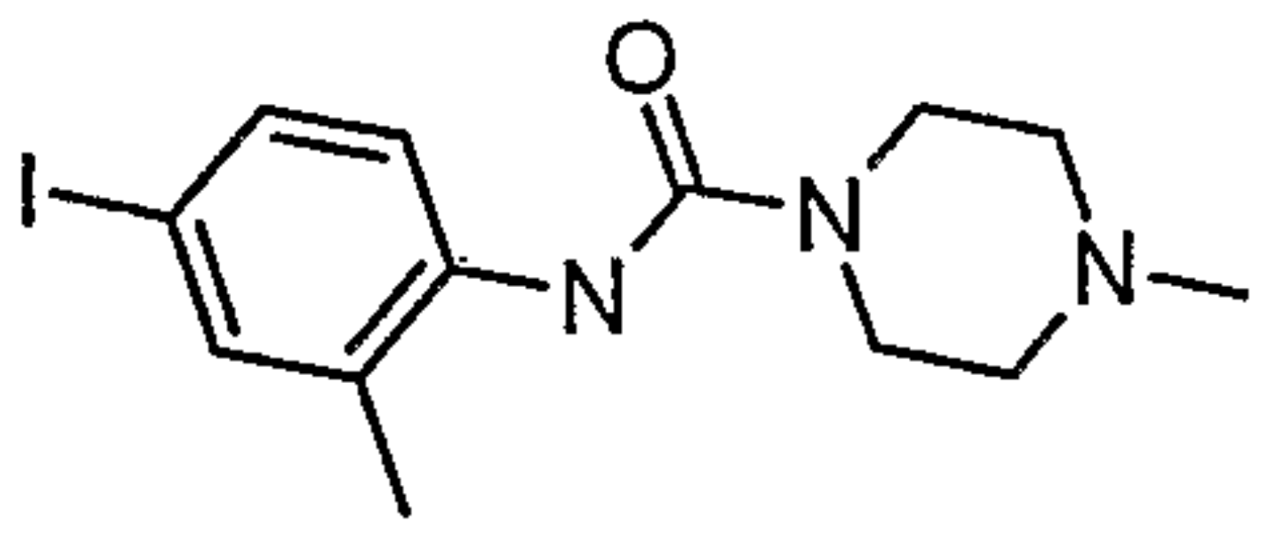
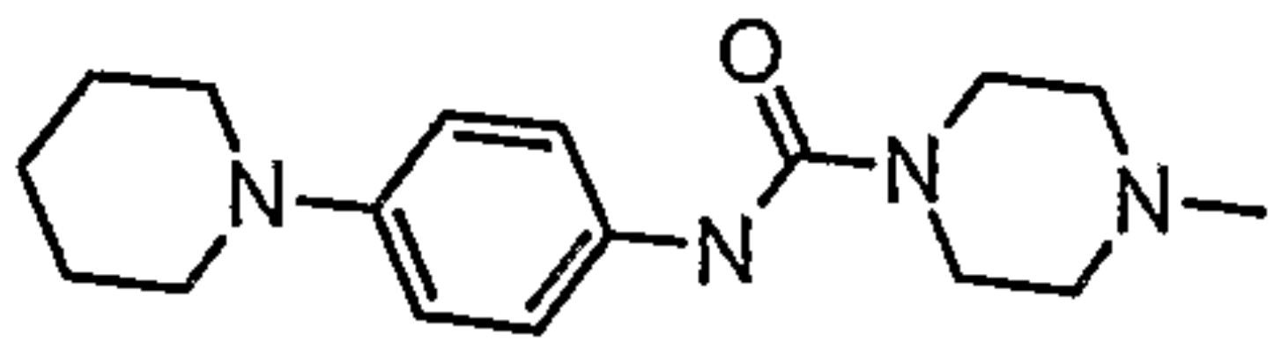
Example No.	STRUCTURE	Name	MW	Exact Mass	MH+
12.		(4-(7-bromoquinolin-3-ylsulfonyl)piperazin-1-yl)(4-(pyridin-4-yl)piperazin-1-yl)methanone	545.46	544.1	545.1
13.		(4-(4-bromobenzyl)piperazin-1-yl)(4-(2-methylpyrimidin-4-yl)piperazin-1-yl)methanone	459.39	458.1	459.2
14.		(4-bromophenyl)(4-(4-(pyridin-4-yl)piperazine-1-carbonyl)piperazin-1-yl)methanone	458.36	457.1	458.1
15.		(4-(4-fluorophenylsulfonyl)piperazin-1-yl)(4-(pyridin-4-yl)piperazin-1-yl)methanone	433.51	433.2	434.2
16.		2-[4-(5H-dibenzo[b,f]azepin-5-ylcarbonyl)piperazin-1-yl]ethanol	349.43	349.2	350.2
17.		4-methyl-N-(4-morpholinobenzyl)piperazine-1-carboxamide	318.42	318.2	319.2
18.		4-methyl-N-(4-(trifluoromethyl)benzyl)piperazine-1-carboxamide	301.31	301.1	302.1
19.		N-(2,5-difluorobenzyl)-4-methylpiperazine-1-carboxamide	269.29	269.1	270.1
20.		N-(2,6-dimethylbenzyl)-4-methylpiperazine-1-carboxamide	261.37	261.2	262.2

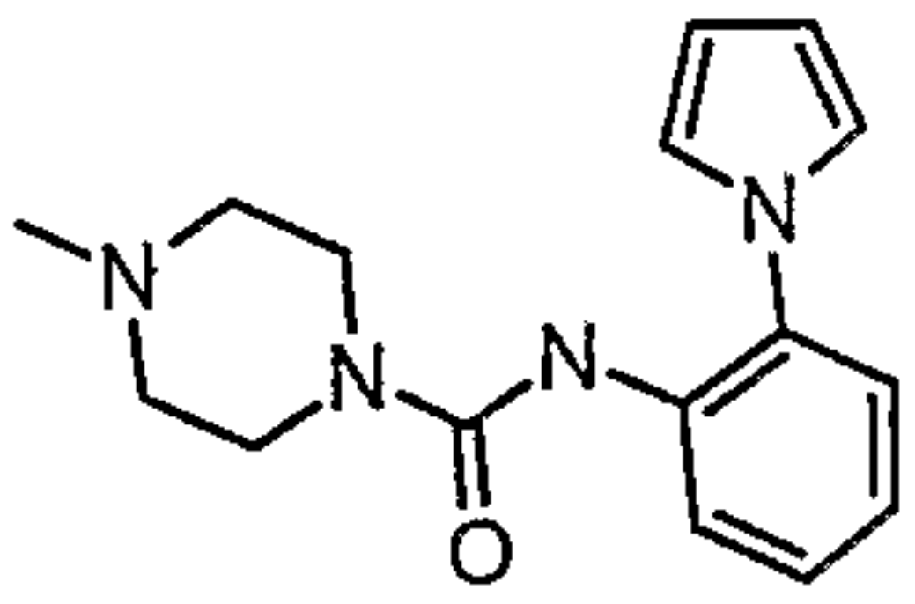
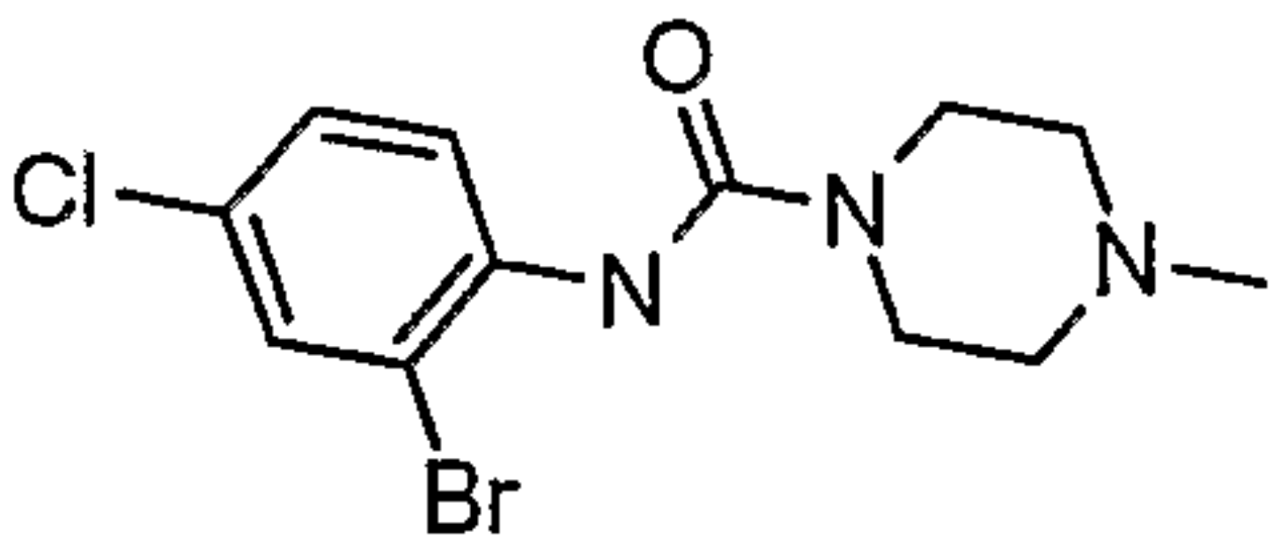
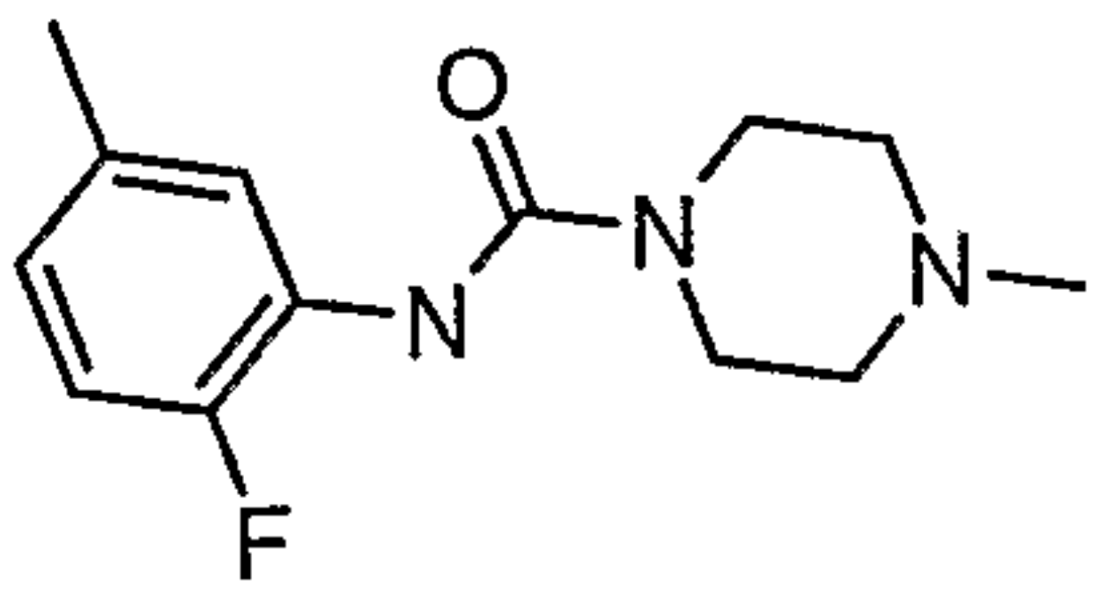
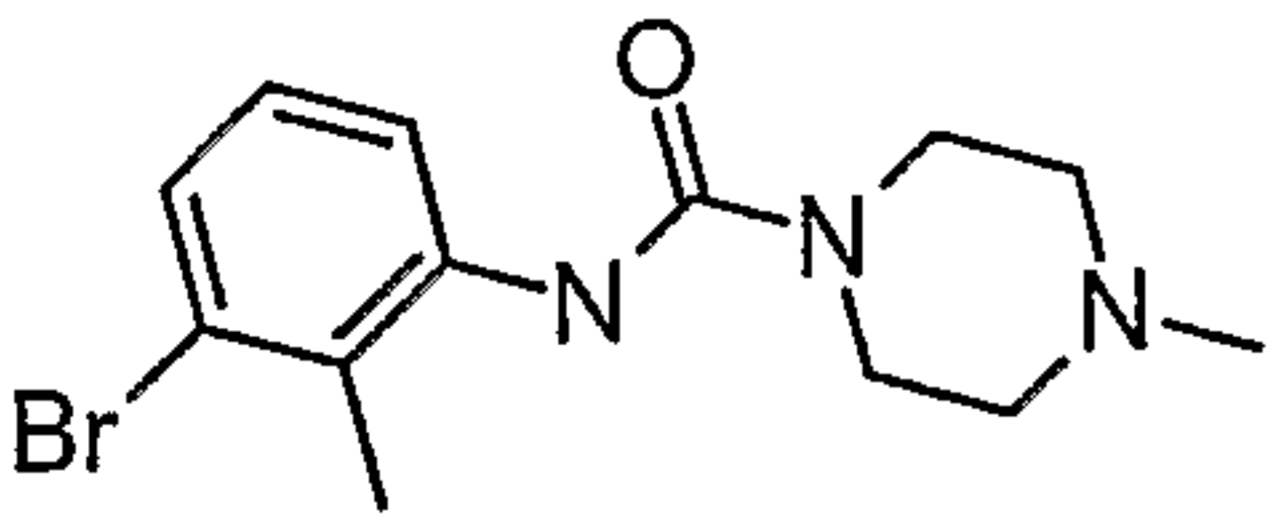
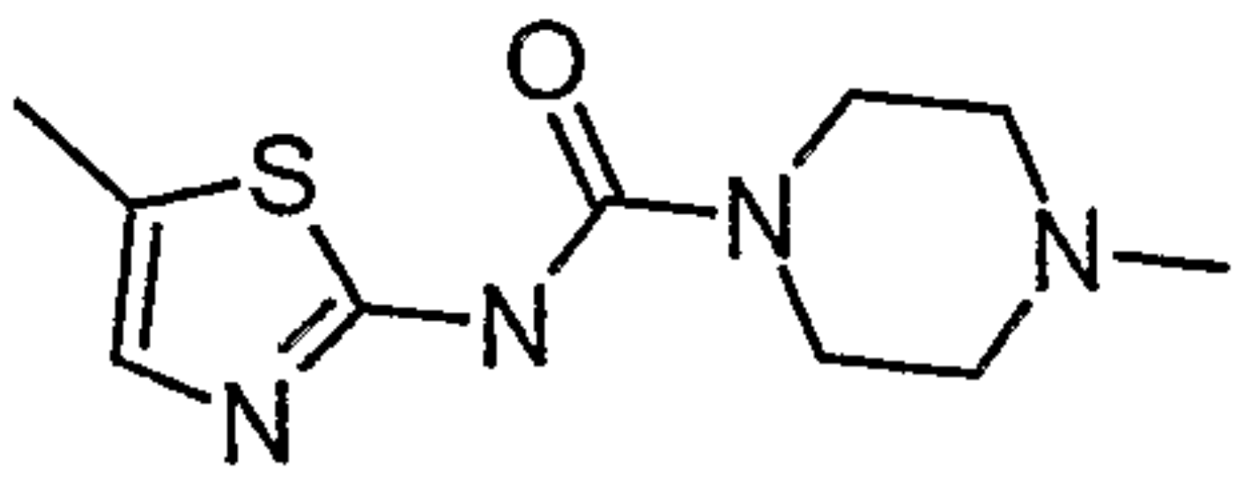
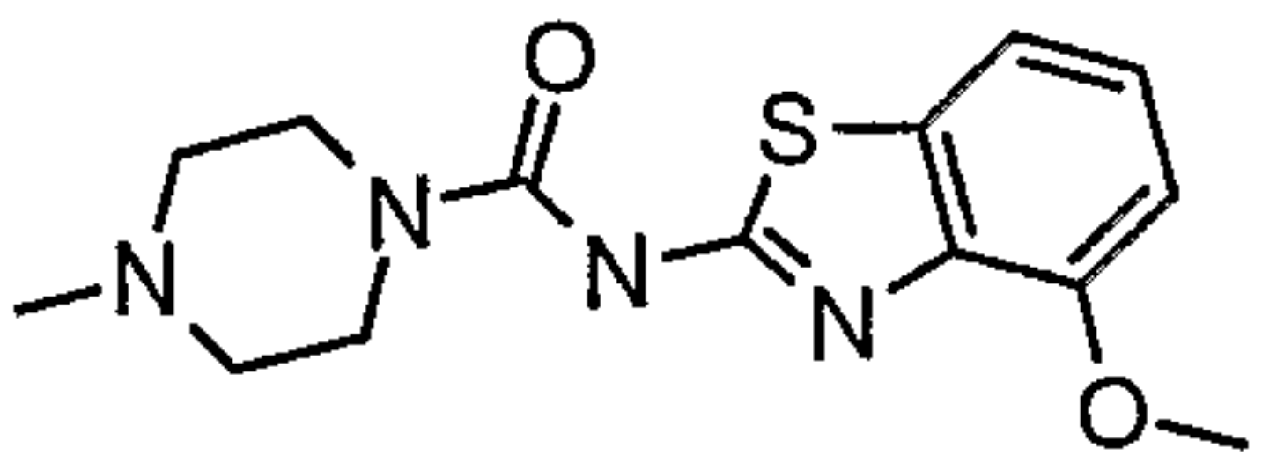
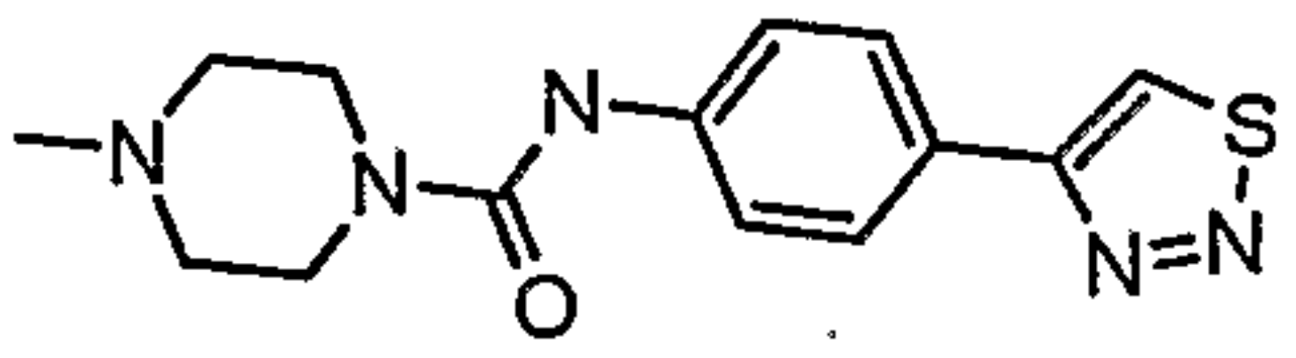
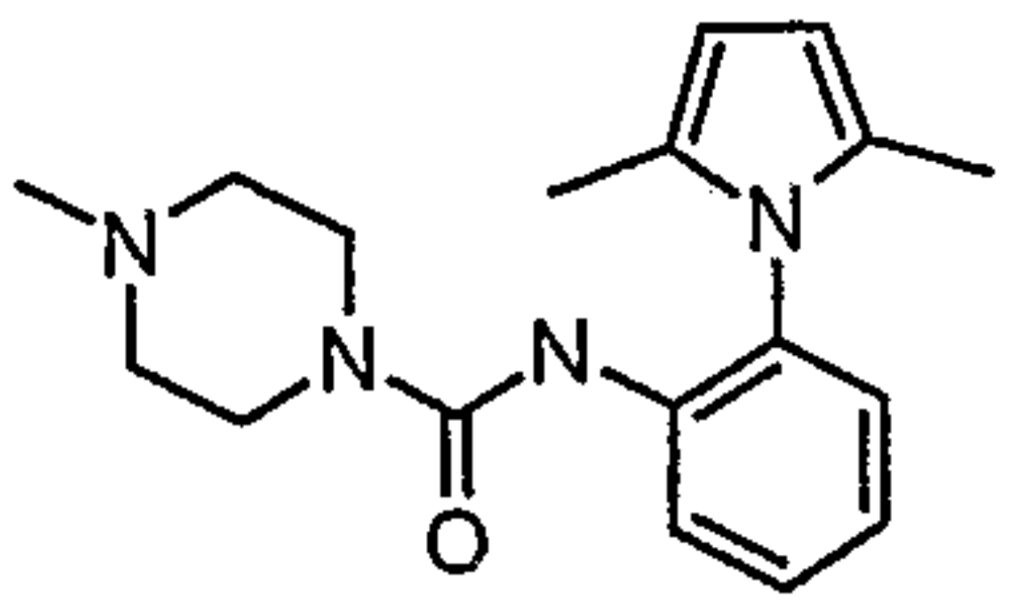
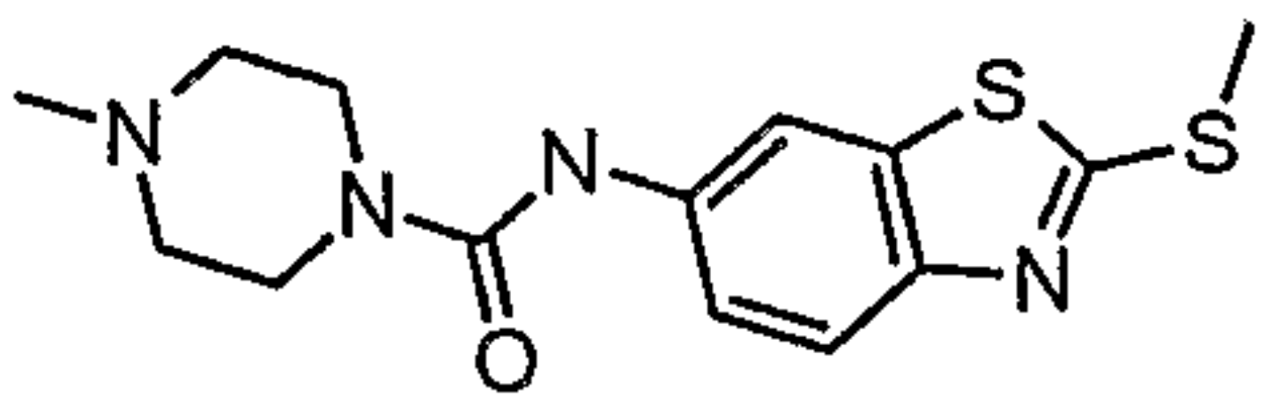
Example No.	STRUCTURE	Name	MW	Exact Mass	MH+
21.		N-(3-fluoro-4-methylbenzyl)-4-methylpiperazine-1-carboxamide	265.33	265.2	266.2
22.		N-(2,4-dichloro-6-methylbenzyl)-4-methylpiperazine-1-carboxamide	316.23	315.1	316.1
23.		N-(3,5-dimethylbenzyl)-4-methylpiperazine-1-carboxamide	261.37	261.2	262.2
24.		N-(2-fluoro-6-(4-methoxyphenoxy)benzyl)-4-methylpiperazine-1-carboxamide	373.43	373.2	374.2
25.		4-methyl-N-(4-(methylthio)benzyl)piperazine-1-carboxamide	279.41	279.1	280.1
26.		4-methyl-N-(4-phenoxybenzyl)piperazine-1-carboxamide	325.41	325.2	326.2
27.		N-(2-(4-methoxyphenoxy)ethyl)-4-methylpiperazine-1-carboxamide	293.37	293.2	294.2
28.		N-(4-fluorobenzyl)-4-methylpiperazine-1-carboxamide	251.3	251.1	252.2
29.		N-(2-(5-methoxy-1H-indol-3-yl)ethyl)-4-methylpiperazine-1-carboxamide	316.4	316.2	317.2

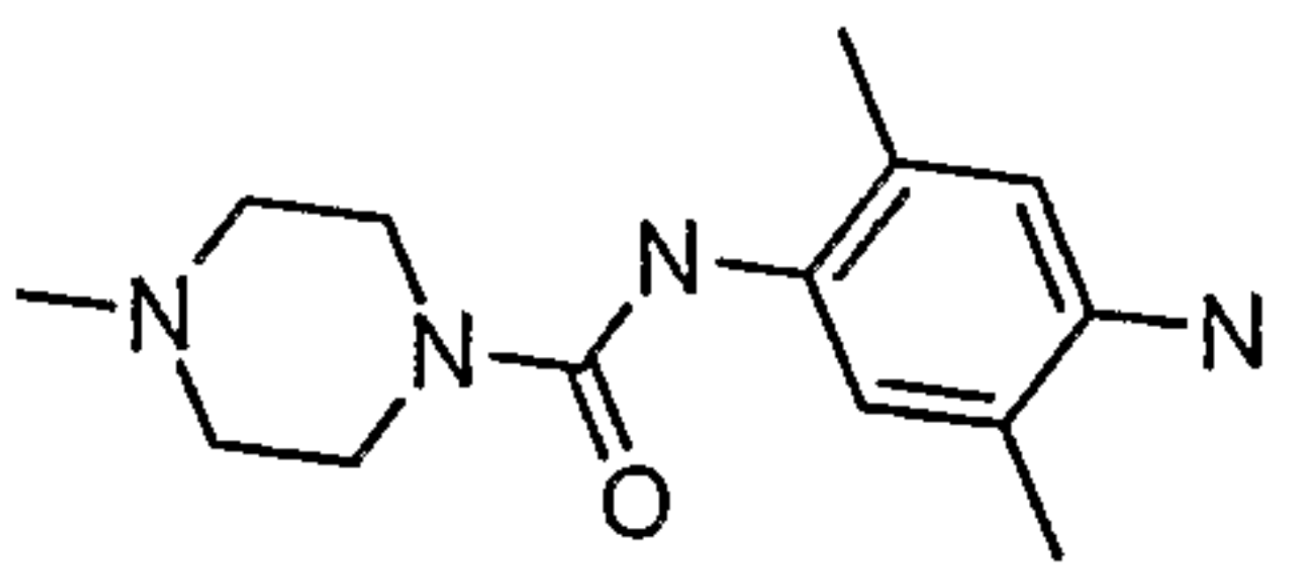
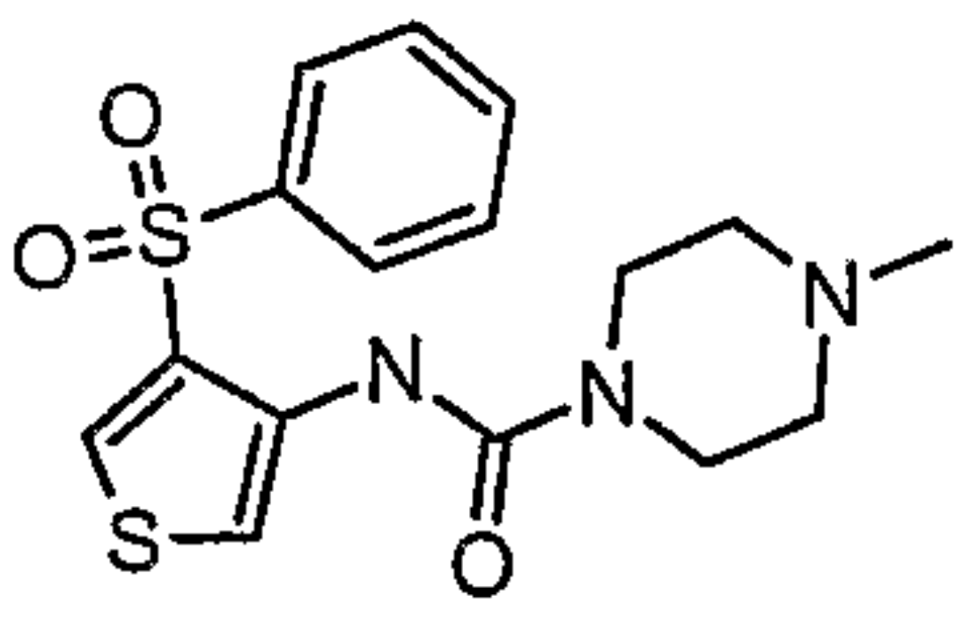
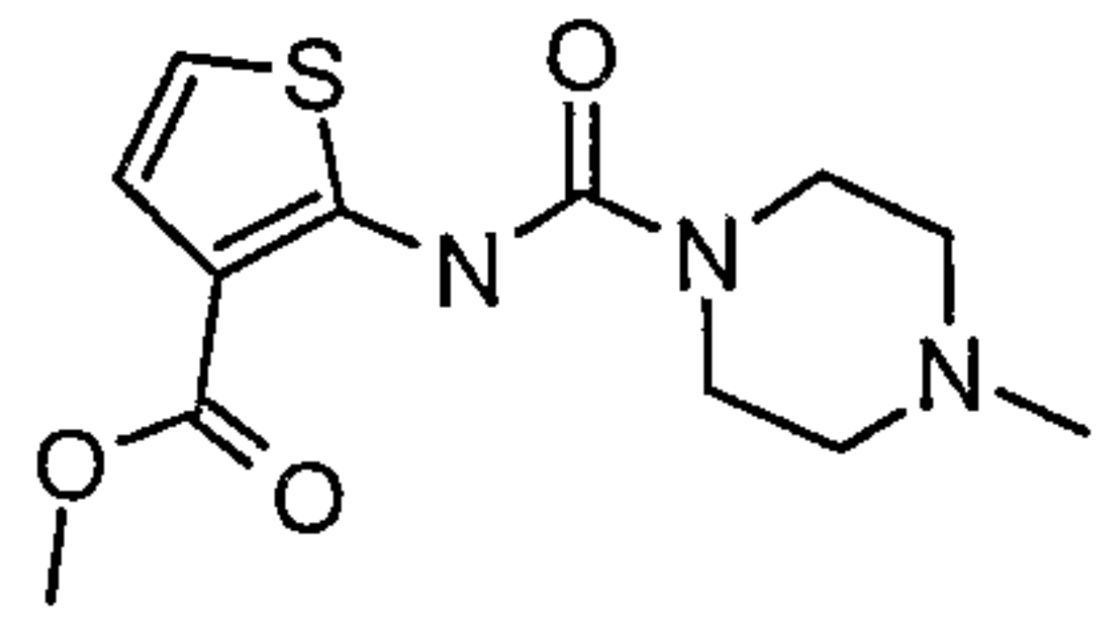
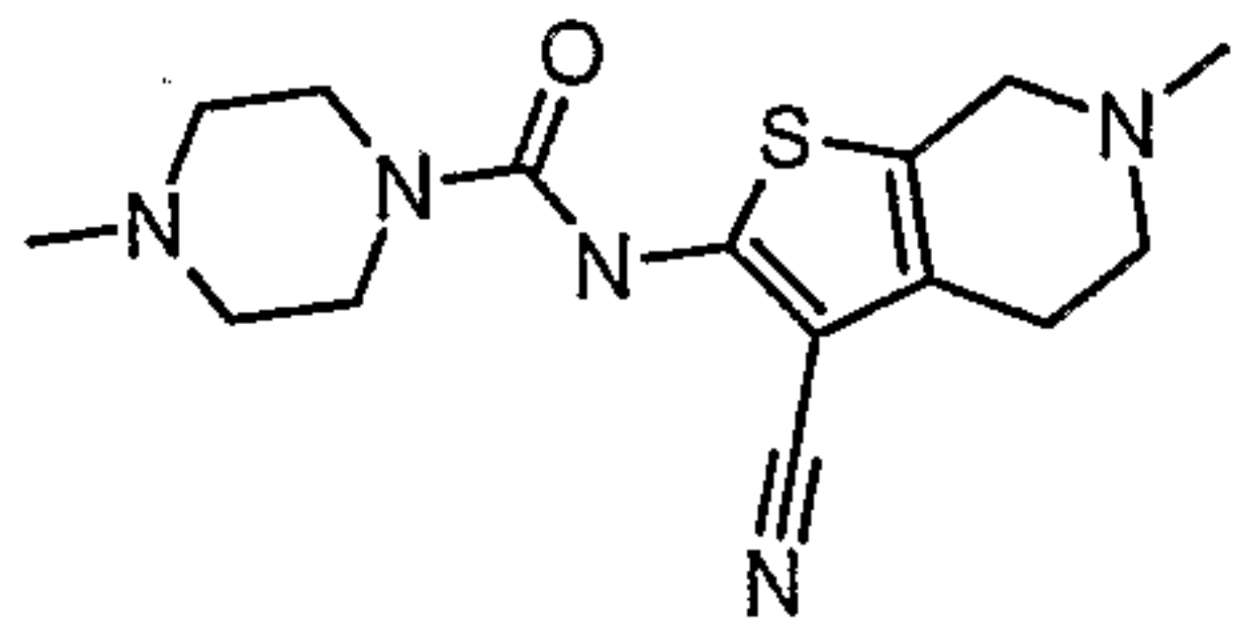
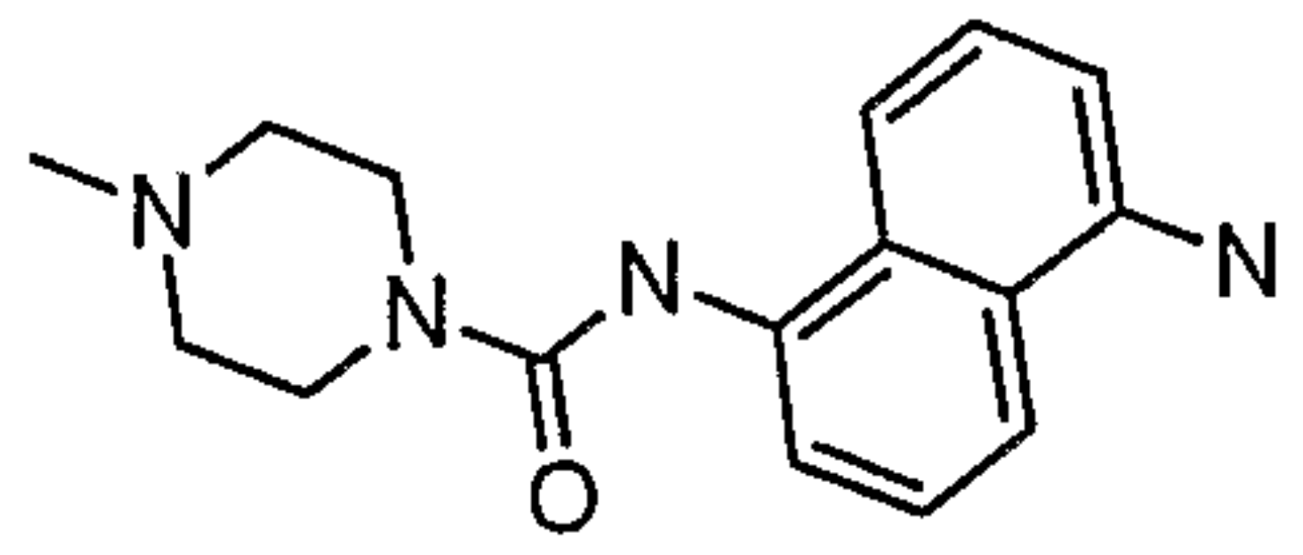
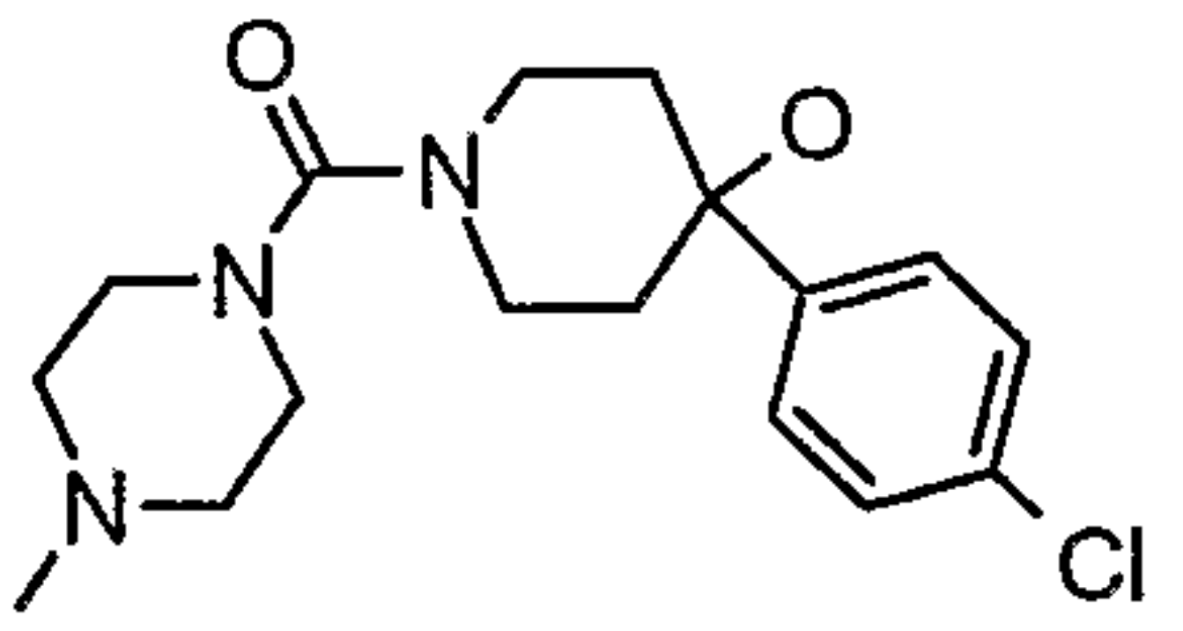
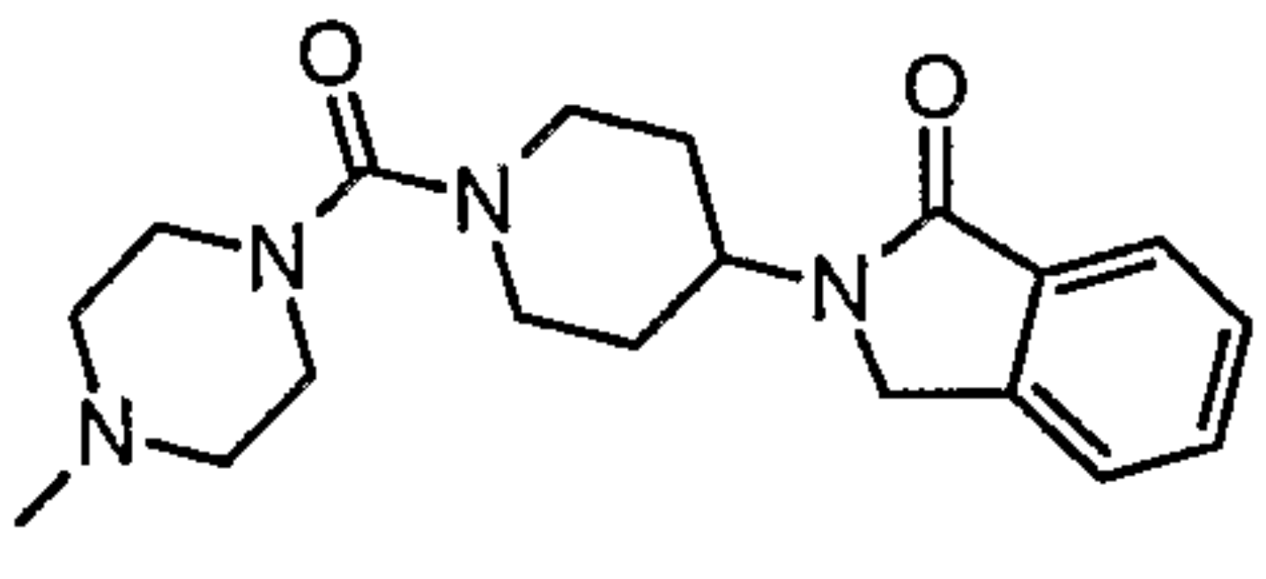
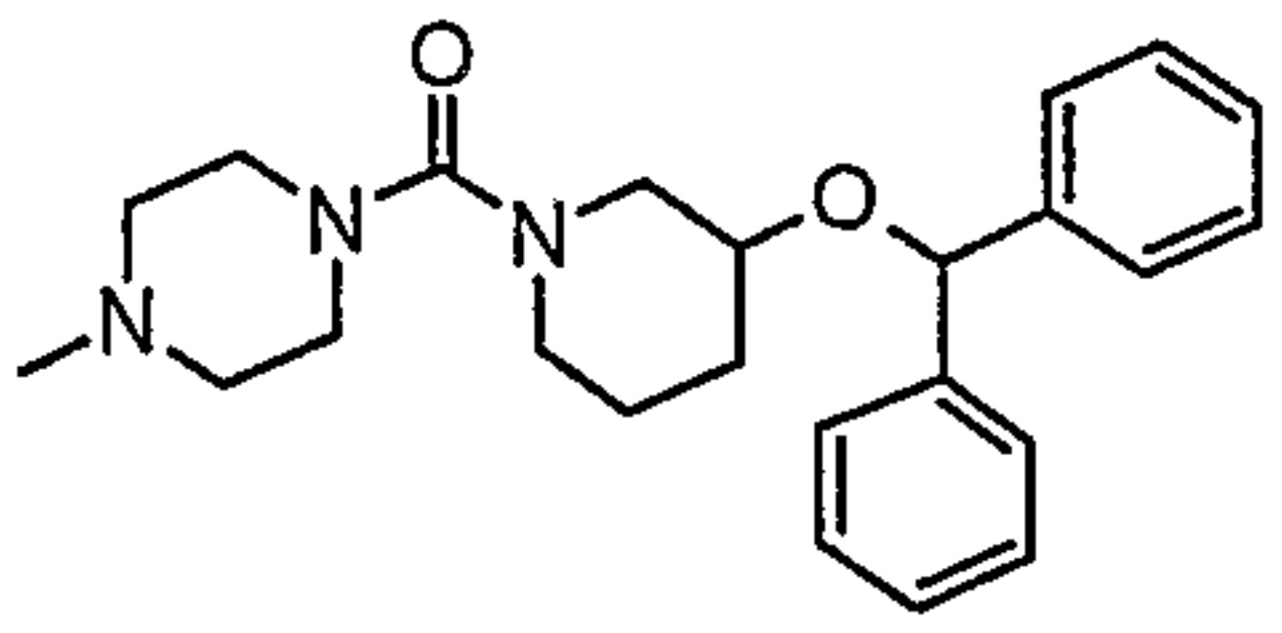
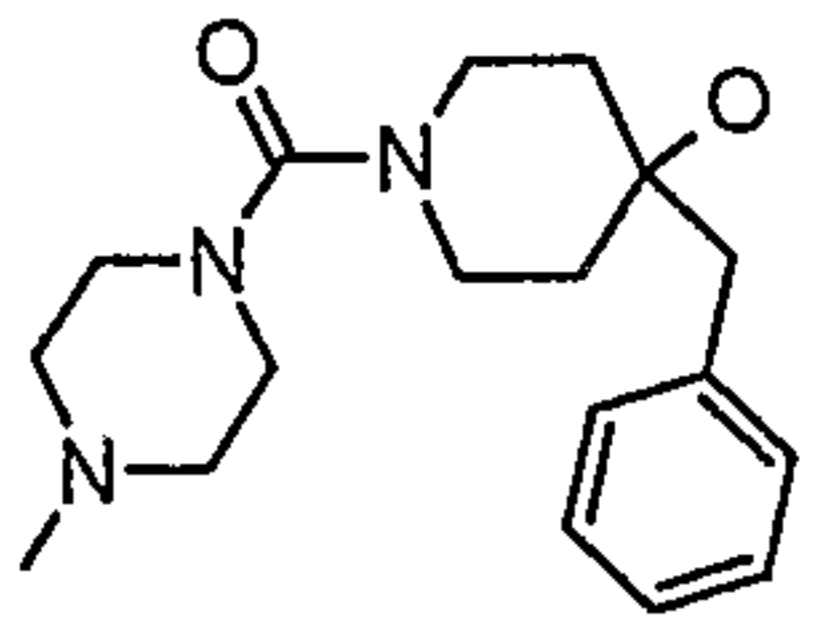
Example No.	STRUCTURE	Name	MW	Exact Mass	MH+
30.		N-(2-(6-methoxy-1H-indol-3-yl)ethyl)-4-methylpiperazine-1-carboxamide	316.4	316.2	317.2
31.		N-(3-bromo-4-methoxyphenethyl)-4-methylpiperazine-1-carboxamide	356.26	355.1	356.1
32.		4-methyl-N-phenethylpiperazine-1-carboxamide	247.34	247.2	248.2
33.		N-(3,4-dimethoxyphenethyl)-4-methylpiperazine-1-carboxamide	307.39	307.2	308.2
34.		N-(2-(1H-indol-3-yl)ethyl)-4-methylpiperazine-1-carboxamide	286.38	286.2	287.2
35.		N-(3-chlorobenzyl)-4-methylpiperazine-1-carboxamide	267.76	267.1	268.1
36.		N-(2,3-dimethoxybenzyl)-4-methylpiperazine-1-carboxamide	293.37	293.2	294.2
37.		4-methyl-N-(thiophen-2-ylmethyl)piperazine-1-carboxamide	239.34	239.1	240.1
38.		N-(benzo[d][1,3]dioxol-5-ylmethyl)-4-methylpiperazine-1-carboxamide	277.32	277.1	278.2

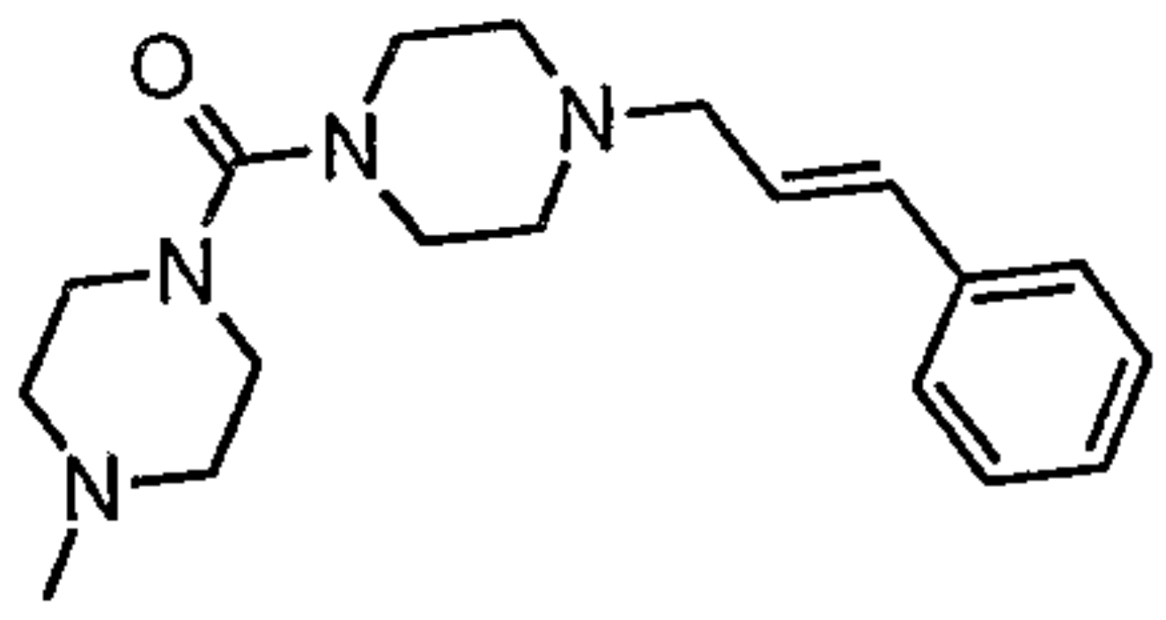
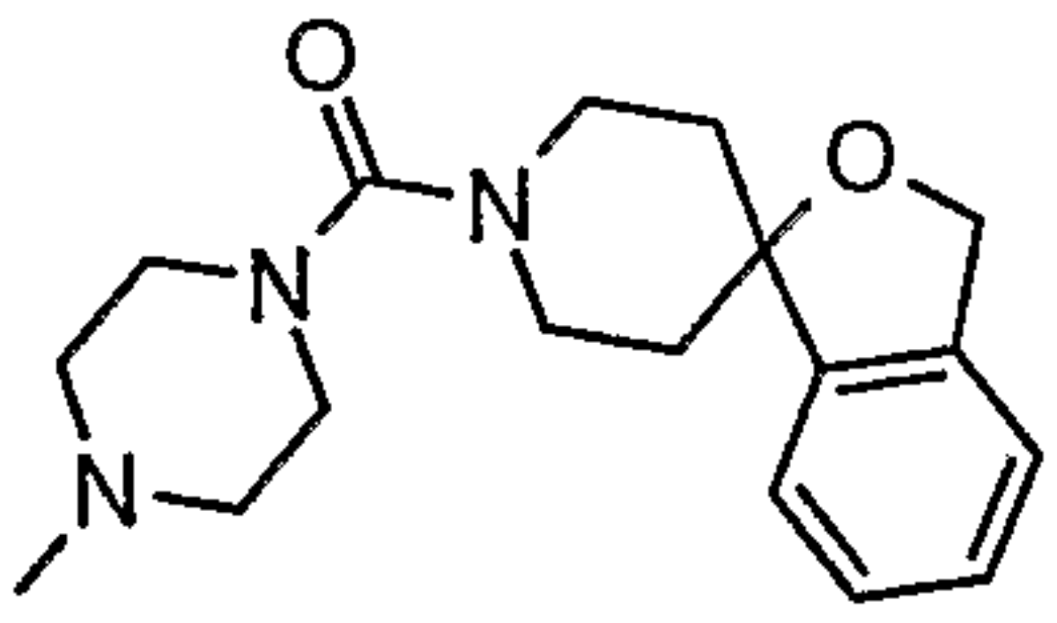
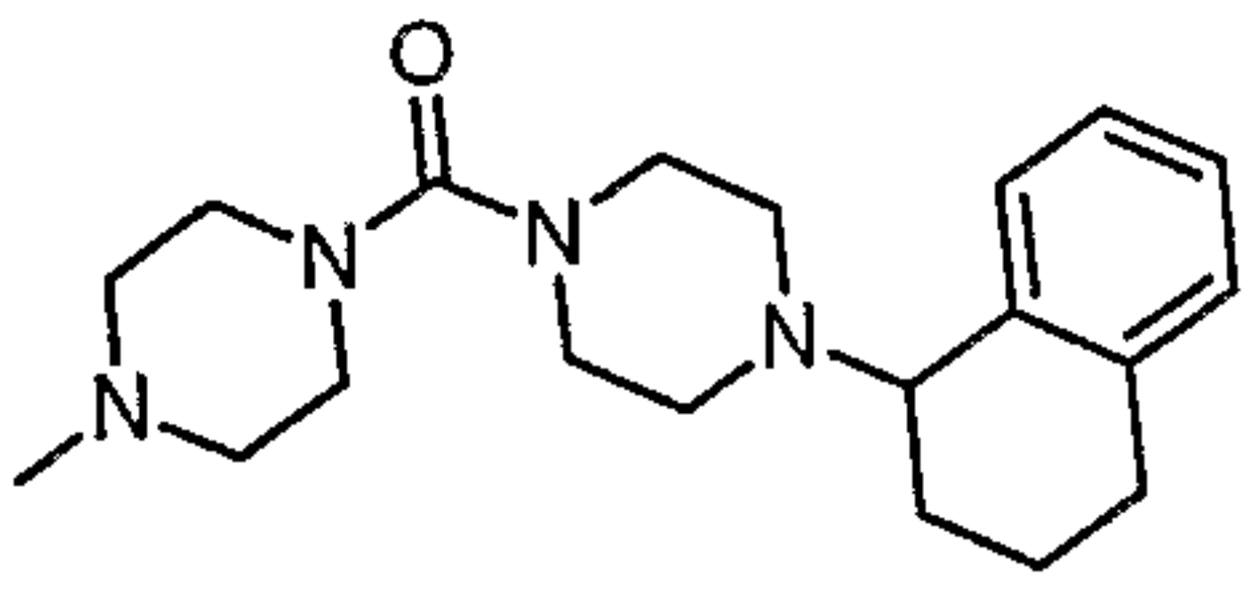
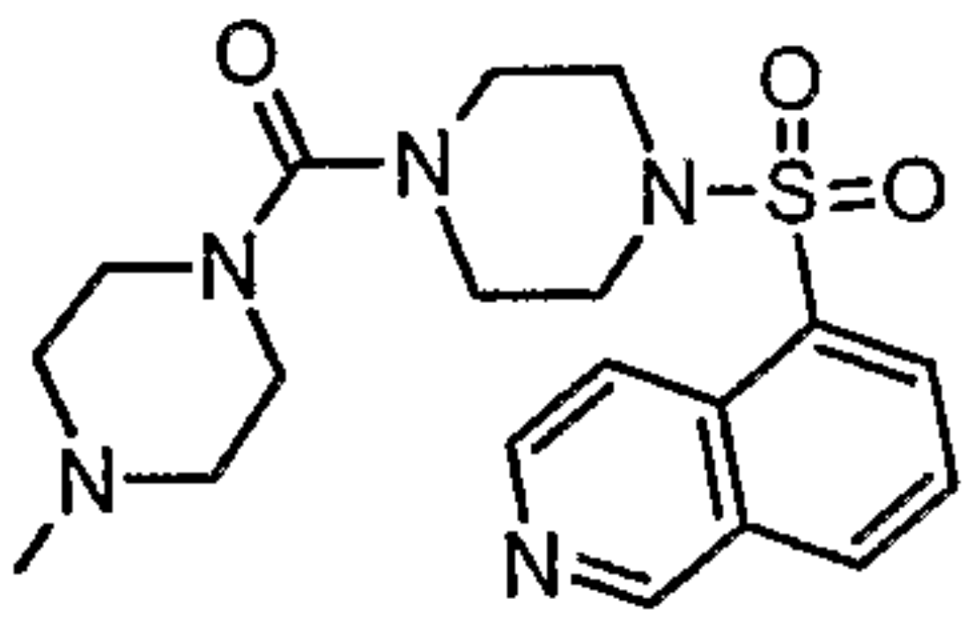
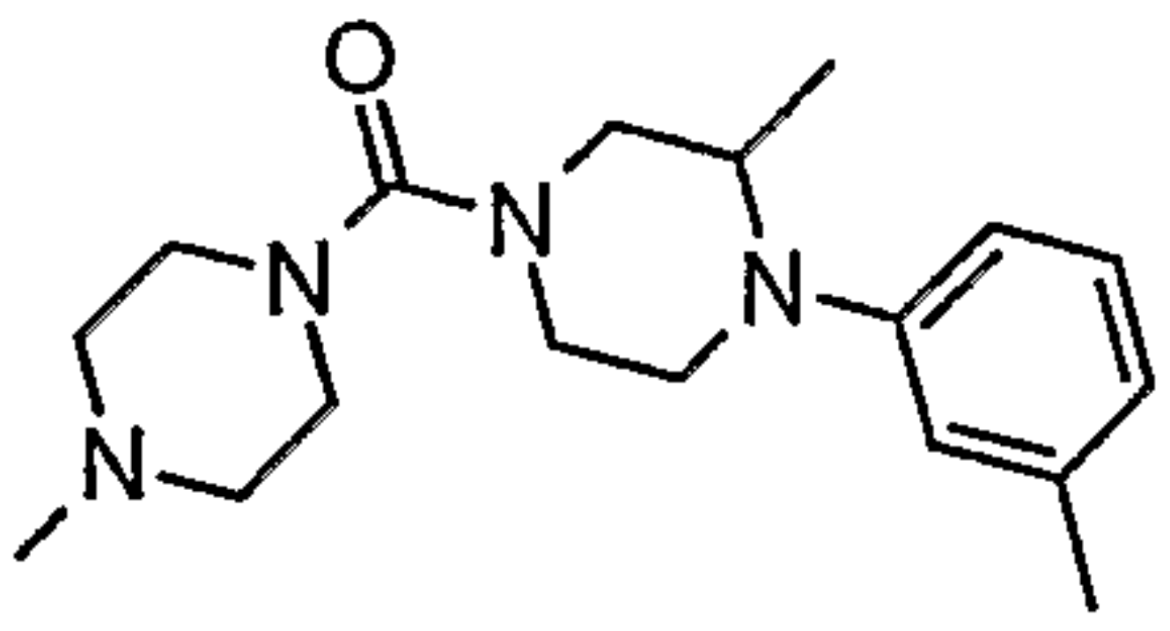
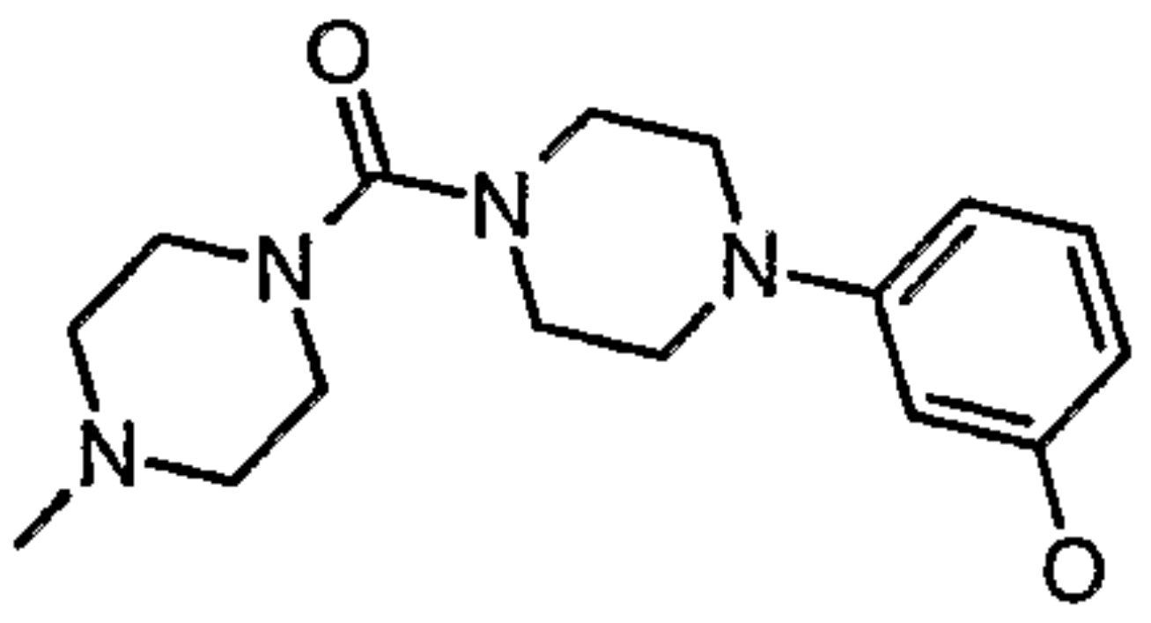
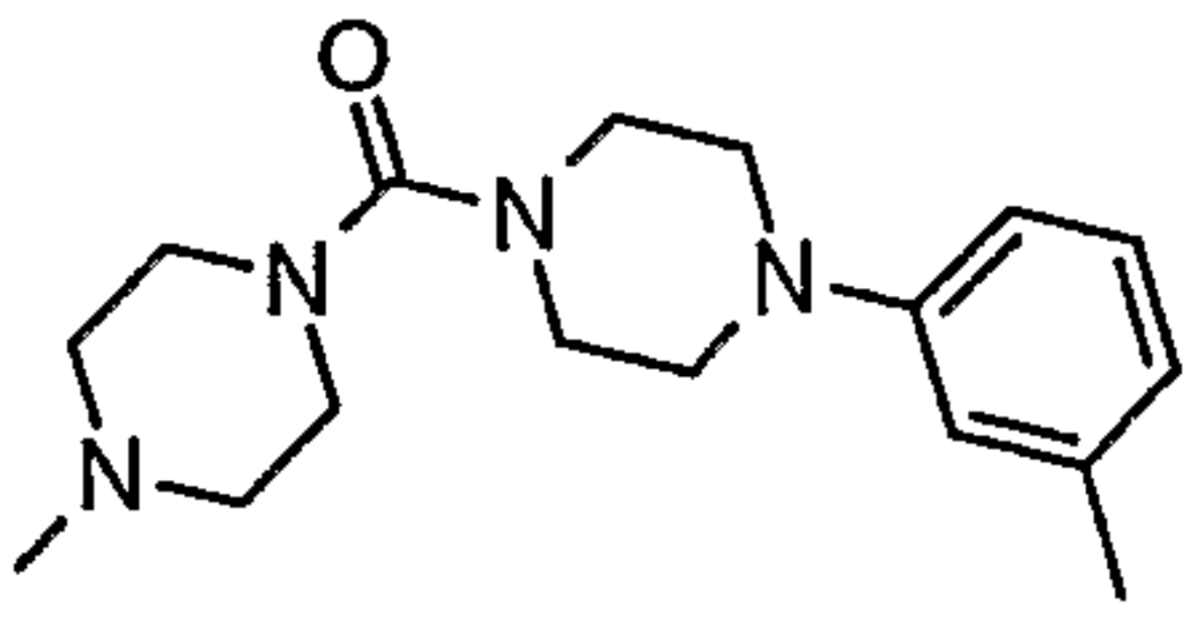
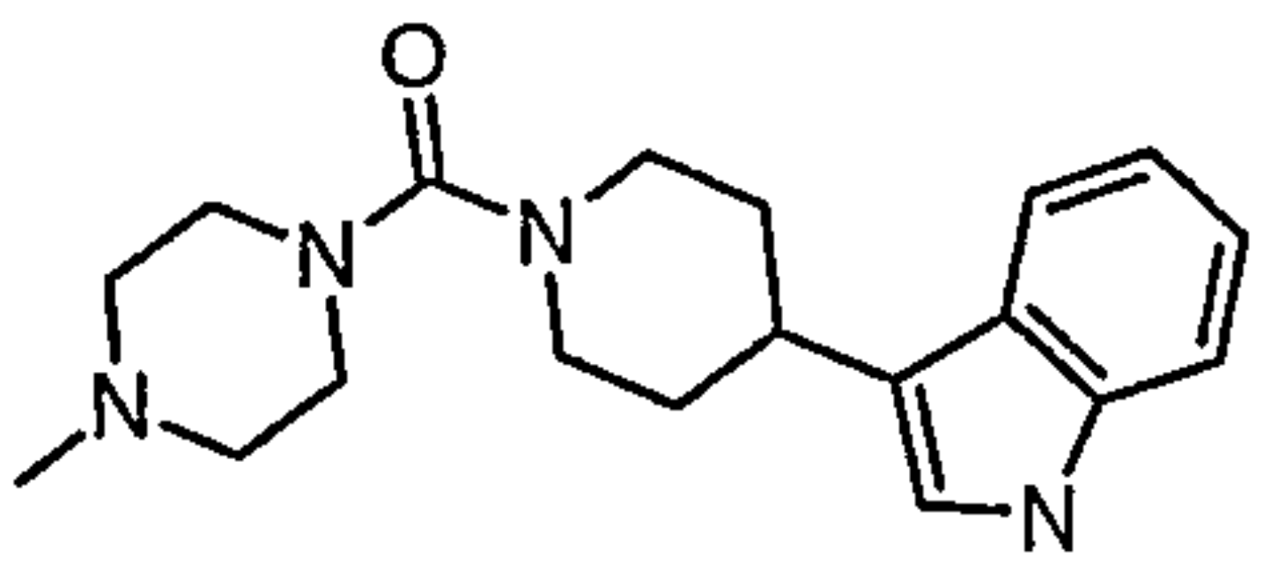
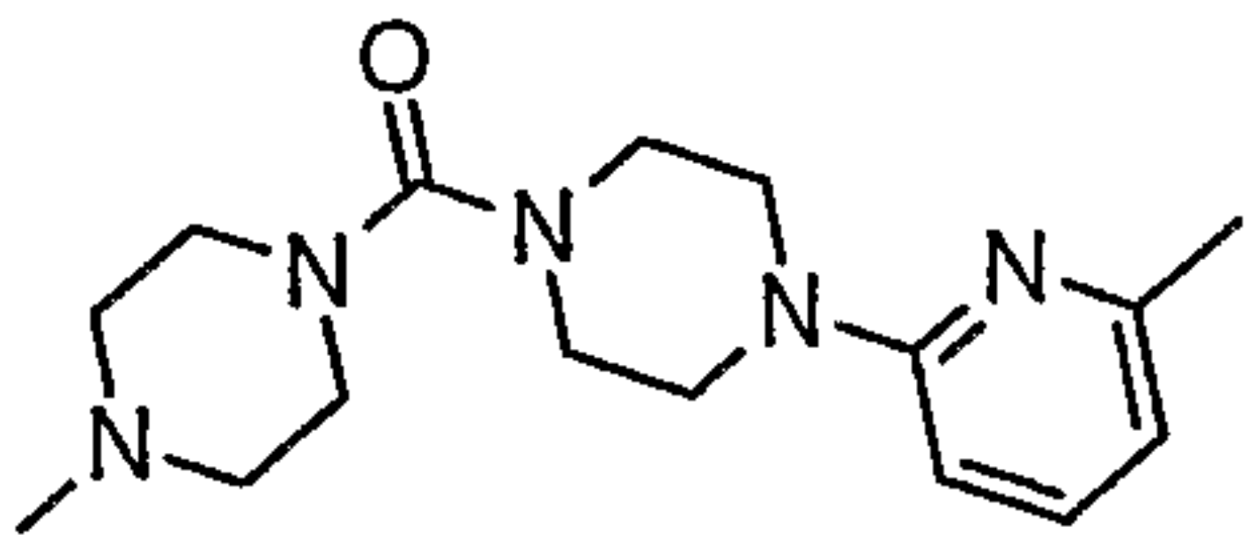
Example No.	STRUCTURE	Name	MW	Exact Mass	MH+
39.		N-(2-chloro-6-fluorobenzyl)-4-methylpiperazine-1-carboxamide	285.75	285.1	286.1
40.		N-(2,3-dichlorobenzyl)-4-methylpiperazine-1-carboxamide	302.2	301.1	302.1
41.		N-(2,5-dichlorobenzyl)-4-methylpiperazine-1-carboxamide	302.2	301.1	302.1
42.		N-(2-methoxybenzyl)-4-methylpiperazine-1-carboxamide	263.34	263.2	264.2
43.		4-methyl-N-(2-phenoxyethyl)piperazine-1-carboxamide	263.34	263.2	264.2
44.		N-(3-chloro-4-methylbenzyl)-4-methylpiperazine-1-carboxamide	281.79	281.1	282.1
45.		N-(2-chloro-6-phenoxybenzyl)-4-methylpiperazine-1-carboxamide	359.86	359.1	360.1
46.		N-(2,5-dimethoxybenzyl)-4-methylpiperazine-1-carboxamide	293.37	293.2	294.2
47.		N-(2,6-dichlorobenzyl)-4-methylpiperazine-1-carboxamide	302.2	301.1	302.1

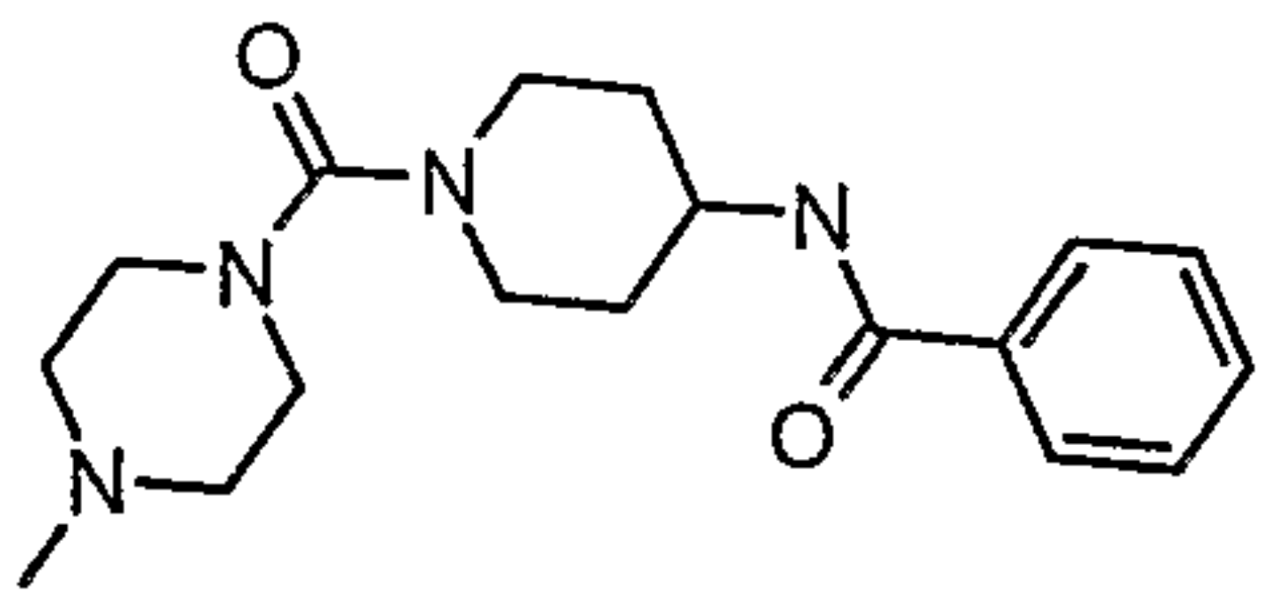
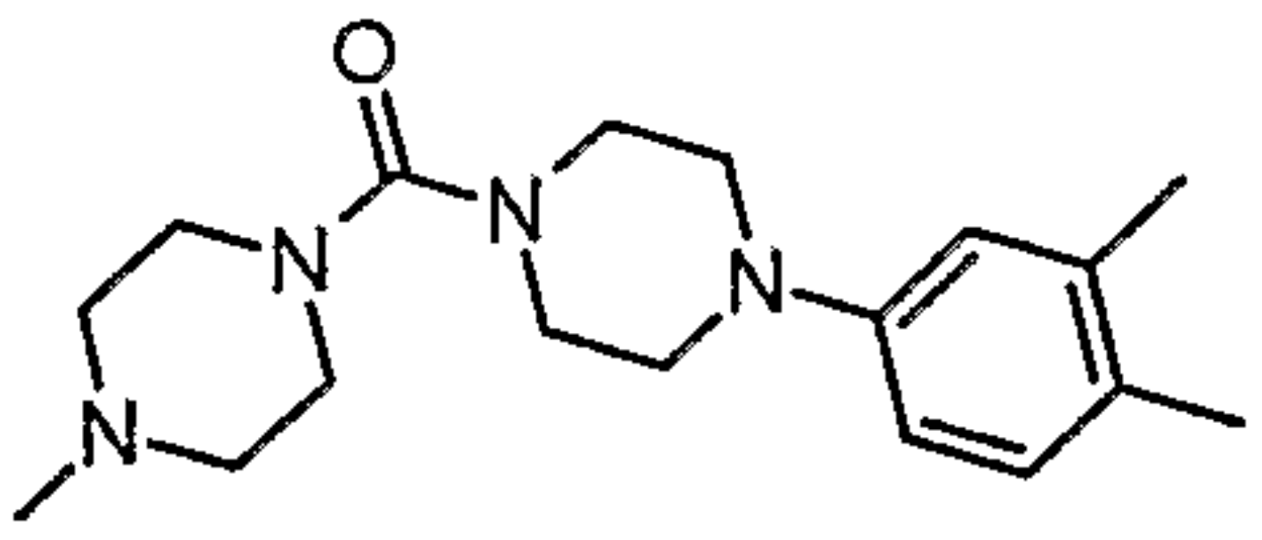
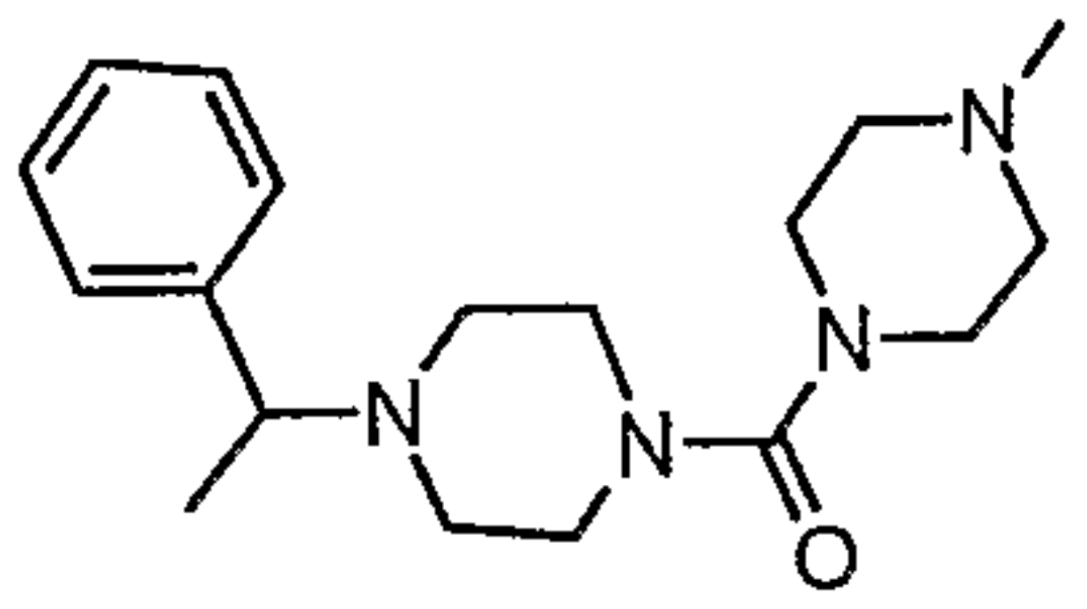
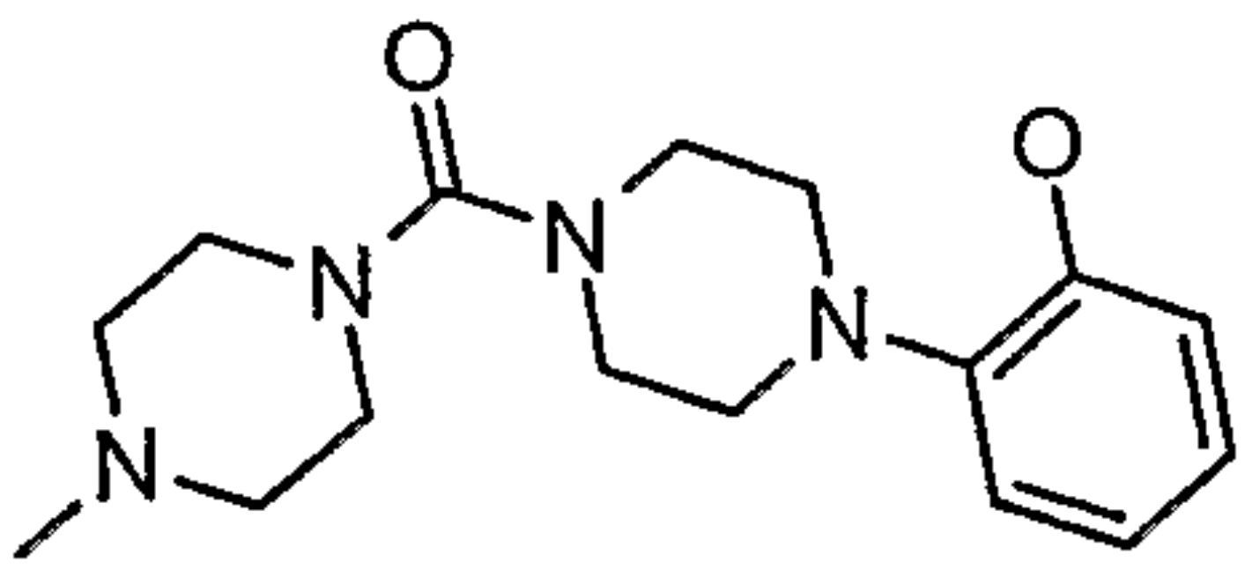
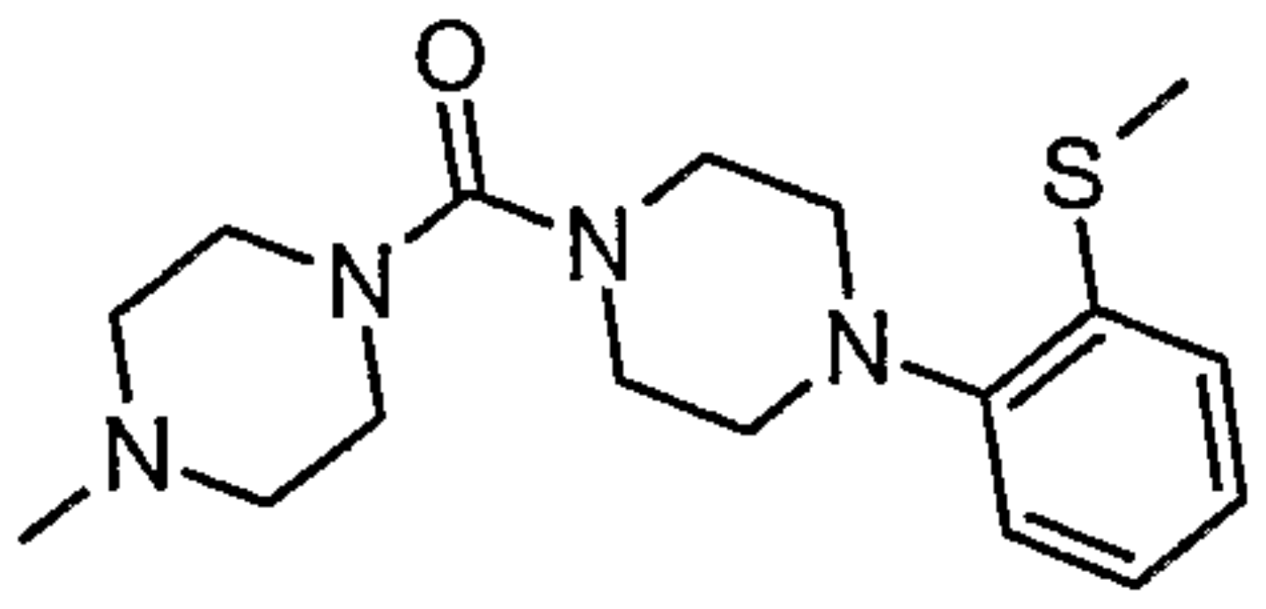
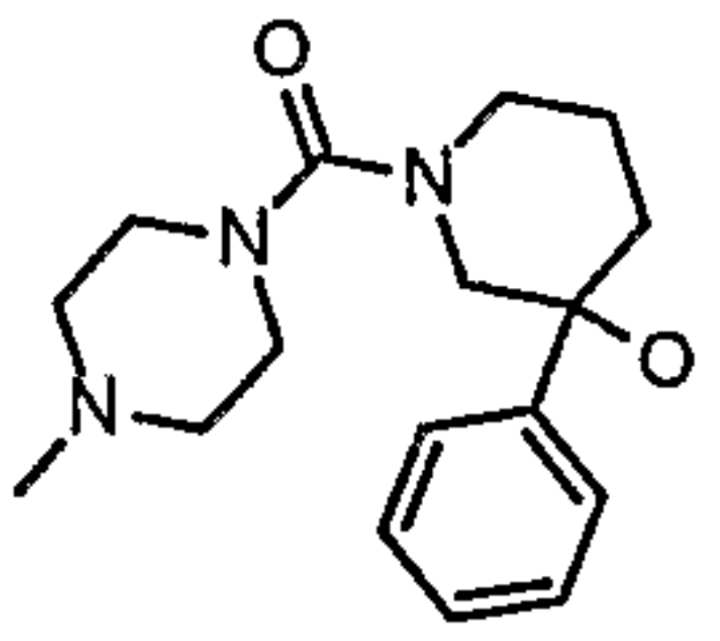
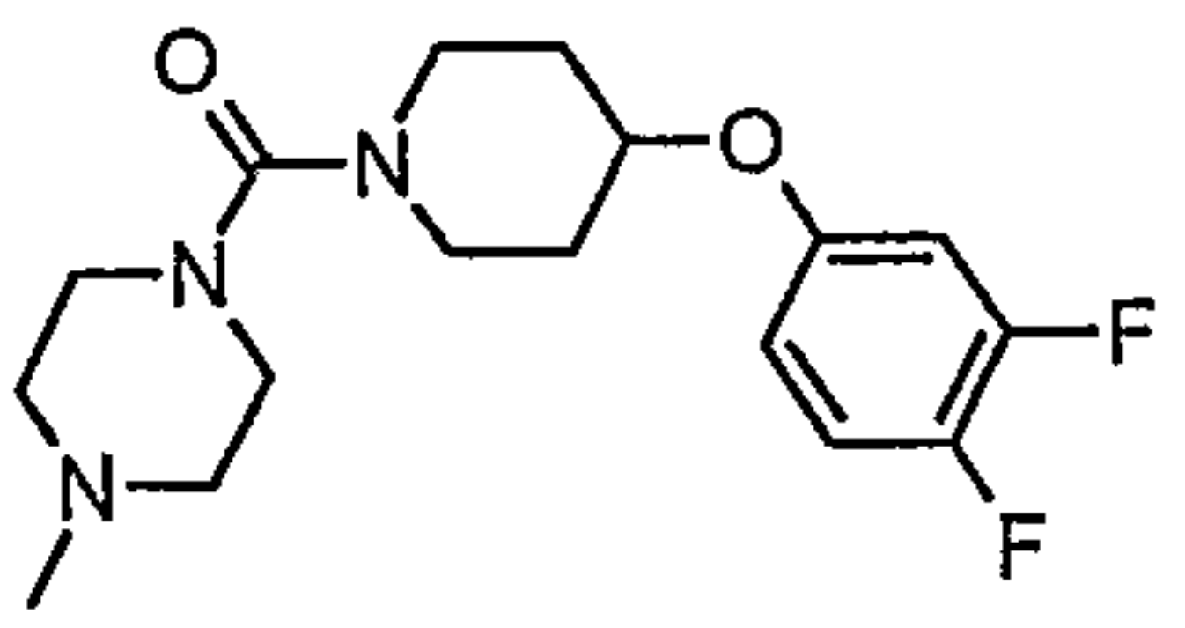
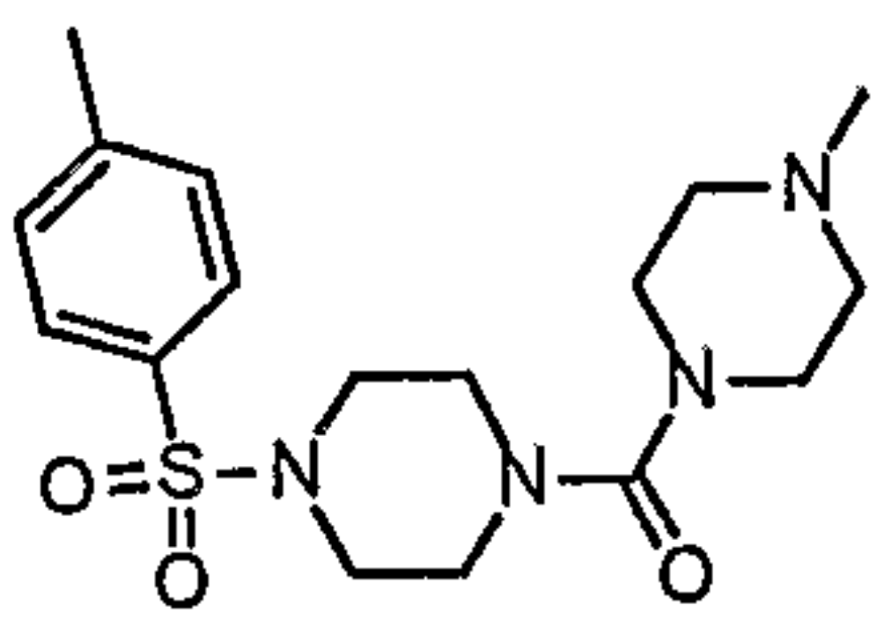
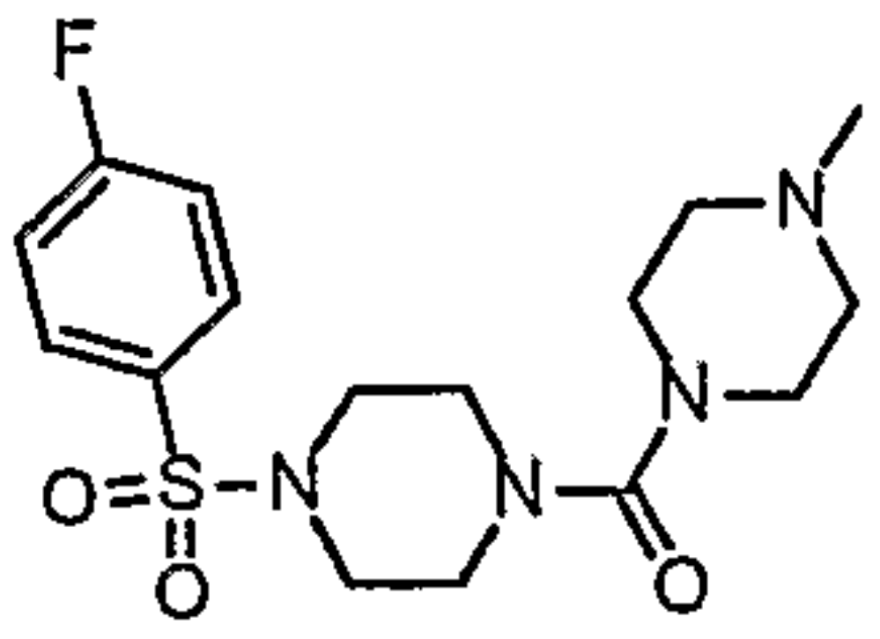
Example No.	STRUCTURE	Name	MW	Exact Mass	MH+
48.		4-methyl-N-(2-(trifluoromethyl)benzyl)piperazine-1-carboxamide	301.31	301.1	302.1
49.		4-methyl-N-(3-(trifluoromethyl)benzyl)piperazine-1-carboxamide	301.31	301.1	302.1
50.		4-methyl-N-(3-(trifluoromethoxy)benzyl)piperazine-1-carboxamide	317.31	317.1	318.1
51.		N-(3-fluorobenzyl)-4-methylpiperazine-1-carboxamide	251.3	251.1	252.2
52.		N-(3,5-difluorobenzyl)-4-methylpiperazine-1-carboxamide	269.29	269.1	270.1
53.		4-methyl-N-(2-methylbenzyl)piperazine-1-carboxamide	247.34	247.2	248.2
54.		4-methyl-N-(4-methylbenzyl)piperazine-1-carboxamide	247.34	247.2	248.2
55.		N-(2-ethoxybenzyl)-4-methylpiperazine-1-carboxamide	277.37	277.2	278.2
56.		N-(furan-2-ylmethyl)-4-methylpiperazine-1-carboxamide	223.27	223.1	224.1

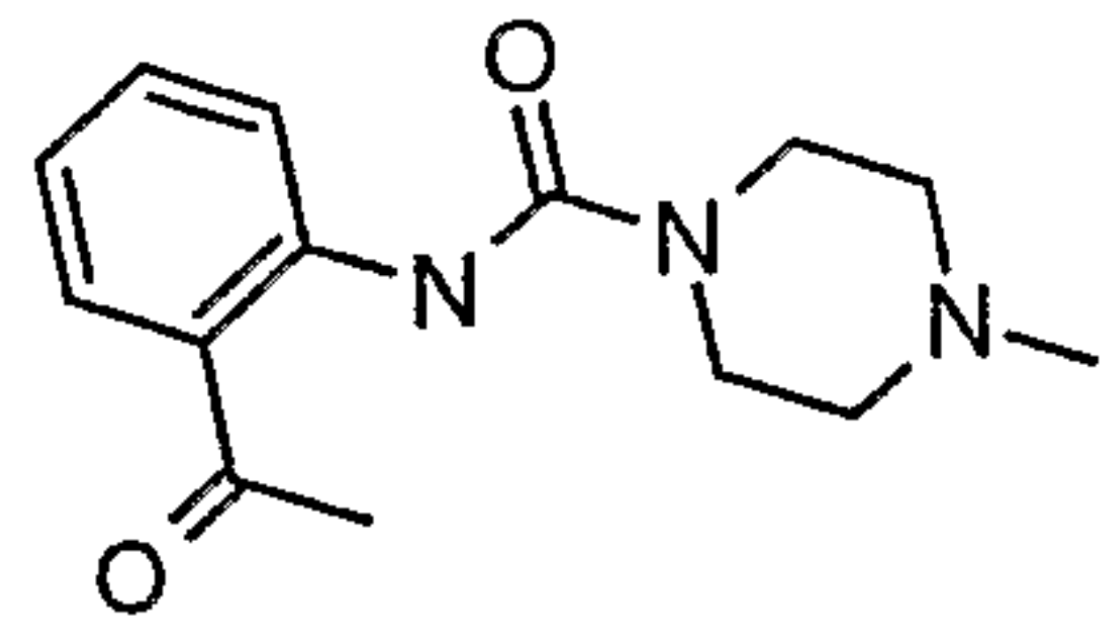
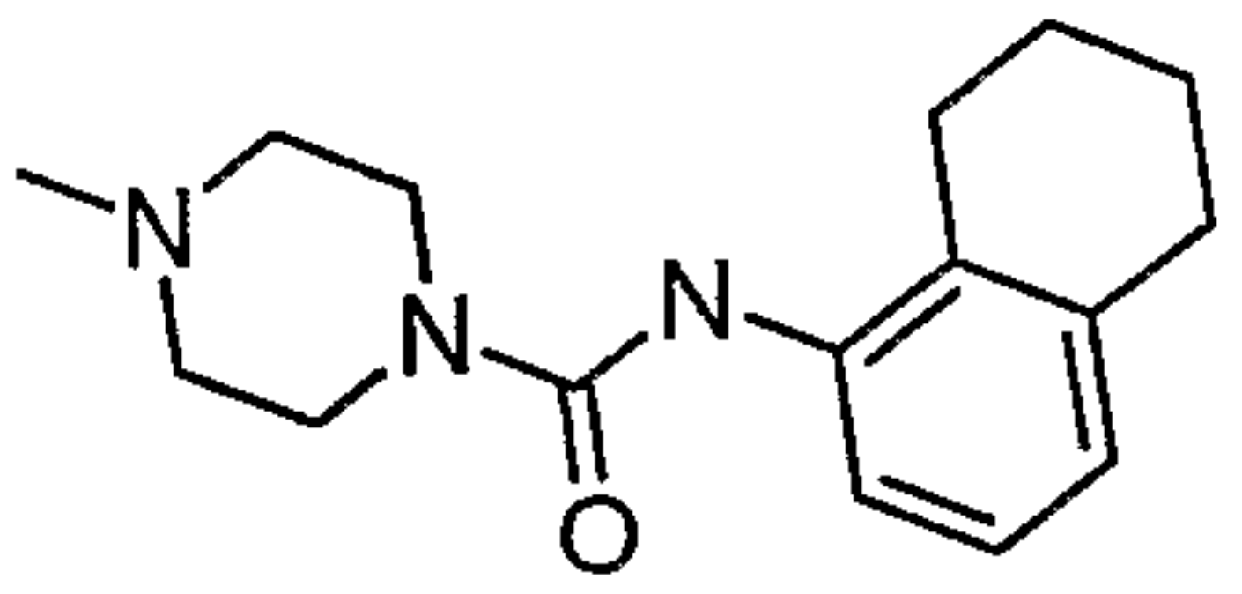
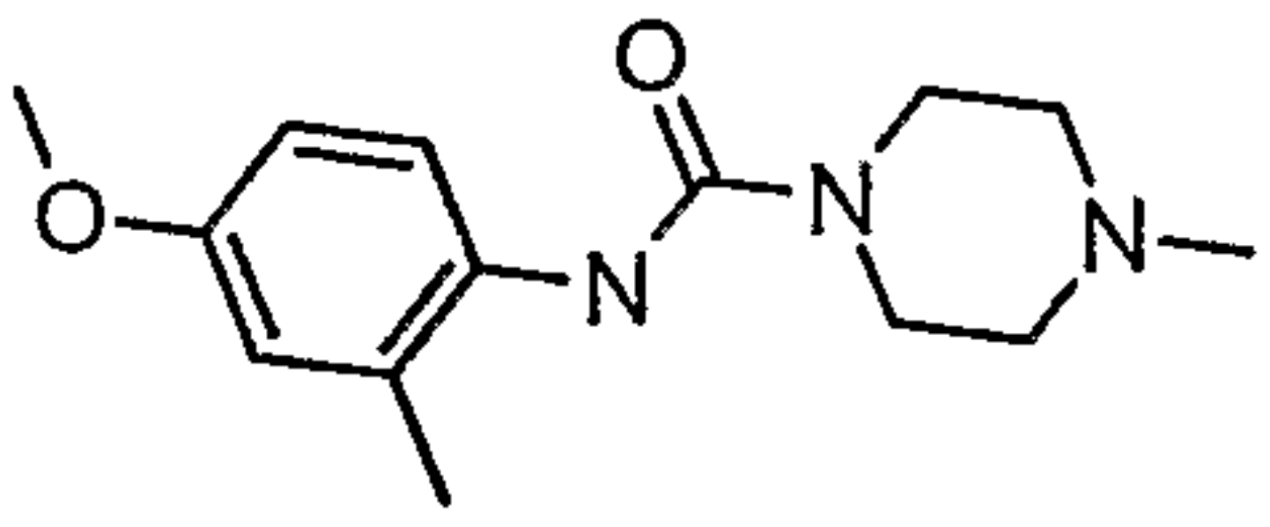
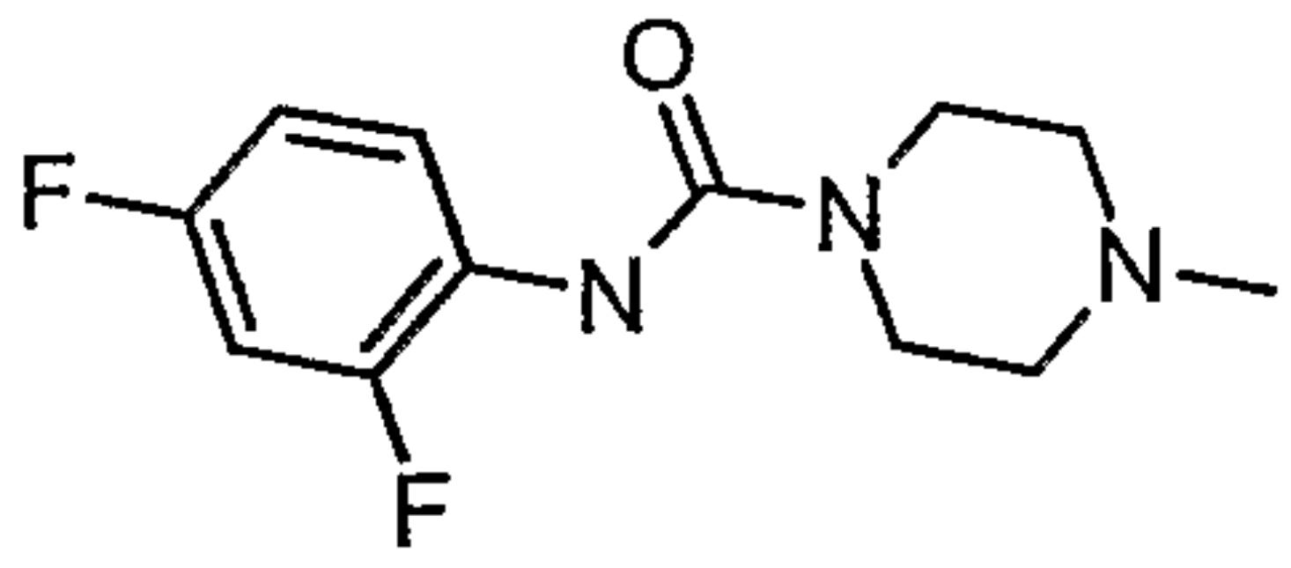
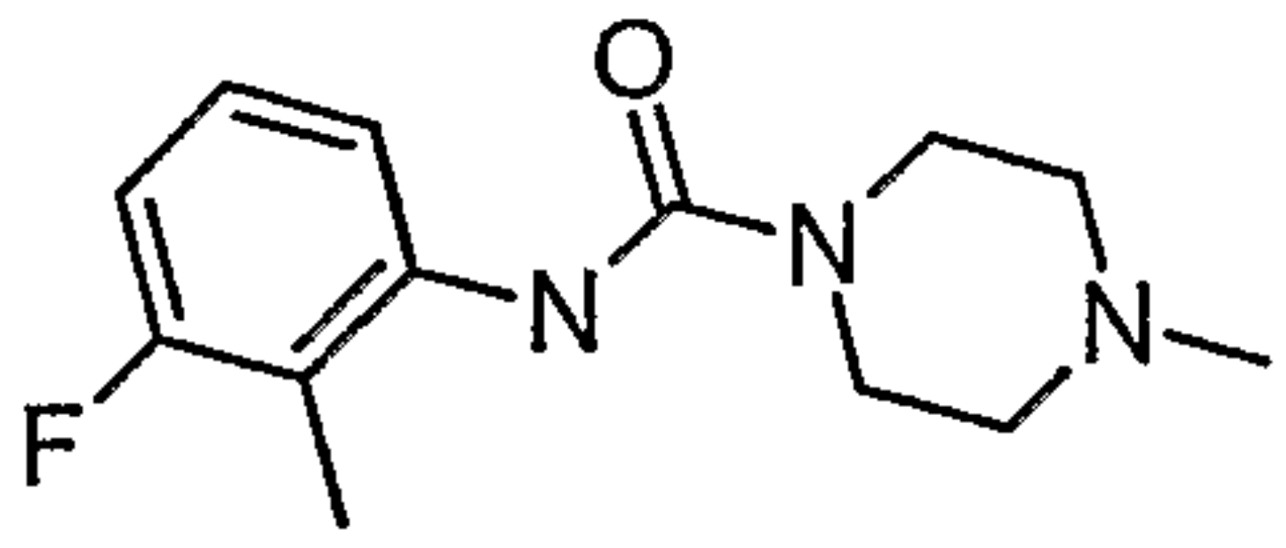
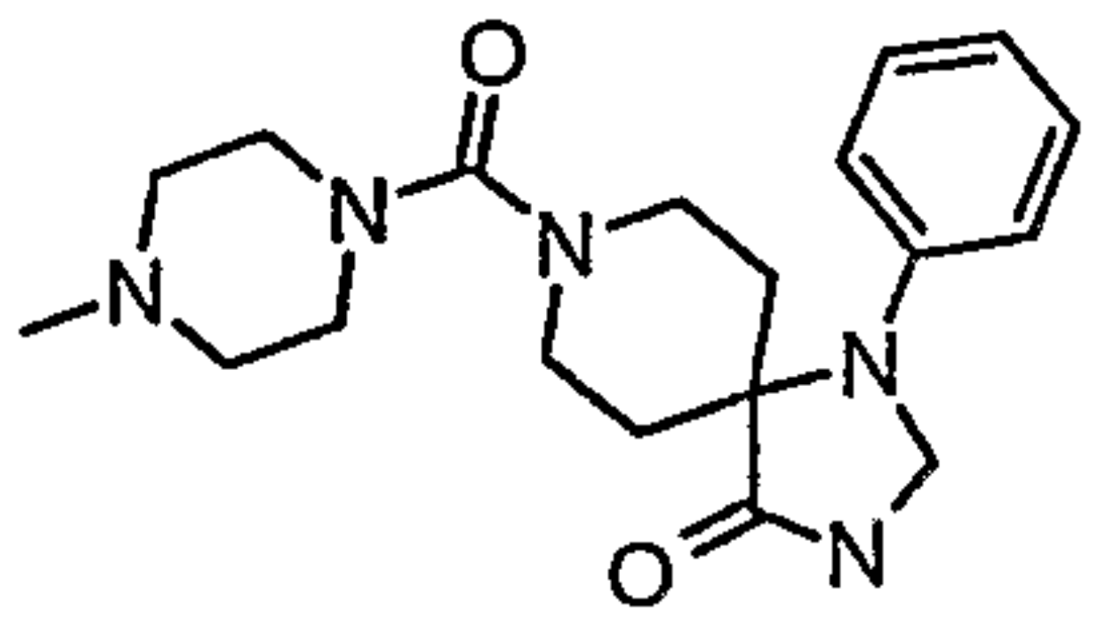
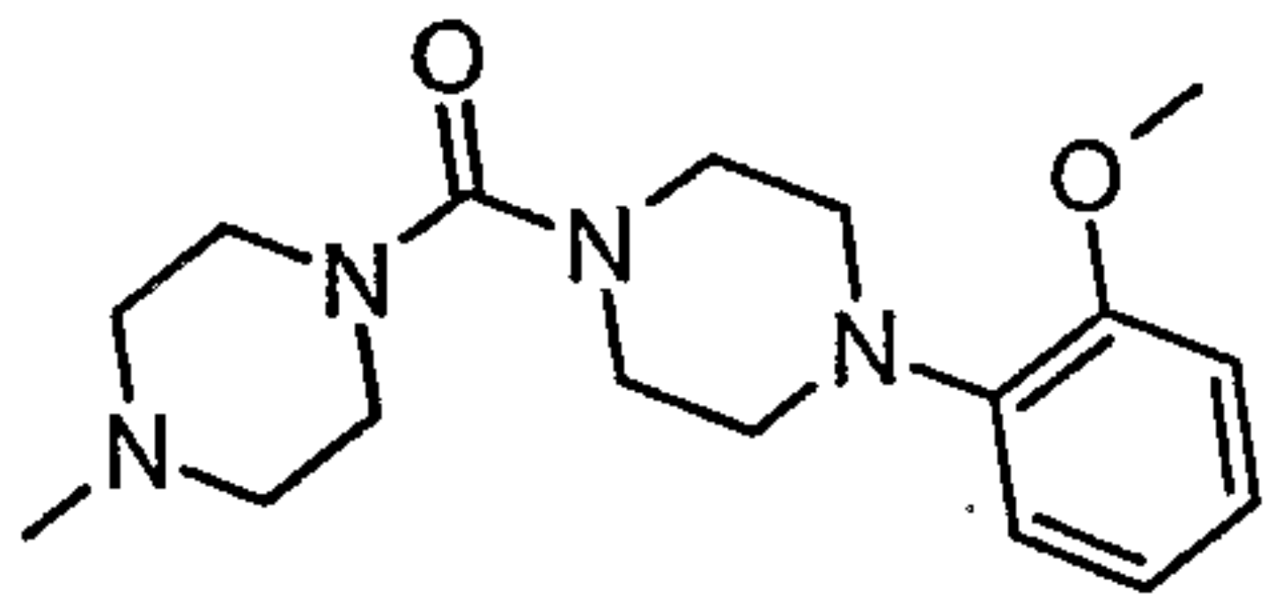
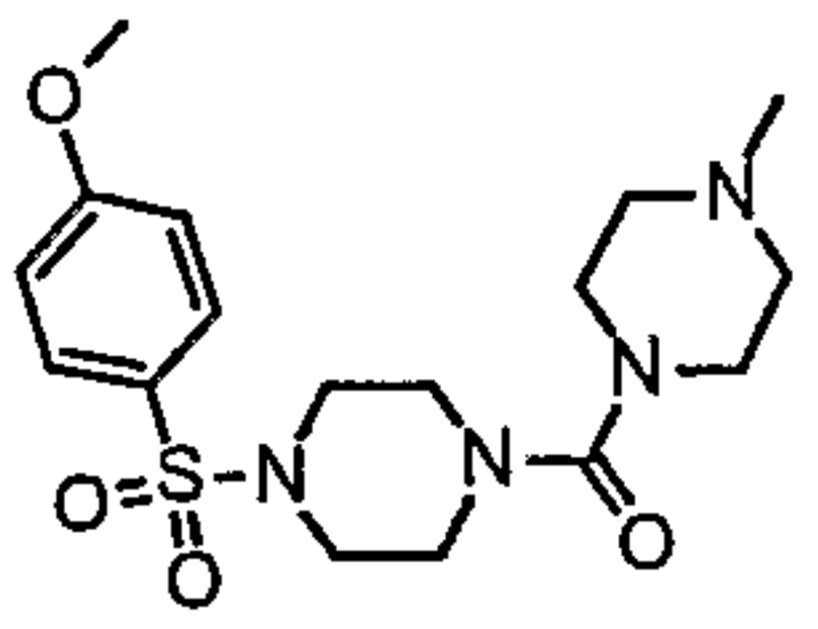
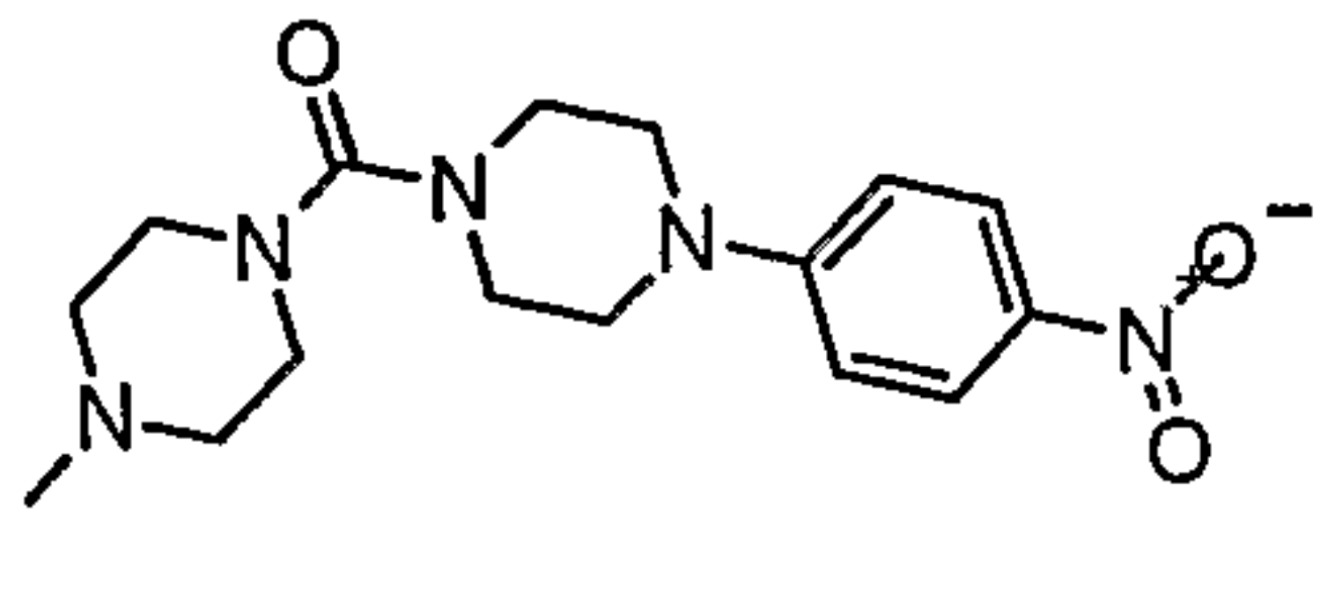
Example No.	STRUCTURE	Name	MW	Exact Mass	MH+
57.		N-(4-chlorobenzyl)-4-methylpiperazine-1-carboxamide	267.76	267.1	268.1
58.		N-(2-chlorobenzyl)-4-methylpiperazine-1-carboxamide	267.76	267.1	268.1
59.		N-(3-methoxybenzyl)-4-methylpiperazine-1-carboxamide	263.34	263.2	264.2
60.		N-(4-methoxybenzyl)-4-methylpiperazine-1-carboxamide	263.34	263.2	264.2
61.		N-(3,5-dichlorophenyl)-4-methylpiperazine-1-carboxamide	288.18	287.1	288.1
62.		N-(2-chloro-4-methylphenyl)-4-methylpiperazine-1-carboxamide	267.76	267.1	268.1
63.		N-(2-chloro-5-methoxyphenyl)-4-methylpiperazine-1-carboxamide	283.76	283.1	284.1
64.		N-(4-iodo-2-methylphenyl)-4-methylpiperazine-1-carboxamide	359.21	359.0	360.1
65.		4-methyl-N-(4-(piperidin-1-yl)phenyl)piperazine-1-carboxamide	302.42	302.2	303.2

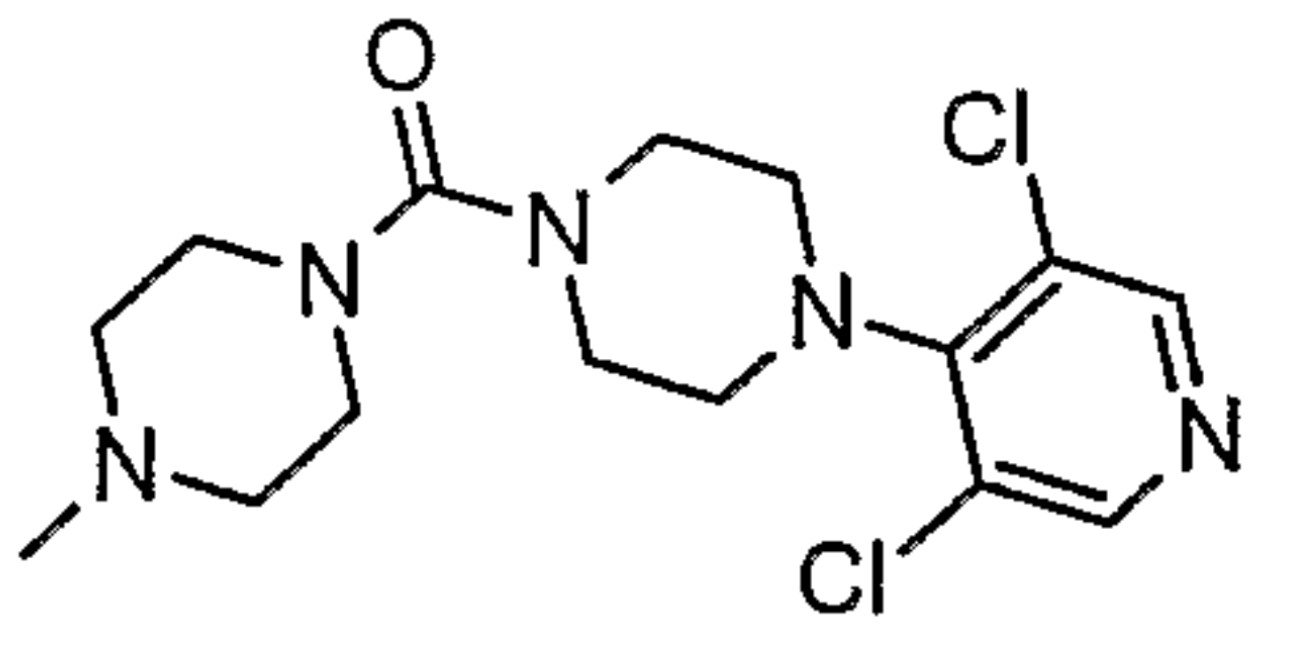
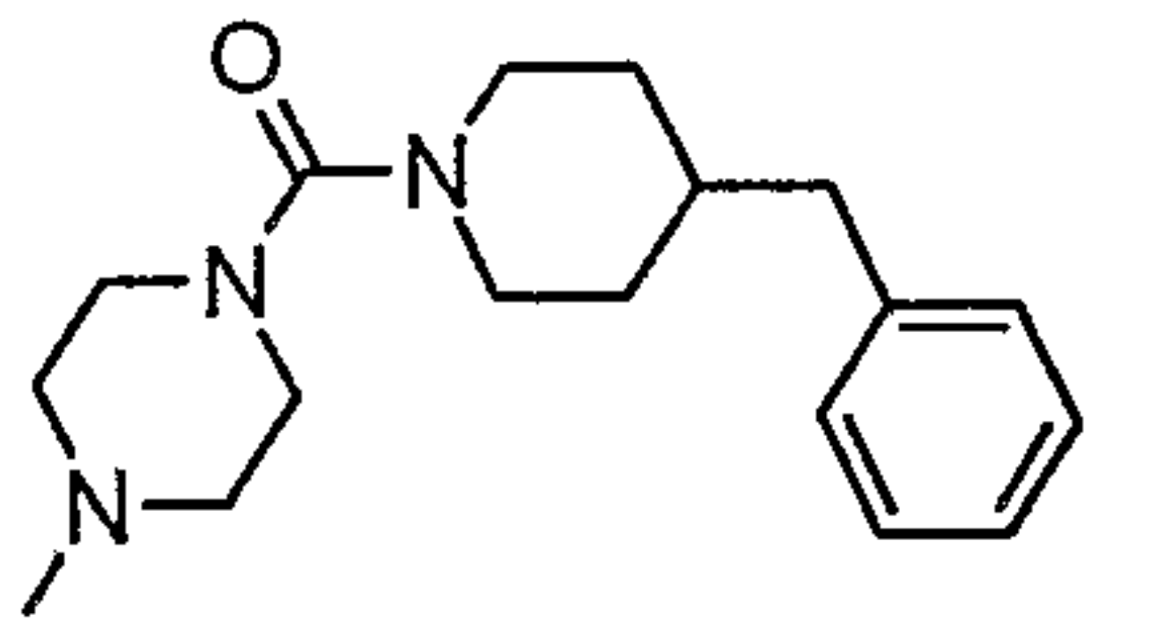
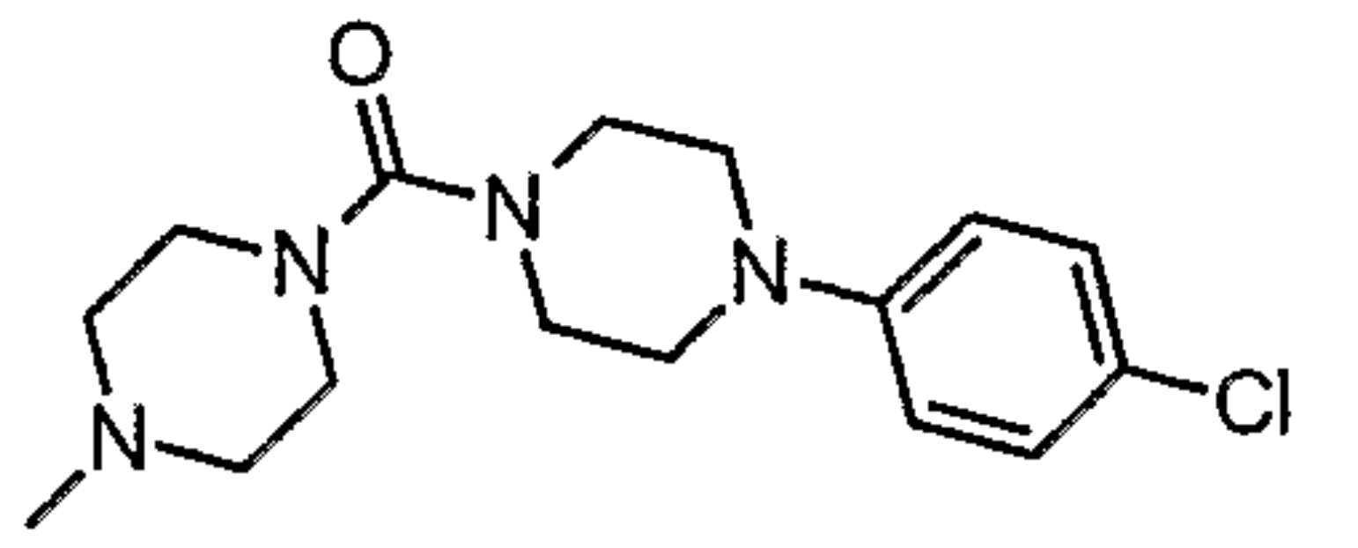
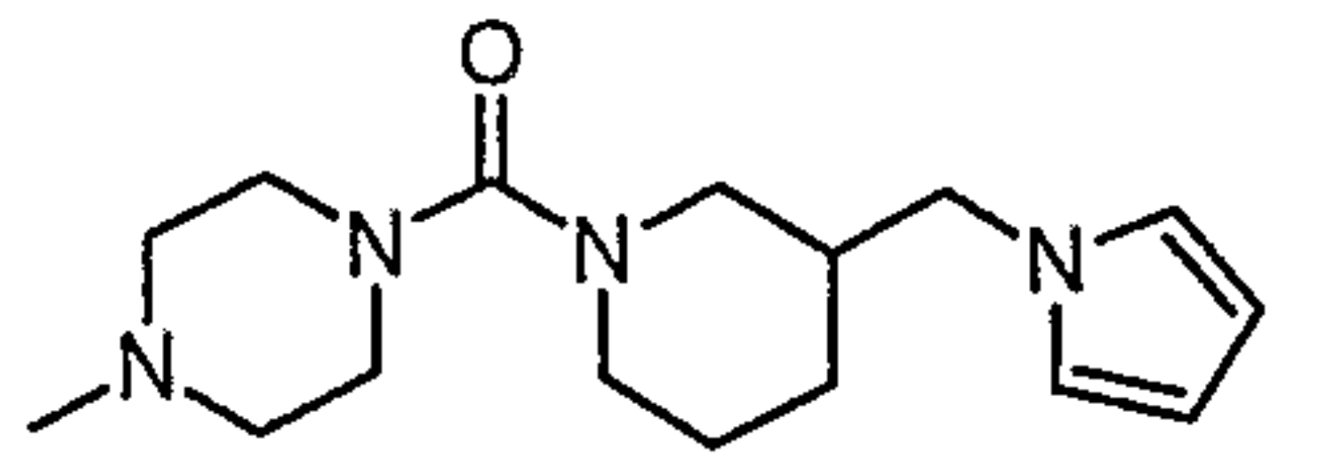
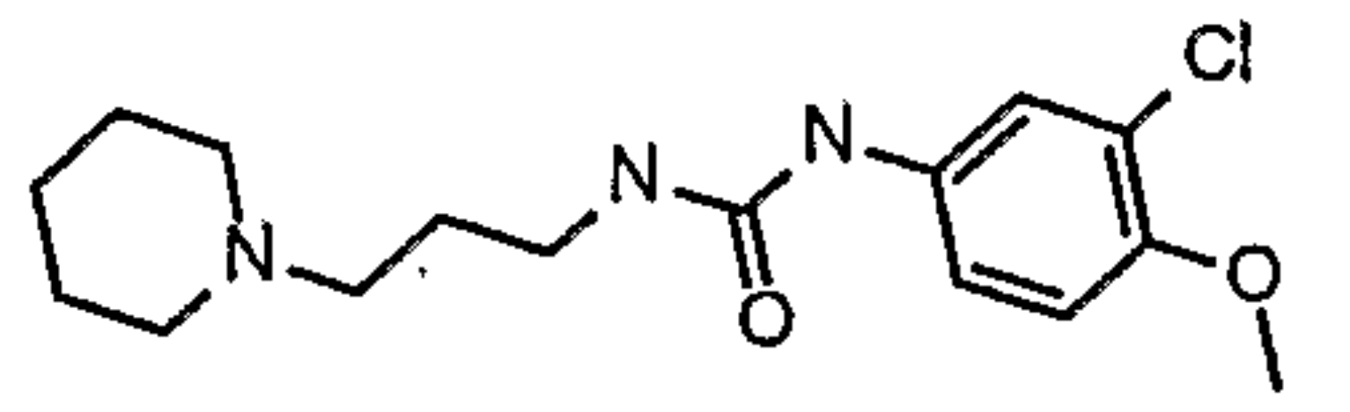
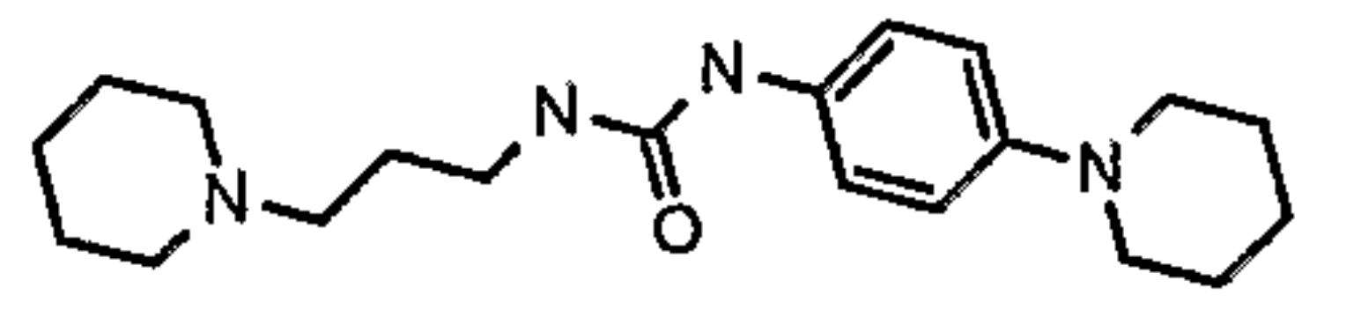
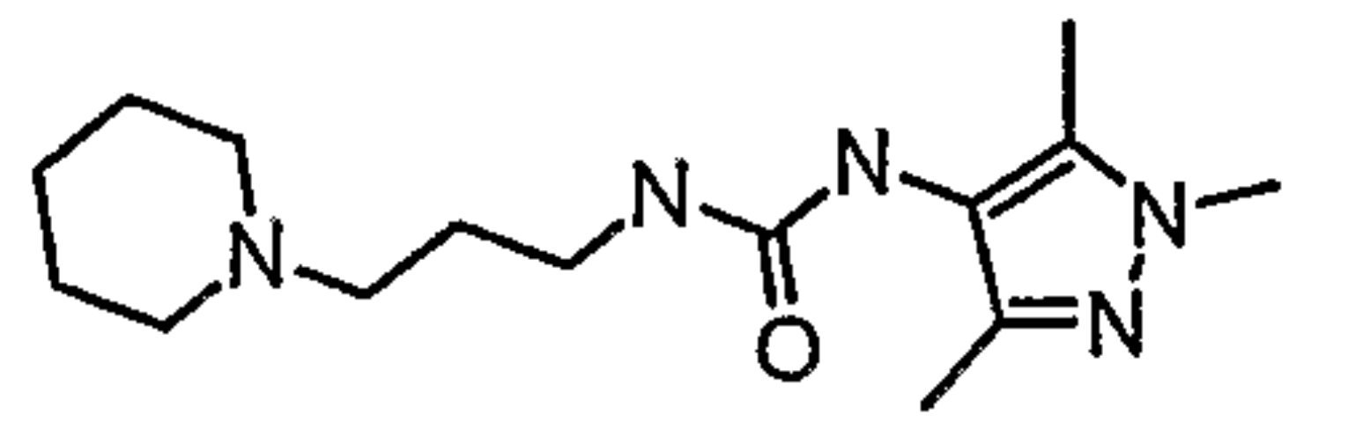
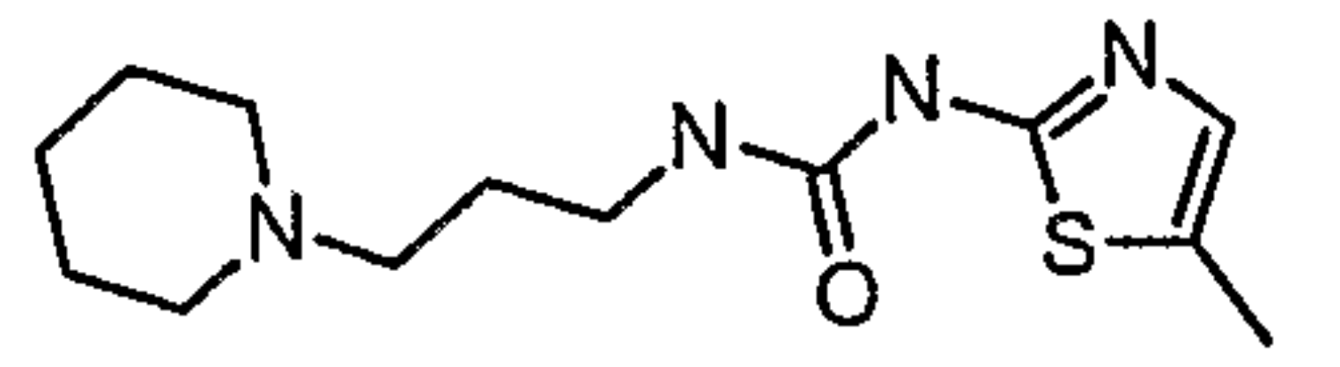
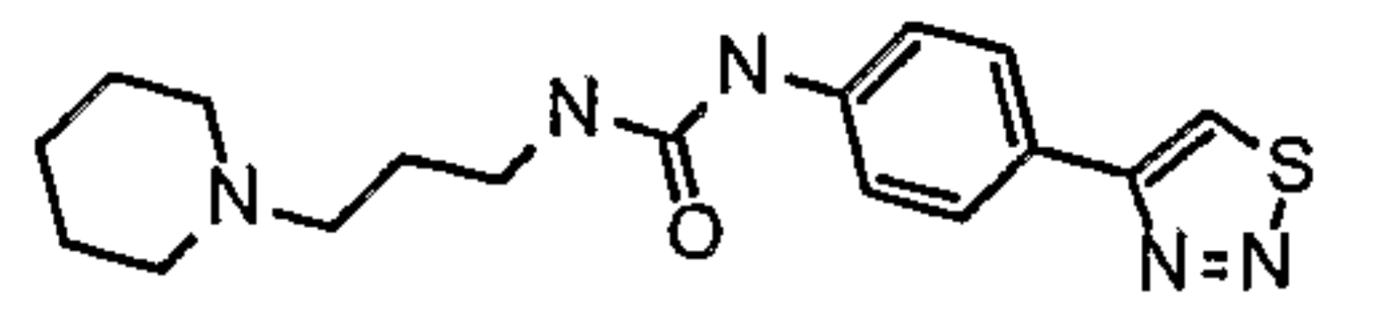
Example No.	STRUCTURE	Name	MW	Exact Mass	MH+
66.		N-(2-(1H-pyrrol-1-yl)phenyl)-4-methylpiperazine-1-carboxamide	284.36	284.2	285.2
67.		N-(2-bromo-4-chlorophenyl)-4-methylpiperazine-1-carboxamide	332.63	331.0	332.0
68.		N-(2-fluoro-5-methylphenyl)-4-methylpiperazine-1-carboxamide	251.3	251.1	252.2
69.		N-(3-bromo-2-methylphenyl)-4-methylpiperazine-1-carboxamide	312.21	311.1	312.1
70.		4-methyl-N-(5-methylthiazol-2-yl)piperazine-1-carboxamide	240.33	240.1	241.1
71.		N-(4-methoxybenzo[d]thiazol-2-yl)-4-methylpiperazine-1-carboxamide	306.39	306.1	307.1
72.		N-(4-(1,2,3-thiadiazol-4-yl)phenyl)-4-methylpiperazine-1-carboxamide	303.39	303.1	304.1
73.		N-(2-(2,5-dimethyl-1H-pyrrol-1-yl)phenyl)-4-methylpiperazine-1-carboxamide	312.42	312.2	313.2
74.		4-methyl-N-(2-(methylthio)benzo[d]thiazol-6-yl)piperazine-1-carboxamide	322.46	322.1	323.1

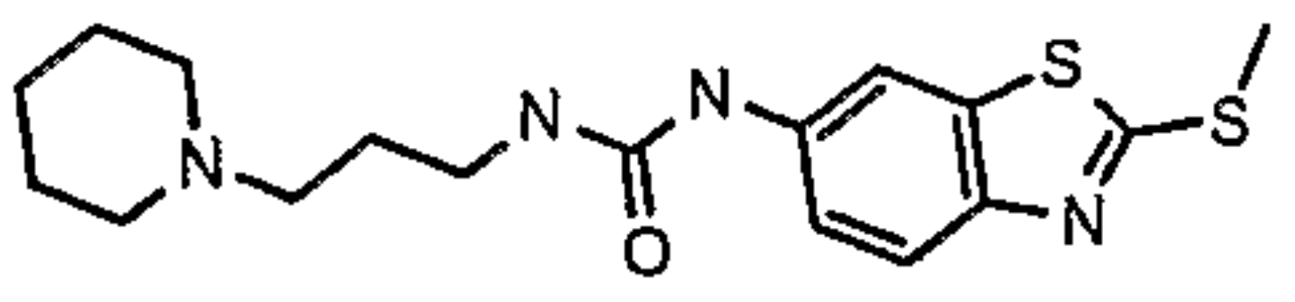
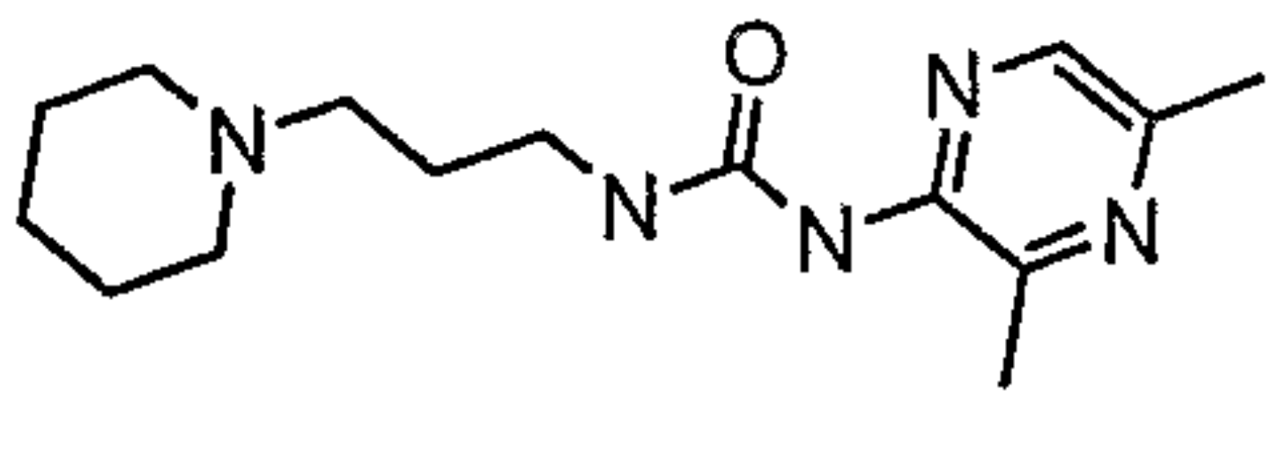
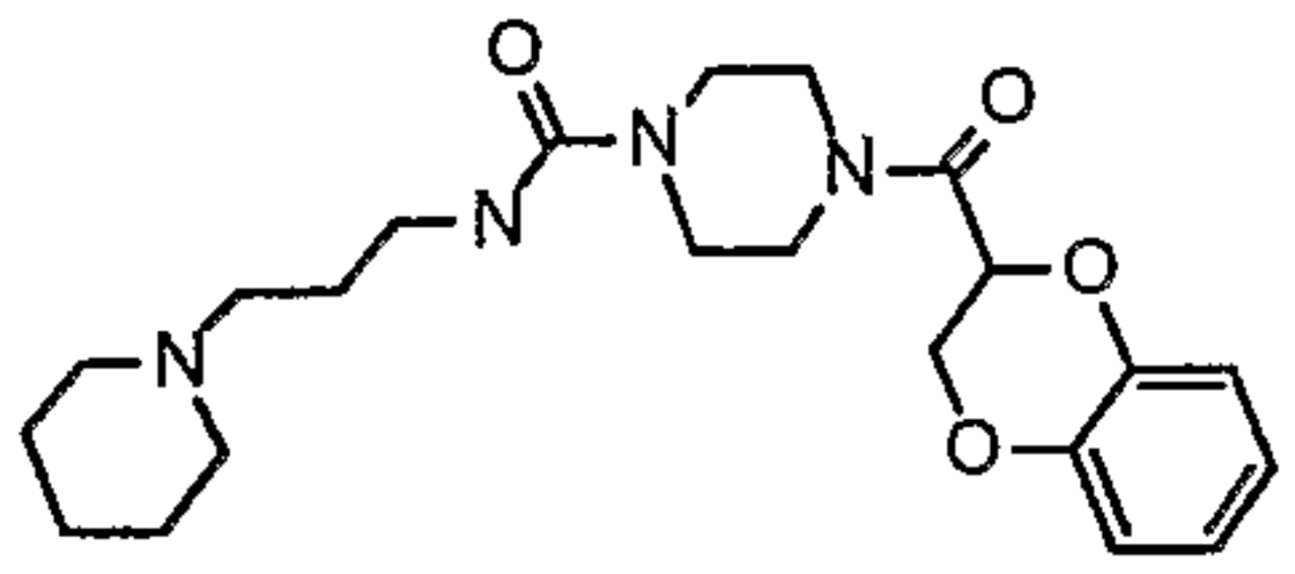
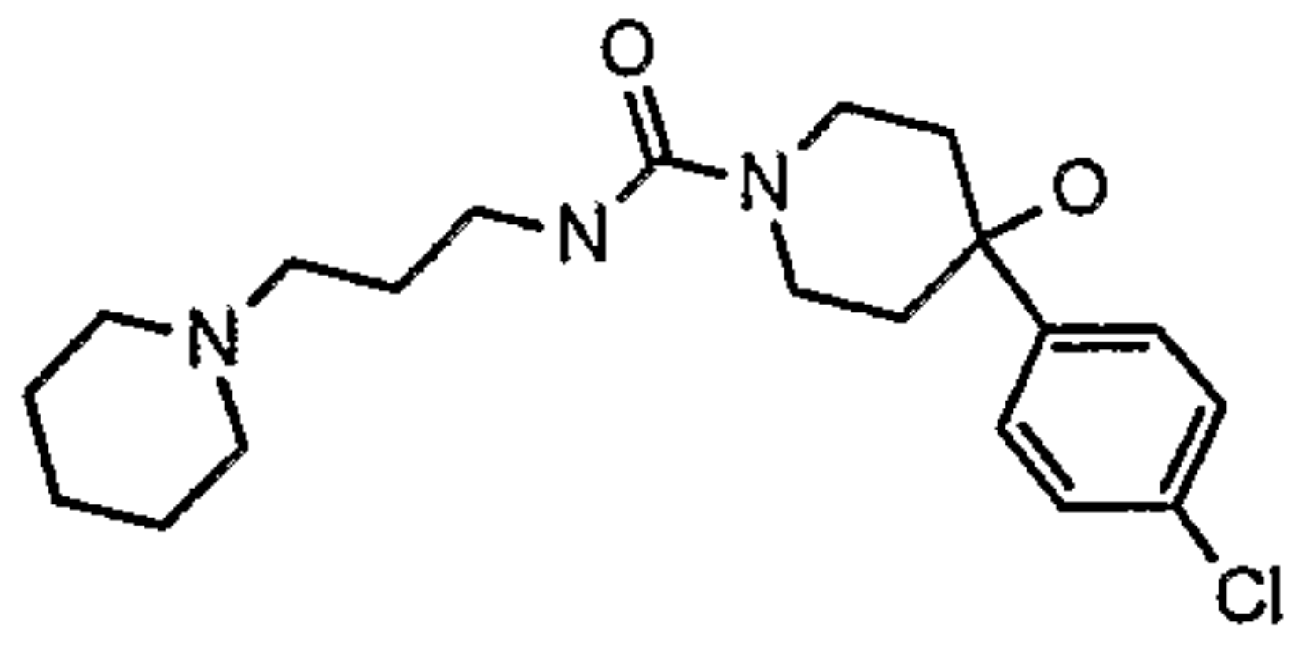
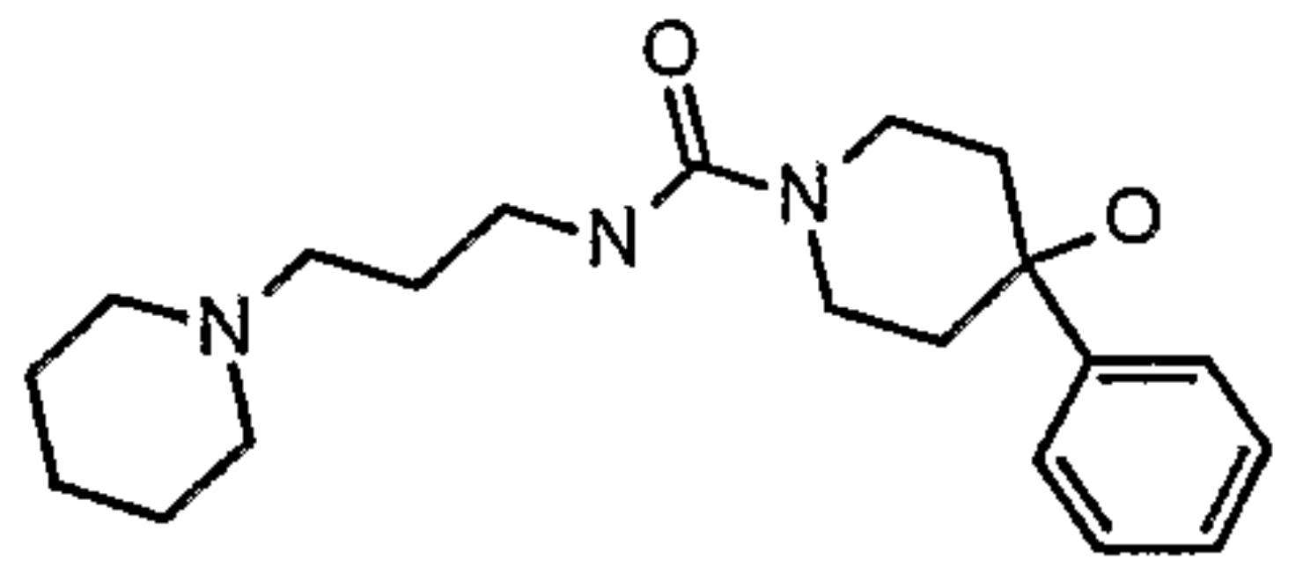
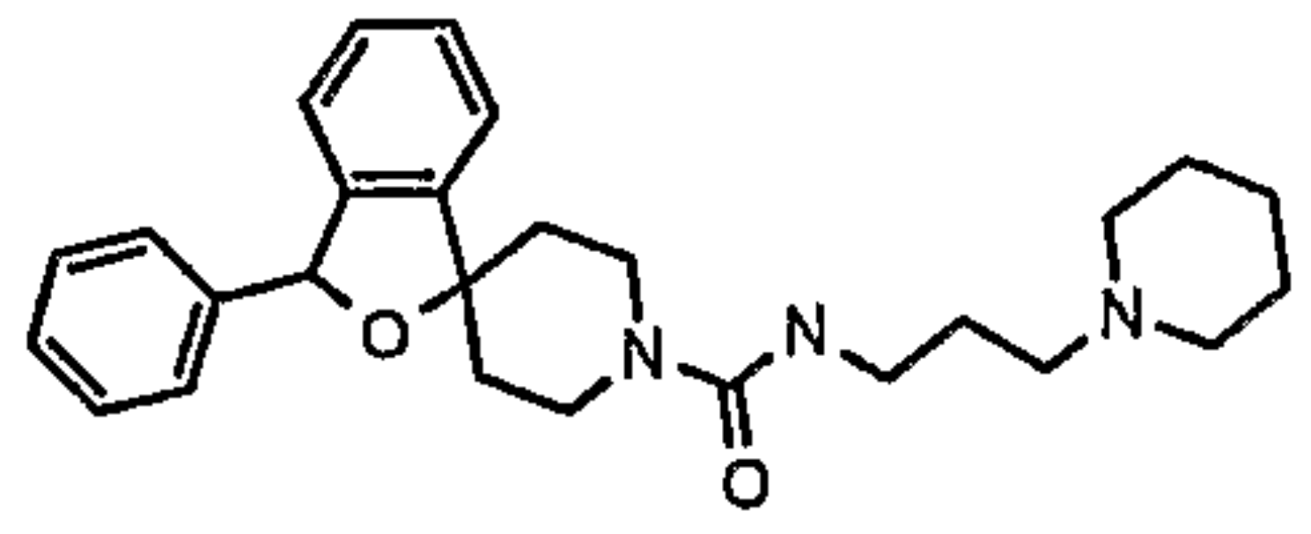
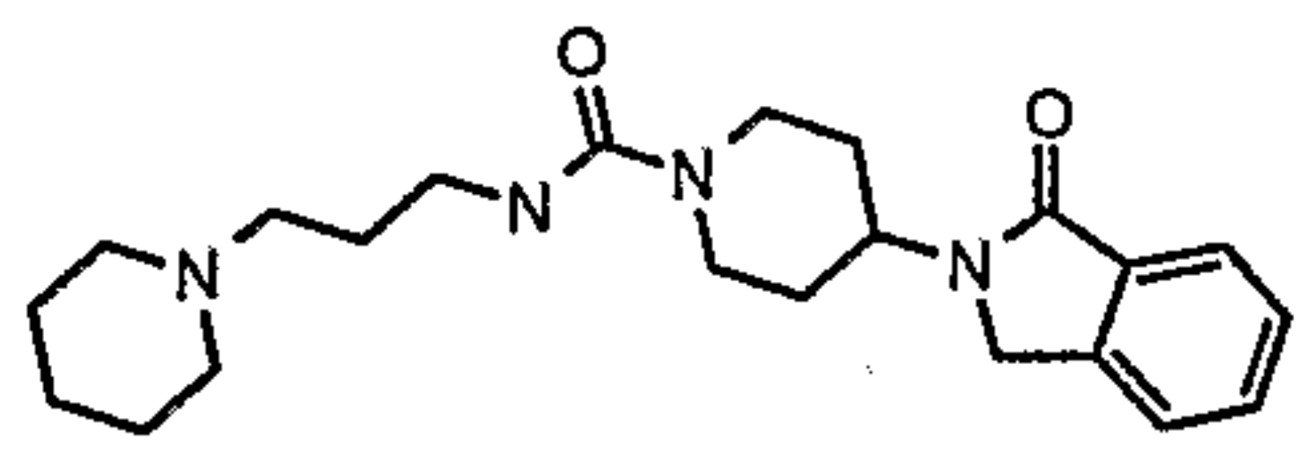
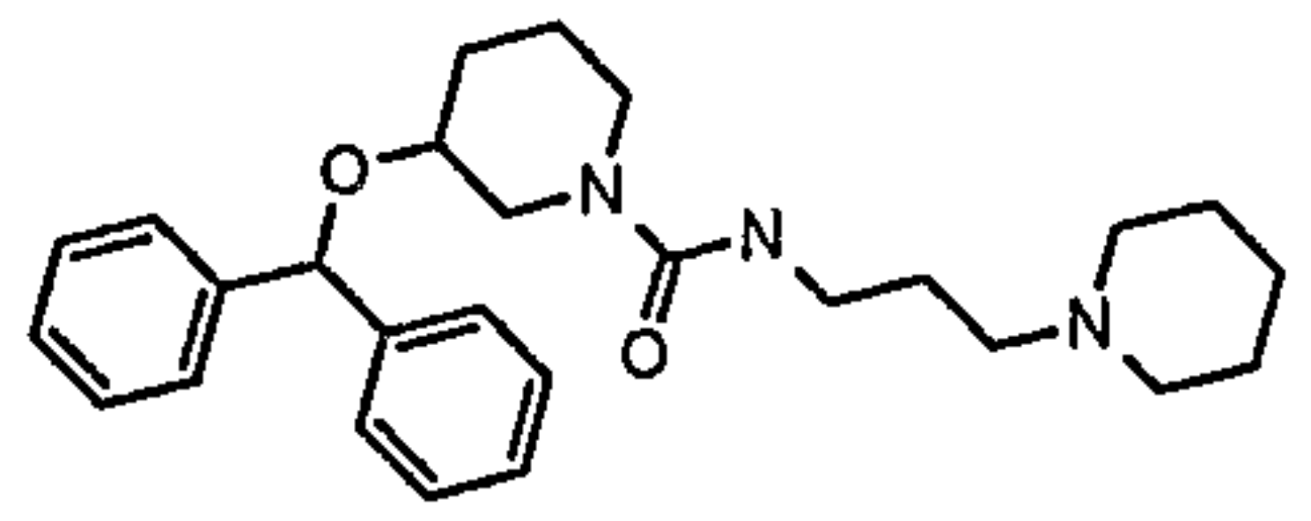
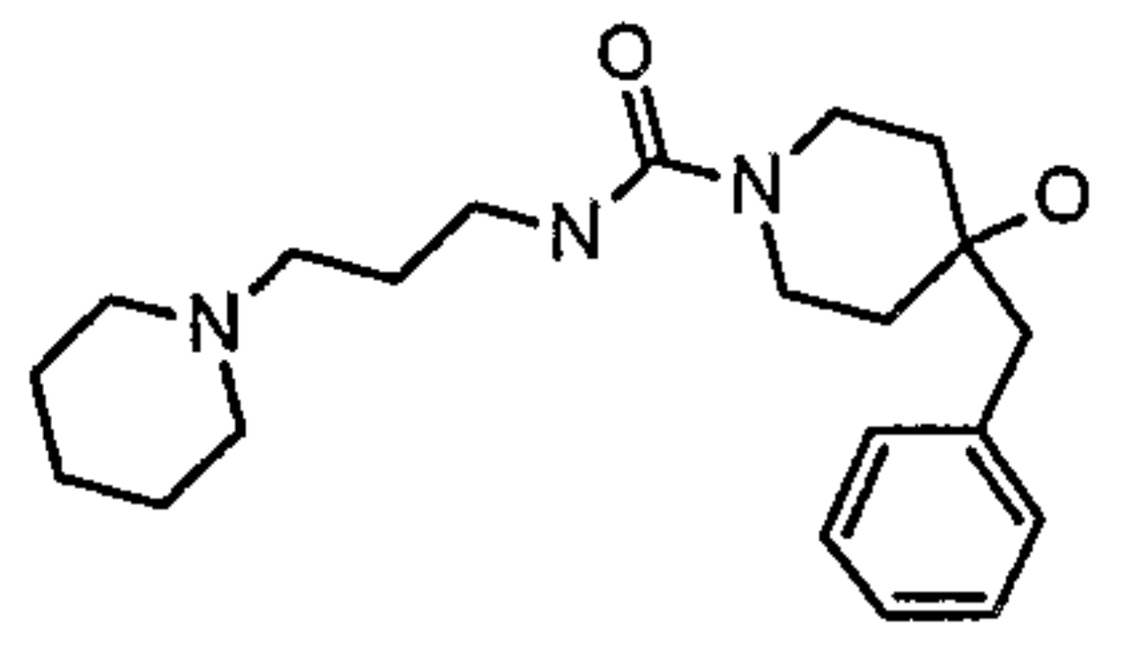
Example No.	STRUCTURE	Name	MW	Exact Mass	MH+
75.		N-(4-amino-2,5-dimethylphenyl)-4-methylpiperazine-1-carboxamide	262.36	262.2	263.2
76.		4-methyl-N-(4-(phenylsulfonyl)thiophen-3-yl)piperazine-1-carboxamide	365.48	365.1	366.1
77.		methyl 2-{[(4-methylpiperazin-1-yl)carbonyl]amino}thiophene-3-carboxylate	283.35	283.1	284.1
78.		N-(3-cyano-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)-4-methylpiperazine-1-carboxamide	319.43	319.1	320.2
79.		N-(5-aminonaphthalen-1-yl)-4-methylpiperazine-1-carboxamide	284.36	284.2	285.2
80.		(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)(4-methylpiperazin-1-yl)methanone	337.85	337.2	338.2
81.		2-(1-(4-methylpiperazine-1-carbonyl)piperidin-4-yl)isoindolin-1-one	342.44	342.2	343.2
82.		(3-(benzhydryloxy)piperidin-1-yl)(4-methylpiperazin-1-yl)methanone	393.53	393.2	394.2
83.		(4-benzyl-4-hydroxypiperidin-1-yl)(4-methylpiperazin-1-yl)methanone	317.43	317.2	318.2

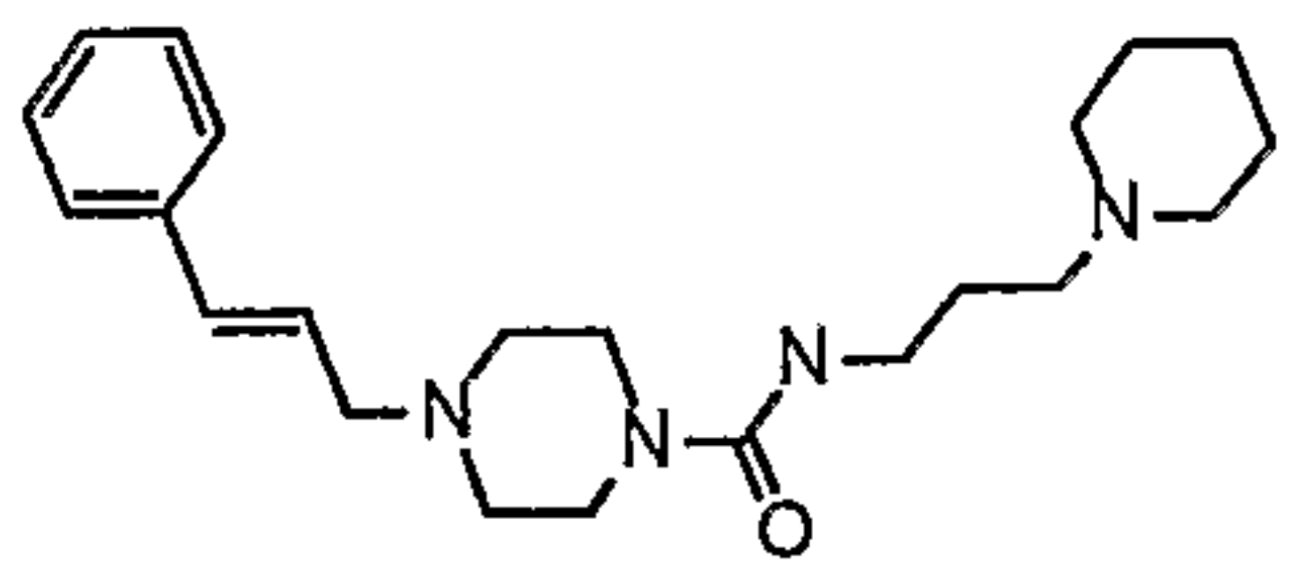
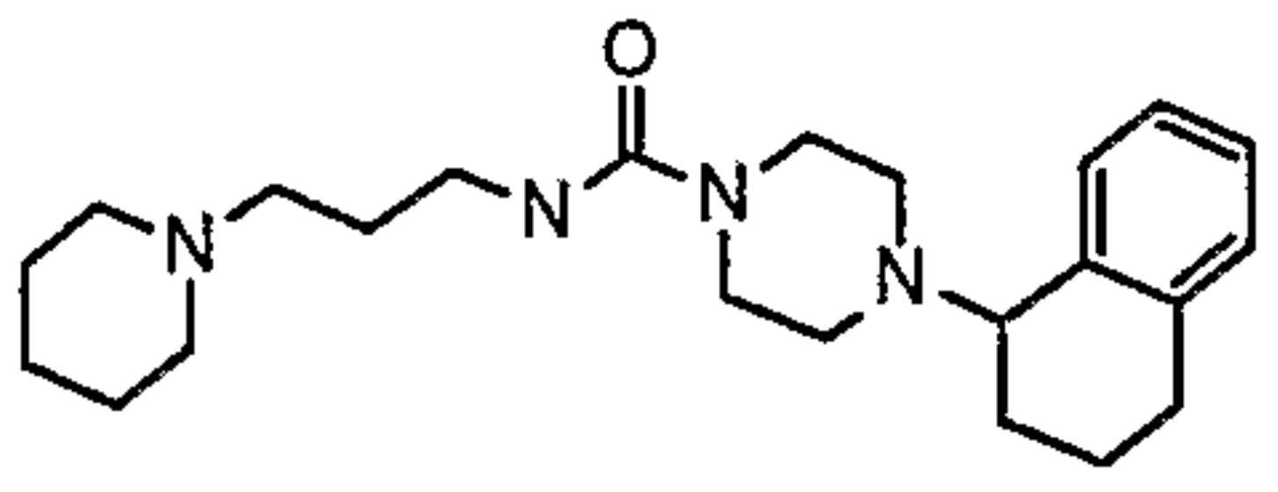
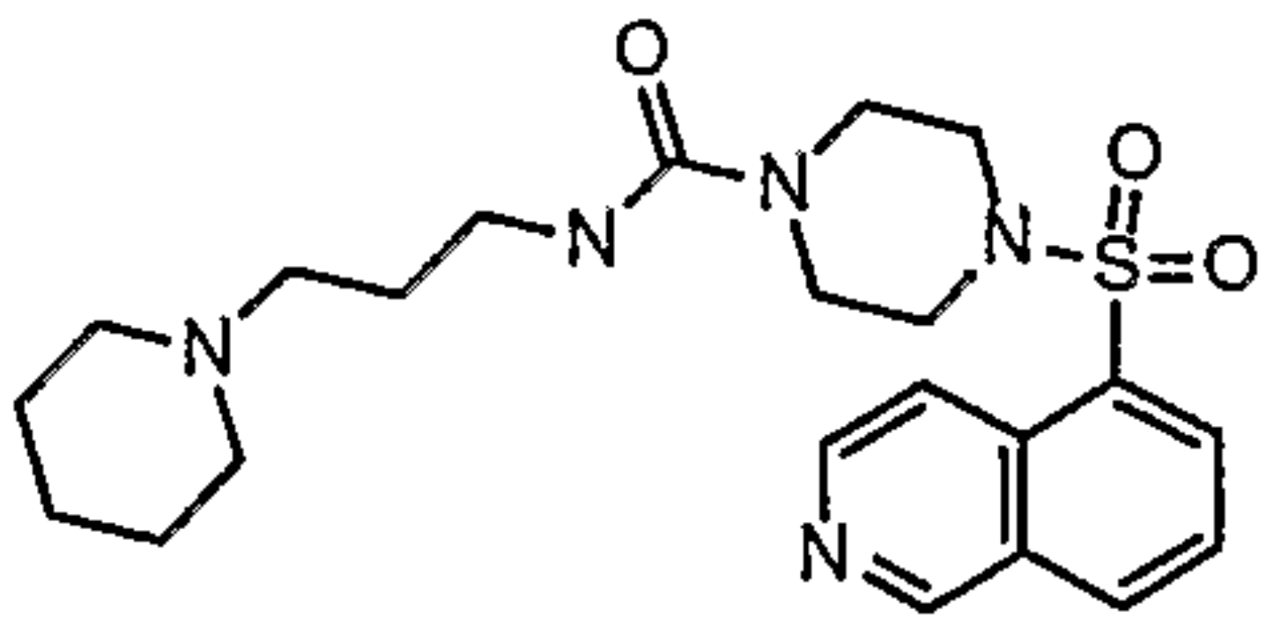
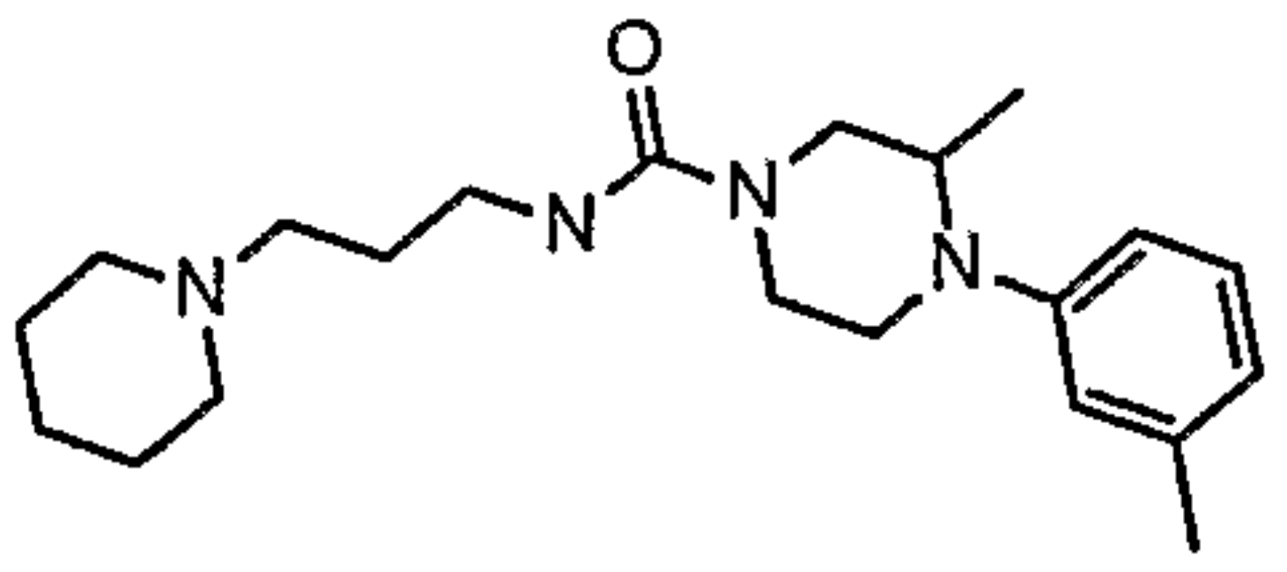
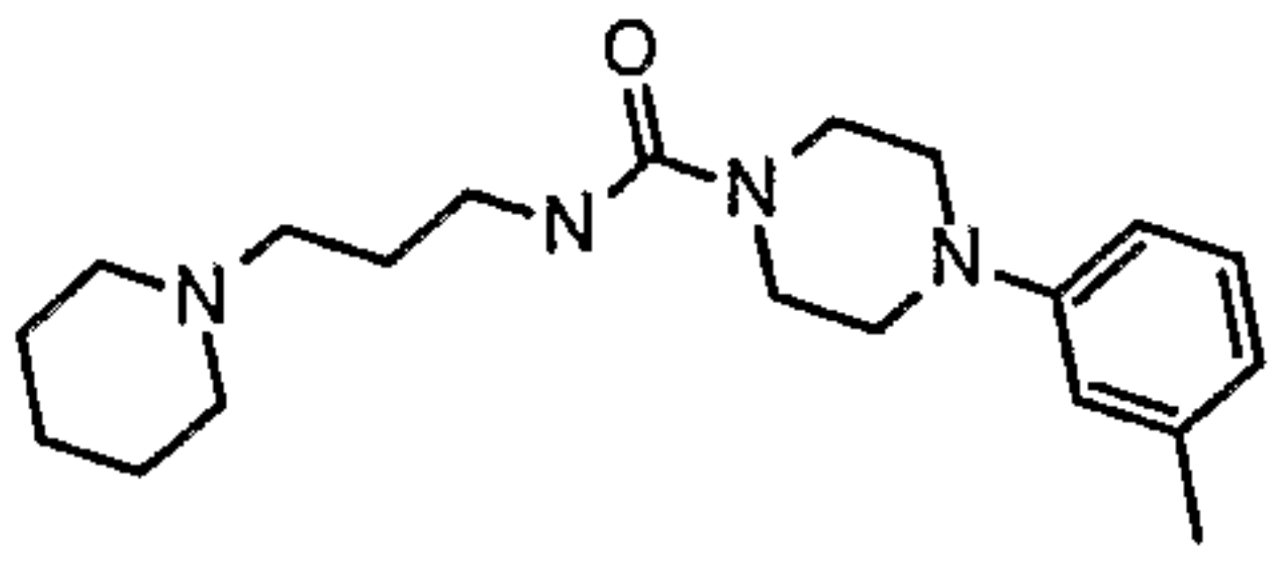
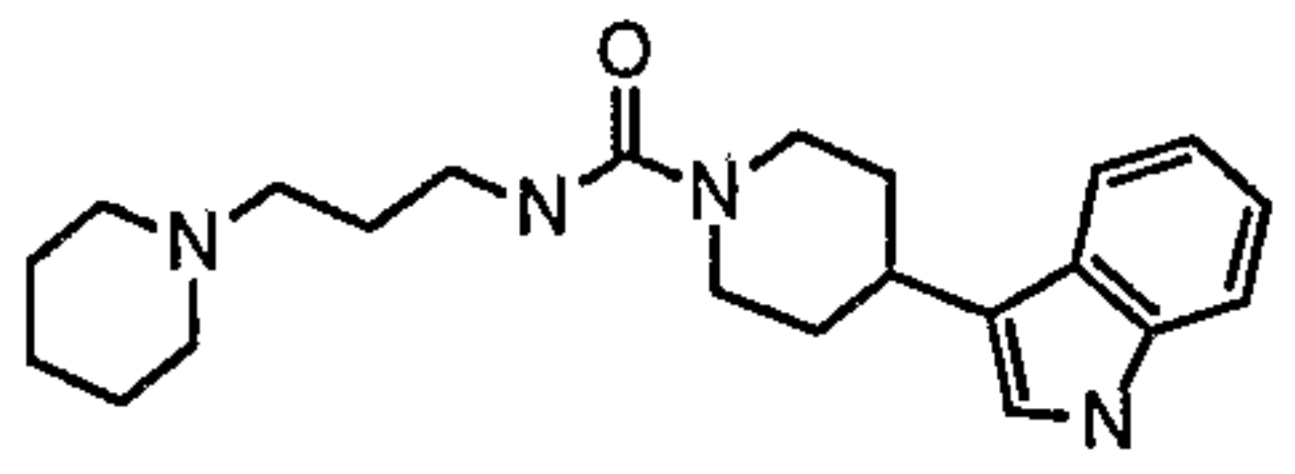
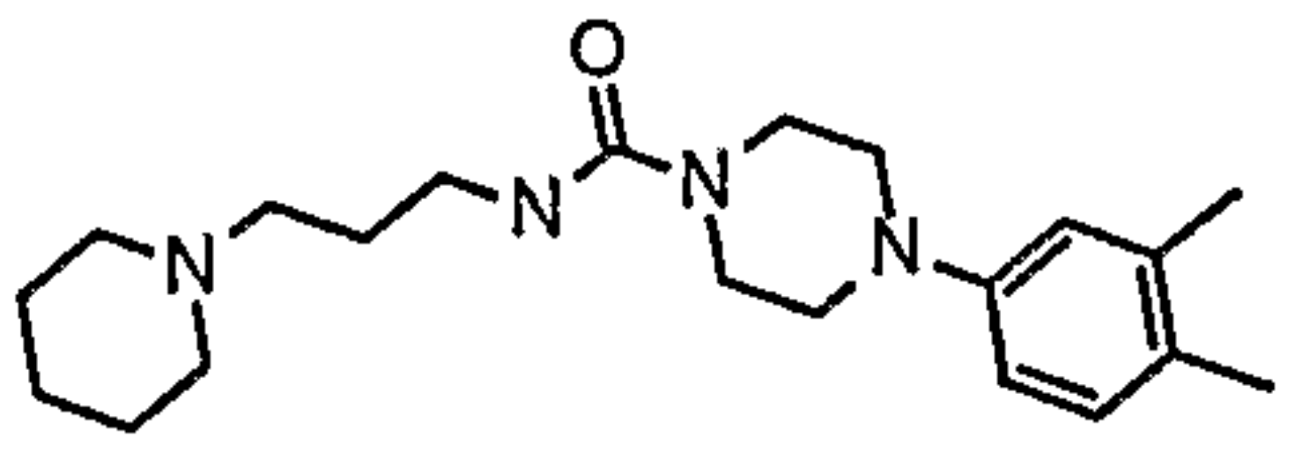
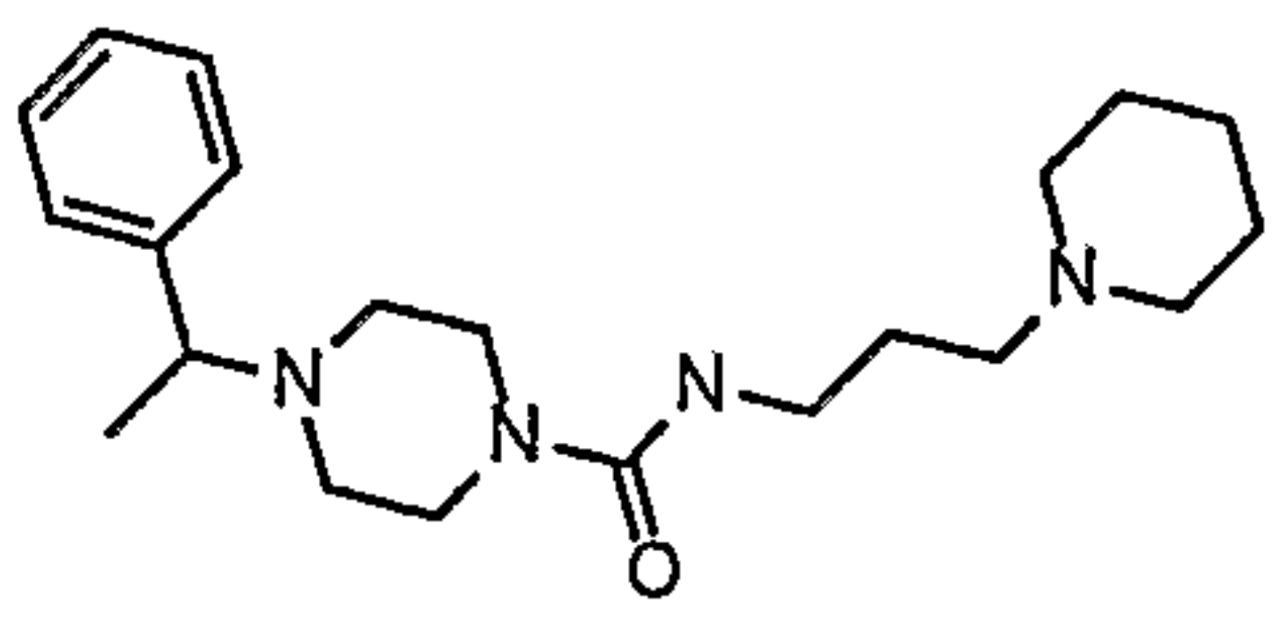
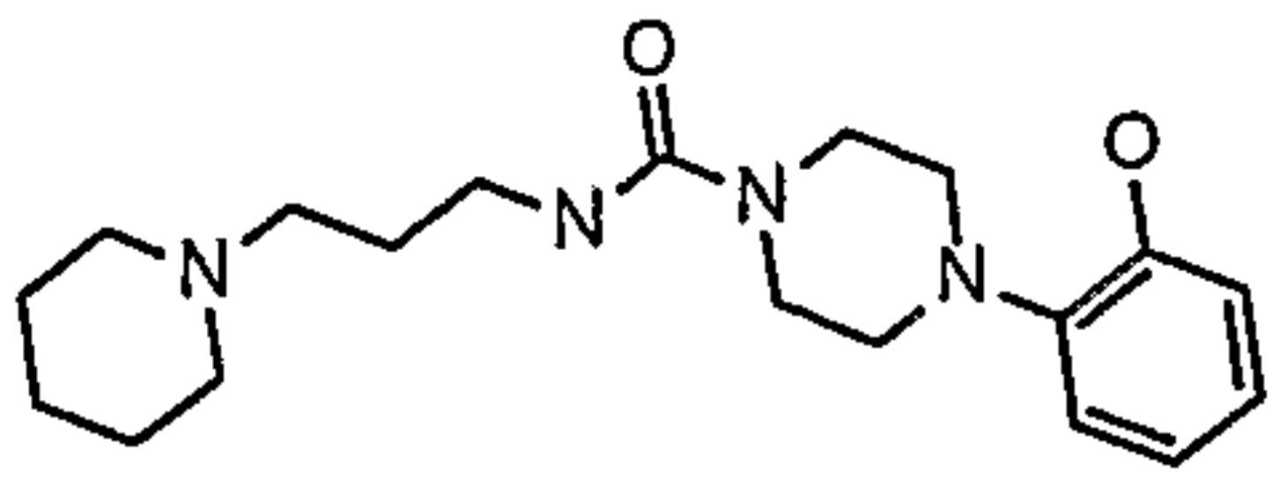
Example No.	STRUCTURE	Name	MW	Exact Mass	MH+
84.		(E)-(4-cinnamylpiperazin-1-yl)(4-methylpiperazin-1-yl)methanone	328.46	328.2	329.2
85.		(4-methylpiperazin-1-yl)(3H-spiro[isobenzofuran-1,4'-piperidine]-1'-yl)methanone	315.41	315.2	316.2
86.		(4-methylpiperazin-1-yl)(4-(1,2,3,4-tetrahydronaphthalen-1-yl)piperazin-1-yl)methanone	342.48	342.2	343.2
87.		(4-(isoquinolin-5-ylsulfonyl)piperazin-1-yl)(4-methylpiperazin-1-yl)methanone	403.5	403.2	404.2
88.		(3-methyl-4-m-tolylpiperazin-1-yl)(4-methylpiperazin-1-yl)methanone	316.45	316.2	317.2
89.		(4-(3-hydroxyphenyl)piperazin-1-yl)(4-methylpiperazin-1-yl)methanone	304.39	304.2	305.2
90.		(4-methylpiperazin-1-yl)(4-m-tolylpiperazin-1-yl)methanone	302.42	302.2	303.2
91.		(4-(1H-indol-3-yl)piperidin-1-yl)(4-methylpiperazin-1-yl)methanone	326.44	326.2	327.2
92.		(4-methylpiperazin-1-yl)(4-(6-methylpyridin-2-yl)piperazin-1-yl)methanone	303.41	303.2	304.2

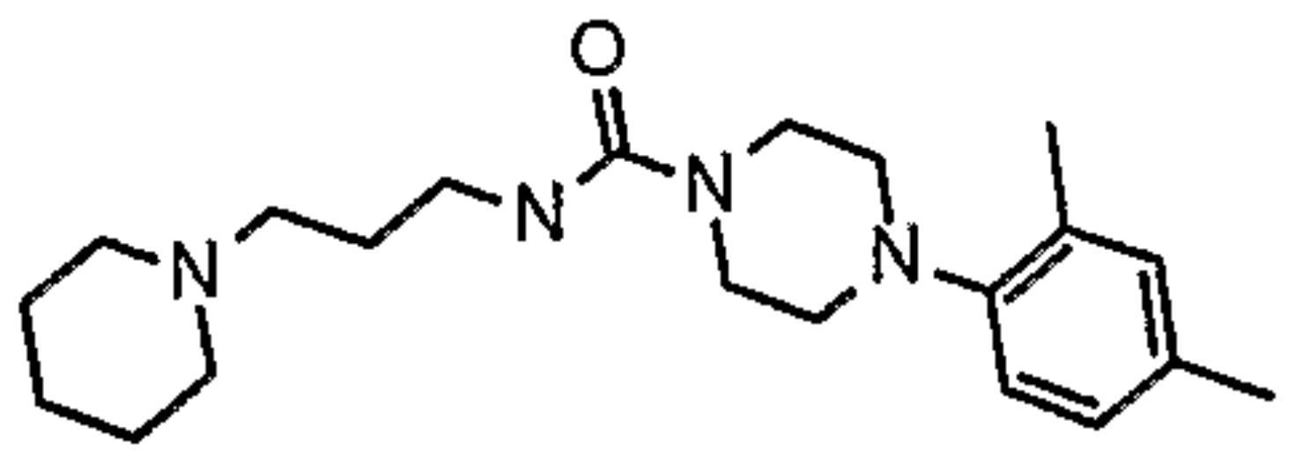
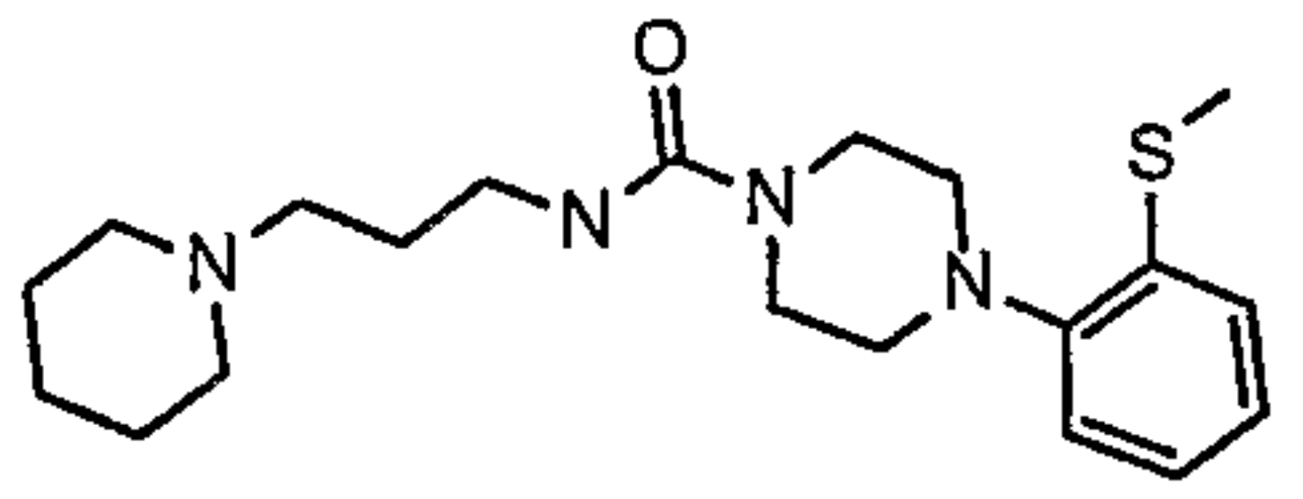
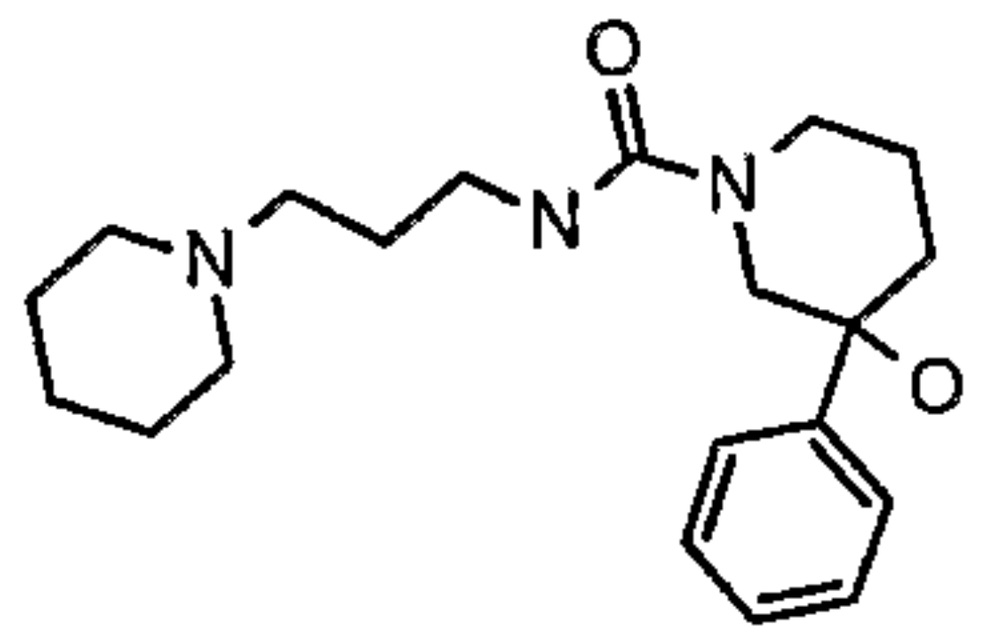
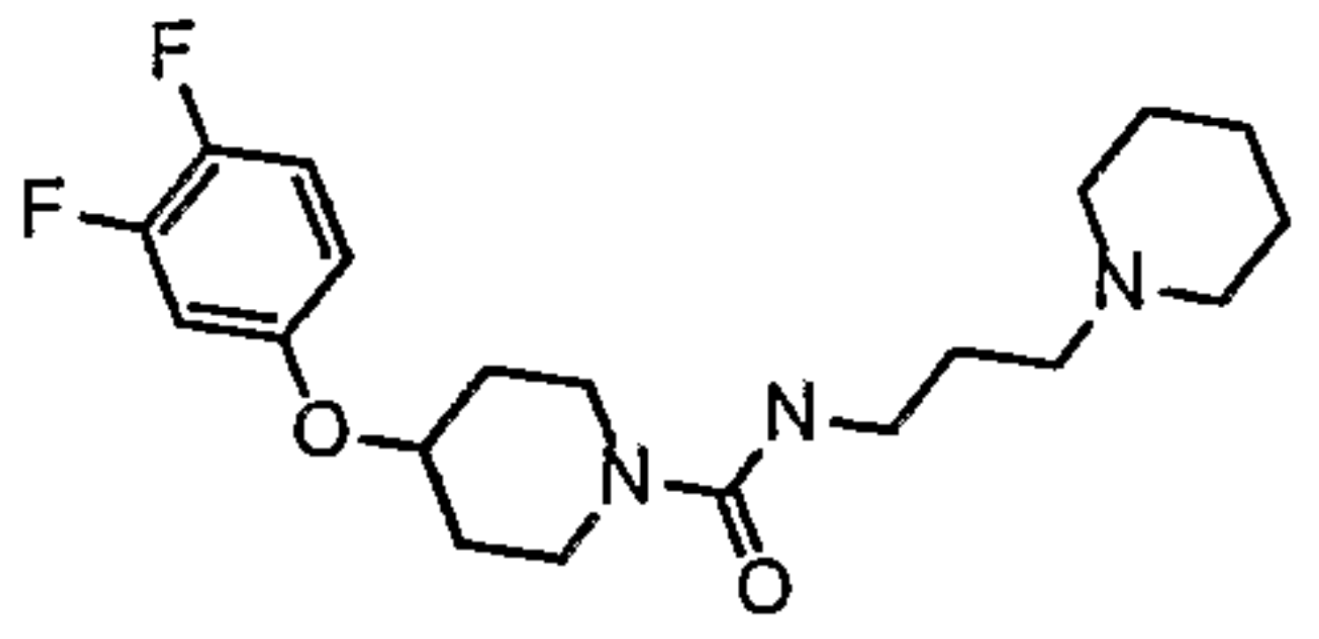
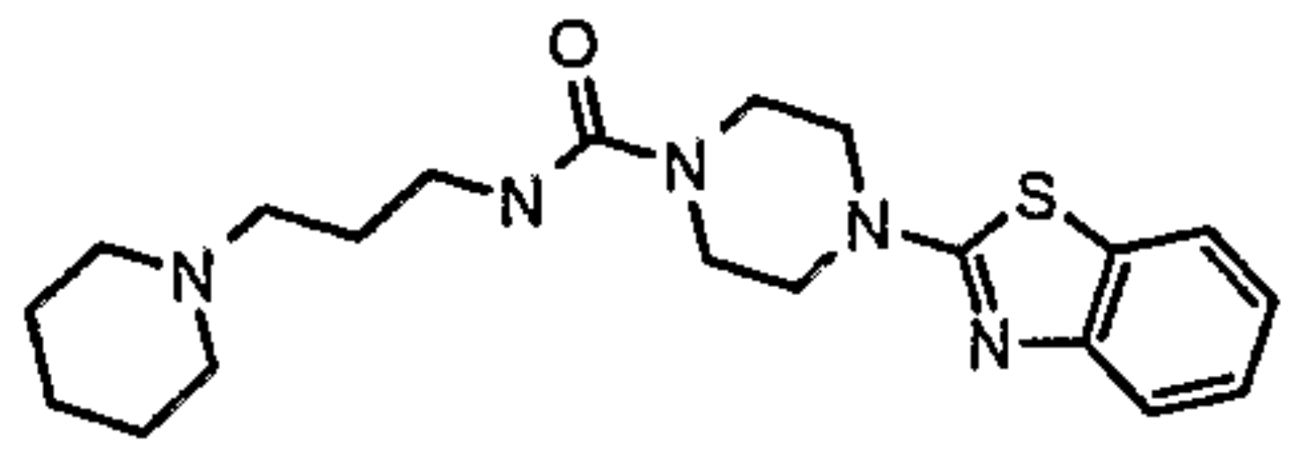
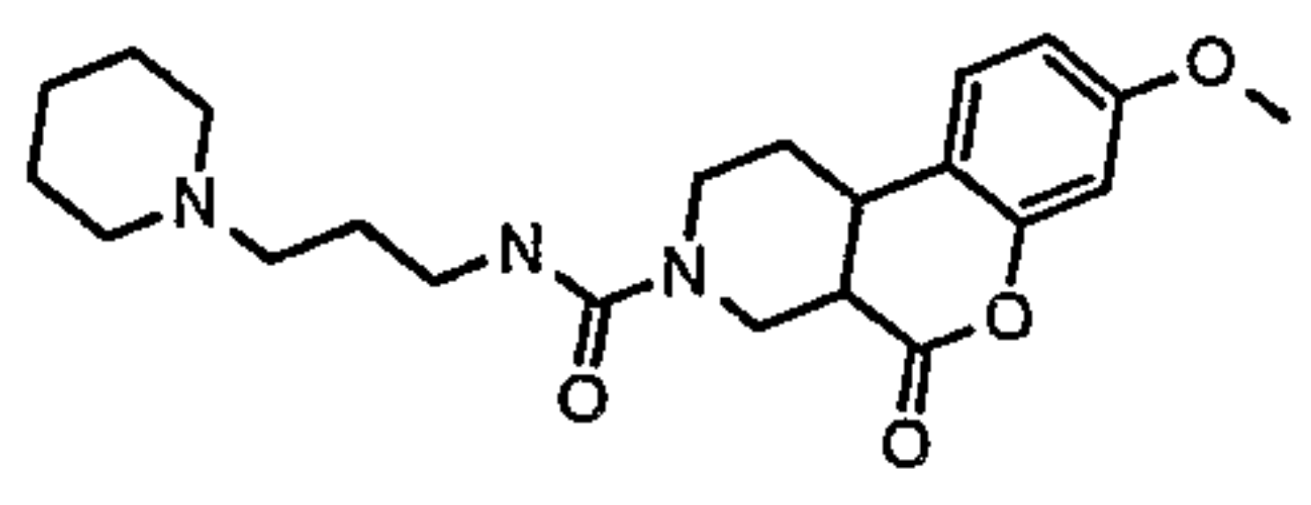
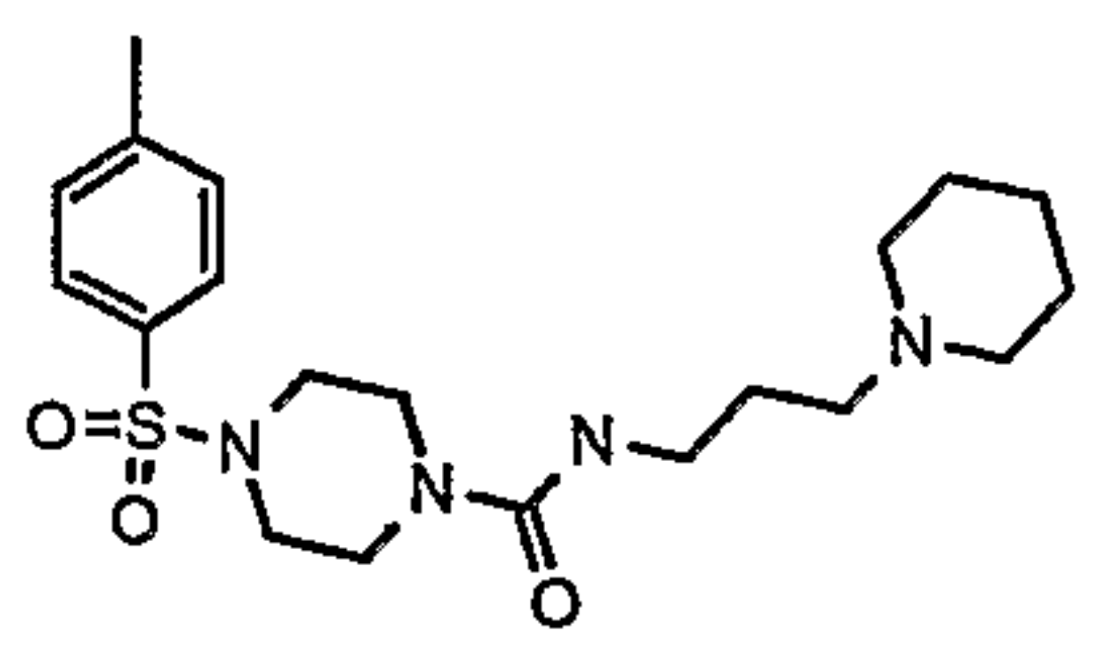
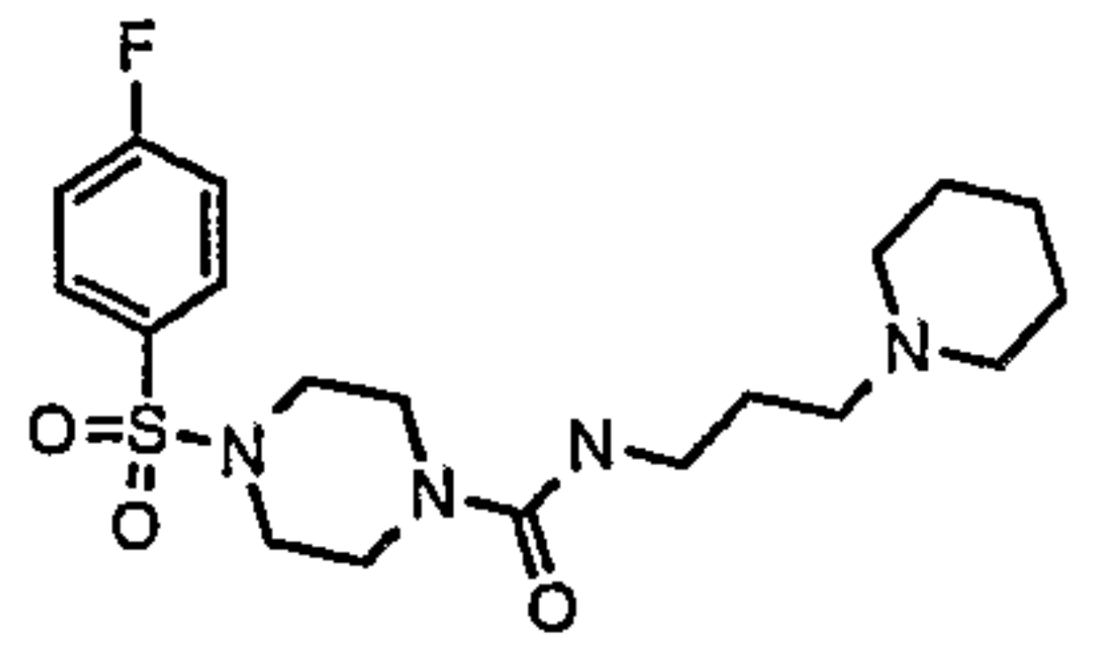
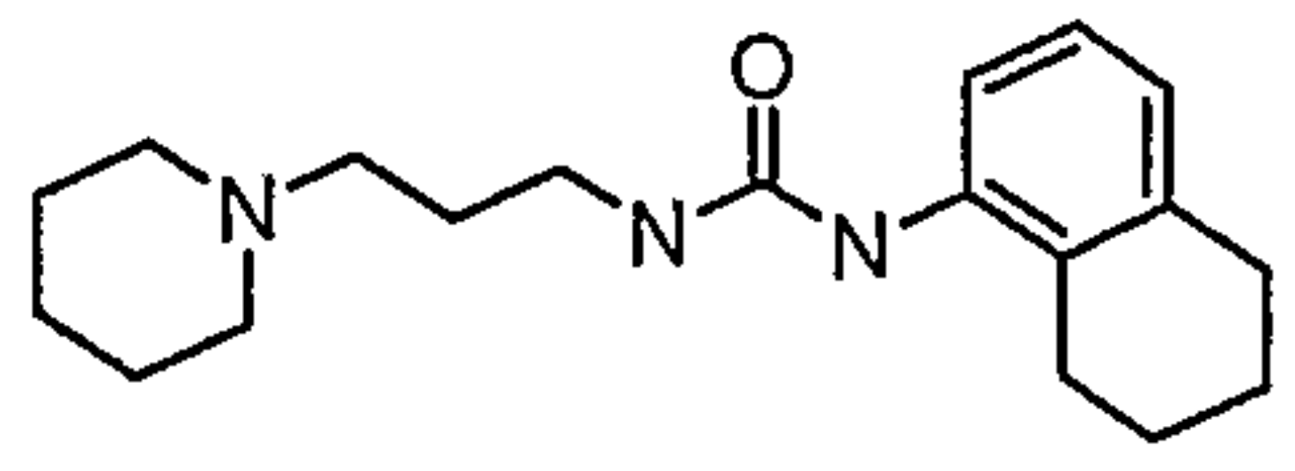
Example No.	STRUCTURE	Name	MW	Exact Mass	MH+
93.		N-(1-(4-methylpiperazine-1-carbonyl)piperidin-4-yl)benzamide	330.43	330.2	331.2
94.		(4-(3,4-dimethylphenyl)piperazin-1-yl)(4-methylpiperazin-1-yl)methanone	316.45	316.2	317.2
95.		(4-methylpiperazin-1-yl)(4-(1-phenylethyl)piperazin-1-yl)methanone	316.45	316.2	317.2
96.		(4-(2-hydroxyphenyl)piperazin-1-yl)(4-methylpiperazin-1-yl)methanone	304.39	304.2	305.2
97.		(4-methylpiperazin-1-yl)(4-(2-(methylthio)phenyl)piperazin-1-yl)methanone	334.49	334.2	335.2
98.		(3-hydroxy-3-phenylpiperidin-1-yl)(4-methylpiperazin-1-yl)methanone	303.4	303.2	304.2
99.		(4-(3,4-difluorophenoxy)piperidin-1-yl)(4-methylpiperazin-1-yl)methanone	339.38	339.2	340.2
100.		(4-methylpiperazin-1-yl)(4-tosylpiperazin-1-yl)methanone	366.48	366.2	367.2
101.		(4-(4-fluorophenylsulfonyl)piperazin-1-yl)(4-methylpiperazin-1-yl)methanone	370.45	370.1	371.2

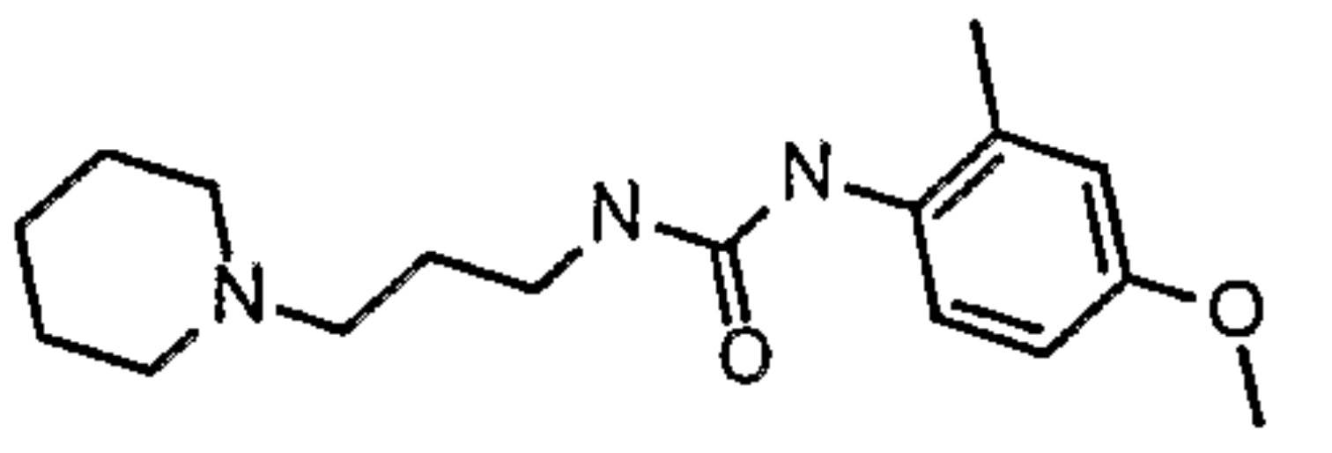
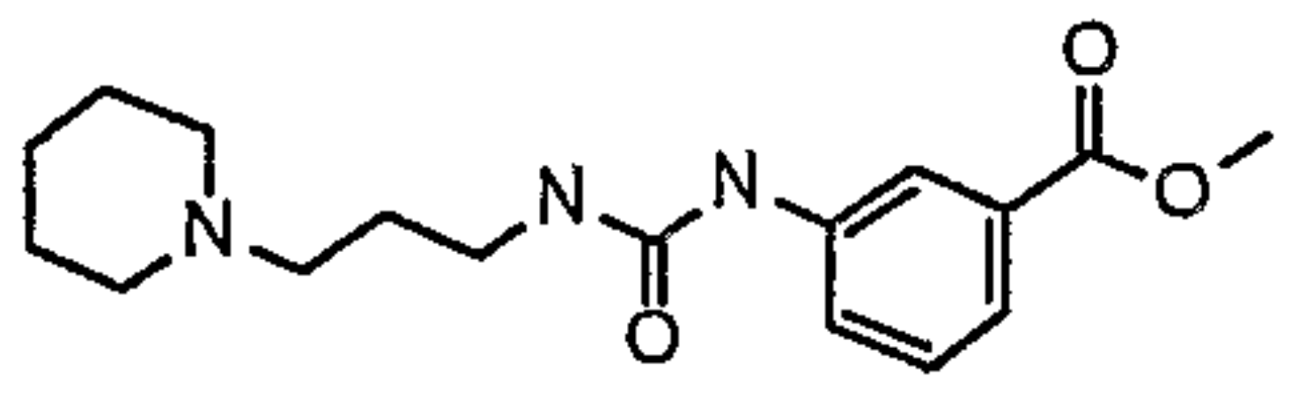
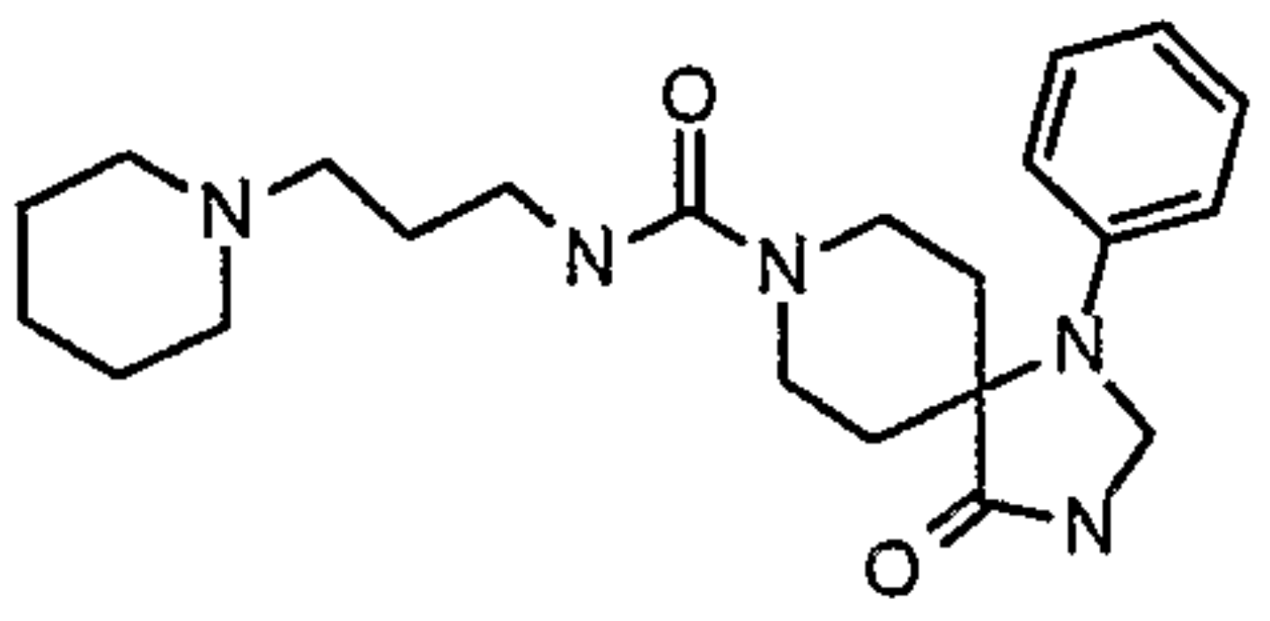
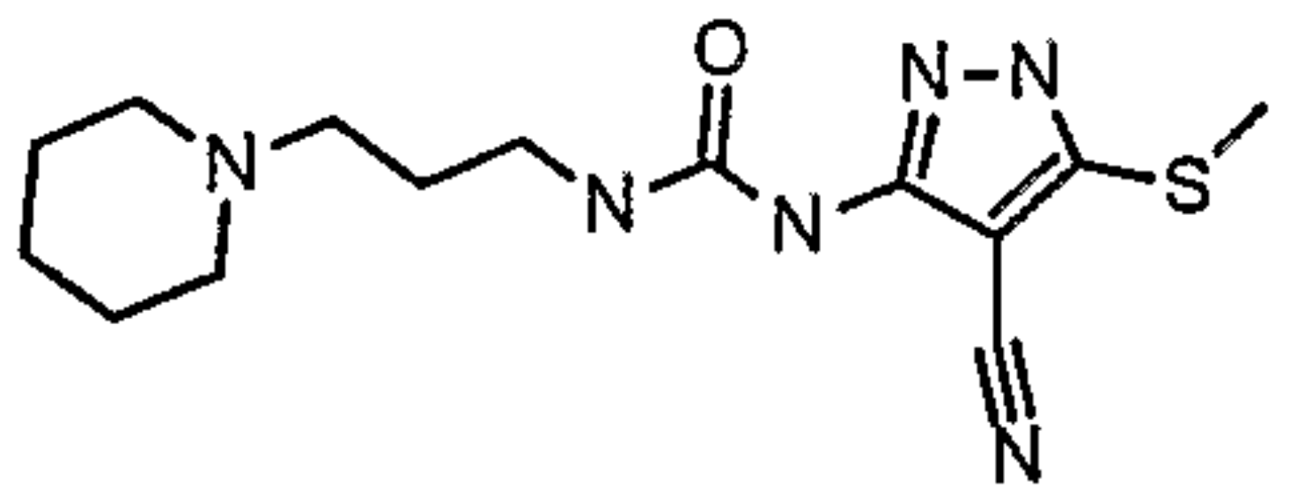
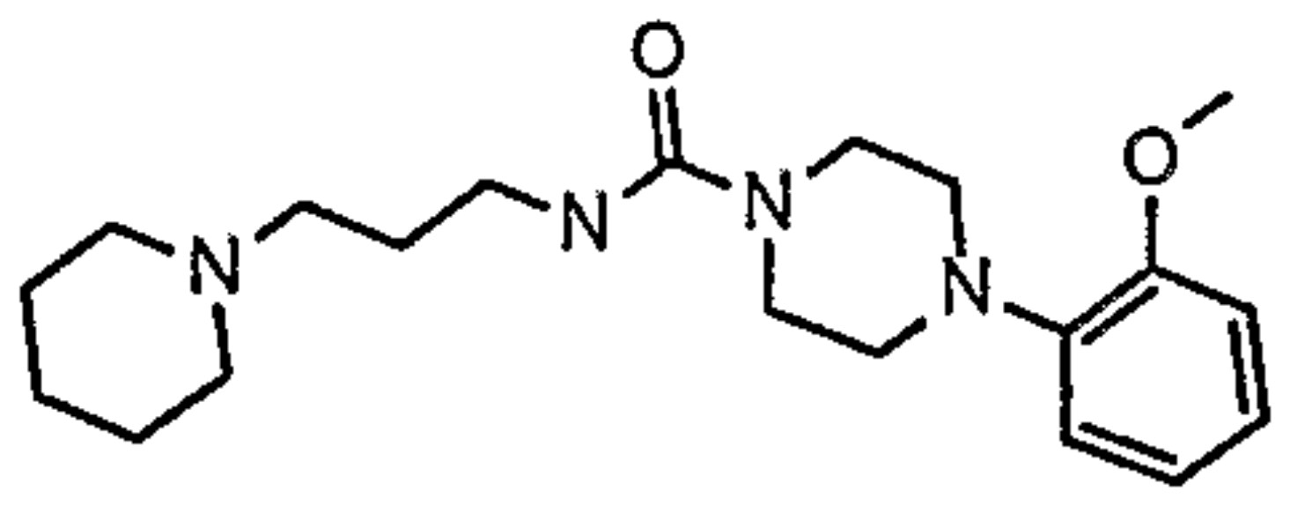
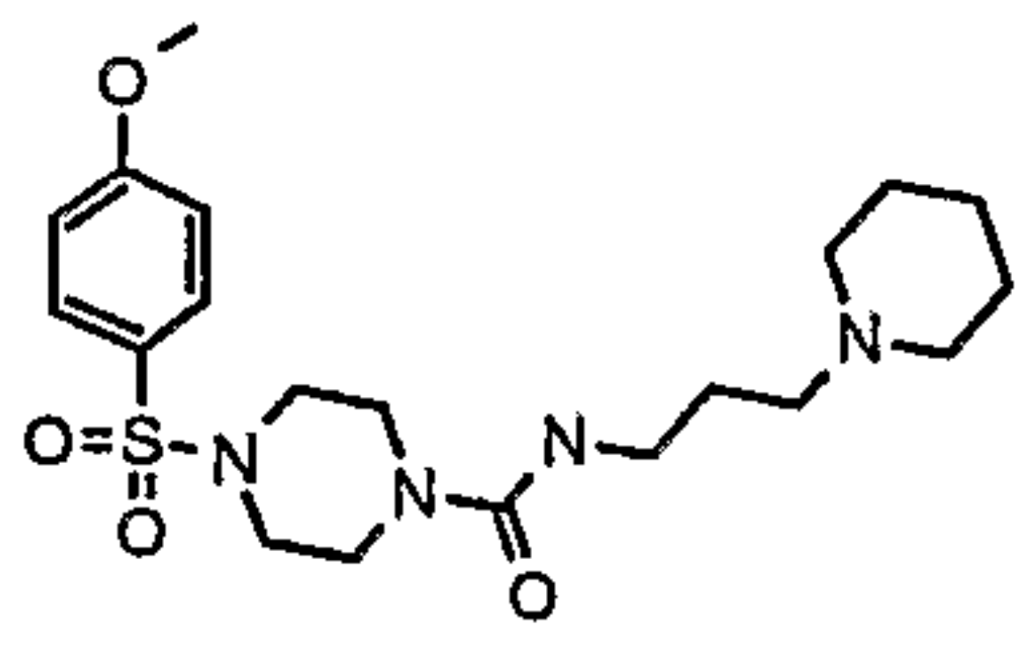
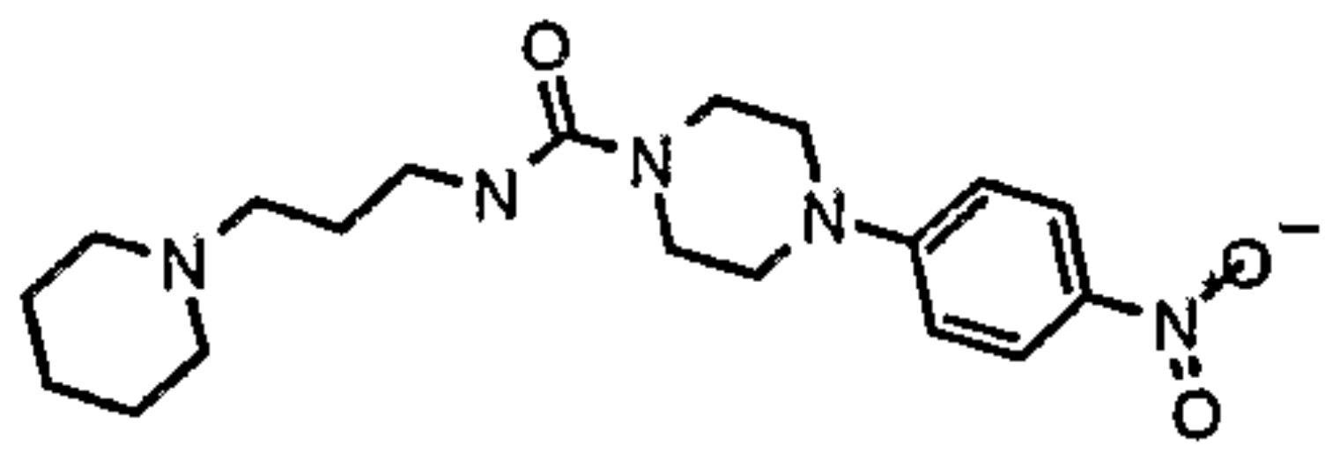
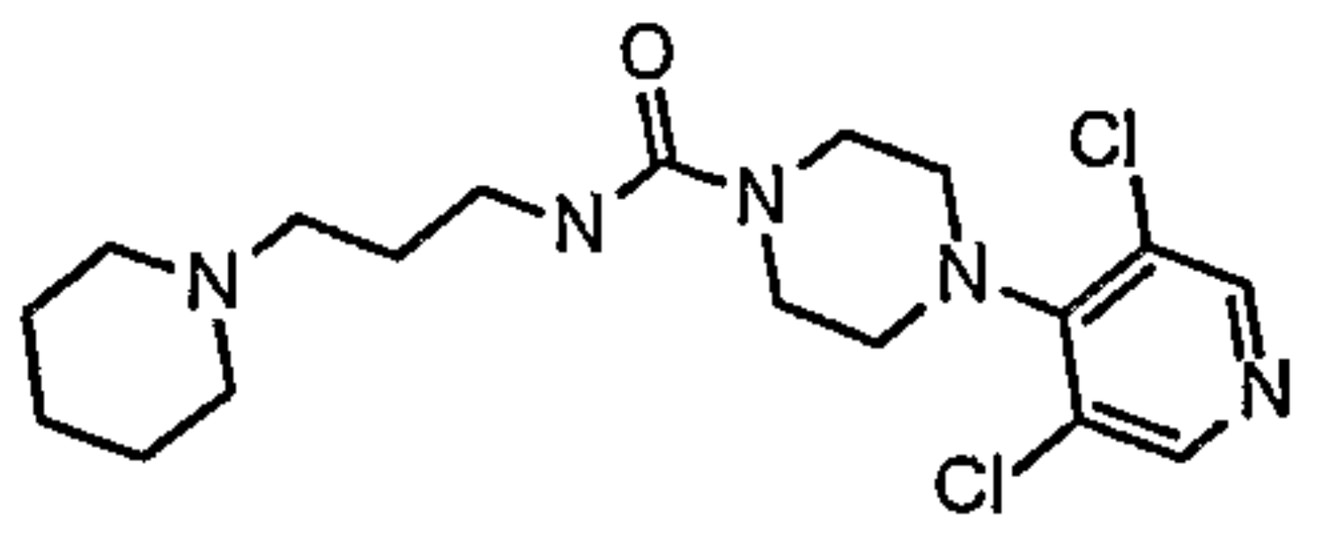
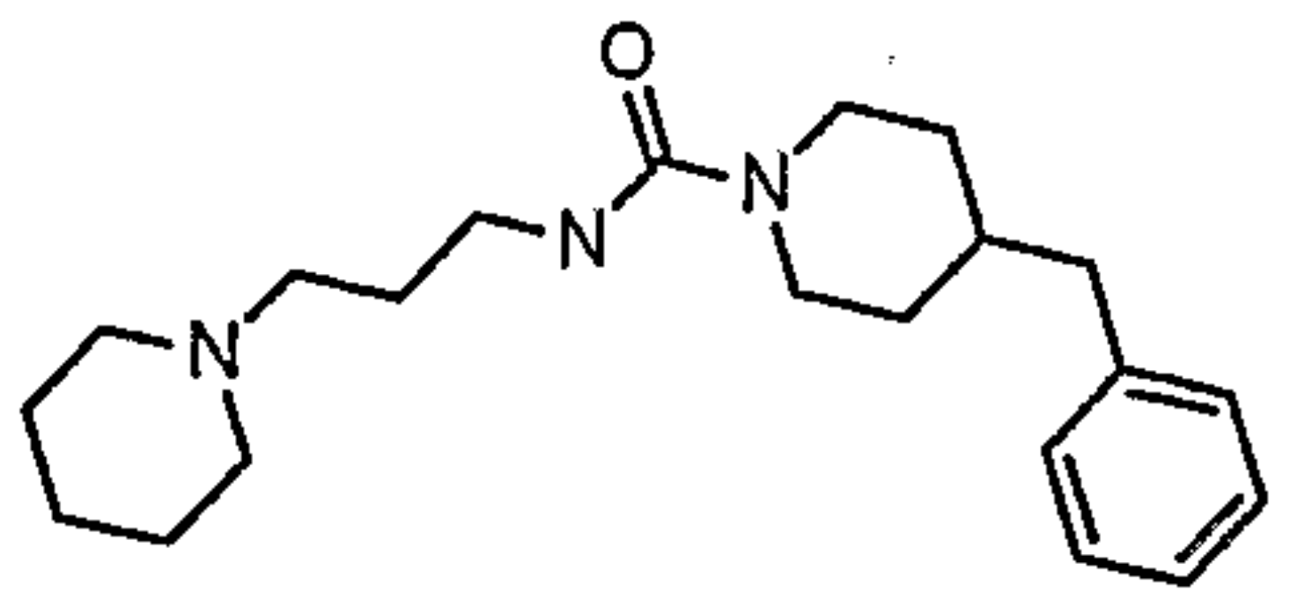
Example No.	STRUCTURE	Name	MW	Exact Mass	MH+
102.		N-(2-ethanoylphenyl)-4-methylpiperazine-1-carboxamide	261.32	261.1	262.2
103.		4-methyl-N-(5,6,7,8-tetrahydronaphthalen-1-yl)piperazine-1-carboxamide	273.38	273.2	274.2
104.		N-(4-methoxy-2-methylphenyl)-4-methylpiperazine-1-carboxamide	263.34	263.2	264.2
105.		N-(2,4-difluorophenyl)-4-methylpiperazine-1-carboxamide	255.27	255.1	256.1
106.		N-(3-fluoro-2-methylphenyl)-4-methylpiperazine-1-carboxamide	251.3	251.1	252.2
107.		8-(4-methylpiperazine-1-carbonyl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one	357.46	357.2	358.2
108.		(4-(2-methoxyphenyl)piperazin-1-yl)(4-methylpiperazin-1-yl)methanone	318.42	318.2	319.2
109.		(4-(4-methoxyphenylsulfonyl)piperazin-1-yl)(4-methylpiperazin-1-yl)methanone	382.48	382.2	383.2
110.		(4-methylpiperazin-1-yl)(4-(4-nitrophenyl)piperazin-1-yl)methanone	333.39	333.2	334.2

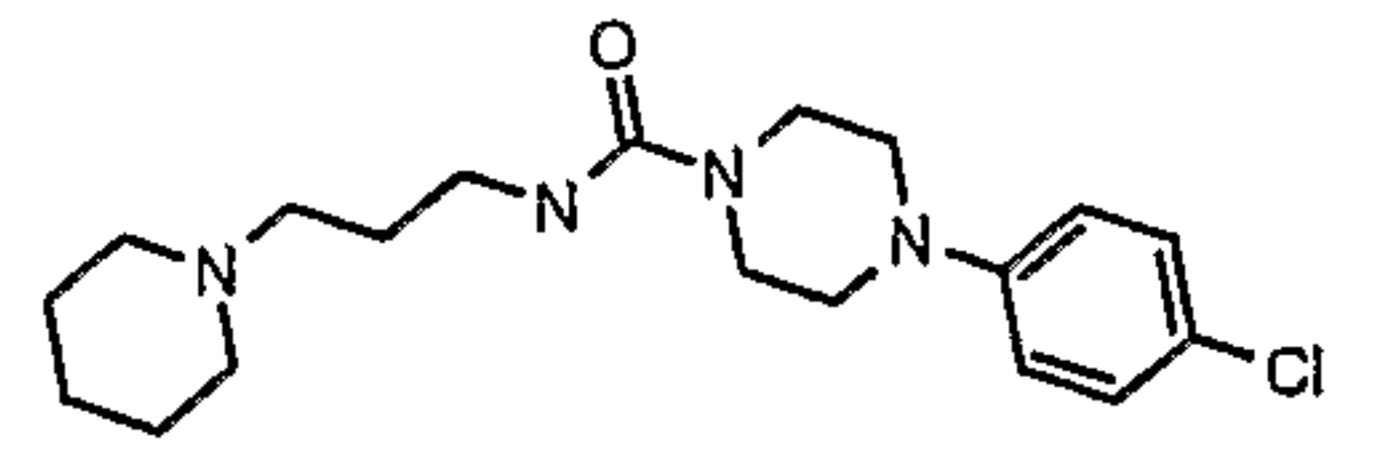
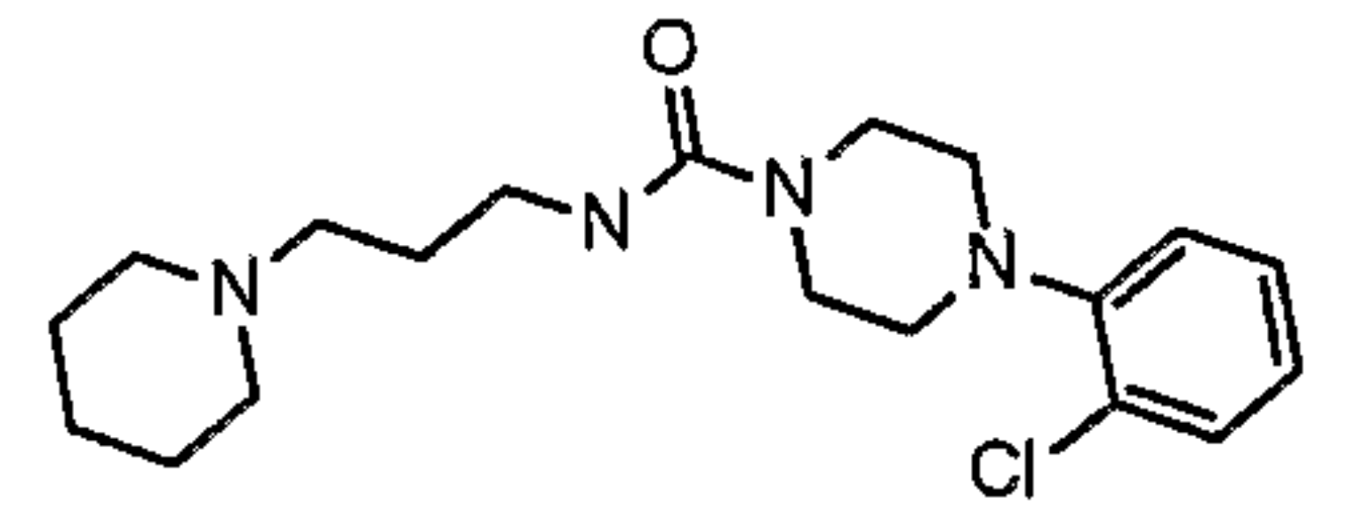
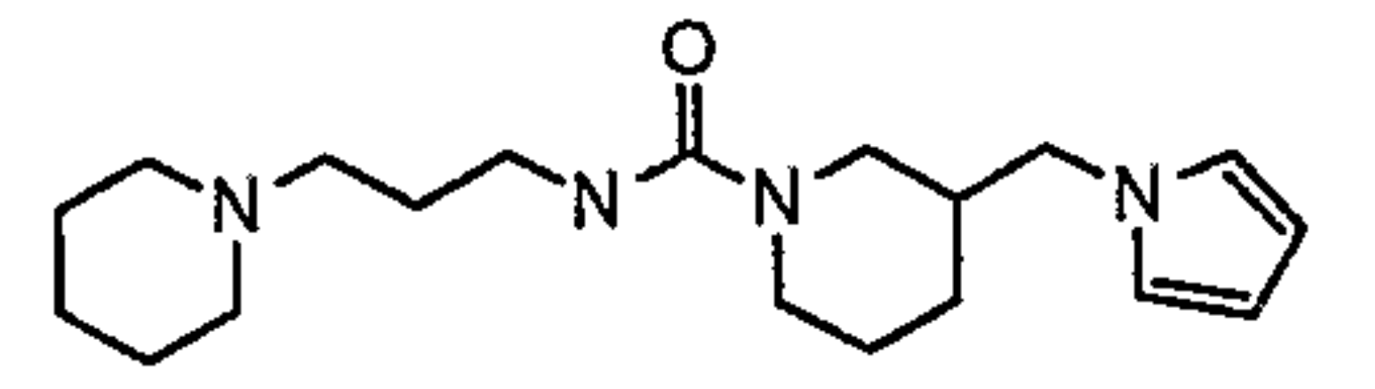
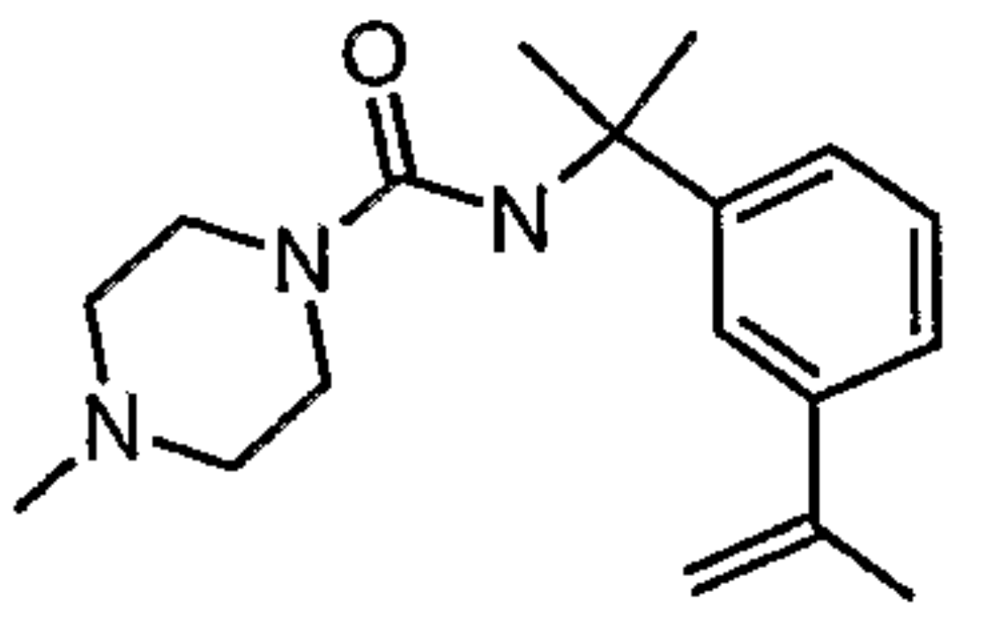
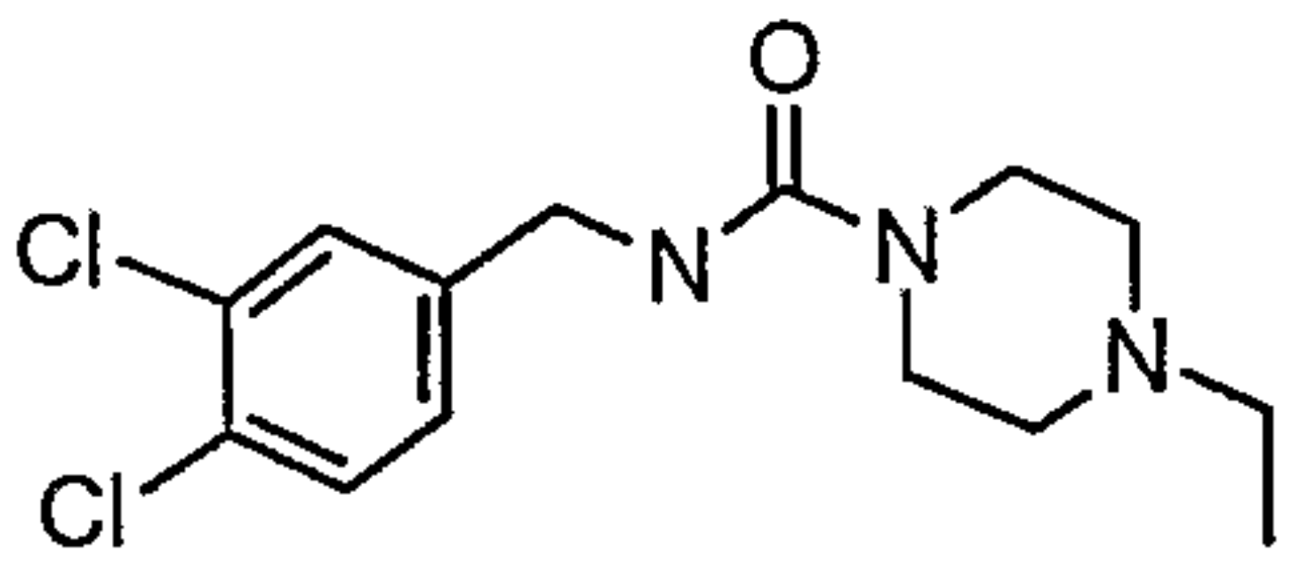
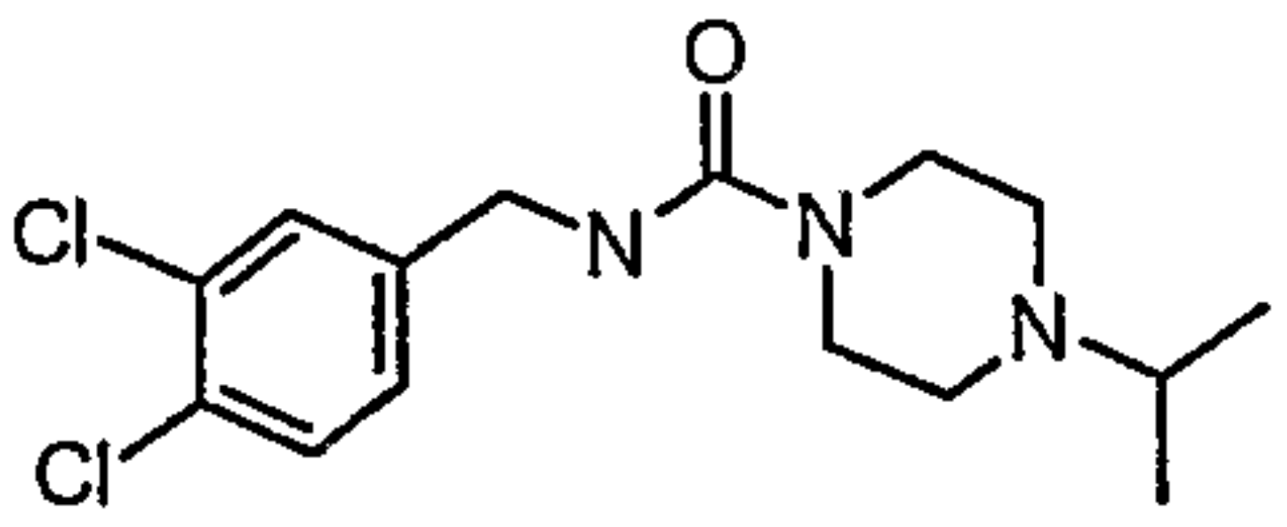
Example No.	STRUCTURE	Name	MW	Exact Mass	MH+
111.		(4-(3,5-dichloropyridin-4-yl)piperazin-1-yl)(4-methylpiperazin-1-yl)methanone	358.27	357.1	358.1
112.		(4-benzylpiperidin-1-yl)(4-methylpiperazin-1-yl)methanone	301.43	301.2	302.2
113.		(4-(4-chlorophenyl)piperazin-1-yl)(4-methylpiperazin-1-yl)methanone	322.84	322.2	323.2
114.		(3-((1H-pyrrol-1-yl)methyl)piperidin-1-yl)(4-methylpiperazin-1-yl)methanone	290.41	290.2	291.2
115.		1-(3-chloro-4-methoxyphenyl)-3-(3-(piperidin-1-yl)propyl)urea	325.84	325.2	326.2
116.		1-(4-(piperidin-1-yl)phenyl)-3-(3-(piperidin-1-yl)propyl)urea	344.5	344.3	345.3
117.		1-(3-(piperidin-1-yl)propyl)-3-(1,3,5-trimethyl-1H-pyrazol-4-yl)urea	293.41	293.2	294.2
118.		1-(5-methylthiazol-2-yl)-3-(3-(piperidin-1-yl)propyl)urea	282.41	282.2	283.2
119.		1-(4-(1,2,3-thiadiazol-4-yl)phenyl)-3-(3-(piperidin-1-yl)propyl)urea	345.47	345.2	346.2

Example No.	STRUCTURE	Name	MW	Exact Mass	MH+
120.		1-(2-(methylthio)benzo[d]thiazol-6-yl)-3-(3-(piperidin-1-yl)propyl)urea	364.54	364.1	365.1
121.		1-(3,5-dimethylpyrazin-2-yl)-3-(3-(piperidin-1-yl)propyl)urea	291.4	291.2	292.2
122.		4-(2,3-dihydrobenzo[b][1,4]dioxine-2-carbonyl)-N-(3-(piperidin-1-yl)propyl)piperazine-1-carboxamide	416.52	416.2	417.3
123.		4-(4-chlorophenyl)-4-hydroxy-N-(3-(piperidin-1-yl)propyl)piperidine-1-carboxamide	379.93	379.2	380.2
124.		4-hydroxy-4-phenyl-N-(3-(piperidin-1-yl)propyl)piperidine-1-carboxamide	345.48	345.2	346.2
125.		3-phenyl-N-(3-(piperidin-1-yl)propyl)-3H-spiro[isobenzofuran-1,4'-piperidine]-1'-carboxamide	433.59	433.3	434.3
126.		4-(1-oxoisoindolin-2-yl)-N-(3-(piperidin-1-yl)propyl)piperidine-1-carboxamide	384.52	384.3	385.3
127.		3-(benzhydryloxy)-N-(3-(piperidin-1-yl)propyl)piperidine-1-carboxamide	435.61	435.3	436.3
128.		4-benzyl-4-hydroxy-N-(3-(piperidin-1-yl)propyl)piperidine-1-carboxamide	359.51	359.3	360.3

Example No.	STRUCTURE	Name	MW	Exact Mass	MH+
129.		4-cinnamyl-N-(3-(piperidin-1-yl)propyl)piperazine-1-carboxamide	370.54	370.3	371.3
130.		N-(3-(piperidin-1-yl)propyl)-4-(1,2,3,4-tetrahydronaphthalen-1-yl)piperazine-1-carboxamide	384.56	384.3	385.3
131.		4-(isoquinolin-5-ylsulfonyl)-N-(3-(piperidin-1-yl)propyl)piperazine-1-carboxamide	445.59	445.2	446.2
132.		3-methyl-N-(3-(piperidin-1-yl)propyl)-4-m-tolylpiperazine-1-carboxamide	358.53	358.3	359.3
133.		N-(3-(piperidin-1-yl)propyl)-4-m-tolylpiperazine-1-carboxamide	344.5	344.3	345.3
134.		4-(1H-indol-3-yl)-N-(3-(piperidin-1-yl)propyl)piperidine-1-carboxamide	368.52	368.3	369.3
135.		4-(3,4-dimethylphenyl)-N-(3-(piperidin-1-yl)propyl)piperazine-1-carboxamide	358.53	358.3	359.3
136.		4-(1-phenylethyl)-N-(3-(piperidin-1-yl)propyl)piperazine-1-carboxamide	358.53	358.3	359.3
137.		4-(2-hydroxyphenyl)-N-(3-(piperidin-1-yl)propyl)piperazine-1-carboxamide	346.47	346.2	347.2

Example No.	STRUCTURE	Name	MW	Exact Mass	MH+
138.		4-(2,4-dimethylphenyl)-N-(3-(piperidin-1-yl)propyl)piperazine-1-carboxamide	358.53	358.3	359.3
139.		4-(2-(methylthio)phenyl)-N-(3-(piperidin-1-yl)propyl)piperazine-1-carboxamide	376.57	376.2	377.2
140.		3-hydroxy-3-phenyl-N-(3-(piperidin-1-yl)propyl)piperidine-1-carboxamide	345.48	345.2	346.2
141.		4-(3,4-difluorophenoxy)-N-(3-(piperidin-1-yl)propyl)piperidine-1-carboxamide	381.46	381.2	382.2
142.		4-(benzo[d]thiazol-2-yl)-N-(3-(piperidin-1-yl)propyl)piperazine-1-carboxamide	387.55	387.2	388.2
143.		8-methoxy-5-oxo-N-(3-piperidin-1-ylpropyl)-1,4a,5,10b-tetrahydro-2H-chromeno[3,4-c]pyridine-3(4H)-carboxamide	401.5	401.2	402.2
144.		N-(3-(piperidin-1-yl)propyl)-4-tosylpiperazine-1-carboxamide	408.56	408.2	409.2
145.		4-(4-fluorophenylsulfonyl)-N-(3-(piperidin-1-yl)propyl)piperazine-1-carboxamide	412.53	412.2	413.2
146.		1-(3-(piperidin-1-yl)propyl)-3-(5,6,7,8-tetrahydronaphthalen-1-yl)urea	315.46	315.2	316.2

Example No.	STRUCTURE	Name	MW	Exact Mass	MH+
147.		1-(4-methoxy-2-methylphenyl)-3-(3-(piperidin-1-yl)propyl)urea	305.42	305.2	306.2
148.		methyl 3-(3-(3-(piperidin-1-yl)propyl)ureido)benzoate	319.4	319.2	320.2
149.		4-oxo-1-phenyl-N-(3-(piperidin-1-yl)propyl)-1,3,8-triazaspiro[4.5]decane-8-carboxamide	399.54	399.3	400.3
150.		1-(4-cyano-5-(methylthio)-1H-pyrazol-3-yl)-3-(3-(piperidin-1-yl)propyl)urea	322.44	322.2	323.2
151.		4-(2-methoxyphenyl)-N-(3-(piperidin-1-yl)propyl)piperazine-1-carboxamide	360.5	360.3	361.3
152.		4-(4-methoxyphenylsulfonyl)-N-(3-(piperidin-1-yl)propyl)piperazine-1-carboxamide	424.56	424.2	425.2
153.		4-(4-nitrophenyl)-N-(3-(piperidin-1-yl)propyl)piperazine-1-carboxamide	375.47	375.2	376.2
154.		4-(3,5-dichloropyridin-4-yl)-N-(3-(piperidin-1-yl)propyl)piperazine-1-carboxamide	400.35	399.2	400.2
155.		4-benzyl-N-(3-(piperidin-1-yl)propyl)piperidine-1-carboxamide	343.51	343.3	344.3

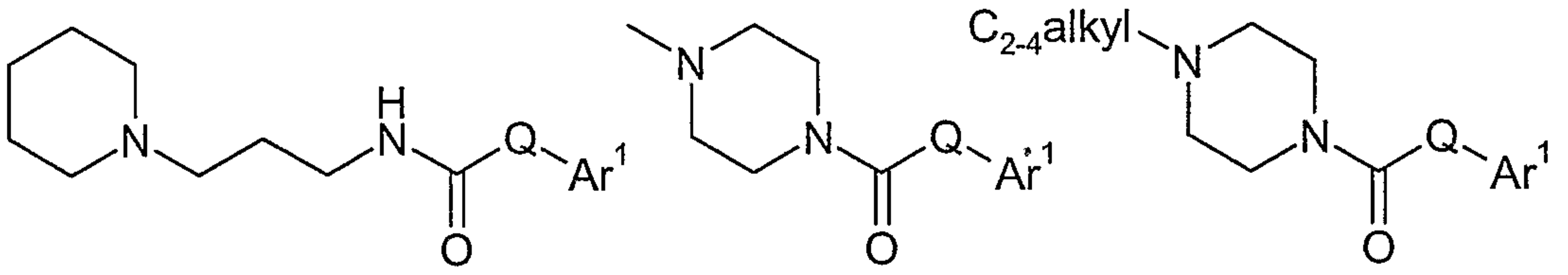
Example No.	STRUCTURE	Name	MW	Exact Mass	MH+
156.		4-(4-chlorophenyl)-N-(3-(piperidin-1-yl)propyl)piperazine-1-carboxamide	364.92	364.2	365.2
157.		4-(2-chlorophenyl)-N-(3-(piperidin-1-yl)propyl)piperazine-1-carboxamide	364.92	364.2	365.2
158.		3-((1H-pyrrol-1-yl)methyl)-N-(3-(piperidin-1-yl)propyl)piperidine-1-carboxamide	332.49	332.3	333.3
159.		4-methyl-N-(2-(3-(prop-1-en-2-yl)phenyl)propan-2-yl)piperazine-1-carboxamide	301.43	301.2	302.2
160.		N-(3,4-dichlorobenzyl)-4-ethylpiperazine-1-carboxamide	316.23	315.1	316.1
161.		N-(3,4-dichlorobenzyl)-4-isopropylpiperazine-1-carboxamide	330.26	329.1	330.1

*High Resolution analytical MS method: Data were acquired in positive ion electrospray mode on an electrospray orthogonal time-of-flight mass spectrometer at a resolution of about 6500. Measurements were made with reversed phase HPLC sample introduction using a linear ACN/water gradient with 0.1% formic acid as the modifier. The experiment was performed using the lockspray accessory with reserpine as the lock mass compound.

In addition, the procedure of Example 1 may be used to prepare all the compounds described earlier in the present specification.

What is claimed is :

1. A compound of formula I, II or III, a pharmaceutically acceptable salt thereof, diastereomers, enantiomers, or mixtures thereof:

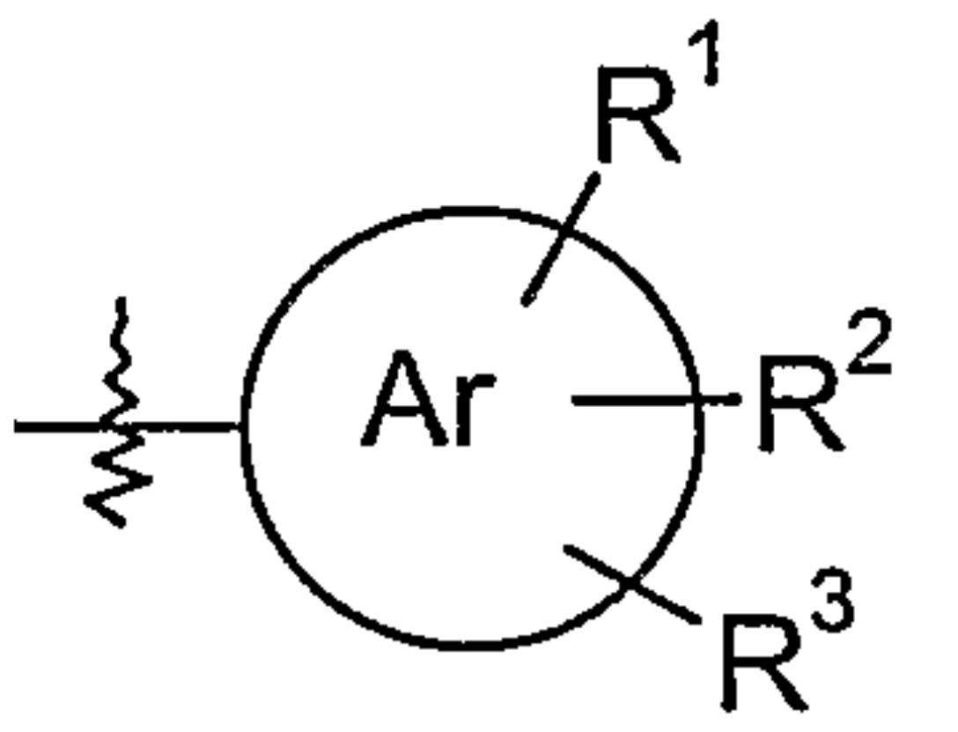


I II III

wherein

Ar^1 is selected from $C_{6\text{-}10}$aryl and $C_{2\text{-}9}$heteroaryl, wherein said $C_{6\text{-}10}$aryl and $C_{2\text{-}9}$heteroaryl are optionally substituted with one or more groups selected from -R, –NO_2, -OR, -Cl, -Br, -I, -F, -CF_3, -OCF_3, -C(=O)R, -C(=O)OH, -NH_2, -SH, -NHR, -NR_2, -SR, -SO_3H, -SO_2R, -SO_2NR, -S(=O)R, -CN, -OH, -C(=O)OR, -C(=O)NR_2, -NRC(=O)R, and -NRC(=O)-OR, wherein R is, independently, a hydrogen, $C_{3\text{-}6}$cycloalkyl, $C_{3\text{-}6}$heterocyclyl, phenyl, benzyl, $C_{1\text{-}6}$alkyl or $C_{2\text{-}6}$alkenyl and wherein said R is further optionally substituted with one or more groups selected from methyl, methoxy, hydroxy and halogen; and

Q is a divalent or trivalent group that connects the carbonyl with Ar^1, wherein said divalent or trivalent group contains at least one nitrogen, said nitrogen is directly connected to the carbonyl group of formula I, II or III to form an amide bond therebetween, and said trivalent group is fused with Ar^1, or Ar^1 is represented by



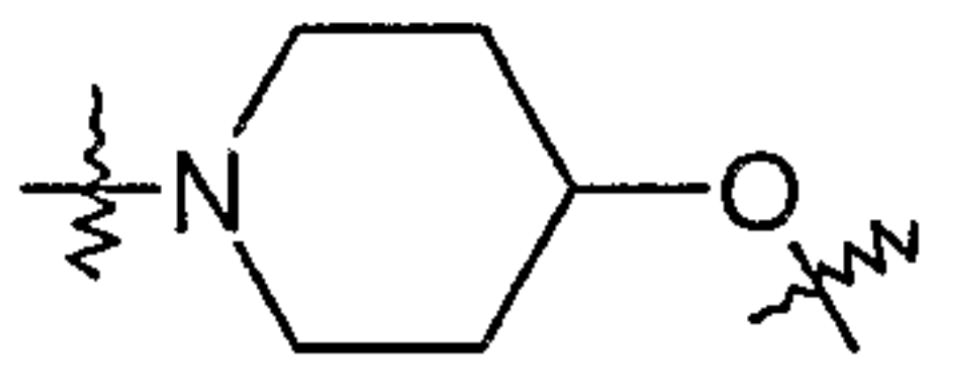
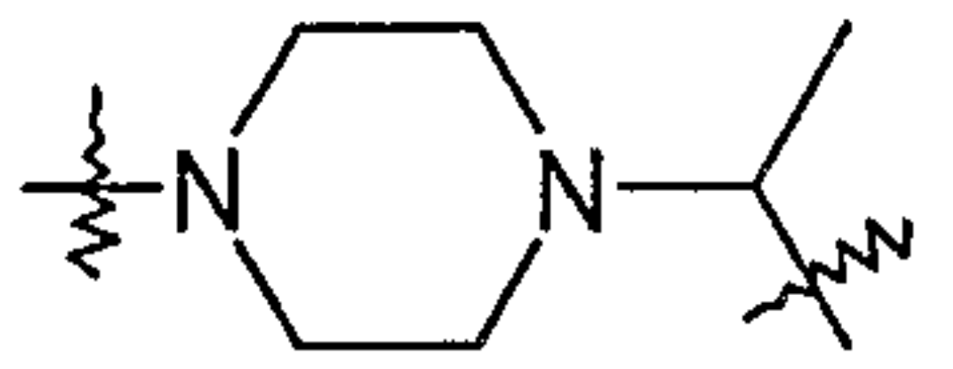
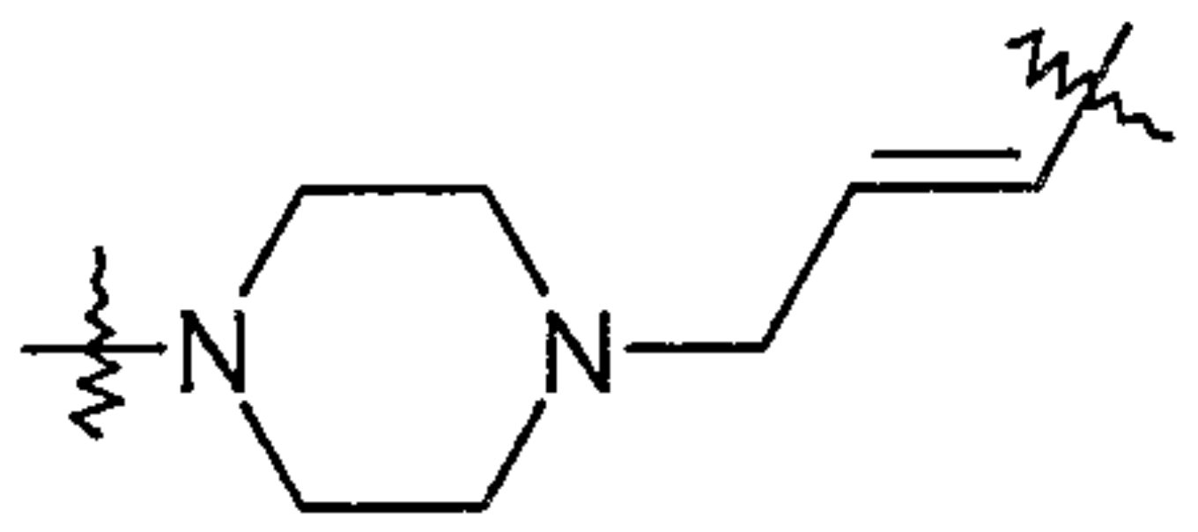
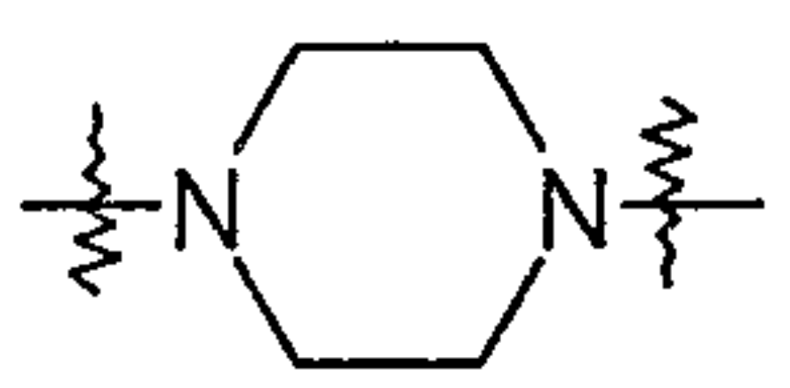
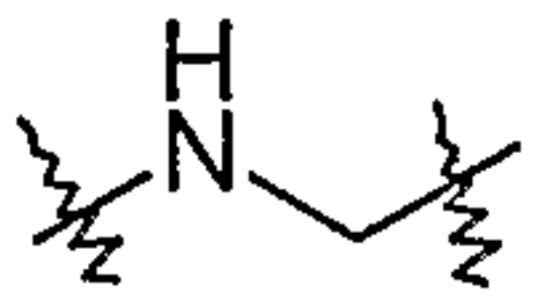
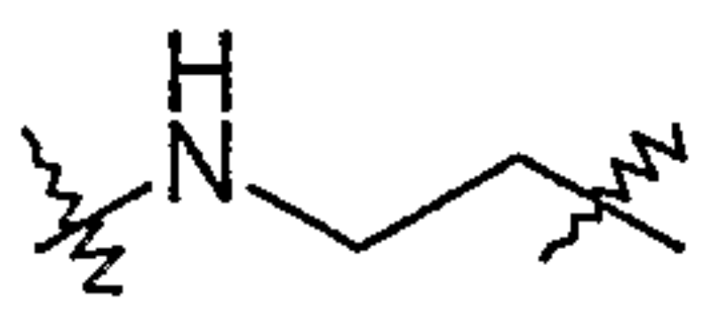
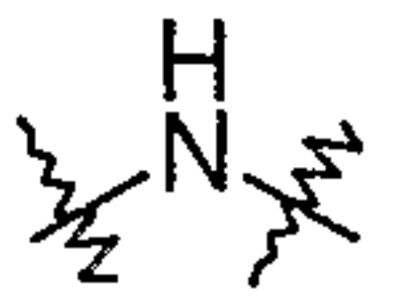
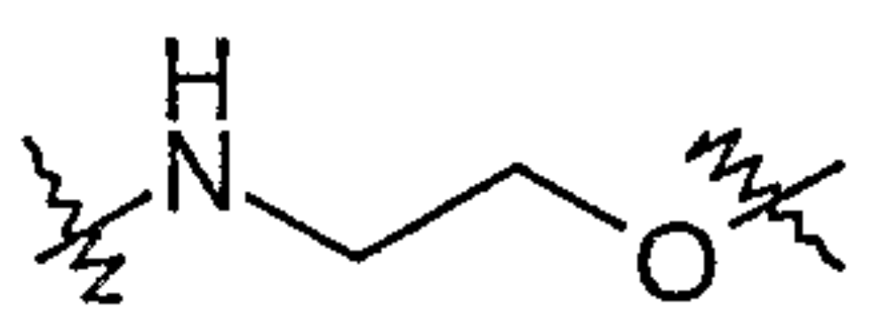
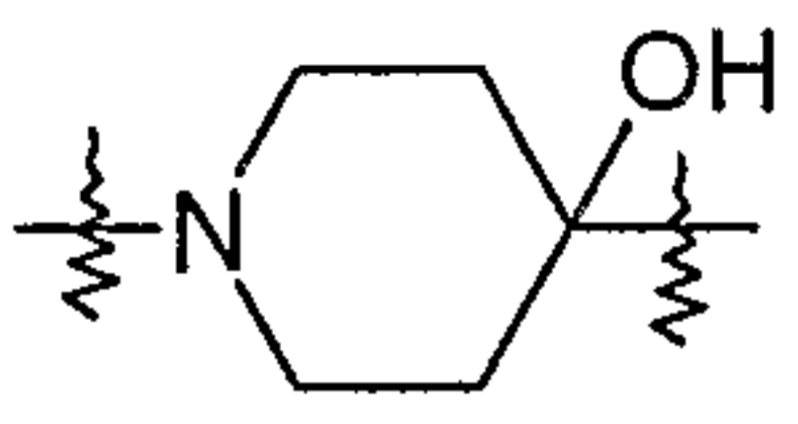
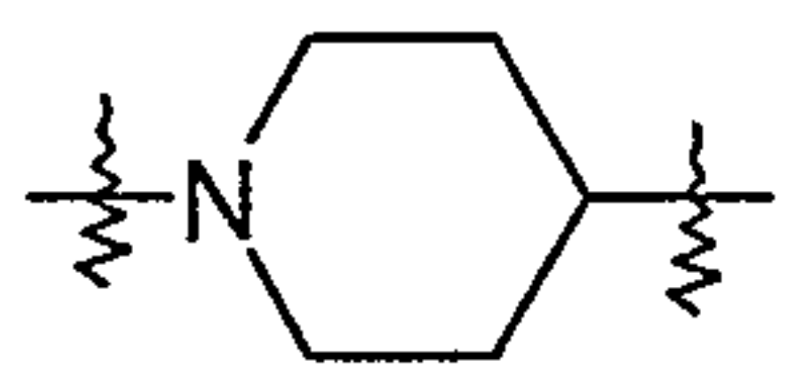
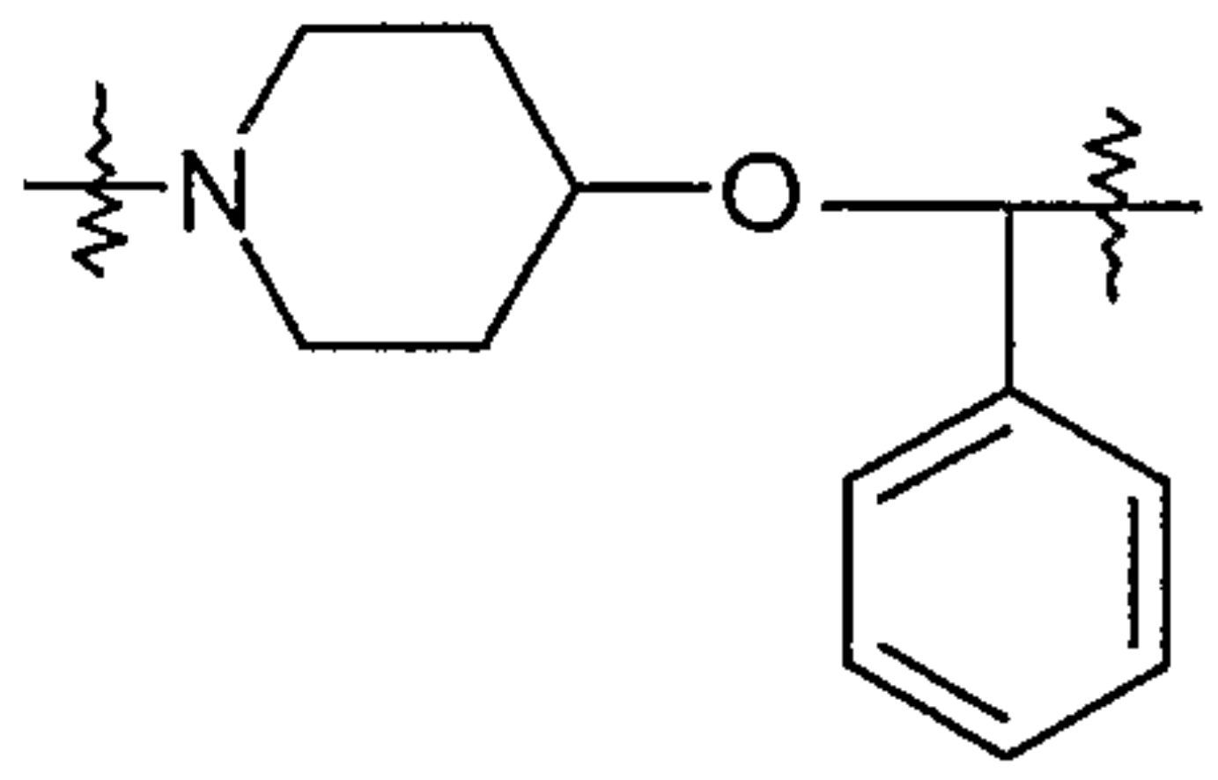
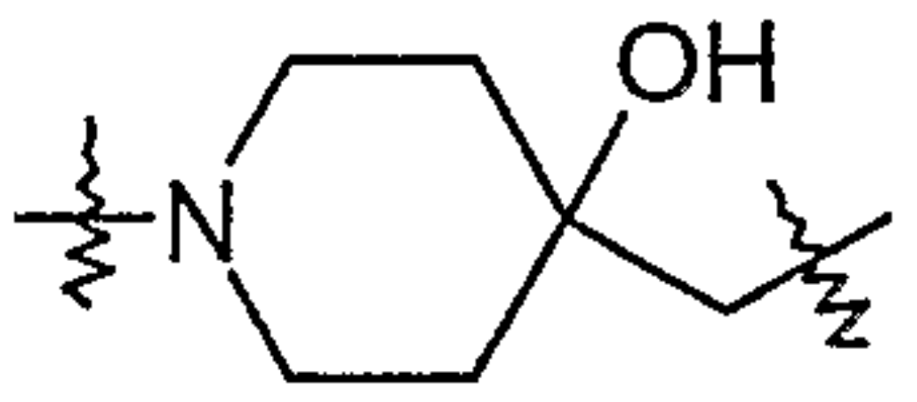
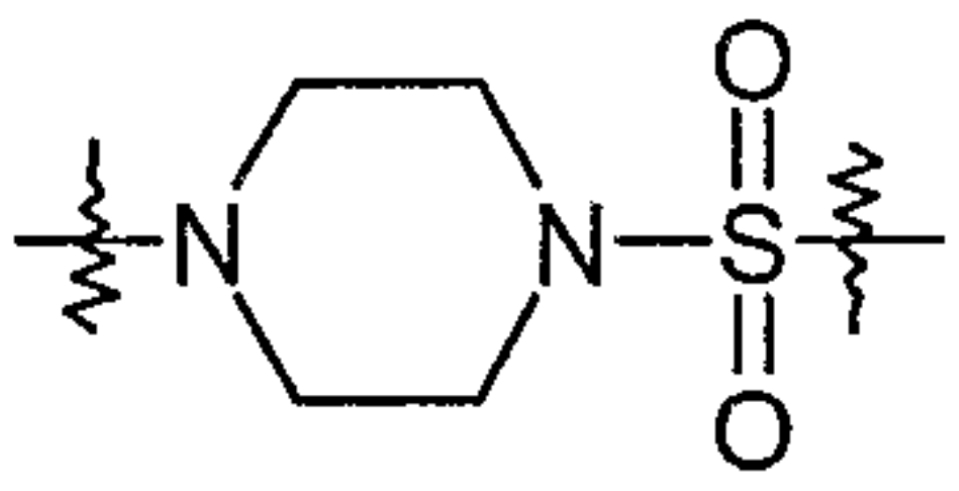
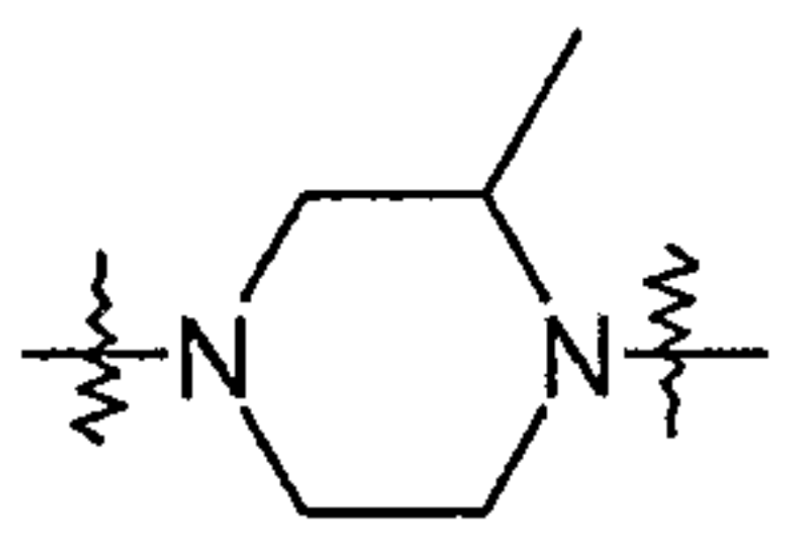
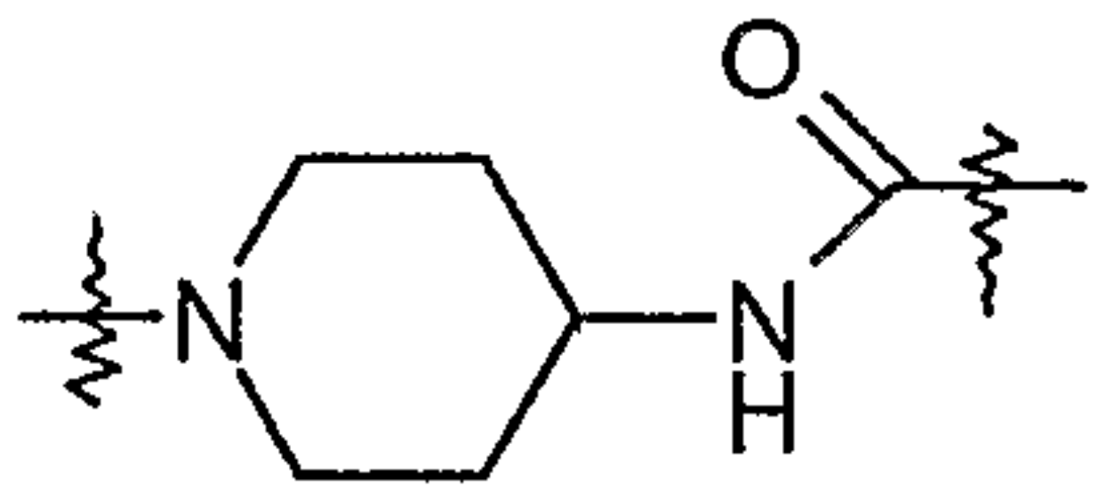
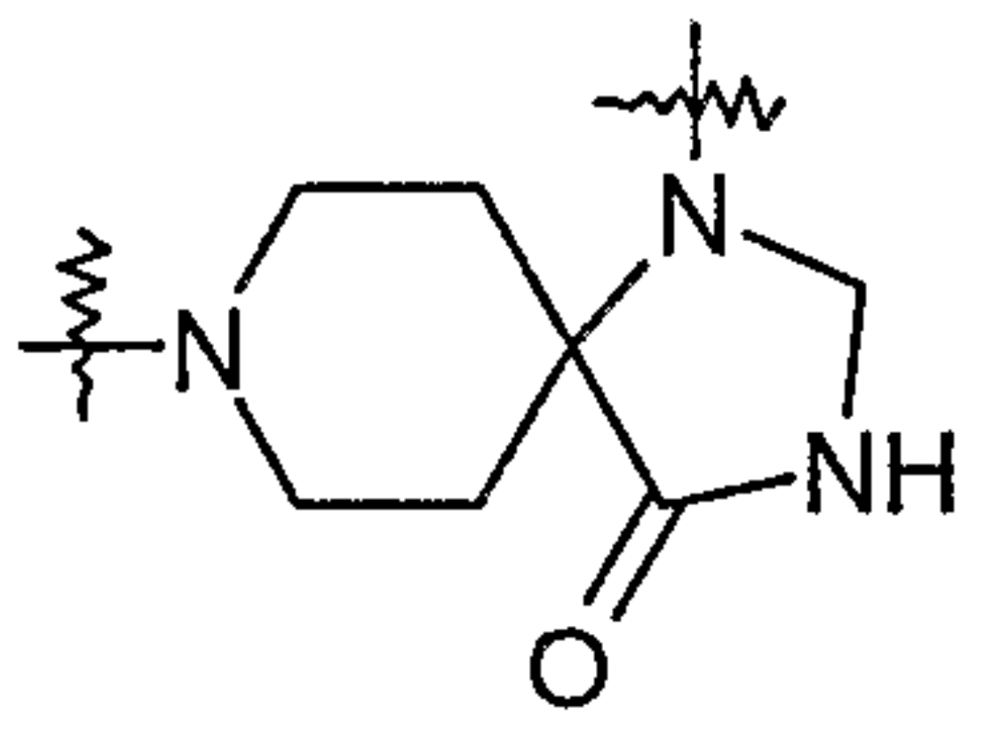
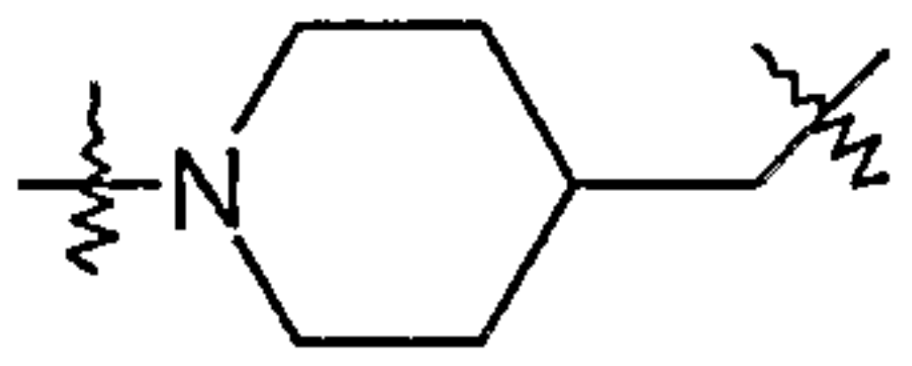
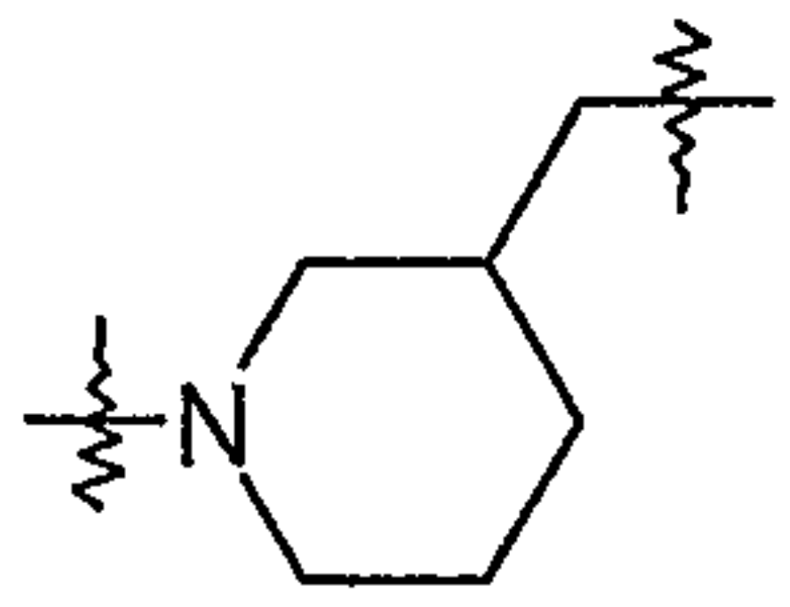
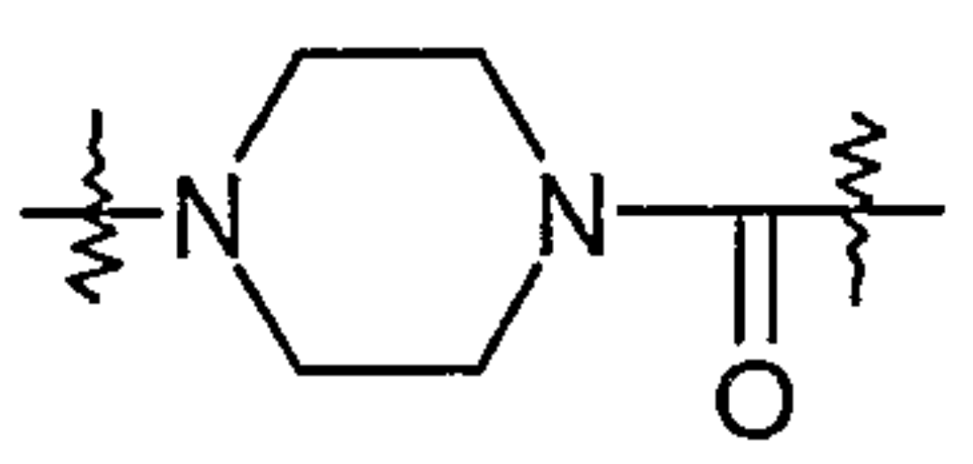
,

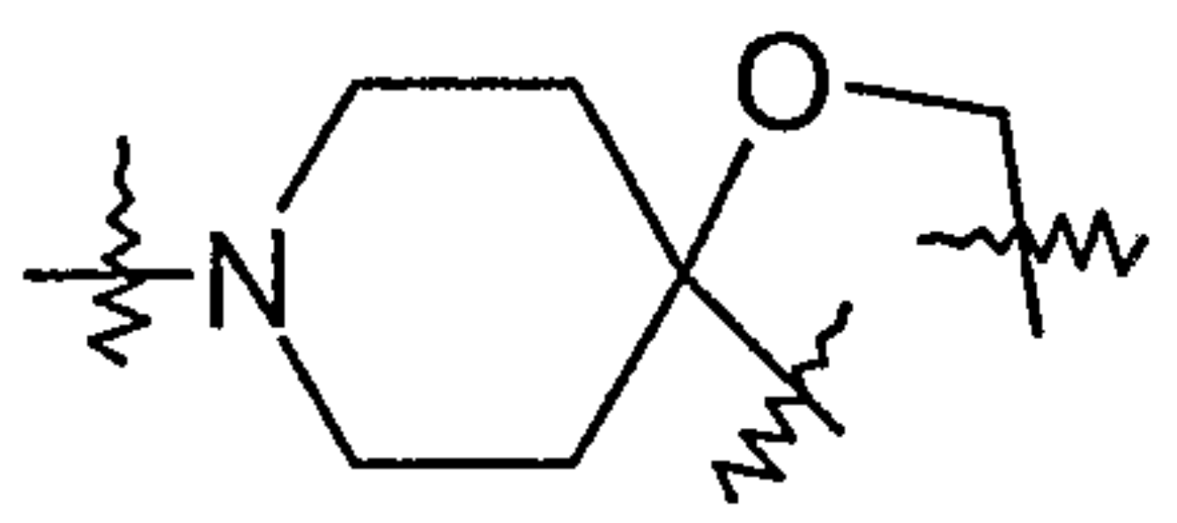
wherein Ar is selected from phenyl, pyridyl, naphthyl, 1,2,3,4-tetrahydro-naphthyl; thienyl, furyl, thiazolyl, benzo[1,3]dioxolyl, 4,5,6,7-tetrahydro-thieno[2,3-c]pyridinyl; 2,3-dihydro-benzo[1,4]dioxinyl; quinolyl; isoquinolyl; indolyl; pyrroyl, benzotriazolyl; benzoimidazolyl, 2,3-dihydro-benzofuranyl; 2,3-dihydro-isoindol-1-on-yl; benzo[1,2,3]thiadiazolyl, benzothiazolyl, and 4H-benzo[1,4]oxazin-3-on-yl;

R^1, R^2 and R^3 are independently selected from -R, –NO_2, -OR, -Cl, -Br, -I, -F, -CF_3, -C(=O)R, -C(=O)OH, -NH_2, -SH, -NHR, -NR_2, -SR, -SO_3H, -SO_2R, -SO_2NR, -S(=O)R, -CN,

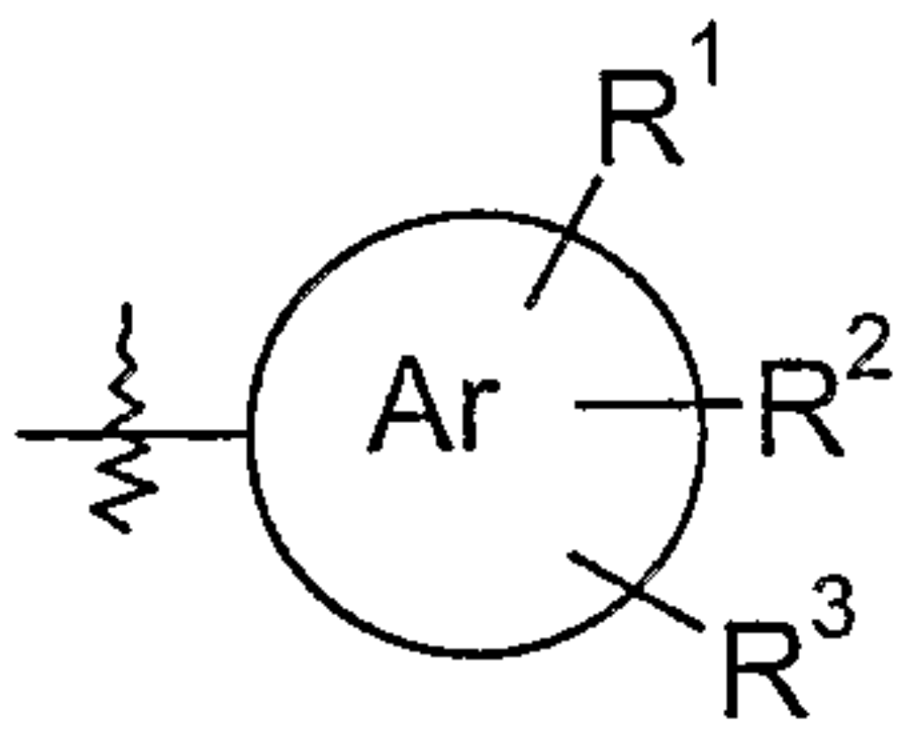
-OH, -C(=O)OR, -C(=O)NR$_2$, -NRC(=O)R, and -NRC(=O)-OR, wherein R is, independently, a hydrogen, C$_{5-6}$cycloalkyl, C$_{3-5}$heterocyclyl, phenyl, benzyl, C$_{1-4}$alkyl or C$_{2-4}$alkenyl, and wherein said R is further optionally substituted with one or more groups selected from methyl, methoxy, hydroxy and halogen;

Q is selected from:

or Q may be a trivalent group such as  , which is fused with Ar^1, wherein Ar^1 is a divalent aromatic group such as 1,2-phenylene.

2. A compound according to claim 1, wherein Ar^1 is represented by

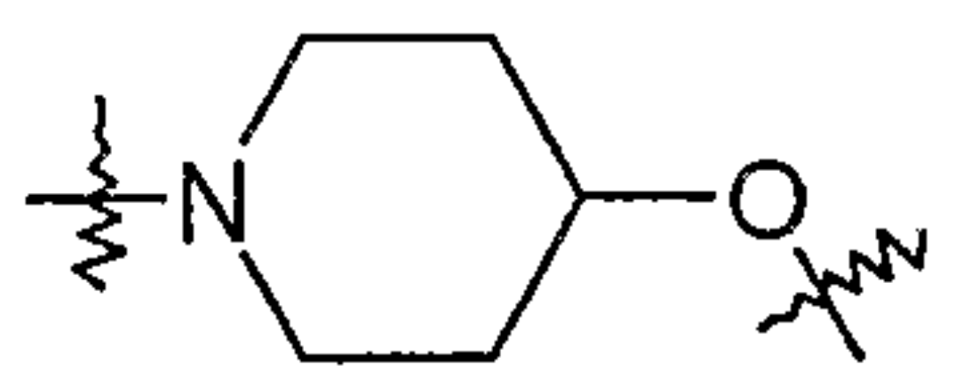


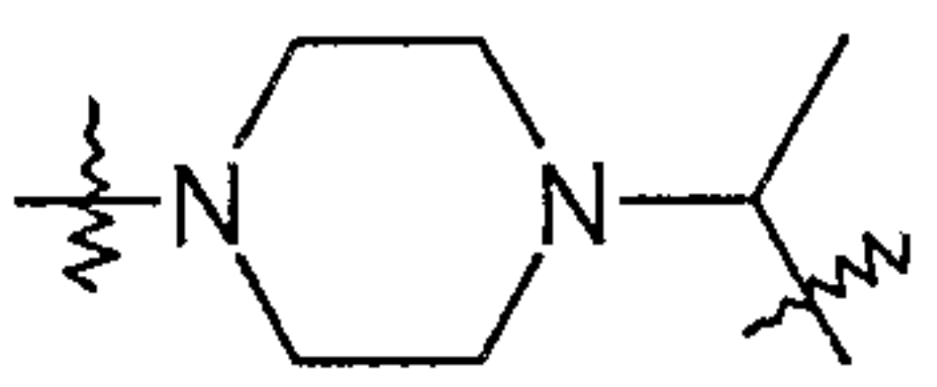
,

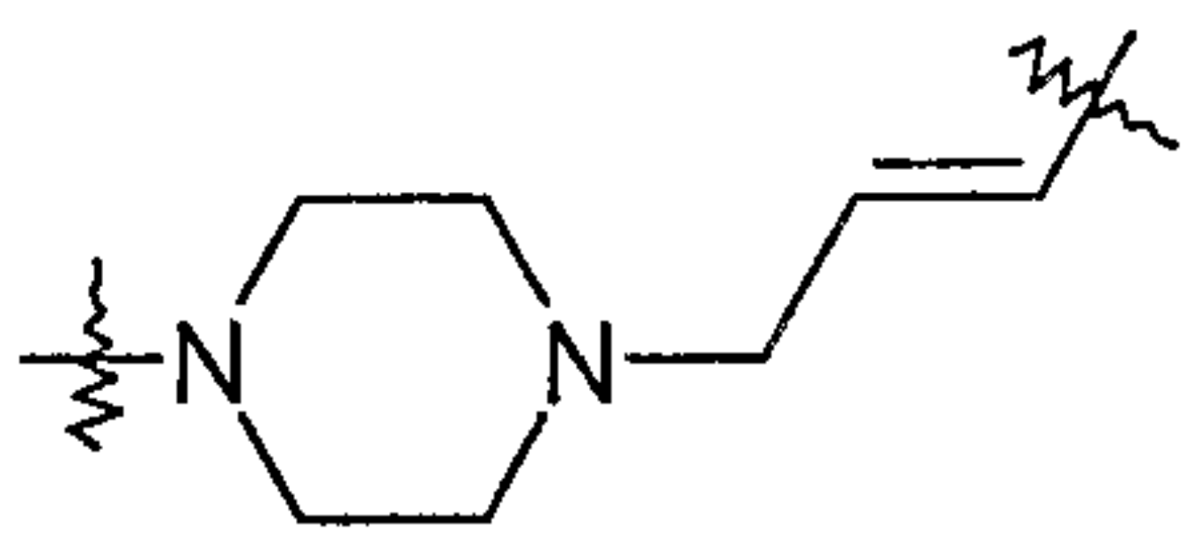
wherein Ar is selected from phenyl, pyridyl, naphthyl, 1,2,3,4-tetrahydro-naphthyl; thienyl, furyl, thiazolyl, benzo[1,3]dioxolyl, 4,5,6,7-tetrahydro-thieno[2,3-c]pyridinyl; 2,3-dihydro-benzo[1,4]dioxinyl; quinolyl; isoquinolyl; indolyl; pyrroyl, benzotriazolyl; benzoimidazolyl, 2,3-dihydro-benzofuranyl; 2,3-dihydro-isoindol-1-on-yl; benzo[1,2,3]thiadiazolyl, benzothiazolyl, and 4H-benzo[1,4]oxazin-3-on-yl;

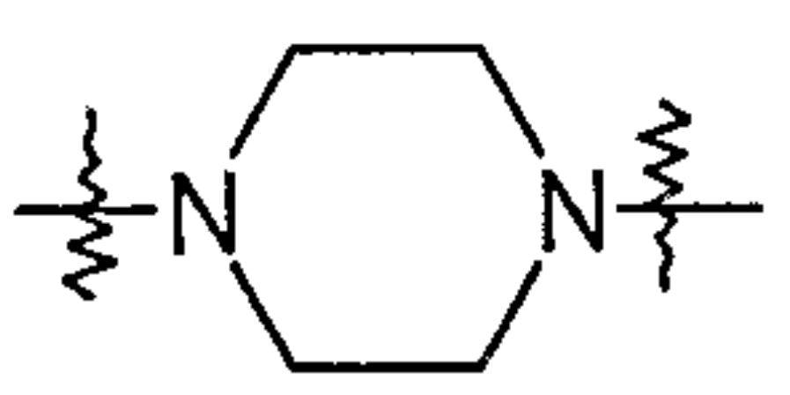
R^1, R^2 and R^3 are independently selected from -R, $-NO_2$, -OR, -Cl, -Br, -I, -F, $-CF_3$, -C(=O)R, -C(=O)OH, $-NH_2$, -SH, -NHR, $-NR_2$, -SR, $-SO_3H$, $-SO_2R$, $-SO_2NR$, -S(=O)R, -CN, -OH, -C(=O)OR, $-C(=O)NR_2$, -NRC(=O)R, and -NRC(=O)-OR, wherein R is, independently, a hydrogen, C_{5-6}cycloalkyl, C_{3-5}heterocyclyl, phenyl, benzyl, C_{1-4}alkyl or C_{2-4}alkenyl, and wherein said R is further optionally substituted with one or more groups selected from methyl, methoxy, hydroxy and halogen;

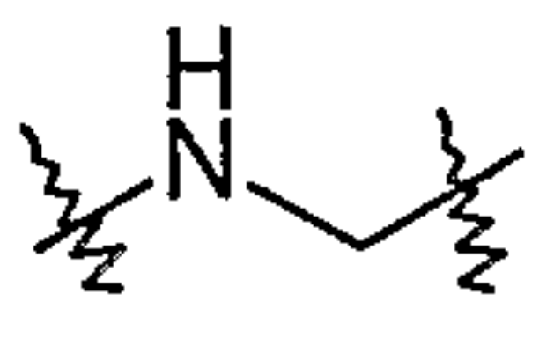
Q is selected from:

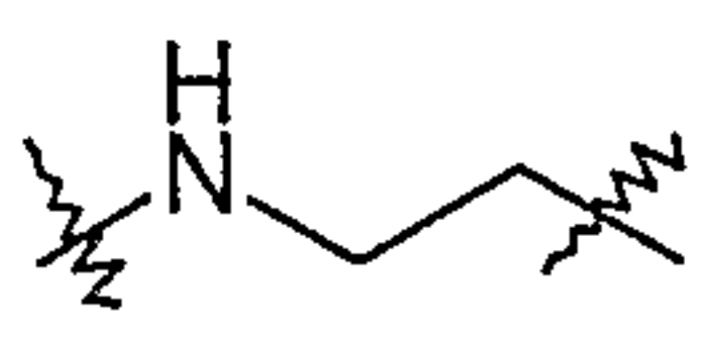


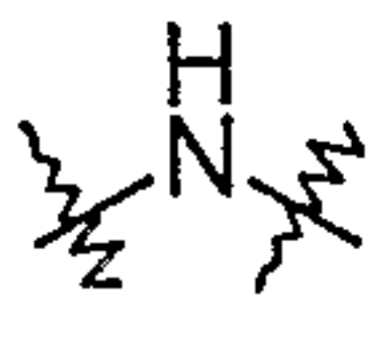


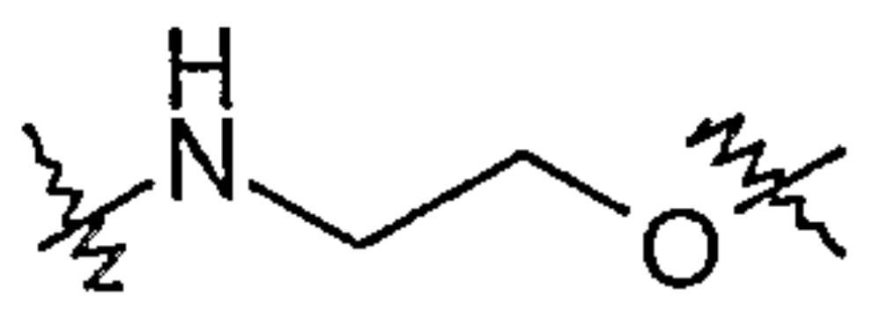


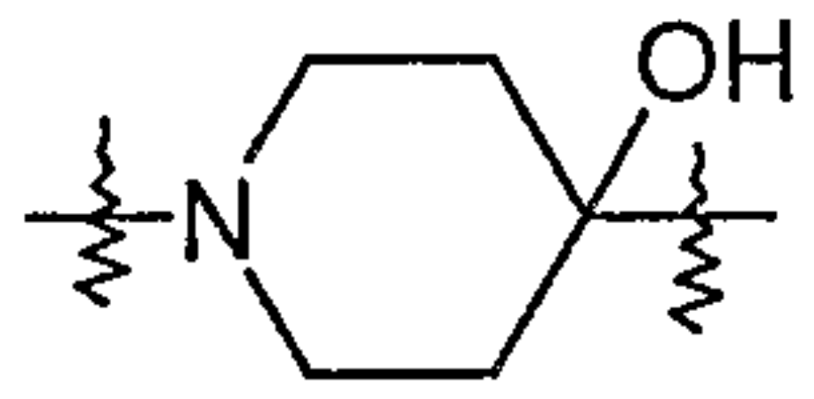


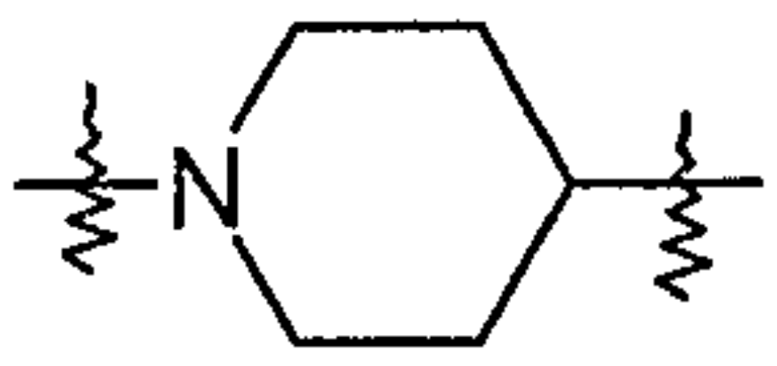


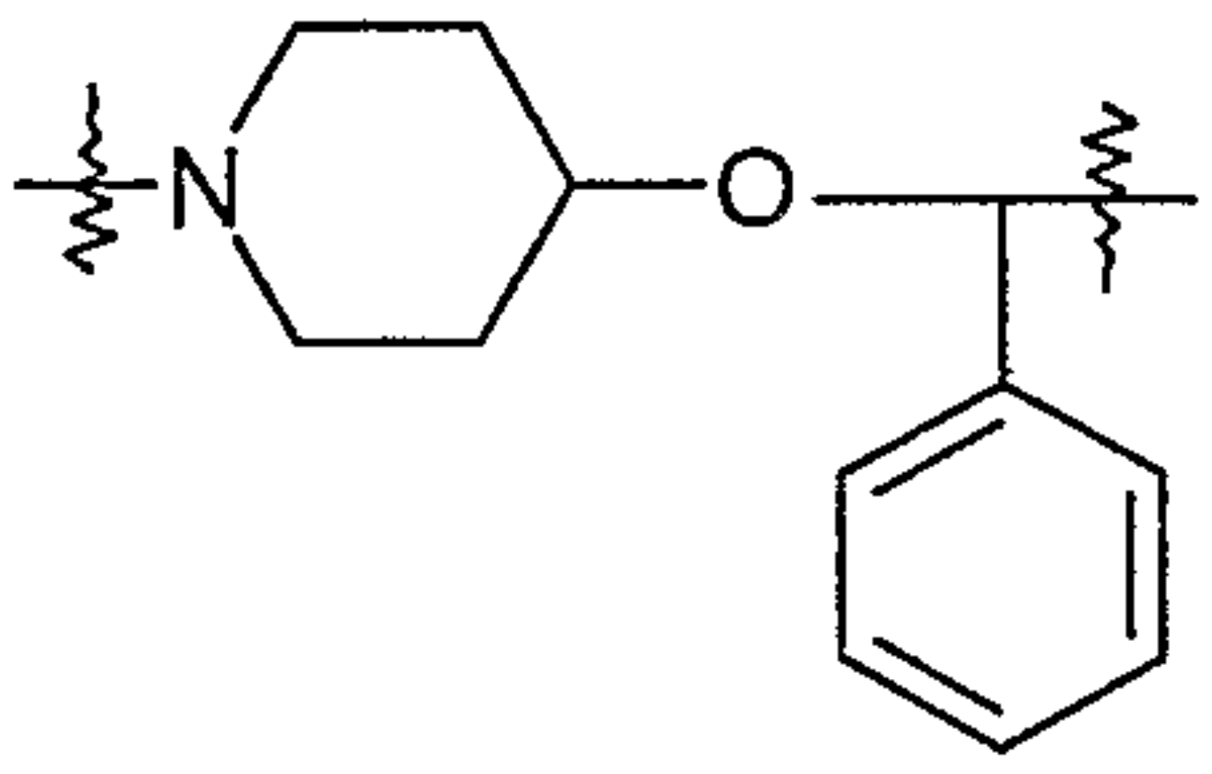


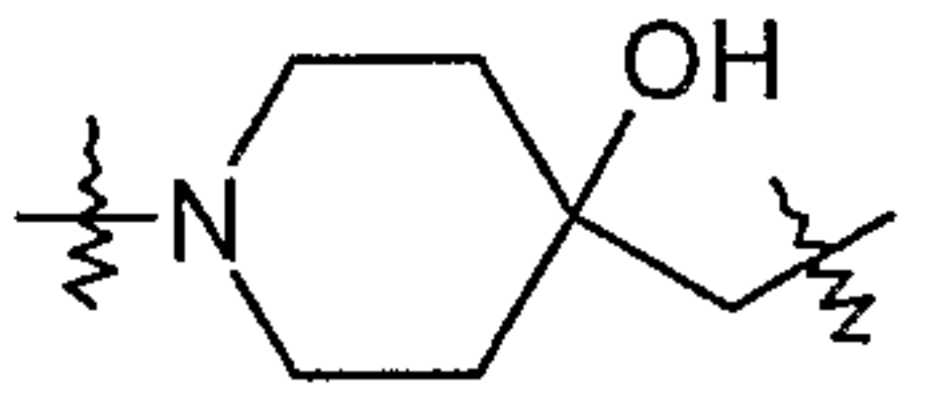


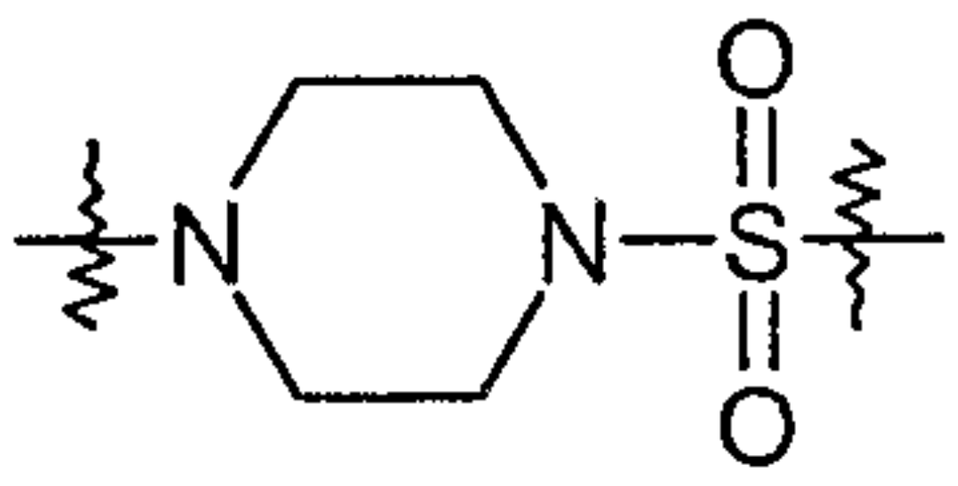


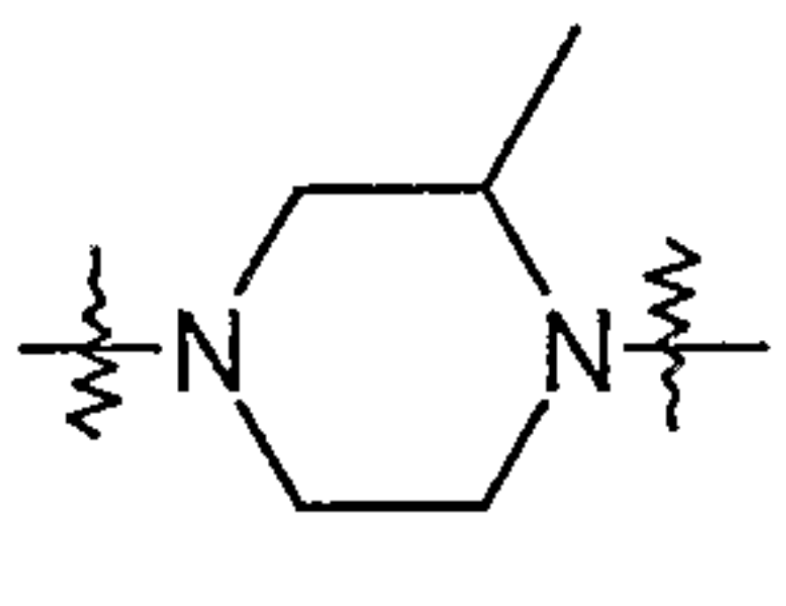


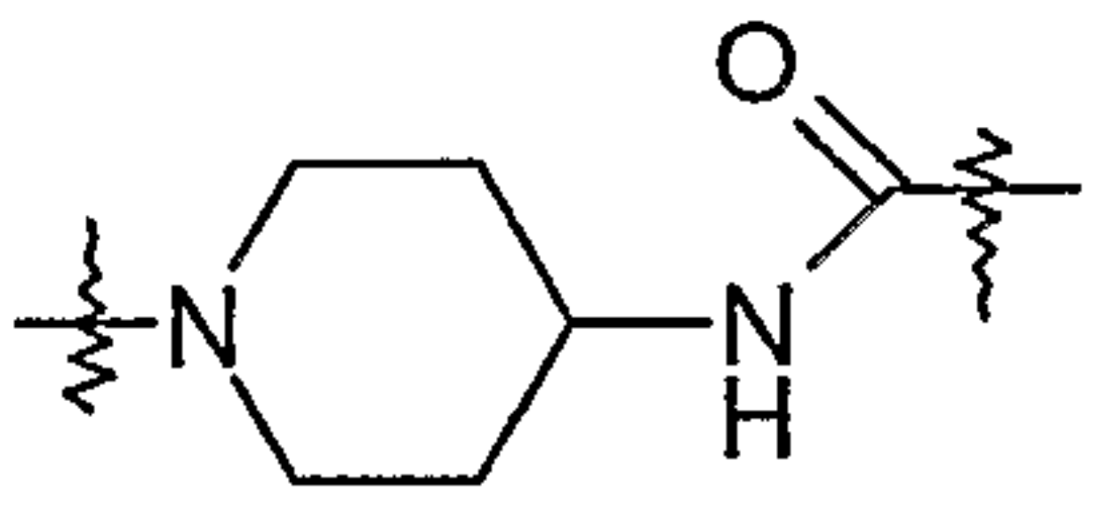


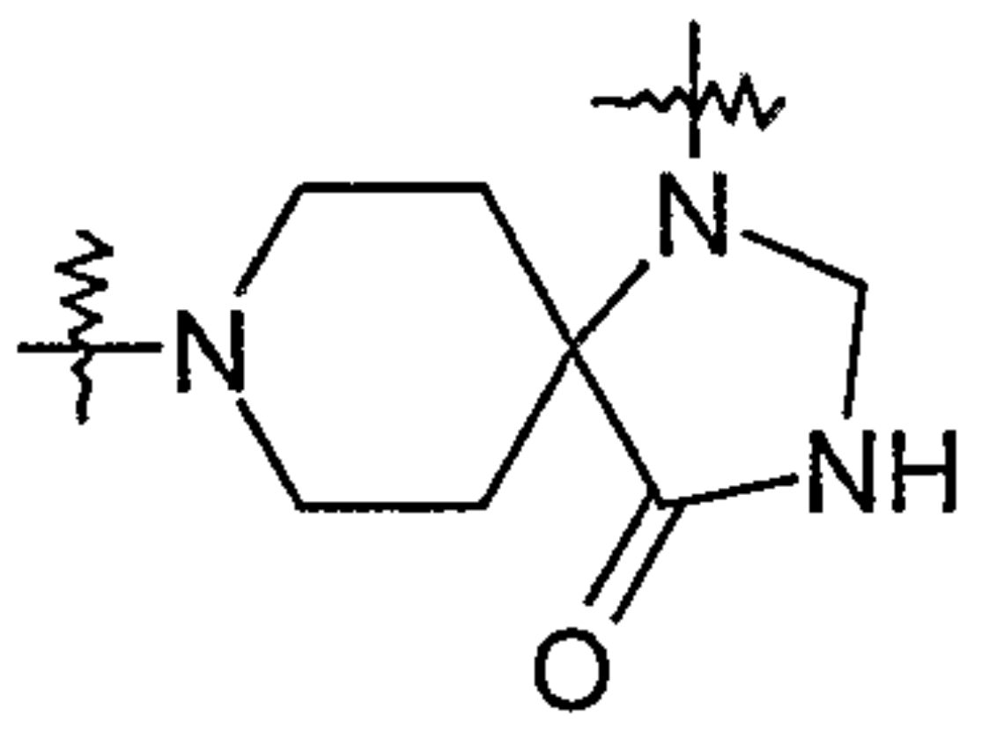


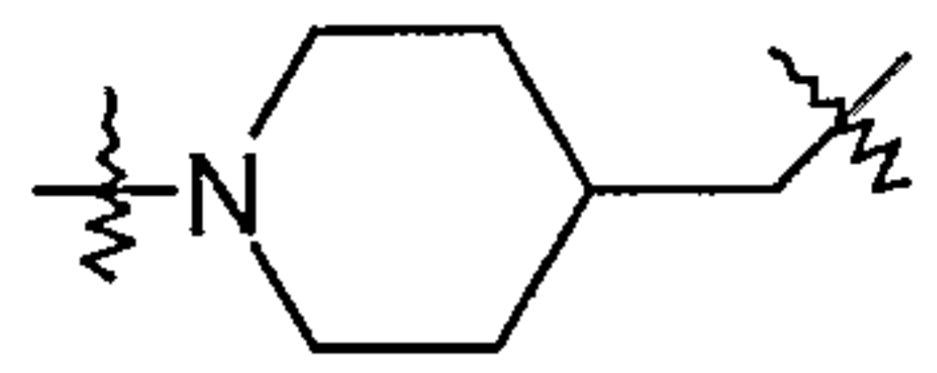


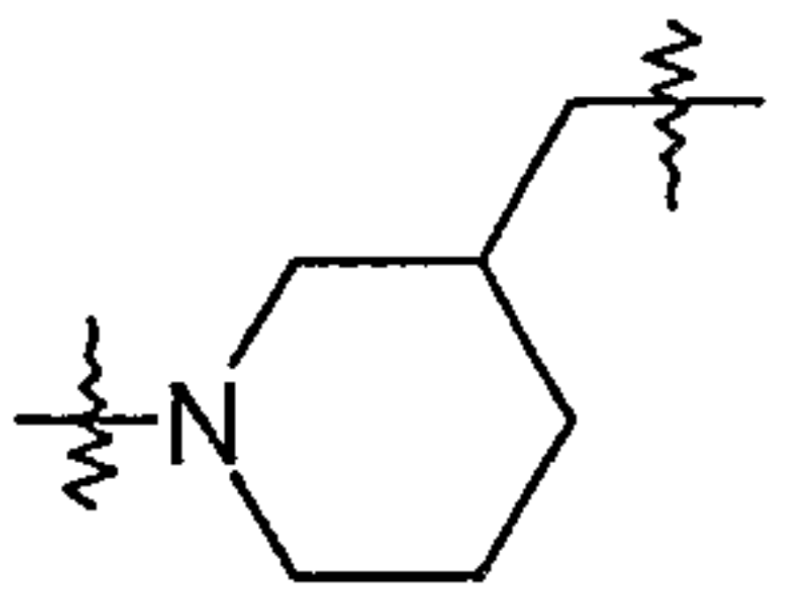


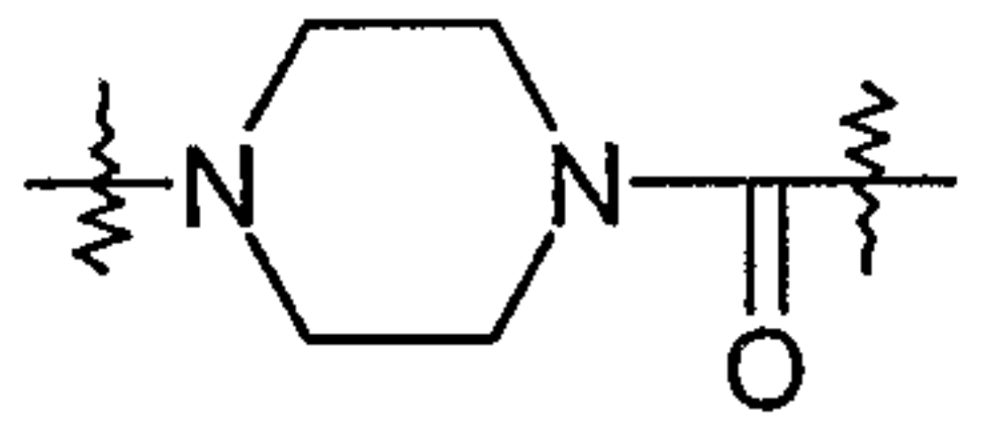


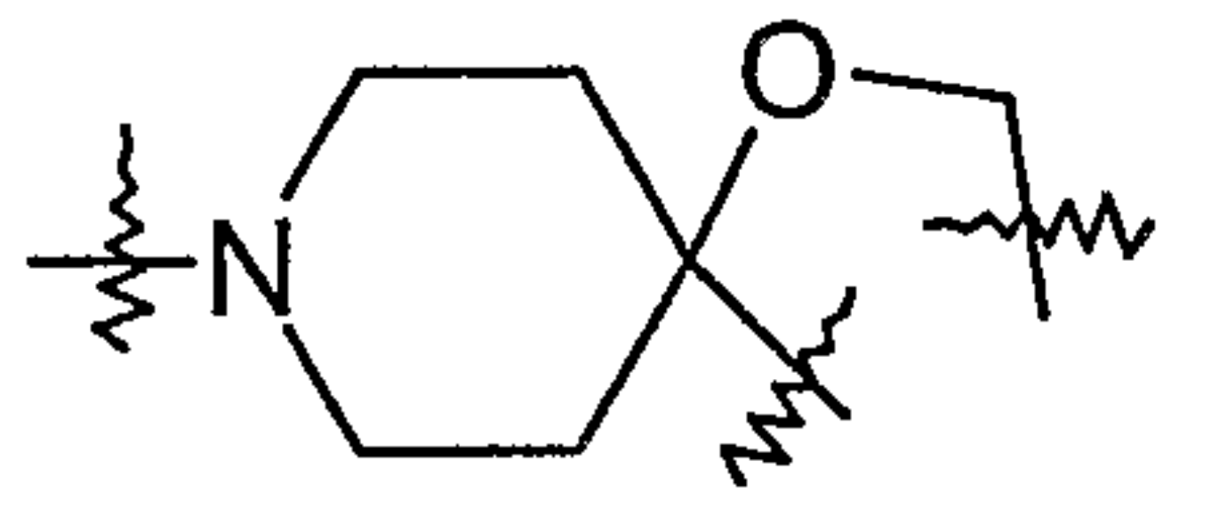








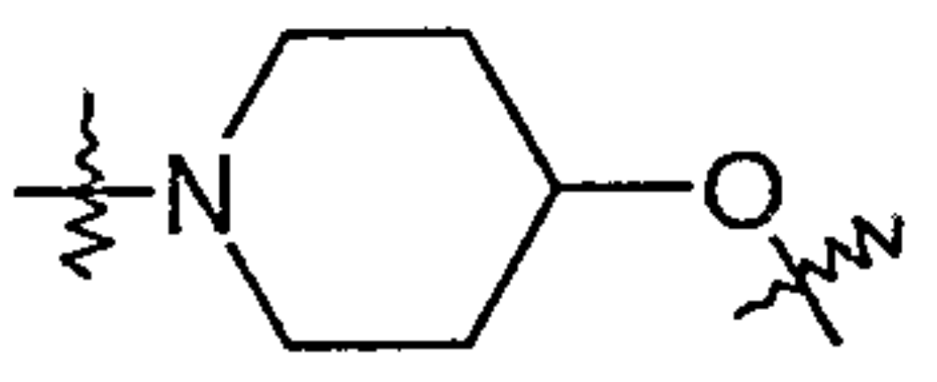


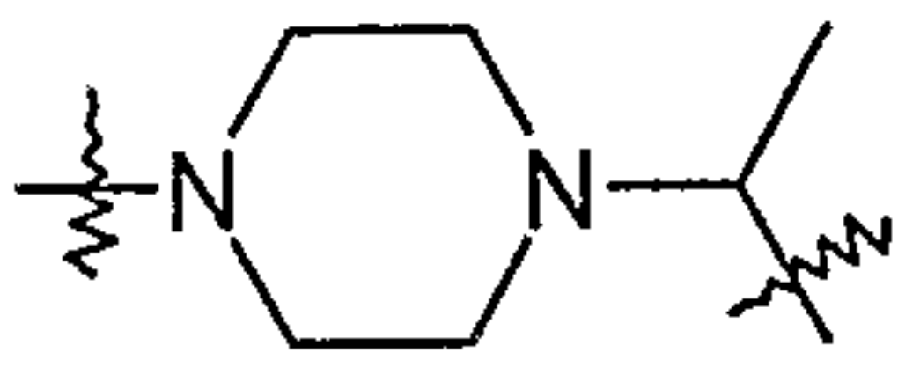
or Q may be a trivalent group such as  , which is fused with Ar^1, wherein Ar^1 is a divalent aromatic group such as 1,2-phenylene.

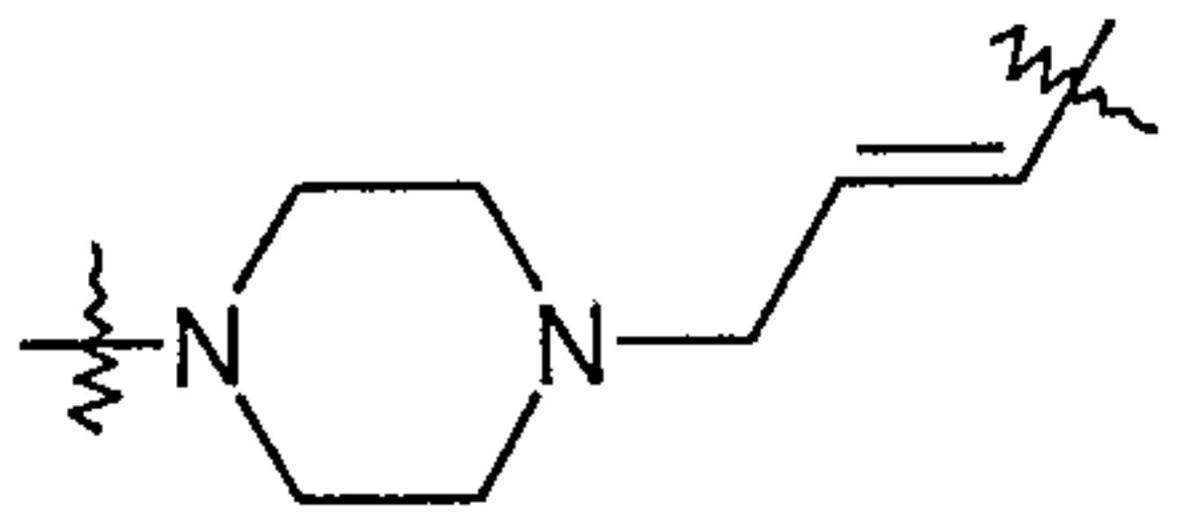
3. A compound according to claim 1,

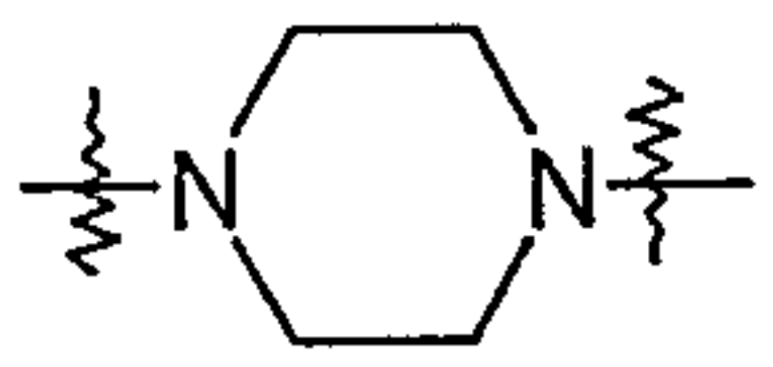
wherein Ar^1 is selected from phenyl, 2-pyridyl, 4-pyridyl; 1-naphthyl, 2-naphthyl, 1,2,3,4-tetrahydro-naphth-1-yl; 1,2,3,4-tetrahydro-naphth-5-yl; 2-thienyl, 3-thienyl, 2-furyl, 2-thiazolyl, benzo[1,3]dioxol-5-yl, 4,5,6,7-tetrahydro-thieno[2,3-c]pyridin-2-yl; 2,3-dihydro-benzo[1,4]dioxin-6-yl; 2,3-dihydro-benzo[1,4]dioxin-2-yl; quinol-2-yl, isoquinol-5-yl; 1H-indol-4-yl, 1H-indol-3-yl, 1H-indol-2-yl, 1H-indol-7-yl, 1-pyrroyl, 1H-benzotriazol-5-yl, 1Hbenzoimidazol-5-yl, 2,3-dihydro-benzofuran-5-yl, 2,3-dihydro-isoindol-1-on-2-yl; benzo[1,2,3]thiadiazol-5-yl, benzo[1,2,3]thiadiazol-6-yl, benzothiazol-6-yl, benzothiazol-2-yl, and 4H-benzo[1,4]oxazin-3-on-7-yl, wherein Ar^1 is further optionally substituted with one or more groups selected from C_{1-4}alkyl, C_{2-4}alkenyl, C_{1-4}alkoxy, C_{1-4}alkenyloxy, phenoxy, 4-methoxyphenoxy, benzyl, acetoamino, methylsulfonyl, methoxycarbonyl, nitro, chloro, fluoro, bromo, iodo, 1-pyrroyl, 2-methyl-pyrro-1-yl, amino, phenylsulfonyl, aceto,1-piperidinyl, [1,2,3]thiadiazol-4-yl, 4-morpholinyl, methoxy, ethoxy, isopropyloxy, methythio, cyano, dimethylamino, hydroxy, methylaminosulfonyl, trifluoromethyl, trifluoromethoxy, phenyl, phenoxy, benzyl, 4-hydroxyl-phenyl, diethylamino, methylsulfonyl, aminosulfonyl, cyclohexyl, 1-pyrrolyl, 1H-pyrazol-3-yl, 5-tetrazolyl, 1-piperidinyl, 1-pyrazolyl, methylsulfonylmethyl, 3,5-dimethyl-pyrazolyl, pyrrolidin-2-on-1-yl; and

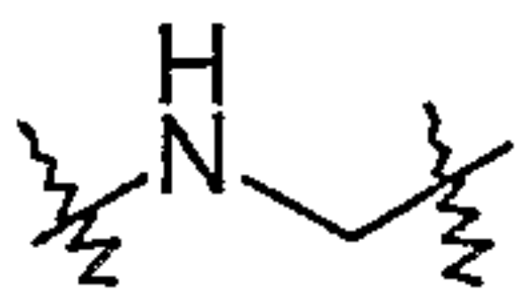
Q is selected from

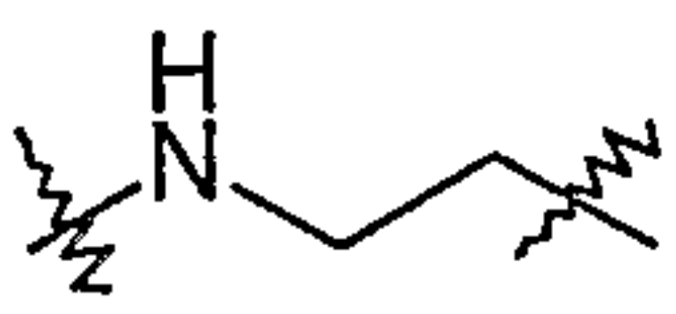


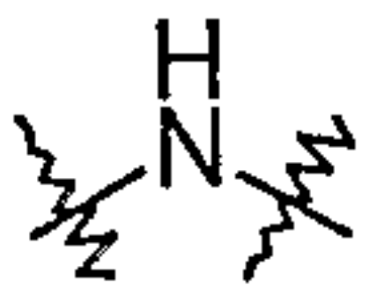


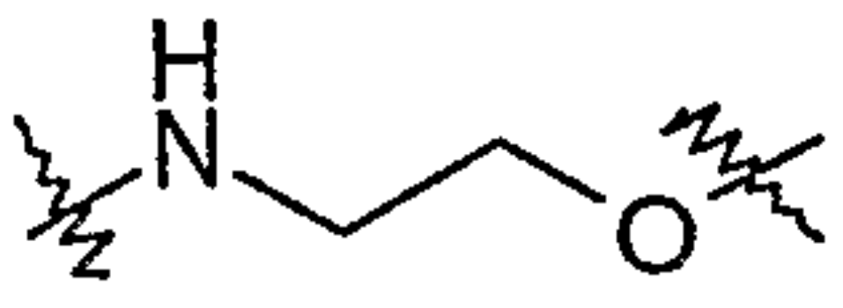


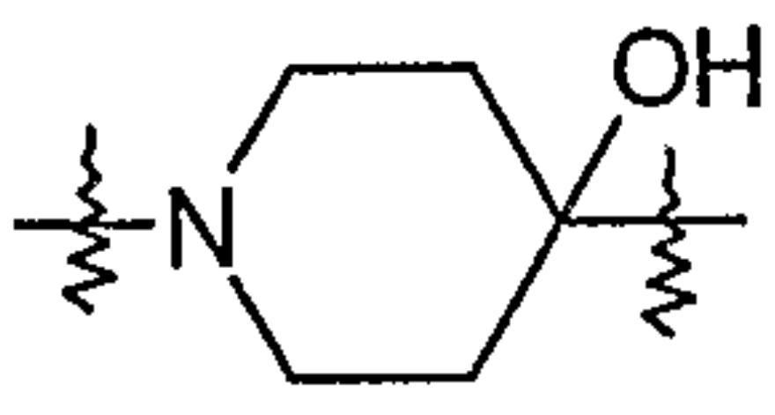


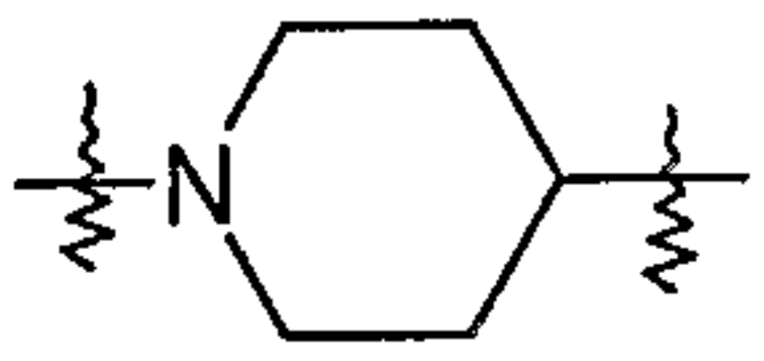


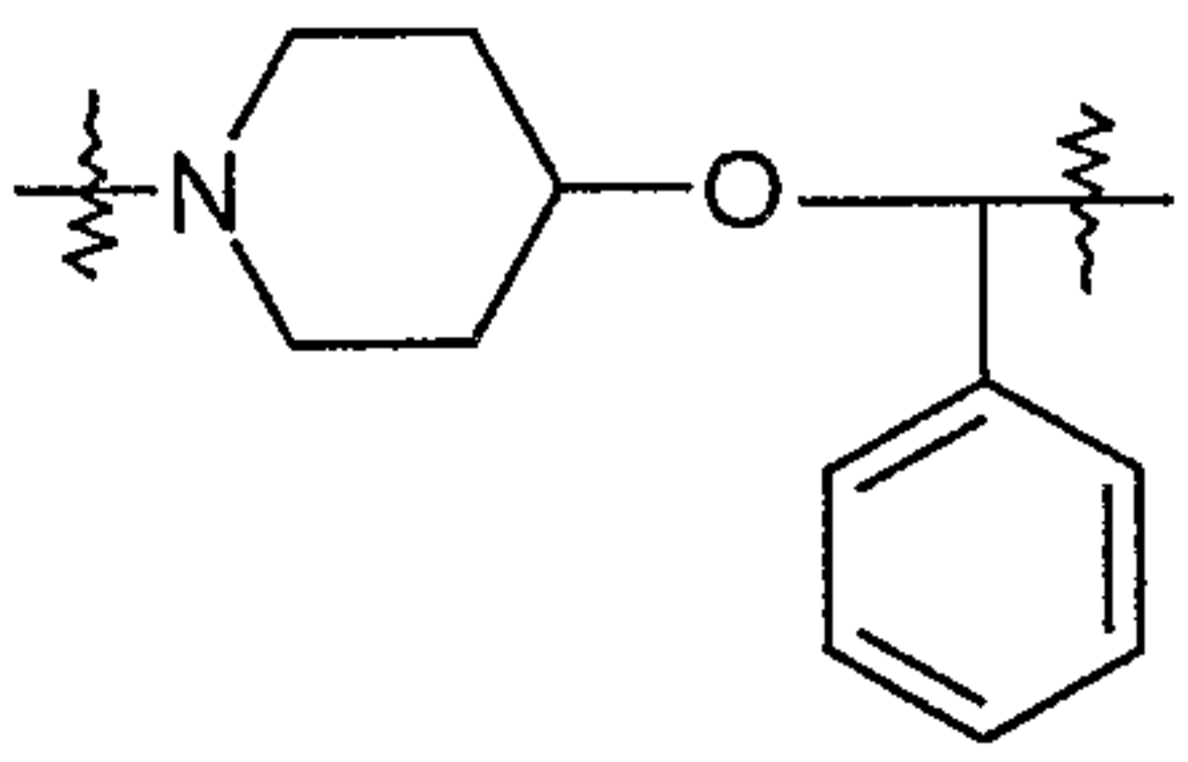


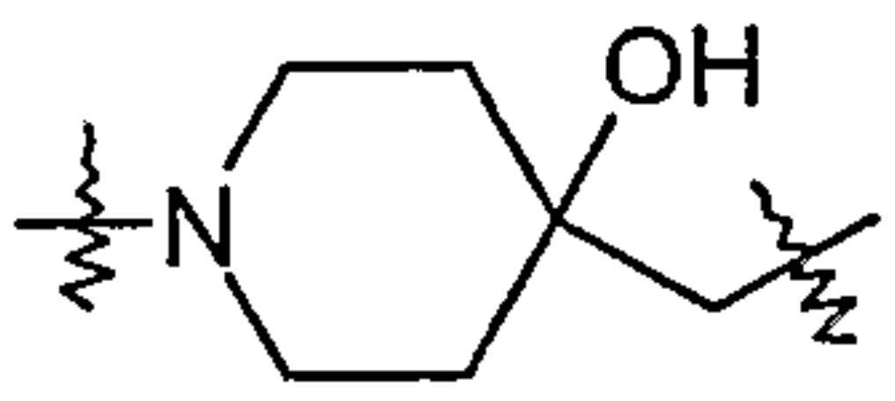


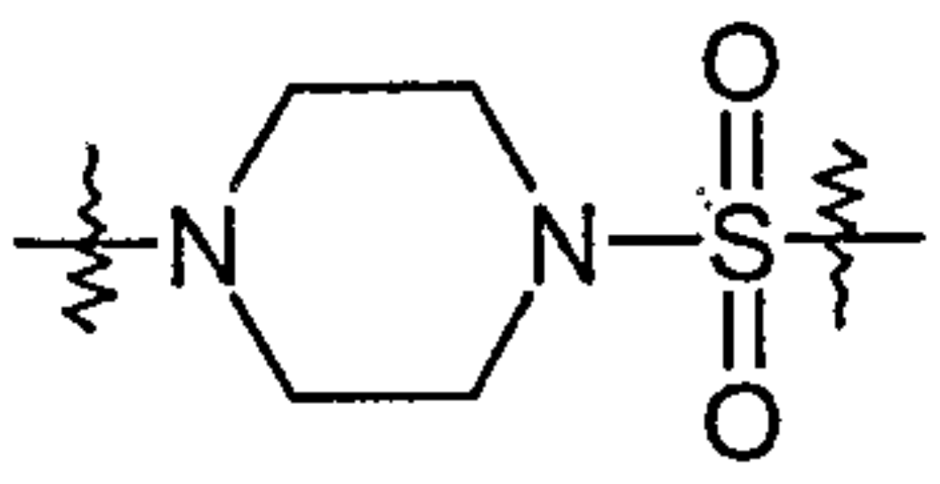


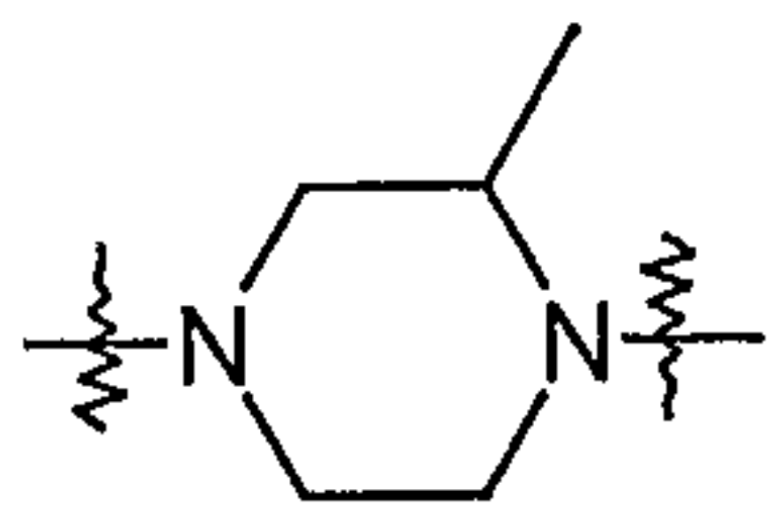


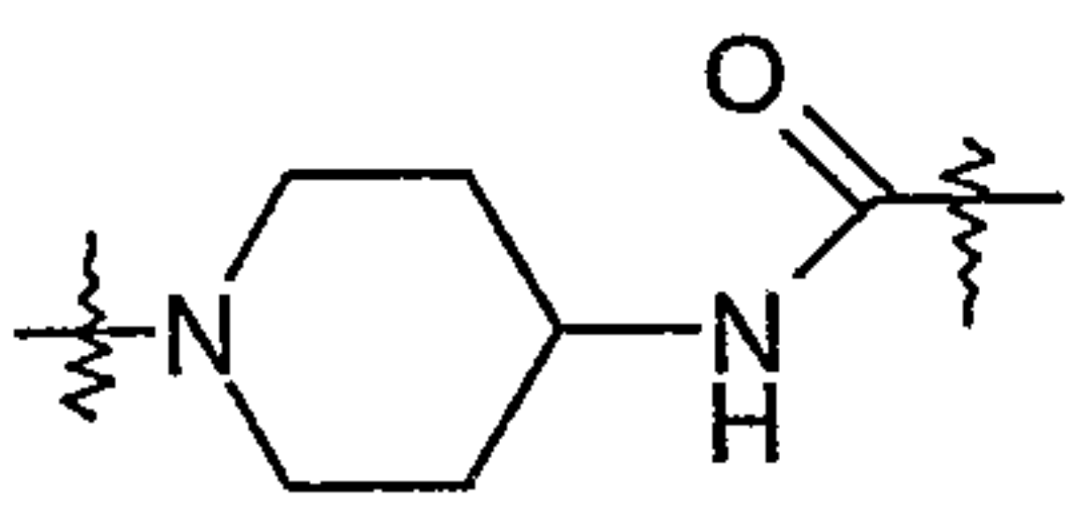


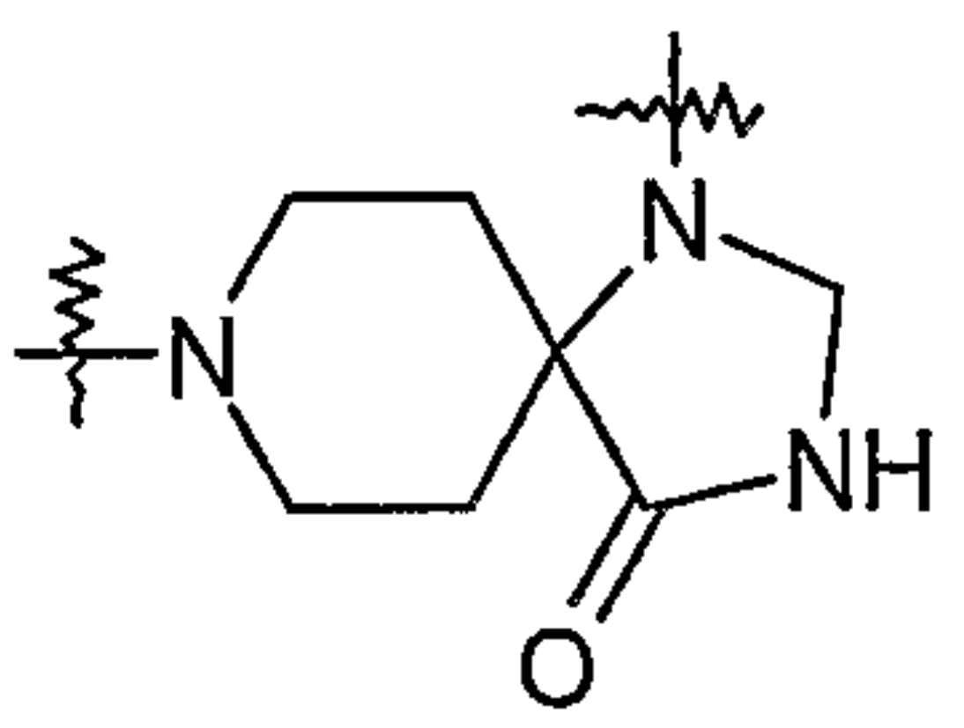


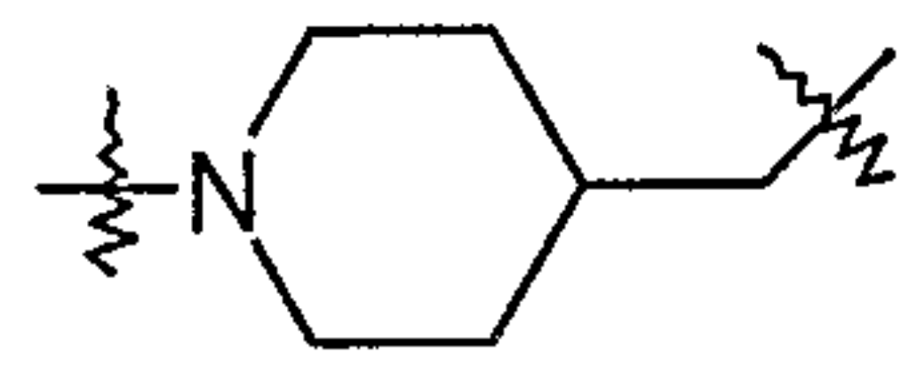


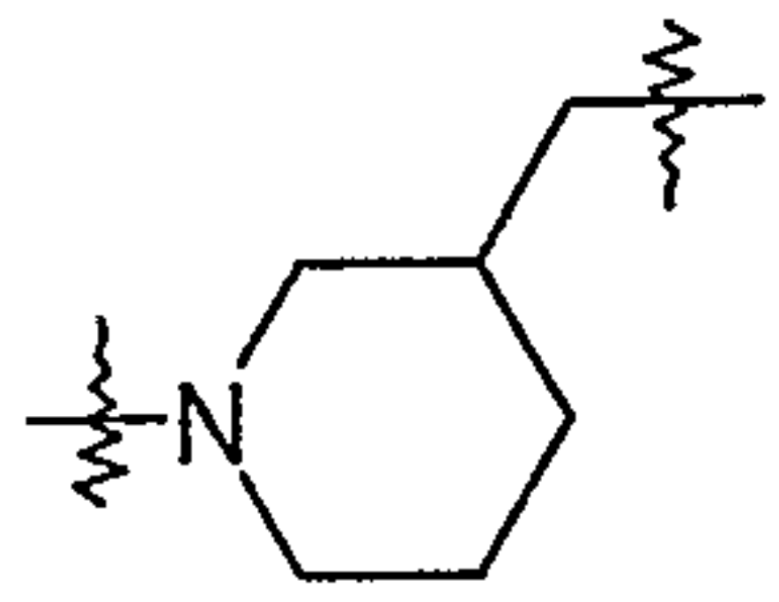


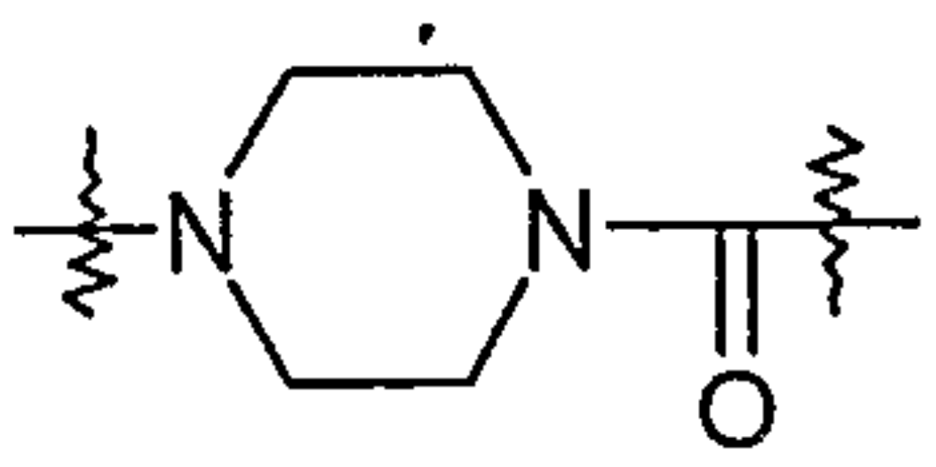




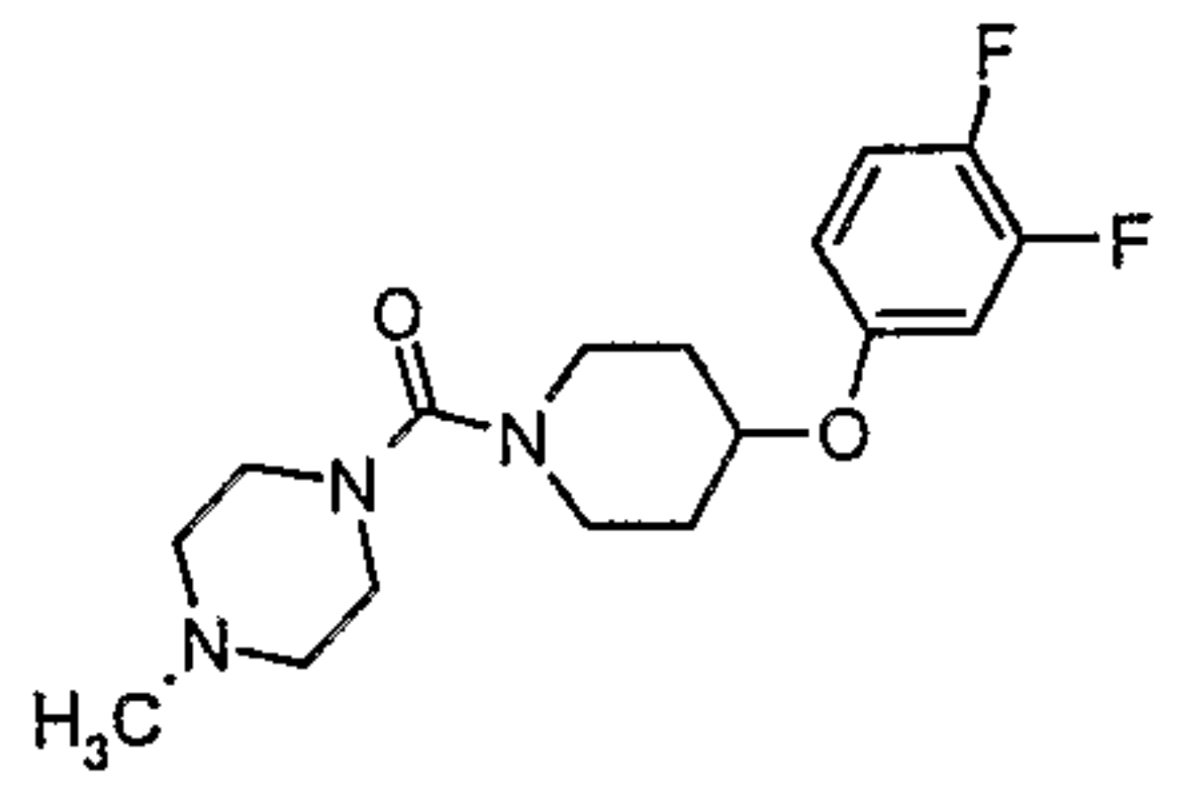








4. A compound selected from: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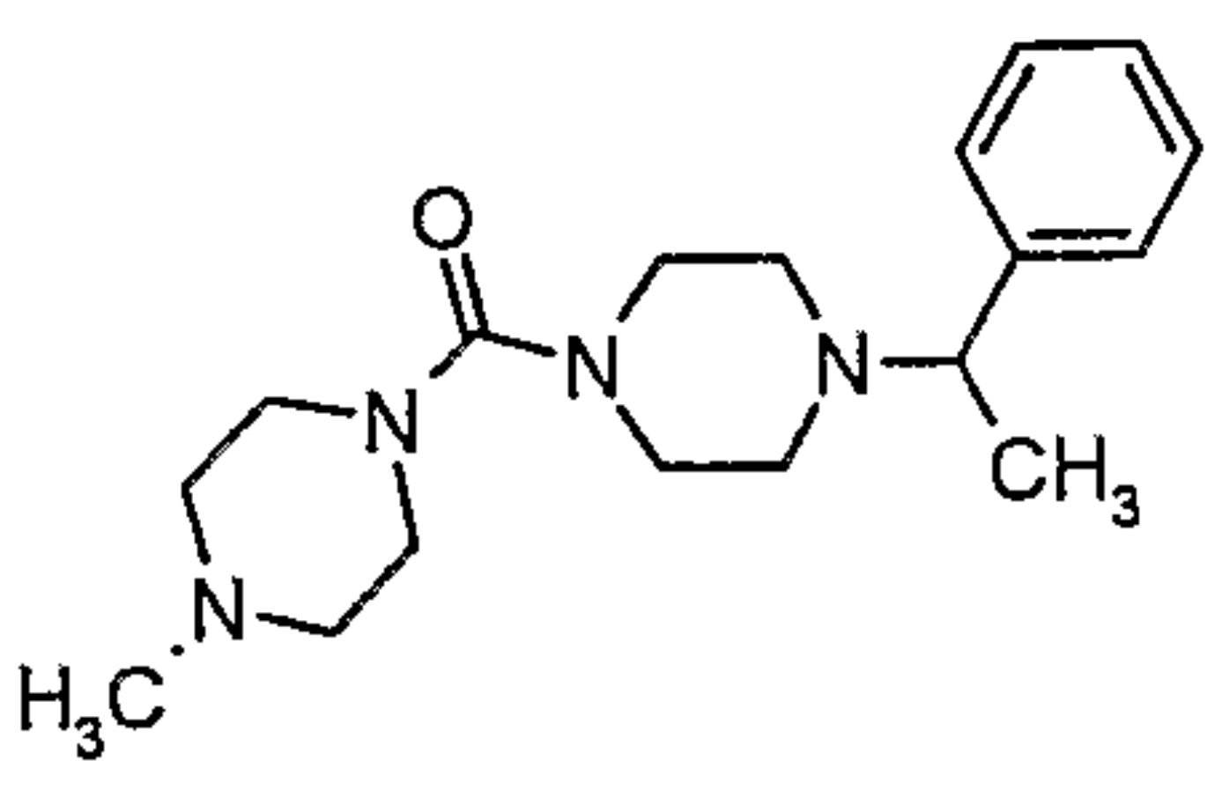
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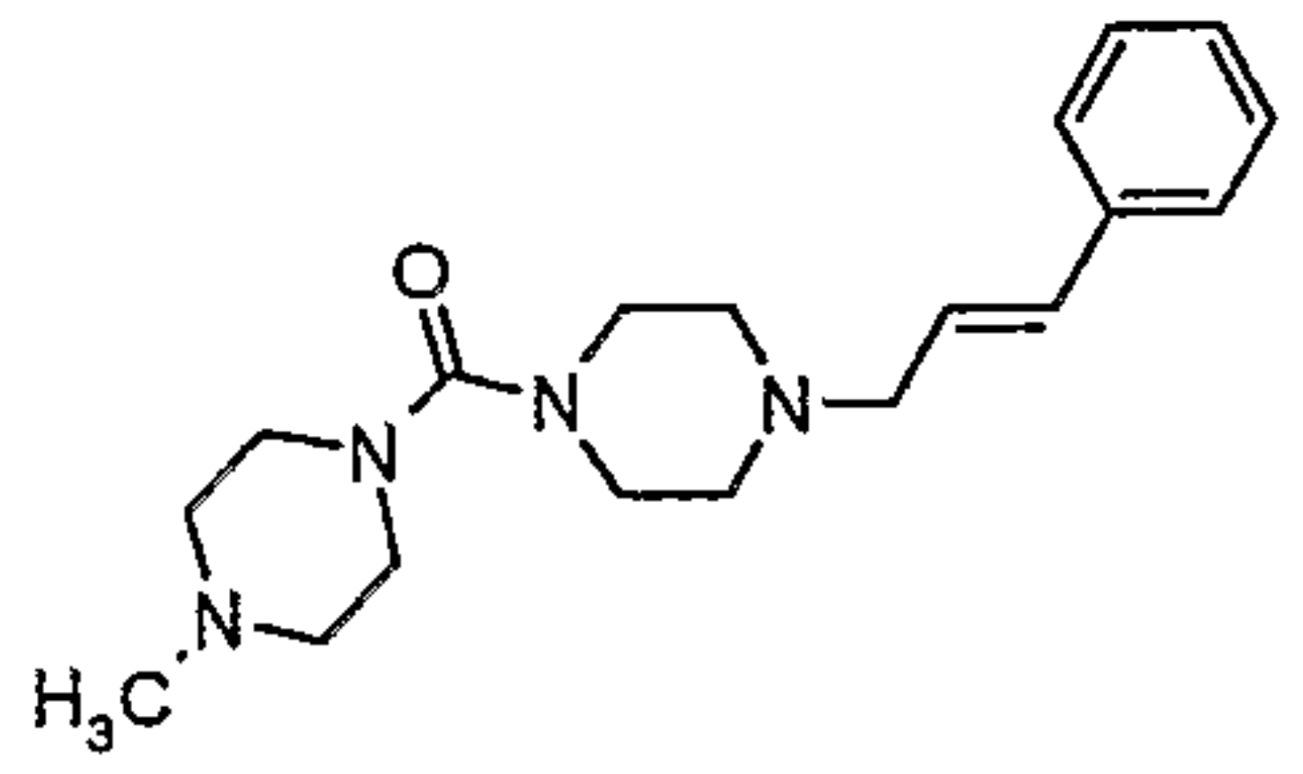
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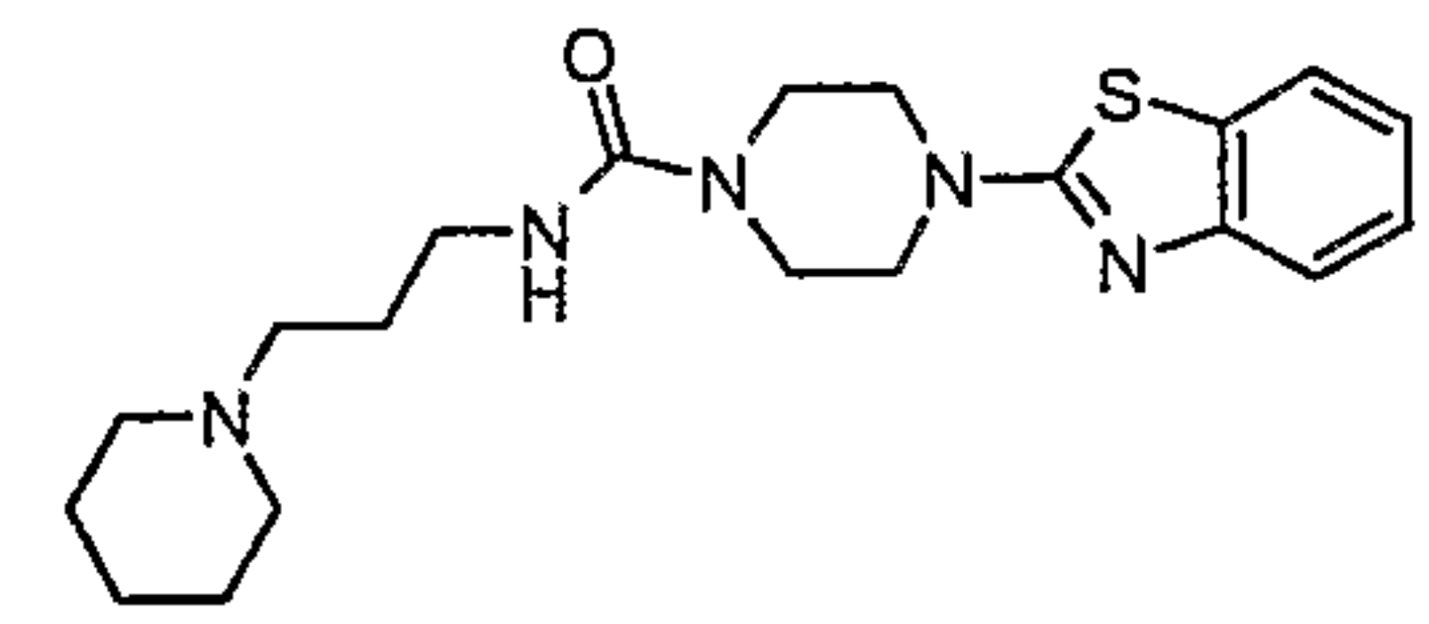
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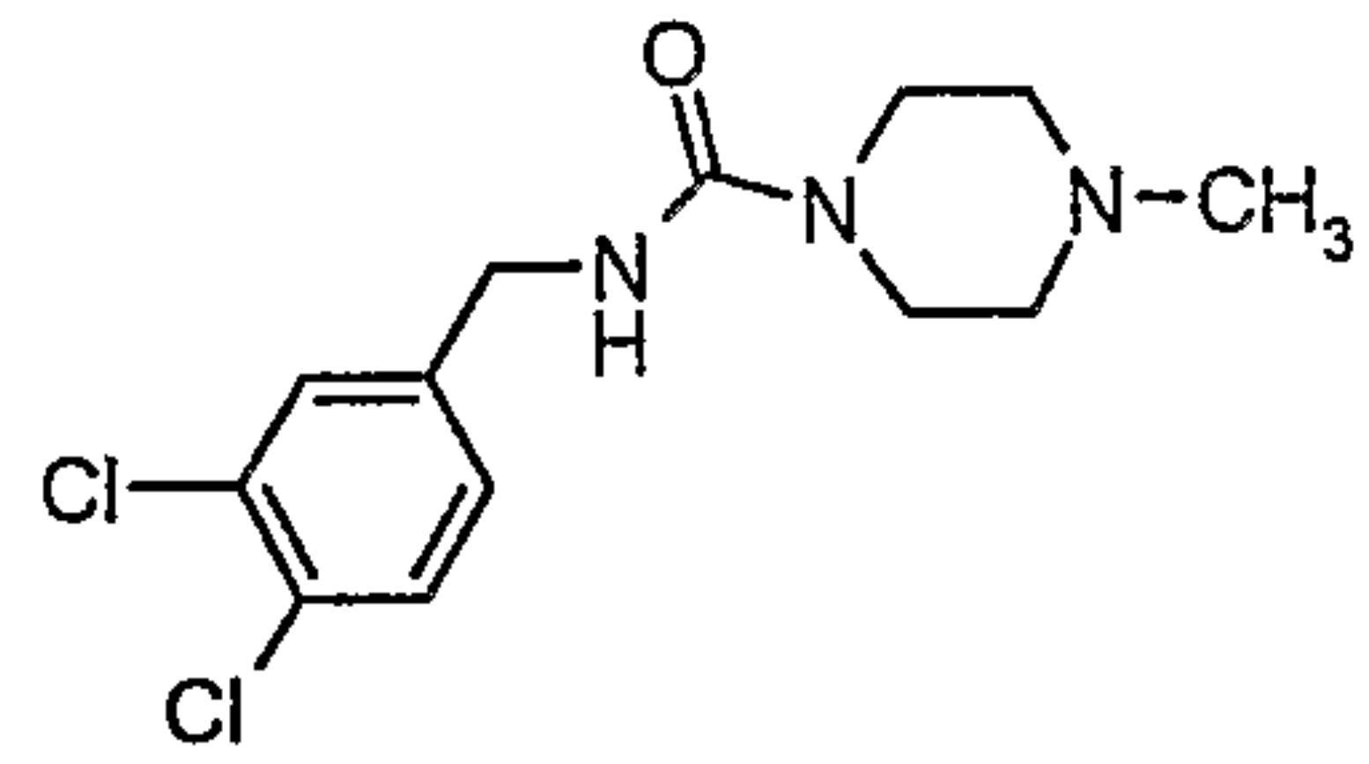
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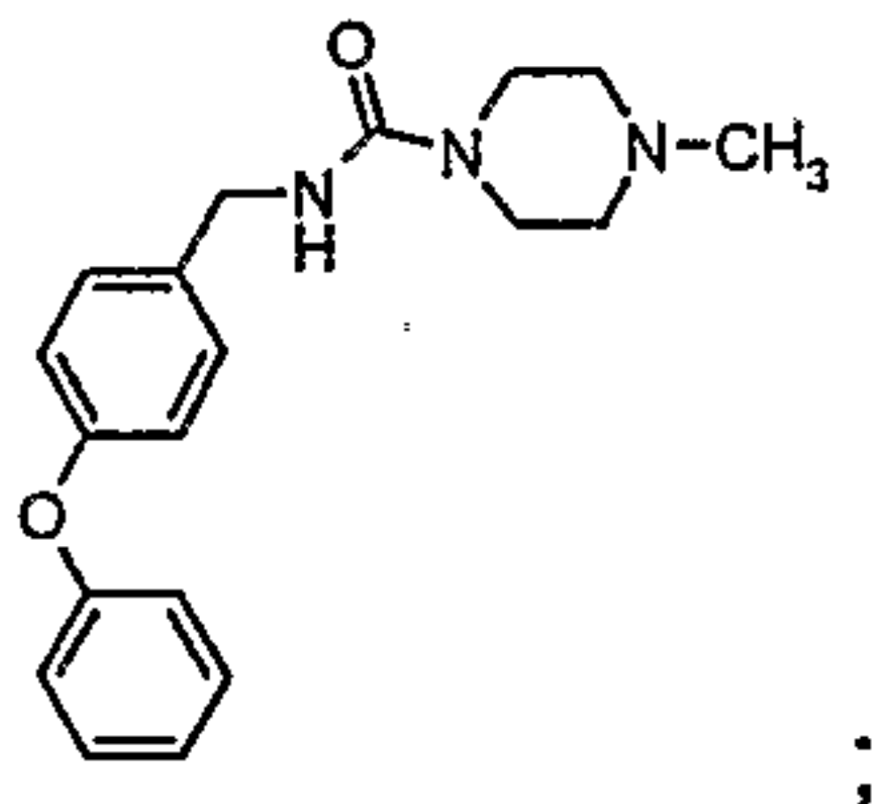
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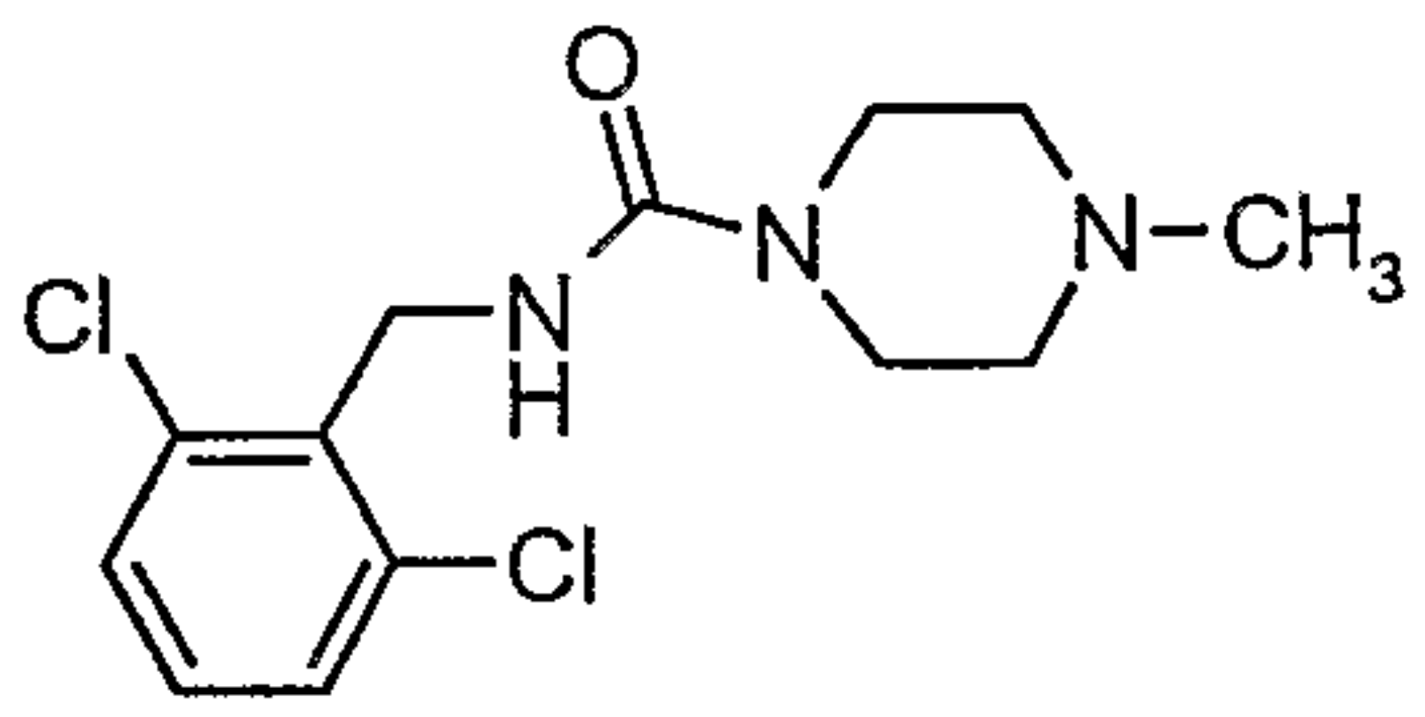
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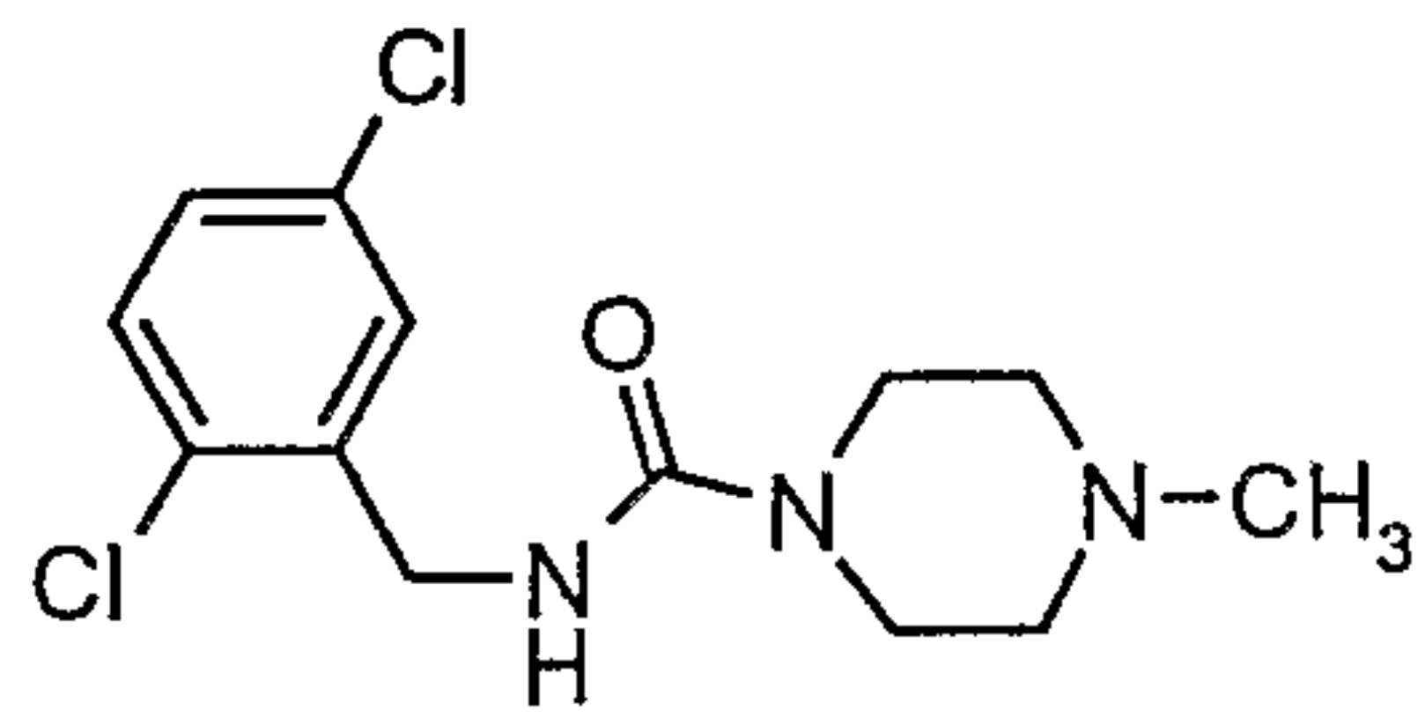
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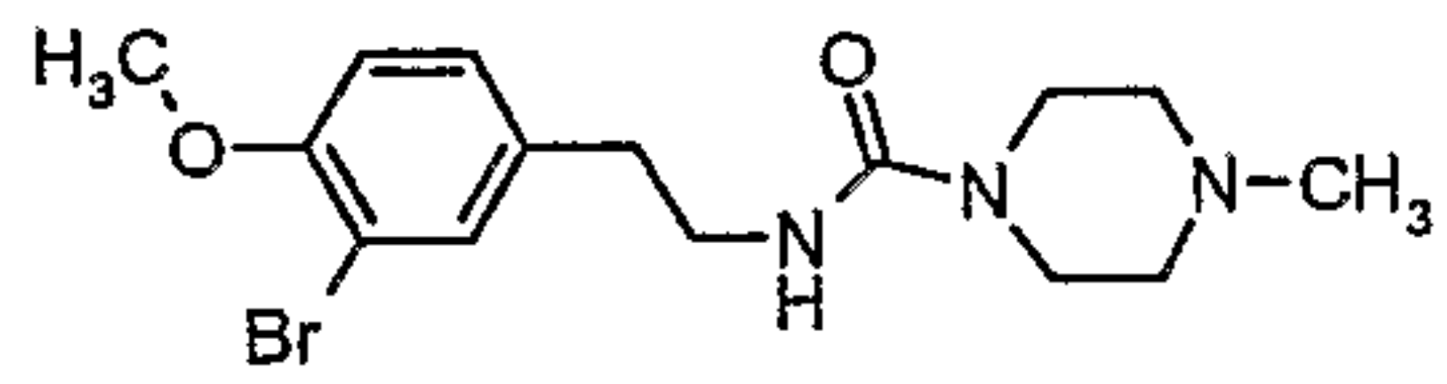
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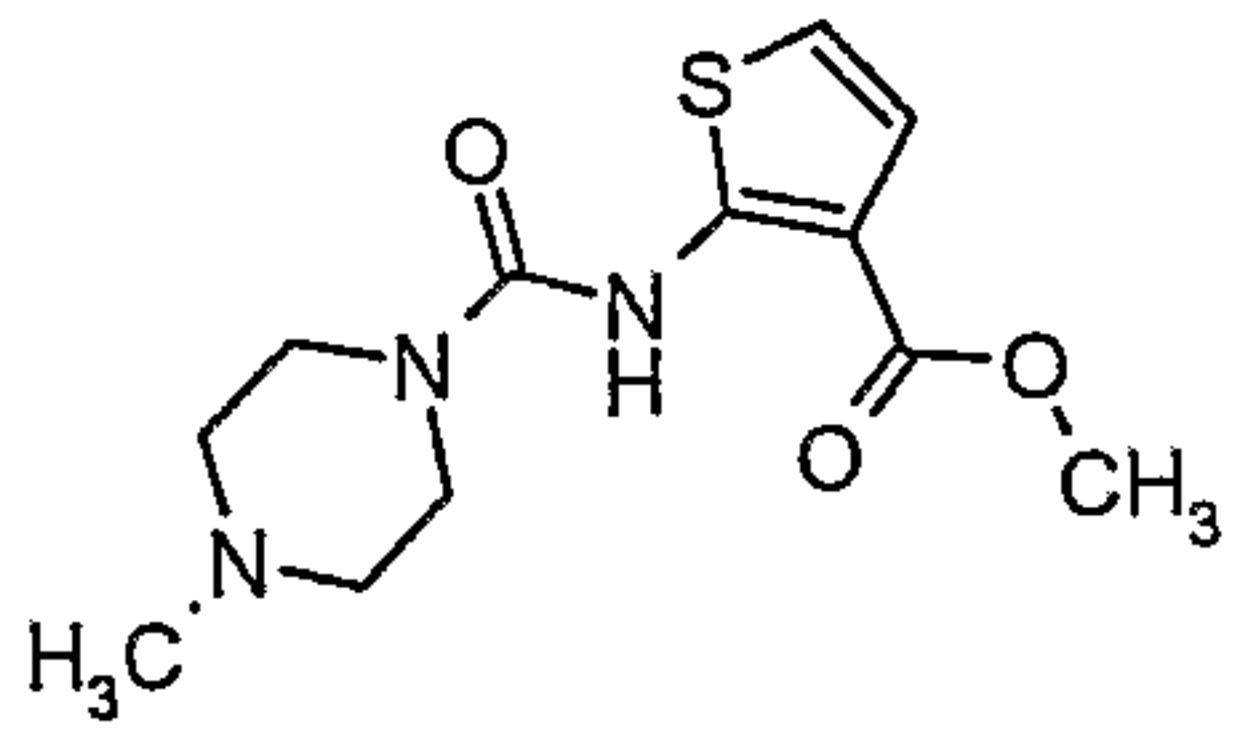
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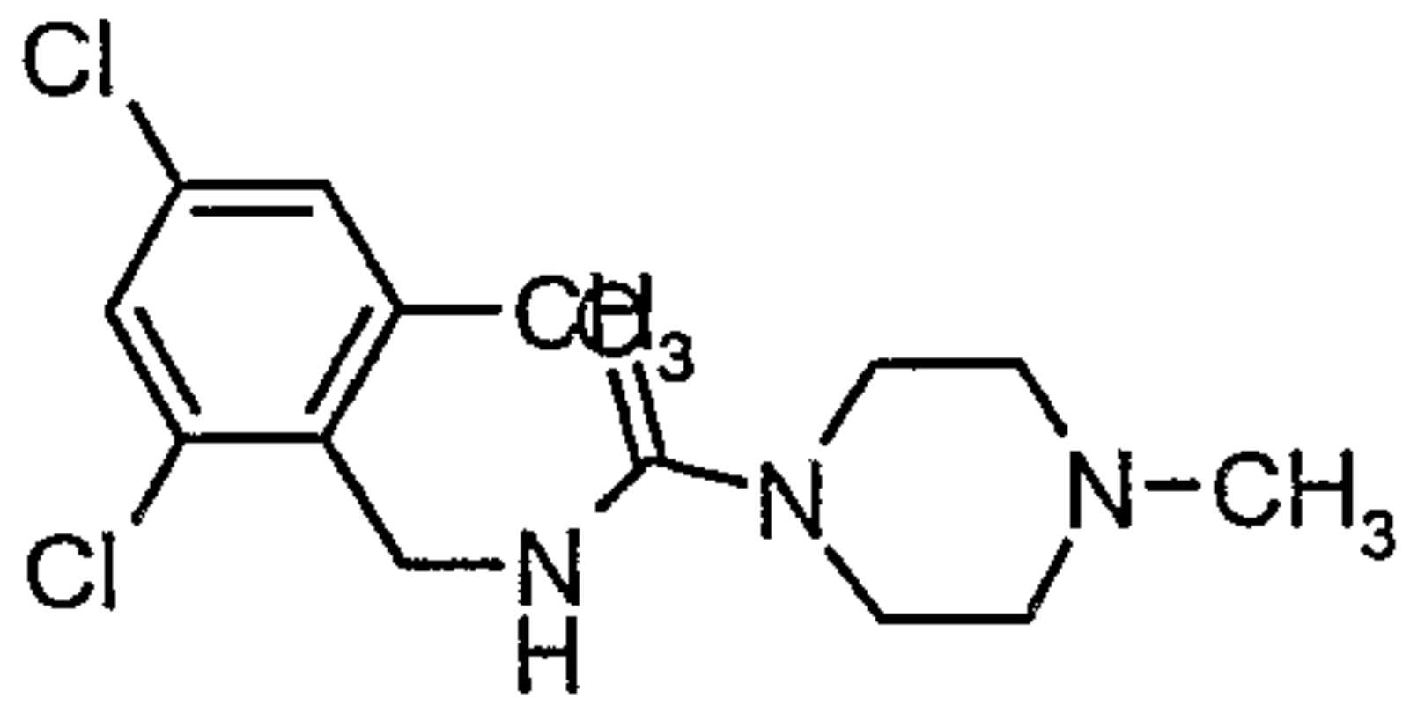
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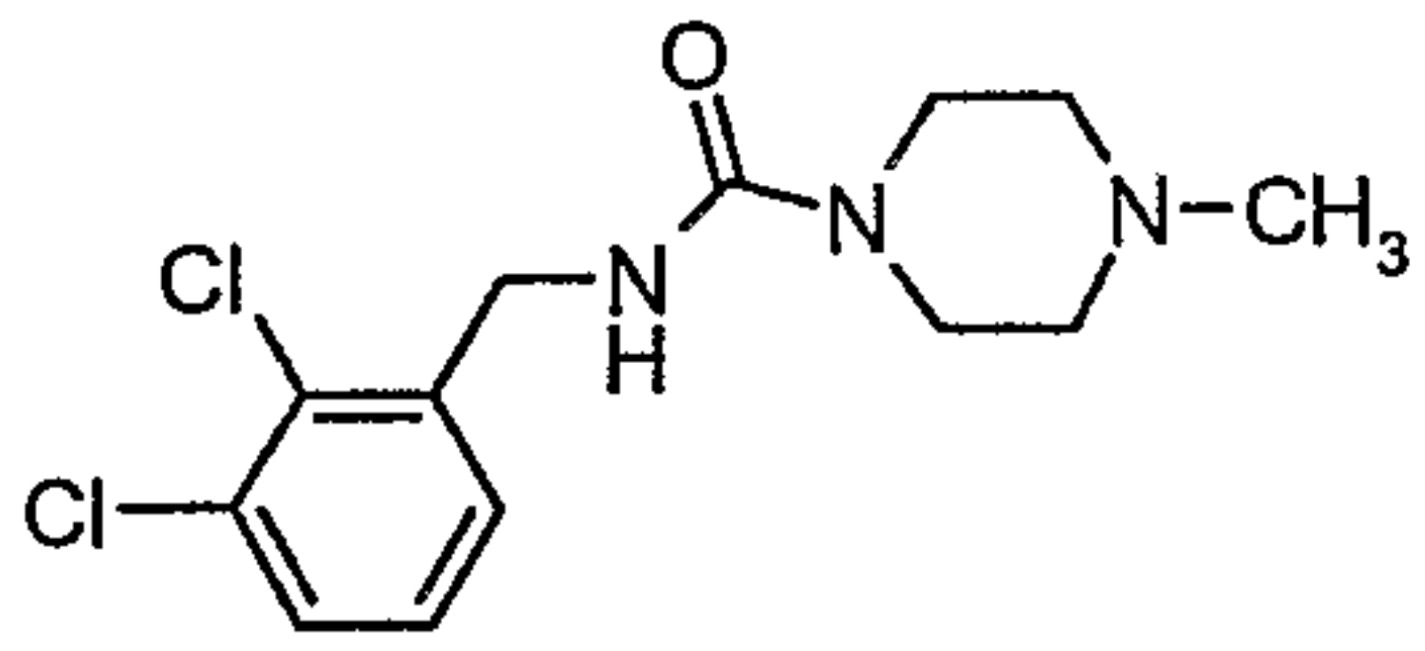
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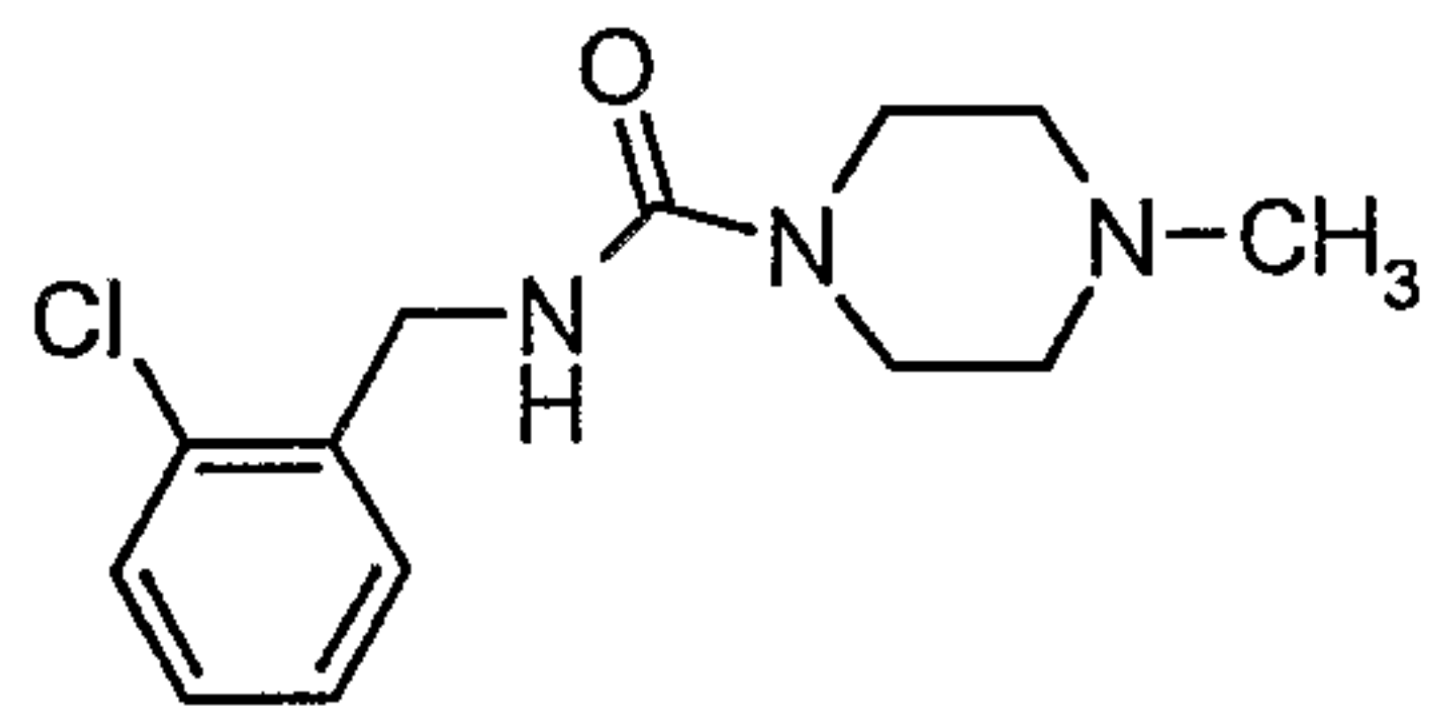
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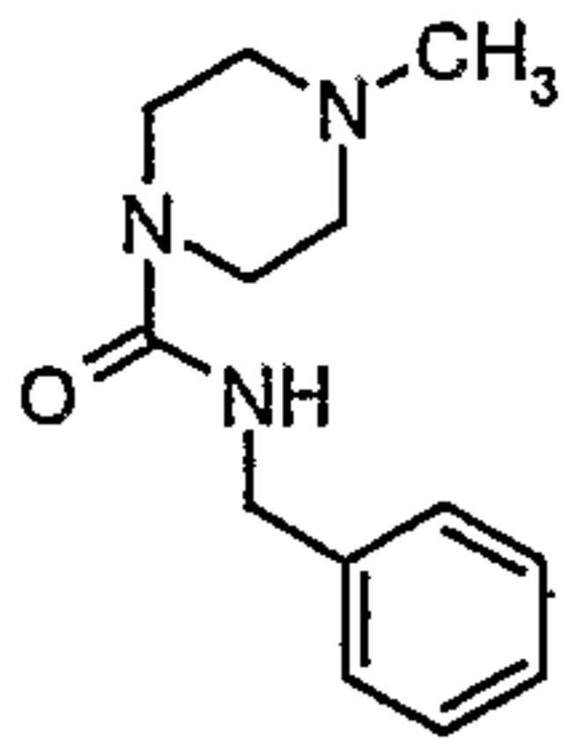
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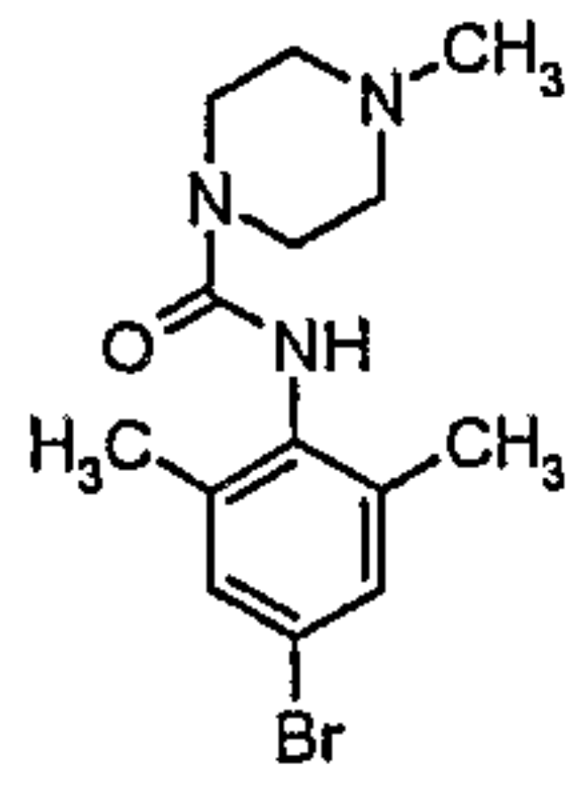
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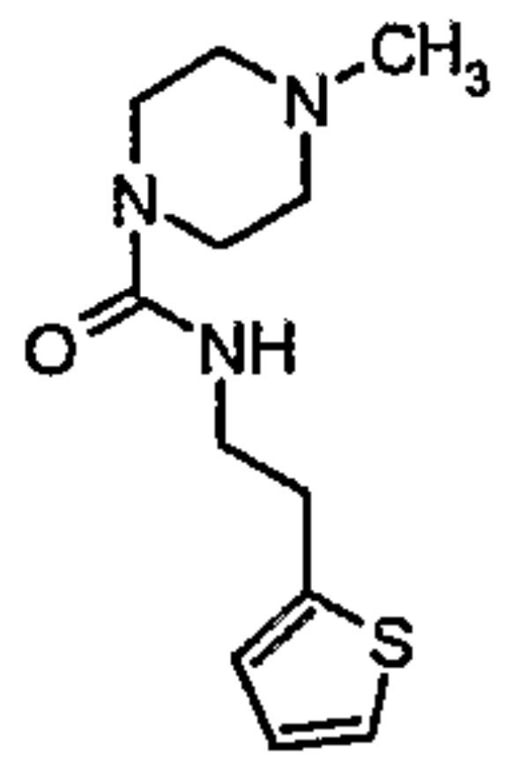
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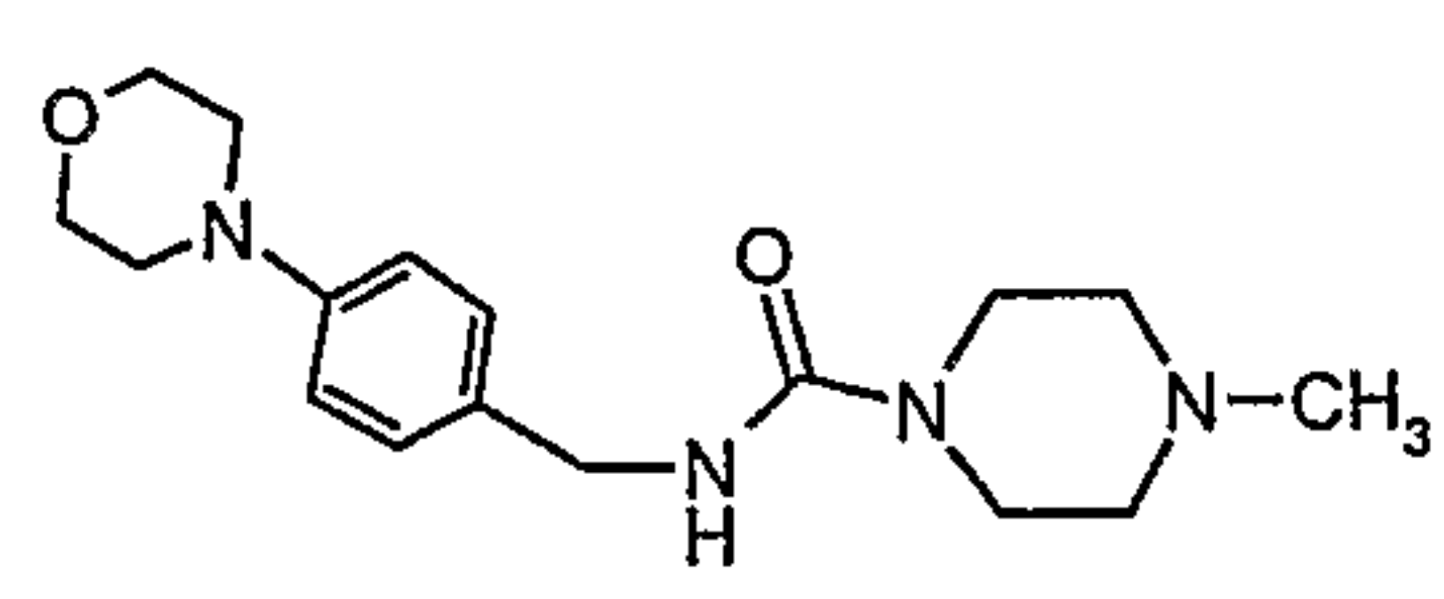
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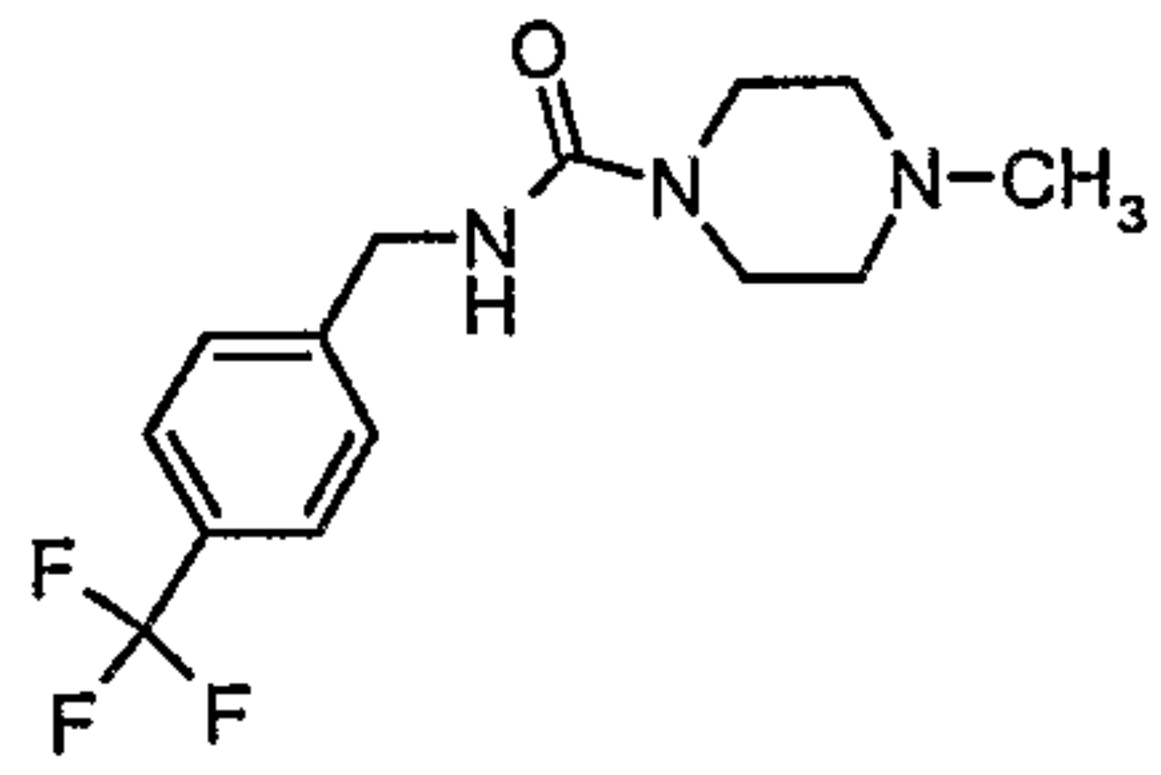
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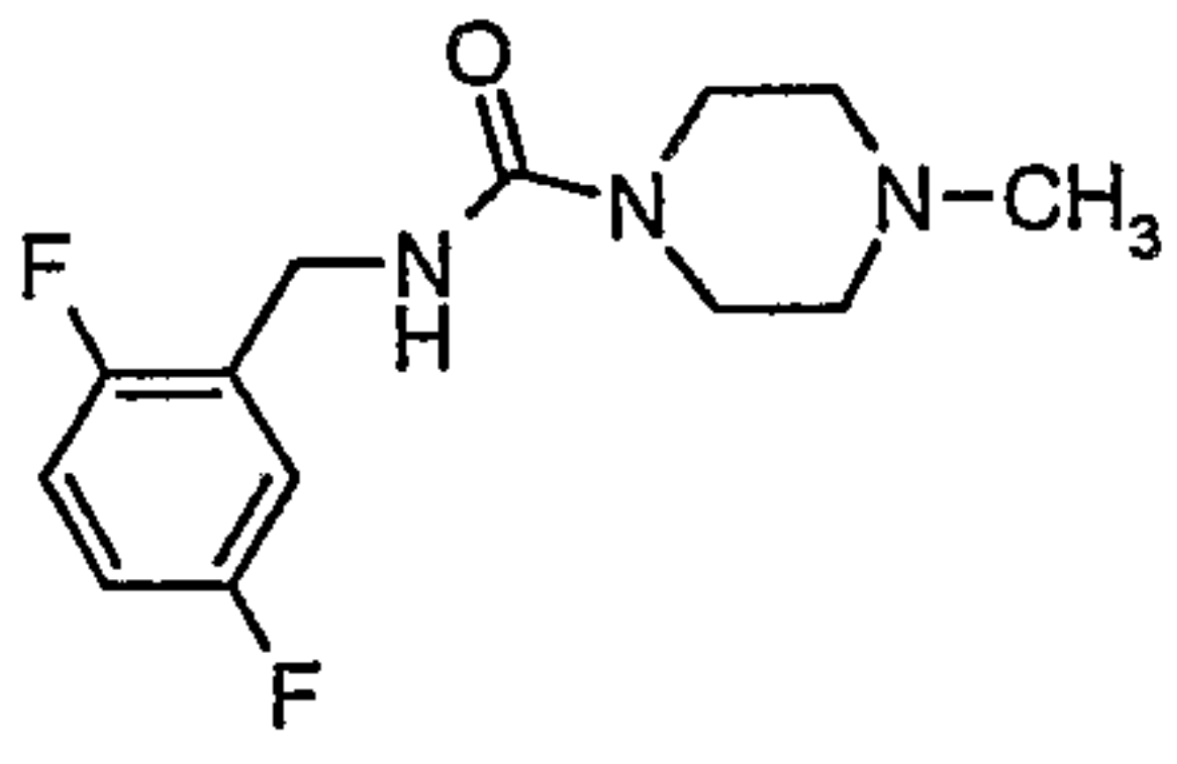
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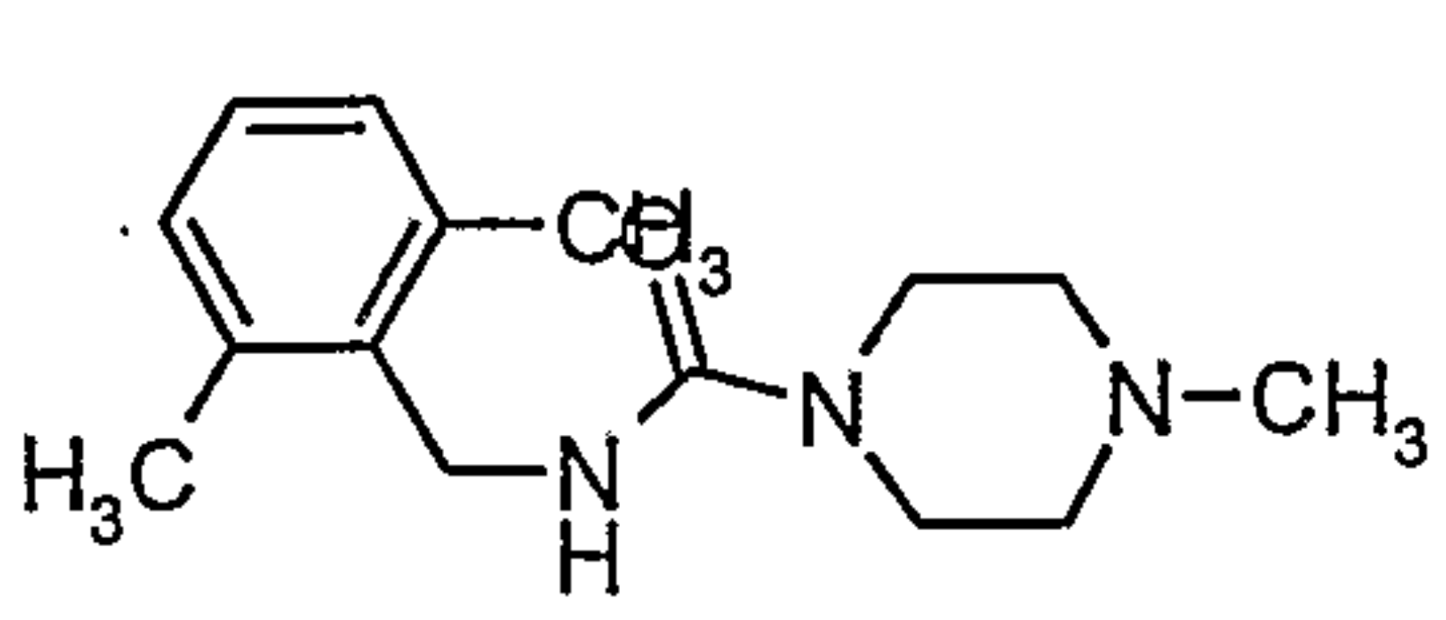
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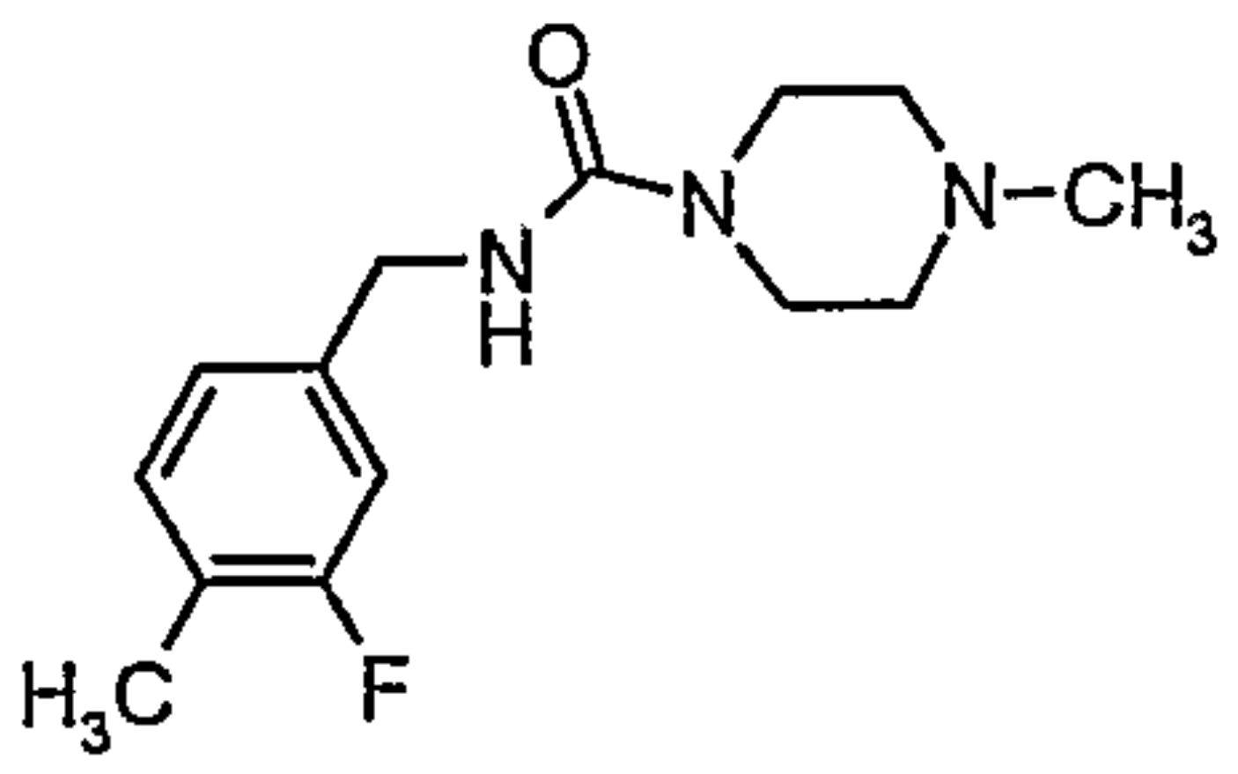
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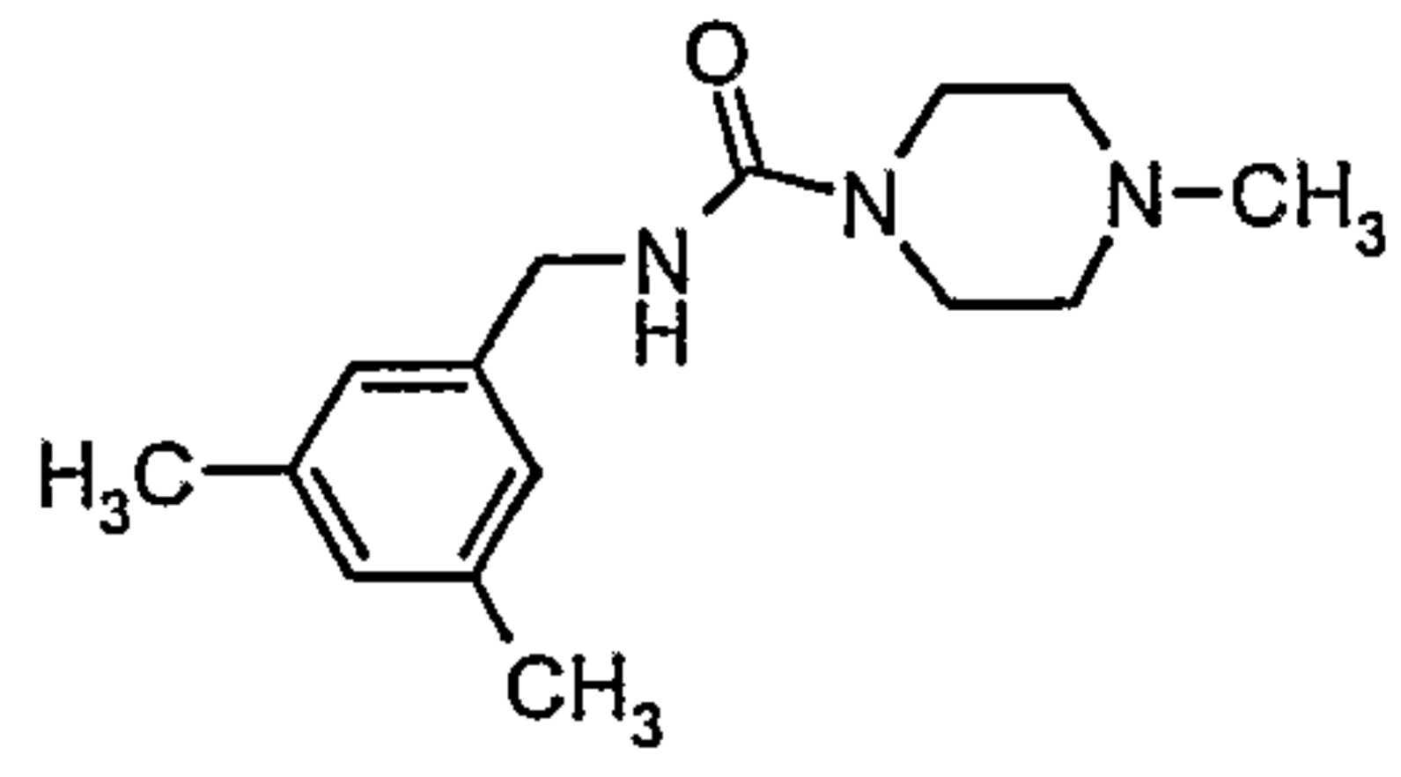
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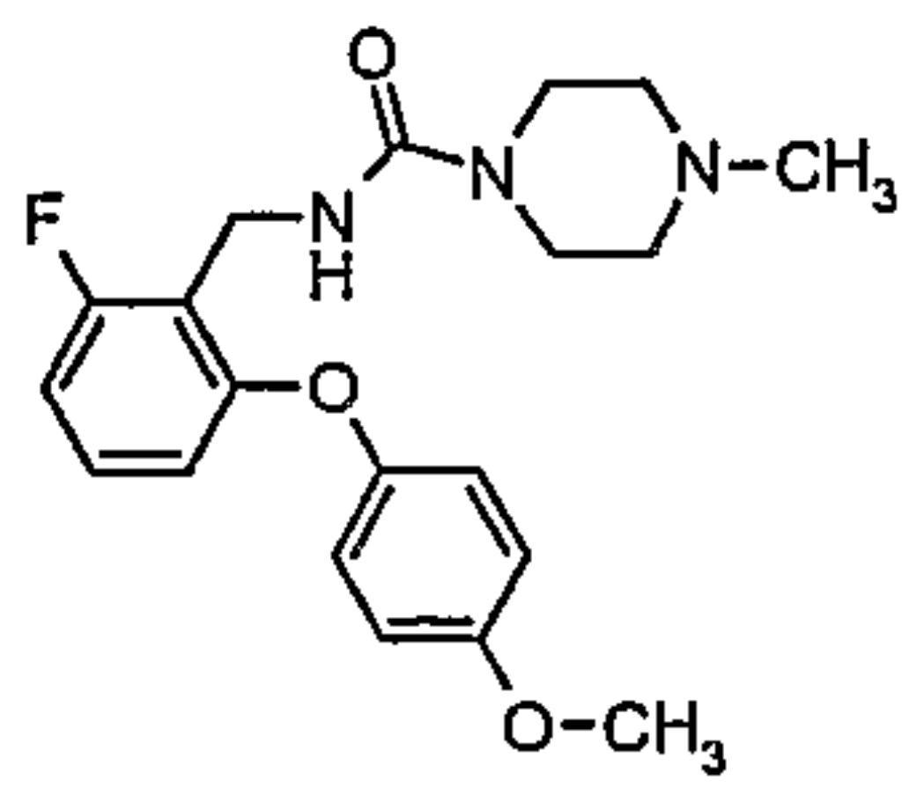
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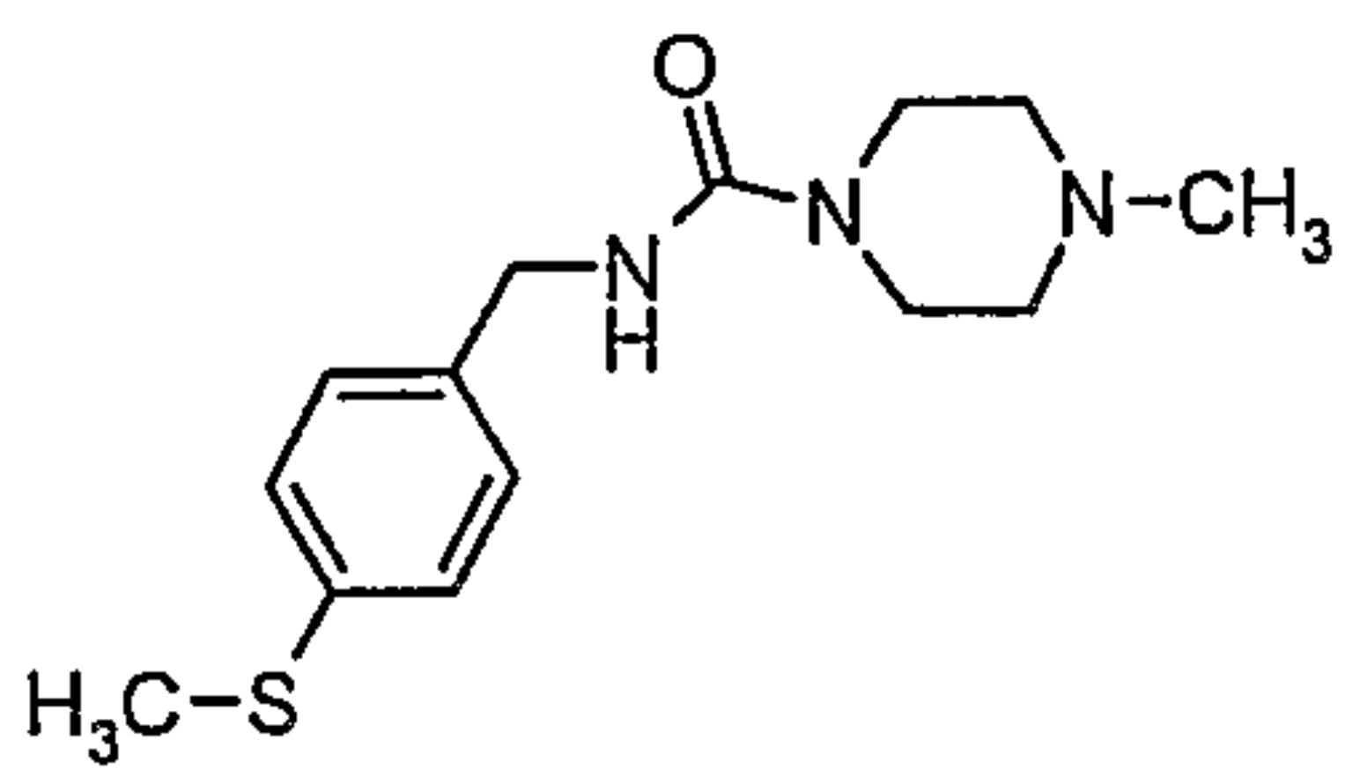
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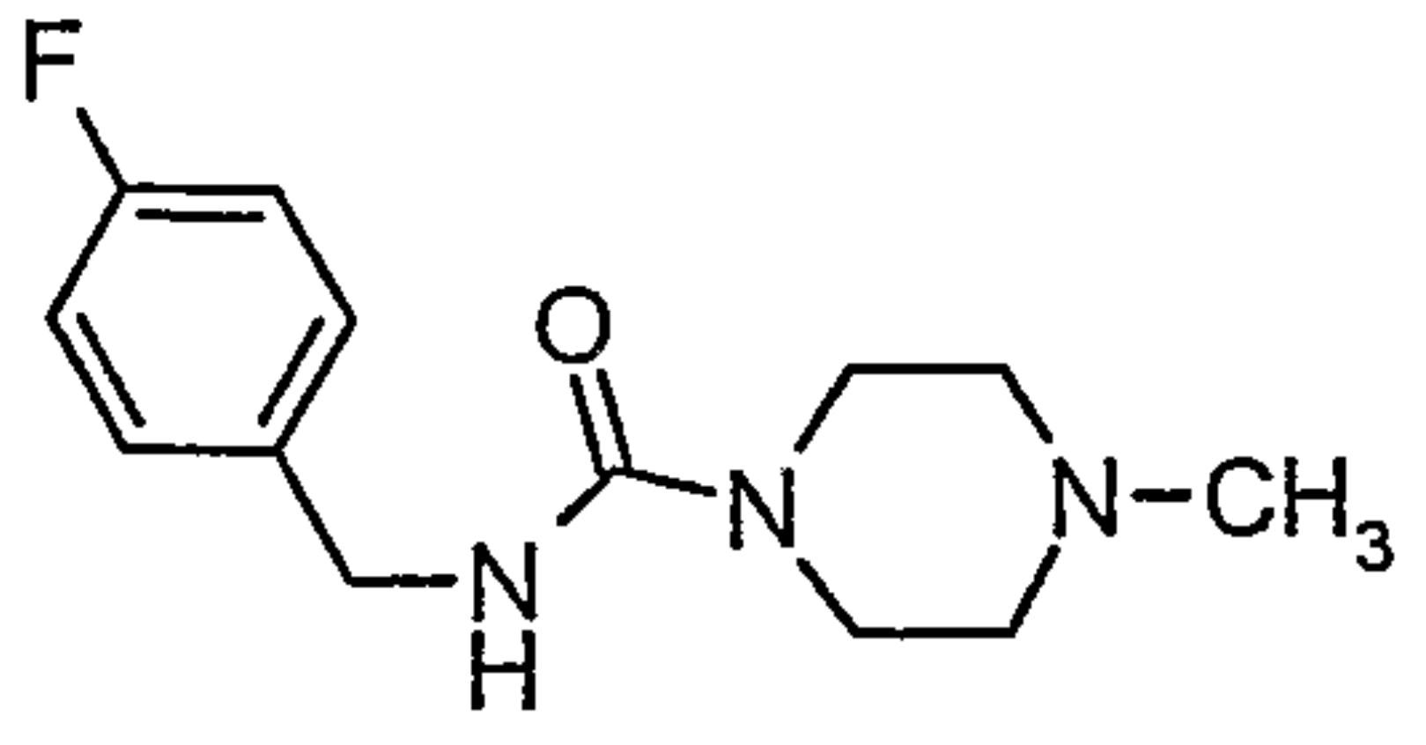
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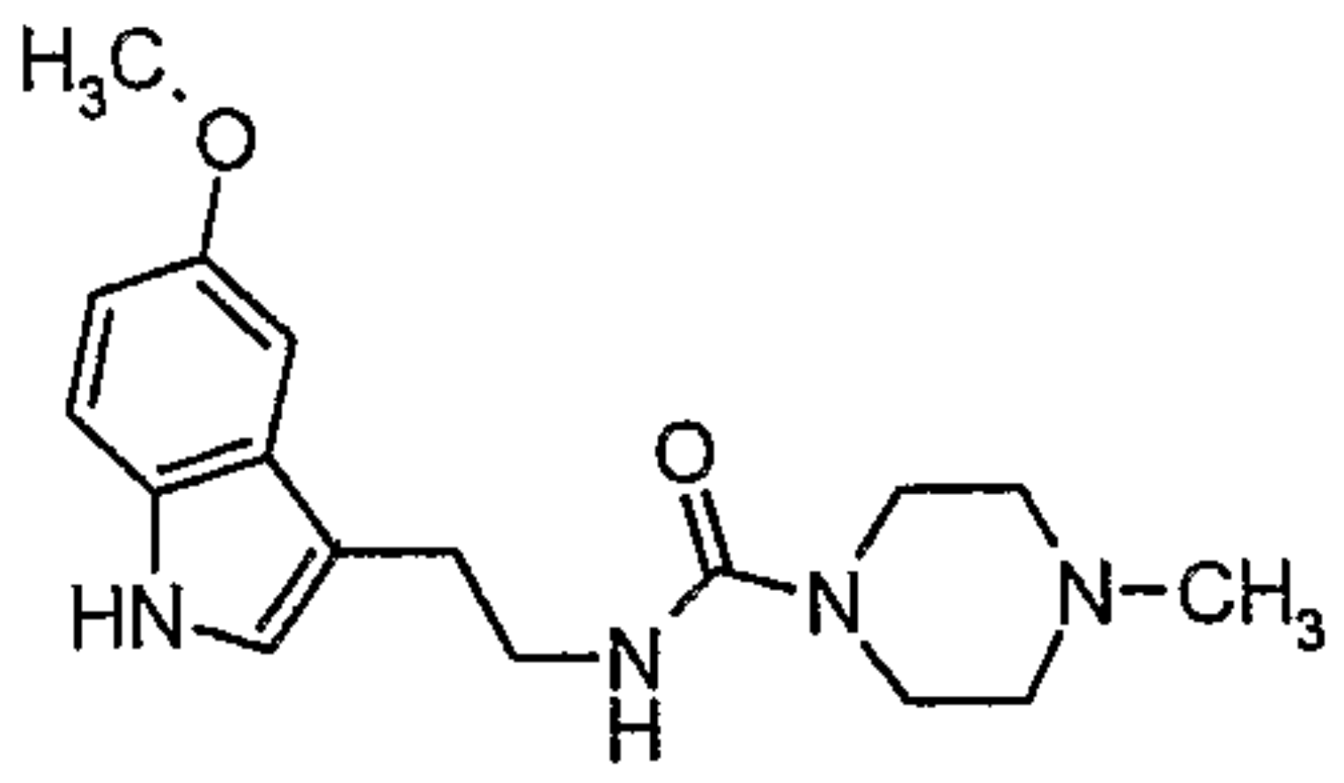
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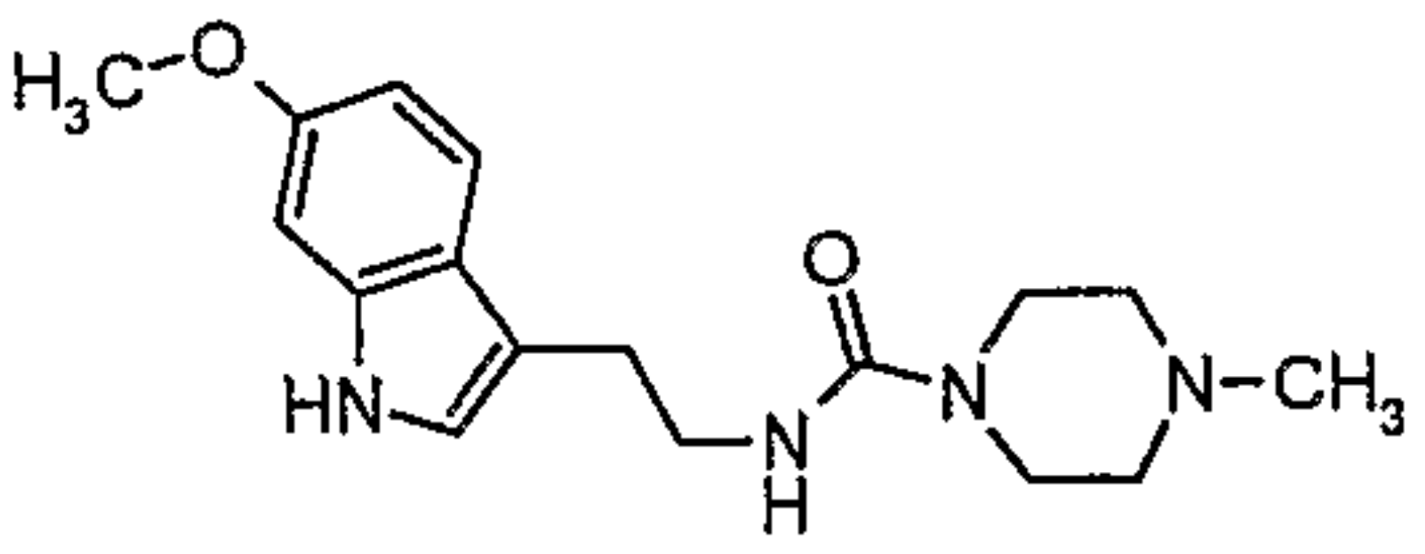
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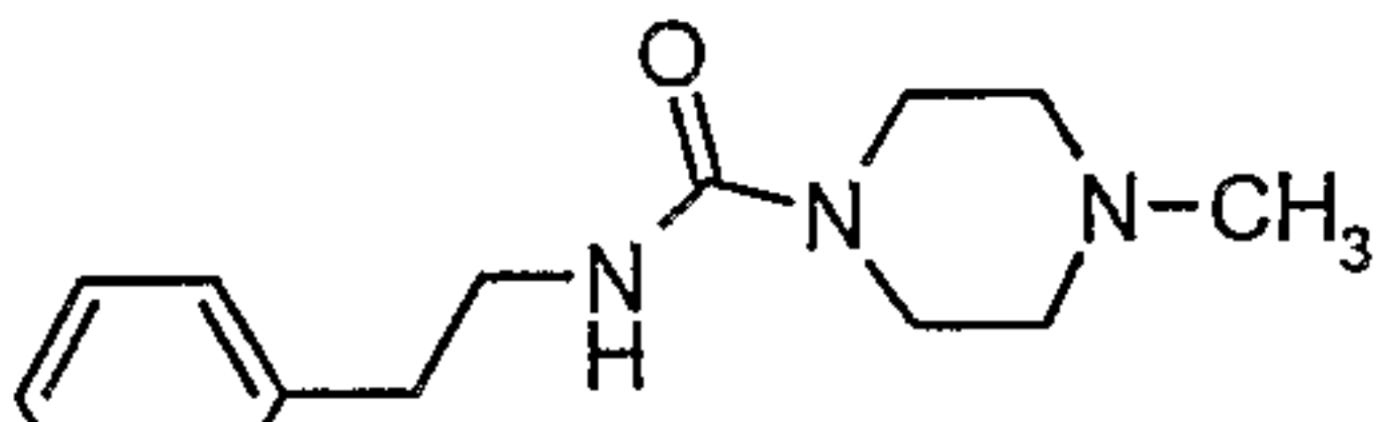
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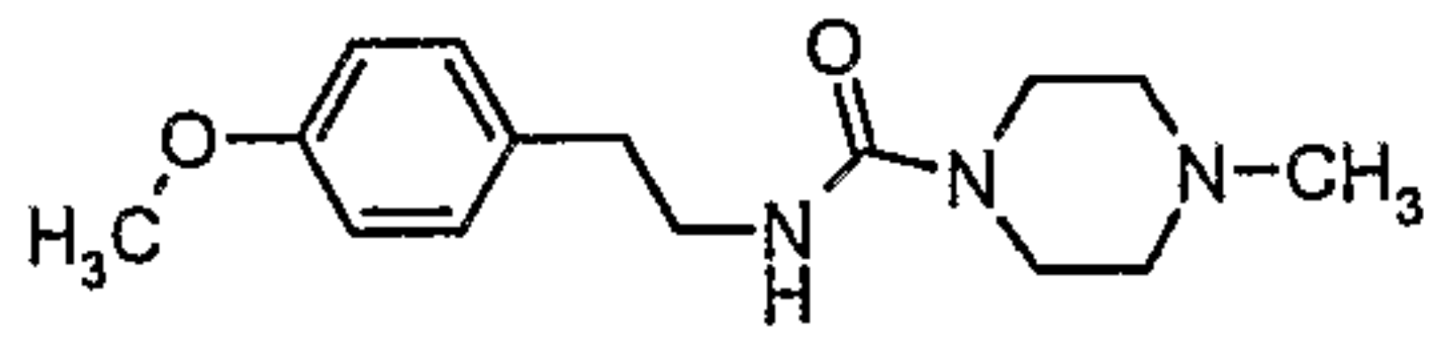
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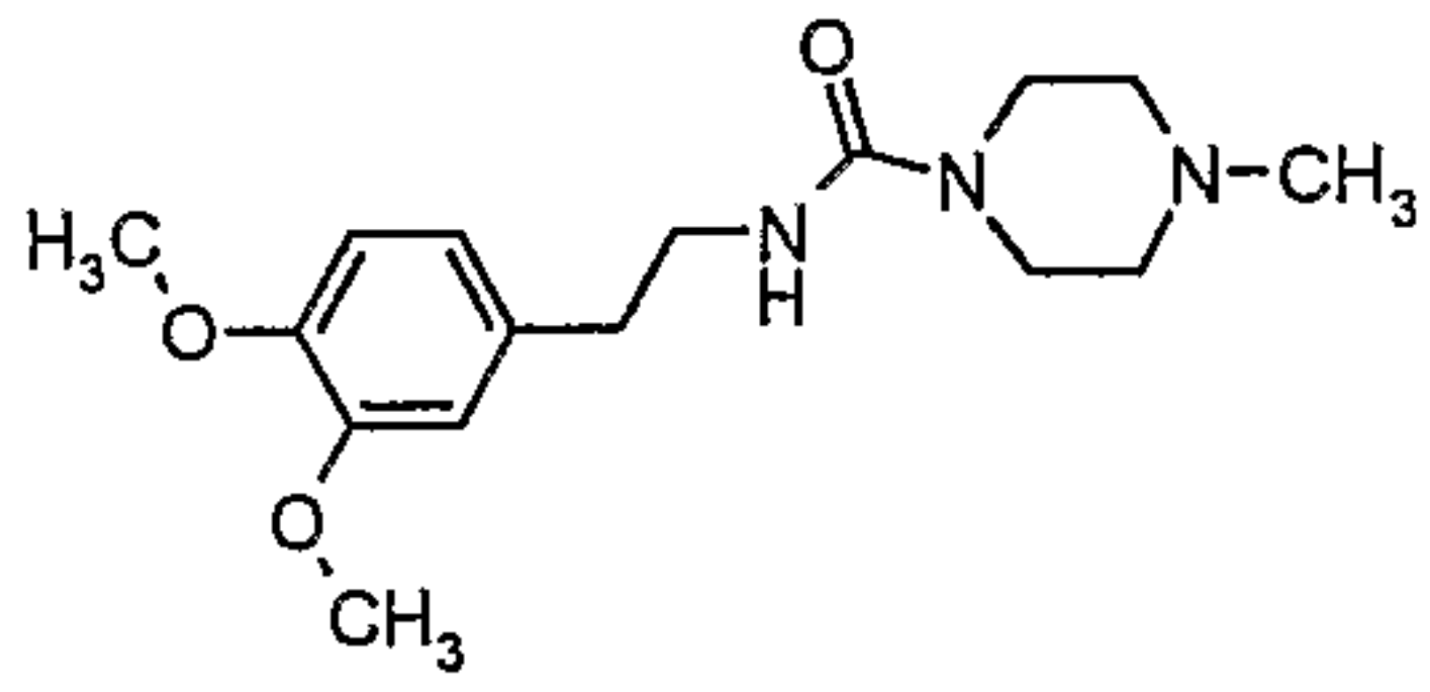
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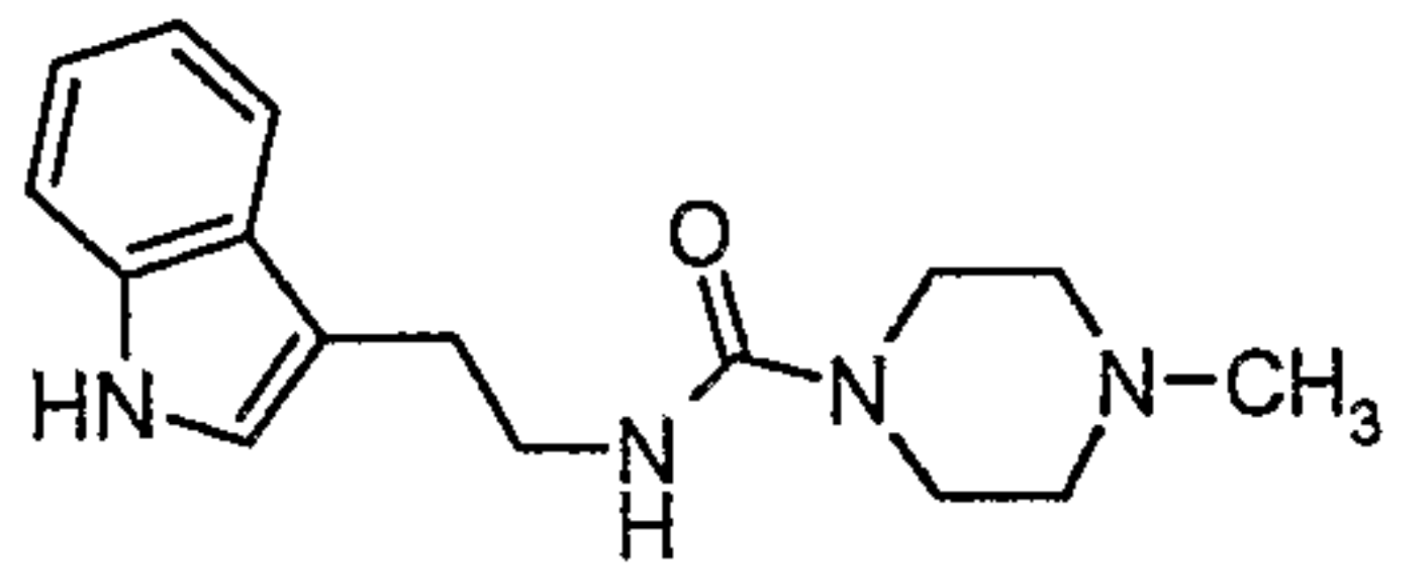
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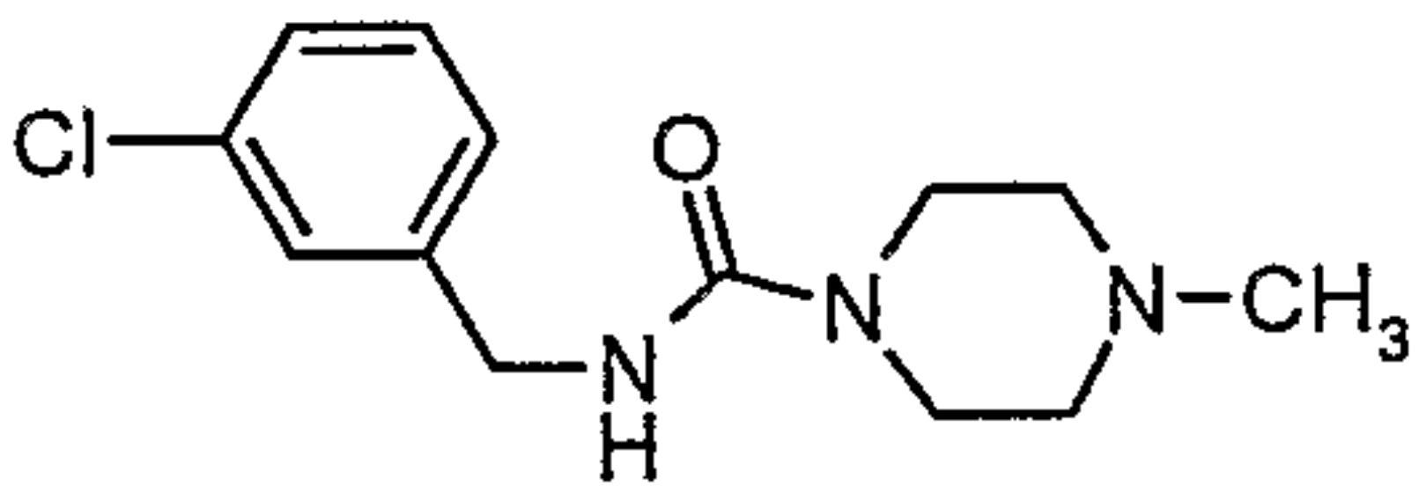
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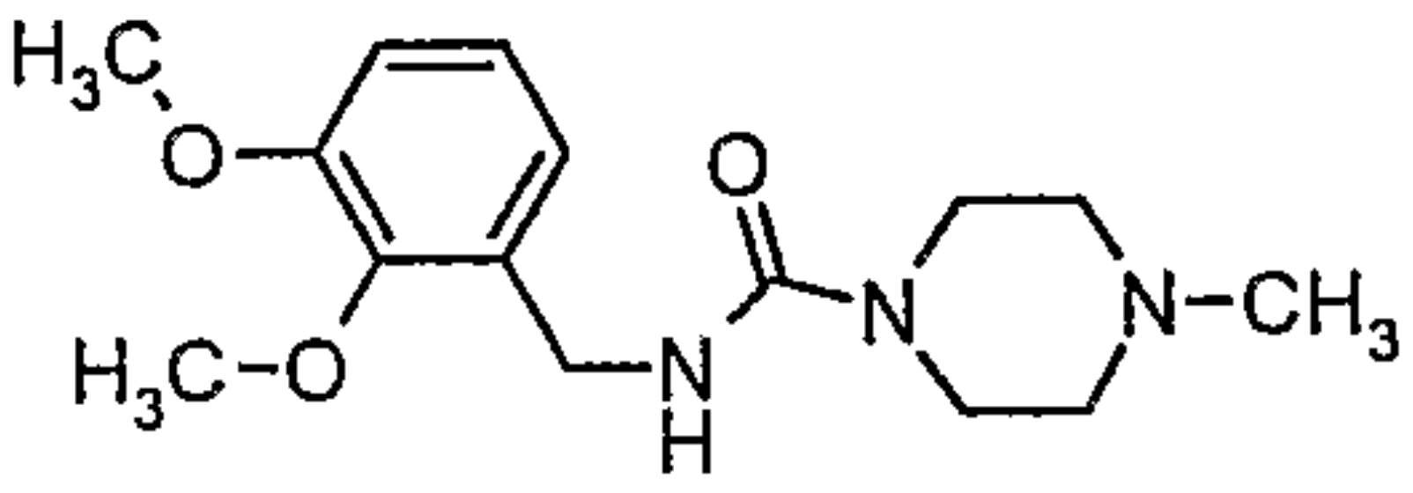
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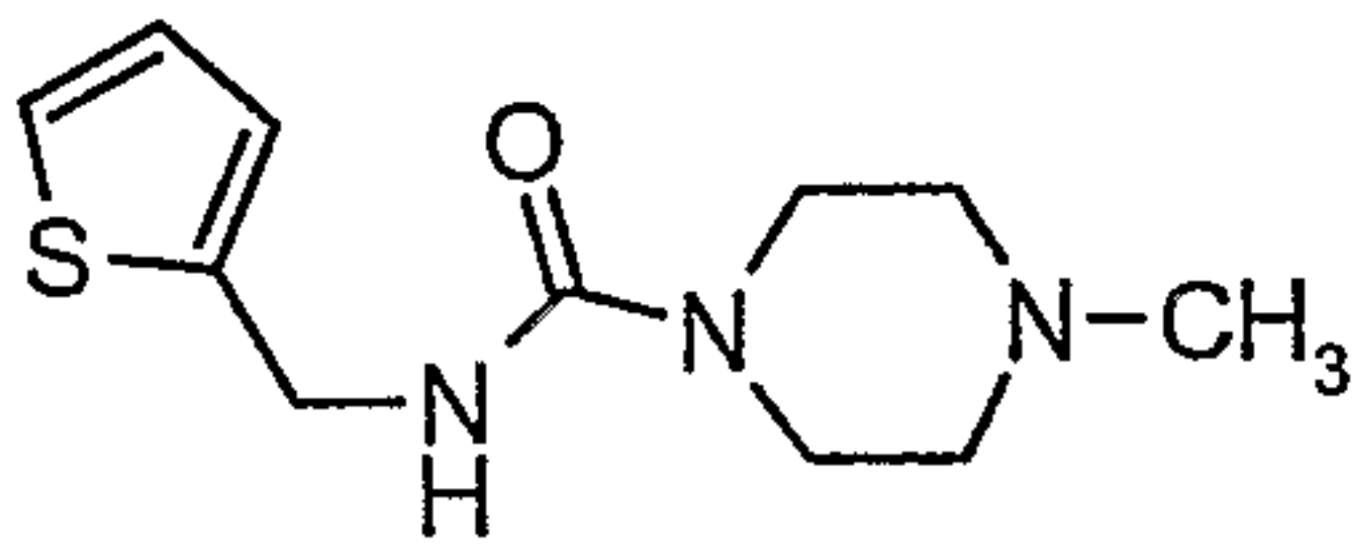
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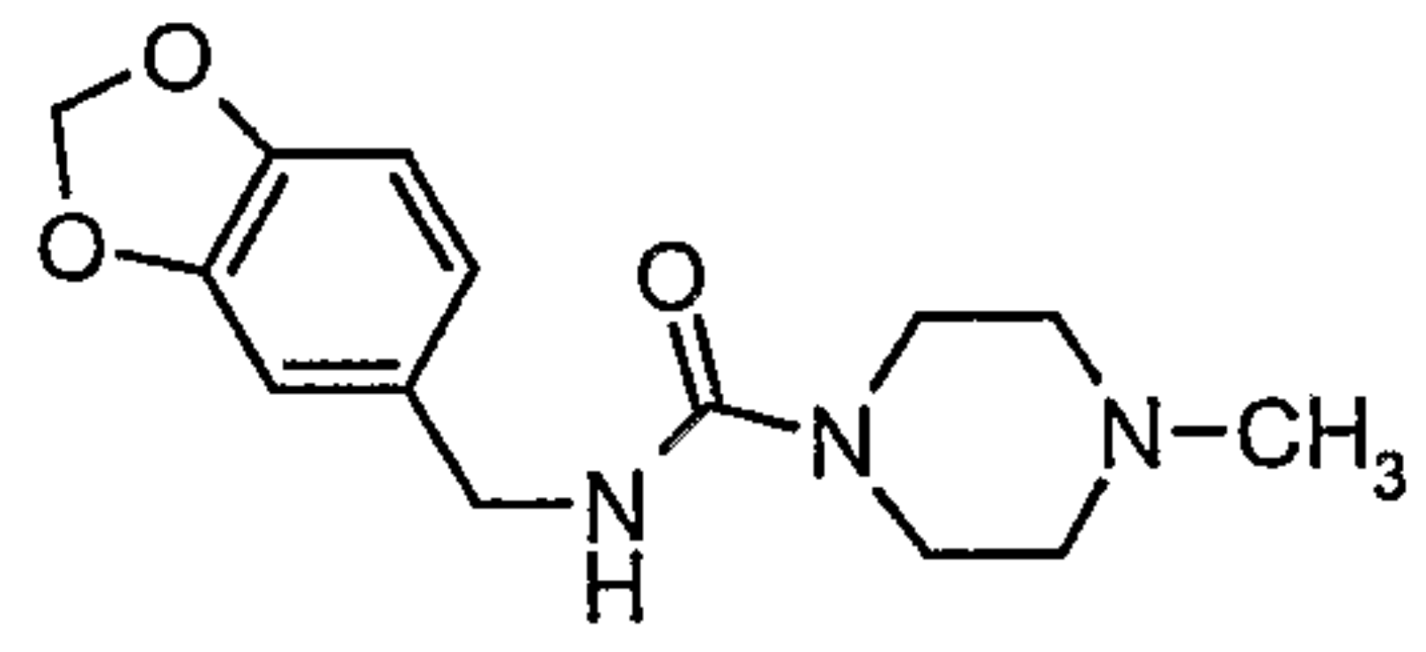
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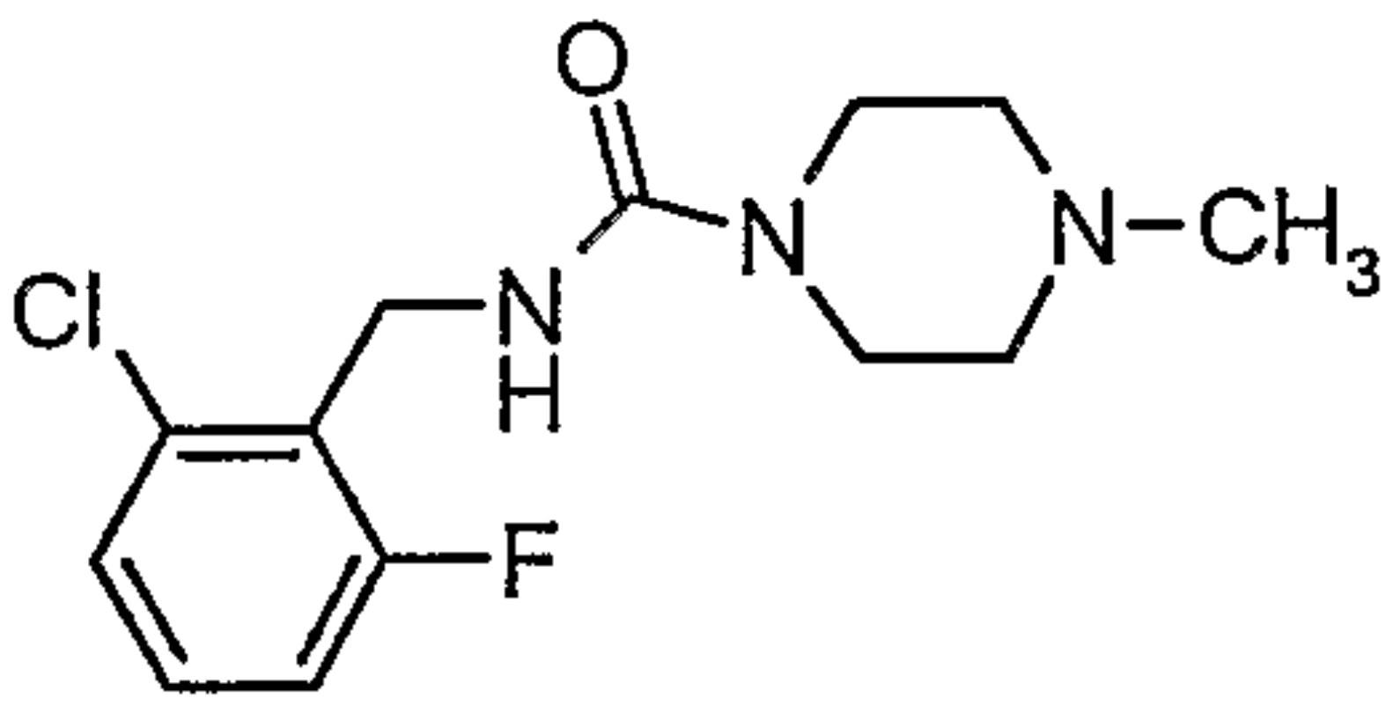
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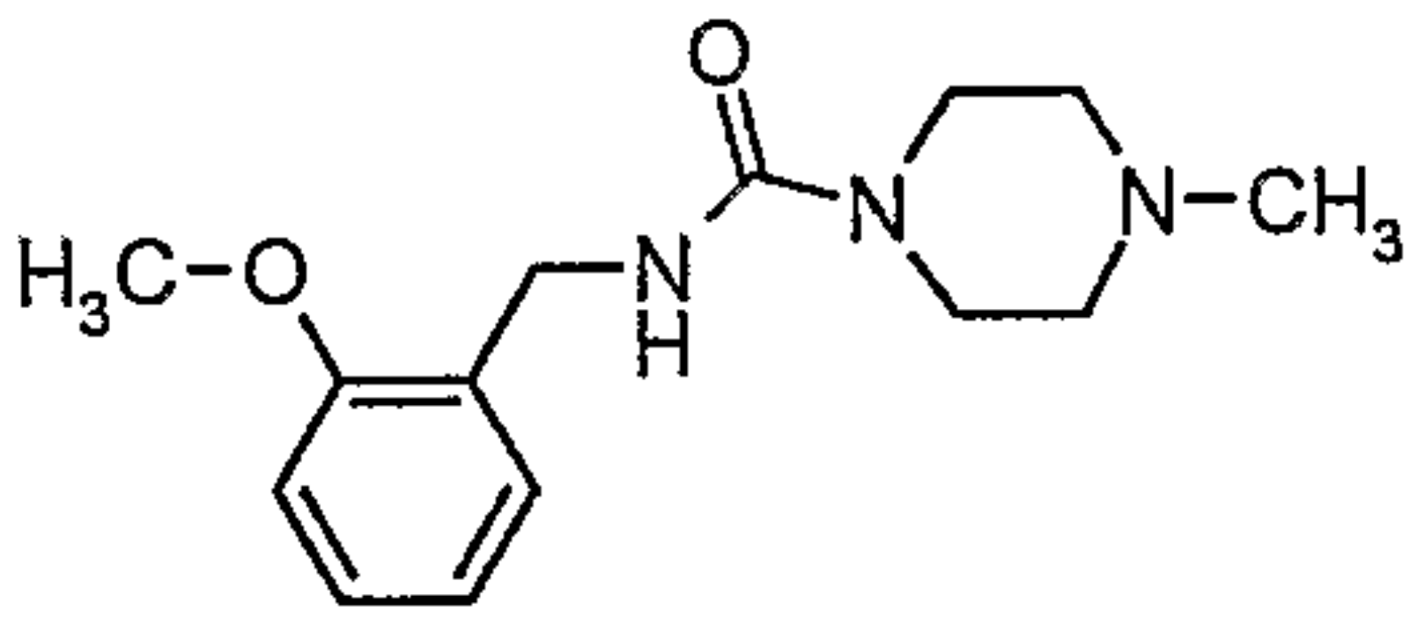
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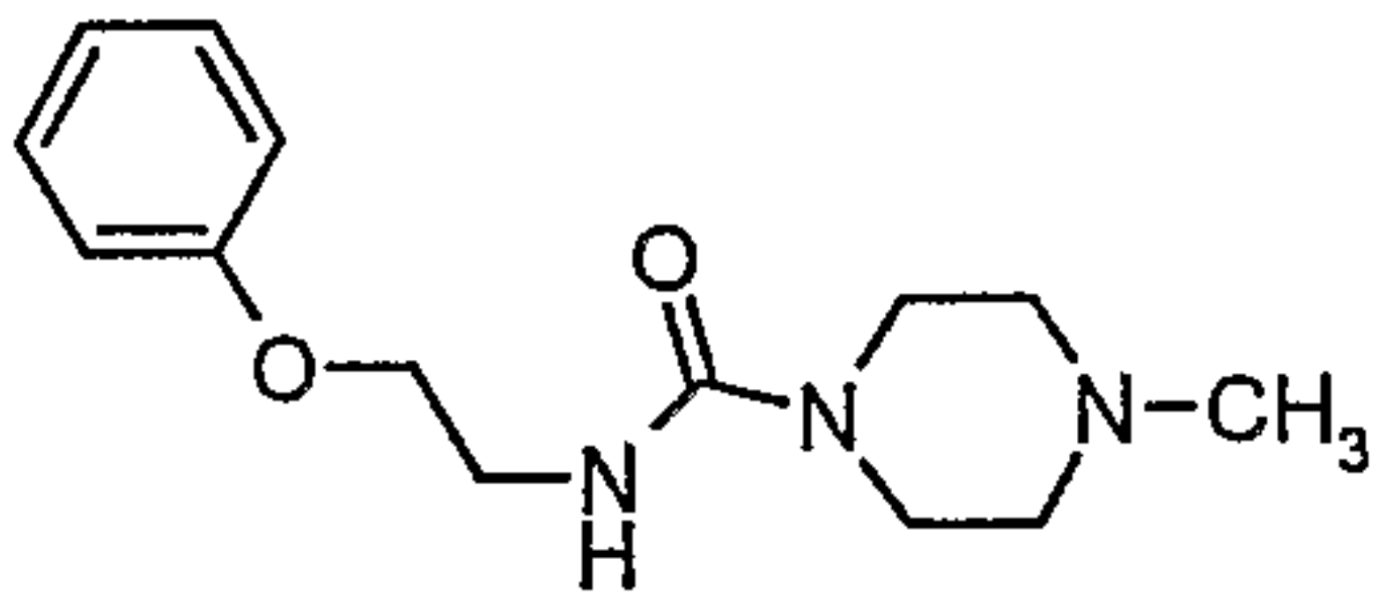
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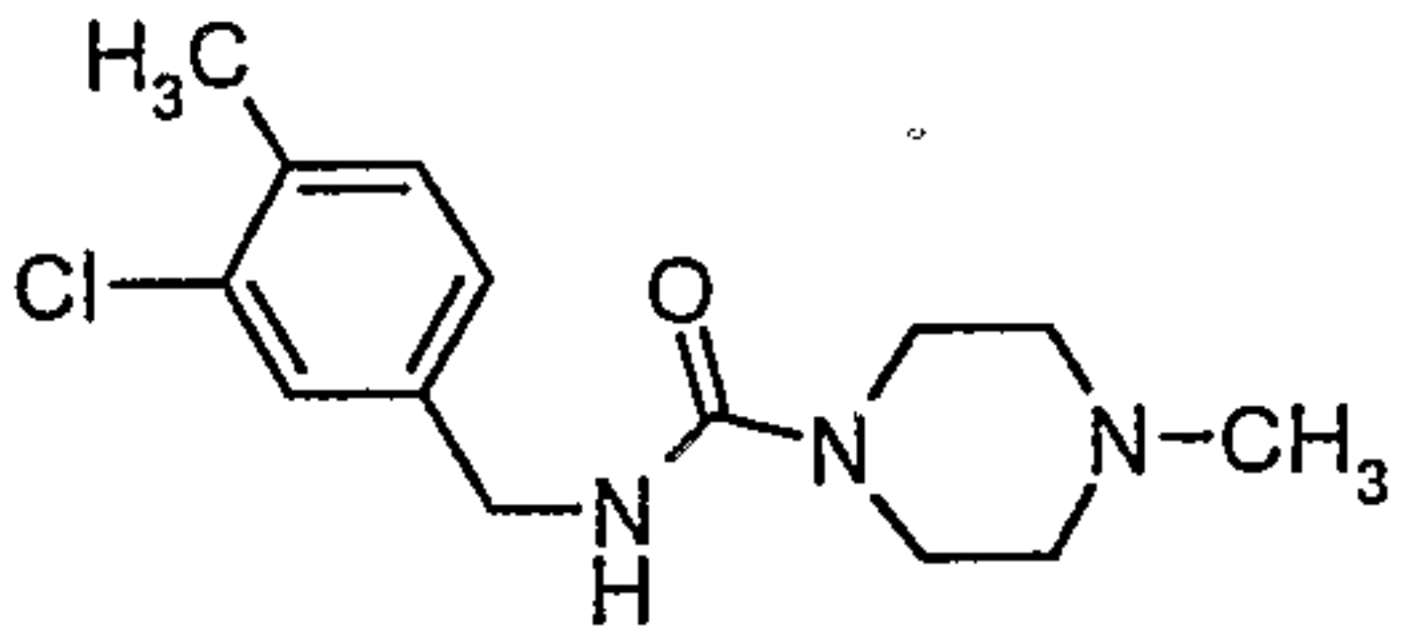
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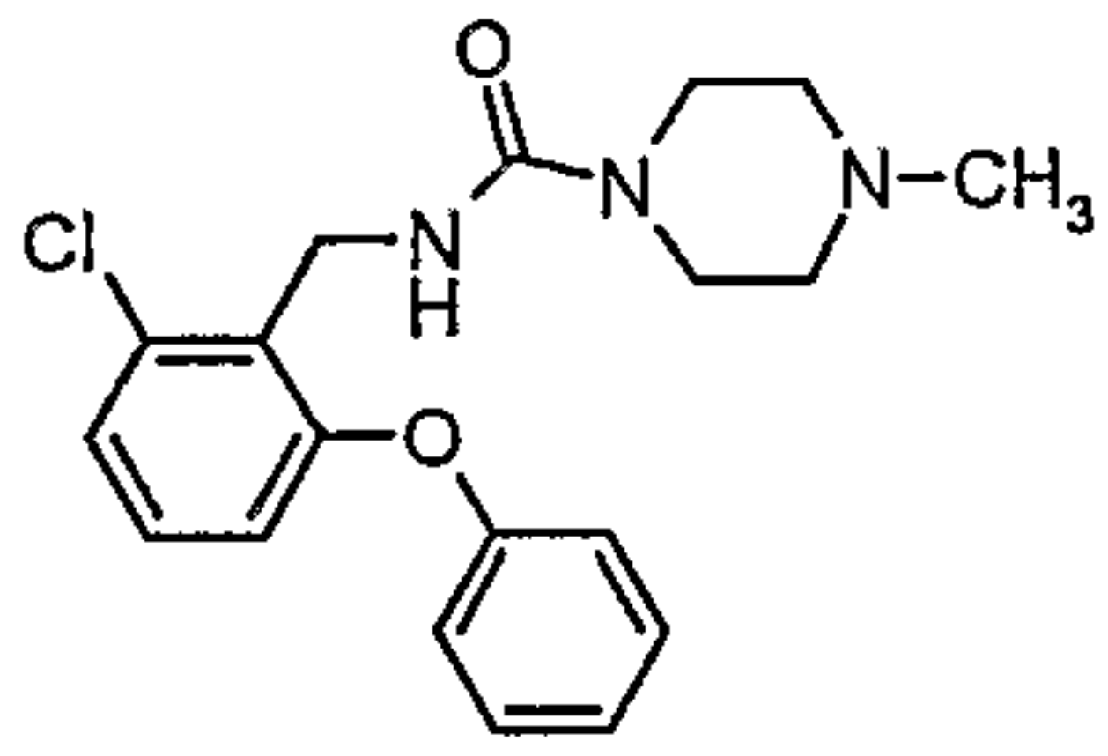
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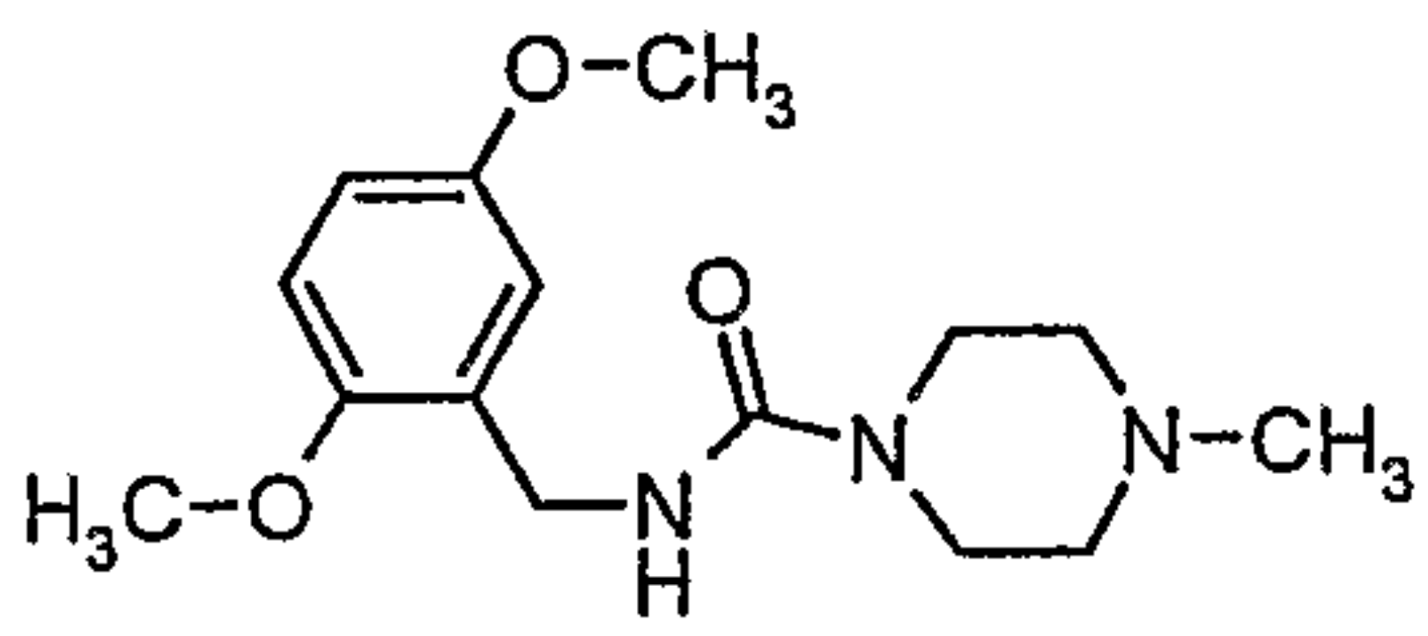
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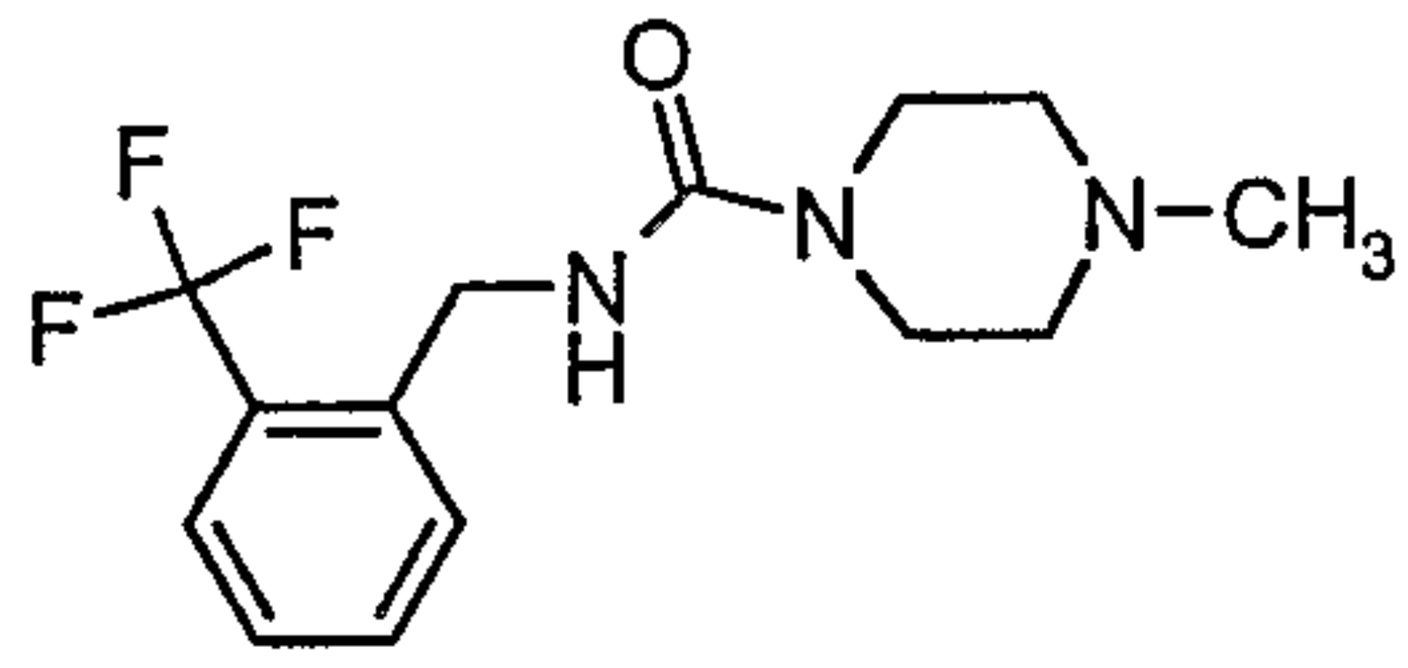
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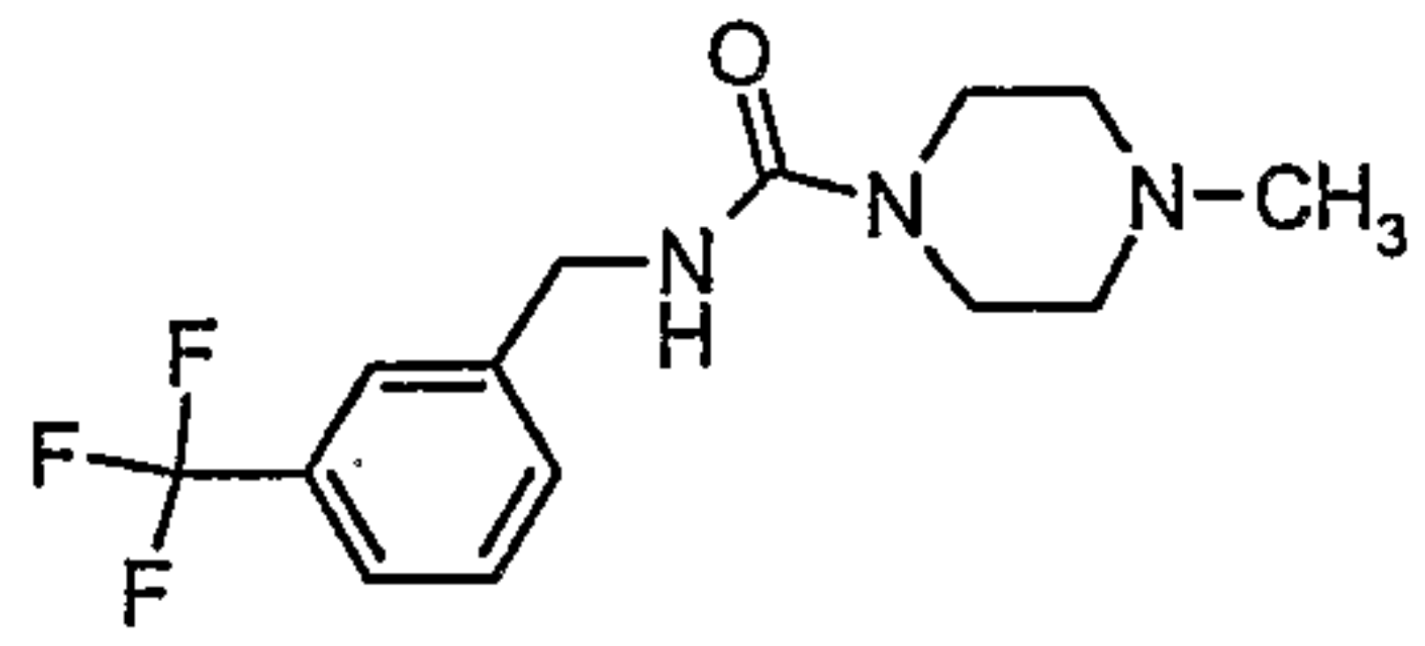
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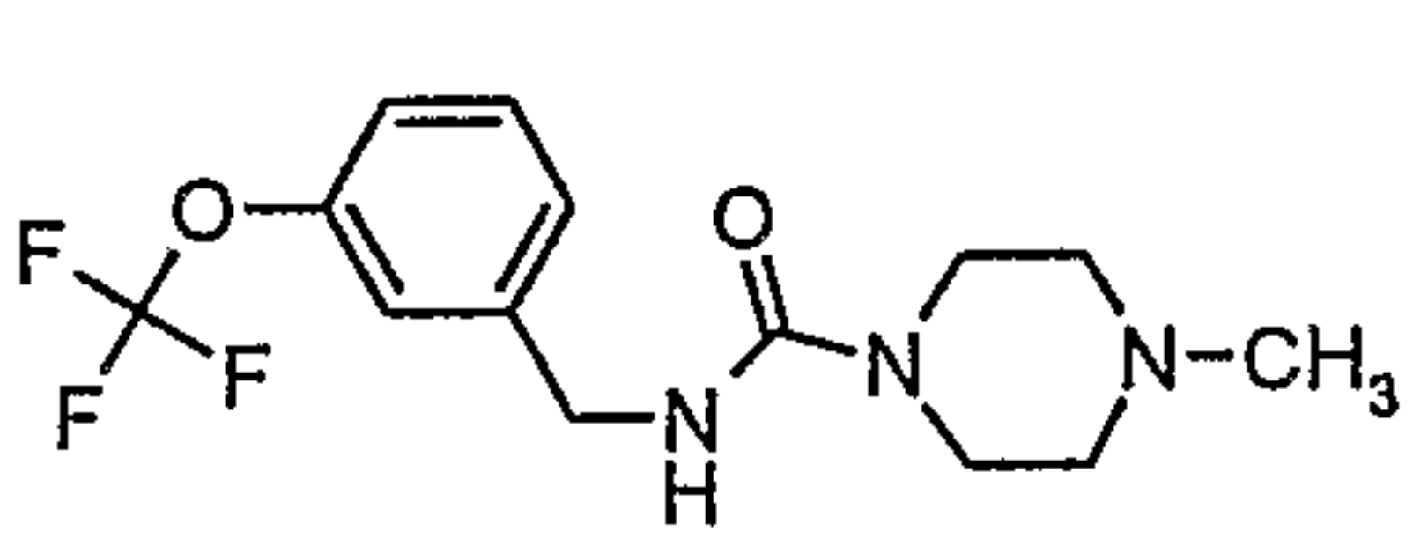
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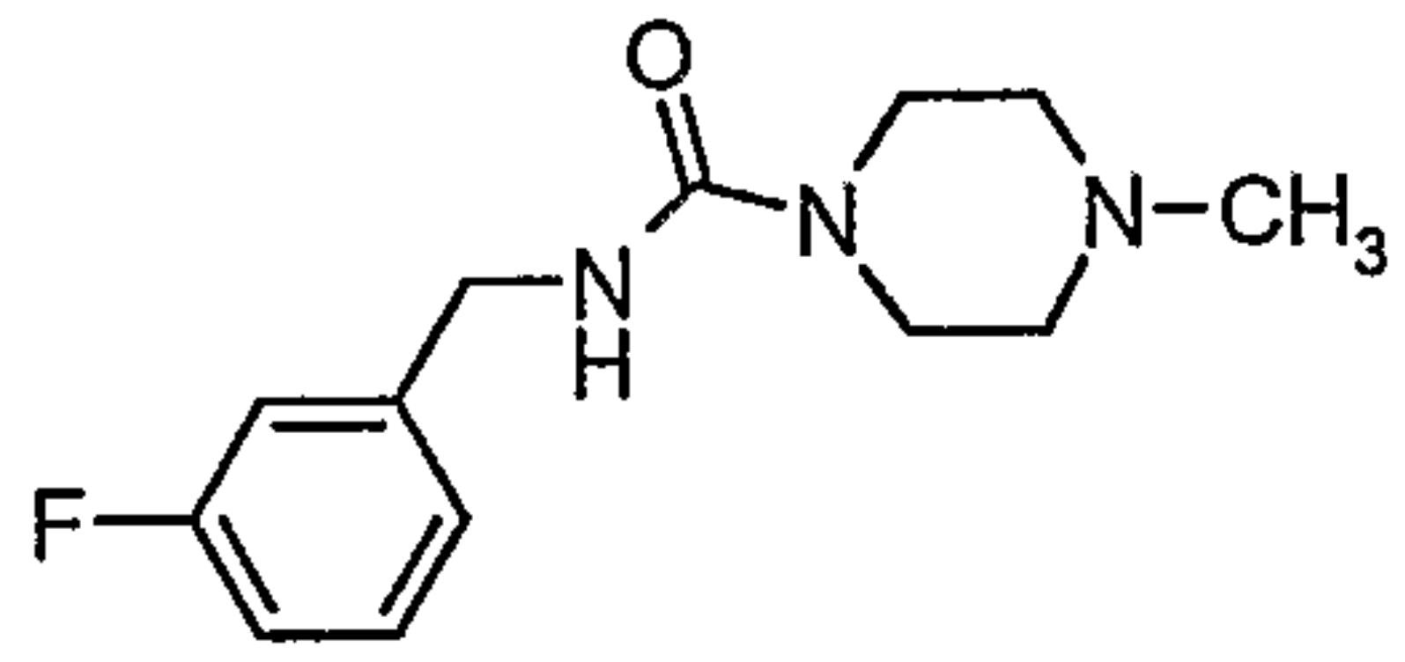
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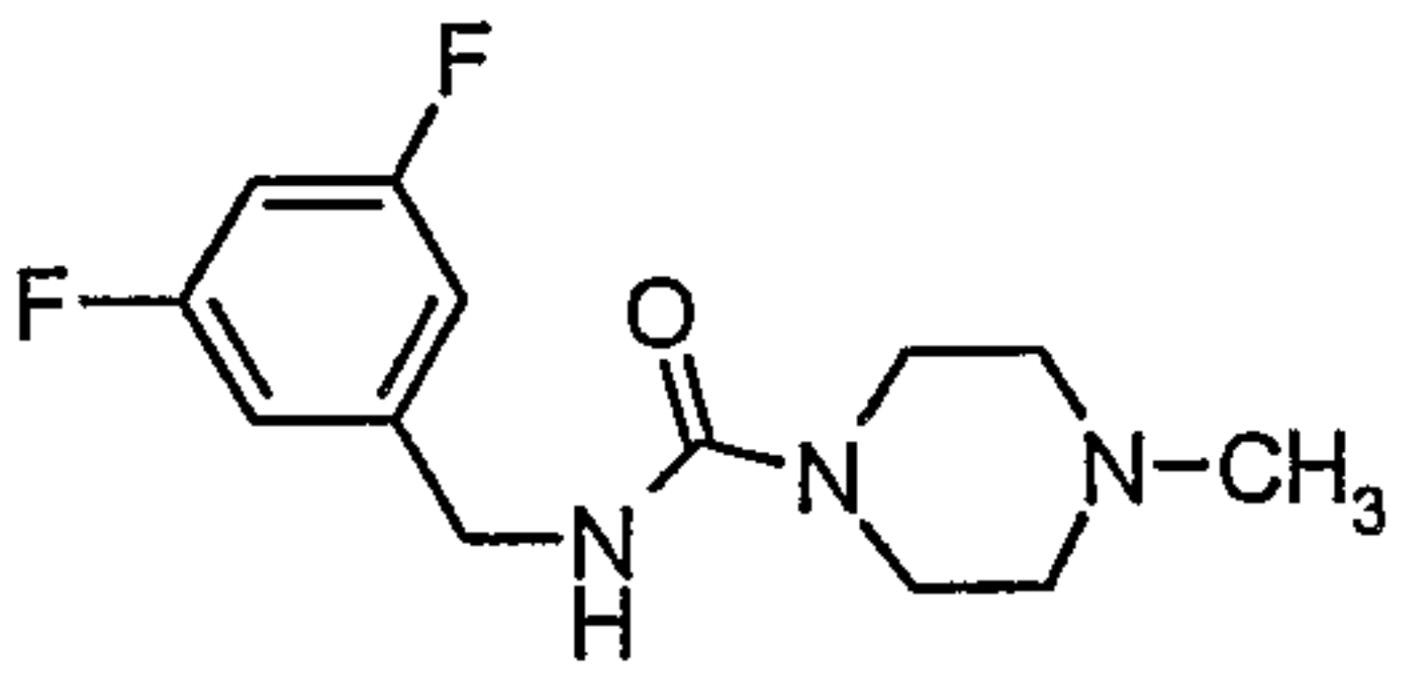
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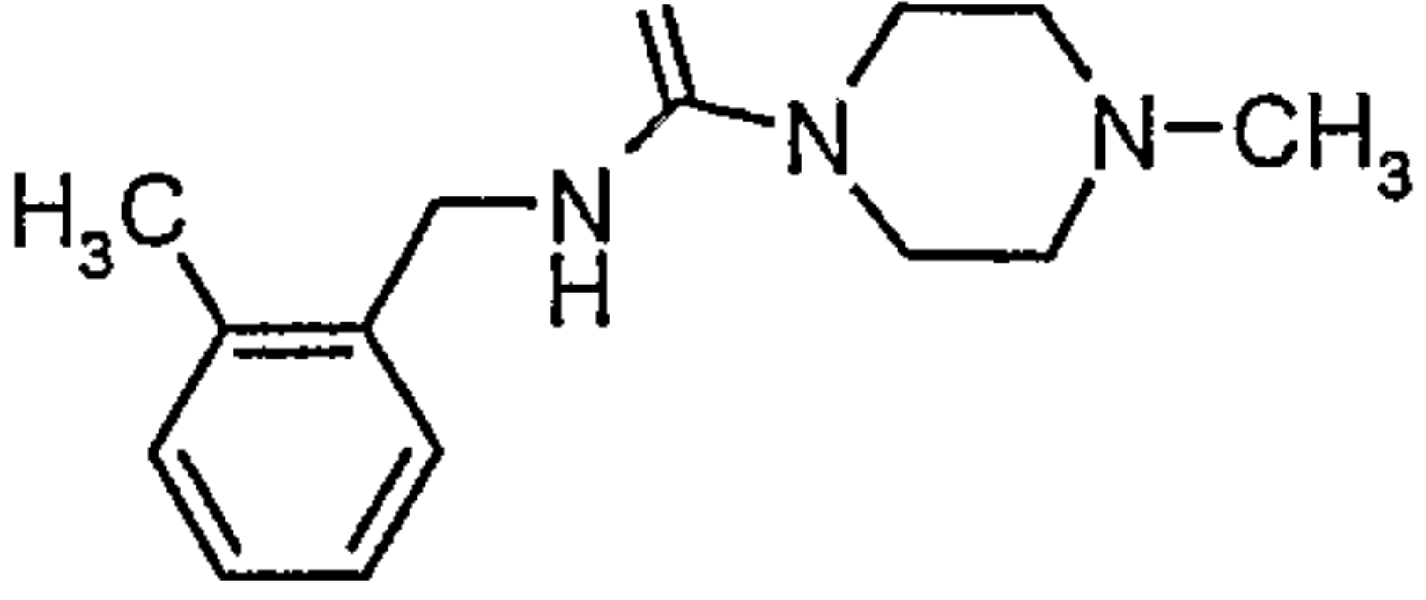
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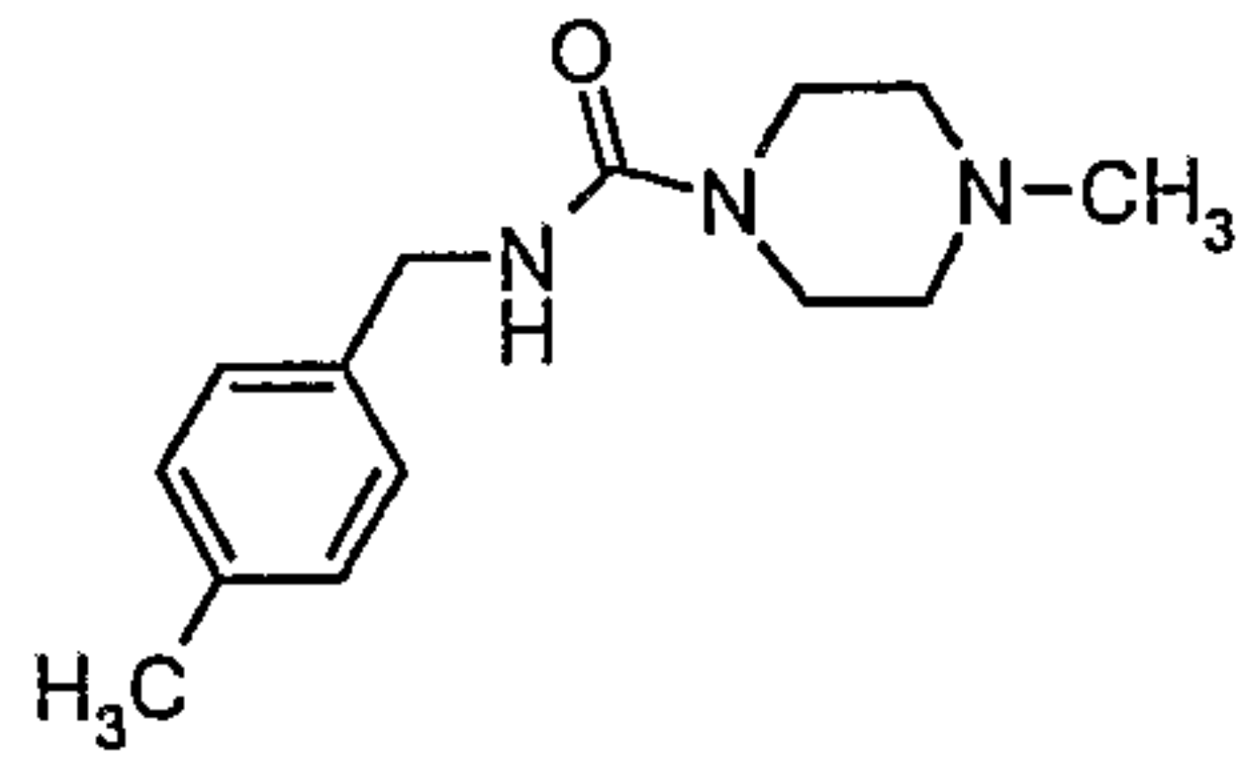
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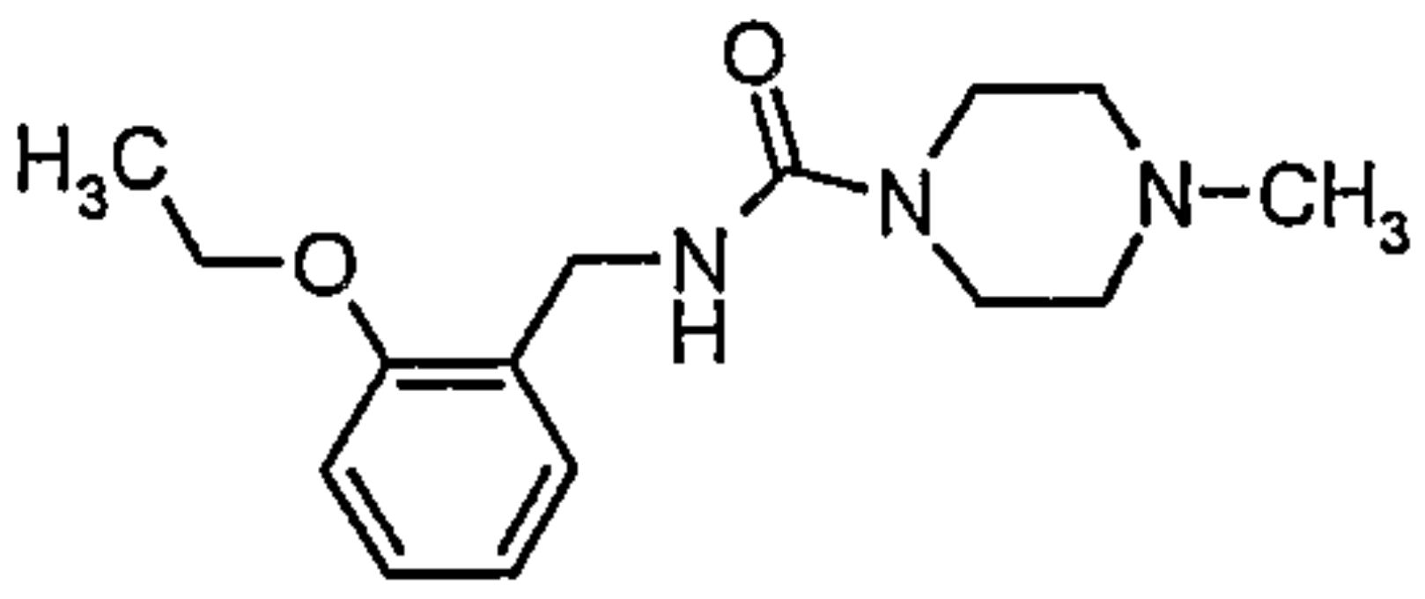
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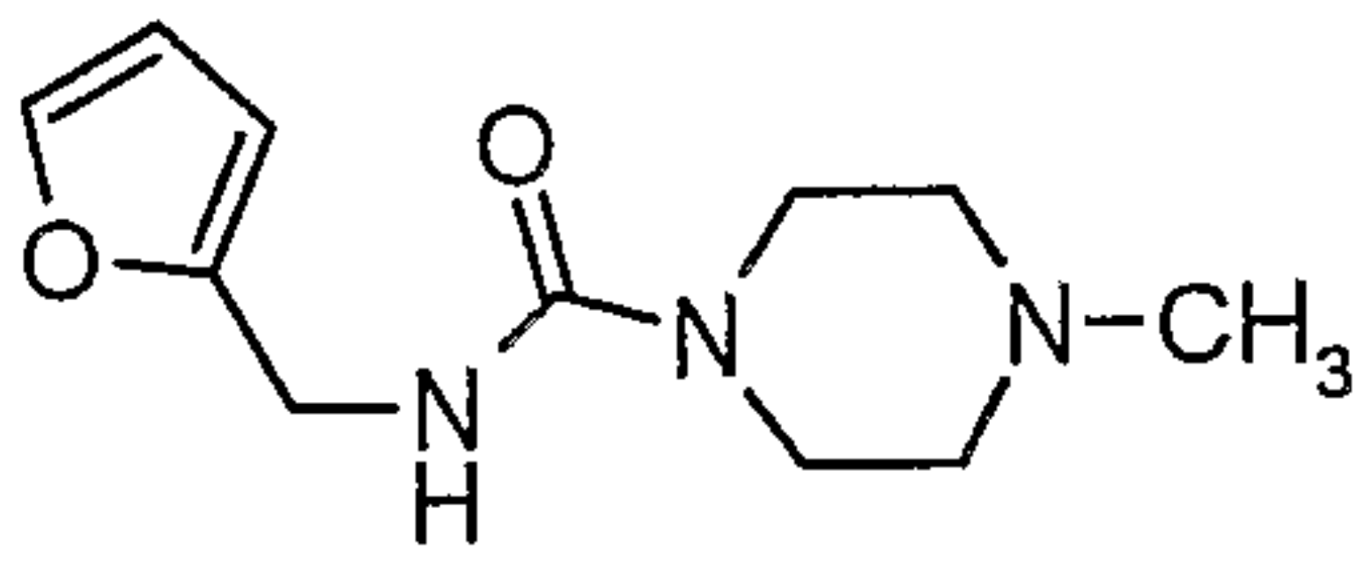
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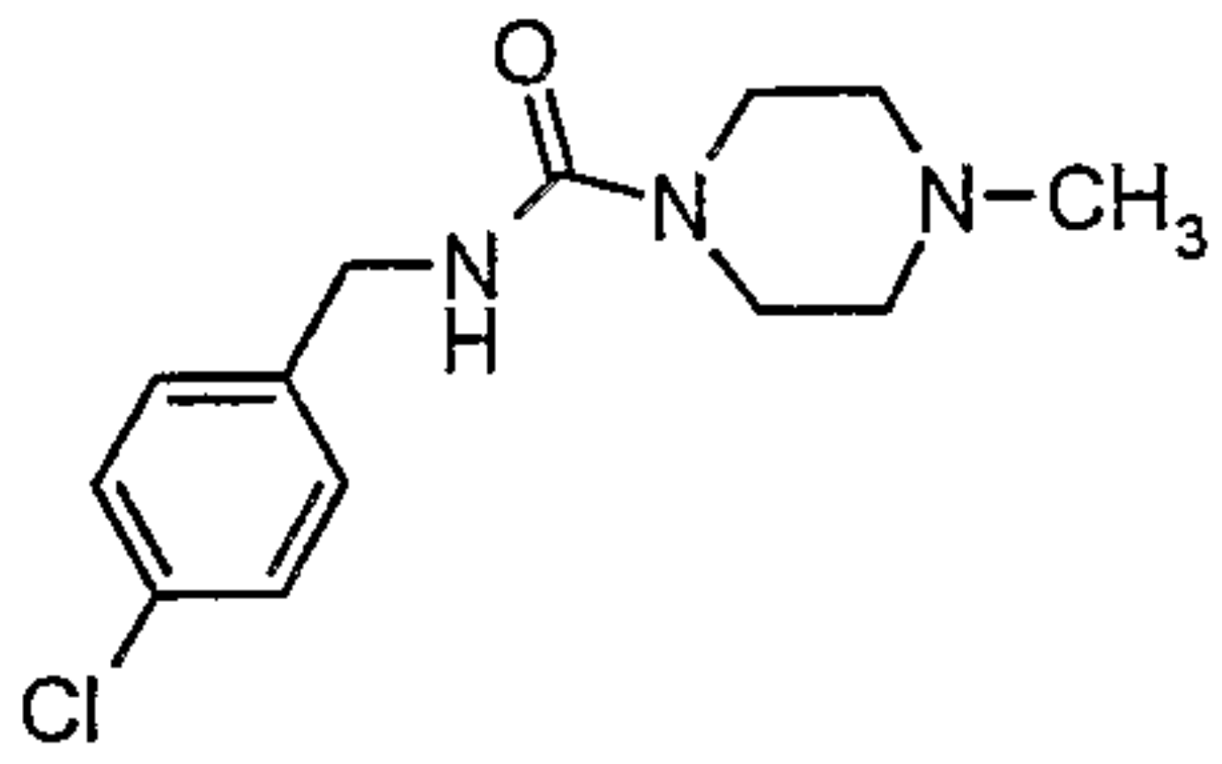
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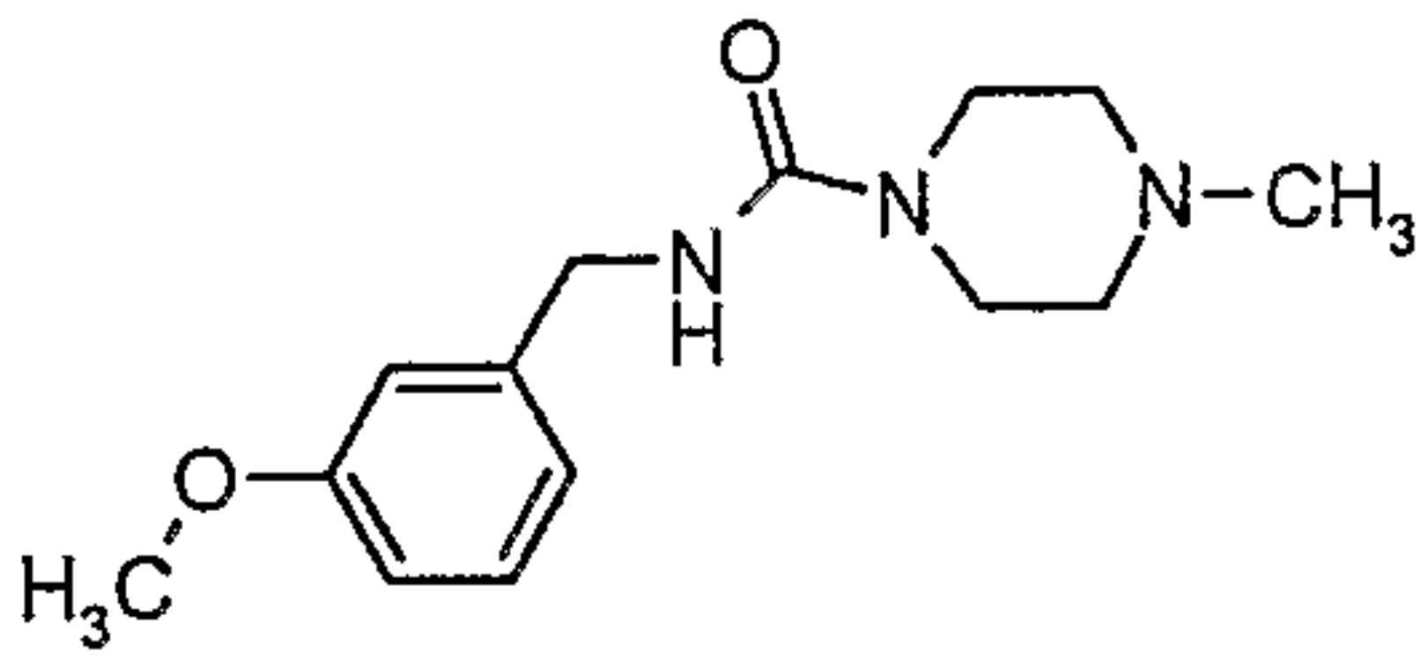
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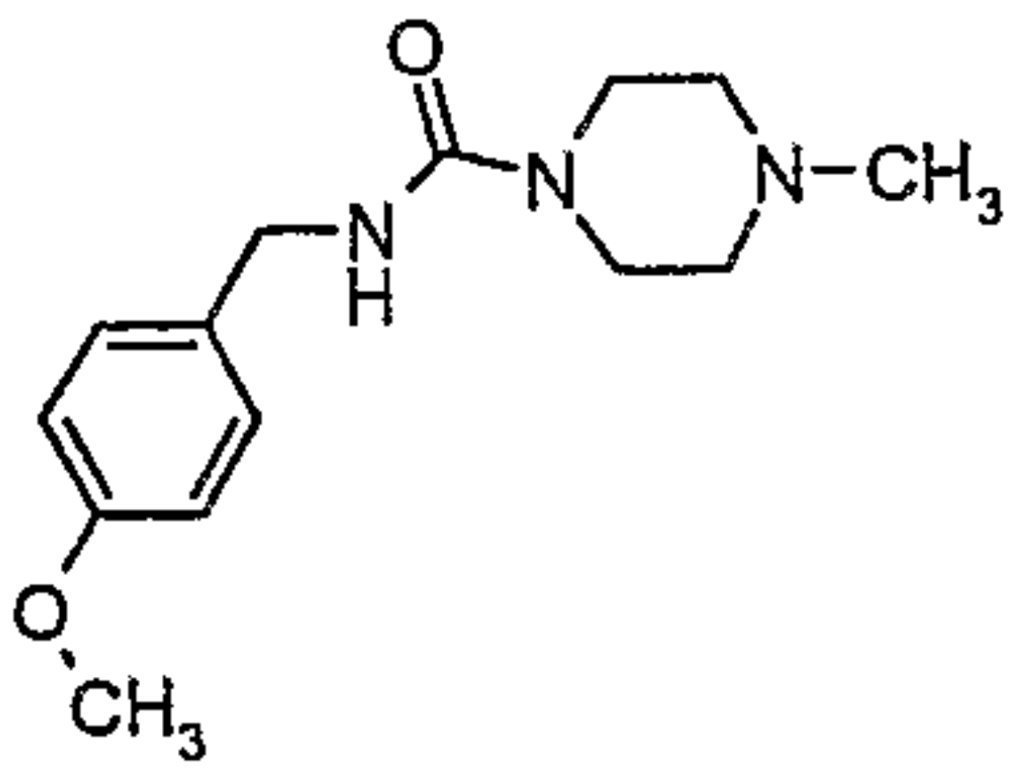
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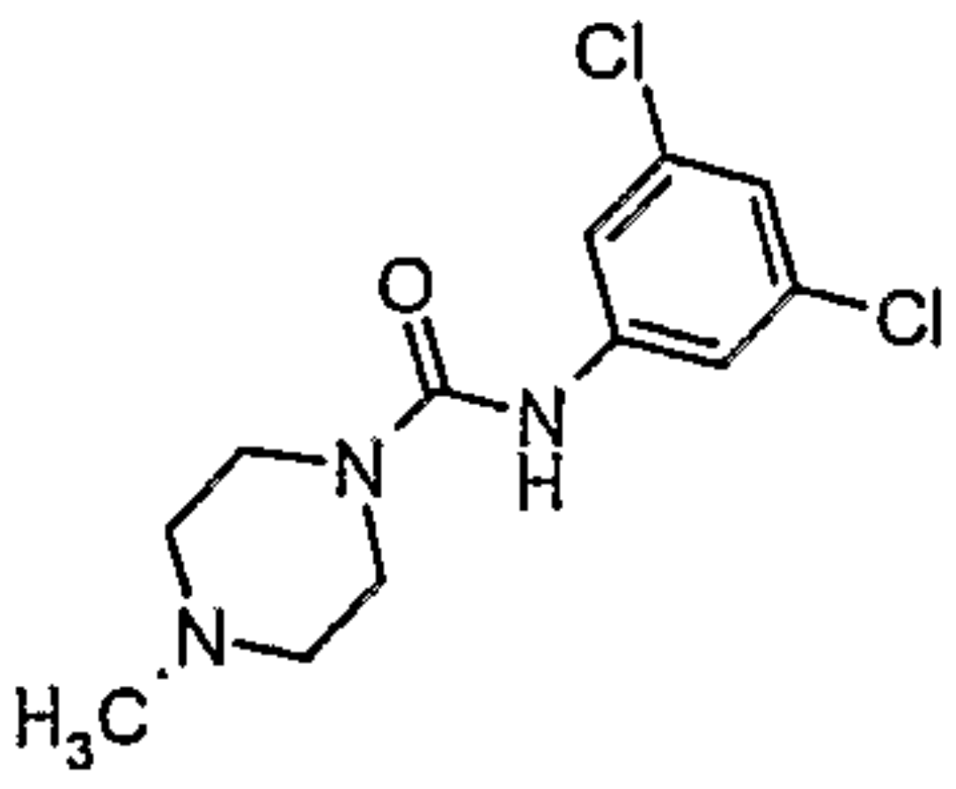
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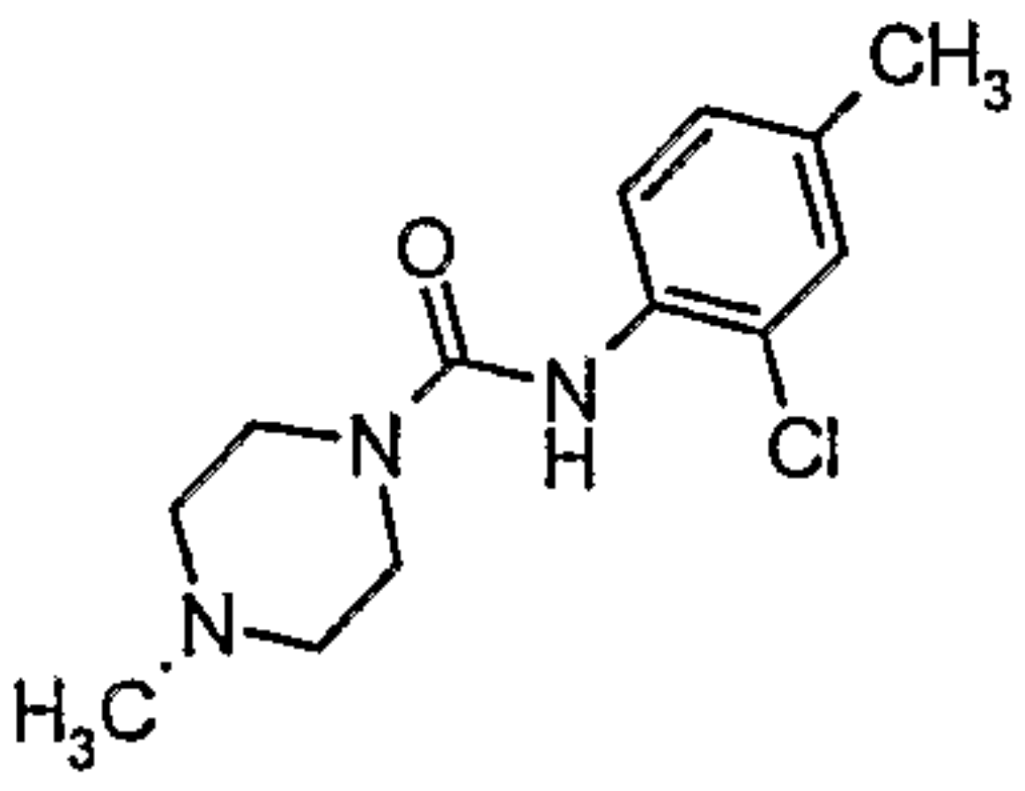
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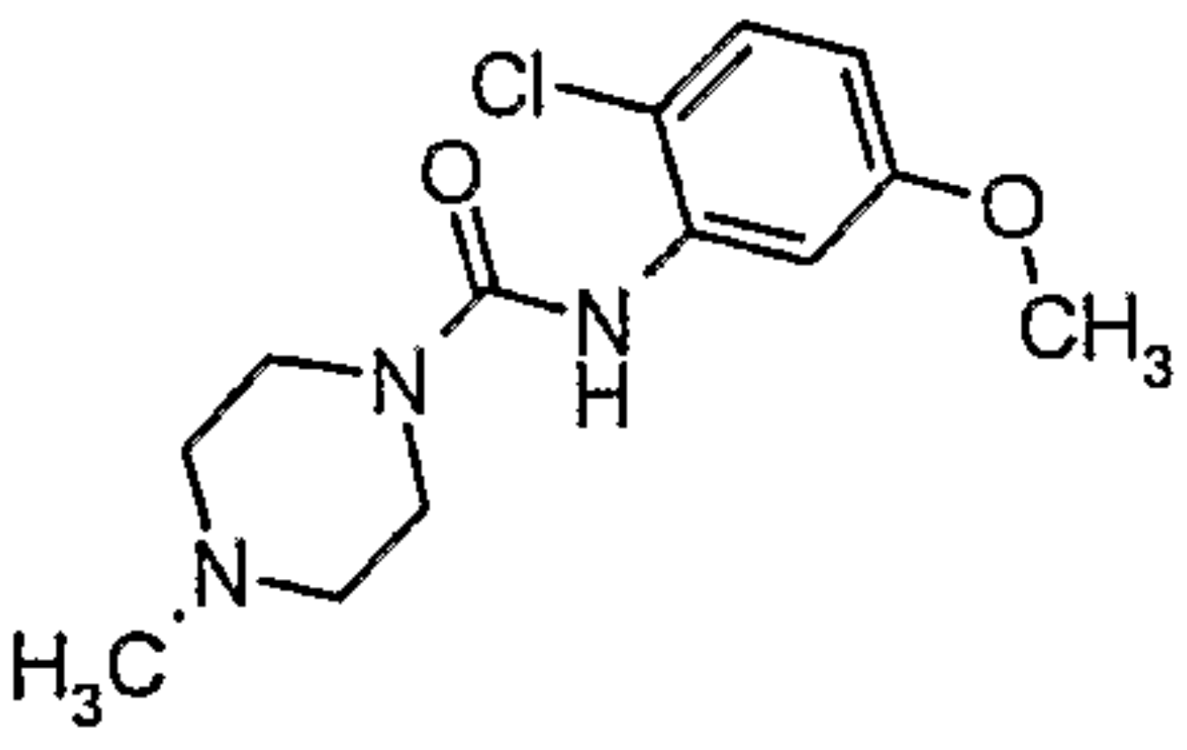
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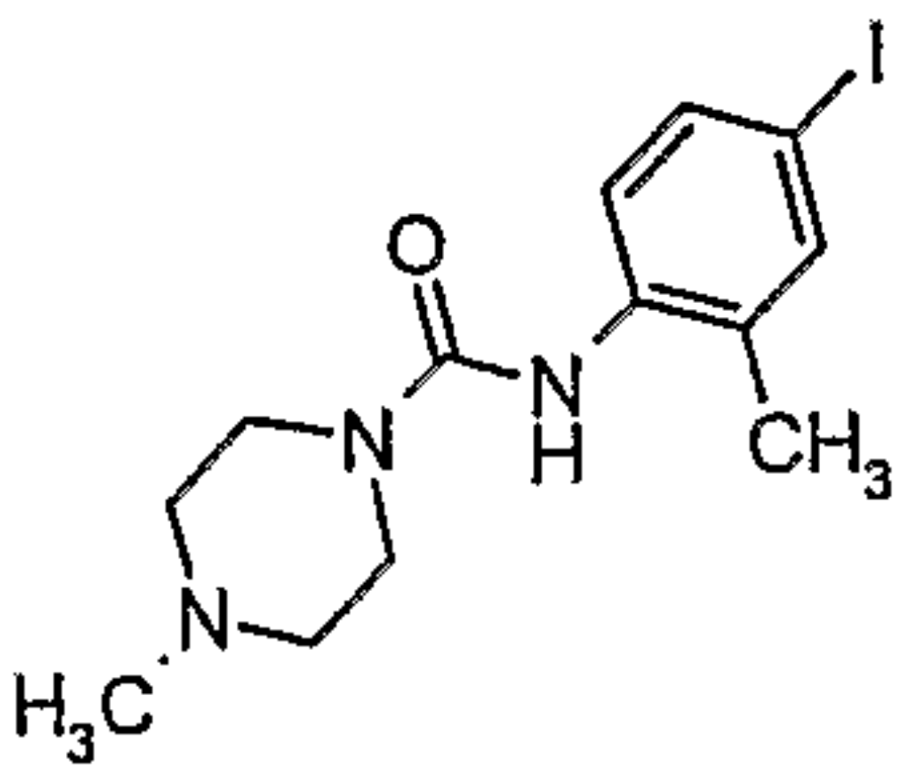
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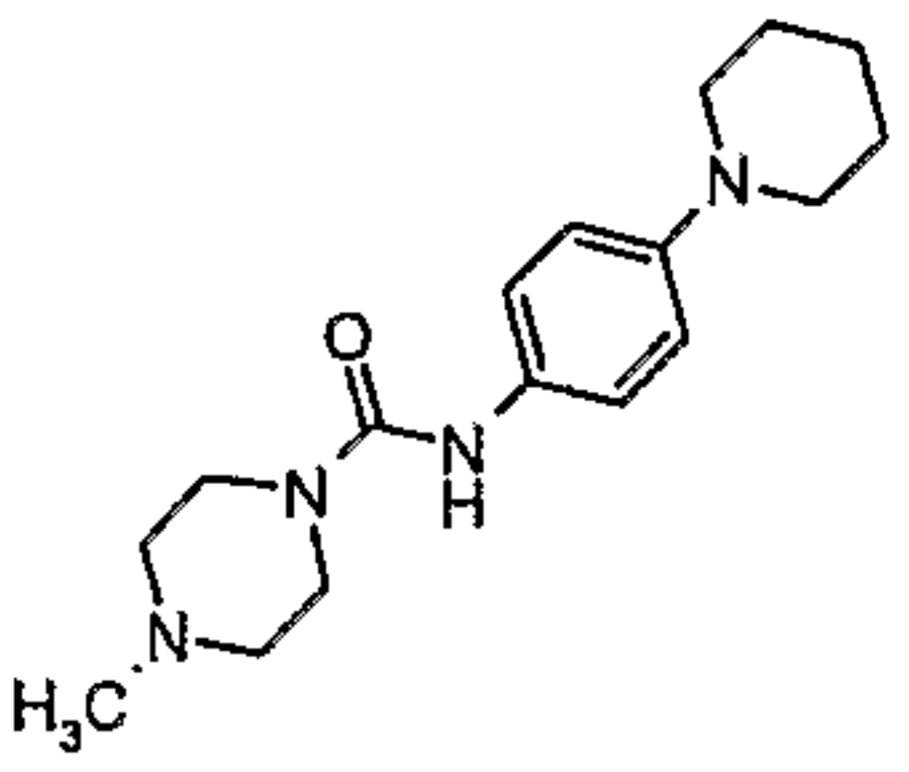
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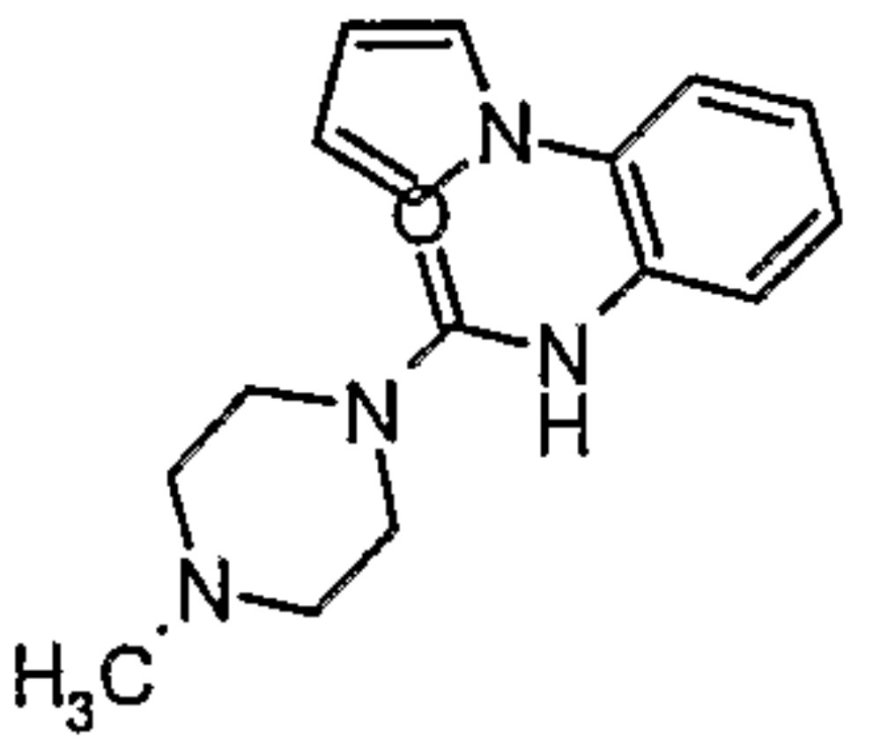
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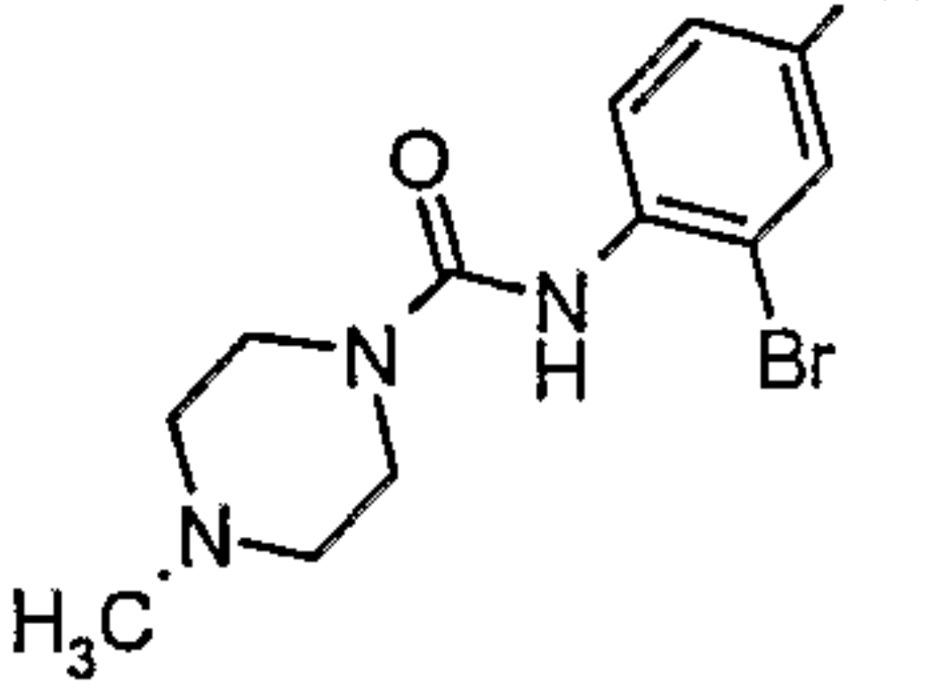
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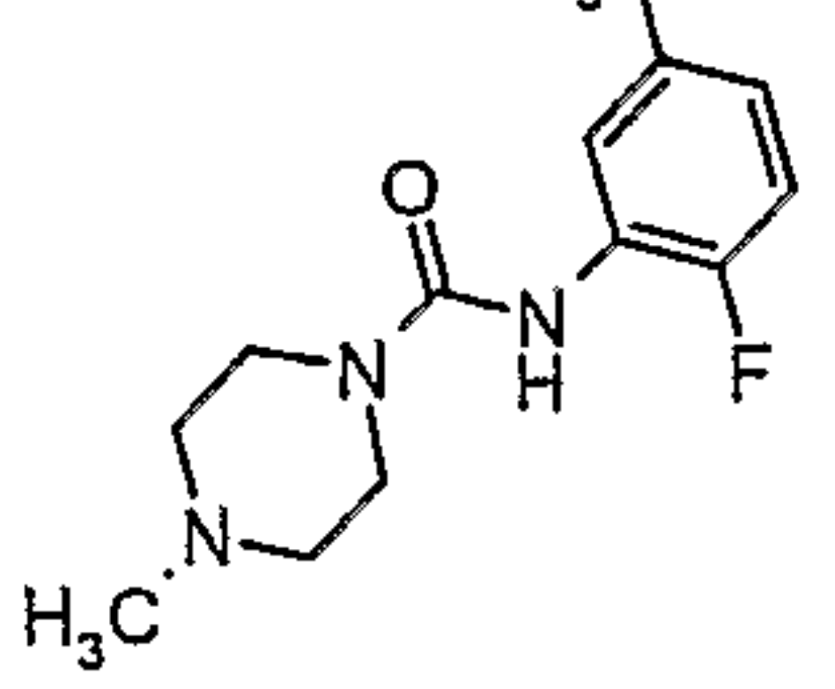
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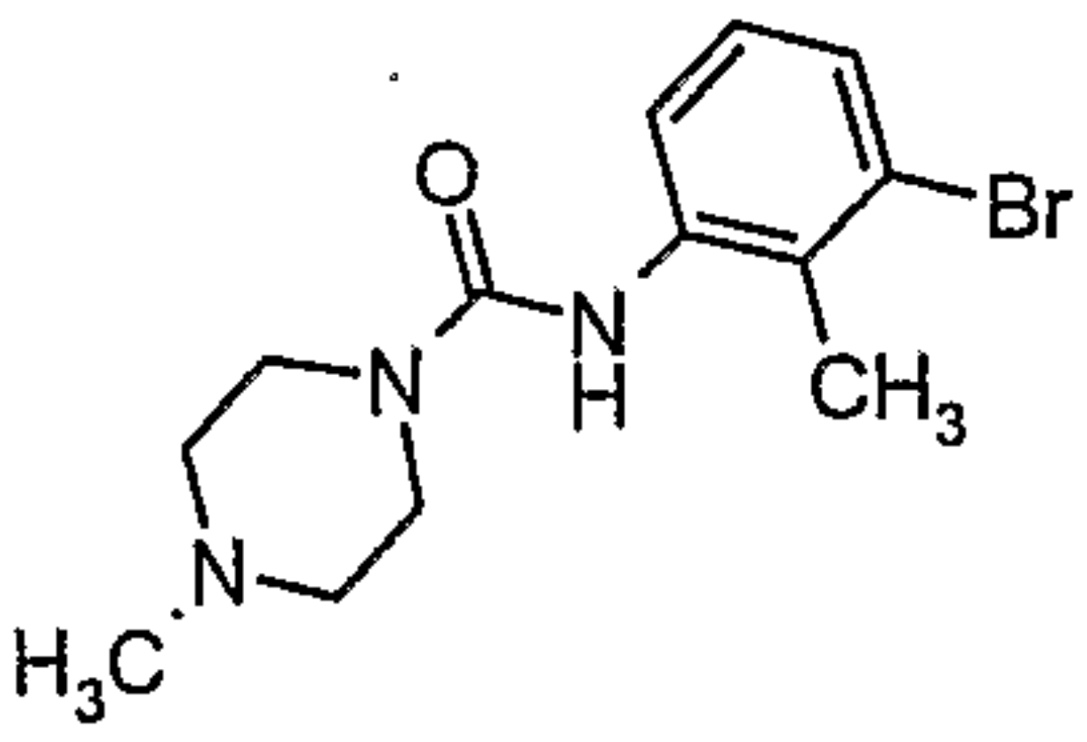
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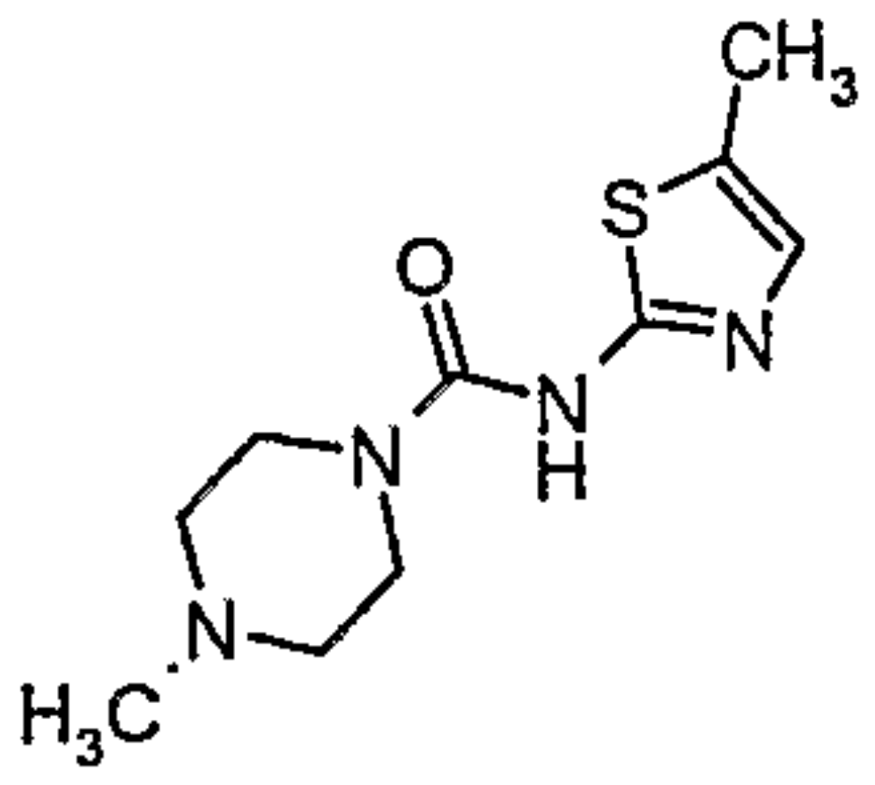
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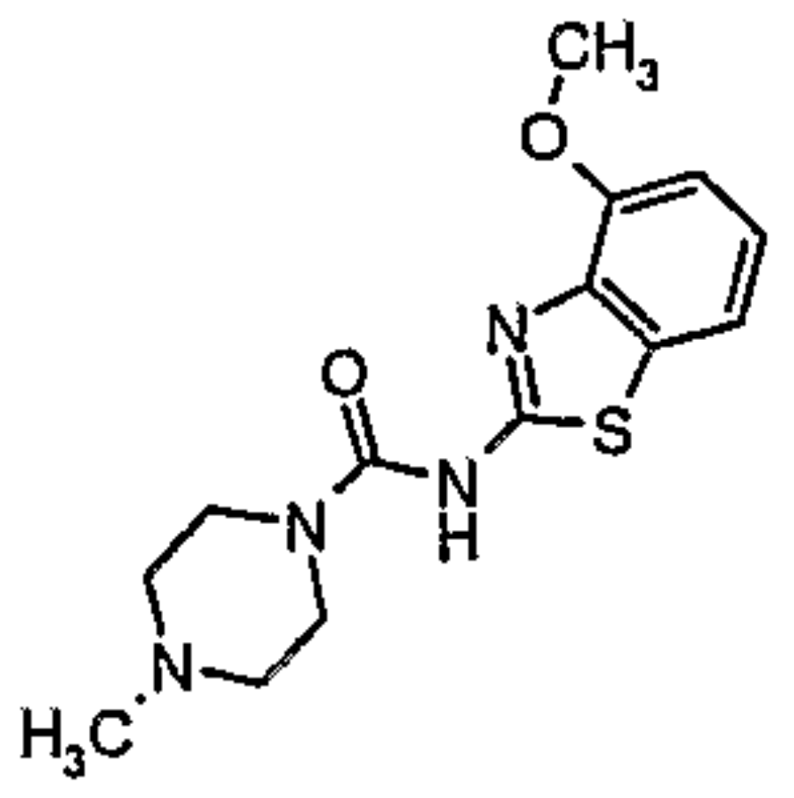
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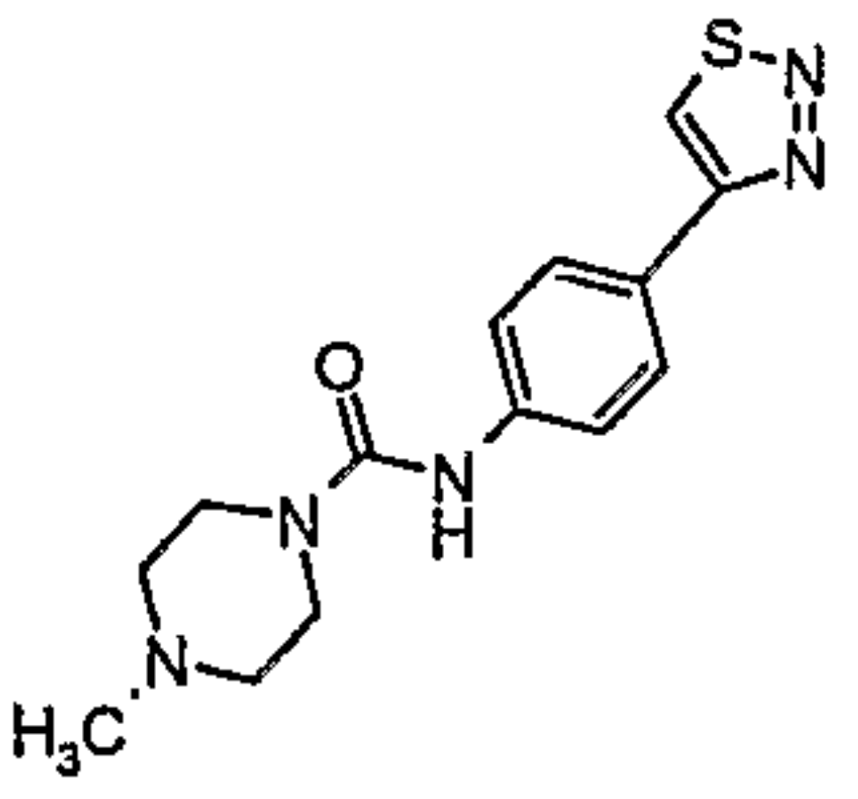
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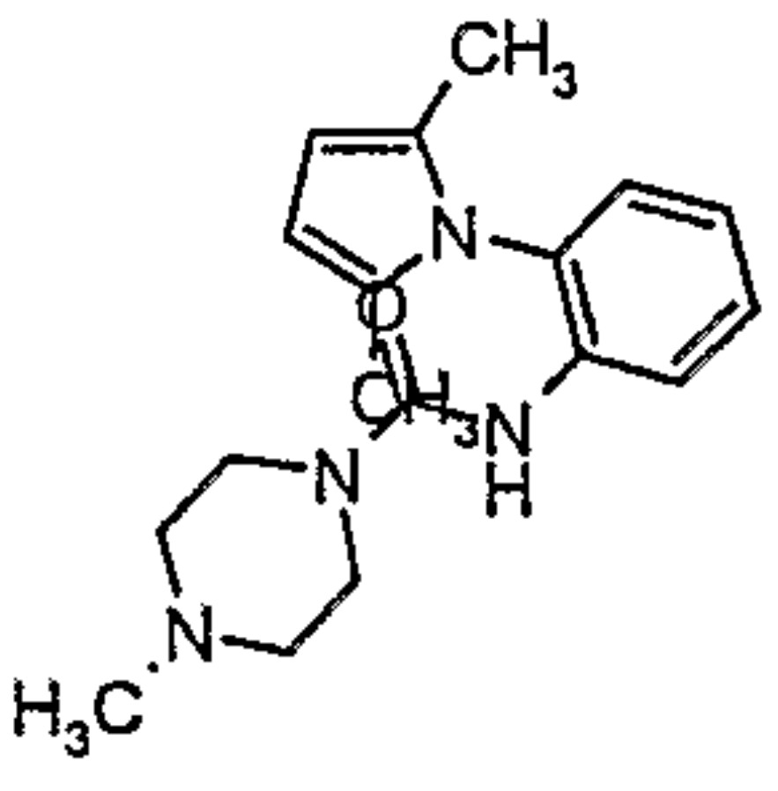
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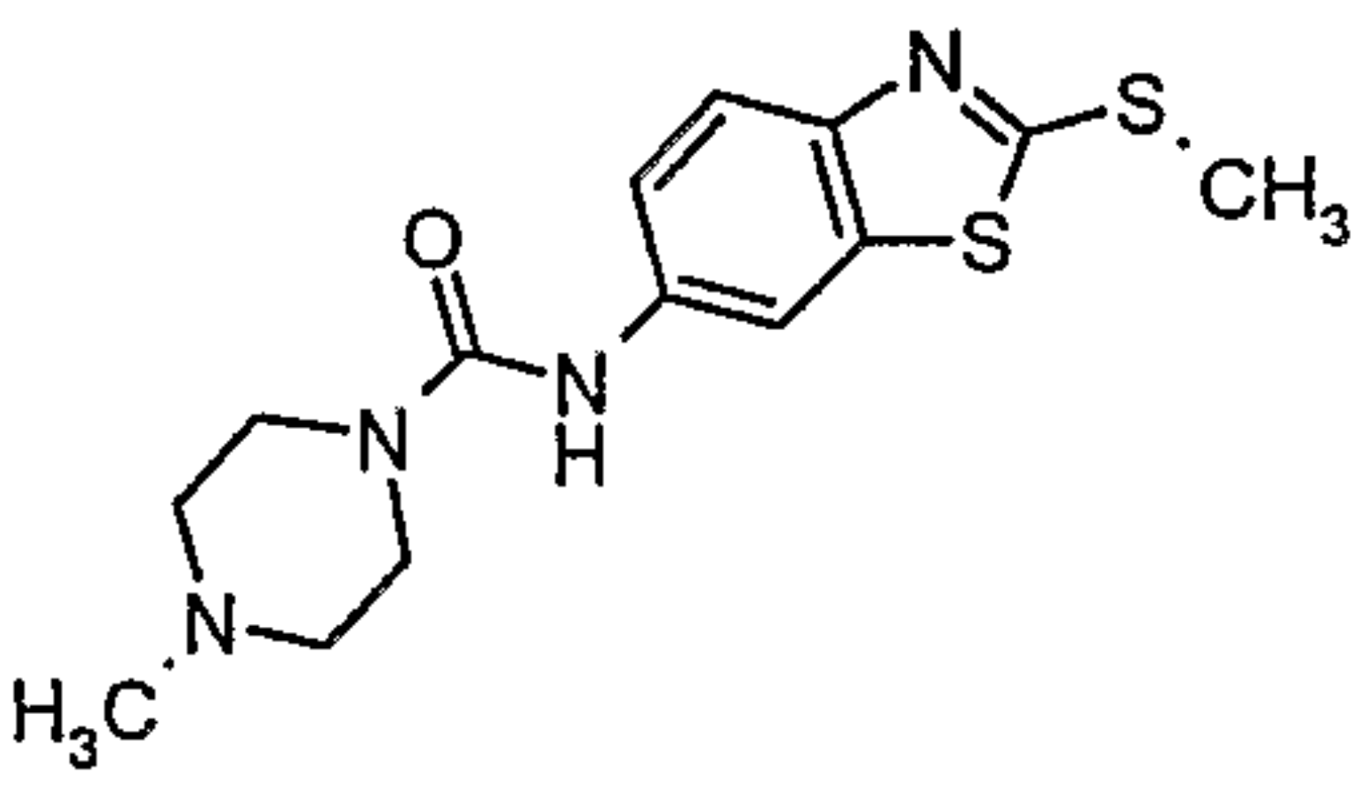
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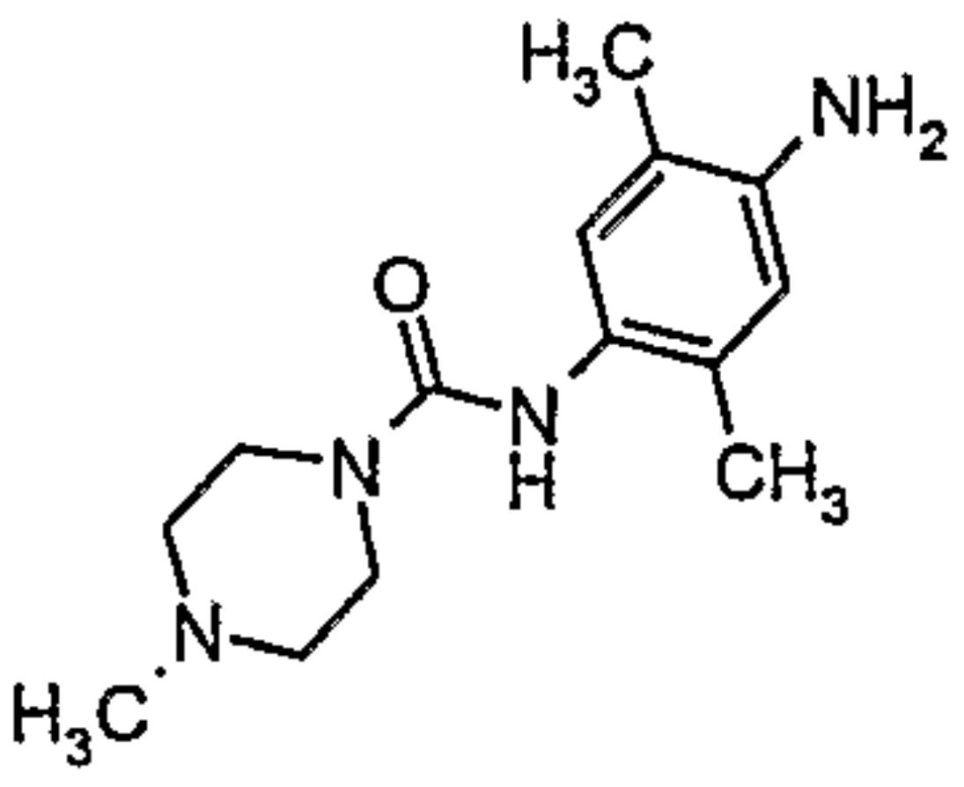
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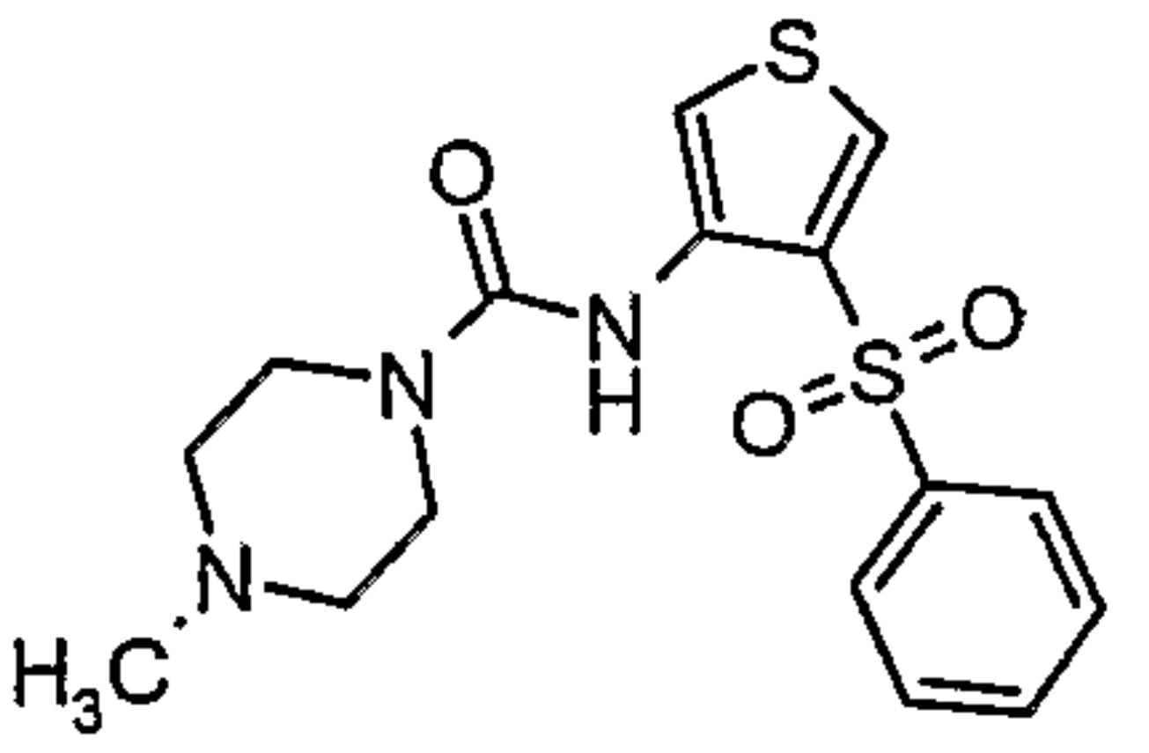
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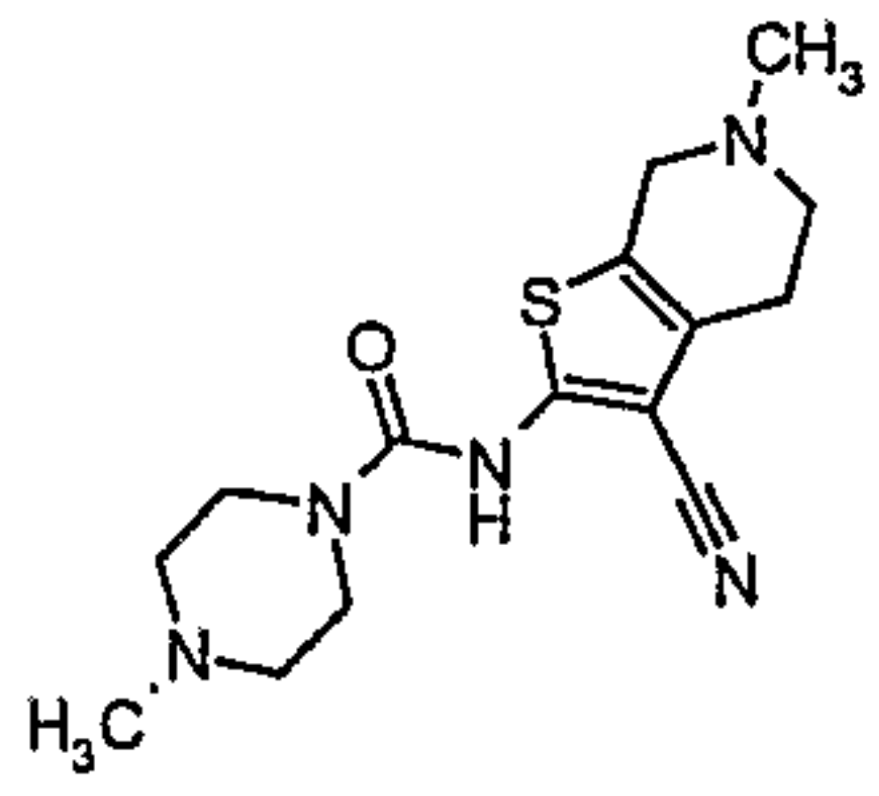
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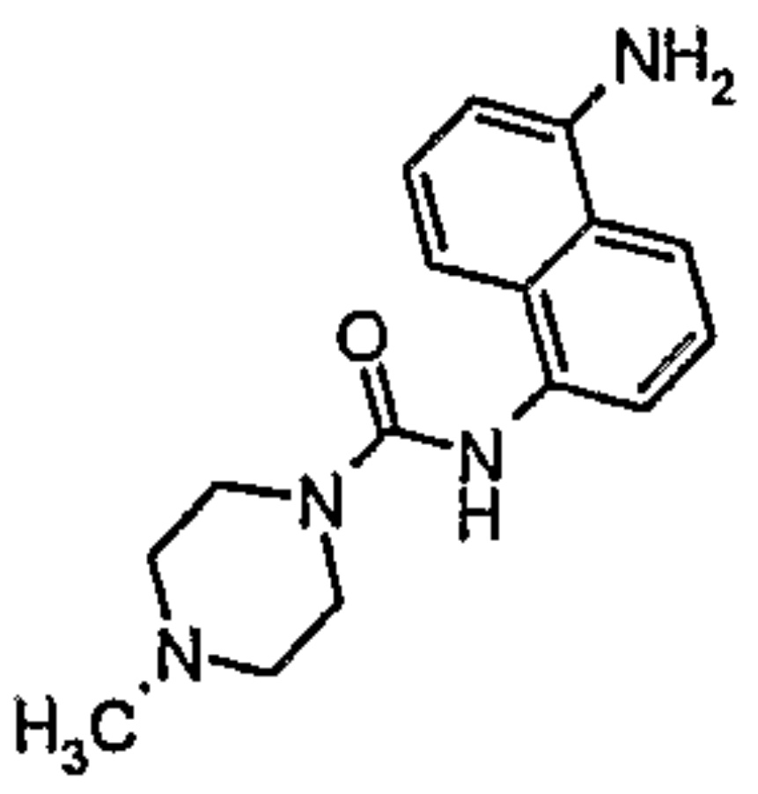
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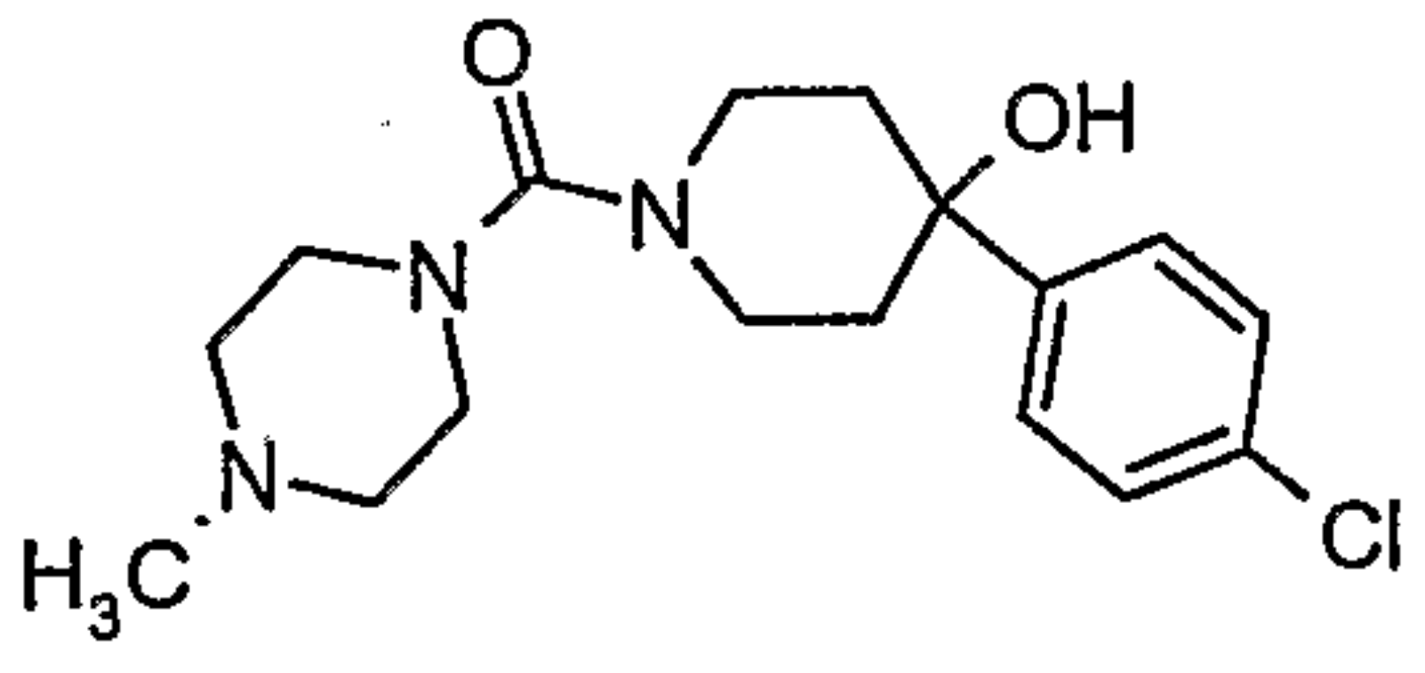
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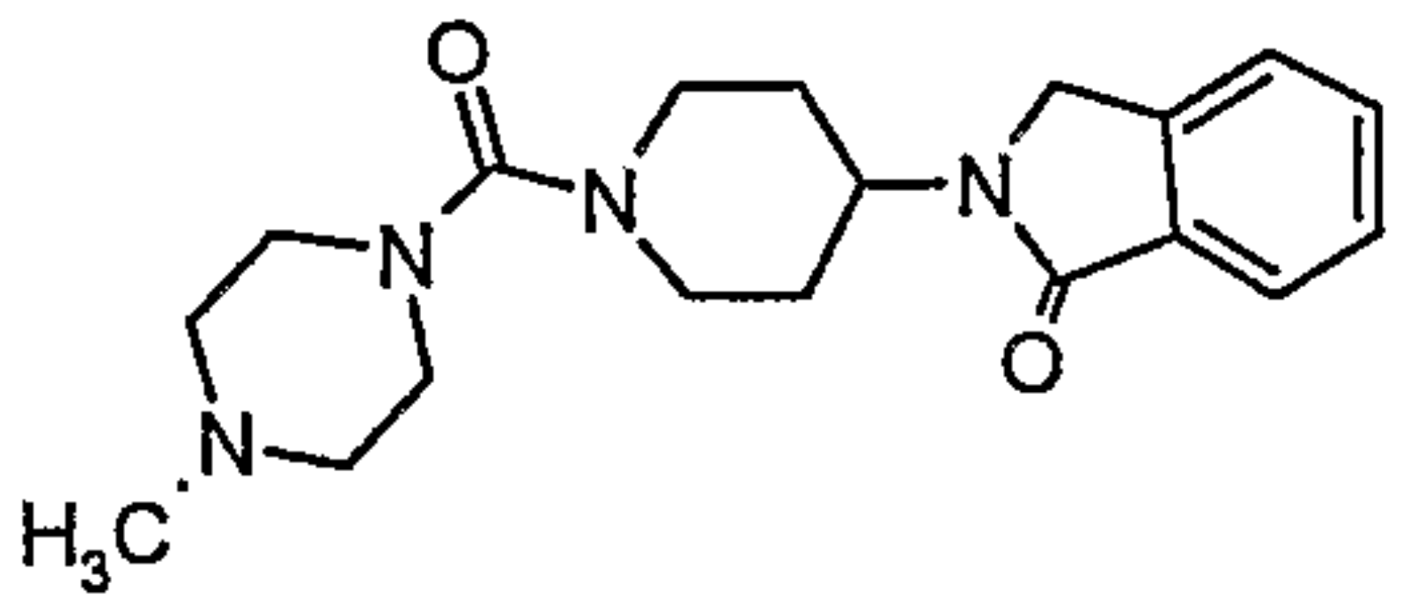
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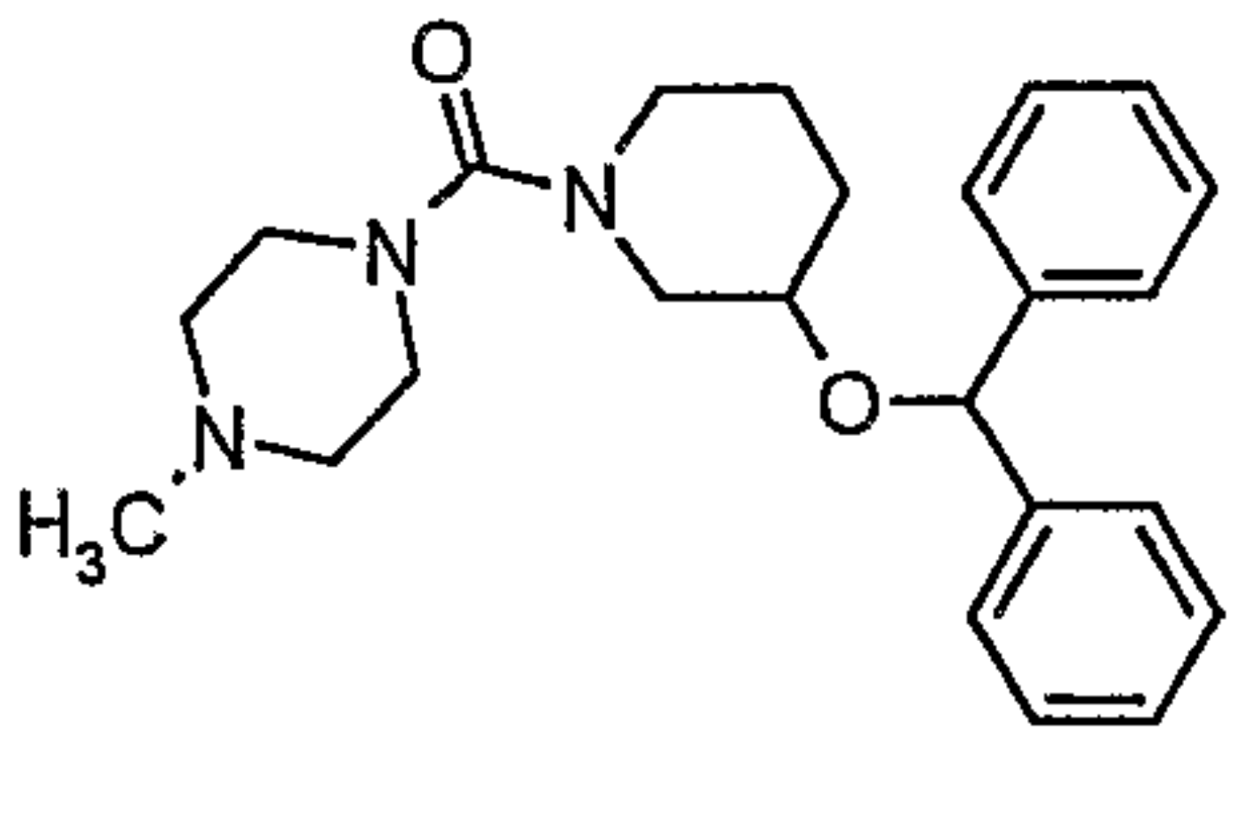
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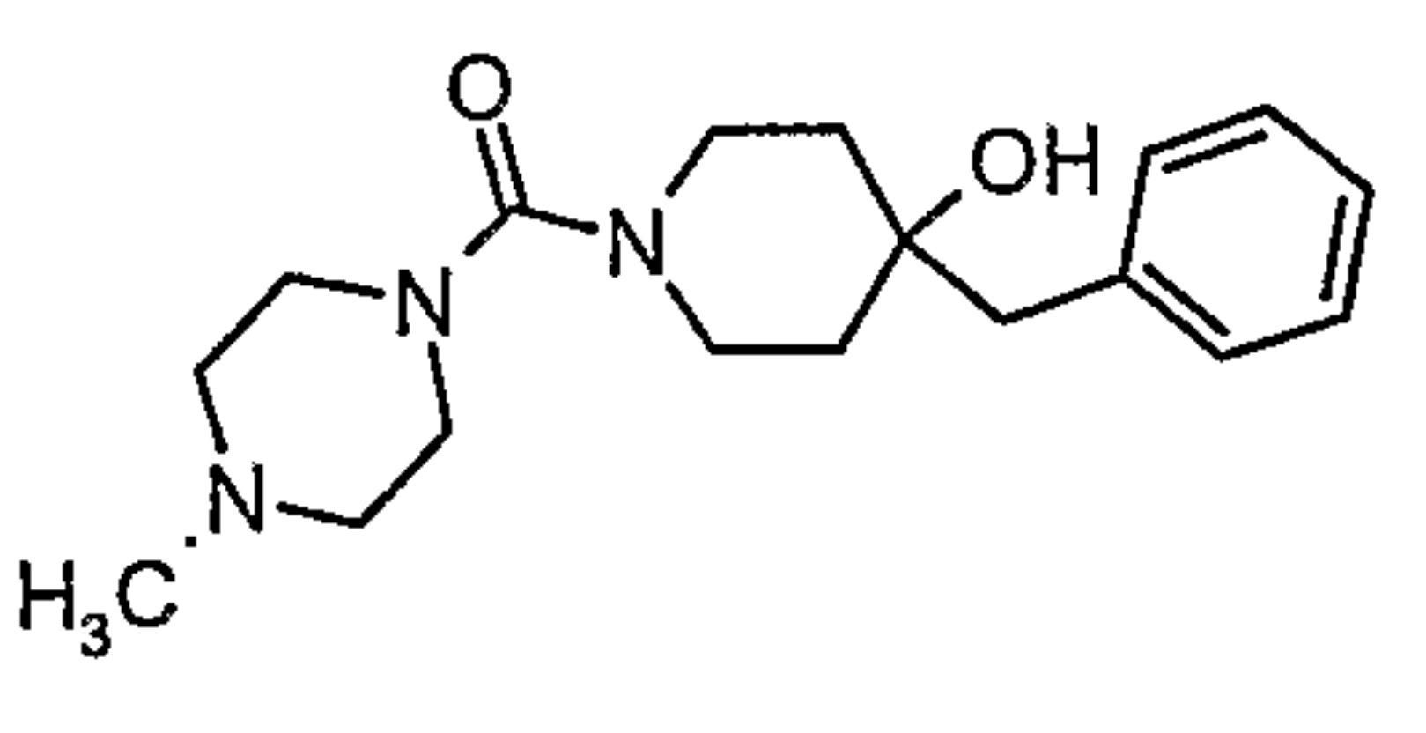
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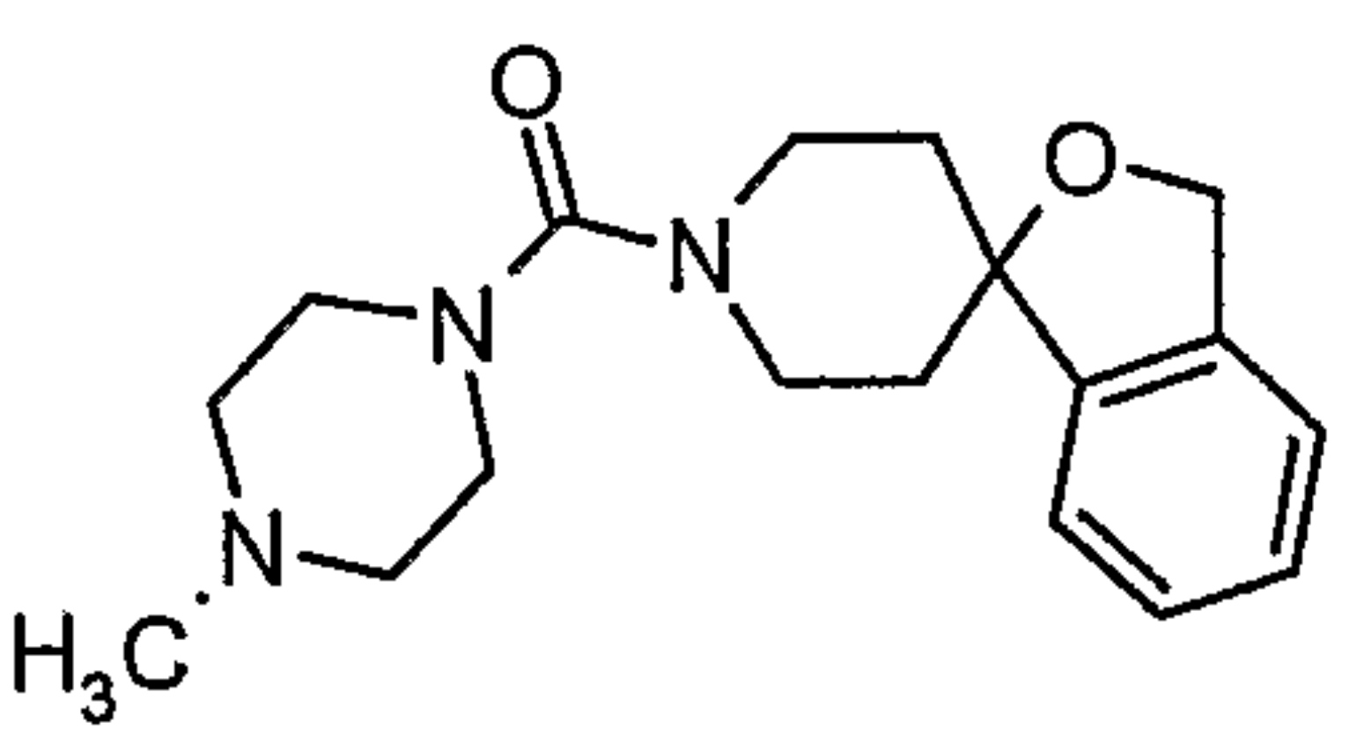
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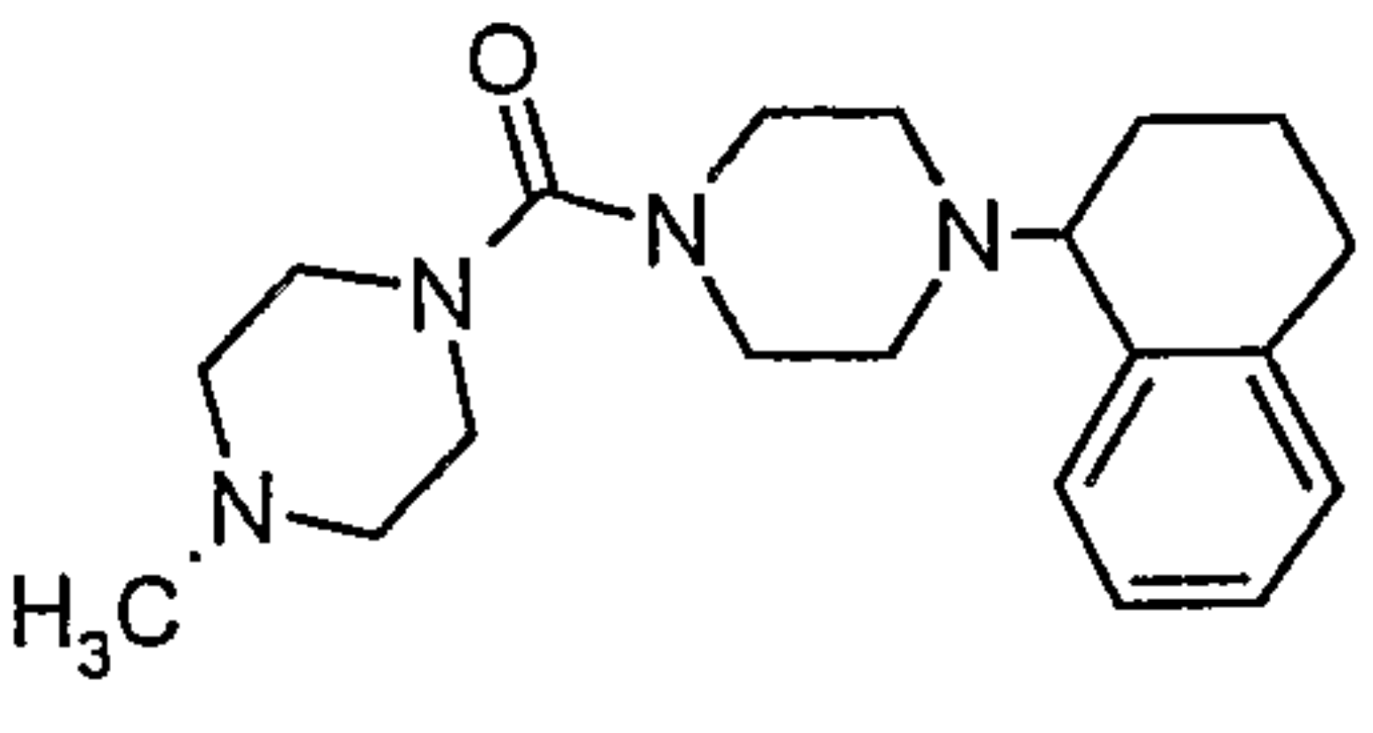
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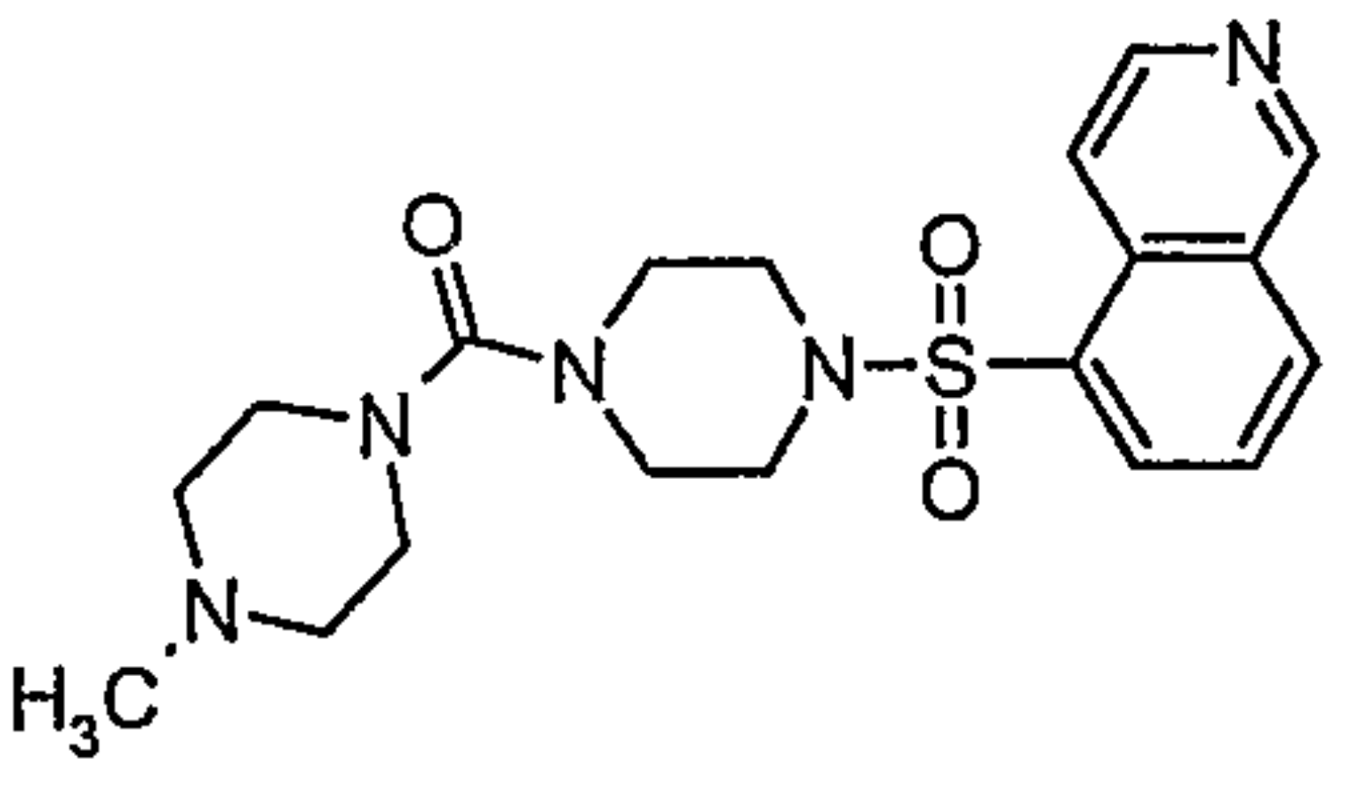
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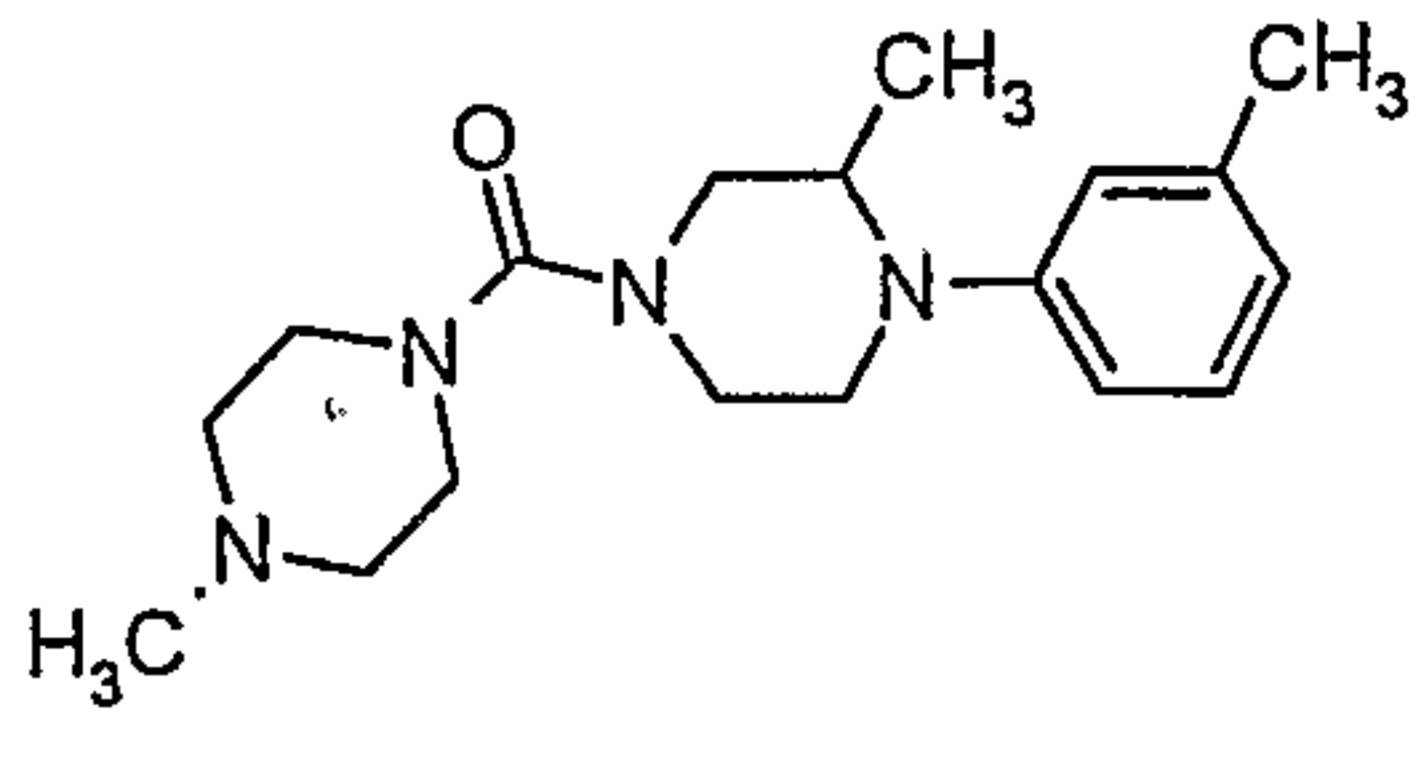
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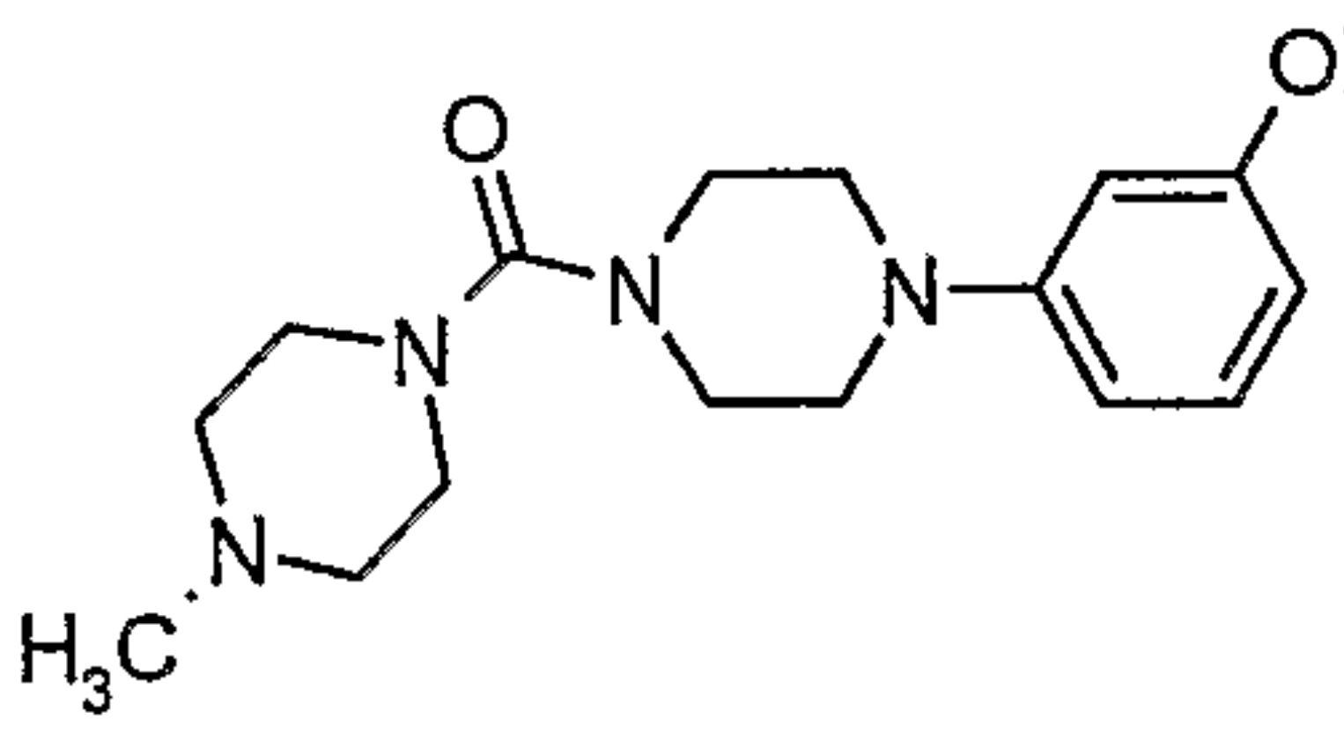
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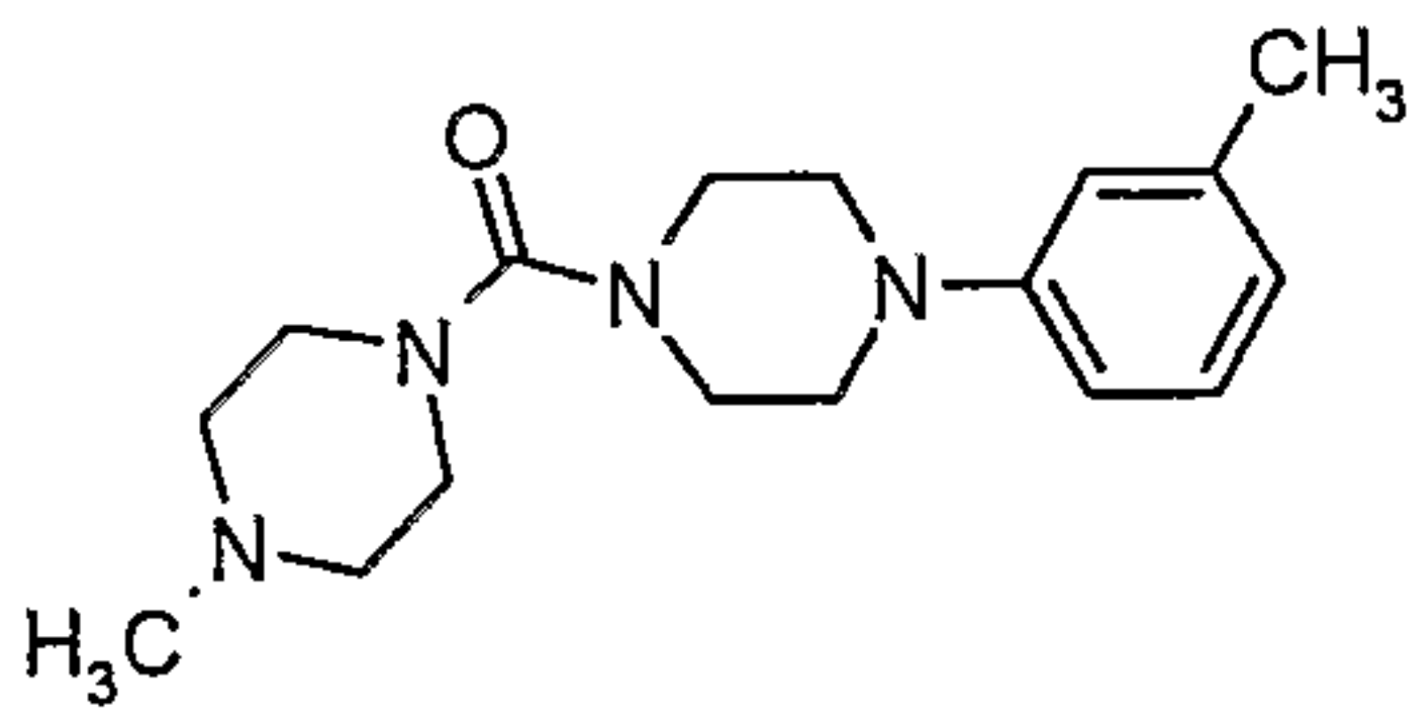
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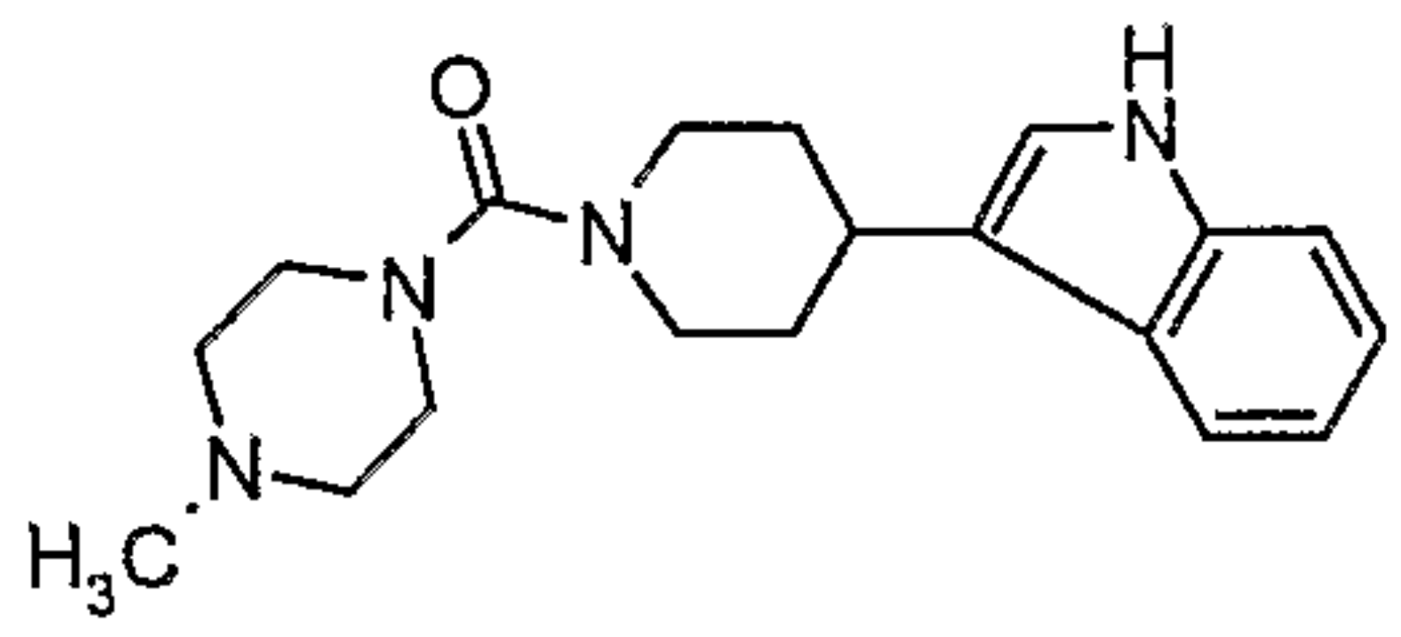
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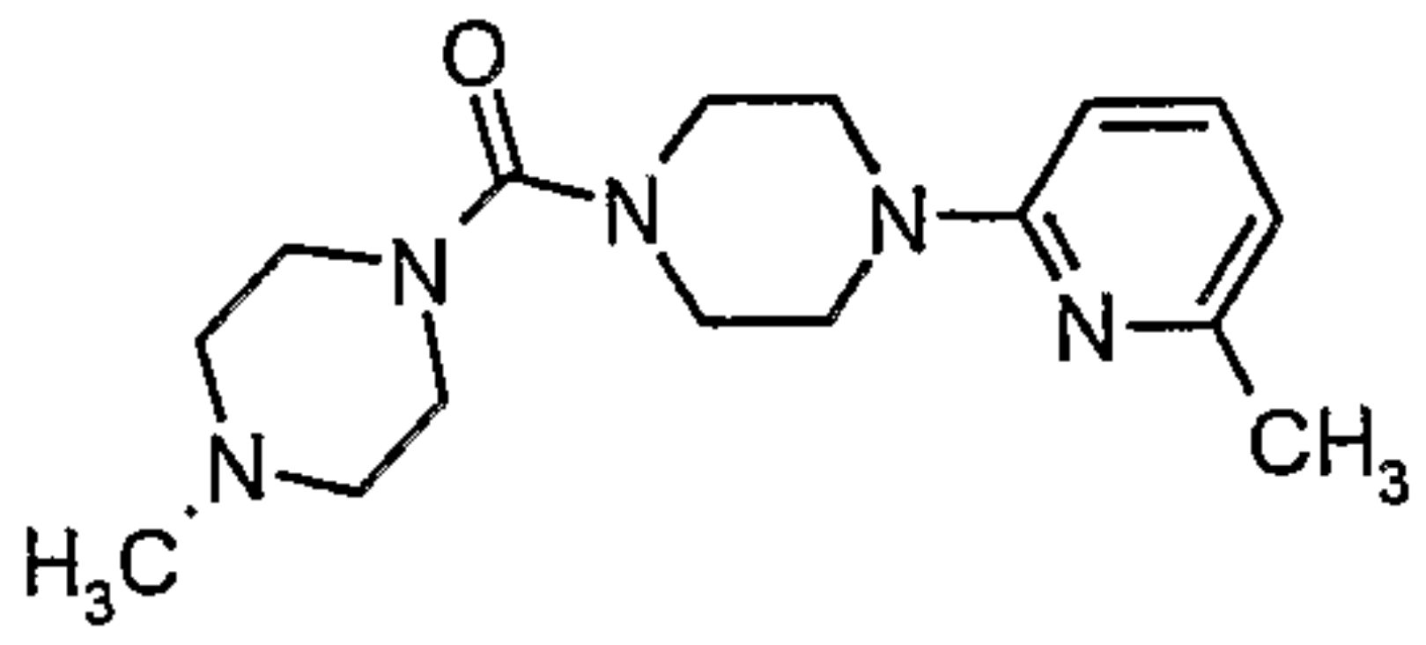
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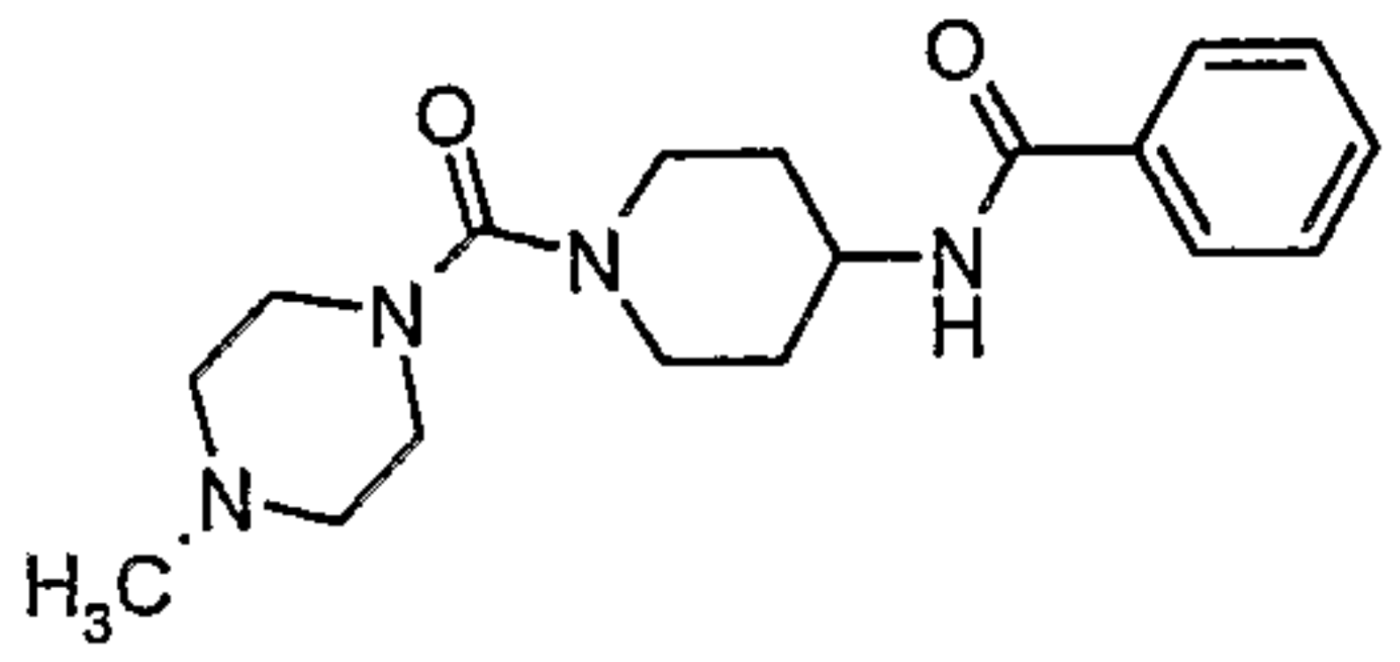
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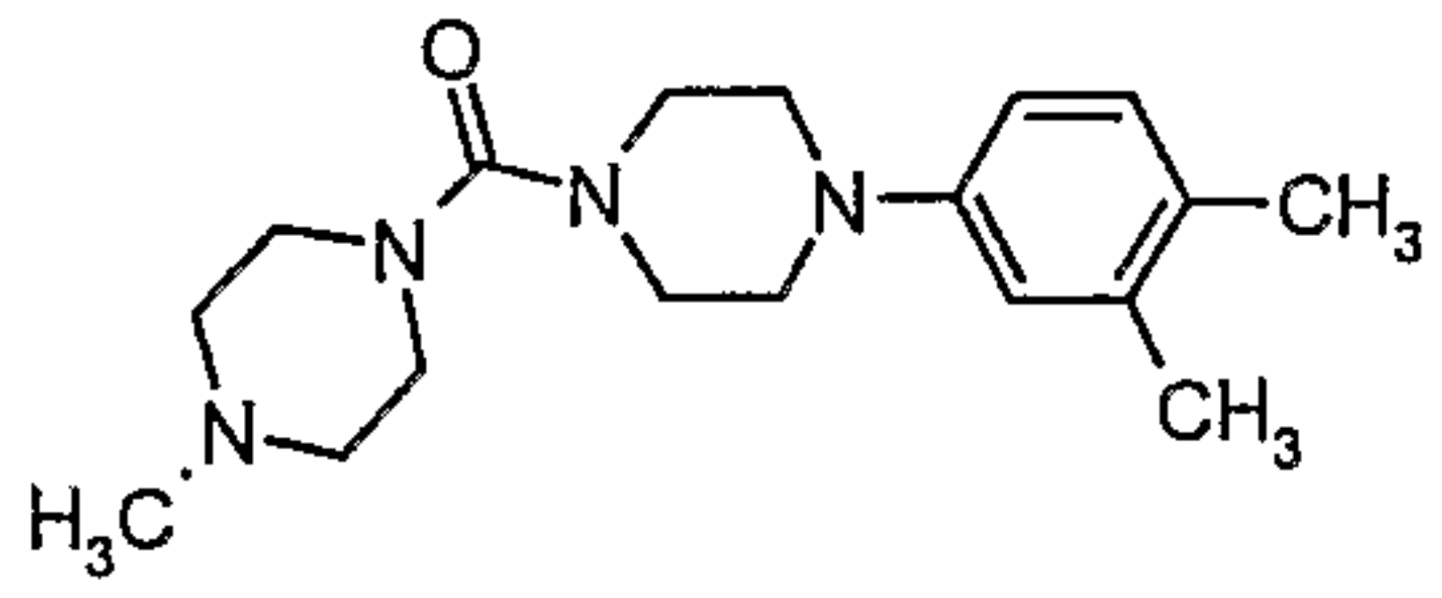
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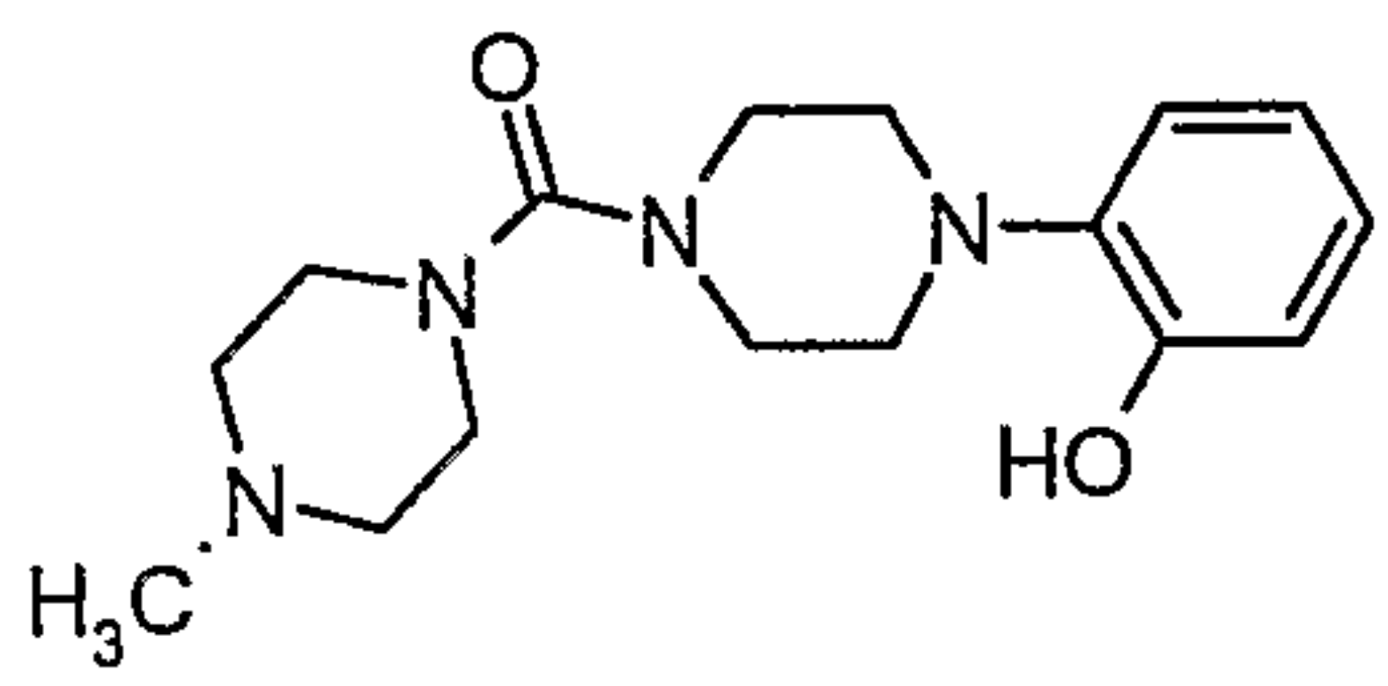
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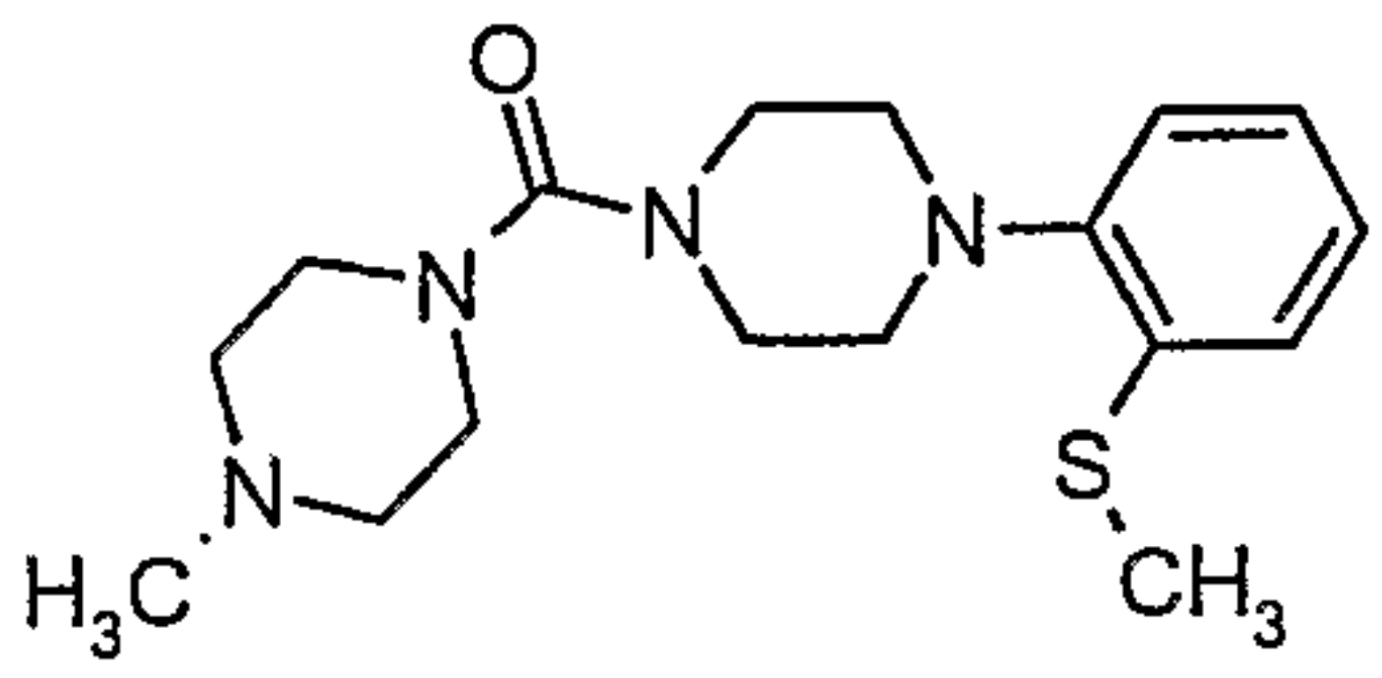
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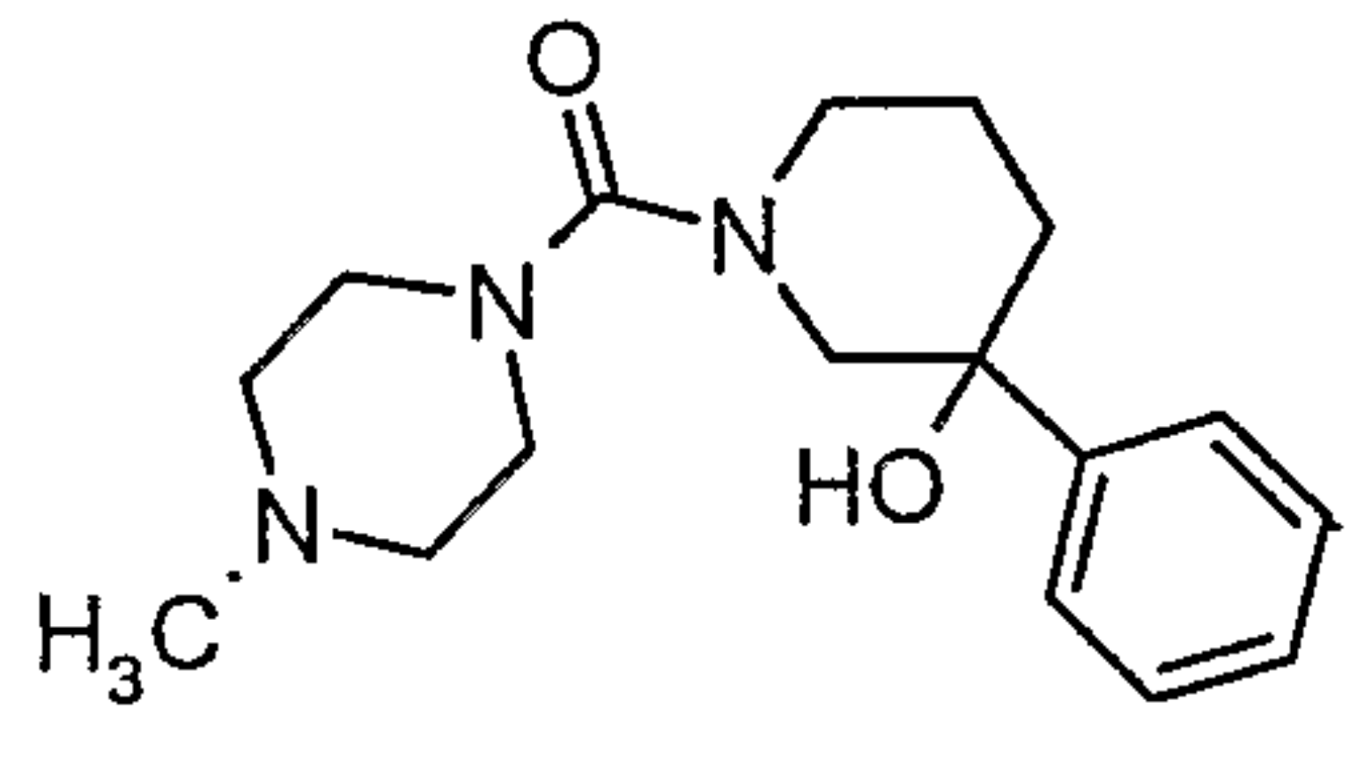
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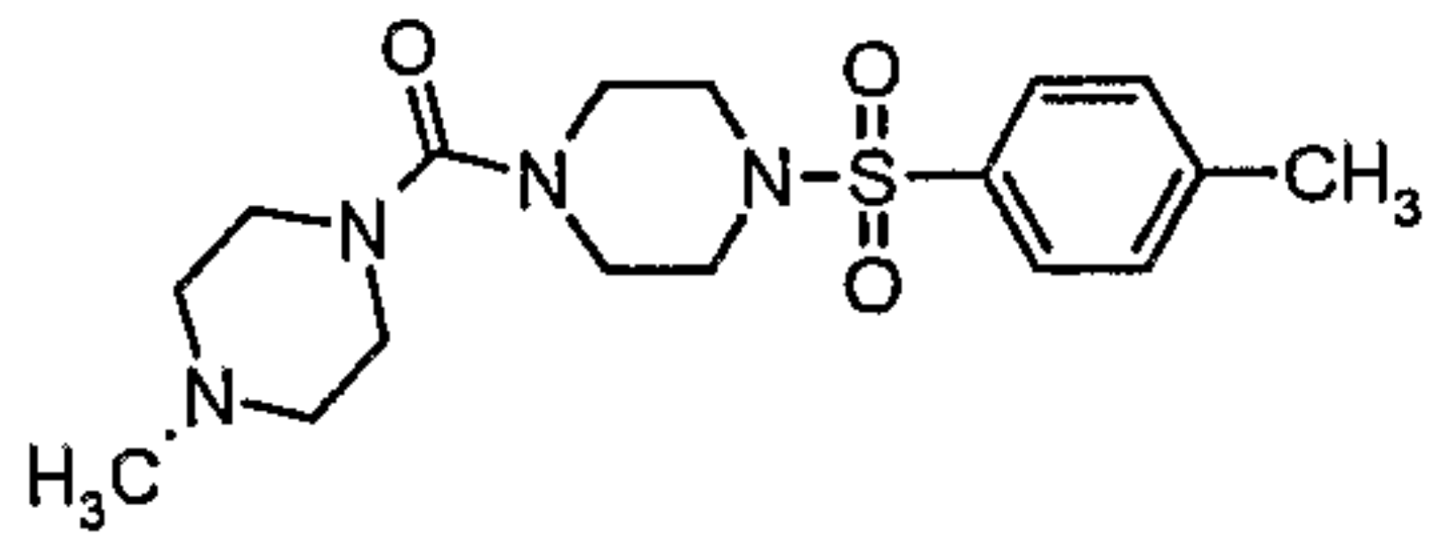
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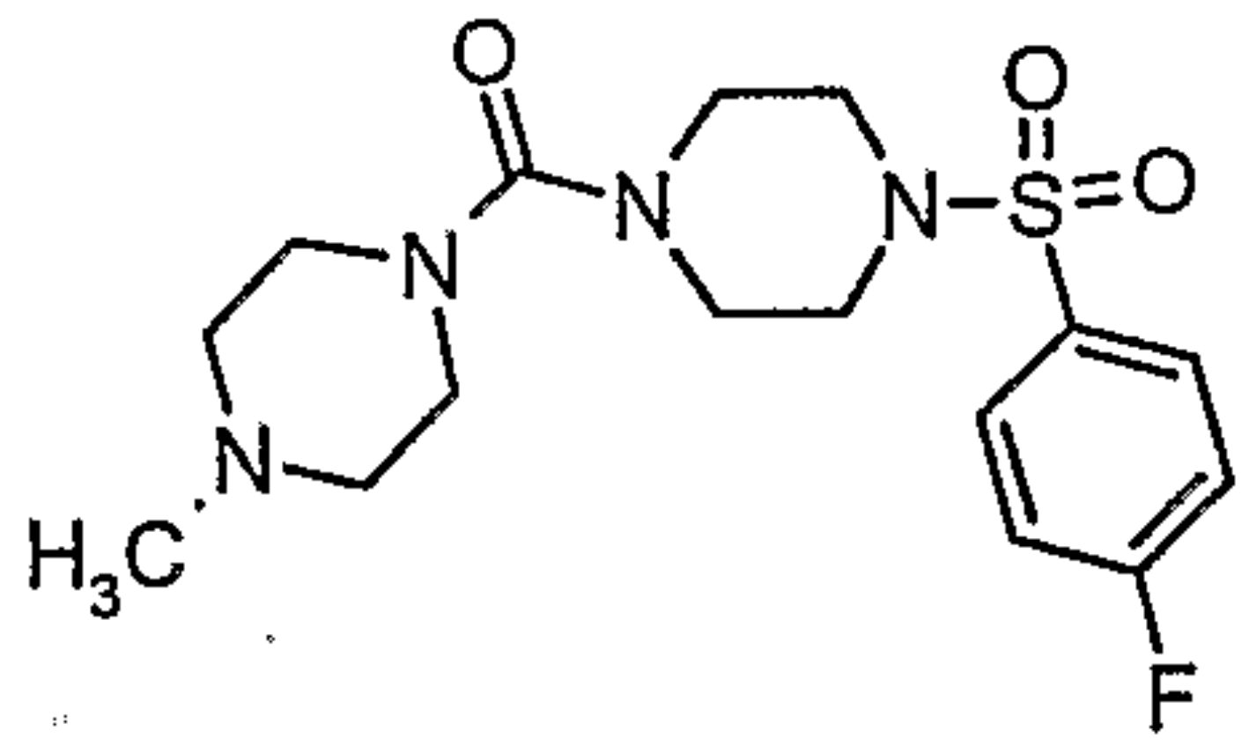
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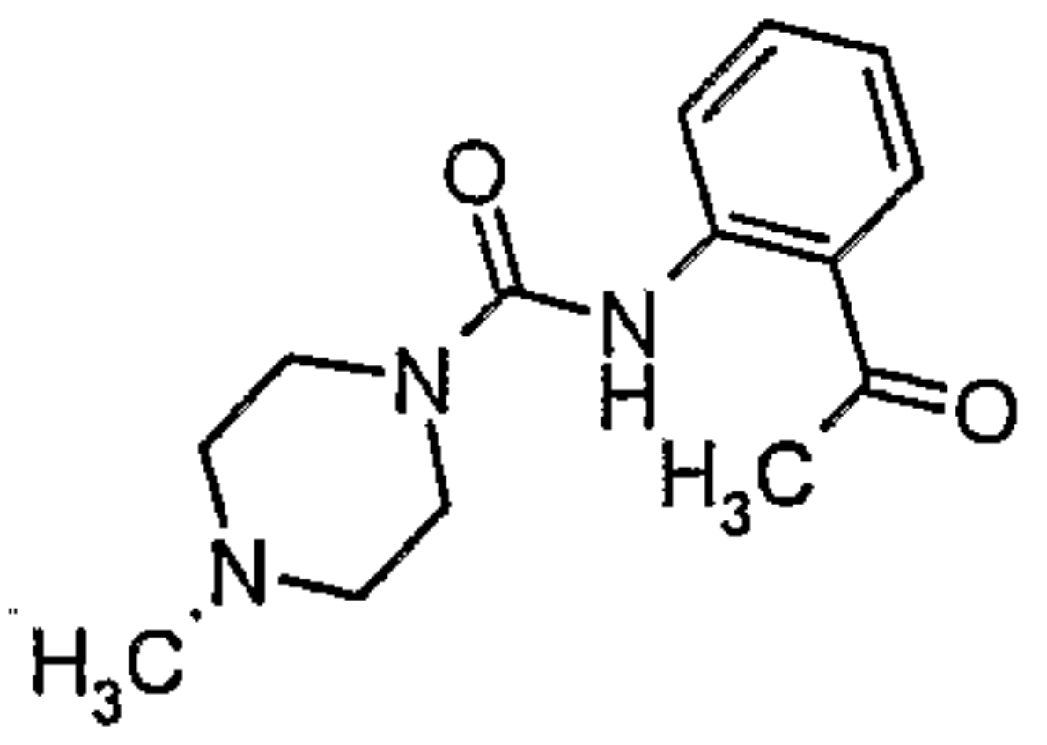
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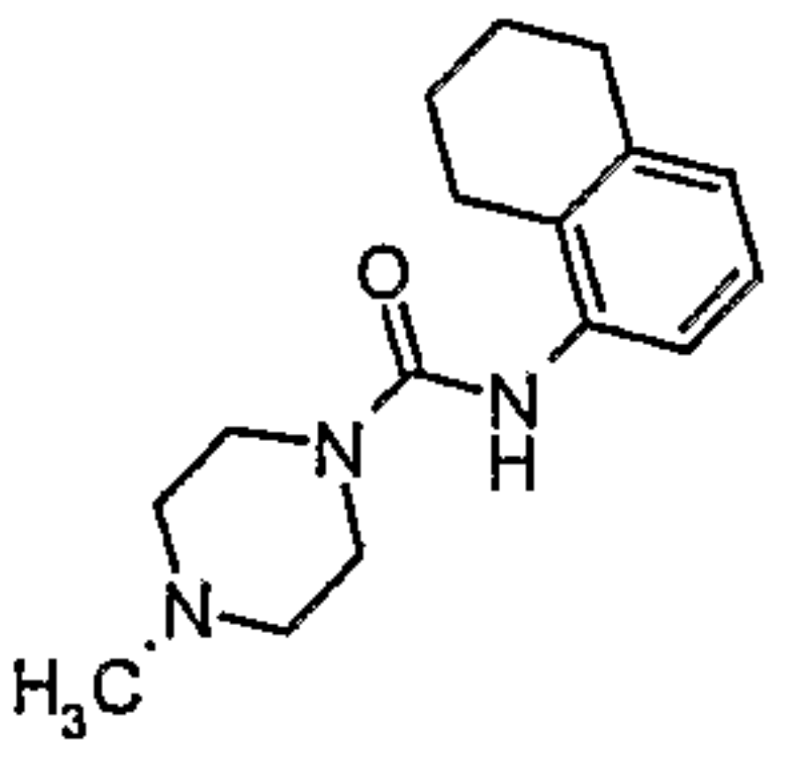
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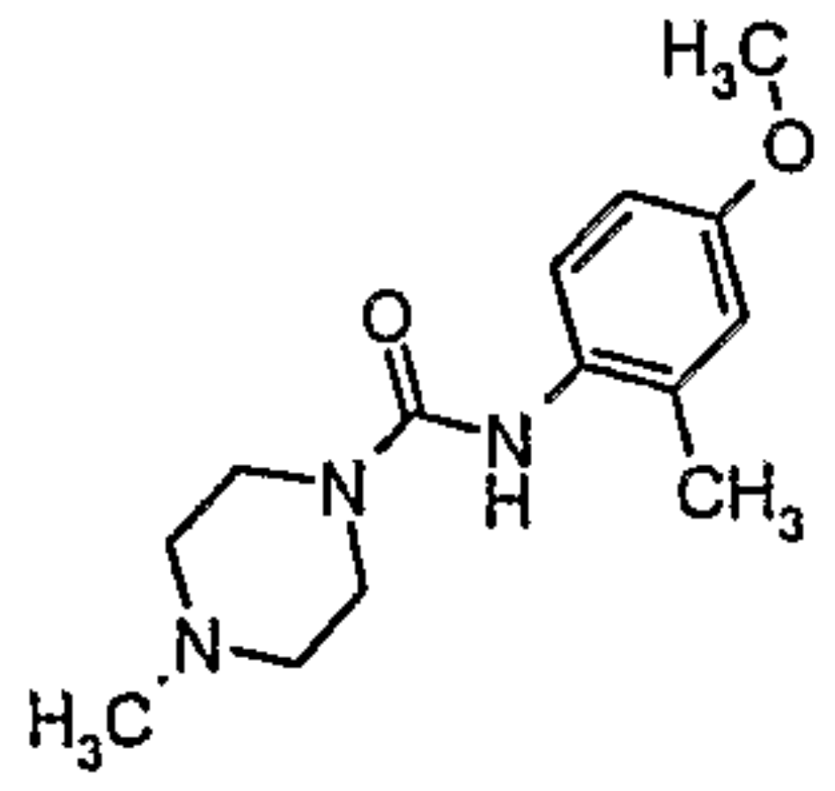
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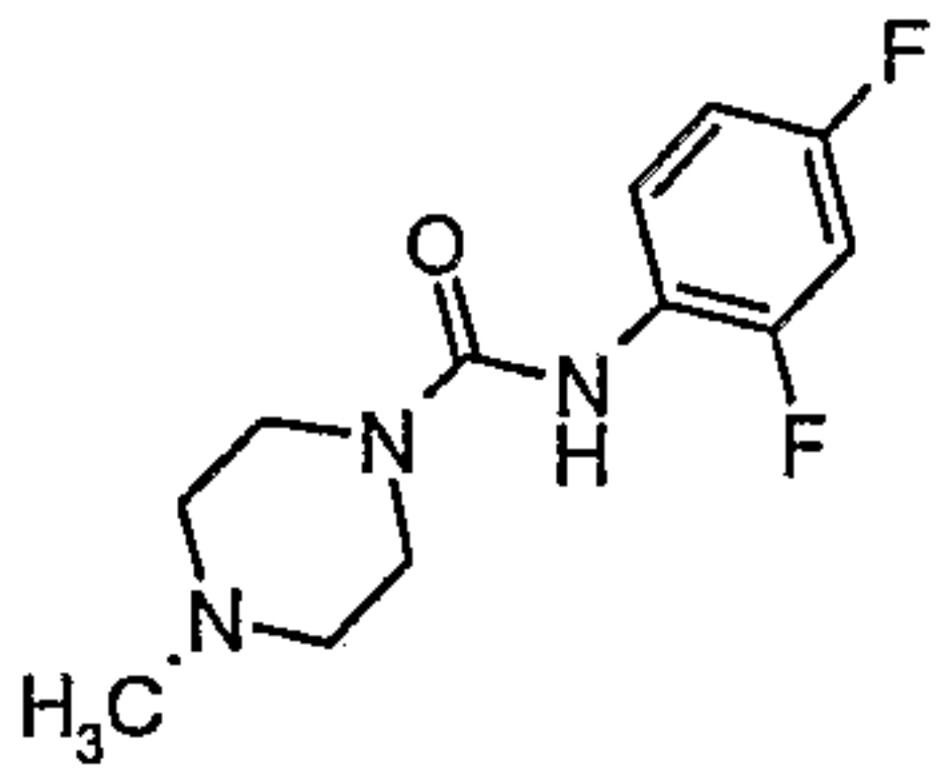
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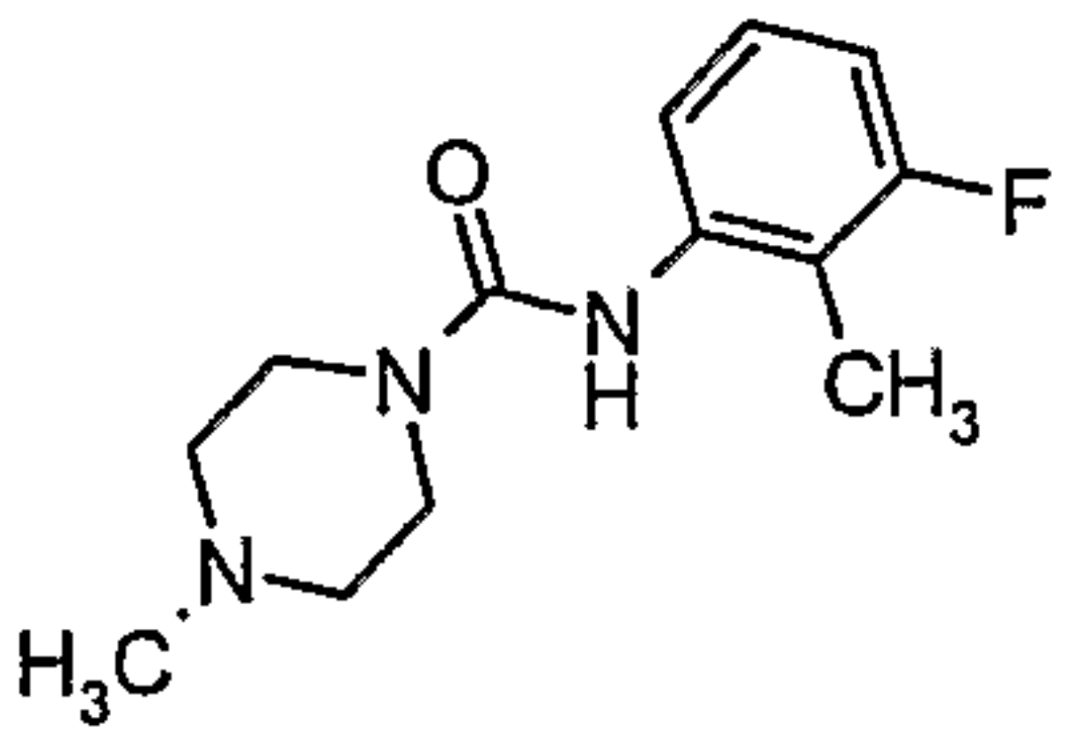
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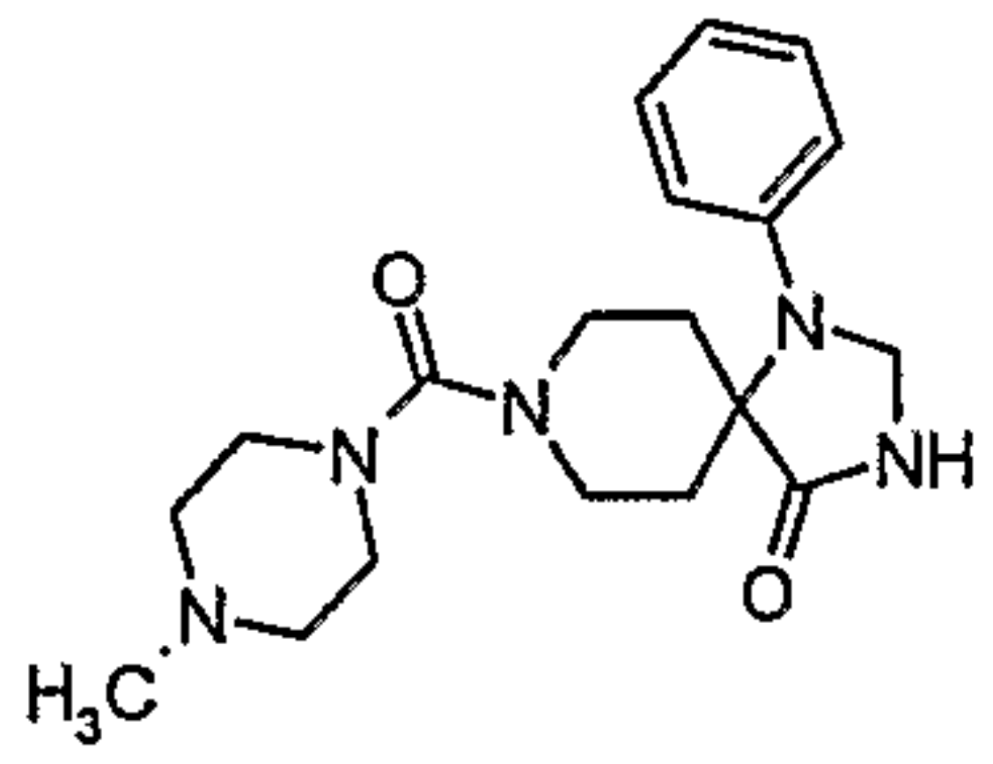
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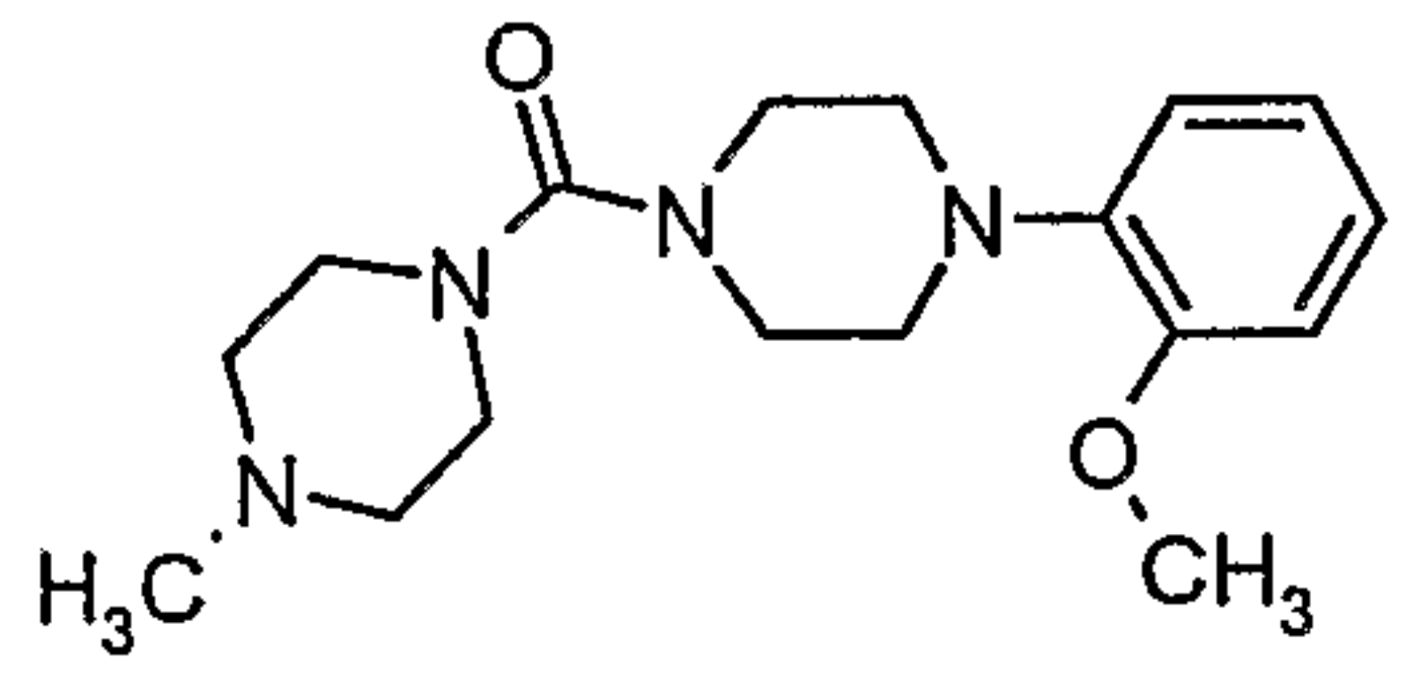
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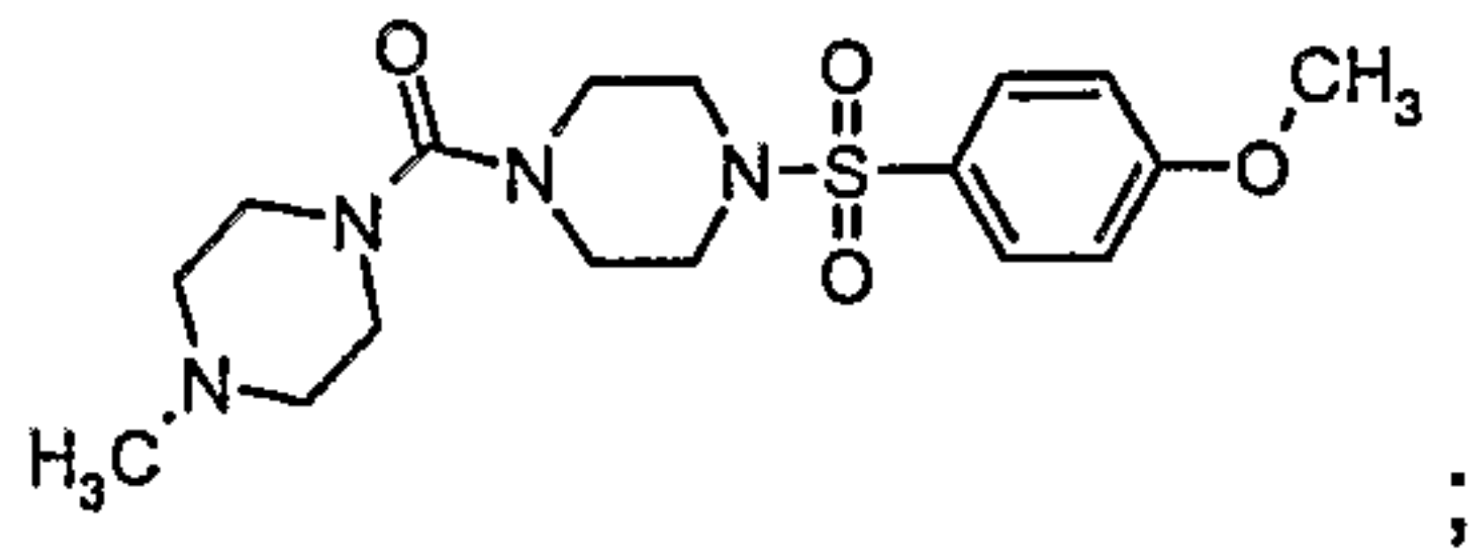
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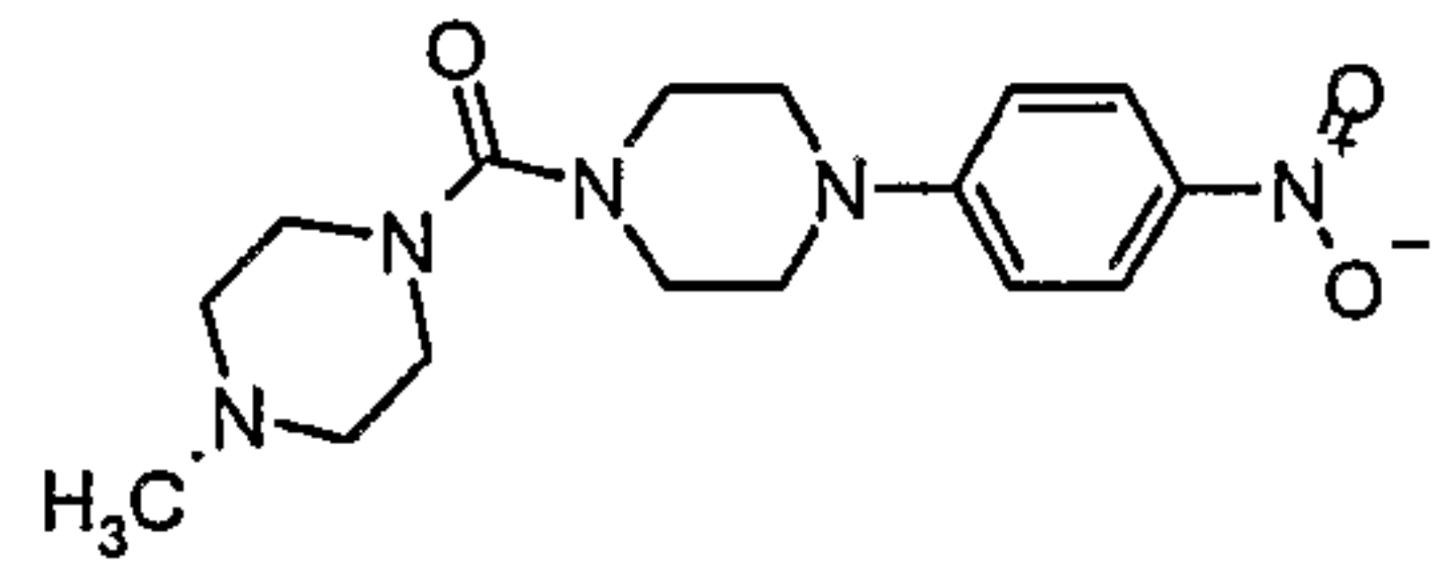
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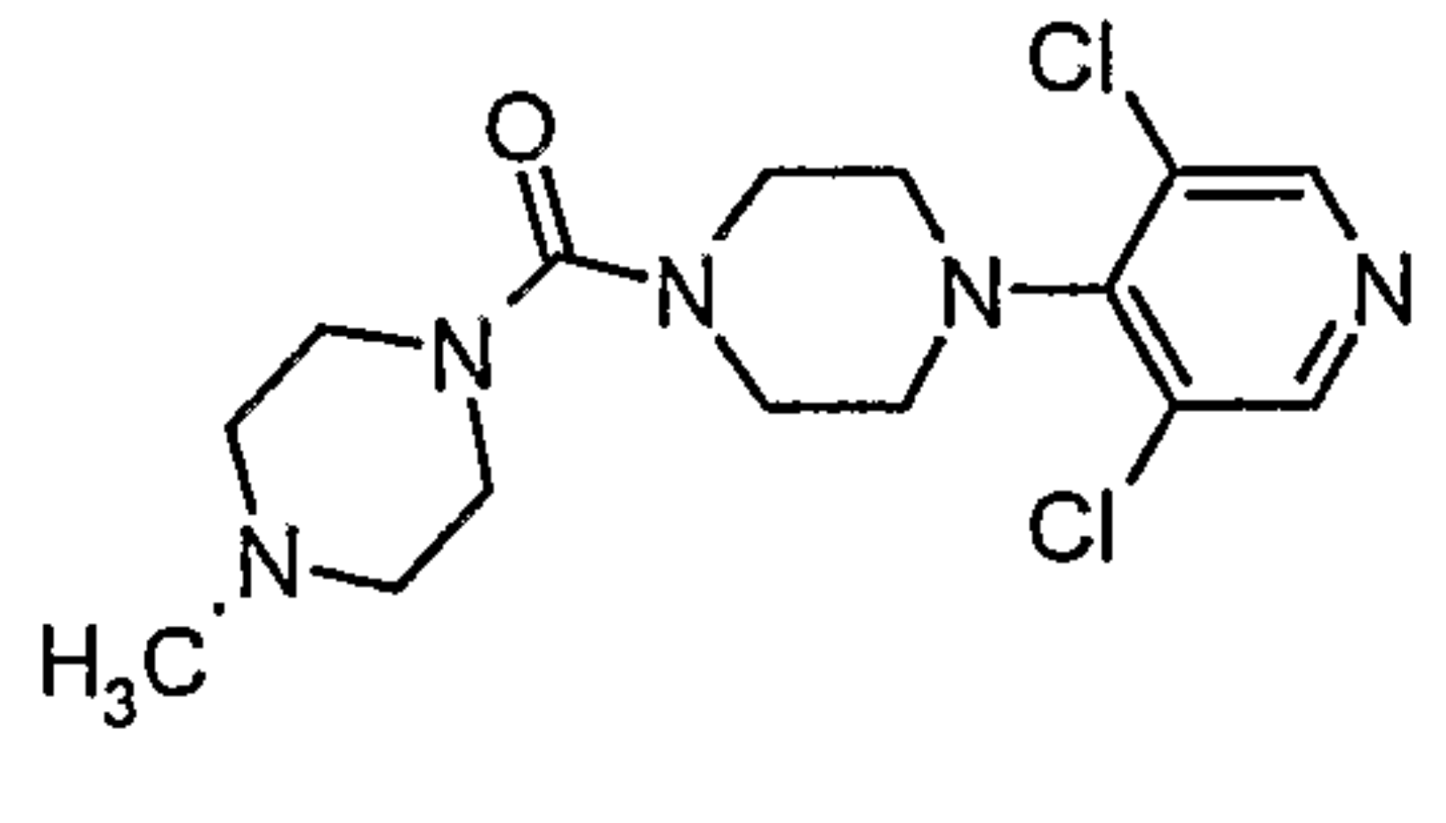
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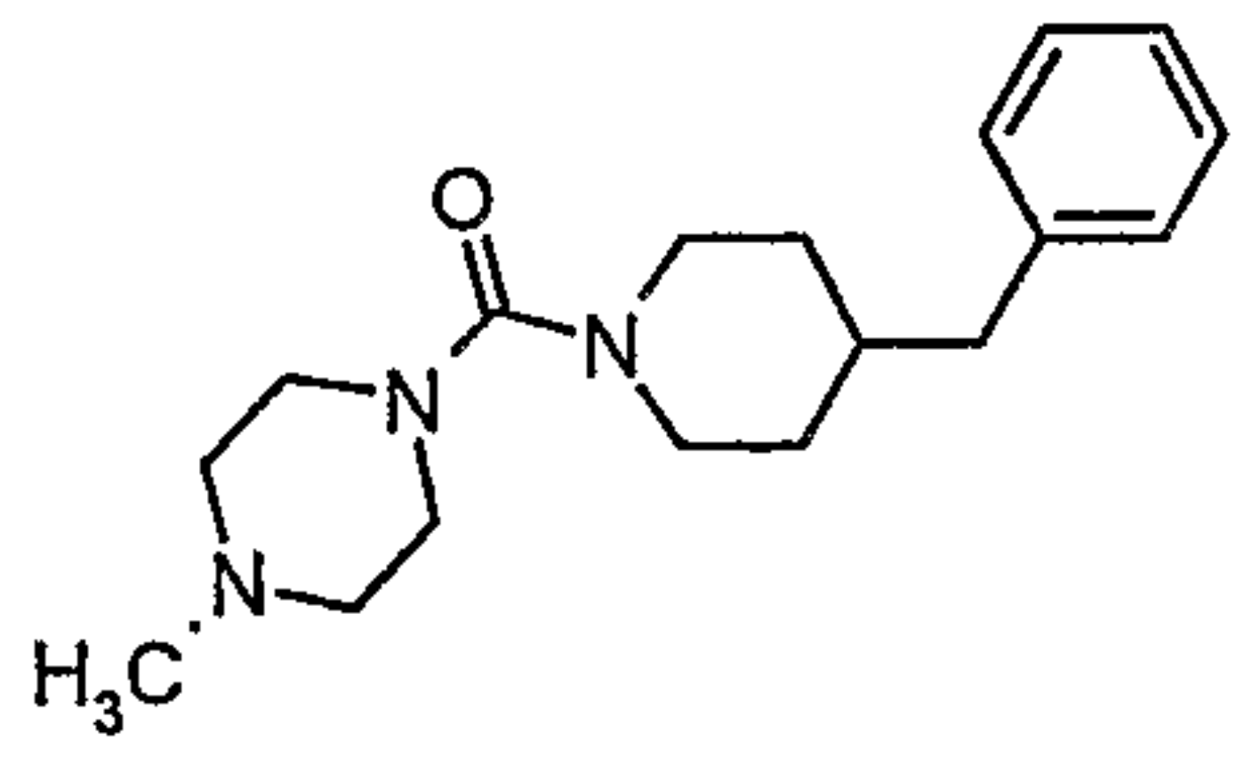
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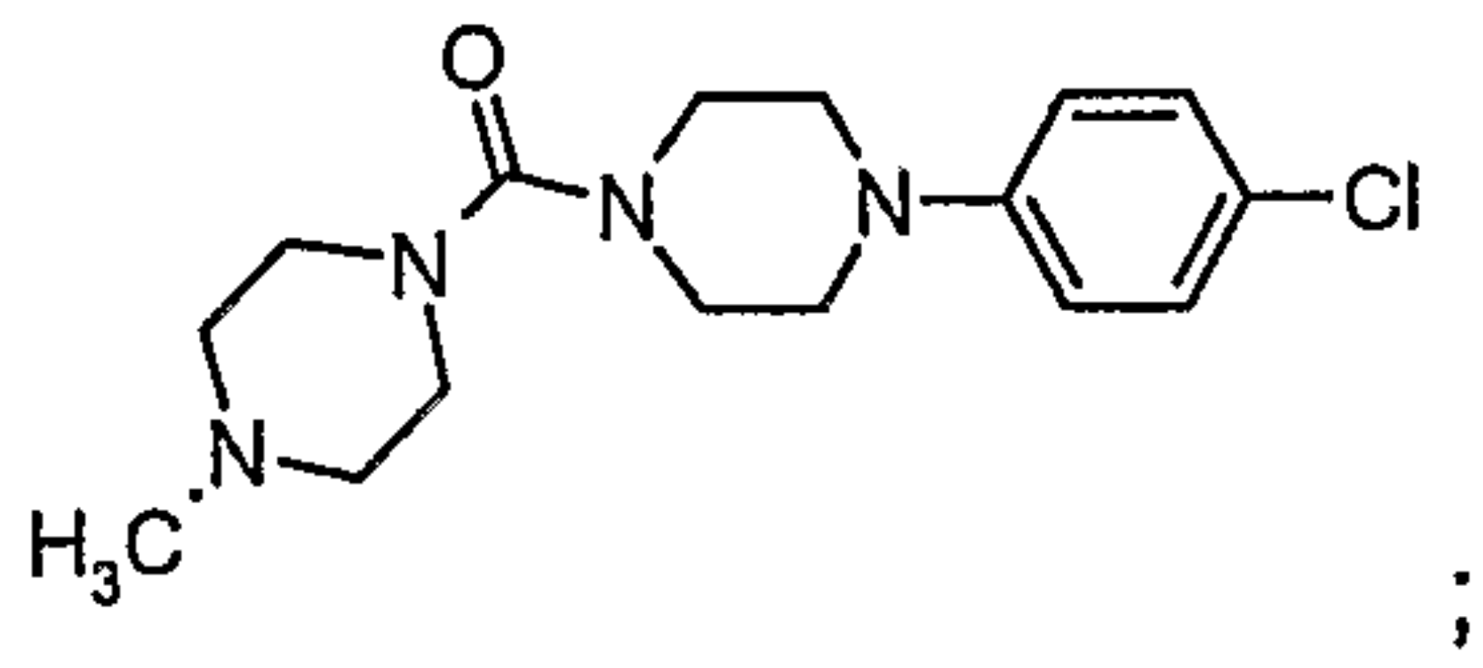
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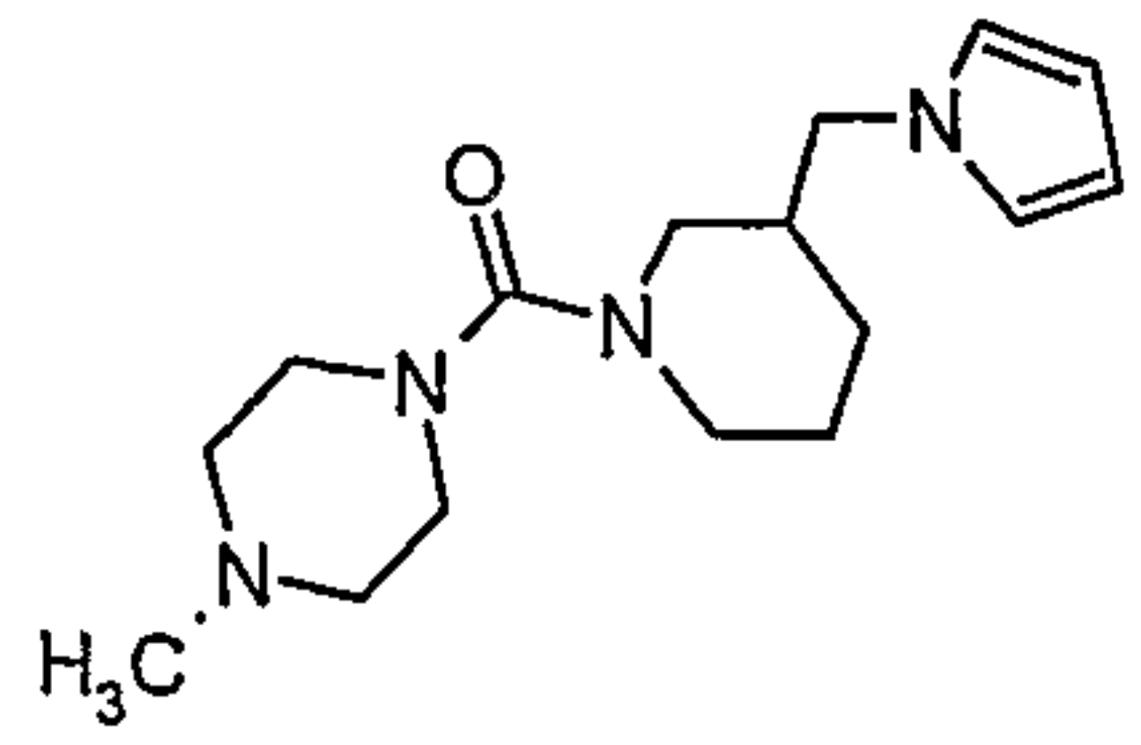
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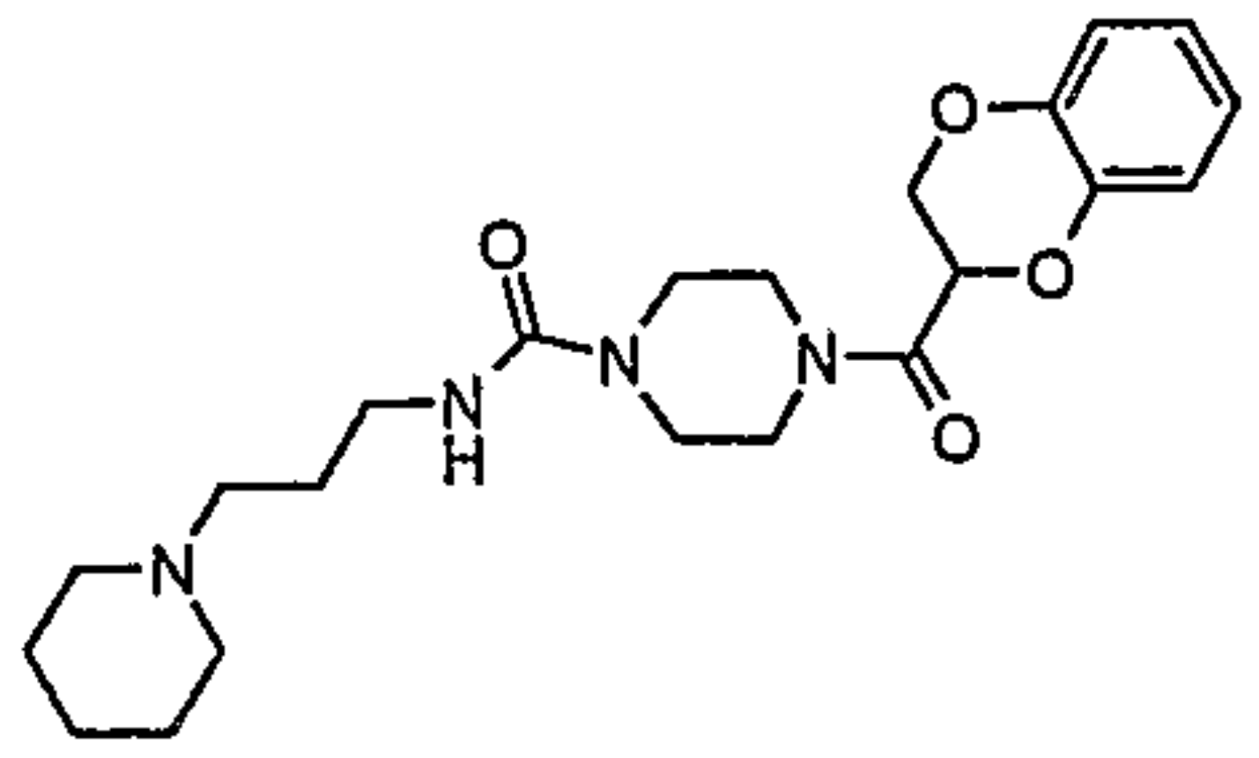
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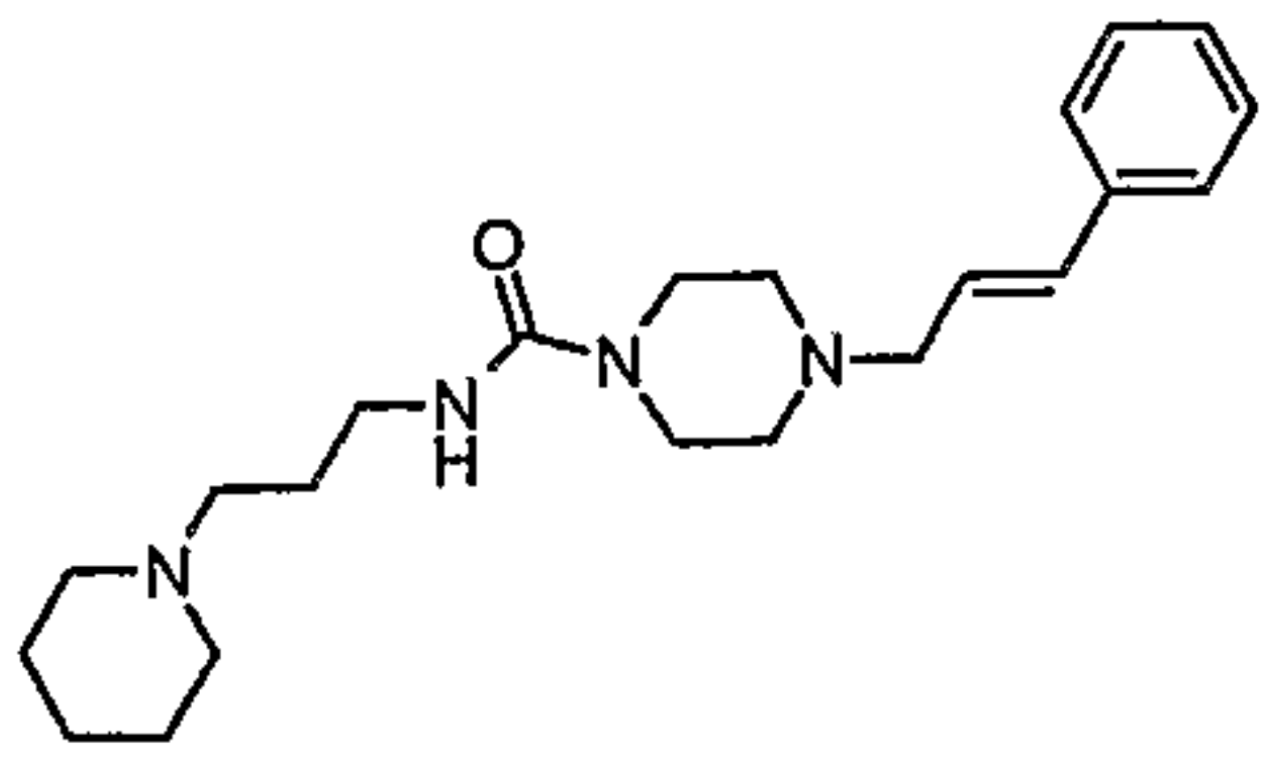
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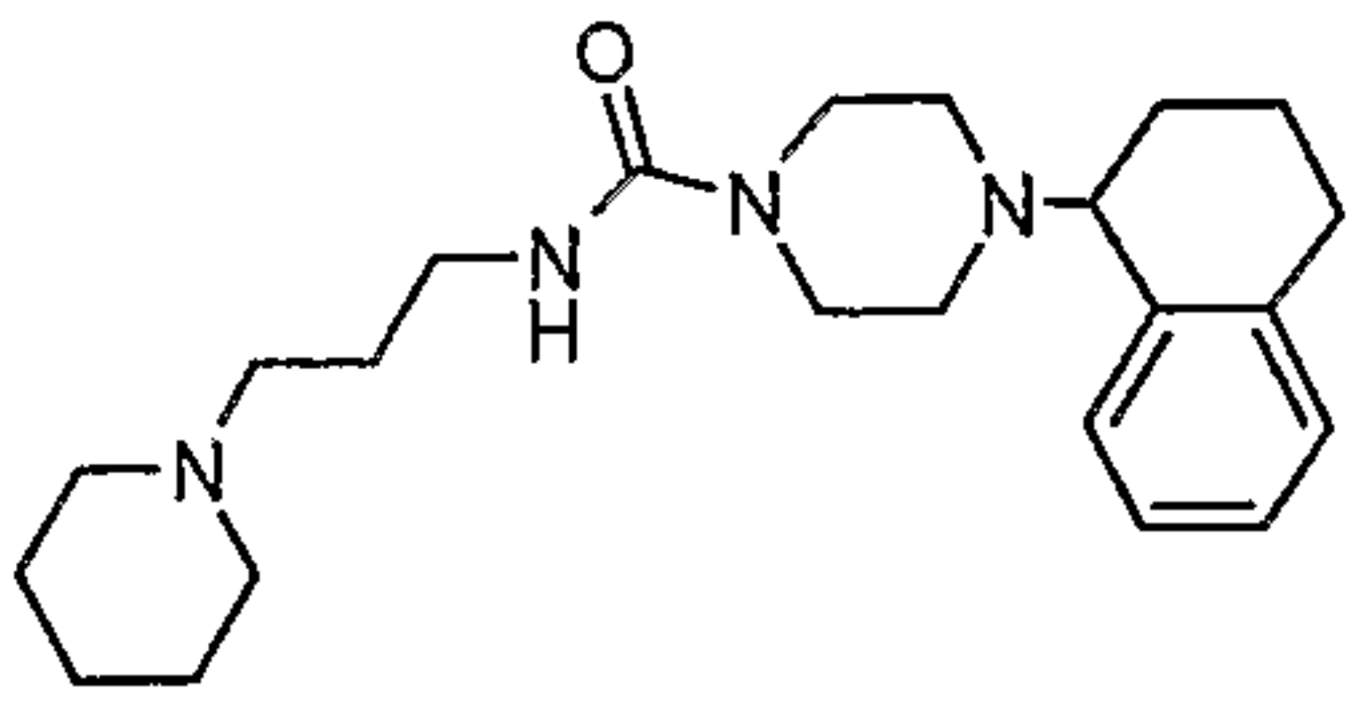
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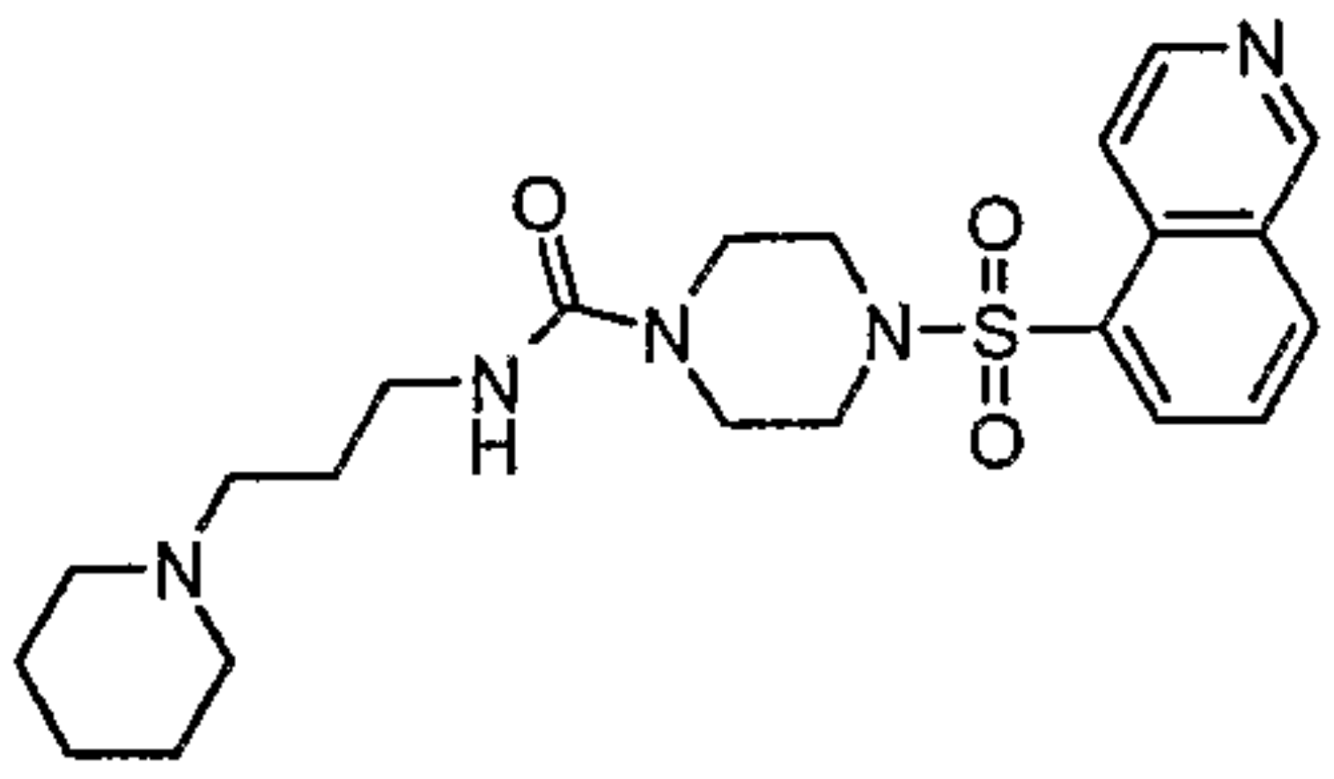
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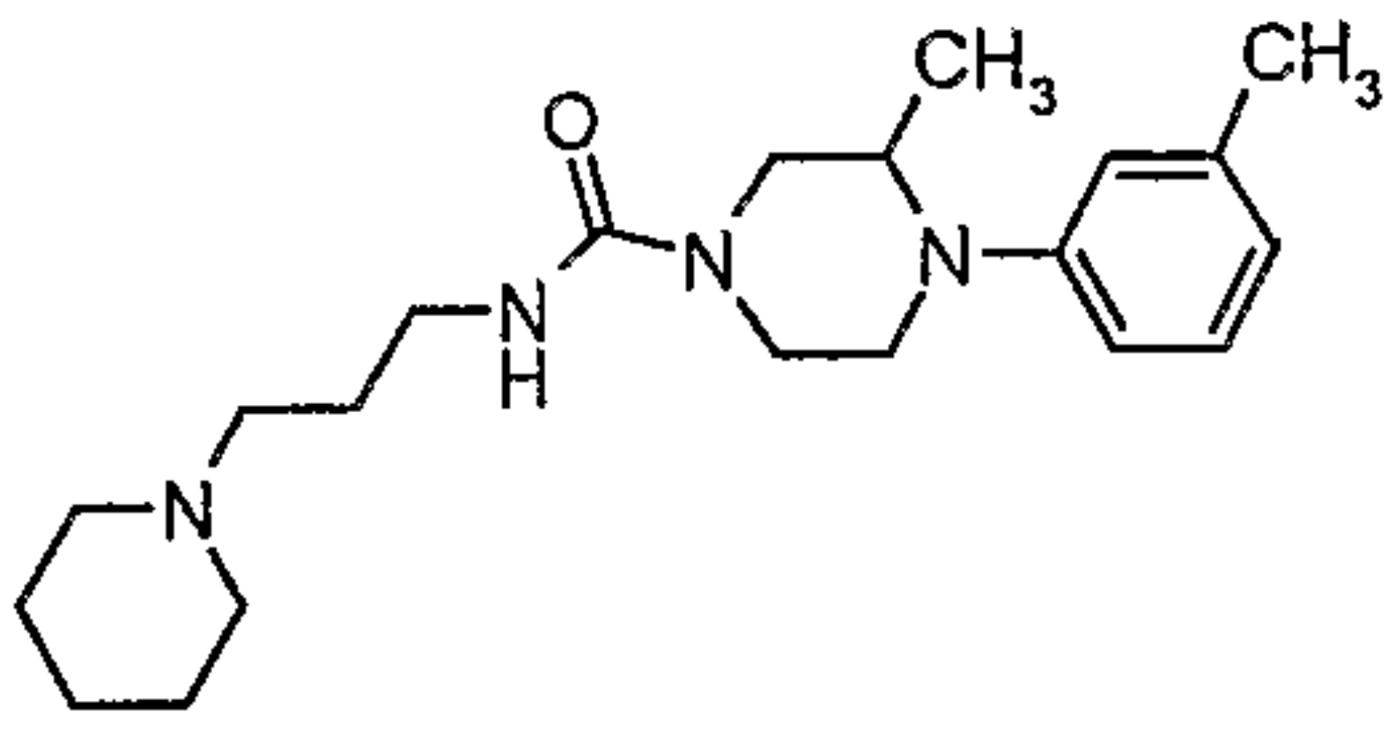
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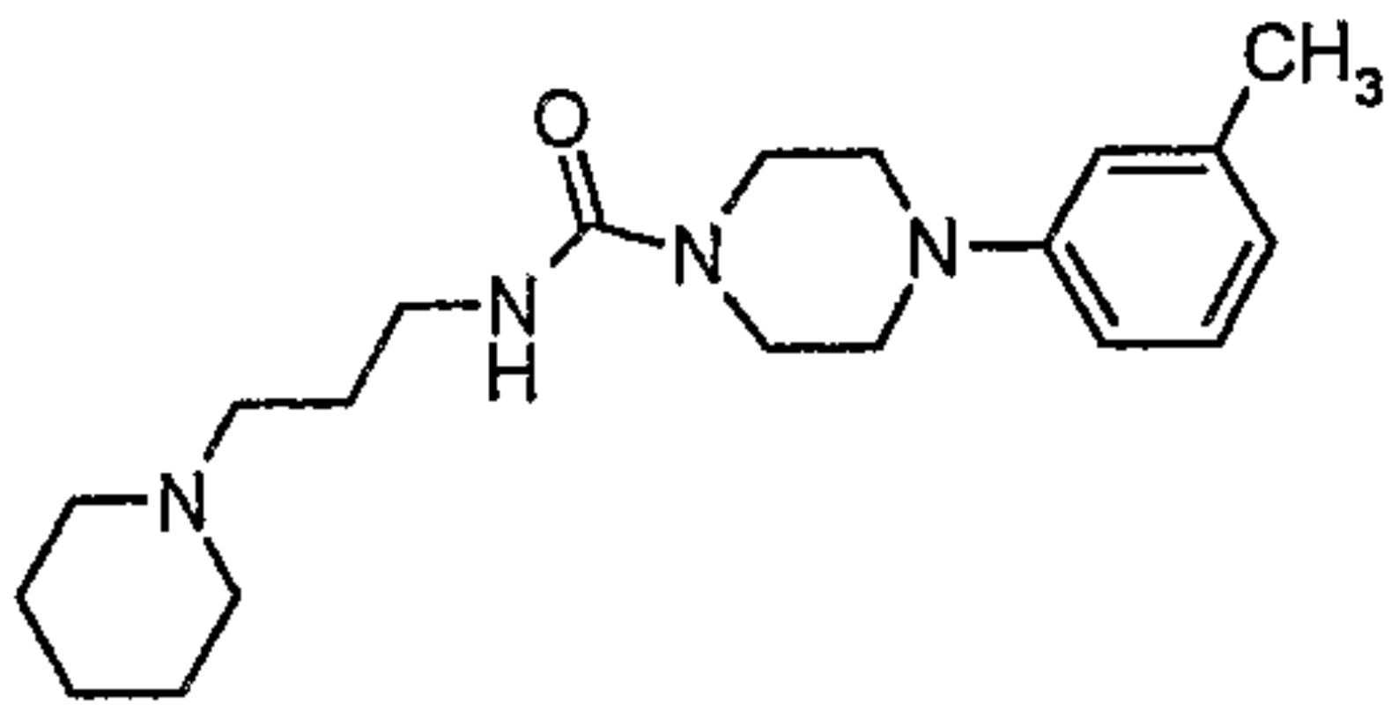
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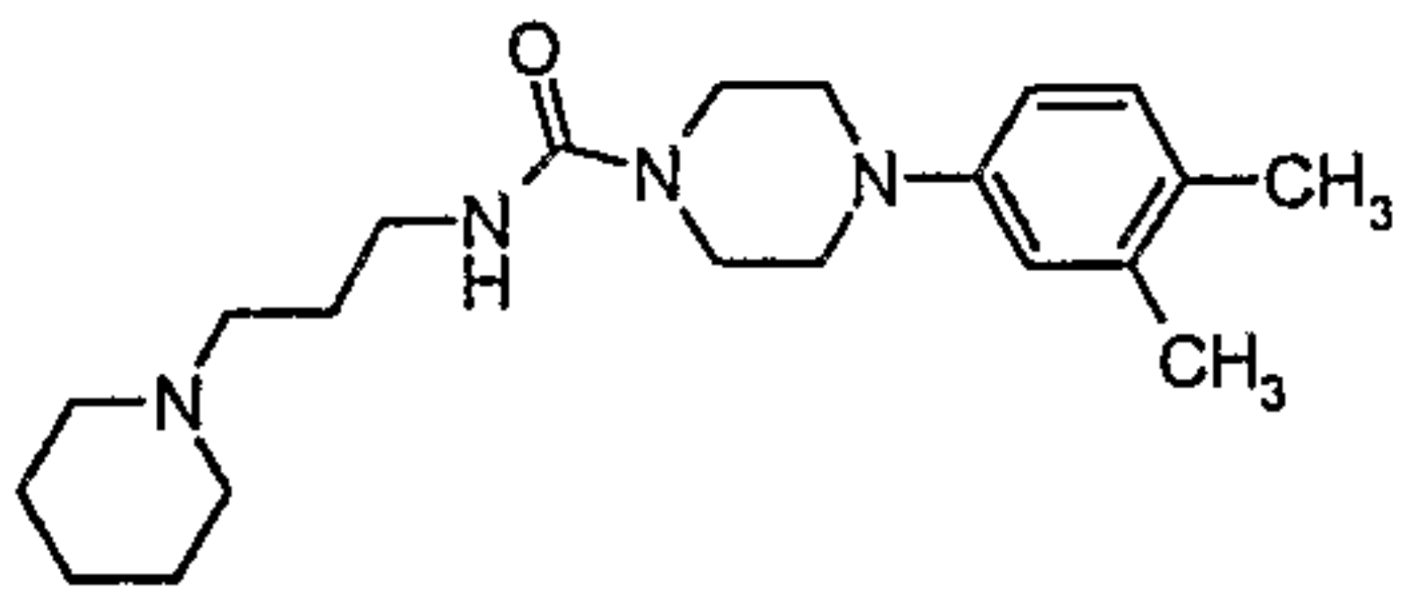
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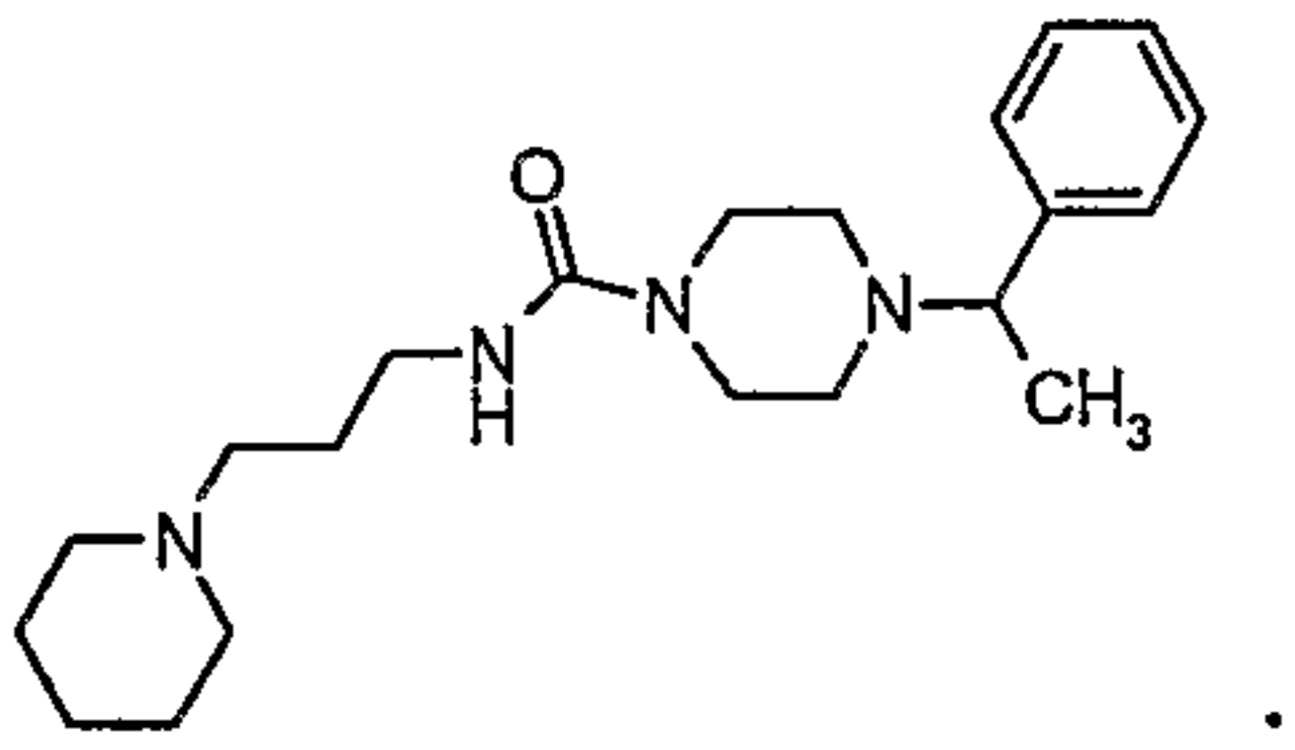
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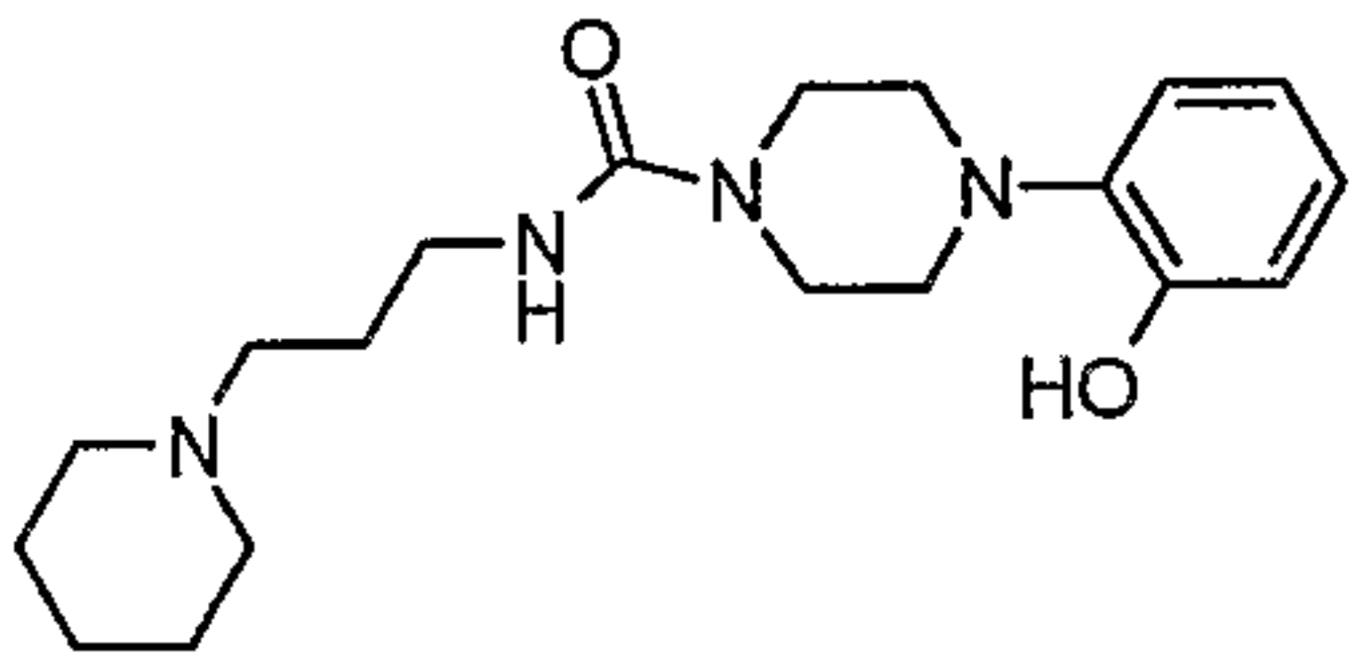
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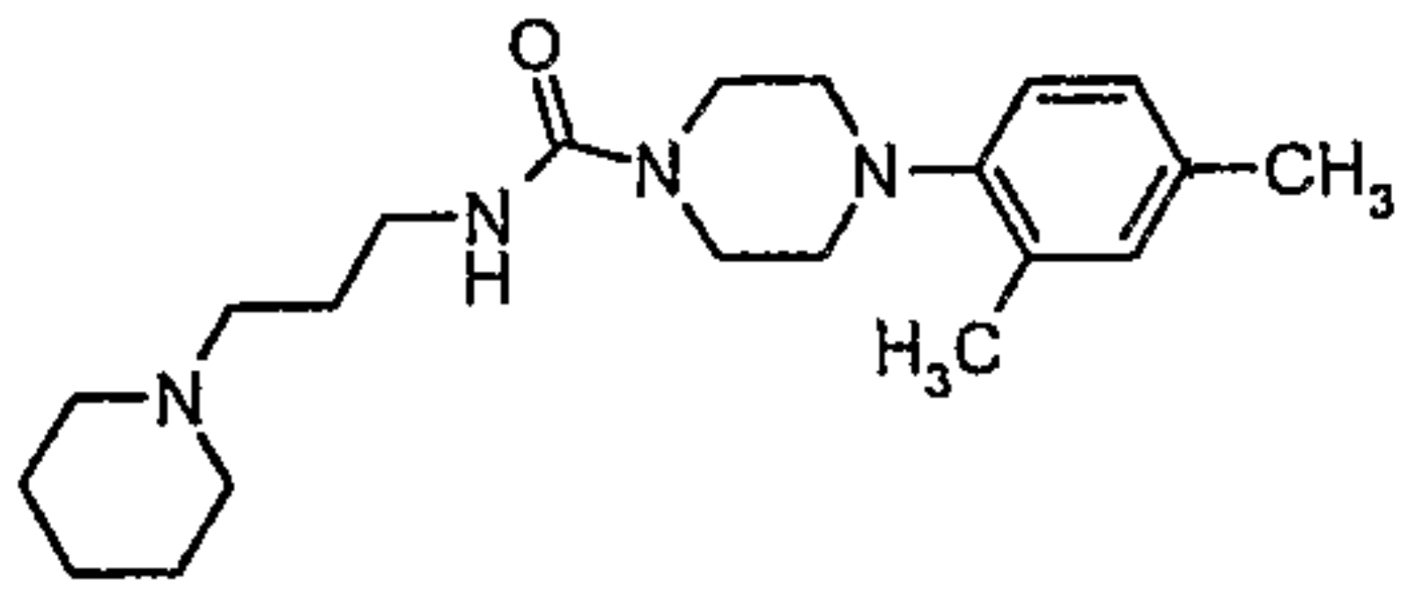
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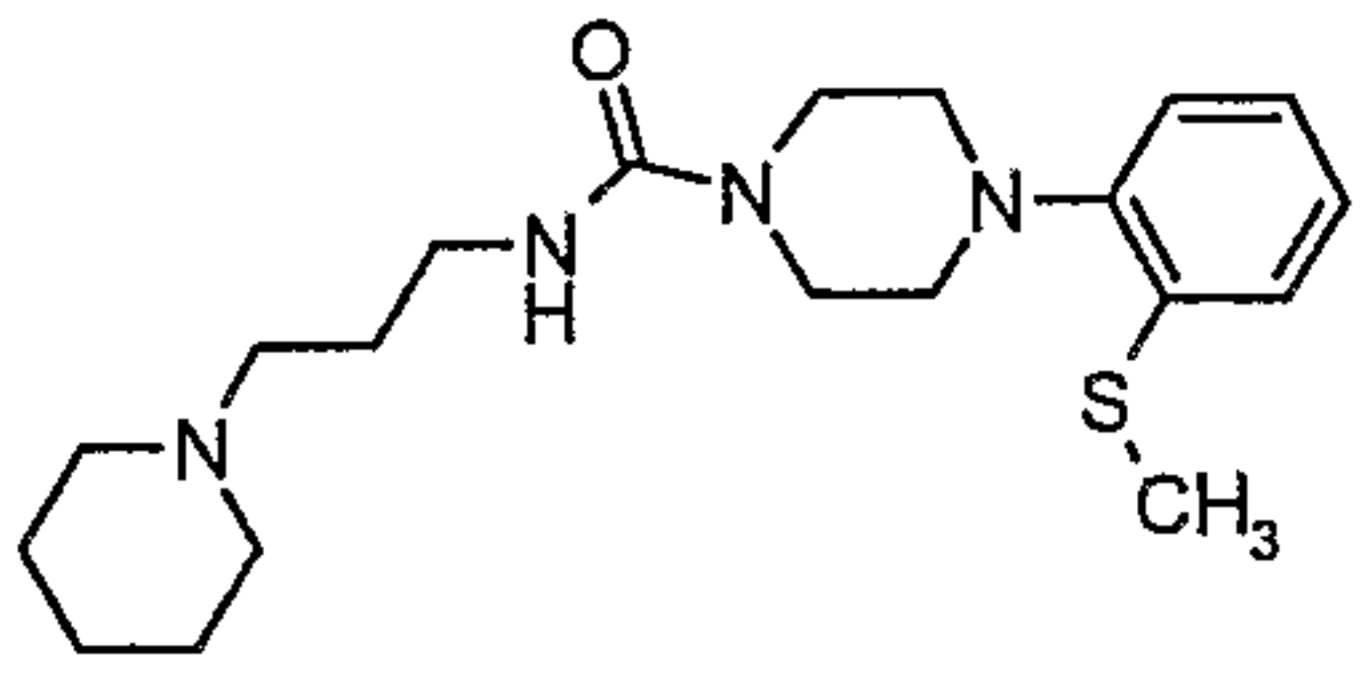
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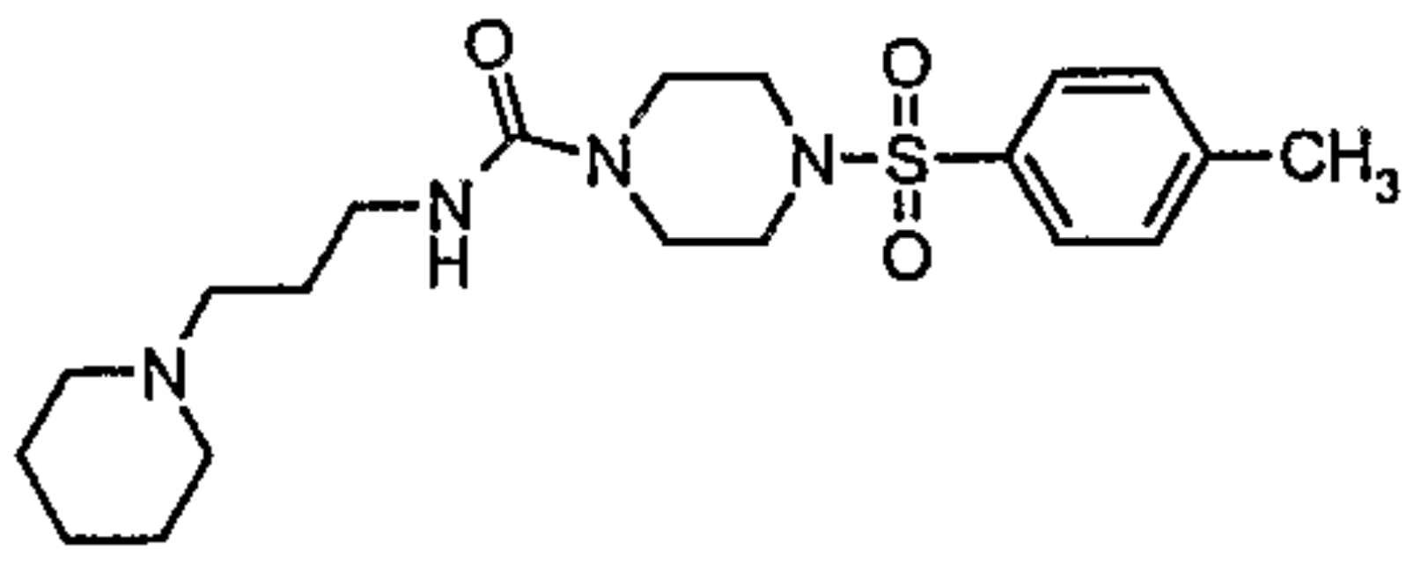
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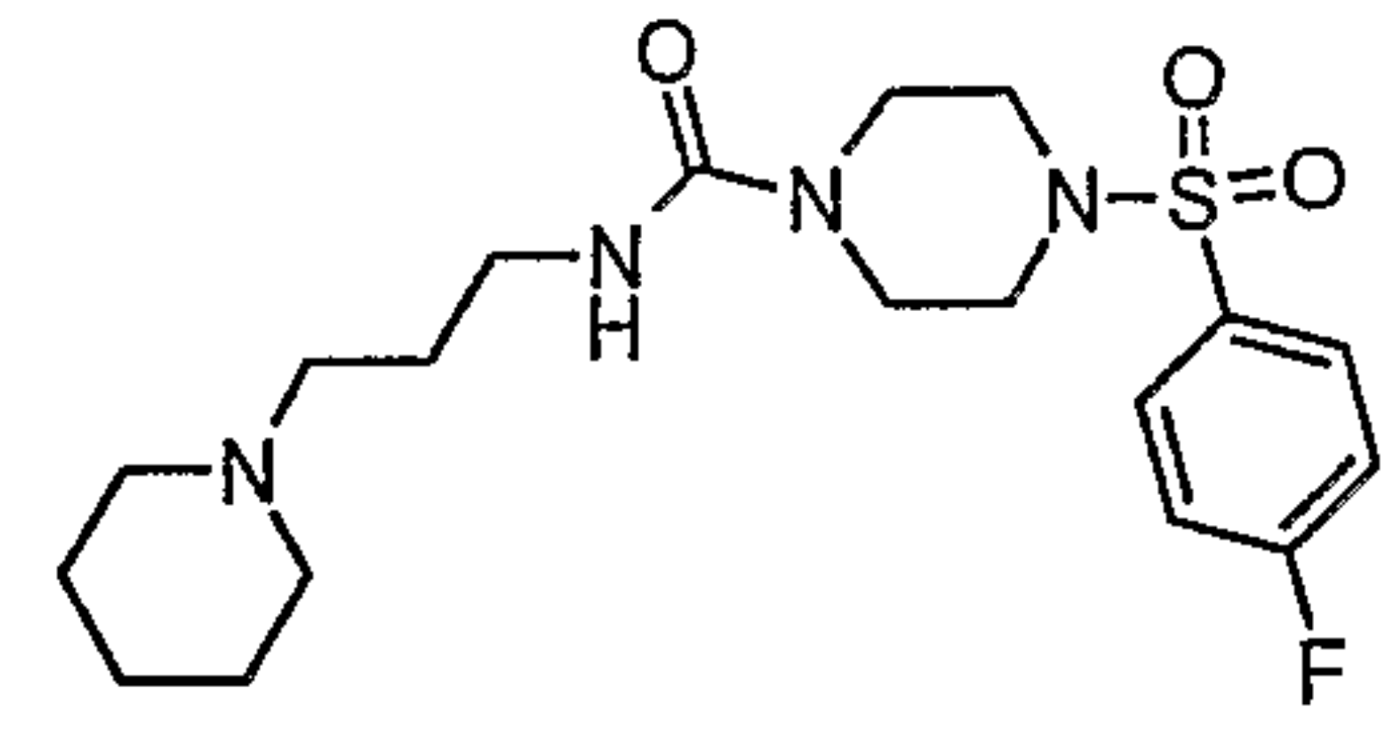
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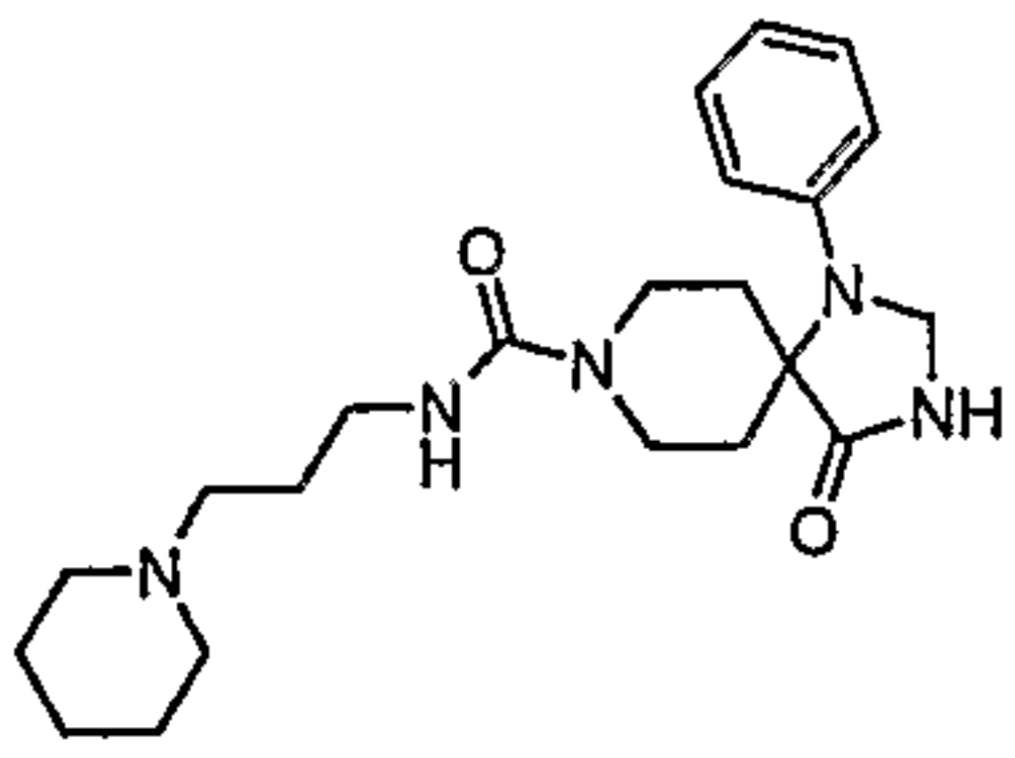
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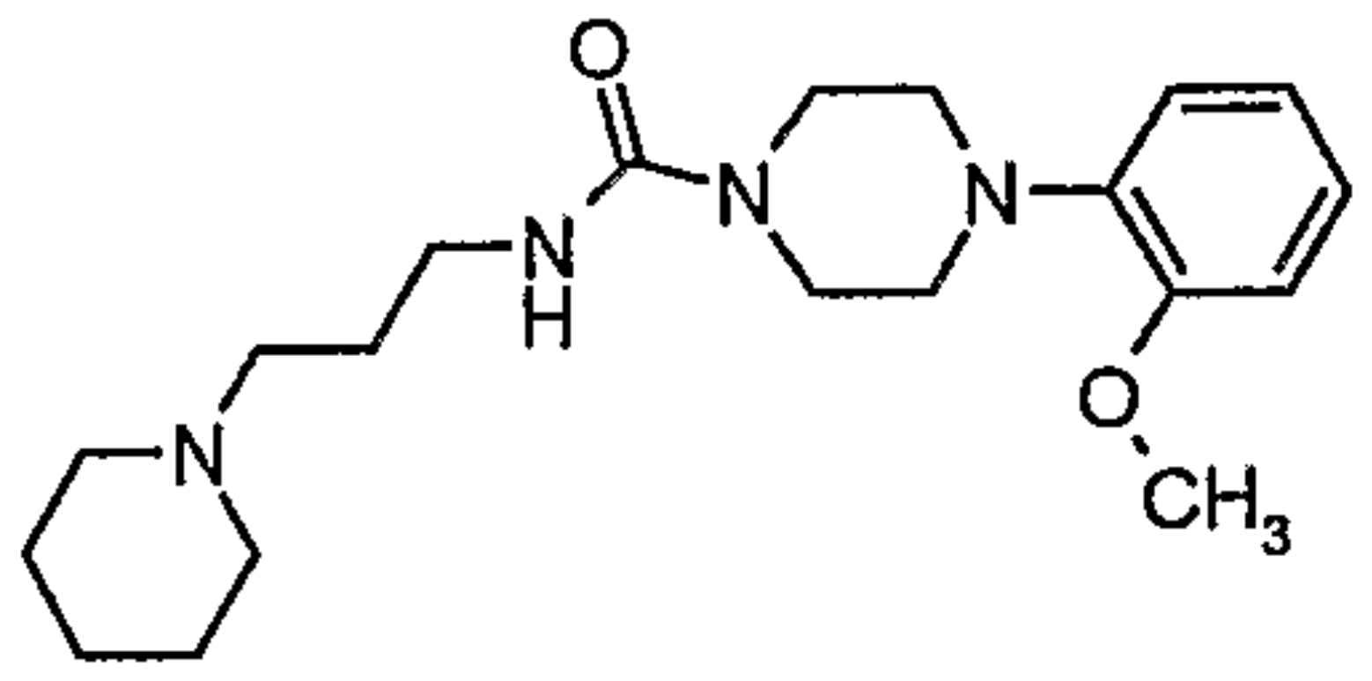
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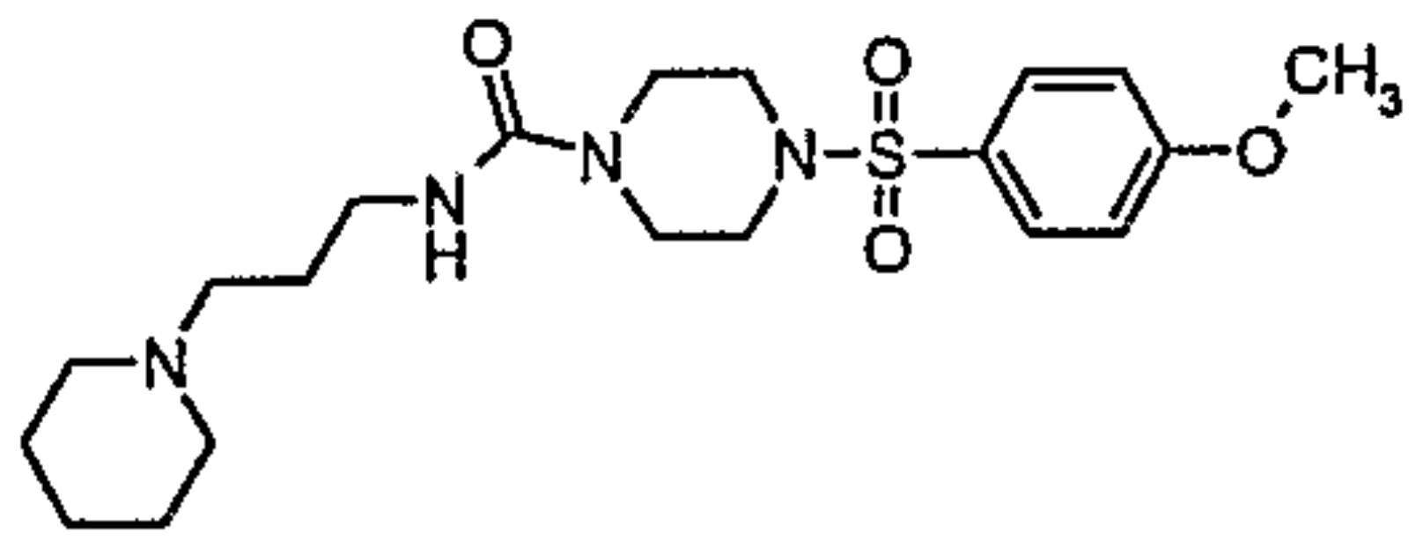
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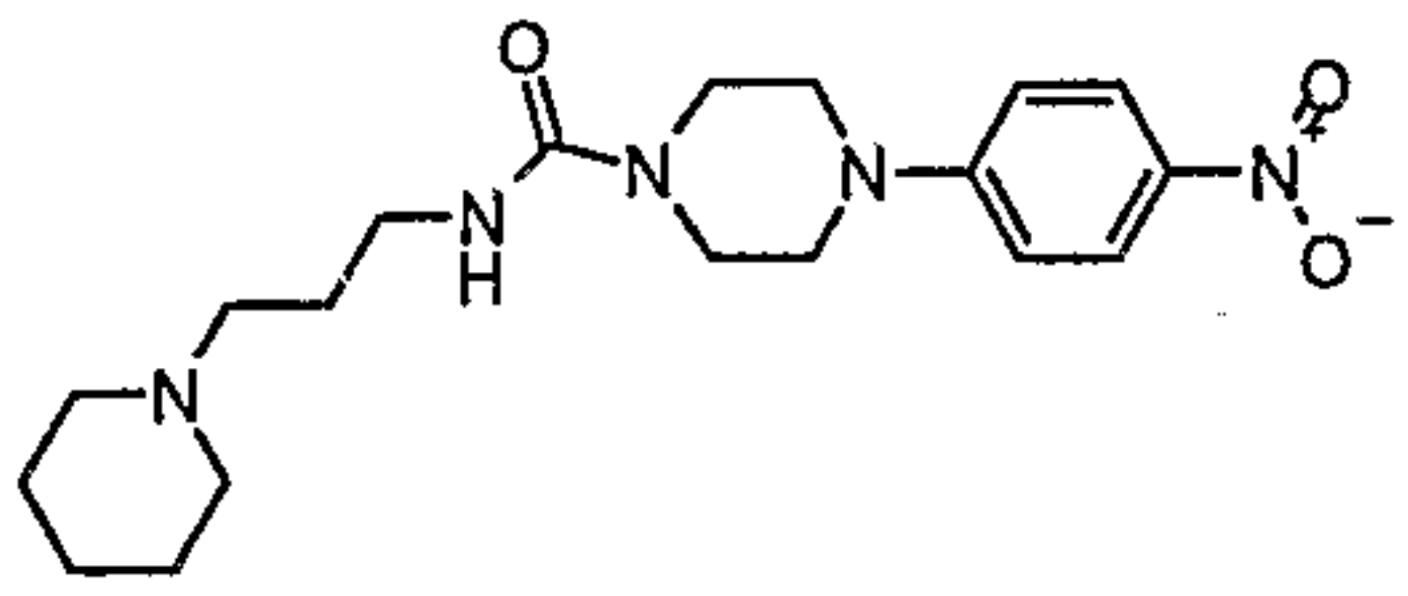
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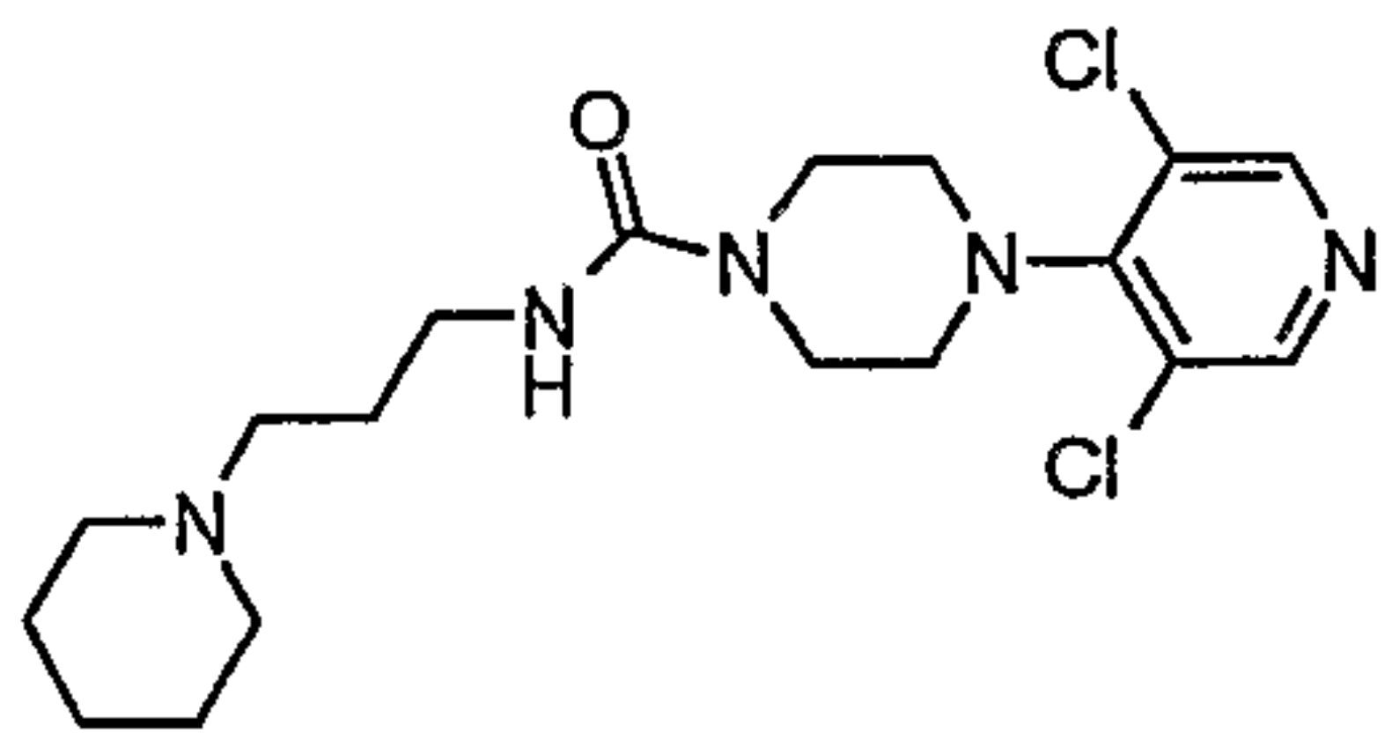
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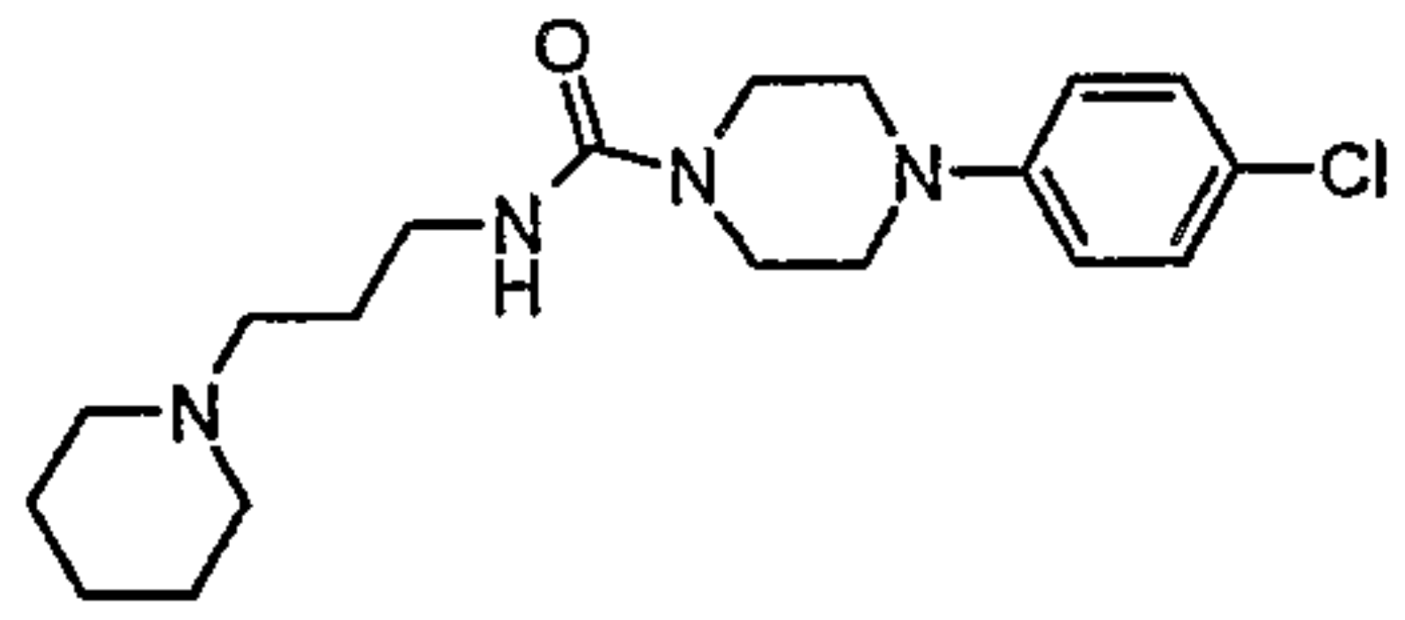
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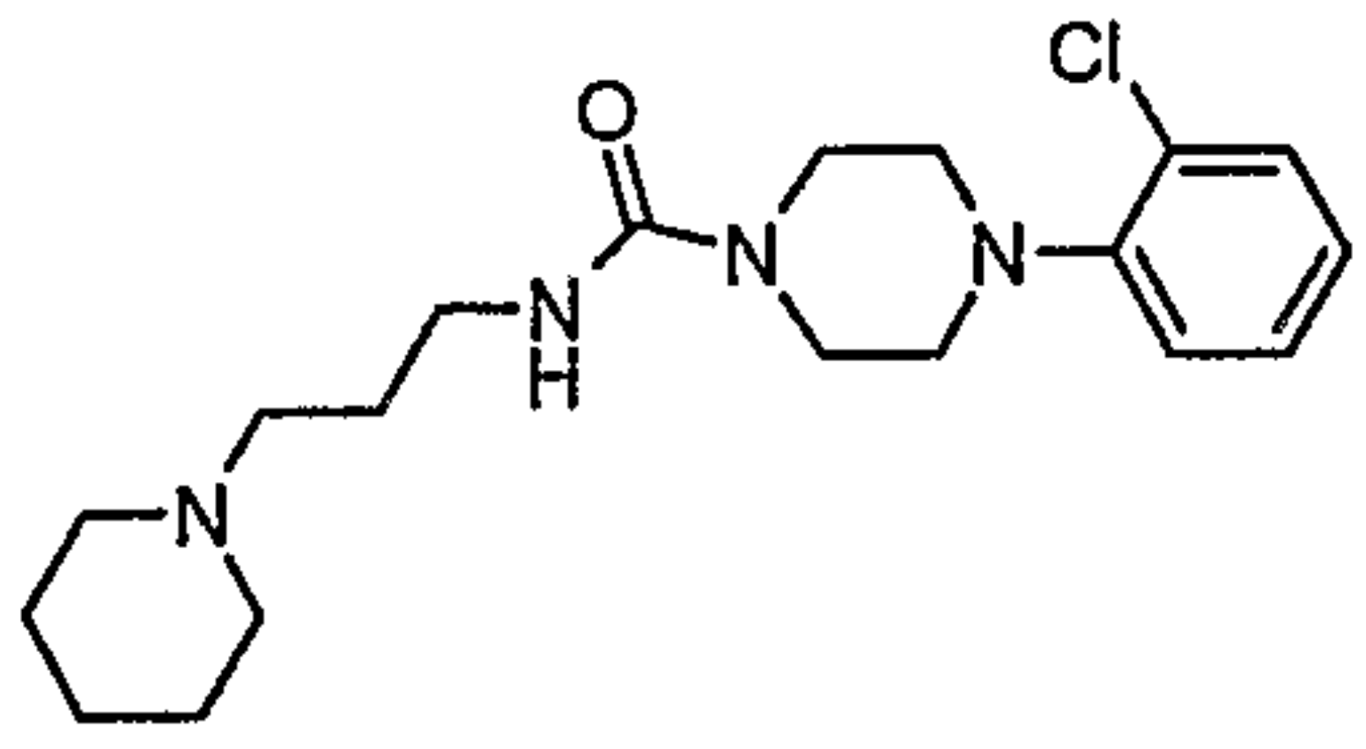
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and pharmaceutically acceptable salts thereof.

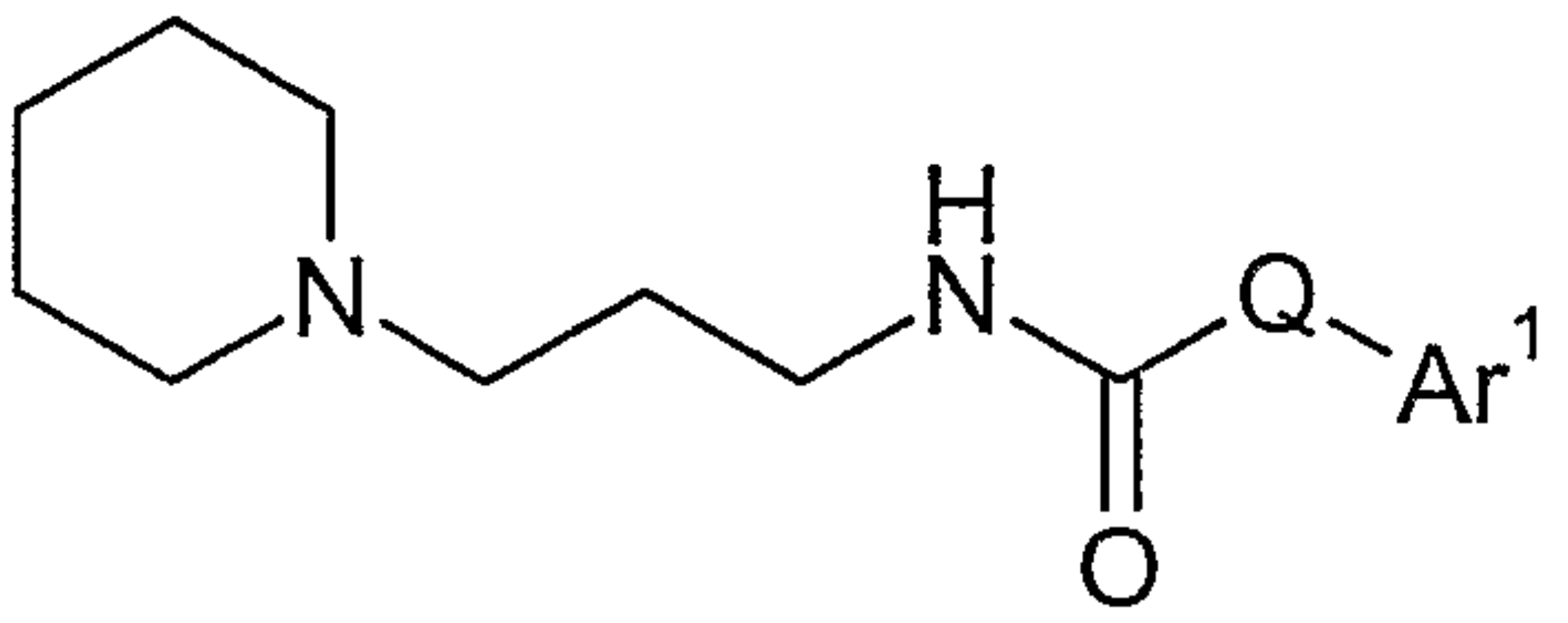
5. A compound according to any one of claims 1-4 for use as a medicament.

6. The use of a compound according to any one of claims 1-4 in the manufacture of a medicament for the therapy of depression.

7. A pharmaceutical composition comprising a compound according to any one of claims 1-4 and a pharmaceutically acceptable carrier.

8. A method for the therapy of depression in a warm-blooded animal, comprising the step of administering to said animal in need of such therapy a therapeutically effective amount of a compound according to any one of claims 1-4.

9. A process for preparing a compound of formula I, comprising:



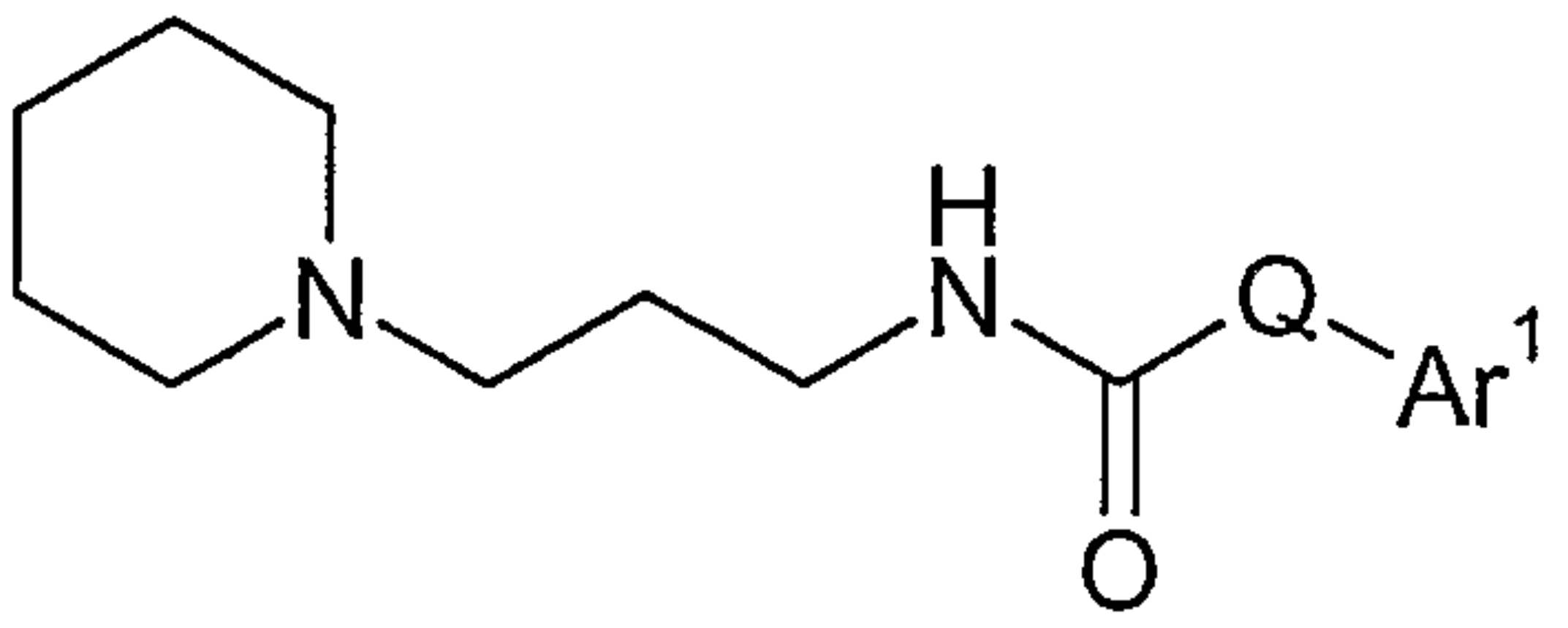
I

reacting Ar^1-Q-H with 3-(1-piperidino)propylamine and a haloformate,

Ar^1 is selected from C_{6-10}aryl and C_{2-9}heteroaryl, wherein said C_{6-10}aryl and C_{2-9}heteroaryl are optionally substituted with one or more groups selected from -R, –NO_2, -OR, -Cl, -Br, -I, -F, -CF_3, -OCF_3, -C(=O)R, -C(=O)OH, -NH_2, -SH, -NHR, -NR_2, -SR, -SO_3H, -SO_2R, -SO_2NR, -S(=O)R, -CN, -OH, -C(=O)OR, -C(=O)NR_2, -NRC(=O)R, and -NRC(=O)-OR, wherein R is, independently, a hydrogen, C_{3-6}cycloalkyl, C_{3-6}heterocyclyl, phenyl, benzyl, C_{1-6}alkyl or C_{2-6}alkenyl and wherein said R is further optionally substituted with one or more groups selected from methyl, methoxy, hydroxy and halogen;

Q is a divalent or trivalent group that connects the carbonyl with Ar^1, wherein said divalent or trivalent group contains at least one nitrogen, wherein said nitrogen of Q is connected to the H in Ar^1-Q-H to form an amino, and said trivalent group is fused with Ar^1; and said Q-H of Ar^1-Q-H forms an amino group.

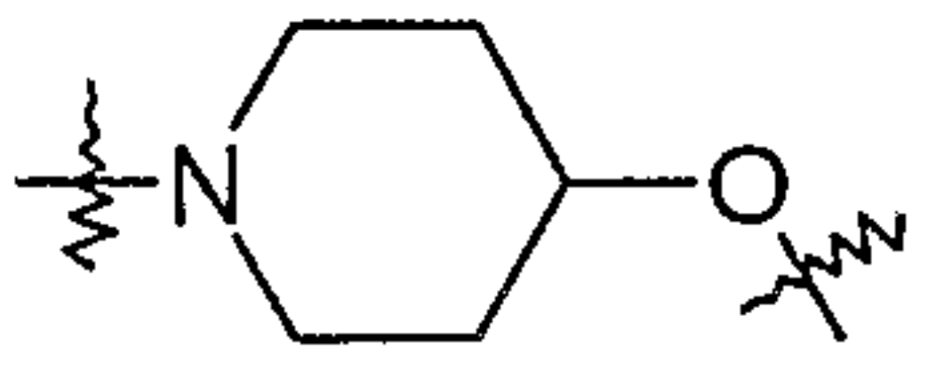
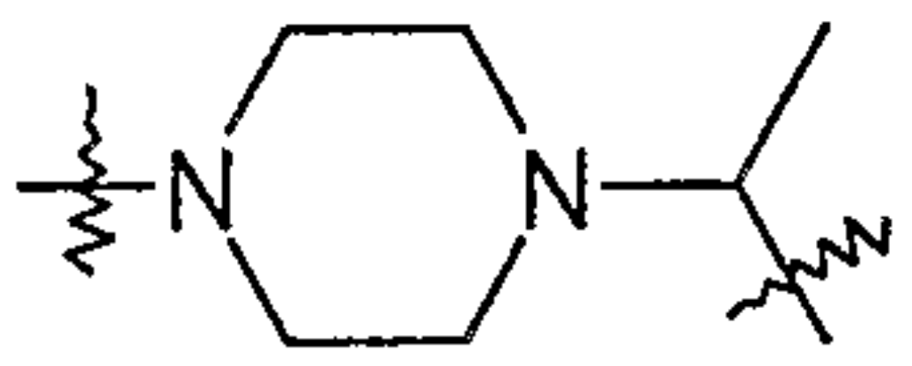
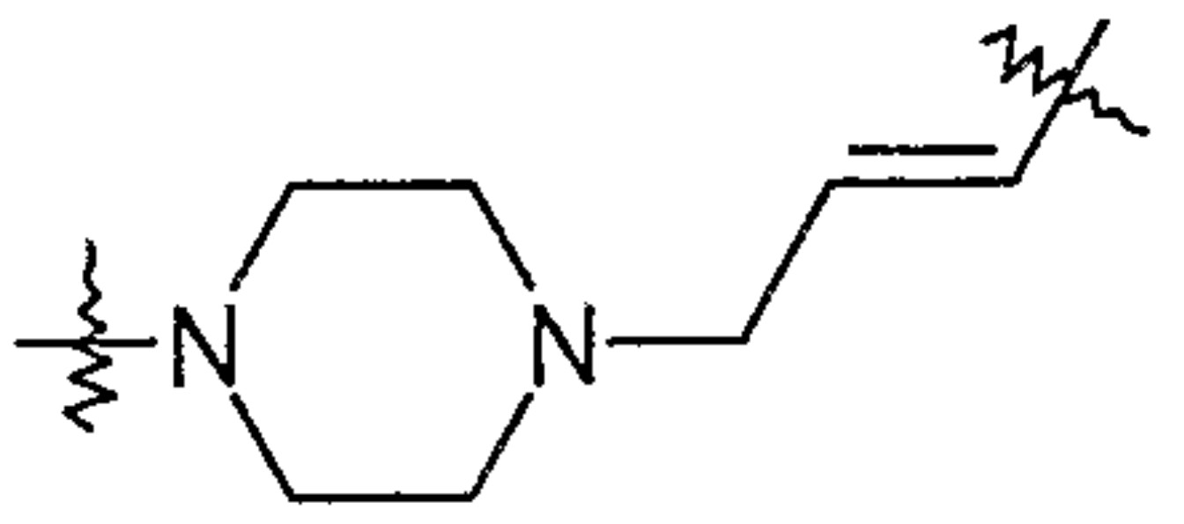
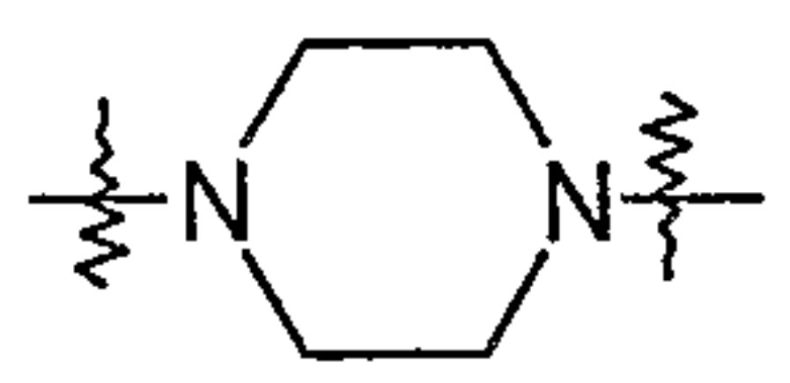
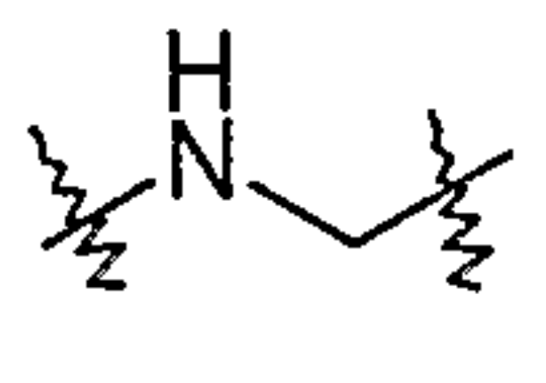
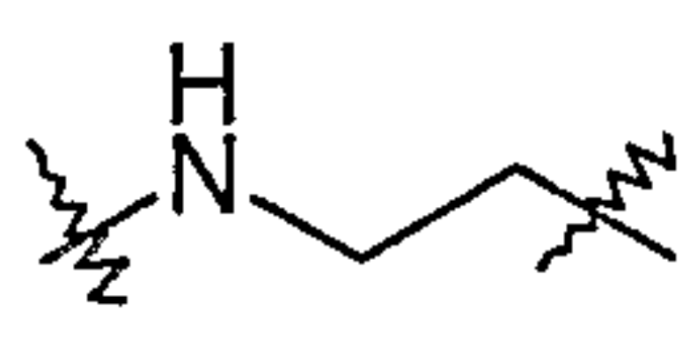
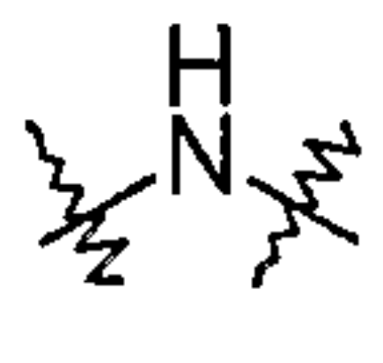
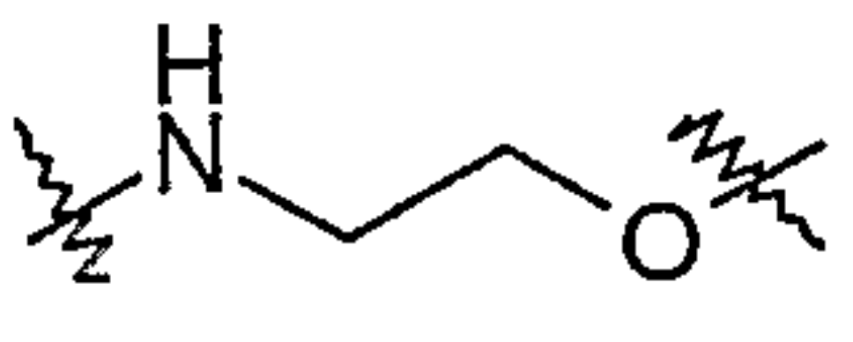
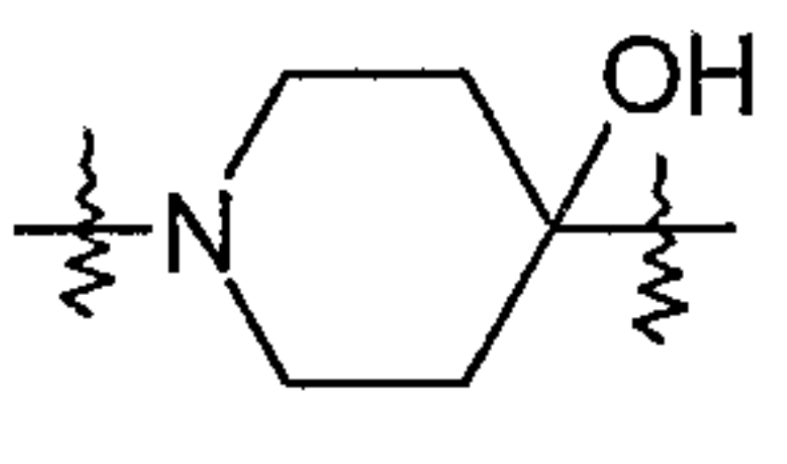
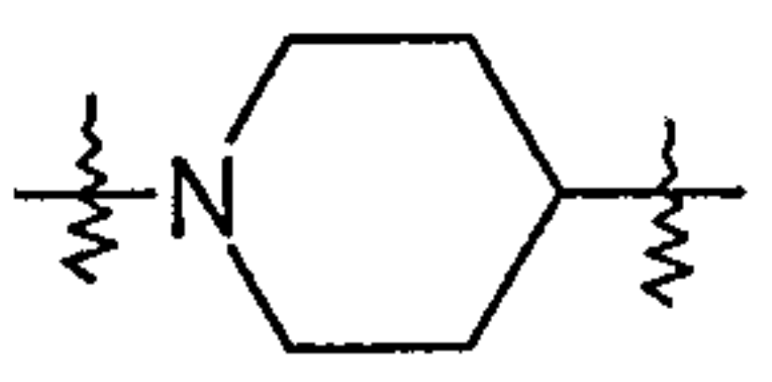
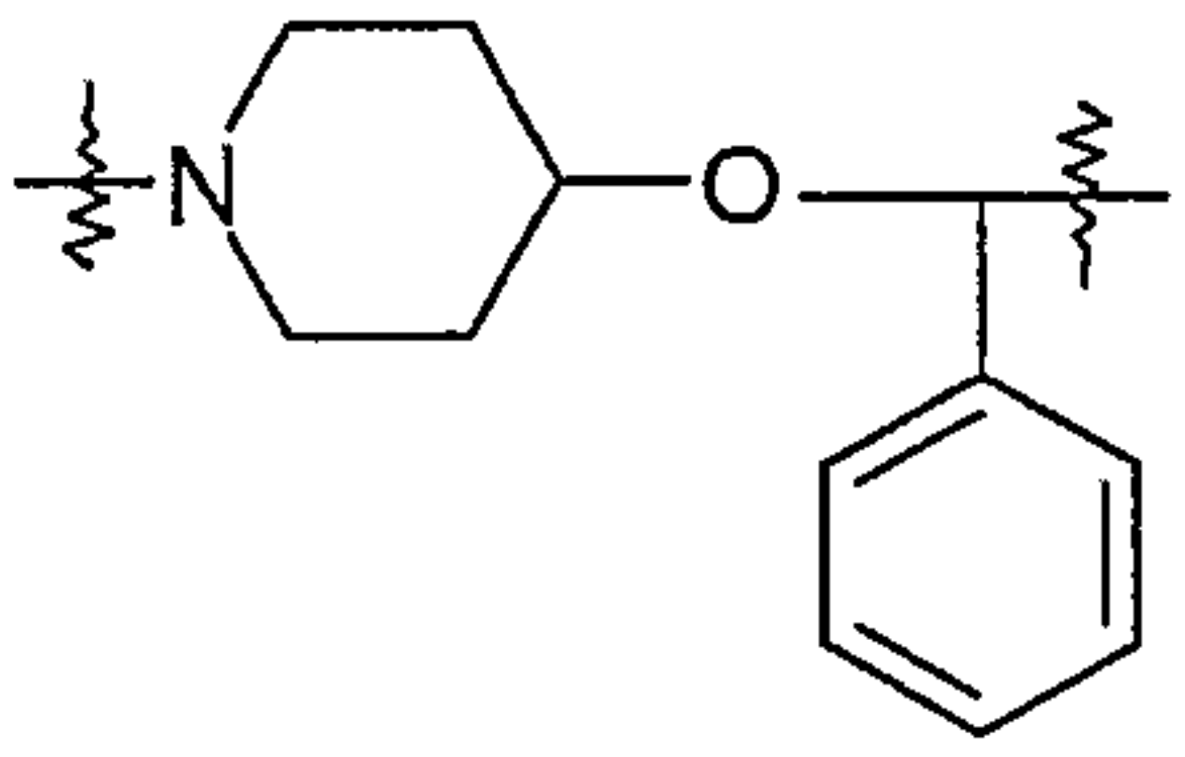
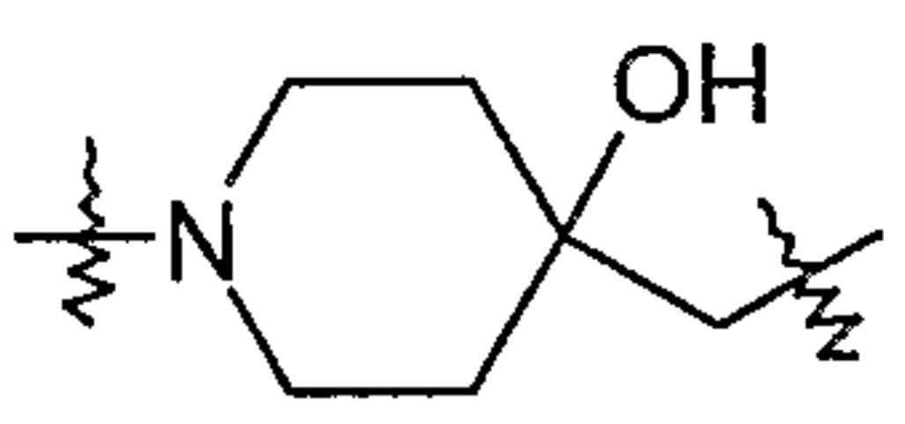
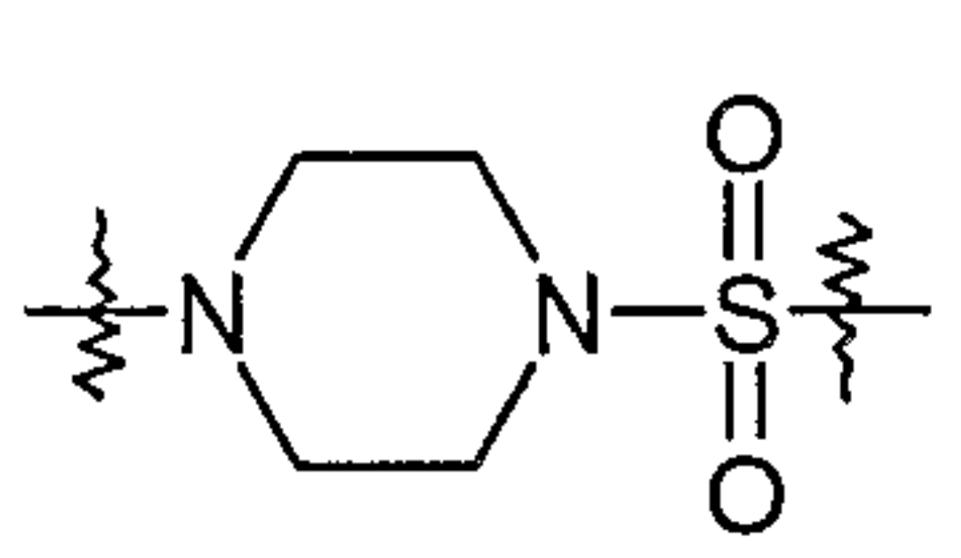
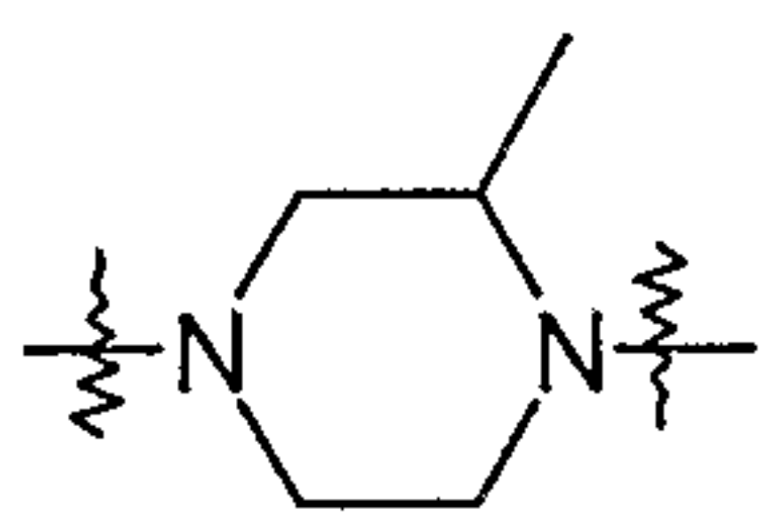
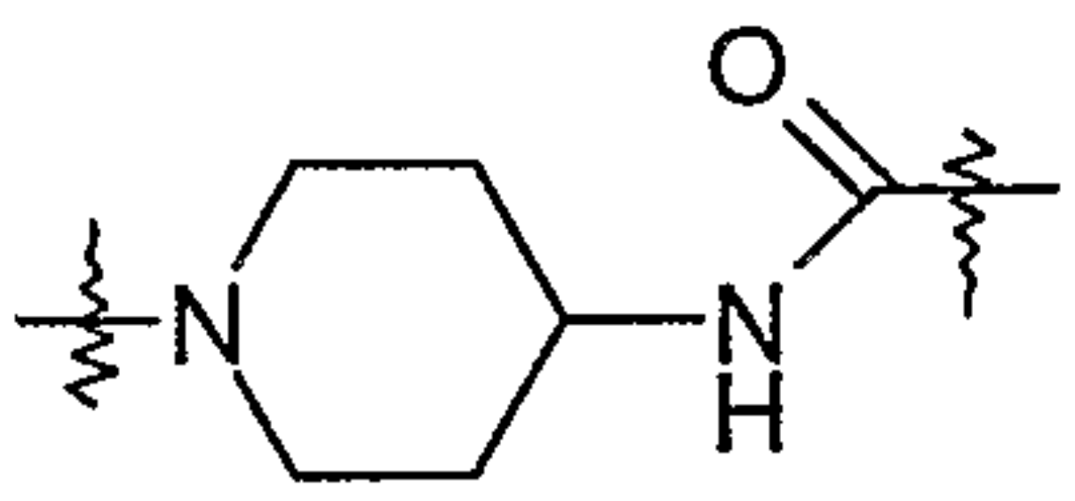
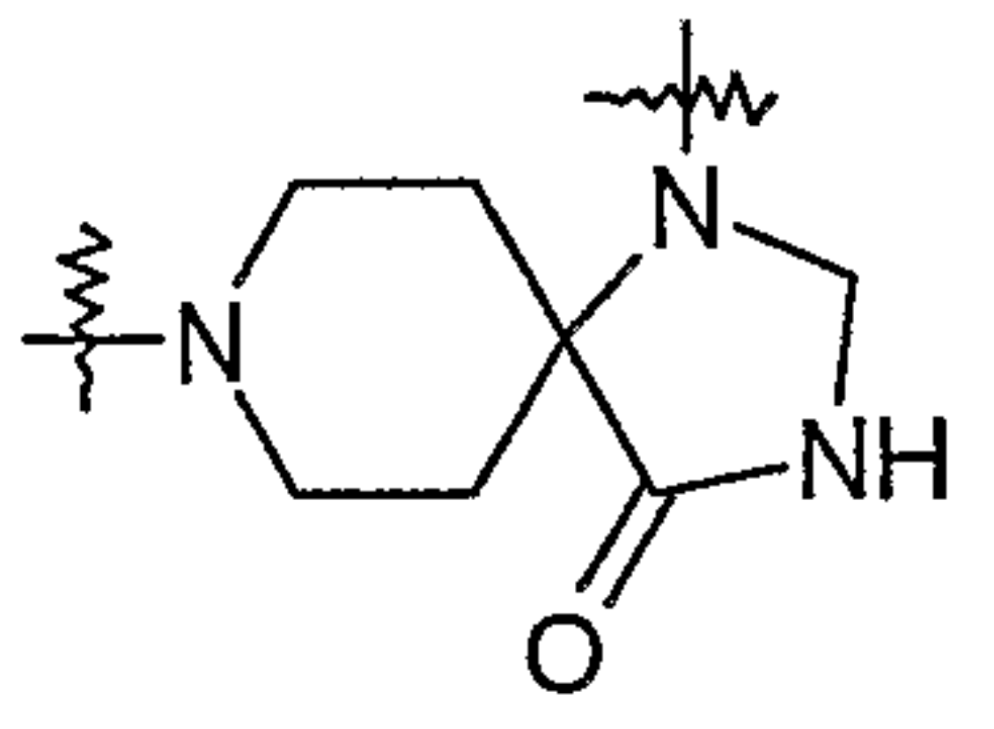
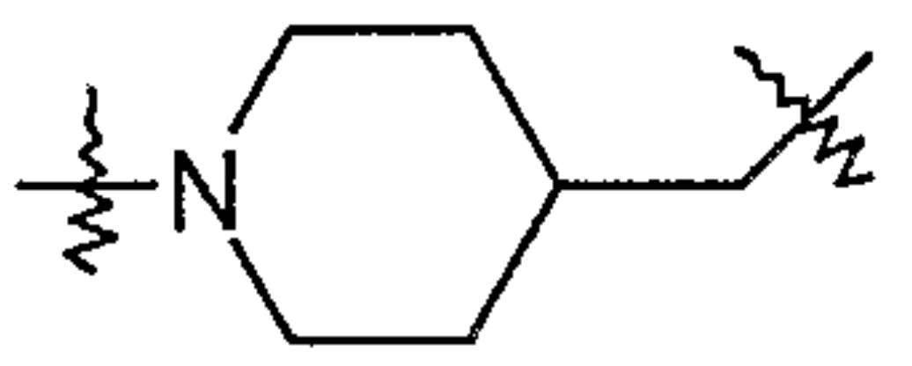
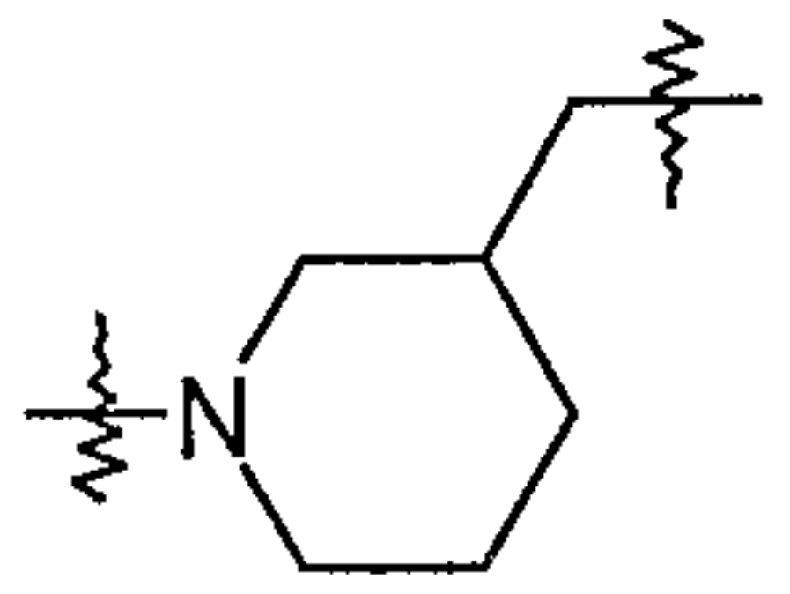
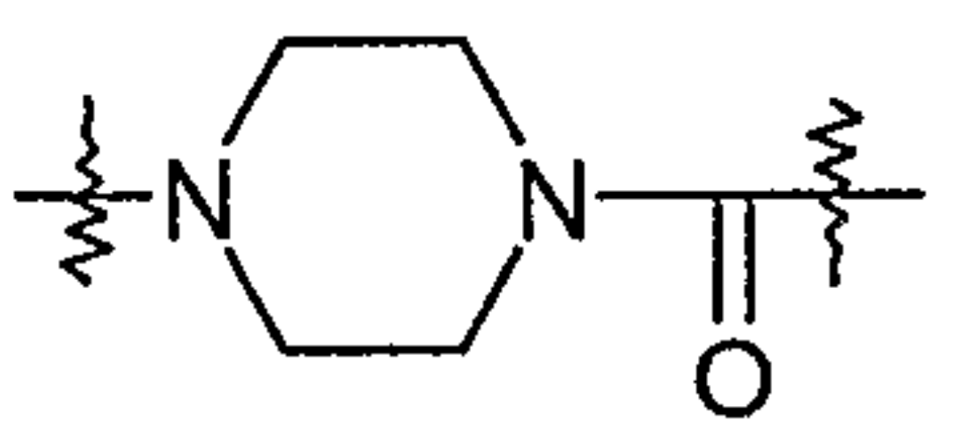
10. A process for preparing a compound of formula I, comprising:



I

combining Ar^1-Q-H with 3-(1-piperidino)propylamine and a haloformate, wherein Ar^1 is selected from phenyl, 2-pyridyl, 4-pyridyl; 1-naphthyl, 2-naphthyl, 1,2,3,4-tetrahydro-naphth-1-yl; 1,2,3,4-tetrahydro-naphth-5-yl; 2-thienyl, 3-thienyl, 2-furyl, 2-thiazolyl, benzo[1,3]dioxol-5-yl, 4,5,6,7-tetrahydro-thieno[2,3-c]pyridin-2-yl; 2,3-dihydro-benzo[1,4]dioxin-6-yl; 2,3-dihydro-benzo[1,4]dioxin-2-yl; quinol-2-yl, isoquinol-5-yl; 1H-indol-4-yl, 1H-indol-3-yl, 1H-indol-2-yl, 1H-indol-7-yl, 1-pyrroyl, 1H-benzotriazol-5-yl, 1H-benzoimidazol-5-yl, 2,3-dihydro-benzofuran-5-yl, 2,3-dihydro-isoindol-1-on-2-yl; benzo[1,2,3]thiadiazol-5-yl, benzo[1,2,3]thiadiazol-6-yl, benzothiazol-6-yl, benzothiazol-2-yl, and 4H-benzo[1,4]oxazin-3-on-7-yl, wherein Ar^1 is further optionally substituted with one or more groups selected from C_{1-4}alkyl, C_{2-4}alkenyl, C_{1-4}alkoxy, C_{1-4}alkenyloxy, phenoxy, 4-methoxyphenoxy, benzyl, acetoamino, methylsulfonyl, methoxycarbonyl, nitro, chloro, fluoro, bromo, iodo, 1-pyrroyl, 2-methyl-pyrro-1-yl, amino, phenylsulfonyl, aceto,1-piperidinyl, [1,2,3]thiadiazol-4-yl, 4-morpholinyl, methoxy, ethoxy, isopropyloxy, methythio, cyano, dimethylamino, hydroxy, methylaminosulfonyl, trifluoromethyl, trifluoromethoxy, phenyl, phenoxy, benzyl, 4-hydroxyl-phenyl, diethylamino, methylsulfonyl, aminosulfonyl, cyclohexyl, 1-pyrrolyl, 1H-pyrazol-3-yl, 5-tetrazolyl, 1-piperidinyl, 1-pyrazolyl, methylsulfonylmethyl, 3,5-dimethyl-pyrazolyl, pyrrolidin-2-on-1-yl; and

Q is selected from

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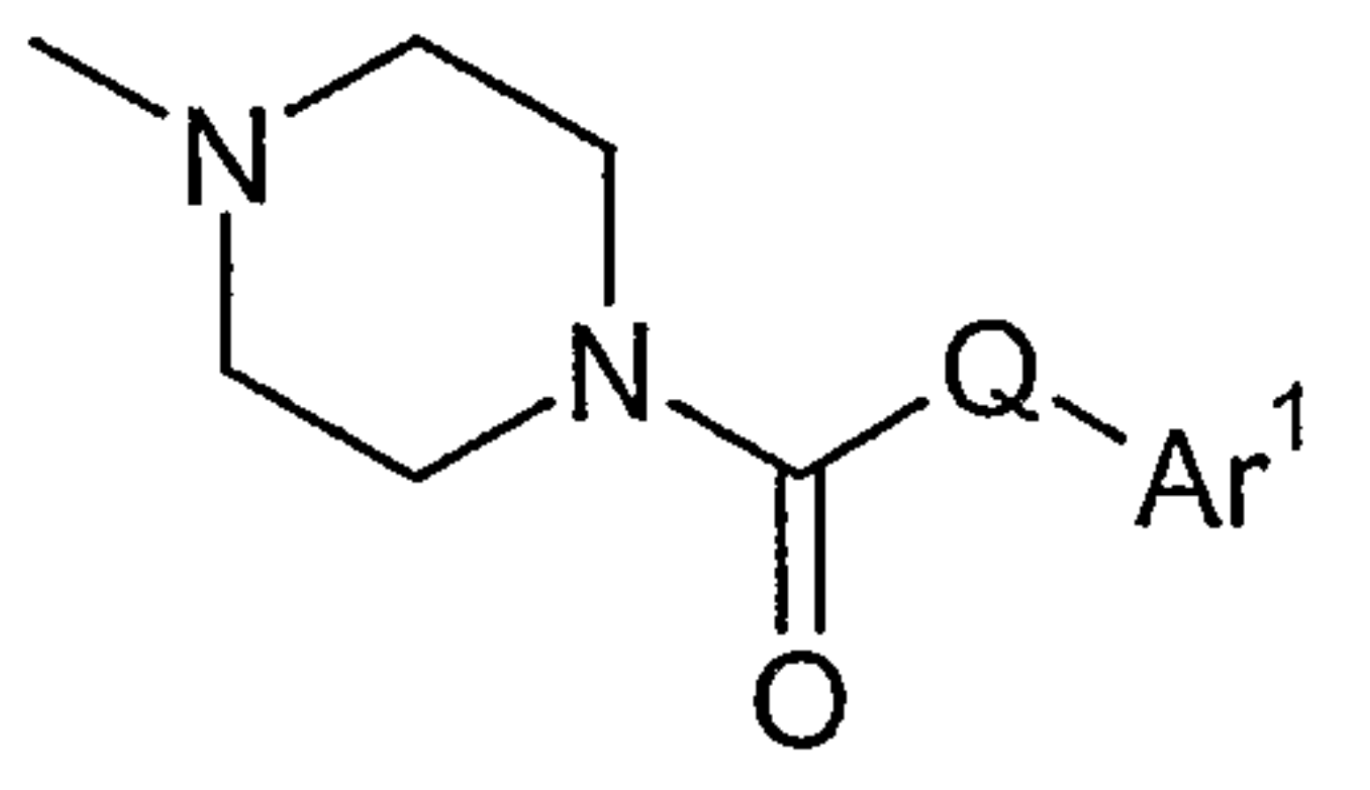
and wherein the left side nitrogen atom in the above-identified structures of Q is connected to the H in Ar^1-Q-H to form an amino group.

11. A process for preparing a compound of formula II, comprising:



II

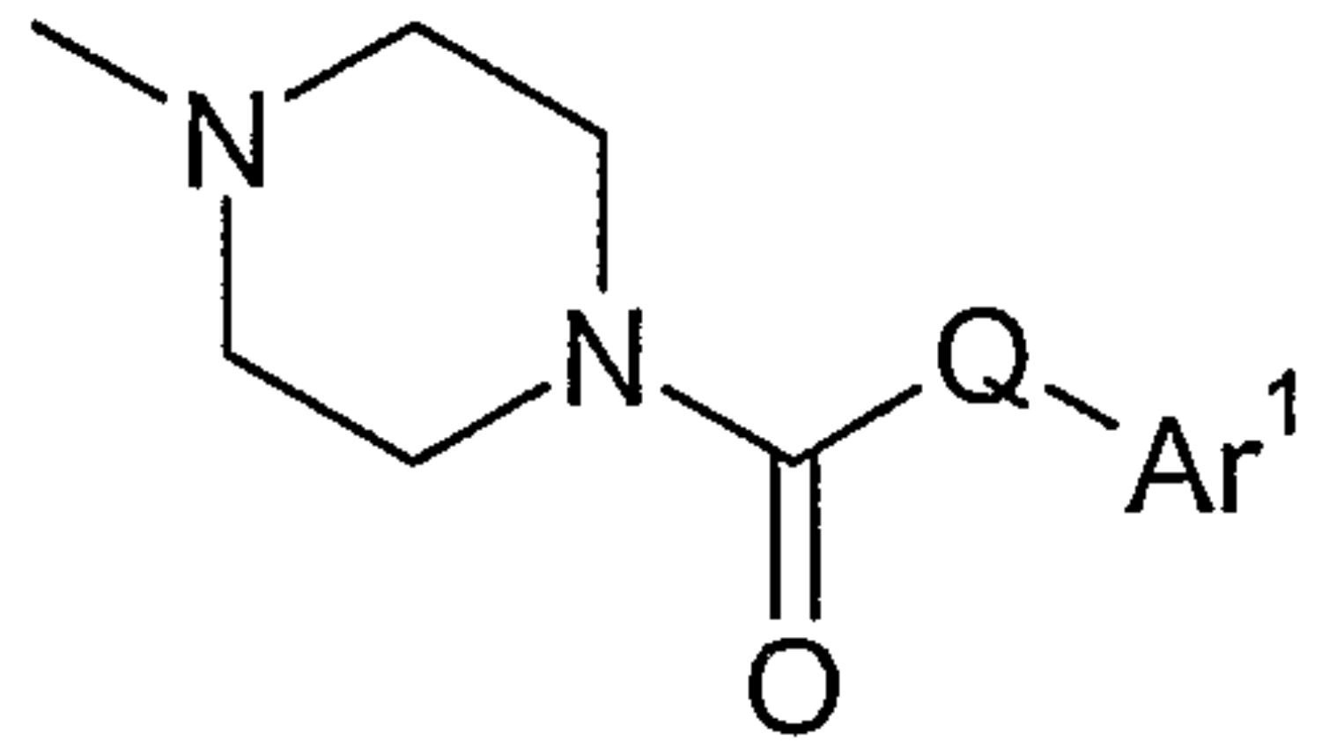
reacting Ar^1-Q-H with N-methyl piperazine and a haloformate,

Ar^1 is selected from C_{6-10}aryl and C_{2-9}heteroaryl, wherein said C_{6-10}aryl and C_{2-9}heteroaryl are optionally substituted with one or more groups selected from -R, $-NO_2$,

-OR, -Cl, -Br, -I, -F, $-CF_3$, $-OCF_3$, -C(=O)R, -C(=O)OH, $-NH_2$, -SH, -NHR, $-NR_2$, -SR, $-SO_3H$, $-SO_2R$, $-SO_2NR$, -S(=O)R, -CN, -OH, -C(=O)OR, $-C(=O)NR_2$, -NRC(=O)R, and -NRC(=O)-OR, wherein R is, independently, a hydrogen, C_{3-6}cycloalkyl, C_{3-6}heterocyclyl, phenyl, benzyl, C_{1-6}alkyl or C_{2-6}alkenyl and wherein said R is further optionally substituted with one or more groups selected from methyl, methoxy, hydroxy and halogen;

Q is a divalent or trivalent group that connects the carbonyl with Ar^1, wherein said divalent or trivalent group contains at least one nitrogen, wherein said nitrogen of Q is connected to the H in Ar^1-Q-H to form an amino, and said trivalent group is fused with Ar^1; and said Q-H of Ar^1-Q-H forms an amino group.

12. A process of preparing a compound of formula II, comprising:



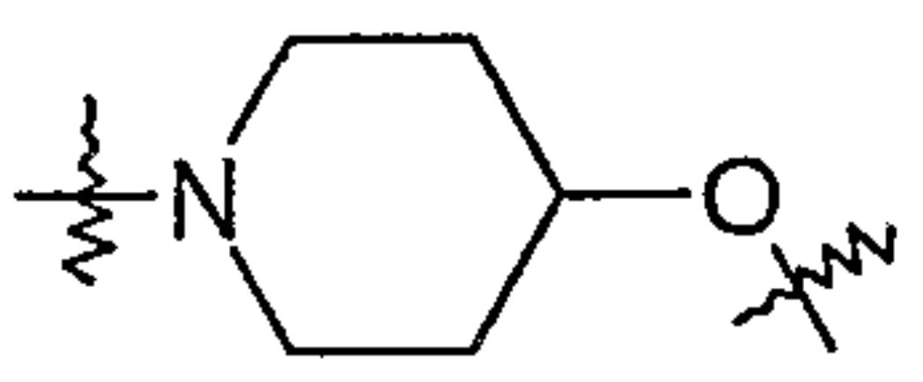
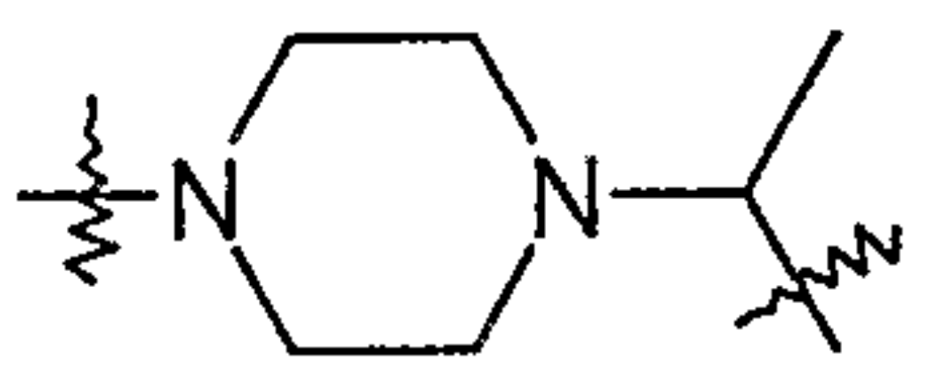
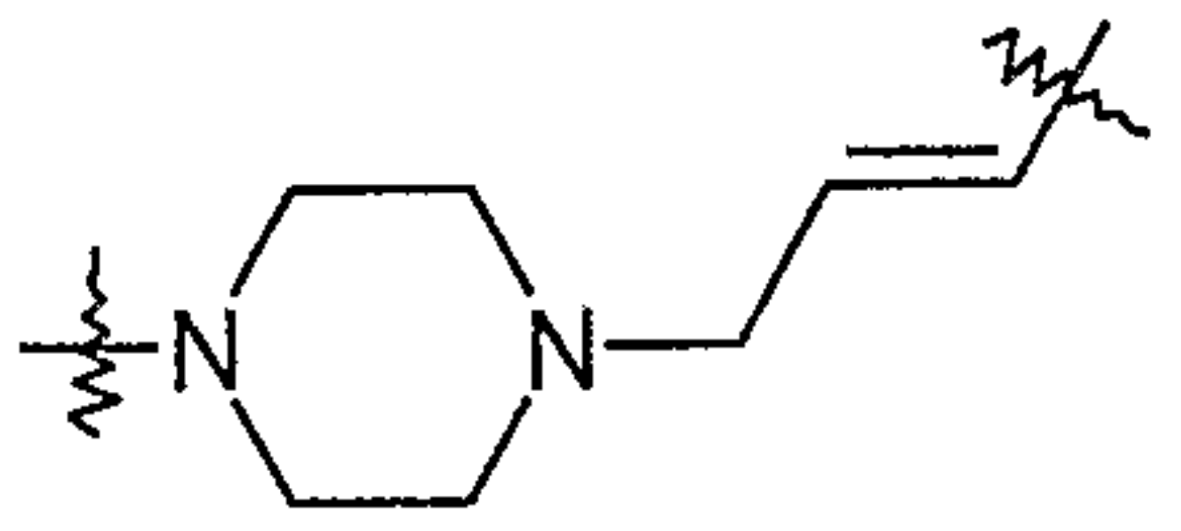
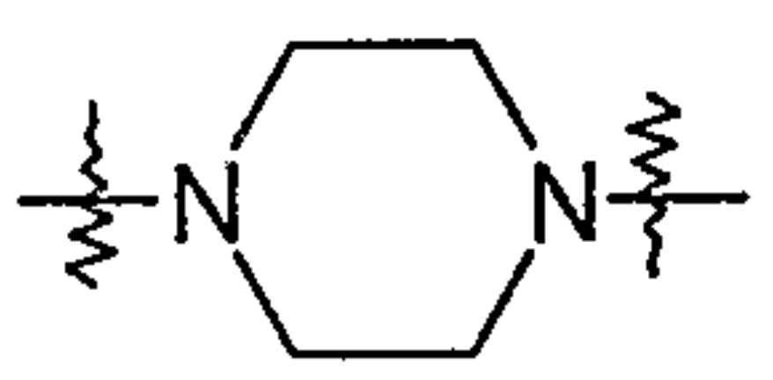
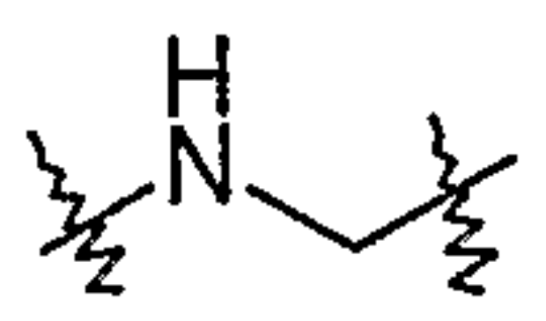
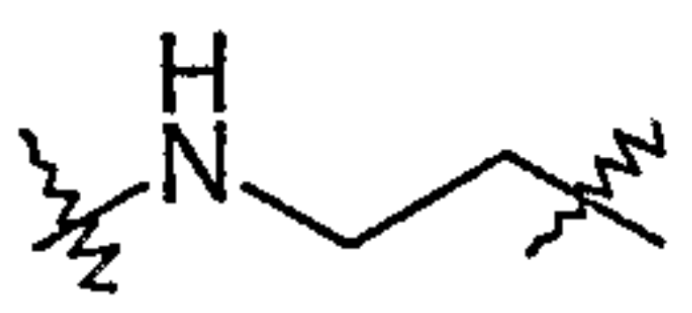
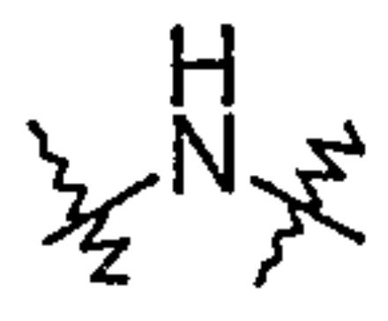
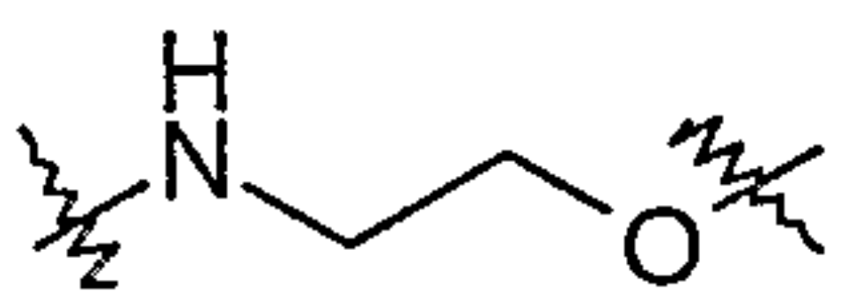
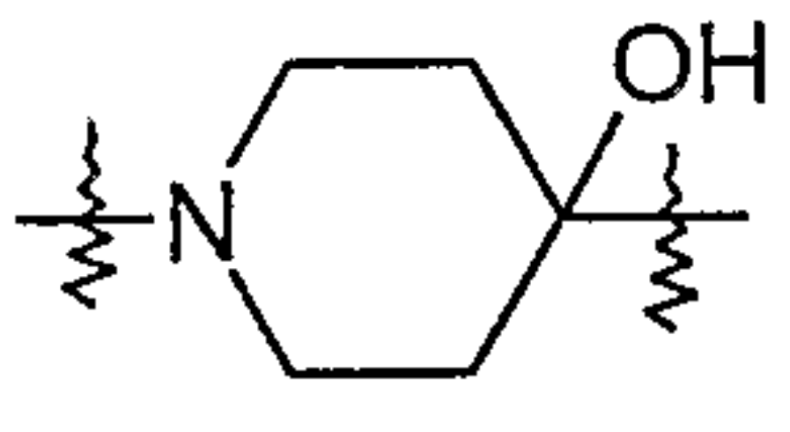
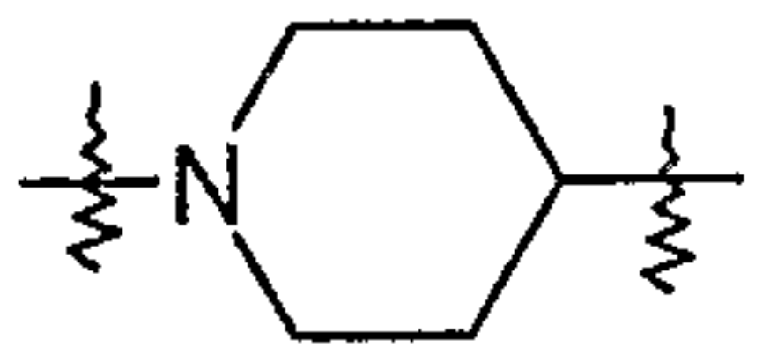
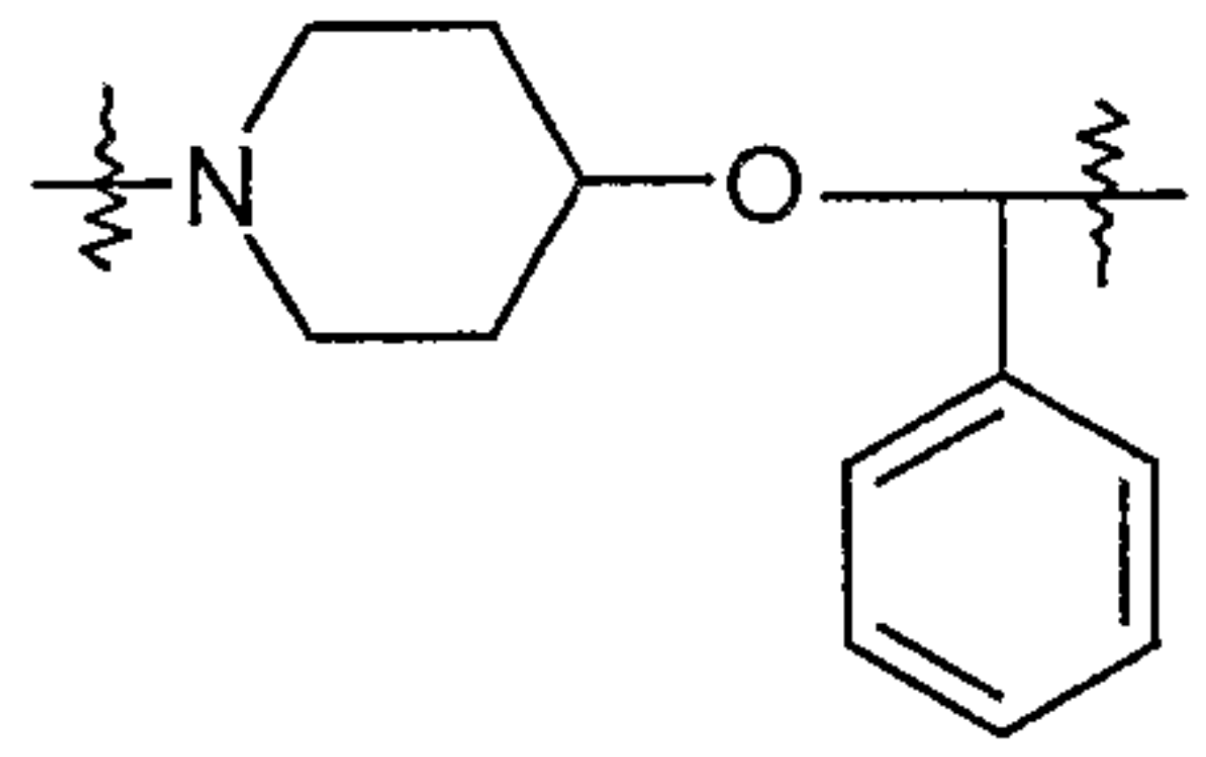
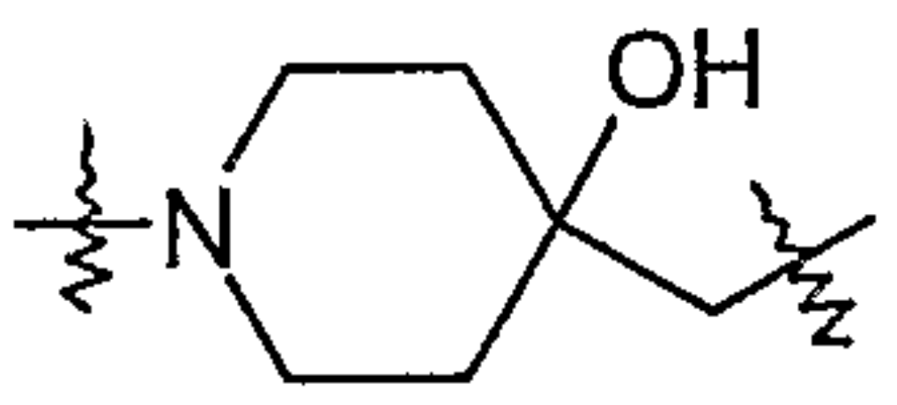
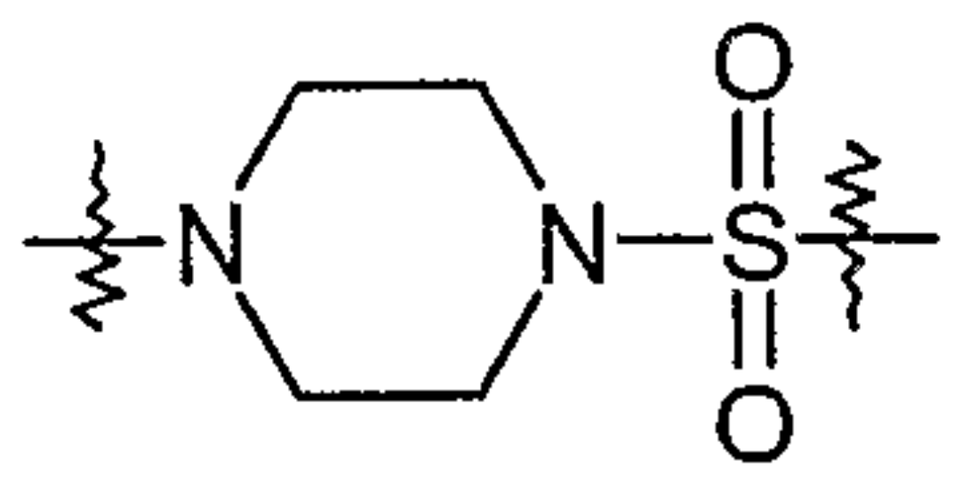
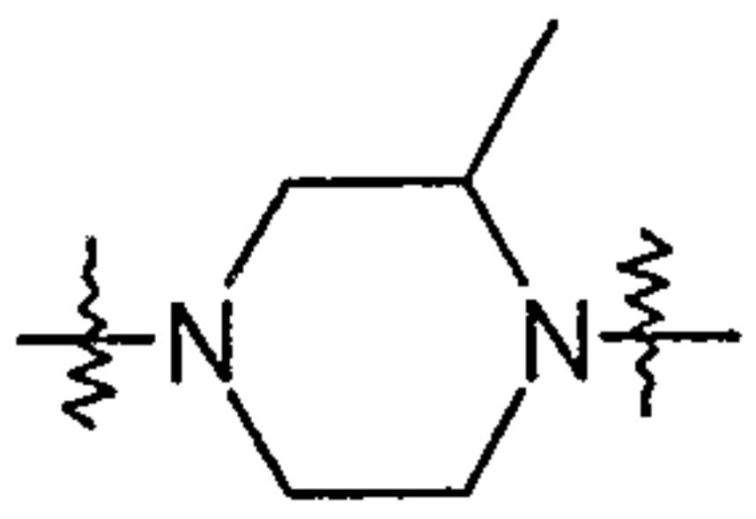
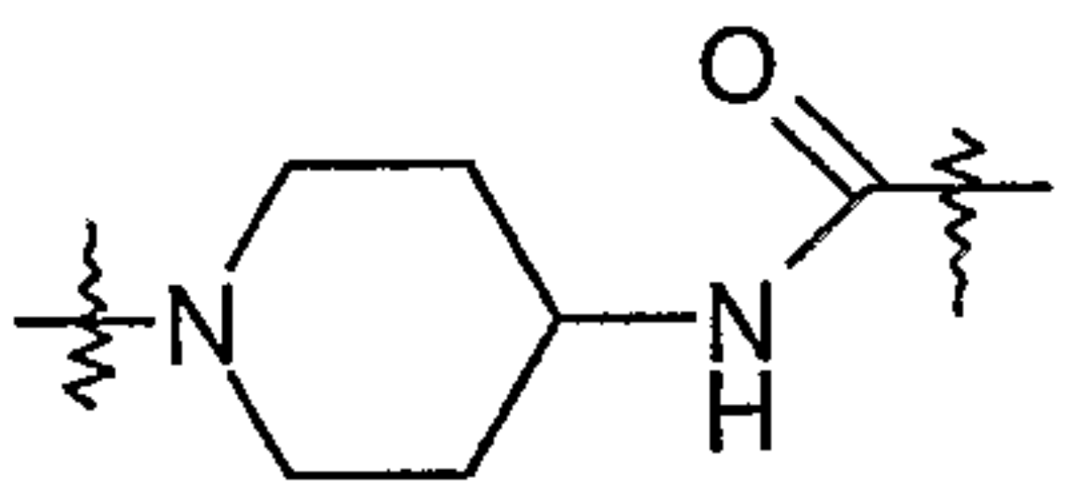
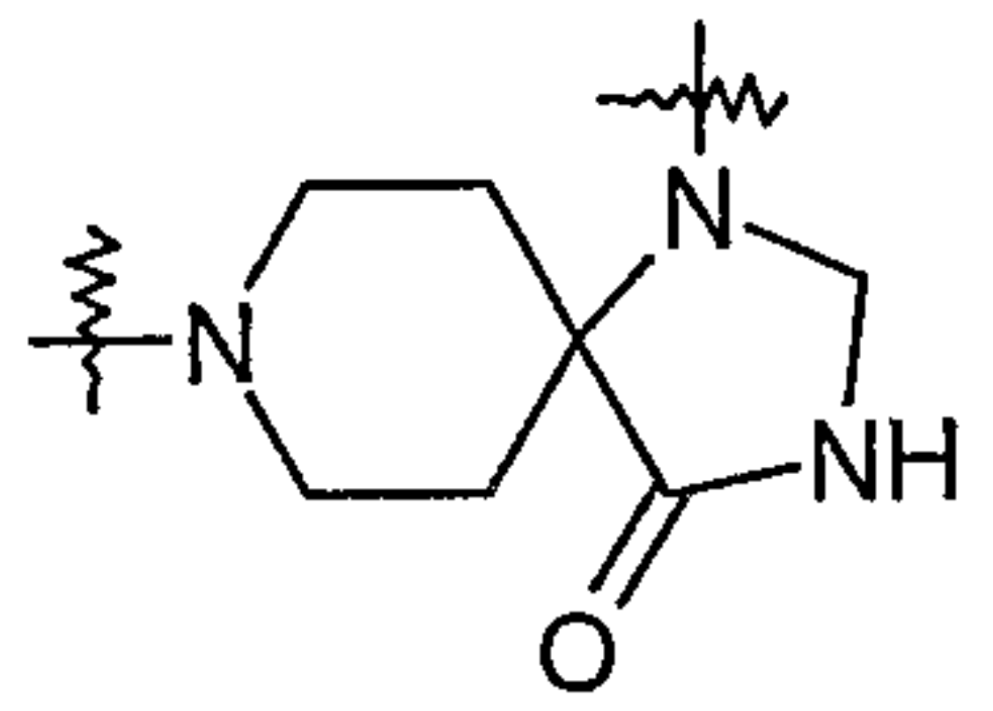
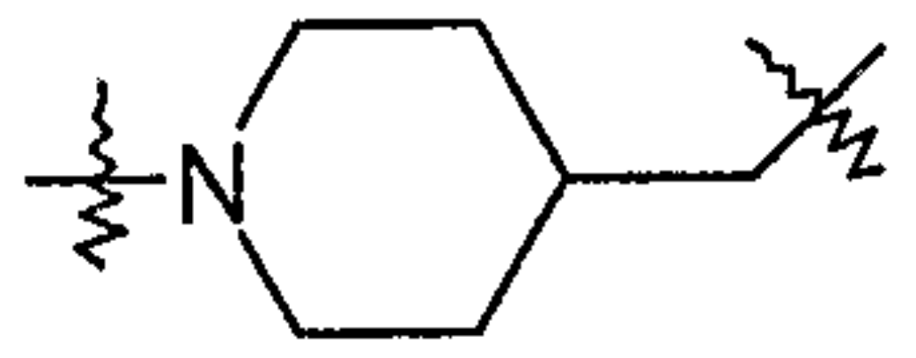
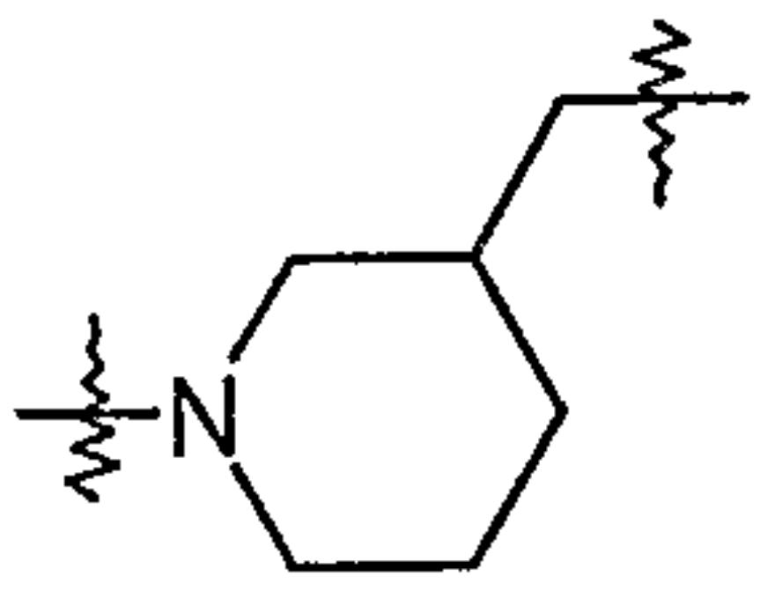
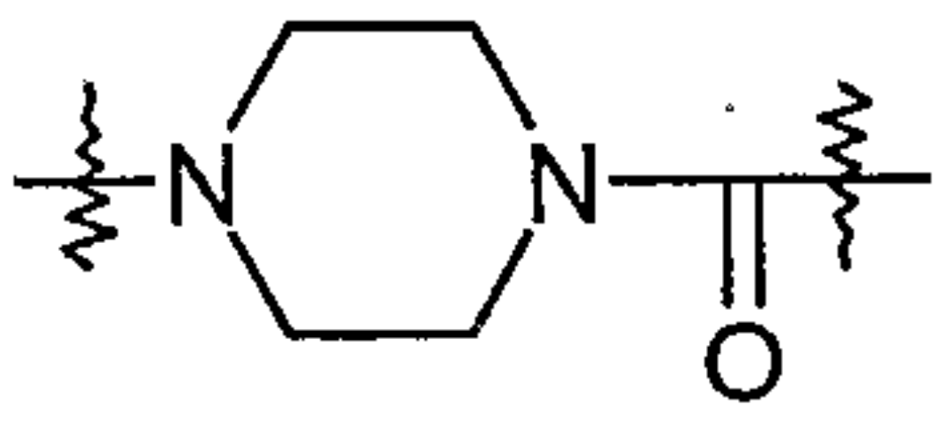
II

combining Ar^1-Q-H with N-methyl piperazine and a haloformate,

wherein Ar^1 is selected from phenyl, 2-pyridyl, 4-pyridyl; 1-naphthyl, 2-naphthyl, 1,2,3,4-tetrahydro-naphth-1-yl; 1,2,3,4-tetrahydro-naphth-5-yl; 2-thienyl, 3-thienyl, 2-furyl, 2-thiazolyl, benzo[1,3]dioxol-5-yl, 4,5,6,7-tetrahydro-thieno[2,3-c]pyridin-2-yl; 2,3-dihydro-benzo[1,4]dioxin-6-yl; 2,3-dihydro-benzo[1,4]dioxin-2-yl; quinol-2-yl, isoquinol-5-yl; 1H-indol-4-yl, 1H-indol-3-yl, 1H-indol-2-yl, 1H-indol-7-yl, 1-pyrroyl, 1H-benzotriazol-5-yl, 1H-benzoimidazol-5-yl, 2,3-dihydro-benzofuran-5-yl, 2,3-dihydro-isoindol-1-on-2-yl; benzo[1,2,3]thiadiazol-5-yl, benzo[1,2,3]thiadiazol-6-yl, benzothiazol-6-yl, benzothiazol-2-yl, and 4H-benzo[1,4]oxazin-3-on-7-yl, wherein Ar^1 is further optionally substituted with one or more groups selected from C_{1-4}alkyl, C_{2-4}alkenyl, C_{1-4}alkoxy, C_{1-4}alkenyloxy, phenoxy, 4-methoxyphenoxy, benzyl, acetoamino, methylsulfonyl, methoxycarbonyl, nitro, chloro, fluoro, bromo, iodo, 1-pyrroyl, 2-methyl-pyrro-1-yl, amino, phenylsulfonyl, aceto, 1-piperidinyl, [1,2,3]thiadiazol-4-yl, 4-morpholinyl, methoxy, ethoxy, isopropyloxy, methythio, cyano, dimethylamino, hydroxy, methylaminosulfonyl, trifluoromethyl, trifluoromethoxy, phenyl, phenoxy, benzyl, 4-hydroxyl-phenyl, diethylamino, methylsulfonyl, aminosulfonyl, cyclohexyl, 1-pyrrolyl, 1H-pyrazol-3-yl, 5-tetrazolyl, 1-

piperidinyl, 1-pyrazolyl, methylsulfonylmethyl, 3,5-dimethyl-pyrazolyl, pyrrolidin-2-on-1-yl; and

Q is selected from

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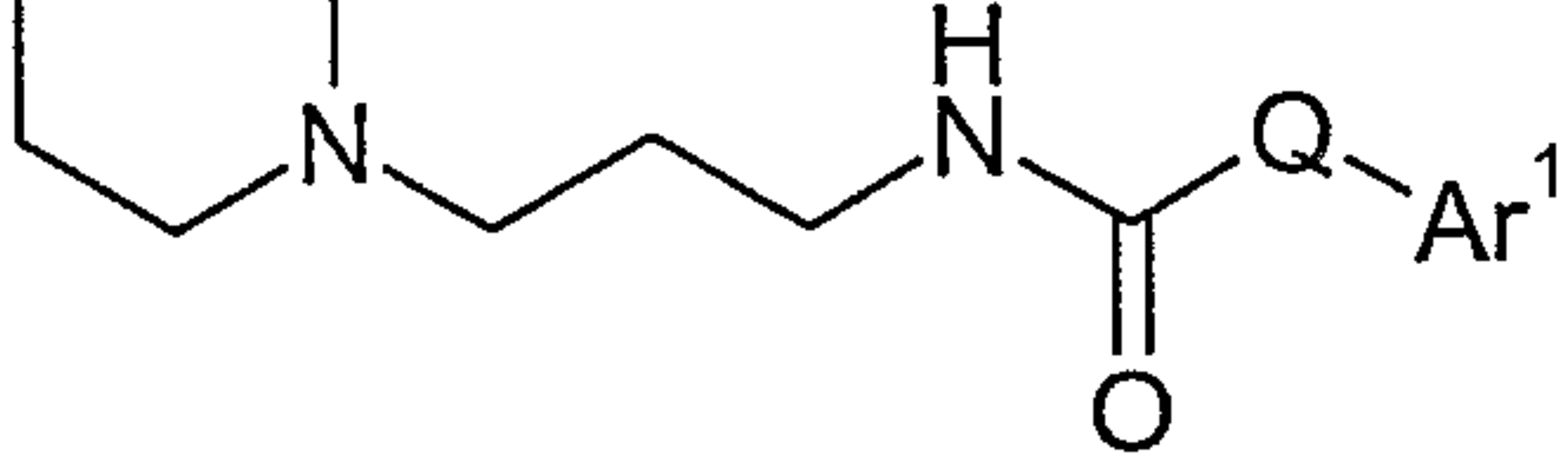
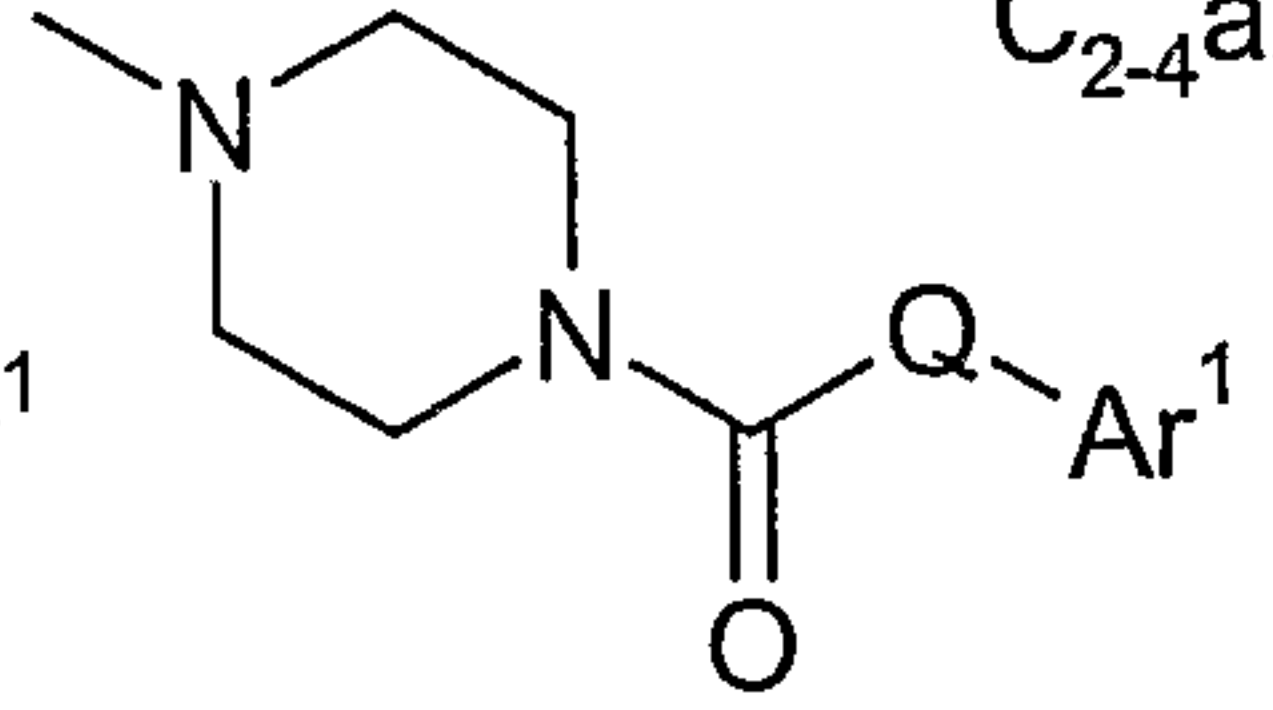
and wherein the left side nitrogen atom in the above-identified structures of Q is connected to the H in Ar^1-Q-H to form an amino group.



(I)



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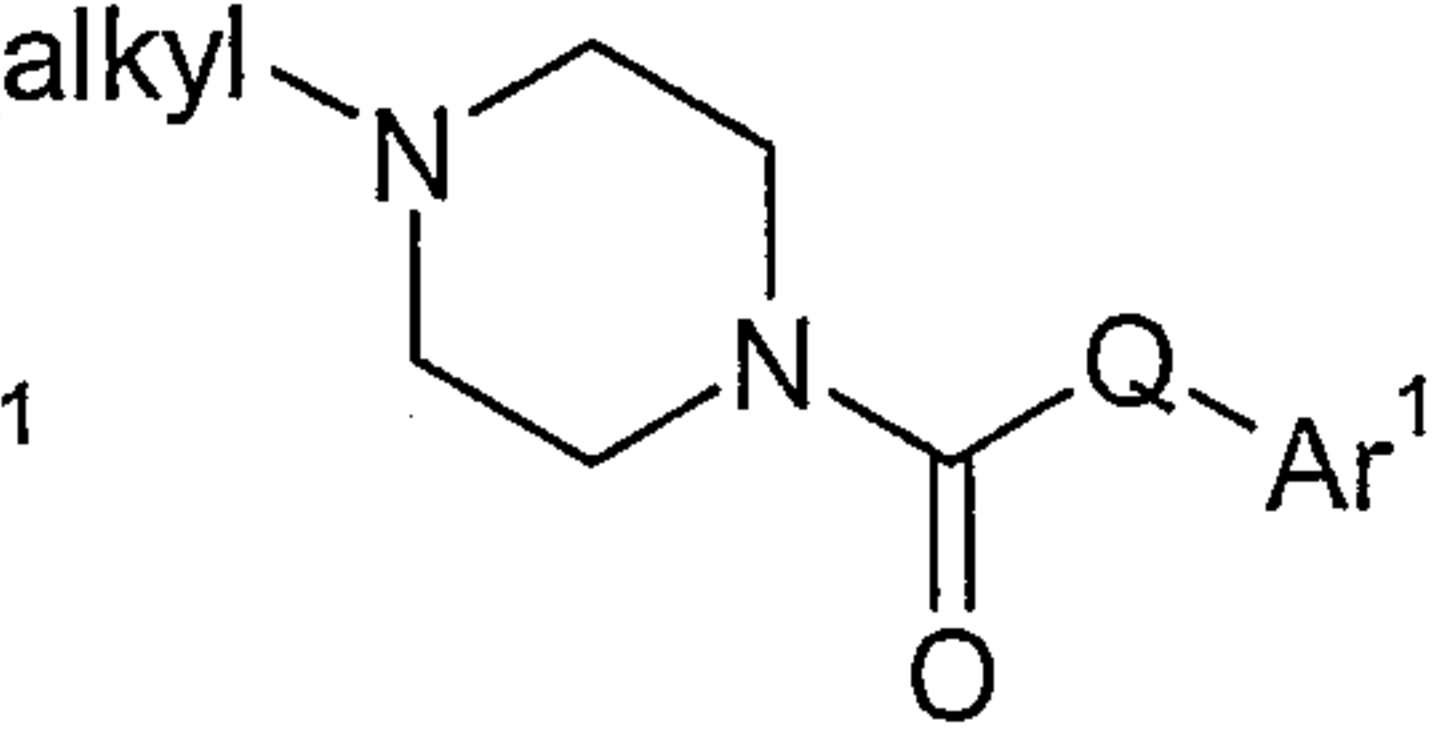

(III)