SUBSTITUTED PIPERAZINES AS CB1 ANTAGONISTS

BACKGROUND OF THE INVENTION

The CB_1 receptor is one of the most abundant neuromodulatory receptors in the brain, and is expressed at high levels in the hippocampus, cortex, cerebellum, and basal ganglia (e.g., Wilson et al., *Science*, **2002**, vol. 296, 678-682). Selective CB_1 receptor antagonists, for example pyrazole derivatives such as rimonabant (e.g., U.S. 6,432,984), can be used to treat various conditions, such as obesity and metabolic syndrome (e.g., Bensaid et al., *Molecular Pharmacology*, **2003** vol. 63, no. 4, pp. 908-914; Trillou et al., *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2002** vol. 284, R345-R353; Kirkham, *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2002** vol. 284, R343-R344), neuroinflammatory disorders (e.g., Adam, et al., *Expert Opin. Ther. Patents*, **2002**, vol. 12, no. 10, 1475-1489; U.S. 6,642,258), cognitive disorders and psychosis (e.g., Adam et al., *Expert Opin. Ther. Pat.*, **2002**, vol. 12, pp. 1475-1489), addiction (e.g., smoking cessation; U.S. Patent Publ. 2003/0087933), gastrointestinal disorders (e.g., Lange et al., *J. Med. Chem.* **2004**, vol. 47, 627-643) and cardiovascular conditions (e.g., Porter et al., *Pharmacology and Therapeutics*, **2001** vol. 90, 45-60; Sanofi-Aventis Publication, Bear Stearns Conference, New York, September 14, 2004, pages 19-24).

However, there is still a need for improved cannabinoid agents, particularly selective CB_1 receptor antagonists, with fewer side-effects and improved efficacy. It is therefore an object of the present invention to provide substituted piperazines useful in the treatment of diseases or conditions mediated by CB_1 receptors.

WO 95/25443, U.S. 5,464,788, and U.S. 5,756,504 describe N-arylpiperazine compounds useful for treating preterm labor, stopping labor, and dysmenorrhea. However, none of the N-aryl piperazines exemplified therein have an aryl and/or heteroaryl substituent at both the 1- and 2-positions of the piperazine ring.

WO 01/02372 and U.S. Published Application No. 2003/0186960 describe cyclized amino acid derivatives for treating or preventing neuronal damage associated with neurological diseases. However, none of the 3-aryl piperazine 2-ones exemplified therein have an aryl and/or heteroaryl substituent at both the 1- and 2-positions of the piperazine ring.

WO 96/01656 describes radiolabelled substituted piperazines useful in pharmacological screening procedures, including labeled N-aryl piperazines. However, none of the N-aryl piperazines exemplified therein have an aryl and/or heteroaryl substituent at both the 1- and 2-positions of the piperazine ring.

U.S. 5,780,480 describes N-aryl piperazines useful as fibrinogen receptor antagonists for inhibiting the binding of fibrinogen to blood platelets, and for inhibiting the aggregation of blood platelets. However, none of the N-aryl piperazines exemplified therein have an aryl and/or heteroaryl substituent at both the 1- and 2-positions of the piperazine ring.

WO 03/008559 describes choline analogs useful for treating conditions or disorders. However, the only substituted piperazine derivative exemplified is N-(2-hydroxyethyl)-N'-(2-pyridylmethyl)-piperazine.

JP 3-200758, JP 4-26683, and JP 4-364175 describe N,N'-diarylpiperazines (i.e., 1,4-diarylpiperazines) prepared by reacting bis(2-hydroxyethyl)arylamines with an amine such as aniline. However, no 1,2-disubstituted piperazines are exemplified.

WO 97/22597 describes various 1,2,4-trisubstituted piperazine derivatives as tachykinin antagonists for treating tachykinin-mediated diseases such as asthma, bronchitis, rhinitis, cough, expectoration, etc. However, none of the 1,2,4-trisubstituted piperazine derivatives exemplified therein have an aryl and/or heteroaryl substituent at both the 1- and 2-positions of the piperazine ring.

EP 0268222, WO 88/01131, U.S. 4,917,896, and U.S. 5,073,544 describe compositions for enhancing the penetration of active agents through the skin, comprising azacyclohexanes, including N-acyl and N,N'-diacylpiperazines. However, none of the N-acyl or N,N'-diacylpiperazines exemplified therein have an aryl and/or heteroaryl substituent at both the 1- and 2-positions of the piperazine ring.

U.S. 6,528,529 describes compounds, including N,N'-disubstituted piperazines, which are selective for muscarinic acetylcholine receptors and are

useful for treating diseases such as Alzheimer's disease. However, none of the N,N'-disubstituted piperazines exemplified therein have an aryl and/or heteroaryl substituent at both the 1- and 2-positions of the piperazine ring.

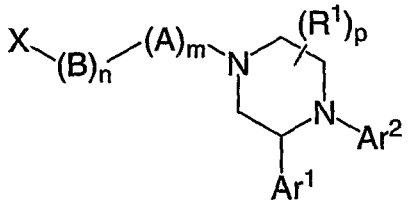
NL 6603256 describes various biologically active piperazine derivatives. However, none of the piperazine derivatives exemplified therein have a substituted aryl and/or heteroaryl substituent at both the 1- and 2-positions of the piperazine ring.

Wikström et al., J. Med. Chem. 2002, 45, 3280-3285, describe the synthesis of 1,2,3,4,10,14b-hexahydro-6-methoxy-2-methyldibnzo[c,f]pyrazine[1,2-a]azepin. However, none of the piperazine intermediates described therein have a substituted aryl and/or heteroaryl substituent at both the 1- and 2-positions of the piperazine ring.

BRIEF SUMMARY OF THE INVENTION

In its many embodiments, the present invention provides a novel class of substituted piperazine compounds as selective CB_1 receptor antagonists for treating various conditions including, but not limited to metabolic syndrome (e.g., obesity, waist circumference, lipid profile, and insulin sensitivity), neuroinflammatory disorders, cognitive disorders, psychosis, addictive behavior, gastrointestinal disorders, and cardiovascular conditions.

The selective CB_1 receptor antagonists of the present invention are piperazine derivatives having the structure of Formula (I):



(I)

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

Ar^1 and Ar^2 are independently aryl or heteroaryl,

wherein said aryl and heteroaryl are substituted with one or more groups Y^1;

n and m are independently 0 or 1;

A is selected from the group consisting of –C(O)-, $-S(O)_2-$, $-C(=N-OR^2)-$, and $-(C(R^2)_2)_q-$ wherein q is 1, 2, or 3;

B is selected from the group consisting of $-N(R^2)-$, -C(O)-, and $-(C(R^3)_2)_r-$ wherein r is 1 or 2,

with the proviso that when B is –C(O)-, then A is –C(O)- or $-(C(R^2)_2)_q-$;

X is selected from the group consisting of H, alkyl, -S-alkyl, $-S(O)_2$-alkyl, $-S(O)_2$-cycloalkyl, $-S(O)_2$-aryl, $-S(O)_2$-heteroaryl, cycloalkyl, benzo-fused cycloalkyl, benzo-fused heterocycloalkyl, benzo-fused heterocycloalkenyl, heterocycloalkyl, $-C(R^2)=C(R^2)$-aryl, $-C(R^2)=C(R^2)$-heteroaryl, $-OR^2$, -O-alkylene-O-alkyl, -S-aryl, $-N(R^4)_2$, $-(C(R^2)_2)_s$-heteroaryl, -C(O)-O-alkyl, -C(O)-aryl, -C(O)-heteroaryl, -N=O, -C(S-alkyl)=N-$S(O)_2$-aryl, $-C(N(R^2)_2)=N-S(O)_2$-aryl, and $-(C(R^2)_2)_s$-aryl wherein s is 0, 1, or 2,

wherein the heteroaryl portion of said $-(C(R^2)_2)_s$-heteroaryl, the aryl portion of said $-C(R^2)=C(R^2)$-aryl, the heteroaryl portion of said $-C(R^2)=C(R^2)$-heteroaryl, the aryl portion of said -S-aryl, the aryl portion of said $-S(O)_2$-aryl, the heteroaryl portion of said $-S(O)_2$-heteroaryl, the aryl portion of said -C(O)-aryl, the heteroaryl portion of said -C(O)-heteroaryl, the aryl portion of said $-(C(R^2)_2)_s$-aryl, the aryl portion of said -C(S-alkyl)=N-$S(O)_2$-aryl, the aryl portion of said $-C(N(R^2)_2)=N-S(O)_2$-aryl, the benzo portion of said benzo-fused cycloalkyl, the benzo portion of said benzo-fused heterocycloalkyl, and the benzo portion of said benzo-fused heterocycloalkenyl of X are unsubstituted or substituted with one or more groups Y^1, and

said cycloalkyl, the cycloalkyl portion of said $-S(O)_2$-cycloalkyl, said heterocycloalkyl, the cycloalkyl portion of said benzo-fused cycloalkyl, the heterocycloalkyl portion of said benzo-fused heterocycloalkyl, and the heterocycloalkenyl portion of said benzo-fused heterocycloalkenyl of X are unsubstituted or substituted with one or more groups Y^2;

each R^1 is independently selected from the group consisting of alkyl, haloalkyl, -alkylene-$N(R^5)_2$, -alkylene-OR^2, alkylene-N_3, -alkylene-CN, and alkylene-O-$S(O)_2$-alkyl; or

two R^1 groups attached to the same ring carbon atom form a carbonyl group;

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

each R^2 is independently H, alkyl, or aryl,

wherein said aryl of R^2 is unsubstituted or substituted with one or more groups Y^1;

each R^3 is selected from the group consisting of H, alkyl, unsubstituted aryl, aryl substituted with one or more Y^1 groups, $-OR^2$, -alkylene-O-alkyl, and -alkylene-OH;

each R^4 is selected from the group consisting of H, alkyl, aryl,–C(O)-O-alkyl, -C(O)-alkyl, -C(O)-aryl, and $–S(O)_2$aryl,

wherein said aryl, the aryl portion of said –C(O)-aryl, and the aryl portion of said $–S(O)_2$aryl of R^4 are unsubstituted or substituted with one or more Y^1 groups;

each R^5 is selected from the group consisting of H, alkyl, aryl, $-S(O)_2$-alkyl, $-S(O)_2$-cycloalkyl, $-S(O)_2$-aryl, $-C(O)-N(R^2)_2$, -C(O)-alkyl, and –alkylene-OH,

wherein said aryl and the aryl portion of said $–S(O)_2$-aryl of R^5 are unsubstituted or substituted with one or more Z groups;

each Y^1 is independently selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, benzyl, aryl, heteroaryl, -O-aryl, -S-aryl, $-S(O)_2$-alkyl, $-S(O)_2$-cycloalkyl, $-S(O)_2$-aryl, -alkylene-CN, -CN, -C(O)-alkyl, -C(O)-aryl, -C(O)-haloalkyl, -C(O)O-alkyl, $-N(R^2)C(O)$-alkyl, $-N(R^2)C(O)-N(R^2)_2$, -OH, -O-alkyl, -O-haloalkyl, -O-alkylene-C(O)OH, -S-alkyl, -S-haloalkyl, -alkylene-OH, -alkylene-C(O)-O-alkyl, -O-alkylene-aryl, and $-N(R^5)_2$,

wherein said aryl, heteroaryl, the aryl portion of said –O-aryl, the aryl portion of said -S-aryl, the aryl portion of said $–S(O)_2$-aryl, the aryl portion of said benzyl, the aryl portion of said –C(O)-aryl, and the aryl portion of said -O-alkylene-aryl of Y^1 are unsubstituted or substituted with one or more groups Z; or

two groups Y^1 form a $–O-CH_2-O-$ group;

each Y^2 is independently selected from the group consisting of alkyl, haloalkyl, aryl, -alkylene-aryl, -CN, -C(O)-alkyl, $-S(O)_2$-cycloalkyl, -alkylene-$N(R^2)_2$, $-C(O)$-alkylene-$N(R^4)_2$, -C(O)-O-alkyl, -C(O)-aryl, and –C(O)-haloalkyl,

wherein said aryl and the aryl portion of said –C(O)-aryl of Y^2 are unsubstituted or substituted with one or more groups Z; or

two groups Y^2 form a $-O-CH_2CH_2-O-$ group; or

two of said Y^2 substituents attached to the same ring carbon atom of a cycloalkyl, benzo-fused cycloalkyl, benzo-fused heterocycloalkyl, benzo-fused

heterocycloalkenyl, or heterocycloalkyl ring, together with the ring carbon atom to which they are both attached, form a carbonyl group; and

each Z is independently selected from the group consisting of alkyl, halo, haloalkyl, -OH, -O-alkyl, and -CN.

In another embodiment, the present invention also provides for compositions comprising at least one selective CB_1 receptor antagonist compound of Formula (I), above, or a pharmaceutically acceptable salt, solvate, or ester thereof, and a pharmaceutically acceptable carrier.

In another embodiment, the present invention also provides for compositions comprising at least on selective CB_1 receptor antagonist compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or ester thereof, in combination with at least one cholesterol lowering compound.

In yet another embodiment, the present invention also provides for a method of treating, reducing, or ameliorating metabolic syndrome, obesity, waist circumference, lipid profile, insulin sensitivity, neuroinflammatory disorders, cognitive disorders, psychosis, addictive behavior, gastrointestinal disorders, and cardiovascular conditions by administering an effective amount of at least one compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or ester thereof, to a patient in need thereof.

In yet another embodiment, the present invention also provides for a method of treating vascular conditions, hyperlipidaemia, atherosclerosis, hypercholesterolemia, sitosterolemia, vascular inflammation, metabolic syndrome, stroke, diabetes, obesity and/or reducing the level of sterol(s) by administering an effective amount of a composition comprising a combination of at least one compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or ester thereof, and at least one cholesterol lowering compound.

DETAILED DESCRIPTION OF THE INVENTION

The selective CB_1 receptor antagonist compounds of the present invention are selective CB_1 receptor antagonists of mammalian CB_1 receptors, preferably human CB_1 receptors, and variants thereof. Mammalian CB_1 receptors also include CB_1 receptors found in rodents, primates, and other mammalian species.

In one embodiment, the selective CB_1 receptor antagonist compounds of the present invention are selective CB_1 receptor antagonists that bind to a CB_1

receptor with a binding affinity ($K_{i(CB1)}$, measured as described herein) of about 400 nM or less, or about 200 nM or less, or about 100 nM or less, or about 10 nM or less. These ranges are inclusive of all values and subranges therebetween.

In one embodiment, the selective CB_1 receptor antagonist compounds of the present invention are selective CB_1 receptor antagonists that have a ratio of CB_1 receptor affinity to CB_2 receptor affinity ($K_{i(CB1)}$:$K_{i(CB2)}$, measured as described herein) of about 1:2 or better, or about 1:10 or better, or about 1:25 or better, or about 1:50 or better, or about 1:75 or better, or about 1:90 or better. These ranges are inclusive of all values and subranges therebetween.

Thus, in one embodiment, a selective CB_1 receptor antagonist of the present invention has an affinity for the CB_1 receptor, measured as described herein, of at least 400 nM or less, and a ratio of CB_1 to CB_2 receptor affinity (i.e., $K_{i(CB1)}$:$K_{i(CB2)}$) of at least 1:2 or better. In another embodiment the CB_1 receptor affinity is about 200 nM or less, and the $K_{i(CB1)}$:$K_{i(CB2)}$ is about 1:10 or better. In another embodiment the CB_1 affinity is about 100 nM or less, and the $K_{i(CB1)}$:$K_{i(CB2)}$ is about 1:25 or better. In another embodiment the CB_1 affinity is about 10 nM or less, and the $K_{i(CB1)}$:$K_{i(CB2)}$ is about 1:75 or better. In another embodiment the CB_1 affinity is about 10 nM or less, and the $K_{i(CB1)}$:$K_{i(CB2)}$ is about 1:90 or better. These ranges are inclusive of all values and subranges therebetween.

In one embodiment, the present invention provides for a selective CB_1 receptor antagonist compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or ester thereof, wherein the various substituent groups (i.e., X, Ar^1, Ar^2, etc.) are as defined herein.

In another embodiment of the compound of the present invention, or a pharmaceutically acceptable salt, solvate, or ester thereof,

Ar^1 and Ar^2 are independently $(C_6$-$C_{10})$aryl or $(C_2$-$C_{10})$heteroaryl,

wherein said $(C_6$-$C_{10})$aryl and $(C_2$-$C_{10})$heteroaryl are substituted with one or more groups Y^1;

n and m are independently 0 or 1;

A is selected from the group consisting of –C(O)-, $-S(O)_2-$, $-C(=N-OR^2)-$, and $-(C(R^2)_2)_q-$ wherein q is 1, 2, or 3;

B is selected from the group consisting of $-N(R^2)-$, -C(O)-, and $-(C(R^3)_2)_r-$ wherein r is 1 or 2,

with the proviso that when B is –C(O)-, then A is –C(O)- or -$(C(R^2)_2)_q$-;

X is selected from the group consisting of H, $(C_1$-$C_6)$alkyl, -S-$(C_1$-$C_6)$alkyl, -$S(O)_2$-$(C_1$-$C_6)$alkyl, -$S(O)_2$-$(C_3$-$C_{10})$cycloalkyl, -$S(O)_2$-$(C_6$-$C_{10})$aryl, -$S(O)_2$-$(C_2$-$C_{10})$heteroaryl, $(C_3$-$C_{10})$cycloalkyl, benzo-fused $(C_3$-$C_{10})$cycloalkyl, benzo-fused $(C_2$-$C_{10})$heterocycloalkyl, benzo-fused $(C_2$-$C_{10})$heterocycloalkenyl, $(C_2$-$C_{10})$heterocycloalkyl, -$C(R^2)$=$C(R^2)$-$(C_6$-$C_{10})$aryl, -$C(R^2)$=$C(R^2)$-$(C_2$-$C_{10})$heteroaryl, -OR^2, -O-$(C_1$-$C_6)$alkylene-O-$(C_1$-$C_6)$alkyl, -S-$(C_6$-$C_{10})$aryl, -$N(R^4)_2$, -$(C(R^2)_2)_s$-$(C_2$-$C_{10})$heteroaryl, -C(O)-O-$(C_1$-$C_6)$alkyl, -C(O)-$(C_6$-$C_{10})$aryl, -C(O)-$(C_2$-$C_{10})$heteroaryl, -N=O, -C(S-$(C_1$-$C_6)$alkyl)=N-$S(O)_2$-$(C_6$-$C_{10})$aryl, -$C(N(R^2)_2)$=N-$S(O)_2$-$(C_6$-$C_{10})$aryl, and -$(C(R^2)_2)_s$-$(C_6$-$C_{10})$aryl wherein s is 0, 1, or 2,

wherein the $(C_2$-$C_{10})$heteroaryl portion of said -$(C(R^2)_2)_s$-$(C_2$-$C_{10})$heteroaryl, the $(C_6$-$C_{10})$aryl portion of said -$C(R^2)$=$C(R^2)$-$(C_6$-$C_{10})$aryl, the $(C_2$-$C_{10})$heteroaryl portion of said -$C(R^2)$=$C(R^2)$-$(C_2$-$C_{10})$heteroaryl, the $(C_6$-$C_{10})$aryl portion of said -S-$(C_6$-$C_{10})$aryl, the $(C_6$-$C_{10})$aryl portion of said -$S(O)_2$-$(C_6$-$C_{10})$aryl, the $(C_2$-$C_{10})$heteroaryl portion of said -$S(O)_2$-$(C_2$-$C_{10})$heteroaryl, the $(C_6$-$C_{10})$aryl portion of said -C(O)-$(C_6$-$C_{10})$aryl, the $(C_2$-$C_{10})$heteroaryl portion of said -C(O)-$(C_2$-$C_{10})$heteroaryl, the $(C_6$-$C_{10})$aryl portion of said -$(C(R^3)_2)_s$-$(C_6$-$C_{10})$aryl, the $(C_6$-$C_{10})$aryl portion of said -C(S-$(C_1$-$C_6)$alkyl)=N-$S(O)_2$-$(C_6$-$C_{10})$aryl, the $(C_6$-$C_{10})$aryl portion of said -$C(N(R^2)_2)$=N-$S(O)_2$-$(C_6$-$C_{10})$aryl, the benzo portion of said benzo-fused $(C_3$-$C_{10})$cycloalkyl, the benzo portion of said benzo-fused $(C_2$-$C_{10})$heterocycloalkyl, and the benzo portion of said benzo-fused $(C_2$-$C_{10})$heterocycloalkenyl of X are unsubstituted or substituted with one or more groups Y^1, and

said $(C_3$-$C_{10})$cycloalkyl, the $(C_3$-$C_{10})$cycloalkyl portion of said -$S(O)_2$-$(C_3$-$C_{10})$cycloalkyl, said $(C_2$-$C_{10})$heterocycloalkyl, the $(C_3$-$C_{10})$cycloalkyl portion of said benzo-fused $(C_3$-$C_{10})$cycloalkyl, the $(C_2$-$C_{10})$heterocycloalkyl portion of said benzo-fused $(C_2$-$C_{10})$heterocycloalkyl, and the $(C_2$-$C_{10})$heterocycloalkenyl portion of said benzo-fused $(C_2$-$C_{10})$heterocycloalkenyl of X are unsubstituted or substituted with one or more groups Y^2;

each R^1 is independently selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $-(C_1\text{-}C_6)$alkylene-$N(R^5)_2$, $-(C_1\text{-}C_6)$alkylene-OR^2, $(C_1\text{-}C_6)$alkylene-N_3, and $(C_1\text{-}C_6)$alkylene-O-$S(O)_2$-$(C_1\text{-}C_6)$alkyl; or

two R^1 groups attached to the same ring carbon atom form a carbonyl group;

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

each R^2 is independently H, $(C_1\text{-}C_6)$alkyl, or $(C_6\text{-}C_{10})$aryl,

wherein said $(C_6\text{-}C_{10})$aryl of R^2 is unsubstituted or substituted with one or more groups Y^1;

each R^3 is selected from the group consisting of H, $(C_1\text{-}C_6)$alkyl, unsubstituted $(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl substituted with one or more Y^1 groups, $-OR^2$, $-(C_1\text{-}C_6)$alkylene-O-$(C_1\text{-}C_6)$alkyl, and $-(C_1\text{-}C_6)$alkylene-OH;

each R^4 is selected from the group consisting of H, $(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl, $-C(O)\text{-}O\text{-}(C_1\text{-}C_6)$alkyl,–$C(O)\text{-}(C_1\text{-}C_6)$alkyl, $-C(O)\text{-}(C_6\text{-}C_{10})$aryl, and $-S(O)_2\text{-}(C_6\text{-}C_{10})$aryl,

wherein said $(C_6\text{-}C_{10})$aryl, the $(C_6\text{-}C_{10})$aryl portion of said $–C(O)\text{-}(C_6\text{-}C_{10})$aryl, and the $(C_6\text{-}C_{10})$aryl portion of said $–S(O)_2\text{-}(C_6\text{-}C_{10})$aryl of R^4 are unsubstituted or substituted with one or more Y^1 groups;

each R^5 is selected from the group consisting of H, $(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl, $-S(O)_2\text{-}(C_1\text{-}C_6)$alkyl, $-S(O)_2\text{-}(C_3\text{-}C_{10})$cycloalkyl, $-S(O)_2$-aryl, $-C(O)\text{-}N(R^2)_2$, $-C(O)\text{-}(C_1\text{-}C_6)$alkyl, and $-(C_1\text{-}C_6)$alkylene-OH,

wherein said $(C_6\text{-}C_{10})$aryl and the $(C_6\text{-}C_{10})$aryl portion of said $–S(O)_2\text{-}(C_6\text{-}C_{10})$aryl of R^5 are unsubstituted or substituted with one or more Z groups;

each Y^1 is independently selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_2\text{-}C_{10})$heterocycloalkyl, $(C_2\text{-}C_{10})$heterocycloalkenyl, halo, $(C_1\text{-}C_6)$haloalkyl, benzyl, $(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_{10})$heteroaryl, $-O\text{-}(C_6\text{-}C_{10})$aryl, $-S\text{-}(C_6\text{-}C_{10})$aryl, $-S(O)_2\text{-}(C_1\text{-}C_6)$alkyl, $-S(O)_2\text{-}(C_3\text{-}C_{10})$cycloalkyl, $-S(O)_2\text{-}(C_6\text{-}C_{10})$aryl, $-(C_1\text{-}C_6)$alkylene-CN, -CN, $-C(O)\text{-}(C_1\text{-}C_6)$alkyl, $-C(O)\text{-}(C_6\text{-}C_{10})$aryl, $-C(O)\text{-}(C_1\text{-}C_6)$alkyl, $-C(O)\text{-}(C_1\text{-}C_6)$haloalkyl, $-C(O)O\text{-}(C_1\text{-}C_6)$alkyl, $-N(R^2)C(O)\text{-}(C_1\text{-}C_6)$alkyl, $-N(R^2)C(O)\text{-}N(R^2)_2$, -OH, $-O\text{-}(C_1\text{-}C_6)$alkyl, $-O\text{-}(C_1\text{-}C_6)$haloalkyl, $-O\text{-}(C_1\text{-}C_6)$alkylene-C(O)OH, $-S\text{-}(C_1\text{-}C_6)$alkyl, $-S\text{-}(C_1\text{-}C_6)$haloalkyl, $-(C_1\text{-}C_6)$alkylene-OH, $-(C_1\text{-}C_6)$alkylene-$C(O)\text{-}O\text{-}(C_1\text{-}C_6)$alkyl, $-O\text{-}(C_1\text{-}C_6)$alkylene-$(C_6\text{-}C_{10})$aryl, and $-N(R^5)_2$,

wherein said (C_6-C_{10})aryl, said (C_2-C_{10})heteroaryl, the (C_6-C_{10})aryl portion of said -O-(C_6-C_{10})aryl, the (C_6-C_{10})aryl portion of said -S-(C_6-C_{10})aryl, the (C_6-C_{10})aryl portion of said –$S(O)_2$-(C_6-C_{10})aryl, said benzyl, the (C_6-C_{10})aryl portion of said –C(O)-(C_6-C_{10})aryl, and the (C_6-C_{10})aryl portion of said -O-(C_1-C_6)alkylene-(C_6-C_{10})aryl of Y^1 are unsubstituted or substituted with one or more groups Z; or

two groups Y^1 form a –O-CH_2-O- group;

each Y^2 is independently selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_6-C_{10})aryl, -(C_1-C_6)alkylene-(C_6-C_{10})aryl, -CN, -C(O)-(C_1-C_6)alkyl, -$S(O)_2$-(C_3-C_{10})cycloalkyl, -(C_1-C_6)alkylene-$N(R^2)_2$, -C(O)-(C_1-C_6)alkylene-$N(R^4)_2$, -C(O)-O-(C_1-C_6)alkyl, -C(O)- (C_6-C_{10})aryl, and -C(O)- (C_1-C_6)haloalkyl,

wherein said aryl and the (C_6-C_{10})aryl portion of said –C(O)- (C_6-C_{10})aryl of Y^2 are unsubstituted or substituted with one or more groups Z; or

two groups Y^2 form a -O-CH_2CH_2-O- group; or

two of said Y^2 substituents attached to the same ring carbon atom of a (C_3-C_{10})cycloalkyl, benzo-fused (C_3-C_{10})cycloalkyl, benzo-fused (C_2-C_{10})heterocycloalkyl, benzo-fused (C_2-C_{10})heterocycloalkenyl, or (C_2-C_{10})heterocycloalkyl ring, together with the ring carbon atom to which they are both attached, form a carbonyl group; and

eand Z is independently selected from the group consisting of (C_1-C_6)alkyl, halo, (C_1-C_6)haloalkyl, -OH, -O-(C_1-C_6)alkyl, and -CN.

In another embodiment of the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, Ar^1 and Ar^2 are independently aryl substituted with one or more groups Y^1.

In another embodiment of the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, Ar^1 and Ar^2 are independently aryl substituted with one or more groups Y^1, m is 1; and A is -C(O)-.

In another embodiment of the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, Ar^1 and Ar^2 are independently aryl substituted with one or more groups Y^1, m is 1; n is 0; and A is -C(O)-.

In another embodiment of the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, Ar^1 and Ar^2 are independently aryl substituted with one or more groups Y^1, m is 1; n is 1; B is –NH-; and A is -C(O)-.

In another embodiment of the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, Ar^1 and Ar^2 are independently aryl substituted with one or more groups Y^1, m is 1; n is 1; B is $-(C(R^2)_2)_r-$ wherein r is 1 or 2; and A is -C(O)-.

In another embodiment of the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, Ar^1 and Ar^2 are independently aryl substituted with one or more groups Y^1, m is 1; n is 1; B is $-N(R^2)-$ wherein r is 1 or 2; and A is -C(O)-.

In another embodiment of the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, m is 1; and A is $-S(O)_2-$.

In another embodiment of the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, m is 1; n is 0; and A is $-S(O)_2-$.

In another embodiment of the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, m is 1; n is 1; B is $-N(R^2)-$; and A is $-S(O)_2-$.

In another embodiment of the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, m is 1; A is $-C(=N-OR^2)-$; and n is 0.

In another embodiment of the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, m is 1; A is $-(C(R^2)_2)_q-$ wherein q is 1, 2, or 3; and n is 0.

In another embodiment of the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, X is aryl or heteroaryl, and said aryl or heteroaryl of X is unsubstituted or substituted with one or more Y^1 groups; m is 1; A is $-(C(R^2)_2)_q-$ wherein q is 1, 2, or 3; and n is 0.

In another embodiment of the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, X is aryl or

heteroaryl, and said aryl or heteroaryl of X is unsubstituted or substituted with one or more Y^1 groups; m is 1; A is $-(C(R^2)_2)_q-$ wherein q is 1 or 2; and n is 0.

In another embodiment of the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, m is 0; B is $-(C(R^3)_2)_r-$ wherein r is 1, 2, or 3; and A is $-(C(R^2)_2)_q-$ wherein q is 1, 2, or 3.

In another embodiment of the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, m and n are both 1; B is $-(C(R^3)_2)_r-$ wherein r is 1, 2, or 3; and n is 1.

In another embodiment of the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, m and n are both 0.

In another embodiment of the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, X is $-(C(R^2)_2)_s$-aryl wherein s is 0, 1, or 2.

In another embodiment of the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, X is heteroaryl.

In another embodiment of the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, X is cycloalkyl.

In another embodiment of the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, X is heterocycloalkyl.

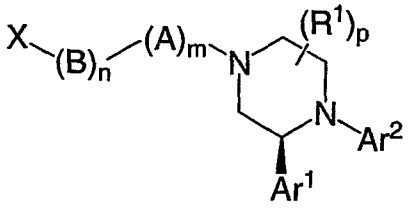
In another embodiment of the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, X is alkyl.

In another embodiment of the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, X is $-N(R^4)_2$.

In another embodiment of the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, m and n are both 1; B is $-(C(R^3)_2)_r-$ wherein r is 1, 2, or 3; and A is –C(O)-.

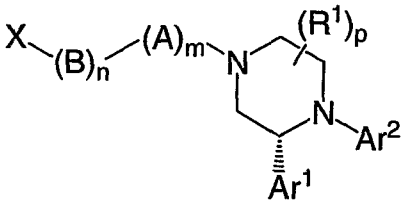
In another embodiment of the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, m and n are both 1; A is –C(O)-; and B is –NH-.

In yet another embodiment the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, have the following Formula (IA):



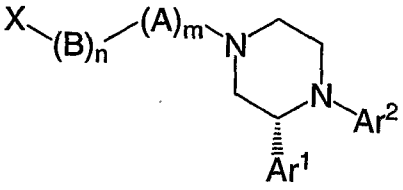
(IA) .

In yet another embodiment the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, have the following Formula (IB):



(IB) .

In yet another embodiment the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, have the following Formula (IC):



(IC) .

In yet another embodiment, the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, have the Formula (IC) above, wherein m is 1 and A is –C(O)-.

In yet another embodiment, the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, have the Formula (IC) above, wherein m is 1, n is 0, and A is –C(O)-.

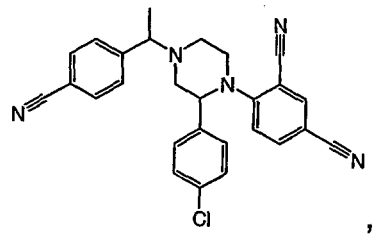
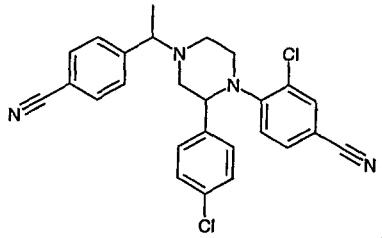
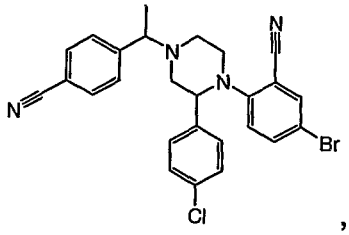
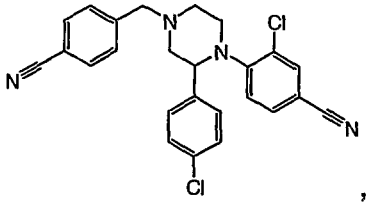
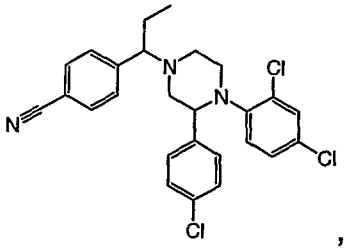
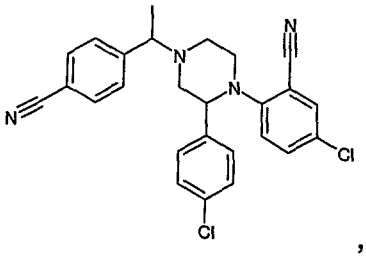
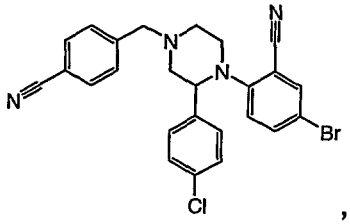
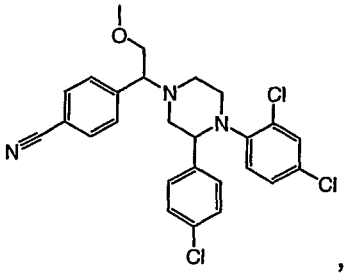
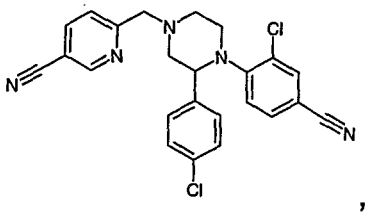
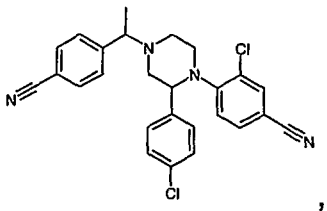
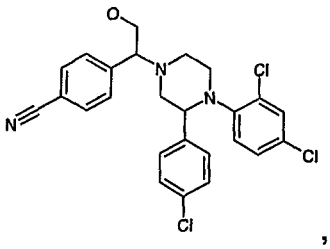
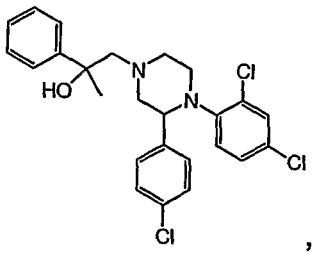
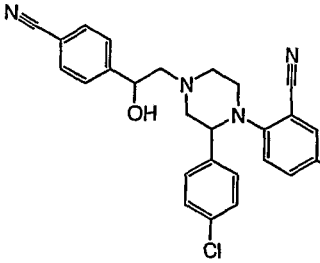
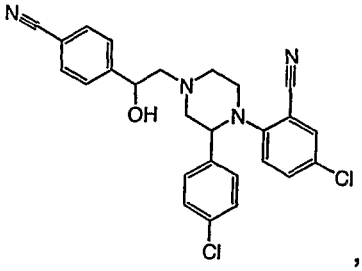
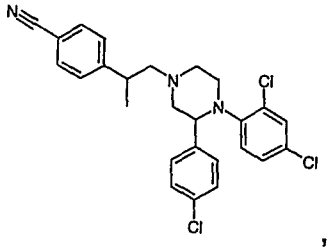
In yet another embodiment, the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, have the Formula (IC) above, wherein m is 1, n is 1, A is –C(O)-, and B is $-N(R^2)-$.

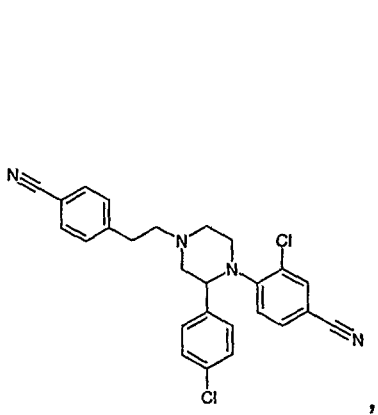
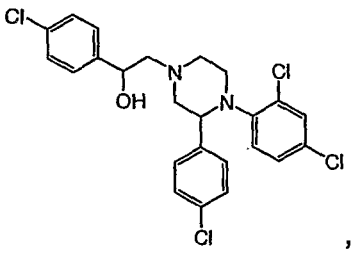
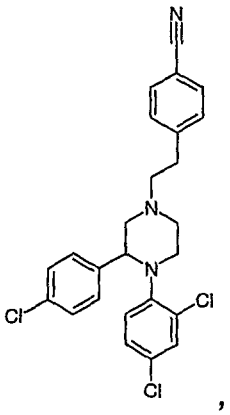
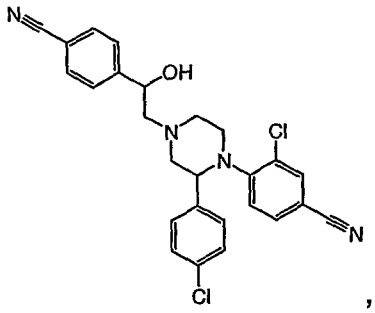
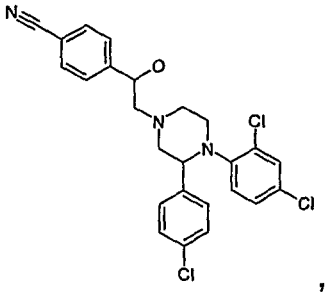
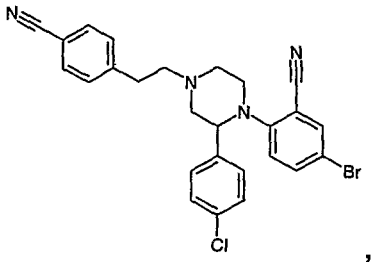
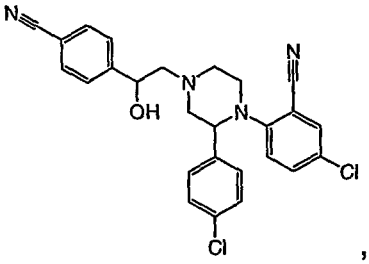
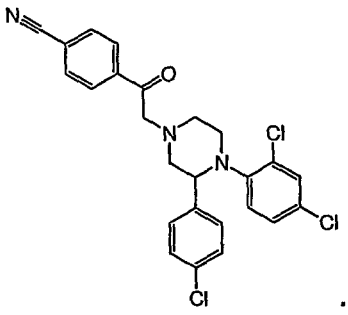
In yet another embodiment, the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, have the Formula (IC) above, wherein m is 1 and A is $-S(O)_2-$.

In yet another embodiment, the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, have the Formula (IC) above, wherein m is 1, n is 0, and A is $-S(O)_2-$.

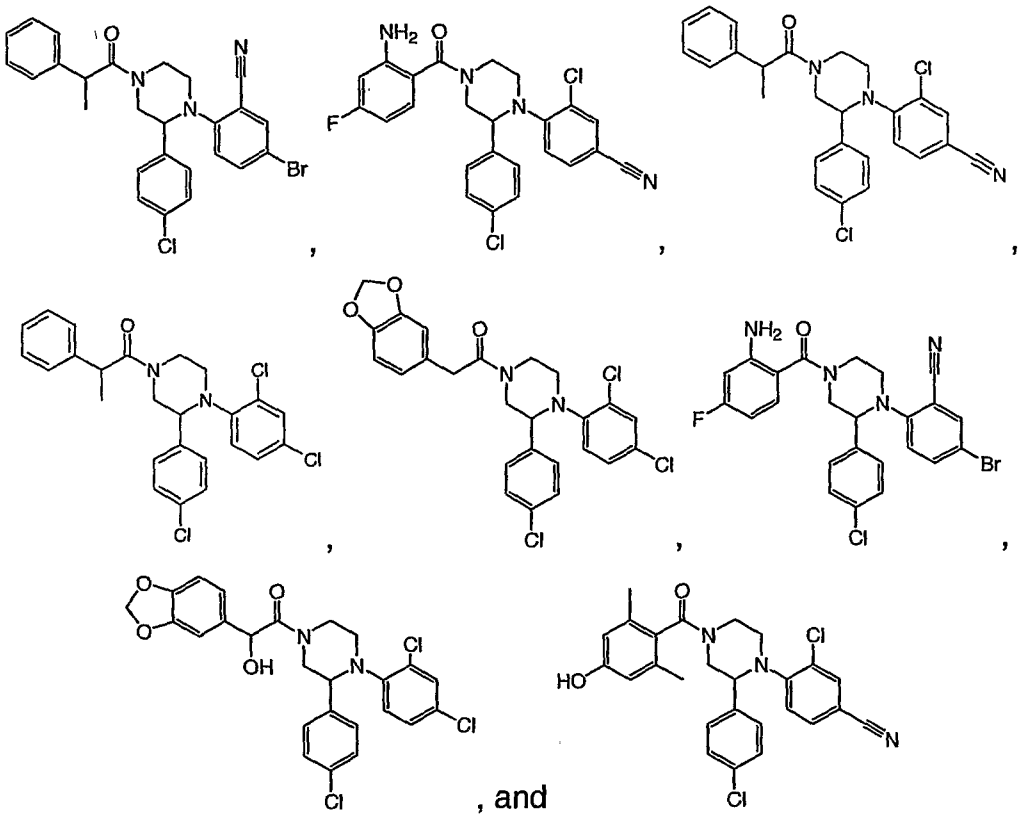
In yet another embodiment, the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, have the Formula (IC) above, wherein m is 1, ni 1, B is $-N(R^2)-$, and A is $-S(O)_2-$.

In yet another embodiment, the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof are selected from the group consisting of:


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. One of ordinary skill will recognize that the compounds shown above have stereogenic centers. Thus, the compounds shown above include all possible stereoisomers.

In yet another embodiment, the compounds of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof are selected from the group consisting of:



, and

or a pharmaceutically acceptable salt, solvate, or ester thereof. One of ordinary skill will recognize that the compounds shown above have stereogenic centers. Thus, the compounds shown above include all possible stereoisomers.

Ar^1 and Ar^2 are independently aryl or heteroaryl, wherein said aryl and heteroaryl are substituted with one or more groups Y^1. Non-limiting examples of said aryl of Ar^1 and/or Ar^2 include, for example, phenyl, naphthyl, pyridyl (e.g., 2-, 3-, and 4-pyridyl), quinolyl, etc. substituted with one or more (e.g., 1, 2, 3, or 4) Y^1 groups as defined herein.

A is selected from the group consisting of –C(O)-, $-S(O)_2-$, $-C(=N-OR^2)-$, and $-(C(R^2)_2)_q-$ wherein q is 1, 2, or 3. Non-limiting examples of A when A is $-(C(R^2)_2)_q-$ include, for example, $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)CH_2-$, $-CH_2CH(CH_3)-$, $-CH(CH_3)-(CH_2)_2-$, $-(CH_2)_2-CH(CH_3)-$, -CH(phenyl)-CH_2-, $-CH_2-$CH(phenyl)-, -CH(phenyl)-, etc. Non-limiting examples of A when A is $-C(=N-OR^2)-$ include -C(=N-OH)-, $-C(=N-OCH_3)-$, $-C(=N-OCH_2CH_3)-$, $-C(=N-OCH(CH_3)_2)-$, $-C(=N-OC(CH_3)_3)-$, -C(=N-O-phenyl), etc.

B is selected from the group consisting of $–N(R^2)-$, -C(O)-, and $-(C(R^3)_2)_r-$ wherein r is 1 or 2. Non-limiting examples of B when B is $-(C(R^3)_2)_r-$ include, for example, $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH(CH(CH_3)_2)-$,

-CH($CH_2CH(CH_3)_2$)-, -$CH_2CH_2CH_2$-, -CH(CH_3)CH_2-, -$CH_2CH(CH_3)$-, -CH(CH_3)-(CH_2)$_2$-, -(CH_2)$_2$-CH(CH_3)-, -CH(phenyl)-CH_2-, -CH_2-CH(phenyl)-, -CH(phenyl)-, -CH(OH)-, -C(CH_3)(OH)-, -CH(OH)CH_2-, -$CH_2CH(OH)$-, -CH(OH)$CH_2CH(CH_3)$-, -CH(CH(OH)(CH_3))-, -CH(CH_3)$CH_2CH(OH)$-, -CH(CH_2OH)-, -CH(OCH_3)-, -CH(OCH_3)CH_2-, -$CH_2CH(OCH_3)$-, -CH(OCH_3)$CH_2CH(CH_3)$-, -CH(CH_3)$CH_2CH(OCH_3)$-, -CH(CH_2OCH_3)-, -CH(OCH_3)-, -CH(OCH_2CH_3)CH_2-, -$CH_2CH(OCH_2CH_3)$-, -CH(OCH_2CH_3)$CH_2CH(CH_3)$-, -CH(CH_3)$CH_2CH(OCH_2CH_3)$-, -CH($CH_2OCH_2CH_3$)-, etc. Non-limiting examples of B when B is –N(R^2)- include –NH-, –N(alkyl)-, –N(aryl)-, wherein the terms "alkyl" and "aryl" are as defined above.

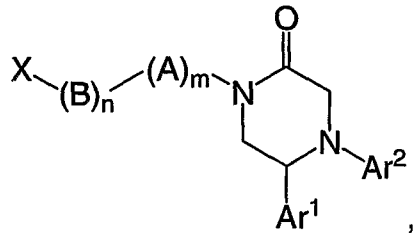
X is selected from the group consisting of H, alkyl, -S-alkyl, -S(O)$_2$-alkyl, -S(O)$_2$-cycloalkyl, -S(O)$_2$-aryl, -S(O)$_2$-heteroaryl, cycloalkyl, benzo-fused cycloalkyl, benzo-fused heterocycloalkyl, benzo-fused heterocycloalkenyl, heterocycloalkyl, -C(R^2)=C(R^2)-aryl, -C(R^2)=C(R^2)-heteroaryl, -OR^2, -O-alkylene-O-alkyl, -S-aryl, -N(R^4)$_2$, -(C(R^2)$_2$)$_s$-heteroaryl, -C(O)-O-alkyl, -C(O)-aryl, -C(O)-heteroaryl, -N=O, -C(S-alkyl)=N-S(O)$_2$-aryl, -C(N(R^2)$_2$)=N-S(O)$_2$-aryl, and -(C(R^2)$_2$)$_s$-aryl wherein s is 0, 1, or 2. Non-limiting examples of X when X is alkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, neo-pentyl, n-hexyl, iso-hexyl, etc. Non-limiting examples of X when X is-S-alkyl include –S-methyl, -S-ethyl, -S-(n-propyl), –S-(iso-propyl), –S-(n-butyl), –S-(iso-butyl), –S-(sec-butyl), –S-(tert-butyl), –S-(n-pentyl), –S-(iso-pentyl), –S-(neo-pentyl), –S-(n-hexyl), -S-(iso-hexyl), etc. Non-limiting examples of X when X is -S(O)$_2$-alkyl include -S(O)$_2$-methyl, –S(O)$_2$-ethyl, -S(O)$_2$-(n-propyl), –S(O)$_2$-(iso-propyl), –S(O)$_2$-(n-butyl), –S(O)$_2$-(iso-butyl), –S(O)$_2$-(sec-butyl), –S(O)$_2$-(tert-butyl), –S(O)$_2$-(n-pentyl), –S(O)$_2$-(iso-pentyl), –S(O)$_2$-(neo-pentyl), –S(O)$_2$-(n-hexyl), –S(O)$_2$-(iso-hexyl), etc. Non-limiting examples of X when X is -S(O)$_2$-cycloalkyl include -S(O)$_2$-cyclopropyl, -S(O)$_2$-cyclobutyl, -S(O)$_2$-cyclopentyl, -S(O)$_2$-cyclohexyl, -S(O)$_2$-cycloheptyl, -S(O)$_2$-adamantyl, -S(O)$_2$-(bicyclo[2.1.1]hexanyl) , -S(O)$_2$-(bicyclo[2.2.1]heptenyl) , -S(O)$_2$-(bicyclo[3.1.1]heptenyl) , -S(O)$_2$-(bicyclo[2.2.2]octenyl) , -S(O)$_2$-(bicyclo[3.2.1]octenyl), etc. Non-limiting examples of X when X is -S(O)$_2$-aryl includes -S(O)$_2$-phenyl, -S(O)$_2$-naphthyl, etc. Non-limiting examples of X when X is -S(O)$_2$-heteroaryl include -S(O)$_2$-pyridyl, -S(O)$_2$-azaindolyl, -S(O)$_2$-benzimidazolyl, -S(O)$_2$-benzofuranyl, -S(O)$_2$-furanyl, -S(O)$_2$-indolyl, etc.

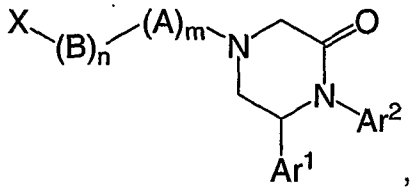
Non-limiting examples of X when X is cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, bicyclo[2.1.1]hexanyl, bicyclo[2.2.1]heptenyl, bicyclo[3.1.1]heptenyl, bicyclo[2.2.2]octenyl, bicyclo[3.2.1]octenyl, etc. Non-limiting examples of X when X is benzo-fused cycloalkyl include 1,2,3,4-tetrahydronaphthyl, indanyl, bicyclo[4.2.0]octa-1,3,5-trienyl, etc. Non-limiting examples of X when X is benzo-fused heterocycloalkyl includes 3,4-dihydro-2*H*-benzo[1,4]oxazinyl, chromanyl, 2,3-dihydro-1*H*-indolyl, 2,3-dihydro-1*H*-isoindolyl, 2,3-dihydro-benzofuranyl, 1,3-dihydro-isobenzofuranyl, 2,3-dihydro-benzo[*b*]thiophenyl, 1,3-dihydro-benzo[*c*]thiophenyl, etc. Non-limiting examples of X when X is benzo-fused heterocycloalkenyl include 2*H*-benzo[1,4]oxazinyl, 4H-chromenyl, 4*H*-chromenyl, 3*H*-indolyl, 1*H*-isoindolyl, 4*H*-benzo[1,4]oxazinyl, etc. Non-limiting examples of X when X is heterocycloalkyl include morpholinyl, piperazinyl, piperidinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydropyranyl, azetidinyl, etc. When X is $-C(R^2)=C(R^2)$-aryl, non-limiting examples of X include -CH=CH-aryl, $-C(CH_3)$=CH-aryl, -CH=$C(CH_3)$-aryl, $-C(CH_3)=C(CH_3)$-aryl, -C(phenyl)=CH-aryl, -C(phenyl)=$C(CH_3)$-aryl, where "aryl" includes, for example, the aryl groups listed above. When X is $-C(R^2)=C(R^2)$-heteroaryl, non-limiting examples of X include -CH=CH-heteroaryl, $-C(CH_3)$=CH-heteroaryl, -CH=$C(CH_3)$- heteroaryl, $-C(CH_3)=C(CH_3)$- heteroaryl, -C(phenyl)=CH-heteroaryl, -C(phenyl)=$C(CH_3)$-heteroaryl, where "heteroaryl" includes, for example, the heteroaryl groups listed above. When X is $-OR^2$, R^2 is defined as described herein. Thus, X includes -OH, -O-alkyl (where the term "alkyl" is defined as described above), and –O-aryl (where the term "aryl" is defined as described above). When X is -O-alkylene-O-alkyl, non-limiting examples of X include $-O-CH_2-O-CH_3$, $-O-CH(CH_3)-O-CH_3$, $-O-CH_2CH_2-O-CH_3$, $-O-CH_2CH_2-O-CH_2CH_3$, $-O-CH(OCH_3)CH_2CH(CH_3)_2$, $-O-CH(CH_3)CH_2CH_2-O-CH_3$, $-O-CH_2CH_2-O-CH_2CH_3$, etc. Non-limiting examples of X when X is -S-aryl includes -S-phenyl, -S-naphthyl, etc. Non-limiting examples of X when X is $-N(R^4)_2$ include $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, -NH(aryl), -N(alkyl)(aryl), $-N(aryl)_2$, -NH–C(O)-O-alkyl, -N(alkyl)–C(O)-O-alkyl, -N(aryl)-C(O)-O-alkyl, -NH-C(O)alkyl, -N(alkyl)-C(O)alkyl, and -N(aryl)–C(O)alkyl where the terms "alkyl" and "aryl" are defined as described above. Non-limiting examples of X when X is $-(C(R^2)_2)_s$-heteroaryl, include heteroaryl, $-C(R^2)_2$-heteroaryl, $-(C(R^2)_2)_2$-heteroaryl, where R^2 and the

term "heteroaryl" are as defined herein, and "-$(C(R^2)_2)_s$-" includes -CH_2-, -CH_2CH_2-, -$CH(CH_3)$-, -$C(CH_3)_2$-, -$CH(CH(CH_3)_2)$-, -$CH(CH_2CH(CH_3)_2)$-, -$CH_2CH_2CH_2$-, -$CH(CH_3)CH_2$-, -$CH_2CH(CH_3)$-, -$CH(CH_3)$-$(CH_2)_2$-, -$(CH_2)_2$-$CH(CH_3)$-, -CH(phenyl)-CH_2-, -CH_2-CH(phenyl)-, -CH(phenyl)-, etc. Non-limiting examples of X when X is -C(O)-O-alkyl include -C(O)-O-(methyl), -C(O)-O-(ethyl), -C(O)-O-(n-propyl), -C(O)-O-(iso-propyl), -C(O)-O-(n-butyl), -C(O)-O-(iso-butyl), -C(O)-O-(sec-butyl), -C(O)-O-(tert-butyl), -C(O)-O-(n-pentyl), -C(O)-O-(iso-pentyl), -C(O)-O-(neo-pentyl), etc. Non-limiting examples of X when X is -C(O)-aryl include -C(O)-phenyl, -C(O)-naphthyl, etc. Non-limiting examples of X when X is -C(O)-heteroaryl include -C(O)-pyridyl, -C(O)-azaindolyl, -C(O)-benzimidazolyl, -C(O)-benzothiophenyl, -C(O)-furanyl, -C(O)-furazanyl, -C(O)-indolyl, -C(O)-isoquinolyl, etc. When X is -C(S-alkyl)=N-$S(O)_2$-aryl, the "alkyl" and "aryl" portions thereof can independently include any of the alkyl and aryl groups described herein. Likewise, when X is -$C(N(R^2)_2)$=N-$S(O)_2$-aryl said R^2 groups and the "aryl" portion are as defined herein. Non-limiting examples of X when X is -$(C(R^2)_2)_s$-aryl, include aryl, -$C(R^2)_2$-aryl, -$(C(R^2)_2)_2$-aryl, where R^2 and the term "aryl" are as defined herein, and "-$(C(R^2)_2)_s$-" is as defined above. Said heteroaryl, the heteroaryl portion of said -$(C(R^2)_2)_s$-heteroaryl, the aryl portion of said -$C(R^2)$=$C(R^2)$-aryl, the heteroaryl portion of said -$C(R^2)$=$C(R^2)$-heteroaryl, the aryl portion of said -S-aryl, the aryl portion of said -$S(O)_2$-aryl, the heteroaryl portion of said -$S(O)_2$-heteroaryl, the aryl portion of said -C(O)-aryl, the heteroaryl portion of said -C(O)-heteroaryl, the aryl portion of said -$(C(R^2)_2)_s$-aryl, the benzo portion of said benzo-fused cycloalkyl, the benzo portion of said benzo-fused heterocycloalkyl, and the benzo portion of said benzo-fused heterocycloalkenyl of X are unsubstituted or substituted with one or more groups Y^1, where Y^1 is defined as described herein, and said cycloalkyl, the cycloalkyl portion of said -$S(O)_2$-cycloalkyl, said heterocycloalkyl, the cycloalkyl portion of said benzo-fused cycloalkyl, the heterocycloalkyl portion of said benzo-fused heterocycloalkyl, and the heterocycloalkenyl portion of said benzo-fused heterocycloalkenyl of X are unsubstituted or substituted with one or more groups Y^2 where Y^2 is defined as described herein.

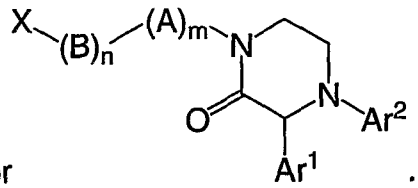
Each R^1 is independently selected from the group consisting of alkyl, haloalkyl, -alkylene-$N(R^5)_2$, -alkylene-OR^2, alkylene-N_3, and alkylene-O-$S(O)_2$-alkyl. Non-limiting examples of R^1 when R^1 is alkyl include

methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, neo-pentyl, n-hexyl, iso-hexyl, etc. Non-limiting examples of R^1 when R^1 is haloalkyl include $-CF_3$, $-CHF_2$, $-CH_2F$, $-CH_2CF_3$, $-CF_2CF_3$, $-CH_2Br$, $-CH_2Cl$, $-CCl_3$, etc. When R^1 is alkylene-N_3 or alkylene-O-$S(O)_2$-alkyl, the alkylene portion thereof can include any of the alkylene groups described herein (e.g., $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)CH_2CH_2-$, etc. Similarly, the "alkyl" portion of alkylene-O-$S(O)_2$-alkyl can include any alkyl group described herein (e.g., methyl, ethyl, propyl, butyl, pentyl, etc.) Non-limiting examples of R^1 when R^1 is -alkylene-$N(R^5)_2$ include $-CH_2-N(R^5)_2$, $-CH(CH_3)-N(R^5)_2$, $-CH_2CH_2-N(R^5)_2$, $-CH_2CH_2CH_2-N(R^5)_2$, $-CH(CH_3)CH_2CH_2-N(R^5)_2$, etc., wherein each R^5 is independently defined as described herein. For example, the "$-N(R^5)_2$" portion of -alkylene-$N(R^5)_2$ of R^1 can be $-NH_2$, $-N(CH_3)_2$, $-NH(CH_3)$, -NH(phenyl), $-N(phenyl)_2$, $-NH-S(O)_2-CH_3$, -NH-$S(O)_2$-cyclopropyl, $-NH-C(O)-NH_2$, $-NH-C(O)-N(CH_3)_2$, $-NH-C(O)-CH_3$, $-NH-CH_2CH_2-OH$, etc. Non-limiting examples of R^1 when R^1 is -alkylene-OR^2 include $-CH_2-OR^2$, $-CH(CH_3)-OR^2$, $-CH_2CH_2-OR^2$, $-CH(OR^2)CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_2-OR^2$, wherein R^2 is defined as described herein. For example, the "$-OR^2$" portion of said -alkylene-OR^2 of R^1 can be $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, -O-phenyl. Alternatively, two R^1 groups attached to the same ring carbon atom can form a carbonyl group, for example as shown below:



,


,



or .

Each R^2 is independently H, alkyl, or aryl. Non-limiting examples of R^2 when R^2 is alkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, neo-pentyl, n-hexyl, iso-hexyl, etc. Non-limiting examples of R^2 when R^2 is aryl include phenyl, naphthyl, etc., wherein

said aryl may be unsubstituted or substituted with one or more Y^1 groups as defined herein.

Each R^3 is selected from the group consisting of H, alkyl, unsubstituted aryl, aryl substituted with one or more Y^1 groups, $-OR^2$, -alkylene-O-alkyl, and -alkylene-OH. Non-limiting examples of R^3 when R^3 is alkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, neo-pentyl, n-hexyl, iso-hexyl, etc. Non-limiting examples of R^3 when R^3 is aryl include phenyl, naphthyl, etc., wherein said aryl may be unsubstituted or substituted with one or more Y^1 groups as defined herein. Non-limiting examples of R^3 when R^3 is $-OR^2$ include –OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, -O-phenyl, etc. Non-limiting examples of R^3 when R^3 is -alkylene-O-alkyl include $-O-CH_2-O-CH_3$, $-O-CH_2CH_2-O-C(CH_3)_3$, $-O-CH(CH_3)-O-CH_3$, $-O-CH_2CH_2-O-CH_3$, $-O-CH_2CH_2-O-CH_2CH_3$, $-O-CH(OCH_3)CH_2CH(CH_3)_2$, $-O-CH(CH_3)CH_2CH_2-O-CH_3$, $-O-CH_2CH_2-O-CH_2CH_3$, etc. Non-limiting examples of R^3 when R^3 is -alkylene-OH include $-CH_2-OH$, $-CH_2CH_2-OH$, $-CH_2CH_2CH_2-OH$, $-CH(OH)CH_3$, $-CH_2CH(OH)CH_3$, etc.

Each R^4 is selected from the group consisting of H, alkyl, aryl,–C(O)-O-alkyl, -C(O)-alkyl, -C(O)-aryl, and $–S(O)_2$aryl. Non-limiting examples of R^4 when R^4 is alkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, neo-pentyl, n-hexyl, iso-hexyl, etc. Non-limiting examples of R^4 when R^4 is aryl include phenyl, naphthyl, etc., wherein said aryl may be unsubstituted or substituted with one or more Y^1 groups as defined herein. Non-limiting examples of R^4 when R^4 is -C(O)-O-alkyl include $-C(O)-O-CH_3$, $-C(O)-O-CH_2CH_3$, $-C(O)-O-CH_2CH_2CH_3$, $-C(O)-O-CH(CH_3)_2$, $-C(O)-O-CH_2CH_2CH_2CH_3$, $-C(O)-O-CH_2CH(CH_3)_2$, $-C(O)-O-CH(CH_3)CH_2CH_3$, $-C(O)-O-C(CH_3)_3$, $-C(O)-O-CH_2CH_2CH_2CH_2CH_3$, $-C(O)-O-CH_2CH(CH_3)CH_2CH_3$, $-C(O)-O-CH_2CH_2CH(CH_3)_2$, $-C(O)-O-CH_2CH_2CH_2CH_2CH_2CH_3$, $-C(O)-O-CH(CH_3)CH_2CH_2CH_2CH_3$, $-C(O)-O-CH_2CH(CH_3)CH_2CH_2CH_3$, $-C(O)-O-CH_2CH_2CH(CH_3)CH_2CH_3$, $-C(O)-O-CH_2CH_2CH_2CH(CH_3)_2$, etc. Non-limiting examples of R^4 when R^4 is -C(O)-alkyl include $-C(O)-CH_3$, $-C(O)-CH_2CH_3$, $-C(O)-CH_2CH_2CH_3$, $-C(O)-CH(CH_3)_2$, $-C(O)-CH_2CH_2CH_2CH_3$, $-C(O)-CH_2CH(CH_3)_2$, $-C(O)-CH(CH_3)CH_2CH_3$, $-C(O)-C(CH_3)_3$, $-C(O)-CH_2CH_2CH_2CH_2CH_3$, $-C(O)-CH_2CH(CH_3)CH_2CH_3$, $-C(O)-CH_2CH_2CH(CH_3)_2$, $-C(O)-CH_2CH_2CH_2CH_2CH_2CH_3$,

-C(O)-CH(CH_3)$CH_2CH_2CH_2CH_3$, -C(O)-CH_2CH(CH_3)$CH_2CH_2CH_3$, -C(O)-CH_2CH_2CH(CH_3)CH_2CH_3, -C(O)-$CH_2CH_2CH_2$CH(CH_3)$_2$, etc. Non-limiting examples of R^4 when R^4 is -C(O)-aryl include -C(O)-phenyl, -C(O)-naphthyl, etc., optionally substituted with one or more Y^1 groups. Non-limiting examples of R^4 when R^4 is –S(O)$_2$aryl include –S(O)$_2$-phenyl, –S(O)$_2$-naphthyl, etc., optionally substituted with one or more Y^1 groups.

Each R^5 is selected from the group consisting of H, alkyl, aryl, -S(O)$_2$-alkyl, -S(O)$_2$-cycloalkyl, -S(O)$_2$-aryl, -C(O)-N(R^2)$_2$, -C(O)-alkyl, and –alkylene-OH. Non-limiting examples of R^5 when R^5 is alkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, neo-pentyl, n-hexyl, iso-hexyl, etc. Non-limiting examples of R^5 when R^5 is aryl include phenyl, naphthyl, etc., wherein said aryl may be unsubstituted or substituted with one or more Z groups as defined herein. Non-limiting examples of R^5 when R^5 is -S(O)$_2$-alkyl include -S(O)$_2$-CH_3, -S(O)$_2$-CH_2CH_3, -S(O)$_2$-$CH_2CH_2CH_3$, -S(O)$_2$-CH(CH_3)$_2$, -S(O)$_2$-$CH_2CH_2CH_2CH_3$, -S(O)$_2$-CH_2CH(CH_3)$_2$, -S(O)$_2$-CH(CH_3)CH_2CH_3, -S(O)$_2$-C(CH_3)$_3$, -S(O)$_2$-$CH_2CH_2CH_2CH_2CH_3$, -S(O)$_2$-CH_2CH(CH_3)CH_2CH_3, -S(O)$_2$-CH_2CH_2CH(CH_3)$_2$, -S(O)$_2$-$CH_2CH_2CH_2CH_2CH_2CH_3$, -S(O)$_2$-CH(CH_3)$CH_2CH_2CH_2CH_3$, -S(O)$_2$-CH_2CH(CH_3)$CH_2CH_2CH_3$, -S(O)$_2$-CH_2CH_2CH(CH_3)CH_2CH_3, -S(O)$_2$-$CH_2CH_2CH_2$CH(CH_3)$_2$, etc. Non-limiting examples of R^5 when R^5 is -S(O)$_2$-cycloalkyl include -S(O)$_2$-cyclopropyl, -S(O)$_2$-cyclobutyl, -S(O)$_2$-cyclopentyl, -S(O)$_2$-cyclohexyl, -S(O)$_2$-adamantyl, -S(O)$_2$-norbornyl, -S(O)$_2$-decalyl, etc. Non-limiting examples of R^5 when R^5 is -C(O)-N(R^2)$_2$ include –C(O)-NH_2, –C(O)-NH(alkyl), -C(O)-N(alkyl)$_2$, -C(O)-NH(aryl), -C(O)-N(alkyl)(aryl), -C(O)-N(aryl)$_2$, wherein the terms "aryl" and "alkyl" are as defined above, and said "aryl" may be unsubstituted or substituted with one or more Y^1 groups as defined herein. Non-limiting examples of R^5 when R^5 is -C(O)-alkyl include -C(O)-CH_3, -C(O)-CH_2CH_3, -C(O)-$CH_2CH_2CH_3$, -C(O)-CH(CH_3)$_2$, -C(O)-$CH_2CH_2CH_2CH_3$, -C(O)-CH_2CH(CH_3)$_2$, -C(O)-CH(CH_3)CH_2CH_3, -C(O)-C(CH_3)$_3$, -C(O)-$CH_2CH_2CH_2CH_2CH_3$, -C(O)-CH_2CH(CH_3)CH_2CH_3, -C(O)-CH_2CH_2CH(CH_3)$_2$, -C(O)-$CH_2CH_2CH_2CH_2CH_2CH_3$, -C(O)-CH(CH_3)$CH_2CH_2CH_2CH_3$, -C(O)-CH_2CH(CH_3)$CH_2CH_2CH_3$, -C(O)-CH_2CH_2CH(CH_3)CH_2CH_3, -C(O)-$CH_2CH_2CH_2$CH(CH_3)$_2$, etc. Non-limiting examples of R^5 when R^5 is

-alkylene-OH include –CH_2-OH, -CH_2CH_2-OH, -$CH_2CH_2CH_2$-OH, -CH(OH)CH_3, -CH_2CH(OH)CH_3, etc. Non-limiting examples of R^5 when R^5 is –$S(O)_2$aryl include –$S(O)_2$-phenyl, –$S(O)_2$-naphthyl, etc., optionally substituted with one or more Y^1 groups.

Each Y^1 is independently selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, benzyl, aryl, heteroaryl, -O-aryl, -S-aryl, -$S(O)_2$-alkyl, -$S(O)_2$-cycloalkyl, -$S(O)_2$-aryl, -alkylene-CN, -CN, -C(O)-alkyl, -C(O)-aryl, -C(O)-haloalkyl, -C(O)O-alkyl, -$N(R^2)$C(O)-alkyl, -$N(R^2)$C(O)-$N(R^2)_2$, -OH, -O-alkyl, -O-haloalkyl, -O-alkylene-C(O)OH, -S-alkyl, -S-haloalkyl, -alkylene-OH, -alkylene-C(O)-O-alkyl, -O-alkylene-aryl, and -$N(R^5)_2$. Non-limiting examples of Y^1 when Y^1 is alkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, neo-pentyl, n-hexyl, iso-hexyl, etc. Non-limiting examples of Y^1 when Y^1 is cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, norbornyl, etc. Non-limiting examples of Y^1 when Y^1 is heterocycloalkyl include morpholinyl, piperazinyl, piperidinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydropyranyl, azetidinyl, etc. Non-limiting examples of Y^1 when Y^1 is heterocycloalkenyl include 2*H*-benzo[1,4]oxazinyl, 4H-chromenyl, 4*H*-chromenyl, 3*H*-indolyl, 1*H*-isoindolyl, 4*H*-benzo[1,4]oxazinyl, etc. Non-limiting examples of Y^1 when Y^1 is halo include chloro, bromo, and iodo. Non-limiting examples of Y^1 when Y^1 is haloalkyl include –CF_3, -CHF_2, -CH_2F, -CH_2CF_3, -CF_2CF_3, -CH_2Br, -CH_2Cl, -CCl_3, etc. Non-limiting examples of Y^1 when Y^1 is aryl include phenyl, naphthyl, etc. Non-limiting examples of Y^1 when Y^1 is heteroaryl include azaindolyl, benzimidazolyl, benzofuranyl, furanyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, furazanyl, indolyl, quinolyl, isoquinolyl, phthalazinyl, pyrazinyl, pyridazinyl, pyrimidyl, pyrrolyl, quinoxalinyl, thiophenyl, isoxazolyl, triazolyl, thiazolyl, indazolyl, thiadiazolyl, imidazolyl, benzo[*b*]thiophenyl, tetrazolyl, pyrazolyl, etc. Non-limiting examples of Y^1 when Y^1 is -O-aryl include –O-phenyl, –O-naphthyl, etc.. Non-limiting examples of Y^1 when Y^1 is-S-aryl include –S-phenyl, –S-naphthyl, etc. Non-limiting examples of Y^1 when Y^1 is -$S(O)_2$-alkyl include -$S(O)_2$-CH_3, -$S(O)_2$-CH_2CH_3, -$S(O)_2$-$CH_2CH_2CH_3$, -$S(O)_2$-$CH(CH_3)_2$, -$S(O)_2$-$CH_2CH_2CH_2CH_3$, -$S(O)_2$-$CH_2CH(CH_3)_2$, -$S(O)_2$-$CH(CH_3)CH_2CH_3$, -$S(O)_2$-$C(CH_3)_3$, -$S(O)_2$-$CH_2CH_2CH_2CH_2CH_3$, -$S(O)_2$-$CH_2CH(CH_3)CH_2CH_3$,

$-S(O)_2-CH_2CH_2CH(CH_3)_2$, $-S(O)_2-CH_2CH_2CH_2CH_2CH_2CH_3$, $-S(O)_2-CH(CH_3)CH_2CH_2CH_2CH_3$, $-S(O)_2-CH_2CH(CH_3)CH_2CH_2CH_3$, $-S(O)_2-CH_2CH_2CH(CH_3)CH_2CH_3$, $-S(O)_2-CH_2CH_2CH_2CH(CH_3)_2$, etc. Non-limiting examples of Y^1 when Y^1 is -S(O)$_2$-cycloalkyl include -S(O)$_2$-cyclopropyl, -S(O)$_2$-cyclobutyl, -S(O)$_2$-cyclopentyl, -S(O)$_2$-cyclohexyl, -S(O)$_2$-adamantyl, -S(O)$_2$-norbornyl, etc. Non-limiting examples of Y^1 when Y^1 is -S(O)$_2$-aryl include -S(O)$_2$-phenyl, -S(O)$_2$-naphthyl, etc. Non-limiting examples of Y^1 when Y^1 is -alkylene-CN include $-O-CH_2-CN$, $-O-CH_2CH_2-CN$, $-CH_2CH_2CH_2CN$, $-O-CH(CH_3)-CN$, $-O-CH(CN)CH_2CH(CH_3)_2$, $-O-CH(CH_3)CH_2CH_2-CN$, etc. Non-limiting examples of Y^1 when Y^1 is -C(O)-alkyl include $-C(O)-CH_3$, $-C(O)-CH_2CH_3$, $-C(O)-CH_2CH_2CH_3$, $-C(O)-CH(CH_3)_2$, $-C(O)-CH_2CH_2CH_2CH_3$, $-C(O)-CH_2CH(CH_3)_2$, $-C(O)-CH(CH_3)CH_2CH_3$, $-C(O)-C(CH_3)_3$, $-C(O)-CH_2CH_2CH_2CH_2CH_3$, $-C(O)-CH_2CH(CH_3)CH_2CH_3$, $-C(O)-CH_2CH_2CH(CH_3)_2$, $-C(O)-CH_2CH_2CH_2CH_2CH_2CH_3$, $-C(O)-CH(CH_3)CH_2CH_2CH_2CH_3$, $-C(O)-CH_2CH(CH_3)CH_2CH_2CH_3$, $-C(O)-CH_2CH_2CH(CH_3)CH_2CH_3$, $-C(O)-CH_2CH_2CH_2CH(CH_3)_2$, etc. Non-limiting examples of Y^1 when Y^1 is -alkylene-OH include $-CH_2-OH$, $-CH_2CH_2-OH$, $-CH_2CH_2CH_2-OH$, $-CH(OH)CH_3$, $-CH_2CH(OH)CH_3$, etc. Non-limiting examples of Y^1 when Y^1 is –C(O)-aryl include –C(O)-phenyl, –C(O)-naphthyl, etc.. Non-limiting examples of Y^1 when Y^1 is -C(O)-haloalkyl include $-C(O)-CF_3$, $-C(O)-CHF_2$, $-C(O)-CH_2F$, $-C(O)-CH_2CF_3$, $-C(O)-CF_2CF_3$, $-C(O)-CH_2Br$, $-C(O)-CH_2Cl$, $-C(O)-CCl_3$, etc. Non-limiting examples of Y^1 when Y^1 is -C(O)O-alkyl include $-C(O)-O-CH_3$, $-C(O)-O-CH_2CH_3$, $-C(O)-O-CH_2CH_2CH_3$, $-C(O)-O-CH(CH_3)_2$, $-C(O)-O-CH_2CH_2CH_2CH_3$, $-C(O)-O-CH_2CH(CH_3)_2$, $-C(O)-O-CH(CH_3)CH_2CH_3$, $-C(O)-O-C(CH_3)_3$, $-C(O)-O-CH_2CH_2CH_2CH_2CH_3$, $-C(O)-O-CH_2CH(CH_3)CH_2CH_3$, $-C(O)-O-CH_2CH_2CH(CH_3)_2$, $-C(O)-O-CH_2CH_2CH_2CH_2CH_2CH_3$, $-C(O)-O-CH(CH_3)CH_2CH_2CH_2CH_3$, $-C(O)-O-CH_2CH(CH_3)CH_2CH_2CH_3$, $-C(O)-O-CH_2CH_2CH(CH_3)CH_2CH_3$, $-C(O)-O-CH_2CH_2CH_2CH(CH_3)_2$, etc. Non-limiting examples of Y^1 when Y^1 is -N(R^2)C(O)-alkyl include –NH-C(O)-alkyl, -N(alkyl)-C(O)-alkyl, and -N(aryl)-C(O)-alkyl wherein the terms "alkyl" and "aryl" are as defined above. Non-limiting examples of Y^1 when Y^1 is -N(R^2)C(O)-N(R^2)$_2$ include $-NHC(O)-NH_2$, -NHC(O)-N(alkyl)$_2$, -NHC(O)-N(aryl)$_2$, -NHC(O)-NH-alkyl, -NHC(O)-NH-aryl, -N(alkyl)C(O)-NH-alkyl, -N(alkyl)C(O)-NH-aryl, -N(aryl)C(O)-NH-aryl,

-N(aryl)C(O)-NH-aryl, etc. Non-limiting examples of Y^1 when Y^1 is -O-alkyl include -O-CH_3, -O-CH_2CH_3, -O-$CH_2CH_2CH_3$, -O-$CH(CH_3)_2$, -O-$CH_2CH_2CH_2CH_3$, -O-$CH_2CH(CH_3)_2$, -O-$CH(CH_3)CH_2CH_3$, -O-$C(CH_3)_3$, -O-$CH_2CH_2CH_2CH_2CH_3$, -O-$CH_2CH(CH_3)CH_2CH_3$, -O-$CH_2CH_2CH(CH_3)_2$, -O-$CH_2CH_2CH_2CH_2CH_2CH_3$, -O-$CH(CH_3)CH_2CH_2CH_2CH_3$, -O-$CH_2CH(CH_3)CH_2CH_2CH_3$, -O-$CH_2CH_2CH(CH_3)CH_2CH_3$, -O-$CH_2CH_2CH_2CH(CH_3)_2$, etc. Non-limiting examples of Y^1 when Y^1 is -O-haloalkyl include -O-CF_3, -O-CHF_2, –O-CH_2F, -O-CH_2CF_3, –O-CF_2CF_3, –O-CH_2Br, -O-CH_2Cl, –O-CCl_3, etc. Non-limiting examples of Y^1 when Y^1 is -O-alkylene-C(O)OH include -O-CH_2-C(O)OH, -O-CH_2CH_2-C(O)OH, -$CH_2CH_2CH_2C$(O)OH, -O-$CH(CH_3)$-C(O)OH, -O-CH(C(O)OH)$CH_2CH(CH_3)_2$, -O-$CH(CH_3)CH_2CH_2$-C(O)OH, etc. Non-limiting examples of Y^1 when Y^1 is -S-alkyl include -S-CH_3, -S-CH_2CH_3, -S-$CH_2CH_2CH_3$, -S-$CH(CH_3)_2$, -S-$CH_2CH_2CH_2CH_3$, -S-$CH_2CH(CH_3)_2$, -S-$CH(CH_3)CH_2CH_3$, -S-$C(CH_3)_3$, -S-$CH_2CH_2CH_2CH_2CH_3$, -S-$CH_2CH(CH_3)CH_2CH_3$, -S-$CH_2CH_2CH(CH_3)_2$, -S-$CH_2CH_2CH_2CH_2CH_2CH_3$, -S-$CH(CH_3)CH_2CH_2CH_2CH_3$, -S-$CH_2CH(CH_3)CH_2CH_2CH_3$, -S-$CH_2CH_2CH(CH_3)CH_2CH_3$, -S-$CH_2CH_2CH_2CH(CH_3)_2$, etc. Non-limiting examples of Y^1 when Y^1 is -S-haloalkyl include -S-CF_3, -S-CHF_2, –S-CH_2F, -S-CH_2CF_3, –S-CF_2CF_3, -S-CH_2Br, -S-CH_2Cl, –S-CCl_3, etc. Non-limiting examples of Y^1 when Y^1 is -alkylene-OH include –CH_2-OH, -CH_2CH_2-OH, -$CH_2CH_2CH_2$-OH, -CH(OH)CH_3, -CH_2CH(OH)CH_3, etc. Non-limiting examples of Y^1 when Y^1 is -alkylene-C(O)-O-alkyl include -O-CH_2-C(O)O-CH_3, -O-CH_2-C(O)O-CH_2CH_3, -O-CH_2CH_2-C(O)O-CH_2CH_3, -O-$CH_2CH_2CH_2$-C(O)O-CH_3, -O-CH_2CH_2-C(O)O-$C(CH_3)_3$, -O-$CH(CH_3)$-C(O)O-CH_3, -O-CH_2CH_2-C(O)O-CH_3, -O-CH(C(O)OCH_3)$CH_2CH(CH_3)_2$, -O-$CH(CH_3)CH_2CH_2$-C(O)O-CH_3, etc. Non-limiting examples of Y^1 when Y^1 is -O-alkylene-aryl include –O-CH_2-phenyl, -O-CH_2CH_2-phenyl, -O-$CH(CH_3)$-phenyl, -O-$CH_2CH(CH_3)$-phenyl, -O$C(CH_3)_2$-phenyl, -O-$CH(CH_2CH_3)$-phenyl, etc. Non-limiting examples of Y^1 when Y^1 is -N(R^5)$_2$ include –NH_2, -N(CH_3)$_2$, -NH(CH_3), -NH(phenyl), -N(phenyl)$_2$, -NH-S(O)$_2$-CH_3, -NH-S(O)$_2$-cyclopropyl, -NH-C(O)-NH_2, -NH-C(O)-N(CH_3)$_2$, -NH-C(O)-CH_3, -NH-CH_2CH_2-OH, etc. The aryl or heteroaryl portions of any of the groups of Y^1 may be unsubstituted or substituted with one or more Z groups as defined herein.

Each Y^2 is independently selected from the group consisting of alkyl, haloalkyl, aryl, -alkylene-aryl, -CN, -C(O)-alkyl, -$S(O)_2$-cycloalkyl, -alkylene-$N(R^2)_2$, -C(O)-alkylene-$N(R^4)_2$, -C(O)-O-alkyl, -C(O)-aryl, and -C(O)-haloalkyl. Non-limiting examples of Y^2 when Y^2 is alkyl include $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-(CH_3)_3$, $-CH_2CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)CH_2CH_3$, $-CH_2CH_2CH(CH_3)_2$, $-CH_2CH_2CH_2CH_2CH_2CH_3$, $-CH(CH_3)CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)CH_2CH_2CH_3$, $-CH_2CH_2CH(CH_3)CH_2CH_3$, $-CH_2CH_2CH_2CH(CH_3)_2$, etc. Non-limiting examples of Y^2 when Y^2 is aryl include phenyl, naphthyl, etc. Non-limiting examples of Y^2 when Y^2 is -alkylene-aryl include $-CH_2$-phenyl, $-CH_2CH_2$-phenyl, $-CH(CH_3)$-phenyl, $-CH_2CH(CH_3)$-phenyl, $-C(CH_3)_2$-phenyl, $-CH(CH_2CH_3)$-phenyl, etc. Non-limiting examples of Y^2 when Y^2 is -C(O)-alkyl include $-C(O)-CH_3$, $-C(O)-CH_2CH_3$, $-C(O)-CH_2CH_2CH_3$, $-C(O)-CH(CH_3)_2$, $-C(O)-CH_2CH_2CH_2CH_3$, $-C(O)-CH_2CH(CH_3)_2$, $-C(O)-CH(CH_3)CH_2CH_3$, $-C(O)-C(CH_3)_3$, $-C(O)-CH_2CH_2CH_2CH_2CH_3$, $-C(O)-CH_2CH(CH_3)CH_2CH_3$, $-C(O)-CH_2CH_2CH(CH_3)_2$, $-C(O)-CH_2CH_2CH_2CH_2CH_2CH_3$, $-C(O)-CH(CH_3)CH_2CH_2CH_2CH_3$, $-C(O)-CH_2CH(CH_3)CH_2CH_2CH_3$, $-C(O)-CH_2CH_2CH(CH_3)CH_2CH_3$, $-C(O)-CH_2CH_2CH_2CH(CH_3)_2$, etc. Non-limiting examples of Y^2 when Y^2 is -$S(O)_2$-cycloalkyl include -$S(O)_2$-cyclopropyl, -$S(O)_2$-cyclobutyl, -$S(O)_2$-cyclopentyl, -$S(O)_2$-cyclohexyl, -$S(O)_2$-norbornyl, -$S(O)_2$-adamantyl, etc. Non-limiting examples of Y^2 when Y^2 is -alkylene-$N(R^2)_2$ include -alkylene-$N(R^2)_2$ include $-CH_2$-$N(R^2)_2$, $-CH(CH_3)$-$N(R^2)_2$, $-CH_2CH_2$-$N(R^2)_2$, $-CH_2CH_2CH_2$-$N(R^2)_2$, $-CH(CH_3)CH_2CH_2$-$N(R^2)_2$, etc., wherein each R^2 is independently defined as described herein. For example, the "-$N(R^2)_2$" portion of -alkylene-$N(R^2)_2$ of Y^2 can be $-NH_2$, $-N(CH_3)_2$, $-NH(CH_3)$, -NH(phenyl), -N(phenyl)$_2$, $-N(CH_2CH_3)_2$, $-NH(CH_2CH_3)$, etc. Non-limiting examples of Y^2 when Y^2 is -C(O)-alkylene-$N(R^4)_2$ include -C(O)-CH_2-$N(R^4)_2$, -C(O)-$CH(CH_3)$-$N(R^4)_2$, -C(O)-CH_2CH_2-$N(R^4)_2$, -C(O)-$CH_2CH_2CH_2$-$N(R^4)_2$, -C(O)-$CH(CH_3)CH_2CH_2$-$N(R^4)_2$, etc., wherein each R^4 is independently defined as described herein. For example the "-$N(R^4)_2$" portion of -C(O)-alkylene-$N(R^4)_2$ of Y^2 can be $-NH_2$, $-N(CH_3)_2$, $-NH(CH_3)$, -NH(phenyl), -N(phenyl)$_2$, $-N(CH_2CH_3)_2$, $-NH(CH_2CH_3)$, $-NH-C(O)-O-CH_3$, $-NH-C(O)-O-CH_2CH_3$, $-N(CH_3)-C(O)-O-CH_3$, $-N(CH_3)-C(O)-O-CH_2CH_3$, $-NH-C(O)-CH_3$, $-NH-C(O)-CH_2CH_3$, $-N(CH_3)-C(O)-CH_3$, $-N(CH_3)-C(O)-CH_2CH_3$, etc. Non-limiting examples of Y^2 when Y^2 is

-C(O)-O-alkyl include -C(O)-O-CH_3, -C(O)-O-CH_2CH_3, -C(O)-O-$CH_2CH_2CH_3$, -C(O)-O-$CH(CH_3)_2$, -C(O)-O-$CH_2CH_2CH_2CH_3$, -C(O)-O-$CH_2CH(CH_3)_2$, -C(O)-O-$CH(CH_3)CH_2CH_3$, -C(O)-O-$C(CH_3)_3$, -C(O)-O-$CH_2CH_2CH_2CH_2CH_3$, -C(O)-O-$CH_2CH(CH_3)CH_2CH_3$, -C(O)-O-$CH_2CH_2CH(CH_3)_2$, -C(O)-O-$CH_2CH_2CH_2CH_2CH_2CH_3$, -C(O)-O-$CH(CH_3)CH_2CH_2CH_2CH_3$, -C(O)-O-$CH_2CH(CH_3)CH_2CH_2CH_3$, -C(O)-O-$CH_2CH_2CH(CH_3)CH_2CH_3$, -C(O)-O-$CH_2CH_2CH_2CH(CH_3)_2$, etc. Non-limiting examples of Y^2 when Y^2 is -C(O)-aryl include -C(O)-phenyl, -C(O)-naphthyl, etc., optionally substituted with one or more Z groups. Non-limiting examples of Y^2 when Y^2 is –C(O)-haloalkyl include –C(O)-CF_3, –C(O)-CHF_2, –C(O)-CH_2F, –C(O)-CH_2CF_3, –C(O)-CF_2CF_3, -C(O)-CH_2Br, –C(O)-CH_2Cl, –C(O)-CCl_3, etc.

Each Z is independently selected from the group consisting of alkyl, halo, haloalkyl, -OH, -O-alkyl, and –CN. The terms “alkyl”, “halo”, aloalkyl”, and “-O-alkyl” are as defined above.

As used throughout the specification, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"Patient" includes both human and animals.

“Mammal” means humans and other mammalian animals.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. In one embodiment alkyl groups contain about 1 to about 12 carbon atoms in the chain. In another embodiment alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, heptyl, nonyl, or decyl.

“Alkylene” means a divalent group obtained by removal of a hydrogen atom from an alkyl group that is defined above. Non-limiting examples of alkylene include methylene, ethylene and propylene. “Lower alkylene” means an alkylene having about 1 to 6 carbon atoms in the chain, which may be straight or branched.

"Alkenyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and

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

"Alkenylene" means a divalent group obtained by removal of a hydrogen atom from an alkenyl group that is defined above.

"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. In one embodiment alkynyl groups have about 2 to about 12 carbon atoms in the chain. In another embodiment alkynyl groups have about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl, 3-methylbutynyl, n-pentynyl, and decynyl. The term "substituted alkynyl" means that the alkynyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, aryl and cycloalkyl.

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

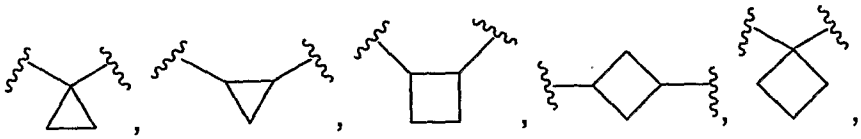
"Aryloxy" means a –O-aryl group, wherein aryl is defined as above. the aryloxy group is attached to the parent moiety through the ether oxygen.

"Arylene" means a divalent aryl group obtained by the removal of a hydrogen atom from an aryl group as defined above. Non-limiting examples of arylenes include, for example, 1,2-phenylene, 1,3-phenylene, or 1,4-phenylene.

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

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 13 carbon atoms, or about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalin, norbornyl, adamantyl and the like.

"Cycloalkylene" means a divalent cycloalkyl group obtained by the removal of a hydrogen atom from a cycloalkyl group as defined above. Non-limiting examples of cycloalkylenes include:

 , etc.

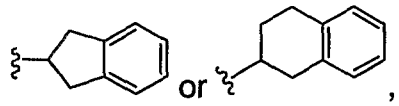
"Heterocycloalkyl" means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, or about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. In one embodiment heterocycloalkyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocycloalkyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The heterocycloalkyl can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocycloalkyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocycloalkyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

"Heterocycloalkenyl" means a non-aromatic unsaturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, or about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Heterocycloalkenyls have at least one double bond, wherein said double bond may be between two ring carbon atoms, between a ring carbon atom and a ring heteroatom (e.g., between a ring carbon atom and a ring nitrogen atom), or between two ring heteroatoms (e.g., between two ring nitrogen atoms). If more than one double bond is present in the ring, each double bond is independently defined as described herein. In another embodiment heterocycloalkenyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocycloalkenyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The heterocycloalkenyl can be optionally substituted by one or more "ring system

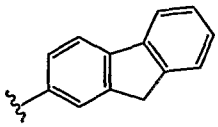
substituents" which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocycloalkenyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocycloalkenyl rings include thiazolinyl, 2,3-dihydro-1H-pyrrolyl, 2,5-dihydro-1H-pyrrolyl, 3,4-dihydro-2H-pyrrolyl, 2,3-dihydro-furan, 2,5-dihydro-furan, etc.

"Benzo-fused heterocycloalkenyl" means a heterocycloalkenyl, as defined above, to which one or more phenyl rings has been fused, so that each phenyl ring shares two ring carbon atoms with the cycloalkyl ring. Non-limiting examples of benzo-fused cycloalkyls are 4H-chromene, chromene-4-one, 1H-isochromene, etc.

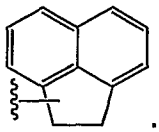
"Benzo-fused cycloalkyl" means a cycloalkyl, as defined above, to which one or more phenyl rings has been fused, so that each phenyl ring shares two ring carbon atoms with the cycloalkyl ring. Non-limiting examples of benzo-fused cycloalkyls are indanyl and tetradehydronaphthyl:



and non-limiting examples of a dibenzo-fused cycloalkyls are fluorenyl:


and

acenaphthenyl:



"Benzo-fused heterocycloalkyl" means a heterocycloalkyl, as defined above, to which one or more phenyl rings has been fused, so that each phenyl ring shares two ring carbon atoms with the heterocycloalkyl ring. A non-limiting example of a benzo-fused heterocycloalkyls is 2,3-dihydro-benzo[1,4]dioxinyl.

"Cycloalkenyl" means a non-aromatic mono or multicyclic ring system comprising about 3 to about 10 carbon atoms, or about 5 to about 10 carbon atoms, which contains at least one carbon-carbon double bond. In one embodiment cycloalkenyl rings contain about 5 to about 7 ring atoms. The cycloalkenyl can be optionally substituted with one or more "ring system

substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkenyls include cyclopentenyl, cyclohexenyl, cycloheptenyl, and the like. Non-limiting example of a suitable multicyclic cycloalkenyl is norbornylenyl.

"Halo" (or "halogeno" or "halogen") means fluoro, chloro, bromo, or iodo groups. Preferred are fluoro, chloro or bromo, and more preferred are fluoro and chloro.

"Haloalkyl" means an alkyl as defined above wherein one or more hydrogen atoms on the alkyl are replaced by a halo group as defined above.

"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, and are defined as described herein.

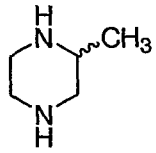
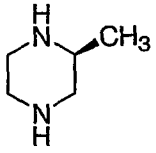
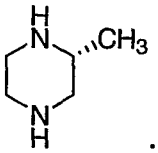
"Alkoxy" means an –O-alkyl group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy and heptoxy. The bond to the parent moiety is through the ether oxygen.

With reference to the number of moieties (e.g., substituents, groups or rings) in a compound, unless otherwise defined, the phrases "one or more" and "at least one" mean that there can be as many moieties as chemically permitted, and the determination of the maximum number of such moieties is well within the knowledge of those skilled in the art.

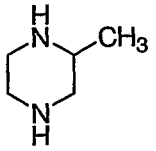
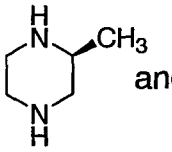
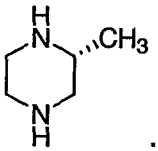
When used herein, the term "independently", in reference to the substitution of a parent moiety with one or more substituents, means that the parent moiety may be substituted with any of the listed substituents, either individually or in combination, and any number of chemically possible substituents may be used. As a non-limiting example, a phenyl independently substituted with one or more alkyl or halo substituents can include, chlorophenyl, dichlorophenyl, trichlorophenyl, tolyl, xylyl, 2-chloro-3-methylphenyl, 2,3-dichloro-4-methylphenyl, etc.

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

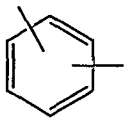
The wavy line ∿∿∿ as a bond generally indicates a mixture of, or either of, the possible isomers, e.g., containing (R)- and (S)- stereochemistry. For example,


means containing both

and

.

Moreover, when the stereochemistry of a chiral center (or stereogenic center) is not expressly indicated, a mixture of, or any of the individual possible isomers are contemplated. Thus, for example,

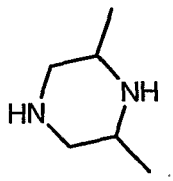
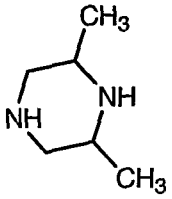

means containing

and/or

.

Lines drawn into the ring systems, such as, for example:



indicate that the indicated line (bond) may be attached to any of the substitutable ring carbon atoms.

As well known in the art, a bond drawn from a particular atom wherein no moiety is depicted at the terminal end of the bond indicates a methyl group bound through that bond to the atom, unless stated otherwise. For example:


represents

.

It should also be noted that any carbon or heteroatom with unsatisfied valences in the text, schemes, examples, structural formulae, and any Tables herein is assumed to have the hydrogen atom or atoms to satisfy the valences.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound' or "stable

structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

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

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

When any variable (e.g., aryl, heterocycle, R^2, etc.) occurs more than one time in any constituent or in any Formula (e.g., Formula I), its definition on each occurrence is independent of its definition at every other occurrence.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term "prodrug", as employed herein, denotes a compound that is a drug precursor which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of formula I or a salt and/or solvate thereof. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) Volume 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design,* (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, both of which are incorporated herein by reference thereto.

"Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain

instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

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

The compounds of Formula (I) form salts that are also within the scope of this invention. Reference to a compound of Formula (I) herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula (I) contains both a basic moiety, such as, but not limited to a piperazine, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds of the Formula (I) may be formed, for example, by reacting a compound of Formula (I) with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization. Acids (and bases) which are generally considered suitable for the formation of pharmaceutically useful salts from basic (or acidic) pharmaceutical compounds are discussed, for example, by

S. Berge *et al, Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al, The Practice of Medicinal Chemistry* (1996), Academic Press, New York; in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website); and P. Heinrich Stahl, Camille G. Wermuth (Eds.), *Handbook of Pharmaceutical Salts: Properties, Selection, and Use*, (2002) Int'l. Union of Pure and Applied Chemistry, pp. 330-331. These disclosures are incorporated herein by reference thereto.

Exemplary acid addition salts include acetates, adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides, hydrobromides, hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates, methanesulfonates, methyl sulfates, 2-naphthalenesulfonates, nicotinates, nitrates, oxalates, pamoates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates, sulfonates (such as those mentioned herein), tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) undecanoates, and the like.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, aluminum salts, zinc salts, salts with organic bases (for example, organic amines) such as benzathines, diethylamine, dicyclohexylamines, hydrabamines (formed with N,N-bis(dehydroabietyl)ethylenediamine), N-methyl-D-glucamines, N-methyl-D-glucamides, t-butyl amines, piperazine, phenylcyclohexylamine, choline, tromethamine, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g. methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g. decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are

considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Compounds of Formula (I), and salts, solvates and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates and prodrugs of the compounds as well as the salts and solvates of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate" "prodrug" and the like, is intended to equally apply to the salt, solvate and prodrug of enantiomers, stereoisomers, rotamers, tautomers, racemates or prodrugs of the inventive compounds.

Polymorphic forms of the compounds of Formula (I), and of the salts, solvates and prodrugs of the compounds of Formula (I), are intended to be included in the present invention.

In still another embodiment, the present invention provides a composition comprising at least one compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or ester thereof, and a pharmaceutically acceptable carrier.

The term "pharmaceutical composition" is also intended to encompass both the bulk composition and individual dosage units comprised of more than one (e.g., two) pharmaceutically active agents such as, for example, a compound of the present invention and an additional agent selected from the lists of the additional agents described herein, along with any pharmaceutically inactive excipients. The bulk composition and each individual dosage unit can contain fixed amounts of the afore-said "more than one pharmaceutically active agents".

The bulk composition is material that has not yet been formed into individual dosage units. An illustrative dosage unit is an oral dosage unit such as tablets, pills and the like. Similarly, the herein-described method of treating a patient by administering a pharmaceutical composition of the present invention is also intended to encompass the administration of the afore-said bulk composition and individual dosage units.

Unit dosage forms, without limitation, can include tablets, pills, capsules, sustained release pills, sustained release tablets, sustained release capsules, powders, granules, or in the form of solutions or mixtures (i.e., elixirs, tinctures, syrups, emulsions, suspensions). For example, one or more compounds of Formula (I), or salts or solvates thereof, may be combined, without limitation, with one or more pharmaceutically acceptable liquid carriers such as ethanol, glycerol, or water, and/or one or more solid binders such as, for example, starch, gelatin, natural sugars (e.g., glucose or β-lactose), and/or natural or synthetic gums (e.g., acacia, tragacanth, or sodium alginate), carboxymethylcellulose, polyethylene glycol, waxes and the like, and/or disintegrants, buffers, preservatives, anti-oxidants, lubricants, flavorings, thickeners, coloring agents, emulsifiers and the like. In addition, the unit dosage forms can include, without limitation, pharmaceutically acceptable lubricants (e.g., sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, and sodium chloride) and disintegrators (e.g., starch, methyl cellulose, agar, bentonite, and xanthan gum).

The amount of excipient or additive can range from about 0.1 to about 90 weight percent of the total weight of the treatment composition or therapeutic combination. One skilled in the art would understand that the amount of carrier(s), excipients and additives (if present) can vary.

In another embodiment, the present invention provides a method of treating, reducing, or ameliorating a disease or condition selected from the group consisting of metabolic syndrome, obesity, waist circumference, lipid profile, insulin sensitivity, neuroinflammatory disorders, cognitive disorders, psychosis, addictive behavior, gastrointestinal disorders, and cardiovascular conditions, in a patient in need thereof, comprising administering to said patient an effective amount of at least one compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or ester thereof.

In yet another embodiment, the present invention provides a method of treating, reducing, or ameliorating obesity, in a patient in need thereof, comprising administering to said patient an effective amount of at least one compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or ester thereof.

In yet another embodiment, the present invention provides a method of treating, reducing, or ameliorating metabolic syndrome, obesity, waist circumference, lipid profile, insulin sensitivity, neuroinflammatory disorders, cognitive disorders, psychosis, addictive behavior, gastrointestinal disorders, and cardiovascular conditions, in a patient in need thereof, comprising administering to said patient an effective amount of a composition comprising at least one compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or ester thereof and a pharmaceutically acceptable carrier.

In yet another embodiment, the present invention provides a method of treating, reducing, or ameliorating obesity, in a patient in need thereof, comprising administering to said patient an effective amount of a composition comprising at least one compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or ester thereof and a pharmaceutically acceptable carrier.

The compounds of Formula (I) can be useful as CB_1 receptor antagonists for treating, reducing, or ameliorating metabolic syndrome, obesity, waist circumference, lipid profile, insulin sensitivity, neuroinflammatory disorders, cognitive disorders, psychosis, addictive behavior (e.g., smoking cessation), gastrointestinal disorders, and cardiovascular conditions (e.g., elevated cholesterol and triglyceride levels). It is contemplated that the compounds of Formula (I) of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof, can be useful in treating one or more the conditions or diseases listed above. In particular, the compounds of Formula (I) of the present invention are useful in treating obesity.

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in antagonizing a CB_1 receptor and thus producing the desired therapeutic effect in a suitable patient.

The selective CB_1 receptor antagonist compound of Formula (I), or a

pharmaceutically acceptable salt, solvate, or ester thereof, can be administered in a therapeutically effective amount and manner to treat the specified condition. The daily dose of the selective CB_1 receptor antagonist of Formula (I) (or pharmaceutically acceptable salts, solvates, or esters thereof) administered to a mammalian patient or subject can range from about 1 mg/kg to about 50 mg/kg (where the units mg/kg refer to the amount of selective CB_1 receptor antagonist compound of Formula (I) per kg body weight of the patient), or about 1 mg/kg to about 25 mg/kg, or about 1 mg/kg to about 10 mg/kg.

Alternatively, the daily dose can range from about 1 mg to about 50 mg, or about 1 mg to about 25 mg, or about 5 mg to about 20 mg. Although a single administration of the selective CB_1 receptor antagonist compound of Formula (I), or salts, solvates, or esters thereof, can be efficacious, multiple dosages can also be administered. The exact dose, however, can readily be determined by the attending clinician and will depend on such factors as the potency of the compound administered, the age, weight, condition and response of the patient.

The treatment compositions of the present invention can be administered in any conventional dosage form, preferably an oral dosage form such as a capsule, tablet, powder, cachet, suspension or solution. The formulations and pharmaceutical compositions can be prepared using conventional pharmaceutically acceptable and conventional techniques.

In still yet another embodiment, the present invention provides a composition comprising: (a) at least one compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or ester thereof, and (b) at least one cholesterol lowering compound.

Therapeutic combinations also are provided comprising: (a) a first amount of at least one selective CB_1 receptor antagonist, or a pharmaceutically acceptable salt, solvate, or ester thereof; and (b) a second amount of at least one cholesterol lowering compound, wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity, hyperlipidemia, metabolic syndrome, or lowering a concentration of a sterol in the plasma of a subject.

Pharmaceutical compositions for the treatment or prevention of a vascular condition, diabetes, obesity, hyperlipidemia, metabolic syndrome, or lowering a concentration of a sterol in the plasma of a subject comprising a therapeutically

effective amount of the above compositions or therapeutic combinations and a pharmaceutically acceptable carrier also are provided.

In still yet another embodiment, the compositions and combinations of the present invention comprise at least one compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or ester thereof, and at least one sterol absorption inhibitor or at least one 5α-stanol absorption inhibitor.

In still yet another embodiment of the present invention, there is provided a therapeutic combination comprising: (a) a first amount of at least one compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or ester thereof; and (b) a second amount of at least one cholesterol lowering compound; wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of one or more of a vascular condition, diabetes, obesity, metabolic syndrome, or lowering a concentration of a sterol in the plasma of a subject.

In still yet another embodiment, the present invention provides for a pharmaceutical composition for the treatment or prevention of one or more of a vascular condition, diabetes, obesity, metabolic syndrome, or lowering a concentration of a sterol in the plasma of a subject, comprising a therapeutically effective amount of a composition or therapeutic combination comprising: (a) at least one compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or ester thereof; (b) a cholesterol lowering compound; and (c) a pharmaceutically acceptable carrier.

As used herein, "therapeutic combination" or "combination therapy" means the administration of two or more therapeutic agents, such as a compound according to Formula (I) of the present invention, and a cholesterol lowering compound such as one or more substituted azetidinone or one or more substituted β-lactam, to prevent or treat a condition, for example a vascular condition, such as hyperlipidaemia (for example atherosclerosis, hypercholesterolemia or sitosterolemia), vascular inflammation, metabolic syndrome, stroke, diabetes, obesity and/or reduce the level of sterol(s) (such as cholesterol) in the plasma or tissue. As used herein, "vascular" comprises cardiovascular, cerebrovascular and combinations thereof. The compositions, combinations and treatments of the present invention can be administered by any

suitable means which produce contact of these compounds with the site of action in the body, for example in the plasma, liver, small intestine, or brain (e.g., hippocampus, cortex, cerebellum, and basal ganglia) of a subject (mammal or human or other animal). Such administration includes co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single tablet or capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each therapeutic agent. Also, such administration includes the administration of each type of therapeutic agent in a sequential manner. In either case, the treatment using the combination therapy will provide beneficial effects in treating the condition. A potential advantage of the combination therapy disclosed herein may be a reduction in the required amount of an individual therapeutic compound or the overall total amount of therapeutic compounds that are effective in treating the condition. By using a combination of therapeutic agents, the side effects of the individual compounds can be reduced as compared to a monotherapy, which can improve patient compliance. Also, therapeutic agents can be selected to provide a broader range of complimentary effects or complimentary modes of action.

As discussed above, the compositions, pharmaceutical compositions and therapeutic combinations of the present invention comprise: (a) one or more compounds according to Formula (I) of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof; and (b) one or more cholesterol lowering agents. A non-limiting list of cholesterol lowering agents useful in the present invention include HMG CoA reductase inhibitor compounds such as lovastatin (for example MEVACOR® which is available from Merck & Co.), simvastatin (for example ZOCOR® which is available from Merck & Co.), pravastatin (for example PRAVACHOL® which is available from Bristol Meyers Squibb), atorvastatin, fluvastatin, cerivastatin, CI-981, rivastatin (sodium 7-(4-fluorophenyl)-2,6-diisopropyl-5-methoxymethylpyridin-3-yl)-3,5-dihydroxy-6-heptanoate), rosuvastatin calcium (CRESTOR® from AstraZeneca Pharmaceuticals), pitavastatin (such as NK-104 of Negma Kowa of Japan); HMG CoA synthetase inhibitors, for example L-659,699 ((E,E)-11-[3'R-(hydroxy-methyl)-4'-oxo-2'R-oxetanyl]-3,5,7R-trimethyl-2,4-undecadienoic acid); squalene synthesis inhibitors, for example squalestatin 1; squalene epoxidase inhibitors,

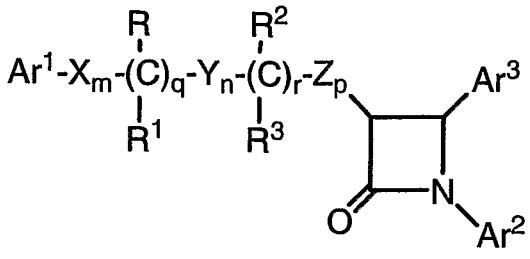
for example, NB-598 ((E)-N-ethyl-N-(6,6-dimethyl-2-hepten-4-ynyl)-3-[(3,3'-bithiophen-5-yl)methoxy]benzene-methanamine hydrochloride); sterol (e.g., cholesterol) biosynthesis inhibitors such as DMP-565; nicotinic acid derivatives (e.g., compounds comprising a pyridine-3-carboxylate structure or a pyrazine-2-carboxylate structure, including acid forms, salts, esters, zwitterions and tautomers) such as niceritrol, nicofuranose and acipimox (5-methyl pyrazine-2-carboxylic acid 4-oxide); clofibrate; gemfibrazol; bile acid sequestrants such as cholestyramine (a styrene-divinylbenzene copolymer containing quaternary ammonium cationic groups capable of binding bile acids, such as QUESTRAN® or QUESTRAN LIGHT® cholestyramine which are available from Bristol-Myers Squibb), colestipol (a copolymer of diethylenetriamine and 1-chloro-2,3-epoxypropane, such as COLESTID® tablets which are available from Pharmacia), colesevelam hydrochloride (such as WelChol® Tablets (poly(allylamine hydrochloride) cross-linked with epichlorohydrin and alkylated with 1-bromodecane and (6-bromohexyl)-trimethylammonium bromide) which are available from Sankyo), water soluble derivatives such as 3,3-ioene, N-(cycloalkyl) alkylamines and poliglusam, insoluble quaternized polystyrenes, saponins and mixtures thereof; inorganic cholesterol sequestrants such as bismuth salicylate plus montmorillonite clay, aluminum hydroxide and calcium carbonate antacids; ileal bile acid transport ("IBAT") inhibitors (or apical sodium co-dependent bile acid transport ("ASBT") inhibitors) such as benzothiepines, for example the therapeutic compounds comprising a 2,3,4,5-tetrahydro-1-benzothiepine 1,1-dioxide structure such as are disclosed in PCT Patent Application WO 00/38727 which is incorporated herein by reference; AcylCoA:Cholesterol *O*-acyltransferase ("ACAT") Inhibitors such as avasimibe ([[2,4,6-tris(1-methylethyl)phenyl]acetyl]sulfamic acid, 2,6-bis(1-methylethyl)phenyl ester, formerly known as CI-1011), HL-004, lecimibide (DuP-128) and CL-277082 (*N*-(2,4-difluorophenyl)-*N*-[[4-(2,2-dimethylpropyl)phenyl]methyl]-*N*-heptylurea), and the compounds described in P. Chang et al., "Current, New and Future Treatments in Dyslipidaemia and Atherosclerosis", Drugs 2000 Jul;60(1); 55-93, which is incorporated by reference herein; Cholesteryl Ester Transfer Protein ("CETP") Inhibitors such as those disclosed in PCT Patent Application No. WO 00/38721 and U.S. Patent No.

6,147,090, which are incorporated herein by reference; probucol or derivatives thereof, such as AGI-1067 and other derivatives disclosed in U.S. Patents Nos. 6,121,319 and 6,147,250, herein incorporated by reference; low-density lipoprotein (LDL) receptor activators such as HOE-402, an imidazolidinyl-pyrimidine derivative that directly stimulates LDL receptor activity, described in M. Huettinger et al., "Hypolipidemic activity of HOE-402 is Mediated by Stimulation of the LDL Receptor Pathway", Arterioscler. Thromb. 1993; 13:1005-12, herein incorporated by reference; fish oils containing Omega 3 fatty acids (3-PUFA); natural water soluble fibers, such as psyllium, guar, oat and pectin; plant stanols and/or fatty acid esters of plant stanols, such as sitostanol ester used in BENECOL® margarine; nicotinic acid receptor agonists (e.g., agonists of the HM74 and HM74A receptor which receptor is described in US 2004/0142377, US 2005/0004178, US 2005/0154029, US 6902902, WO 2004/071378, WO 2004/071394, WO 01/77320, US 2003/0139343, WO 01/94385, WO 2004/083388, US 2004/254224, US 2004/0254224, US 2003/0109673 and WO 98/56820) for example those described in WO 2004/033431, WO 2005/011677, WO 2005/051937, US 2005/0187280, US 2005/0187263, WO 2005/077950, WO 2005/016867, and WO 2005/016870; and the substituted azetidinone or substituted β-lactam sterol absorption inhibitors discussed in detail below.

As used herein, "sterol absorption inhibitor" means a compound capable of inhibiting the absorption of one or more sterols, including but not limited to cholesterol, phytosterols (such as sitosterol, campesterol, stigmasterol and avenosterol), 5α-stanols (such as cholestanol, 5α-campestanol, 5α-sitostanol), and/or mixtures thereof, when administered in a therapeutically effective (sterol and/or 5α-stanol absorption inhibiting) amount to a mammal or human.

Substituted Azetidinones of Formula (II)

In one embodiment, substituted azetidinones useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (II) below:



(II)

or pharmaceutically acceptable salts, solvates, or esters of the compounds of Formula (II), wherein, in Formula (II) above:

Ar^1 and Ar^2 are independently selected from the group consisting of aryl and R^4-substituted aryl;

Ar^3 is aryl or R^5-substituted aryl;

X, Y and Z are independently selected from the group consisting of $-CH_2-$, -CH(lower alkyl)- and $-C(\text{lower alkyl})_2-$;

R and R^2 are independently selected from the group consisting of $-OR^6$, $-OC(O)R^6$, $-OC(O)OR^9$ and $-OC(O)NR^6R^7$;

R^1 and R^3 are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

q is 0 or 1; r is 0 or 1; m, n and p are independently selected from 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;

R^4 is 1-5 substituents independently selected from the group consisting of lower alkyl, $-OR^6$, $-OC(O)R^6$, $-OC(O)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-OC(O)NR^6R^7$, $-NR^6R^7$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^9$, $-NR^6C(O)NR^7R^8$, $-NR^6SO_2R^9$, $-C(O)OR^6$, $-C(O)NR^6R^7$, $-C(O)R^6$, $-S(O)_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-C(O)OR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$, $-CH=CH-C(O)OR^6$, $-CF_3$, -CN, $-NO_2$ and halogen;

R^5 is 1-5 substituents independently selected from the group consisting of $-OR^6$, $-OC(O)R^6$, $-OC(O)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-OC(O)NR^6R^7$, $-NR^6R^7$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^9$, $-NR^6C(O)NR^7R^8$, $-NR^6S(O)_2R^9$, $-C(O)OR^6$, $-C(O)NR^6R^7$, $-C(O)R^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-C(O)OR^6$, $-O(CH_2)_{1-10}C(O)NR^6R^7$, -(lower alkylene)$C(O)OR^6$ and $-CH=CH-C(O)OR^6$;

R^6, R^7 and R^8 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

R^9 is lower alkyl, aryl or aryl-substituted lower alkyl.

Preferably, R^4 is 1-3 independently selected substituents, and R^5 is preferably 1-3 independently selected substituents.

Certain compounds useful in the therapeutic compositions or combinations of the invention may have at least one asymmetrical carbon atom and therefore all isomers, including enantiomers, diastereomers, stereoisomers, rotamers, tautomers and racemates of the compounds of Formula II-XIII (where they exist) are contemplated as being part of this invention. The invention includes d and l isomers in both pure form and in admixture, including racemic mixtures. Isomers can be prepared using conventional techniques, either by reacting optically pure or optically enriched starting materials or by separating isomers of a compound of the Formulae II-XIII. Isomers may also include geometric isomers, e.g., when a double bond is present.

Those skilled in the art will appreciate that for some of the compounds of the Formulae II-XIII, one isomer may show greater pharmacological activity than other isomers.

Preferred compounds of Formula (II) are those in which Ar^1 is phenyl or R^4-substituted phenyl, more preferably (4-R^4)-substituted phenyl. Ar^2 is preferably phenyl or R^4-substituted phenyl, more preferably (4-R^4)-substituted phenyl. Ar^3 is preferably R^5-substituted phenyl, more preferably (4-R^5)-substituted phenyl. When Ar^1 is (4-R^4)-substituted phenyl, R^4 is preferably a halogen. When Ar^2 and Ar^3 are R^4- and R^5-substituted phenyl, respectively, R^4 is preferably halogen or -OR^6 and R^5 is preferably -OR^6, wherein R^6 is lower alkyl or hydrogen. Especially preferred are compounds wherein each of Ar^1 and Ar^2 is 4-fluorophenyl and Ar^3 is 4-hydroxyphenyl or 4-methoxyphenyl.

X, Y and Z are each preferably -CH_2-. R^1 and R^3 are each preferably hydrogen. R and R^2 are preferably -OR^6 wherein R^6 is hydrogen, or a group readily metabolizable to a hydroxyl (such as -OC(O)R^6, -OC(O)OR^9 and -OC(O)NR^6R^7, defined above).

The sum of m, n, p, q and r is preferably 2, 3 or 4, more preferably 3. Preferred are compounds OF Formula (II) wherein m, n and r are each zero, q is 1 and p is 2.

Also preferred are compounds of Formula (II) in which p, q and n are each zero, r is 1 and m is 2 or 3. More preferred are compounds wherein m, n and r

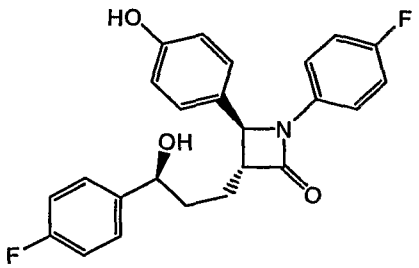
are each zero, q is 1, p is 2, Z is -CH_2- and R is -OR^6, especially when R^6 is hydrogen.

Also more preferred are compounds of Formula (II) wherein p, q and n are each zero, r is 1, m is 2, X is -CH_2- and R^2 is -OR^6, especially when R^6 is hydrogen.

Another group of preferred compounds of Formula (II) is that in which Ar^1 is phenyl or R^4-substituted phenyl, Ar^2 is phenyl or R^4-substituted phenyl and Ar^3 is R^5-substituted phenyl. Also preferred are compounds in which Ar^1 is phenyl or R^4-substituted phenyl, Ar^2 is phenyl or R^4-substituted phenyl, Ar^3 is R^5-substituted phenyl, and the sum of m, n, p, q and r is 2, 3 or 4, more preferably 3. More preferred are compounds wherein Ar^1 is phenyl or R^4-substituted phenyl, Ar^2 is phenyl or R^4-substituted phenyl, Ar^3 is R^5-substituted phenyl, and wherein m, n and r are each zero, q is 1 and p is 2, or wherein p, q and n are each zero, r is 1 and m is 2 or 3.

Substituted Azetidinones of Formula (III)

In a preferred embodiment, a substituted azetidinone of Formula (II) useful in the compositions, therapeutic combinations and methods of the present invention is represented by Formula (III) (ezetimibe) below:



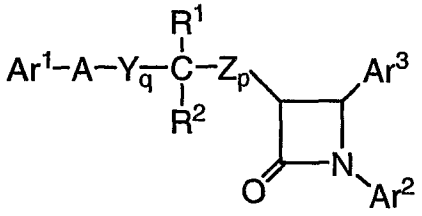
(III)

or pharmaceutically acceptable salts, solvates, or esters of the compound of Formula (III). The compound of Formula (III) can be in anhydrous or hydrated form. A product containing ezetimibe compound is commercially available as ZETIA® ezetimibe formulation from MSP Pharmaceuticals.

Compounds of Formula (II) can be prepared by a variety of methods well known to those skilled in the art, for example such as are disclosed in U.S. Patents Nos. 5,631,365, 5,767,115, 5,846,966, 6,207,822, 6,627,757, 6,093,812, 5,306,817, 5,561,227, 5,688,785, and 5,688,787, each of which is incorporated herein by reference.

Substituted Azetidinones of Formula (IV)

Alternative substituted azetidinones useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (IV) below:



(IV)

or a pharmaceutically acceptable salt thereof or a solvate thereof, or an ester thereof, wherein, in Formula (IV) above:

Ar^1 is R^3-substituted aryl;

Ar^2 is R^4-substituted aryl;

Ar^3 is R^5-substituted aryl;

Y and Z are independently selected from the group consisting of $-CH_2-$, -CH(lower alkyl)- and $-C(\text{lower alkyl})_2-$;

A is selected from -O-, -S-, -S(O)- or $-S(O)_2-$;

R^1 is selected from the group consisting of $-OR^6$, $-OC(O)R^6$, $-OC(O)OR^9$ and $-OC(O)NR^6R^7$;

R^2 is selected from the group consisting of hydrogen, lower alkyl and aryl; or R^1 and R^2 together are =O;

q is 1, 2 or 3;

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

R^5 is 1-3 substituents independently selected from the group consisting of $-OR^6$, $-OC(O)R^6$, $-OC(O)OR^9$, $-O(CH_2)_{1-5}OR^9$, $-OC(O)NR^6R^7$, $-NR^6R^7$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^9$, $-NR^6C(O)NR^7R^8$, $-NR^6S(O)_2$-lower alkyl, $-NR^6S(O)_2$-aryl, $-C(O)NR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}$-alkyl, $S(O)_{0-2}$-aryl, $-O(CH_2)_{1-10}$-$C(O)OR^6$, $-O(CH_2)_{1-10}C(O)NR^6R^7$, o-halogeno, m-halogeno, o-lower alkyl, m-lower alkyl, -(lower alkylene)-$C(O)OR^6$, and $-CH{=}CH$-$C(O)OR^6$;

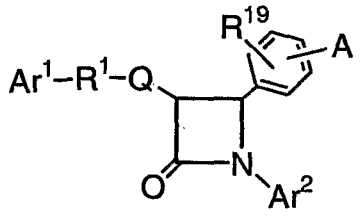
R^3 and R^4 are independently 1-3 substituents independently selected from the group consisting of R^5, hydrogen, p-lower alkyl, aryl, $-NO_2$, $-CF_3$ and p-halogeno;

R^6, R^7 and R^8 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and R^9 is lower alkyl, aryl or aryl-substituted lower alkyl.

Methods for making compounds of Formula (IV) are well known to those skilled in the art. Non-limiting examples of suitable methods are disclosed in U.S. Patent No. 5,688,990, which is incorporated herein by reference.

Substituted Azetidinones of Formula (V)

In another embodiment, substituted azetidinones useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (V):



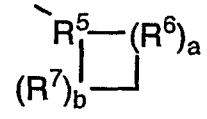
(V)

or a pharmaceutically acceptable salt thereof or a solvate thereof, or an ester thereof, wherein, in Formula (V) above:

A is selected from the group consisting of R^2-substituted heterocycloalkyl, R^2-substituted heteroaryl, R^2-substituted benzo-fused heterocycloalkyl, and R^2-substituted benzo-fused heteroaryl;

Ar^1 is aryl or R^3-substituted aryl;

Ar^2 is aryl or R^4-substituted aryl;

Q is a bond or, with the 3-position ring carbon of the azetidinone, forms the spiro group  ; and

R^1 is selected from the group consisting of:

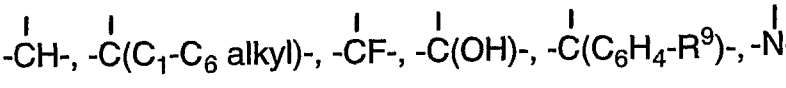
$-(CH_2)_q-$, wherein q is 2-6, provided that when Q forms a spiro ring, q can also be zero or 1;

$-(CH_2)_e-G-(CH_2)_r-$, wherein G is -O-, -C(O)-, phenylene, $-NR^8-$ or $-S(O)_{0-2}-$, e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;

$-(C_2-C_6$ alkenylene)-; and

$-(CH_2)_f-V-(CH_2)_g-$, wherein V is C_3-C_6 cycloalkylene, f is 1-5 and g is 0-5, provided that the sum of f and g is 1-6;

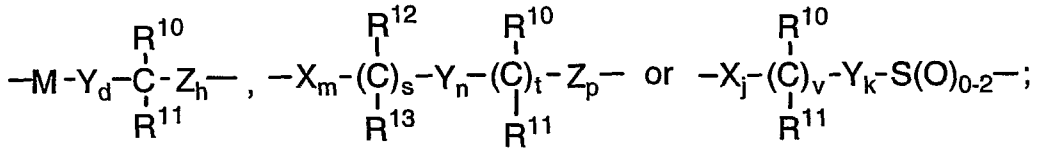
R^5 is selected from:



R^6 and R^7 are independently selected from the group consisting of $-CH_2-$, $-CH(C_1-C_6$ alkyl)-, $-C(di-(C_1-C_6)$ alkyl), -CH=CH- and $-C(C_1-C_6$ alkyl)=CH-; or R^5 together with an adjacent R^6, or R^5 together with an adjacent R^7, form a -CH=CH- or a $-CH=C(C_1-C_6$ alkyl)- group;

a and b are independently 0, 1, 2 or 3, provided both are not zero; provided that when R^6 is -CH=CH- or $-C(C_1-C_6$ alkyl)=CH-, a is 1; provided that when R^7 is -CH=CH- or $-C(C_1-C_6$ alkyl)=CH-, b is 1; provided that when a is 2 or 3, the R^6's can be the same or different; and provided that when b is 2 or 3, the R^7's can be the same or different;

and when Q is a bond, R^1 also can be selected from:



where M is -O-, -S-, -S(O)- or $-S(O)_2-$;

X, Y and Z are independently selected from the group consisting of $-CH_2-$, $-CH(C_1-C_6$ alkyl)- and $-C(di-(C_1-C_6)$ alkyl);

R^{10} and R^{12} are independently selected from the group consisting of $-OR^{14}$, $-OC(O)R^{14}$, $-OC(O)OR^{16}$ and $-OC(O)NR^{14}R^{15}$;

R^{11} and R^{13} are independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl and aryl; or R^{10} and R^{11} together are =O, or R^{12} and R^{13} together are =O;

d is 1, 2 or 3;

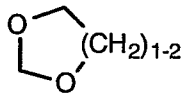
h is 0, 1, 2, 3 or 4;

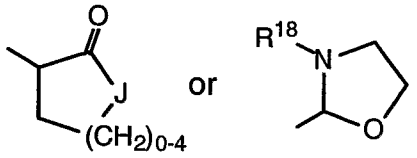
s is 0 or 1; t is 0 or 1; m, n and p are independently 0-4; provided that at least one of s and t is 1, and the sum of m, n, p, s and t is 1-6; provided that when p is 0 and t is 1, the sum of m, s and n is 1-5; and provided that when p is 0 and s is 1, the sum of m, t and n is 1-5;

v is 0 or 1;

j and k are independently 1-5, provided that the sum of j, k and v is 1-5;

R^2 is 1-3 substituents on the ring carbon atoms selected from the group consisting of hydrogen, $(C_1\text{-}C_{10})$alkyl, $(C_2\text{-}C_{10})$alkenyl, $(C_2\text{-}C_{10})$alkynyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkenyl, R^{17}-substituted aryl, R^{17}-substituted benzyl, R^{17}-substituted benzyloxy, R^{17}-substituted aryloxy, halogeno, $-NR^{14}R^{15}$, $NR^{14}R^{15}(C_1\text{-}C_6$ alkylene)-, $NR^{14}R^{15}C(O)(C_1\text{-}C_6$ alkylene)-, $-NHC(O)R^{16}$, OH, $C_1\text{-}C_6$ alkoxy, $-OC(O)R^{16}$, $-C(O)R^{14}$, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, NO_2, $-S(O)_{0\text{-}2}R^{16}$, $-S(O)_2NR^{14}R^{15}$ and $-(C_1\text{-}C_6$ alkylene$)C(O)OR^{14}$; when R^2 is a substituent on a heterocycloalkyl ring, R^2 is as defined, or R^2 is =O

or  ; and, where R^2 is a substituent on a substitutable ring nitrogen, R^2 is hydrogen, $(C_1\text{-}C_6)$alkyl, aryl, $(C_1\text{-}C_6)$alkoxy, aryloxy, $(C_1\text{-}C_6)$alkylcarbonyl, arylcarbonyl, hydroxy, $-(CH_2)_{1\text{-}6}CONR^{18}R^{18}$,



;

wherein J is -O-, -NH-, $-NR^{18}$- or $-CH_2$-;

R^3 and R^4 are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $-OR^{14}$, $-OC(O)R^{14}$, $-OC(O)OR^{16}$, $-O(CH_2)_{1\text{-}5}OR^{14}$, $-OC(O)NR^{14}R^{15}$, $-NR^{14}R^{15}$, $-NR^{14}C(O)R^{15}$, $-NR^{14}C(O)OR^{16}$, $-NR^{14}C(O)NR^{15}R^{19}$, $-NR^{14}S(O)_2R^{16}$, $-C(O)OR^{14}$, $-C(O)NR^{14}R^{15}$, $-C(O)R^{14}$, $-S(O)_2NR^{14}R^{15}$, $S(O)_{0\text{-}2}R^{16}$, $-O(CH_2)_{1\text{-}10}$-$C(O)OR^{14}$, $-O(CH_2)_{1\text{-}10}C(O)NR^{14}R^{15}$, $-(C_1\text{-}C_6$ alkylene$)$-$C(O)OR^{14}$, $-CH{=}CH$-$C(O)OR^{14}$, $-CF_3$, -CN, $-NO_2$ and halogen;

R^8 is hydrogen, $(C_1\text{-}C_6)$alkyl, aryl $(C_1\text{-}C_6)$alkyl, $-C(O)R^{14}$ or $-C(O)OR^{14}$;

R^9 and R^{17} are independently 1-3 groups independently selected from the group consisting of hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, -C(O)OH, NO_2, $-NR^{14}R^{15}$, OH and halogeno;

R^{14} and R^{15} are independently selected from the group consisting of hydrogen, $(C_1\text{-}C_6)$alkyl, aryl and aryl-substituted $(C_1\text{-}C_6)$alkyl;

R^{16} is $(C_1\text{-}C_6)$alkyl, aryl or R^{17}-substituted aryl;

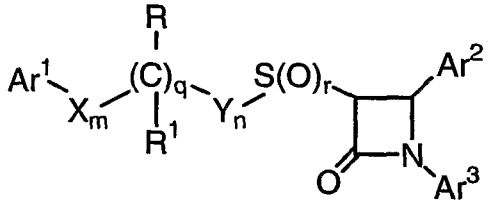
R^{18} is hydrogen or $(C_1\text{-}C_6)$alkyl; and

R^{19} is hydrogen, hydroxy or $(C_1\text{-}C_6)$alkoxy.

Methods for making compounds of Formula (V) are well known to those skilled in the art. Non-limiting examples of suitable methods are disclosed in U.S. Patent No. 5,656,624, which is incorporated herein by reference.

Substituted Azetidinones of Formula (VI)

In another embodiment, substituted azetidinones useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (VI):



(VI)

or a pharmaceutically acceptable salt thereof or a solvate thereof, or an ester thereof, wherein, in Formula (VI) above:

Ar^1 is aryl, R^{10}-substituted aryl or heteroaryl;

Ar^2 is aryl or R^4-substituted aryl;

Ar^3 is aryl or R^5-substituted aryl;

X and Y are independently selected from the group consisting of $-CH_2-$, -CH(lower alkyl)- and $-C(lower\ alkyl)_2-$;

R is $-OR^6$, $-OC(O)R^6$, $-OC(O)OR^9$ or $-OC(O)NR^6R^7$; R^1 is hydrogen, lower alkyl or aryl; or R and R^1 together are =O;

q is 0 or 1;

r is 0, 1 or 2;

m and n are independently 0, 1, 2, 3, 4 or 5; provided that the sum of m, n and q is 1, 2, 3, 4 or 5;

R^4 is 1-5 substituents independently selected from the group consisting of lower alkyl, $-OR^6$, $-OC(O)R^6$, $-OC(O)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-OC(O)NR^6R^7$, $-NR^6R^7$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^9$, $-NR^6C(O)NR^7R^8$, $-NR^6S(O)_2R^9$, $-C(O)OR^6$, $-C(O)NR^6R^7$, $-C(O)R^6$, $-S(O)_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-C(O)OR^6$, $-O(CH_2)_{1-10}C(O)NR^6R^7$, -(lower alkylene)$C(O)OR^6$ and $-CH=CH-C(O)OR^6$;

R^5 is 1-5 substituents independently selected from the group consisting of $-OR^6$, $-OC(O)R^6$, $-OC(O)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-OC(O)NR^6R^7$, $-NR^6R^7$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^9$, $-NR^6C(O)NR^7R^8$, $-NR^6S(O)_2R^9$, $-C(O)OR^6$, $-C(O)NR^6R^7$, $-C(O)R^6$, $-S(O)_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-C(O)OR^6$,

$-O(CH_2)_{1-10}C(O)NR^6R^7$, $-CF_3$, -CN, $-NO_2$, halogen, -(lower alkylene)$C(O)OR^6$ and $-CH=CH-C(O)OR^6$;

R^6, R^7 and R^8 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl;

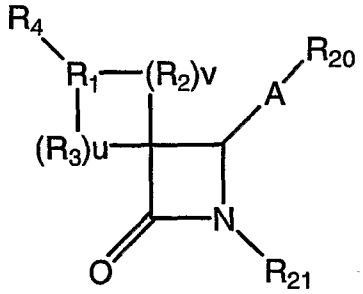
R^9 is lower alkyl, aryl or aryl-substituted lower alkyl; and

R^{10} is 1-5 substituents independently selected from the group consisting of lower alkyl, $-OR^6$, $-OC(O)R^6$, $-OC(O)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-OC(O)NR^6R^7$, $-NR^6R^7$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^9$, $-NR^6C(O)NR^7R^8$, $-NR^6S(O)_2R^9$, $-C(O)OR^6$, $-C(O)NR^6R^7$, $-C(O)R^6$, $-S(O)_2NR^6R^7$, $-S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}$-$C(O)OR^6$, $-O(CH_2)_{1-10}C(O)NR^6R^7$, $-CF_3$, -CN, $-NO_2$ and halogen.

Methods for making compounds of Formula (VI) are well known to those skilled in the art. Non-limiting examples of suitable methods are disclosed in U.S. Patent No. 5,624,920, which is incorporated herein by reference.

Substituted Azetidinones of Formula (VII)

In another embodiment, substituted azetidinones useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (VII):



(VII)

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

R^1 is:

$-\overset{|}{C}H-$, $-\overset{|}{C}$(lower alkyl)-, $-\overset{|}{C}F-$, $-\overset{|}{C}(OH)-$, $-\overset{|}{C}(C_6H_5)-$, $-\overset{|}{C}(C_6H_4-R_{15})-$,

$-\overset{|}{N}-$ or $-\overset{|}{\overset{+}{N}}O^-$;

R^2 and R^3 are independently selected from the group consisting of: $-CH_2-$, -CH(lower alkyl)-, $-C(\text{lower alkyl})_2-$, -CH=CH- and -C(lower alkyl)=CH-; or R^1 together with an adjacent R^2, or R^1 together with an adjacent R^3, form a -CH=CH- or a -CH=C(lower alkyl)- group;

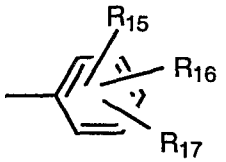
u and v are independently 0, 1, 2 or 3, provided both are not zero; provided that when R^2 is -CH=CH- or -C(lower alkyl)=CH-, v is 1; provided that when R^3 is -CH=CH- or -C(lower alkyl)=CH-, u is 1; provided that when v is 2 or 3, each R^2 can be the same or different; and provided that when u is 2 or 3, each R^3 can be the same or different;

R^4 is selected from B-$(CH_2)_m$C(O)-, wherein m is 0, 1, 2, 3, 4 or 5; B-$(CH_2)_q$-, wherein q is 0, 1, 2, 3, 4, 5 or 6; B-$(CH_2)_e$-Z-$(CH_2)_r$-, wherein Z is -O-, -C(O)-, phenylene, -N(R^8)- or -S(O)$_{0-2}$-, e is 0, 1, 2, 3, 4 or 5 and r is 0, 1, 2, 3, 4 or 5, provided that the sum of e and r is 0, 1, 2, 3, 4, 5 or 6; B-(C_2-C_6 alkenylene)-; B-(C_4-C_6 alkadienylene)-; B-$(CH_2)_t$-Z-(C_2-C_6 alkenylene)-, wherein Z is as defined above, and wherein t is 0, 1, 2 or 3, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6; B-$(CH_2)_f$-V-$(CH_2)_g$-, wherein V is C_3-C_6 cycloalkylene, f is 1, 2, 3, 4 or 5 and g is 0, 1, 2, 3, 4 or 5, provided that the sum of f and g is 1, 2, 3, 4, 5 or 6; B-$(CH_2)_t$-V-(C_2-C_6 alkenylene)- or B-(C_2-C_6 alkenylene)-V-$(CH_2)_t$-, wherein V and t are as defined above, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6;

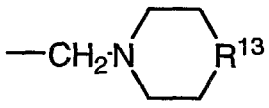
B-$(CH_2)_a$-Z-$(CH_2)_b$-V-$(CH_2)_d$-, wherein Z and V are as defined above and a, b and d are independently 0, 1, 2, 3, 4, 5 or 6, provided that the sum of a, b and d is 0, 1, 2, 3, 4, 5 or 6; or T-$(CH_2)_s$-, wherein T is a C_3-C_6 cycloalkyl and s is 0, 1, 2, 3, 4, 5 or 6; or

R^1 and R^4 together form the group B-CH=$\overset{|}{C}$- ;

B is selected from indanyl, indenyl, naphthyl, tetrahydronaphthyl, heteroaryl or W-substituted heteroaryl, wherein heteroaryl is selected from the group consisting of pyrrolyl, pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, imidazolyl, thiazolyl, pyrazolyl, thienyl, oxazolyl and furanyl, and for nitrogen-containing heteroaryls, the N-oxides thereof, or



W is 1 to 3 substituents independently selected from the group consisting of lower alkyl, hydroxy lower alkyl, lower alkoxy, alkoxyalkyl, alkoxyalkoxy, alkoxycarbonylalkoxy, (lower alkoxyimino)-lower alkyl, lower

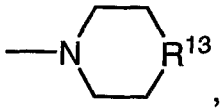
alkanedioyl, lower alkyl lower alkanedioyl, allyloxy, -CF_3, -OCF_3, benzyl, R^7-benzyl, benzyloxy, R^7-benzyloxy, phenoxy, R^7-phenoxy, dioxolanyl, NO_2, -$N(R^8)(R^9)$, $N(R^8)(R^9)$-lower alkylene-, $N(R^8)(R^9)$-lower alkylenyloxy-, OH, halogeno, -CN, -N_3, -$NHC(O)OR^{10}$, -$NHC(O)R^{10}$, $R^{11}(O)_2SNH$-, $(R^{11}(O)_2S)_2N$-, -$S(O)_2NH_2$, -$S(O)_{0-2}R^8$, tert-butyldimethyl-silyloxymethyl, -$C(O)R^{12}$, -$C(O)OR^{19}$, -$C(O)N(R^8)(R^9)$, -$CH{=}CHC(O)R^{12}$, -lower alkylene-$C(O)R^{12}$, $R^{10}C(O)$(lower alkylenyloxy)-, $N(R^8)(R^9)C(O)$(lower alkylenyloxy)- and  for substitution on ring carbon atoms, and the substituents on the substituted heteroaryl ring nitrogen atoms, when present, are selected from the group consisting of lower alkyl, lower alkoxy, -$C(O)OR^{10}$, -$C(O)R^{10}$, OH, $N(R^8)(R^9)$-lower alkylene-, $N(R^8)(R^9)$-lower alkylenyloxy-, -$S(O)_2NH_2$ and 2-(trimethylsilyl)-ethoxymethyl;

R^7 is 1-3 groups independently selected from the group consisting of lower alkyl, lower alkoxy, -C(O)OH, NO_2, -$N(R^8)(R^9)$, OH, and halogeno;

R^8 and R^9 are independently selected from H or lower alkyl;

R^{10} is selected from lower alkyl, phenyl, R^7-phenyl, benzyl or R^7-benzyl;

R^{11} is selected from OH, lower alkyl, phenyl, benzyl, R^7-phenyl or R^7-benzyl;

R^{12} is selected from H, OH, alkoxy, phenoxy, benzyloxy,  , -$N(R^8)(R^9)$, lower alkyl, phenyl or R^7-phenyl;

R^{13} is selected from -O-, -CH_2-, -NH-, -N(lower alkyl)- or -$NC(O)R^{19}$;

R^{15}, R^{16} and R^{17} are independently selected from the group consisting of H and the groups defined for W; or R^{15} is hydrogen and R^{16} and R^{17}, together with adjacent carbon atoms to which they are attached, form a dioxolanyl ring;

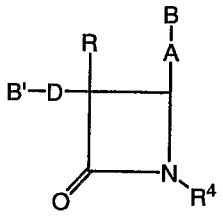
R^{19} is H, lower alkyl, phenyl or phenyl lower alkyl; and

R^{20} and R^{21} are independently selected from the group consisting of phenyl, W-substituted phenyl, naphthyl, W-substituted naphthyl, indanyl, indenyl, tetrahydronaphthyl, benzodioxolyl, heteroaryl, W-substituted heteroaryl, benzo-fused heteroaryl, W-substituted benzo-fused heteroaryl and cyclopropyl, wherein heteroaryl is as defined above.

Methods for making compounds of Formula (VII) are well known to those skilled in the art. Non-limiting examples of suitable methods are disclosed in U.S. Patent No. 5,698,548, which is incorporated herein by reference.

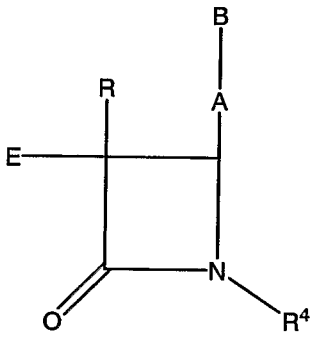
Substituted Azetidinones of Formula (VIII)

In another embodiment, substituted azetidinones useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formulas (VIIIA) and (VIIIB):



(VIIIA)

and



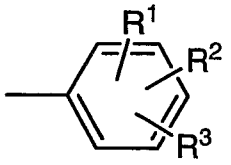
(VIIIB)

or a pharmaceutically acceptable salt, solvate, or ester thereof,

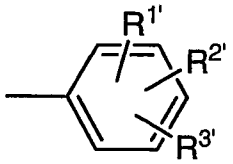
wherein:

A is -CH=CH-, -C≡C- or -$(CH_2)_p$- wherein p is 0, 1 or 2;

B is



B' is



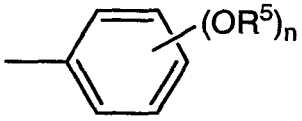
D is -$(CH_2)_m$C(O)- or -$(CH_2)_q$- wherein m is 1, 2, 3 or 4 and q is 2, 3 or 4;

E is C_{10} to C_{20} alkyl or -C(O)-(C_9 to C_{19})-alkyl, wherein the alkyl is straight or branched, saturated or containing one or more double bonds;

R is hydrogen, C_1-C_{15} alkyl, straight or branched, saturated or containing one or more double bonds, or B-$(CH_2)_r$ -, wherein r is 0, 1, 2, or 3;

R^1, R^2, R^3, $R^{1'}$, $R^{2'}$, and $R^{3'}$ are independently selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, carboxy, NO_2, NH_2, OH, halogeno, lower alkylamino, dilower alkylamino, -NHC(O)OR^5, $R^6(O)_2SNH$- and -$S(O)_2NH_2$;

R^4 is



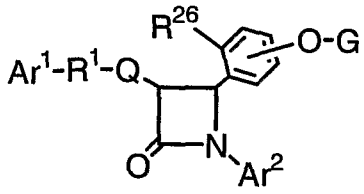
wherein n is 0, 1, 2 or 3;

R^5 is lower alkyl; and

R^6 is OH, lower alkyl, phenyl, benzyl or substituted phenyl wherein the substituents are 1-3 groups independently selected from the group consisting of lower alkyl, lower alkoxy, carboxy, NO_2, NH_2, OH, halogeno, lower alkylamino and dilower alkylamino; or a pharmaceutically acceptable salt, solvate, or ester thereof.

Sterol Absorption Inhibitors of Formula (IX)

In another embodiment, sterol absorption inhibitors useful in the compositions and methods of the present invention are represented by Formula (IX):

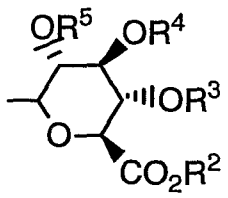
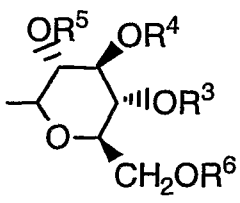
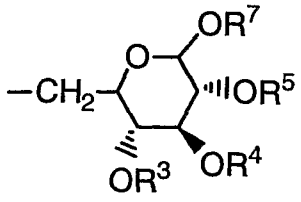


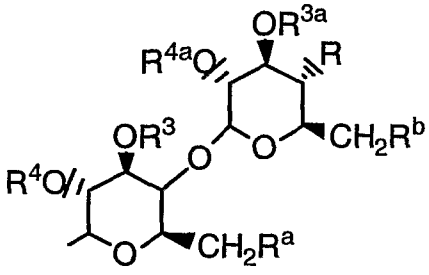
(IX)

or a pharmaceutically acceptable salt, solvate, or ester thereof, wherein, in Formula (IX) above,

R^{26} is H or OG^1;

G and G^1 are independently selected from the group consisting of

H,  ,  , 

and  ; provided that when R^{26} is H or OH, G is not H;

R, R^a and R^b are independently selected from the group consisting of H, -OH, halogeno, $-NH_2$, azido, (C_1-C_6)alkoxy(C_1-C_6)-alkoxy or -W-R^{30};

W is independently selected from the group consisting of -NH-C(O)-, -O-C(O)-, -O-C(O)-N(R^{31})-, -NH-C(O)-N(R^{31})- and -O-C(S)-N(R^{31})-;

R^2 and R^6 are independently selected from the group consisting of H, (C_1-C_6)alkyl, aryl and aryl(C_1-C_6)alkyl;

R^3, R^4, R^5, R^7, R^{3a} and R^{4a} are independently selected from the group consisting of H, (C_1-C_6)alkyl, aryl(C_1-C_6)alkyl, -C(O)(C_1-C_6)alkyl and -C(O)aryl;

R^{30} is selected from the group consisting of R^{32}-substituted T, R^{32}-substituted-T-(C_1-C_6)alkyl, R^{32}-substituted-(C_2-C_4)alkenyl, R^{32}-substituted-(C_1-C_6)alkyl, R^{32}-substituted-(C_3-C_7)cycloalkyl and R^{32}-substituted-(C_3-C_7)cycloalkyl(C_1-C_6)alkyl;

R^{31} is selected from the group consisting of H and (C_1-C_4)alkyl;

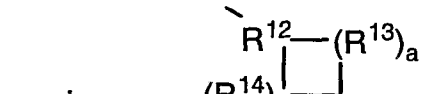
T is selected from the group consisting of phenyl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, iosthiazolyl, benzothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl and pyridyl;

R^{32} is independently selected from 1-3 substituents independently selected from the group consisting of halogeno, (C_1-C_4)alkyl, -OH, phenoxy, $-CF_3$, $-NO_2$, (C_1-C_4)alkoxy, methylenedioxy, oxo, (C_1-C_4)alkylsulfanyl, (C_1-C_4)alkylsulfinyl, (C_1-C_4)alkylsulfonyl, $-N(CH_3)_2$, -C(O)-NH(C_1-C_4)alkyl, -C(O)-N$((C_1-C_4)$alkyl$)_2$, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkoxy and pyrrolidinylcarbonyl; or

R^{32} is a covalent bond and R^{31}, the nitrogen to which it is attached and R^{32} form a pyrrolidinyl, piperidinyl, N-methyl-piperazinyl, indolinyl or morpholinyl group, or a (C_1-C_4)alkoxycarbonyl-substituted pyrrolidinyl, piperidinyl, N-methylpiperazinyl, indolinyl or morpholinyl group;

Ar^1 is aryl or R^{10}-substituted aryl;

Ar^2 is aryl or R^{11}-substituted aryl;

Q is a bond or, with the 3-position ring carbon of the azetidinone, forms the spiro group  ; and

R^1 is selected from the group consisting of

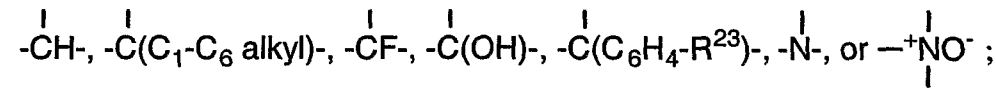
$-(CH_2)_q-$, wherein q is 2-6, provided that when Q forms a spiro ring, q can also be zero or 1;

$-(CH_2)_e-E-(CH_2)_r-$, wherein E is -O-, -C(O)-, phenylene, $-NR^{22}-$ or $-S(O)_{0-2}-$, e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;

$-(C_2-C_6)$alkenylene-; and

$-(CH_2)_f-V-(CH_2)_g-$, wherein V is C_3-C_6 cycloalkylene, f is 1-5 and g is 0-5, provided that the sum of f and g is 1-6;

R^{12} is:



R^{13} and R^{14} are independently selected from the group consisting of

$-CH_2-$, $-CH((C_1-C_6)$ alkyl)-, $-C((C_1-C_6)$ alkyl)$_2$, -CH=CH- and $-C((C_1-C_6)$ alkyl)=CH-; or

R^{12} together with an adjacent R^{13}, or R^{12} together with an adjacent R^{14}, form a -CH=CH- or a $-CH=C(C_1-C_6$ alkyl)- group;

a and b are independently 0, 1, 2 or 3, provided both are not zero;

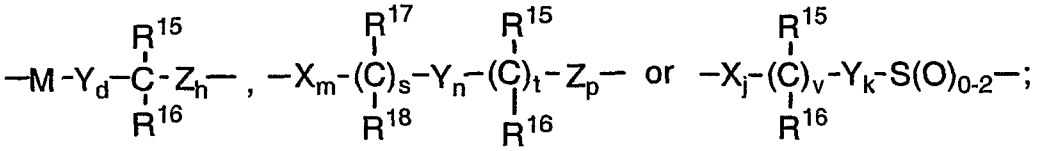
provided that when R^{13} is -CH=CH- or $-C(C_1-C_6$ alkyl)=CH-, a is 1;

provided that when R^{14} is -CH=CH- or $-C(C_1-C_6$ alkyl)=CH-, b is 1;

provided that when a is 2 or 3, each R^{13} can be the same or different; and

provided that when b is 2 or 3, each R^{14} can be the same or different;

and when Q is a bond, R^1 also can be:



M is -O-, -S-, -S(O)- or -$S(O)_2$-;

X, Y and Z are independently selected from the group consisting of -CH_2-, -$CH(C_1$-$C_6)$alkyl- and -$C((C_1$-$C_6)$alkyl$)_2$;

R^{10} and R^{11} are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of $(C_1$-$C_6)$alkyl, -OR^{19}, -$OC(O)R^{19}$, -$OC(O)OR^{21}$, -$O(CH_2)_{1-5}OR^{19}$, -$OC(O)NR^{19}R^{20}$, -$NR^{19}R^{20}$, -$NR_{19}C(O)R^{20}$, -$NR^{19}C(O)OR^{21}$, -$NR^{19}C(O)NR^{20}R^{25}$, -$NR^{19}S(O)_2R^{21}$, -$C(O)OR^{19}$, -$C(O)NR^{19}R^{20}$, -$C(O)R^{19}$, -$S(O)_2NR^{19}R^{20}$, $S(O)_{0-2}R^{21}$, -$O(CH_2)_{1-10}$-$C(O)OR^{19}$, -$O(CH_2)_{1-10}C(O)NR^{19}R^{20}$, -$(C_1$-$C_6$ alkylene)-$C(O)OR^{19}$, -CH=CH-$C(O)OR^{19}$, -CF_3, -CN, -NO_2 and halogen;

R^{15} and R^{17} are independently selected from the group consisting of -OR^{19}, -$OC(O)R^{19}$, -$OC(O)OR^{21}$ and -$OC(O)NR^{19}R^{20}$;

R^{16} and R^{18} are independently selected from the group consisting of H, $(C_1$-$C_6)$alkyl and aryl; or R^{15} and R^{16} together are =O, or R^{17} and R^{18} together are =O;

d is 1, 2 or 3;

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

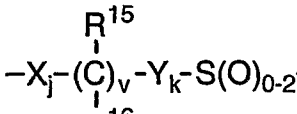
s is 0 or 1; t is 0 or 1; m, n and p are independently 0-4;

provided that at least one of s and t is 1, and the sum of m, n, p, s and t is 1-6;

provided that when p is 0 and t is 1, the sum of m, s and n is 1-5; and provided that when p is 0 and s is 1, the sum of m, t and n is 1-5;

v is 0 or 1;

j and k are independently 1-5, provided that the sum of j, k and v is 1-5;

and when Q is a bond and R^1 is  , Ar^1 can also be pyridyl, isoxazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, pyrazinyl, pyrimidinyl or pyridazinyl;

R^{19} and R^{20} are independently selected from the group consisting of H, $(C_1\text{-}C_6)$alkyl, aryl and aryl-substituted $(C_1\text{-}C_6)$alkyl;

R^{21} is $(C_1\text{-}C_6)$alkyl, aryl or R^{24}-substituted aryl;

R^{22} is H, $(C_1\text{-}C_6)$alkyl, aryl $(C_1\text{-}C_6)$alkyl, $-C(O)R^{19}$ or $-C(O)OR^{19}$;

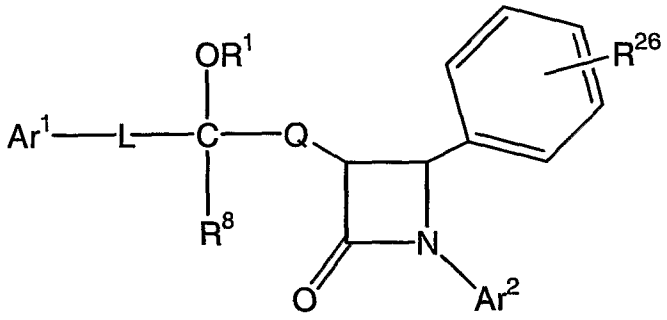
R^{23} and R^{24} are independently 1-3 groups independently selected from the group consisting of H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, -C(O)OH, NO_2, $-NR^{19}R^{20}$, -OH and halogeno; and

R^{25} is H, -OH or $(C_1\text{-}C_6)$alkoxy.

Methods for making compounds of Formula (IX) are well known to those skilled in the art. Non-limiting examples of suitable methods are disclosed in U.S. Patent No. 5,756,470, which is incorporated herein by reference.

Substituted Azetidinones of Formula (X)

In another embodiment, substituted azetidinones useful in the compositions and methods of the present invention are represented by Formula (X) below:

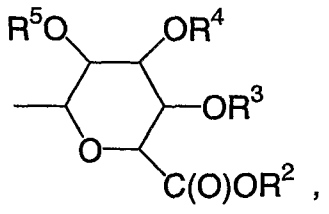
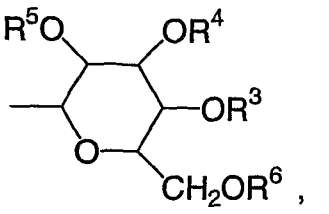
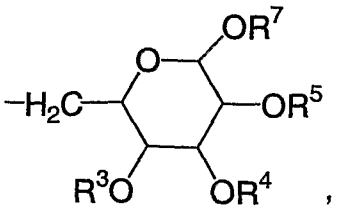
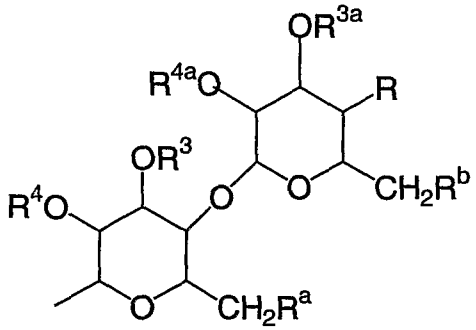
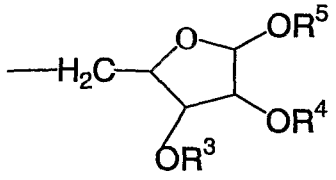


(X)

or a pharmaceutically acceptable salt, solvate, or ester thereof, wherein in Formula (X):

R^1 is selected from the group consisting of H, G, G^1, G^2, $-SO_3H$ and $-PO_3H$;

G is selected from the group consisting of: H,





and


(sugar derivatives)

wherein R, R^a and R^b are each independently selected from the group consisting of H, -OH, halo, $-NH_2$, azido, (C_1-C_6)alkoxy(C_1-C_6)alkoxy or $-W-R^{30}$;

W is independently selected from the group consisting of -NH-C(O)-, -O-C(O)-, -O-C(O)-N(R^{31})-, -NH-C(O)-N(R^{31})- and -O-C(S)-N(R^{31})-;

R^2 and R^6 are each independently selected from the group consisting of H, (C_1-C_6)alkyl, acetyl, aryl and aryl(C_1-C_6)alkyl;

R^3, R^4, R^5, R^7, R^{3a} and R^{4a} are each independently selected from the group consisting of H, (C_1-C_6)alkyl, acetyl, aryl(C_1-C_6)alkyl, -C(O)(C_1-C_6)alkyl and -C(O)aryl;

R^{30} is independently selected from the group consisting of R^{32}-substituted T, R^{32}-substituted-T-(C_1-C_6)alkyl, R^{32}-substituted-(C_2-C_4)alkenyl, R^{32}-substituted-(C_1-C_6)alkyl, R^{32}-substituted-(C_3-C_7)cycloalkyl and R^{32}-substituted-(C_3-C_7)cycloalkyl(C_1-C_6)alkyl;

R^{31} is independently selected from the group consisting of H and (C_1-C_4)alkyl;

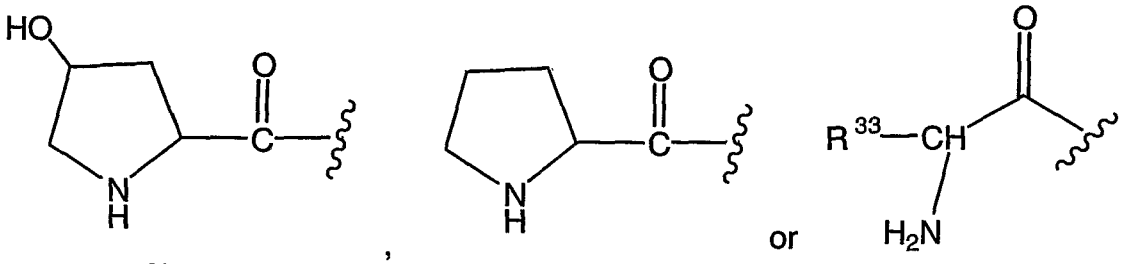
T is independently selected from the group consisting of phenyl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl and pyridyl;

R^{32} is independently selected from 1-3 substituents which are each independently selected from the group consisting of H, halo, (C_1-C_4)alkyl, -OH, phenoxy, $-CF_3$, $-NO_2$, (C_1-C_4)alkoxy, methylenedioxy, oxo, (C_1-C_4)alkylsulfanyl, (C_1-C_4)alkylsulfinyl, (C_1-C_4)alkylsulfonyl, $-N(CH_3)_2$, -C(O)-NH(C_1-C_4)alkyl,

-C(O)-N(C_1-C_4)alkyl)$_2$, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkoxy and pyrrolidinylcarbonyl; or

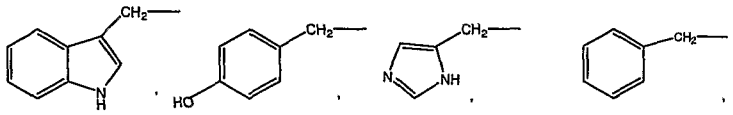
R^{32} is a covalent bond and R^{31}, the nitrogen to which it is attached and R^{32} form a pyrrolidinyl, piperidinyl, N-methyl-piperazinyl, indolinyl or morpholinyl group, or a (C_1-C_4)alkoxycarbonyl-substituted pyrrolidinyl, piperidinyl, N-methylpiperazinyl, indolinyl or morpholinyl group;

G^1 is represented by the structure:



or

wherein R^{33} is independently selected from the group consisting of unsubstituted alkyl, R^{34}-substituted alkyl, (R^{35})(R^{36})alkyl-,

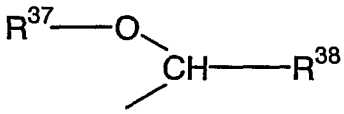


R^{34} is one to three substituents, each R^{34} being independently selected from the group consisting of HO(O)C-, HO-, HS-, (CH_3)S-, H_2N-, (NH_2)(NH)C(NH)-, (NH_2)C(O)- and HO(O)CCH(NH_3^+)CH_2SS-;

R^{35} is independently selected from the group consisting of H and NH_2-;

R^{36} is independently selected from the group consisting of H, unsubstituted alkyl, R^{34}-substituted alkyl, unsubstituted cycloalkyl and R^{34}-substituted cycloalkyl;

G^2 is represented by the structure:



wherein R^{37} and R^{38} are each independently selected from the group consisting of (C_1-C_6)alkyl and aryl;

R^{26} is one to five substituents, each R^{26} being independently selected from the group consisting of:

a) H;

b) -OH;

c) $-OCH_3$;

d) fluorine;

e) chlorine;

f) –O-G;

g) $-O-G^1$;

h) $-O-G^2$;

i) $-SO_3H$; and

j) $-PO_3H$;

provided that when R^1 is H, R^{26} is not H, –OH, $-OCH_3$ or –O-G;

Ar^1 is aryl, R^{10}-substituted aryl, heteroaryl or R^{10}-substituted heteroaryl;

Ar^2 is aryl, R^{11}-substituted aryl, heteroaryl or R^{11}-substituted heteroaryl;

L is selected from the group consisting of:

a) a covalent bond;

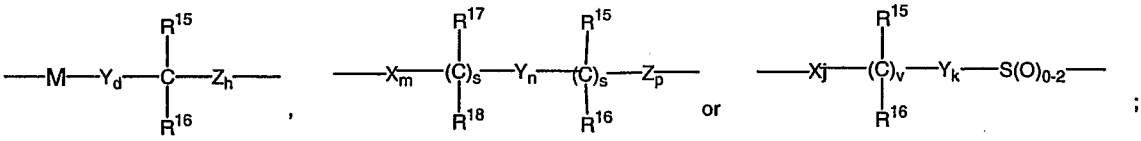
b) $-(CH_2)_q-$, wherein q is 1-6;

c) $-(CH_2)_e-E-(CH_2)_r-$, wherein E is –O-, -C(O)-, phenylene, $-NR^{22}-$ or $-S(O)_{0-2}-$, e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;

d) $-(C_2-C_6)$alkenylene-;

e) $-(CH_2)_f-V-(CH_2)_g-$, wherein V is C_3-C_6cycloalkylene, f is 1-5 and g is 0-5, provided that the sum of f and g is 1-6; and

f)



wherein M is –O-, -S-, -S(O)- or $-S(O)_2-$;

X, Y and Z are each independently selected from the group consisting of $-CH_2-$, $-CH(C_1-C_6)$alkyl- and $-C((C_1-C_6)alkyl)_2-$;

R^8 is selected from the group consisting of H and alkyl;

R^{10} and R^{11} are each independently selected from the group consisting of 1-3 substituents which are each independently selected from the group consisting of (C_1-C_6)alkyl, $-OR^{19}$, $-OC(O)R^{19}$, $-OC(O)OR^{21}$, $-O(CH_2)_{1-5}OR^{19}$, $-OC(O)NR^{19}R^{20}$,

$-NR^{19}R^{20}$, $-NR^{19}C(O)R^{20}$, $-NR^{19}C(O)OR^{21}$, $-NR^{19}C(O)NR^{20}R^{25}$, $-NR^{19}S(O)_2R^{21}$, $-C(O)OR^{19}$, $-C(O)NR^{19}R^{20}$, $-C(O)R^{19}$, $-S(O)_2NR^{19}R^{20}$, $S(O)_{0-2}R^{21}$, $-O(CH_2)_{1-10}-C(O)OR^{19}$, $-O(CH_2)_{1-10}C(O)NR^{19}R^{20}$, $-(C_1-C_6$ alkylene$)-C(O)OR^{19}$, $-CH=CH-C(O)OR^{19}$, $-CF_3$, $-CN$, $-NO_2$ and halo;

R^{15} and R^{17} are each independently selected from the group consisting of $-OR^{19}$, $-OC(O)R^{19}$, $-OC(O)OR^{21}$, $-OC(O)NR^{19}R^{20}$;

R^{16} and $R^{18}$are each independently selected from the group consisting of H, (C_1-C_6)alkyl and aryl; or

R^{15} and R^{16} together are =O, or $R^{17}$and R^{18} together are =O;

d is 1, 2 or 3;

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

s is 0 or 1;

t is 0 or 1;

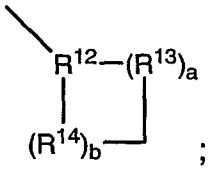
m, n and p are each independently selected from 0-4;

provided that at least one of s and t is 1, and the sum of m, n, p, s and t is 1-6; provided that when p is 0 and t is 1, the sum of m, n and p is 1-5; and provided that when p is 0 and s is 1, the sum of m, t and n is 1-5;

v is 0 or 1;

j and k are each independently 1-5, provided that the sum of j, k and v is 1-5;

Q is a bond, $-(CH_2)_q-$, wherein q is 1-6, or, with the 3-position ring carbon of the azetidinone, forms the spiro group



;

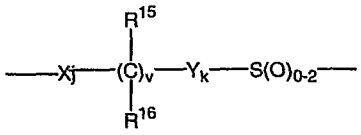
wherein R^{12} is

$-CH-$, $-C(C_1-C_6$ alkyl$)-$, $-CF-$, $-C(OH)-$, $-C(C_6H_4-R^{23})-$, $-N-$, or $-{}^{+}N(O^{-})-$;

R^{13} and R^{14} are each independently selected from the group consisting of $-CH_2-$, $-CH(C_1-C_6$ alkyl$)-$, $-C((C_1-C_6)$ alkyl$)_2$, $-CH=CH-$ and $-C(C_1-C_6$ alkyl$)=CH-$; or R^{12} together with an adjacent R^{13}, or R^{12} together with an adjacent R^{14}, form a $-CH=CH-$ or a $-CH=C(C_1-C_6$ alkyl$)-$ group;

a and b are each independently 0, 1, 2 or 3, provided both are not zero; provided that when R^{13} is -CH=CH- or -C(C_1-C_6 alkyl)=CH-, a is 1; provided that when R^{14} is -CH=CH- or -C(C_1-C_6 alkyl)=CH-, b is 1; provided that when a is 2 or 3, each R^{13} can be the same or different; and provided that when b is 2 or 3, each R^{14} can be the same or different;

and when Q is a bond and L is



then Ar^1 can also be pyridyl, isoxazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, pyrazinyl, pyrimidinyl or pyridazinyl;

R^{19} and R^{20} are each independently selected from the group consisting of H, (C_1-C_6)alkyl, aryl and aryl-substituted (C_1-C_6)alkyl;

R^{21} is (C_1-C_6)alkyl, aryl or R^{24}-substituted aryl;

R^{22} is H, (C_1-C_6)alkyl, aryl (C_1-C_6)alkyl, -C(O)R^{19} or –C(O)OR^{19};

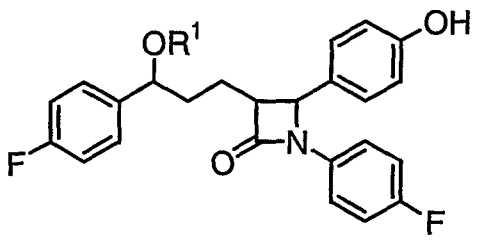
R^{23} and R^{24} are each independently selected from the group consisting of 1-3 substituents which are each independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, -C(O)OH, NO_2, -$NR^{19}R^{20}$, -OH and halo; and

R^{25} is H, -OH or (C_1-C_6)alkoxy.

Examples of compounds of Formula (X) which are useful in the methods and combinations of the present invention and methods for making such compounds are disclosed in U.S. Patent Application Serial No. 10/166,942, filed June 11, 2002, incorporated herein by reference.

Substituted Azetidinones of Formulae (XI)-(XIII)

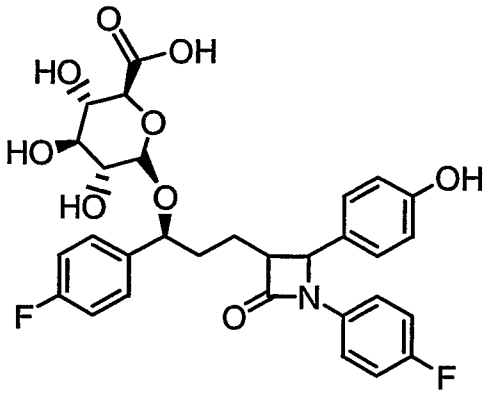
An example of a useful substituted azetidinone is one represented by the Formula (XI):



(XI)

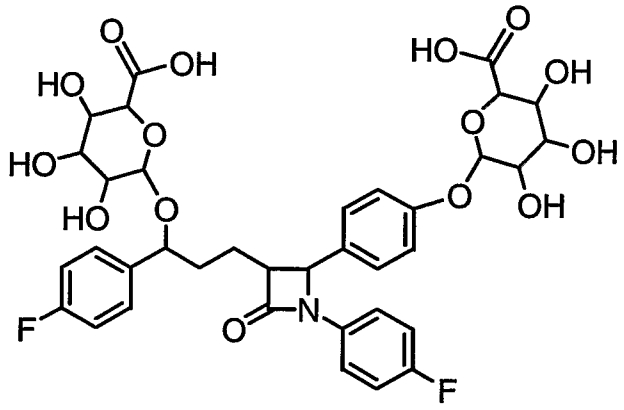
wherein R^1 is defined as above.

A more preferred compound is one represented by Formula (XII):



(XII).

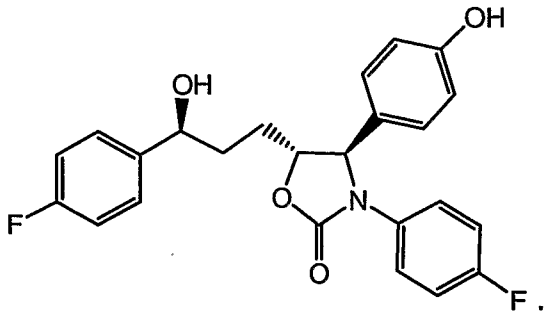
Another useful compound is represented by Formula (XIII):



(XIII)

Other useful substituted azetidinone compounds include N-sulfonyl-2-azetidinones such as are disclosed in U.S. Patent No. 4,983,597, ethyl 4-(2-oxoazetidin-4-yl)phenoxy-alkanoates such as are disclosed in Ram et al., Indian J. Chem. Sect. B. 29B, 12 (1990), p. 1134-7, diphenyl azetidinones and derivatives disclosed in U.S. Patent Publication Nos. 2002/0039774, 2002/0128252, 2002/0128253 and 2002/0137689, 2004/063929, WO 2002/066464, U.S. Patent Nos. 6,498,156 and 6,703,386, each of which is incorporated by reference herein.

Other sterol absorption inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are described in WO 2004/005247, WO 2004/000803, WO 2004/000804, WO 2004/000805, WO 0250027, U.S. published application 2002/0137689, and the compounds described in L. Kværnø et al., Angew. Chem. Int. Ed., **2004**, vol. 43, pp. 4653-4656, all of which are incorporated herein by reference. An illustrative compound of Kværnø et al. is:



The compounds of Formulae II-XIII can be prepared by known methods, including the methods discussed above and, for example, in WO 93/02048, U.S. 5,306,817 and 5,561,227, herein incorporated by reference, which describe the preparation of compounds wherein -R^1-Q- is alkylene, alkenylene or alkylene interrupted by a hetero atom, phenylene or cycloalkylene; WO 94/17038 and U.S. 5,698,548, herein incorporated by reference, describe the preparation of compounds wherein Q is a spirocyclic group; WO 95/08532, U.S. 5,631,365, U.S. 5,767,115, U.S. 5,846,966, and U.S. R.E. 37,721, herein incorporated by reference, describe the preparation of compounds wherein -R^1-Q- is a hydroxy-substituted alkylene group; PCT/US95/03196, herein incorporated by reference, describes compounds wherein -R^1-Q- is a hydroxy-substituted alkylene attached to the Ar^1 moiety through an -O- or $S(O)_{0-2}$- group; and U.S. Serial No. 08/463,619, filed June 5, 1995, herein incorporated by reference, describes the preparation of compounds wherein -R^1-Q- is a hydroxy-substituted alkylene group attached to the azetidinone ring by a -$S(O)_{0-2}$- group. Each of the above patents or publications are herein incorporated by reference in their entirety.

The daily dose of the sterol absorption inhibitor(s) administered to the subject can range from about 0.1 to about 1000 mg per day, preferably about 0.25 to about 50 mg/day, and more preferably about 10 mg per day, given in a single dose or 2-4 divided doses. The exact dose, however, is determined by the

attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient.

For administration of pharmaceutically acceptable salts of the above compounds, the weights indicated above refer to the weight of the acid equivalent or the base equivalent of the therapeutic compound derived from the salt.

In another embodiment of the present invention, the compositions or therapeutic combinations described above comprise one or more selective CB_1 receptor antagonist compounds of Formula (I) in combination with one or more cholesterol biosynthesis inhibitors and/or lipid-lowering compounds discussed below.

Generally, a total daily dosage of cholesterol biosynthesis inhibitor(s) can range from about 0.1 to about 160 mg per day, and preferably about 0.2 to about 80 mg/day in single or 2-3 divided doses.

In another alternative embodiment, the compositions, therapeutic combinations or methods of the present invention can comprise at least one compound of Formula (I), or pharmaceutically acceptable salts, solvates, or esters thereof, and one or more bile acid sequestrants (insoluble anion exchange resins), co-administered with or in combination with the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or ester thereof, and a substituted azetidinone or a substituted β-lactam discussed above.

Bile acid sequestrants bind bile acids in the intestine, interrupting the enterohepatic circulation of bile acids and causing an increase in the faecal excretion of steroids. Use of bile acid sequestrants is desirable because of their non-systemic mode of action. Bile acid sequestrants can lower intrahepatic cholesterol and promote the synthesis of apo B/E (LDL) receptors that bind LDL from plasma to further reduce cholesterol levels in the blood.

Generally, a total daily dosage of bile acid sequestrant(s) can range from about 1 to about 50 grams per day, and preferably about 2 to about 16 grams per day in single or 2-4 divided doses.

In an alternative embodiment, the compositions or treatments of the present invention can comprise at least one compound of Formula (I), or pharmaceutically acceptable salts, solvates, or esters thereof, and one or more IBAT inhibitors. The IBAT inhibitors can inhibit bile acid transport to reduce LDL

cholesterol levels. Generally, a total daily dosage of IBAT inhibitor(s) can range from about 0.01 to about 1000 mg/day, and preferably about 0.1 to about 50 mg/day in single or 2-4 divided doses.

In another alternative embodiment, the compositions or treatments of the present invention can comprise at least one compound of Formula (I), or pharmaceutically acceptable salts, solvates, or esters thereof, and nicotinic acid (niacin) and/or derivatives thereof. Nicotinic acid and its derivatives inhibit hepatic production of VLDL and its metabolite LDL and increases HDL and apo A-1 levels. An example of a suitable nicotinic acid product is NIASPAN® (niacin extended-release tablets) which are available from Kos.

Generally, a total daily dosage of nicotinic acid or a derivative thereof can range from about 500 to about 10,000 mg/day, preferably about 1000 to about 8000 mg/day, and more preferably about 3000 to about 6000 mg/day in single or divided doses.

In another alternative embodiment, the compositions or treatments of the present invention can comprise at least one compound of Formula (I), or pharmaceutically acceptable salts, solvates, or estes thereof, and one or more AcylCoA:Cholesterol *O*-acyltransferase ("ACAT") Inhibitors, which can reduce LDL and VLDL levels. ACAT is an enzyme responsible for esterifying excess intracellular cholesterol and may reduce the synthesis of VLDL, which is a product of cholesterol esterification, and overproduction of apo B-100-containing lipoproteins. Generally, a total daily dosage of ACAT inhibitor(s) can range from about 0.1 to about 1000 mg/day in single or 2-4 divided doses.

In another alternative embodiment, the compositions or treatments of the present invention can comprise at least one compound of Formula (I), or pharmaceutically acceptable salts, solvates, or esters thereof, and one or more Cholesteryl Ester Transfer Protein ("CETP") Inhibitors. CETP is responsible for the exchange or transfer of cholesteryl ester carrying HDL and triglycerides in VLDL. Pancreatic cholesteryl ester hydrolase (pCEH) inhibitors such as WAY-121898 also can be co-administered with or in combination.

Generally, a total daily dosage of CETP inhibitor(s) can range from about 0.01 to about 1000 mg/day, and preferably about 0.5 to about 20 mg/kg body weight/day in single or divided doses.

In another alternative embodiment, the compositions or treatments of the present invention can comprise at least one compound of Formula (I), or pharmaceutically acceptable salts, solvates, or esters thereof, and probucol or derivatives thereof, which can reduce LDL levels.

Generally, a total daily dosage of probucol or derivatives thereof can range from about 10 to about 2000 mg/day, and preferably about 500 to about 1500 mg/day in single or 2-4 divided doses.

In another alternative embodiment, the compositions or treatments of the present invention can comprise at least one compound of Formula (I), or pharmaceutically acceptable salts, solvates, or esters thereof, and low-density lipoprotein (LDL) receptor activators.

Generally, a total daily dosage of LDL receptor activator(s) can range from about 1 to about 1000 mg/day in single or 2-4 divided doses.

In another alternative embodiment, the compositions or treatments of the present invention can comprise at least one compound of Formula (I), or pharmaceutically acceptable salts, solvates, or esters thereof, and fish oil. Generally, a total daily dosage of fish oil or Omega 3 fatty acids can range from about 1 to about 30 grams per day in single or 2-4 divided doses.

In another alternative embodiment, the compositions or treatments of the present invention can further comprise at least one compound of Formula (I), or pharmaceutically acceptable salts, solvates, or esters thereof, and natural water soluble fibers, such as psyllium, guar, oat and pectin, which can reduce cholesterol levels. Generally, a total daily dosage of natural water soluble fibers can range from about 0.1 to about 10 grams per day in single or 2-4 divided doses.

In another alternative embodiment, the compositions or treatments of the present invention can comprise at least one compound of Formula (I), or pharmaceutically acceptable salts, solvates, or esters thereof, and plant sterols, plant stanols and/or fatty acid esters of plant stanols, such as sitostanol ester used in BENECOL® margarine, which can reduce cholesterol levels. Generally, a total daily dosage of plant sterols, plant stanols and/or fatty acid esters of plant stanols can range from about 0.5 to about 20 grams per day in single or 2-4 divided doses.

In another alternative embodiment, the compositions or treatments of the present invention can comprise at least one compound of Formula (I), or pharmaceutically acceptable salts, solvates, or esters thereof, and antioxidants, such as probucol, tocopherol, ascorbic acid, β-carotene and selenium, or vitamins such as vitamin B_6 or vitamin B_{12}. Generally, a total daily dosage of antioxidants or vitamins can range from about 0.05 to about 10 grams per day in single or 2-4 divided doses.

In another alternative embodiment, the compositions or treatments of the present invention can comprise at least one compound of Formula (I), or pharmaceutically acceptable salts, solvates, or esters thereof, and monocyte and macrophage inhibitors such as polyunsaturated fatty acids (PUFA), thyroid hormones including throxine analogues such as CGS-26214 (a thyroxine compound with a fluorinated ring), gene therapy and use of recombinant proteins such as recombinant apo E. Generally, a total daily dosage of these agents can range from about 0.01 to about 1000 mg/day in single or 2-4 divided doses.

Also useful with the present invention are compositions or therapeutic combinations that further comprise hormone replacement agents and compositions. Useful hormone agents and compositions for hormone replacement therapy of the present invention include androgens, estrogens, progestins, their pharmaceutically acceptable salts and derivatives thereof. Combinations of these agents and compositions are also useful.

The dosage of androgen and estrogen combinations vary, desirably from about 1 mg to about 4 mg androgen and from about 1 mg to about 3 mg estrogen. Examples include, but are not limited to, androgen and estrogen combinations such as the combination of esterified estrogens (sodium estrone sulfate and sodium equilin sulfate) and methyltestosterone (17-hydroxy-17-methyl-, (17B)- androst-4-en-3-one) available from Solvay Pharmaceuticals, Inc., Marietta, GA, under the tradename Estratest.

Estrogens and estrogen combinations may vary in dosage from about 0.01 mg up to 8 mg, desirably from about 0.3 mg to about 3.0 mg. Examples of useful estrogens and estrogen combinations include:

(a) the blend of nine (9) synthetic estrogenic substances including sodium estrone sulfate, sodium equilin sulfate, sodium 17 α -dihydroequilin

sulfate, sodium 17 α -estradiol sulfate, sodium 17 β -dihydroequilin sulfate, sodium 17 α -dihydroequilenin sulfate, sodium 17 β -dihydroequilenin sulfate, sodium equilenin sulfate and sodium 17 β -estradiol sulfate; available from Duramed Pharmaceuticals, Inc., Cincinnati, OH, under the tradename Cenestin;

(b) ethinyl estradiol (19-nor-17 α -pregna-1,3,5(10)-trien-20-yne-3,17-diol; available by Schering Plough Corporation, Kenilworth, NJ, under the tradename Estinyl;

(c) esterified estrogen combinations such as sodium estrone sulfate and sodium equilin sulfate; available from Solvay under the tradename Estratab and from Monarch Pharmaceuticals, Bristol, TN, under the tradename Menest;

(d) estropipate (piperazine estra-1,3,5(10)-trien-17-one, 3-(sulfooxy)-estrone sulfate); available from Pharmacia & Upjohn, Peapack, NJ, under the tradename Ogen and from Women First Health Care, Inc., San Diego, CA, under the tradename Ortho-Est; and

(e) conjugated estrogens (17 α-dihydroequilin, 17 α-estradiol, and 17 β-dihydroequilin); available from Wyeth-Ayerst Pharmaceuticals, Philadelphia, PA, under the tradename Premarin.

Progestins and estrogens may also be administered with a variety of dosages, generally from about 0.05 to about 2.0 mg progestin and about 0.001 mg to about 2 mg estrogen, desirably from about 0.1 mg to about 1 mg progestin and about 0.01 mg to about 0.5 mg estrogen. Examples of progestin and estrogen combinations that may vary in dosage and regimen include:

(a) the combination of estradiol (estra-1, 3, 5 (10)-triene-3, 17 β-diol hemihydrate) and norethindrone (17 β-acetoxy-19-nor-17 α-pregn-4-en-20-yn-3-one); which is available from Pharmacia & Upjohn, Peapack, NJ, under the tradename Activella;

(b) the combination of levonorgestrel (d(-)-13 β-ethyl-17 α-ethinyl-17 β-hydroxygon- 4-en-3-one) and ethinyl estradial; available from Wyeth-Ayerst under the tradename Alesse, from Watson Laboratories, Inc., Corona, CA, under the tradenames Levora and Trivora, Monarch Pharmaceuticals, under the tradename Nordette, and from Wyeth-Ayerst under the tradename Triphasil;

(c) the combination of ethynodiol diacetate (19-nor-17 α-pregn-4-en-20-yne-3 β, 17-diol diacetate) and ethinyl estradiol; available from G.D. Searle &

Co., Chicago, IL, under the tradename Demulen and from Watson under the tradename Zovia;

(d) the combination of desogestrel (13-ethyl-11- methylene-18,19-dinor-17 α-pregn- 4-en- 20-yn-17-ol) and ethinyl estradiol; available from Organon under the tradenames Desogen and Mircette, and from Ortho-McNeil Pharmaceutical, Raritan, NJ, under the tradename Ortho-Cept;

(e) the combination of norethindrone and ethinyl estradiol; available from Parke-Davis, Morris Plains, NJ, under the tradenames Estrostep and FemHRT, from Watson under the tradenames Microgestin, Necon, and Tri-Norinyl, from Ortho-McNeil under the tradenames Modicon and Ortho-Novum, and from Warner Chilcott Laboratories, Rockaway, NJ, under the tradename Ovcon;

(f) the combination of norgestrel ((±)-13-ethyl-17-hydroxy-18, 19-dinor-17 α-preg-4-en-20-yn-3-one) and ethinyl estradiol; available from Wyeth-Ayerst under the tradenames Ovral and Lo/Ovral, and from Watson under the tradenames Ogestrel and Low-Ogestrel;

(g) the combination of norethindrone, ethinyl estradiol, and mestranol (3-methoxy-19-nor-17 α-pregna-1,3,5(10)-trien-20-yn-17-ol); available from Watson under the tradenames Brevicon and Norinyl;

(h) the combination of 17 β-estradiol (estra-1,3,5(10)-triene-3,17 β-diol) and micronized norgestimate (17 α-17-(Acetyloxyl)-13-ethyl-18,19-dinorpregn-4-en-20-yn-3-one3-oxime); available from Ortho-McNeil under the tradename Ortho-Prefest;

(i) the combination of norgestimate (18,19-dinor-17-pregn-4-en-20-yn-3-one, 17--(acetyloxy)-13-ethyl-,oxime, (17(α)-(+)-) and ethinyl estradiol; available from Ortho-McNeil under the tradenames Ortho Cyclen and Ortho Tri-Cyclen; and

(j) the combination of conjugated estrogens (sodium estrone sulfate and sodium equilin sulfate) and medroxyprogesterone acetate (20-dione, 17-(acetyloxy)-6-methyl-, (6(α))- pregn-4-ene-3); available from Wyeth-Ayerst under the tradenames Premphase and Prempro.

In general, a dosage of progestins may vary from about .05 mg to about 10 mg or up to about 200 mg if microsized progesterone is administered. Examples of progestins include norethindrone; available from ESI Lederle, Inc.,

Philadelphia, PA, under the tradename Aygestin, from Ortho-McNeil under the tradename Micronor, and from Watson under the tradename Nor-QD; norgestrel; available from Wyeth-Ayerst under the tradename Ovrette; micronized progesterone (pregn-4-ene-3, 20-dione); available from Solvay under the tradename Prometrium; and medroxyprogesterone acetate; available from Pharmacia & Upjohn under the tradename Provera.

In another alternative embodiment, the compositions, therapeutic combinations or methods of the present invention can comprise at least one compound of Formula (I), or pharmaceutically acceptable salts, solvates, or esters thereof, and one or more obesity control medications. Useful obesity control medications include, but are not limited to, drugs that reduce energy intake or suppress appetite, drugs that increase energy expenditure and nutrient-partitioning agents. Suitable obesity control medications include, but are not limited to, noradrenergic agents (such as diethylpropion, mazindol, phenylpropanolamine, phentermine, phendimetrazine, phendamine tartrate, methamphetamine, phendimetrazine and tartrate); serotonergic agents (such as sibutramine, fenfluramine, dexfenfluramine, fluoxetine, fluvoxamine and paroxtine); thermogenic agents (such as ephedrine, caffeine, theophylline, and selective β3-adrenergic agonists); alpha-blocking agents; kainite or AMPA receptor antagonists; leptin-lipolysis stimulated receptors; phosphodiesterase enzyme inhibitors; compounds having nucleotide sequences of the mahogany gene; fibroblast growth factor-10 polypeptides; monoamine oxidase inhibitors (such as befloxatone, moclobemide, brofaromine, phenoxathine, esuprone, befol, toloxatone, pirlindol, amiflamine, sercloremine, bazinaprine, lazabemide, milacemide and caroxazone); compounds for increasing lipid metabolism (such as evodiamine compounds); and lipase inhibitors (such as orlistat). Generally, a total dosage of the above-described obesity control medications can range from 1 to 3,000 mg/day, desirably from about 1 to 1,000 mg/day and more desirably from about 1 to 200 mg/day in single or 2-4 divided doses.

The compositions, therapeutic combinations or methods of the present invention can comprise at least one compound of Formula (I), or pharmaceutically acceptable salts, solvates, or esters thereof, and one or more blood modifiers which are chemically different from the substituted azetidinone

and substituted β-lactam compounds (such as compounds II-XIII above) and the lipid modulating agents discussed above, for example, they contain one or more different atoms, have a different arrangement of atoms or a different number of one or more atoms than the sterol absorption inhibitor(s) or lipid modulating agents discussed above. Useful blood modifiers include but are not limited to anti-coagulants (argatroban, bivalirudin, dalteparin sodium, desirudin, dicumarol, lyapolate sodium, nafamostat mesylate, phenprocoumon, tinzaparin sodium, warfarin sodium); antithrombotic (anagrelide hydrochloride, bivalirudin, cilostazol, dalteparin sodium, danaparoid sodium, dazoxiben hydrochloride, efegatran sulfate, enoxaparin sodium, fluretofen, ifetroban, ifetroban sodium, lamifiban, lotrafiban hydrochloride, napsagatran, orbofiban acetate, roxifiban acetate, sibrafiban, tinzaparin sodium, trifenagrel, abciximab, zolimomab aritox); fibrinogen receptor antagonists (roxifiban acetate, fradafiban, orbofiban, lotrafiban hydrochloride, tirofiban, xemilofiban, monoclonal antibody 7E3, sibrafiban); platelet inhibitors (cilostazol, clopidogrel bisulfate, epoprostenol, epoprostenol sodium, ticlopidine hydrochloride, aspirin, ibuprofen, naproxen, sulindae, idomethacin, mefenamate, droxicam, diclofenac, sulfinpyrazone, piroxicam, dipyridamole); platelet aggregation inhibitors (acadesine, beraprost, beraprost sodium, ciprostene calcium, itazigrel, lifarizine, lotrafiban hydrochloride, orbofiban acetate, oxagrelate, fradafiban, orbofiban, tirofiban, xemilofiban); hemorrheologic agents (pentoxifylline); lipoprotein associated coagulation inhibitors; Factor VIIa inhibitors (4H-31-benzoxazin-4-ones, 4H-3,1-benzoxazin-4-thiones, quinazolin-4-ones, quinazolin-4-thiones, benzothiazin-4-ones, imidazolyl-boronic acid-derived peptide analogues TFPI-derived peptides, naphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)-benzyl]-2-oxo-pyrrolidin-3-(S)-yl} amide trifluoroacetate, dibenzofuran-2-sulfonic acid {1-[3-(aminomethyl)-benzyl]-5-oxo-pyrrolidin-3-yl}-amide, tolulene-4-sulfonic acid {1-[3-(aminoiminomethyl)-benzyl]-2-oxo-pyrrolidin-3-(S)-yl}-amide trifluoroacetate, 3,4-dihydro-1H-isoquinoline-2-sulfonic acid {1-[3-(aminoiminomethyl)-benzyl]-2-oxo-pyrrolin-3-(S)-yl}-amide trifluoroacetate); Factor Xa inhibitors (disubstituted pyrazolines, disubstituted triazolines, substituted n-[(aminoiminomethyl)phenyl] propylamides, substituted n-[(aminomethyl)phenyl] propylamides, tissue factor pathway inhibitor (TFPI), low molecular weight heparins, heparinoids, benzimidazolines, benzoxazolinones,

benzopiperazinones, indanones, dibasic (amidinoaryl) propanoic acid derivatives, amidinophenyl-pyrrolidines, amidinophenyl-pyrrolines, amidinophenyl-isoxazolidines, amidinoindoles, amidinoazoles, bis-arlysulfonylaminobenzamide derivatives, peptidic Factor Xa inhibitors).

The compositions, therapeutic combinations or methods of the present invention can comprise at least one compound of Formula (I), or pharmaceutically acceptable salts, solvates, or esters thereof, and one or more cardiovascular agents which are chemically different from the substituted azetidinone and substituted β-lactam compounds (such as compounds II-XIII above) and the lipid modulating agents discussed above, for example, they contain one or more different atoms, have a different arrangement of atoms or a different number of one or more atoms than the sterol absorption inhibitor(s) or PPAR receptor activators discussed above. Useful cardiovascular agents include but are not limited to calcium channel blockers (clentiazem maleate, amlodipine besylate, isradipine, nimodipine, felodipine, nilvadipine, nifedipine, teludipine hydrochloride, diltiazem hydrochloride, belfosdil, verapamil hydrochloride, fostedil); adrenergic blockers (fenspiride hydrochloride, labetalol hydrochloride, proroxan, alfuzosin hydrochloride, acebutolol, acebutolol hydrochloride, alprenolol hydrochloride, atenolol, bunolol hydrochloride, carteolol hydrochloride, celiprolol hydrochloride, cetamolol hydrochloride, cicloprolol hydrochloride, dexpropranolol hydrochloride, diacetolol hydrochloride, dilevalol hydrochloride, esmolol hydrochloride, exaprolol hydrochloride, flestolol sulfate, labetalol hydrochloride, levobetaxolol hydrochloride, levobunolol hydrochloride, metalol hydrochloride, metoprolol, metoprolol tartrate, nadolol, pamatolol sulfate, penbutolol sulfate, practolol, propranolol hydrochloride, sotalol hydrochloride, timolol, timolol maleate, tiprenolol hydrochloride, tolamolol, bisoprolol, bisoprolol fumarate, nebivolol); adrenergic stimulants; angiotensin converting enzyme (ACE) inhibitors (benazepril hydrochloride, benazeprilat, captopril, delapril hydrochloride, fosinopril sodium, libenzapril, moexipril hydrochloride, pentopril, perindopril, quinapril hydrochloride, quinaprilat, ramipril, spirapril hydrochloride, spiraprilat, teprotide, enalapril maleate, lisinopril, zofenopril calcium, perindopril erbumine); antihypertensive agents (althiazide, benzthiazide, captopril, carvedilol, chlorothiazide sodium, clonidine hydrochloride, cyclothiazide, delapril

hydrochloride, dilevalol hydrochloride, doxazosin mesylate, fosinopril sodium, guanfacine hydrochloride, methyldopa, metoprolol succinate, moexipril hydrochloride, monatepil maleate, pelanserin hydrochloride, phenoxybenzamine hydrochloride, prazosin hydrochloride, primidolol, quinapril hydrochloride, quinaprilat, ramipril, terazosin hydrochloride, candesartan, candesartan cilexetil, telmisartan, amlodipine besylate, amlodipine maleate, bevantolol hydrochloride); angiotensin II receptor antagonists (candesartan, irbesartan, losartan potassium, candesartan cilexetil, telmisartan); anti-anginal agents (amlodipine besylate, amlodipine maleate, betaxolol hydrochloride, bevantolol hydrochloride, butoprozine hydrochloride, carvedilol, cinepazet maleate, metoprolol succinate, molsidomine, monatepil maleate, primidolol, ranolazine hydrochoride, tosifen, verapamil hydrochloride); coronary vasodilators (fostedil, azaclorzine hydrochloride, chromonar hydrochloride, clonitrate, diltiazem hydrochloride, dipyridamole, droprenilamine, erythrityl tetranitrate, isosorbide dinitrate, isosorbide mononitrate, lidoflazine, mioflazine hydrochloride, mixidine, molsidomine, nicorandil, nifedipine, nisoldipine, nitroglycerine, oxprenolol hydrochloride, pentrinitrol, perhexiline maleate, prenylamine, propatyl nitrate, terodiline hydrochloride, tolamolol, verapamil); diuretics (the combination product of hydrochlorothiazide and spironolactone and the combination product of hydrochlorothiazide and triamterene).

The compositions, therapeutic combinations or methods of the present invention can comprise at least one compound of Formula (I), or pharmaceutically acceptable salts, solvates, or esters thereof, and one or more antidiabetic medications for reducing blood glucose levels in a human. Useful antidiabetic medications include, but are not limited to, drugs that reduce energy intake or suppress appetite, drugs that increase energy expenditure and nutrient-partitioning agents. Suitable antidiabetic medications include, but are not limited to, sulfonylurea (such as acetohexamide, chlorpropamide, gliamilide, gliclazide, glimepiride, glipizide, glyburide, glibenclamide, tolazamide, and tolbutamide), meglitinide (such as repaglinide and nateglinide), biguanide (such as metformin and buformin), alpha-glucosidase inhibitor (such as acarbose, miglitol, camiglibose, and voglibose), certain peptides (such as amlintide, pramlintide, exendin, and GLP-1 agonistic peptides), and orally administrable insulin or insulin composition for intestinal delivery thereof. Generally, a total dosage of the

above-described antidiabetic medications can range from 0.1 to 1,000 mg/day in single or 2-4 divided doses.

Mixtures of two, three, four or more of any of the pharmacological or therapeutic agents described above can be used in the compositions and therapeutic combinations of the present invention.

Since the present invention relates to treating conditions as discussed above, by treatment with a combination of active ingredients wherein the active ingredients may be administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form. That is, a kit is contemplated wherein two separate units are combined: a pharmaceutical composition comprising at least one selective CB_1 receptor antagonist of Formula (I), or a pharmaceutically acceptable salt, solvate, or ester thereof, and a separate pharmaceutical composition comprising at least one cholesterol lowering compound as described above. The kit will preferably include directions for the administration of the separate components. The kit form is particularly advantageous when the separate components must be administered in different dosage forms (e.g., oral and parenteral) or are administered at different dosage intervals.

In yet another embodiment, the present invention provides a method of treating, reducing, or ameliorating a disease or condition selected from the group consisting of metabolic syndrome, obesity, waist circumference, lipid profile, insulin sensitivity, neuroinflammatory disorders, cognitive disorders, psychosis, addictive behavior, gastrointestinal disorders, vascular conditions, hyperlipidaemia, atherosclerosis, hypercholesterolemia, sitosterolemia, vascular inflammation, stroke, diabetes, and cardiovascular conditions, and/or reduce the level of sterol(s) in a patient in need thereof, comprising administering to said patient an effective amount of at least one compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or ester thereof, and one or more cholesterol lowering compound.

The treatment compositions and therapeutic combinations comprising at least one compound of Formula (I) and at least one cholesterol lowering agent can inhibit the intestinal absorption of cholesterol in mammals can be useful in the treatment and/or prevention of conditions, for example vascular conditions, such as atherosclerosis, hypercholesterolemia and sitosterolemia, stroke, obesity

and lowering of plasma levels of cholesterol in mammals, in particular in mammals.

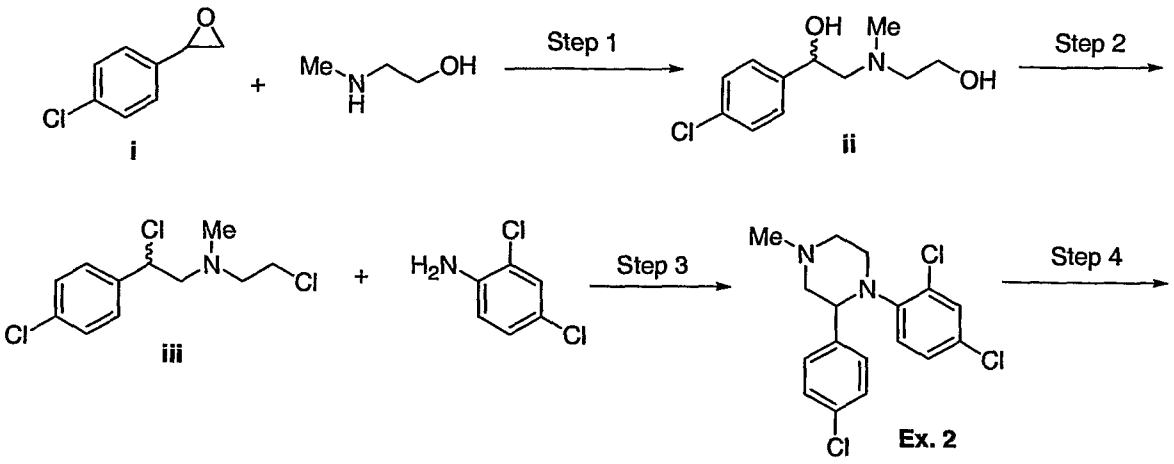
In another embodiment of the present invention, the compositions and therapeutic combinations of the present invention can inhibit sterol or 5α-stanol absorption or reduce plasma concentration of at least one sterol selected from the group consisting of phytosterols (such as sitosterol, campesterol, stigmasterol and avenosterol) and/or 5α-stanol (such as cholestanol, 5α-campestanol, 5α-sitostanol), cholesterol and mixtures thereof. The plasma concentration can be reduced by administering to a mammal in need of such treatment an effective amount of at least one treatment composition or therapeutic combination comprising at least one selective CB_1 receptor antagonist and at least one cholesterol lowering compound, for example a sterol absorption inhibitor described above. The reduction in plasma concentration of sterols or 5α-stanols can range from about 1 to about 70 percent, and preferably about 10 to about 50 percent. Methods of measuring serum total blood cholesterol and total LDL cholesterol are well known to those skilled in the art and for example include those disclosed in PCT WO 99/38498 at page 11, incorporated by reference herein. Methods of determining levels of other sterols in serum are disclosed in H. Gylling et al., "Serum Sterols During Stanol Ester Feeding in a Mildly Hypercholesterolemic Population", J. Lipid Res. 40: 593-600 (1999), incorporated by reference herein.

The treatments of the present invention can also reduce the size or presence of plaque deposits in vascular vessels. The plaque volume can be measured using (IVUS), in which a tiny ultrasound probe is inserted into an artery to directly image and measure the size of atherosclerotic plaques, in a manner well know to those skilled in the art.

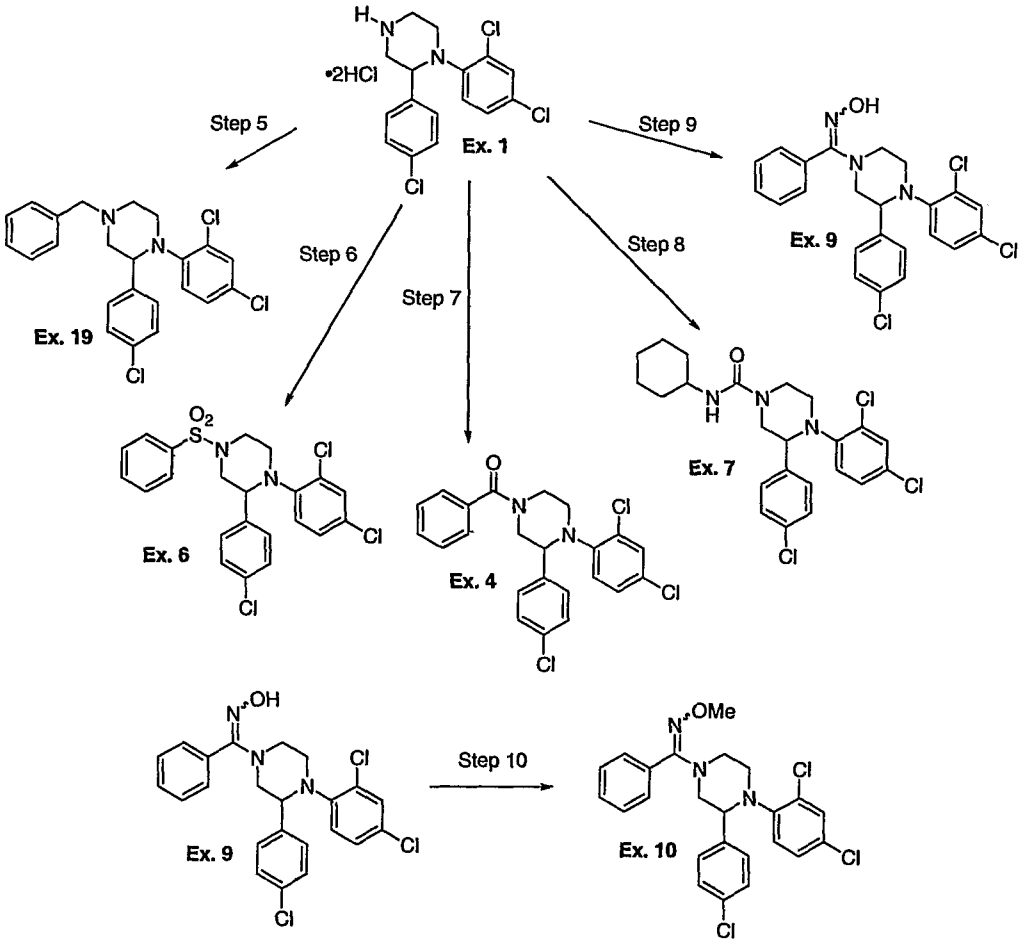
EXAMPLES

Preparation of Examples 1, 2, 4, 6, 7, 9, 19, and 10

Scheme 1



Scheme 2



Step 1:

To neat 2-(4-chlorophenyl)oxirane **i** (10.1 g, 65.4 mmol) was added *N*-methylethanolamine (7.36 g, 98.1 mmol). The reaction mixture was warmed to

130°C and stirred for 15 h. The reaction mixture was then cooled to room temperature (approximately 21°C) and purified directly by silica gel chromatography (8% MeOH/CH_2Cl_2) to provide the diol **ii** (13.1 g, 57.2 mmol).

Step 2:

To a solution of the diol **ii** (13.1 g, 57.2 mmol) in $CHCl_3$ (110 mL) at 0°C was added a solution of $SOCl_2$ (57 mL) in $CHCl_3$ (100 mL), dropwise, over 20 minutes. After the addition of the $SOCl_2$ solution was complete, the reaction mixture was warmed to reflux and stirred for 3.5 h. The reaction was cooled to room temperature and then concentrated *in vacuo*. The resulting oil was taken up into CH_2Cl_2 and stirred vigorously with saturated aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2 and the combined CH_2Cl_2 layers were washed with water and brine, then dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide **iii** (14.2 g, 53.2 mmol). The chloride **iii** was used directly, or converted to its HCl salt. The HCl salt of chloride **iii** was prepared by dissolving chloride **iii** in CH_2Cl_2 and adding excess 2N HCl/diethyl ether. After stirring the mixture for 5 minutes, the solvent was removed *in vacuo* to provide the HCl salt of chloride **iii** as a solid.

Step 3:

To a solution of **iii** (3.27 g, 12.3 mmol) in propionitrile (40 mL) was added 2,4-dichloroaniline (5.97 g, 36.9 mmol). The reaction mixture was warmed to reflux and stirred for 18 h. The reaction mixture was then cooled to room temperature and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (5% MeOH/CH_2Cl_2) provided the piperazine **Example 2** (2.92 g, 8.21 mmol).

Step 4:

To a solution of the piperazine **Example 2** (2.92 g, 8.21 mmol) in dichloroethane (27 mL) at room temperature was added Proton-Sponge® (1,8-bis(dimethylamino)naphthalene; available from Aldrich) (0.52 g, 2.46 mmol) and 1-chloroethylchloroformate (2.35 g, 16.4 mmol). The reaction mixture was warmed to reflux and stirred for 21 h. The dichloroethane was removed *in vacuo* and MeOH (30 mL) was then added. The reaction mixture was then warmed to reflux and stirred for 7 h. The reaction mixture was concentrated *in vacuo* and the resulting oil was taken up into CH_2Cl_2. Saturated aqueous $NaHCO_3$ was added, and the mixture was stirred vigorously, then extracted with CH_2Cl_2. The

organic layers were combined and washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide the piperazine **Example 1** (2.11 g, 6.19 mmol).

Step 5:

To a solution of piperazine **Example 1** (0.135 g, 0.33 mmol) in dichloroethane (1.3 mL) was added triethylamine (0.07 g, 0.66 mmol), benzaldehyde (0.052 g, 0.49 mmol), and sodium triacetoxyborohydride (0.14 g, 0.66 mmol). The reaction was stirred for 18 h at room temperature. CH_2Cl_2 was added, and the solution was then washed with saturated aqueous $NaHCO_3$, water, and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide a residue that was adsorbed on excess PS-TsOH resin in CH_2Cl_2. After 2 h, the resin was filtered and washed with CH_2Cl_2 and MeOH. The resin was then stirred with 7N NH_3/MeOH for 1 h, filtered, and washed with CH_2Cl_2. The filtrate was concentrated *in vacuo* to provide **Example 19** (0.086 g, 0.20 mmol).

Step 6:

To a solution of the piperazine **Example 1** (0.10 g, 0.24 mmol) in dichloroethane (1 mL) was added TEA (i.e., triethylamine) (0.09 g, 0.96 mmol) and benzenesulfonyl chloride (0.05 g, 0.3 mmol) at room temperature. The reaction mixture was stirred for 12 h and concentrated *in vacuo*. The resulting residue was purified by silica gel preparative plate TLC (i.e., thin layer chromatography) (2000 μm, 20% EtOAc/hexane) to provide the sulfonamide **Example 6** (0.11 g, 0.22 mmol).

Step 7:

To a solution of the piperazine **Example 1** (0.14 g, 0.33 mmol) in CH_2Cl_2 (1.7 mL) at 0°C was added TEA (0.10 g, 0.10 mmol) followed by benzoyl chloride (0.05 g, 0.37 mmol). The cold bath was allowed to warm slowly to room temperature, and the reaction mixture was stirred for 20 h. CH_2Cl_2 was added and the mixture washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography to provide the amide **Example 4** (0.13 g, 0.29 g).

Step 8:

To a solution of the piperazine **Example 1** (0.18 g, 0.45 mmol) in dichloroethane (2 mL) was added TEA (0.14 g, 1.3 mmol) followed by cyclohexylisocyanate (0.08 g, 0.67 mmol). The reaction mixture was warmed to

reflux and stirred for 17 h, then cooled to room temperature. CH_2Cl_2 was added, and the solution was washed with water and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by silica gel prep plate TLC (2000 μm, 30% EtOAc/hexane) to provide the urea **Example 7** (0.19 g, 0.41 mmol).

Step 9:

To a solution of benzaldehyde (2.00 g, 18.8 mmol) in ethanol (13 mL) was added hydroxyl amine hydrochloride (2.61 g, 37.6 mmol) and pyridine (3.8 mmol). The solution was warmed to reflux and stirred for 18 h. The reaction mixture was concentrated *in vacuo* and the resulting residue was taken up into CH_2Cl_2, washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide the phenyloxime (2.0 g, 16.5 mmol). The phenyloxime was taken up into DMF (i.e., dimethylformamide) (55 mL), and *N*-chlorosuccinimide (2.43 g, 18.2 mmol) was added at room temperature. The reaction mixture was stirred for 23 h and then water was added. The mixture was extracted with EtOAc. The organic layers were combined and washed with water and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide the benzohydroximoyl chloride that was used directly.

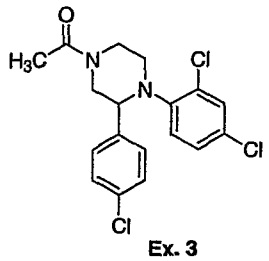
To the piperazine **Example 1** (0.50 g, 1.21 mmol) in CH_2Cl_2 (4 mL) was added diisopropylethylamine (0.55 g, 4.23 mmol) and the benzohydroximoyl chloride prepared as described above (0.28 g, 1.81 mmol), at room temperature. The reaction mixture was stirred for 15 h and CH_2Cl_2 was then added. The solution was then washed with water and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (30% EtOAc/hexane) to provide the amidoxime **Example 9** (0.44 g, 0.95 mmol).

Step 10:

To a solution of the amidoxime **Example 9** (0.074 g, 0.15 mmol) in toluene (0.5 mL) was added 50% aqueous NaOH (0.5 mL), methyl iodide (0.04 g, 0.30 mmol), and tetrabutylammonium iodide (0.003 g, 0.007 mmol). The resulting reaction mixture was stirred at room temperature for 18 h, then water was added and the mixture was extracted with EtOAc. The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel preparative plate TLC (2000 μm,

10% EtOAc/hexane) to provide the *O*-methylamidoxime **Example 10** (0.05 g, 0.10 mmol).

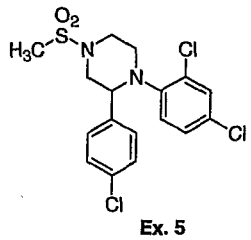
Preparation of Example 3



Ex. 3

Example 3 was prepared from **Example 1** using procedures similar to those used to prepare **Example 4**, except that acetyl chloride was used in Step 7 (above) instead of benzoyl chloride.

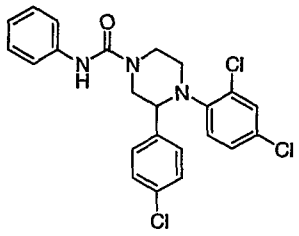
Preparation of Example 5



Ex. 5

Example 5 was prepared from **Example 1** using procedures similar to those used to prepare **Example 6**, except that methanesulfonyl chloride was used in Step 6 (above) instead of benzenesulfonyl chloride.

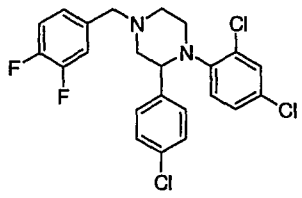
Preparation of Example 8



Ex. 8

Example 8 was prepared from **Example 1** using procedures similar to those used to prepare **Example 7**, except that phenylisocyanate was used in Step 8 (above) instead of cyclohexylisocyanate.

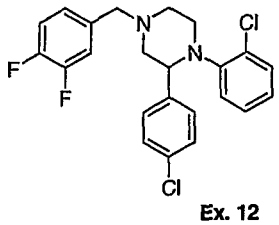
Preparation of Example 11



Ex. 11

Example 11 was prepared from **Example 1** using procedures similar to those used to prepare **Example 19**, except that 3,4-difluorobenzaldehyde was used in Scheme 2, Step 5 (above) instead of benzaldehyde.

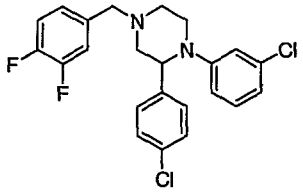
Preparation of Example 12



Ex. 12

Example 12 was prepared using procedures similar to those used to prepare **Example 19**, except that in Scheme 1, Step 3 (above), the HCl salt of **iii** was used instead of **iii**, 2-chloroaniline was used instead of 2,4-dichloroaniline, acetonitrile was used instead of propionitrile, NaI (1 equiv.) and diisopropylethylamine (3 equiv.) was added, and in Scheme 2, Step 5 (above), 3,4-difluorobenzaldehyde was used instead of benzaldehyde..

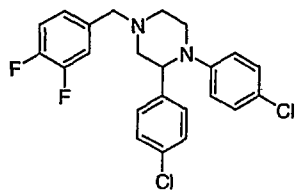
Preparation of Example 13



Ex. 13

Example 13 was prepared using procedures similar to those used to prepare **Example 19**, except that in Scheme 1, Step 3 (above), the HCl salt of **iii** was used instead of **iii**, 3-chloroaniline was used instead of 2,4-dichloroaniline, acetonitrile was used instead of propionitrile, NaI (1 equiv.) and diisopropylethylamine (3 equiv.) was added, and in Scheme 2, Step 5 (above), 3,4-difluorobenzaldehyde was used instead of benzaldehyde.

Preparation of Example 14

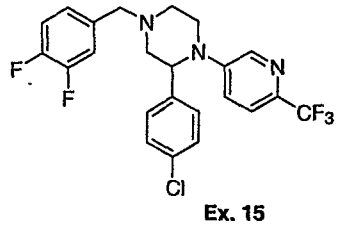


Ex. 14

Example 14 was prepared using procedures similar to those used to prepare **Example 19**, except that in Scheme 1, Step 3 (above), 4-chloroaniline was used instead of 2,4-dichloroaniline, acetonitrile was used instead of

propionitrile, and NaI was added, and in Scheme 2, Step 5 (above), 3,4-difluorobenzaldehyde was used instead of benzaldehyde.

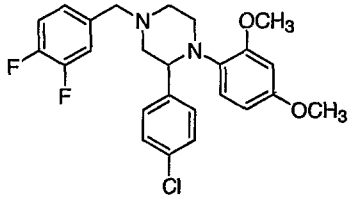
Preparation of Example 15



Ex. 15

Example 15 was prepared using procedures similar to those used to prepare **Example 19**, except that in Scheme 1, Step 3 (above), 6-trifluoromethyl-pyridin-3-ylamine was used instead of 2,4-dichloroaniline, acetonitrile was used instead of propionitrile, NaI (1 equiv.) and diisopropylethylamine (3 equiv.) was added, and in Scheme 2, Step 5 (above), 3,4-difluorobenzaldehyde was used instead of benzaldehyde.

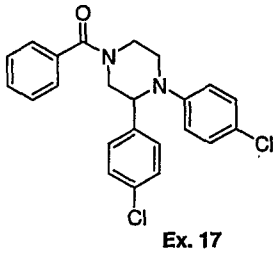
Preparation of Example 16



Ex. 16

Example 16 was prepared using procedures similar to those used to prepare **Example 19**, except that in Scheme 1, Step 3 (above), 2,4-dimethoxyaniline was used instead of 2,4-dichloroaniline, acetonitrile was used instead of propionitrile, NaI (1 equiv.) and diisopropylethylamine (3 equiv.) was added, and in Scheme 2, Step 5 (above), 3,4-difluorobenzaldehyde was used instead of benzaldehyde.

Preparation of Example 17

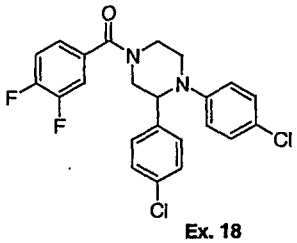


Ex. 17

Example 17 was prepared using procedures similar to those used to prepare **Example 4**, except that in Scheme 1, Step 3 (above), the HCl salt of **iii** was used instead of **iii**, 4-chloroaniline was used instead of 2,4-dichloroaniline,

acetonitrile was used instead of propionitrile, and NaI (1 equiv.) and diisopropylethylamine (3 equiv.) was added.

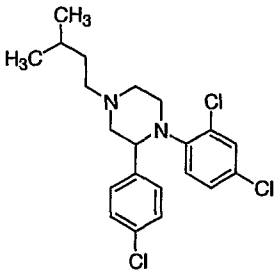
Preparation of Example 18



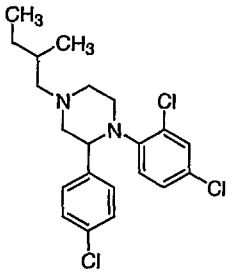
Ex. 18

Example 18 was prepared using procedures similar to those used to prepare **Example 4**, except that in Scheme 1, Step 3 (above), the HCl salt of **iii** was used instead of **iii**, 4-chloroaniline was used instead of 2,4-dichloroaniline, acetonitrile was used instead of propionitrile, NaI (1 equiv.) and diisopropylethylamine (3 equiv.) was added, and in Step 7 (above), 3,4-difluorobenzoyl chloride was used instead of benzoyl chloride.

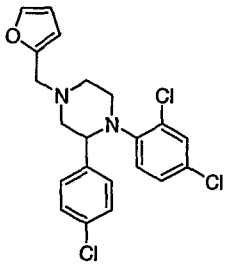
Preparation of Examples 20-110



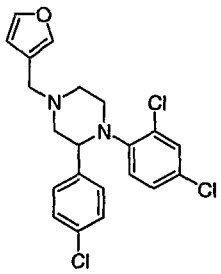
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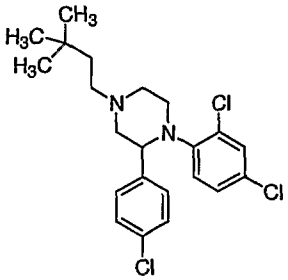
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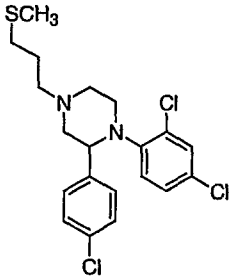
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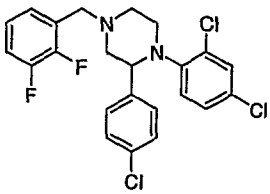
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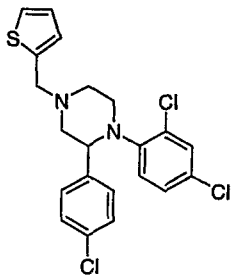
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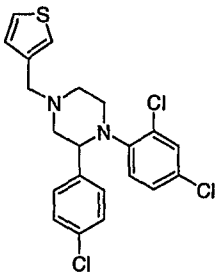
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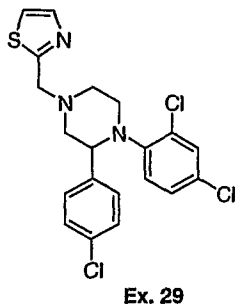
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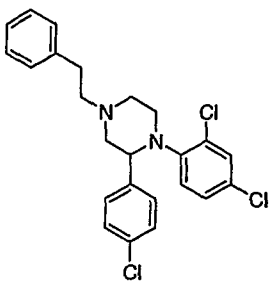
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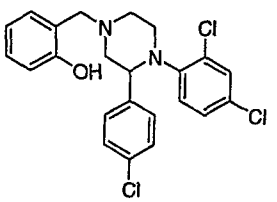
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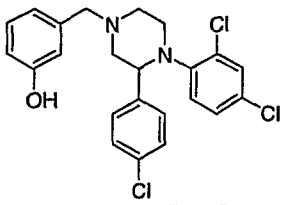
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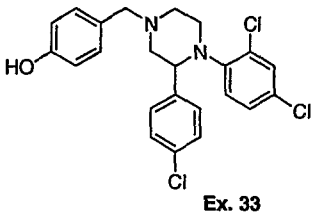


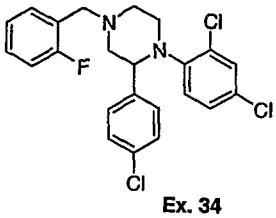
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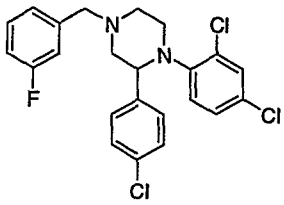


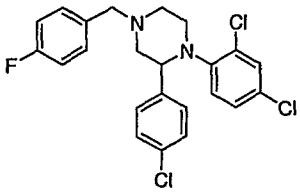
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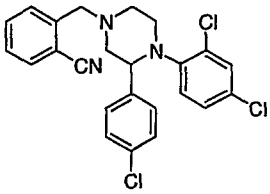

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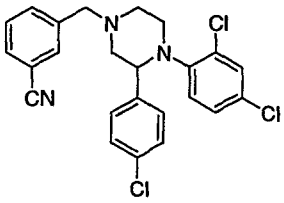

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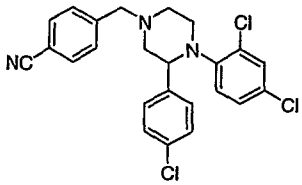

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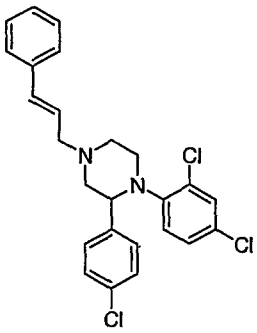

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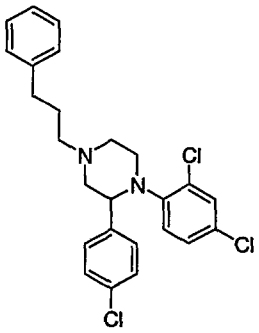

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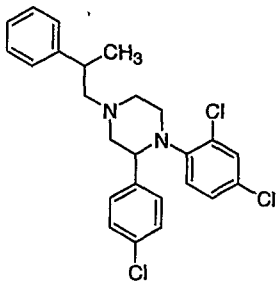

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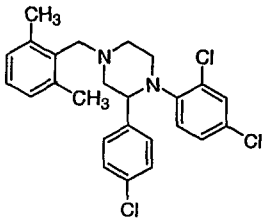

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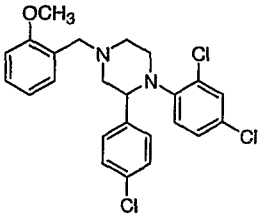

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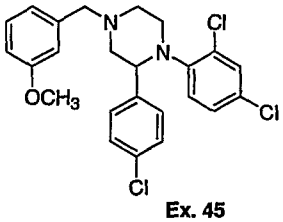

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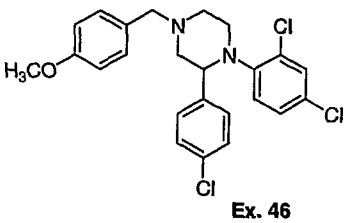

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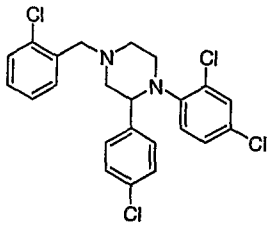

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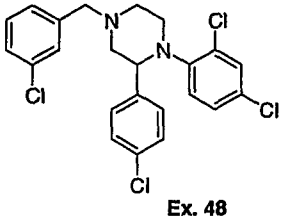

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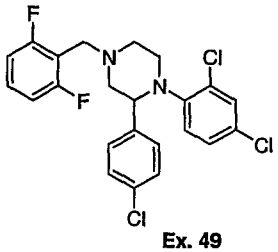

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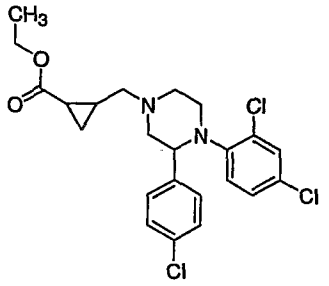

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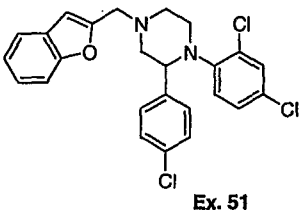

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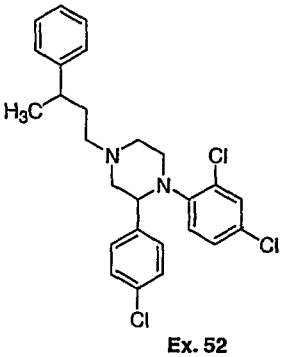

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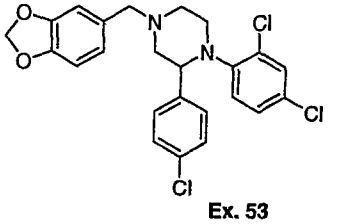

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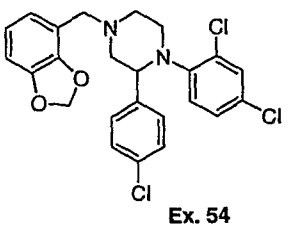

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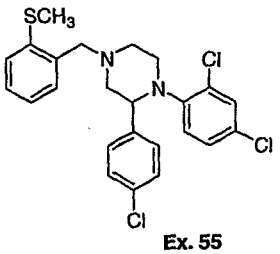

Ex. 50

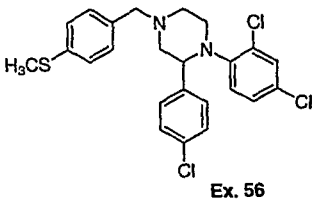

Ex. 51

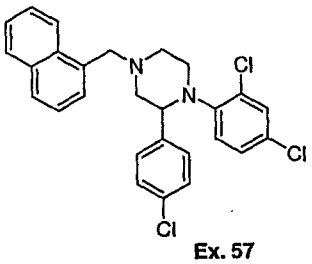

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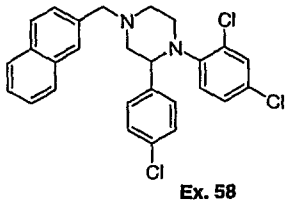

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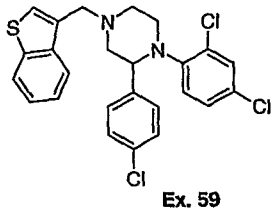

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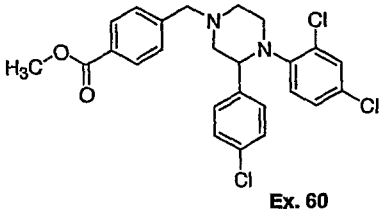

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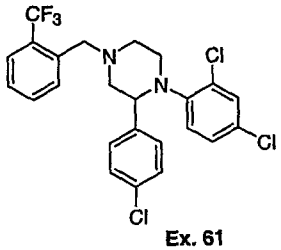

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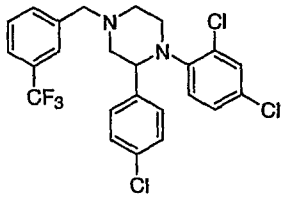

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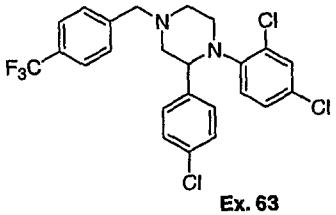

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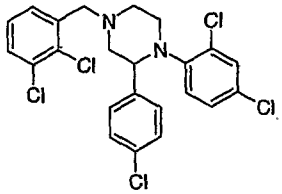

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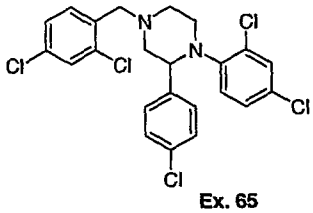

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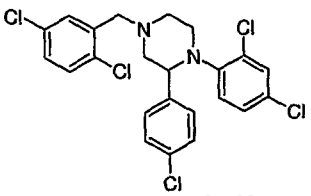

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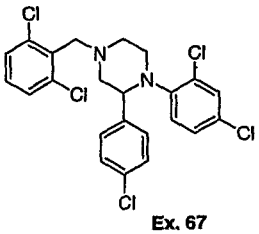

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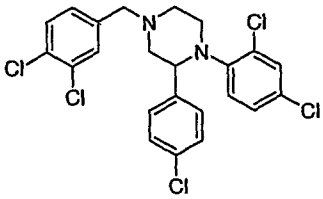

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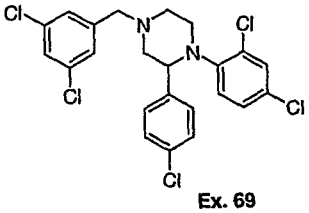

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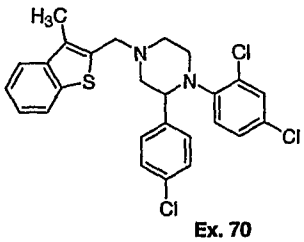

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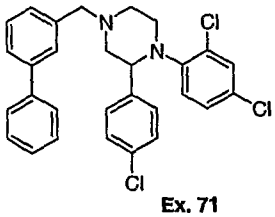

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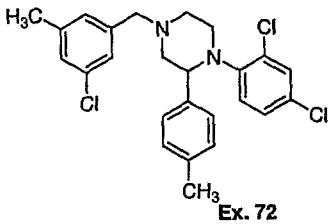

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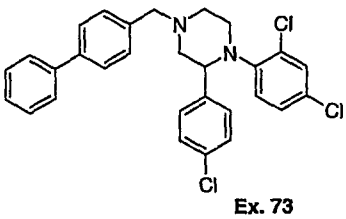

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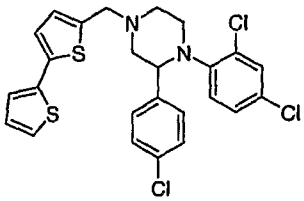

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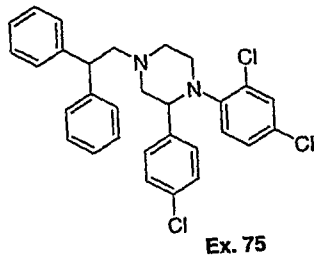

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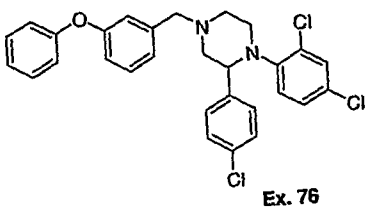

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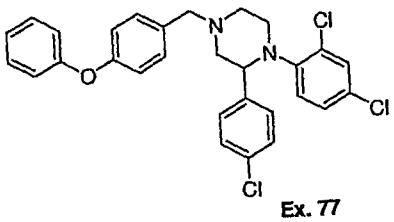

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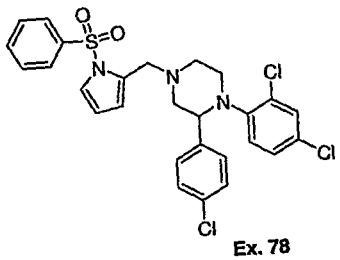

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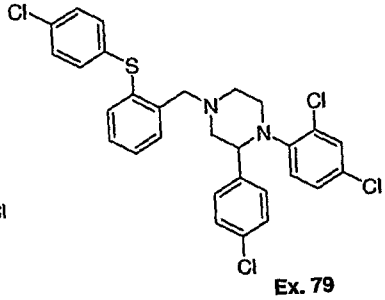

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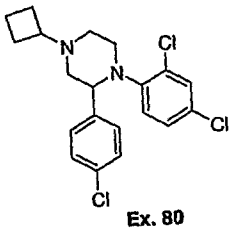

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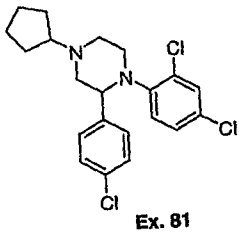

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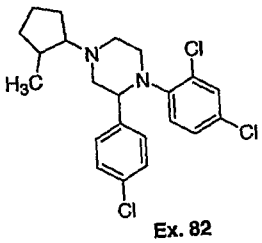

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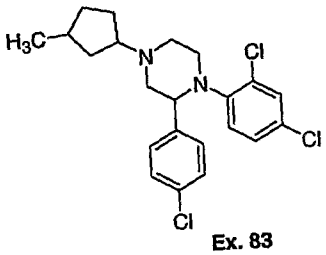

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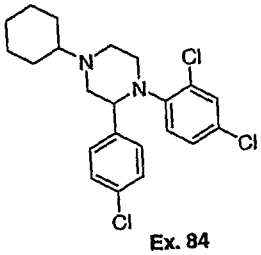

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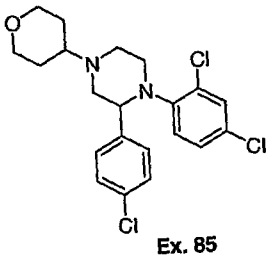

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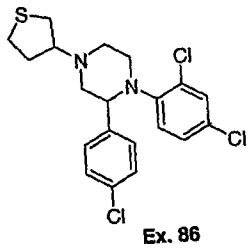

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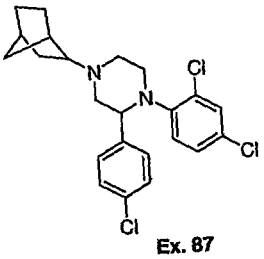

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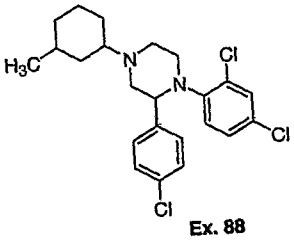

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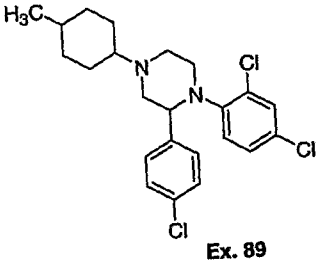

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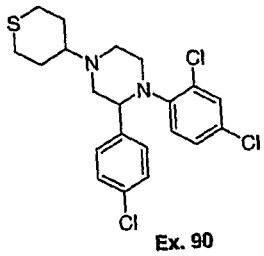

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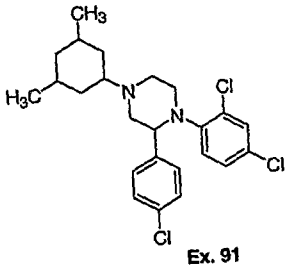

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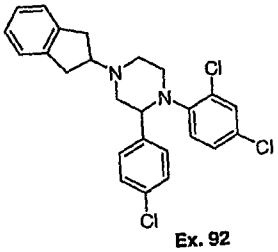

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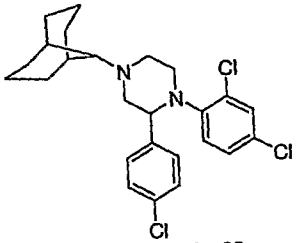

Ex. 88


Ex. 89

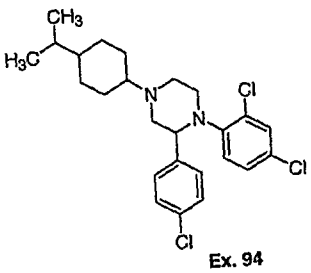

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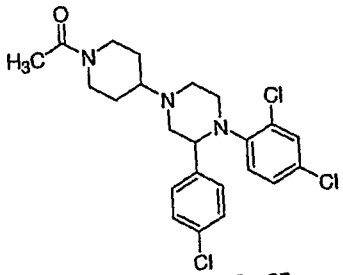

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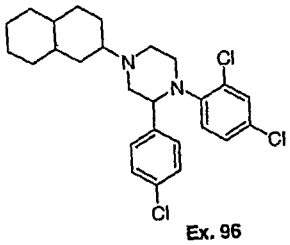

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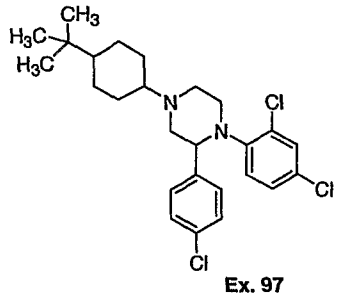

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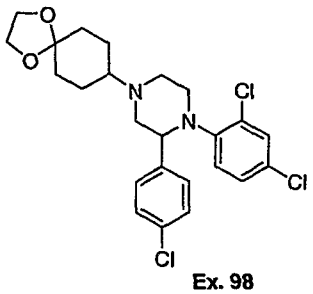
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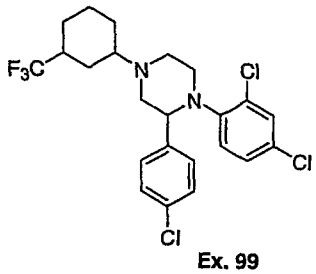

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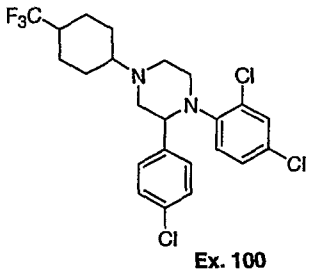

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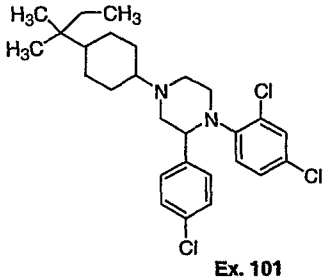

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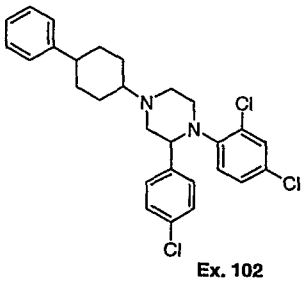

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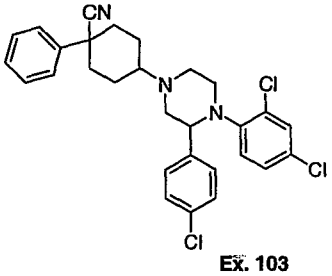

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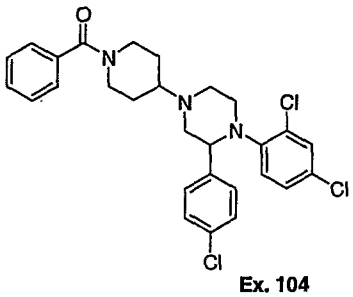

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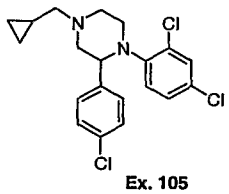

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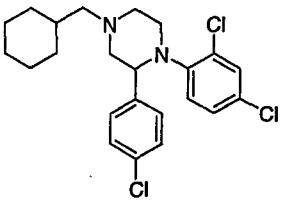

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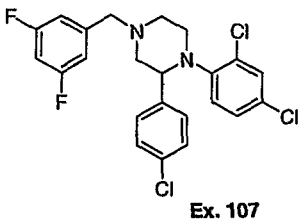

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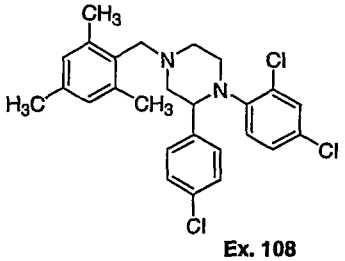

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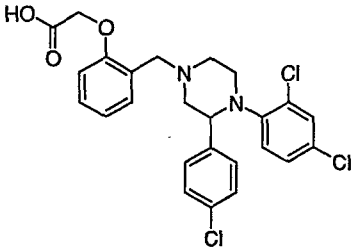

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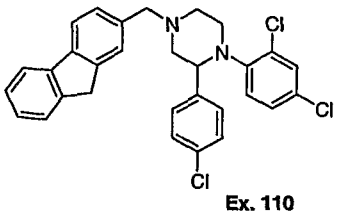

Ex. 105


Ex. 106


Ex. 107

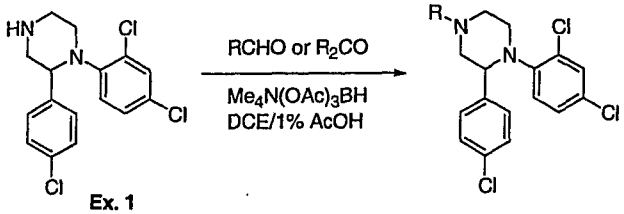

Ex. 108


Ex. 109


Ex. 110

Examples 20-110 were prepared by the following method, using a parallel synthesis approach.

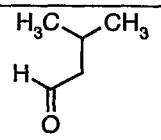
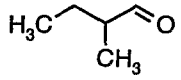
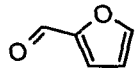
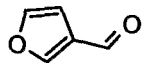
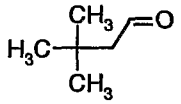
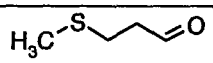
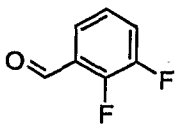
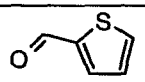
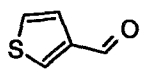
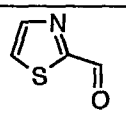
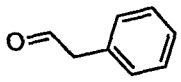
Scheme 3

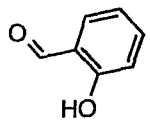
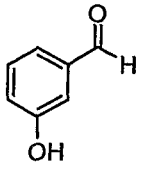
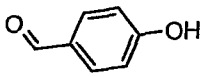
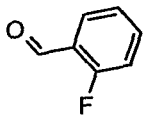
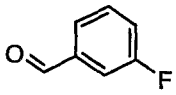
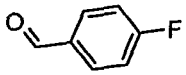
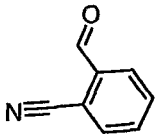
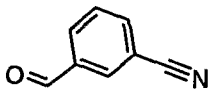
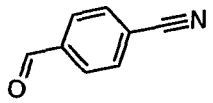
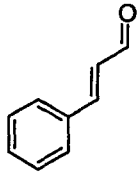
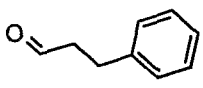
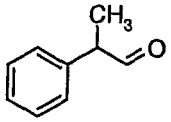


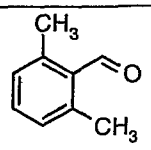
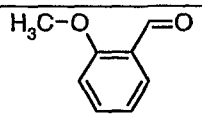
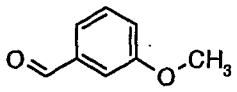
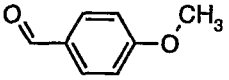
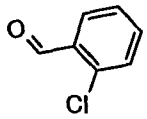
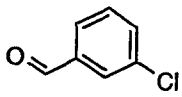
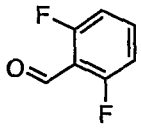
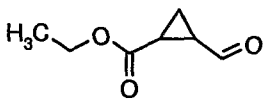
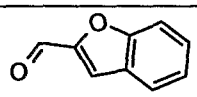
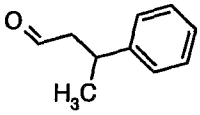
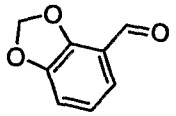
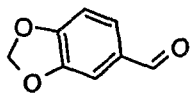
Ex. 1

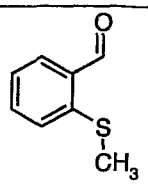
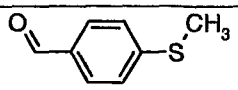
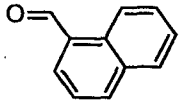
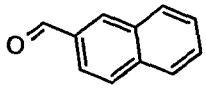
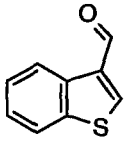
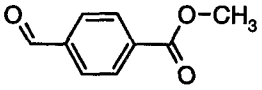
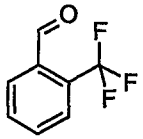
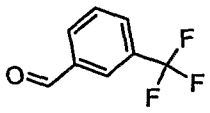
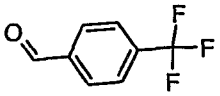
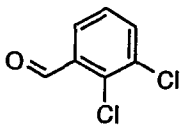
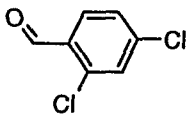
The piperazine **Example 1**, prepared as described above (0.72 g, 2.1 mmol) and $Me_4N(OAc)_3BH$ (1.11g, 4.2 mmol) was dissolved in a 1% acetic acid/dichloroethane (DCE) solution (100 mL). Aliquots (1 mL) of the resulting mixture were added to 96 wells of a deep well polypropylene microtiter plate. To each of the wells was then added one of 96 different aldehydes or ketones (shown in Table I, below) (1.0 M solution in MeCN, 150 μL) via a TECAN liquid handler.

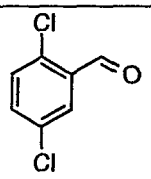
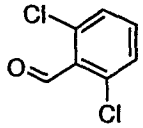
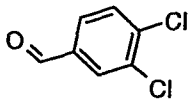
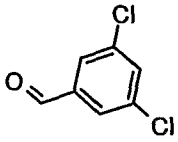
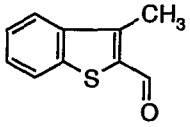
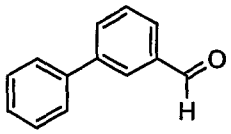
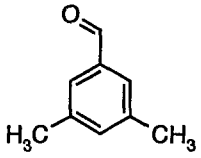
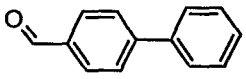
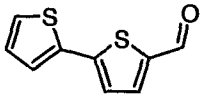
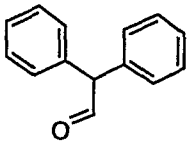
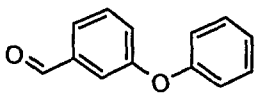
Table I: Aldehydes/Ketones Used

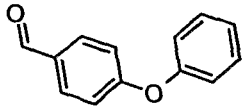
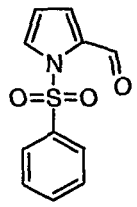
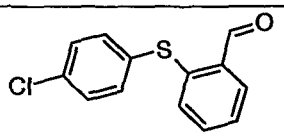
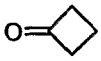
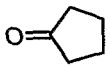
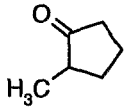
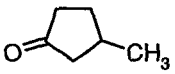
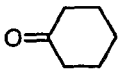
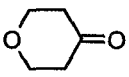
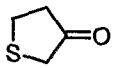
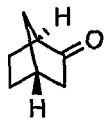
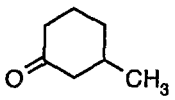
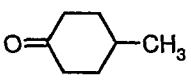
Example	Ketone/Aldehyde
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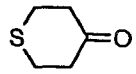
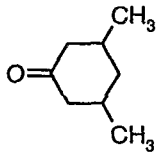
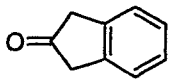
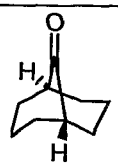
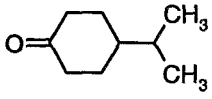
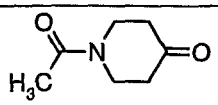
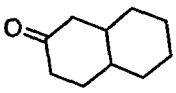
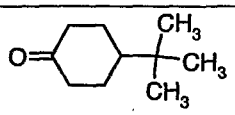
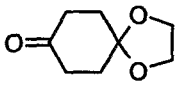
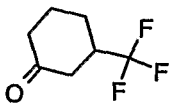
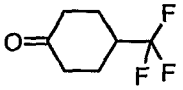
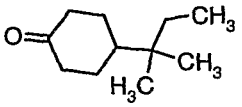
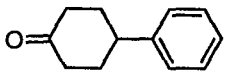
Example	Ketone/Aldehyde
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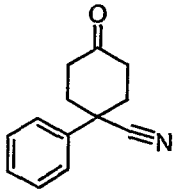
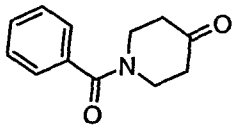
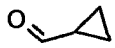
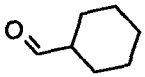
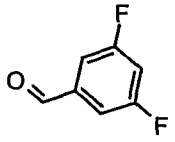
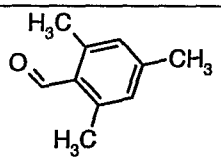
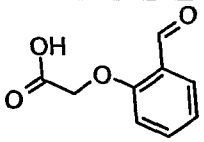
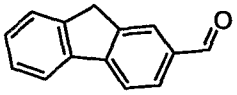
Example	Ketone/Aldehyde
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Example	Ketone/Aldehyde
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Example	Ketone/Aldehyde
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Example	Ketone/Aldehyde
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Example	Ketone/Aldehyde
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Example	Ketone/Aldehyde
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The plate was then sealed and shaken at room temperature for 3 days. MP-TsOH resin (i.e., macroporous resin functionalized with toluenesulfonic acid groups; available from Argonaut Technologies, Inc.) (100 mg) was then added to each well of the plate. The plate was then resealed and shaken for 2 h. The bottom of the plate was opened and the filtrate from each well was collected in the corresponding 2 mL well of a 96-well plate. The resin in each well was washed with CH_2Cl_2 (4X) followed by MeOH (3X). The bottom of the plate was then resealed and an aliquot of 2 N NH_3/MeOH (1.5 mL) was added to each well to remove crude product bound to the MP-TsOH resin. The plate was sealed and

shaken for 2 h. The bottom of the plate was opened and the filtrate from each well was collected in the corresponding 2 mL well of a 96-well plate. The resin in each well was washed with MeOH (1X). An aliquot from each well was removed for LC/MS analysis. The remaining solution from each well was transferred to 96 corresponding 2-dram bar-coded vials using a TECAN liquid handler. The solvent was then removed from each of the vials using a SPEEDVAC concentrator, to provide crude Products I.

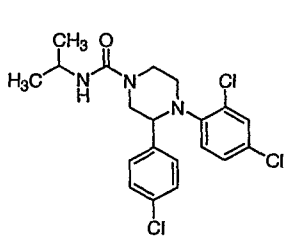
LC/MS analysis showed that most crude Products I contained 10-40% of starting piperazine **Example 1**. The desired product was also determined to be present in the filtrate by TLC (i.e., thin layer chromatography) analysis. The filtrates were then transferred by a TECAN liquid handler to 96 corresponding BOHDAN MINIBLOCK cartridges containing approximately 100 mg of MP-TsOH resin. The cartridges were sealed and shaken for 20 h. The solvent was then removed from each cartridge *in vacuo* and the resin was washed in each cartridge with CH_2Cl_2 (3X) and MeOH (3X, 1.5 mL). A 3.5 N NH_3/MeOH-THF (1:1) solution (1.5 mL) was then added to the resin in each cartridge to remove crude product bound to the MP-TsOH resin. The cartridges were sealed and shaken for 20 h. The solvent from each cartridge was collected by filtration and the resin in each cartridge was treated with 7 N NH_3/MeOH (1.5 mL) for 8 h. The solvent was removed by filtration and the filtrates were combined in 96 corresponding 2-dram bar-coded vials. An aliquot form each vial was analyzed by LC/MS, and the remaining solvent from each vial was removed *in vacuo* to provide crude Products II.

The MP-TsOH resin from Product I was manually transferred with MeOH from the plate to 96 corresponding cartridges of a BOHDAN MINIBLOCK. The solution from each cartridge was then removed by filtration and the resin in each cartridge was treated with 3.5 N NH_3 in MeOH/THF (1:1, 18h, 1.5 mL). The filtrate from each cartridge was collected and the resin in each cartridge was again treated with 3.5 N NH_3 in MeOH/THF (1:1, 8h, 1.5 mL). The filtrates were combined with the corresponding Product I and an aliquot from each combined filtrate was submitted for LC/MS analysis. The solvent from each sample was removed *in vacuo* to provide Product III.

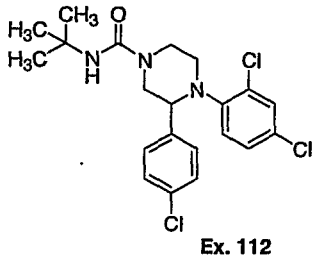
Products II were added to Products III if it was determined by LC/MS analysis that a sufficient quantity of desired product was present in Product II.

The combined products were transferred with DCE/MeCN (i.e. dichloroethane/acetonitrile, 1:1, 3 mL) to 96 corresponding BOHDAN MINIBLOCK cartridges containing PS-NCO resin (polystyrene functionalized with isocyanate groups; available from Argonaut Technologies, Inc.) (6 equiv.). The cartridges were capped and shaken for 3 days. The products were filtered into individual vials and the resin was washed with DCE/MeCN (1:1, 2X, 0.5 mL). An aliquot from each vial was removed for LC/MS analysis, and the remaining solvent was removed using a SPEEDVAC concentrator to provide desired products, **Examples 20-110**.

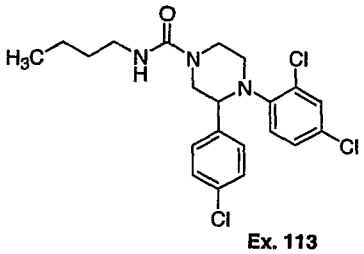
Preparation of Examples 111 – 154 and 171



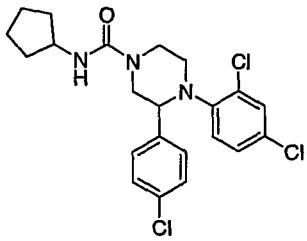
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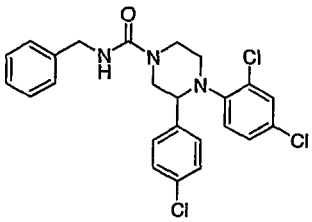
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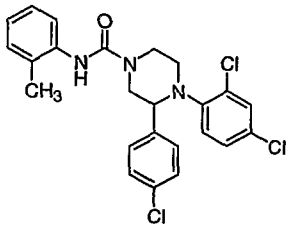
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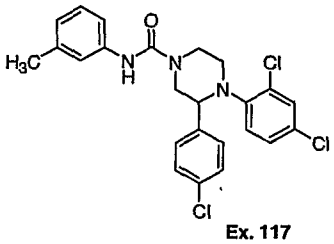
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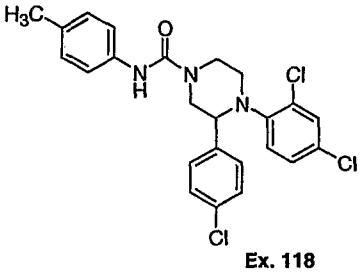
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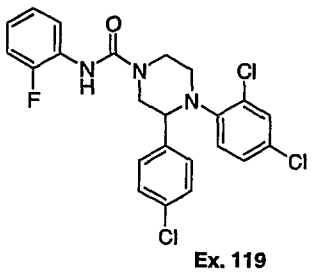
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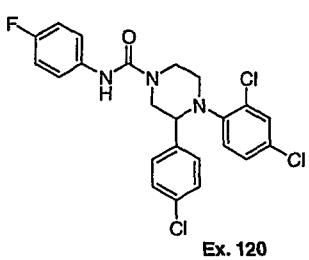
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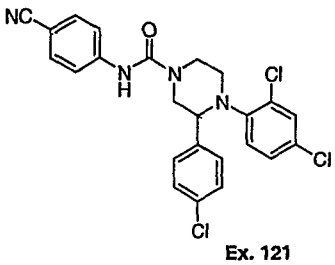
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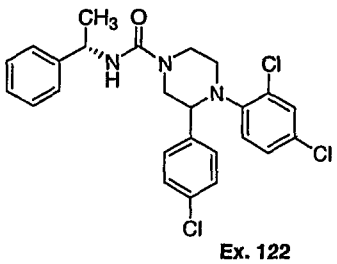
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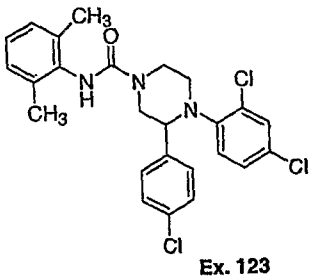
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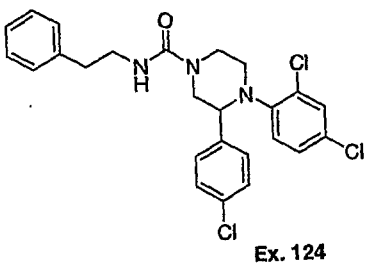


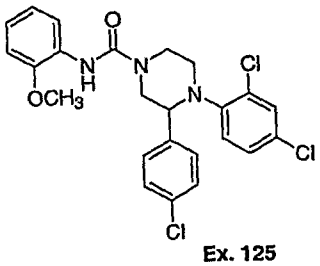
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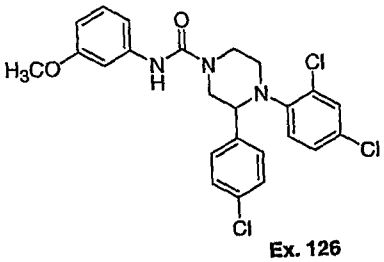


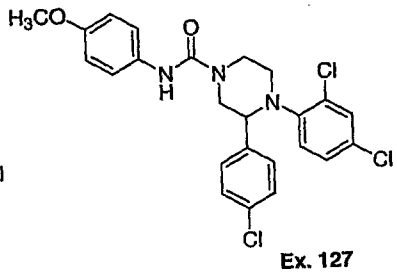
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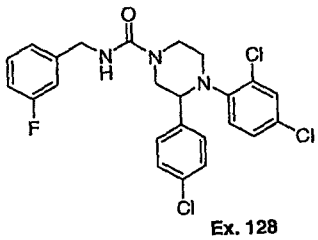

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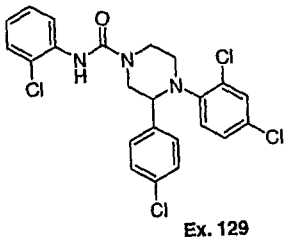

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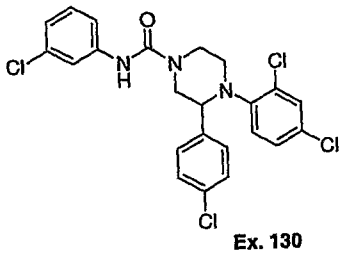

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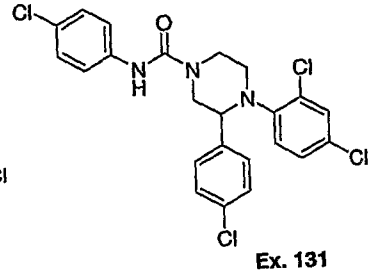

Ex. 126

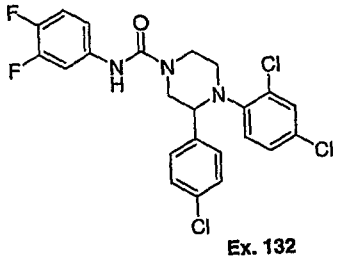

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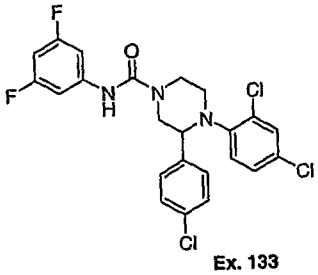

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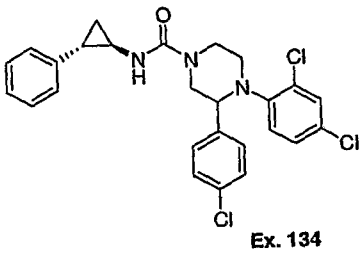

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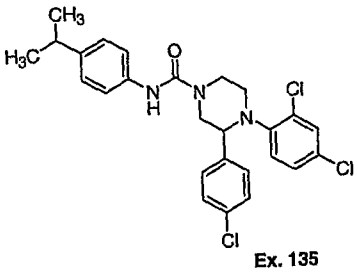

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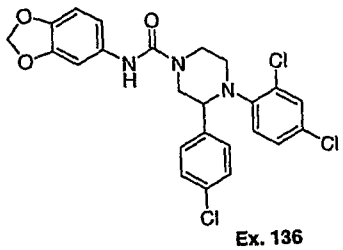

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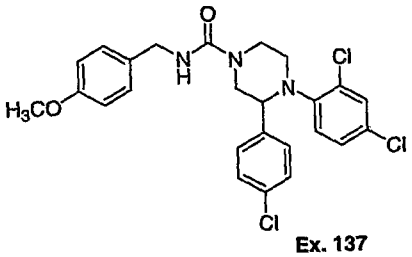

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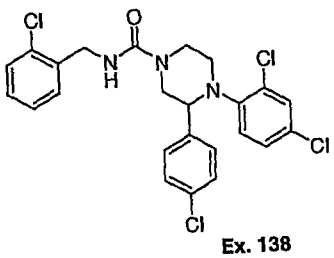

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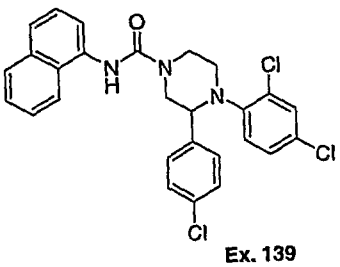

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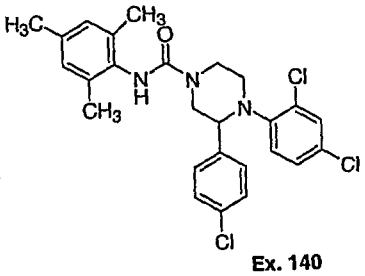

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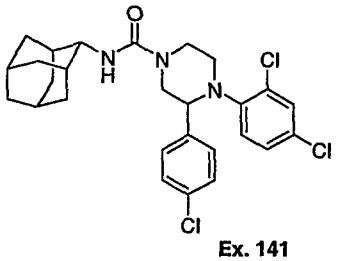

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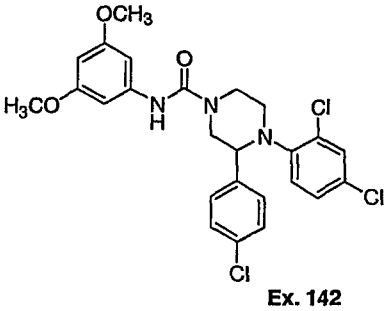

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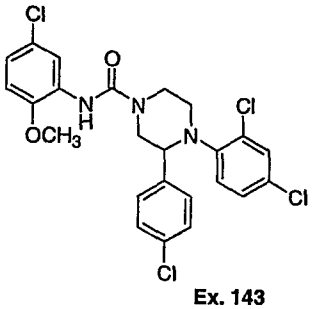

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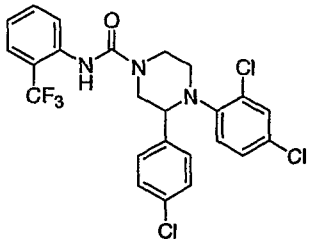
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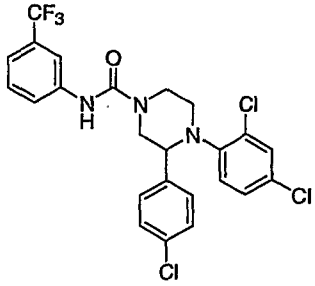
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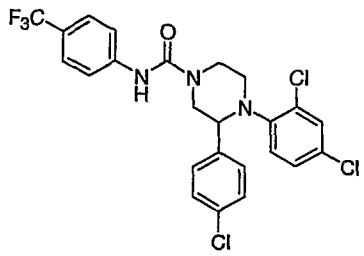
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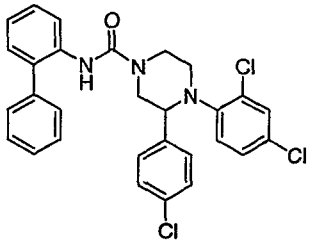
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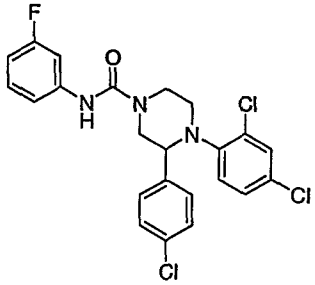
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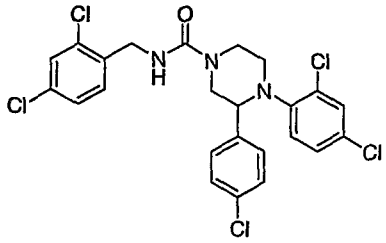
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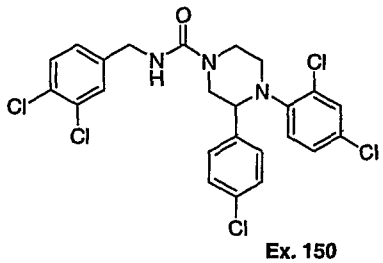
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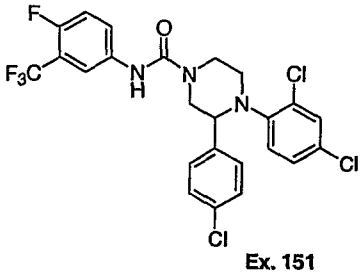
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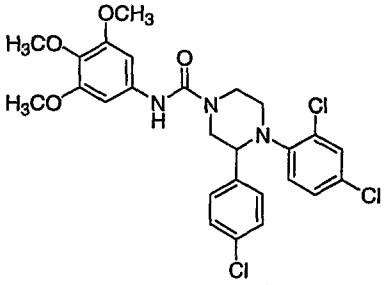
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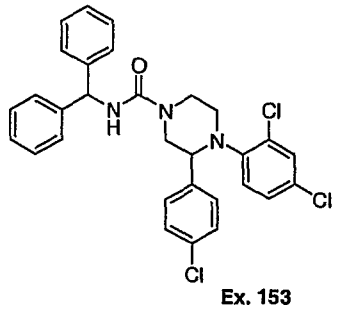
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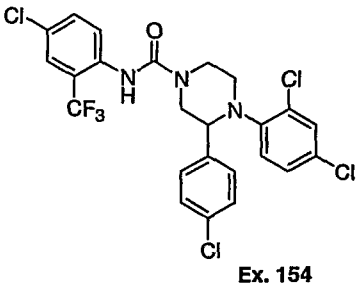
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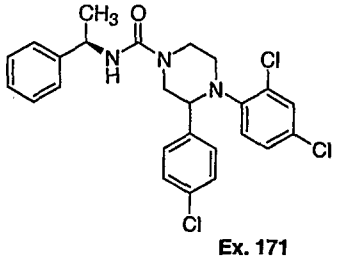
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Ex. 153



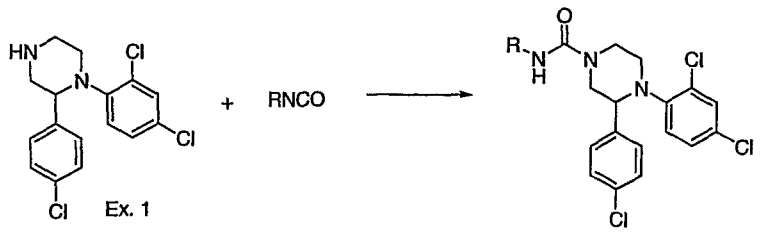
Ex. 154



Ex. 171

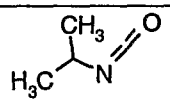
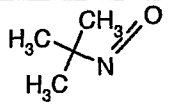
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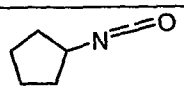
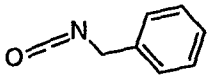
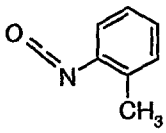
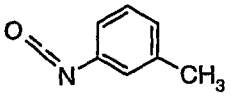
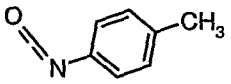
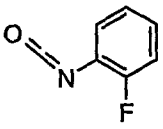
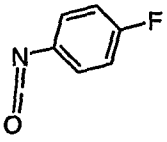
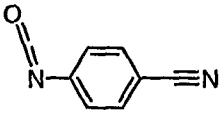
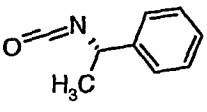
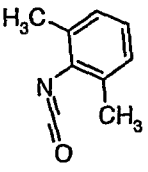
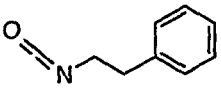
Scheme 4

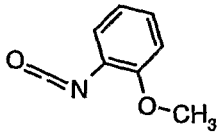
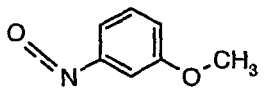
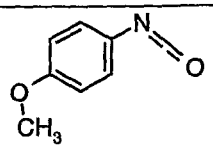
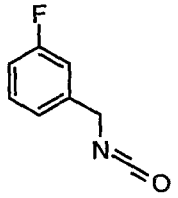
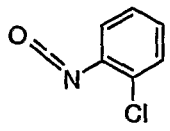
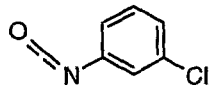
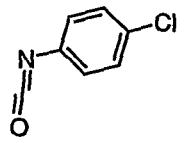
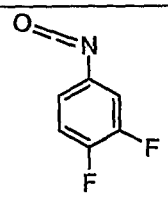
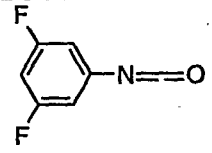


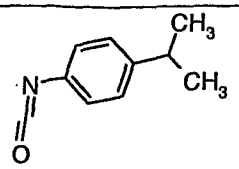
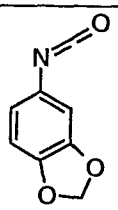
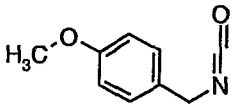
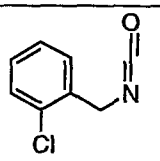
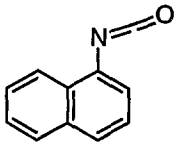
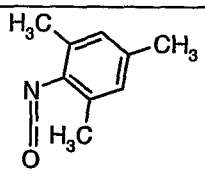
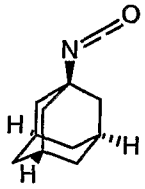
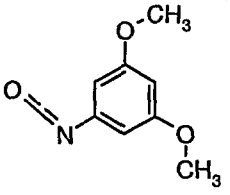
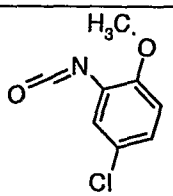
A dichloroethane: acetonitrile (1:1) stock solution of piperazine **Example 1** (1 mL, 0.023 mmol) was added to 48 wells of a deep well polypropylene microtiter plate. 0.5 M stock solutions of each individual isocyanates (RNCO) (Table II, below) in dichloromethane (0.14 mL, 0.07 mmol) were added to the plate, which was then sealed and shaken at 25°C for 20 h. The solutions were then filtered through a polypropylene frit into a second microtiter plate containing PS-Isocyanate resin (i.e., polystyrene resin functionalized with isocyanate groups, available from Argonaut Technologies, Inc.) (0.046 g, 0.07 mmol) and PS-Trisamine resin (i.e., polystyrene resin functionalized with the tris-(2-aminoethyl)amine group, available from Argonaut Technologies, Inc.) (0.042 g, 0.18 mmol). After the top plate was washed with MeCN (acetonitrile) (0.5 mL/well), the plate was removed, the bottom plate sealed, and then shaken for 16 h at 25°C. The solutions were then filtered through a polypropylene frit into a 96-well collection plate. The wells of the top plate were washed with MeCN (0.5 mL/well) and the top plate removed. The resultant solutions in the collection plate were transferred into vials and the solvent removed *in vacuo* using a SPEEDVAC. The resulting samples were evaluated by LC/MS and those that were >70% pure are listed above.

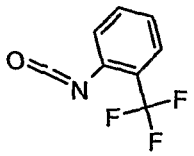
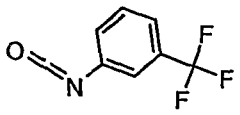
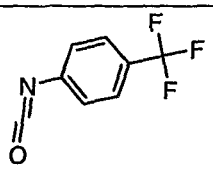
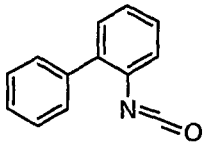
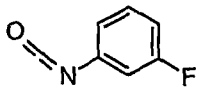
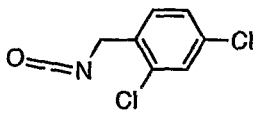
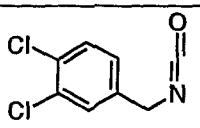
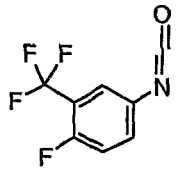
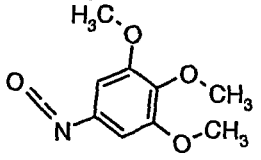
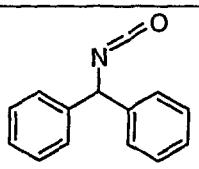
Table II: Isocyanates Used

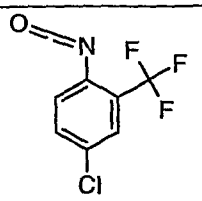
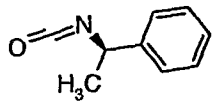
Example	Isocyanate
111	
112	

Example	Isocyanate
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114	
115	
116	
117	
118	
119	
120	
121	
122	
123	
124	

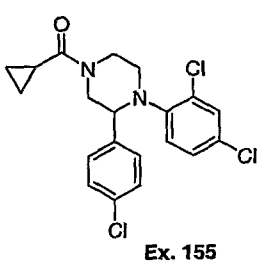
Example	Isocyanate
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126	
127	
128	
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130	
131	
132	
133	
134	

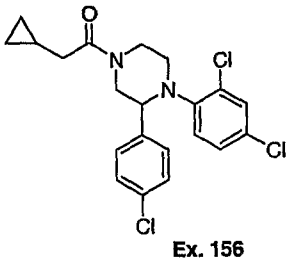
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137	
138	
139	
140	
141	
142	
143	

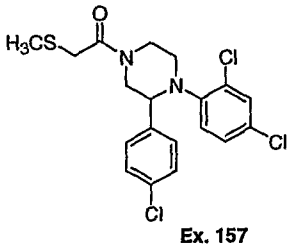
Example	Isocyanate
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146	
147	
148	
149	
150	
151	
152	
153	

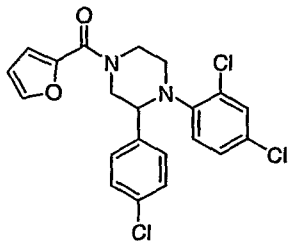
Example	Isocyanate
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171	

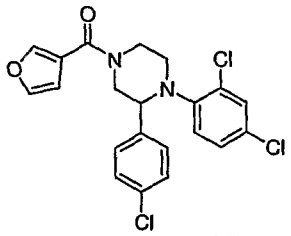
Preparation of Examples 155 – 170 and 172 - 233

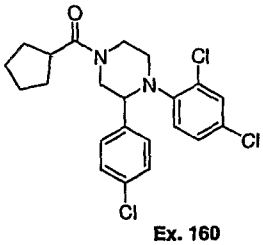

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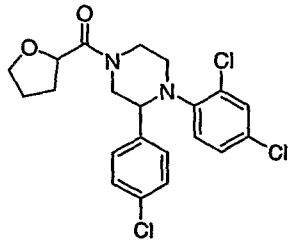

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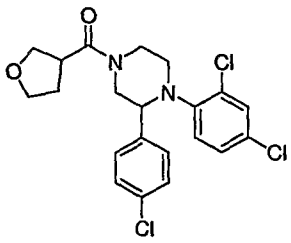

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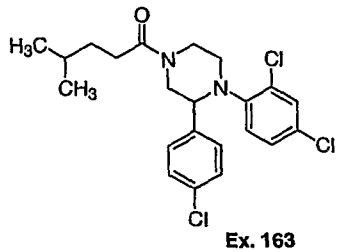

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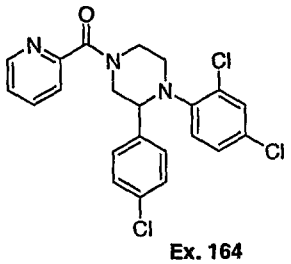

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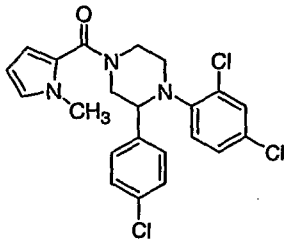

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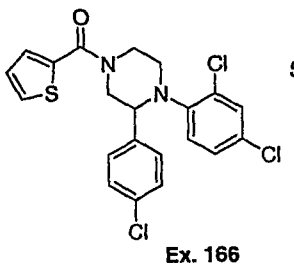

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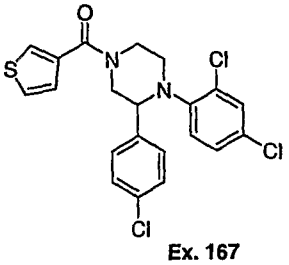

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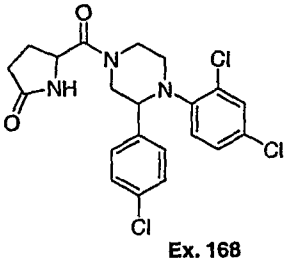

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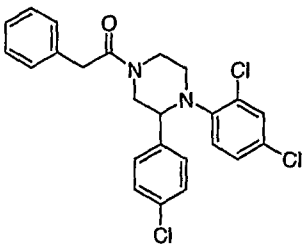

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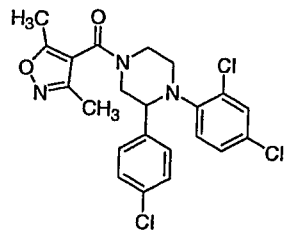

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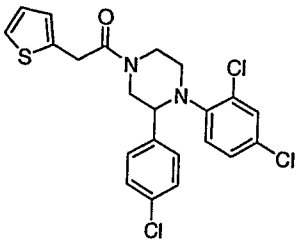

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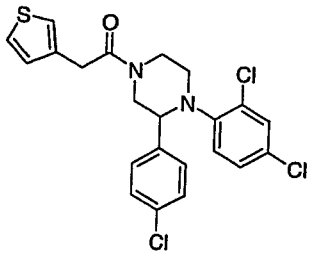

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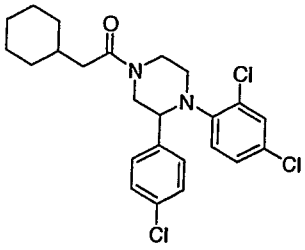

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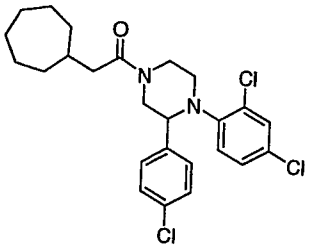

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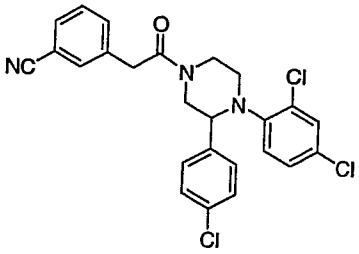

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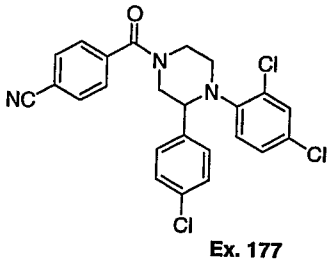

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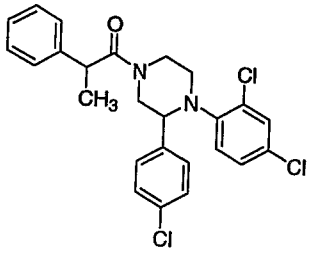

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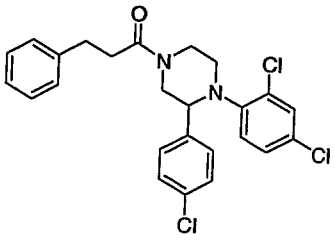

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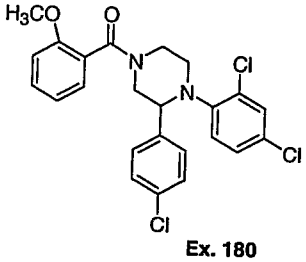

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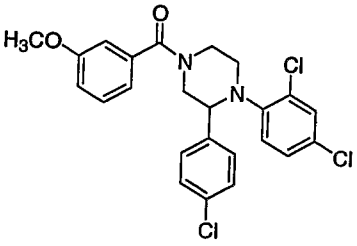

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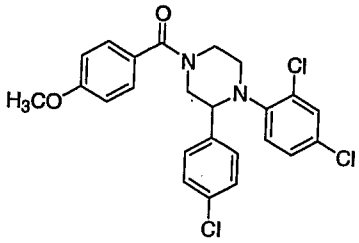

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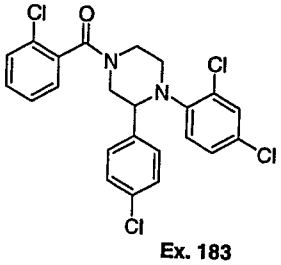

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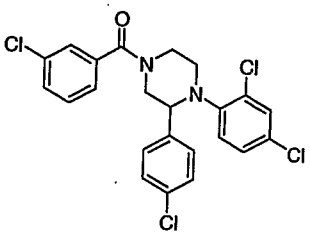

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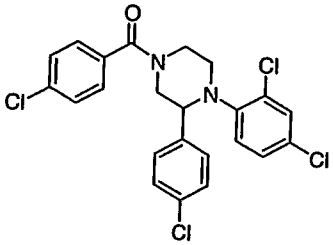

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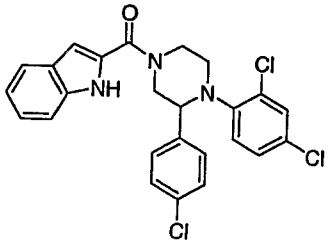

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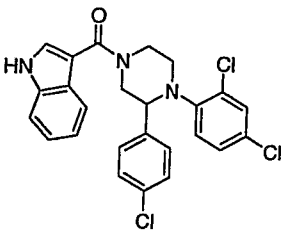

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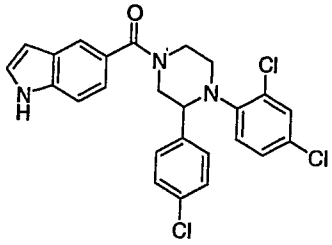

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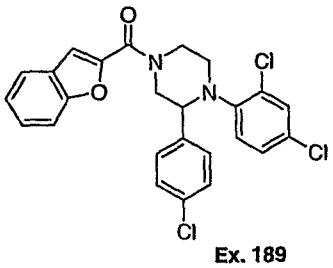

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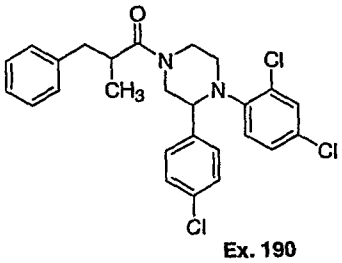

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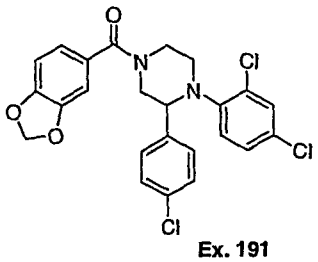

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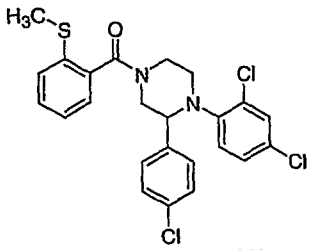

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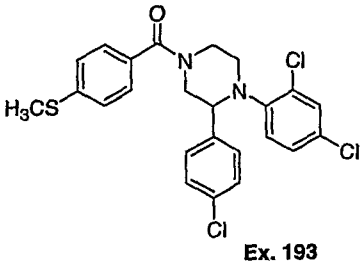
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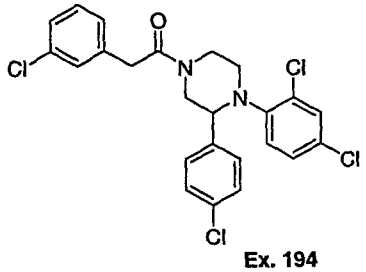

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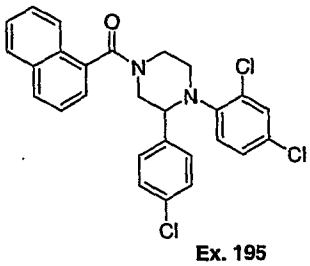

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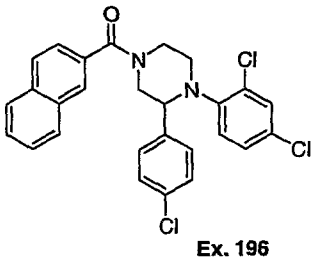

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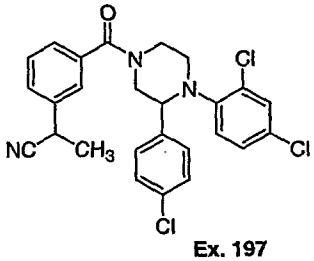

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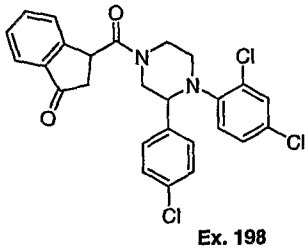

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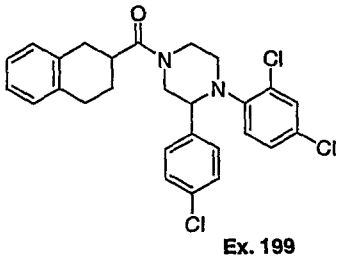

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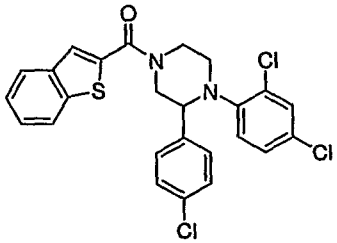

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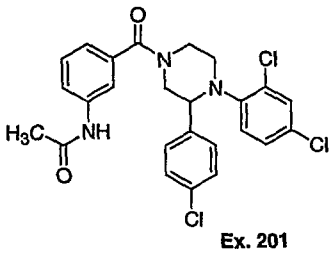

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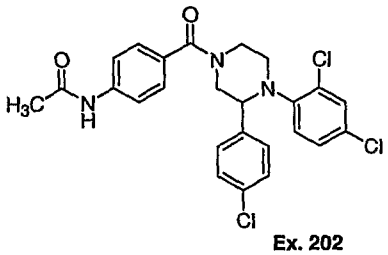

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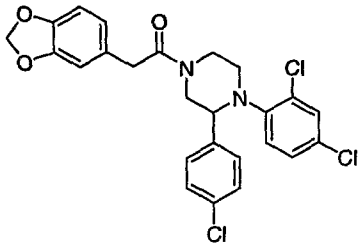

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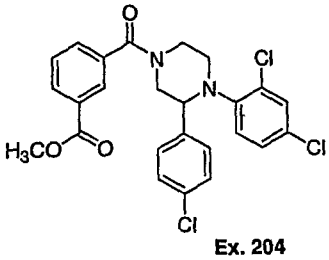

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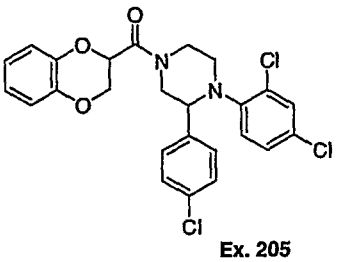

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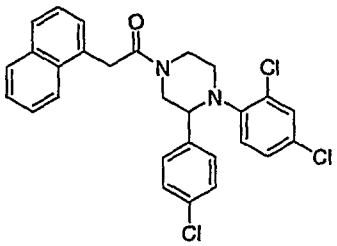

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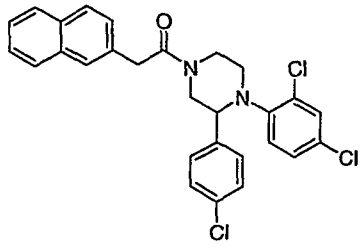

Ex. 202


Ex. 203

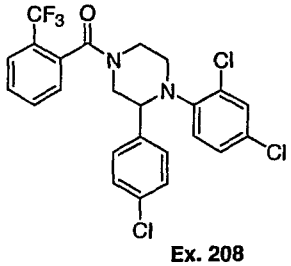

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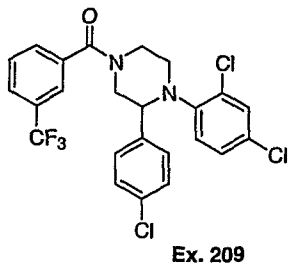

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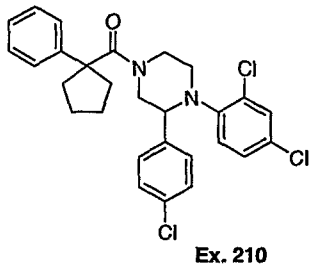
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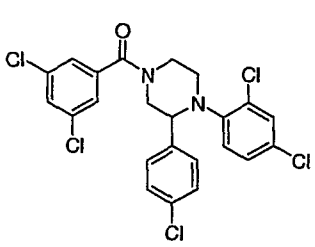
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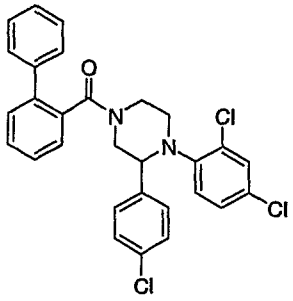
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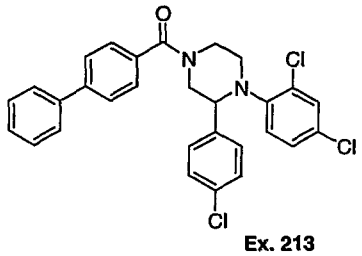
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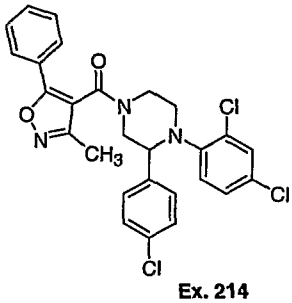
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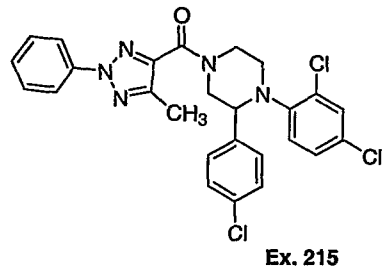
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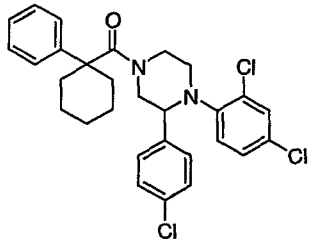
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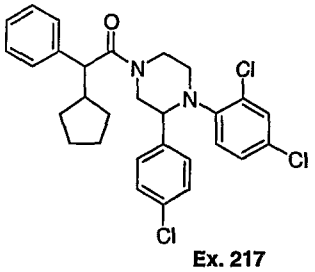
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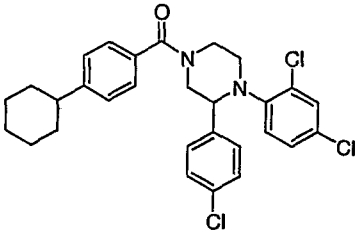
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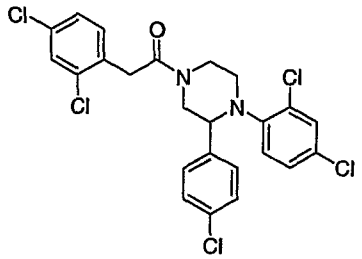
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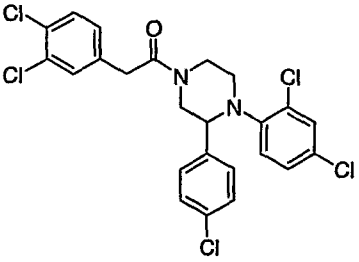
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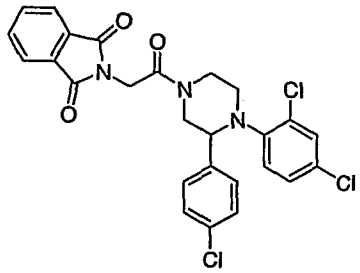
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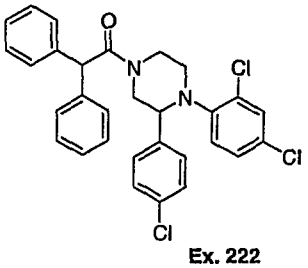
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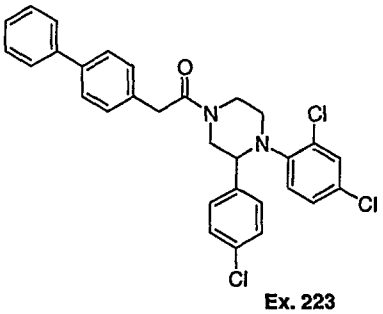
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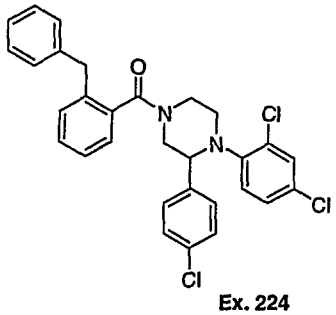
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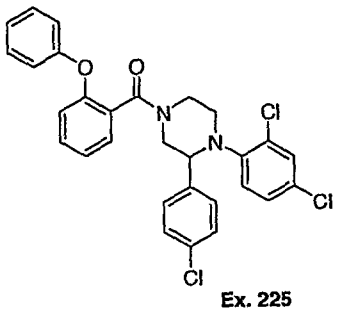
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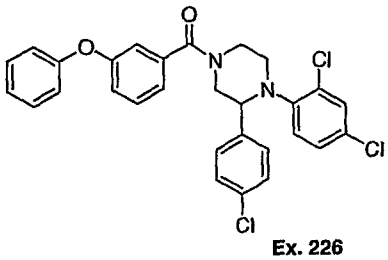


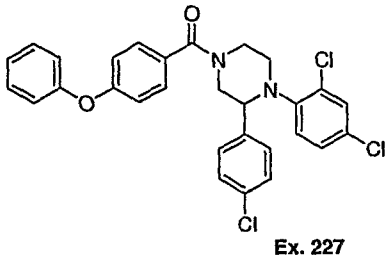
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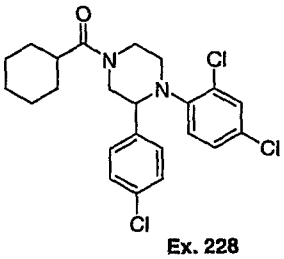


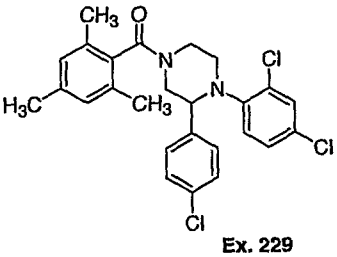
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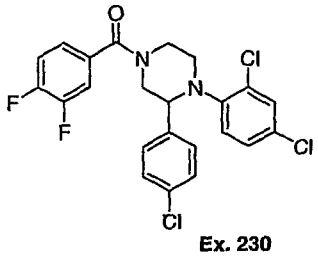

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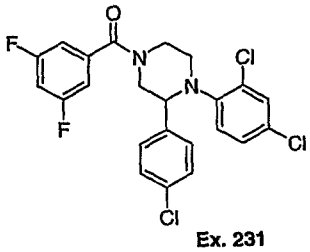

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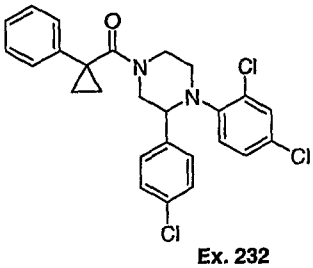

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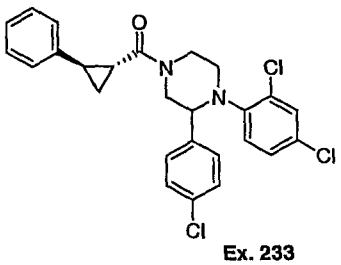

Ex. 228


Ex. 229


Ex. 230

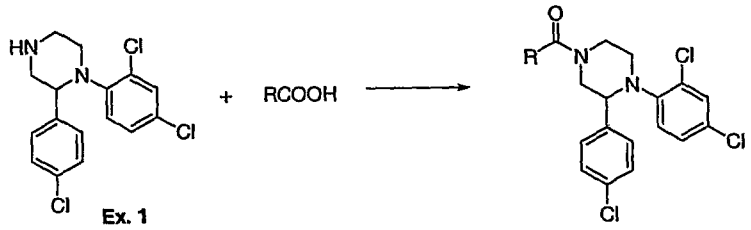

Ex. 231


Ex. 232


Ex. 233

Examples 155 – 170 and 172 – 233 were prepared using the following parallel synthetic method.

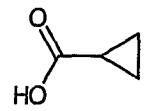
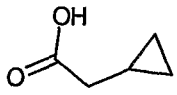
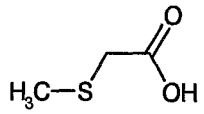
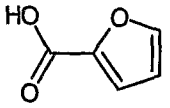
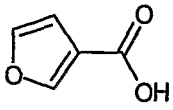
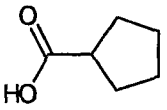
Scheme 5

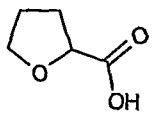
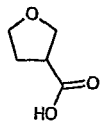
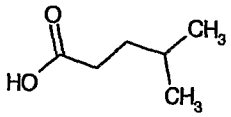
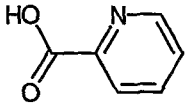
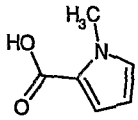
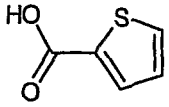
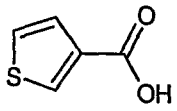
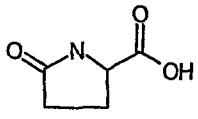

Ex. 1

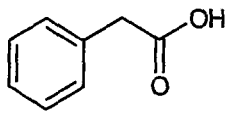
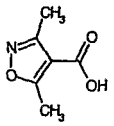
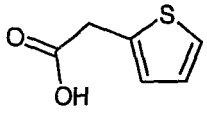
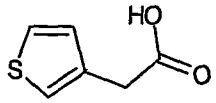
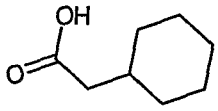
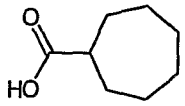
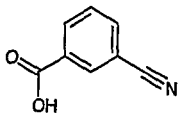
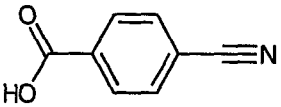
PS-EDC resin (i.e., polystyrene functionalized with EDC - 1-(dimethylaminopropyl)-3-ethylcarbodiimide - available from Polymer Laboratories) (0.082 g, 1.42 mmol) was added to 96 wells of a deep well polypropylene microtiter plate followed by a MeCN/THF (3:2) stock solution (1 mL) of piperazine **Example 1** (0.021 mmol) and HOBt (i.e., 1-hydroxybenzotriazole hydrate) (0.031 mmol). 1 M stock solutions of each of the individual acids (RCOOH) (Table III, below) (0.042 mL, 0.042 mmol) were added to the wells, which were then sealed and shaken at 25°C for 18 h. The solutions were filtered through a polypropylene frit into a second microtiter plate containing PS-Isocyanate resin (3 equiv., 0.07 mmol) and PS-Trisamine resin (8 equiv., 0.17 mmol). After the top plate was

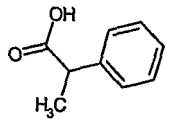
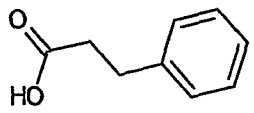
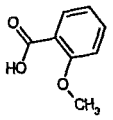
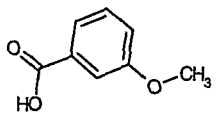
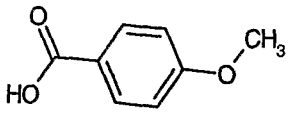
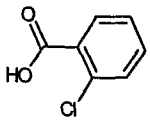
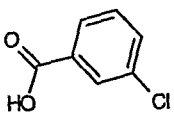
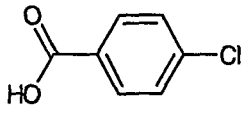
washed with MeCN (0.5 mL/well), the plate was removed, the bottom microtiter plate was sealed and then shaken at 25°C for 16 h. The solutions were filtered through a polypropylene frit into a 96-well collection plate. The wells of the top plate were then washed with MeCN (0.5 mL/well), and the plate removed. The resultant solutions in the collection plate were transferred into vials and the solvent removed *in vacuo* using a SPEEDVAC. The resulting samples were evaluated by LCMS and those that were >70% pure are shown above.

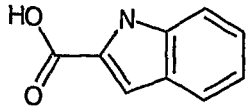
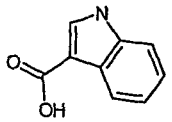
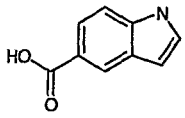
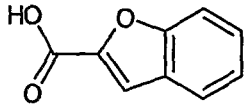
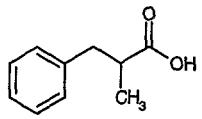
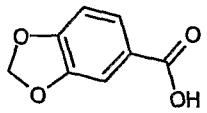
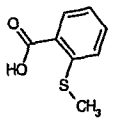
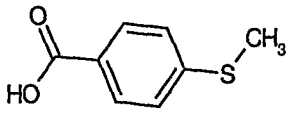
Table III: Carboxylic Acids Used to Prepare Examples 155 – 170 and 172 – 233

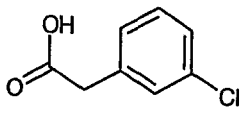
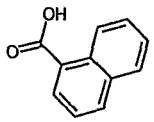
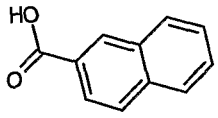
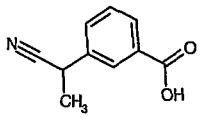
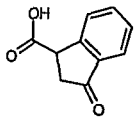
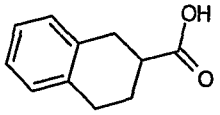
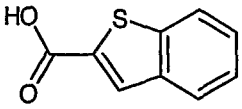
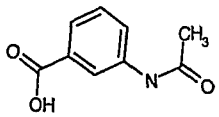
Example	Carboxylic Acid Structure
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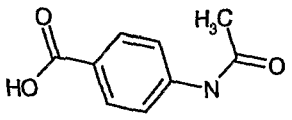
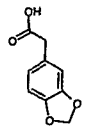
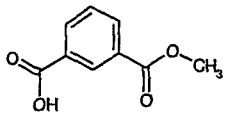
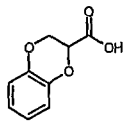
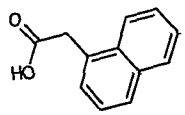
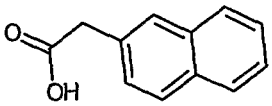
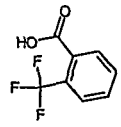
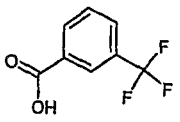
Example	Carboxylic Acid Structure
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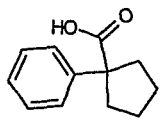
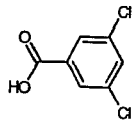
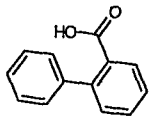
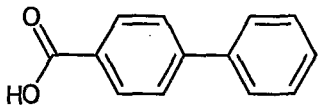
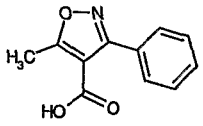
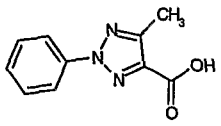
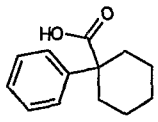
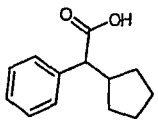
Example	Carboxylic Acid Structure
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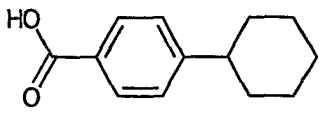
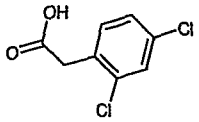
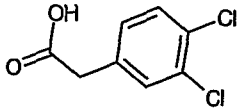
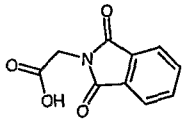
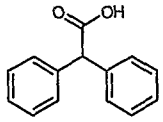
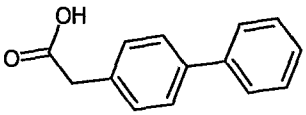
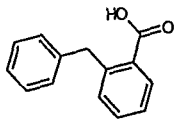
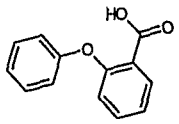
Example	Carboxylic Acid Structure
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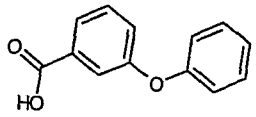
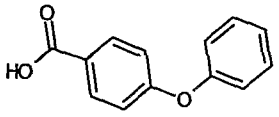
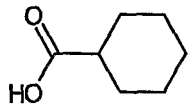
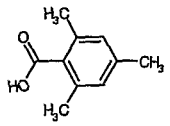
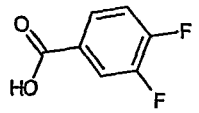
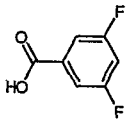
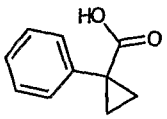
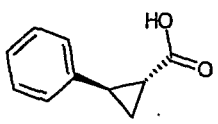
Example	Carboxylic Acid Structure
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Example	Carboxylic Acid Structure
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Example	Carboxylic Acid Structure
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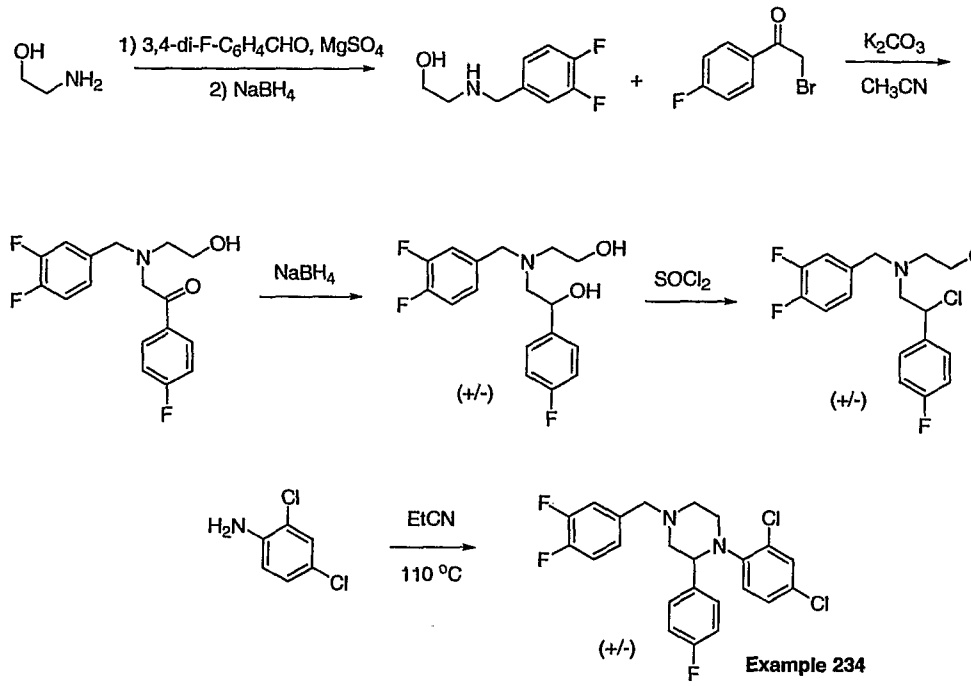
Example	Carboxylic Acid Structure
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Example	Carboxylic Acid Structure
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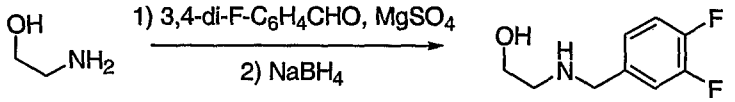
Example	Carboxylic Acid Structure
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Preparation of Examples 234-246

Scheme 6

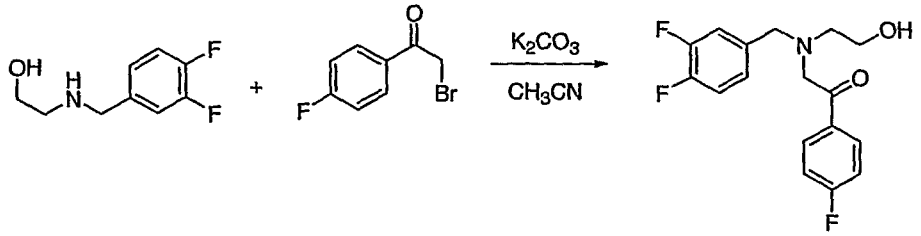


Step 1:



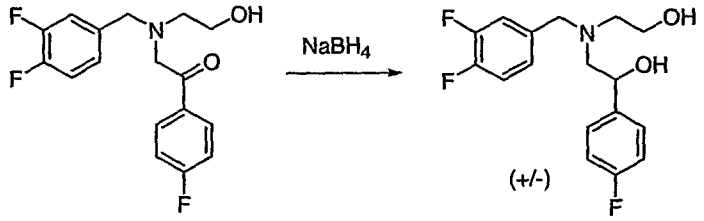
Ethanolamine (3 g), 3,4-difluorobenzaldehyde (7 g), and $MgSO_4$ (15 g) were taken up in CH_2Cl_2 and stirred at 25°C (4 h). The solution was filtered and concentrated, thereby providing the imine as a thick oil. The imine was taken up MeOH and cooled to 0°C. Sodium borohydride (1.9 g) was added in portions at 0°C. After the addition of $NaBH_4$, the reaction was warmed to 25°C and stirred for 0.5 h. The reaction mixture was quenched with 1 N $HCl_{(aq.)}$. The mixture was concentrated to remove MeOH. The residue was extracted with Et_2O. The aqueous layer was cooled to 0°C and made basic via addition of NaOH pellets (pH = 11-12). The aqueous layer was extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were dried ($MgSO_4$), filtered, and concentrated to furnish the amino-alcohol (6.5 g, 70 %) as a thick oil.

Step 2:



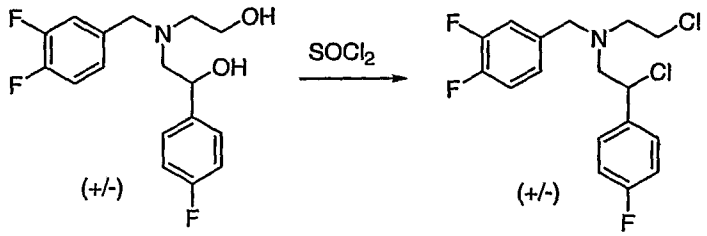
The amino-alcohol (390 mg), bromo-ketone (500 mg), and K_2CO_3 (380 mg) were taken up in CH_3CN and stirred at 25°C (19 h). The solution was concentrated. The residue was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The combined EtOAc layers were washed with brine, dried ($MgSO_4$), and filtered. Concentration gave a yellow oil. Purification via thin-layer preparative chromatography (10 % EtOAc in CH_2Cl_2, SiO_2) gave 610 mg (90 %) of the keto-alcohol as an oil.

Step 3:



The keto-alcohol (610 mg) was taken up in MeOH. Sodium borohydride (90 mg) was added, and the solution was stirred at 25°C (20 h). The solution was quenched with $NaHCO_{3(aq.)}$ and concentrated to remove MeOH. The mixture was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to afford 540 mg (88 %) of the diol as a colorless oil.

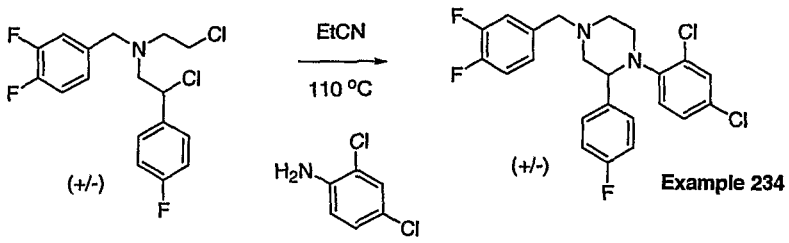
Step 4:



The diol (540 mg) and $SOCl_2$ (493 mg) were taken up in DCE and refluxed for 4 h (85°C). The solution was diluted with CH_2Cl_2 and washed with saturated $NaHCO_{3(aq.)}$. The aqueous layer was extracted with CH_2Cl_2. The combined

organic layers were dried ($MgSO_4$), filtered, and concentrated to give the di-chloro-amine as a yellow oil. This material was used without any further purification.

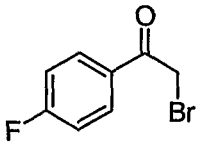
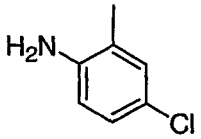
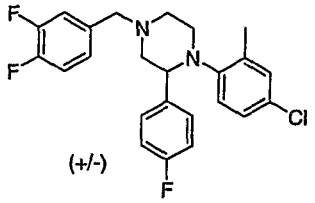
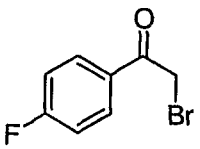
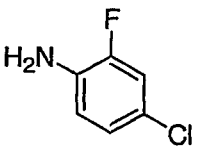
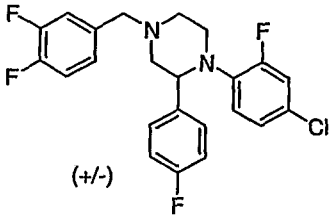
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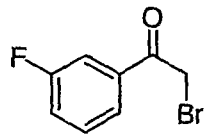
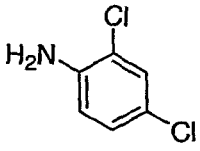
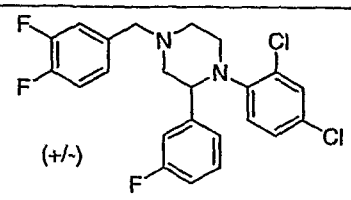
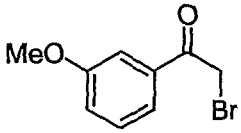
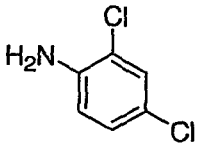
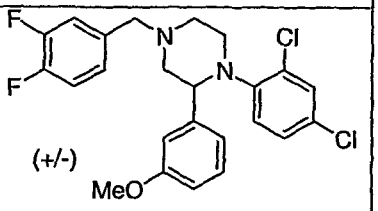
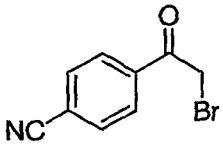
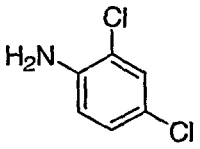
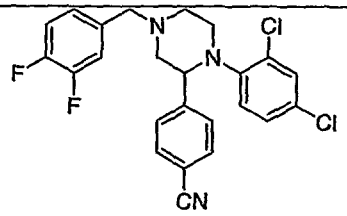
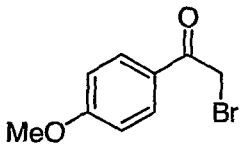
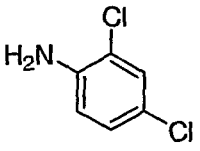
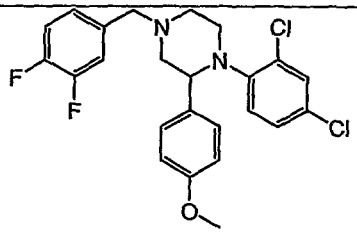
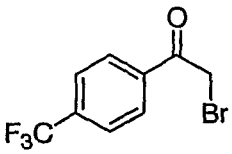
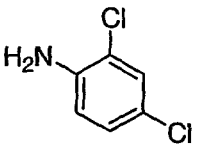
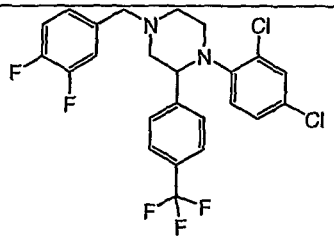
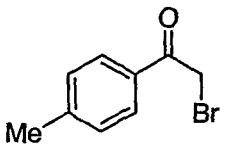
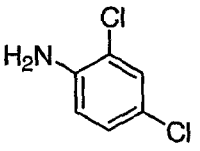
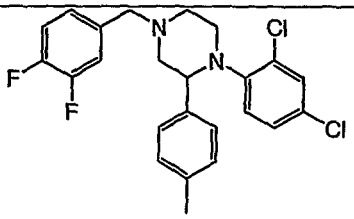
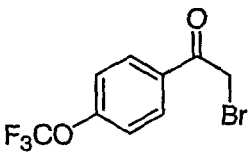
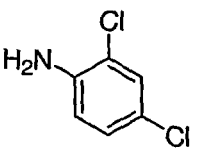
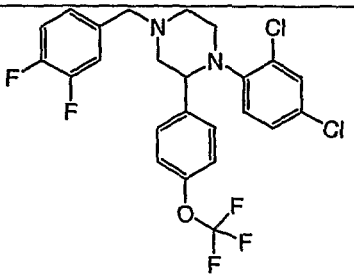
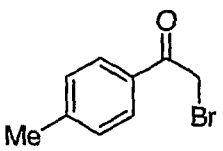
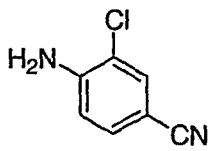
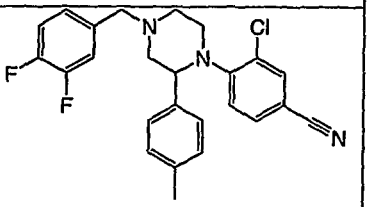


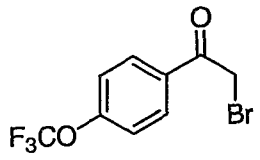
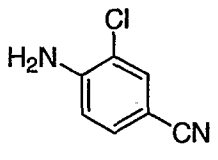
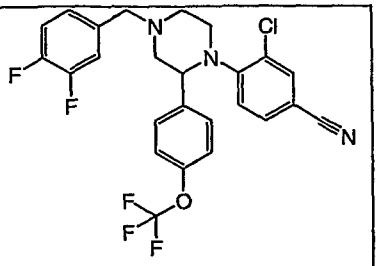
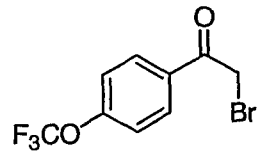
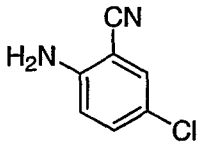
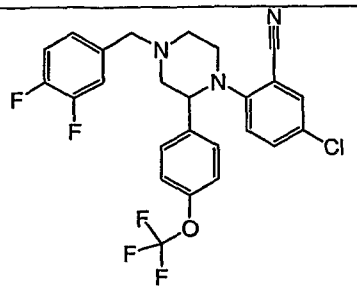
The dichloro-amine (200 mg) and 2,4-dichloroaniline (269 mg) were taken up in EtCN (i.e., propionitrile) and heated at 110°C (18 h). The solution was concentrated. The residue was partitioned between EtOAc and saturated $NaHCO_{3(aq.)}$. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). Filtration and concentration gave a yellow oil. Purification via thin-layer preparative chromatography (15% EtOAc in hexanes, SiO_2) gave 24 mg (10 %) of **Example 234** as a colorless oil.

The following Examples were prepared following the same procedures described in Scheme 6 using the appropriate reagents outlined in **Table IV**. The bromoketones of Table IV are commercially available, e.g. from Aldrich or Acros.

Table IV

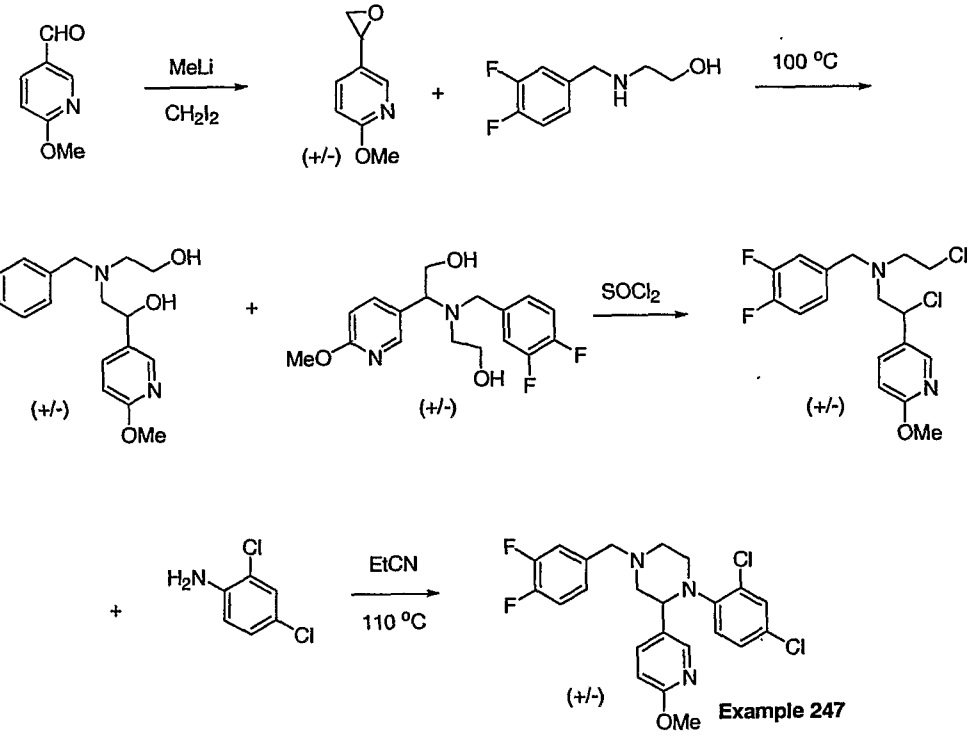
Example	Bromo-Ketone Step 2	Aniline Step 5	Structure
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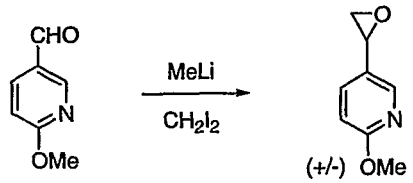
245			
246			

Preparation of Example 247

Scheme 7



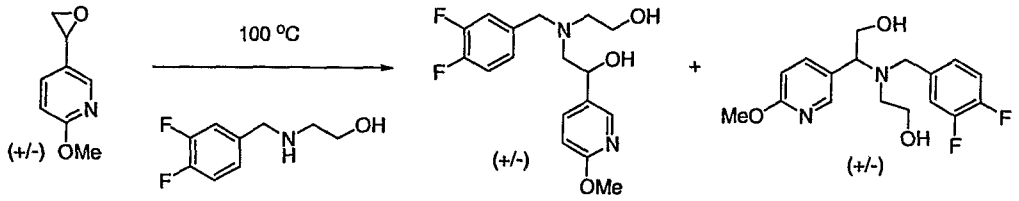
Step 1:



The aldehyde (2 g) and CH_2I_2 (1. 8 mL) were taken up in THF (40 mL) and cooled to 0°C. Methyllithium-LiBr complex (20 mL of a 1.5 M solution in Et_2O) was added dropwise to the reaction. The mixture was stirred at 0°C for 1 h and

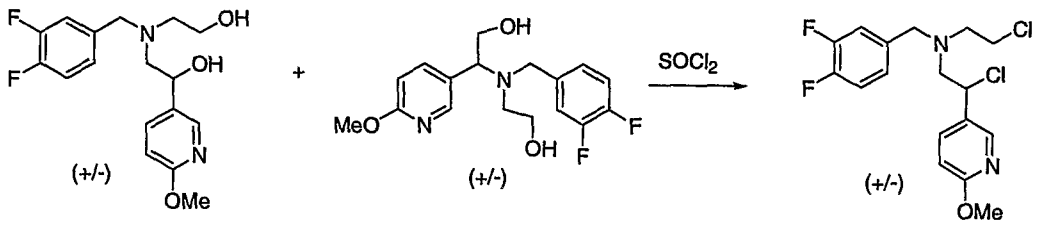
then at 25°C for 1 h. The mixture was poured into ice. The mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). Filtration and concentration gave the epoxide (2.2 g, 100 %) as a yellow oil.

Step 2:



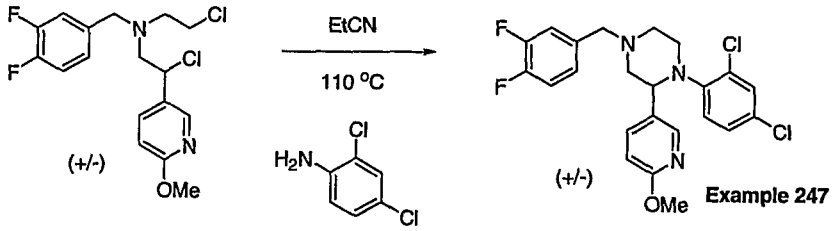
The epoxide (2.4 g) and amino-alcohol (2.97 g) were heated neat at 100°C (18 h). The residue was purified via flash chromatography (3/1 CH_2Cl_2/acetone, SiO_2) to give 3 g (58 %) of the diols as a mixture of isomers.

Step 3:



The mixture of diols (250 mg) and $SOCl_2$ (0.2 mL) were taken up in DCE and heated at 70°C (45 min). The solution was cooled and partitioned between CH_2Cl_2 and 1 N $NaOH_{(aq.)}$. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give 187 mg (67 %) of the dichloro-amine as a yellow oil. This material was used without any further purification.

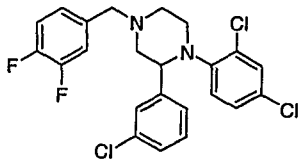
Step 4:



The dichloro-amine (187 mg), 2,4-dichloroaniline (242 mg), and NaI (50 mg) were taken up in EtCN and heated at 100°C (19 h). The solution was concentrated. The residue was partitioned between CH_2Cl_2 and 1 N $NaOH_{(aq.)}$. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The material contained the desired product and the uncyclized intermediate. The residue was taken up in

EtCN and NaI (50 mg) was added. The solution was heated at 100°C (18 h). The solution was worked up as before. Purification via thin-layer preparative chromatography (9/1 hexanes/acetone, SiO_2) gave 47 mg (20 %) of **Example 247** as a yellow oil.

Preparation of Example 248

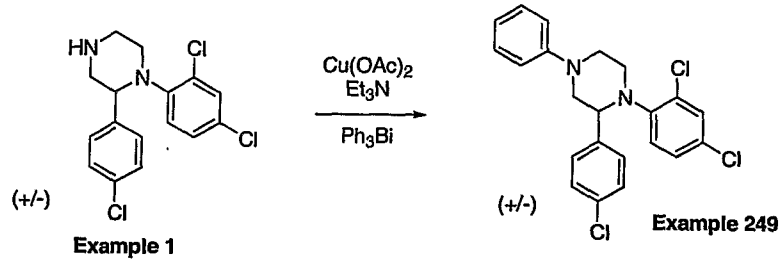


Example 248

The piperazine **Example 248** was prepared in a manner similar to the method used to prepare **Example 247** except that 3-chlorostyrene oxide (prepared as in step 1, Scheme 7) was used instead of the pyridyl epoxide in step 2 of Scheme 7, above.

Preparation of Example 249

Scheme 8

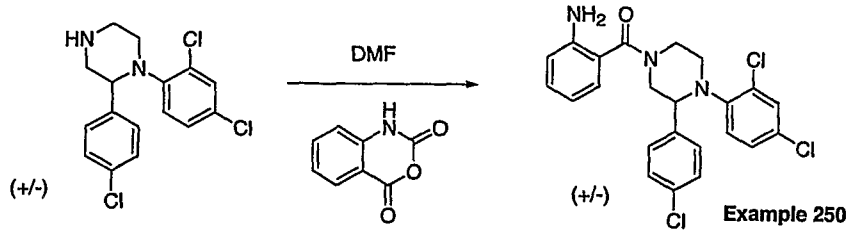


Example 1 **Example 249**

The NH piperazine **Example 1** (100 mg), Ph_3Bi (385 mg), $Cu(OAc)_2$ (106 mg), and Et_3N (0.12 mL) were taken up in toluene and heated at 115°C (18 h). The solution was filtered and concentrated. Purification via thin-layer preparative chromatography (10/1 hexanes/Et_2O, SiO_2) gave 78 mg (64 %) of **Example 249** as a white solid.

Preparation of Example 250

Scheme 9

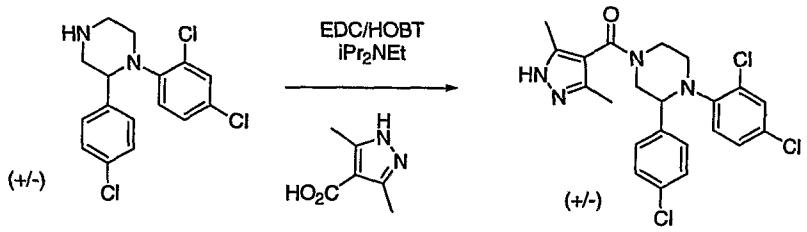


Example 1 **Example 250**

The NH piperazine **Example 1** (540 mg) and isatoic anhydride (410 mg) were stirred at 25°C (18 h). More isatoic anhydride was added (400 mg), and the mixture was stirred at 60°C (18 h). The solution was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). Filtration and concentration gave a yellow oil. Purification via flash chromatography (1/1 EtOAc/hexanes, SiO_2) gave 268 mg (37 %) of **Example 250** as a white solid.

Preparation of Examples 251-253

Scheme 10

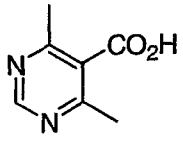
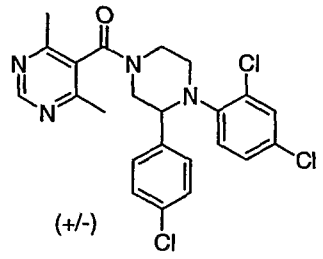
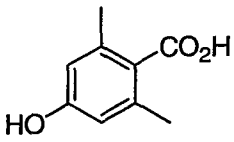
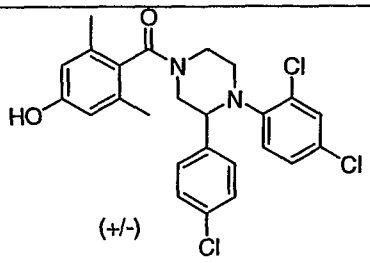


Example 1 **Example 251**

The NH piperazine **Example 1** (220 mg), EDC (i.e., 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride) (245 mg), HOBT (i.e., 1-hydroxybenzotriazole) (172 mg), acid (108 mg), and iPr_2NEt (206 mg) were taken up in CH_3CN and stirred at 25°C (18 h). The solution was partitioned between EtOAc and 1 N $NaOH_{(aq.)}$. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). Filtration and concentration gave a solid. The solid was triturated with Et_2O. The white solid was collected and dried to give 125 mg (42 %) of **Example 251.**

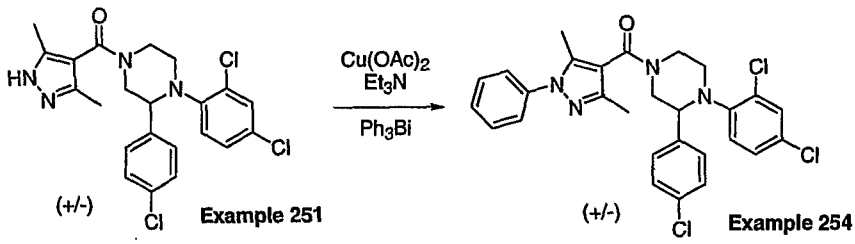
The following examples were prepared according to the procedure described in **Scheme 10** using the appropriate reagents. The carboxylic acids in **Table V** were prepared by methods described in WO 00/66558 or U.S. 6,391,865, both of which are herein incorporated by reference in their entirety.

Table V

Example	Carboxylic Acid	Structure
252		
253		

Preparation of Example 254

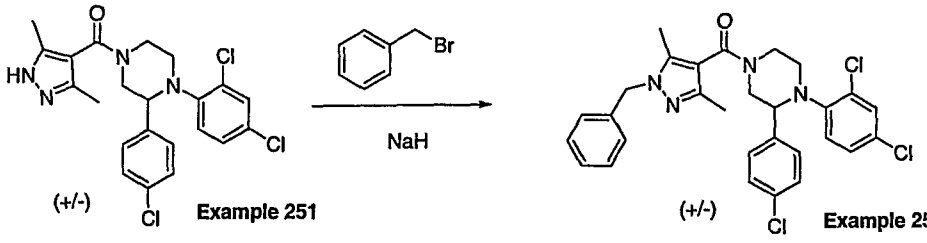
Scheme 11



Example 254 was prepared from **Example 251** using the procedure described above in **Scheme 8.**

Preparation of Example 255

Scheme 12

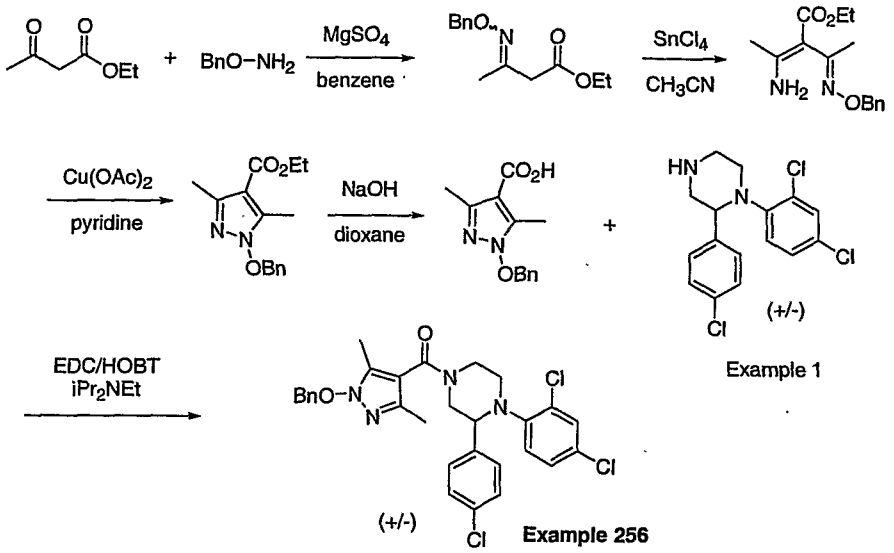


Example 251 (40 mg) was taken up in THF at 25°C. NaH(15 mg of a 60 wt % dispersion in oil) was added. After 10-15 minutes, benzyl bromide (30 mg)

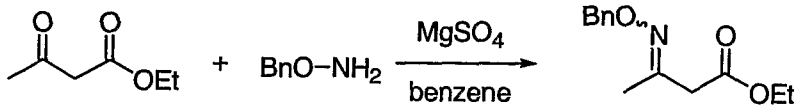
was added, and the solution was stirred at 25°C (18 h). The solution was concentrated, and the residue was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). Filtration and concentration gave a yellow oil. Purification via thin-layer preparative chromatography (5 % MeOH in CH_2Cl_2, SiO_2) gave 14 mg (29 %) of the N-benzyl analog **Example 255** as an oil.

Preparation of Example 256

Scheme 13

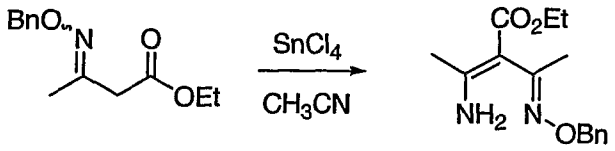


Step 1:



Ethyl acetoacetate (7.5 g, 58 mmol) and O-Benzyl hydroxyl amine (7.1 g, 58 mmol), and $MgSO_4$ (5 g) were taken up in benzene and stirred at 25°C for 24 hours. Filtration and concentration gave the oxime.

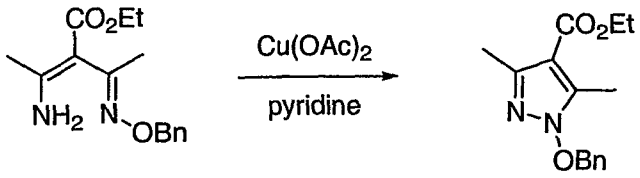
Step 2:



The oxime (1.0 g, 4.25 mmol) was taken up in CH_3CN (8 mL) and cooled to 0°C. $SnCl_4$ (4.3 ml, 1.0 M in CH_2Cl_2) was added dropwise to the solution at 0°C. The solution was stirred at 0°C for one hour. The solution was quenched with saturated Na_2CO_3 (aq.). The mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried (MgSO4). Filtration

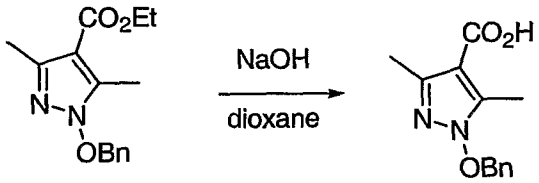
and concentration gave a colorless oil. Purification via flash chromatography (3/1 hexanes/EtOAc, SiO_2) gave 415 mg (35 %) of the enamide as a colorless oil.

Step 3:



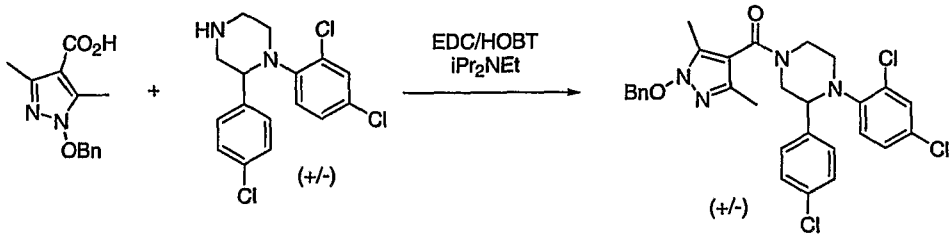
The enamide (415 mg, 1.5 mmol) and $Cu(OAc)_2$ (400 mg) were taken up in pyridine. The mixture was heated at 100°C for 4 hours. The solution was cooled and concentrated. The residue was partitioned between EtOAc and 10% $NH_4OH_{(aq.)}$. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). Filtration and concentration gave a brown oil. Purification via flash chromatography (9/1 hexanes/EtOAc, SiO_2) gave 330 mg (80%) of the pyrazole as a colorless oil.

Step 4:



The ester (545 mg, 1.99 mmol) and 1 N $NaOH_{(aq.)}$ was taken up in dioxane/EtOH. The solution was heated at 75°C for 24 hours. The solution was concentrated. The solution was acidified with 1 M $HCl_{(aq.)}$ (pH = 2-3). The resulting white precipitate was collected and dried under high vacuum. The acid was obtained as a white powder (314 mg, 64 %). ^1H NMR ($CDCl_3$, 400 MHz) δ 2.07 (s, 3H), 2.46 (s, 3 H), 5.26 (s, 2 H), 7.25 – 7.37 (m, 5 H). HRMS calc'd for $C_{13}H_{15}O_3N$ (MH^+) 247.1083; Found: 247.1089.

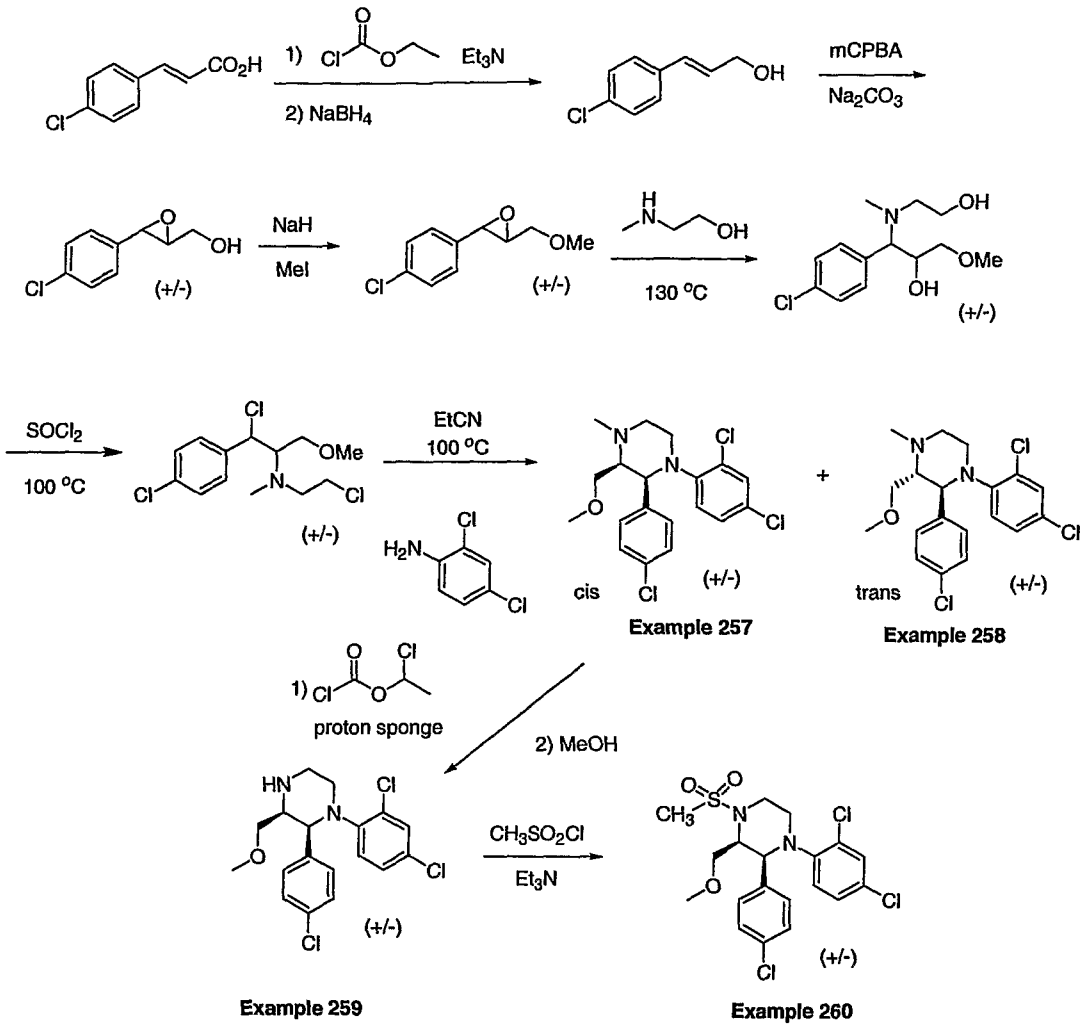
Step 5:



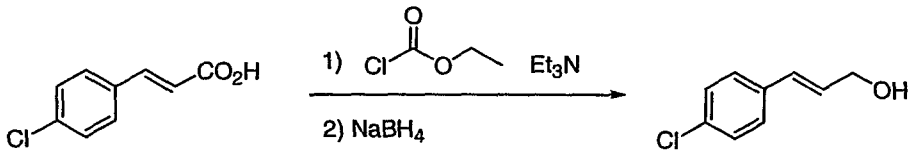
Example 256

Preparation of Examples 257-262

Scheme 14



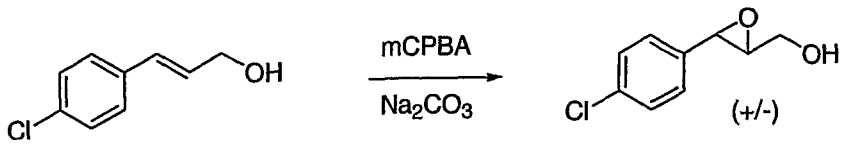
Step 1:



4-Chloro-cinnamic acid (30 g) and Et_3N (18.3 g) were taken up in THF (300 mL) at 0°C. Ethyl chloroformate (17.3 mL) was added dropwise at 0°C. The slurry was stirred at 0°C for one hour. The Et_3NHCl was removed by filtration, and the filtrate was filtered directly into cold water. The filtrate was washed with cold THF. The solution was placed into an ice-bath, and $NaBH_4$ (13.2 g) was added in portions (with gas evolution). The ice bath was removed, and the resulting solution was stirred at 25°C (16 h). The reaction was quenched with 2 M $HCl_{(aq.)}$. Diethyl ether was added, and the mixture was allowed to stir at 25°C for 3 hours. The aqueous layer was extracted with Et_2O. The combined organic

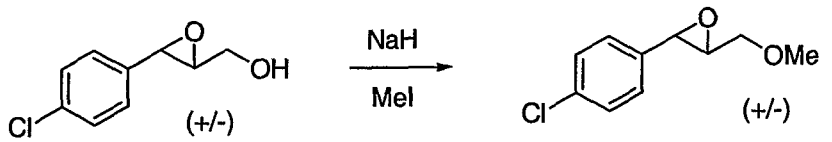
layers were washed with brine and dried ($MgSO_4$). Filtration and concentration gave a yellow oil. Purification via flash chromatography (15 % EtOAc in CH_2Cl_2, SiO_2) gave 23.5 grams (85 % yield) of the alcohol as an oil that slowly solidified.

Step 2:



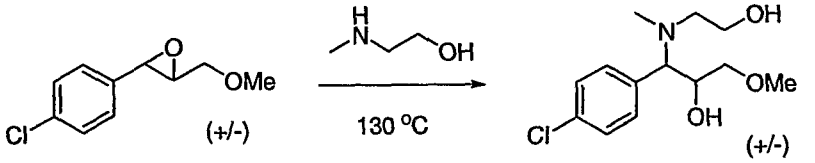
The alcohol (23.5 g) and Na_2CO_3 (17.8 g) were taken up in CH_2Cl_2 (300 mL) and cooled to 0°C (mechanical stirrer). m-CPBA (i.e. m-chloroperoxybenzoic acid) (38 grams) was added in portions at 0°C. The mixture was warmed to 25°C and stirred at that temp for 16 hours. The solution was washed with 10% $Na_2S_2O_{3(aq.)}$ and saturated $NaHCO_{3(aq.)}$. The organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification via flash chromatography (15 % EtOAc in CH_2Cl_2, SiO_2) gave 16.5 grams (64 %) of the racemic epoxide as an oil.

Step 3:



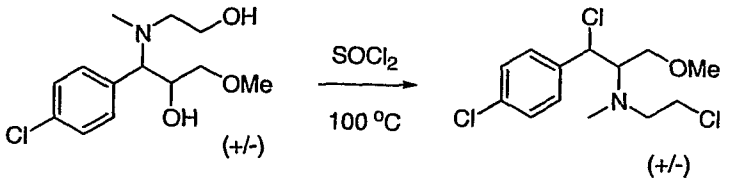
Sodium hydride (4.3 g) was suspended in DMF (100 mL) at -20°C. The epoxy-alcohol (16.5 g) was added, and the reaction mixture was stirred at -20°C for 0.5 h. Iodomethane (19 g) was added at -20°C, and the resulting reaction mixture was stirred at that temperature for 40 minutes. The reaction mixture was allowed to warm to 25°C and stir at that temperature for 3 hours. The reaction mixture was poured into a mixture of EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered which furnished the methyl ether (14.6 g, 82 %). This material was used without any further purification.

Step 4:



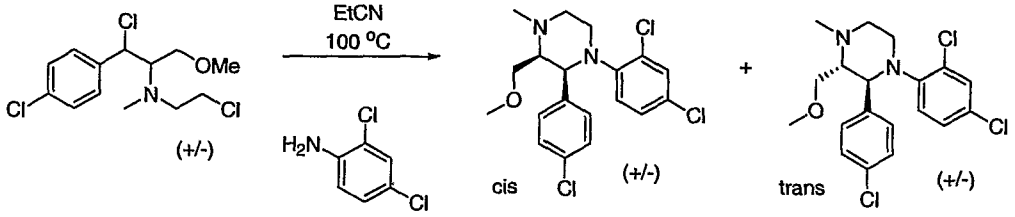
The methyl ether (14.6 g) and N-methyl-ethanolamine (5.5 g) were heated neat (130°C, 24 hours). Purification via flash chromatography (CH_2Cl_2, EtOAc, then 20 % MeOH in EtOAc, SiO_2) furnished the diol (15 g, 75 %) as a viscous oil.

Step 5:



The diol (7 g) and $SOCl_2$ (4.7 mL) were taken up in DCE (50 mL) and the solution was heated to 100°C (3 h). The solution was diluted with CH_2Cl_2 and slowly quenched with saturated $NaHCO_{3(aq.)}$. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to furnish the di-chloro amine (7.2 g, 91 %). This material was used without any further purification.

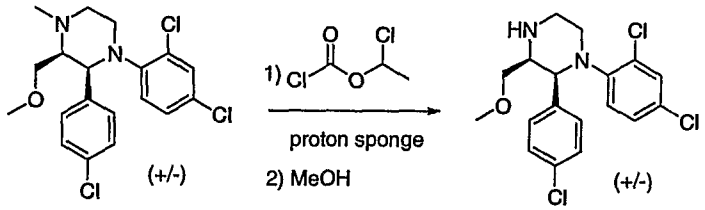
Step 6:



Example 257 Example 258

The dichloro-amine (7.2 g) and 2,4-dichloroaniline (11.5 g) were heated in propionitrile (100°C, 24 h). Solution was evaporated. The residue was partitioned between EtOAc and 2 N $NaOH_{(aq.)}$. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered. Purification via flash chromatography twice (2 % MeOH in CH_2Cl_2 then 10 % acetone in CH_2Cl_2, SiO_2) furnished the cis and trans piperazines, **Examples 257** and **258**, (8.05 grams, 85 % 10/1 cis/trans ratio) as thick oils that solidified on standing.

Step 7:

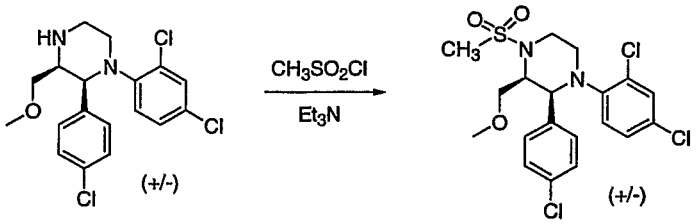


Example 257 Example 259

The cis-N-methyl piperazine **Example 257** (2 g), proton sponge (i.e., N,N,N',N'-tetramethylnaphthalene-1,8-diamine) (0.32 g), and 1-chloroethyl-chloroformate (1.4 g) were heated in DCE (90°C, 20 h). The solution was

concentrated. The residue was taken up in MeOH and heated at reflux for 7 hours. The solution was evaporated. The residue was partitioned between EtOAc and saturated $NaHCO_{3(aq.)}$. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). Filtration and concentration gave a yellow oil. Purification via flash chromatography (5 % MeOH in CH_2Cl_2, SiO_2) gave the NH piperazine **Example 259** (1.3 g, 67 %) as a yellow oil.

Step 8:

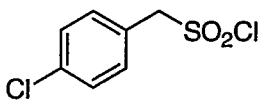
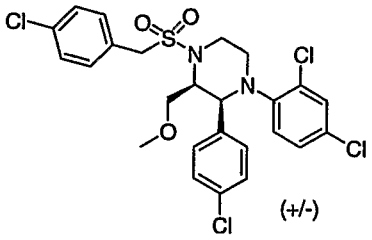


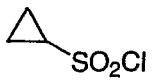
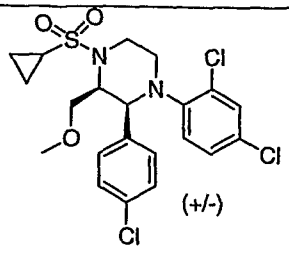
Example 259 Example 260

The NH-piperazine **Example 259** (100 mg) and Et_3N (34 mg) were taken up in CH_2Cl_2. $MeSO_2Cl$ (35 mg) was added, and the solution was stirred at 25°C (16 h). The solution was diluted with CH_2Cl_2 and washed with 1 N $NaOH_{(aq.)}$. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification via thin-layer preparative chromatography (2 % EtOAc in CH_2Cl_2, SiO_2) furnished the sulfonamide **Example 260** (77 mg, 64 %) as a yellow oil.

The following examples were prepared according to Step 8 in **Scheme 14** using the appropriate reagent (**Table VI**).

Table VI

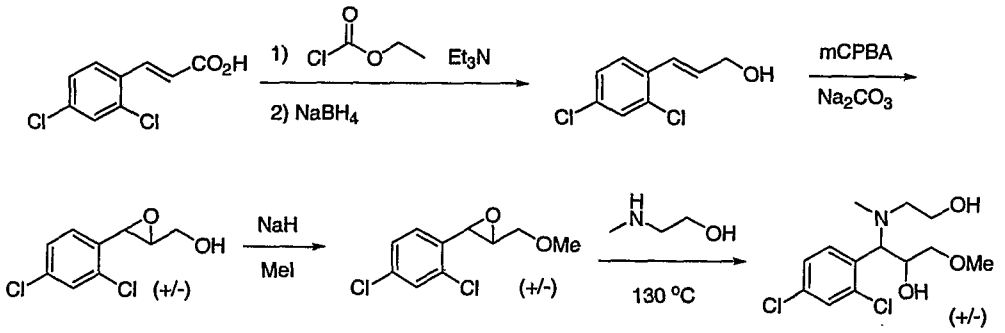
Example	Sulfonyl Chloride	Structure
261		

Example	Sulfonyl Chloride	Structure
262		

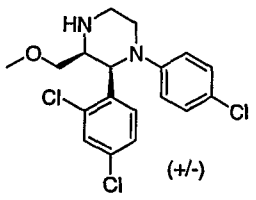
Preparation of Examples 263-266

Examples 263-266 were prepared using procedures similar to those described in **Scheme 14**, as shown in **Scheme 15.**

Scheme 15



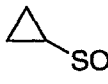
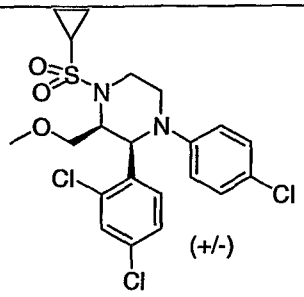
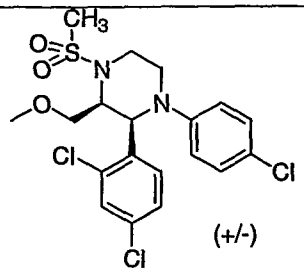
Example 263



Example 264

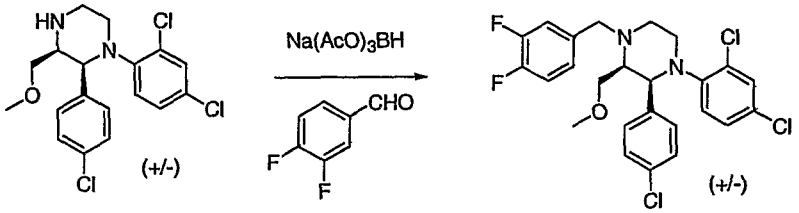
The Examples shown in **Table VII** were prepared from the appropriate sulfonyl chlorides and the piperazine **Example 264** shown in **Scheme 15** according to the procedure outlined in Step 8 of **Scheme 14.**

Table VII

Example	Sulfonyl Chloride Step 7	Structure
265		
266	CH_3SO_2Cl	

Preparation of Examples 267-270

Scheme 16

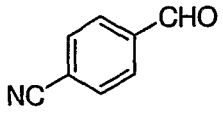
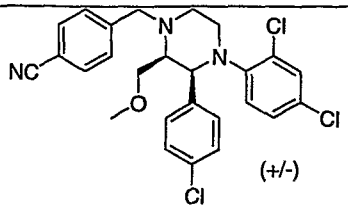


Example 259 Example 267

The NH-piperazine **Example 259** (100 mg), 3,4-difluorobenzaldehyde (40 mg), and $Na(AcO)_3BH$ (110 mg) were stirred in CH_2Cl_2 at 25°C (16 h). The solution was diluted with CH_2Cl_2 and washed with 1 N $NaOH_{(aq.)}$. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$). Filtration and concentration gave a yellow oil. Purification via preparative thin-layer chromatography (2 % EtOAc in CH_2Cl_2, SiO_2) furnished 44 mg (33 %) of **Example 267** as a colorless oil.

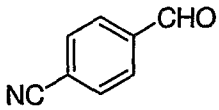
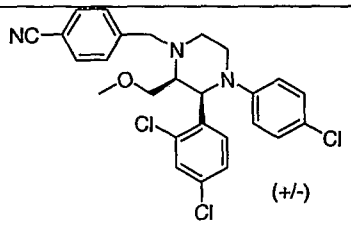
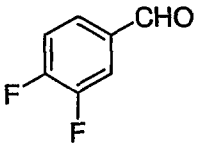
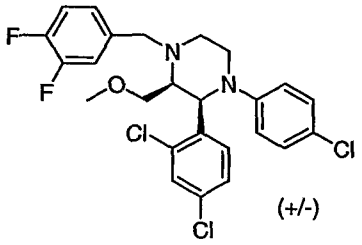
Following the same procedure as described in **Scheme 16** the following Example was prepared from the appropriate aldehyde.

Table VIII

Example	Aldehyde	Structure
268		

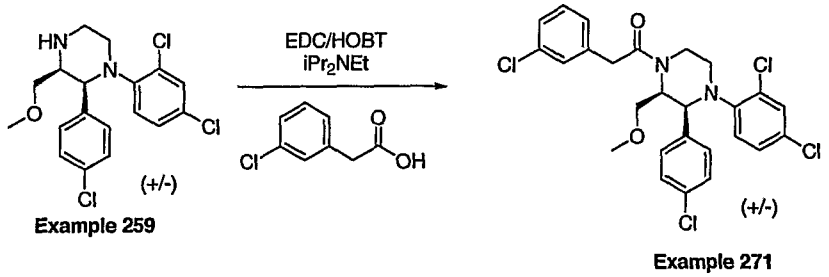
The following Examples were prepared using the piperazine **Example 264** of **Scheme 15** and the procedure of **Scheme 16**. The appropriate reagents are listed below (**Table IX**).

Table IX.

Example	Aldehyde	Structure
269		
270		

Preparation of Examples 271-272

Scheme 17



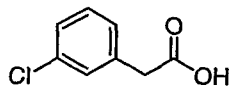
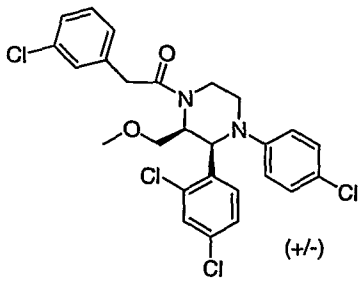
Example 259

Example 271

The NH-piperazine **Example 259** (100 mg), EDC (99 mg), HOBT (69 mg), iPrNEt (67 mg), and the acid (48 mg) were taken up in CH_2Cl_2. The solution was stirred at 25°C (16 h). The solution was diluted with CH_2Cl_2 and washed with 1 N $NaOH_{(aq.)}$. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification via thin-layer preparative chromatography (5 % EtOAc in CH_2Cl_2, SiO_2) furnished the amide **Example 271** (20 mg, 14 %) as a colorless oil.

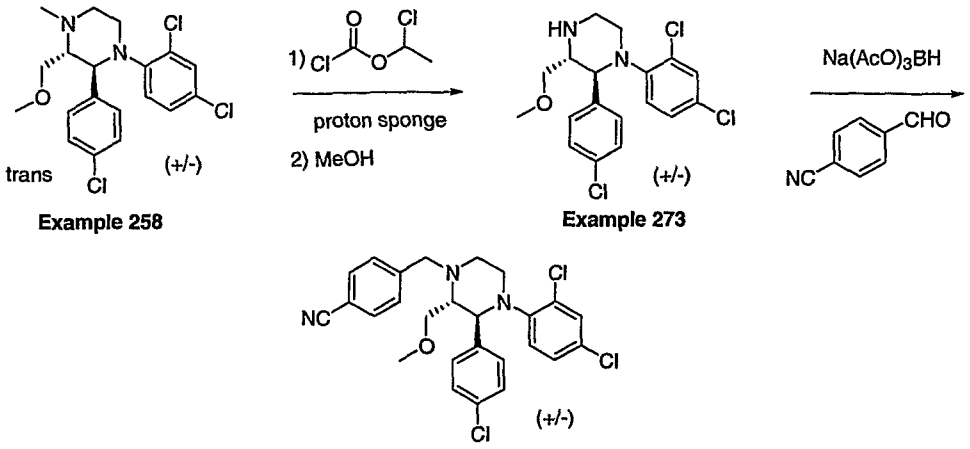
The following Example was prepared according to the procedures described in **Scheme 17** using the piperazine **Example 264** shown in **Scheme 15**. The appropriate reagent is listed below (**Table X**).

Table X

Example	Aldehyde Scheme 2	Structure
272		

Preparation of Examples 273-274

Scheme 18



Example 258

Example 273

Example 274

Step 1:

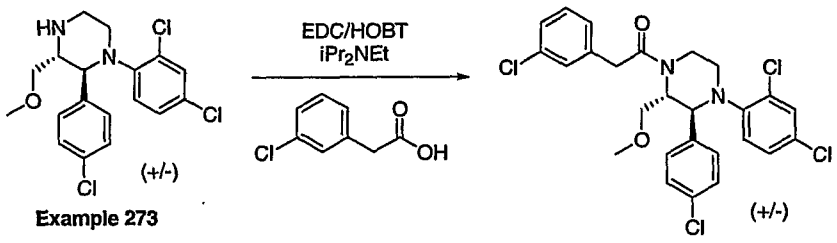
The trans-piperazine **Example 258** was converted into the NH piperazine **Example 273** as described previously in **Scheme 14**, Step 7.

Step 2:

The NH piperazine **Example 273** and 4-cyanobenzaldehyde were reacted following the procedure described in **Scheme 16** to provide **Example 274.**

Preparation of Example 275

Scheme 19



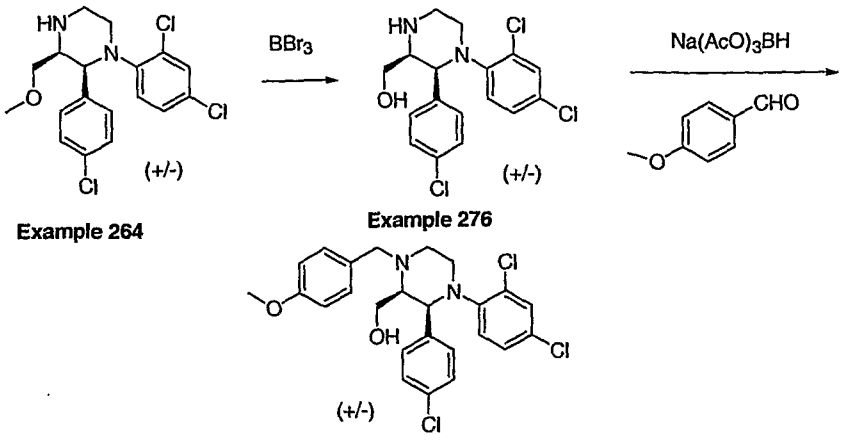
Example 273

Example 275

Example 275 was prepared using the procedure described for the corresponding cis isomer (**Scheme 17**).

Preparation of Examples 276-277

Scheme 20



Example 264

Example 276

Example 277

Step 1:

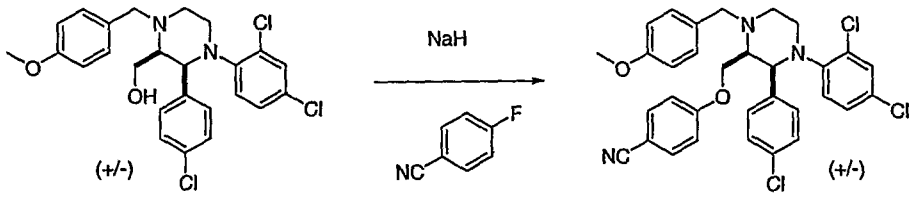
The NH-piperazine **Example 264** (108 mg) was taken up in CH_2Cl_2. Boron tribromide (0.13 mL) was added, and the resulting solution was stirred at 25°C (16 h). The solution was quenched with saturated $NaHCO_{3(aq.)}$. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude product **Example 276** was used without any further purification.

Step 2:

The amino-alcohol **Example 276** (460 mg) and 4-methoxybenzaldehyde were reacted according to the procedure described above (**Scheme 18**) to furnish **Example 277**.

Preparation of Example 278

Scheme 21



Example 277

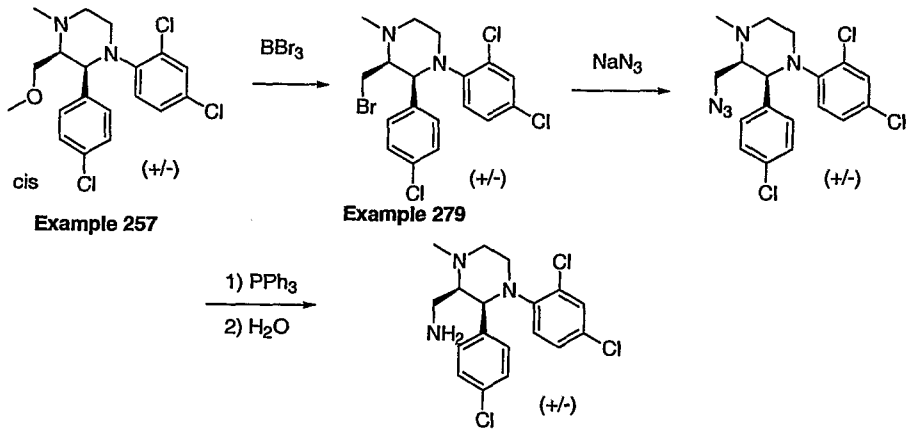
Example 278

The N-benzyl piperazine **Example 277** (160 mg) and NaH (46 mg, 60 wt % oil dispersion) were taken up in DMF. Then 4-fluoro-cyanobenzene (100 mg) was added, and the resulting solution was stirred at 25°C (4 h). The reaction was partitioned between EtOAc and water. The aqueous layers were extracted with

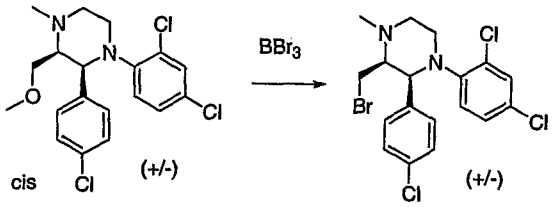
EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). Filtration and concentration gave a yellow oil. Purification via thin-layer preparative chromatography (5/1 hexanes/EtOAc, SiO_2) furnished 4 mg (2 %) of the ether **Example 278** as an oil.

Preparation of Examples 279-280

Scheme 22

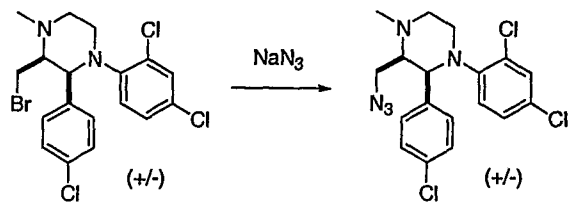


Step 1:



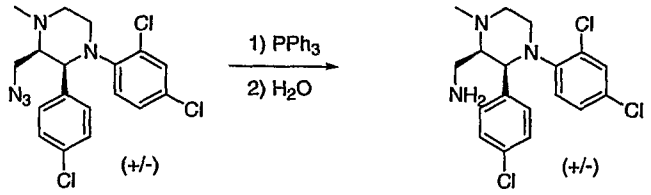
The piperazine **Example 257** (1.3 g) was taken up in CH_2Cl_2. Boron tribromide (17 mL of a 1.0 M solution in CH_2Cl_2) was added, and the solution was stirred at 25°C (16 h). The solution was diluted with CH_2Cl_2 and washed with saturated $NaHCO_{3(aq.)}$. The aqueous layers were extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification via flash chromatography (CH_2Cl_2 then 10 % EtOAc in CH_2Cl_2) furnished the bromide (1.1 g, 70 %).

Step 2:



The bromide (1.2 g) and NaN_3 (340 mg) were taken up in DMSO and stirred at 25°C (72 h). The solution was partitioned between Et_2O and water. The aqueous layers were extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to furnish the azide (1 g, 94 %).

Step 3:

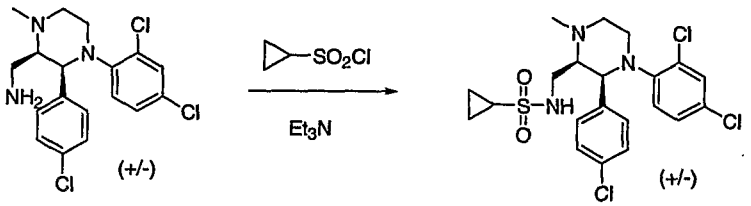


Example 280

The azide (500 mg) and PPh_3 (640 mg) were taken up in THF (4 mL) and heated at reflux (65°C) for 2 hours. Water (4 mL) was added, and the mixture was stirred at 40°C (16 h). The mixture was concentrated. The residue was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Purification via thin-layer preparative chromatography (4 % 7 N NH_3 in MeOH in CH_2Cl_2, SiO_2) furnished the amine (340 mg, 88 %) **Example 280**.

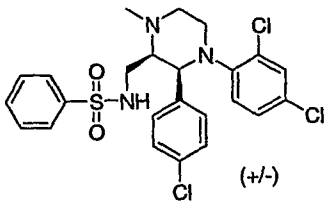
Preparation of Example 281-282

Scheme 23



Example 280 Example 281

The amine **Example 280** (160 mg) and Et_3N (95 mg) were taken up in CH_2Cl_2. Cyclopropylsulfonyl chloride (88 mg) was added, and the solution was stirred at 25°C (16 h). The solution was diluted with CH_2Cl_2 and washed with 1 N $NaOH_{(aq.)}$. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification via thin-layer preparative chromatography (8 % MeOH in CH_2Cl_2, SiO_2) furnished 138 mg (68 %) of **Example 281**.

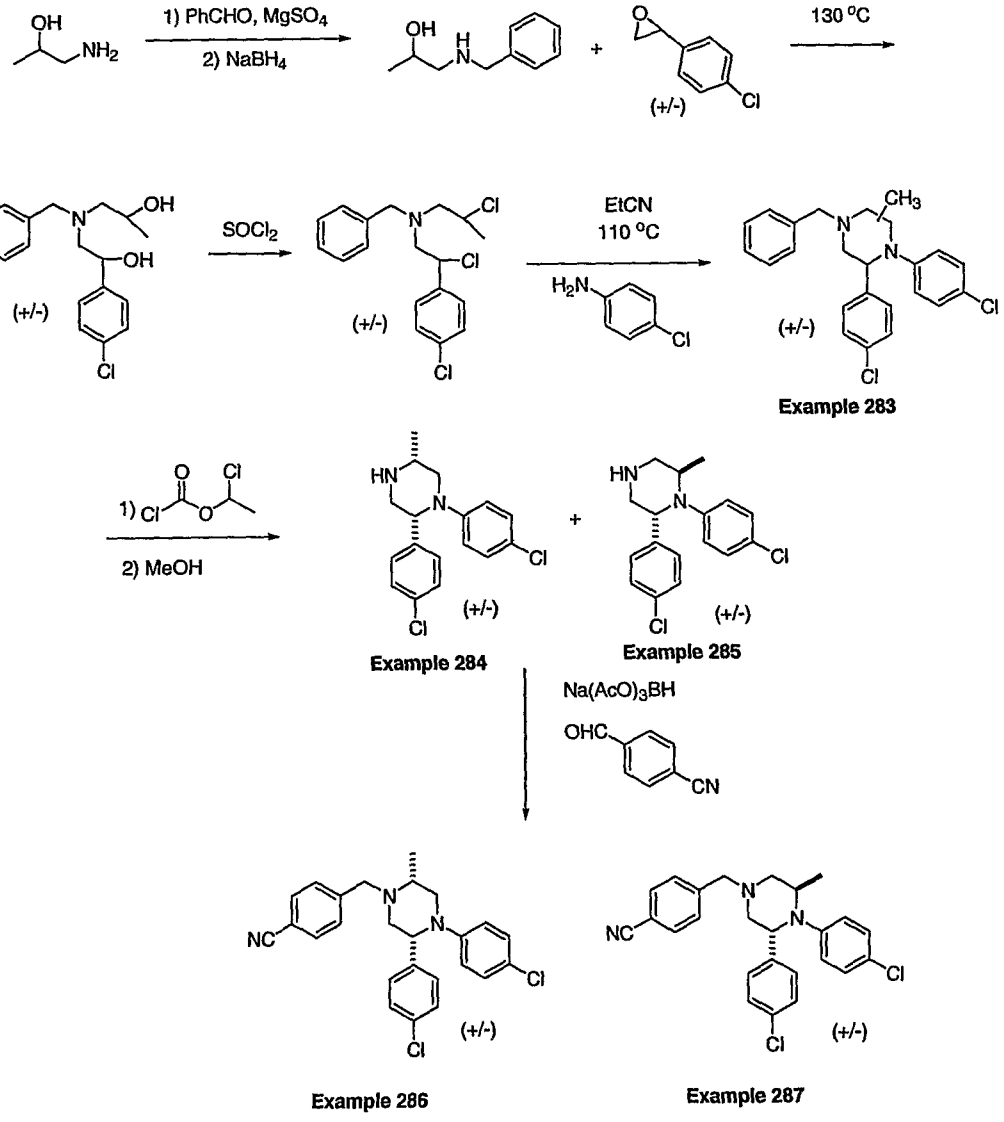


Example 282

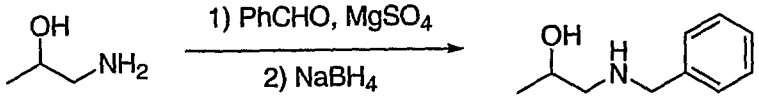
Example 282 was prepared according to the procedure described previously (**Scheme 23**) using benzenesulfonyl chloride.

Preparation of Examples 283-288

Scheme 24

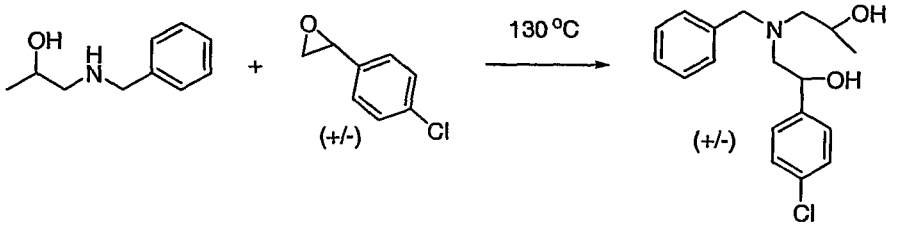


Step 1:



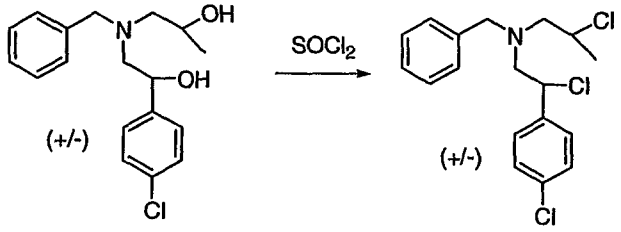
1-Amino-2-isopropanol (2 g), benzaldehyde (2.7 ml), and $MgSO_4$ (8 g) were taken up in CH_2Cl_2 and stirred at 25°C (16 h). The mixture was filtered and concentrated which furnished an imine as a solid. The imine was taken up in MeOH and $NaBH_4$ (1 g) was added in portions. The solution was stirred at 25°C (3 h). The solution was concentrated. The residue was partitioned between Et_2O and 1 M $HCl_{(aq.)}$. The aqueous acidic layer was extracted with Et_2O. The aqueous layer was cooled (0°C) and rendered basic via addition of NaOH pellets (pH = 11-12). The mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated which furnished the amino-alcohol as a thick oil (3.84 g, 87 %).

Step 2:



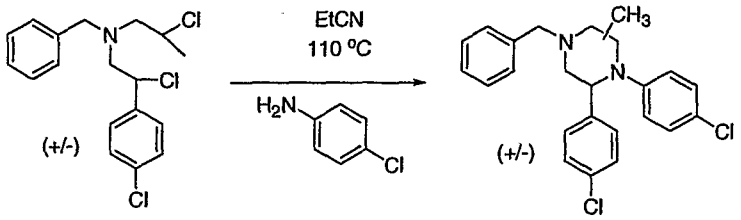
(+/-)-4-chloro-styrene oxide (2.8 mL) and the amino-alcohol (3.8 g) were heated neat at 130°C (18 h) which furnished the diol as a thick gum. The diol was used in Step 3 without any further purification.

Step 3:



The crude diol from Step 2 (23 mmol) was taken up in DCE (i.e., dichloroethane). Thionyl chloride (4.3 mL) was added, and the solution was heated at reflux (85°C, 3.5 h). The solution was cooled and washed with 1 N $NaOH_{(aq.)}$. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated which furnished the dichloro-amine as a thick gum. This material was used without any further purification in Step 4.

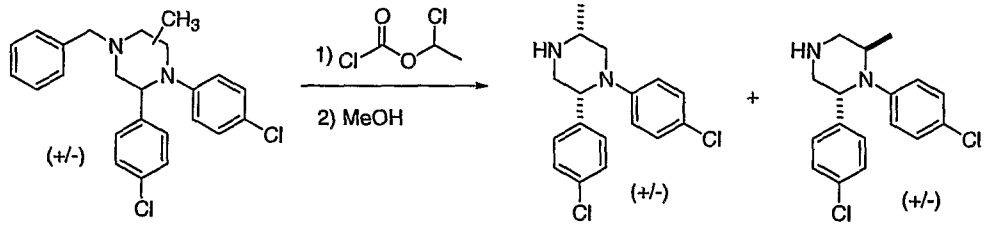
Step 4:



Example 283

The dichloro-amine (7.9 g) and 4-chloroaniline (1.2 g) were taken up in EtCN and heated at 110°C (19 h). The solution was concentrated and partitioned between CH_2Cl_2 and 1 N $NaOH_{(aq.)}$. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification via flash chromatography (9/1 hexanes/Et_2O, SiO_2) gave 1.2 g (35 %) of the piperazine **Example 283** as a mixture of isomers.

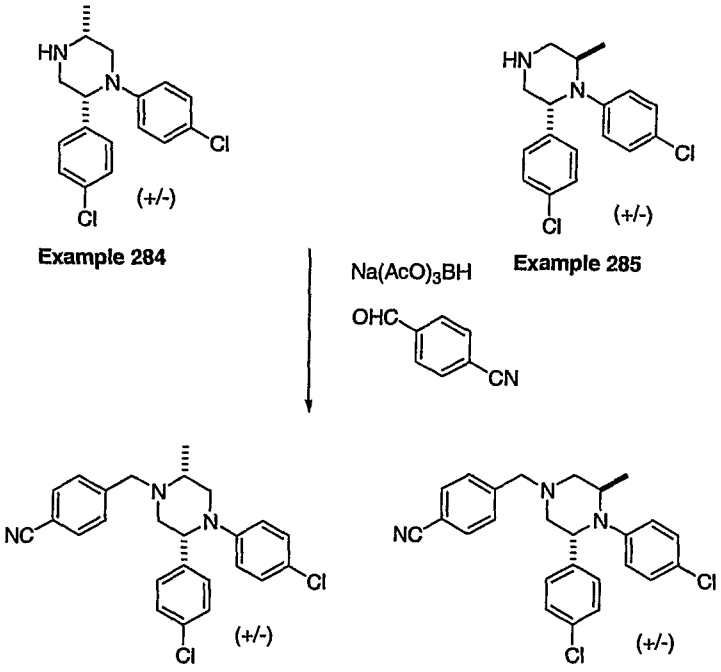
Step 5:



Example 283 Example 284 Example 285

The piperazine **Example 283** (1 g) and 1-chloroethyl-chloroformate ((0.3 mL) were taken up in DCE and heated (85°C, 18 h). The solution was concentrated. The residue was taken up in MeOH and heated at reflux (80°C, 3.5 h). The solution was concentrated. The residue was partitioned between CH_2Cl_2 and 1 N $NaOH_{(aq.)}$. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$). Filtration and concentration gave a yellow oil. Purification via thin-layer preparative chromatography (9/1 CH_2Cl_2/MeOH, SiO_2) gave 100 mg of the 2,5-cis isomer **Example 284** and 50 mg of the 2,6-trans isomer **Example 285**.

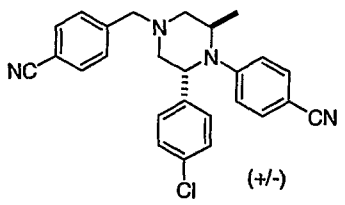
Step 6:



Example 284 Example 285

Example 286 Example 287

The 2,5-cis-NH piperazine **Example 284** (100 mg), 4-cyanobenzaldehyde (48 mg), and $Na(AcO)_3BH$ (127 mg) were taken up in CH_2Cl_2 and stirred at 25°C (19 h). The solution was diluted with CH_2Cl_2 and washed with 1 N $NaOH_{(aq.)}$. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification via thin-layer preparative chromatography (4/1 hexanes/EtOAc, SiO_2) gave 49 mg (37 %) of **Example 286** as a colorless oil. Following the same procedure, the 2,6-trans-NH piperazine **Example 285** was converted into **Example 287**.

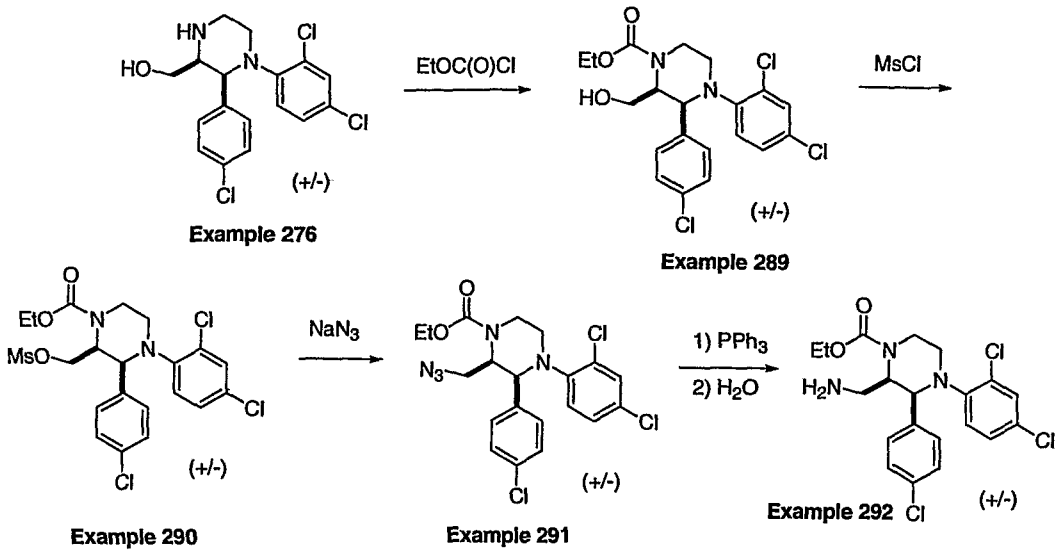


Example 288

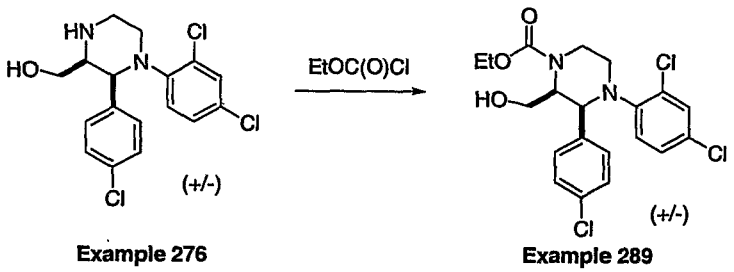
Example 288 was prepared according to conditions described for **Example 287** using 4-cyano-aniline in Step 4 of **Scheme 24**.

Preparation of Examples 289-294

Scheme 25

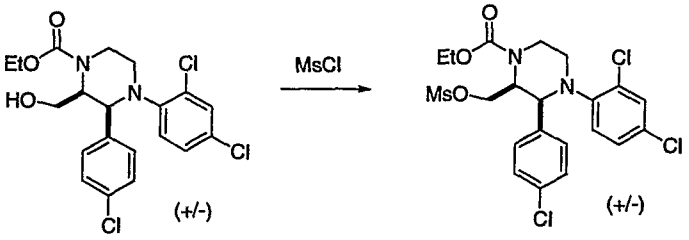


Step 1:



The amino-alcohol **Example 276** from **Scheme 20** (400 mg) and iPr_2NEt (170 mg) were taken up in CH_2Cl_2. Ethyl chloroformate (130 mg) was added, and the solution was stirred at 25 °C for 30 minutes. The solution was diluted with CH_2Cl_2 and washed with saturated $NaHCO_{3\,(aq.)}$. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification via thin-layer preparative chromatography (15 % EtOAc in CH_2Cl_2, SiO_2) furnished the carbamate **Example 289.**

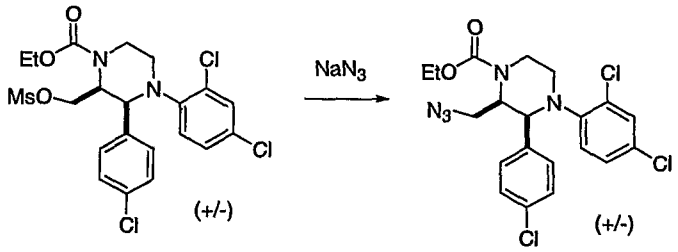
Step 2:



Example 289 Example 290

The carbamate **Example 289** and Et_3N (4 eq.) were taken up in CH_2Cl_2. Methanesulfonyl chloride (4 eq.) was added at 25°C. The solution was stirred at 25°C for 15 minutes. The solution was diluted with CH_2Cl_2 and washed with saturated $NaHCO_{3\,(aq.)}$. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$). Filtration and concentration gave the mesylate **Example 290**, which was used without further purification in Step 3.

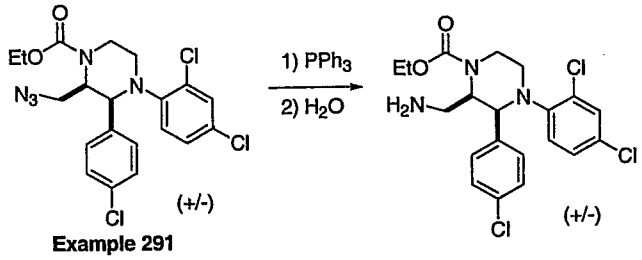
Step 3:



Example 290 Example 291

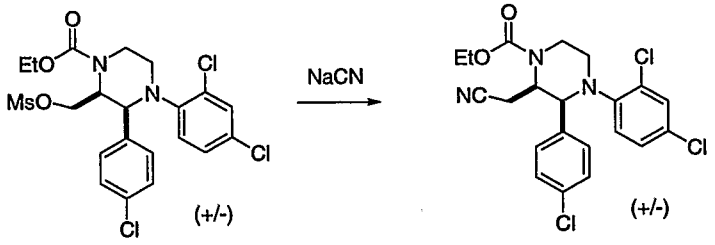
The mesylate **Example 290** from above and sodium azide (130 mg) were taken up in acetone and heated at reflux (60 °C, 18 h). More sodium azide was added (500 mg), and the reaction was heated for an additional 18 h (60°C). The solution was concentrated, and the residue was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). Filtration and concentration gave the azide **Example 291** as a yellow oil (320 mg. 64 % from the amino-alcohol).

Step 4:



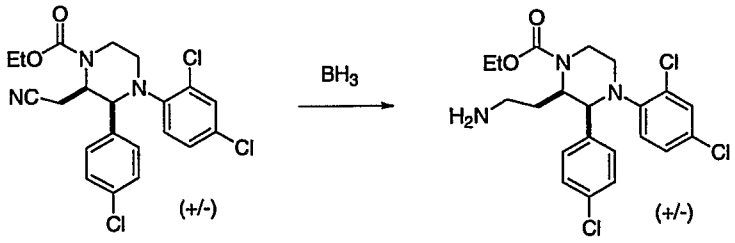
Example 291 Example 292

The azide **Example 291** (320 mg) and PPh_3 (220 mg) were taken up in THF and heated at 65°C (5 h). Water (2 mL) was added, and the solution was heated at reflux (65°C, 18 h). The solution was concentrated, and the residue was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). Filtration and concentration gave the crude amine. Purification via thin-layer preparative chromatography (10 % MeOH in CH_2Cl_2, SiO_2) gave 210 mg (70 %) of the amine **Example 292**.



Example 290 Example 293

The mesylate **Example 290** from **Scheme 25** (300 mg) and NaCN (43 mg) were taken up in DMF and heated at 90°C (18 h). The solution was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). Filtration and concentration gave a yellow oil. Purification via thin-layer preparative chromatography (5 % EtOAc in CH_2Cl_2, SiO_2) gave the cyano-carbamate **Example 293** (130 mg, 50 %) as a white solid.

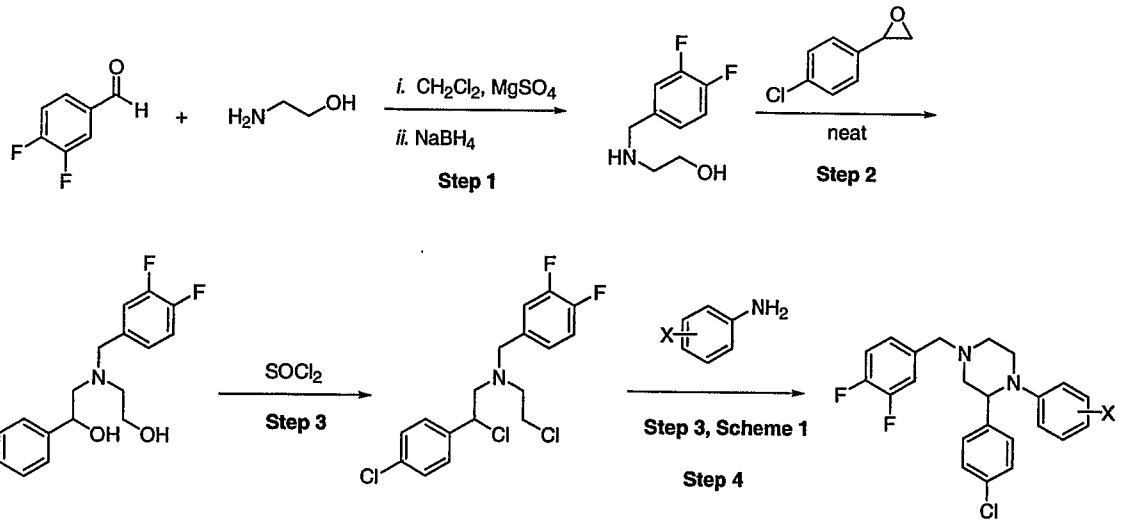


Example 293 Example 294

The cyano-carbamate **Example 293** (120 mg) was taken up in THF. Borane-THF (0.5 mL of a 1.0 M solution in THF) was added, and the solution was heated to reflux (70°C, 5 h). Additional BH_3 (2.2 mL of a 1.0 M solution in THF) was added to the reaction, and the reaction was heated at reflux (70°C, 18 h). The solution was cooled and quenched with 1 M $HCl_{(aq.)}$. The solution was stirred at 25°C (20 minutes) and then rendered basic with 1 N $NaOH_{(aq.)}$. The mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). Filtration and concentration gave a yellow oil. Purification via thin-layer preparative chromatography (15 % MeOH in CH_2Cl_2, SiO_2) gave 100 mg (83 %) of the amine as a yellow oil.

Preparation of Examples 295-301

Scheme 26



Step 1:

To 3,4-difluorobenzaldehyde (15.0 g, 105 mmol) in CH_2Cl_2 (100 mL) was added ethanolamine (6.4 g, 105 mmol) and $MgSO_4$ (32 g). The reaction mixture was stirred for 20 h at room temperature. The reaction was filtered and concentrated *in vacuo*. The residue was taken up into MeOH (100 mL), cooled to 0°C, and $NaBH_4$ was added. The reaction mixture was stirred for 2 h allowing the cold bath to warm to room temperature. The reaction was then concentrated *in vacuo* and 3N HCl was added. The mixture was extracted with ether. The aqueous layer was then rendered basic with 3N NaOH and then extracted with EtOAc. The EtOAc extractions were combined and washed with water and brine.

The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide the corresponding amino-alcohol (14.0 g, 75 mmol).

Step 2:

To the amino-alcohol from step 1 (7.0 g, 37 mmol) was added 4-chlorostryrene oxide (5.0 mL, 41.5 mmol). The neat reaction mixture was warmed to 130°C and stirred for 20 h, cooled to room temperature and purified by silica gel chromatography (3-5% $MeOH/CH_2Cl_2$) to provide the corresponding amino-diol (12.6 g, 36.8 mmol).

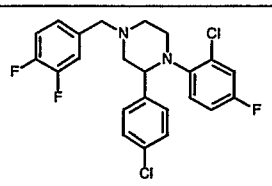
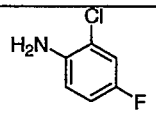
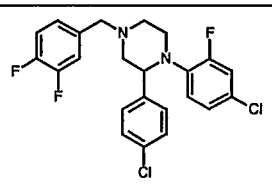
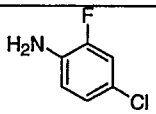
Step 3:

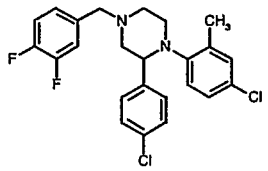
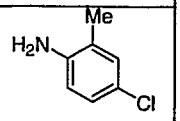
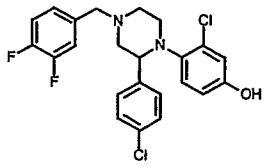
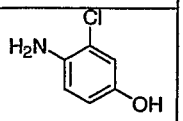
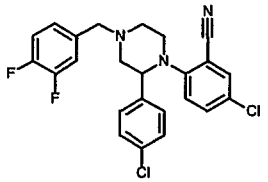
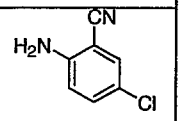
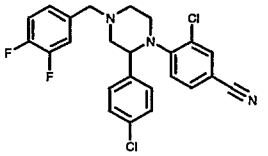
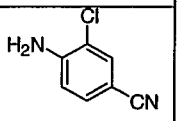
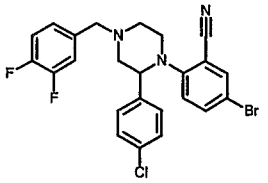
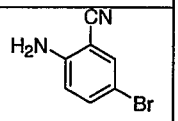
To the amino-diol prepared in step 2 (12.6 g, 37 mmol) in $CHCl_3$ (122 mL) at 0°C was added $SOCl_2$ (61 mL) dropwise. After addition, the reaction mixture was warmed to reflux and stirred for 2h. The reaction was concentrated *in vacuo*. The residue was taken up into CH_2Cl_2 and stirred vigorously with saturated $NaHCO_3$. The organic layer was washed with brine and dried ($MgSO_4$). The organic layer was filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (10% EtOAc/hexane) to provide the corresponding amino-dichloride (10.0 g, 26 mmol).

Step 4:

Following the procedure of step 3 in Scheme 1, the anilines listed in Table XI were used in place of 2,4-dichloroaniline to provide the desired diarylpiperazine compound.

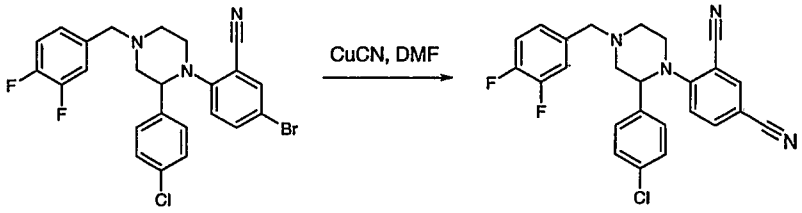
Table XI

Example #	Example Structure	aniline
295		
296		

Example #	Example Structure	aniline
297		
298		
299		
300		
301		

Preparation of Example 302

Scheme 27

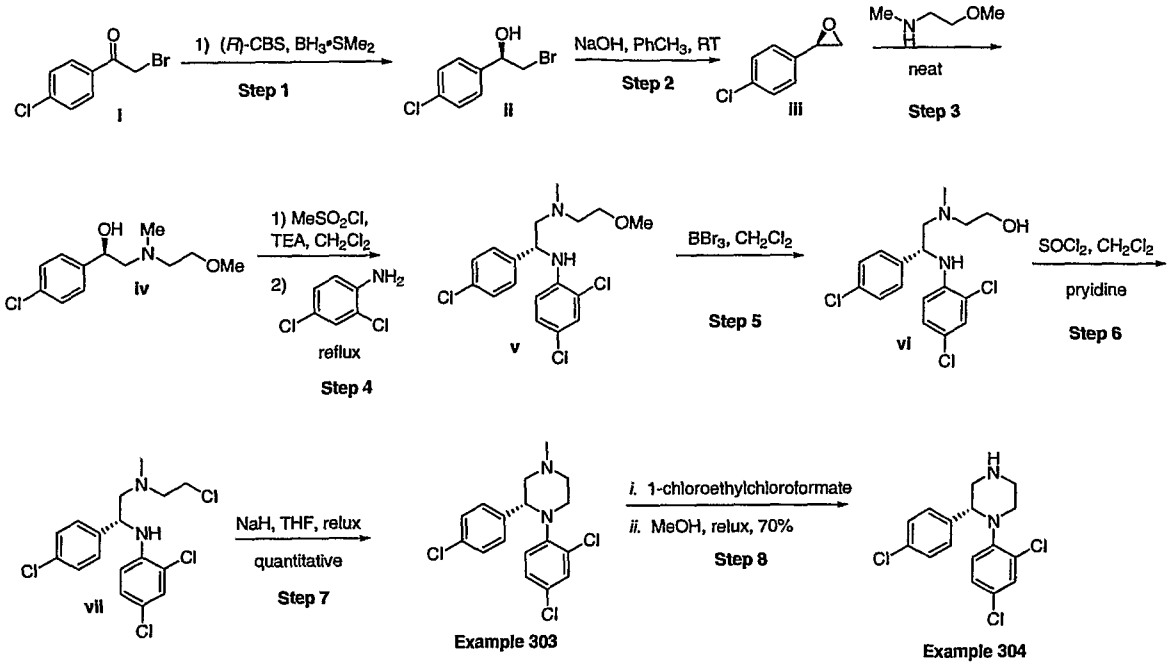


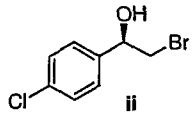
Example 301 Example 302

Example 302 was prepared using the procedure of step 1, Scheme 29 used to prepare **Example 308.**

Preparation of Examples 303-304

Scheme 28

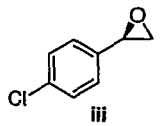




ii

Step 1:

To 2-bromo-4'-chloroacetophenone (233 g, 1000 mmol) in THF (1 L) at 0°C was added (*R*)-2-methyl-CBS-oxazaborolidine (available from Aldrich) (1.0 M in THF, 200 mL, 200 mmol) through an addition funnel. BH_3•SMe_2 (2.0 M in THF, 300 mL, 600 mL) was added slowly over 25 min. The reaction was stirred at room temperature for 2 h. The reaction was cooled to 0°C, and MeOH (200 mL) was added slowly (with gas evolution). The resulting solution was concentrated *in vacuo* and then diluted with CH_2Cl_2 (3.5 L). The organic layer was washed with 1N HCl, water, and brine, then dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide bromo-alcohol **ii** as an oil that solidified on standing (237 g).

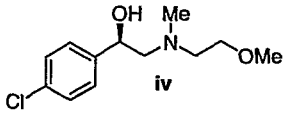


iii

Step 2:

The bromo-alcohol **ii** from step 2 (237 g, 1000 mmol) was dissolved in toluene (3.5 L) and 3N NaOH (3.5 L) was added. The reaction was stirred vigorously at room temperature for 3h. The organic layer was washed with water

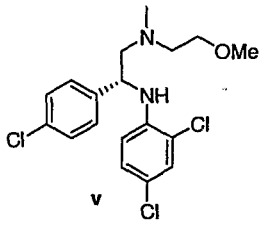
and brine and dried ($MgSO_4$), then filtered and concentrated *in vacuo* to provide the epoxide **iii** (154 g, 1000 mmol). The ee (i.e., enantiomeric excess) of the epoxide was found to be ≥ 96% ee by HPLC [*R,R*-Whelko-O-1, 99.75:0.25 hexane/IPA, 1 mL/min, 220 nm. Isomer A retention time 10.5 min, isomer B (major) 14.1 min)].



iv

Step 3:

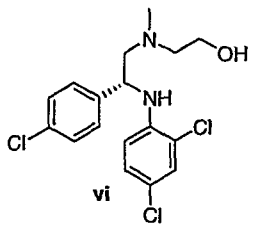
To the epoxide **iii** prepared in step 2 (102 g, 662 mmol) was added *N*-(2-methoxyethyl)methyl amine (83g, 930 mmol). The reaction mixture was heated neat (i.e., without solvent) to 100°C and stirred for 18h. The reaction mixture was cooled to room temperature and then concentrated *in vacuo* to remove the excess amine, thereby providing amino-alcohol **iv** as a mixture of regiosomeric ring opening products (~12:1) (154 g, 96%).



v

Step 4:

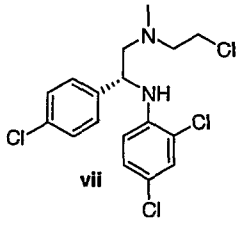
To the amino-alcohol **iv** prepared in step 3 (101 g, 416 mmol) in CH_2Cl_2 (2L) at 0°C was added TEA (i.e., triethylamine) (145 mL, 1040 mmol) followed by methanesulfonyl chloride (52.4 g, 460 mmol). The reaction mixture was stirred at room temperature for 2h and then methanesulfonyl chloride (4 mL, 6 mmol) was added. The reaction mixture was stirred for an additional 1h, then 2,4-dichloroaniline (67.5 g, 416 mmol) was added and the mixture was warmed to reflux. The refluxing mixture was stirred for 20h and cooled to room temperature. CH_2Cl_2 (2 L) was added, and the reaction mixture was washed with saturated $NaHCO_3$, water, and brine, then dried (Mg_2SO_4), filtered, and concentrated *in vacuo* to provide **v** (167 g) as a pale oil that was used directly in the following synthetic step. This process is expected to go with retention of configuration as described in Tetrahedron: *Asymmetry* 10 (1999) 2655-2663 (herein incorporated by reference).



vi

Step 5:

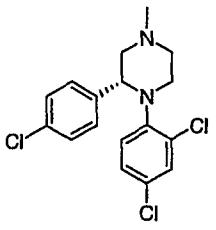
To **v** (167 g, 433 mmol) in CH_2Cl_2 (1.5 L) at 0°C was added BBr_3 (164 g, 433 mmol) over 30 minutes. The reaction was stirred at 0°C for 1 h and then for additional 3.5 h at room temperature. Saturated $NaHCO_3$ (3.5 L) was added slowly with gas evolution from the reaction mixture. The reaction mixture was extracted with CH_2Cl_2. The organic extracts were combined and washed with water (2 L), and brine (2 L), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide a brown oil that was purified by silica gel chromatography (30% EtOAc/hexane) to yield amino-alcohol **vi** (90 g, 241 mmol).



vii

Step 6:

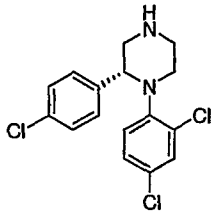
To the amino-alcohol **vi** prepared in step 5(90 g, 240 mmol) in CH_2Cl_2 (1 L) at 0°C was added pyridine (40 mL, 480 mmol) followed by thionyl chloride (53 mL, 720 mmol). The cold bath was removed and the reaction was stirred at room temperature for 4 h and then concentrated *in vacuo* without heating. The sample was taken up into EtOAc, (2 L) and cooled to 0°C. Saturated $NaHCO_3$ (1 L) was cautiously added (with gas evolution). The EtOAc layer was washed with water (1 L), brine (1 L), dried ($MgSO_4/NaSO_4$), filtered and concentrated *in vacuo* to provide a brown oil that was purified by silica gel chromatography (10% EtOAc/hexane) to give chloro-amine **vii** as a pale brown oil (84 g, 89%).



Example 303

Step 7:

To chloro-amine **vii** prepared in step 6 (84 g, 214 mmol) in THF (1 L) was added NaH (60% dispersion in mineral oil) (21.14 g, 535 mmol) in one portion. The reaction mixture was warmed to reflux and stirred for 4 h, then cooled to 0 °C. 1 L of an ice/water mixture was then added (gas evolution). CH_2Cl_2 (2 L) was added and the reaction mixture was stirred. The aqueous phase was washed with CH_2Cl_2, and the CH_2Cl_2 layers were then combined and washed with water (1 L), and brine (1 L). The reaction mixture was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide **Example 303** as a brown oil (83 g) contaminated with mineral oil. The material was used in the following step directly, without further purification.

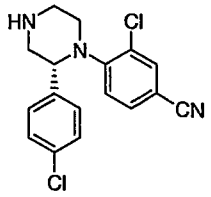


Example 304

Step 8:

To *N*-methylpiperazine **Example 303** (83 g) in DCE (0.8 L) at room temperature was added proton sponge (9.2 g, 43 mmol) followed by 1-chloroethylchloroformate (46.3 mL, 429 mmol). The reaction was warmed to reflux and stirred for 3 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. MeOH (1 L) was added and the reaction mixture was warmed to reflux. The reaction mixture was stirred at reflux for 1.5 h and cooled to room temperature, then concentrated *in vacuo*. CH_2Cl_2 (1.5 L) was added and the reaction mixture was washed with saturated $NaHCO_3$, water, and brine. The reaction mixture was then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The concentrated residue was purified by silica gel chromatography (CH_2Cl_2 then 5% MeOH/CH_2Cl_2) to provide the piperazine **Example 304** (60 g, 214 mmol). The ee was determined to be 98% ee by HPLC analysis (Chiralcel OD column, 94:6 hexane/isopropyl alcohol, 1 mL/min, 254 nm-isomer A retention time 8.4 min, isomer B 10.9 min).

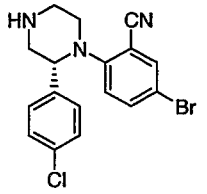
Preparation of Example 305



Example 305

The piperazine **Example 305** was prepared using a procedure similar to the procedure used to prepare **Example 304**, except that 4-amino-3-chlorobenzonitrile was used in place of 2,4-dichloroaniline in Step 4.

Preparation of Example 306

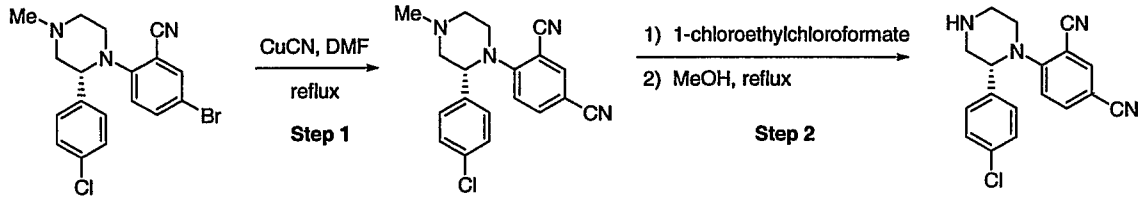


Example 306

The piperazine **Example 306** was prepared using a procedure similar to the procedure used to prepare **Example 304** except that 2-amino-5-bromobenzonitrile was used in place of 2,4-dichloroaniline in Step 4.

Preparation of Examples 307-309

Scheme 29



Example 307 Example 308 Example 309

Step 1:

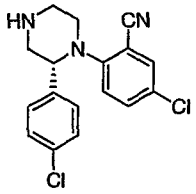
The *N*-methylpiperazine **Example 307** was prepared using a procedure similar to the procedure used to prepare **Example 303** except that 2-amino-5-bromobenzonitrile was used in place of 2,4-dichloroaniline in Step 4. The *N*-methylpiperazine **Example 307** (2.70 g, 7 mmol) in DMF (14 mL) was treated with CuCN (1.88 g, 21 mmol). The reaction mixture was warmed to reflux and stirred for 48 h. The reaction mixture was cooled to room temperature and EtOAc was added followed by saturated NH_4Cl/NH_4OH 9:1 solution. The mixture was stirred vigorously for 15 minutes and then extracted with EtOAc. The organic layers were combined and washed with water, and brine. The organic

layer ($MgSO_4$) was dried, filtered, and concentrated *in vacuo*. The residue was then purified by silica gel chromatograpy (4% MeOH/CH_2Cl_2) to provide the *N*-methylpiperazine **Example 308** (1.0 g, 3.0 mmol).

Step 2:

The *N*-methylpiperazine **Example 308** was demethylated to form **Example 309** as in Step 8 of Scheme 28.

Preparation of Example 310

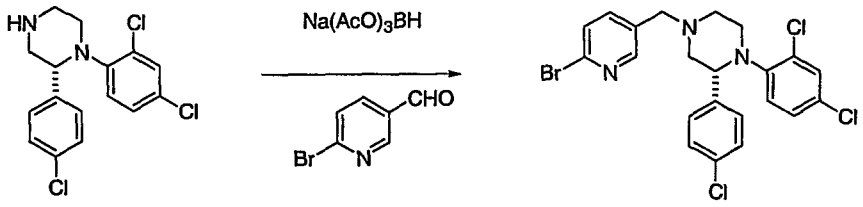


Example 310

The 4-chloro-2-cyanopiperazine **Example 310** was prepared using a procedure similar to the procedure used to prepare **Example 304** of Scheme 28 except that 2-amino-5-chlorobenzonitrile was used in place of 2,4-dichloroaniline in step 4.

Preparation of Example 311

Scheme 30

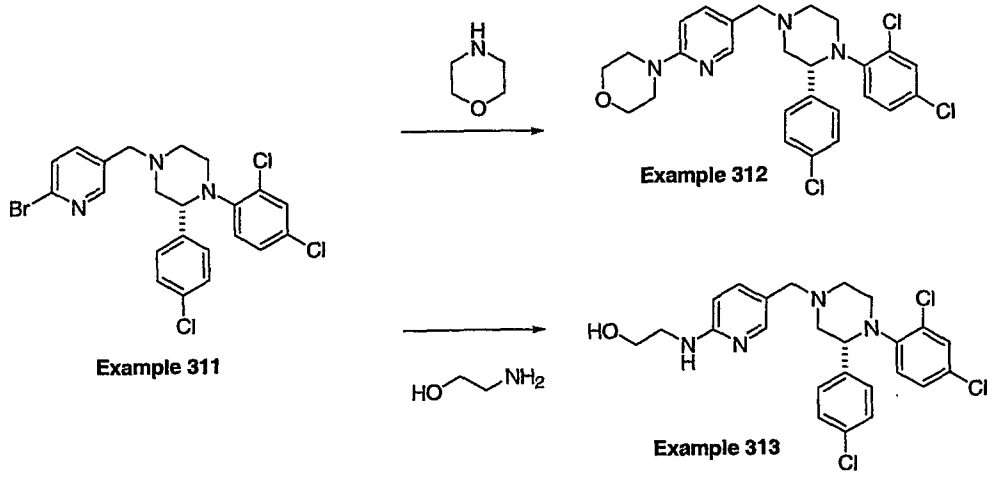


Example 304 **Example 311**

The enantio-enriched piperazine **Example 304** (500 mg), 6-bromo-pyridine-3-carbaldehyde (326 mg), and $Na(AcO)_3BH$ (371 mg) were taken up in CH_2Cl_2 and stirred at 25 °C (18 h). The reaction mixture was diluted with CH_2Cl_2 and washed with 1 N NaOH $_{(aq.)}$. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification via flash chromatography (4/1 hexanes/EtOAc, SiO_2) gave 376 mg (50 %) of the bromo-pyridine **Example 311** as an oil.

Preparation of Examples 312-313

Scheme 31

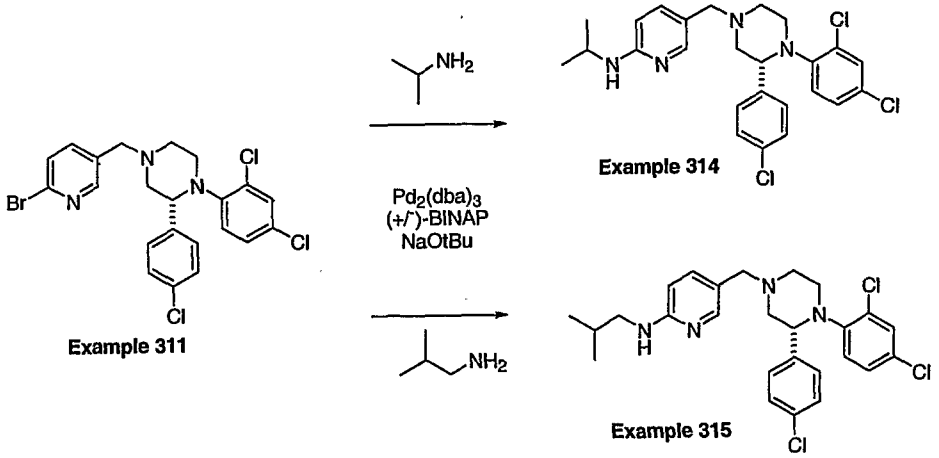


The bromo-pyridine **Example 311** (80 mg) and morpholine (0.3 mL) were heated at 100°C (18 h). The solution was cooled and partitioned between CH_2Cl_2 and 1 N NaOH $_{(aq.)}$. The aqueous solution was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification via thin-layer preparative chromatography (1/1 hexanes/EtOAc, SiO_2) gave 54 mg (65 %) of **Example 312** as a colorless oil.

In a similar manner, the reaction of **Example 311** with ethanol-amine furnished **Example 313** as a colorless oil.

Preparation of Examples 314 and 315

Scheme 32



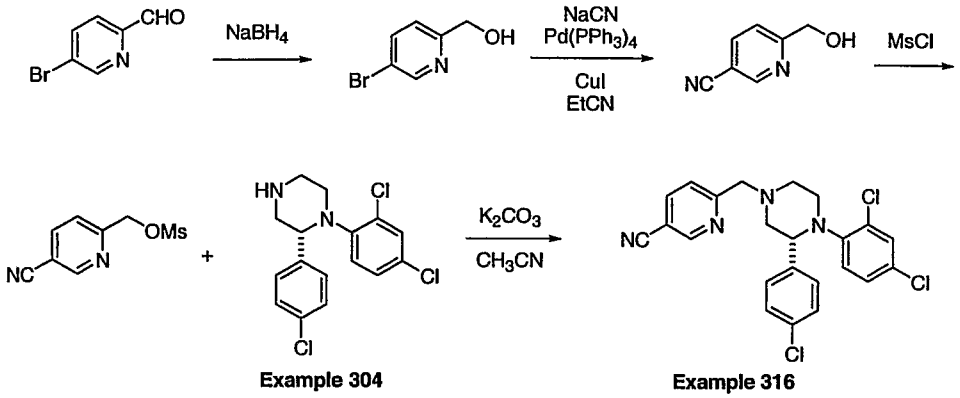
The bromo-pyridine (85 mg) **Example 311**, racemic-BINAP (i.e., 2,2'-bis-diphenylphosphanyl-[1,1']binaphthalenyl; 40 mg), $Pd_2(dba)_3$ (15 mg), and NaOtBu (100 mg) were taken up in iso-propyl amine and heated at 100°C in a sealed tube (18 h). The solution was diluted with Et_2O and filtered through Celite.

Concentration gave the crude product. Purification via thin-layer preparative chromatography (2/1 hexanes/EtOAc, SiO_2) gave 40 mg (48 %) of **Example 314** as an oil.

In a similar manner, the reaction of **Example 311** and iso-butyl amine furnished **Example 315** as an oil.

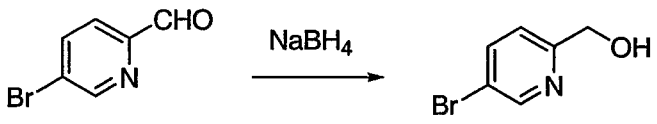
Preparation of Example 316

Scheme 33



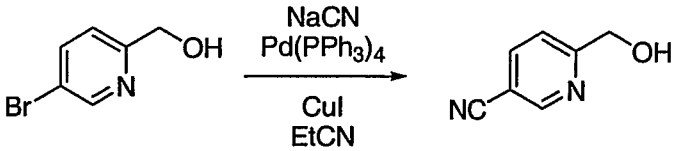
Example 304 Example 316

Step 1:



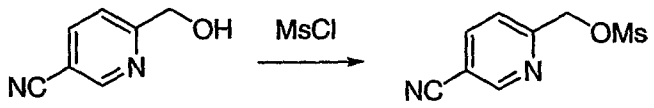
The 5-bromo-pyridine-2-carbaldehyde (2.0 g) was taken up in MeOH and cooled to 0°C. Sodium borohydride (450 mg) was added in portions at 0°C. The solution was warmed to 25°C and stirred at that temperature for 1.5 h. The solution was concentrated, and the residue was quenched with 1 M HCl $_{(aq.)}$. The solution was stirred at 25°C for 0.5 h. The solution was rendered basic via addition of solid K_2CO_3. The mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give (5-bromo-pyridin-2-yl)-methanol as a white solid.

Step 2:



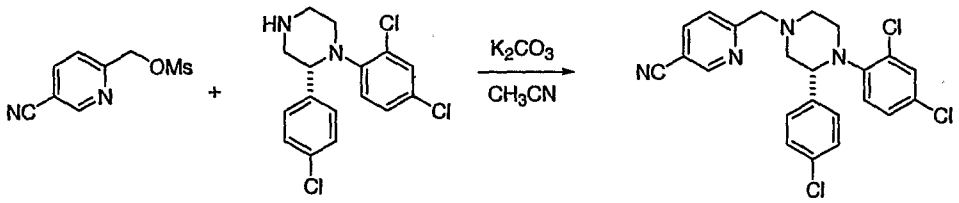
(5-Bromo-pyridin-2-yl)-methanol (1.0 g), NaCN (521 mg), $Pd(PPh_3)_4$ (612 mg), and CuI (200 mg) were taken up in degassed EtCN and heated at 110°C (4 h). The solution was partitioned between EtOAc and 10 % $NH_4OH_{(aq.)}$. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). Filtration and concentration gave a yellow solid. Purification via flash chromatography (1/2 hexanes/EtOAc, SiO_2) gave 341 mg (48 %) of (5-cyano-pyridin-2-yl)-methanol as a white solid.

Step 3:



(5-Cyano-pyridin-2-yl)-methanol (100 mg) and Et_3N (0.14 m) were taken up in CH_2Cl_2 and cooled to 0°C. Methansulfonyl chloride (0.1 mL) was added and the solution was stirred at 0°C for 2 h. The solution was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ (aq.). The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$). Filtration and concentration gave the mesylate as a yellow oil. The mesylate was used in step 4 without further purification.

Step 4:



Example 304

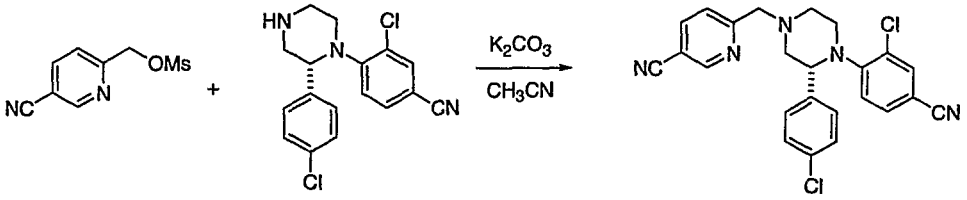
Example 316

The mesylate (0.75 mmol), enantio-enriched piperazine **Example 304** (150 mg), and K_2CO_3 (152 mg) were taken up in CH_3CN and heated at reflux (95°C, 1.5 h). The solution was cooled and partitioned between EtOAc and 1 N $NaOH_{(aq.)}$. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). Filtration and concentration

gave a yellow oil. Purification via thin-layer preparative chromatography (2/1 hexanes/EtOAc, SiO_2) gave 155 mg (77 %) of **Example 316** as a white solid.

Preparation of Example 317

Scheme 34

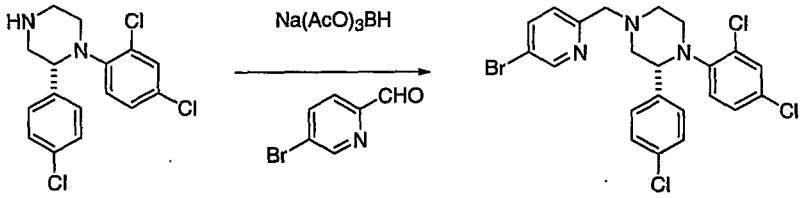


Example 305 Example 317

Example 317 was prepared according to the procedures described in **Scheme 33**, Step 4, above, except that cyano-piperazine **Example 305** was used instead of **Example 304.**

Preparation of Example 318

Scheme 35

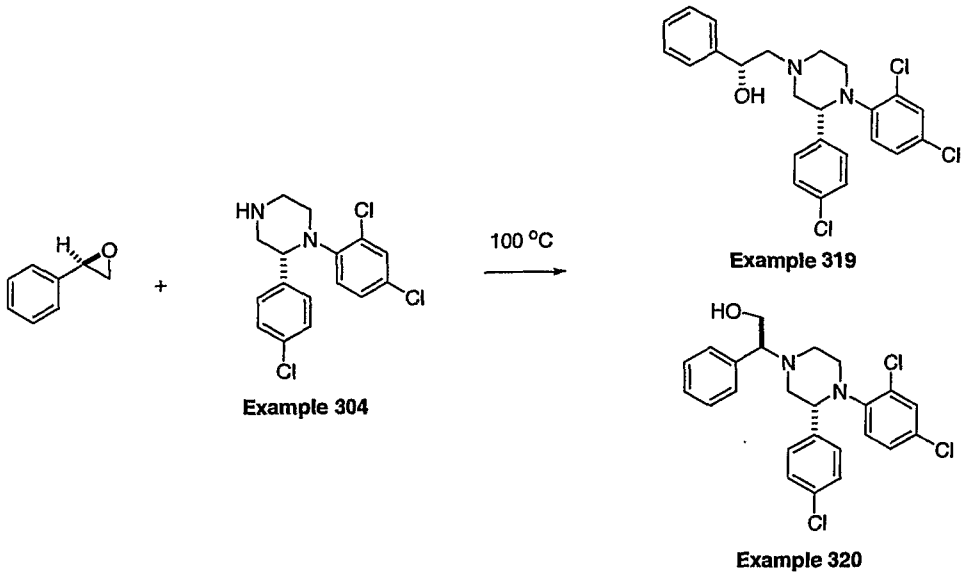


Example 304 Example 318

Example 318 was prepared according to the procedure described in **Scheme 30** except that 5-bromo-pyridine-2-carbaldehyde was used instead of 6-bromo-pyridine-3-carbaldehyde.

Preparation of Examples 319 and 320

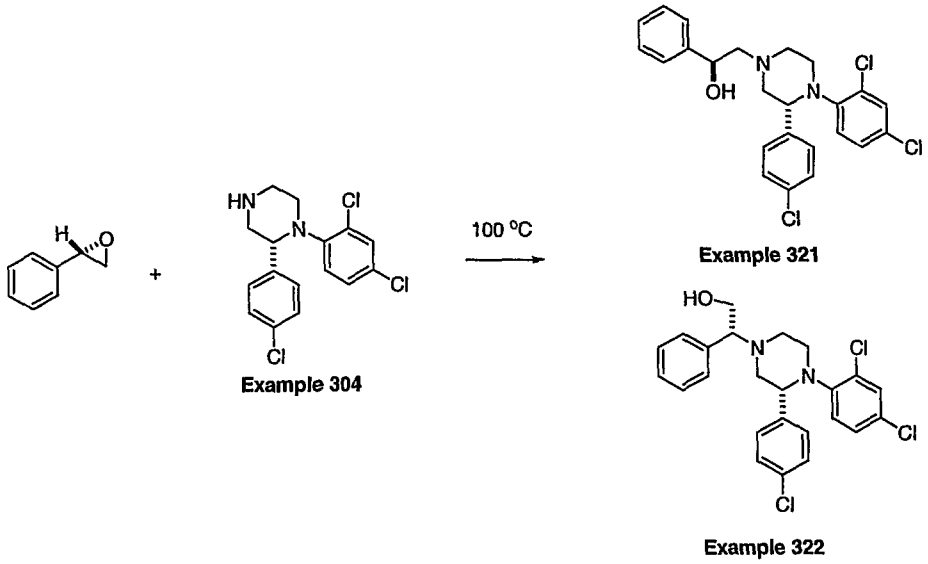
Scheme 36



(R)-Styrene oxide (0.1 mL) and the enantio-enriched piperazine **Example 304** (200 mg) were heated neat at 95°C (4 h). The residue was purified via thin-layer preparative chromatography (3/1 hexanes/EtOAc, SiO_2) to furnish 141 mg (48 %) of **Example 319** and 47 mg (16 %) of **Example 320** as colorless oils.

Preparation of Examples 321 and 322

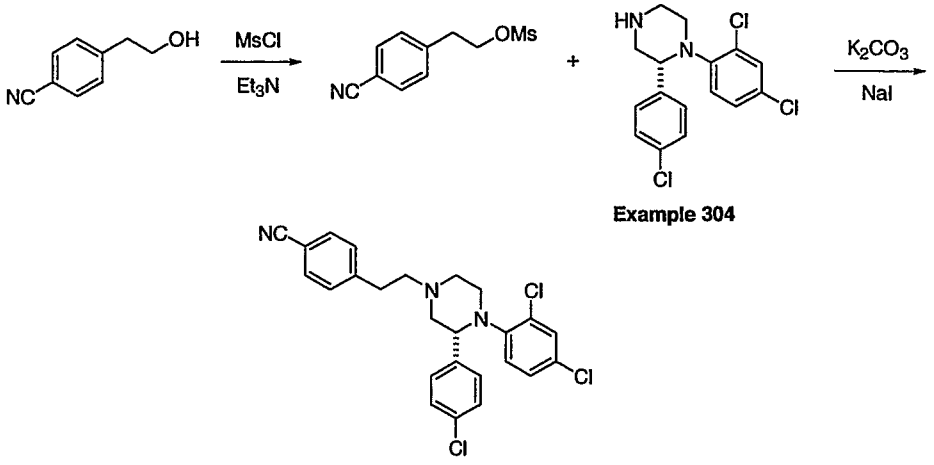
Scheme 37



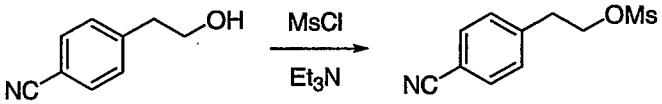
Following the procedure in **Scheme 36**, (S)-styrene oxide and the piperazine **Example 304** gave **Example 321** and **Example 322.**

Preparation of Examples 323-335

Scheme 38

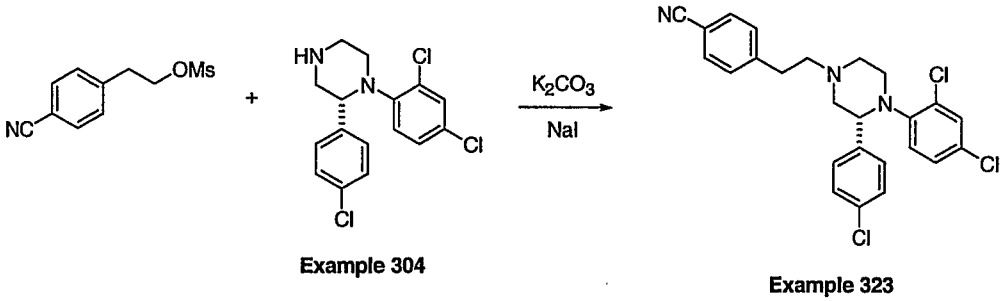


Step 1:



The 4-(2-hydroxyethyl)-benzonitrile (500 mg) and Et_3N (480 mg) were taken up in CH_2Cl_2 at 25°C. Methanesulfonyl chloride (470 mg) was added and the solution was stirred at 25°C (0.5 h). The solution was diluted with CH_2Cl_2 and washed with saturated $NaHCO_{3\,(aq.)}$. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resulting mesylate was used in step 2 without further purification.

Step 2:

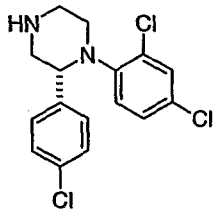
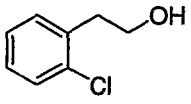
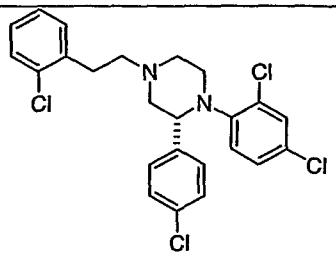
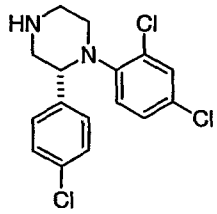
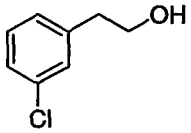
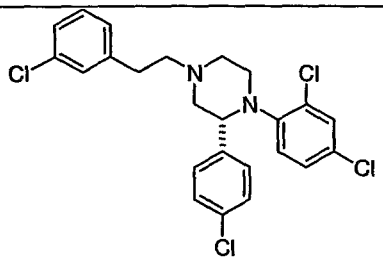
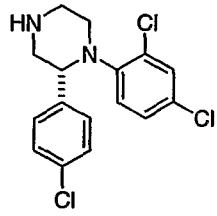
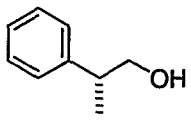
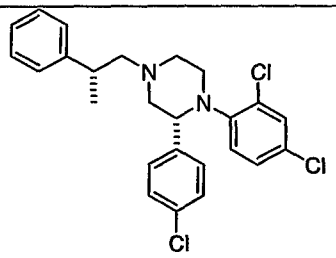
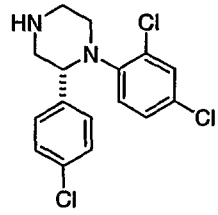
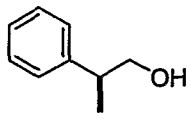
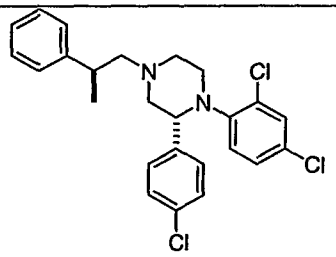
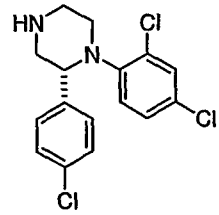
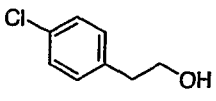
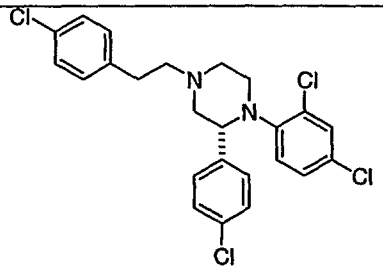


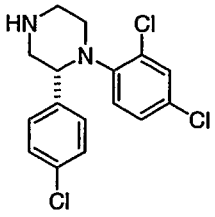
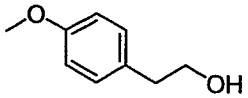
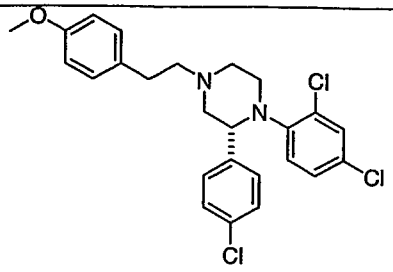
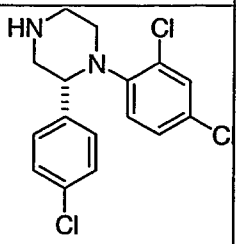
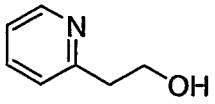
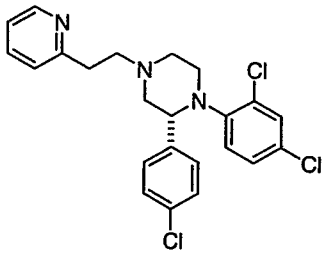
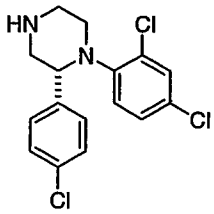
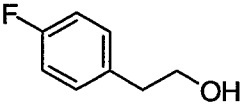
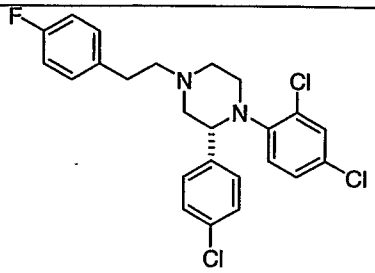
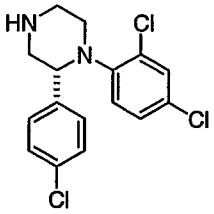
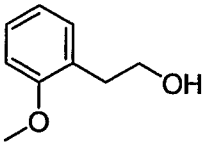
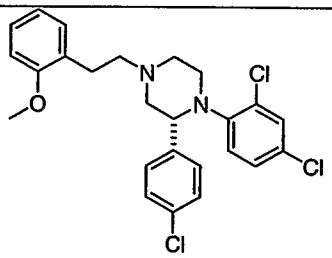
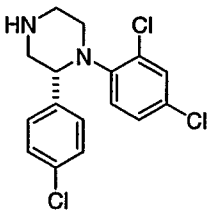
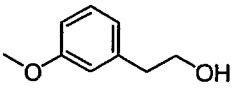
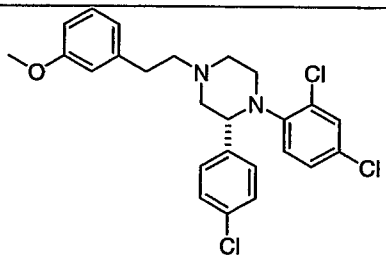
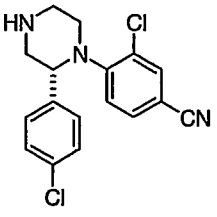
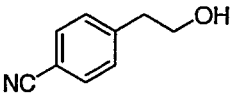
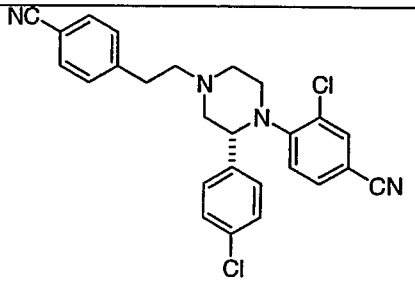
The mesylate prepared in step 1 (63 mg), piperazine **Example 304** (80 mg), K_2CO_3 (97 mg), and NaI (40 mg) were taken up in CH_3CN and heated at reflux (90°C, 18 h). The solution was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). Filtration and concentration gave a yellow

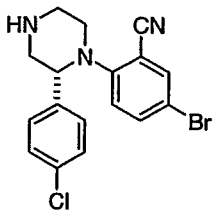
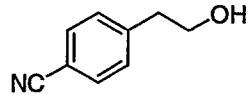
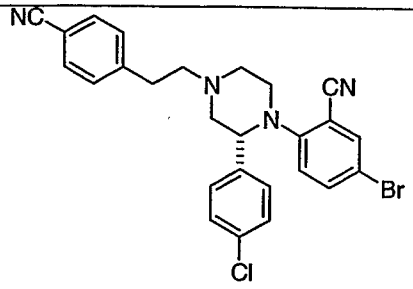
oil. Purification via thin-layer preparative chromatography (7 % EtOAc in CH_2Cl_2, SiO_2) gave 100 mg (90 %) of **Example 323** as a colorless oil.

The following examples were prepared in a similar manner using the appropriate alcohol and piperazine (**Table XII**).

Table XII

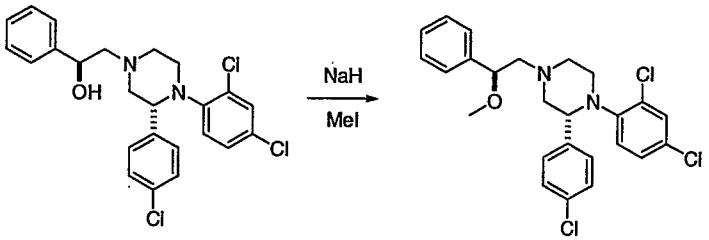
Example #	Piperazine	Alcohol	Example Structure
324			
325			
326			
327			
328			

Example #	Piperazine	Alcohol	Example Structure
329			
330			
331			
332			
333			
334			

Example #	Piperazine	Alcohol	Example Structure
335			

Preparation of Example 336

Scheme 39

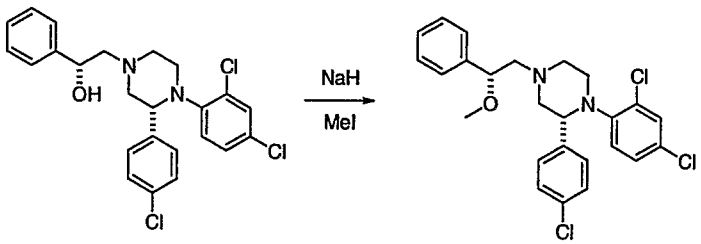


Example 321 Example 336

The alcohol **Example 321** (90 mg) was taken up in THF. Sodium hydride (100 mg of a 60 wt % dispersion in oil) was added. After stirring at 25°C for 10-15 minutes, iodomethane (0.05 mL) was added. The mixture was stirred at 25°C (2 h). The solution was partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). Filtration and concentration gave a yellow oil. Purification via thin-layer preparative chromatography (3/1 hexanes/EtOAc, SiO_2) gave 89 mg (98 %) of **Example 336** as a colorless oil.

Preparation of Example 337

Scheme 40

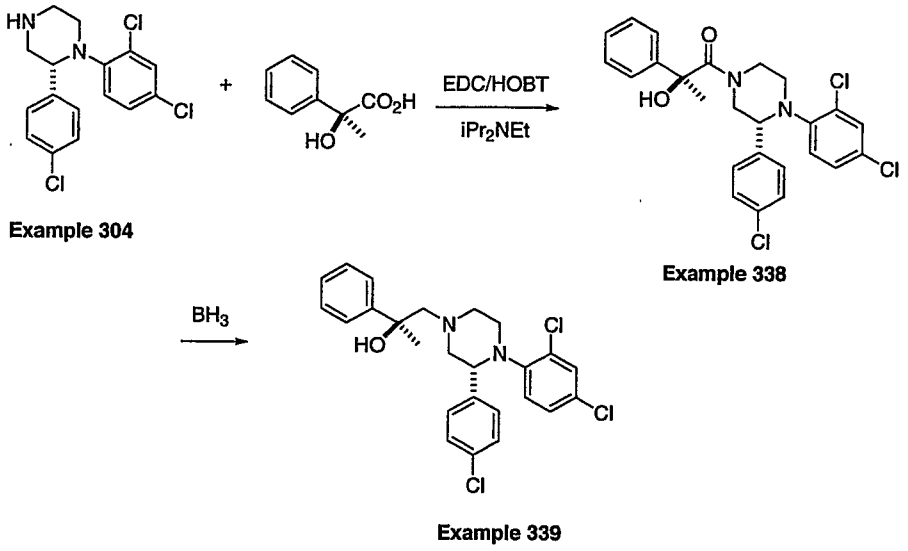


Example 319 Example 337

Using a procedure similar to the procedure described in **Scheme 39**, **Example 319** was converted into **Example 337**.

Preparation of Examples 338-339

Scheme 41

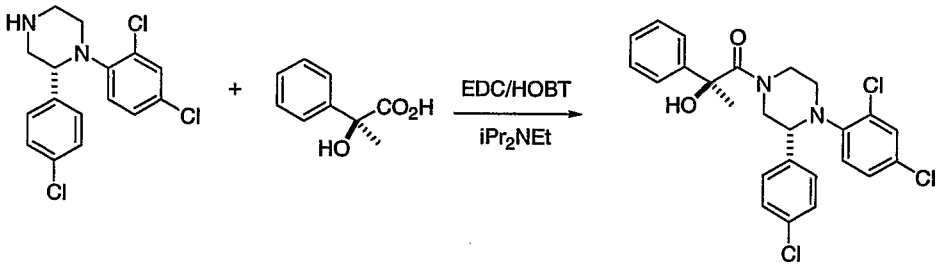


Example 304

Example 338

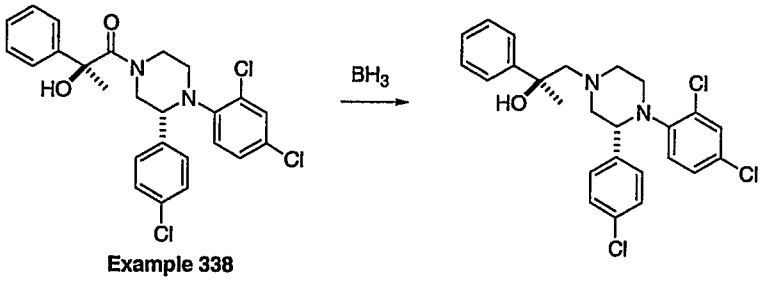
Example 339

Step 1:



The piperazine **Example 304** (300 mg), carboxylic acid (160 mg), EDC (211 mg), HOBT (149 mg), and iPr_2NEt (0.2 mL) were taken up in CH_3CN and heated at 65°C (18 h). The solution was concentrated. The residue was partitioned between EtOAc and 1 N $NaOH_{(aq.)}$. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). Filtration and concentration gave a yellow oil. Purification via flash chromatography (2/1 hexanes/EtOAc, SiO_2) gave 223 mg (52 %) of amide **Example 338** as a colorless oil.

Step 2:



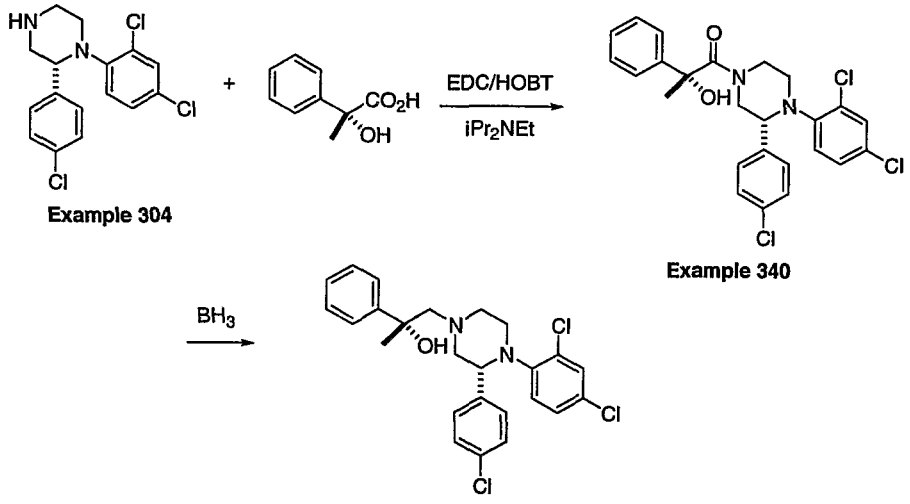
Example 338

Example 339

The amide **Example 338** (223 mg) and BH_3-THF complex (1.0 M BH_3 in THF, 3 mL) were taken up in THF and heated at reflux (65-70°C, 18 h). The solution was cooled and quenched with MeOH (2-3 mL) and 1 M $HCl_{(aq.)}$ (30-40 mL). The solution was stirred at 25°C for 2 h. The solution was cooled and rendered basic with NaOH pellets (pH = 10-12). The mixture was extracted with with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). Filtration and concentration gave a yellow oil. Purification via thin-layer preparative chromatography (6/1 hexanes/EtOAc, SiO_2) gave 133 mg (61 %) of **Example 339** as a colorless oil.

Preparation of Examples 340-341

Scheme 42



Example 304

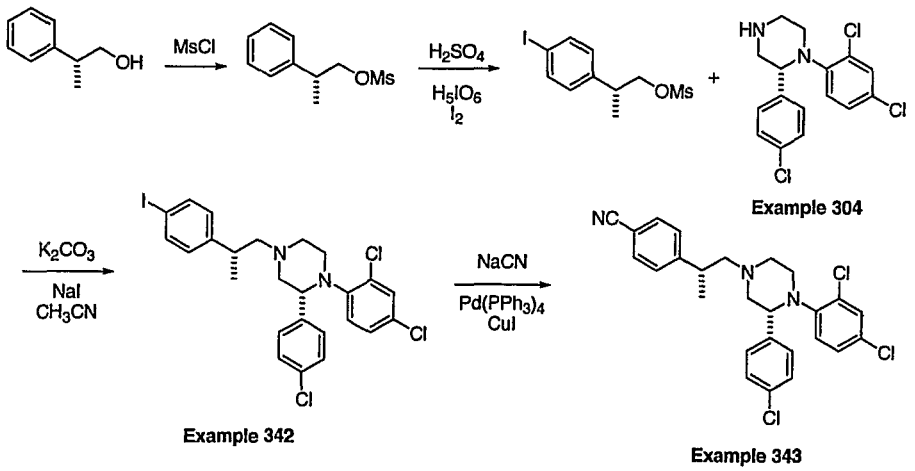
Example 340

Example 341

Using the procedures outlined in **Scheme 41**, **Examples 340** and **341** were prepared from the appropriate piperazine and acid as shown in **Scheme 42.**

Preparation of Examples 342-343

Scheme 43



Example 304

Example 342

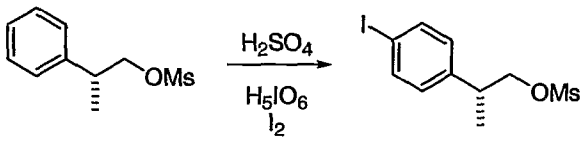
Example 343

Step 1:



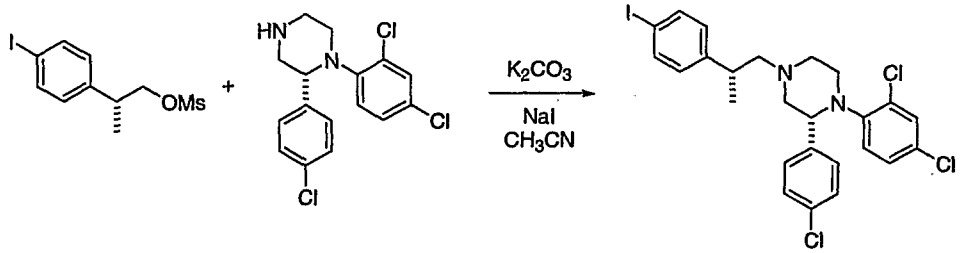
The 2-phenyl-propan-1-ol (500 mg) and Et_3N (0.6 mL) were taken up in CH_2Cl_2 and cooled to 0°C. Methanesulfonyl sulfonyl chloride (0.3 mL) was added at 0°C, and the reaction was warmed to 25°C (3 h). The solution was diluted with CH_2Cl_2 and washed with 1 N NaOH $_{(aq.)}$. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$). Filtration and concentration gave the corresponding mesylate as a yellow oil, which was used without further purification in step 2.

Step 2:



The mesylate prepared in step 1 (798 mg), H_2SO_4 (0.2 mL), H_5IO_6 (212 mg), and I_2 (436 mg) were taken up in glacial acetic acid and stirred at 25°C (18 h). The reaction mixture was heated at 70°C for 3 h. The solution was cooled and rendered basic with 3 N NaOH $_{(aq.)}$. The mixture was treated with 10% $Na_2S_2O_3$ $_{(aq.)}$ to decolorize the I_2 color. The mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification via flash chromatography (4/1 hexanes/EtOAc, SiO_2) gave 800 mg (63 %) of the iodide as a yellow oil.

Step 3:

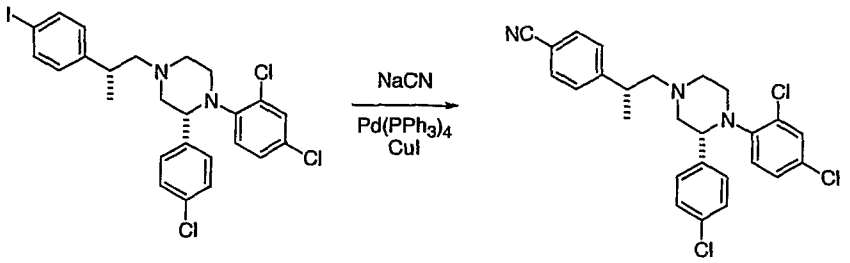


Example 304 Example 342

The iodide prepared in step 2 (394 mg), piperazine **Example 304** (200 mg), K_2CO_3 (240 mg), and NaI (44 mg) were taken up in CH_3CN and heated (85-90°C, 18 h). The reaction mixture was partitioned between EtOAc and 1 N $NaOH_{(aq.)}$. The aqueous layer was extracted with EtOAc. The combined organic

layers were washed with brine and dried ($MgSO_4$). Filtration and concentration gave a yellow oil. Purification via thin-layer preparative chromatography (8/1 hexanes/EtOAc, SiO_2) gave 118 mg (17 %) of the iodo-piperazine **Example 342** as a colorless foam.

Step 4:

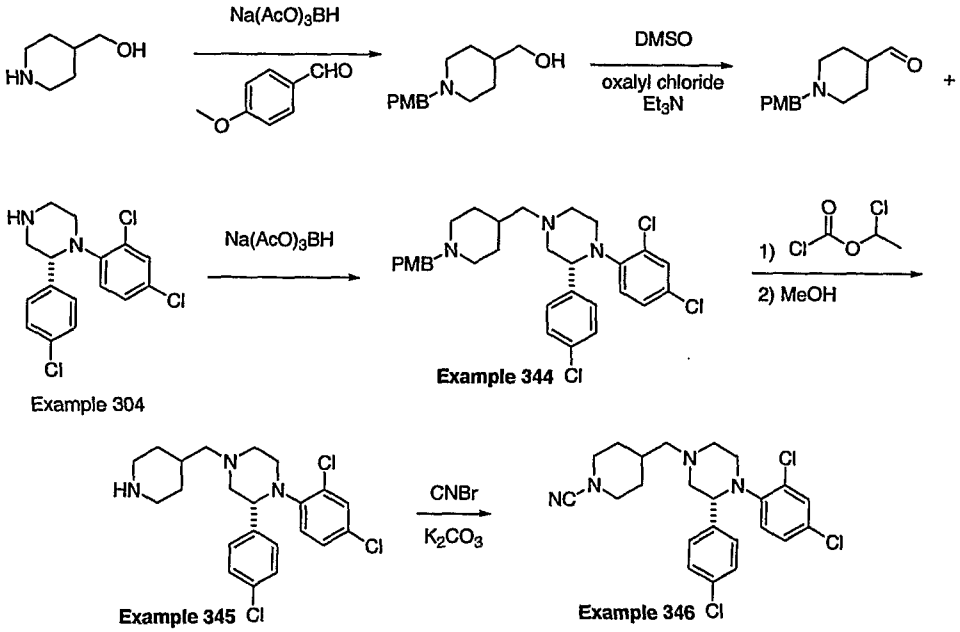


Example 342 **Example 343**

The iodo-piperazine **Example 342** prepared in step 3 (118 mg), NaCN (20 mg), $Pd(PPh_3)_4$ (23 mg), and CuI (8 mg) were taken up in degassed EtCN and heated at 105°C for 1 h. The solution was partitioned between EtOAc and 1 N NaOH $_{(aq.)}$. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). Filtration and concentration gave a yellow oil. Purification via preparative thin-layer chromatography (6/1/ hexanes/EtOAc, SiO_2) gave 58 mg (59 %) of **Example 343.**

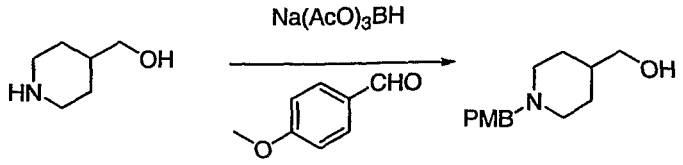
Preparation of Examples 344-346

Scheme 44



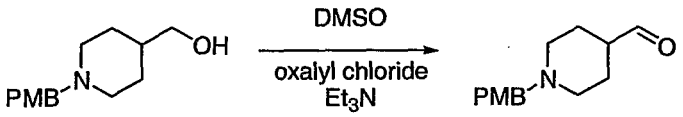
Example 304 **Example 344** **Example 345** **Example 346**

Step 1:



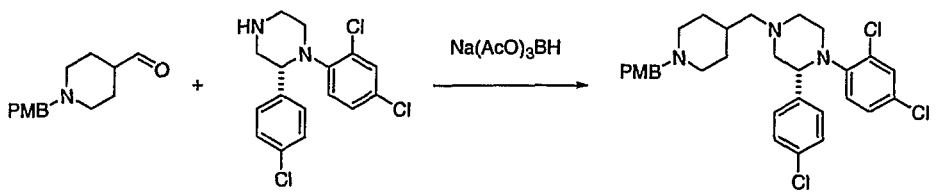
Piperidine-4-yl-methanol (5 g), p-anisaldehyde (6.3 mL), and $Na(AcO)_3BH$ (11 g) were taken up in CH_2Cl_2 and stirred at 25°C (18 h). The solution was diluted with CH_2Cl_2 and washed with 1 N NaOH $_{(aq.)}$. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was partitioned between Et_2O and 1 M HCl $_{(aq.)}$. The aqueous layer was extracted with Et_2O. The aqueous layer was cooled to 0°C and rendered basic via addition of NaOH pellets (pH = 10-12). The mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated which furnished the PMB alcohol (6.35 g, 62 %) as a yellow oil.

Step 2:



DMSO (2.5 mL) was taken up in CH_2Cl_2 (150 mL) and cooled to – 40°C (CH_3CN/CO_2). Oxalyl chloride (3.1 mL) in CH_2Cl_2 (15 mL) was added dropwise to the solution at – 40°C. The solution was stirred at -40°C for 30 minutes. The PMB alcohol prepared in step 1 (6.35 g) in CH_2Cl_2 (15 mL) was added to the solution at -40°C. The resulting solution was stirred at -40°C for 30 minutes. Triethylamine (11.3 mL) was added to the solution at -40°C, and the resulting slurry was warmed to 25°C and stirred at that temperature for 1.5 h. The solution was diluted with CH_2Cl_2 and washed with 1 N NaOH $_{(aq.)}$. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to furnish the aldehyde, which was used without further purification in step 3.

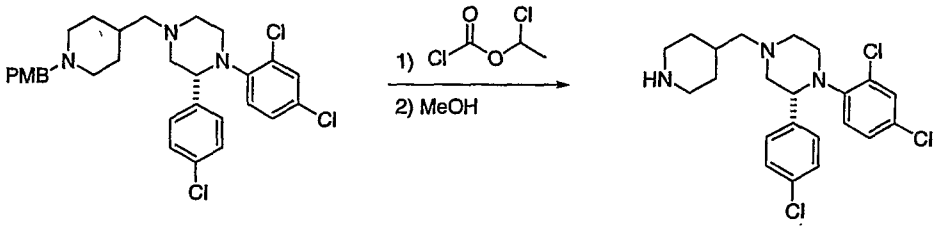
Step 3:



Example 304 Example 344

The piperazine **Example 304** (500 mg), the aldehyde prepared in step 2 (440 mg), and $Na(AcO)_3BH$ (400 mg) were taken up in CH_2Cl_2 and stirred at 25°C (18 h). The solution was diluted with CH_2Cl_2 and washed with 1 N $NaOH_{(aq.)}$. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification via flash chromatography (3/1 hexanes/EtOAc, SiO_2) gave 640 mg (78 %) of **Example 344** as a colorless oil.

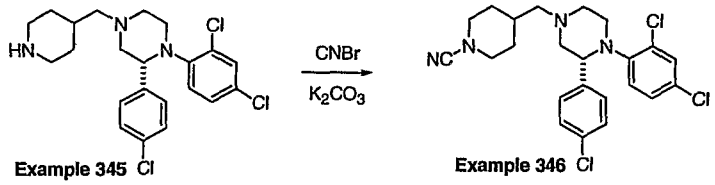
Step 4:



Example 344 Example 345

Example 344 (640 mg) and the chloro-formate shown above in step 4 (0.2 mL) were taken up in CH_2Cl_2 and stirred at 25°C (18 h). The solution was concentrated. The residue was taken up in MeOH and heated at reflux (65°C, 2.5 h). The solution was concentrated, and the residue was partitioned between 1 M $HCl_{(aq.)}$ and Et_2O. The aqueous layer was extracted with with Et_2O. The aqueous layer was cooled (0°C) and made basic via addition of NaOH pellets (pH = 10-12). The solution was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give **Example 345** (367 mg, 74 %) as a yellow oil.

Step 5

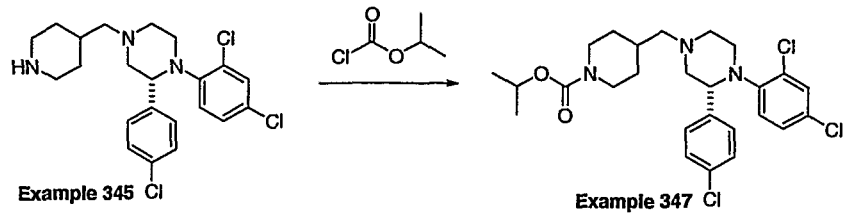


Example 345 Cl Example 346 Cl

Example 345 (70 mg), CNBr (0.2 mL of a 3.0 M solution in CH_2Cl_2), and K_2CO_3 (66 mg) were taken up in CH_3CN and stirred at 25°C (4 h). The solution was partitioned between EtOAc and saturated $NaHCO_{3\ (aq.)}$. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). Filtration and concentration gave a yellow oil. Purification via thin-layer preparative chromatography (3/1 hexanes/EtOAc, SiO_2) gave **Example 346** (25 mg, 34 %) as a colorless oil.

Preparation of Example 347

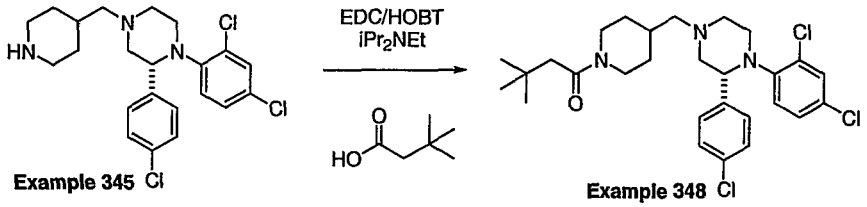
Scheme 45



Example 345 (70 mg) and the chloro-formate shown above in scheme 16 (0.3 mL) were partitioned between CH_2Cl_2 and 1 N NaOH $_{(aq.)}$. The mixture was stirred at 25°C (4 h). The mixture was diluted with water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (MgSO4), filtered, and concentrated. Pufication via thin-layer preparative chromatography (3/1 hexanes/EtOAc, SiO_2) gave **Example 347** (63 mg, 75 %) as a colorless oil.

Preparation of Example 348

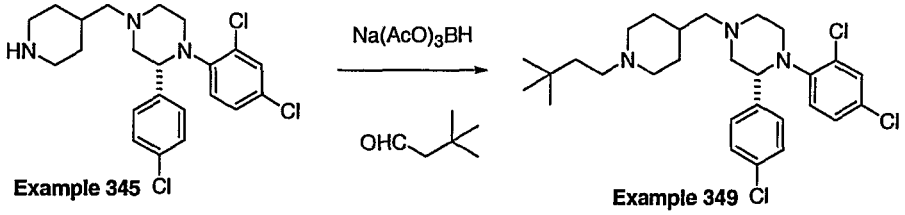
Scheme 46



Example 345 was converted into **Example 348** following the procedure outlined in Step 1 of **Scheme 41** using the appropriate piperidine and acid shown in **Scheme 46.**

Preparation of Example 349

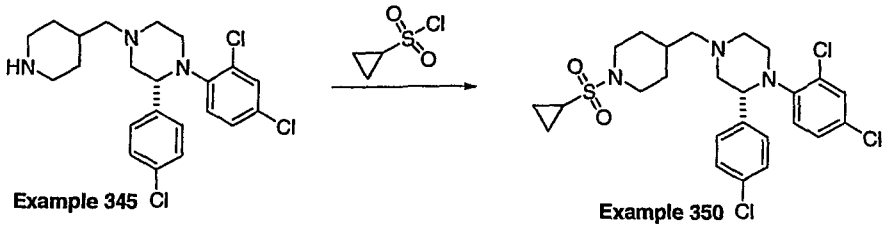
Scheme 47



Example 345 was converted into **Example 349** following the procedure outlined in Step 3 of **Scheme 44** using the appropriate piperidine and aldehyde shown in **Scheme 47.**

Preparation of Example 350

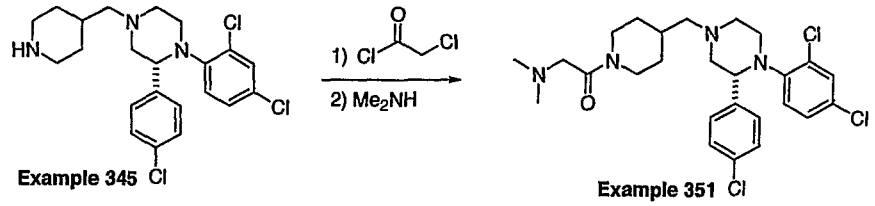
Scheme 48



Example 345 was converted into **Example 350** following the procedure outlined in Step 8 of **Scheme 14** using the appropriate piperidine and sulfonyl chloride shown in **Scheme 48**.

Preparation of Example 351

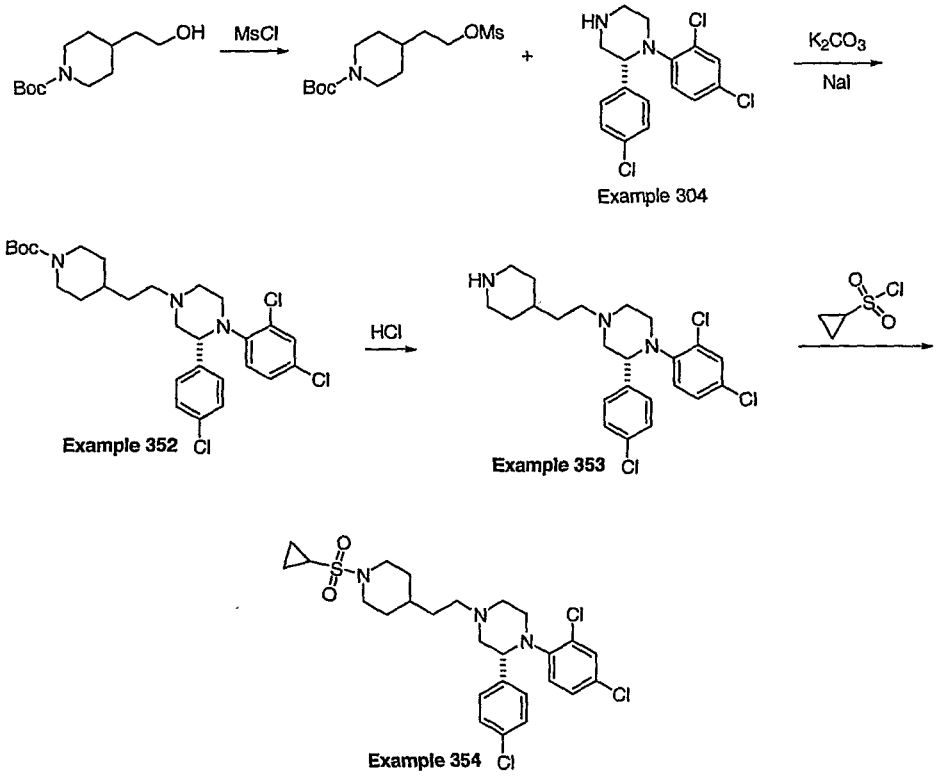
Scheme 49



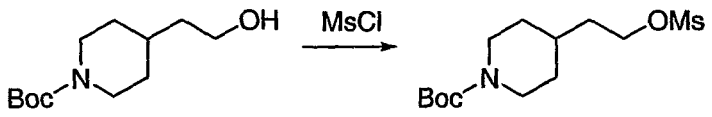
Example 345 (45 mg) and the acid chloride (0.05 mL) were partitioned between CH_2Cl_2 and saturated $NaHCO_{3\,(aq.)}$. The mixture was stirred at 25°C (3 h). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated to furnish the chloro-amide. The chloro-amide was taken up in DMF and 20 mL of a 2.0 M Me_2NH in THF solution was added. The solution was heated in a sealed tube (75°C, 66 h). The solution was concentrated. The residue was partitioned between CH_2Cl_2 and 1 N $NaOH_{(aq.)}$. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification via thin-layer preparative chromatography (20/1 CH_2Cl_2/MeOH, SiO_2) gave 18 mg (34 %) of **Example 351** as a colorless oil.

Preparation of Examples 352-354

Scheme 50

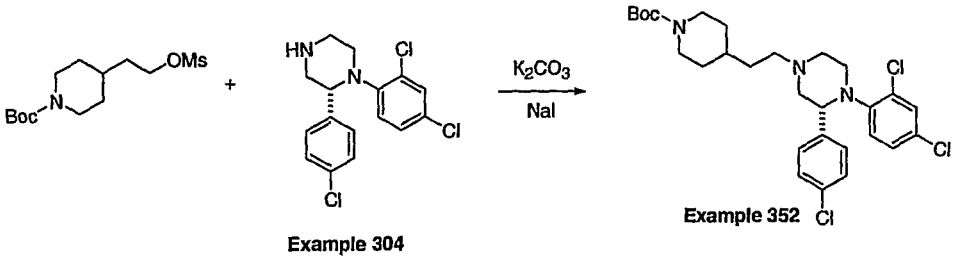


Step 1:



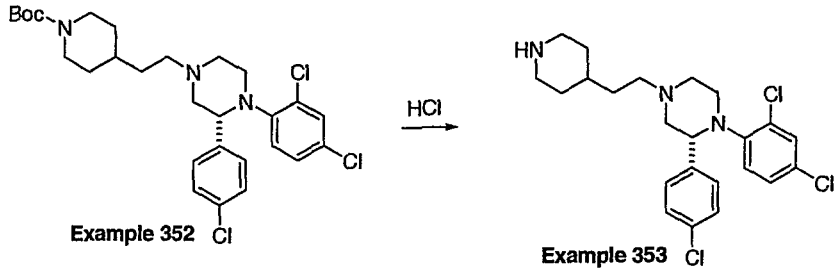
The N-Boc alcohol shown above in **Scheme 50** was converted into the mesylate according to the procedure outlined in Step 1 of **Scheme 43.**

Step 2:



Example 352 was prepared according to the procedure outlined in Step 3 of **Scheme 43** using the appropriate reagents.

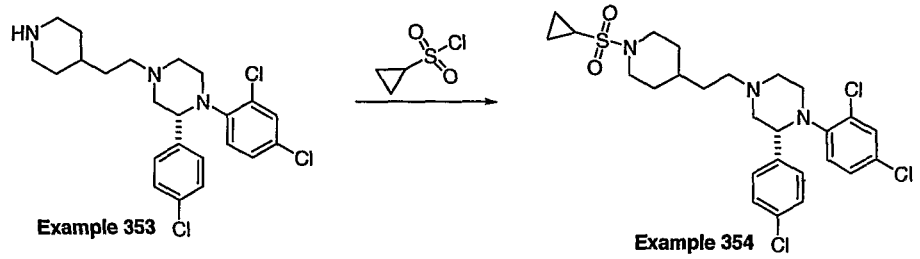
Step 3:



Example 352 Example 353

Example 352 (750 mg) and 4 M HCl $_{(aq.)}$ were taken up in MeOH and stirred at 25 °C (18 h). The solution was concentrated. The residue was taken up in EtOAc and washed with 1 N NaOH $_{(aq.)}$. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). Filtration and concentration gave **Example 353** as a yellow oil.

Step 4:

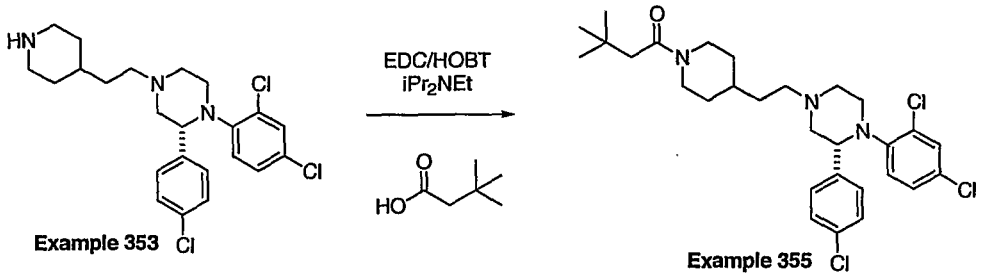


Example 353 Example 354

Example 353 was converted into **Example 354** using the procedures outlined in Step 1 of **Scheme 43** using the appropriate reagents.

Preparation of Example 355

Scheme 51

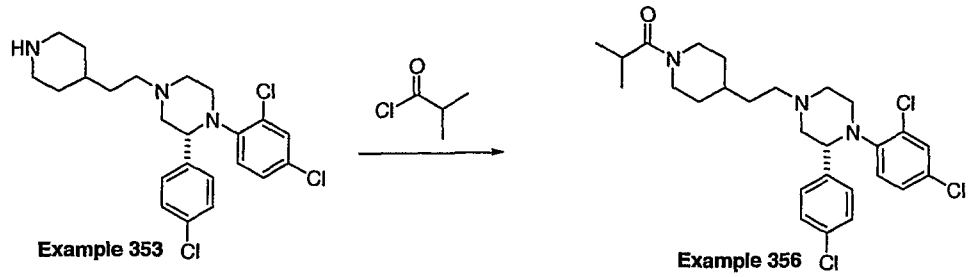


Example 353 Example 355

Example 353 was converted into **Example 355** using the procedure outlined in **Scheme 46** using the appropriate reagents.

Preparation of Example 356

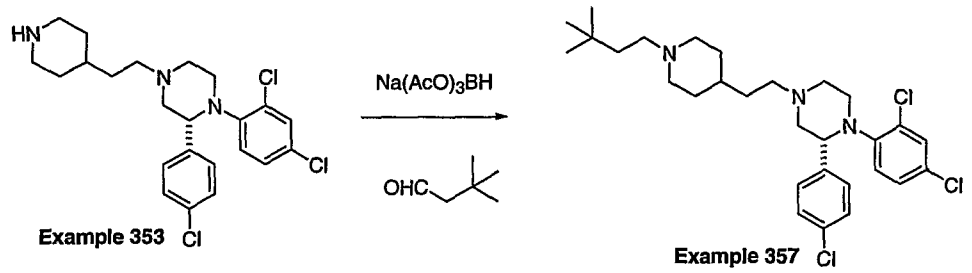
Scheme 52



Example 353 was converted into **Example 356** using the procedure outlined in **Scheme 45** using the appropriate reagents.

Preparation of Example 357

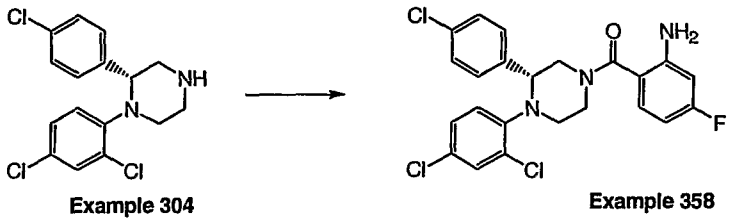
Scheme 53



Example 353 was converted into **Example 357** using the procedure outlined in Step 1 of **Scheme 44** using the appropriate reagents.

Preparation of Example 358

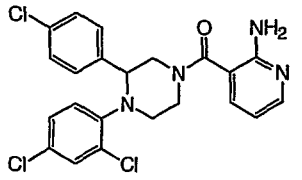
Scheme 54



To a solution of the piperazine **Example 304** in MeCN (3 mL) was added 2-amino-4-fluorobenzoic acid (54mg, 0.35 mmol), EDCI (67 mg, 0.35 mmol), HOBt (47 mg, 0.35 mmol) and iPr_2NEt (160 uL, 0.92 mmol). The solution was allowed to stir at room temperature overnight. The solution was then concentrated. The crude product was partitioned between EtOAc and 1M NaOH. The aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by preparative TLC (SiO_2, 2:1 hexanes:EtOAc) to afford **Example 358** (99 mg). The product was converted to its HCl salt by dissolving

in CH_2Cl_2 followed by the addition of 2N HCl (in ether). The solvent was then removed to provide the salt.

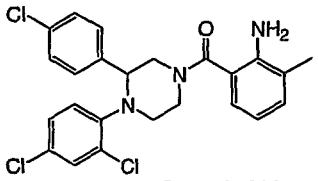
Preparation of Example 359



Example 359

Example 359 was prepared using a procedure similar to that used to prepare **Example 358** except that 2-aminonicotinic acid was coupled with **Example 1** instead of 2-amino-4-fluorobenzoic acid.

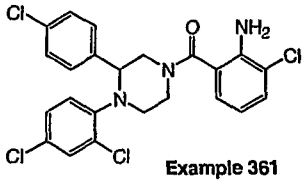
Preparation of Example 360



Example 360

Example 360 was prepared using a procedure similar to that used to prepare **Example 359** except that 2-amino-3-methylbenzoic acid was coupled with **Example 1** instead of 2-amino-4-fluorobenzoic acid.

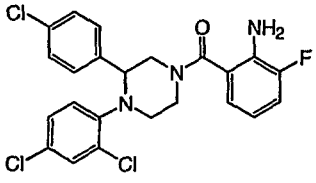
Preparation of Example 361



Example 361

Example 361 was prepared using a procedure similar to that used to prepare **Example 359** except that 2-amino-3-chlorobenzoic acid was coupled with **Example 1** instead of 2-amino-4-fluorobenzoic acid.

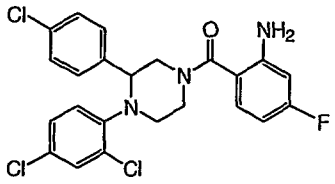
Preparation of Example 362



Example 362

Example 362 was prepared using a procedure similar to that used to prepare **Example 359** except that 2-amino-3-fluorobenzoic acid was coupled with **Example 1** instead of 2-amino-4-fluorobenzoic acid.

Preparation of Example 363

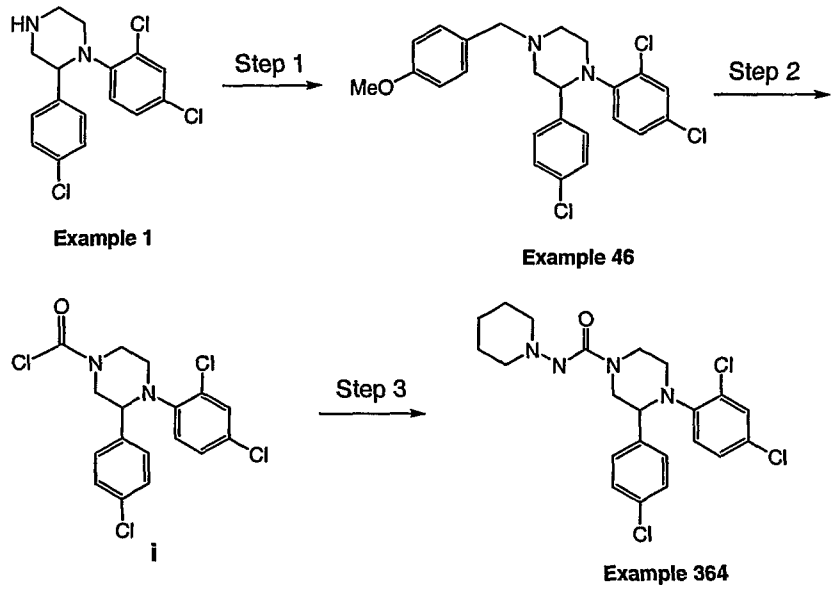


Example 363

Example 363 was prepared using a procedure similar to that used to prepare **Example 359** except that 2-amino-4-fluorobenzoic acid was coupled with **Example 1** instead of 2-amino-4-fluorobenzoic acid.

Preparation of Example 364

Scheme 55



Example 1 Example 46 i Example 364

Step 1:

To a solution of **Example 1** (305 mg, 0.89 mmol) in DCE (5 mL) was added p-anisaldehyde (134 mg, 0.98 mmol), sodium triacetoxyborohydride (208 mg, 0.98 mmol) and acetic acid (59 mg, 0.98 mmol). The solution was stirred at room temperature overnight. The mixture was diluted with CH_2Cl_2 and washed with 1 M NaOH (aq.). The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The

crude product purified by flash chromatography (SiO_2, gradient 100:0 to 60:40 hexanes:EtOAc) to afford **Example 46** (180mg).

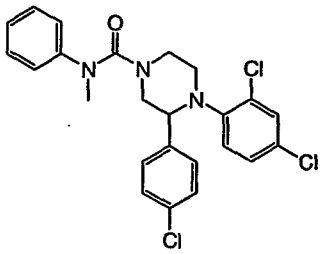
Step 2:

To a solution of **Example 46** (165 mg, 0.36 mmol) in CH_2Cl_2 (5 mL) at 0°C was added triphosgene (33mg, 0.125 mmol) in CH_2Cl_2 (2 mL). The solution was stirred at 0°C for 2 h. The solution was then concentrated *in vacuo* to afford the crude carbamoyl chloride which was used without purification in step 3.

Step 3:

To a solution of the carbamoyl chloride prepared in step 2 (0.36 mmol) in CH_2Cl_2 (5 mL) was added 1-amino piperidine (40 mg, 0.40 mmol) and iPr_2NEt (52 mg, 0.40 mmol). The solution was stirred at room temperature overnight. The solution was diluted with CH_2Cl_2 and washed with $NaHCO_3$ (aq.). The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by preparative TLC (SiO_2; 2:1 EtOAc:hexanes) to afford **Example 364** (38 mg). The product was converted to the HCl salt by dissolving it in CH_2Cl_2 followed by the addition of 2N HCl (in ether). The solvent was then removed to provide the salt.

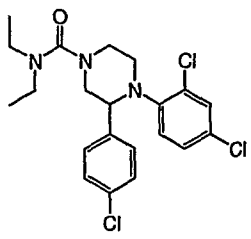
Preparation of Example 365



Example 365

Example 365 was prepared from carbamoyl chloride **i** (**Scheme 55**, step 2) using a procedure similar to that used to prepare **Example 364**, except that N-methylaniline was used in Step 3 (above) instead of 1-aminopiperidine.

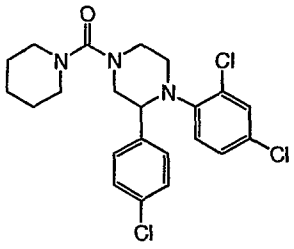
Preparation of Example 366



Example 366

Example 366 was prepared from carbamoyl chloride **i** (**Scheme 55**, Step 2) using a procedure similar to that used to prepare **Example 364**, except that diethylamine was used in Step 3 (above) instead of 1-aminopiperidine.

Preparation of Example 367

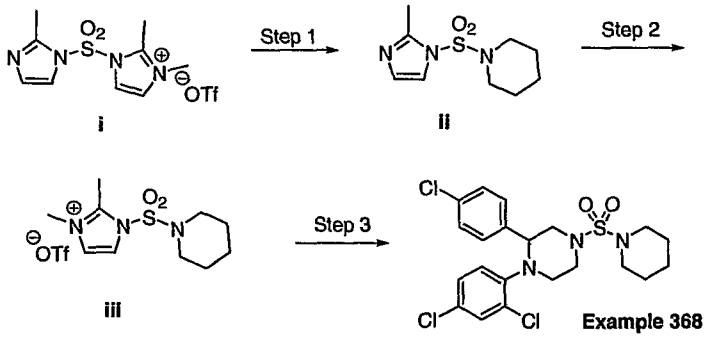


Example 367

Example 367 was prepared from carbamoyl chloride **i** (**Scheme 55**, Step 2) using a procedure similar to that used to prepare **Example 364**, except that piperidine was used in Step 3 (above) instead of 1-aminopiperidine.

Preparation of Example 368

Scheme 56



Step 1:

To a solution of salt **i** (method of J. Organic Chem 68, (2003) 115-119; herein incorporated by reference) (233 mg, 0.64 mmol) in MeCN (5 mL) was added piperidine (37 mg, 0.43 mmol). The solution was allowed to stir overnight at room temperature. The solution was then concentrated and the crude product was purified by filtration through a SiO_2 plug using EtOAc to wash the plug. The filtrate was concentrated to afford **ii** (88 mg) as a white crystalline solid.

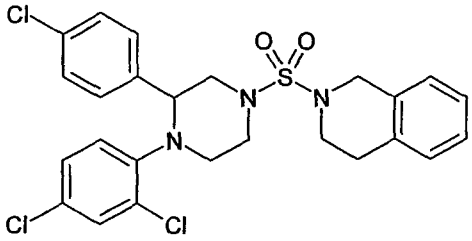
Step 2:

To a solution of **ii** (88 mg, 0.38 mmol) in CH_2Cl_2 (5 mL) at 0°C was added methyl triflate (69 mg, 0.42 mmol). The solution was stirred at 0°C for 2 h. The solution was concentrated to afford **iii** as a white solid.

Step 3:

To a solution of **iii** (0.38 mmol) in MeCN (2 mL) was added **Example 1** (100 mg, 0.29 mmol). The solution was heated to reflux for 16 h. The solution was then concentrated and purified by flash chromatography (SiO_2; gradient elution 100:0 to 80:20 hexanes:EtOAc) to afford **Example 368** (150mg) as a clear oil. The product was converted to the HCl salt by dissolving in CH_2Cl_2 followed by the addition of 2N HCl (in ether). The solvent was then removed to provide the salt.

Preparation of Example 369

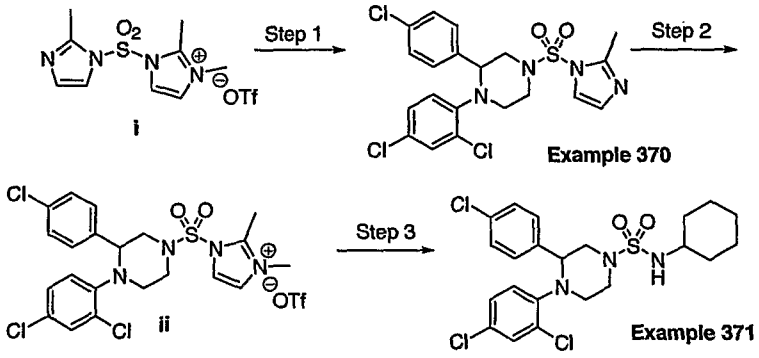


Example 369

Example 369 was prepared from **i** (**Scheme 56**, above) using a procedure similar to that used to prepare **Example 368**, except that tetrahydroquinoline was used in Step 1 (above) instead of piperidine.

Preparation of Examples 370-371

Scheme 57



Step 1:

To a solution of salt **i** (555 mg, 1.53 mmol) in MeCN (10 mL) was added **Example 1** (349 mg, 1.02 mmol). The solution was allowed to stir overnight at room temperature. The solution was concentrated and the crude product was purified via flash chromatography (SiO_2; gradient elution 100:0 to 1:1 hexanes:EtOAc) to afford **Example 370** (252 mg) as a white crystalline solid.

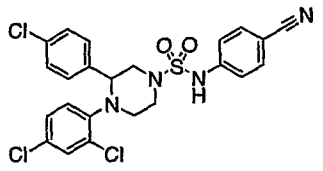
Step 2:

To a solution of **Example 370** (252 mg, 0.52 mmol) in CH_2Cl_2 (15 mL) at 0°C was added methyl triflate (89 mg, 0.54 mmol). The solution was stirred at 0°C for 2 h. The solution was concentrated to afford **ii** as a white solid.

Step 3:

To a solution of **ii** (0.17 mmol) in MeCN (2 mL) was added aminocyclohexane (17 mg, 0.17 mmol). The solution was heated to reflux for 16 h. The solution was then concentrated and purified by preparative TLC (SiO_2 2:1 hexanes:EtOAc) to afford **Example 371** (45 mg) as a clear oil. The product was converted to the HCl salt by dissolving in CH_2Cl_2 followed by the addition of 2N HCl (in ether). The solvent was then removed to provide the salt.

Preparation of Example 372

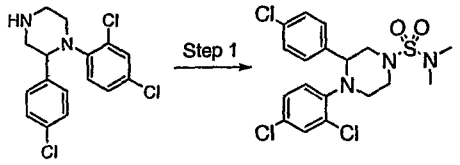


Example 372

Example 372 was prepared using a procedure similar to that used to prepare **Example 371**, except 4-cyanoaniline was used instead of aminocyclohexane in Step 3 (above).

Preparation of Example 373

Scheme 57



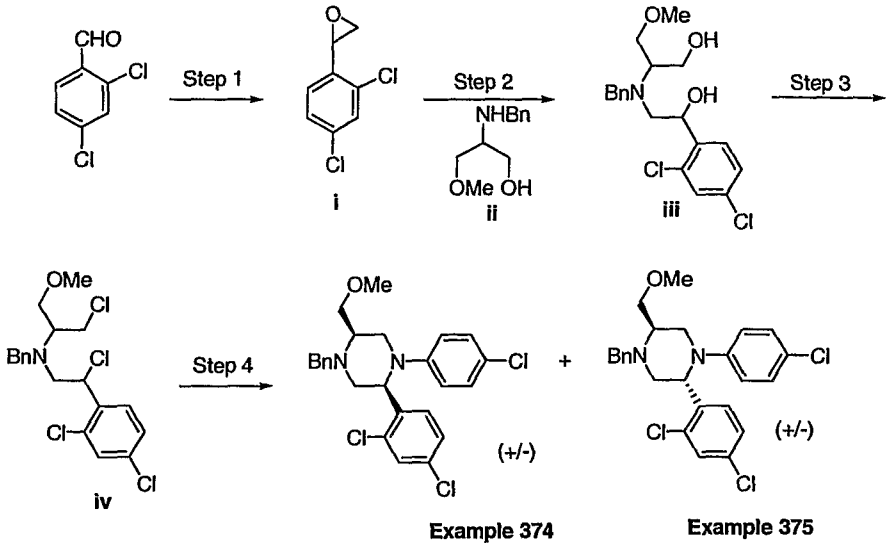
Example 1 **Example 373**

To a solution of **Example 1** (70 mg, 0.20 mmol) in CH_2Cl_2 (2 mL) was added N,N-dimethyl amino sulfonyl chloride (32 mg, 0.23 mol) and iPr_2NEt (31 mg, 0.24 mmol). The solution was stirred at room temperature overnight. The solution was then diluted with CH_2Cl_2 The solution was diluted with CH_2Cl_2 and washed with $NaHCO_3$ (aq.). The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by preparative TLC (SiO_2; 2:1 EtOAc:hexanes) to afford **Example 373** (66 mg). The product was converted to the HCl salt by

dissolving in CH_2Cl_2 followed by the addition of 2N HCl (in ether). The solvent was then removed to provide the salt.

Preparation of Examples 374-375

Scheme 59



Step 1:

To a solution of 2,4-dichlorobenzaldehyde (2.0 g, 11.4 mmol) in anhydrous THF (20 mL) was added diiodomethane (4.59 g, 17.1 mmol). The solution was cooled to 0°C and butyl lithium-lithium bromide complex (1.5 M in Et_2O, 22.8 mmol) was added. The solution was stirred at 0°C for 1 h and the solution was warmed to room temperature and allowed to stir an additional 1 h. To this reaction was slowly added ice. The mixture was then extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford **i** (2.1 g) as an orange oil that was used without purification in Step 2.

Step 2:

To a flask containing **ii** (prepared by the method of Synthesis (1992) 288-292; herein incorporated by reference) (1.55 g, 7.94 mmol) was added **i** (1.5 g, 7.94 mmol). The neat mixture was heated to 130°C for 16 h to afford **iii** (3.0 g), which was used without purification in Step 3.

Step 3:

To a solution of **iii** (1.5 g, 3.9 mmol) in DCE (10 mL) was added thionyl chloride (1.16 g, 9.8 mmol). The resultant solution was heated to reflux for 2 h. The reaction was slowly quenched with $NaHCO_3$ (aq.). The mixture was then extracted with CH_2Cl_2 (3x). The combined organic layers were dried over

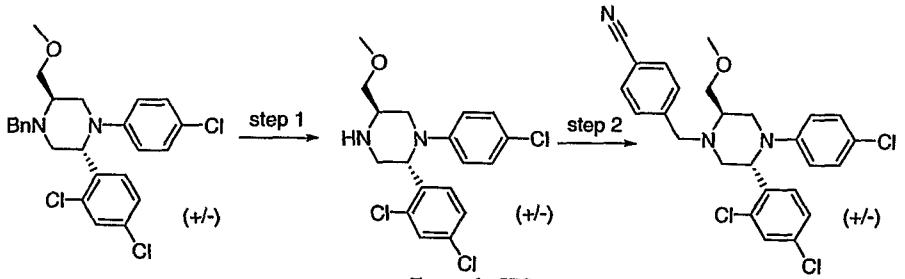
Na_2SO_4, filtered and concentrated to afford **iv** (1.64 g), which was used without purification in Step 4.

Step 4:

To a solution of **iv** (1.64 g, 3.9 mmol) propylnitrile (20 mL) was added 4-chloroaniline (1.49 g, 11.7 mmol). The solution was heated to reflux overnight. The solution was partitioned between $NaHCO_3$ (aq.) and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (SiO_2; gradient elution 100:0 to 9:1 hexanes: EtOAc) to afford **Example 374** (265 mg) and after further purification by preparative TLC (SiO_2; 9:1 hexanes:EtOAc) **Example 375** (60 mg). The products were converted to their HCl salts by dissolving in CH_2Cl_2 followed by the addition of 2N HCl (in ether). The solvent was then removed to provide the salts.

Preparation of Examples 376-377

Scheme 60



Example 375 Example 376 Example 377

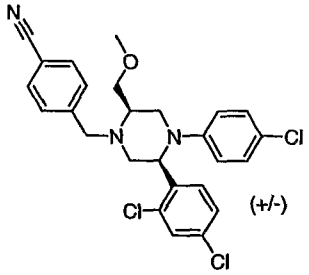
Step 1:

To a solution of **Example 375** (30 mg, 0.064 mmol) in DCE (2 mL) was added 1-chloroethyl chloroformate (10 mg, 0.07 mmol). The solution was heated to reflux for 1 h. Additional 1-chloroethyl chloroformate (8 mg, 0.056 mmol) was added and the solution was heated to reflux for an additional 8 h. The solution was concentrated. To the crude product was added MeOH (1 mL). The resultant solution was heated to reflux for 1.5 h. The solution was concentrated. The material was partitioned between CH_2Cl_2 and $NaHCO_3$ (aq.). The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by preparative TLC (SiO_2 1:1 hexanes:EtOAc) to afford **Example 376** (17 mg).

Step 2:

To a solution of **Example 376** (17 mg, 0.05 mmol) in CH_2Cl_2 (1 mL) was added 4-cyanobenzaldehyde (7 mg, 0.05 mmol) and sodium triacetoxyborohydride (16 mg, 0.075 mmol). The mixture was stirred at room temperature for 16 h. The mixture was partitioned between EtOAc and $NaHCO_3$ (aq.). The aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by preparative TLC (SiO_2 4:1 hexanes:EtOAc) to afford **Example 377**. The product was converted to the HCl salt by dissolving in CH_2Cl_2 followed by the addition of 2N HCl (in ether). The solvent was then removed to provide the salt.

Preparation of Example 378

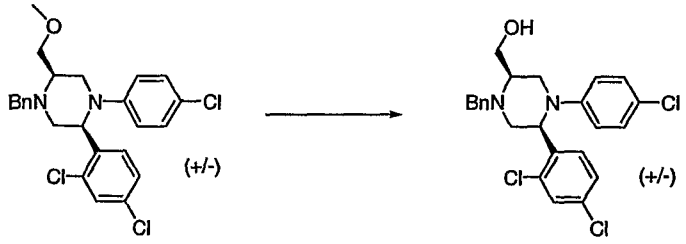


Example 378

Example 378 was prepared using the same procedure used to prepare **Example 377**, except **Example 374** was used as the starting material instead of **Example 375.**

Preparation of Example 379

Scheme 61

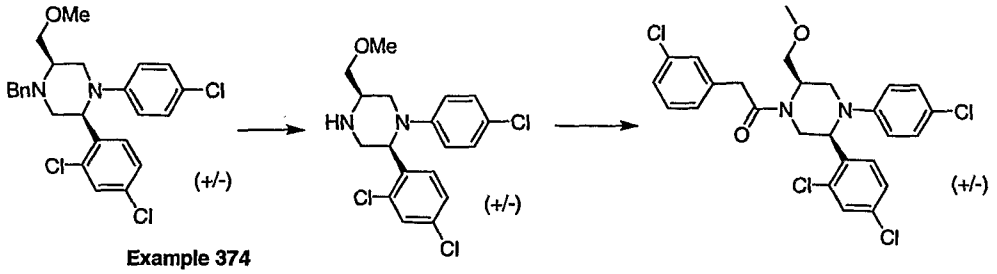


Example 374 **Example 379**

To a solution of **Example 374** (50 mg, 0.1 mmol) in CH_2Cl_2 (5 mL) at 0°C was added BBr_3 (26 mg, 0.15 mmol). The solution was allowed to warm to room temperature and stirred for 3 h. To the solution was added $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by

preparative TLC (SiO_2 4:1 hexanes:EtOAc) to afford **Example 379**. The product was converted to the HCl salt by dissolving in CH_2Cl_2 followed by the addition of 2N HCl (in ether). The solvent was then removed to provide the salt (9 mg).

Preparation of Example 380



Example 374 Example 380

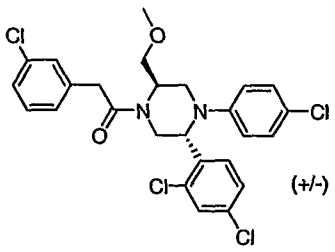
Step 1:

Example 374 was converted to the secondary amine using conditions similar to those used to prepare **Example 376** in Scheme 60.

Step 2:

The secondary amine prepared in step 1 was reacted with 3-chlorophenylacetic acid using conditions similar to those used to prepare **Example 358** in Scheme 54.

Preparation of Example 381

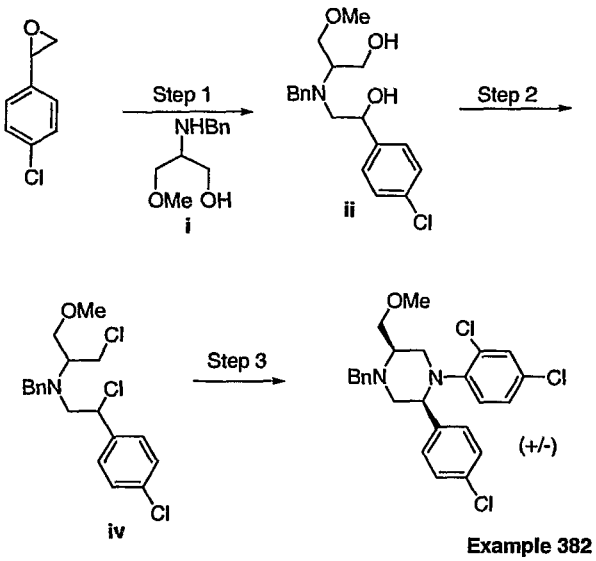


Example 381

Example 381 was prepared using conditions similar to those used to prepare **Example 380**, except that **Example 376** was used instead of **Example 374**.

Preparation of Example 382

Scheme 62



Example 382

Step 1:

To a flask containing **i** (1.0 g, 5.1 mmol) was added 4-chlorostyrene epoxide. The neat mixture was heated to 130°C for 18 h to afford the diol **ii** which was used without purification.

Step 2:

To a solution of **ii** (710 mg, 2.02 mmol) in $CHCl_3$ (15 mL) was added thionyl chloride (603 mg, 5.07 mmol). The resultant solution was heated to reflux for 3 h. The solution was cooled to room temperature and concentrated. The crude mixture was partitioned between CH_2Cl_2 and $NaHCO_3$ (aq.). The mixture was stirred vigorously for 10 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford **iv**, which was used without purification in Step 3.

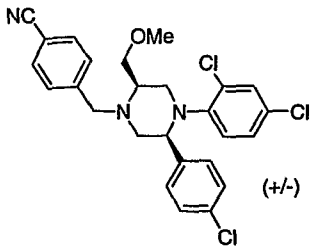
Step 3:

To a solution of the dichloride **iv** (3.0 mmol) in propioniltrile (20 mL) was added 2,4-dichloroaniline (486 mg, 3.0 mmol) and iPr_2NEt (387 mg, 3.0 mmol). The mixture was heated to 100°C for 16 h. Cooled solution to room temperature and concentrated.

The crude material was dissolved in anhydrous THF (10 mL). To this solution was added NaH (60 mg, 60% in oil). The mixture was heated to reflux for 16 h. Additional NaH (60mg, 60% in oil) was added and the mixture was

heated to reflux for an additional 24h. Water was slowly added and the mixture was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by preparative TLC (SiO_2, 4:1 hexanes:EtOAc) to afford **Example 382** (365 mg). The product was converted to the HCl salt by dissolving in CH_2Cl_2 followed by the addition of 2N HCl (in ether). The solvent was then removed to provide the salt.

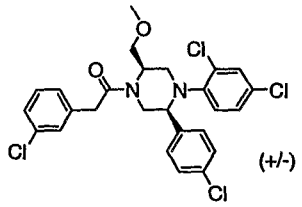
Preparation of Example 383



Example 383

Example 383 was prepared using conditions similar to those used to prepare **Example 377**, except **Example 374** was used as the starting material instead of **Example 375**.

Preparation of Example 385

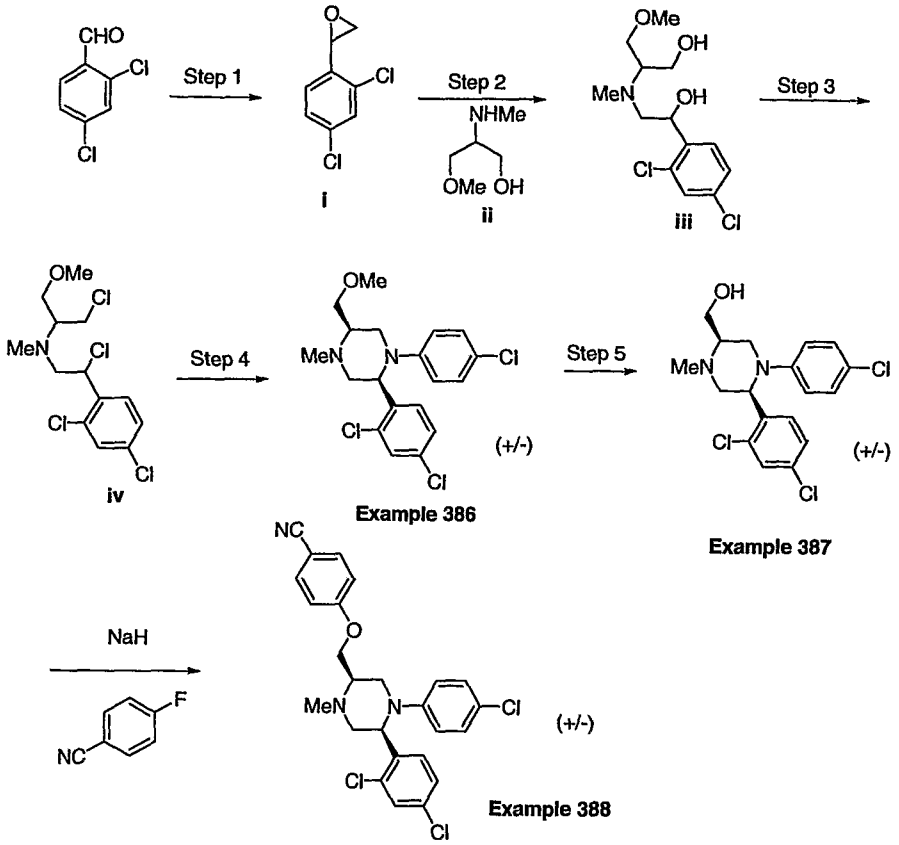


Example 385

Example 385 was prepared using conditions similar to those used to prepare **Example 380**.

Preparation of Examples 386-388

Scheme 63

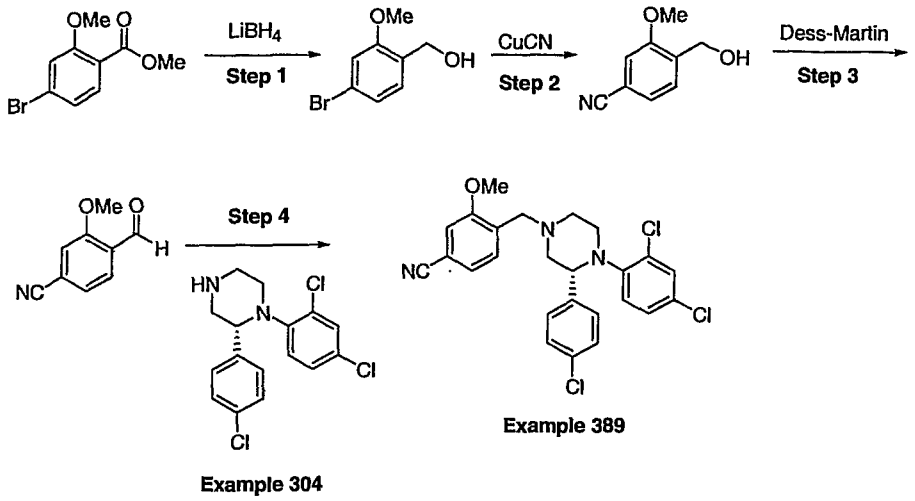


The N-methyl piperazine **Example 386** was prepared using procedures similar to those described above for **Example 374** (Steps 1, 2, 3, and 4). The alcohol **Example 387** was prepared from the N-methyl piperazine **Example 386** using a procedure similar to that used to prepare **Example 379**.

The alcohol **Example 387** (30 mg) was taken up in DMF. Sodium hydride (12 mg of a 60 wt % dispersion in oil) was added. 4-Fluorobenzonitrile (35 mg) was added, and the solution was stirred at 25°C (18 h). The solution was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). Filtration and concentration gave a yellow oil. Purification via thin-layer preparative chromatography (2/1 hexanes/EtOAc, SiO_2) gave 21 mg (45 %) of **Example 388** as an oil.

Preparation of Example 389

Scheme 64



Step 1:

To methyl-4-bromo-2-methoxybenzoate (Aldrich) (1.0 g, 4.1 mmol) in THF (10 mL), was added $LiBH_4$ (0.13 g, 6.1 mmol). Ethanol (2 mL) was added dropwise. The resulting reaction mixture was stirred at room temperature for 20 h. 1 N NaOH was added, and the mixture was extracted with EtOAc. The organic layers were combined and washed with water and brine, then dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide the corresponfing benzyl alcohol (0.86 g, 4.0 mmol).

Step 2:

To the benzyl alcohol prepared in step 1 (0.86 g, 4.0 mmol) in DMF (8 mL) was added CuCN (1.1 g, 12 mmol). The mixture was warmed to 150°C and stirred for 20 h. The mixture was then cooled to room temperature and EtOAc was added, followed by a saturated NH_4Cl/NH_4OH solution. The mixture was stirred vigorously for 10 minutes and extracted with EtOAc, then the organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by silica gel chromatography provided 4-hydroxymethyl-3-methoxy-benzonitrile (0.38 g, 2.3 mmol).

Step 3:

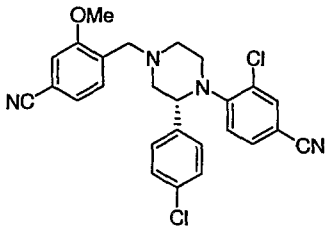
To 4-hydroxymethyl-3-methoxy-benzonitrile prepared in step 2 (0.38 g, 2.3 mmol) in CH_2Cl_2 (8 mL) at room temperature was added Dess-Martin periodinane (1.2 g, 2.8 mmol). The mixture was stirred at room temperature for 20 h. The resulting white precipitate was filtered off and the filtrate concentrated *in vacuo*.

The residue was purified by silica gel chromatography (20% EtOAc/Hex) to provide the corresponding aldehyde (0.32 g, 2.0 mmol).

Step 4:

To the aldehyde prepared in step 3 (0.07 g, 0.44 mmol) in DCE (1 mL) was added the piperazine **Example 304** (0.15 g, 0.44 mmol) followed by $Na(OAc)_3BH$ (0.19 g, 0.88 mmol). The mixture was stirred at room temperature for 20 h. CH_2Cl_2 was added and the mixture was washed with 1 N NaOH, water and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (35% EtOAc/hexane) to provide **Example 389** (0.21 g, 0.44 mmol).

Preparation of Example 390

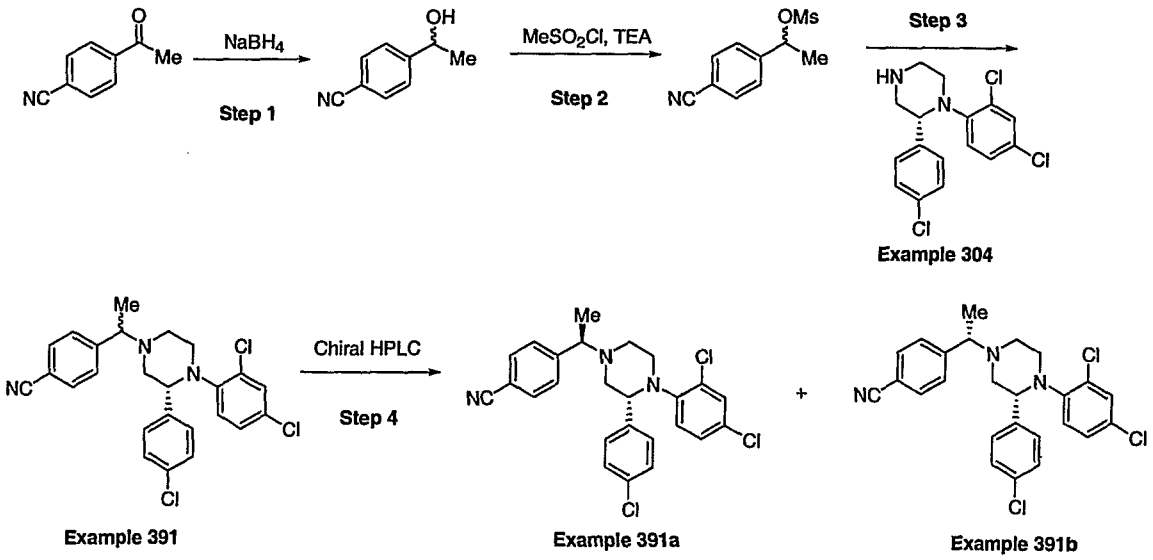


Example 390

Example 390 was prepared in a manner similar to that used to prepare **Example 389** in **Scheme 64**, except that piperazine **Example 305** was used instead of piperazine **Example 304** in step 4.

Preparation of Examples 391, 391a, and 391b

Scheme 65



Step 1:

To 4-acetylcyanobenzene (2.0 g, 13.8 mmol) in MeOH (55 mL) was added $NaBH_4$ (0.52 g, 13.0 mmol) in one portion. The reaction was stirred for 3 h, allowing the cold bath to warm. The reaction mixture was concentrated *in vacuo*. Water was added and the mixture was extracted with ether. The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide the corresponding alcohol (2.0 g, 13.6 mmol).

Step 2:

To the alcohol prepared in step 1 (2.0 g, 13.6 mmol) in CH_2Cl_2 (45 mL) at 0°C was added TEA (2.1 g, 20.4 mmol) followed by $MeSO_2Cl$ (1.87 g, 16.3 mmol). The mixture was stirred for 20 h, allowing the cold bath to warm. CH_2Cl_2 was added and the combined organic layers were washed with saturated $NaHCO_3$, water, and brine, then dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide the corresponding mesylate (2.88 g, 12.8 mmol).

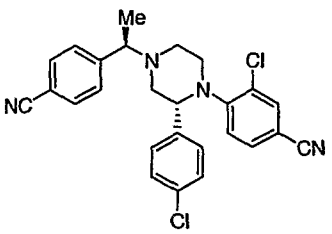
Step 3:

To the mesylate prepared in step 2 (1.1 g, 4.8 mmol) in acetonitrile (13 mL) was added the piperazine **Example 304** (1.3 g, 3.84 mmol) followed by K_2CO_3 (1.33 g, 9.6 mmol). The mixture was warmed to reflux and stirred for 20 h, cooled to room temperature, followed by the addition of water. The mixture was extracted with ethyl acetate, and the combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The concentrate was purified by silica gel chromatography (30% EtOAc/hexane) to provide **Example 391** (1.44 g, 3.1 mmol) as a 1:1 mixture of diastereomers.

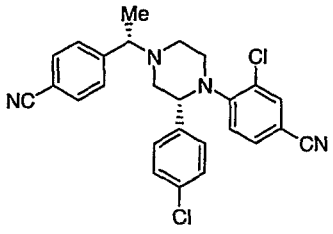
Step 4:

The mixture of diastereomers of **Example 391** were separated by preparative chiral HPLC (Chiralcel OD, 5x50 cm, 3% IPA/hexane, 48 ml/min, 254 nm) to provide a faster eluting and slower eluting stereoisomer.

Preparation of Examples 392a and 392b



Example 392a

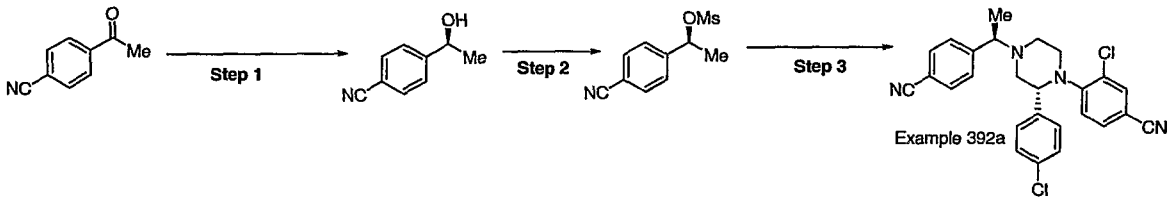


Example 392b

Examples 392a and **392b** were prepared using procedures similar to those used to prepare **Examples 391a and 391b** in **Scheme 65**, above, except that the piperazine **Example 305** was used in step 3 instead of **Example 304.** **Examples 392a** and **392b** were separated by chiral preparative HPLC (Chiralcel OD, 5x50 cm, 10% IPA/hexane, 48 mL/min, 254 nm).

Alternatively, **Example 392a** was prepared by the following method:

Scheme 66



Step 1:

To 4-acetylbenzonitrile (3.0 g, 20.7 mmol) in THF (21 mL) at -18°C (CO_2/ethylene glycol bath) was added (*R*)-2-methyl-CBS-oxazaborolidine (1M in toluene, 2.1 mL) followed by BH_3•SMe_2 (2.0M in THF, 7.2 mL) (following the chiral reduction procedure described in Chem. Rev., 1993, 93, 763-784). The cold bath was allowed to expire while stirring for 18 h. MeOH (~10 mL) was added (with gas evolution) and stirred for 15 minutes. The reaction mixture was concentrated *in vacuo* and taken up into EtOAc. The reaction mixture was then washed with 1N HCL, water, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo.* The residue was purified by silica gel chromatography (5-40% EtOAc/hexanes) to provide the corresponding chiral alcohol (1.85 g, 12.6 mmol).

Step 2:

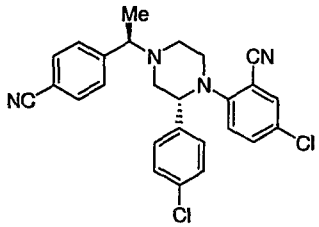
To the alcohol prepared in step 1 (0.70 g, 4.8 mmol) in CH_2Cl_2 (16 mL) at 0°C was added TEA (triethylamine; 0.72 g, 7.1 mmol) followed by methanesulfonyl chloride (0.60 g, 5.2 mmol). The reaction mixture was stirred at

0°C for 1 h. CH_2Cl_2 was added and the mixture was washed with 1N HCL, water, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide the corresponding chiral mesylate (1.1 g, 4.7 mmol) that was used directly in the next step without further purification.

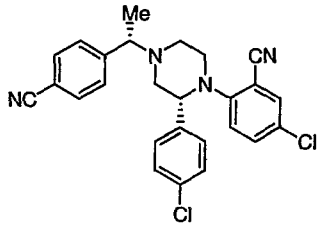
Step 3:

To the piperazine **Example 305** (1.3 g, 4.0 mmol) in acetonitrile (13 mL) was added the mesylate prepared in step 2 (1.0 g, 4.6 mmol) followed by potassium carbonate (1.4 g, 10.1 mmol). The mixture was warmed to reflux and stirred for 36 h. The mixture was cooled to room temperature and water was added. The mixture was extracted with EtOAc. The organic layers were combined and washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (0-10% MeOH/CH_2Cl_2) to provide a mixture of **Example 392a** and **Example 392b** (1.0 g) in ~10:1 ratio as determined by chiral HPLC (Chiralcel OD, 10% IPA/hexanes, 1 mL/min, 254 nm- **Example 392a** retention time=12.0 min; **Example 392b** retention time 13.8 min). **Example 392b** was separated from **Example 392a** by preparative chiral HPLC (Chiralcel OD, 10% IPA/hexanes, 50 mL/min, 254 nm) to provide **Example 392a** (0.68 g, 1.48 mmol).

Preparation of Examples 393a and 393b



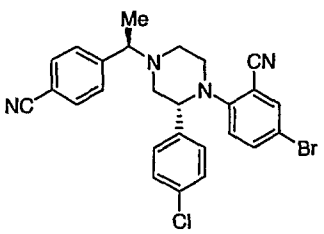
Example 393a



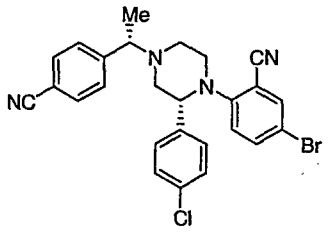
Example 393b

Examples 393a and **393b** were prepared using procedures similar to those used to prepare **Examples 391a and 391b** in **Scheme 65**, above, except that piperazine **Example 310** was used in step 3 instead of **Example 304**. **Examples 393a** and **393b** were separated by chiral preparative HPLC (Chiralcel OD, 5x50 cm, 25% IPA/hexane, 50 mL/min., 254 nm).

Preparation of Examples 394a and 394b



Example 394a

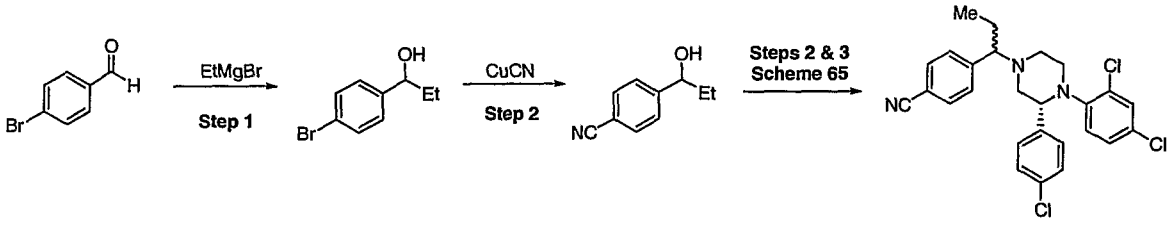


Example 394b

Examples 394a and **394b** were prepared using procedures similar to those used to prepare **Examples 391a and 391b** in **Scheme 65**, above, except that piperazine **Examples 306** was used in step 3 instead of **Example 304**. **Examples 394a** and **394b** were separated by chiral preparative HPLC (Chiralcel OD, 5x50 cm, 5% IPA/hexane, 50 mL/min, 254 nm).

Preparation of Example 395

Scheme 67



Example 395

Step 1:

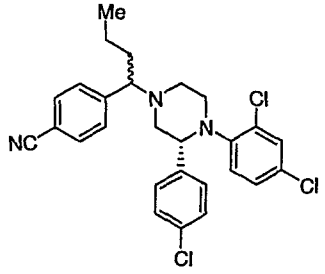
To 4-bromobenzaldehyde (1.0 g, 5.4 mmol) in THF (18 mL) at 0°C was added ethylmagnesium bromide (1.0 M in THF, 5.9 mL). The reaction mixture was stirred for 40 minutes. Water was added, then 25% aqueous sodium citrate solution. The mixture was extracted with EtOAc. The organic layers were combined and washed with water and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (20% EtOAc/hexane) provided the corresponding alcohol (0.81 g, 3.8 mmol).

Step 2:

To the alcohol prepared in step 1 (0.8 g, 3.8 mmol) in DMF (14 mL) was added CuCN (1.16 g, 12.9 mmol). The reaction mixture was warmed the to 150°C, stirred for 18 h and then cooled to room temperature. A NH_4Cl/saturated NH_4OH (9:1) solution was then added and the mixture was extracted with EtOAc. The organic layers were combined and dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (30% EtOAc/hexane)

provided the corresponding nitrile (0.34 g, 2.1 mmol). The nitrile was converted to **Example 395** the procedures described above in steps 2 and 3 of **Scheme 65**.

Preparation of Example 396

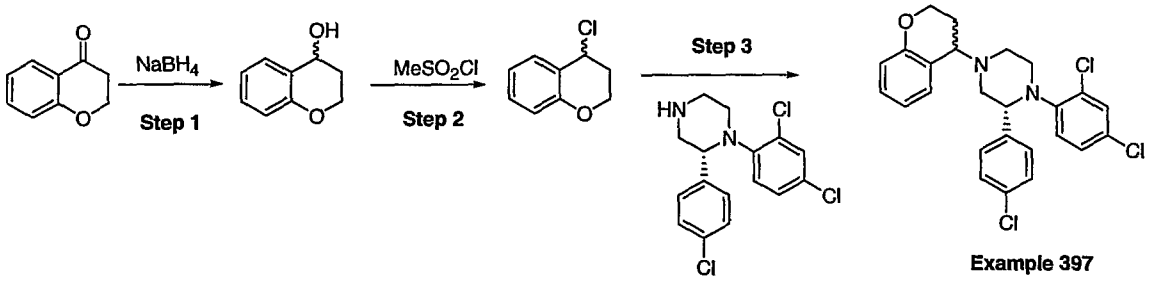


Example 396

The propyl piperazine **Example 396** was prepared using the procedures of Scheme 67 except that propylmagnesium chloride was used instead of ethylmagnesium bromide in step 1.

Preparation of Example 397

Scheme 68



Example 304 **Example 397**

Step 1:

To 4-chromanone (1.0 g, 6.75 mmol) in MeOH (20 mL) was added $NaBH_4$ (0.51 g, 13.5 mmol). The reaction mixture was stirred for 2 h and then concentrated *in vacuo*. 1N HCl was added and the mixture was extracted with EtOAc. The organic layers were combined and washed with water and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide the corresponding alcohol (1.01 g, 6.75 mmol).

Step 2:

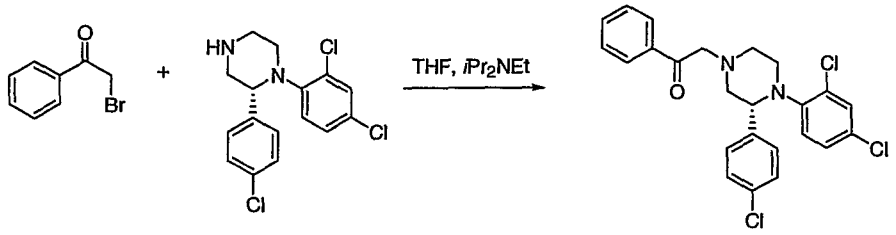
To the alcohol prepared in step 1 (1.1 g, 7.3 mmol) in CH_2Cl_2 (20 mL) at 0°C was added TEA (1.53 mL, 11 mmol) followed by methanesulfonyl chloride (0.68 mL, 8.8 mmol). The reaction mixture was stirred for 1 h and CH_2Cl_2 was added. The mixture was washed with water and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide the corresponding chloride (1.23 g, 5.38 mmol).

Step 3:

To the piperazine **Example 304** (0.10 g, 0.29 mmol) in acetonitrile (1 mL) was added the chloride prepared in step 2 (0.06 g, 0.37 mmol) followed by K_2CO_3 (0.10 g, 0.73 mmol). The mixture was warmed to reflux and stirred for 20 h. The reaction mixture was concentrated *in vacuo* and EtOAc was added. The mixture was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel preparative TLC (2000μm, 10% EtOAc/hexane) to provide **Example 397** (0.80 g, 0.17 mmol).

Preparation of Example 398

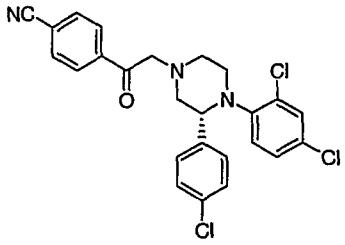
Scheme 69



Example 304 Example 398

To the piperazine **Example 304** (1.0 g, 2.9 mmol) in THF (10 mL) was added diisopropylethyl amine (1.1 g, 8.7 mmol) followed by 2-bromoacetophenone (1.1 g, 5.8 mmol). The mixture was stirred for 75 minutes at room temperature and water was added. The mixture was extracted with ethyl acetate, then the combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (30% EtOAc/hexane) provided **Example 398** (1.1 g, 2.4 mmol).

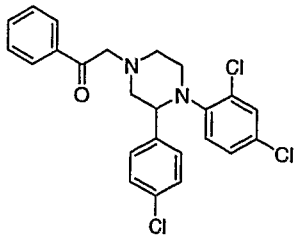
Preparation of Example 399



Example 399

Example 399 was prepared using procedures similar to those used to prepare **Example 398** in **Scheme 69** except that 2-bromo-4'-cyanoacetophenone was used instead of 2-bromoacetophenone.

Preparation of Example 400

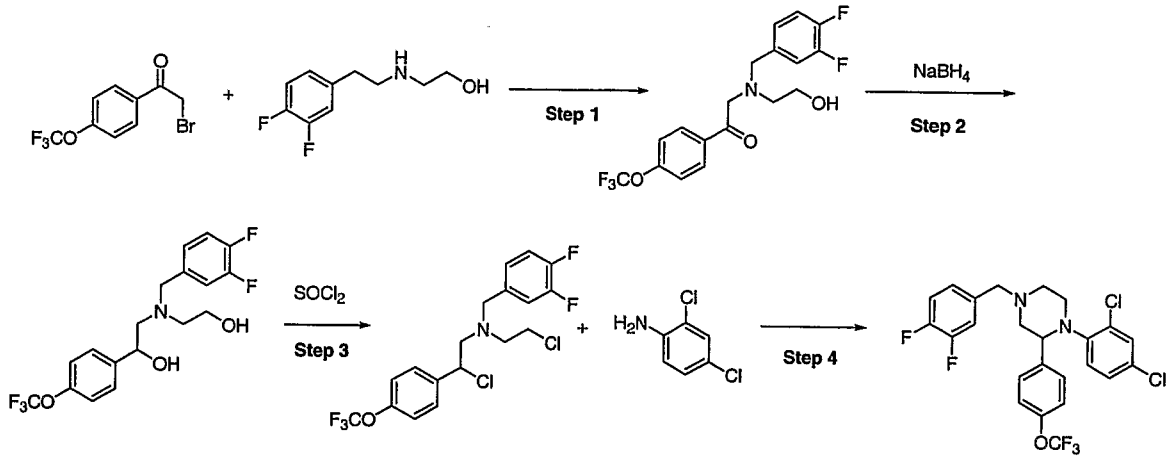


Example 400

Example 400 was prepared using procedures similar to those used to preapre **Example 398** in **Scheme 69** except that the racemic piperazine **Example 1** was used instead of chiral piperazine **Example 304.**

Preparation of Examples 401-410

Scheme 70



Example 401

Step 1:

To the 2-[2-(3,4-difluorophenyl)-ethylamino]-ethanol (0.5 g, 2.7 mmol) in acetonitrile (5 mL) was added 2-bromo-1-(4-trifluoromethoxyphenyl)-ethanone (0.76 g, 2.7 mmol) and K_2CO_3 (0.44 g, 3.2 mmol). The reaction mixture was stirred at room temperature for 20 h, and concentrated *in vacuo*. Water was added to the concentrate, which was then extracted with EtOAc. The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (40% EtOAc/hexane) provided 2-[(3,4-difluorobenzyl)-(2-hydroxyethyl)-amino]-1-(4-trifluoromethoxyphenyl)-ethanone (0.8 g, 2.1 mmol).

Step 2:

To 2-[(3,4-difluorobenzyl)-(2-hydroxyethyl)-amino]-1-(4-trifluoromethoxyphenyl)-ethanone (0.8 g, 2.1 mmol) in MeOH (10 mL) at 0°C was added $NaBH_4$ (0.12 g, 3.1 mmol) in one portion. The mixture was allowed to warm to room temperature and stirred for 20 h. The reaction mixture was concentrated *in vacuo*, and the residue was taken up into CH_2Cl_2 and washed with 1N NaOH, water, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide a diol (0.8 g, 2.1 mmol).

Step 3:

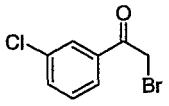
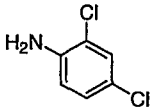
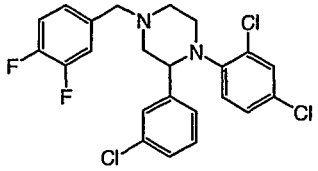
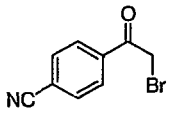
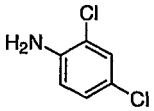
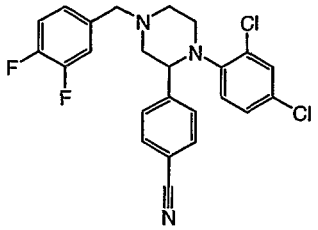
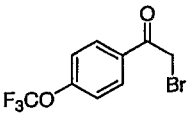
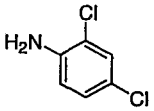
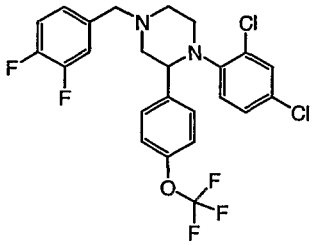
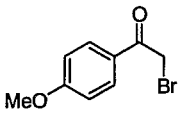
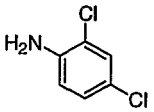
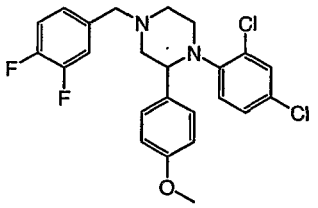
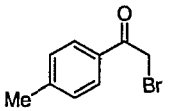
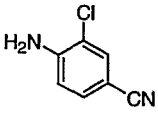
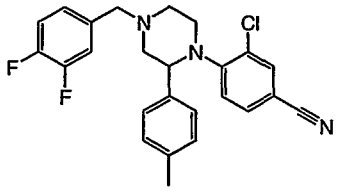
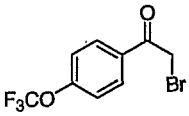
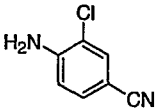
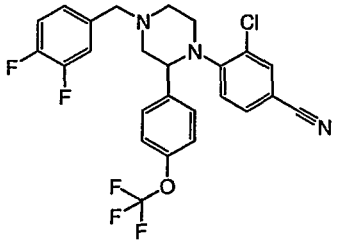
To the diol prepared in step 2 (0.8 g, 2.1 mmol) in $CHCl_3$ (16 mL) at 0°C was added thionyl chloride (4 mL). The reaction mixture was allowed to warm to room temperature and then warmed to reflux and stirred for 2h. The reaction was cooled to room temperature and concentrated *in vacuo*. The residue was taked up into CH_2Cl_2 and stirred vigorously with saturated $NaHCO_{3(aq)}$. The organic layer was washed with water and brine, then dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide the corresponding dichloride (0.74 g).

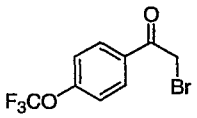
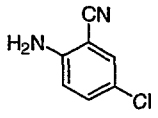
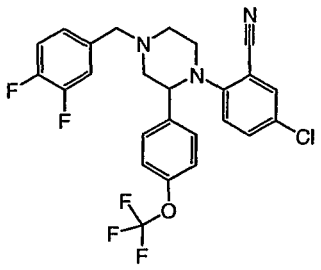
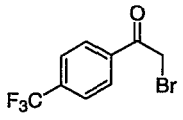
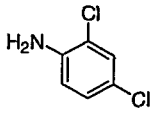
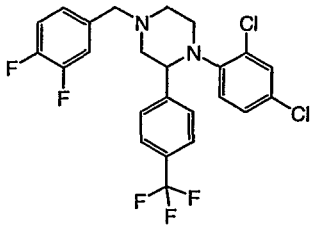
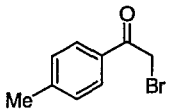
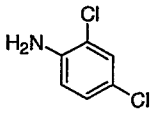
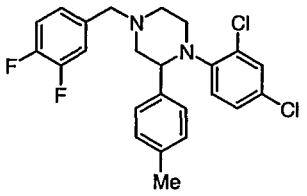
Step 4:

To the dichloride prepared in step 3 (0.15 g, 0.35 mmol) in propionitrile (1.5 mL) was added the aniline (0.17 g, 1.1 mmol). The reaction mixture was warmed to reflux and stirred for 20 h. The reaction was then concentrated *in vacuo*. The residue was taken up into CH_2Cl_2 and washed with saturated $NaHCO_{3(aq)}$, water, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by preparative silica TLC (25% EtOAc/hexane) to provide **Example 401** (0.5 g).

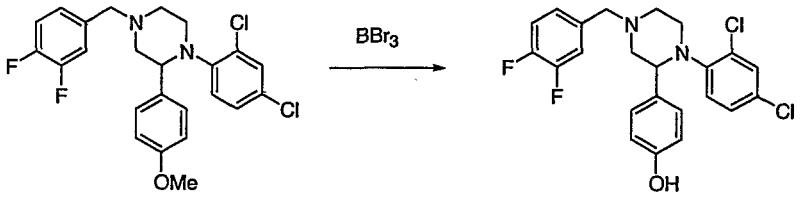
Examples 402-410 listed below in Table XIII were prepared from the appropriate bromoketone and substituted aniline using the general procedure described in Scheme 70.

Table XIII

Example #	Bromoketone	Aniline	Example Structure
402			
403			
404			
405			
406			
407			

Example #	Bromoketone	Aniline	Example Structure
408			
409			
410			

Preparation of Example 411

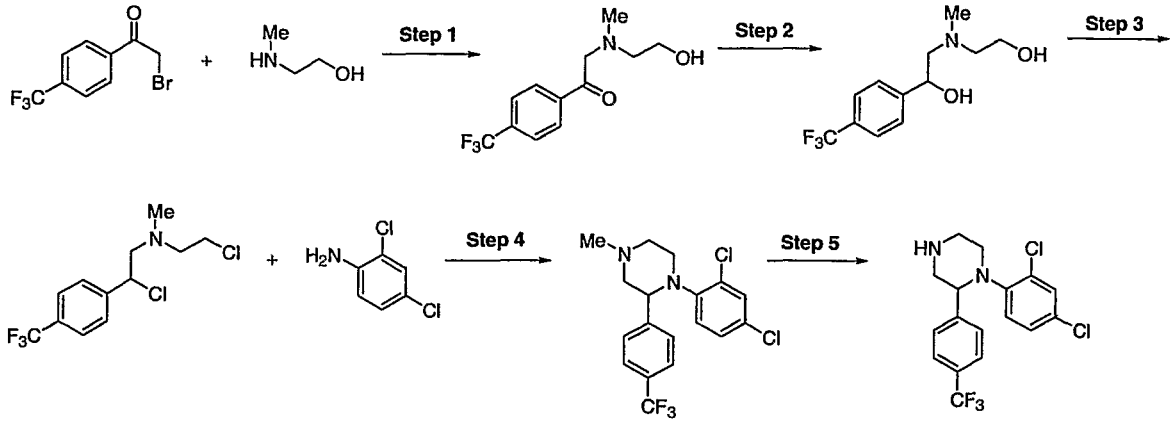


Example 405 Example 411

To the piperazine **Example 405** (0.125 g, 0.27 mmol) in CH_2Cl_2 (1 mL) at -78°C was added boron tribromide (1.0 M in CH_2Cl_2, 0.3 mL). The cold bath was removed from the reaction vessel and the reaction mixture was stirred for 30 minutes. Additional boron tribromide (0.6 mL) was added and the reaction was stirred at room temperature for 20 h. The reaction mixture was diluted with CH_2Cl_2 and poured into cold saturated $NaHCO_{3\,(aq)}$. The mixture was extracted with CH_2Cl_2. The organic layers were combined and washed with water and brine. The organic layer was then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was triturated with ether to provide **Example 411** (0.036 g).

Preparation of Examples 412-415

Scheme 71



Step 1:

To the bromoketone (1.0 g, 3.6 mmol) in acetonitrile (7 mL) was added 2-(methylamino)ethanol (0.3 mL) and K_2CO_3 (0.6 g, 4.35 mmol). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated *in vacuo*. The resulting residue was taken up into EtOAc and then washed with water and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide an amino alcohol (0.85 g) which was used in step 2 without further purification.

Step 2:

To the amino alcohol prepared in step 1 (0.83 g, 3.2 mmol) in MeOH (10 mL) at 0°C was added $NaBH_4$ (0.18 g, 4.8 mmol) in one portion. The reaction mixture was allowed to warm to room temperature while stirring for 20 h. The reaction was concentrated *in vacuo* and taken up into CH_2Cl_2 and washed with 1N NaOH, water, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide the corresponding diol (0.8 g).

Step 3:

To the diol prepared in step 2 (0.8 g, 3.0 mmol) in dichloroethane (24 mL) at 0°C was added thionyl chloride (6 mL). The reaction mixture was allowed to warm to room temperature and then heated to reflux for 2 h. The reaction mixture was concentrated *in vacuo*, taken up into CH_2Cl_2 and stirred vigorously with saturated $NaHCO_{3\,(aq)}$. The organic layer was washed with water and brine

and dried ($MgSO_4$). The organic layer was filtered and concentrated *in vacuo* to provide the corresponding dichloride (0.74 g).

Step 4:

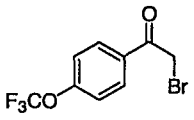
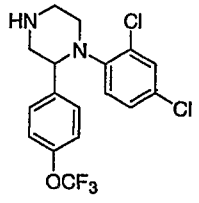
To the dichloride prepared in step 3 (0.2 g, 0.67 mmol) in propionitrile (2 mL) was added 2,4-dichloroaniline (0.32 g). The reaction mixture was warmed to reflux and stirred for 20 h. The reaction was concentrated *in vacuo* and the residue taken up into CH_2Cl_2. The reaction mixture was then washed with 1N NaOH, water, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide a residue that was purified by silica gel chromatography (0-8% MeOH/EtOAc) to provide **Example 412** (0.24 g).

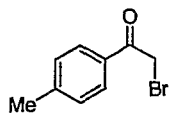
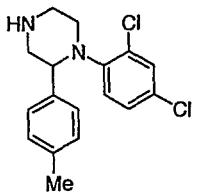
Step 5:

To the piperazine **Example 412** (0.24 g) in dichloroethane (2 mL) was added proton sponge (0.04g) and 1-chloroethylchloroformate (0.13 mL). The reaction mixture was warmed to reflux and stirred for 20 h. The reaction mixture was concentrated *in vacuo* and the residue taken up into MeOH (2 mL). The soution was warmed to reflux and stirred for 3 h. The reaction mixture was concentrated *in vacuo*, the resulting residue taken up into CH_2Cl_2, and then washed with 1N NaOH, water, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (8% MeOH/CH_2Cl_2) to provide the piperazine **Example 413** (0.2 g).

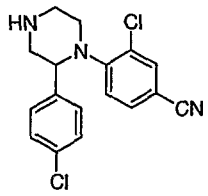
The following piperazines were prepared as in Scheme 71 above using the α-bromoketone listed in Table XIV in step 1.

Table XIV

Example #	α-Bromoketone	Example Structure
414		

Example #	α-Bromoketone	Example Structure
415		

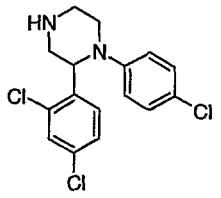
Preparation of Example 416



Example 416

The piperazine **Example 416** was prepared in a manner similar to that used to prepare **Example 1** in Scheme 1 except that 4-amino-3-chlorobenzonitrile was used instead of 2,4-dichloroaniline in step 3.

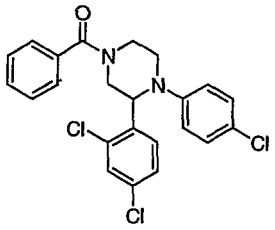
Preparation of Example 417



Example 417

Piperazine **Example 417** was prepared in the same manner as **Example 1** in Scheme 1 except that 2-(2,4-dichlorophenyl)oxirane (prepared from 2,4-dichlorobenzaldehyde as in step 1 of scheme 7) was used instead of 2-(4-chlorophenyl)oxirane in step 1 and 4-chloroaniline was used instead of 2,4-dichloroaniline in step 3.

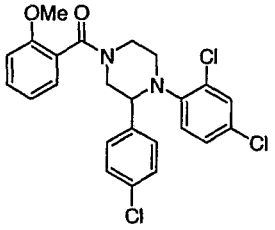
Preparation of Example 418



Example 418

Example 418 was prepared in the same manner as **Example 4** in Scheme 2 except that the piperazine **Example 417** was used instead of **Example 1**.

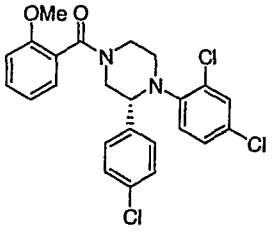
Preparation of Example 419



Example 419

Example 419 was prepared in the same manner as **Example 4** in Scheme 2 except that 2-methoxybenzoyl chloride was used instead of benzoyl chloride.

Preparation of Example 420

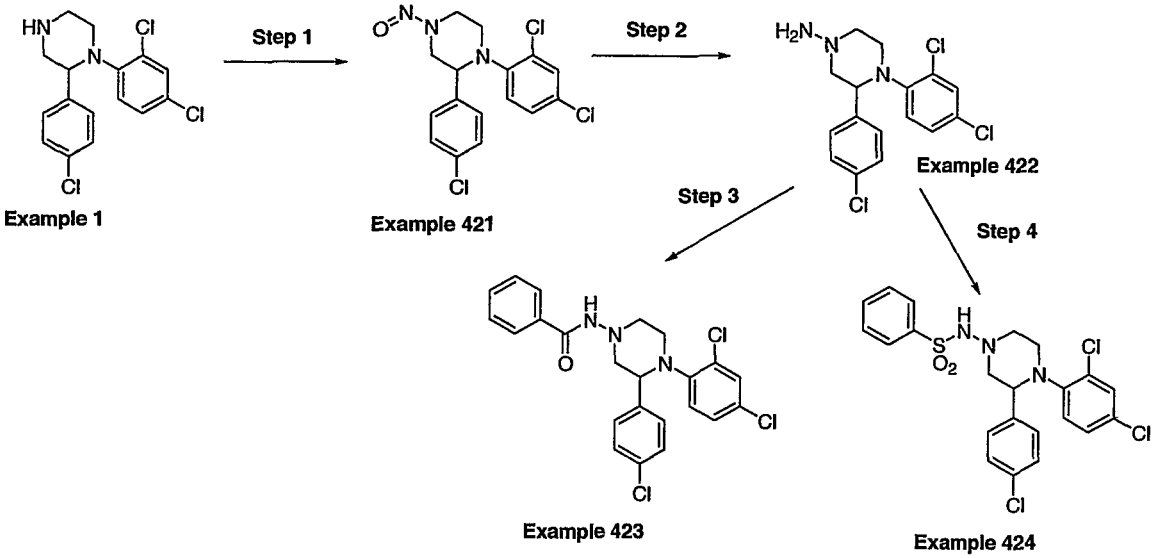


Example 420

Example 420 was prepared in the same manner as **Example 4** in Scheme 2 except that the piperazine **Example 304** was used instead of **Example 1** and 2-methoxybenzoyl chloride was used instead of benzoyl chloride.

Preparation of Examples 421-424

Scheme 72



Step 1:

To the piperazine **Example 1** (0.31 g, 0.89 mmol) in THF (3 mL) at 0°C was added 3N $HCl_{(aq)}$ (1.5 mL). $NaNO_2$ (0.14 g, 2.1 mmol) in water (0.9 mL) was then added and the cold bath was removed from the reaction vessel. The reaction mixture was stirred for 15 h. The reaction mixture was then made basic with 3N NaOH, extracted with EtOAc, and the organic layer was washed with water and brine. The organic layer was then dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide **Example 421** (0.31 g, 085 mmol).

Step 2:

To the piperazine **Example 421** (0.31 g, 0.85 mmol) in AcOH (3 mL) was added water (1.4 mL). Zinc dust was added (0.062 g) in one portion. THF (1 mL) was then added, and the reaction mixture was warmed to 50°C. After 1 h, additional zinc dust (0.3 g) was added. The reaction mixture was stirred at reflux for an additional 1 h. The reaction mixture was cooled to room temperature and filtered. EtOAc was added and the mixture was washed with 3N NaOH, water, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (6% $MeOH/CH_2Cl_2$) to provide **Example 422** (0.17 g).

Step 3:

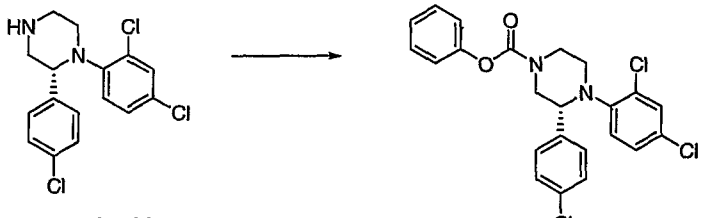
To the aminopiperazine **Example 422** (0.07 g, 0.16 mmol) in dichloroethane (1 mL) was added TEA (0.05 g, 0.48 mmol) and benzoyl chloride (0.03 g, 0.2 mmol). The reaction mixture was stirred at room temperature for 1 h. CH_2Cl_2 was added to the reaction mixture, which was then washed with saturated $NaHCO_3$, water, and brine. The mixture was then dried ($MgSO_4$), filtered, and the organic layer was concentrated *in vacuo*. The concentrate was purified by preparative TLC (SiO_2) (50% EtOAc/hexane) to provide **Example 423** (0.07 g).

Step 4:

To the piperazine **Example 422** (0.074 g, 0.17 mmol) in dichloroethane (1 mL) was added TEA (0.05 g, 0.5 mmol) followed by benzene sulfonyl chloride (0.04 g). The mixture was stirred at room temperature for 2 h and CH_2Cl_2 was added. The mixture was washed with saturated $NaHCO_3$, water, and brine, dried ($MgSO_4$), filtered, and the organic layer was concentrated *in vacuo*. Purification by preparative TLC (SiO_2) (20% EtOAc/hexane) provided **Example 424** (0.05 g).

Preparation of Example 425

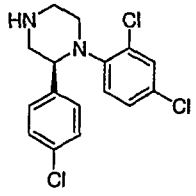
Scheme 73



Example 304 Example 425

The carbamate **Example 425** was prepared in the same manner as **Example 4** in Scheme 2 except that **Example 304** was used as a starting material instead of **Example 1** and phenylchloroformate was used instead of benzoyl chloride.

Preparation of Example 426

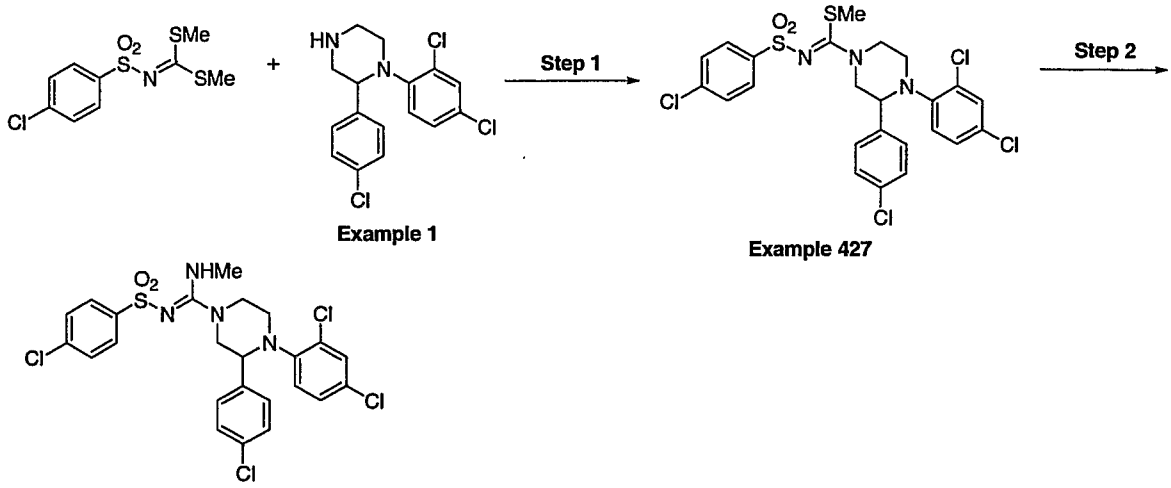


Example 426

The piperazine **Example 426** was prepared in the same manner as the chiral piperazine **Example 304** in Scheme 28 except that (*S*)-2-methyl-CBS-oxazaborolidine was used instead of (*R*)-2-methyl-CBS-oxazaborolidine in step 1.

Preparation of Examples 427-428

Scheme 74



Example 1

Example 427

Example 428

Step 1:

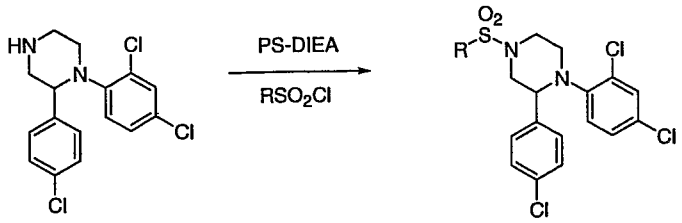
The arylsulfonyldithioimide carbonic acid methyl ester was prepared according to the method of Lange *et. al.* J. Med Chem. 2004, 47, 627-643 (herein incorporated by reference). To the dithioimide (0.39 g, 1.3 mmol) in propionitrile (4 mL) was added the Et_3N (0.43 mL, 3.1 mmol) and the piperazine **Example 1** (0.3 g, 1.3 mmol). The reaction mixture was warmed to reflux and stirred for 20 h, then cooled to room temperature and concentrated *in vacuo*. The residue, **Example 427**, was used in step 2 without further purification.

Step 2:

Example 427 was taken up into MeOH (7 mL) and $MeNH_2$ (40% solution in water, 1.5 mL, 18 mmol) was added. The reaction mixture was stirred at room temperature for 20 h, then concentrated *in vacuo*. The resulting residue was taken up into CH_2Cl_2 and the insoluble precipitate was filtered off. The filtrate was concentrated *in vacuo* and purified by silica gel chromatography (55% EtOAc/hexane) to provide **Example 428** (0.35 g, 0.61 mmol).

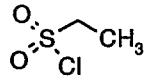
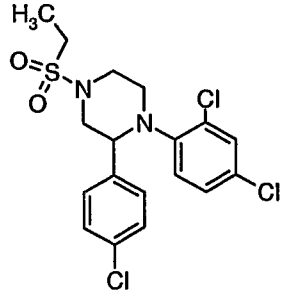
Preparation of Examples 429-494

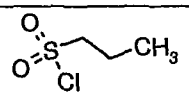
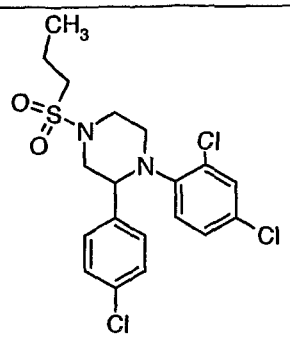
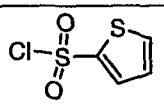
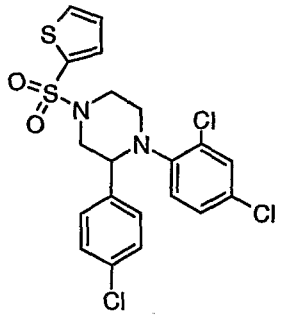
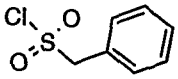
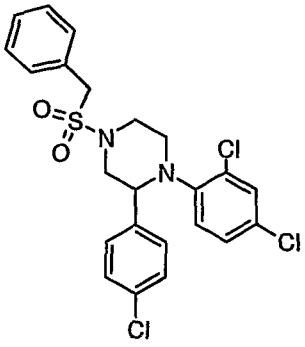
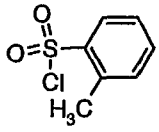
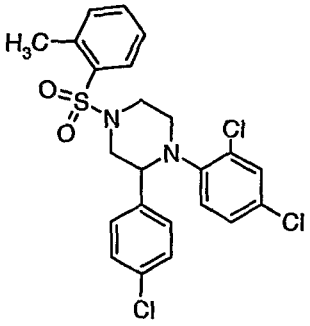
Scheme 75

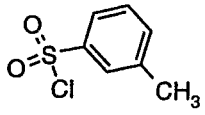
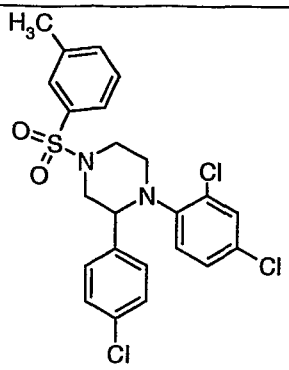
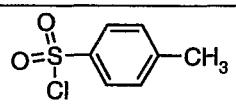
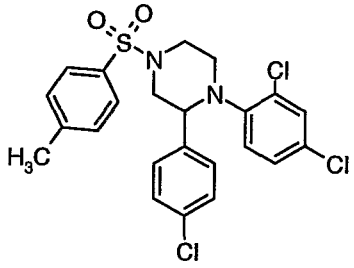
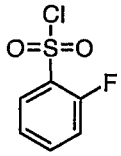
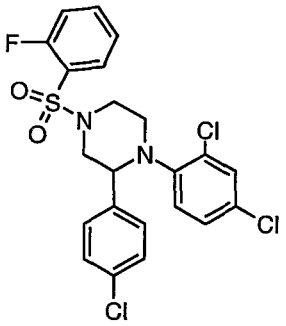
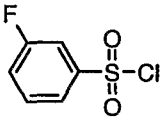
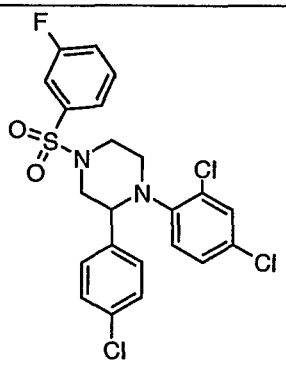
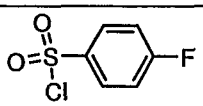
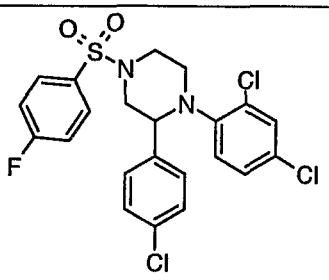


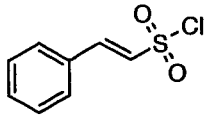
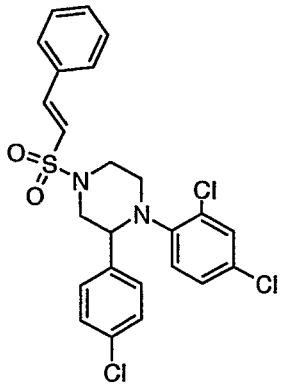
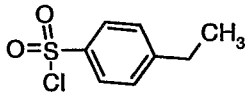
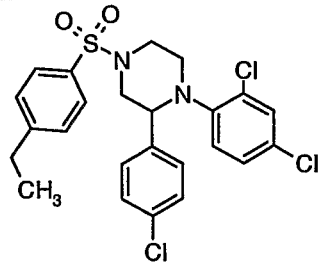
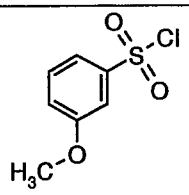
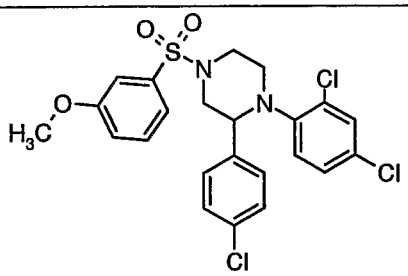
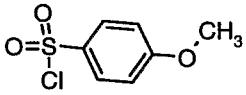
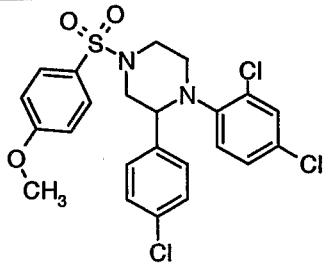
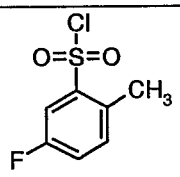
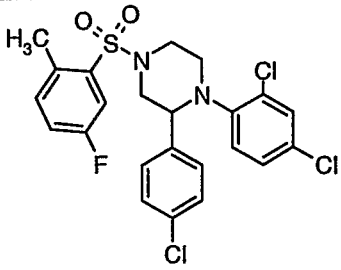
Polystyrene DIEA resin (47 mg, 0.045 mmol) was added to 72-wells of a deep well polypropylene microtiter plate followed by a MeCN/THF (3:2) stock solution (1 mL) of piperazine **Example 1** (0.033 mmol). Then 0.5 M stock solutions of each of the individual sulfonyl chlorides ($R_{1\text{-}66}SO_2Cl$) (0.135 mL, 0.067 mmol) were added to the wells, which was then sealed and shaken at 25°C for 20h. The solutions were filtered thru a polypropylene frit into a second microtiter plate containing polystyrene isocyanate resin (3 equivalents, 0.135 mmol) and polystyrene trisamine resin (6 equivalents, 0.27 mmol). After the top plate was washed with MeCN (0.5 mL), the plate was removed, the bottom microtiter plate sealed and shaken at 25°C for 16h. Then the solutions were filtered thru a polypropylene frit into a 96-well collection plate. The wells of the top plate were then washed with MeCN (0.5 mL), and the plate removed. Then the resultant solutions in the collection plate were transferred into vials and the solvents removed in vacuo via a SpeedVac to provide the sulfonamides shown below in Table XV.

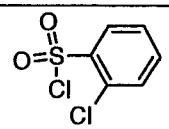
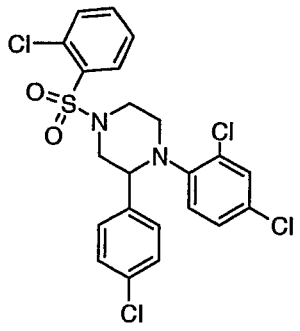
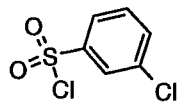
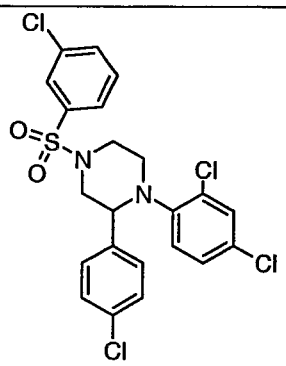
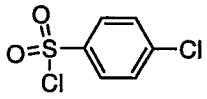
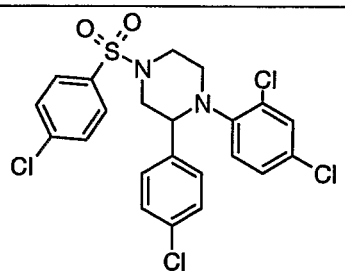
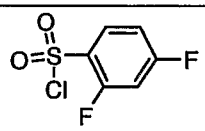
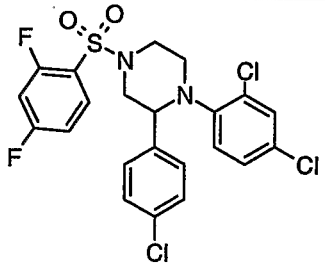
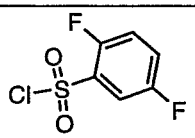
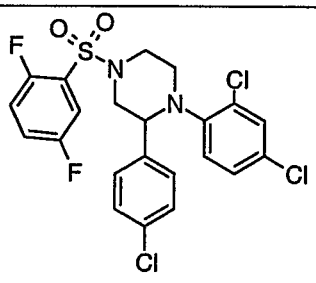
Table XV

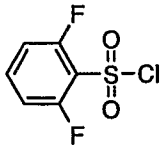
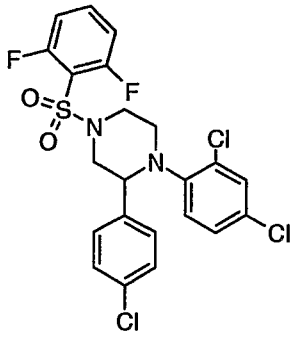
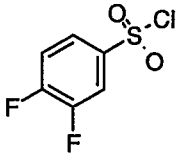
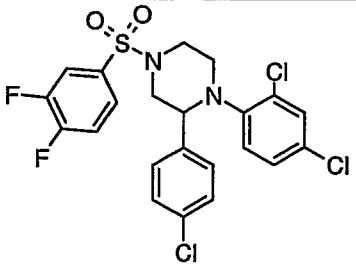
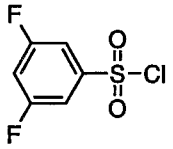
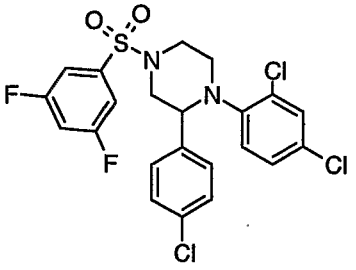
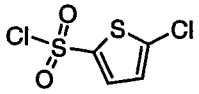
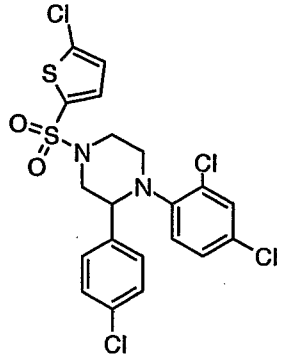
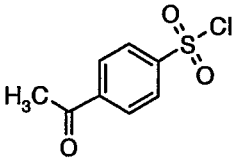
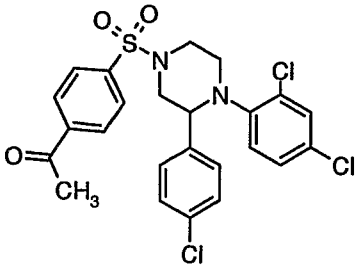
Example #	Sulfonyl Chloride	Example Structure
429		

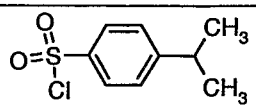
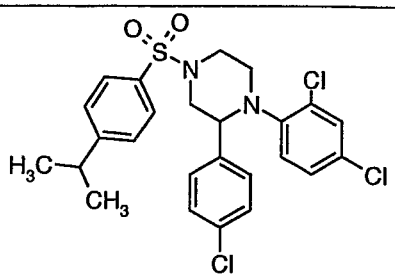
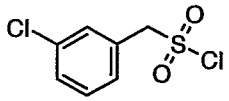
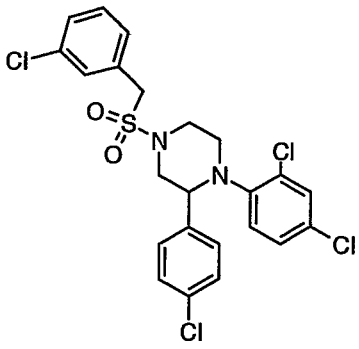
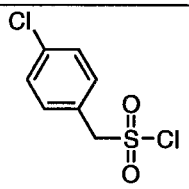
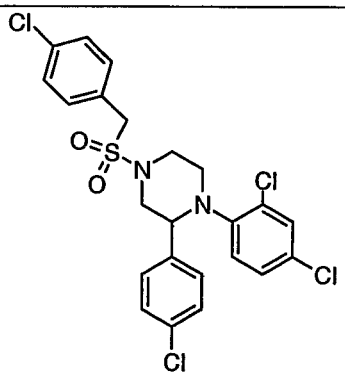
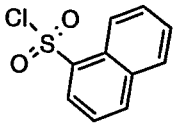
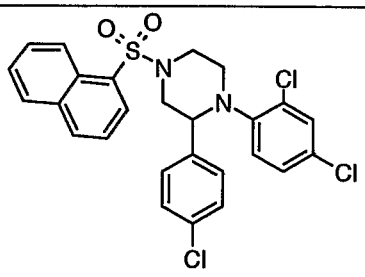
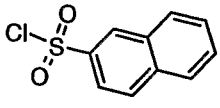
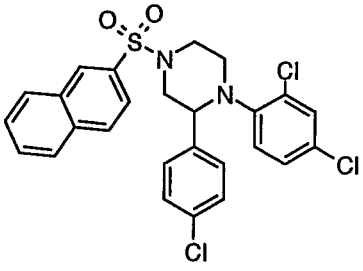
Example #	Sulfonyl Chloride	Example Structure
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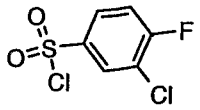
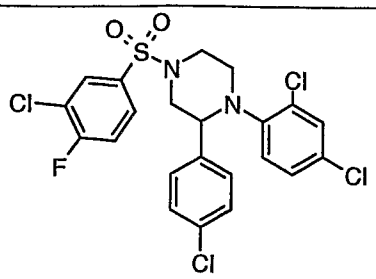
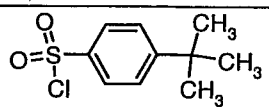
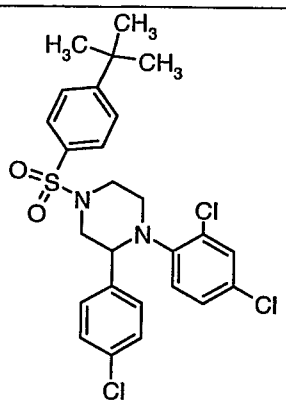
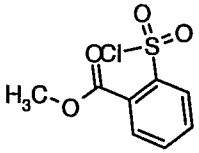
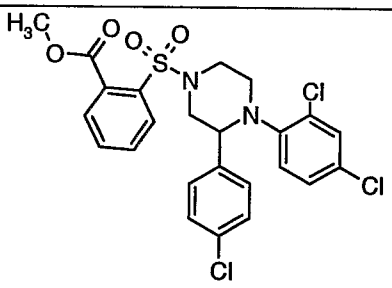
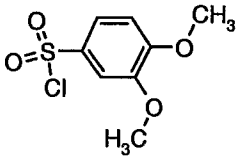
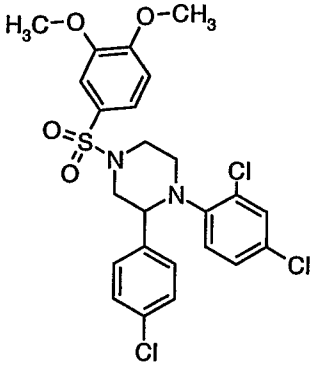
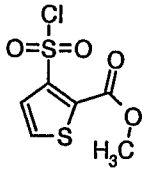
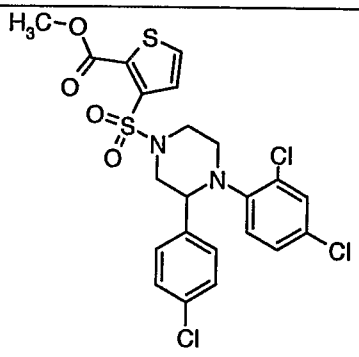
Example #	Sulfonyl Chloride	Example Structure
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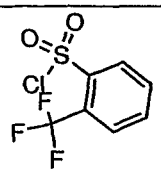
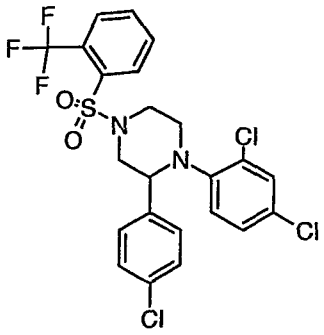
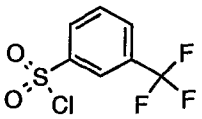
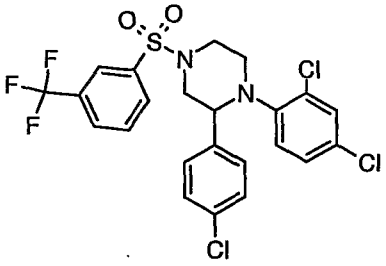
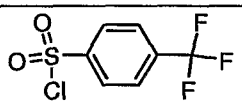
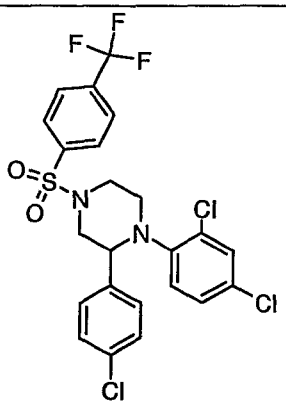
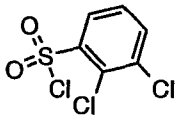
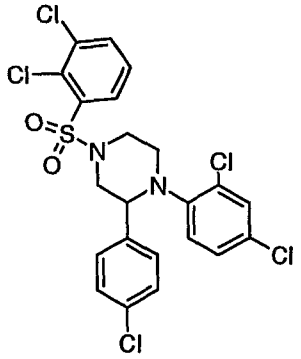
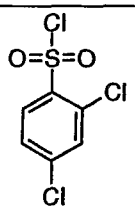
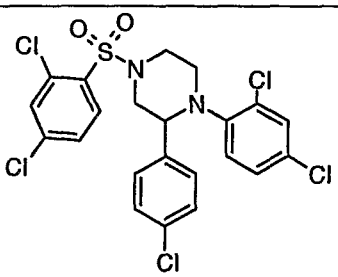
Example #	Sulfonyl Chloride	Example Structure
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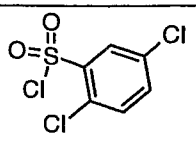
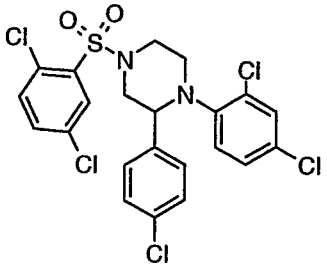
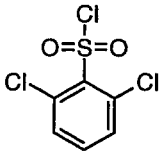
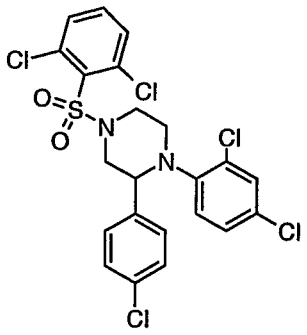
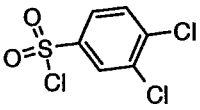
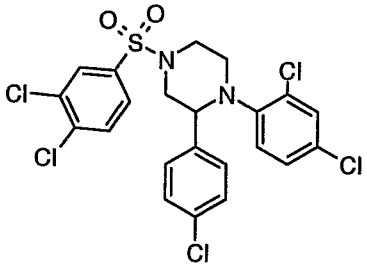
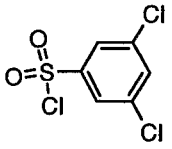
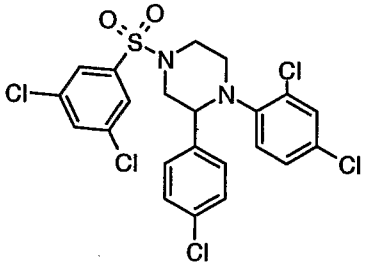
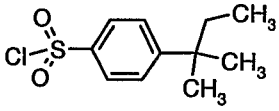
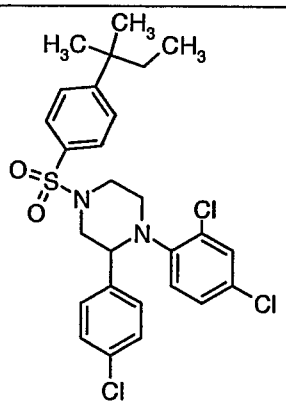
Example #	Sulfonyl Chloride	Example Structure
444		
445		
446		
447		
448		

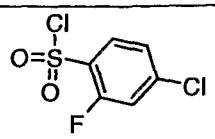
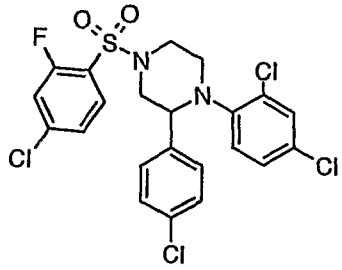
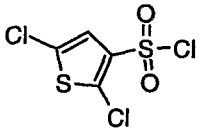
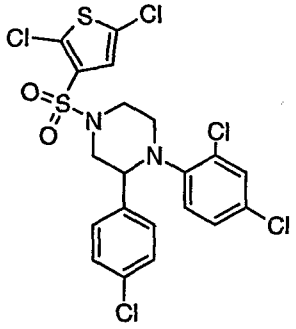
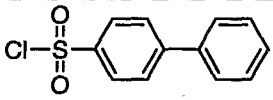
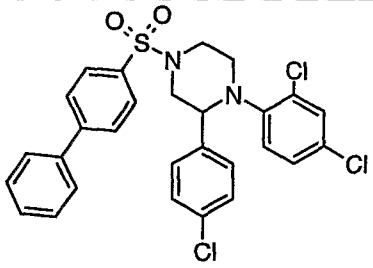
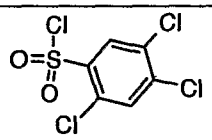
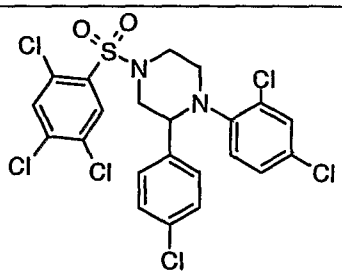
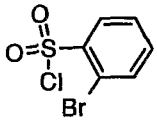
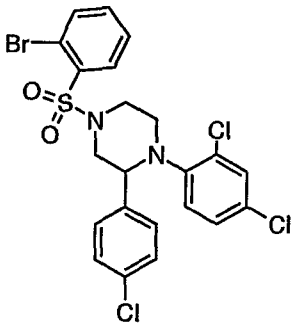
Example #	Sulfonyl Chloride	Example Structure
449		
450		
451		
452		
453		

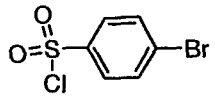
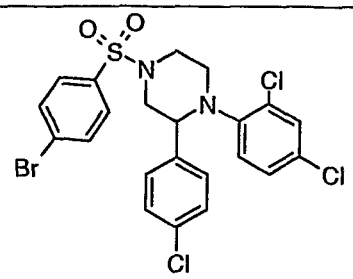
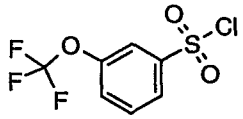
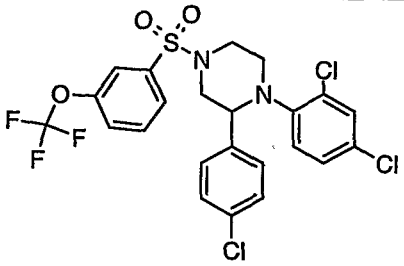
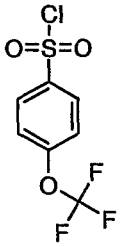
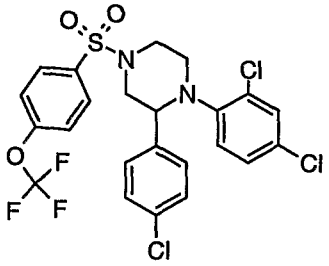
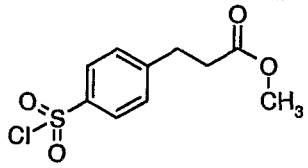
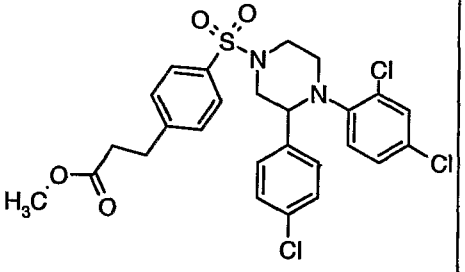
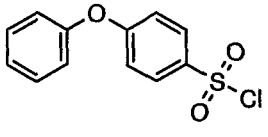
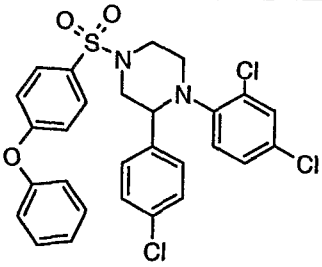
Example #	Sulfonyl Chloride	Example Structure
454		
455		
456		
457		
458		

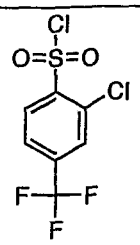
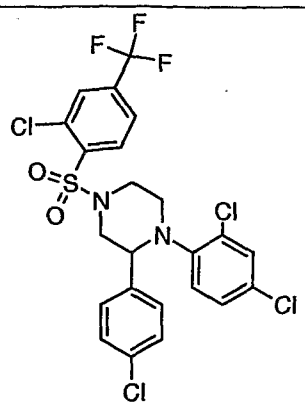
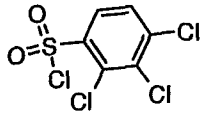
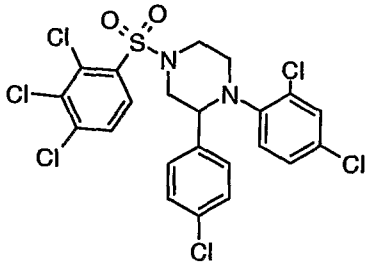
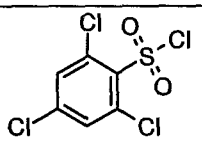
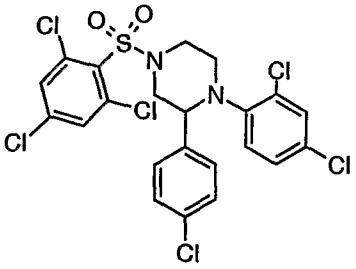
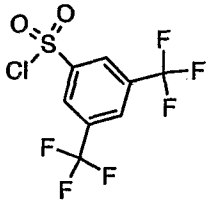
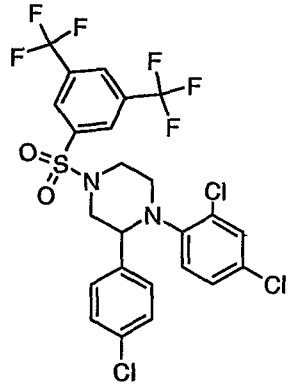
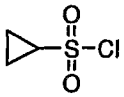
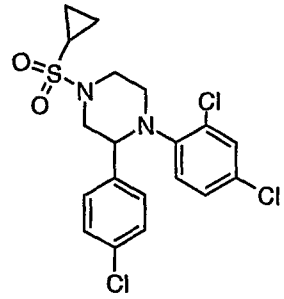
Example #	Sulfonyl Chloride	Example Structure
459		
460		
461		
462		
463		

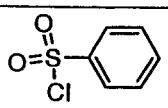
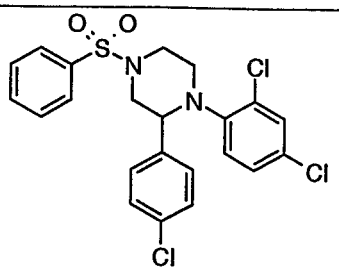
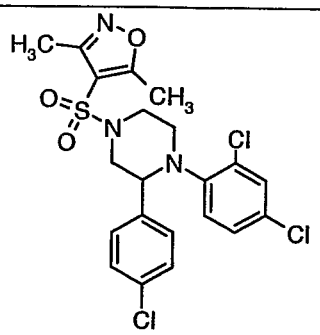
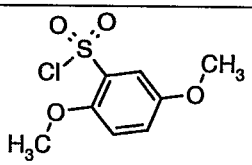
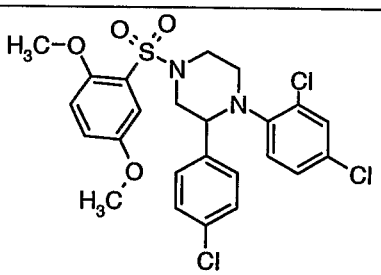
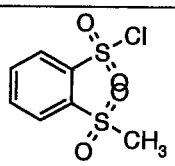
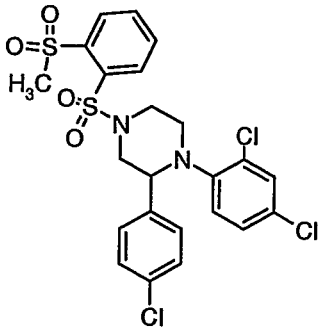
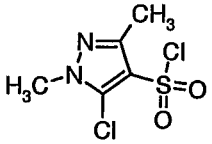
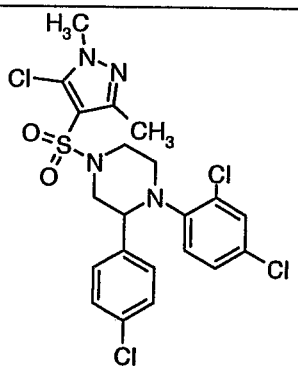
Example #	Sulfonyl Chloride	Example Structure
464		
465		
466		
467		
468		

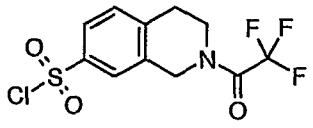
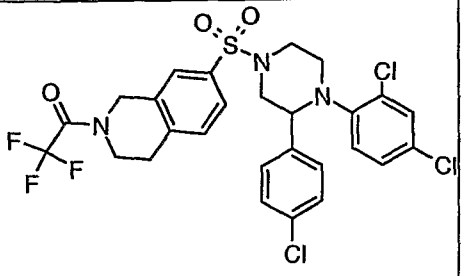
Example #	Sulfonyl Chloride	Example Structure
469		
470		
471		
472		
473		

Example #	Sulfonyl Chloride	Example Structure
474		
475		
476		
477		
478		

Example #	Sulfonyl Chloride	Example Structure
479		
480		
481		
482		
483		

Example #	Sulfonyl Chloride	Example Structure
484		
485		
486		
487		
488		

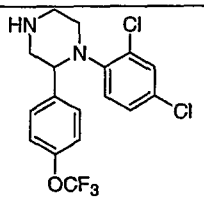
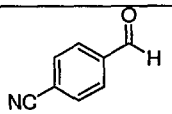
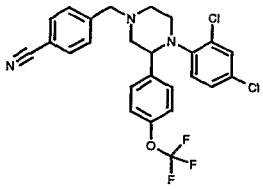
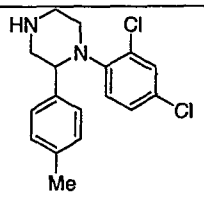
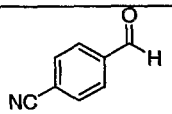
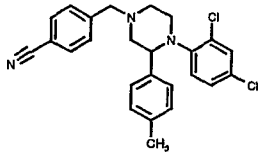
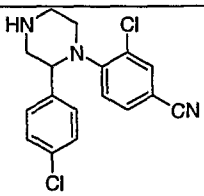
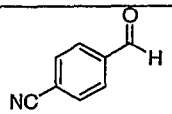
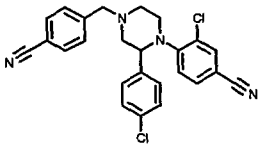
Example #	Sulfonyl Chloride	Example Structure
489		
490		
491		
492		
493		

Example #	Sulfonyl Chloride	Example Structure
494		

Preparation of Examples 495-497

Examples 495-497 were prepared by the reaction of the appropriate piperazine and aldehyde (e.g., by the method of step 4 of Scheme 64), shown in Table XVI, below. The piperazines were prepared, e.g., by the methods described in Scheme 71.

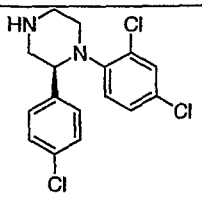
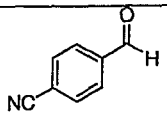
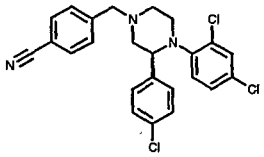
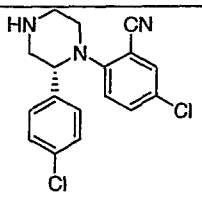
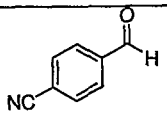
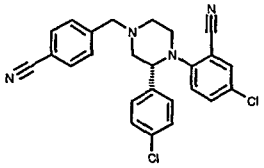
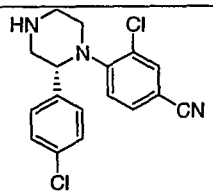
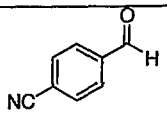
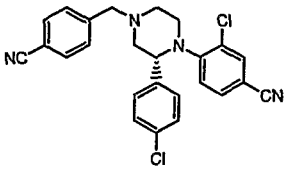
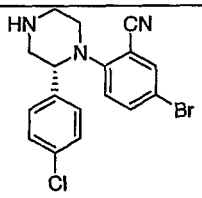
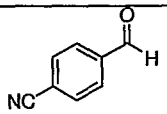
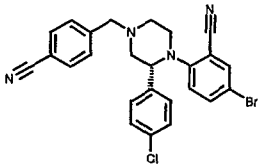
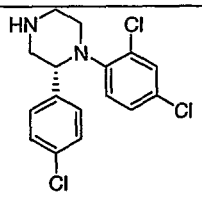
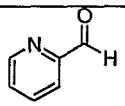
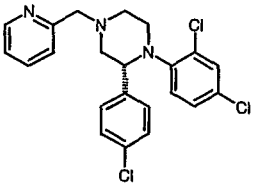
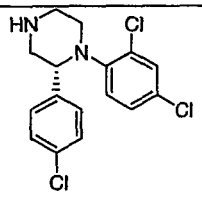
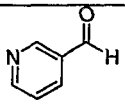
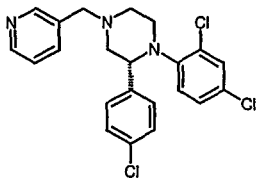
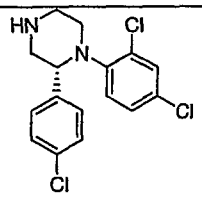
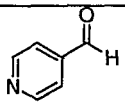
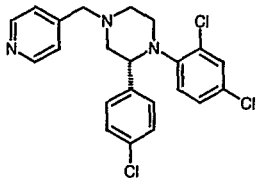
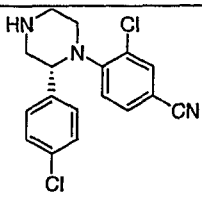
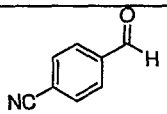
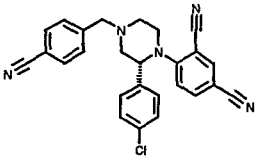
Table XVI

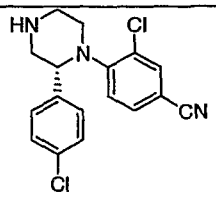
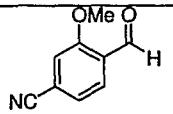
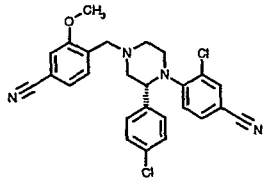
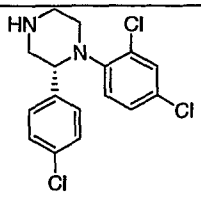
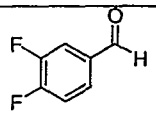
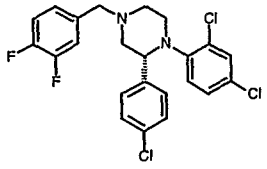
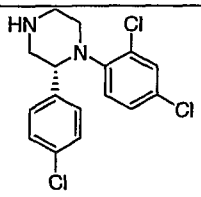
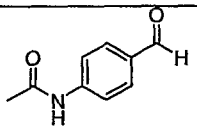
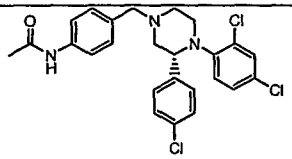
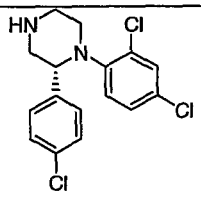
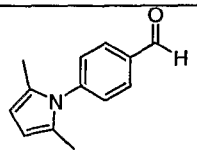
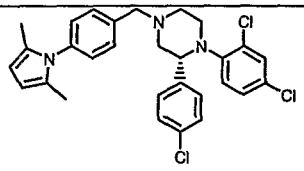
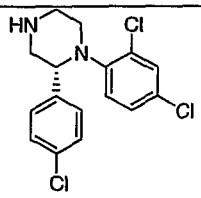
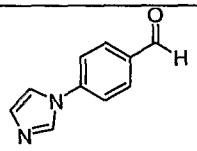
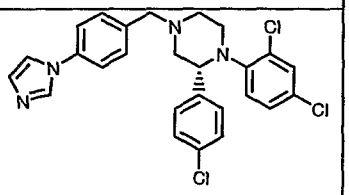
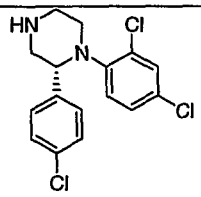
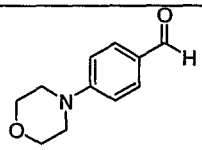
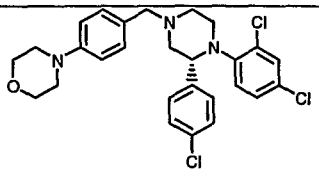
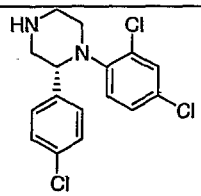
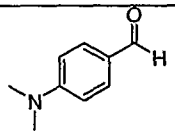
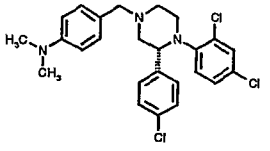
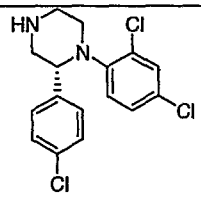
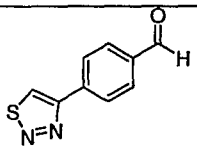
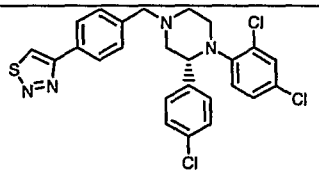
Example #	Piperazine	Aldehyde	Example Structure
495			
496			
497			

Preparation of Examples 498-513

Examples 498-513 were prepared by the reaction of the appropriate piperazine and aldehyde (e.g., by the method of Scheme 64, step 4) shown in Table XVII, below. The piperazines were prepared, e.g, by the method of Scheme 28.

Table XVII

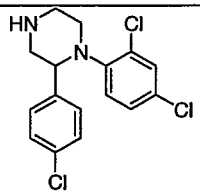
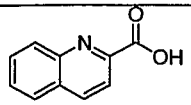
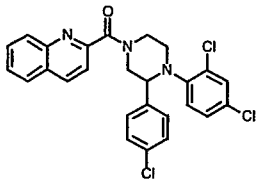
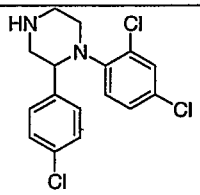
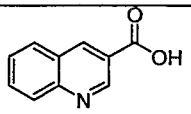
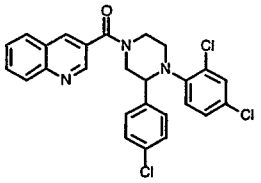
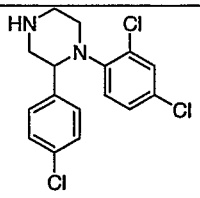
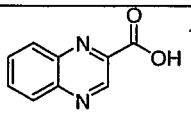
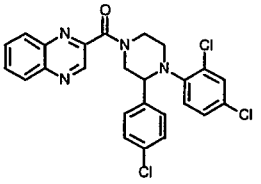
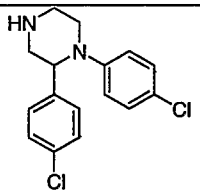
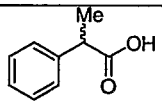
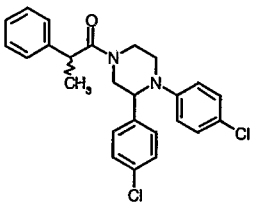
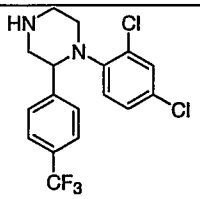
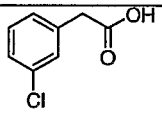
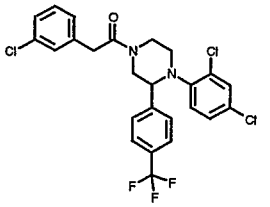
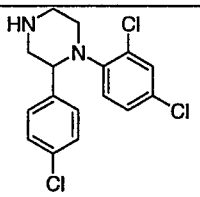
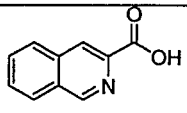
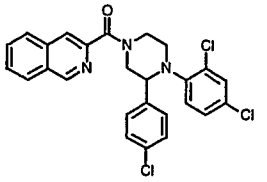
Example #	Piperazine	Aldehyde	Example Structure
498			
499			
500			
501			
502			
503			
504			
505			

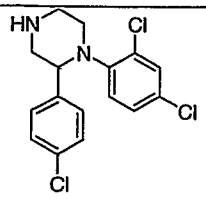
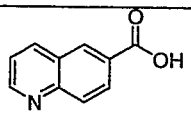
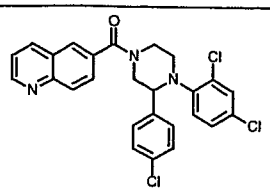
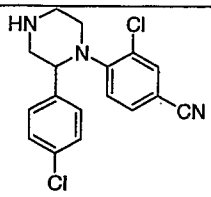
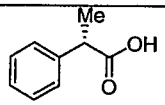
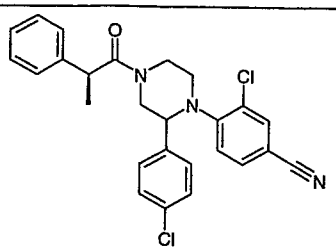
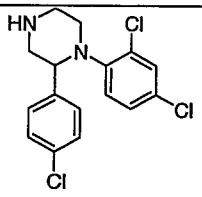
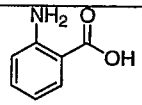
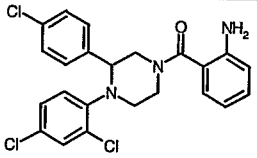
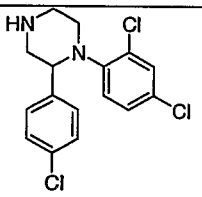
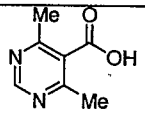
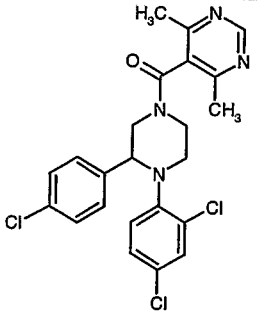
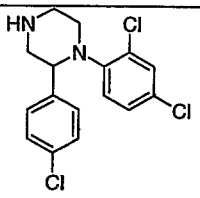
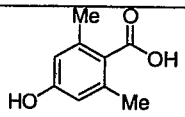
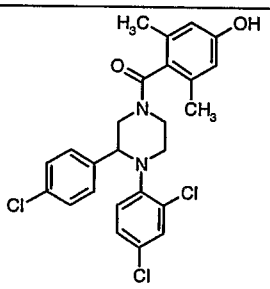
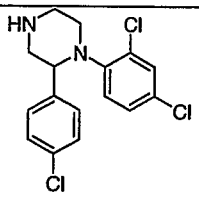
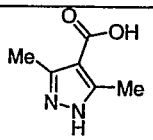
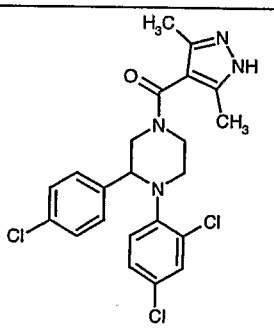
Example #	Piperazine	Aldehyde	Example Structure
506			
507			
508			
509			
510			
511			
512			
513			

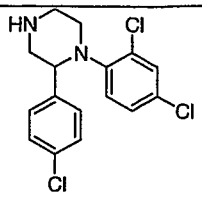
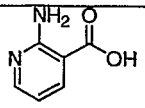
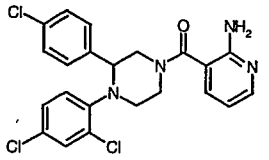
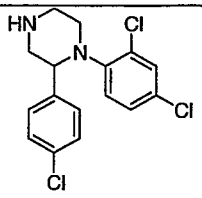
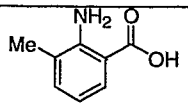
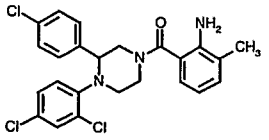
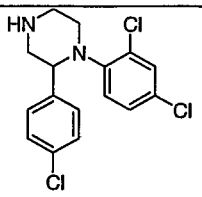
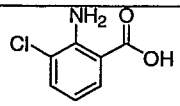
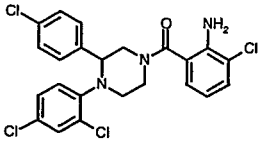
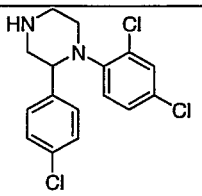
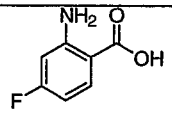
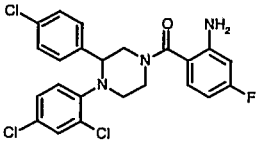
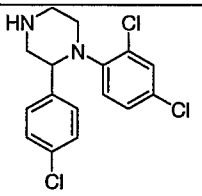
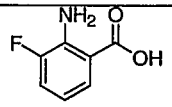
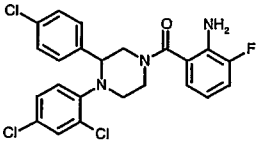
Preparation of Examples 514-530

Examples 514-530 were prepared by the reaction of the appropriate piperazine and carboxylic acid (e.g., the method of Scheme 17) shown in Table XVIII, below.

Table XVIII

Example #	Piperazine	Carboxylic Acid	Example Structure
514			
515			
516			
517			
518			
519			

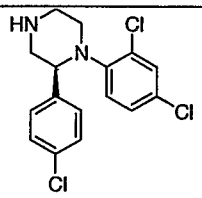
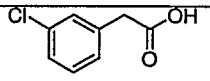
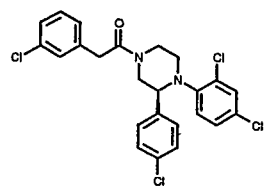
Example #	Piperazine	Carboxylic Acid	Example Structure
520			
521			
522			
523			
524			
525			

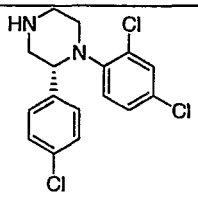
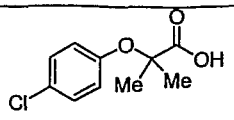
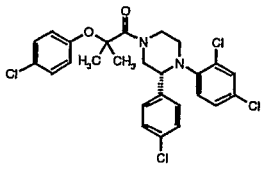
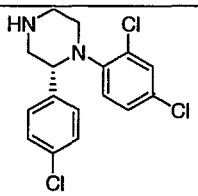
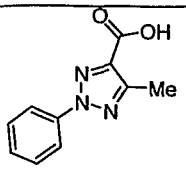
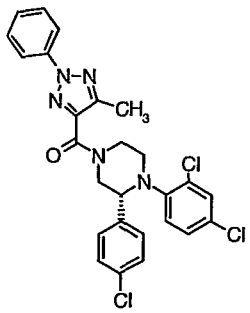
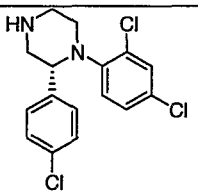
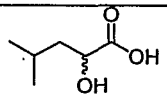
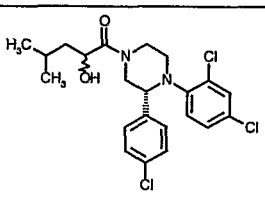
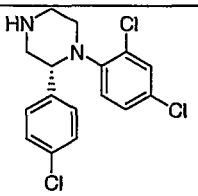
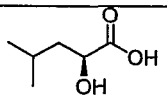
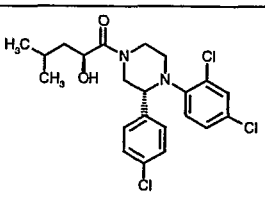
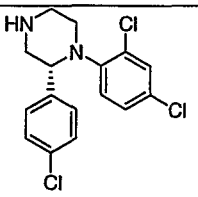
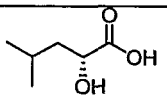
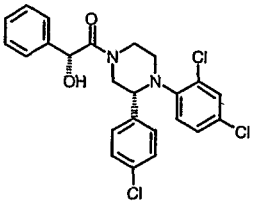
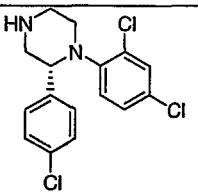
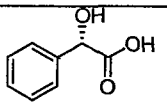
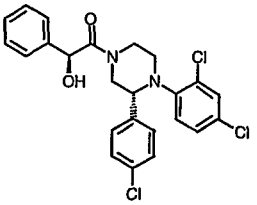
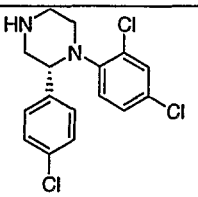
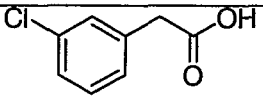
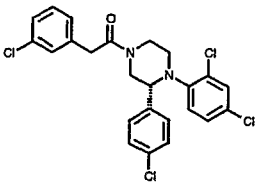
Example #	Piperazine	Carboxylic Acid	Example Structure
526			
527			
528			
529			
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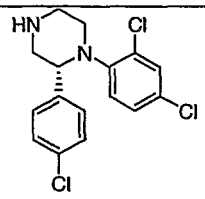
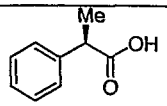
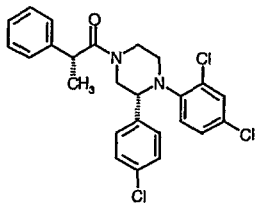
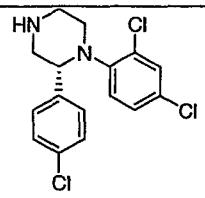
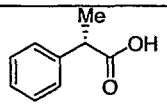
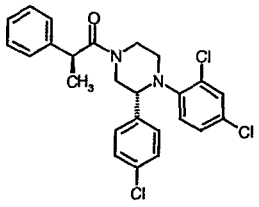
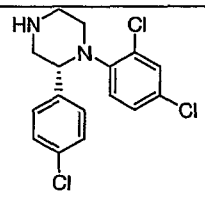
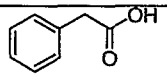
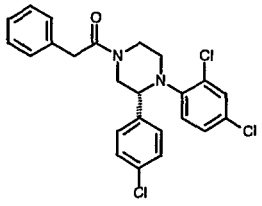
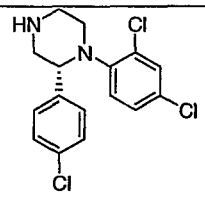
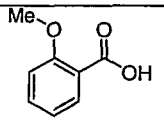
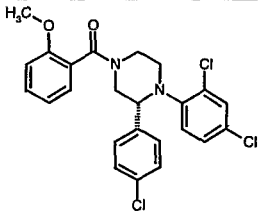
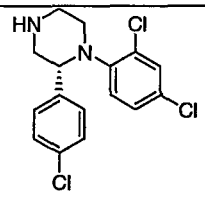
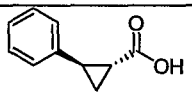
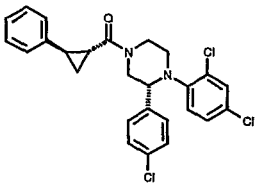
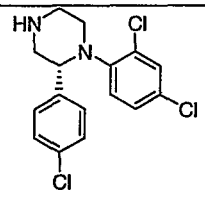
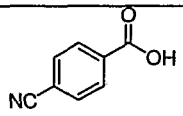
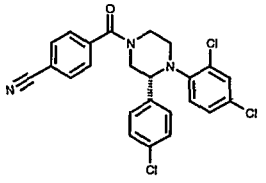
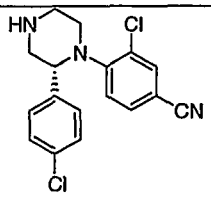
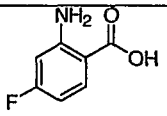
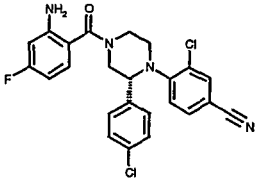
Preparation of Examples 531-570

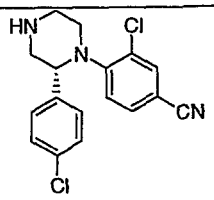
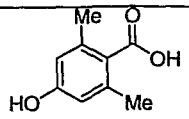
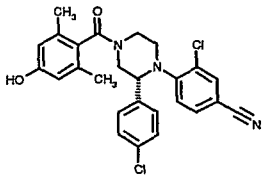
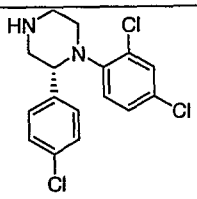
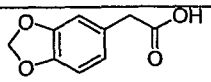
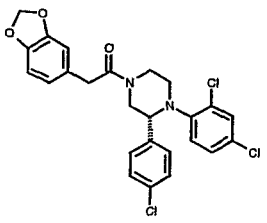
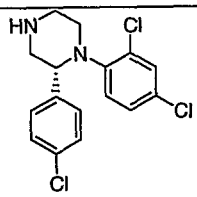
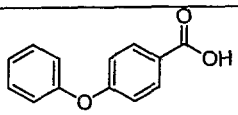
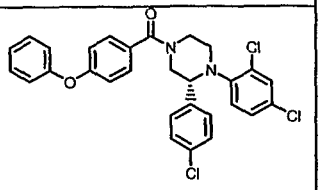
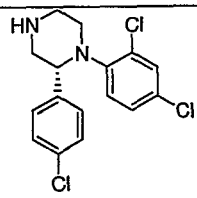
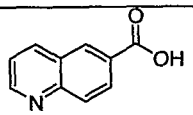
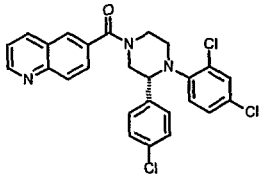
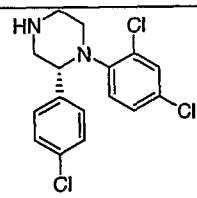
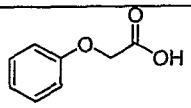
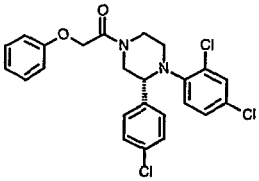
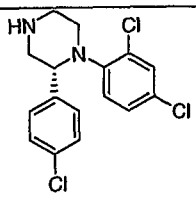
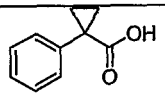
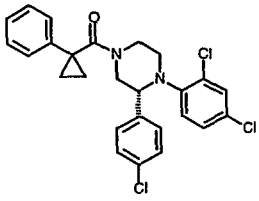
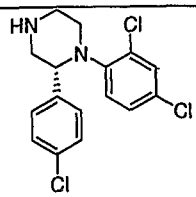
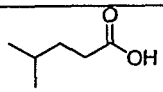
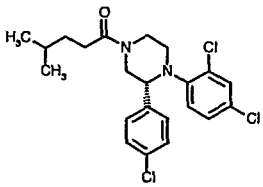
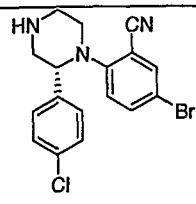
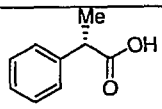
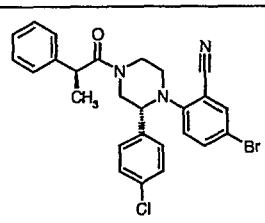
Examples 531-570 were prepared by the reaction of the appropriate piperazine (e.g., **Examples 304** or **426**) and carboxylic acid shown in Table XIX, below (e.g., by the method of Scheme 17).

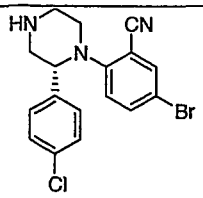
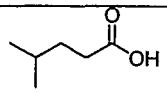
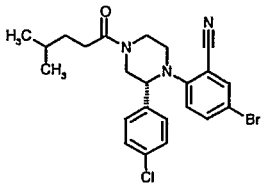
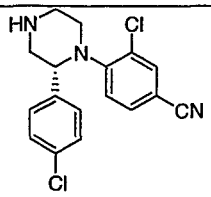
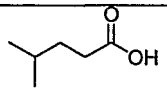
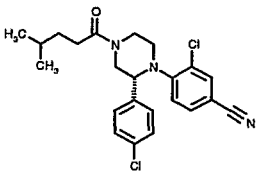
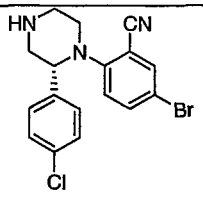
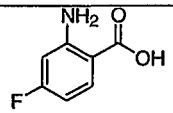
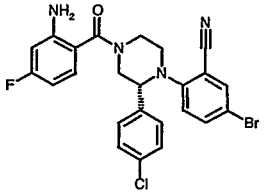
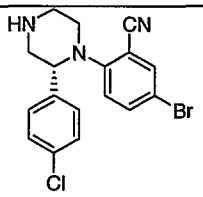
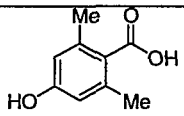
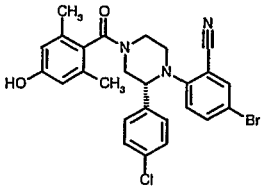
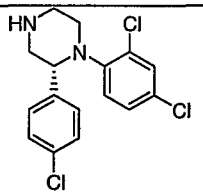
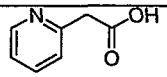
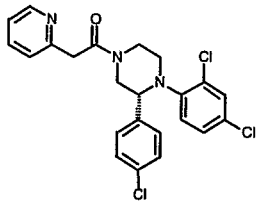
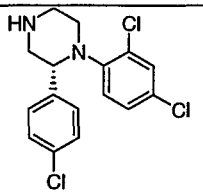
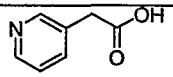
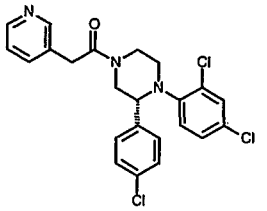
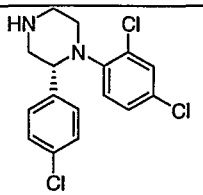
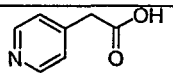
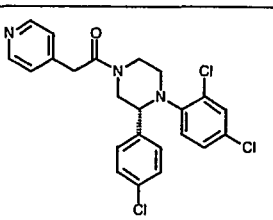
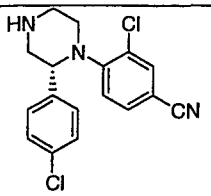
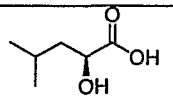
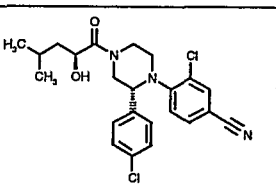
Table XIX

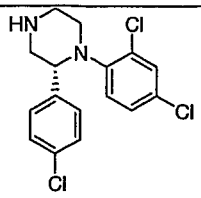
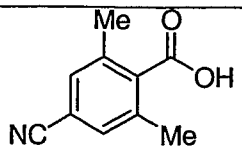
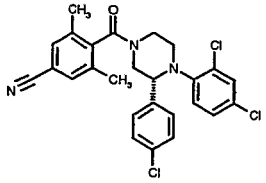
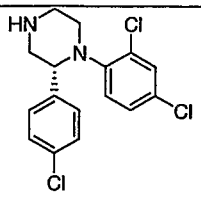
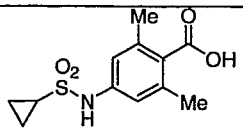
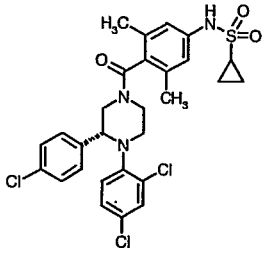
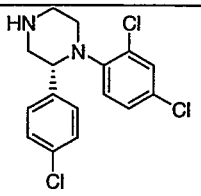
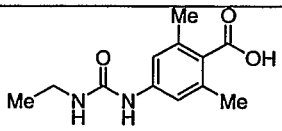
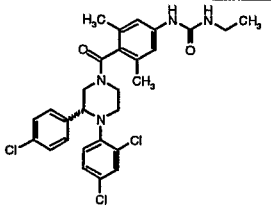
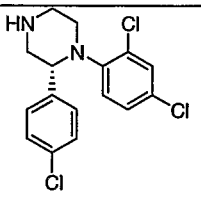
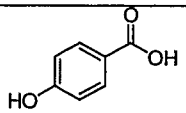
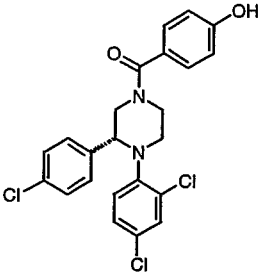
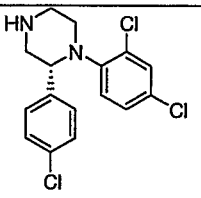
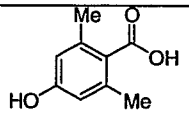
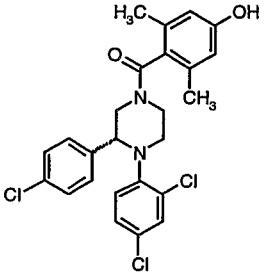
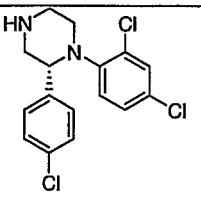
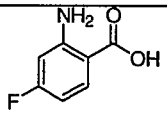
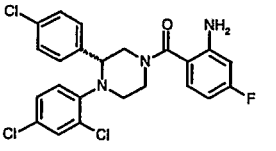
Example #	Piperazine	Carboxylic Acid	Example Structure
531			

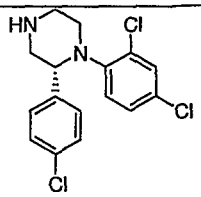
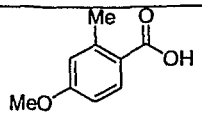
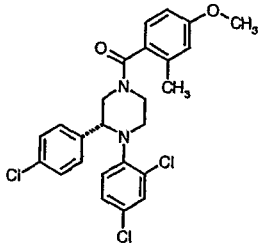
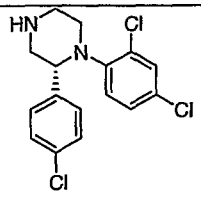
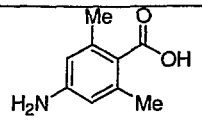
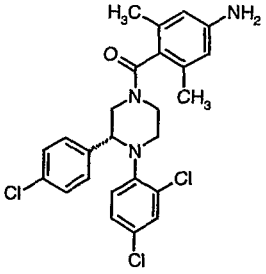
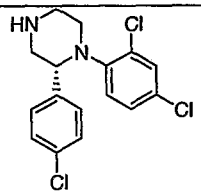
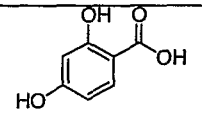
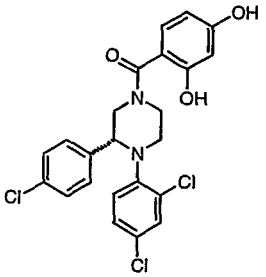
Example #	Piperazine	Carboxylic Acid	Example Structure
532			
533			
534			
535			
536			
537			
538			

Example #	Piperazine	Carboxylic Acid	Example Structure
539			
540			
541			
542			
543			
544			
545			

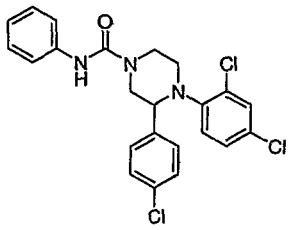
Example #	Piperazine	Carboxylic Acid	Example Structure
546			
547			
548			
549			
550			
551			
552			
553			

Example #	Piperazine	Carboxylic Acid	Example Structure
554			
555			
556			
557			
558			
559			
560			
561			

Example #	Piperazine	Carboxylic Acid	Example Structure
562			
563			
564			
565			
566			
567			

Example #	Piperazine	Carboxylic Acid	Example Structure
568			
569			
570			

Preparation of Example 571



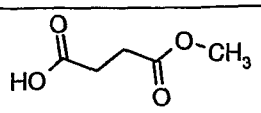
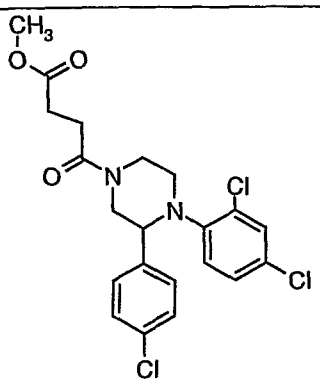
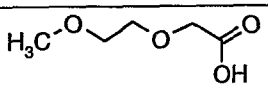
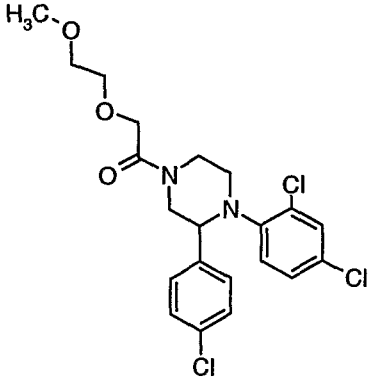
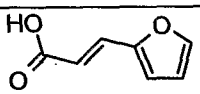
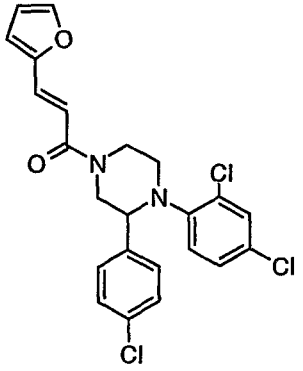
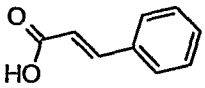
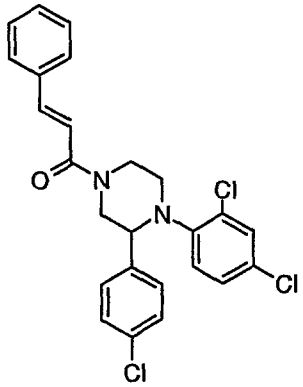
Example 571

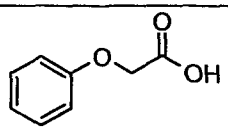
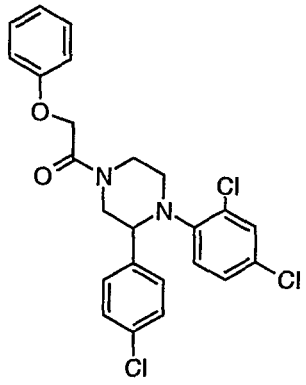
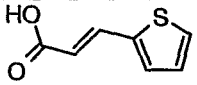
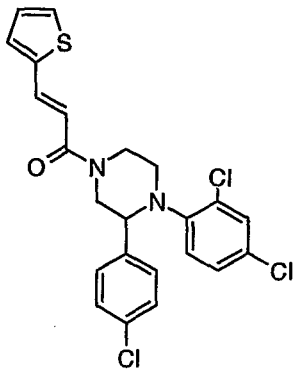
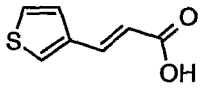
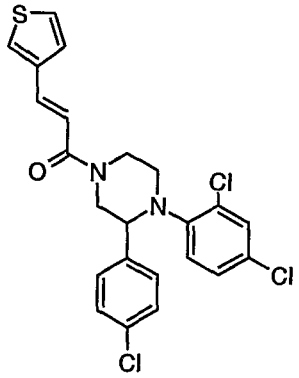
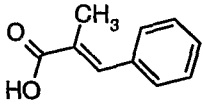
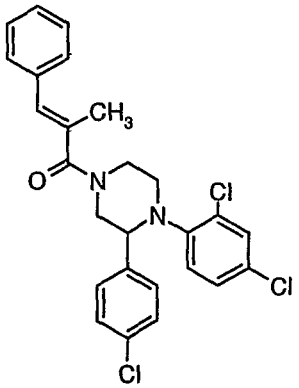
Example 571 was prepared by the reaction of phenyl isocyanate with **Example 1** using procedures similar to those used to prepare **Examples 7,** Scheme 1.

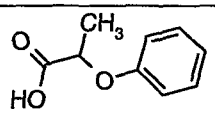
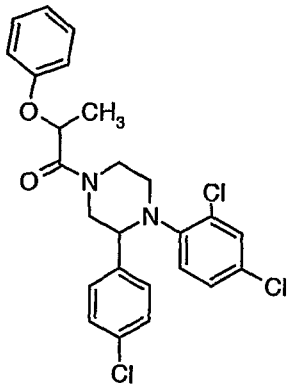
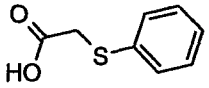
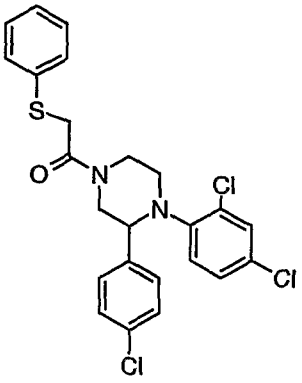
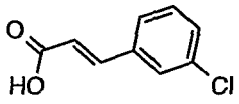
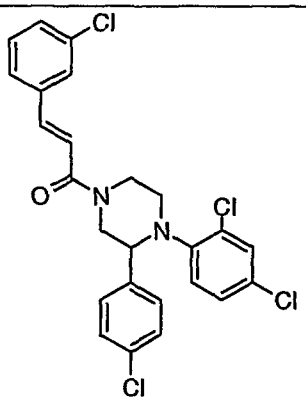
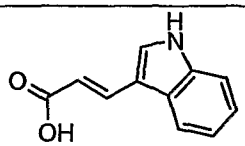
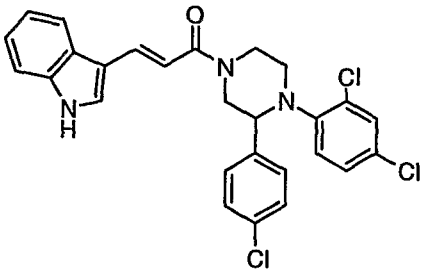
Preparation of Examples 572-685

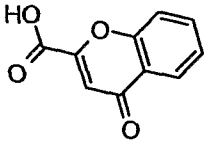
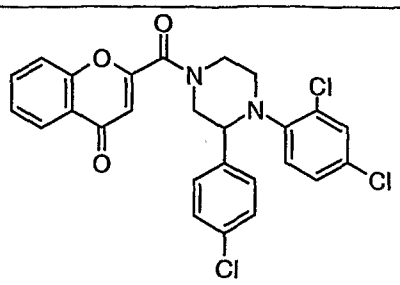
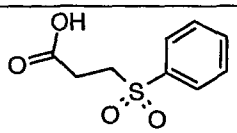
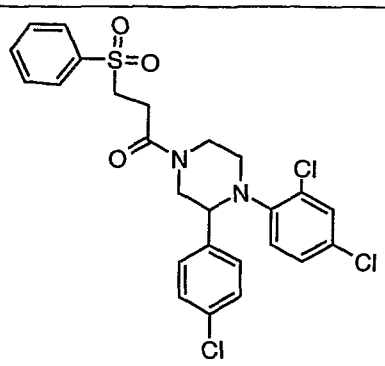
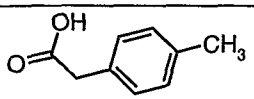
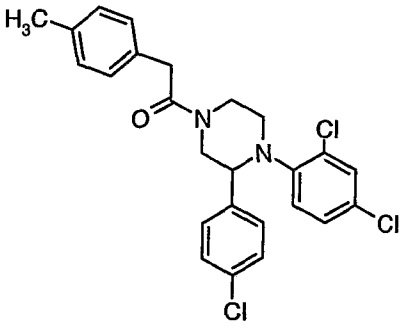
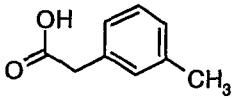
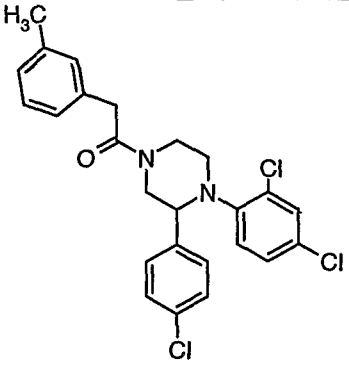
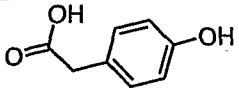
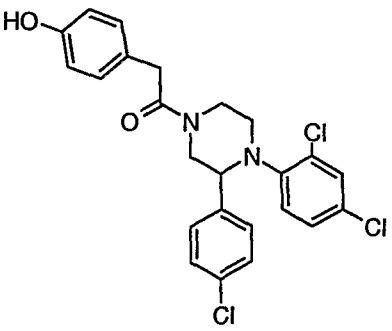
Examples 572-685 were prepared by the reaction of piperazine **Example 1** and the carboxylic acid shown in Table XX, using the procedure of Scheme 5.

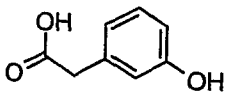
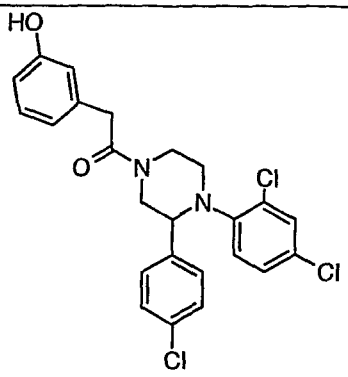
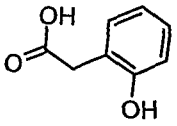
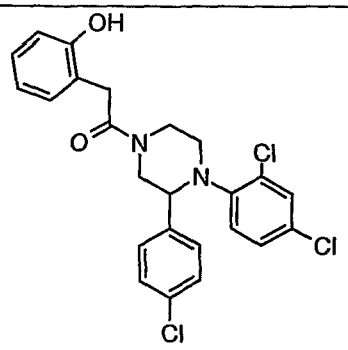
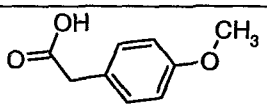
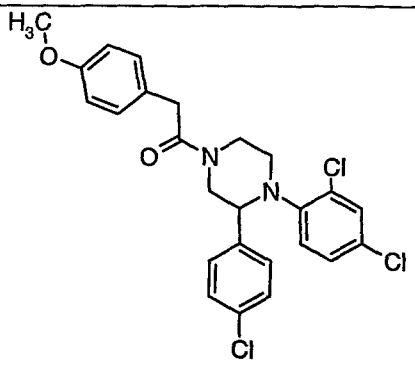
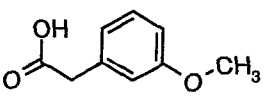
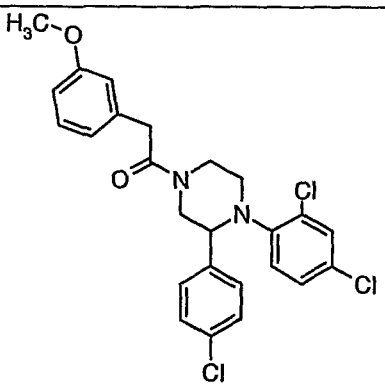
Table XX

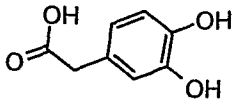
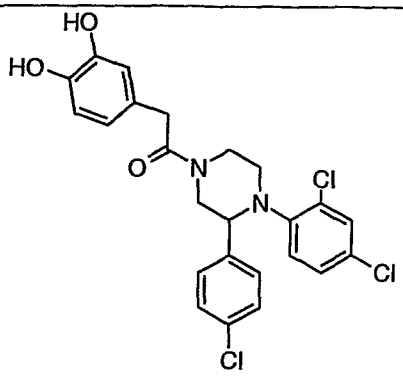
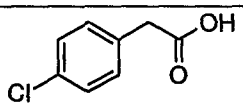
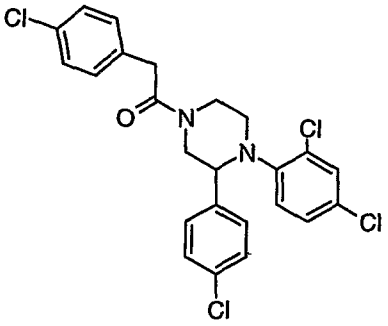
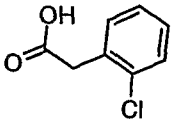
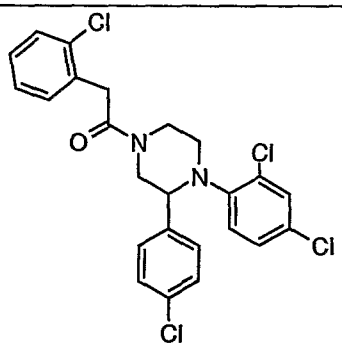
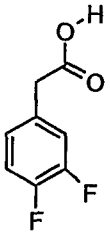
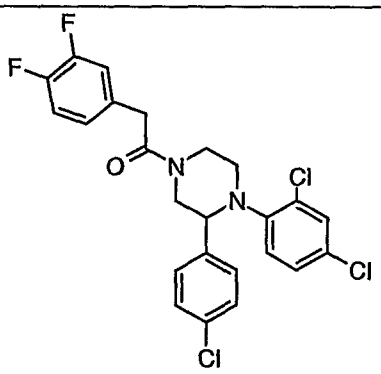
Example #	Carboxylic Acid	Example Structure
572		
573		
574		
575		

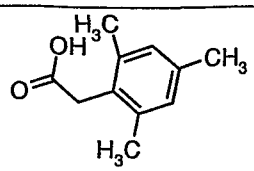
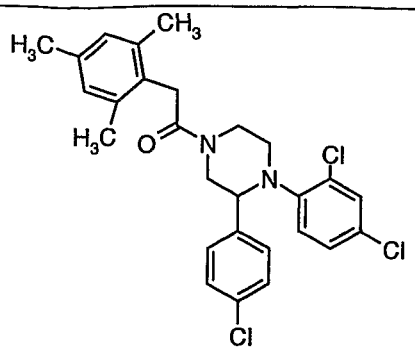
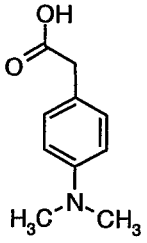
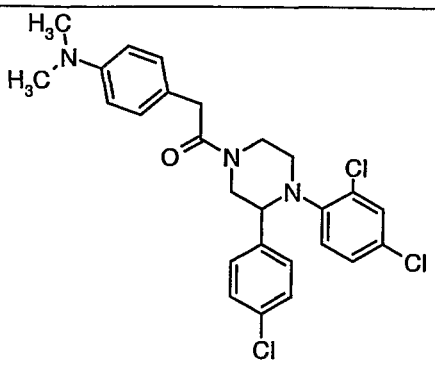
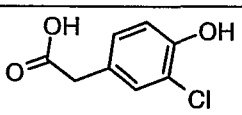
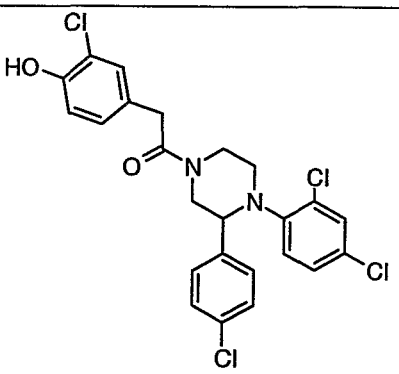
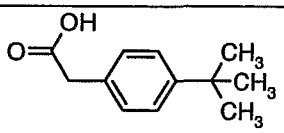
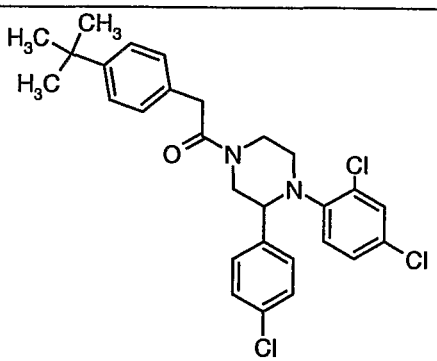
Example #	Carboxylic Acid	Example Structure
576		
577		
578		
579		

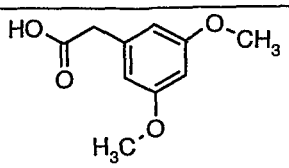
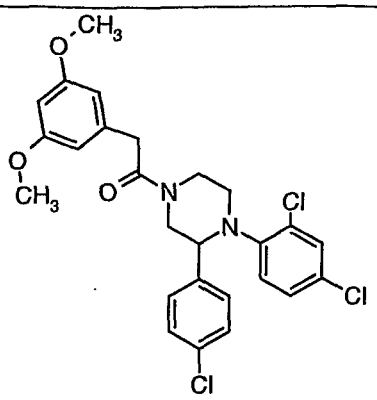
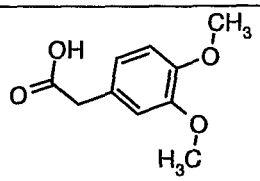
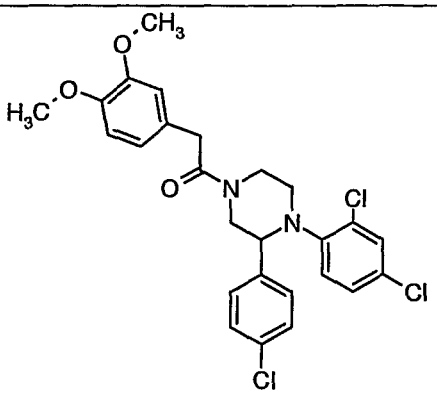
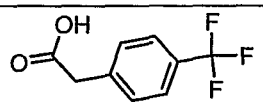
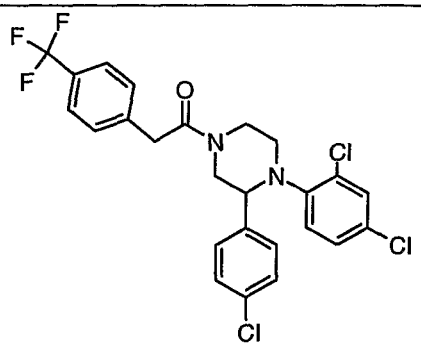
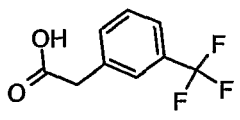
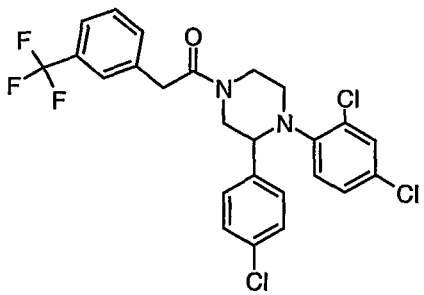
Example #	Carboxylic Acid	Example Structure
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581		
582		
583		

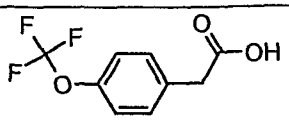
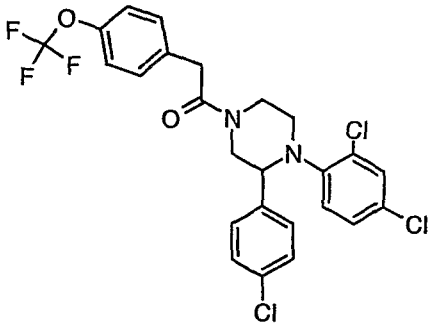
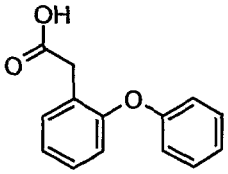
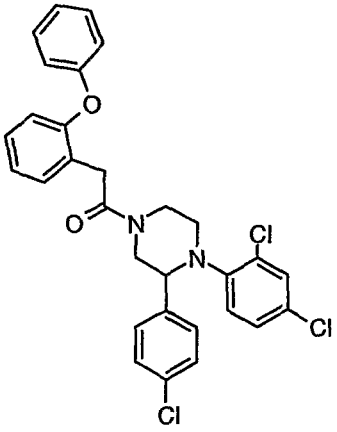
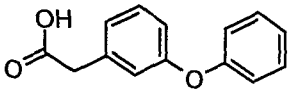
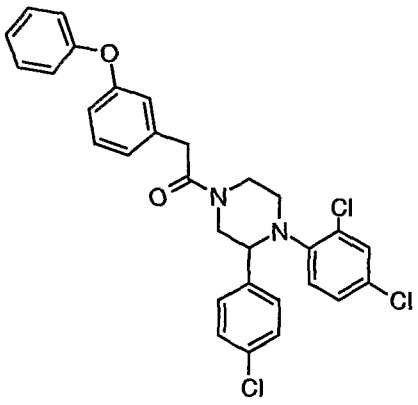
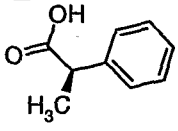
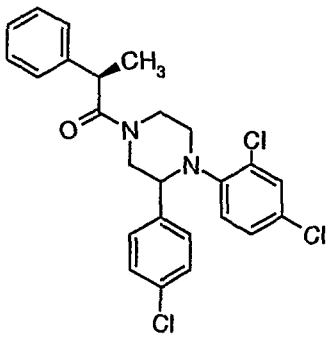
Example #	Carboxylic Acid	Example Structure
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585		
586		
587		
588		

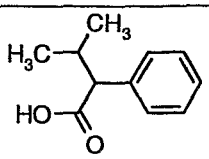
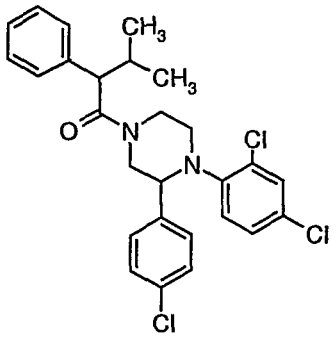
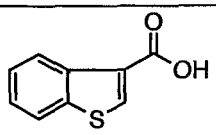
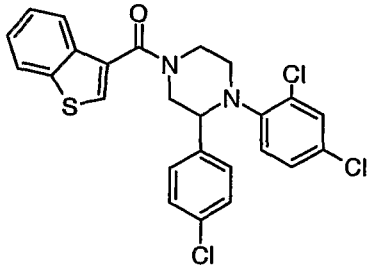
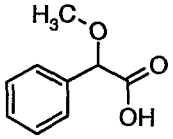
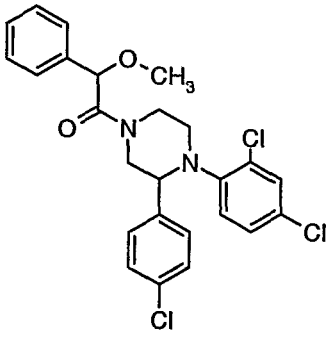
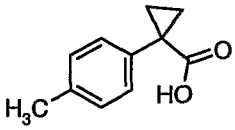
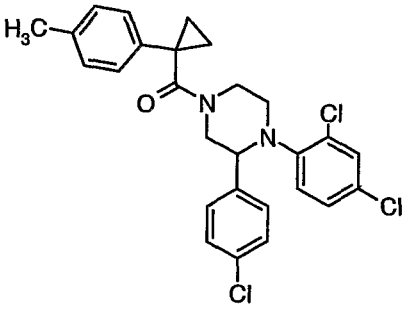
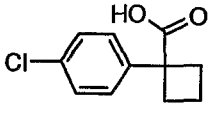
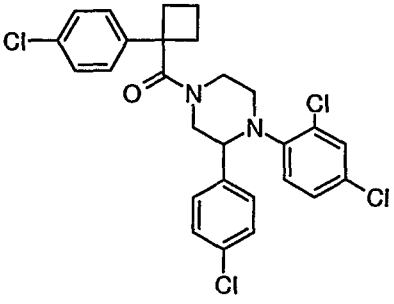
Example #	Carboxylic Acid	Example Structure
589		
590		
591		
592		

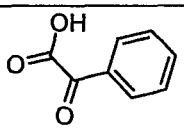
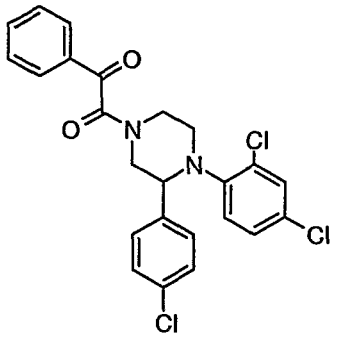
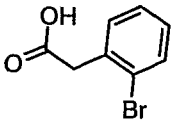
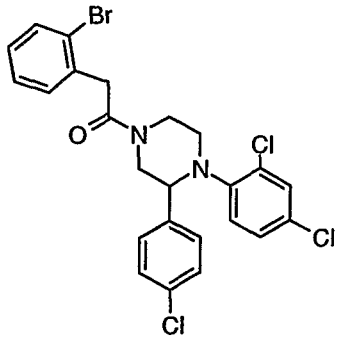
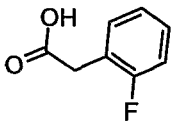
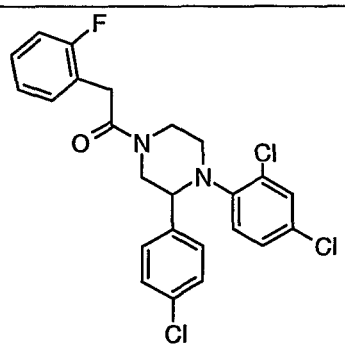
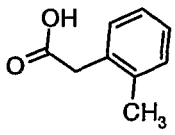
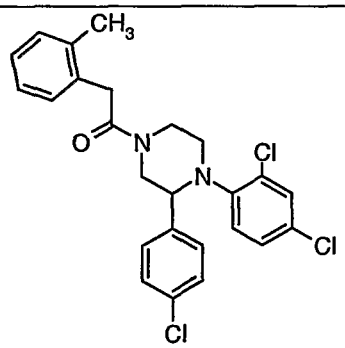
Example #	Carboxylic Acid	Example Structure
593		
594		
595		
596		

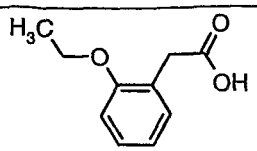
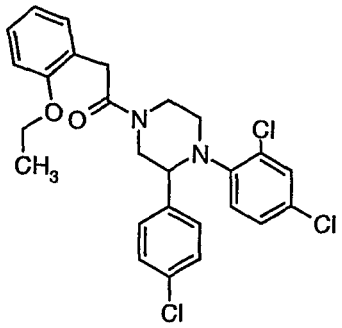
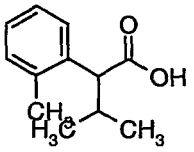
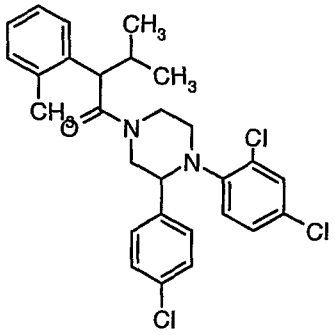
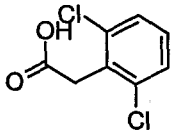
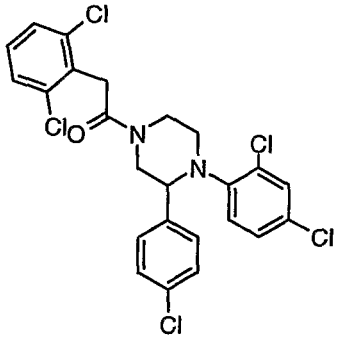
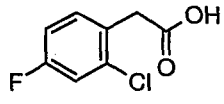
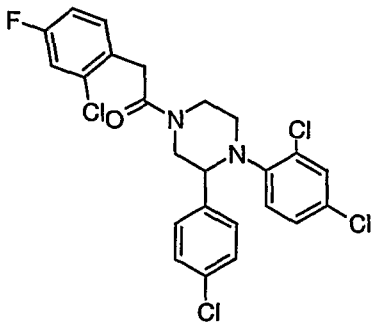
Example #	Carboxylic Acid	Example Structure
597		
598		
599		
600		

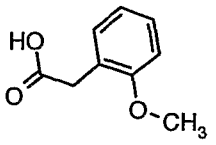
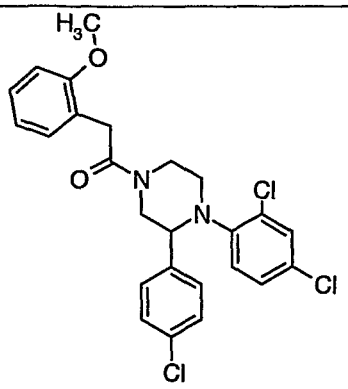
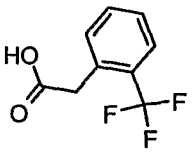
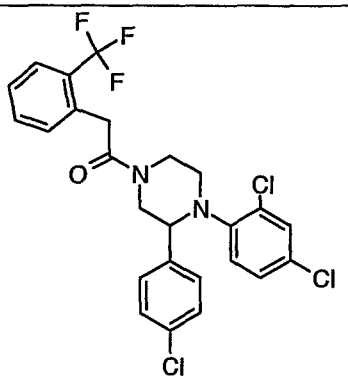
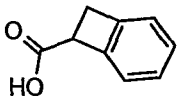
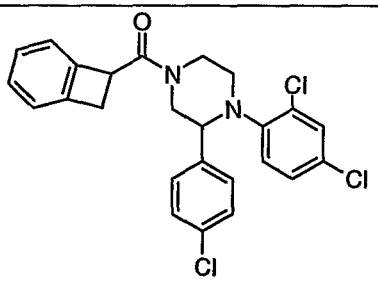
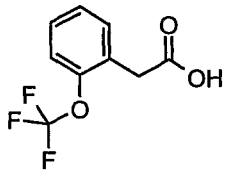
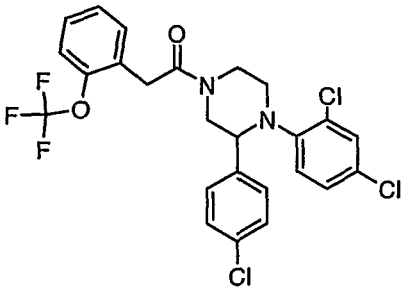
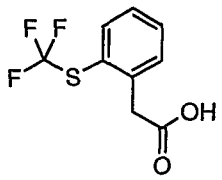
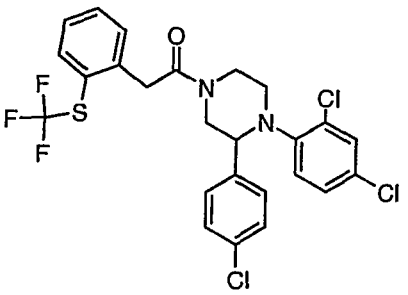
Example #	Carboxylic Acid	Example Structure
601		
602		
603		
604		

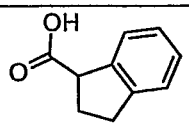
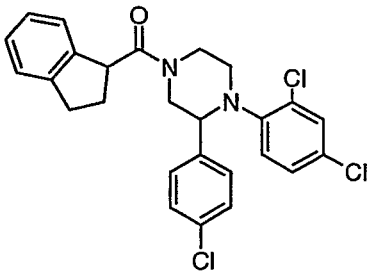
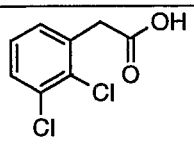
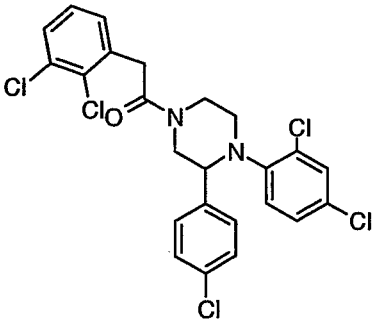
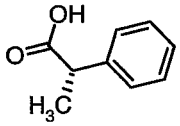
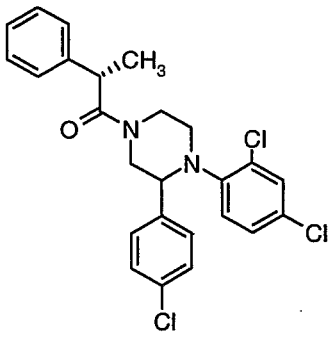
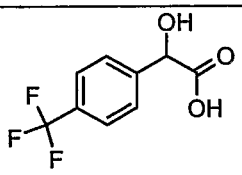
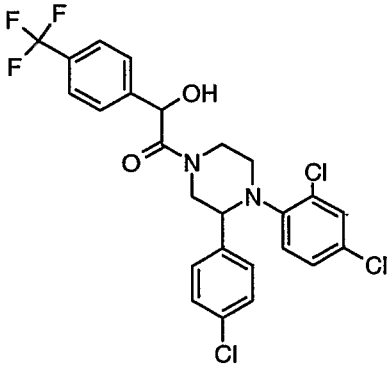
Example #	Carboxylic Acid	Example Structure
605		
606		
607		
608		

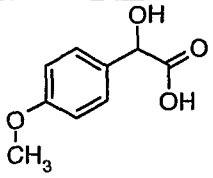
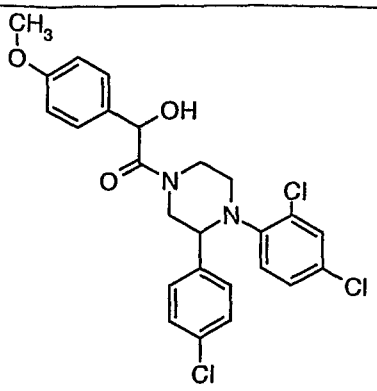
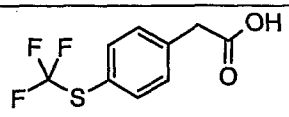
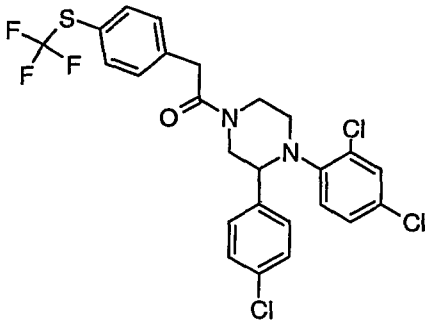
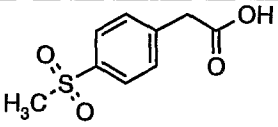
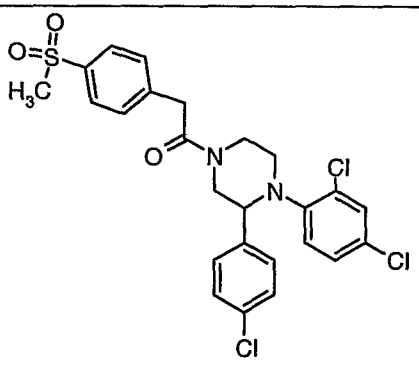
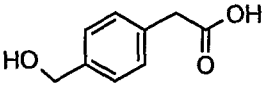
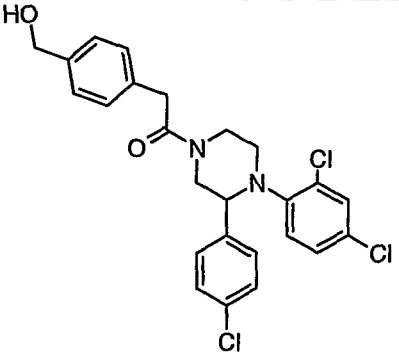
Example #	Carboxylic Acid	Example Structure
609		
610		
611		
612		
613		

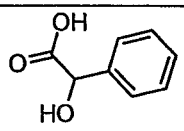
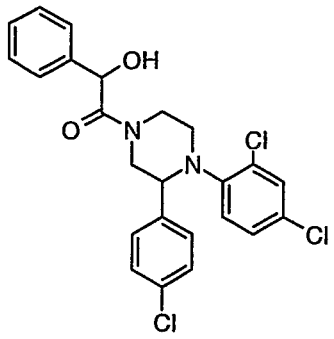
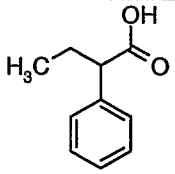
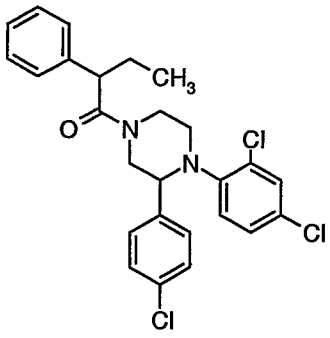
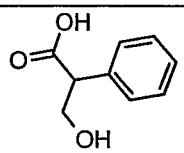
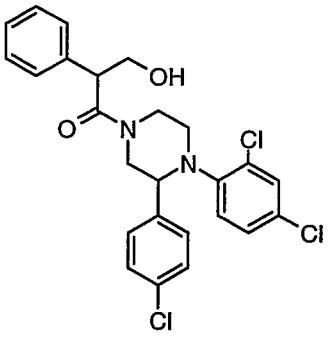
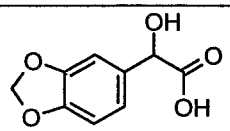
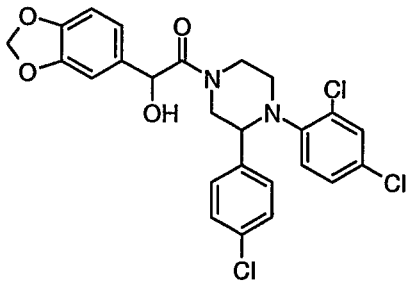
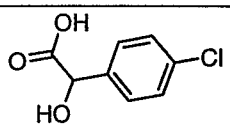
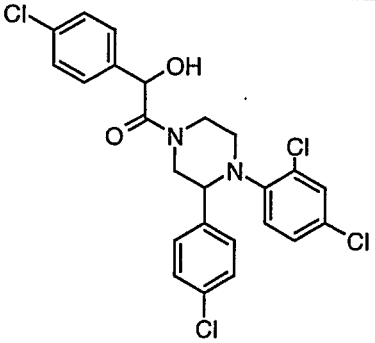
Example #	Carboxylic Acid	Example Structure
614		
615		
616		
617		

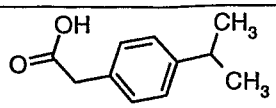
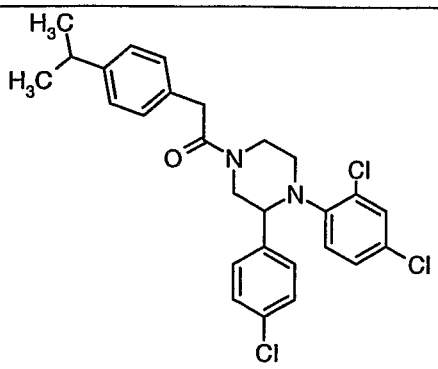
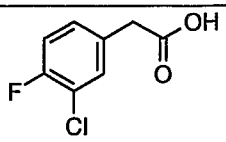
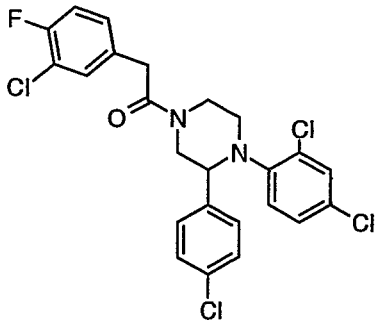
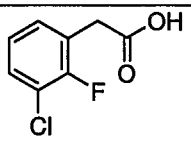
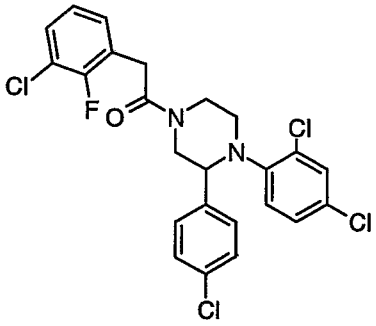
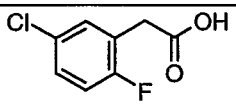
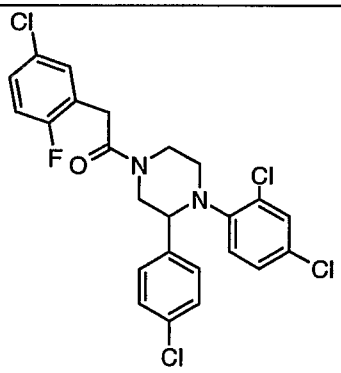
Example #	Carboxylic Acid	Example Structure
618		
619		
620		
621		

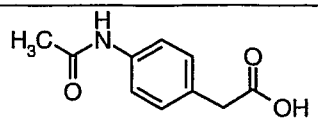
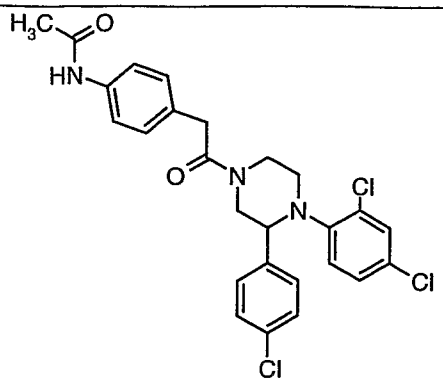
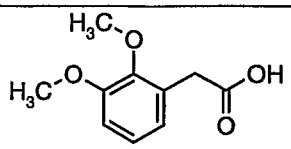
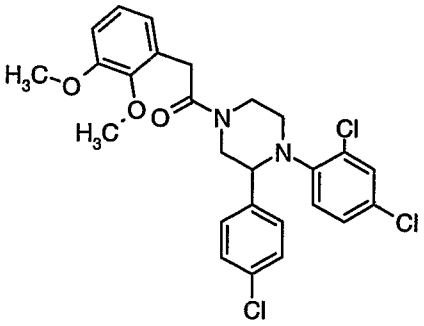
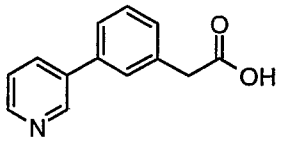
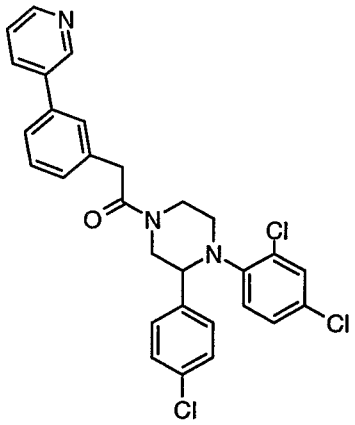
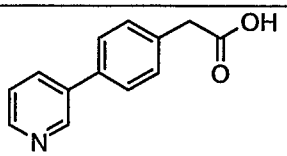
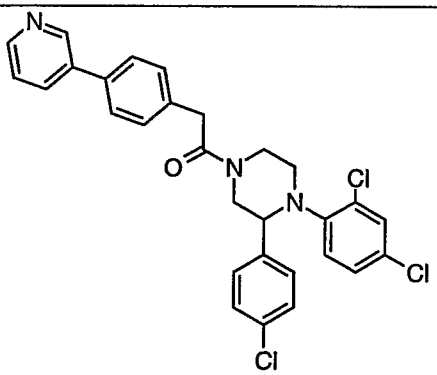
Example #	Carboxylic Acid	Example Structure
622		
623		
624		
625		
626		

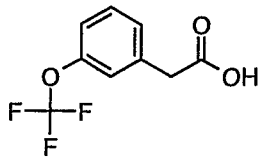
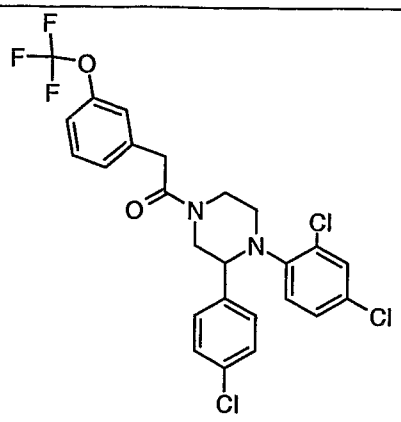
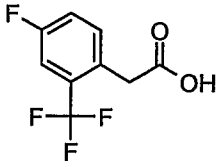
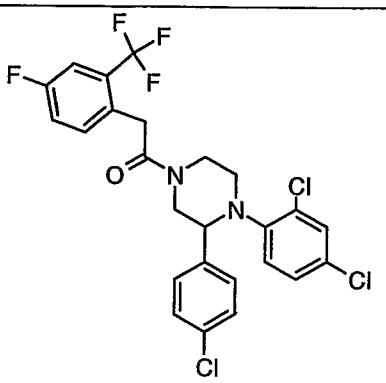
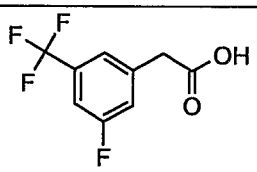
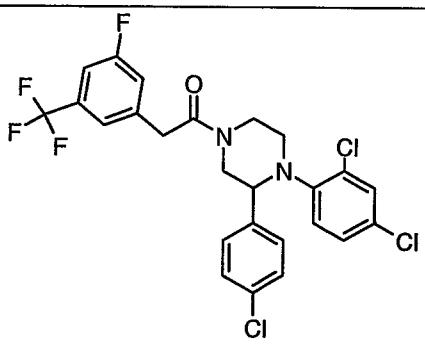
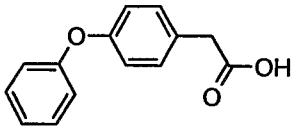
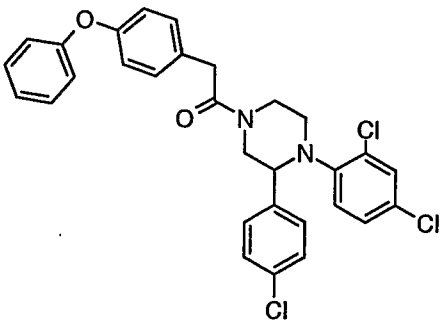
Example #	Carboxylic Acid	Example Structure
627		
628		
629		
630		

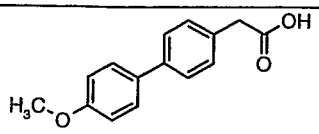
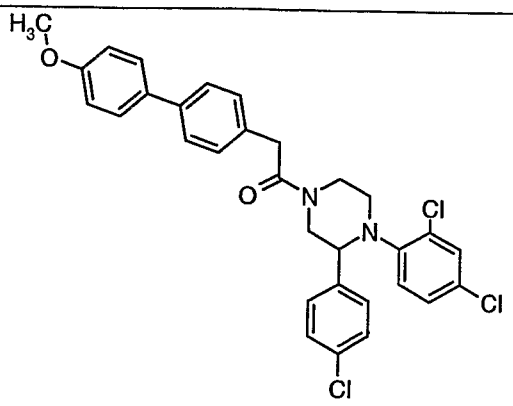
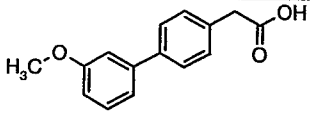
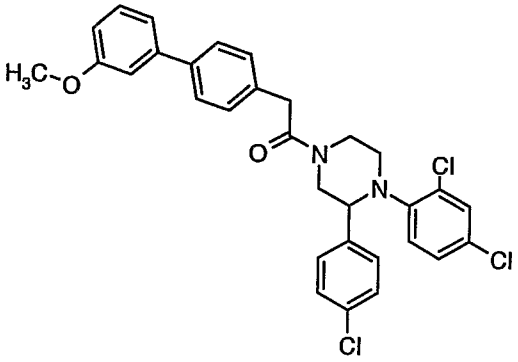
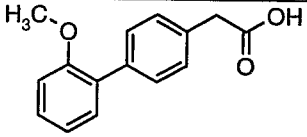
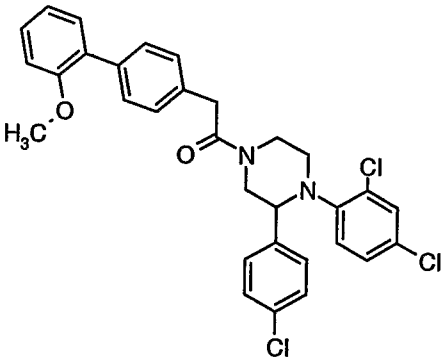
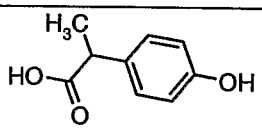
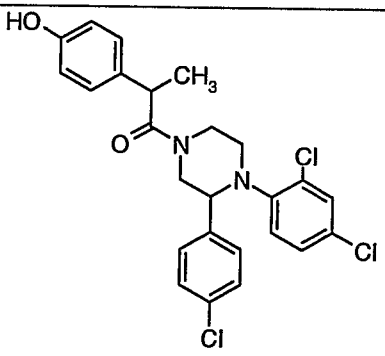
Example #	Carboxylic Acid	Example Structure
631		
632		
633		
634		

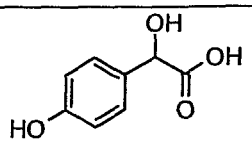
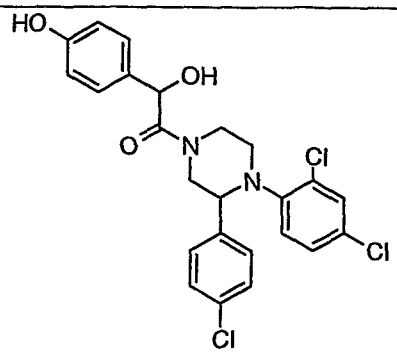
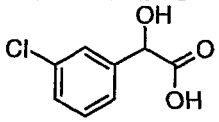
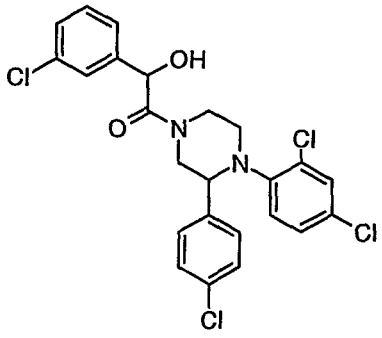
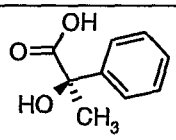
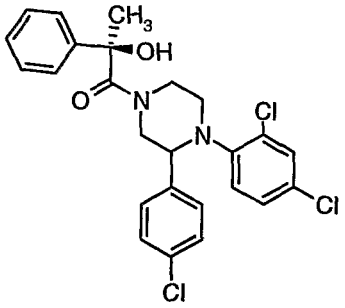
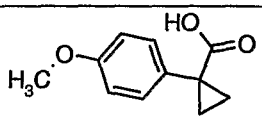
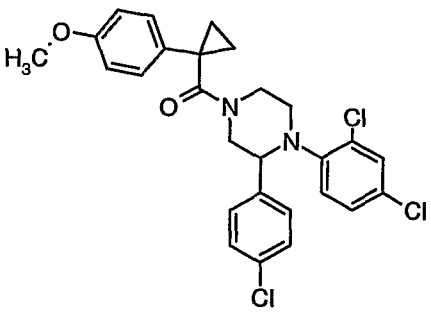
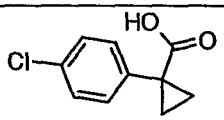
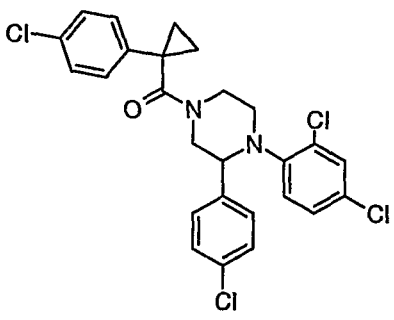
Example #	Carboxylic Acid	Example Structure
635		
636		
637		
638		
639		

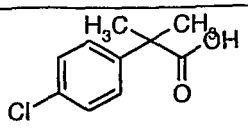
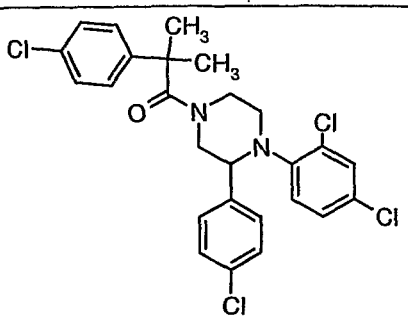
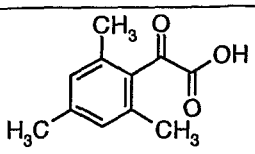
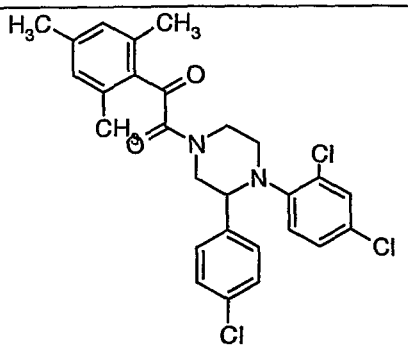
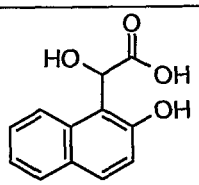
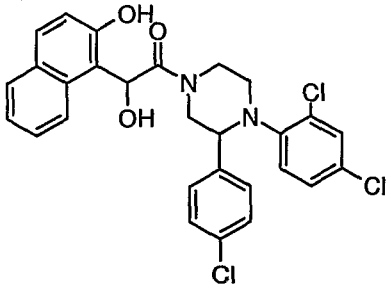
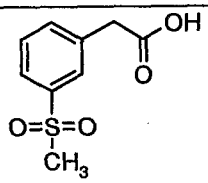
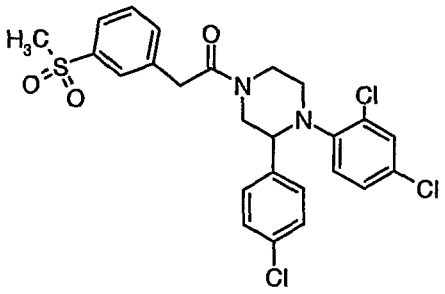
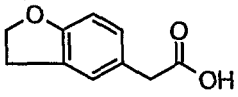
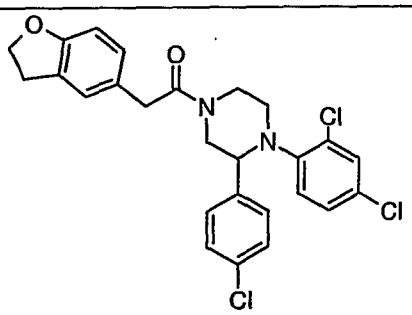
Example #	Carboxylic Acid	Example Structure
640		
641		
642		
643		

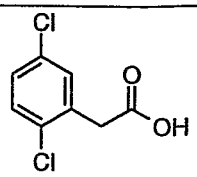
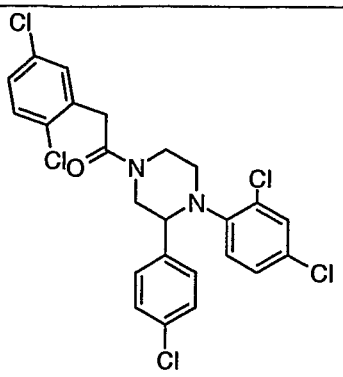
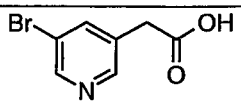
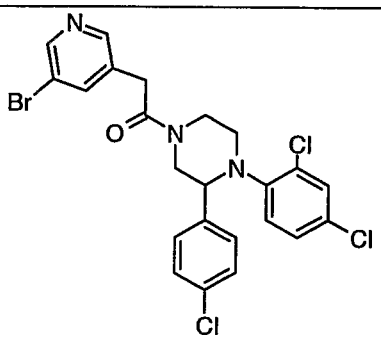
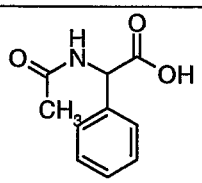
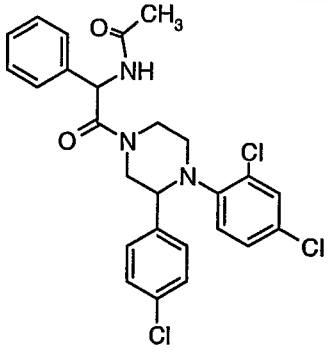
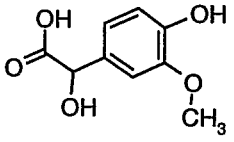
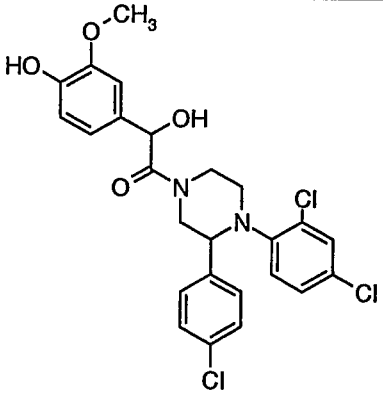
Example #	Carboxylic Acid	Example Structure
644		
645		
646		
647		

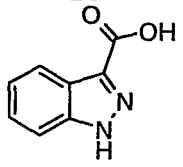
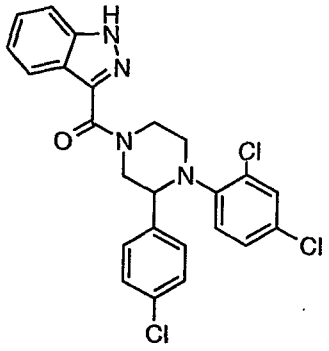
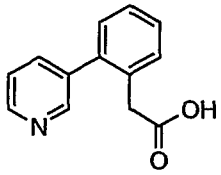
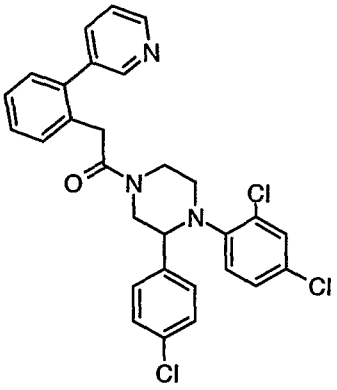
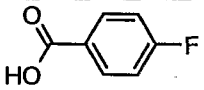
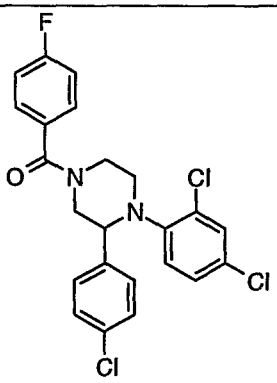
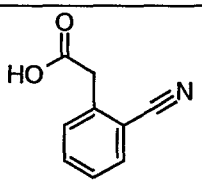
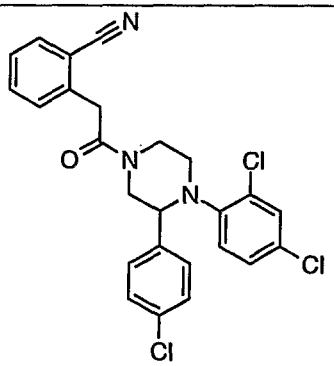
Example #	Carboxylic Acid	Example Structure
648		
649		
650		
651		

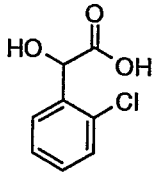
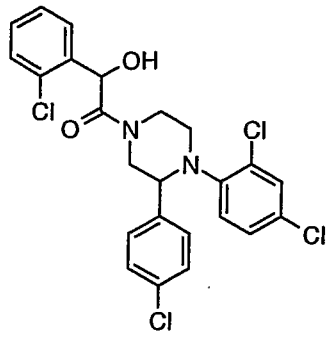
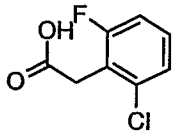
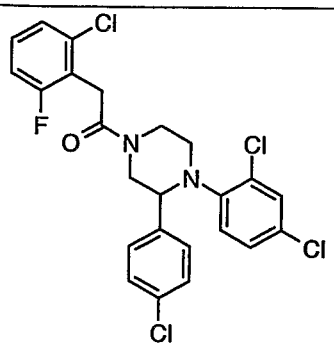
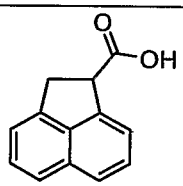
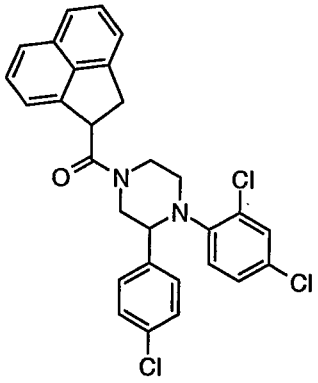
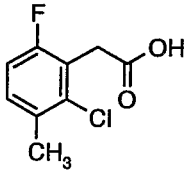
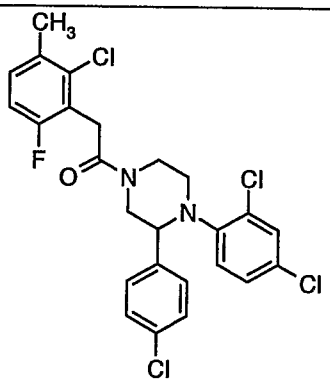
Example #	Carboxylic Acid	Example Structure
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653		
654		
655		

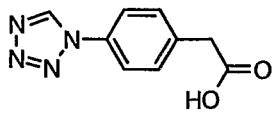
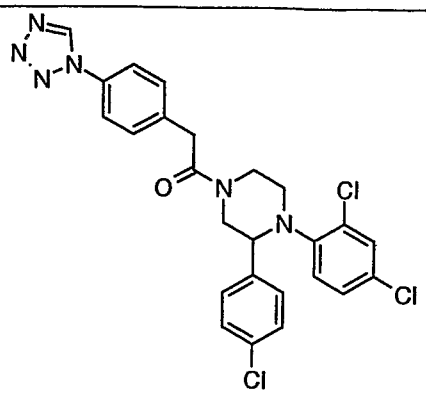
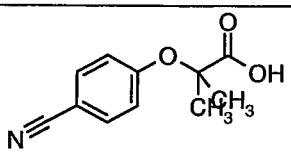
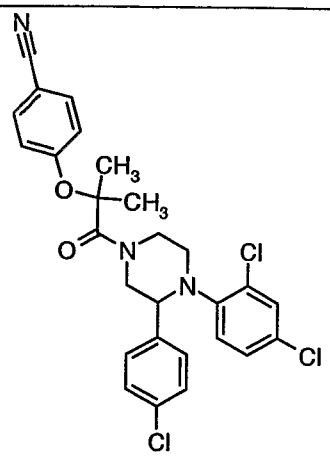
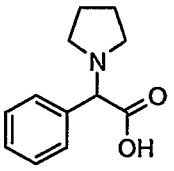
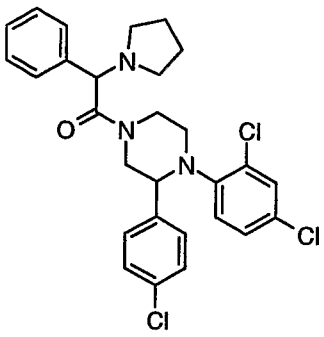
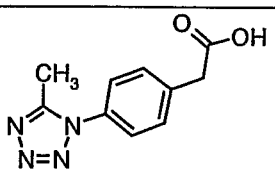
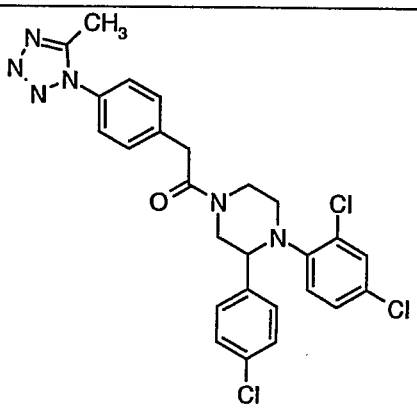
Example #	Carboxylic Acid	Example Structure
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657		
658		
659		
660		

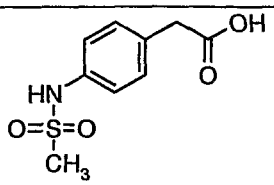
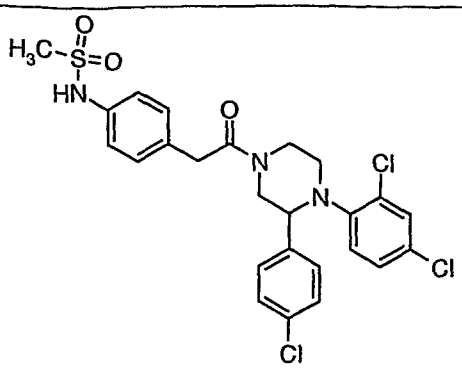
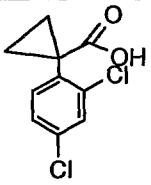
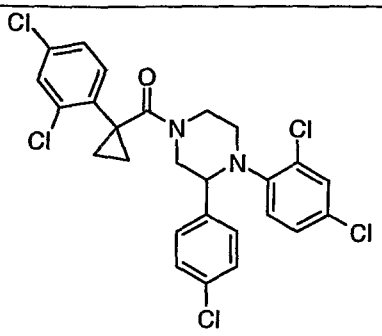
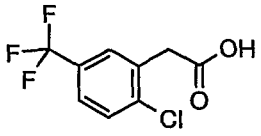
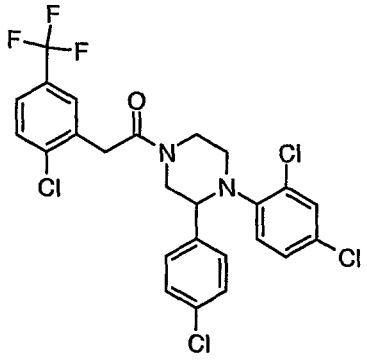
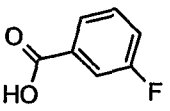
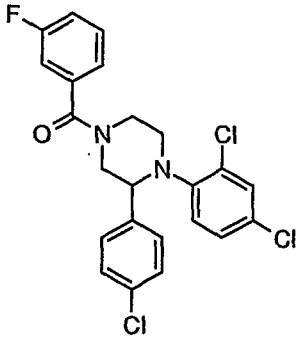
Example #	Carboxylic Acid	Example Structure
661		
662		
663		
664		
665		

Example #	Carboxylic Acid	Example Structure
666		
667		
668		
669		

Example #	Carboxylic Acid	Example Structure
670		
671		
672		
673		

Example #	Carboxylic Acid	Example Structure
674		
675		
676		
677		

Example #	Carboxylic Acid	Example Structure
678		
679		
680		
681		

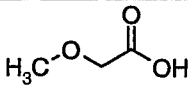
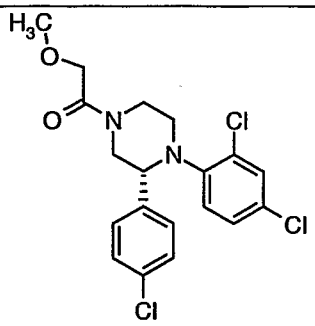
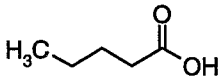
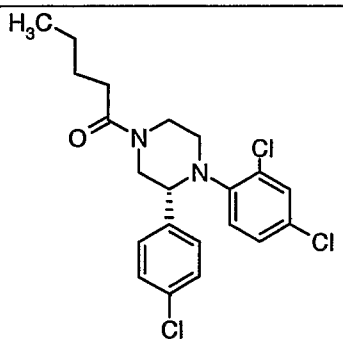
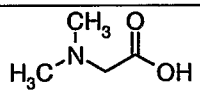
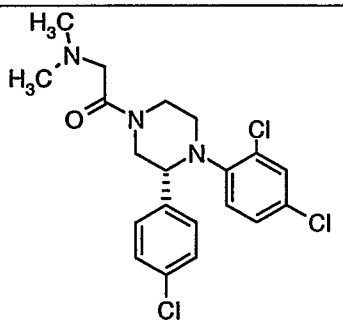
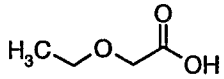
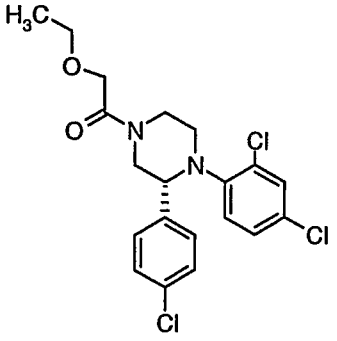
Example #	Carboxylic Acid	Example Structure
682		
683		
684		
685		

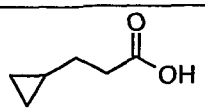
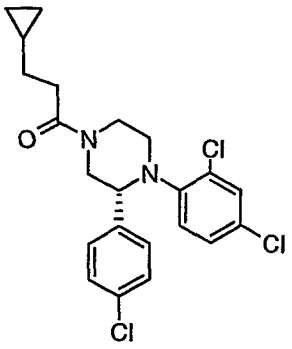
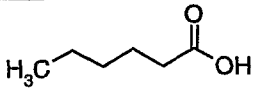
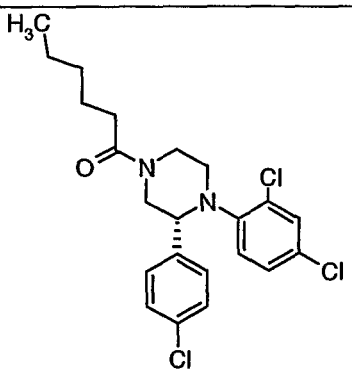
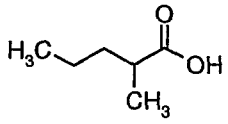
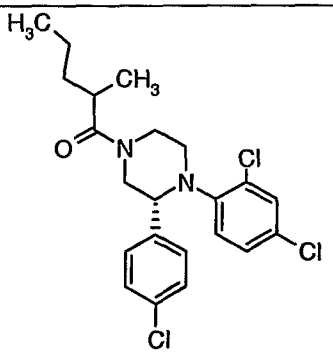
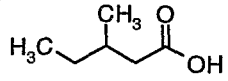
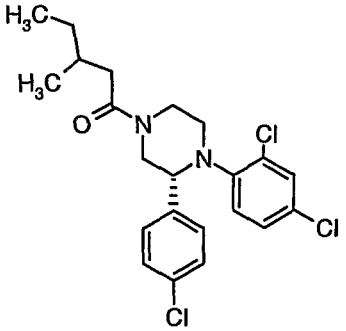
Preparation of Examples 686-766

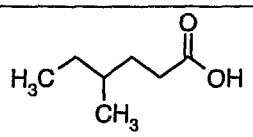
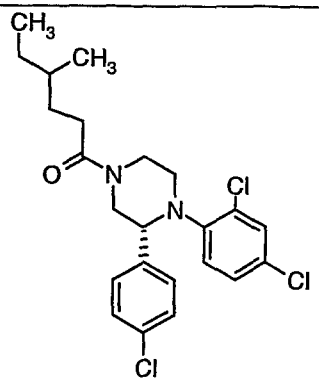
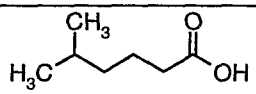
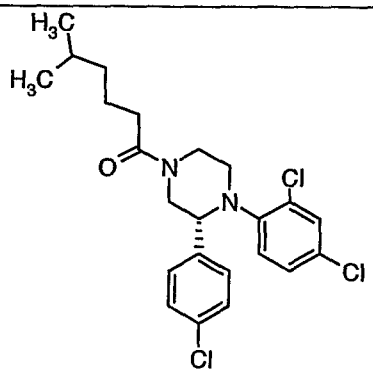
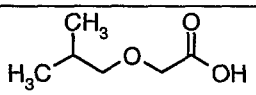
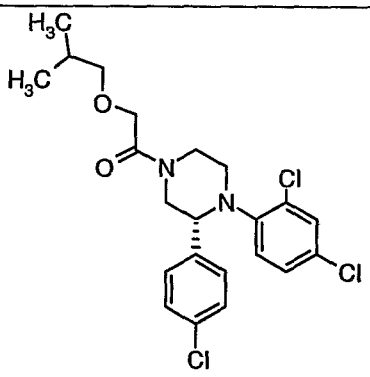
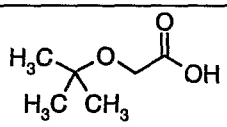
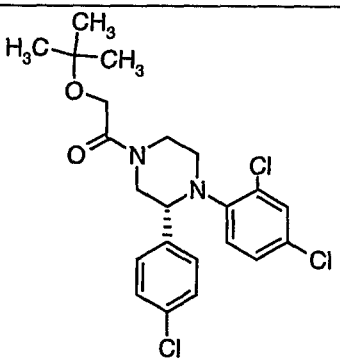
Examples 686-766 were prepared by the reaction of piperazine **Example 304** with the carboxylic acids shown in Table XXI, using the procedure of Scheme 5. **Examples 735, 737, 739, 741, 743, 745, 747, 749, 751, 753, 755, 757, 759, 761, 763,** and **765** prepared from the corresponding Boc carbamate by hydrolysis

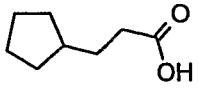
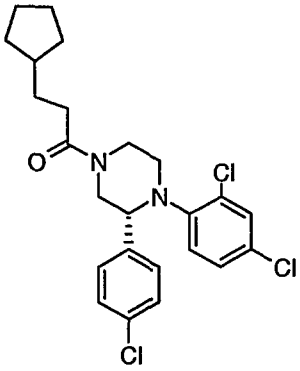
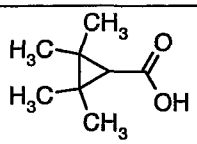
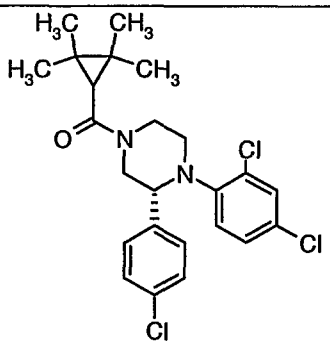
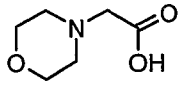
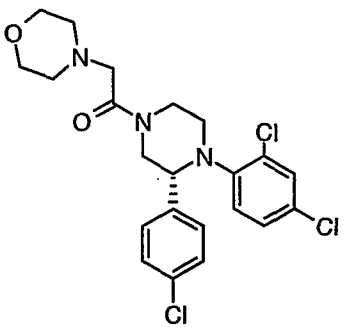
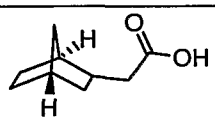
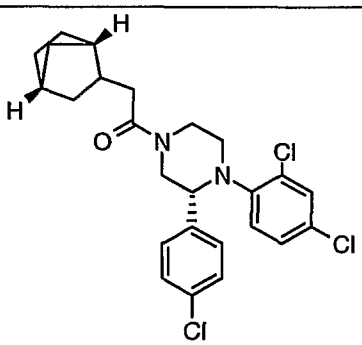
in 95% MeOH/ 5% (95% TFA/ 5% H_2O) solution in pre-weighed vials with shaking for 3 h. The solvent was removed *in vacuo* using a SpeedVac. Methanol and 2N HCl/ether was added and the samples shaken for 3 h. The solvent was removed *in vacuo* on a SpeedVac and the products were isolated as the HCl salt.

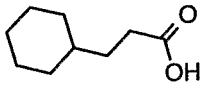
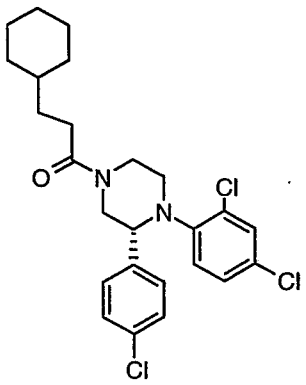
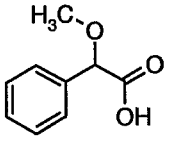
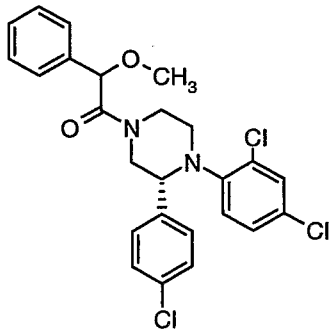
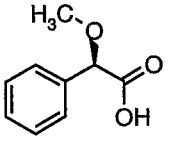
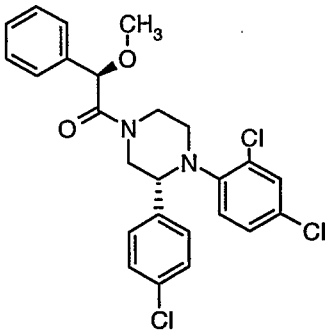
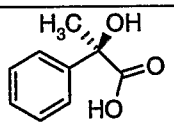
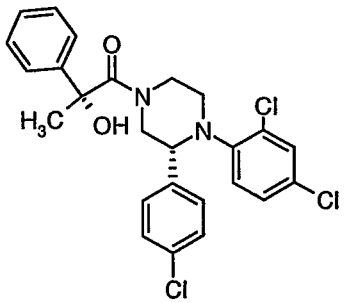
Table XXI

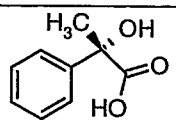
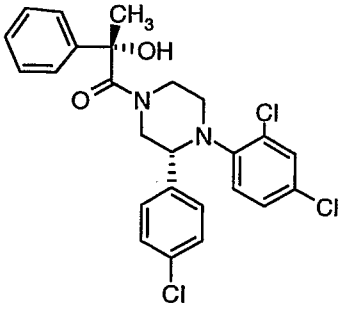
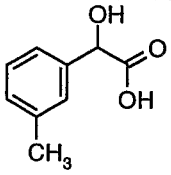
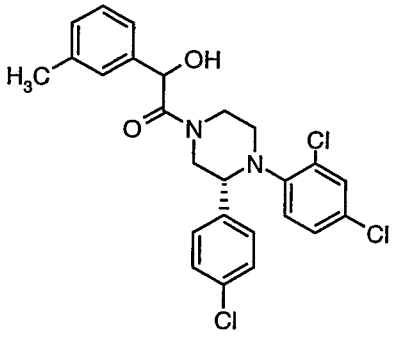
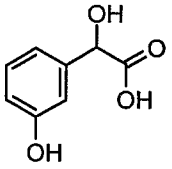
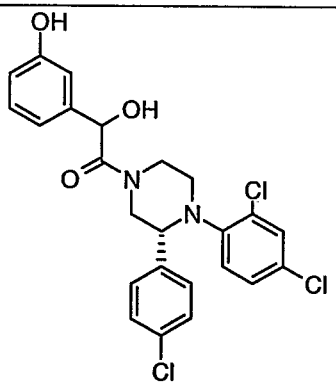
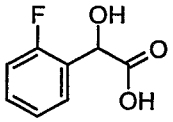
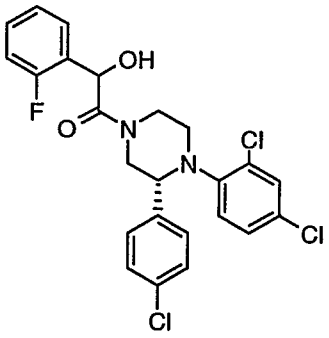
Example #	Carboxylic Acid	Example Structure
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687		
688		
689		

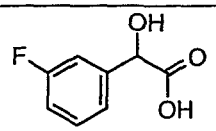
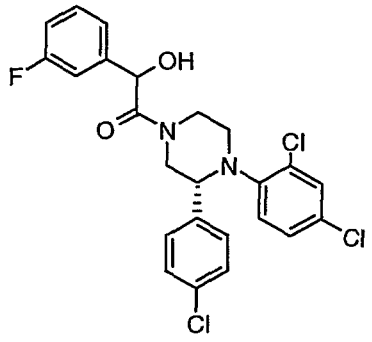
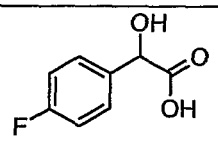
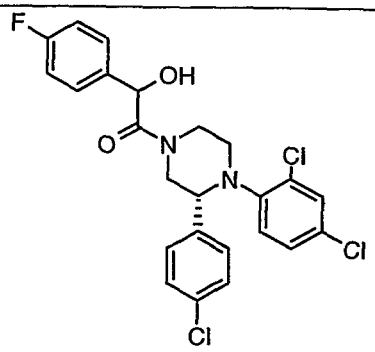
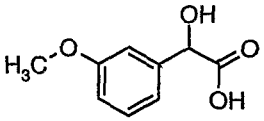
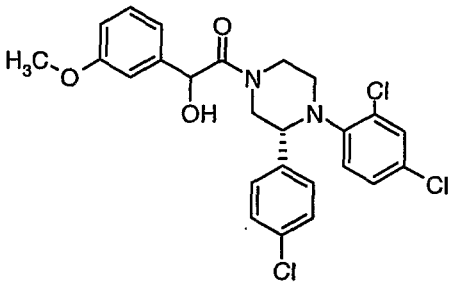
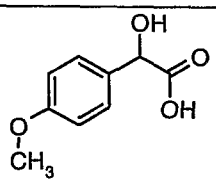
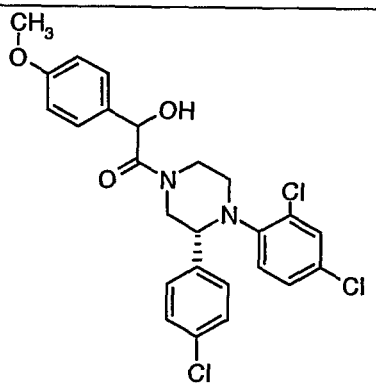
Example #	Carboxylic Acid	Example Structure
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691		
692		
693		

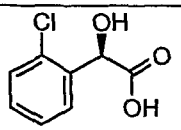
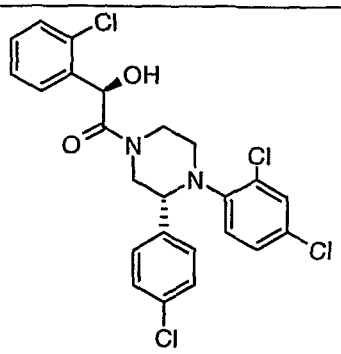
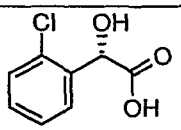
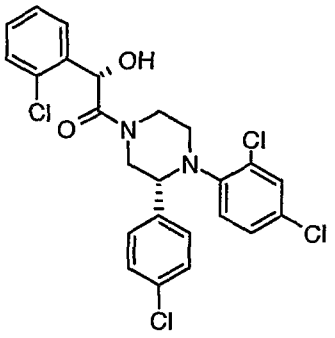
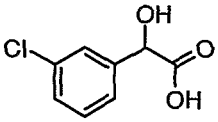
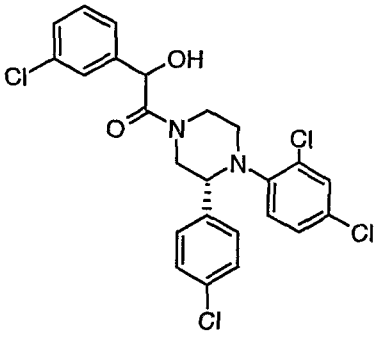
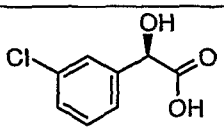
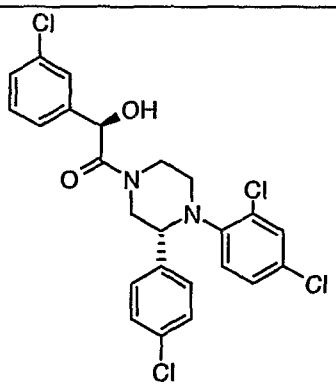
Example #	Carboxylic Acid	Example Structure
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695		
696		
697		

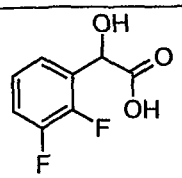
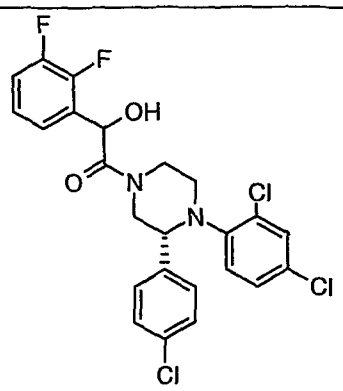
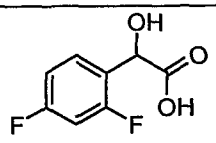
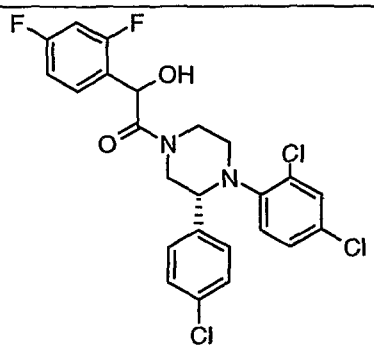
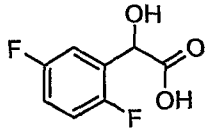
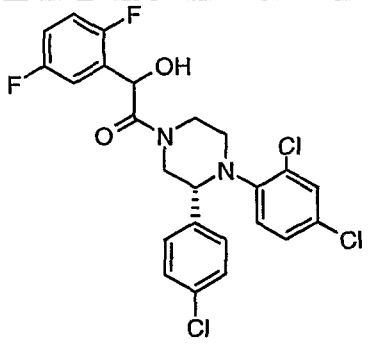
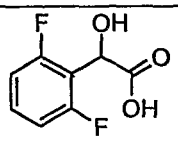
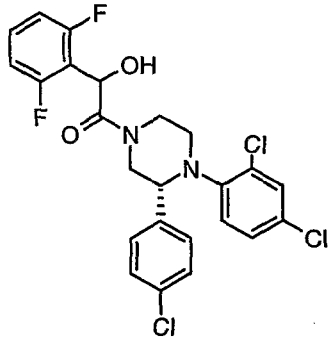
Example #	Carboxylic Acid	Example Structure
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699		
700		
701		

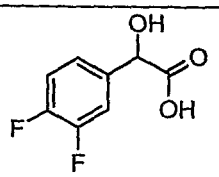
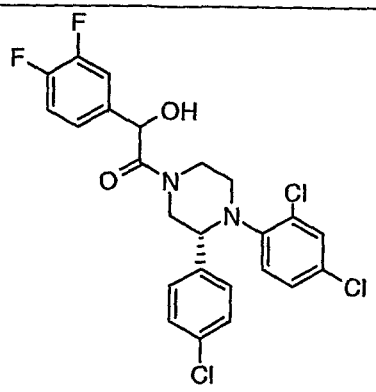
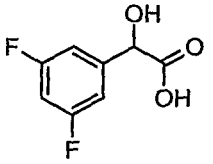
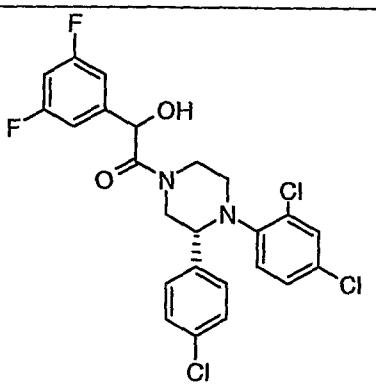
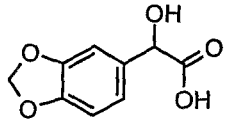
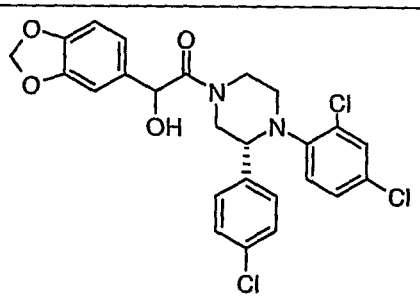
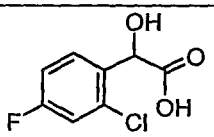
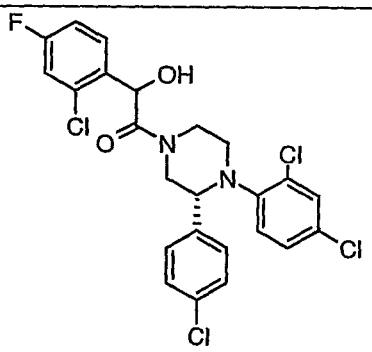
Example #	Carboxylic Acid	Example Structure
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703		
704		
705		

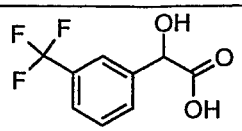
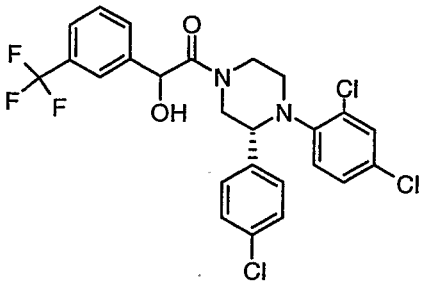
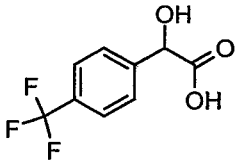
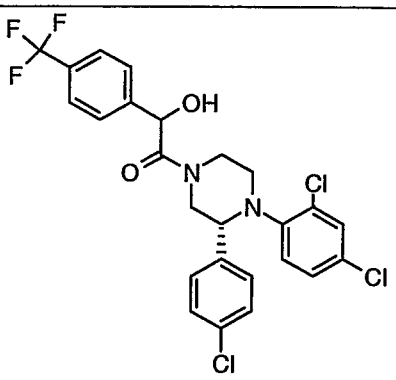
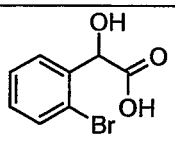
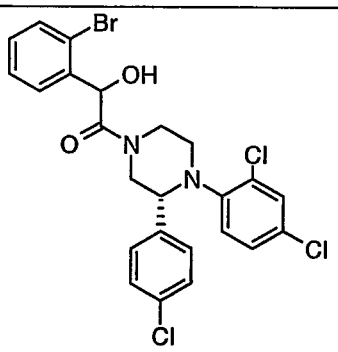
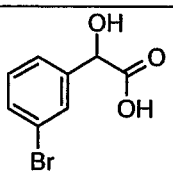
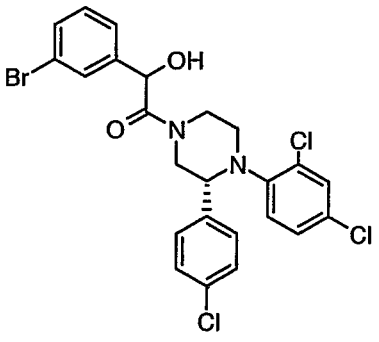
Example #	Carboxylic Acid	Example Structure
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707		
708		
709		

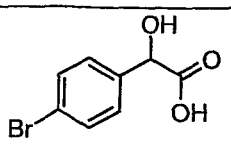
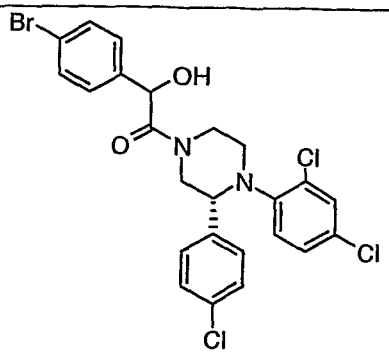
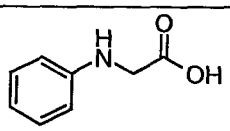
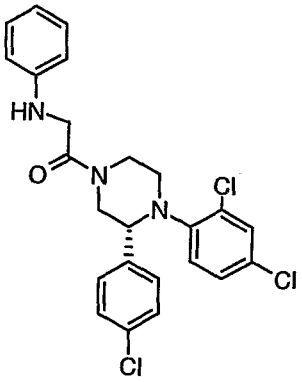
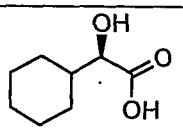
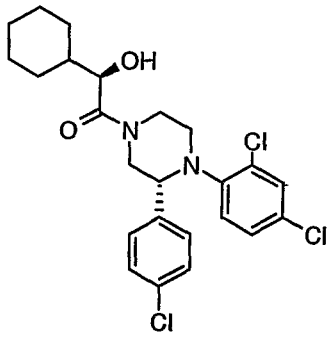
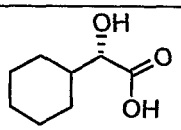
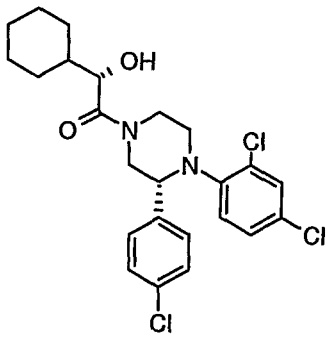
Example #	Carboxylic Acid	Example Structure
710		
711		
712		
713		

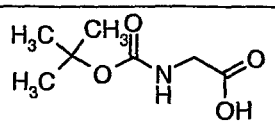
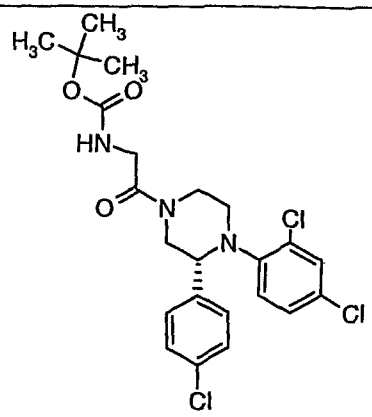
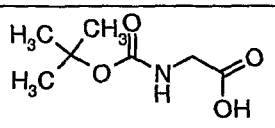
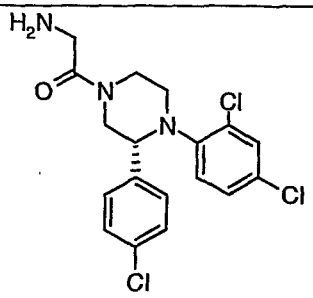
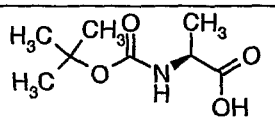
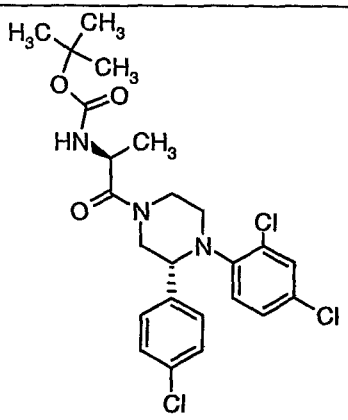
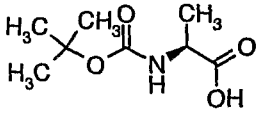
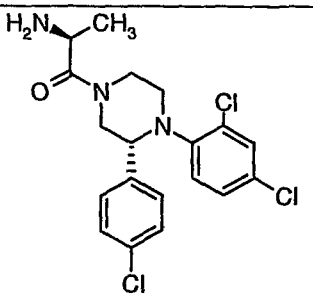
Example #	Carboxylic Acid	Example Structure
714		
715		
716		
717		

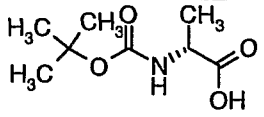
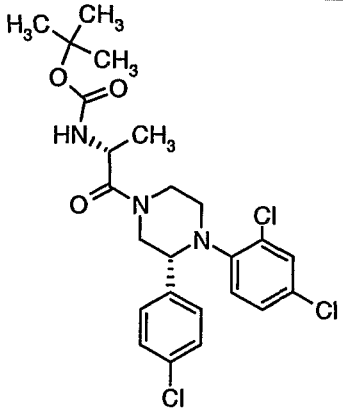
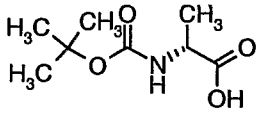
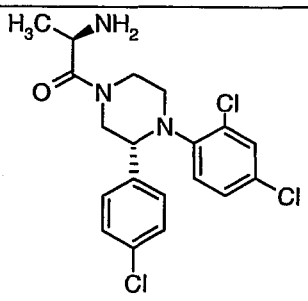
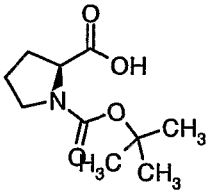
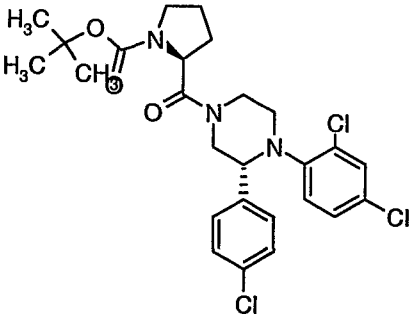
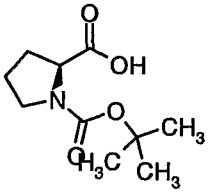
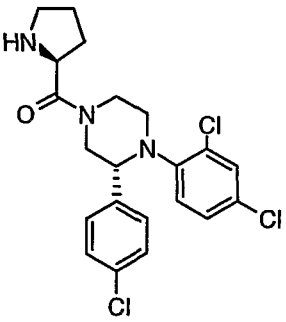
Example #	Carboxylic Acid	Example Structure
718		
719		
720		
721		

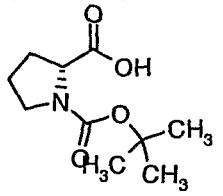
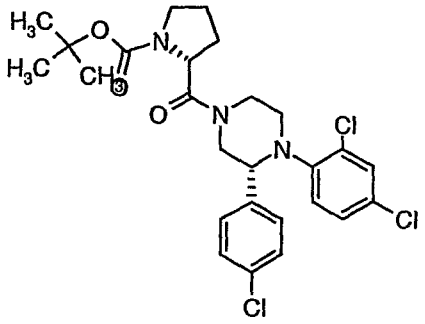
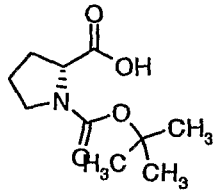
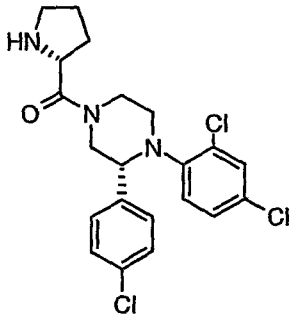
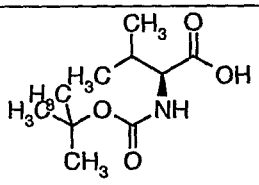
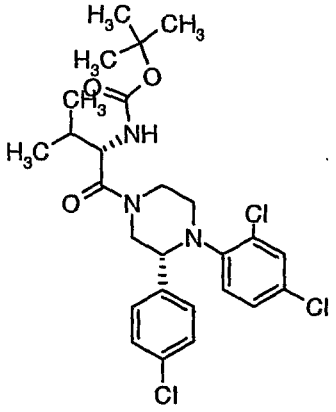
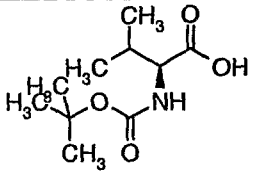
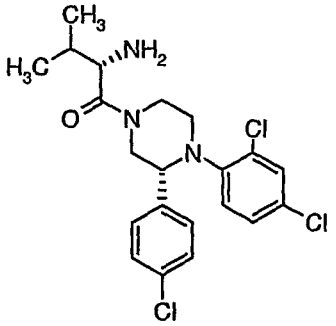
Example #	Carboxylic Acid	Example Structure
722		
723		
724		
725		

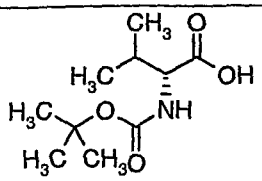
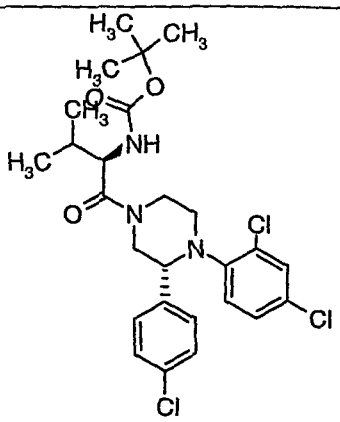
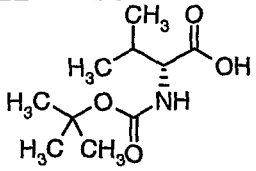
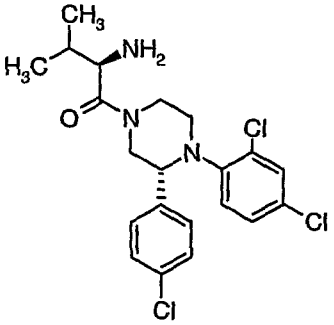
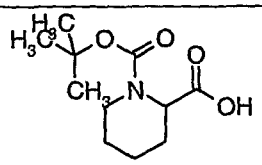
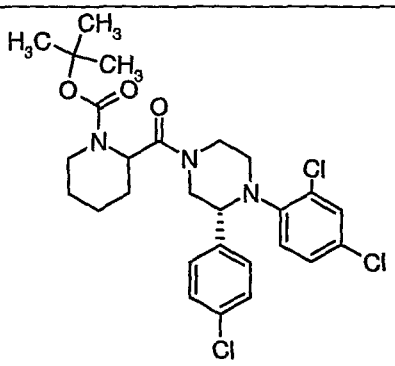
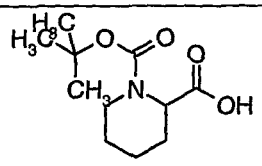
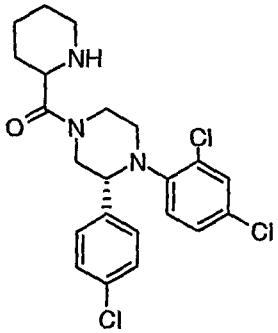
Example #	Carboxylic Acid	Example Structure
726		
727		
728		
729		

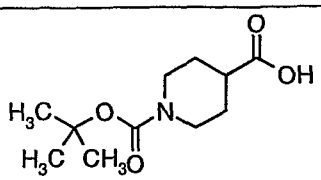
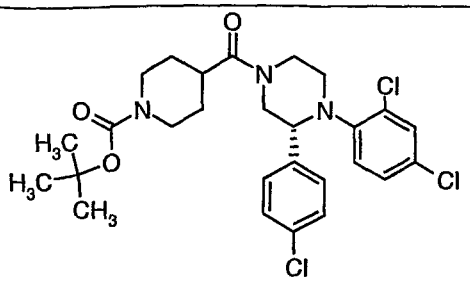
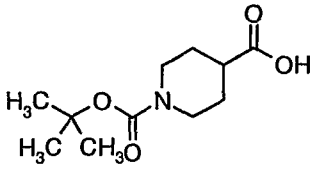
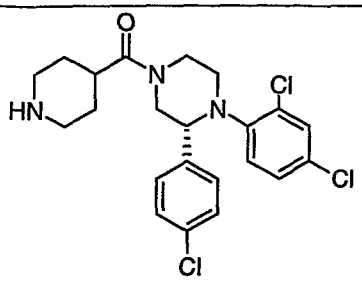
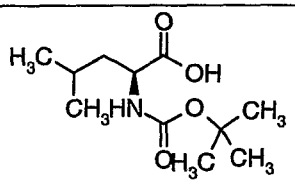
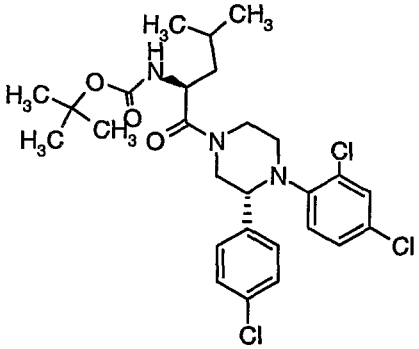
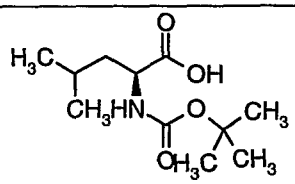
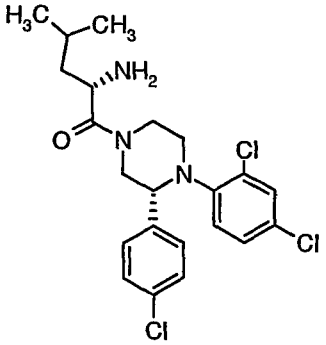
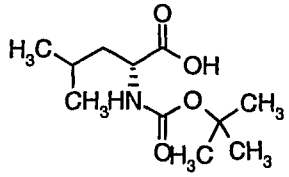
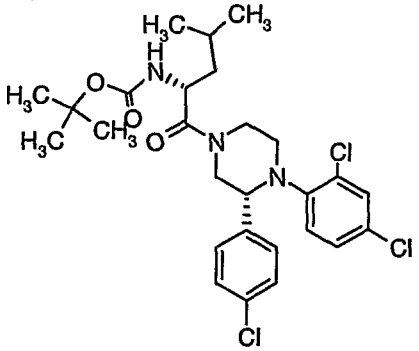
Example #	Carboxylic Acid	Example Structure
730		
731		
732		
733		

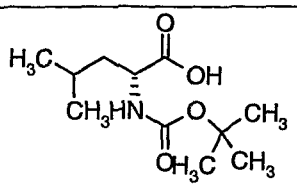
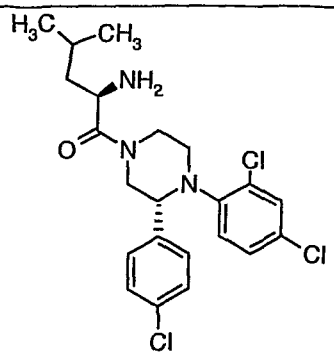
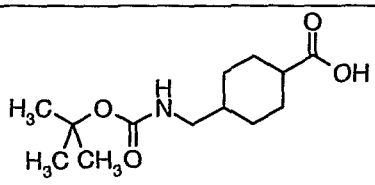
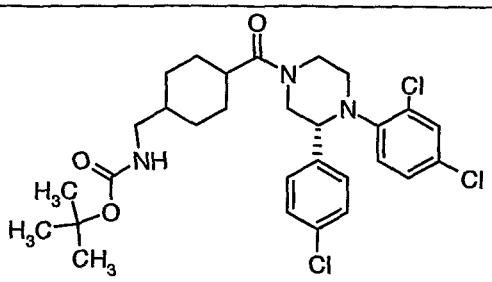
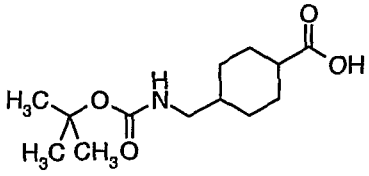
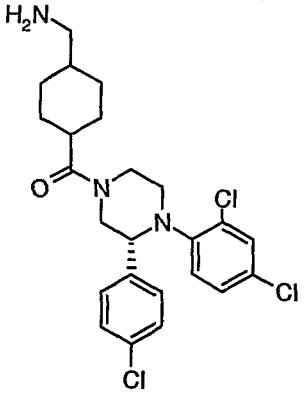
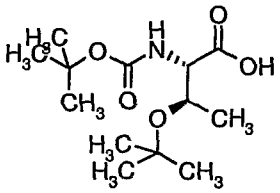
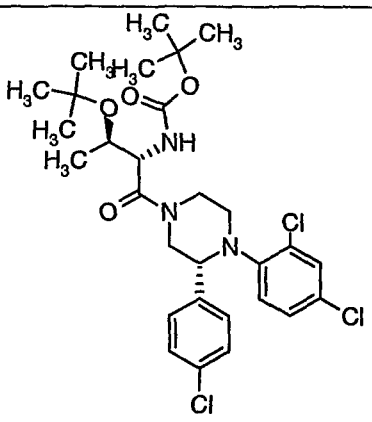
Example #	Carboxylic Acid	Example Structure
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735		
736		
737		

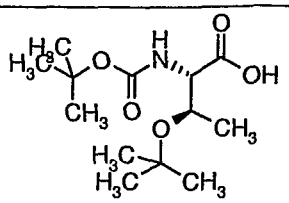
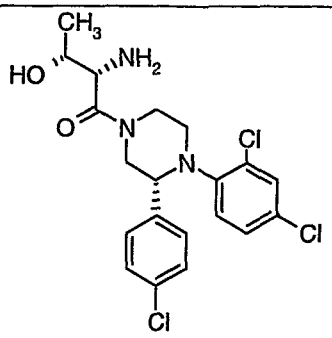
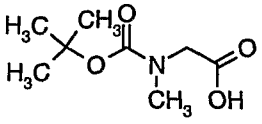
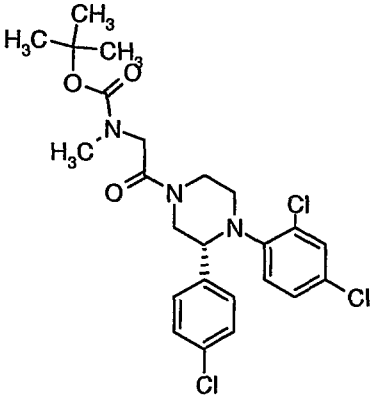
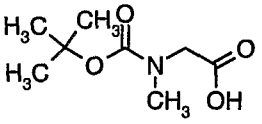
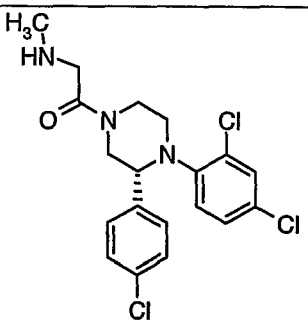
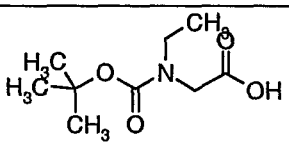
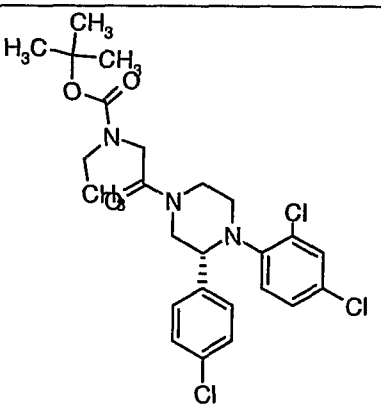
Example #	Carboxylic Acid	Example Structure
738		
739		
740		
741		

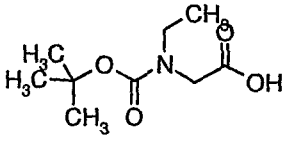
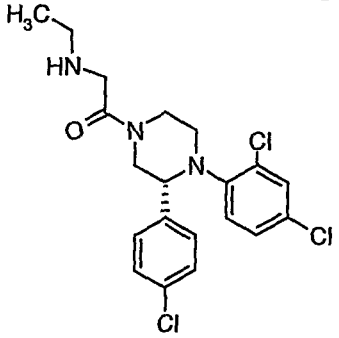
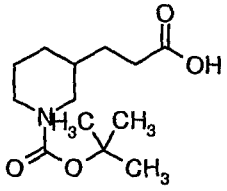
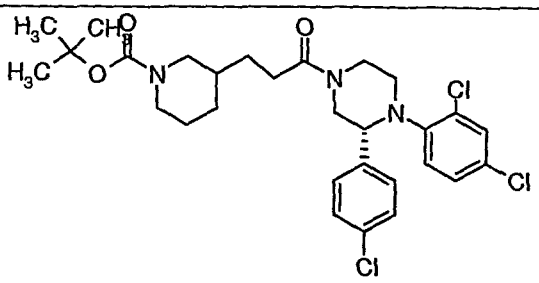
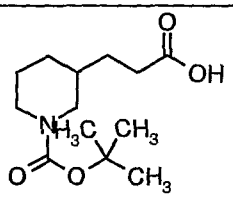
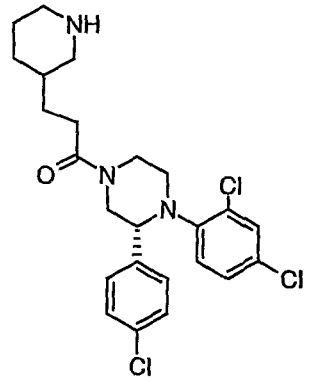
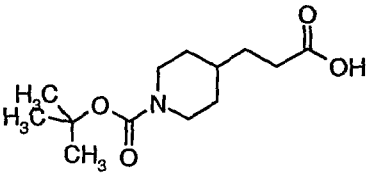
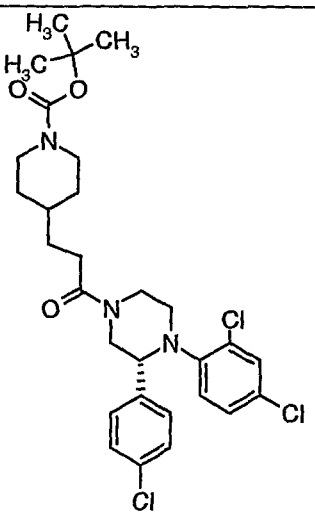
Example #	Carboxylic Acid	Example Structure
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743		
744		
745		

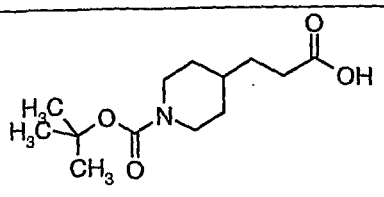
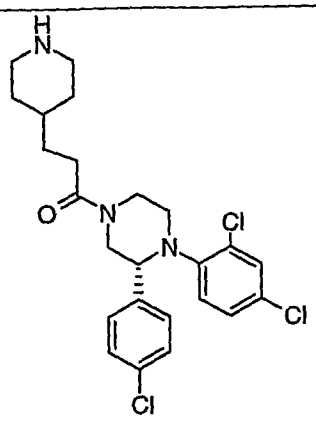
Example #	Carboxylic Acid	Example Structure
746		
747		
748		
749		

Example #	Carboxylic Acid	Example Structure
750		
751		
752		
753		
754		

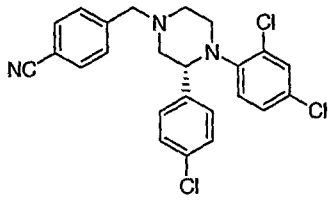
Example #	Carboxylic Acid	Example Structure
755		
756		
757		
758		

Example #	Carboxylic Acid	Example Structure
759		
760		
761		
762		

Example #	Carboxylic Acid	Example Structure
763		
764		
765		
766		

Example #	Carboxylic Acid	Example Structure
767		

Preparation of Example 768

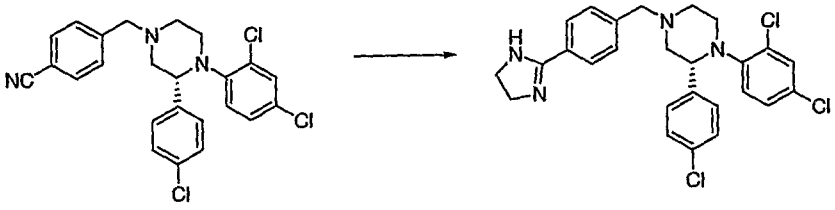


Example 768

Example 768 was prepared by the method of Scheme 1, except that **Example 304** was used instead of **Example 1** and 4-cycanobenzaldehyde was used instead of benzaldehyde.

Preparation of Example 769

Scheme 74



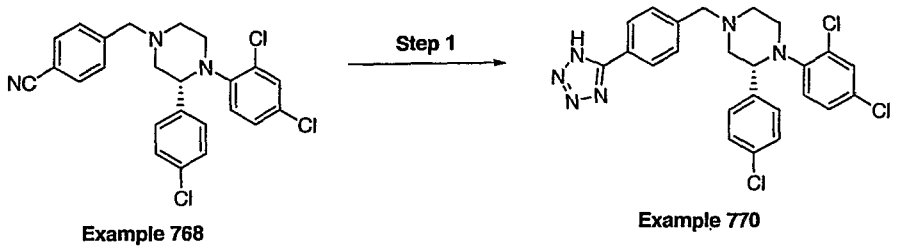
Example 768 Example 769

To the piperazine **Example 768** (0.1 g, 0.22 mmol) in ethylenediamine (15 μL) was added Yttrium (III) trifluoromethane sulfonate (1.2 mg). The mixture was warmed to 100°C and stirred for 20 h. An additional amount of ethylenediamine (0.2 mL) and Yttrium (III) trifluoromethane sulfonate (1 mg) was added, and the mixture was stirred at 100°C for 4 days. Additional ethylenediamine (0.2 mL) and Yttrium (III) trifluoromethane sulfonate (1 mg) were then added, and the mixture stirred for an additional 24 h at 100°C. The reaction mixture was cooled to room

temperature and purified by preparative TLC (25% EtOAc/hexane) to provide **Example 769** (0.022 g).

Preparation of Example 770

Scheme 76



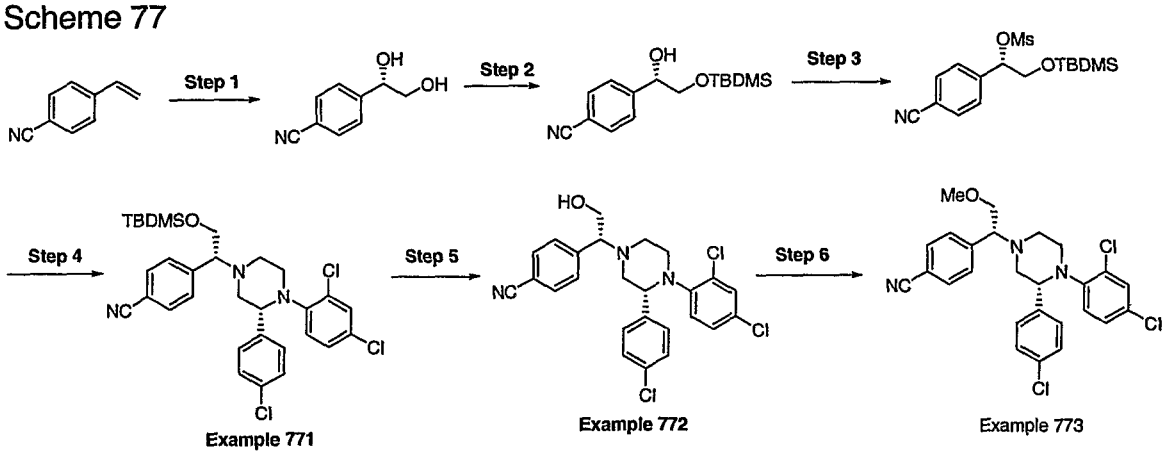
Example 768 Example 770

Step 1:

To the piperazine **Example 768** (0.1 g, 0.22 mmol) in DMF (2.2 mL) in a microwave reactor vial was added NaN_3 (0.17 g, 2.6 mmol) and NH_4Cl (0.14 g, 2.6 mmol). The reaction mixture was capped and irradiated in a microwave reactor at 20W. The reaction temperature reached ~220°C. The reaction was irradiated for 25 minutes and cooled to room temperature. Saturated $NaHCO_3$ was added and the mixture was extracted with EtOAc. The organic layer was washed with water and brine. The organic layer was then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel preparative TLC (5% MeOH/CH_2Cl_2) to provide **Example 770** (0.035 g).

Preparation of Examples 771-773

Scheme 77



Example 771 Example 772 Example 773

Step 1

To AD mix α (available from Aldrich) (10.8 g) in *tert*-butyl alcohol/water (1:1) (78 mL) at 0°C was added 4-cyanostyrene (1.0 g, 7.7 mmol). The reaction was stirred for 20 h, allowing the cold bath to expire. The reaction was cooled to 0°C and solid sodium sulfite (10 g) was added. The mixture was allowed to warm to room temperature while stirring for 1 h. The mixture was then extracted with

EtOAc. The organic layer was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (5% MeOH/CH_2Cl_2) to provide the corresponding diol (1.24 g).

Step 2

To the diol prepared in step 1 (0.62 g, 3.8 mmol) in DMF (10 mL) at 0°C was added imidazole (0.65 g, 9.5 mmol) followed by TBDMS-Cl (i.e., tert-butyldimethylsilyl chloride) (0.69 g, 4.6 mmol). The reaction mixture was stirred for 4h while warming to room temperature. The reaction mixture was poured into brine and then extracted with EtOAc. The organic layer was washed with water, brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (20% EtOAc/hexane) to provide a tert-butyldimethylsilyl ether (0.67 g).

Step 3

To the tert-butyldimethylsilyl ether prepared in step 2 (0.67 g, 2.4 mmol) in CH_2Cl_2 (8 mL) at 0°C was added TEA (i.e., triethylamine) (0.5 mL, 3.6 mmol) followed by $MeSO_2Cl$ (0.22 mL, 2.9 mmol). The reaction mixture was stirred for 2 h and CH_2Cl_2 was added. The mixture was washed with saturated $NaHCO_{3(aq)}$, water, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide a methylsulfonyl ester (0.87 g) that was used directly in step 4 without further purification.

Step 4

To the methylsulfonyl ester prepared in step 3 (0.34 g, 1 mmol) in acetonitrile (3 mL) was added piperazine **Example 304** (0.44 g, 1.25 mmol) and potassium carbonate (0.35 g, 2.5 mmol). The reaction mixture was warmed to reflux and stirred for 24 h. The reaction was cooled to room temperature and EtOAc was added. The mixture was washed with water and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (20% EtOAc/hexane) to provide **Example 771** (0.40 g).

Step 5

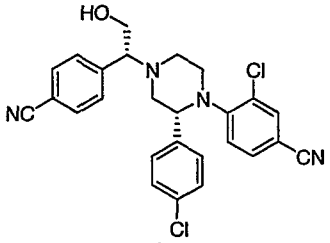
To **Example 771** (0.40 g, 0.66 mmol) in THF (2 mL) at 0°C was added tetrabutylammonium fluoride (1.0 M in THF, 0.74 mL). The reaction was stirred for 20 h while warming to room temperature. EtOAc was added and the mixture washed with water and brine. The organic layer was dried ($MgSO_4$), filtered, and

concentrated *in vacuo*. The residue was purified by silica gel chromatography (60% EtOAc/hex) to provide **Example 772** (0.31 g, 0.64 mmol).

Step 6

To **Example 772** (0.15 g, 0.31 mmol) in THF at room temperature was added NaH (15 mg) (60% dispersion in mineral oil) followed by methyl iodide (0.024 mL, 0.38 mmoL). The reaction was stirred at room temperature for 20 h. Water was added slowly and the mixture was extracted with EtOAc. The organic layer was washed with water, brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (30% EtOAc/hexane) to provide **Example 773** (0.14 g).

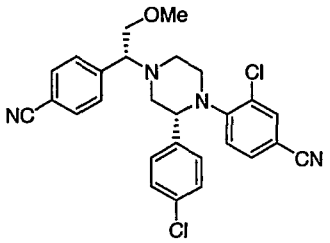
Preparation of Example 774



Example 774

Example 774 was prepared using procedures similar to those used to prepare **Example 772**, except that the piperazine **Example 305** was used instead of **Example 304** in step 4 of Scheme 77.

Preparation of Example 775

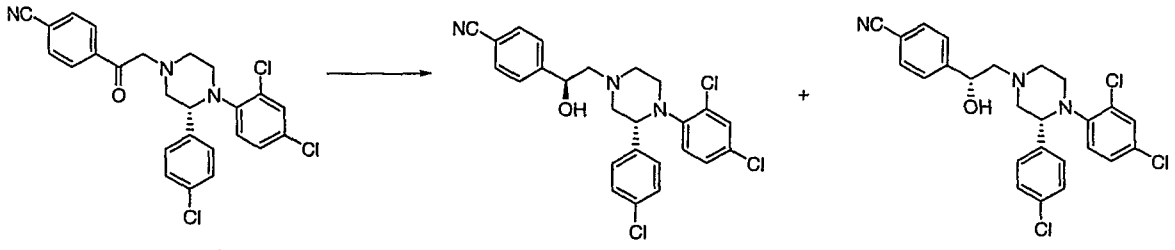


Example 775

Example 775 was prepared using procedures similar to those used to prepare **Example 773**, except that the piperazine **Example 305** was used instead of **Example 304** in step 4 of Scheme 77.

Preparation of Example 776a and 776b

Scheme 78

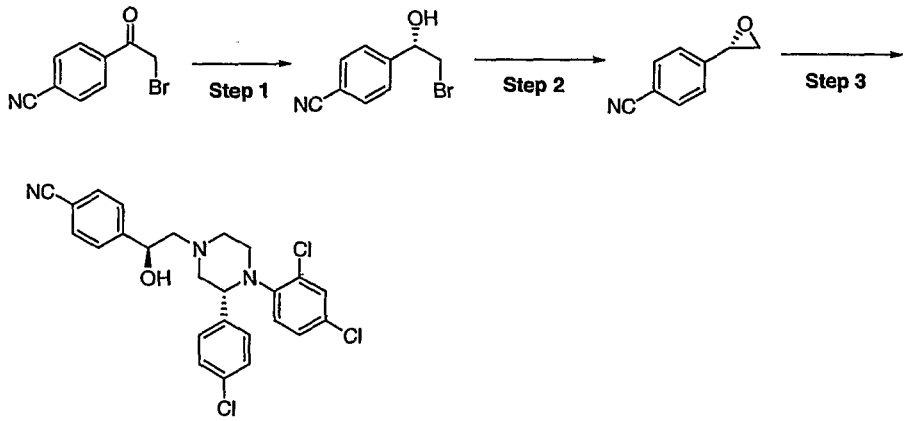


Example 399 Example 776a Example 776b

To **Example 399** (0.16 g, 0.32 mmol) in MeOH (1.5 mL) at 0°C was added $NaBH_4$ (0.012 g, 0.32 mmol) (with gas evolution). The cold bath was removed from the reaction vessel, and the reaction mixture was stirred for 45 minutes. The reaction mixture was concentrated *in vacuo*. Water was added and the reaction mixture was extracted with EtOAc. The organic layers were combined and washed with water, brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromotography (5-50% EtOAc/hexane) to provide the corresponding alcohol as a mixture of diastereomers (0.8 g, 0.16 mmol). The diastereomers were separated by chiral prep HPLC (Chiralcel OD, 85% hexane/IPA, 50 mL/min, 254 nm) to provide **Examples 776a** and **776b**.

Alternatively, **Example 776a** was prepared by the following method:

Scheme 79



Example 776a

Step 1:

To 2-bromo-4'-cyanoacetophenone (1.0 g, 4.5 mmol) in THF (4.5 mL) at 0°C was added (*S*)-2-methyl-CBS-oxazaborolidine (1M in toluene, 0.89 mL) followed by BH_3•SMe_2 (2.0M in THF, 1.3 mL). The mixture was stirred at 0°C for 75 minutes. MeOH (~5 mL) was added (with gas evolution) and the mixture was

stirred for 15 minutes. The reaction mixture was concentrated *in vacuo*. The residue was taken up into CH_2Cl_2 and washed with 1N HCL, water, and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide the corresponding alcohol which was used directly in the next step withour further purification.

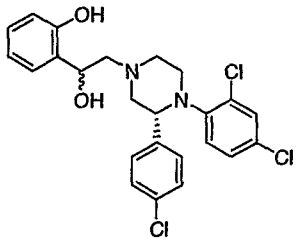
Step 2:

The alcohol prepared in step 1 was taken up into toluene (40 mL). 1N NaOH (40 mL) was added and the mixture was stirred at room temperature for 20 h. The organic layer was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (0-20% EtOAc/hexane) to provide the epoxide (0.52 g, 3.6 mmol).

Step 3:

To the piperazine **Example 304** (0.15 g, 0.44 mmol) was added the epoxide (0.07 g, 0.48 mmol) prepared in step 2. The reaction mixture was heated neat (without solvent) at 100°C for 18 h. The reaction was cooled to room temperature and the reaction mixture purified by silica gel chromatography (5-40% EtOAc/hexanes) to provide a residue (0.14 g) which was further purified by chiral preparative HPLC [Chiralcel OD 85% hexanes/IPA, 50 mL/min, 254 nm] to provide **Example 776a** (0.13 g, 0.29 mmol).

Preparation of Example 777

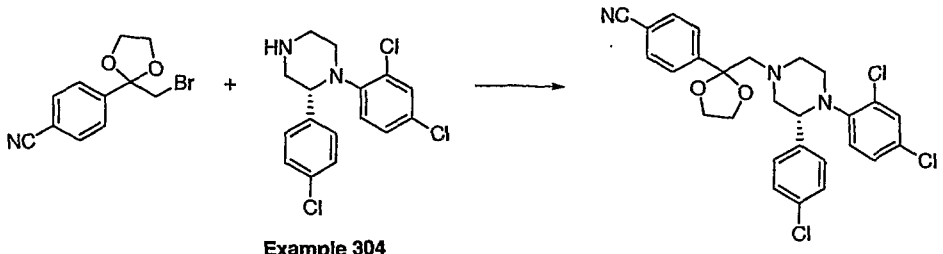


Example 777

Example 777 was prepared from the ketone **Example 780** by reduction with sodium borohyrdide as described above in Scheme 78.

Preparation of Example 778

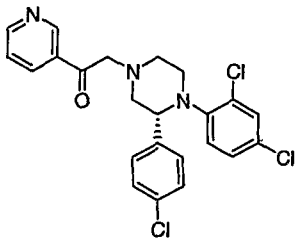
Scheme 80



Example 304 Example 778

To the piperazine **Example 304** (0.15 g, 0.44 mmol) in DMF (1.5 mL) was added potassium carbonate (0.12 g, 0.88 mmol) and 4-[2-(bromomethyl)-1,3-dioxalane-2-yl]benzonitrile (0.15 g, 0.55 mmol) followed by sodium iodide (0.025 g, 0.16 mmol). The reaction mixture was warmed to 150°C and stirred for 4 days. The reaction mixture was then cooled to room temperature and water was added. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with water, brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromoatography (0-25% EtOAc/hex) to provide the ketal **Example 778** (0.10 g).

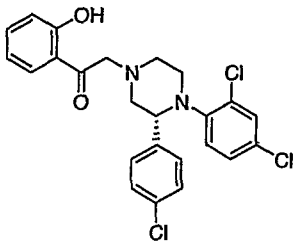
Preparation of Example 779



Example 779

Example 779 was prepared in the same manner as **Example 398** in scheme 69 except that 2-bromo-1-pyridin-3-ylethan-1-one hydrobromide was used instead of 2-bromoacetophenone.

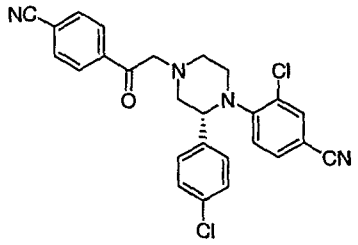
Preparation of Example 780



Example 780

Example 780 was prepared in the same manner as **Example 398** in scheme 69 except that 2-bromo-2'-hydroxyacetophenone was used instead of 2-bromoacetophenone.

Preparation of Example 781

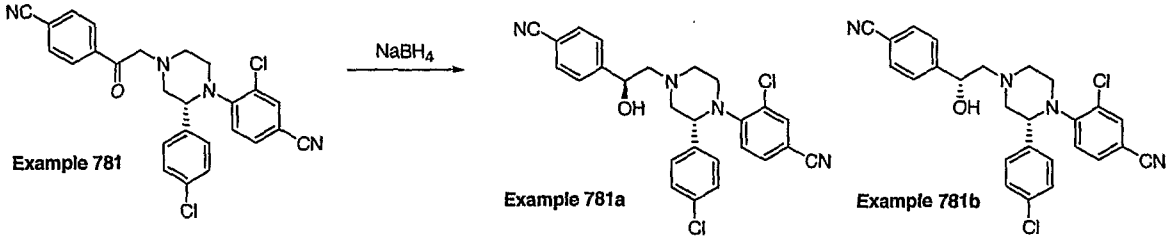


Example 781

The ketone **Example 781** was prepared in the same manner as **Example 399**, except that the piperazine **Example 305** was used instead of **Example 304.**

Preparation of Examples

Scheme 81

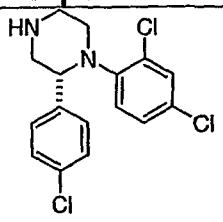
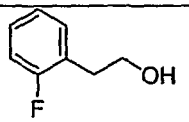
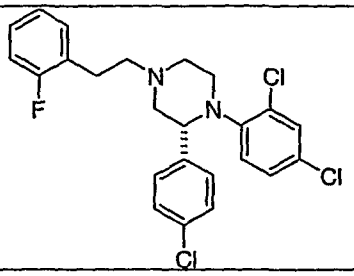


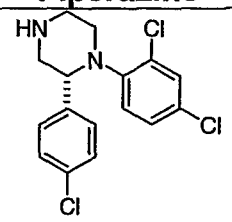
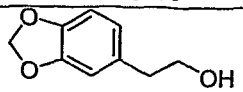
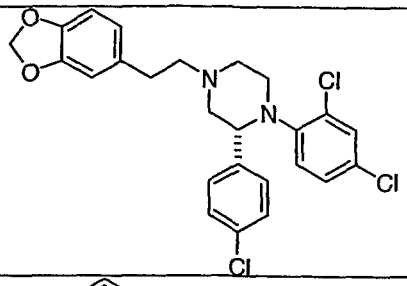
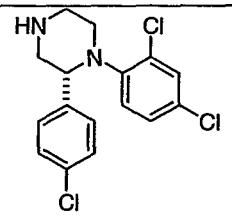
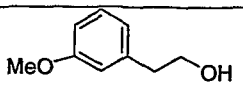
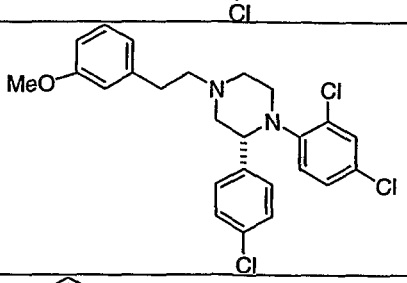
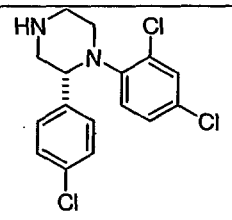
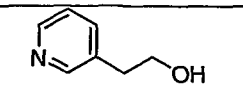
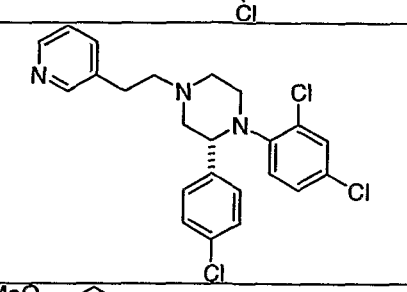
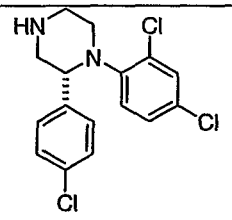
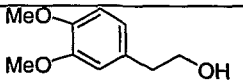
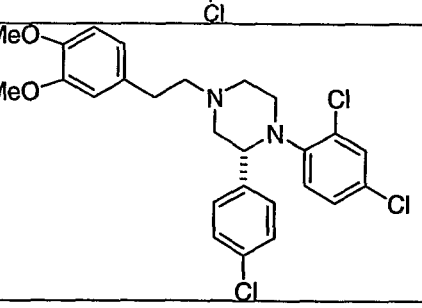
Example 781 was reduced with $NaBH_4$ using the procedure described for the reduction of **Example 399** in Scheme 78 to provide a mixture of diasteromers (**781a** and **781b**) that were separated by chiral preparative HPLC [Chiralcel OD, 25% IPA/hexane, 50 mL/min., 254 nm].

Preparation of Example 782-786

Examples 782-786 were prepared accoriding to the method of Scheme 38, using the appropriate piperazine and alcohol shown in Table XXII, below.

Table XXII

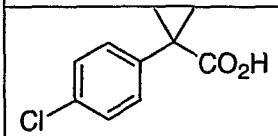
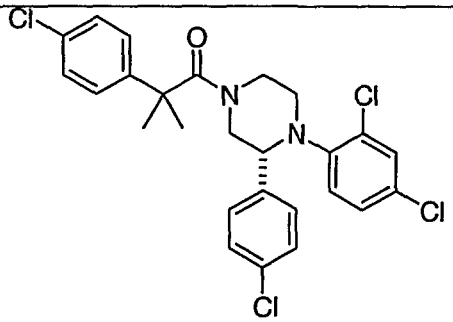
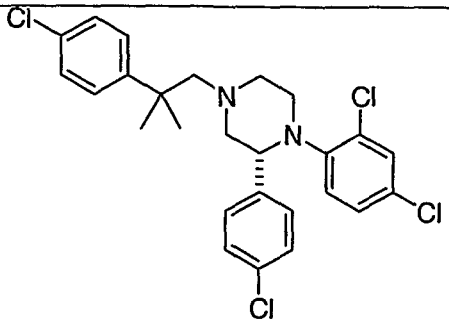
Example #	Piperazine	Alcohol	Structure
782			

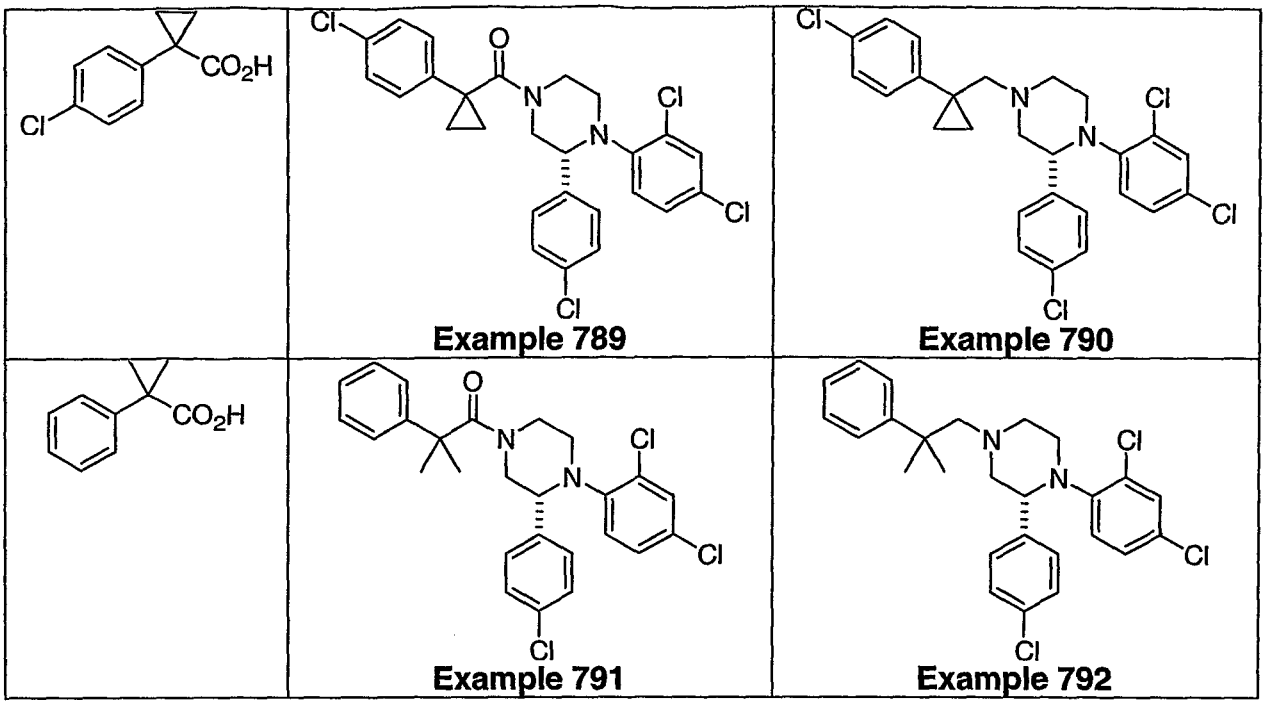
Example #	Piperazine	Alcohol	Structure
783			
784			
785			
786			

Preparation of Examples 787-792

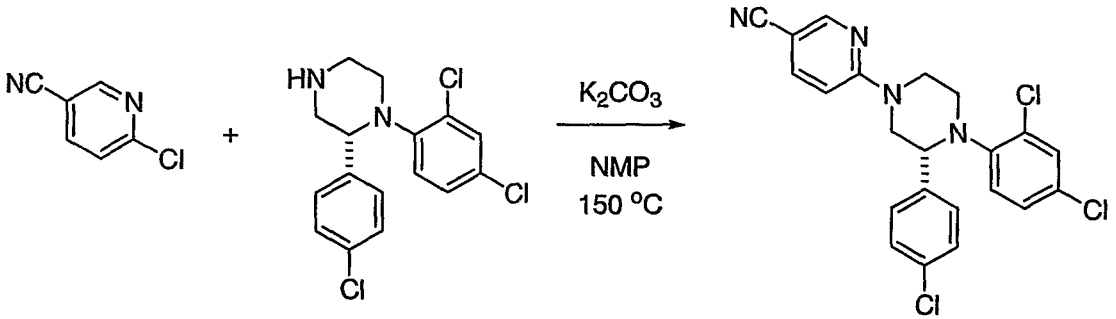
Using the procedures outlined in Scheme 41, the Amide and Amine **Examples 787-792** were prepared from the piperazine **Example 304** and the carboxylic acid indicated in Table XXIII, below.

Table XXIII

Acid	Amide	Amine
	 **Example 787**	 **Example 788**



Preparation of Example 793
Scheme 82

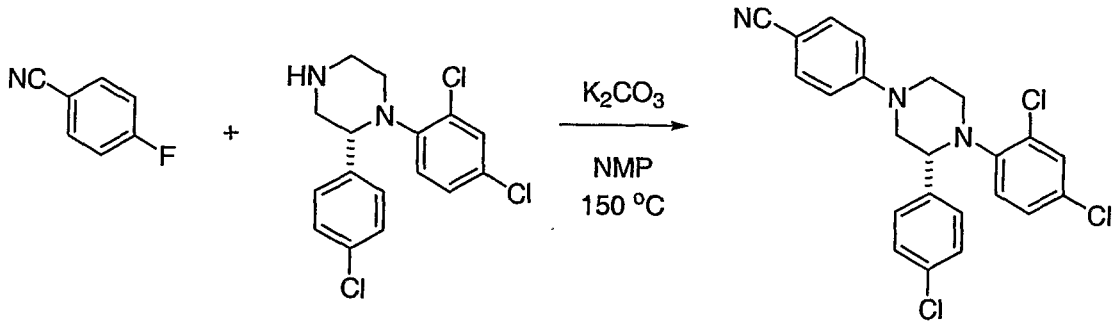


Example 793

2-Chloro-5-cyano-pyridine (56 mg), the piperazine **Example 304** (125 mg), and K_2CO_3 (100 mg) were taken up in 1-methyl-2-pyrrolidinone (NMP) and heated at 120°C for 18 hours. The reaction mixture was heated at 150°C for 5 hours. The reaction mixture was cooled and partitioned between EtOAc and saturated $NaHCO_{3(aq.)}$. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). Filtration and concentration gave a yellow oil. Purification via thin-layer preparative chromatography (1.2/1 CH_2Cl_2/hexanes, SiO_2) furnished 110 mg (63 %) of **Example 793** as a colorless oil.

Preparation of Example 794

Scheme 83

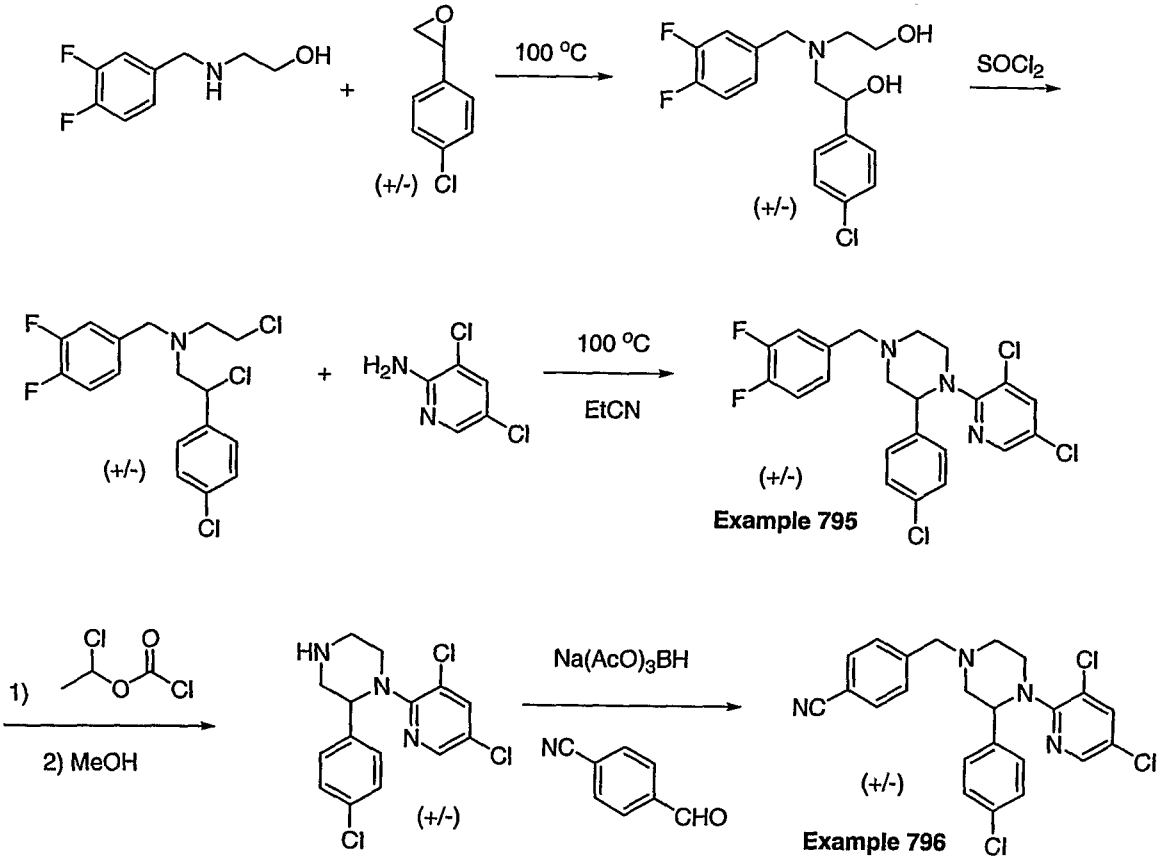


Example 794

Example 794 was prepared according to the procedure outlined above in Scheme 82 using 4-fluoro-benzonitrile in place of 2-chloro-5-cyano-pyridine.

Preparation of Examples 795-796

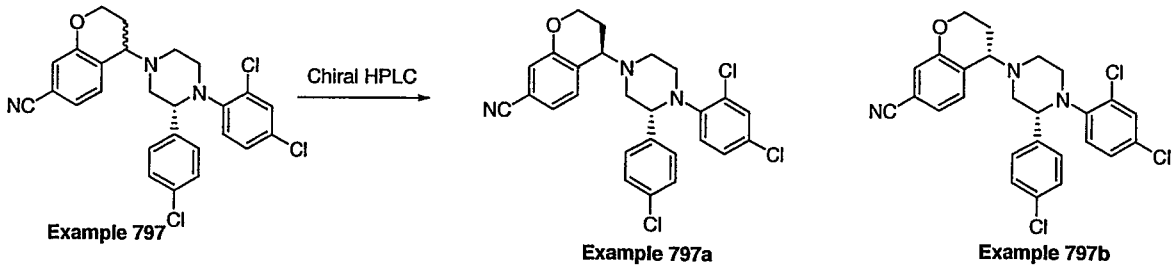
Scheme 84



Example 795 was prepared according to the procedures outlined in Steps 2, 3, and 4 of Scheme 7 using 2-(4-chlorophenyl)oxirane and 2-amino-3,5-dichloropyridine as indicated in Scheme 84, above. **Example 796** was prepared from Example 795 using the procedures outlined in Steps 5 and 6 of Scheme 24.

Preparation of Examples 797, 797a, and 797b

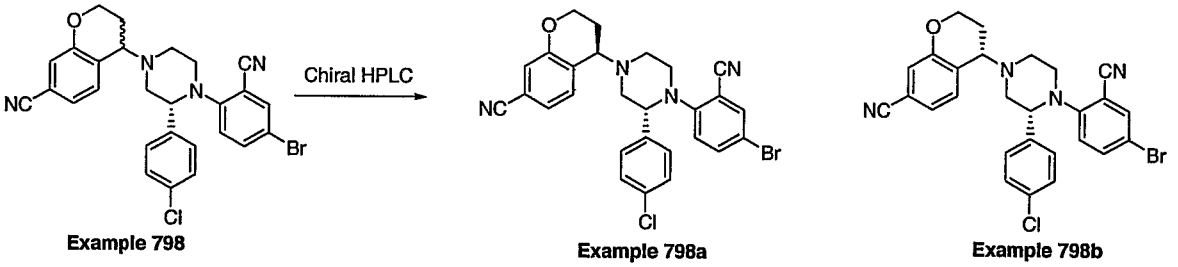
Scheme 85



Example 797 was prepared in the same manner as **Example 397** in Scheme 68 except that 7-cyano-4-chromanone was used instead of 4-chromanone. The 1:1 mixture of diastereomers of **Example 797** was separated by chiral preparative HPLC [Chiralcel OD, 10% IPA/hexane, 40 mL/min, 254 nm] to provide a faster eluting and a slower eluting isomer.

Preparation of Examples 798, 798a, and 798b

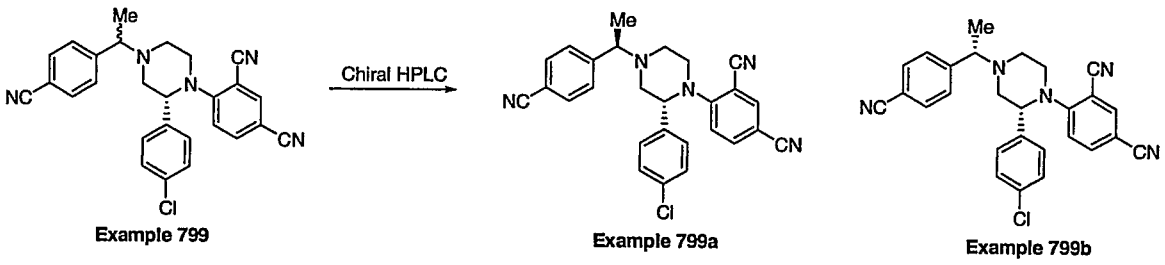
Scheme 86



Example 798 was prepared in the same manner as **Example 397** in scheme 68 except that 7-cyano-4-chromanone was used instead of 4-chromanone in step 1 and **Example 309** was used instead of **Example 304** in step 3. The 1:1 mixture of diastereomers of **Example 798** was separated by chiral preparative HPLC [Chiralcel OD, 20% IPA/hexane, 45 ml/min, 254 nm] to provide a faster eluting and a slower eluting isomer.

Preparation of Examples 799, 799a, and 799b

Scheme 87

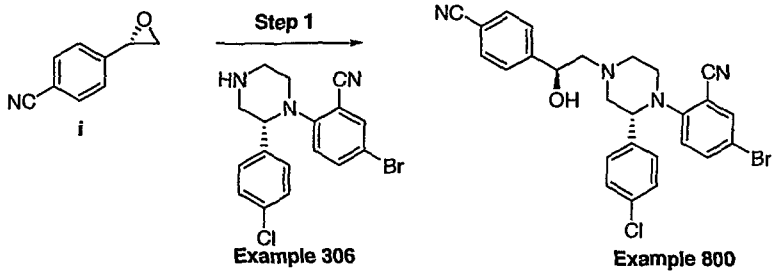


Example 799 was prepared in the same manner as **Example 391** in scheme 65 except that **Example 309** was used instead of **Example 304** in step

3. The 1:1 mixture of diastereomers of **Example 799** was separated by chiral preparative HPLC [Chiralcel OD, 25% IPA/hexane, 50 mL/min, 254 nm] to provide a faster eluting and a slower eluting isomer.

Preparation of Example 800

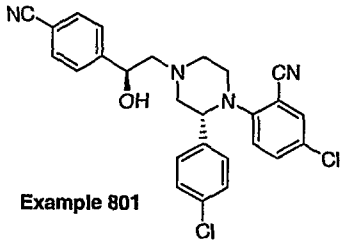
Scheme 88



Step 1:

The epoxide **i** was prepared in the same manner as **iii** in Scheme 28 except that 2-bromo-4'-cyanoacetophenone was used instead of 2-bromo-4'-chloroacetophenone and (*S*)-CBS-oxazaborolidine was used instead of (*R*)-CBS-oxazaborolidine in step 1. The epoxide **i** (0.05 g, 0.36 mmol) was heated neat (without solvent) with the piperazine **Example 306** (0.13 g, 0.33 mmol) at 100°C for 18 h. The reaction mixture was cooled to room temperature and purified by silica gel chromatography (60% EtOAc/hexane). The residue, which contained a small amount of the minor diastereomer, was purified by chiral preparative HPLC [Chiralcel OD, 20% IPA/hexane, 50 mL/min, 254 nm] to provide **Example 800** (0.11 g).

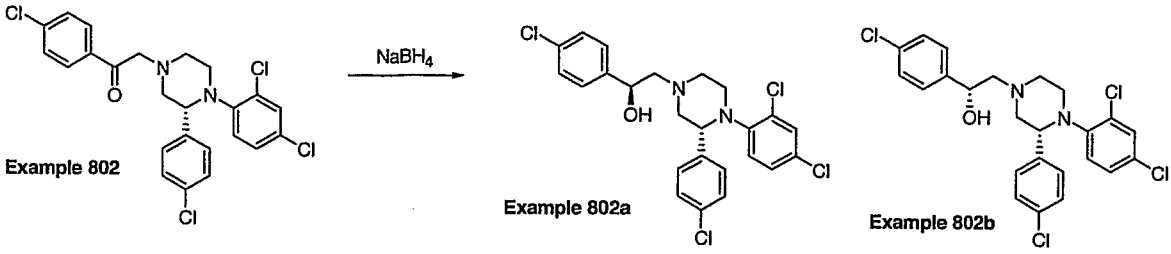
Preparation of Example 801



Example 801 was prepared in the same manner as **Example 800** except that **Example 305** was used instead of **Example 306** in Scheme 88.

Preparation of Examples 802, 802a, and 802b

Scheme 89



The ketone **Example 802** was prepared in the same manner as **Example 398** in Scheme 69 except that 2-bromo-4'-cyanoacetophenone was used instead of 2-bromoacetophenone. **Example 802a** and **Example 802b** were prepared in the same manner as **Example 776a** and **Example 776b** in Scheme 78 except that **Example 802** was used instead of **Example 399**.

Method for evaluating Cannabinoid CB_1 and CB affinity

Competition binding assays for cannabinoid CB_1 and CB_2 affinity were performed by incubating commercially purchased membranes prepared from cells expressing each receptor subtype (8 μg pro) with 0.5 nM ^{3}H-CP55,940, a non-selective cannabinoid agonist, along with concentrations of drug ranging from 0.0001-3 μM in Buffer A (5 mM $MgCl_2$, 2.5 mM EDTA and 013% BSA). Non-specific binding was defined in the presence of 10 μM CP55,940. For saturation studies, concentrations of ^{3}H-CP55,940 ranging from 0.1-5 nM were incubated with membranes in the presence and absence of 10 μM CP55,940. Assays were terminated after incubation for 1 ½ hours by rapid filtration onto 0.3 % polyethylenamine treated GF/C filterplates using a BRANDEL cell harvester. The plates were dried and MICROSCINT scintillation cocktail was added, after which the bound radioactivity was quantified using a TOPCOUNT scintillation counter.

The dissociation constant (K_d) of ^{3}H-CP55,940 at the CB_1 and CB_2 receptor were determined by plotting specific binding at each concentration of radioligand, and analysis by non-linear regression. For competition studies, the concentration of each drug that inhibited 50 percent of ^{3}H-CP55,940 binding (IC_{50}) was determined by non-linear regression analysis of the radioligand displacement curves. Affinity constants (K_i) were calculated using the equation derived by Cheng and Prusoff (1973), defined as: $IC_{50}/1+[\text{conc. ligand} / K_d]$.

GTPγS Binding Protocol

The functional efficacy of compounds to activate second messengers within the cell was determined utilizing the GTPγS binding assay. Guanine nucleotides are phosphorylated within the plasma membrane of the cell following binding and activation by agonists. A radiolabelled derivative of guanine triphosphate (GTP) is utilized in this assay as it cannot be dephosphorylated and therefore accumulates following agonist binding. The simultaneous presence of an antagonist into this system will shift the agonist concentration curve to the right, with increasing concentrations of antagonist producing a greater rightward shift in the dose-response curve of the agonist.

Commercially purchased membranes were incubated with 10 mM GDP to allow sufficient substrate for phosphorylation in the presence of agonist. The membranes were then pre-incubated with increasing concentrations of test compound for 30 minutes to determine if they were capable of stimulating phosphorylation alone. Increasing concentrations of the non-selective cannabinoid agonist WIN55,122 were then added in the presence or absence of each concentration of test compound. The assay was then incubated for 1 hour at room temperature. To complete the assay, ^{35}S-GTPγS was added and the assay incubated for another 30 minutes. Assays were terminated by rapid filtration onto 10 mM sodium phosphate-treated GF/C filterplates using a Brandel cell harvester. The plates were dried and Microscint scintillation cocktail was added, after which the bound radioactivity was quantified using a Topcount scintillation counter.

The stimulation of ^{35}S-GTPγS binding as a function of the concentration of the agonist WIN55,122, in the absence and presence of test compound, was plotted and the EC_{50} determined by nonlinear regression analysis using GraphPad Prism software. A Schild analysis of the rightward shift in the dose response curve of WIN55,122 in the presence of test compound was determined by plotting the concentration of test compound against the negative log of the dose ratio [1-(EC_{50} agonist + test compound/EC50 of agonist alone)]. A linear regression analysis yields the Kb, defined as the X-intercept of the linear equation.

Preparation of Compound of Formula (II)

Step 1): To a solution of (S)-4-phenyl-2-oxazolidinone (41 g, 0.25 mol) in CH_2Cl_2 (200 mL), was added 4-dimethylaminopyridine (2.5 g, 0.02 mol) and triethylamine (84.7 mL, 0.61 mol) and the reaction mixture was cooled to 0°C. Methyl-4-(chloroformyl)butyrate (50 g, 0.3 mol) was added as a solution in CH_2Cl_2 (375 mL) dropwise over 1 h, and the reaction was allowed to warm to 22°C. After 17 h, water and H_2SO_4 (2N, 100 mL), was added the layers were separated, and the organic layer was washed sequentially with NaOH (10%), NaCl (sat'd) and water. The organic layer was dried over $MgSO_4$ and concentrated to obtain a semicrystalline product.

Step 2): To a solution of $TiCl_4$ (18.2 mL, 0.165 mol) in CH_2Cl_2 (600 mL) at 0°C, was added titanium isopropoxide (16.5 mL, 0.055 mol). After 15 min, the product of Step 1 (49.0 g, 0.17 mol) was added as a solution in CH_2Cl_2 (100 mL). After 5 min., diisopropylethylamine (DIPEA) (65.2 mL, 0.37 mol) was added and the reaction mixture was stirred at 0°C for 1 h, the reaction mixture was cooled to -20°C, and 4-benzyloxybenzylidine(4-fluoro)aniline (114.3 g, 0.37 mol) was added as a solid. The reaction mixture was stirred vigorously for 4 h at -20°C, then acetic acid was added as a solution in CH_2Cl_2 dropwise over 15 min, the reaction mixture was allowed to warm to 0°C, and H_2SO_4 (2N) was added. The reaction mixture was stirred an additional 1 h, the layers were separated, washed with water, separated and the organic layer was dried. The crude product was crystallized from ethanol/water to obtain the pure intermediate.

Step 3): To a solution of the product of Step 2 (8.9 g, 14.9 mmol) in toluene (100 mL) at 50°C, was added N,O-bis(trimethylsilyl)acetamide (BSA) (7.50 mL, 30.3 mmol). After 0.5 h, solid TBAF (0.39 g, 1.5 mmol) was added and the reaction mixture stirred at 50°C for an additional 3 h. The reaction mixture was cooled to 22°C, CH_3OH (10 mL), was added. The reaction mixture was washed with HCl (1N), $NaHCO_3$ (1N) and NaCl (sat'd.), and the organic layer was dried over $MgSO_4$.

Step 4): To a solution of the product of Step 3 (0.94 g, 2.2 mmol) in CH_3OH (3 mL), was added water (1 mL) and $LiOH•H_2O$ (102 mg, 2.4 mmole). The reaction mixture was stirred at 22°C for 1 h and then additional $LiOH•H_2O$ (54 mg, 1.3 mmole) was added. After a total of 2 h, HCl (1N) and EtOAc was added, the layers were separated, the organic layer was dried and concentrated in *vacuo*. To a solution of the resultant product (0.91 g, 2.2 mmol) in CH_2Cl_2 at

22°C, was added ClC(O)C(O)Cl (0.29 mL, 3.3 mmol) and the mixture stirred for 16 h. The solvent was removed in *vacuo*.

Step 5): To an efficiently stirred suspension of 4-fluorophenylzinc chloride (4.4 mmol) prepared from 4-fluorophenylmagnesium bromide (1M in THF, 4.4 mL, 4.4 mmol) and $ZnCl_2$ (0.6 g, 4.4 mmol) at 4°C, was added tetrakis(triphenylphosphine)palladium (0.25 g, 0.21 mmol) followed by the product of Step 4 (0.94 g, 2.2 mmol) as a solution in THF (2 mL). The reaction was stirred for 1 h at 0°C and then for 0.5 h at 22°C. HCl (1N, 5 mL) was added and the mixture was extracted with EtOAc. The organic layer was concentrated to an oil and purified by silica gel chromatography to obtain 1-(4-fluorophenyl)-4(S)-(4-hydroxyphenyl)-3(R)-(3-oxo-3-phenylpropyl)-2-azetidinone:
HRMS calc'd for $C_{24}H_{19}F_2NO_3$ = 408.1429, found 408.1411.

Step 6): To the product of Step 5 (0.95 g, 1.91 mmol) in THF (3 mL), was added (R)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo-[1,2-c][1,3,2] oxazaborole (120 mg, 0.43 mmol) and the mixture was cooled to -20°C. After 5 min, borohydride-dimethylsulfide complex (2M in THF, 0.85 mL, 1.7 mmol) was added dropwise over 0.5 h. After a total of 1.5 h, CH_3OH was added followed by HCl (1 N) and the reaction mixture was extracted with EtOAc to obtain 1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl)]-4(S)-[4-(phenylmethoxy)phenyl]-2-azetidinone (compound 6A-1) as an oil. ^1H in $CDCl_3$ d H3 = 4.68. J = 2.3 Hz. CI (M+H) 500.

Use of (S)-tetra-hydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo-[1,2-c][1,3,2] oxazaborole gives the corresponding 3(R)-hydroxypropyl azetidinone (compound 6B-1). ^1H in $CDCl_3$ d H3 = 4.69. J = 2.3 Hz. CI (M+H) 500.

To a solution of compound 6A-1 (0.4 g, 0.8 mmol) in ethanol (2 mL), was added 10% Pd/C (0.03 g) and the reaction mixture was stirred under a pressure (60 psi) of H_2 gas for 16 h. The reaction mixture was filtered and the solvent was concentrated to obtain compound 6A. Mp 164-166°C; CI (M+H) 410.

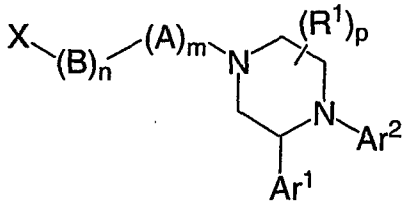
$[\alpha]_D^{25}$ = -28.1° (c 3, CH_3OH) . Elemental analysis calc'd for $C_{24}H_{21}F_2NO_3$: C 70.41; H 5.17; N 3.42; found C 70.25; H 5.19; N 3.54.

Similarly treat compound 6B-1 to obtain compound 6B.
Mp 129.5-132.5°C; CI (M+H) 410. Elemental analysis calc'd for $C_{24}H_{21}F2NO_3$: C 70.41; H 5.17; N 3.42; found C 70.30; H 5.14; N 3.52.

Step 6' (Alternative): To a solution of the product of Step 5 (0.14 g, 0.3 mmol) in ethanol (2 mL), was added 10% Pd/C (0.03 g) and the reaction was stirred under a pressure (60 psi) of H_2 gas for 16 h. The reaction mixture was filtered and the solvent was concentrated to afford a 1:1 mixture of compounds 6A and 6B.

WE CLAIM:

1. A compound of Formula (I):



(I)

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

Ar^1 and Ar^2 are independently aryl or heteroaryl,

wherein said aryl and heteroaryl are substituted with one or more groups Y^1;

n and m are independently 0 or 1;

A is selected from the group consisting of –C(O)-, $-S(O)_2-$, $-C(=N-OR^2)-$, and $-(C(R^2)_2)_q-$ wherein q is 1, 2, or 3;

B is selected from the group consisting of $-N(R^2)-$, -C(O)-, and $-(C(R^3)_2)_r-$ wherein r is 1 or 2,

with the proviso that when B is –C(O)-, then A is –C(O)- or $-(C(R^2)_2)_q-$;

X is selected from the group consisting of H, alkyl, -S-alkyl, $-S(O)_2$-alkyl, $-S(O)_2$-cycloalkyl, $-S(O)_2$-aryl, $-S(O)_2$-heteroaryl, cycloalkyl, benzo-fused cycloalkyl, benzo-fused heterocycloalkyl, benzo-fused heterocycloalkenyl, heterocycloalkyl, $-C(R^2)=C(R^2)$-aryl, $-C(R^2)=C(R^2)$-heteroaryl, $-OR^2$, -O-alkylene-O-alkyl, -S-aryl, $-N(R^4)_2$, $-(C(R^2)_2)_s$-heteroaryl, -C(O)-O-alkyl, -C(O)-aryl, -C(O)-heteroaryl, -N=O, -C(S-alkyl)=N-$S(O)_2$-aryl, $-C(N(R^2)_2)=N-S(O)_2$-aryl, and $-(C(R^2)_2)_s$-aryl wherein s is 0, 1, or 2,

wherein the heteroaryl portion of said $-(C(R^2)_2)_s$-heteroaryl, the aryl portion of said $-C(R^2)=C(R^2)$-aryl, the heteroaryl portion of said $-C(R^2)=C(R^2)$-heteroaryl, the aryl portion of said -S-aryl, the aryl portion of said $-S(O)_2$-aryl, the heteroaryl portion of said $-S(O)_2$-heteroaryl, the aryl portion of said -C(O)-aryl, the heteroaryl portion of said -C(O)-heteroaryl, the aryl portion of said $-(C(R^2)_2)_s$-aryl, the aryl portion of said -C(S-alkyl)=N-$S(O)_2$-aryl, the aryl portion of said $-C(N(R^2)_2)=N-S(O)_2$-aryl, the benzo portion of said benzo-fused cycloalkyl, the benzo portion of said benzo-fused heterocycloalkyl, and

the benzo portion of said benzo-fused heterocycloalkenyl of X are unsubstituted or substituted with one or more groups Y^1, and

said cycloalkyl, the cycloalkyl portion of said -$S(O)_2$-cycloalkyl, said heterocycloalkyl, the cycloalkyl portion of said benzo-fused cycloalkyl, the heterocycloalkyl portion of said benzo-fused heterocycloalkyl, and the heterocycloalkenyl portion of said benzo-fused heterocycloalkenyl of X are unsubstituted or substituted with one or more groups Y^2;

each R^1 is independently selected from the group consisting of alkyl, haloalkyl, -alkylene-$N(R^5)_2$, -alkylene-OR^2, alkylene-N_3, -alkylene-CN, and alkylene-O-$S(O)_2$-alkyl; or

two R^1 groups attached to the same ring carbon atom form a carbonyl group;

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

each R^2 is independently H, alkyl, or aryl,

wherein said aryl of R^2 is unsubstituted or substituted with one or more groups Y^1;

each R^3 is independently selected from the group consisting of H, alkyl, unsubstituted aryl, aryl substituted with one or more Y^1 groups, -OR^2, -alkylene-O-alkyl, and -alkylene-OH;

each R^4 is independently selected from the group consisting of H, alkyl, aryl, -C(O)-O-alkyl, -C(O)-alkyl, -C(O)-aryl, and –$S(O)_2$aryl,

wherein said aryl, the aryl portion of said –C(O)-aryl, and the aryl portion of said –$S(O)_2$aryl of R^4 are unsubstituted or substituted with one or more Y^1 groups;

each R^5 is independently selected from the group consisting of H, alkyl, aryl, -$S(O)_2$-alkyl, -$S(O)_2$-cycloalkyl, -$S(O)_2$-aryl, -C(O)-$N(R^2)_2$, -C(O)-alkyl, and –alkylene-OH,

wherein said aryl and the aryl portion of said –$S(O)_2$-aryl of R^5 are unsubstituted or substituted with one or more Z groups;

each Y^1 is independently selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, benzyl, aryl, heteroaryl, -O-aryl, -S-aryl, -$S(O)_2$-alkyl, -$S(O)_2$-cycloalkyl, -$S(O)_2$-aryl, -alkylene-CN, -CN, -C(O)-alkyl, -C(O)-aryl, -C(O)-haloalkyl, -C(O)O-alkyl, -$N(R^2)$C(O)-alkyl, -$N(R^2)$C(O)-$N(R^2)_2$, -OH, -O-alkyl, -O-haloalkyl, -O-alkylene-C(O)OH, -S-alkyl,

-S-haloalkyl, -alkylene-OH, -alkylene-C(O)-O-alkyl, -O-alkylene-aryl, and $-N(R^5)_2$,

wherein said aryl, heteroaryl, the aryl portion of said –O-aryl, the aryl portion of said -S-aryl, the aryl portion of said $–S(O)_2$-aryl, the aryl portion of said benzyl, the aryl portion of said –C(O)-aryl, and the aryl portion of said -O-alkylene-aryl of Y^1 are unsubstituted or substituted with one or more groups Z; or

two groups Y^1 form a $–O-CH_2-O-$ group;

each Y^2 is independently selected from the group consisting of alkyl, haloalkyl, aryl, -alkylene-aryl, -CN, -C(O)-alkyl, $-S(O)_2$-cycloalkyl, -alkylene-$N(R^4)_2$, -C(O)-alkylene-$N(R^4)_2$, -C(O)-O-alkyl, -C(O)-aryl, and –C(O)-haloalkyl,

wherein said aryl and the aryl portion of said –C(O)-aryl of Y^2 are unsubstituted or substituted with one or more groups Z; or

two groups Y^2 form a $-O-CH_2CH_2-O-$ group; or

two of said Y^2 substituents attached to the same ring carbon atom of a cycloalkyl, benzo-fused cycloalkyl, benzo-fused heterocycloalkyl, benzo-fused heterocycloalkenyl, or heterocycloalkyl ring, together with the ring carbon atom to which they are both attached, form a carbonyl group; and

each Z is independently selected from the group consisting of alkyl, halo, haloalkyl, -OH, -O-alkyl, and -CN.

2. The compound of Claim 1, or a pharmaceutically acceptable salt, solvate, or ester thereof, wherein:

Ar^1 and Ar^2 are independently (C_6-C_{10})aryl or (C_2-C_{10})heteroaryl,

wherein said (C_6-C_{10})aryl and (C_2-C_{10})heteroaryl are substituted with one or more groups Y^1;

n and m are independently 0 or 1;

A is selected from the group consisting of –C(O)-, $-S(O)_2-$, $-C(=N-OR^2)-$, and $-(C(R^2)_2)_q-$ wherein q is 1, 2, or 3;

B is selected from the group consisting of $–N(R^2)-$, -C(O)-, and $-(C(R^3)_2)_r-$ wherein r is 1 or 2,

with the proviso that when B is –C(O)-, then A is –C(O)- or $-(C(R^2)_2)_q-$;

X is selected from the group consisting of H, (C_1-C_6)alkyl, -S-(C_1-C_6)alkyl, $-S(O)_2-(C_1-C_6)$alkyl, $-S(O)_2-(C_3-C_{10})$cycloalkyl, $-S(O)_2-(C_6-C_{10})$aryl,

$-S(O)_2-(C_2-C_{10})$heteroaryl, (C_3-C_{10})cycloalkyl, benzo-fused (C_3-C_{10})cycloalkyl, benzo-fused (C_2-C_{10})heterocycloalkyl, benzo-fused (C_2-C_{10})heterocycloalkenyl, (C_2-C_{10})heterocycloalkyl, $-C(R^2)=C(R^2)-(C_6-C_{10})$aryl, $-C(R^2)=C(R^2)-(C_2-C_{10})$heteroaryl, $-OR^2$, $-O-(C_1-C_6)$alkylene-$O-(C_1-C_6)$alkyl, $-S-(C_6-C_{10})$aryl, $-N(R^4)_2$, $-(C(R^2)_2)_s-(C_2-C_{10})$heteroaryl, $-C(O)-O-(C_1-C_6)$alkyl, $-C(O)-(C_6-C_{10})$aryl, $-C(O)-(C_2-C_{10})$heteroaryl, $-N=O$, $-C(S-(C_1-C_6)alkyl)=N-S(O)_2-(C_6-C_{10})$aryl, $-C(N(R^2)_2)=N-S(O)_2-(C_6-C_{10})$aryl, and $-(C(R^2)_2)_s-(C_6-C_{10})$aryl wherein s is 0, 1, or 2,

wherein the (C_2-C_{10})heteroaryl portion of said $-(C(R^2)_2)_s-(C_2-C_{10})$heteroaryl, the (C_6-C_{10})aryl portion of said $-C(R^2)=C(R^2)-(C_6-C_{10})$aryl, the (C_2-C_{10})heteroaryl portion of said $-C(R^2)=C(R^2)-(C_2-C_{10})$heteroaryl, the (C_6-C_{10})aryl portion of said $-S-(C_6-C_{10})$aryl, the (C_6-C_{10})aryl portion of said $-S(O)_2-(C_6-C_{10})$aryl, the (C_2-C_{10})heteroaryl portion of said $-S(O)_2-(C_2-C_{10})$heteroaryl, the (C_6-C_{10})aryl portion of said $-C(O)-(C_6-C_{10})$aryl, the (C_2-C_{10})heteroaryl portion of said $-C(O)-(C_2-C_{10})$heteroaryl, the (C_6-C_{10})aryl portion of said $-(C(R^3)_2)_s-(C_6-C_{10})$aryl, the (C_6-C_{10})aryl portion of said $-C(S-(C_1-C_6)alkyl)=N-S(O)_2-(C_6-C_{10})$aryl, the (C_6-C_{10})aryl portion of said $-C(N(R^2)_2)=N-S(O)_2-(C_6-C_{10})$aryl, the benzo portion of said benzo-fused (C_3-C_{10})cycloalkyl, the benzo portion of said benzo-fused (C_2-C_{10})heterocycloalkyl, and the benzo portion of said benzo-fused (C_2-C_{10})heterocycloalkenyl of X are unsubstituted or substituted with one or more groups Y^1, and

said (C_3-C_{10})cycloalkyl, the (C_3-C_{10})cycloalkyl portion of said $-S(O)_2-(C_3-C_{10})$cycloalkyl, said (C_2-C_{10})heterocycloalkyl, the (C_3-C_{10})cycloalkyl portion of said benzo-fused (C_3-C_{10})cycloalkyl, the (C_2-C_{10})heterocycloalkyl portion of said benzo-fused (C_2-C_{10})heterocycloalkyl, and the (C_2-C_{10})heterocycloalkenyl portion of said benzo-fused (C_2-C_{10})heterocycloalkenyl of X are unsubstituted or substituted with one or more groups Y^2;

each R^1 is independently selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, $-(C_1-C_6)$alkylene-$N(R^5)_2$, $-(C_1-C_6)$alkylene-OR^2,

$-(C_1-C_6)$alkylene-N_3, $-(C_1-C_6)$alkylene-CN, and
(C_1-C_6)alkylene-O-$S(O)_2$-(C_1-C_6)alkyl; or
two R^1 groups attached to the same ring carbon atom form a carbonyl group;
p is 0, 1, 2, 3, or 4;
each R^2 is independently H, (C_1-C_6)alkyl, or (C_6-C_{10})aryl,
wherein said (C_6-C_{10})aryl of R^2 is unsubstituted or substituted with one or more groups Y^1;
each R^3 is independently selected from the group consisting of H, (C_1-C_6)alkyl, unsubstituted (C_6-C_{10})aryl, (C_6-C_{10})aryl substituted with one or more Y^1 groups, $-OR^2$, $-(C_1-C_6)$alkylene-O-(C_1-C_6)alkyl, and $-(C_1-C_6)$alkylene-OH;
each R^4 is independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_6-C_{10})aryl, -C(O)-O-(C_1-C_6)alkyl,–C(O)-(C_1-C_6)alkyl, -C(O)-(C_6-C_{10})aryl, and $-S(O)_2$-(C_6-C_{10})aryl,
wherein said (C_6-C_{10})aryl, the (C_6-C_{10})aryl portion of said –C(O)-(C_6-C_{10})aryl, and the (C_6-C_{10})aryl portion of said $–S(O)_2$-(C_6-C_{10})aryl of R^4 are unsubstituted or substituted with one or more Y^1 groups;
each R^5 is independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_6-C_{10})aryl, $-S(O)_2$-(C_1-C_6)alkyl, $-S(O)_2$-(C_3-C_{10})cycloalkyl, $-S(O)_2$-aryl, -C(O)-$N(R^2)_2$, -C(O)-(C_1-C_6)alkyl, and $-(C_1-C_6)$alkylene-OH,
wherein said (C_6-C_{10})aryl and the (C_6-C_{10})aryl portion of said $–S(O)_2$-(C_6-C_{10})aryl of R^5 are unsubstituted or substituted with one or more Z groups;
each Y^1 is independently selected from the group consisting of (C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocycloalkyl, (C_2-C_{10})heterocycloalkenyl, halo, (C_1-C_6)haloalkyl, benzyl, (C_6-C_{10})aryl, (C_2-C_{10})heteroaryl, -O-(C_6-C_{10})aryl, -S-(C_6-C_{10})aryl, $-S(O)_2$-(C_1-C_6)alkyl, $-S(O)_2$-(C_3-C_{10})cycloalkyl, $-S(O)_2$-(C_6-C_{10})aryl, $-(C_1-C_6)$alkylene-CN, -CN, -C(O)-(C_1-C_6)alkyl, -C(O)-(C_6-C_{10})aryl, -C(O)-(C_1-C_6)haloalkyl, -C(O)O-(C_1-C_6)alkyl, $-N(R^2)$C(O)-(C_1-C_6)alkyl, $-N(R^2)$C(O)-$N(R^2)_2$, -OH, -O-(C_1-C_6)alkyl, -O-(C_1-C_6)haloalkyl, -O-(C_1-C_6)alkylene-C(O)OH, -S-(C_1-C_6)alkyl, -S-(C_1-C_6)haloalkyl, $-(C_1-C_6)$alkylene-OH, $-(C_1-C_6)$alkylene-C(O)-O-(C_1-C_6)alkyl, -O-(C_1-C_6)alkylene-(C_6-C_{10})aryl, and $-N(R^5)_2$,
wherein said (C_6-C_{10})aryl, said (C_2-C_{10})heteroaryl, the (C_6-C_{10})aryl portion of said -O-(C_6-C_{10})aryl, the (C_6-C_{10})aryl portion of said -S-(C_6-C_{10})aryl,

the $(C_6$-$C_{10})$aryl portion of said $-S(O)_2$-$(C_6$-$C_{10})$aryl, said benzyl, the $(C_6$-$C_{10})$aryl portion of said $-C(O)$-$(C_6$-$C_{10})$aryl, and the $(C_6$-$C_{10})$aryl portion of said -O-$(C_1$-$C_6)$alkylene-$(C_6$-$C_{10})$aryl of Y^1 are unsubstituted or substituted with one or more groups Z; or

two groups Y^1 form a $-O-CH_2-O-$ group;

each Y^2 is independently selected from the group consisting of $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_6$-$C_{10})$aryl, -$(C_1$-$C_6)$alkylene-$(C_6$-$C_{10})$aryl, -CN, -C(O)-$(C_1$-$C_6)$alkyl, $-S(O)_2$-$(C_3$-$C_{10})$cycloalkyl, -$(C_1$-$C_6)$alkylene-$N(R^2)_2$, -C(O)-$(C_1$-$C_6)$alkylene-$N(R^4)_2$, -C(O)-O-$(C_1$-$C_6)$alkyl, -C(O)-$(C_6$-$C_{10})$aryl, and -C(O)-$(C_1$-$C_6)$haloalkyl,

wherein said $(C_6$-$C_{10})$aryl and the $(C_6$-$C_{10})$aryl portion of said -C(O)-$(C_6$-$C_{10})$aryl of Y^2 are unsubstituted or substituted with one or more groups Z; or

two groups Y^2 form a $-O-CH_2CH_2-O-$ group; or

two of said Y^2 substituents attached to the same ring carbon atom of a $(C_3$-$C_{10})$cycloalkyl, benzo-fused $(C_3$-$C_{10})$cycloalkyl, benzo-fused $(C_2$-$C_{10})$heterocycloalkyl, benzo-fused $(C_2$-$C_{10})$heterocycloalkenyl, or $(C_2$-$C_{10})$heterocycloalkyl ring, together with the ring carbon atom to which they are both attached, form a carbonyl group; and

each Z is independently selected from the group consisting of $(C_1$-$C_6)$alkyl, halo, $(C_1$-$C_6)$haloalkyl, -OH, -O-$(C_1$-$C_6)$alkyl, and -CN.

3. The compound of Claim 1, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

Ar^1 and Ar^2 are independently aryl substituted with one or more groups Y^1.

4. The compound of Claim 3, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

Ar^2 is a phenyl independently substituted with 2 Y^1 groups.

5. The compound of Claim 4, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

Ar^2 is a phenyl independently substituted with two Y^1 groups at the 2- and 4-position.

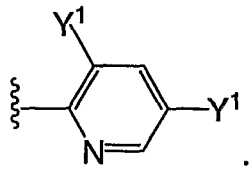
6. The compound of Claim 3, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:
Ar^1 is a phenyl substituted with one Y^1 group at the 4-position.

7. The compound of Claim 6, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:
Ar^2 is a phenyl independently substituted with two Y^1 groups at the 2- and 4-position.

8. The compound of Claim 3, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:
Ar^2 is pyridyl.

9. The compound of Claim 3, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:
Ar^2 is pyridyl independently substituted with two Y^1 groups.

10. The compound of Claim 3, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:
Ar^2 is:



11. The compound according to Claim 3, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:
m is 1; and
A is -C(O)-.

12. The compound according to Claim 11, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:
n is 0.

13. The compound according to Claim 11, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:
n is 1; and
B is –NH-;

14. The compound according to Claim 11, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:
n is 1; and
B is $-(C(R^2)_2)_r-$ wherein r is 1 or 2.

15. The compound according to Claim 11, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:
n is 1; and
B is $-N(R^2)-$.

16. The compound according to Claim 1, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:
m is 1; and
A is $-S(O)_2-$.

17. The compound according to Claim 16, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:
n is 0.

18. The compound according to Claim 16, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:
n is 1; and
B is $-N(R^2)-$.

19. The compound according to Claim 1, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:
m is 1;
A is $-C(=N-OR^2)-$; and

n is 0.

20. The compound according to Claim 1, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:
m is 1;
A is -$(C(R^2)_2)_q$- wherein q is 1, 2, or 3; and
n is 0.

21. The compound according to Claim 20, wherein X is aryl or heteroaryl, and said aryl or heteroaryl of X is unsubstituted or substituted with one or more Y^1 groups.

22. The compound according to Claim 21, wherein q is 1 or 2.

23. The compound according to Claim 1, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:
m is 0;
B is -$(C(R^3)_2)_r$- wherein r is 1, 2, or 3.

24. The compound according to Claim 1, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:
m and n are both 1; and
B is -$(C(R^3)_2)_r$- wherein r is 1, 2, or 3.

25. The compound according to Claim 1, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:
m and n are both 0.

26. The compound according to Claim 1, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:
X is -$(C(R^2)_2)_s$-aryl wherein s is 0, 1, or 2.

27. The compound according to Claim 1, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

X is heteroaryl.

28. The compound according to Claim 1, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:
X is cycloalkyl.

29. The compound according to Claim 1, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:
X is heterocycloalkyl.

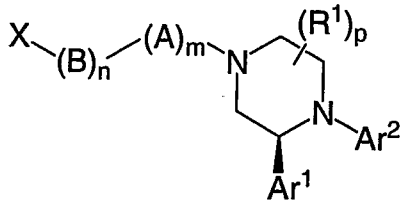
30. The compound according to Claim 1, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:
X is alkyl.

31. The compound according to Claim 1, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:
X is $-N(R^4)_2$.

32. The compound according to Claim 24, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:
A is –C(O)-.

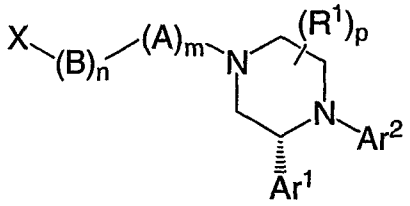
33. The compound according to Claim 1, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:
m and n are both 1;
A is –C(O)-; and
B is –NH-.

34. The compound according to Claim 1, or a pharmaceutically acceptable salt, solvate or ester thereof, having the following Formula (IA):



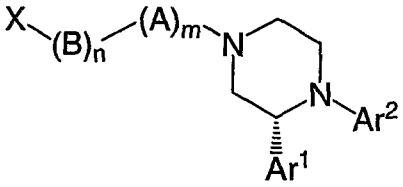
(IA)

35. The compound according to Claim 1, or a pharmaceutically acceptable salt, solvate or ester thereof, having the following Formula (IA):



(IB) .

36. The compound according to Claim 1, or a pharmaceutically acceptable salt, solvate or ester thereof, having the following Formula (IB):



(IC) .

37. The compound according to Claim 36, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:
m is 1; and
A is -C(O)-.

38. The compound according to Claim 37, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein n is 0.

39. The compound according to Claim 37, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:
n is 1; and
B is $-N(R^2)-$.

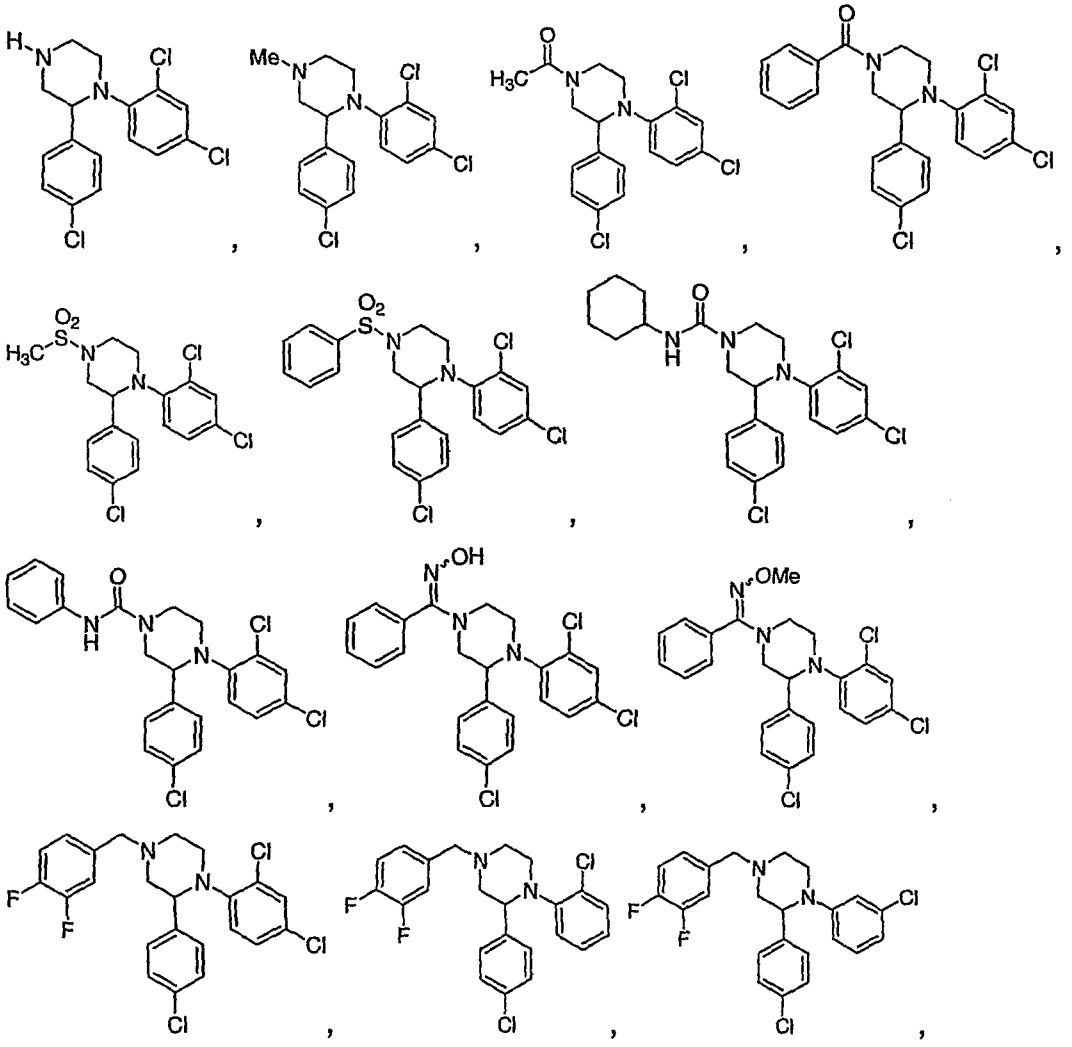
40. The compound according to Claim 36, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:
m is 1;

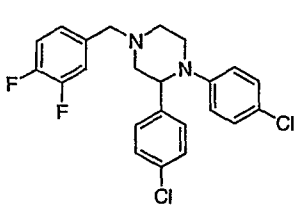
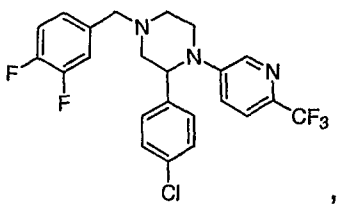
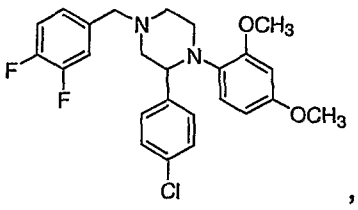
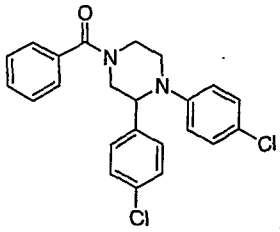
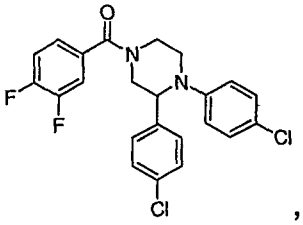
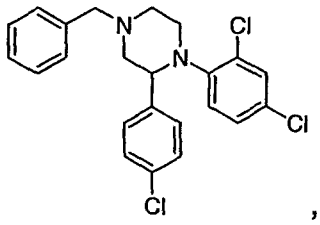
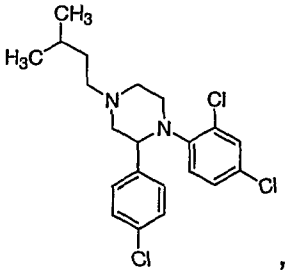
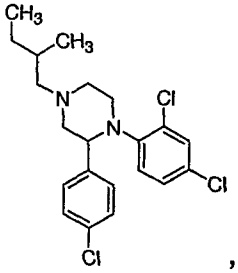
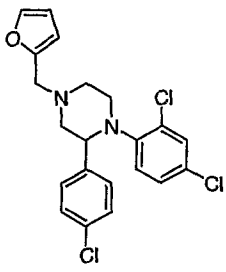
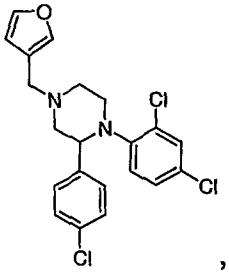
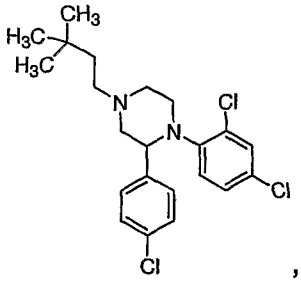
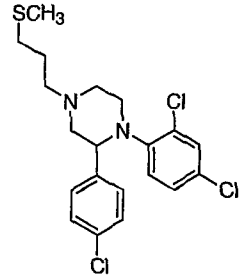
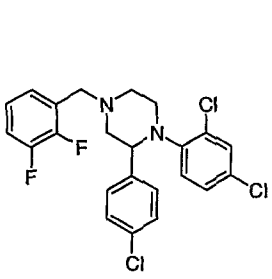
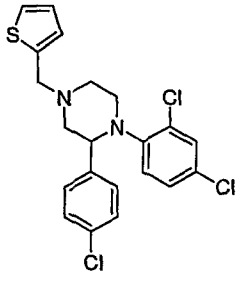
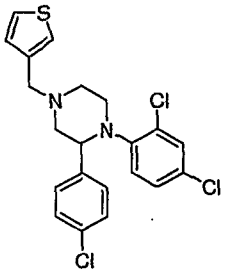
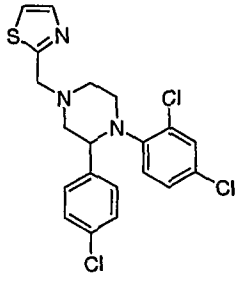
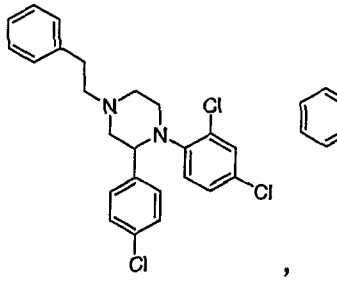
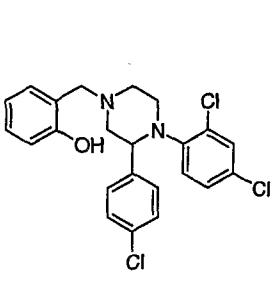
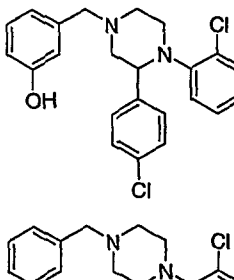
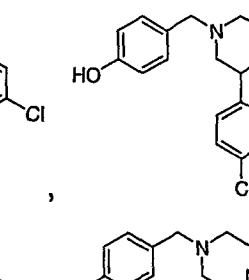
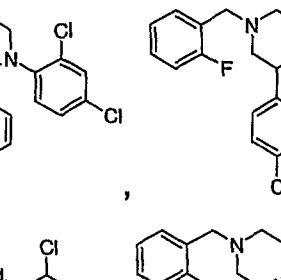
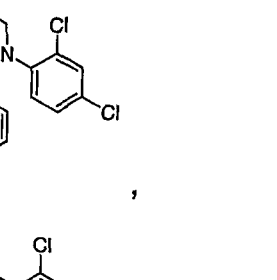
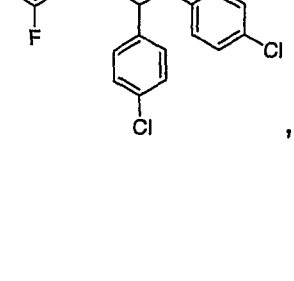
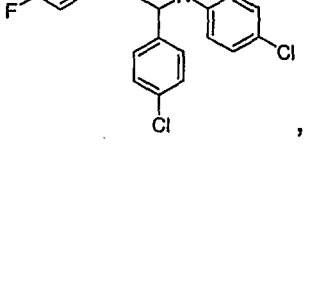
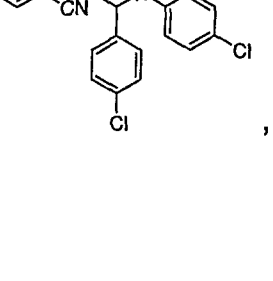
A is -$S(O)_2$-.

41. The compound according to Claim 40, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein n is 0.

42. The compound according to Claim 40, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:
n is 1; and
B is –$N(R^2)$-.

43. A compound according to Claim 1, or a pharmaceutically acceptable salt, solvate or ester thereof, selected from the group consisting of:

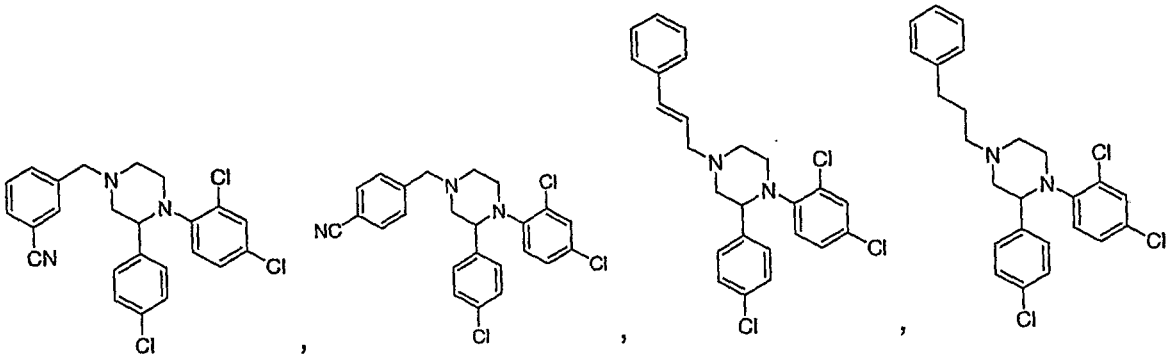
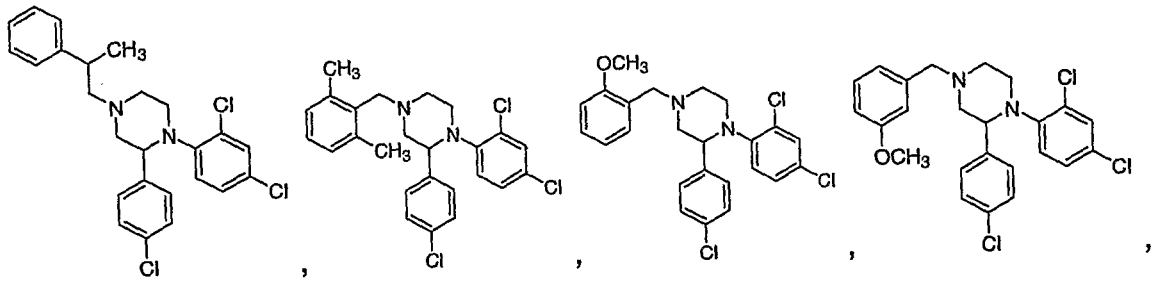
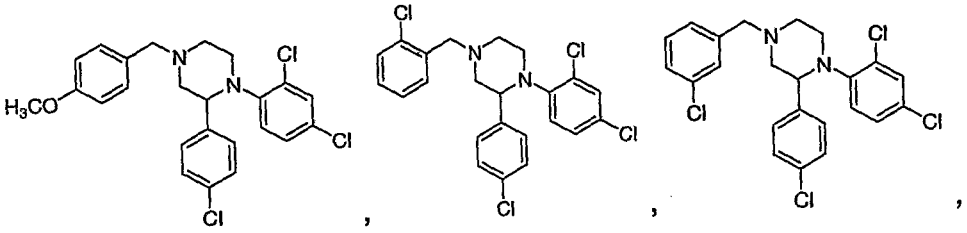
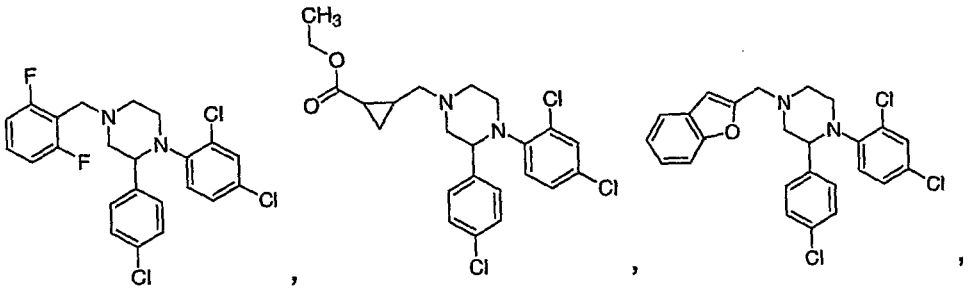
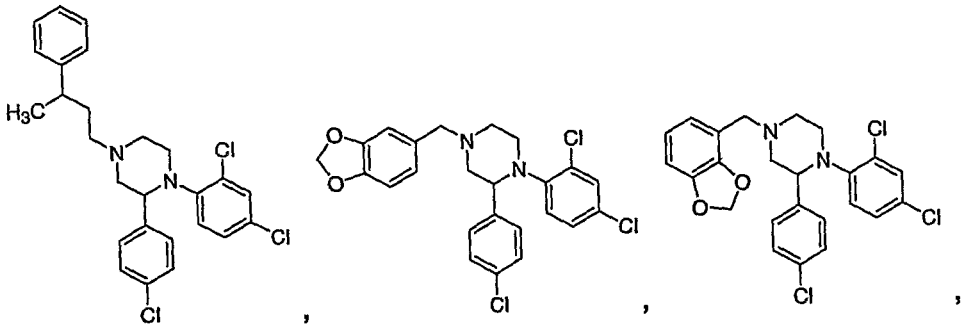
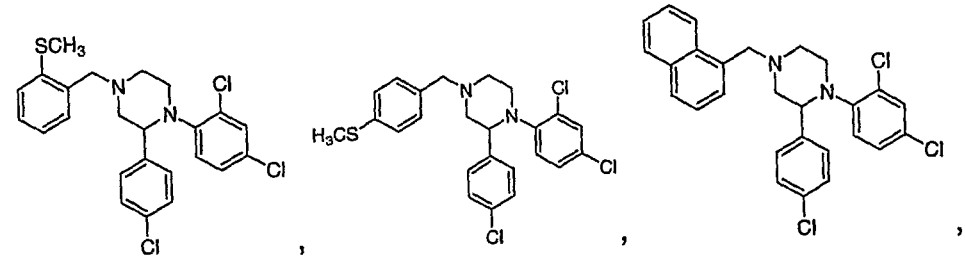


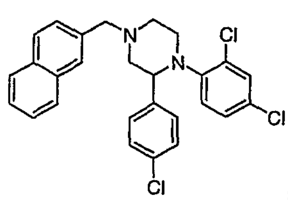
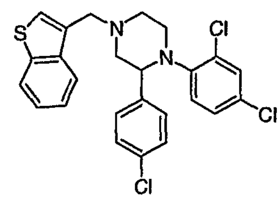
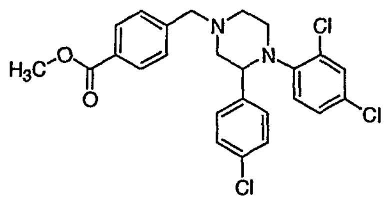

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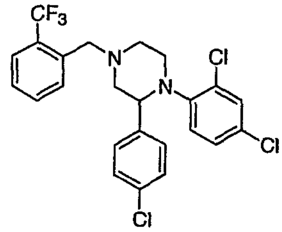
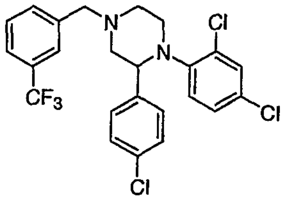
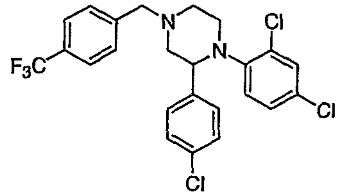
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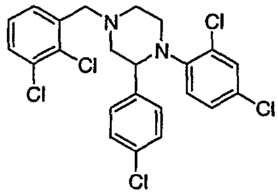
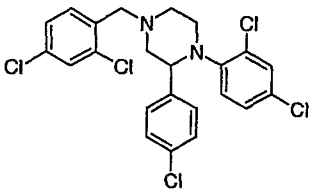
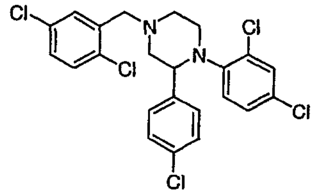
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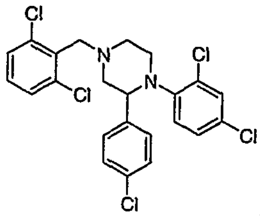
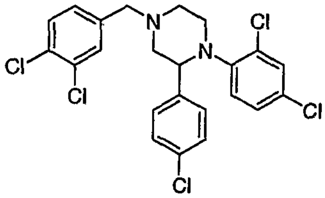
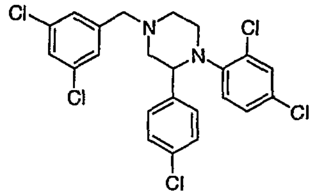
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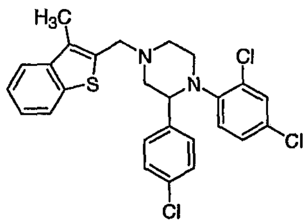
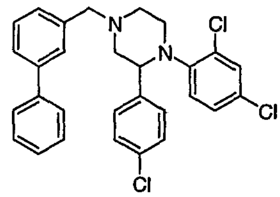
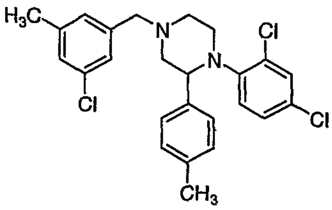







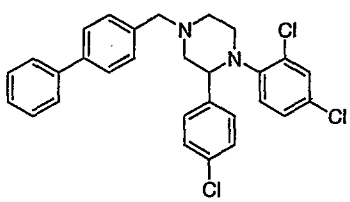
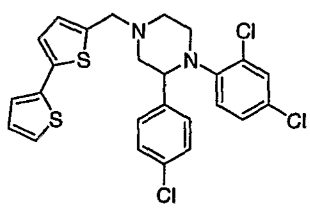
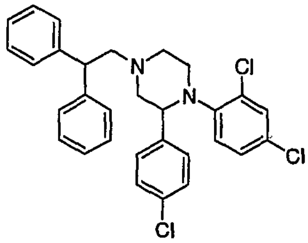
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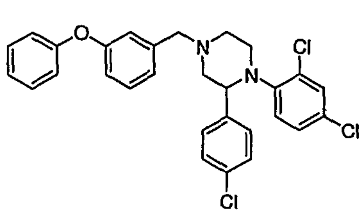
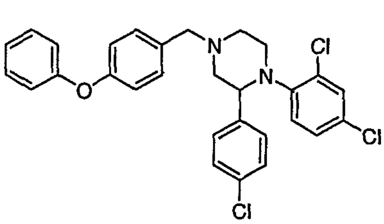
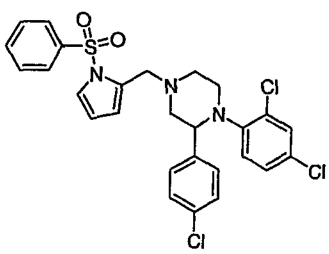
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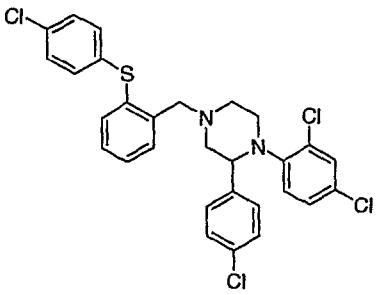
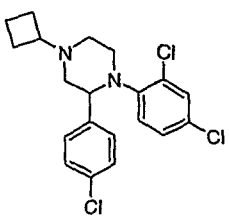
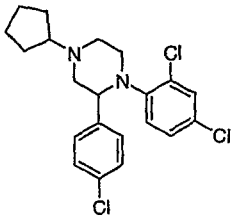
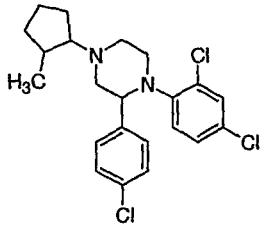
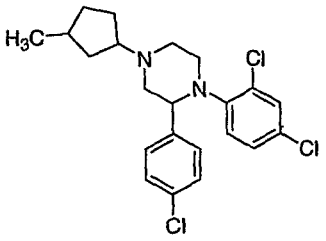
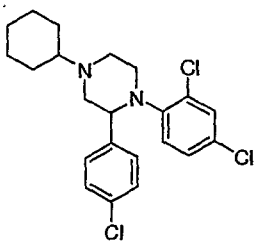
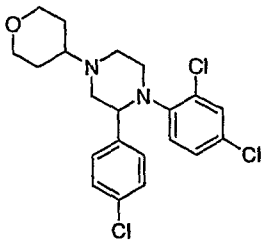
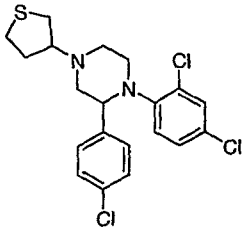
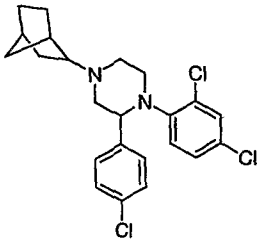
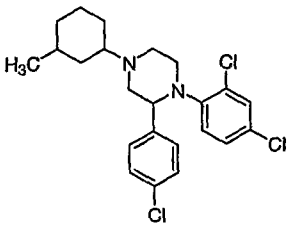
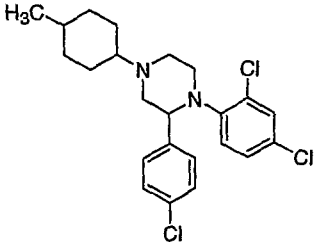
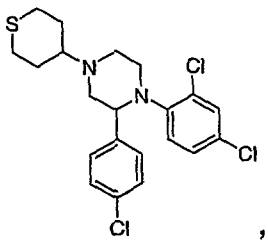
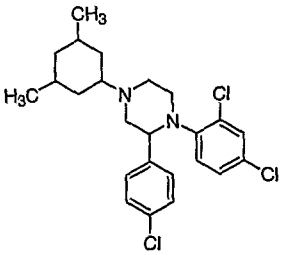
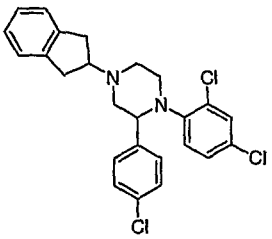
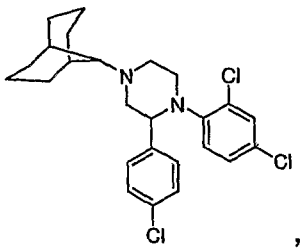
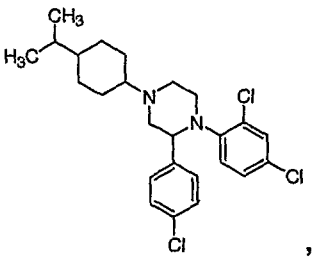
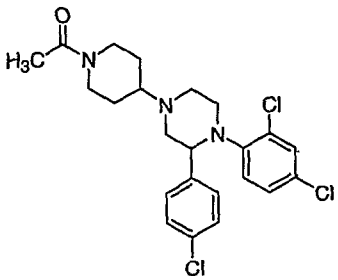
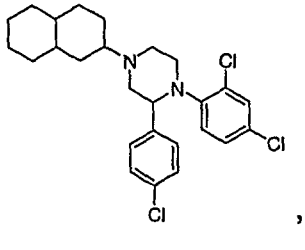
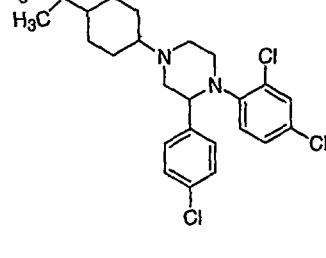
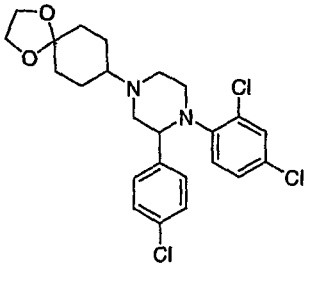
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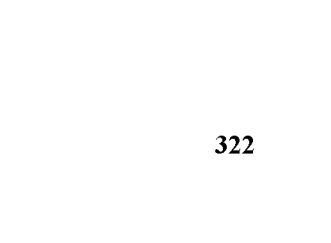
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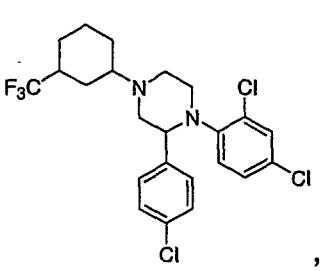
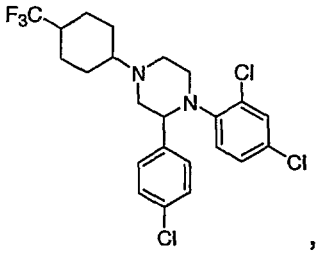
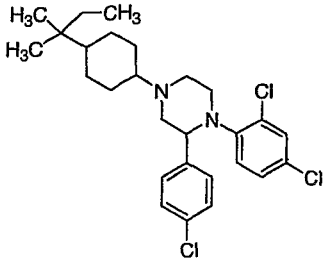
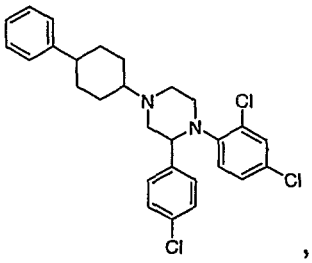
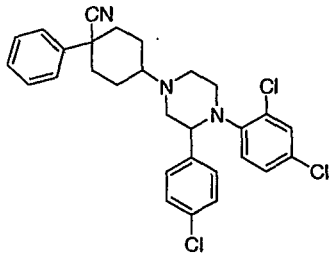
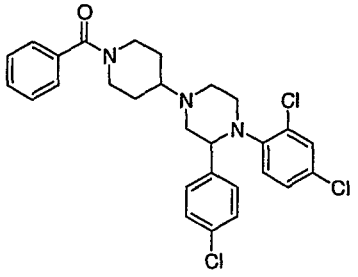
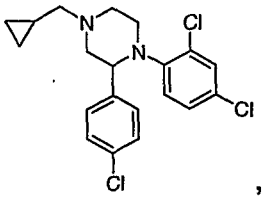
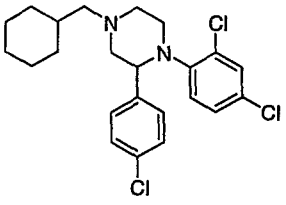
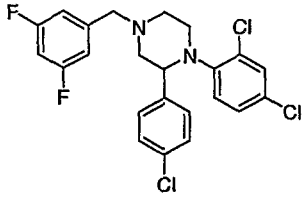
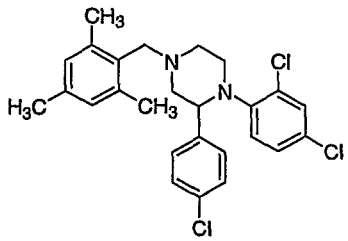
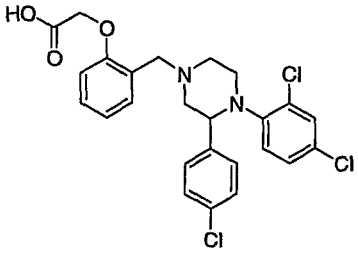
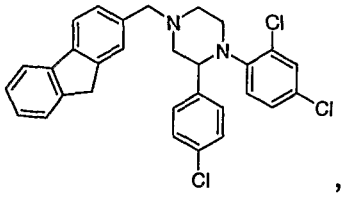
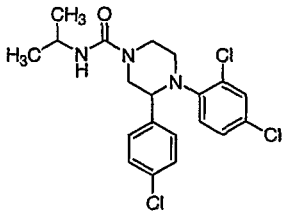
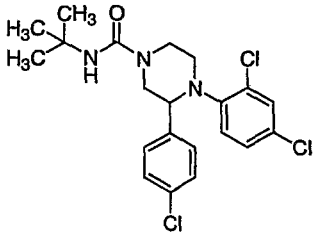
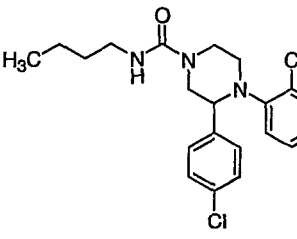
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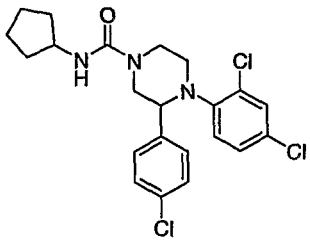
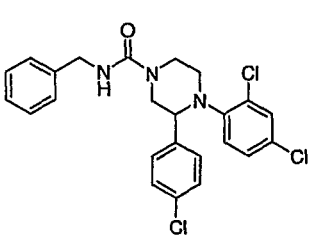
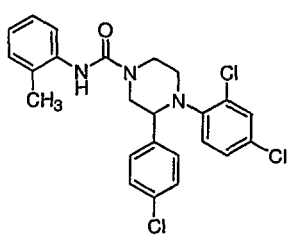
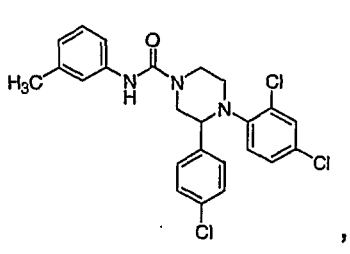
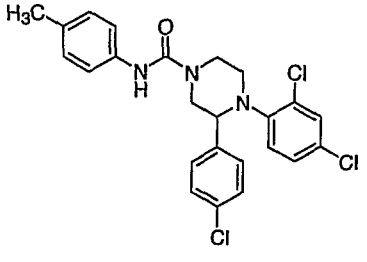
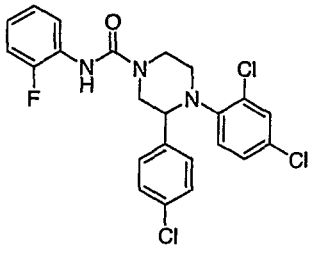
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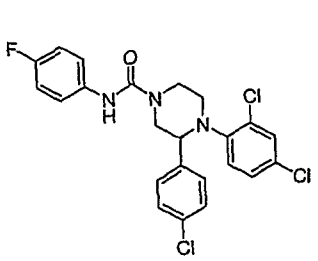
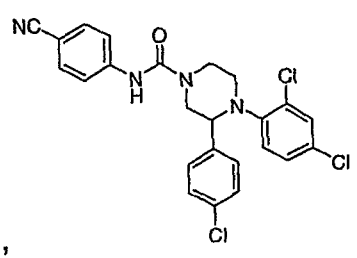
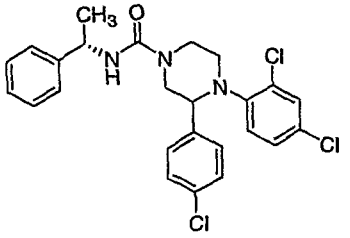
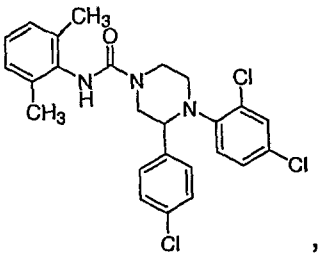
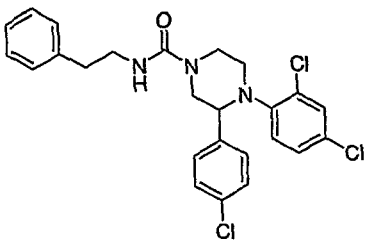
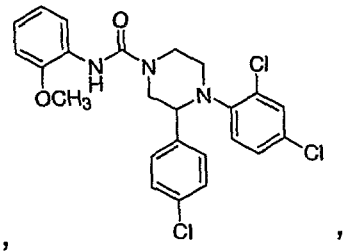
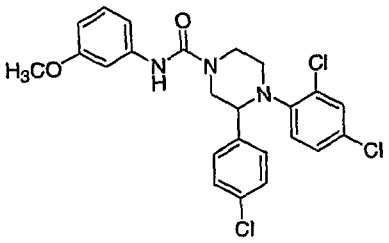
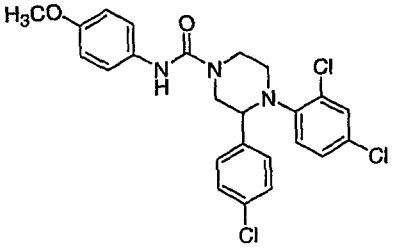
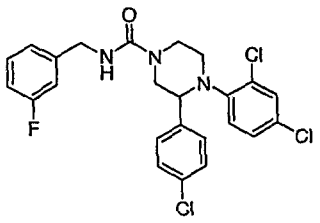
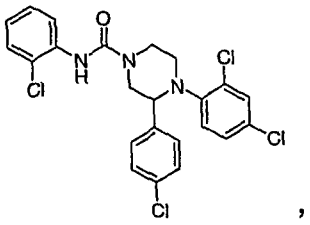
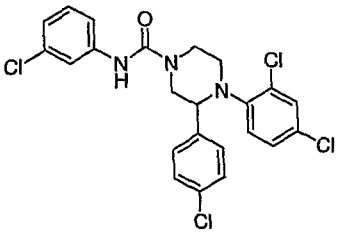
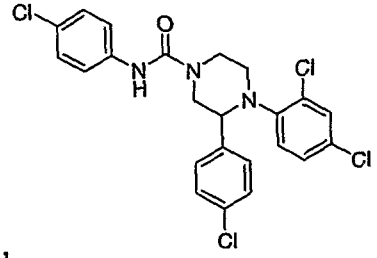
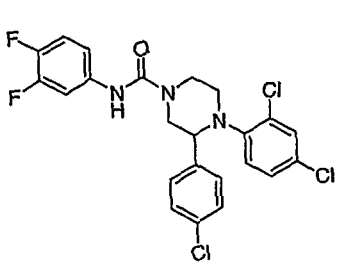
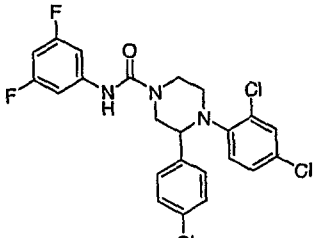
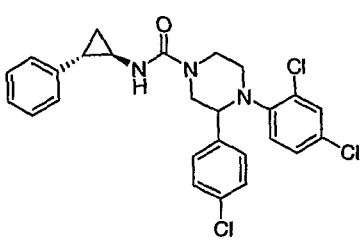
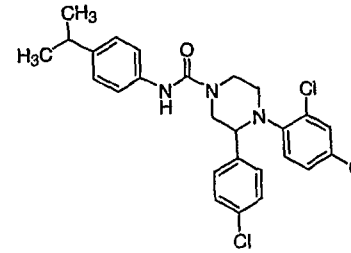
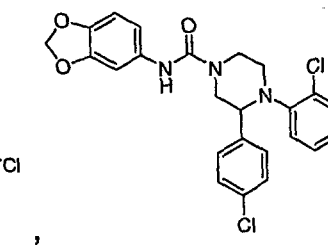
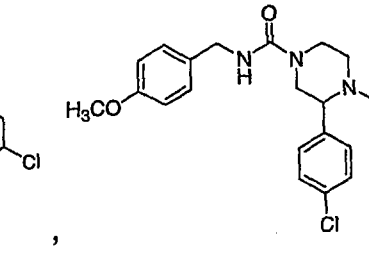

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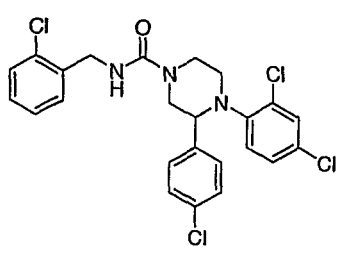
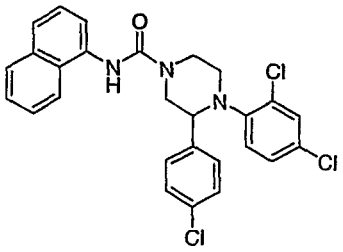
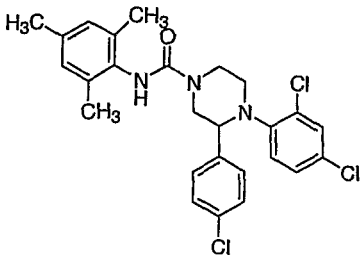
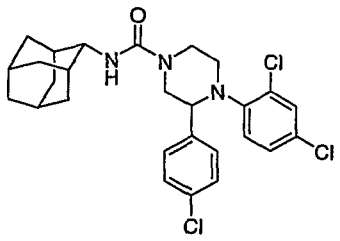
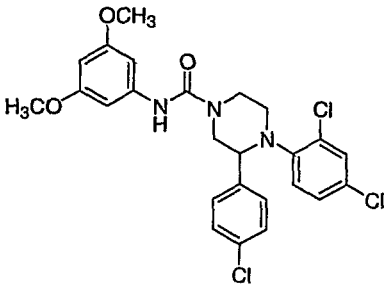
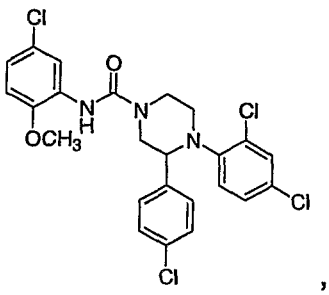
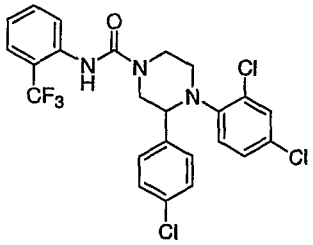
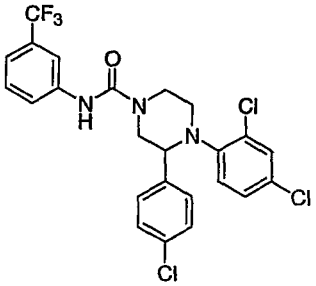
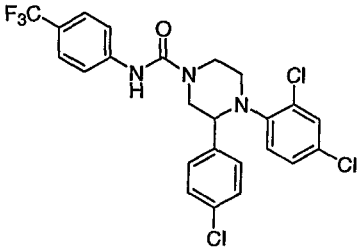
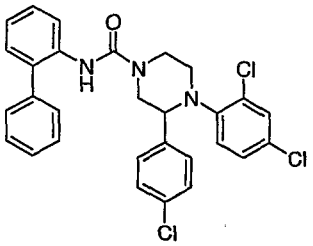
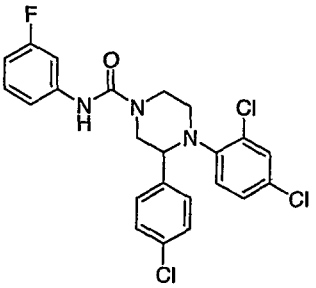
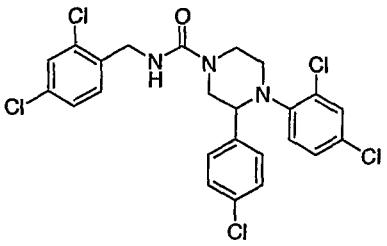
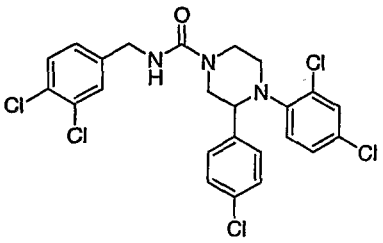
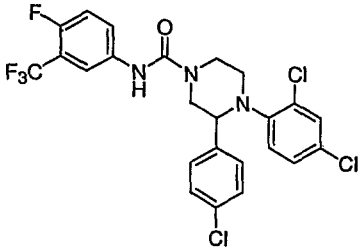
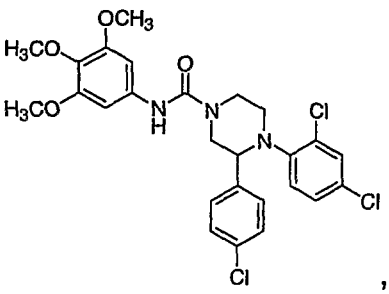
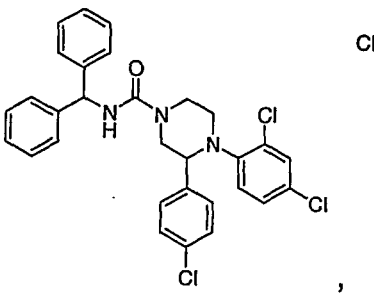
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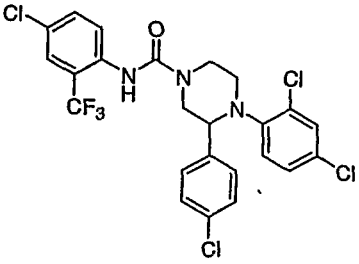
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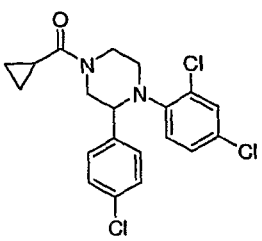
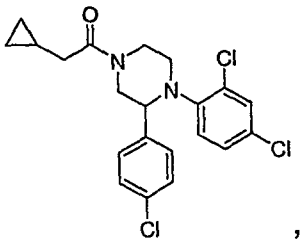
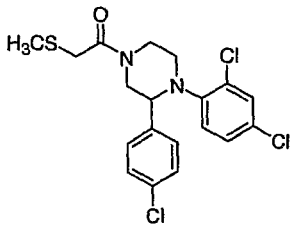
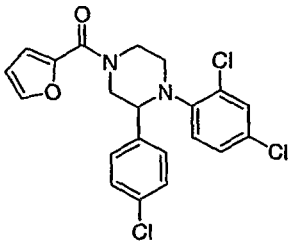
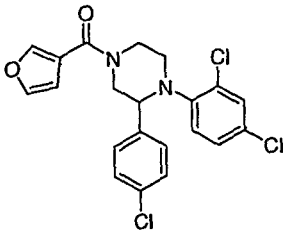
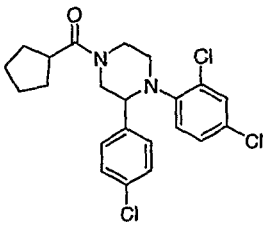
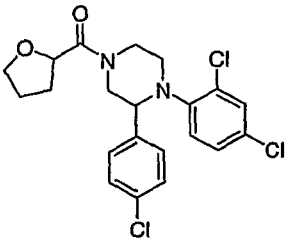
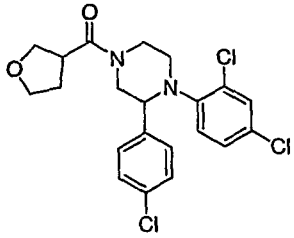
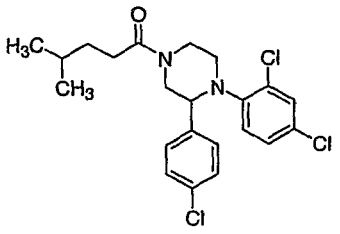
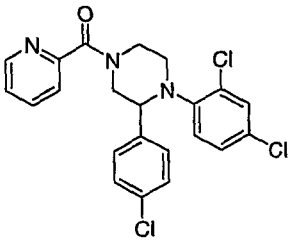
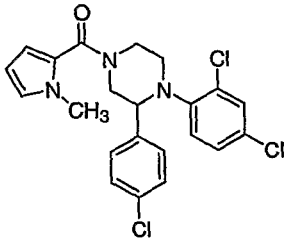
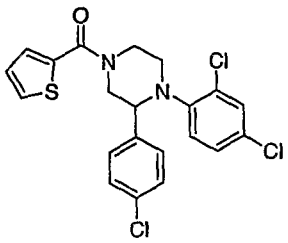
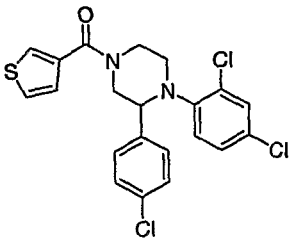
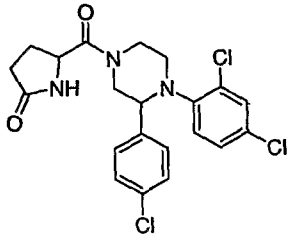
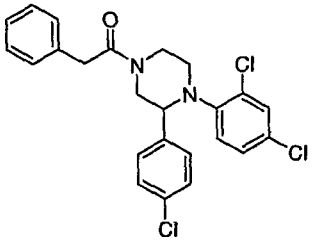
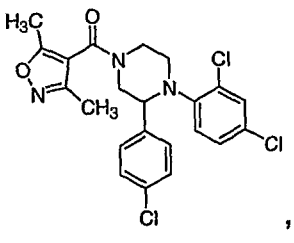
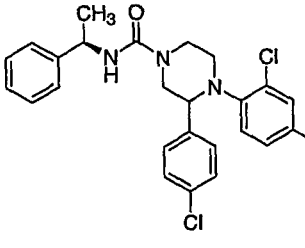
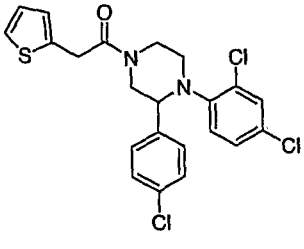
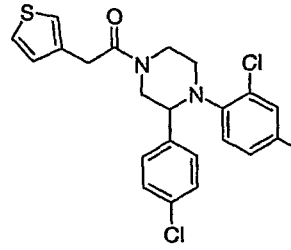
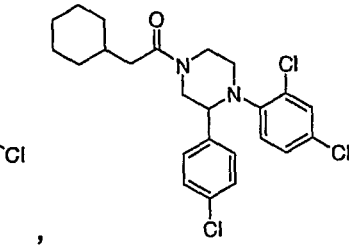
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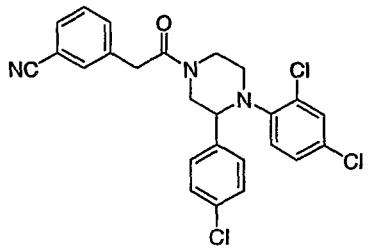
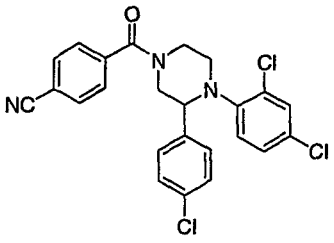
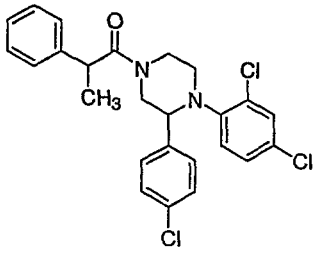
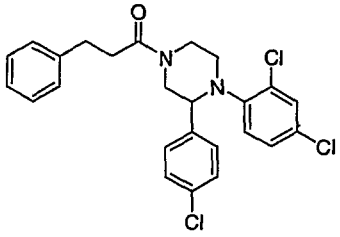
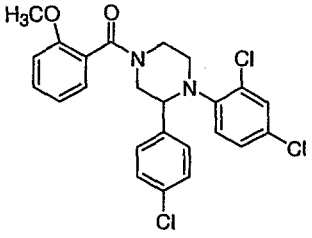
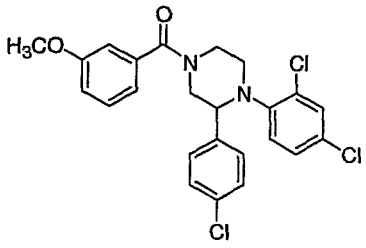
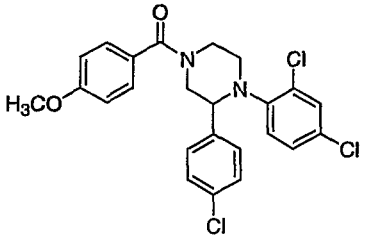
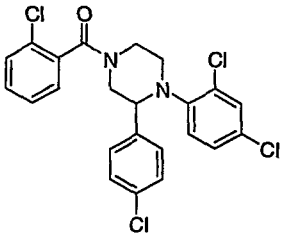
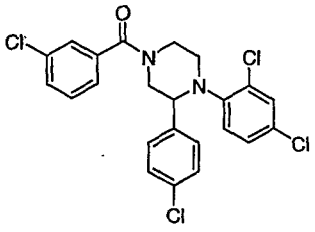
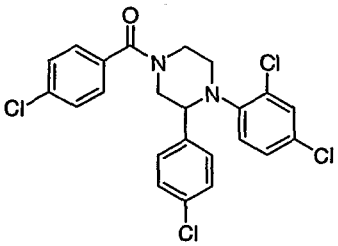
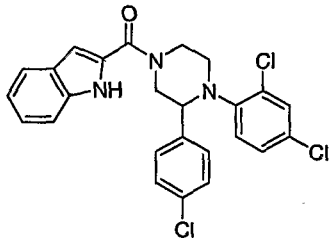
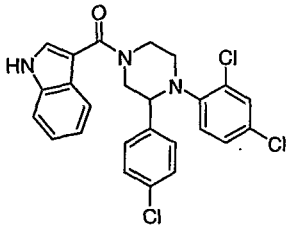
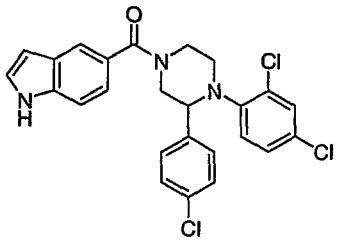
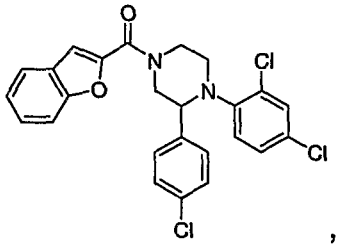
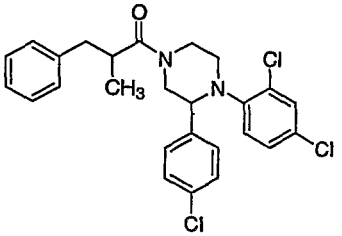
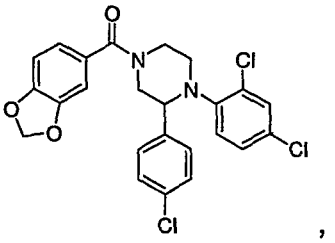
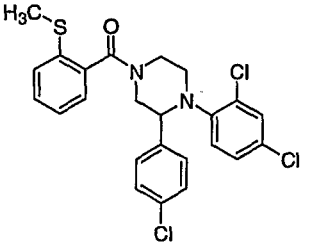
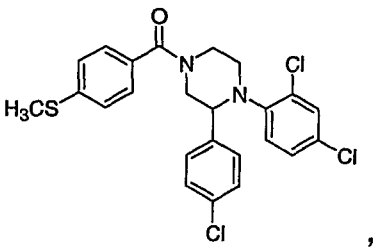
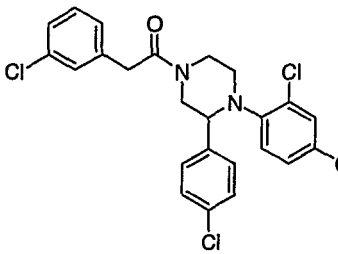
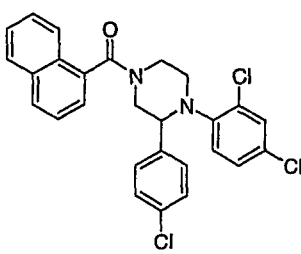
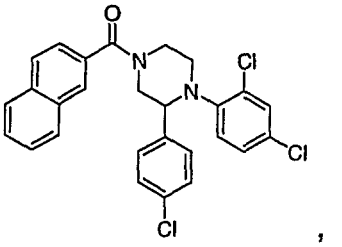

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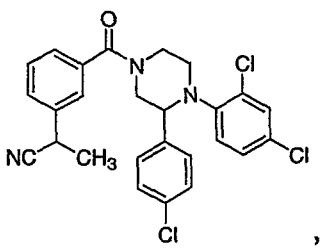
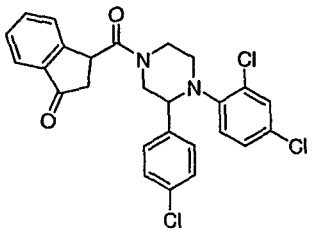
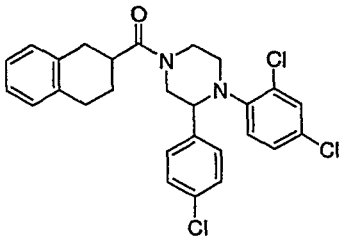
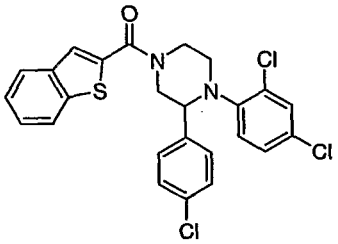
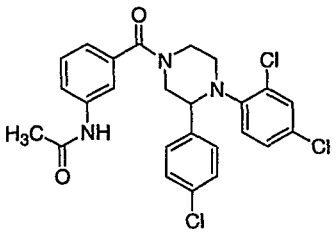
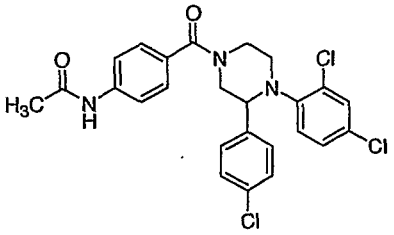
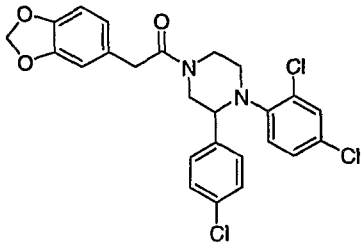
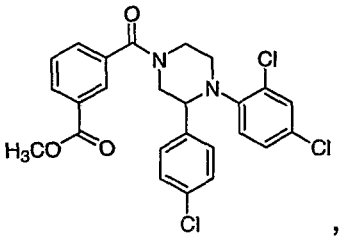
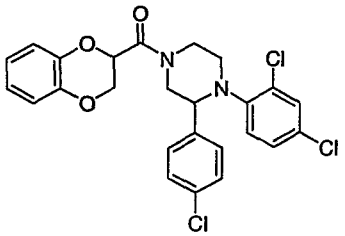
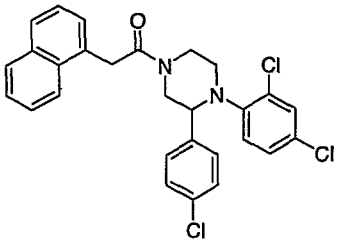
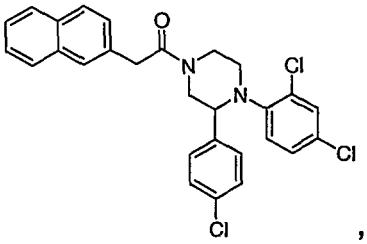
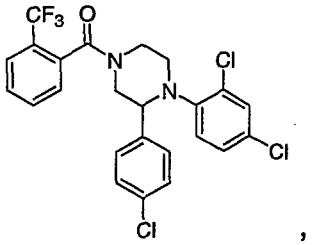
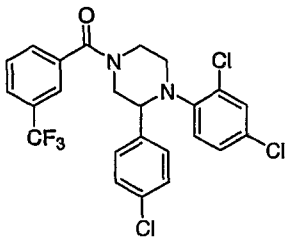
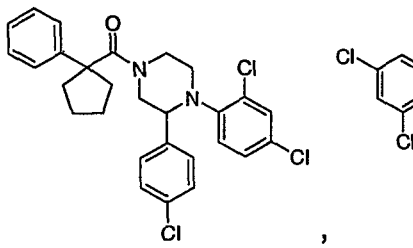
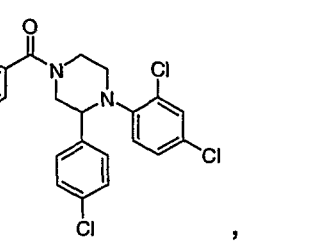
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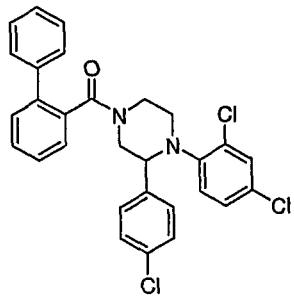
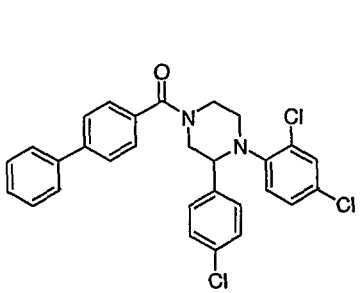
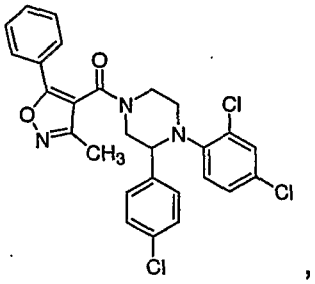
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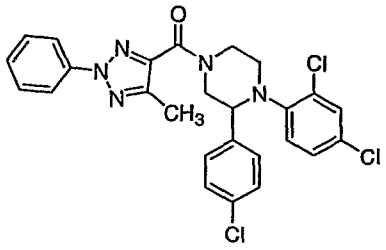
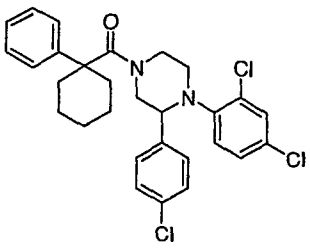
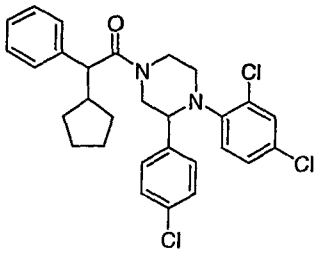
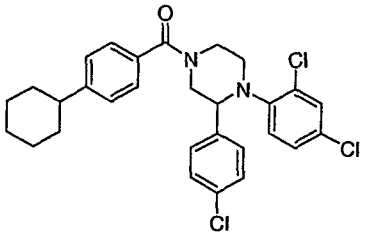
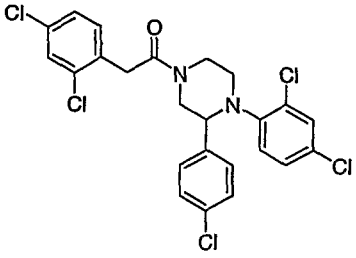
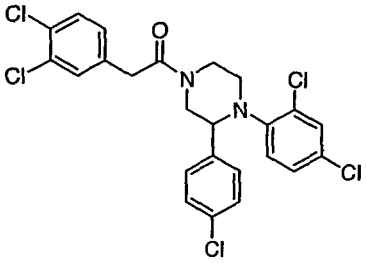
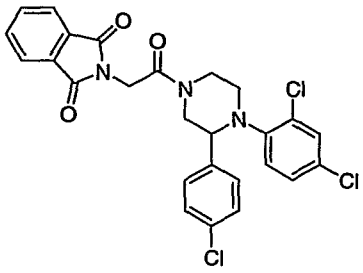
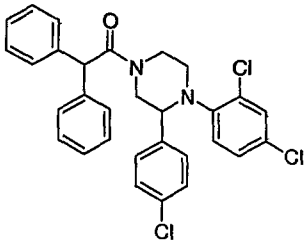
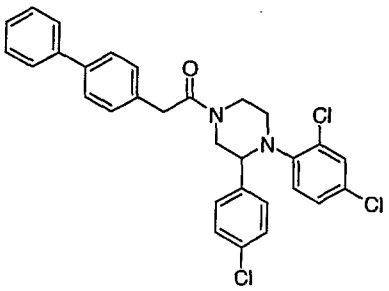
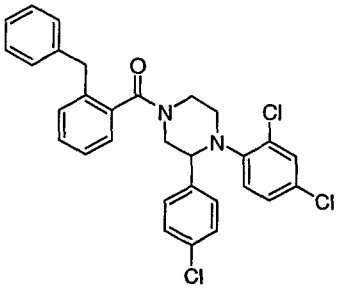
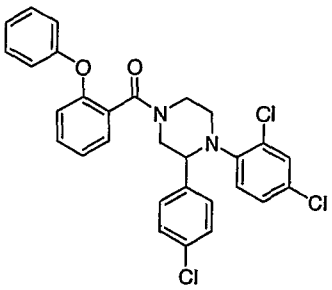
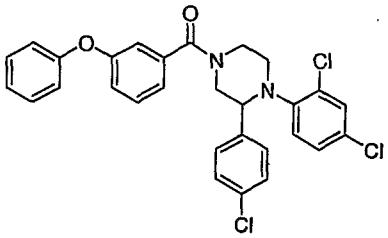
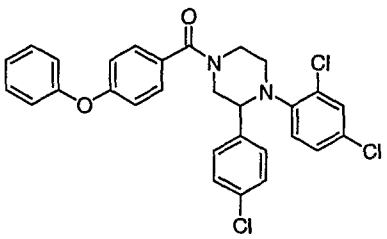
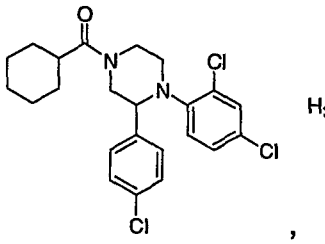
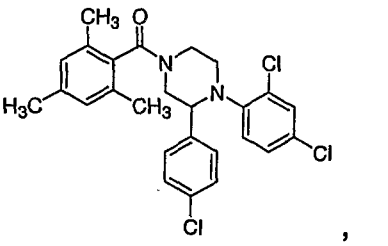
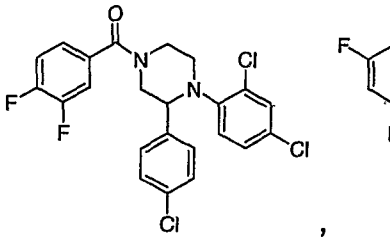
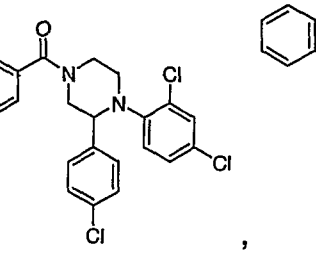
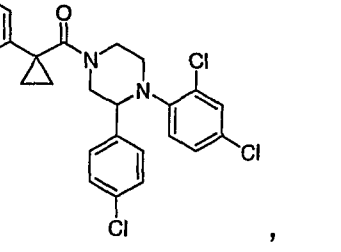

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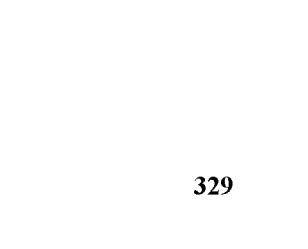

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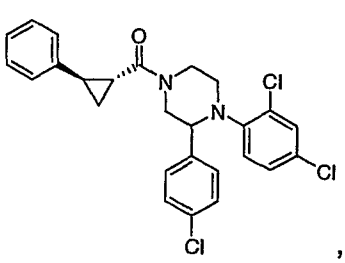
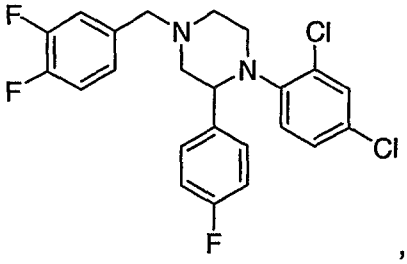
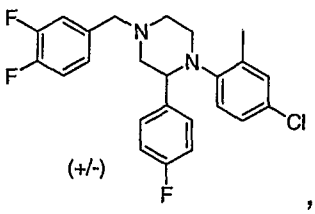
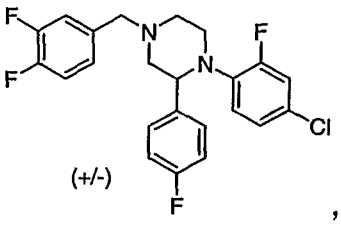
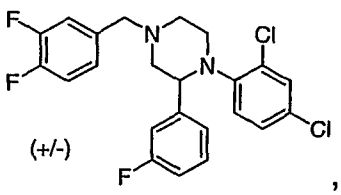
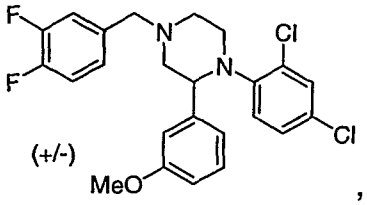
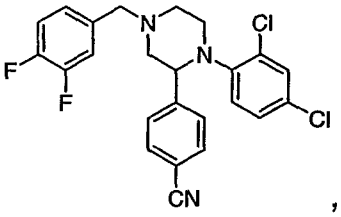
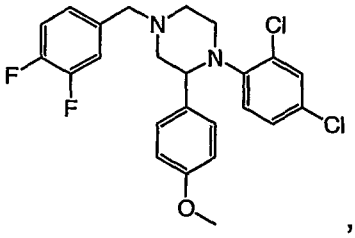
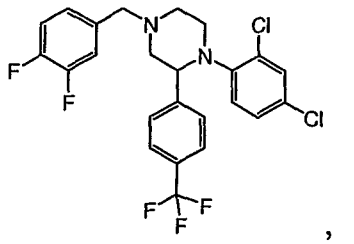
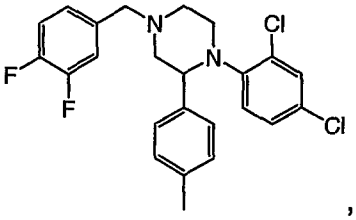
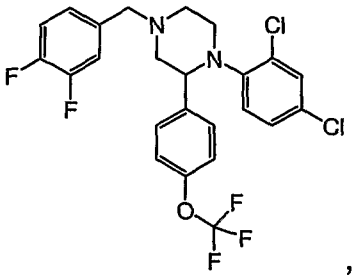
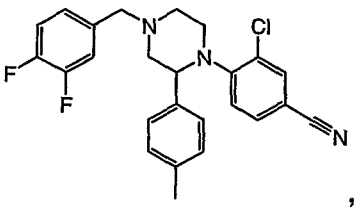
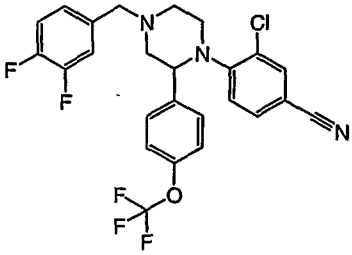
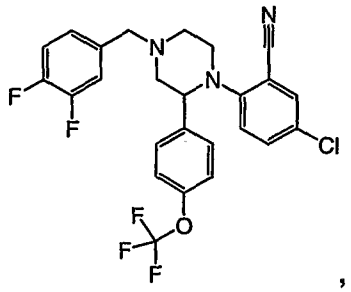
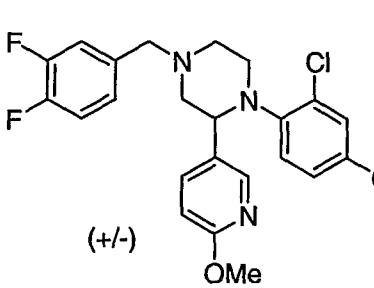
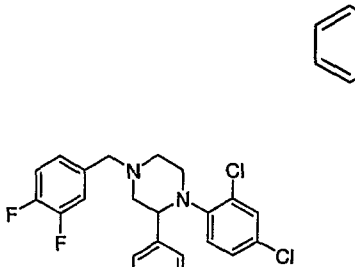
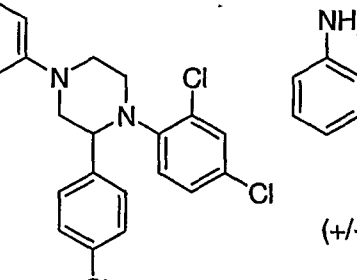
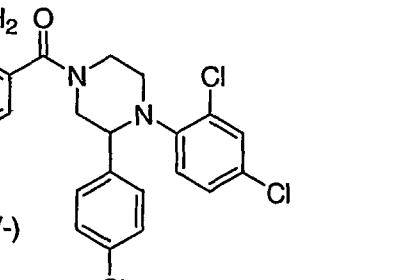
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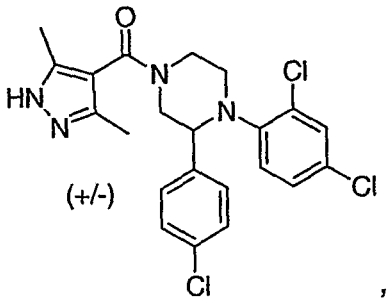
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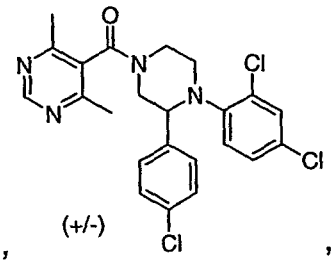
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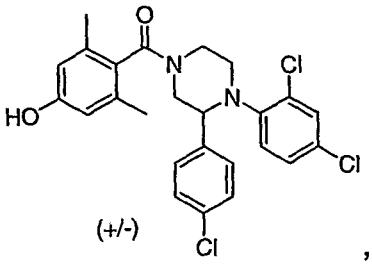
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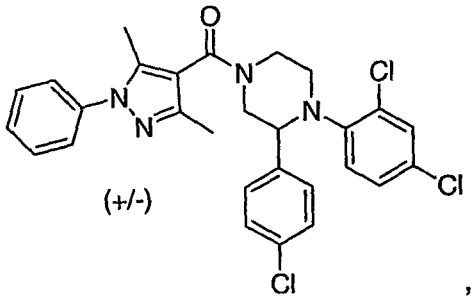
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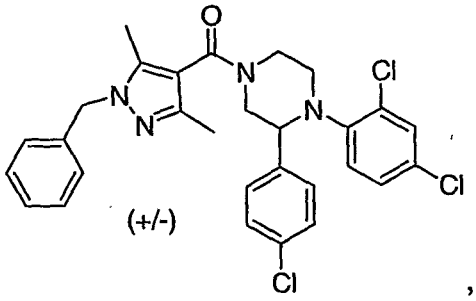
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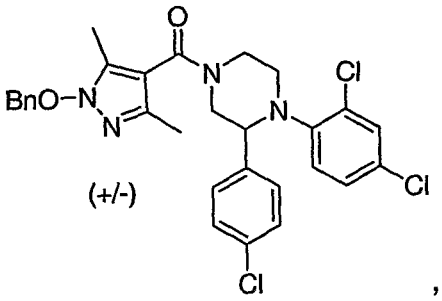
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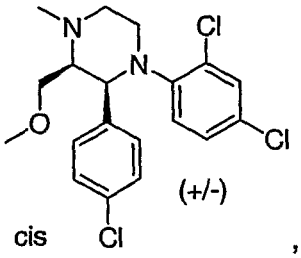
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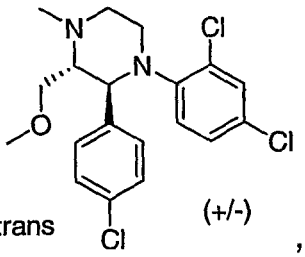
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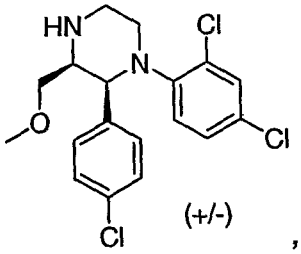
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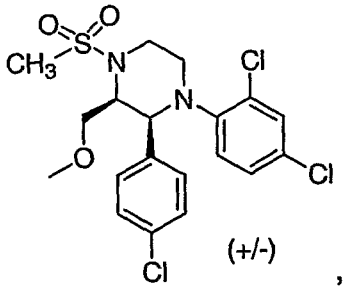
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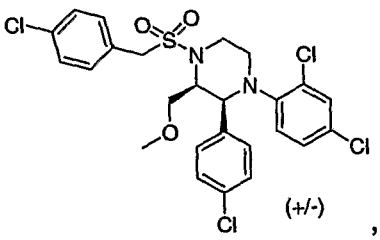
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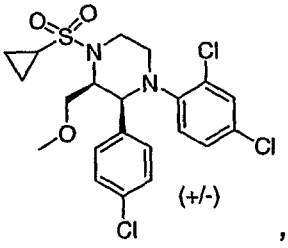
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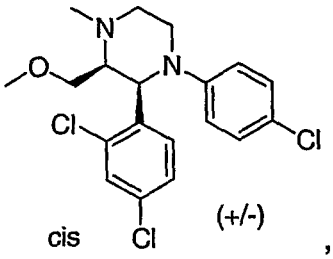
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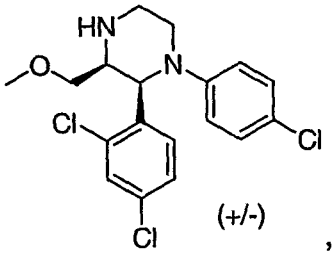
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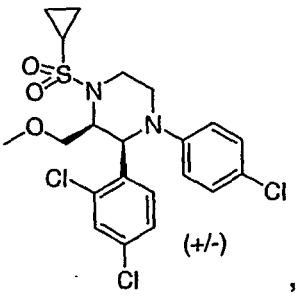
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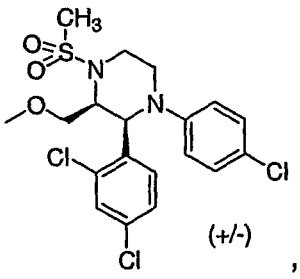
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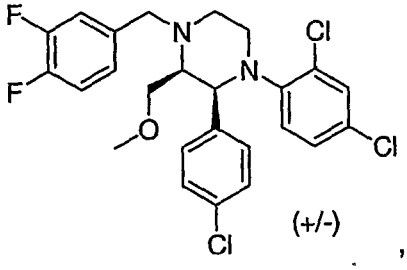
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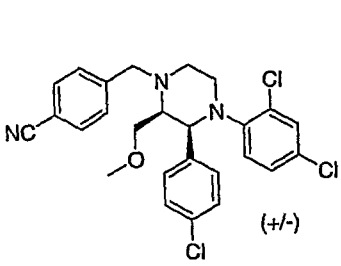
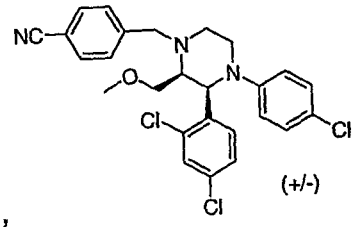
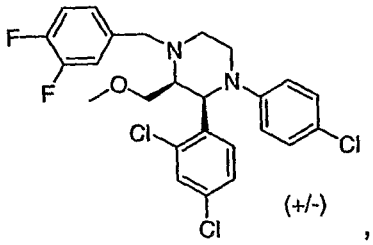
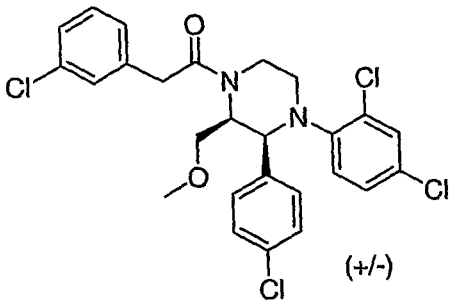
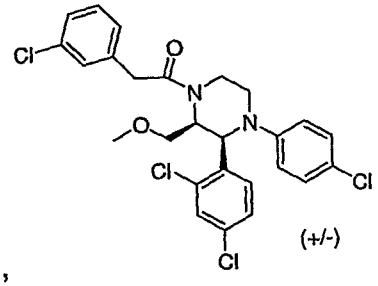
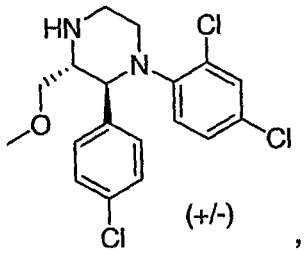
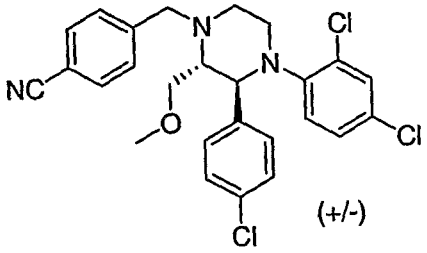
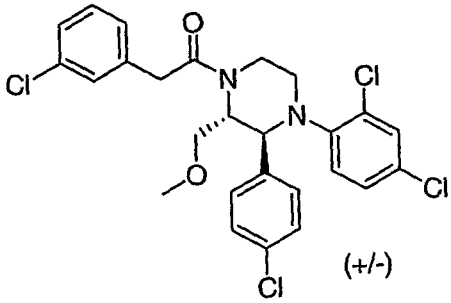
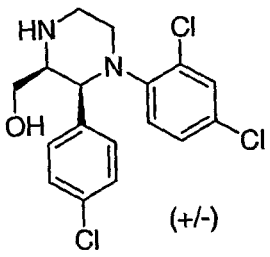
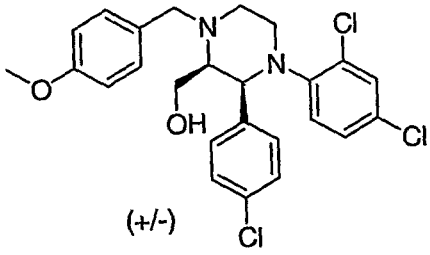
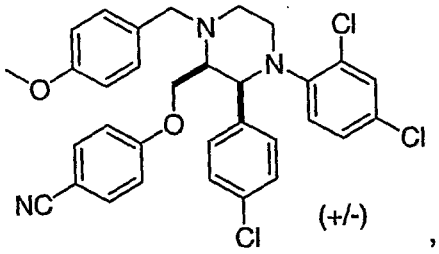
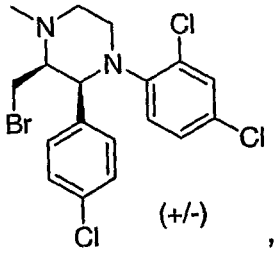
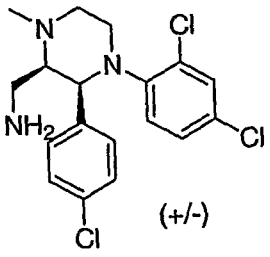
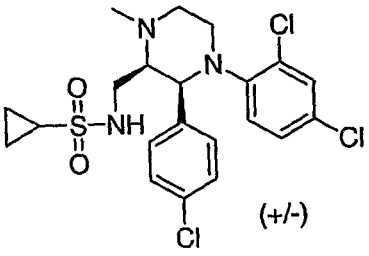
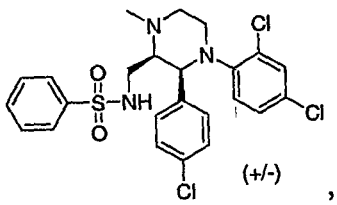
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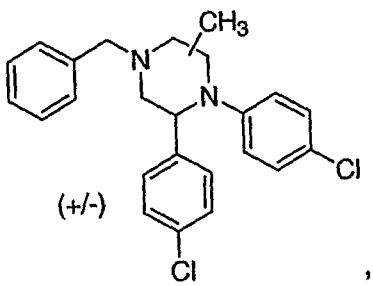
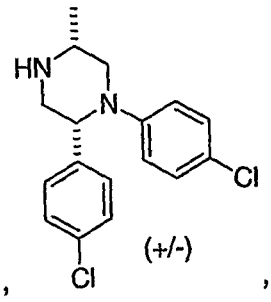
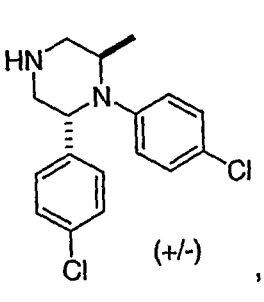
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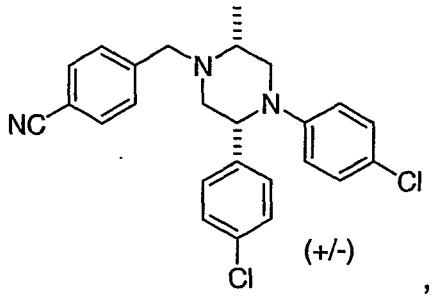
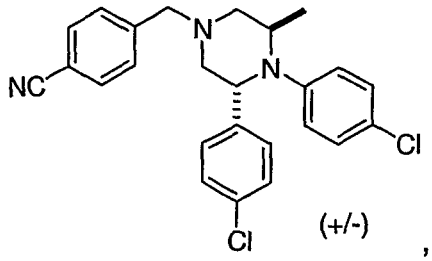
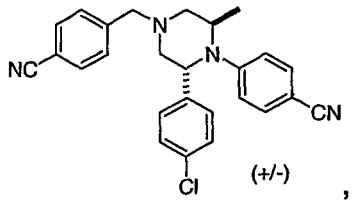
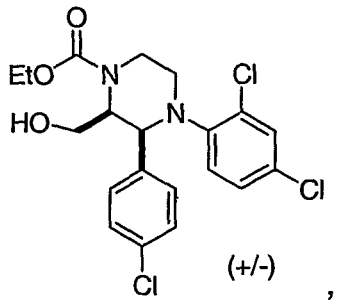
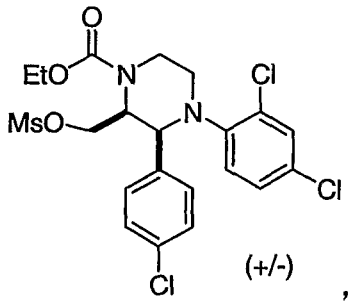
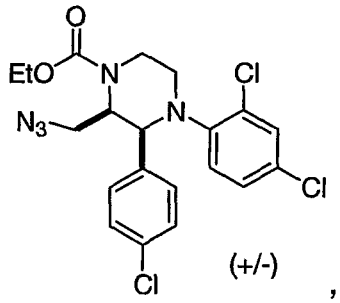
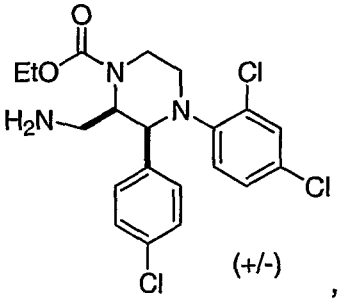
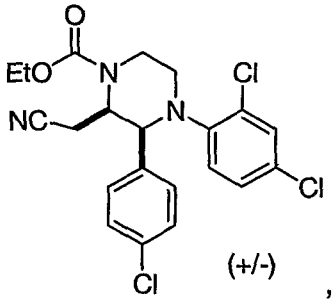
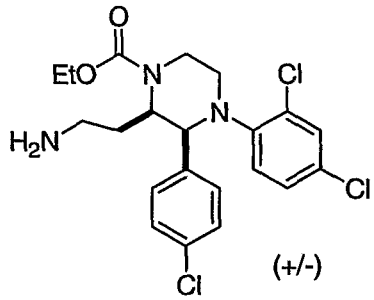
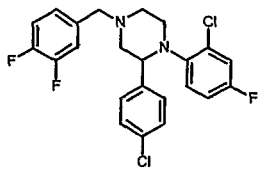
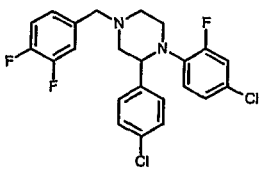
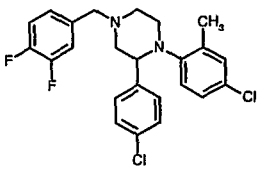
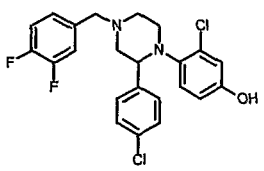
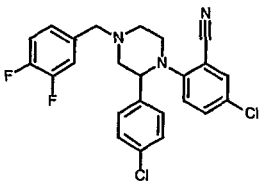
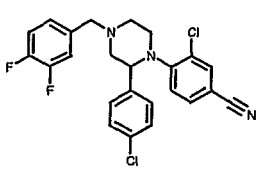
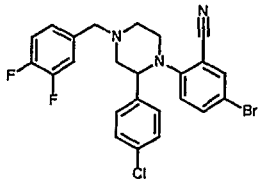
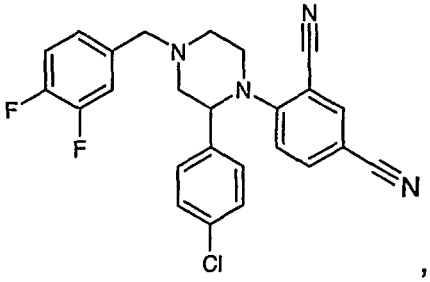
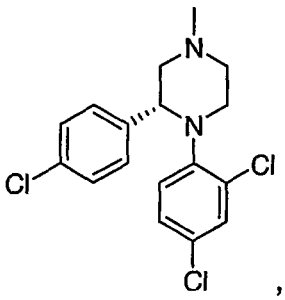

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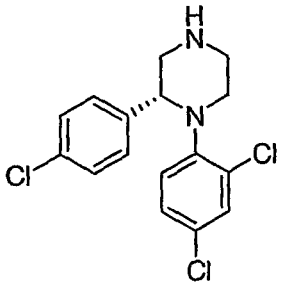
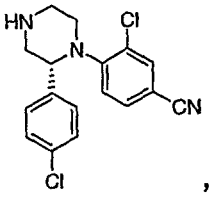
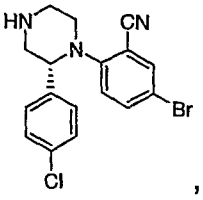
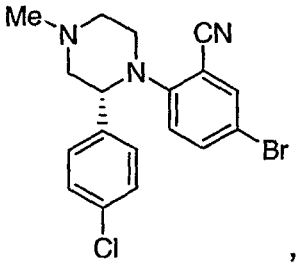
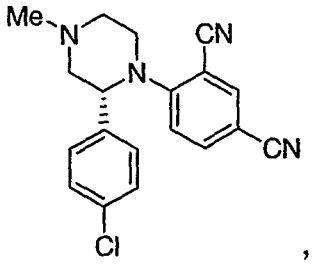
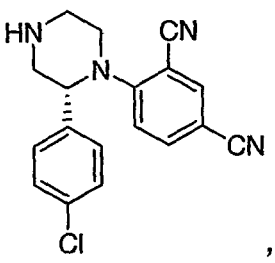
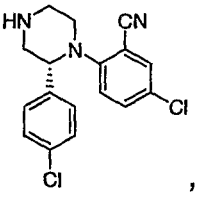
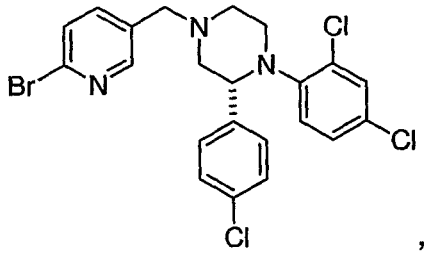
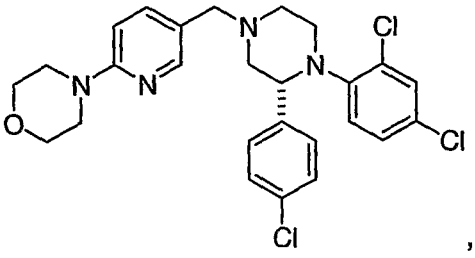
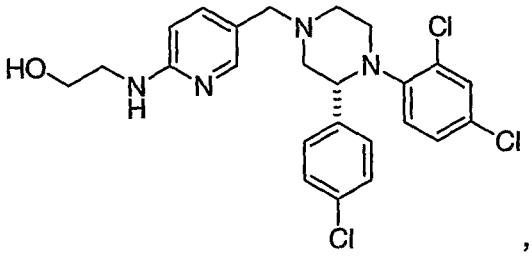
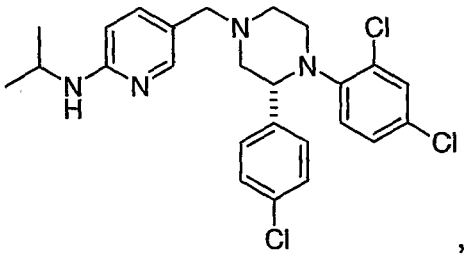
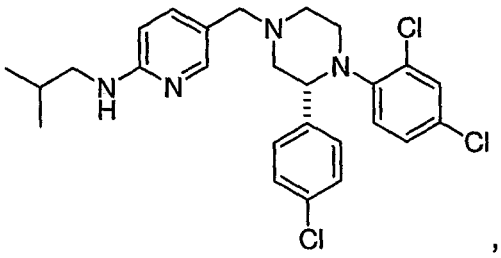
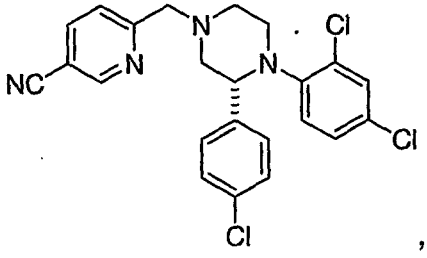
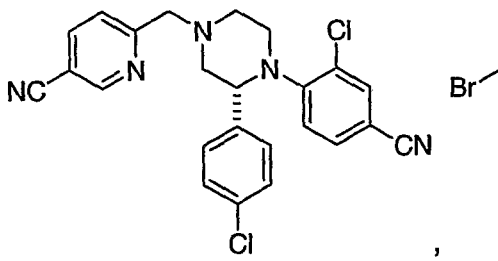
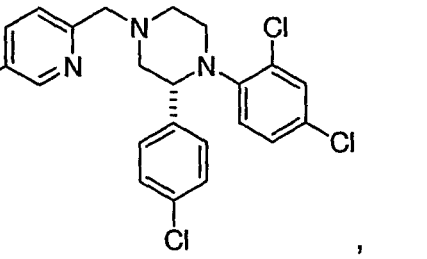
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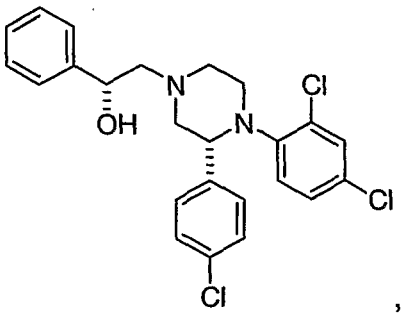
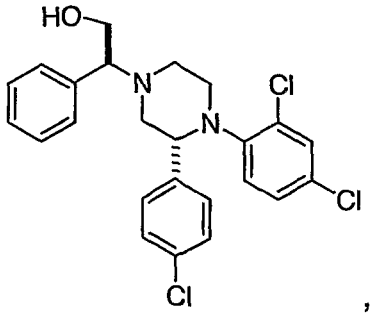
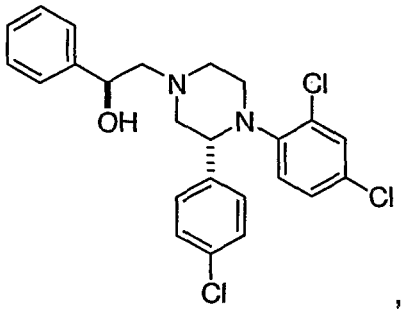
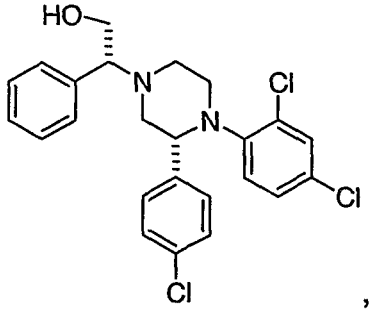
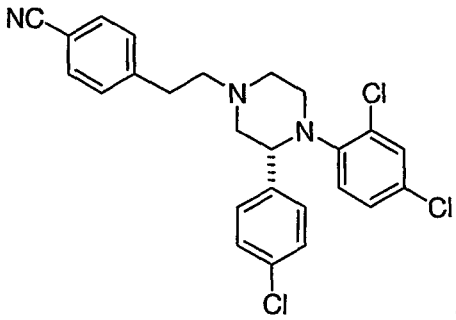
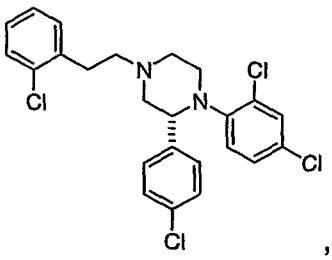
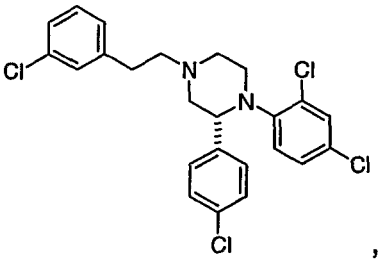
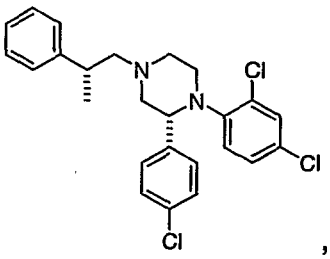
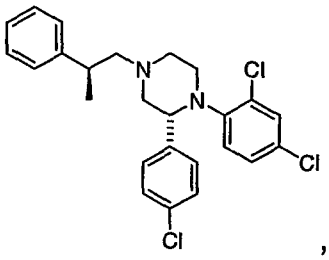
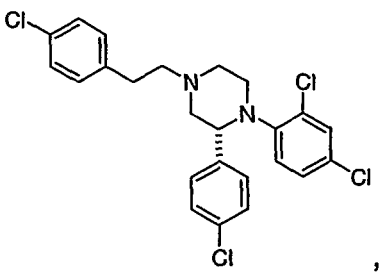
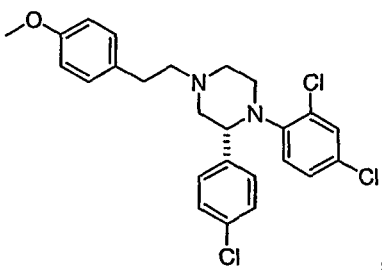
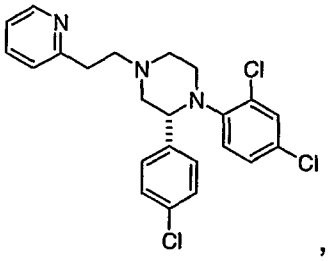
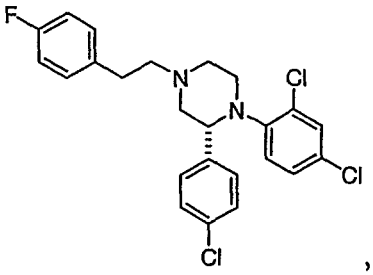
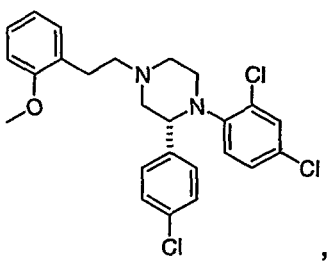
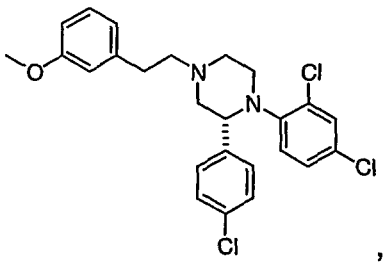
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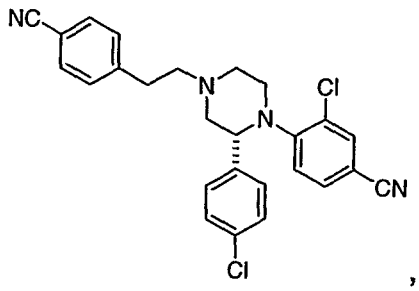
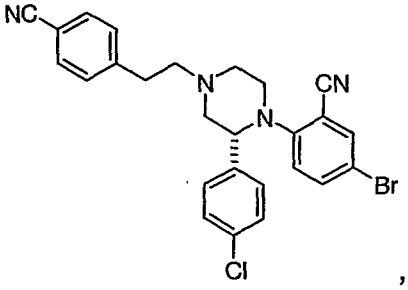
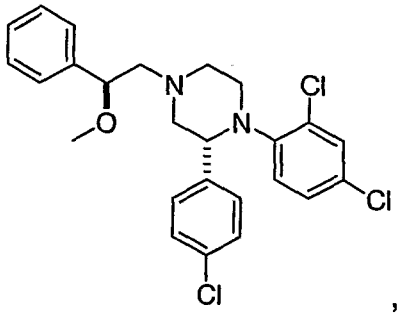
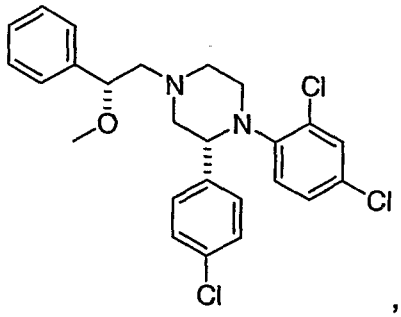
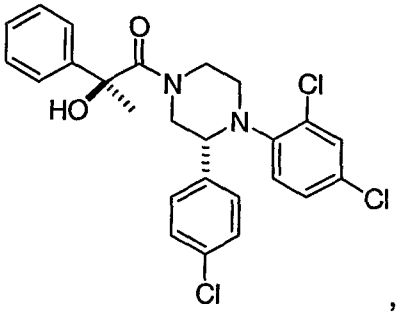
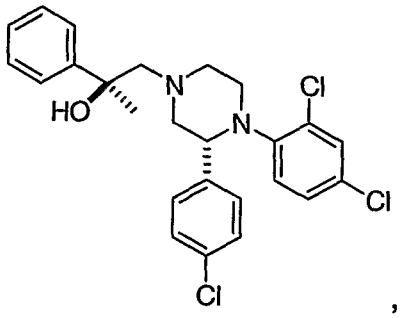
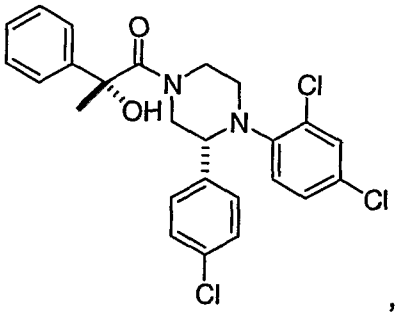
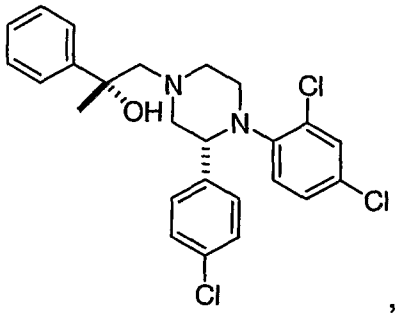
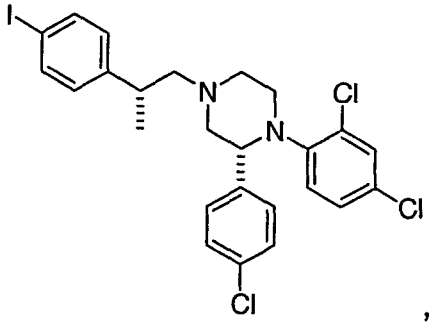
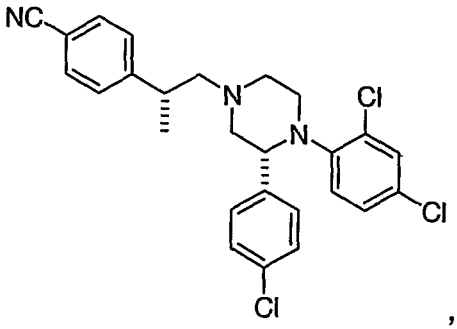
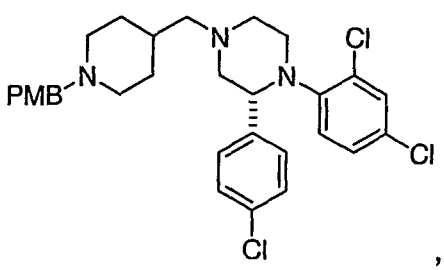
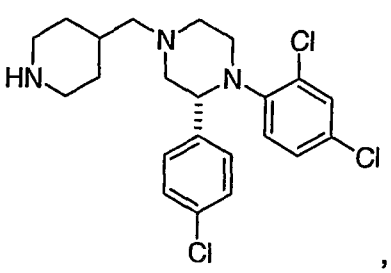

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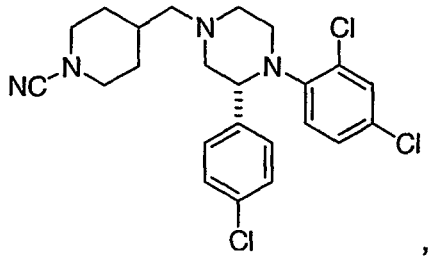
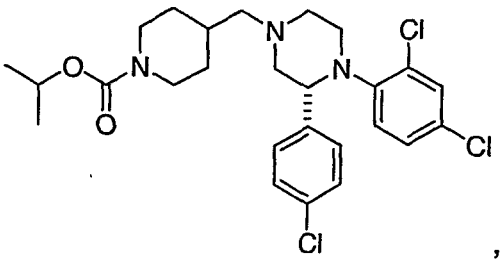
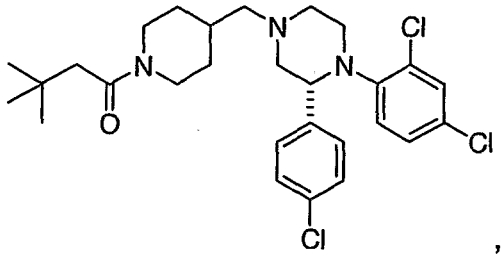
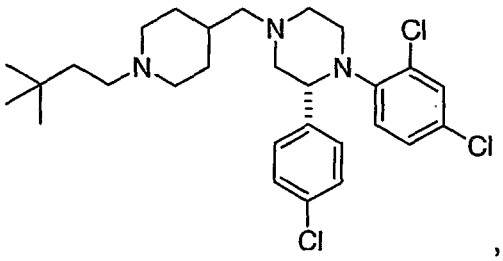
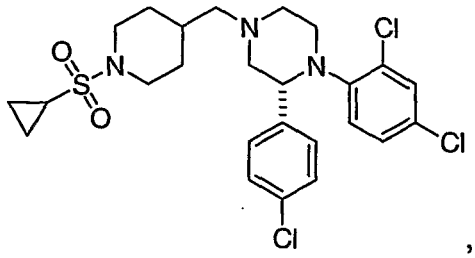
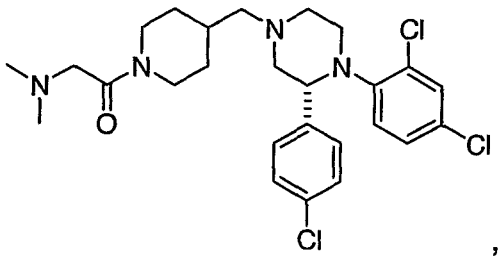
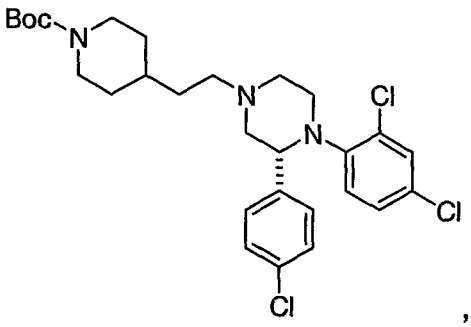
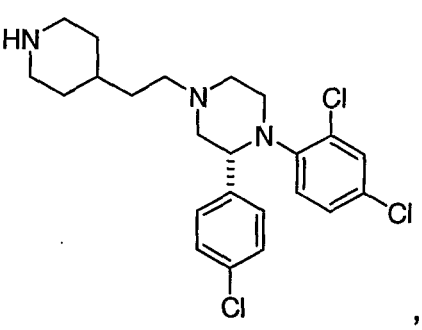
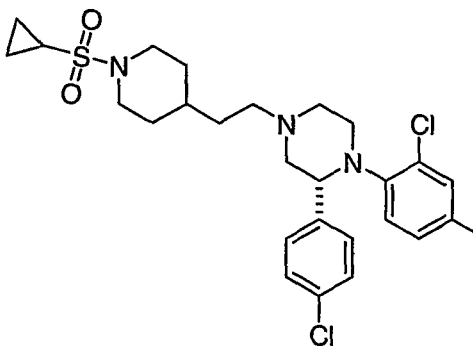

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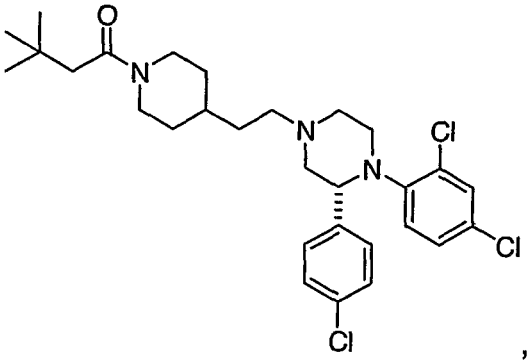
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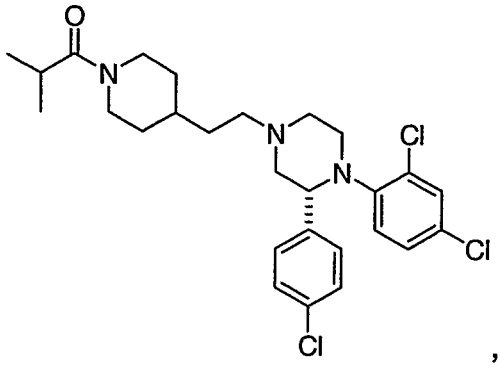
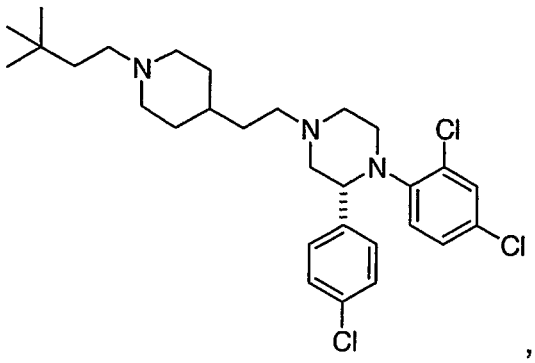
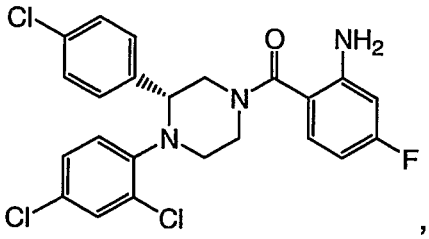
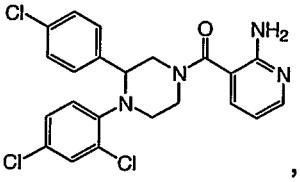
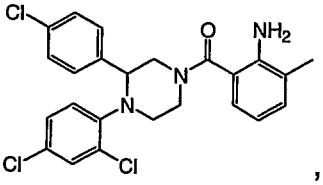
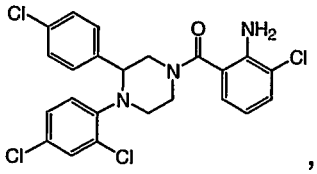
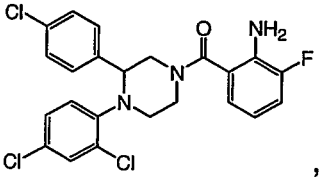
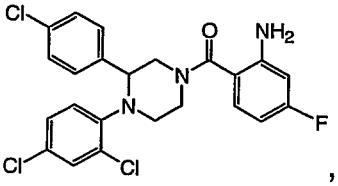
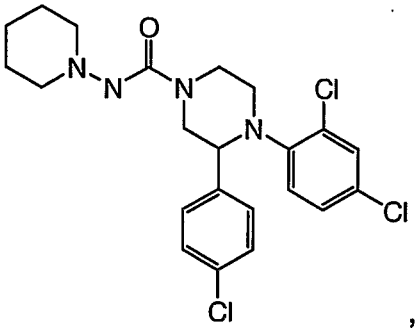
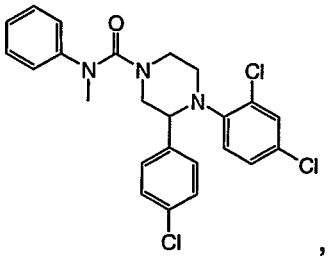
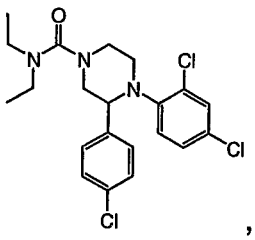
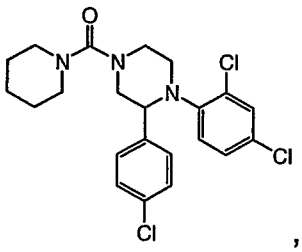
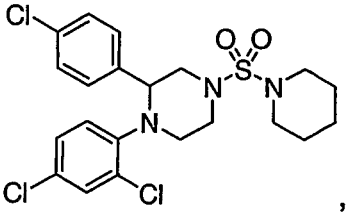
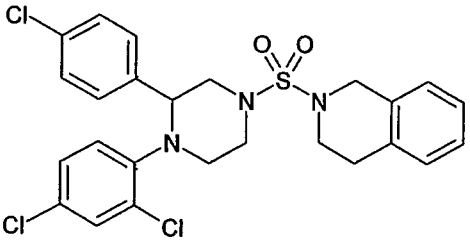
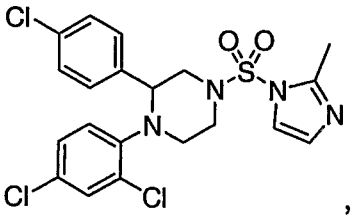
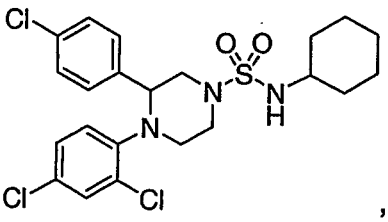
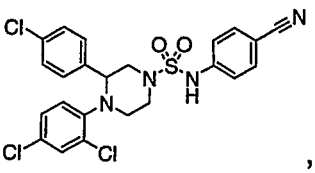

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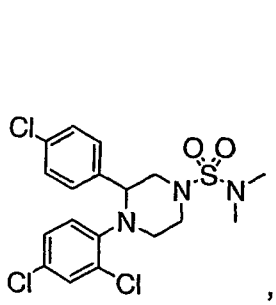
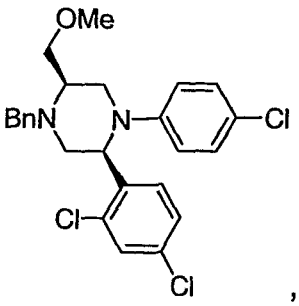
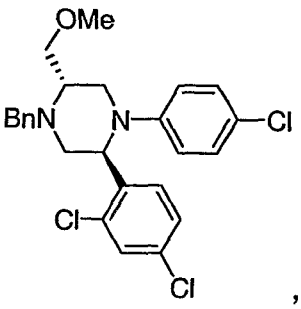
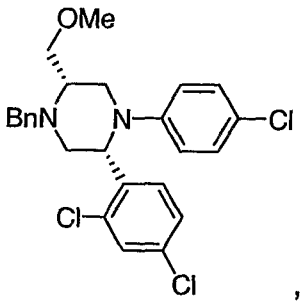
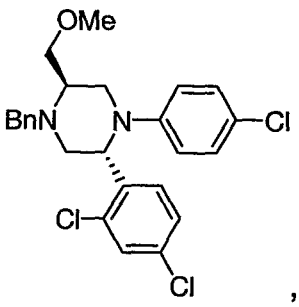
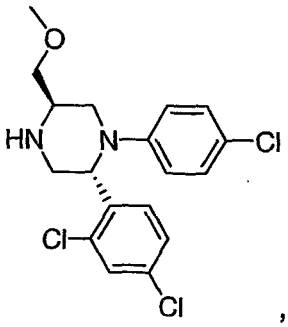
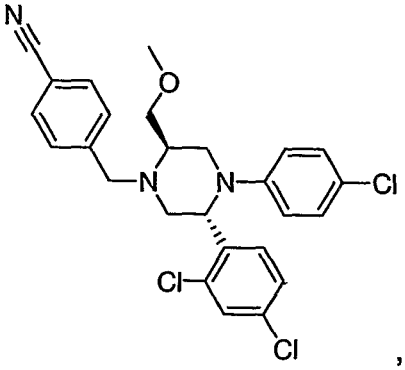
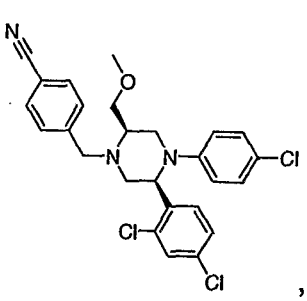
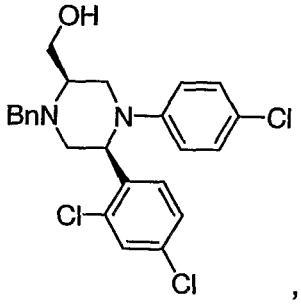
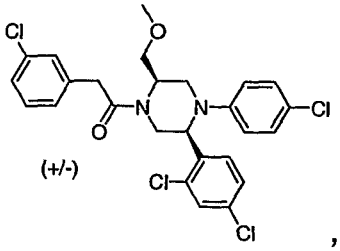
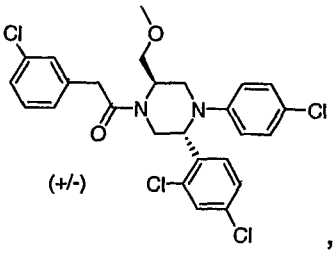
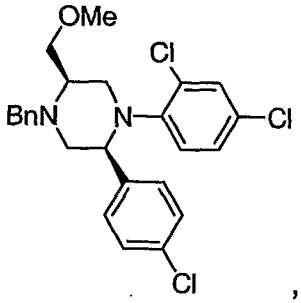
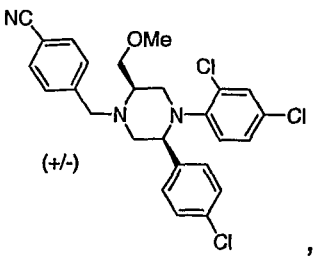
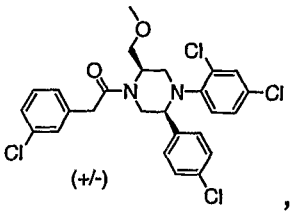
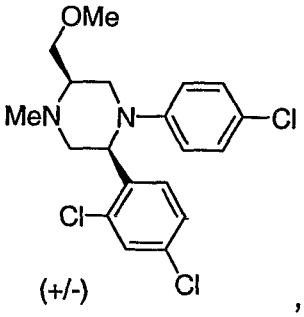












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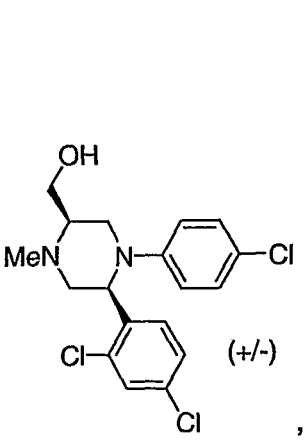
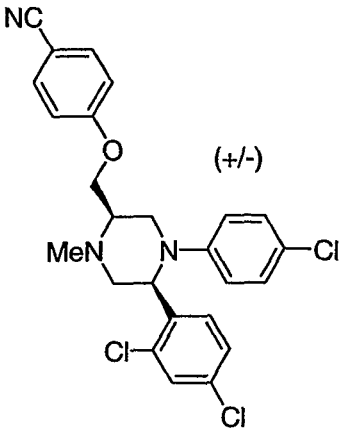
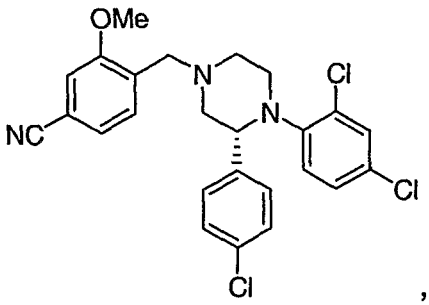
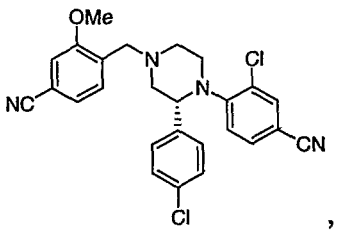
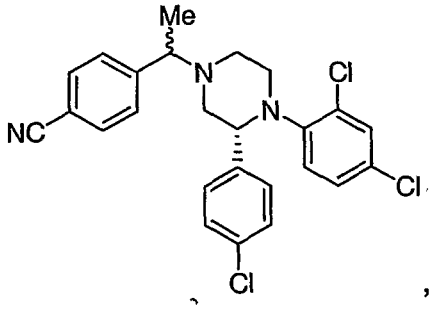
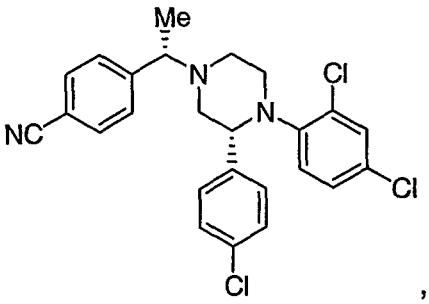
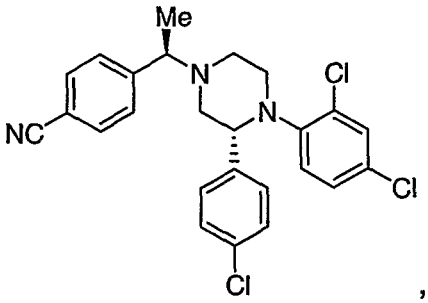
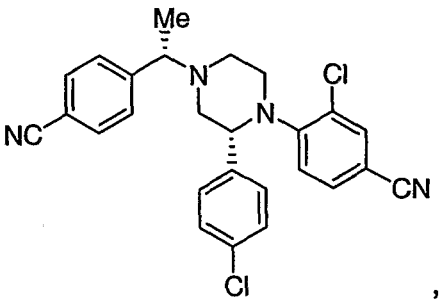
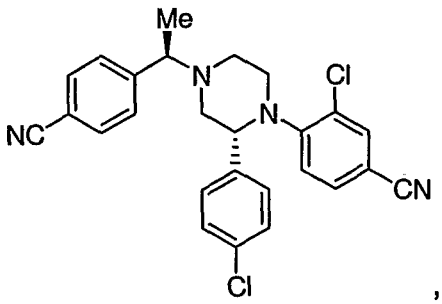
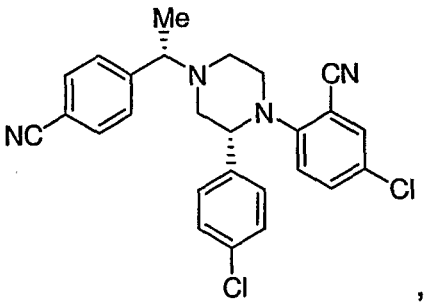
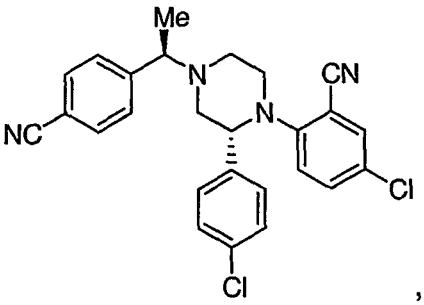
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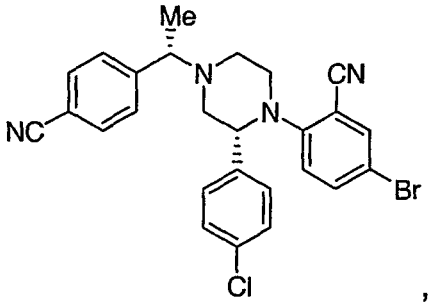
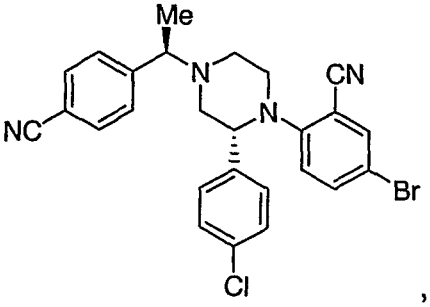
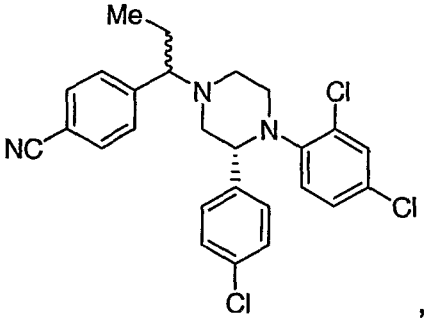
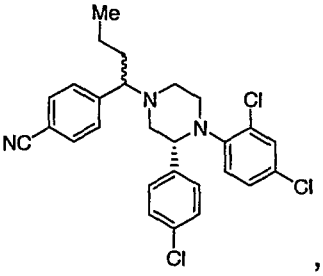
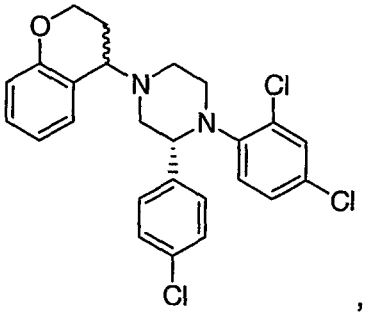
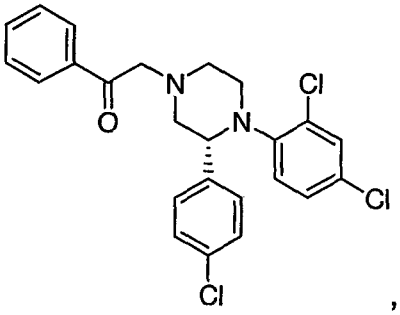
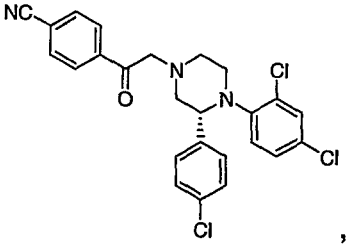
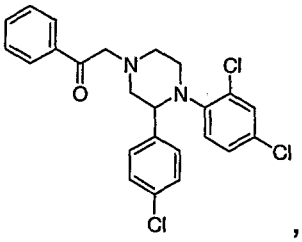
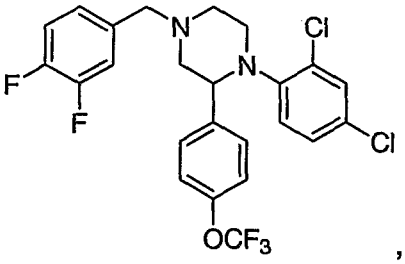
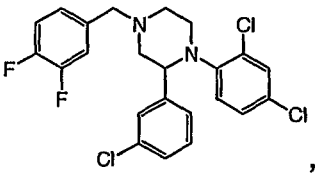
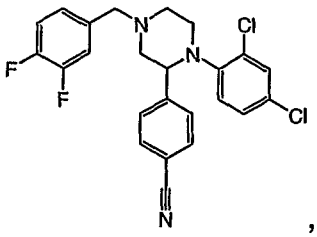
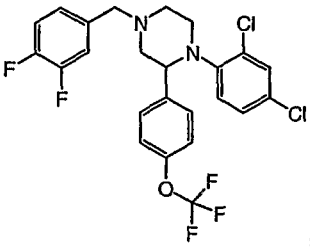
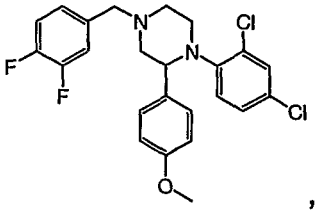
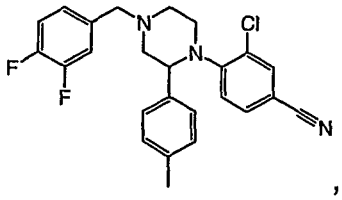
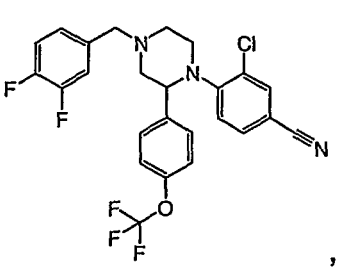
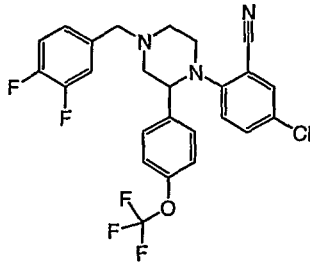
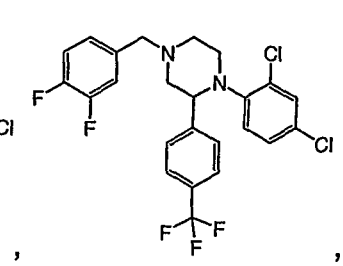

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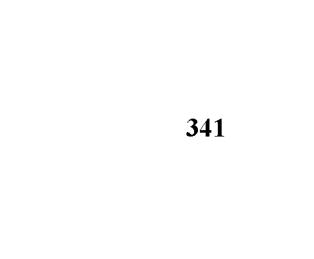
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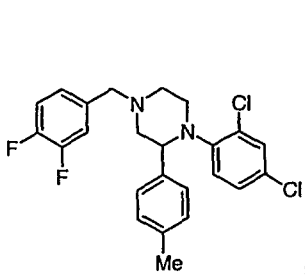
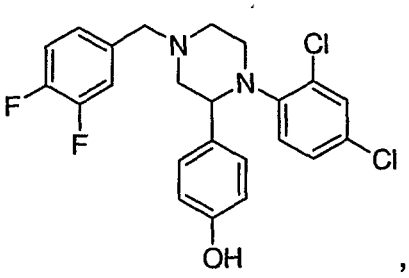
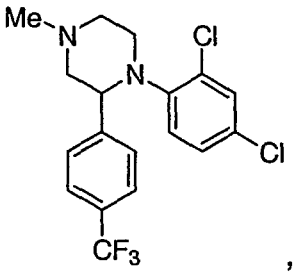
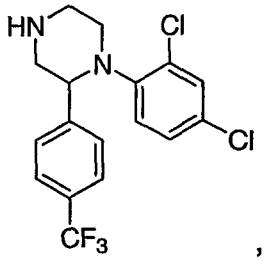
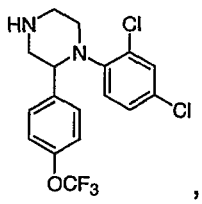
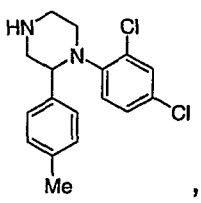
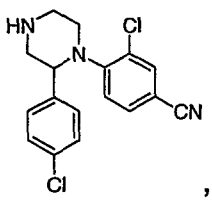
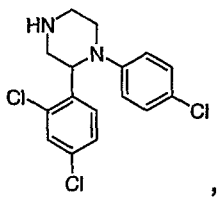
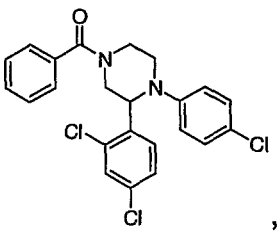
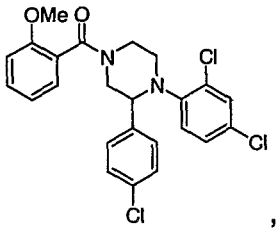
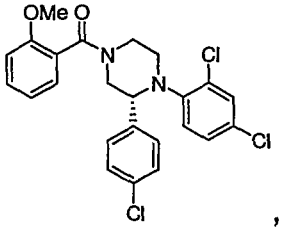
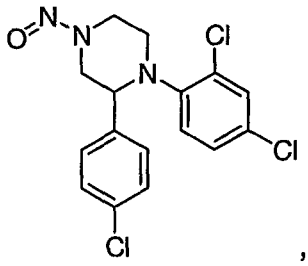
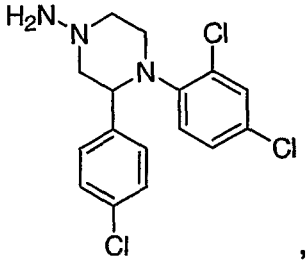
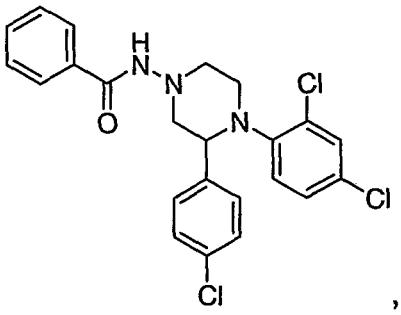
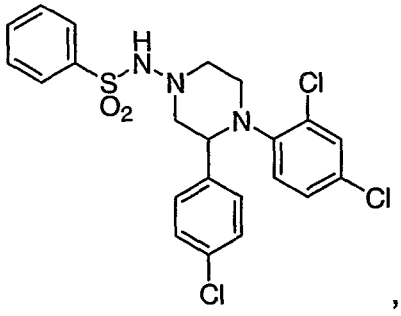
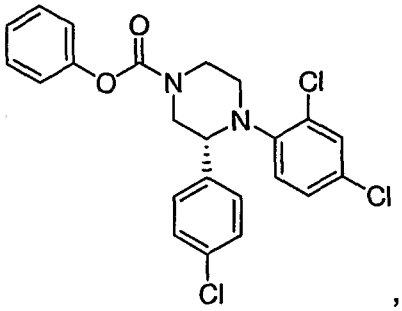
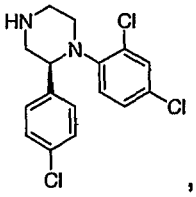
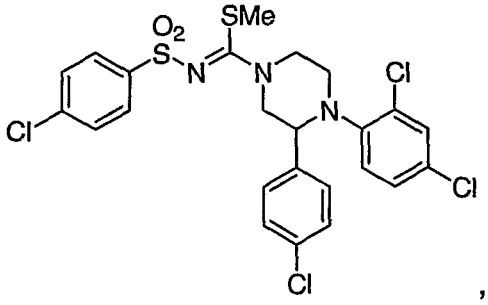
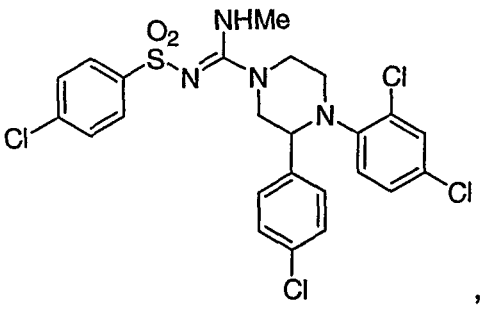
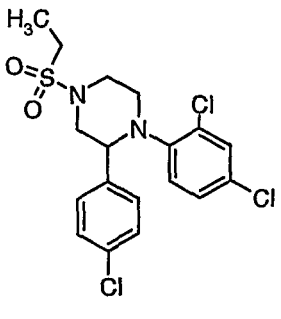
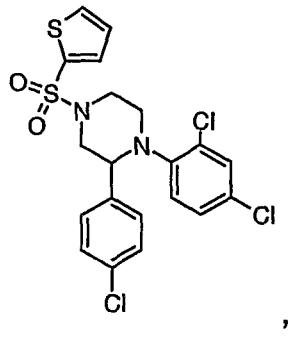
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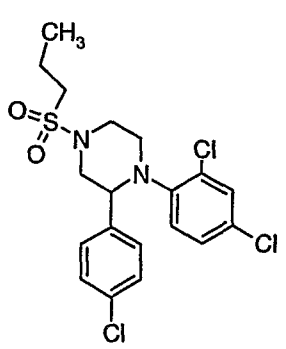
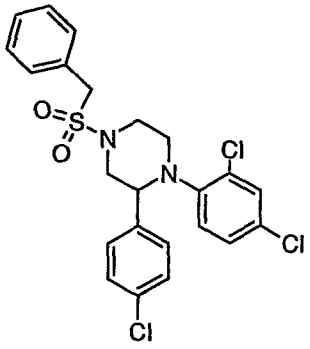
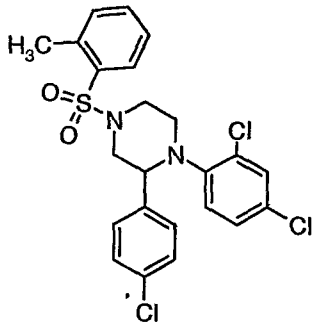
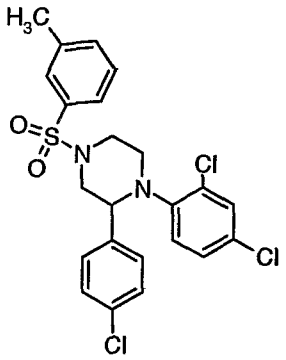
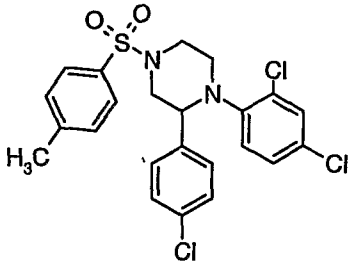
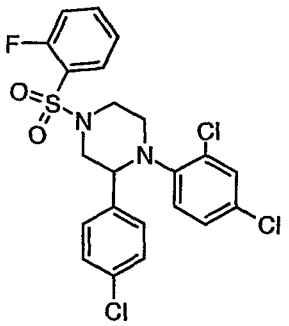
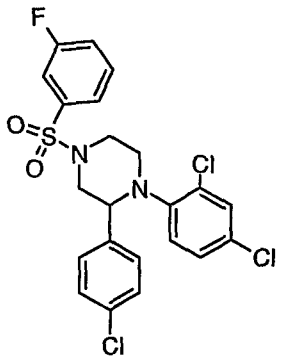
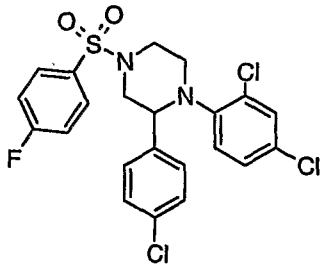
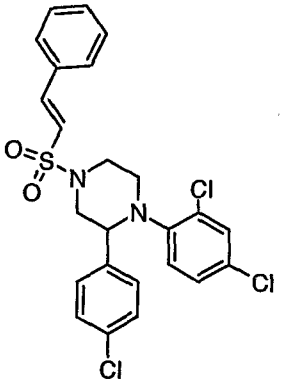
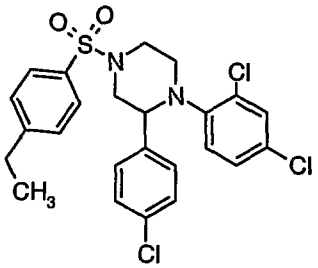
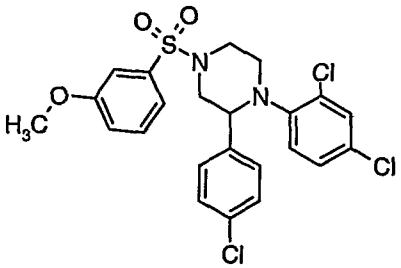
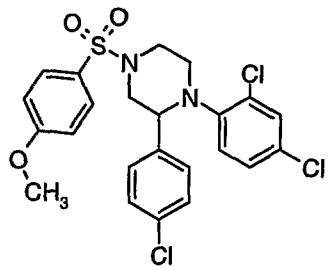












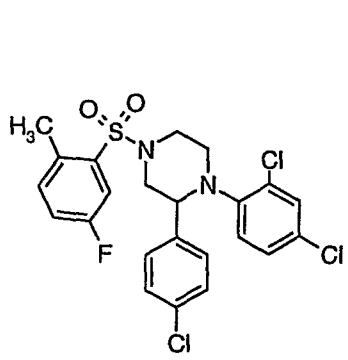
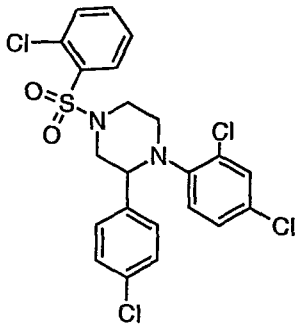
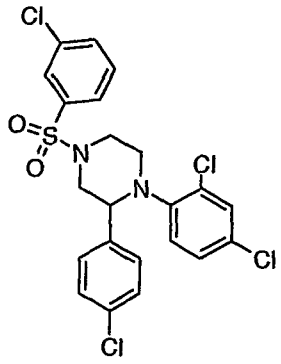
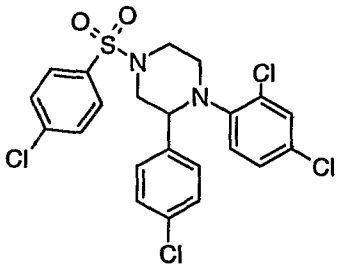
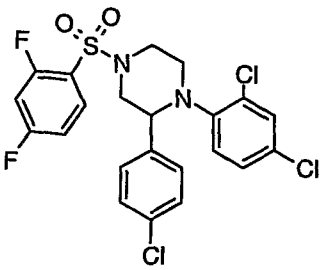
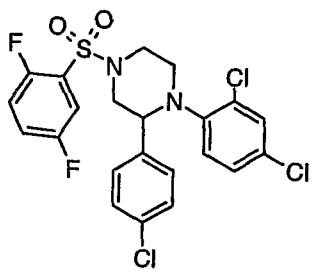
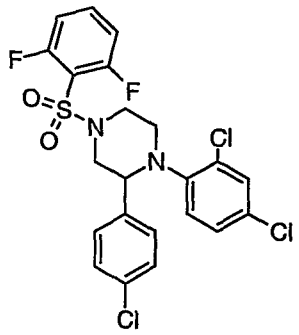
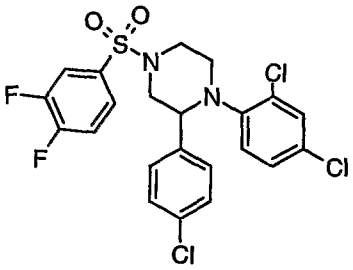
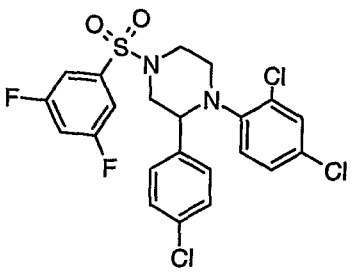
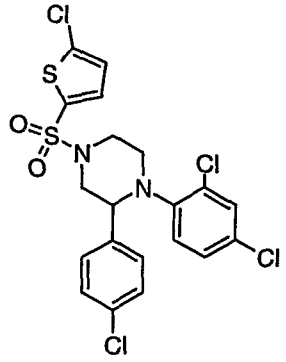
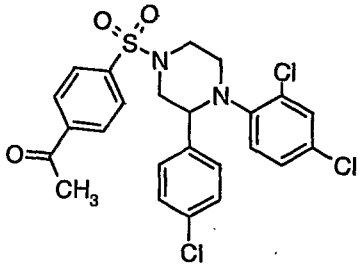
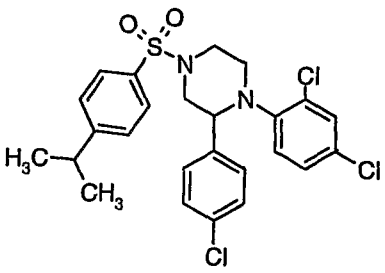
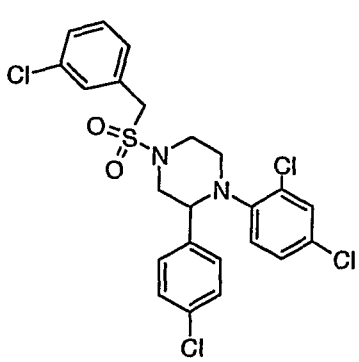
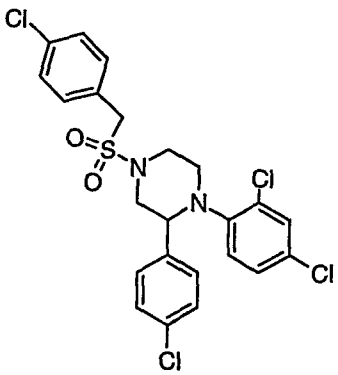
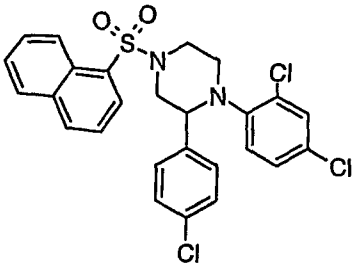




















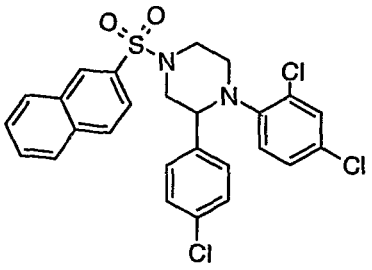
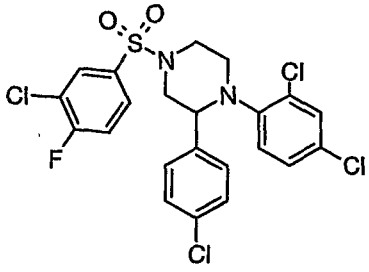
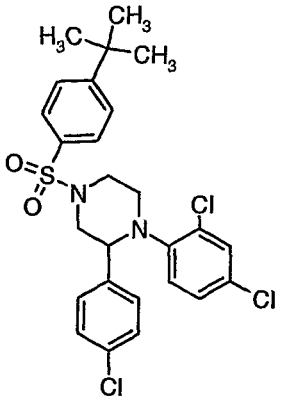
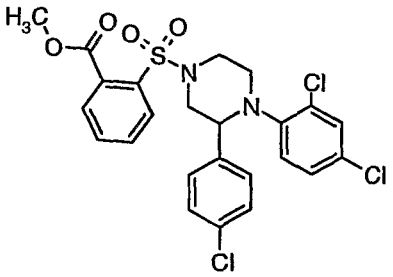
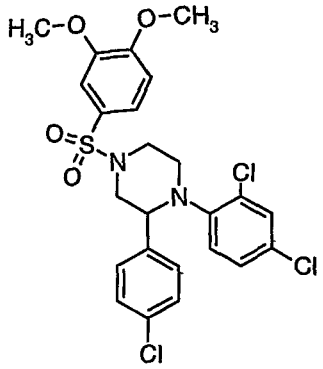
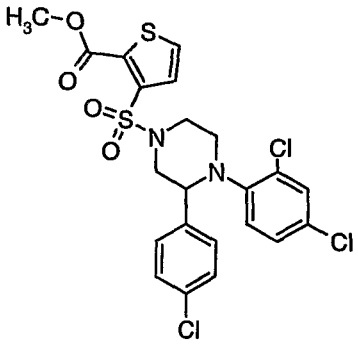
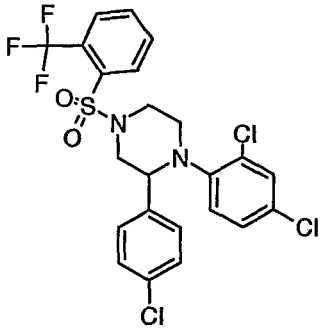
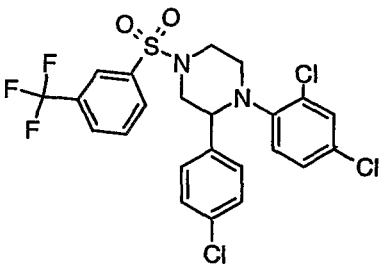
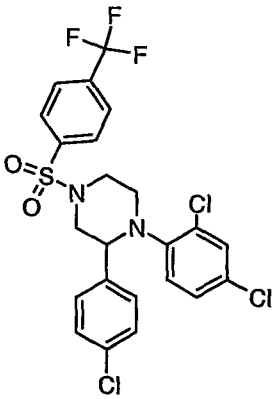
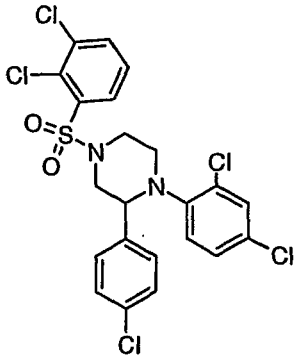
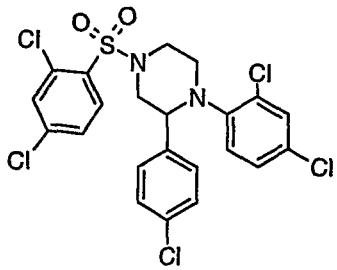
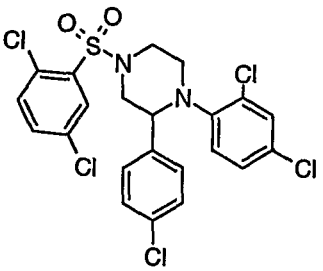
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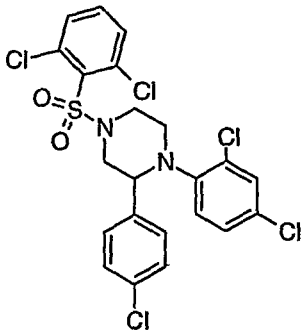
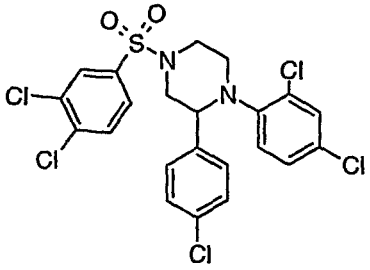
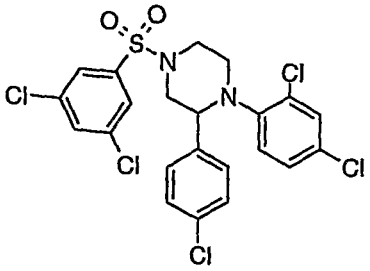
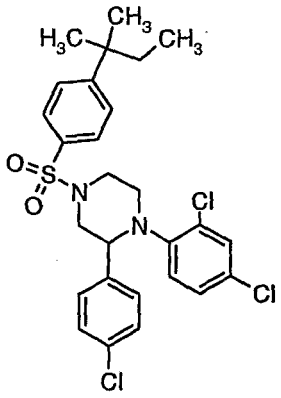
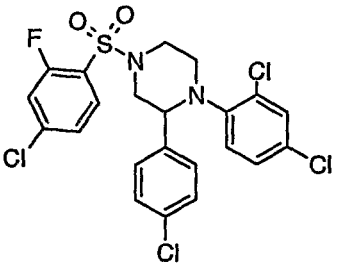
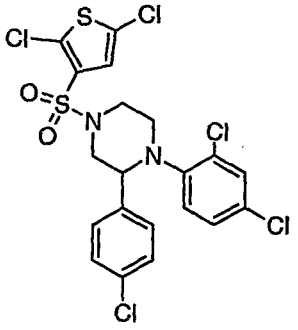
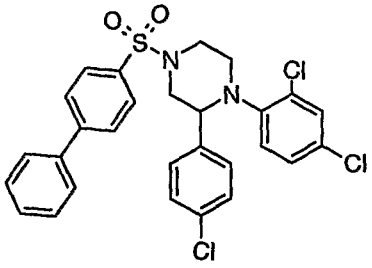
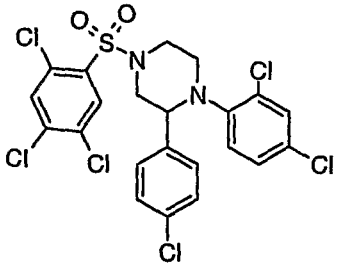
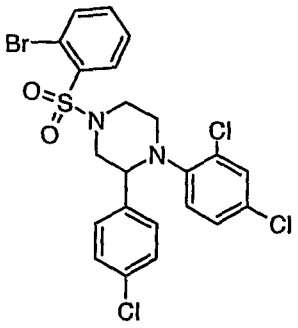
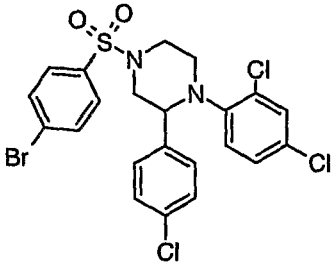
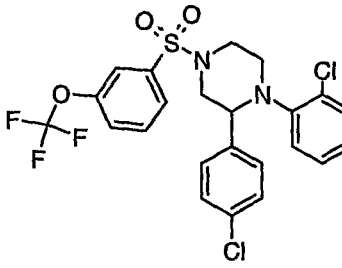
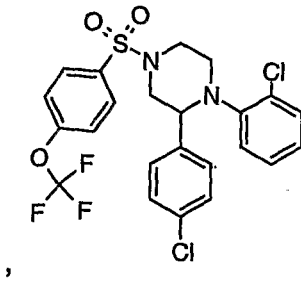

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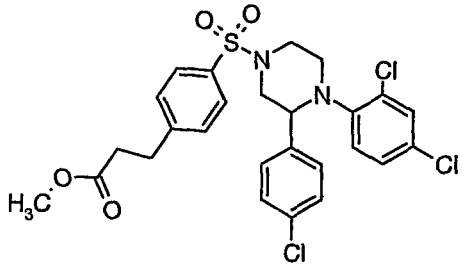
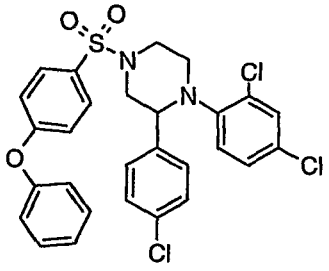
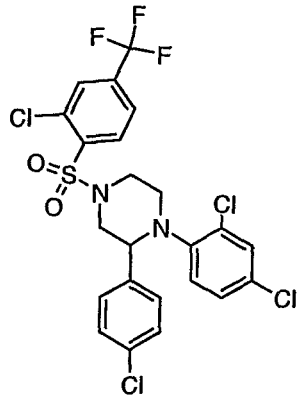
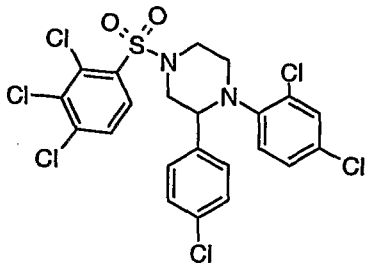
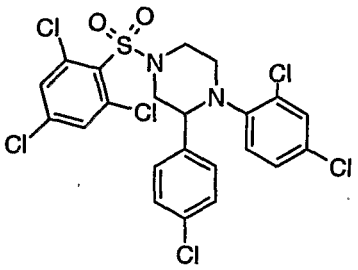
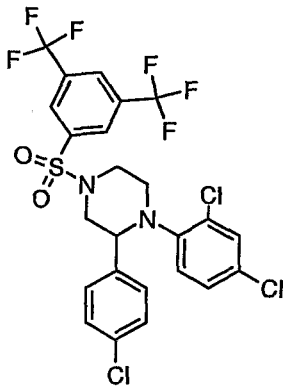
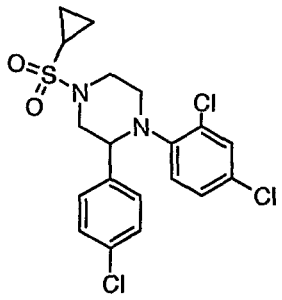
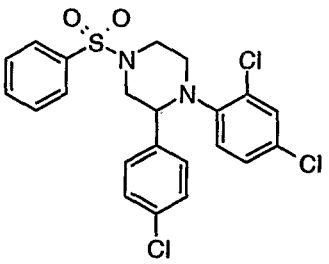
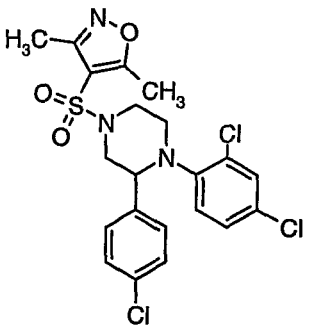
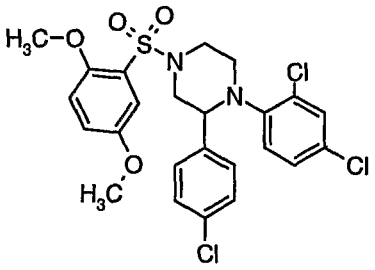
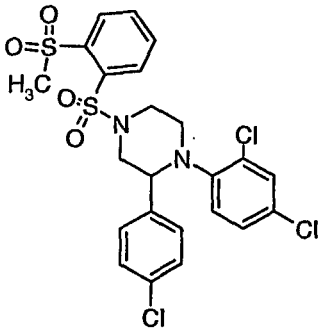
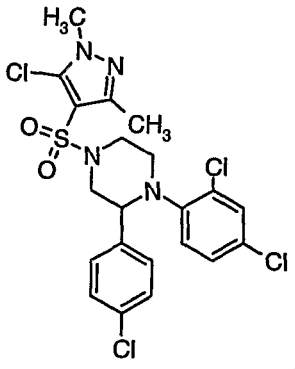

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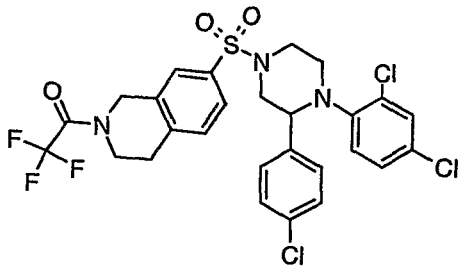
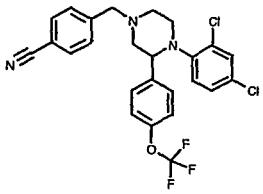
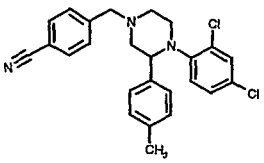
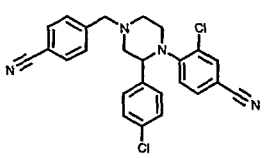
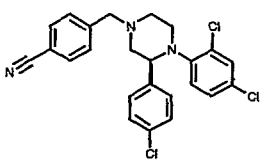
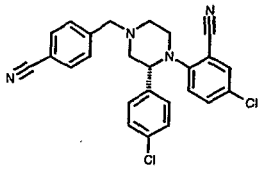
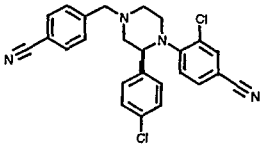
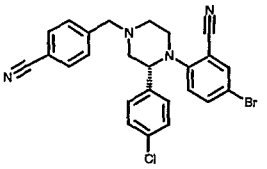
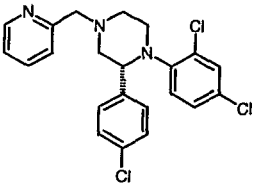
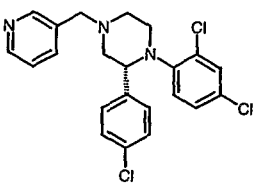
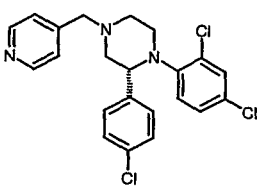
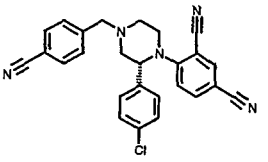
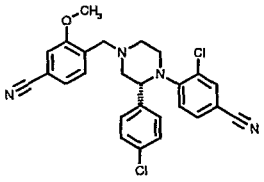
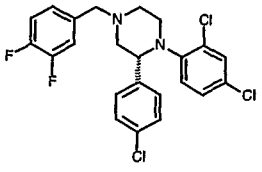
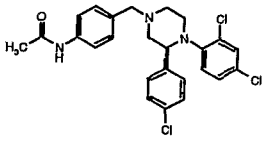
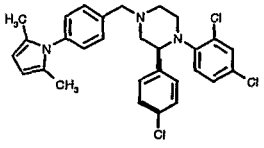
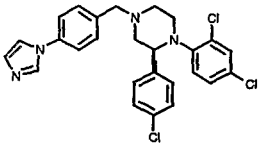
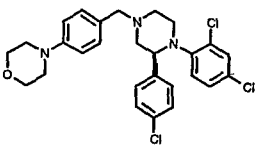
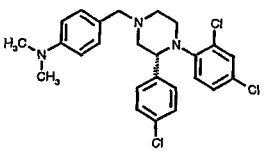
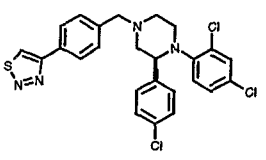
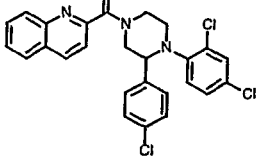
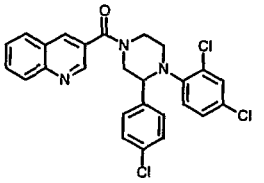
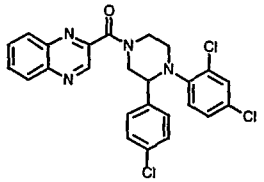
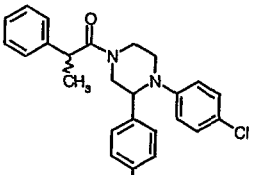
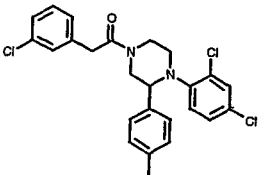
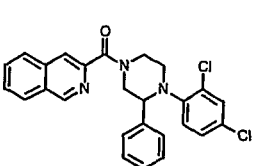
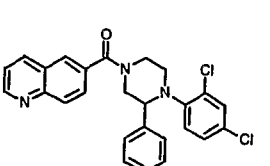

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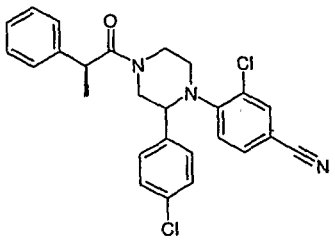
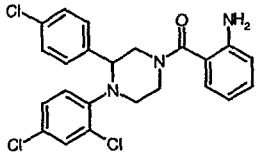
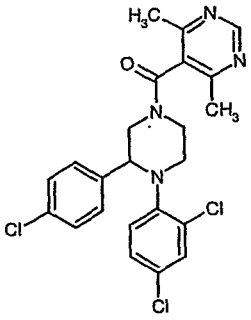
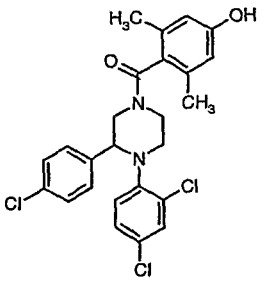
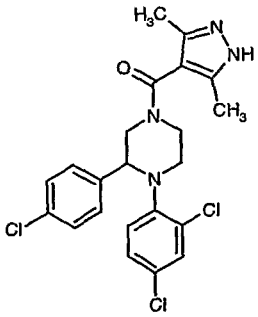
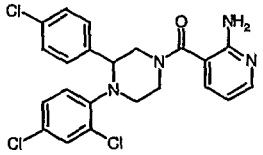
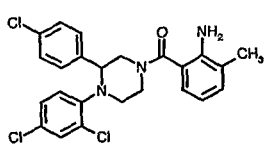
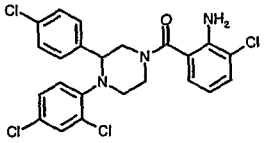
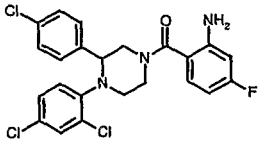
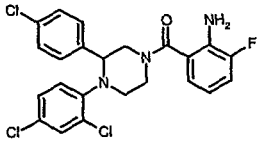
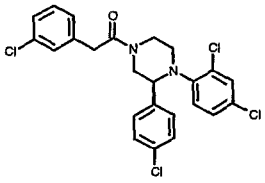
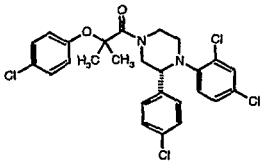
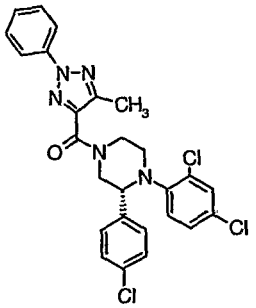
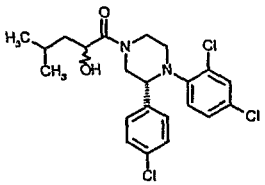
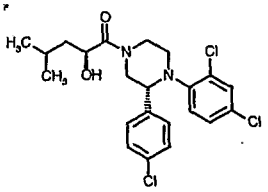
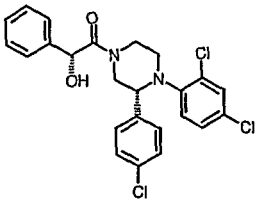
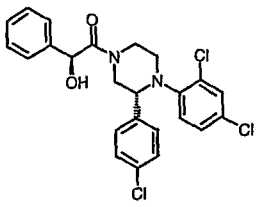
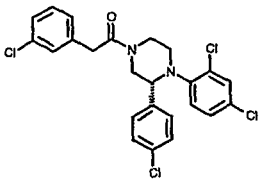
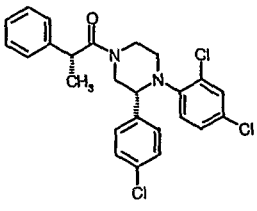
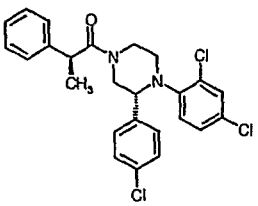
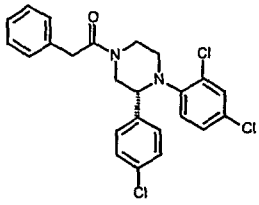
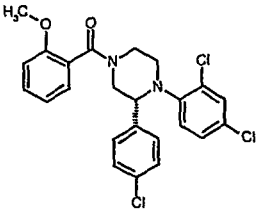
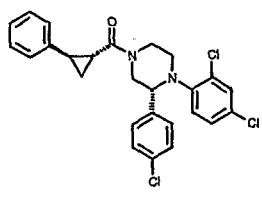

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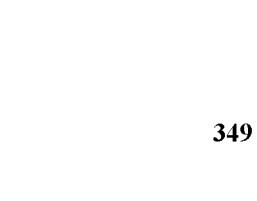
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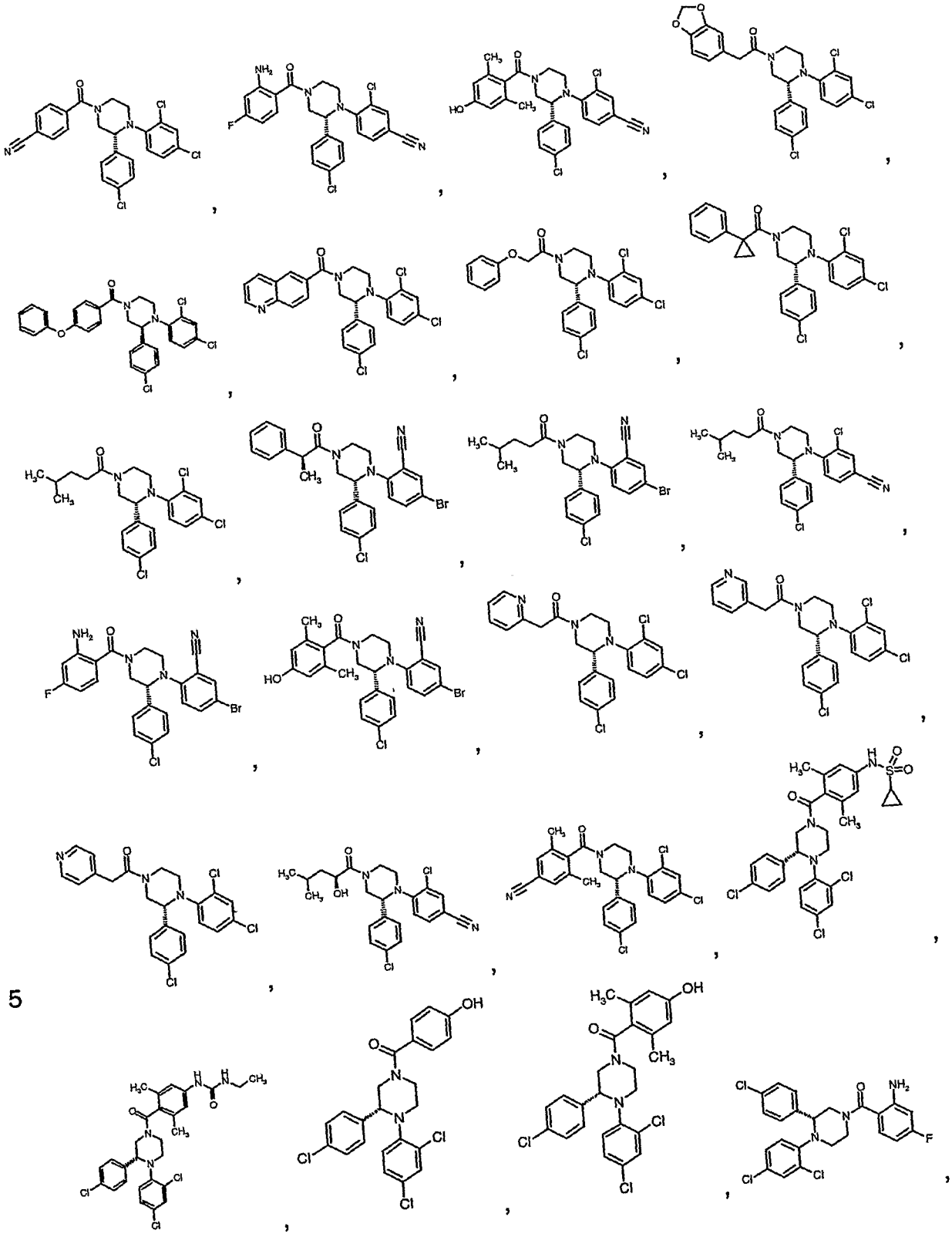

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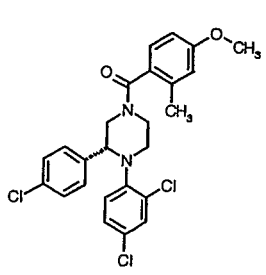
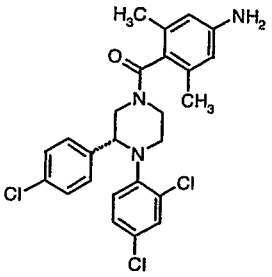
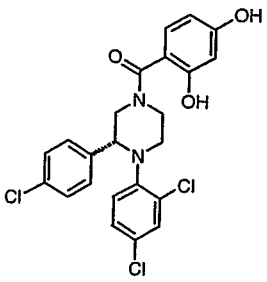
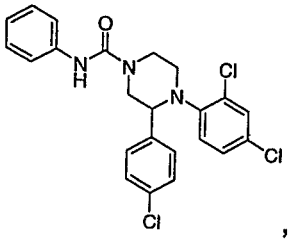
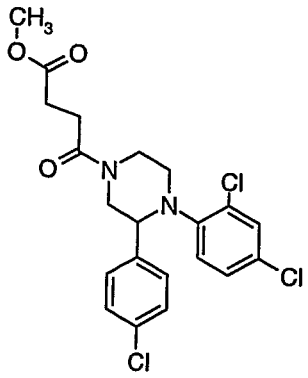
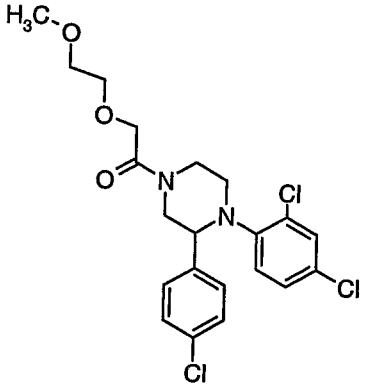
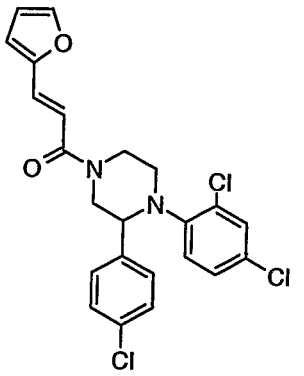
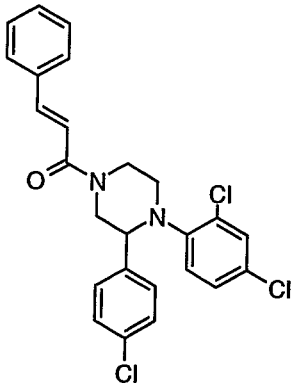
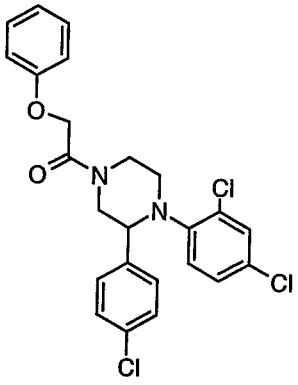
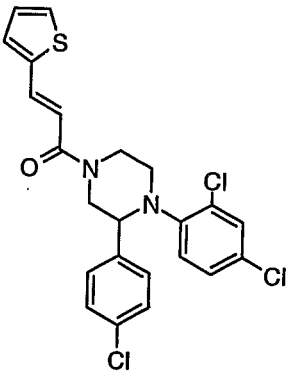
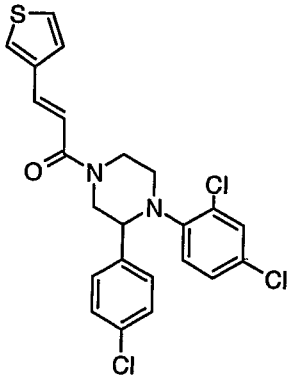
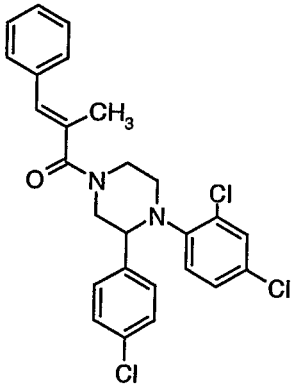
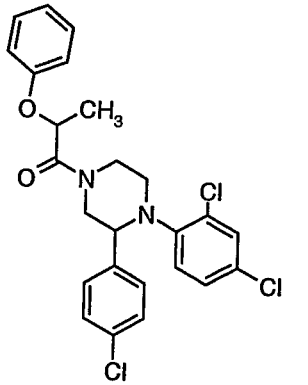
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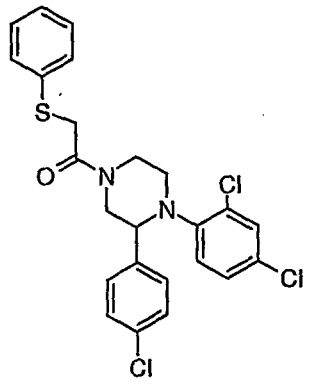
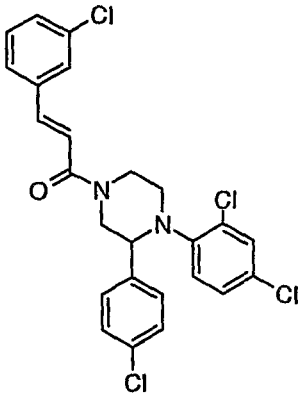
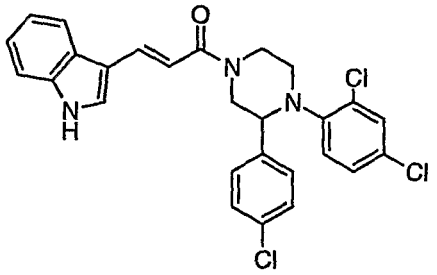
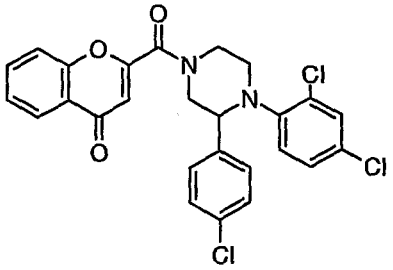
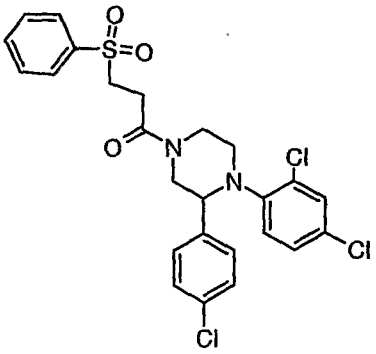
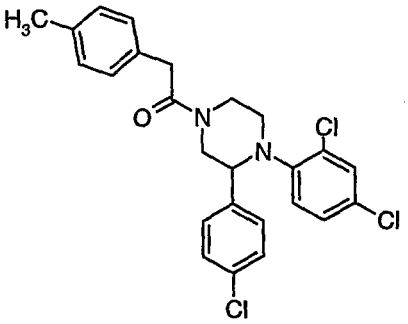
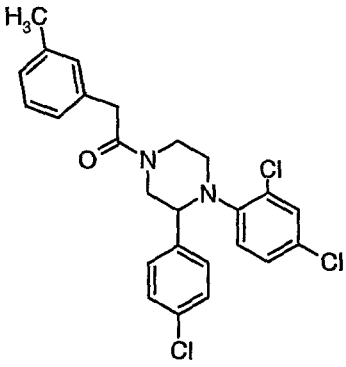
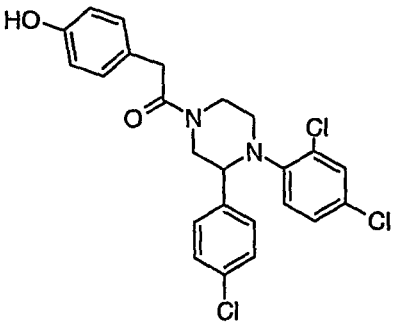
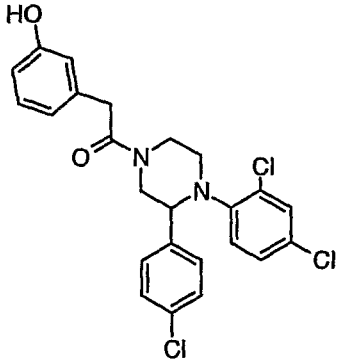
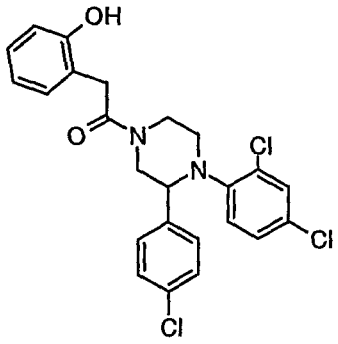


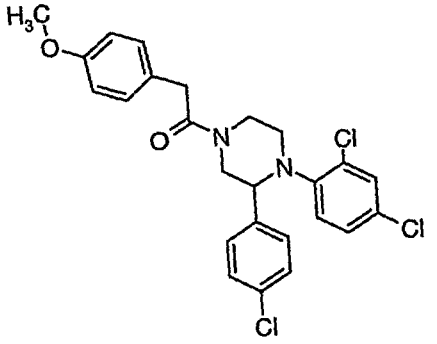
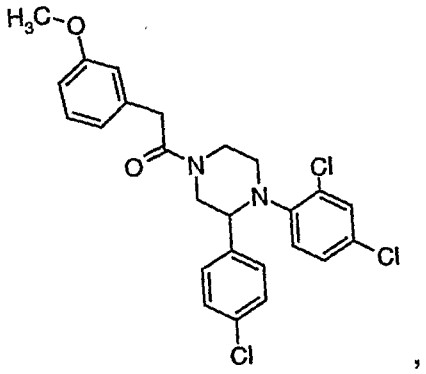
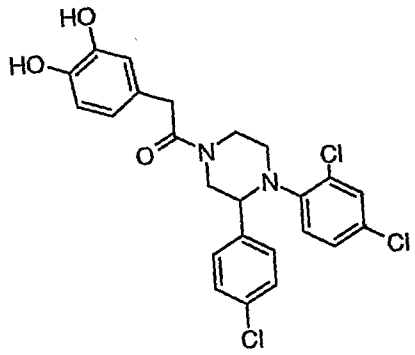
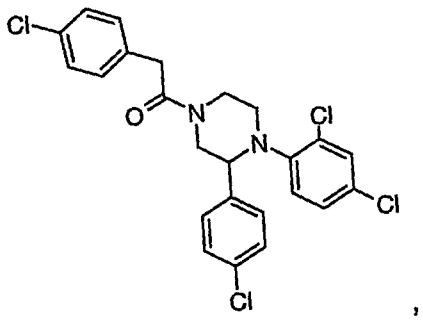
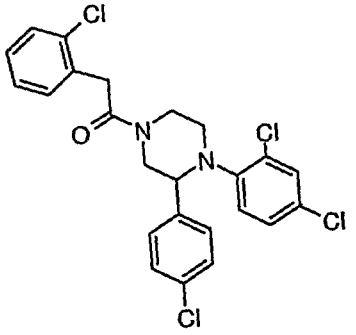
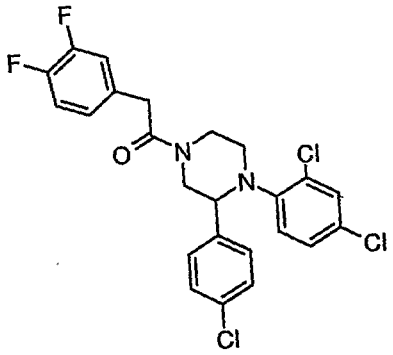
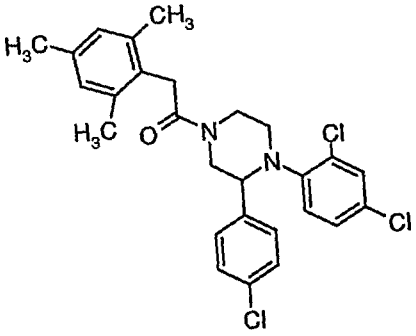
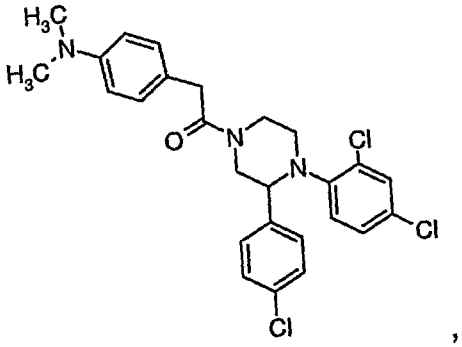

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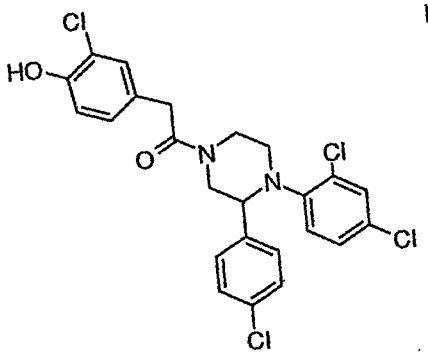
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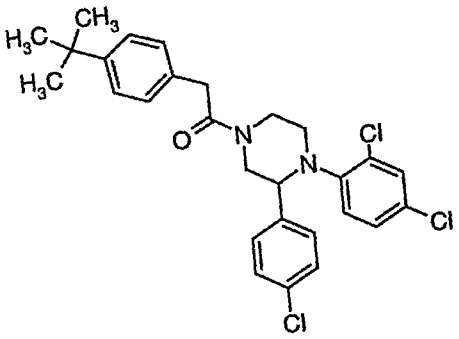
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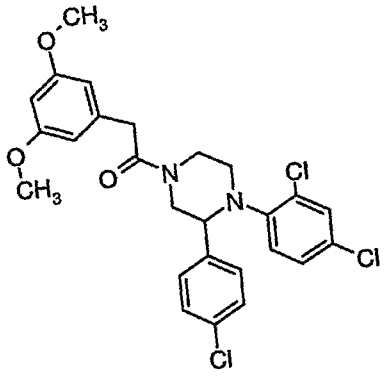

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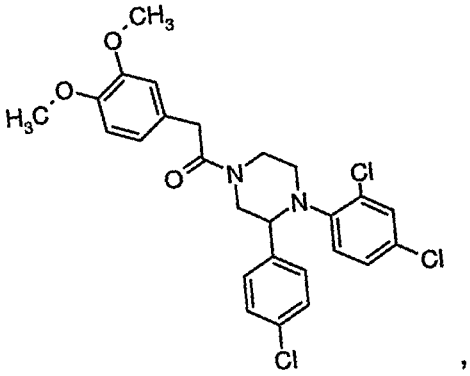
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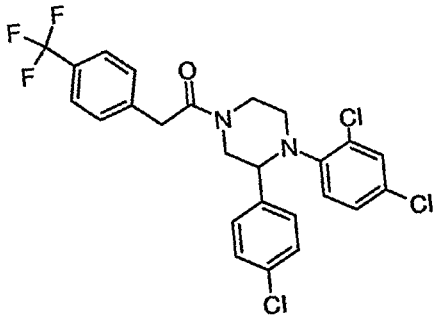
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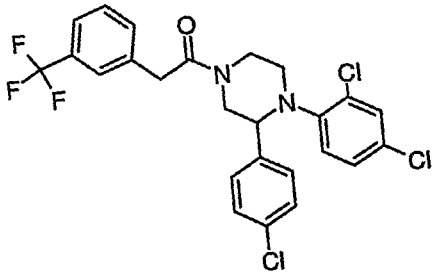
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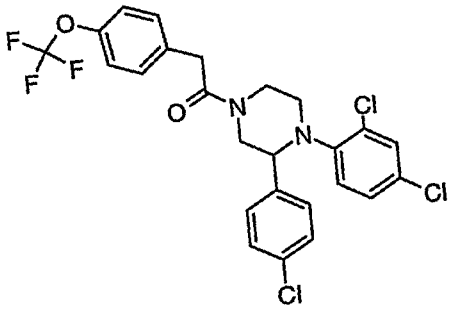
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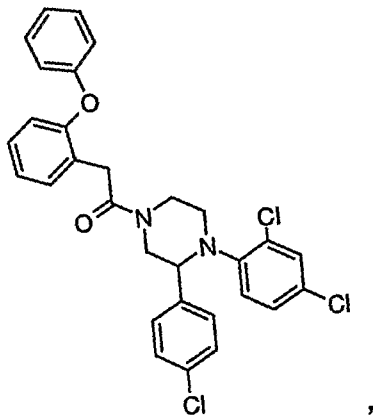
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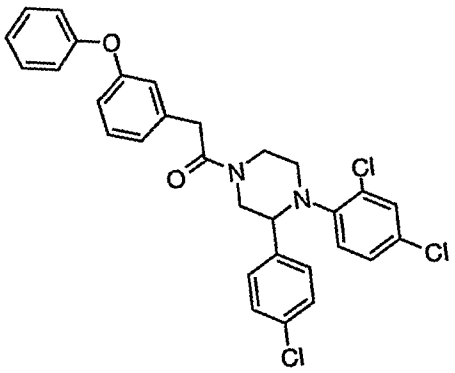
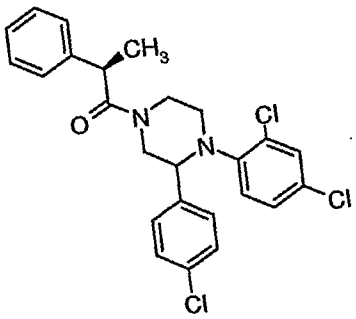
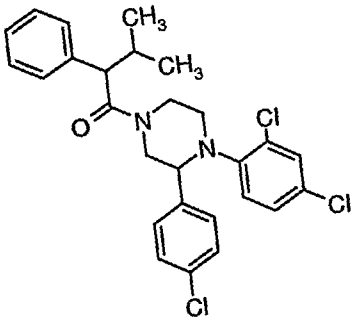
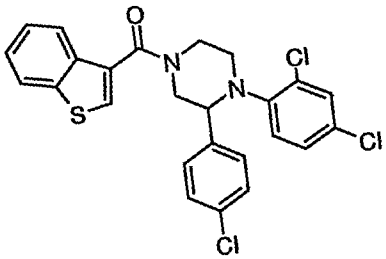
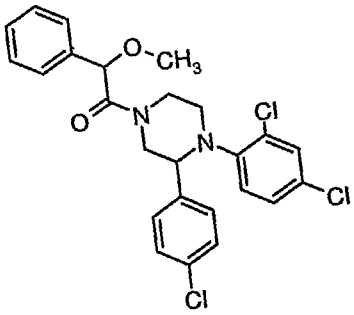
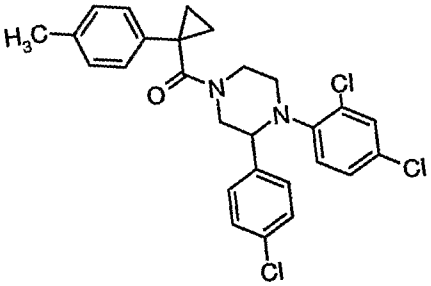
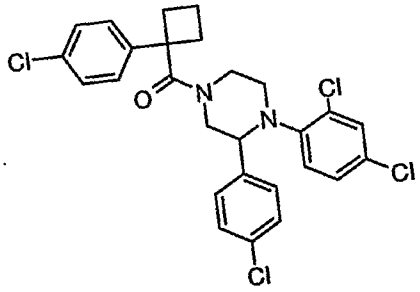
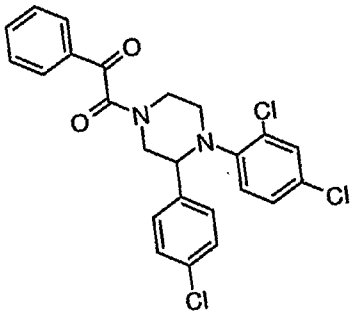
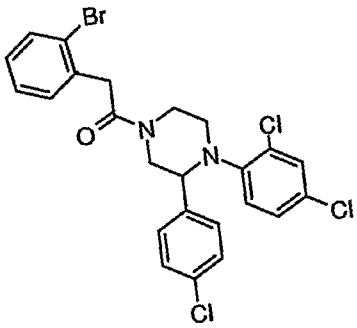
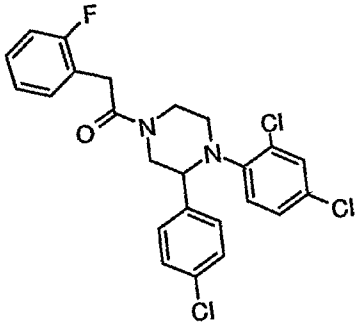


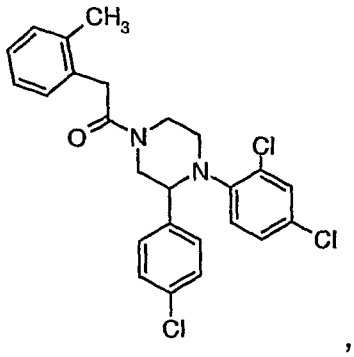
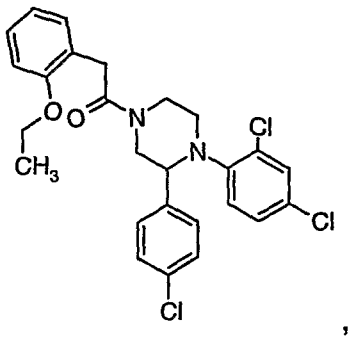
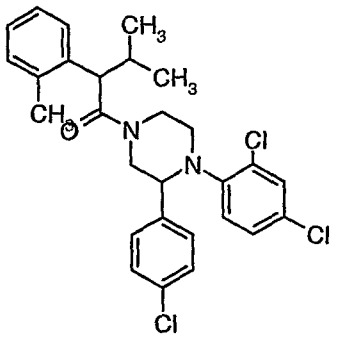
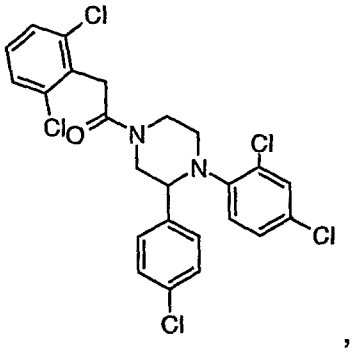
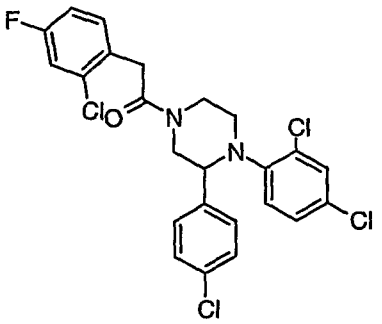
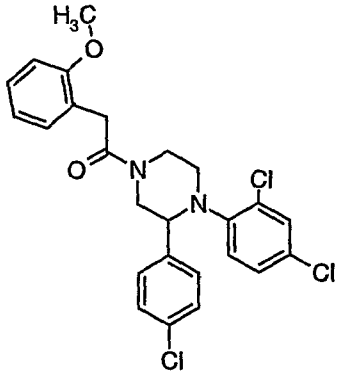
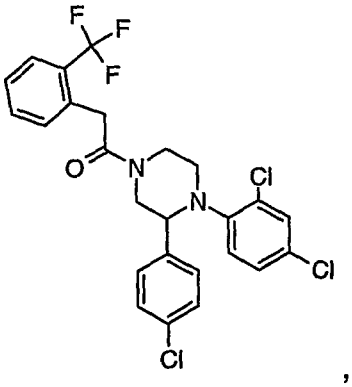
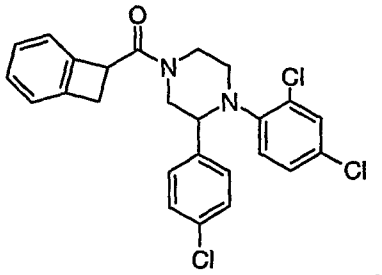
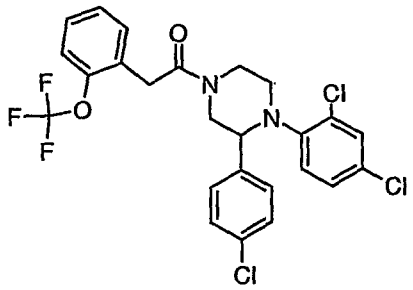
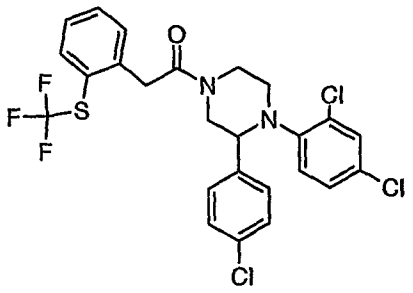
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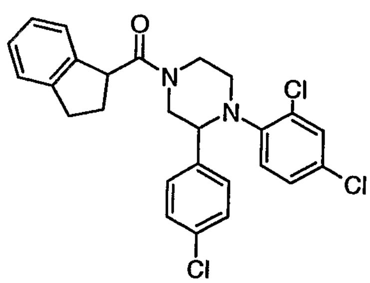
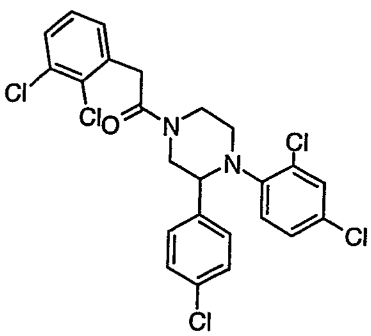
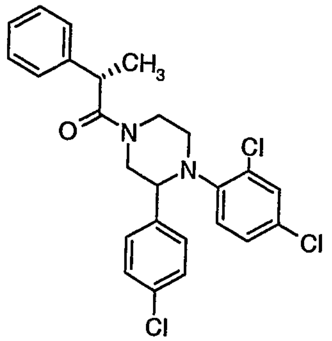


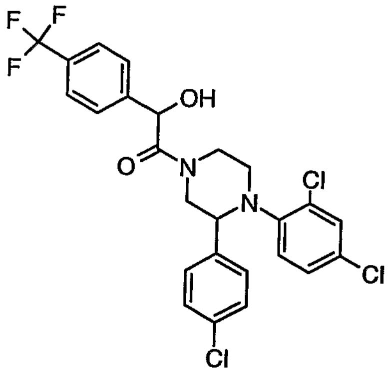
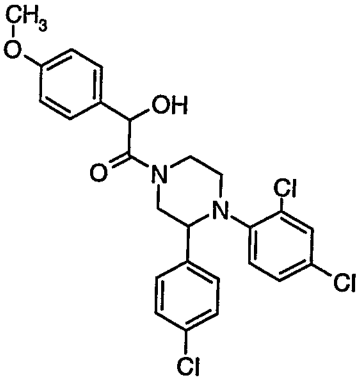
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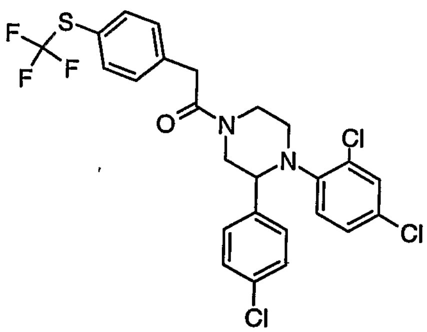
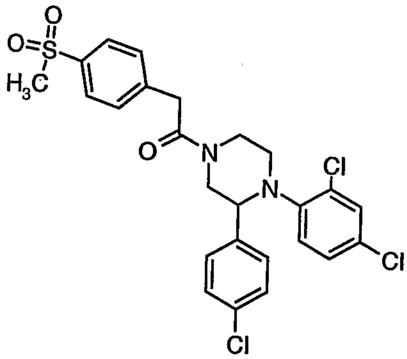


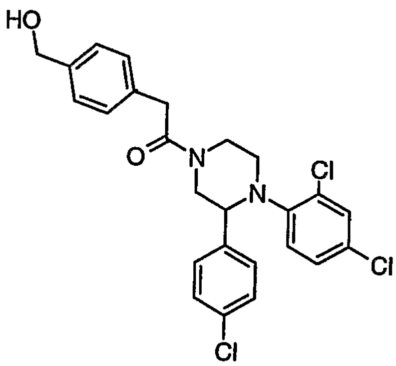
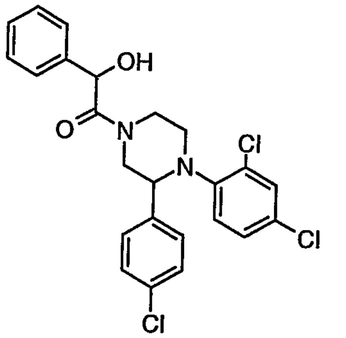
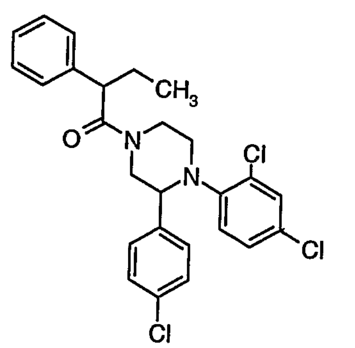

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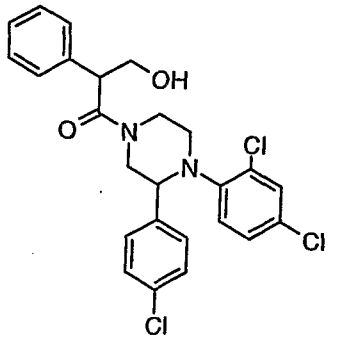
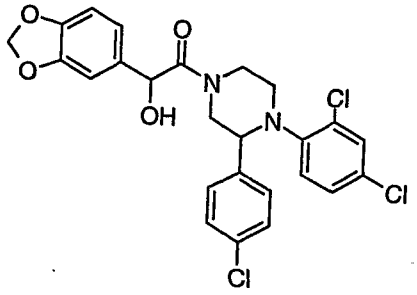
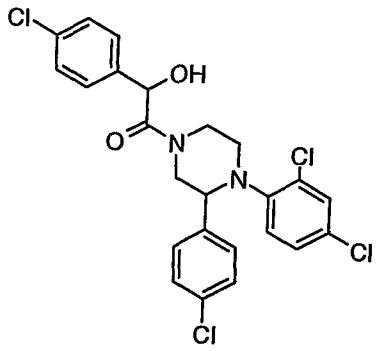
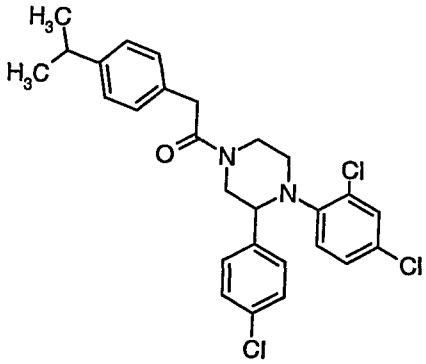
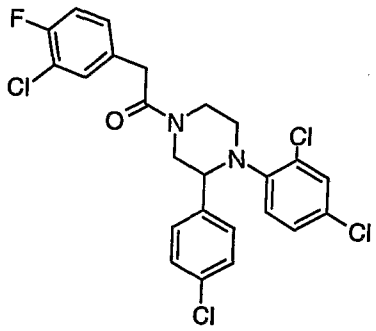
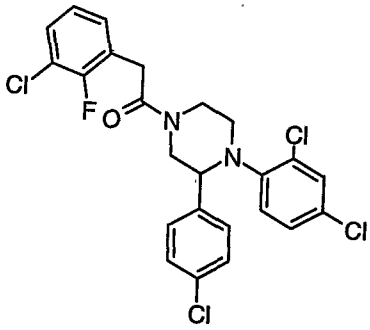
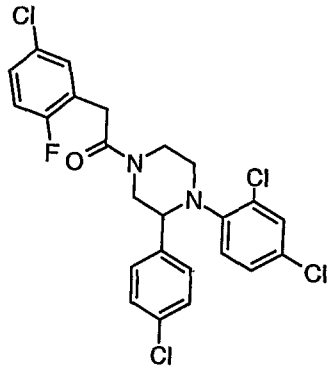
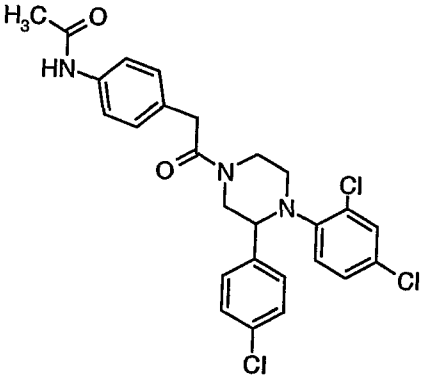
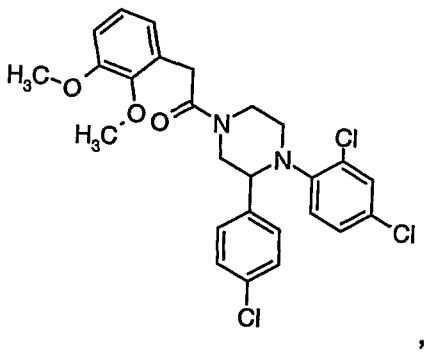

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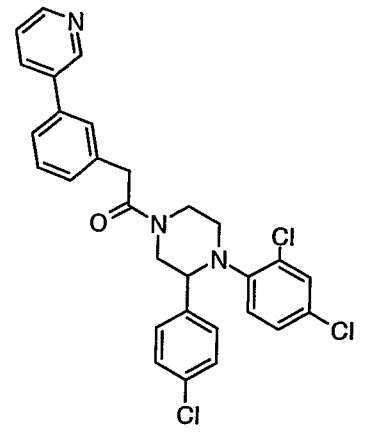
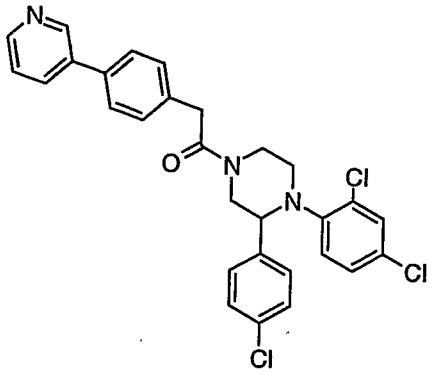
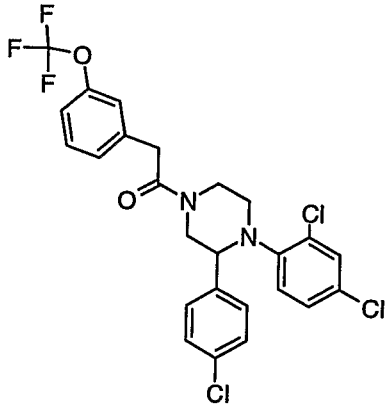
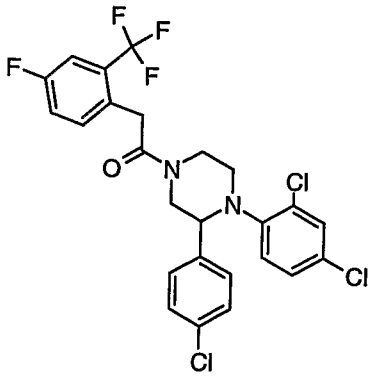
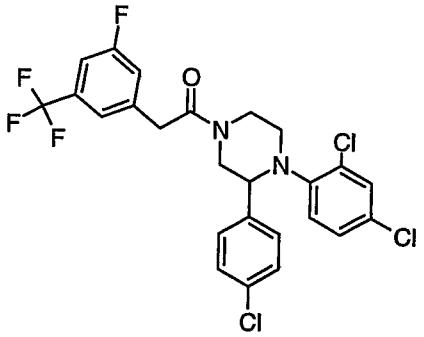
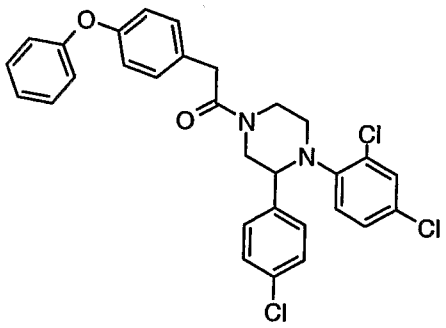
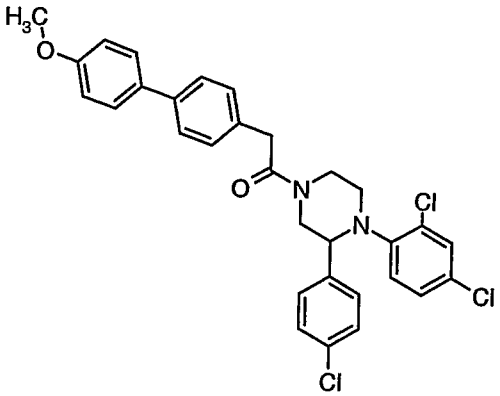
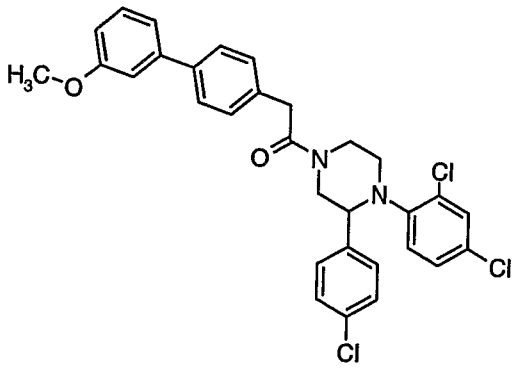

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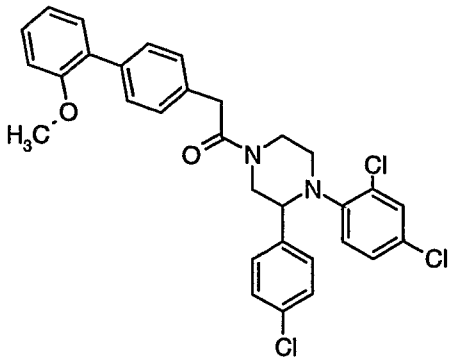
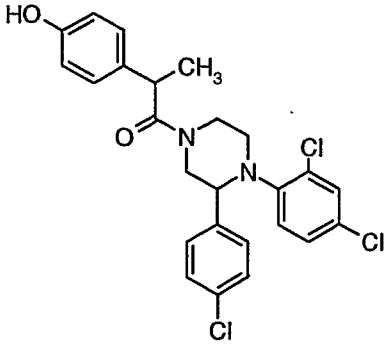
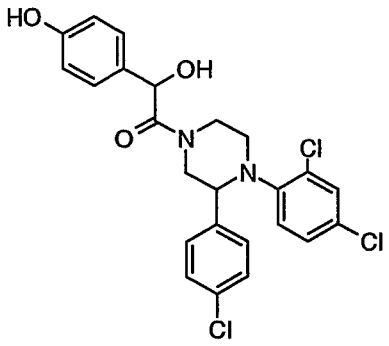
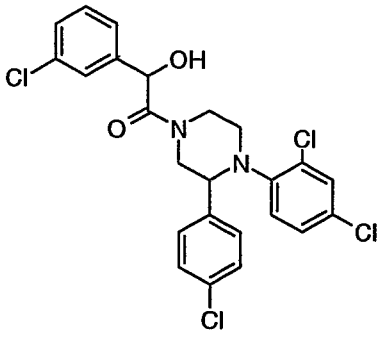
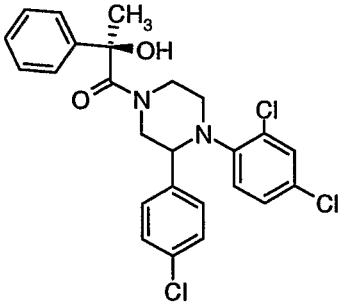
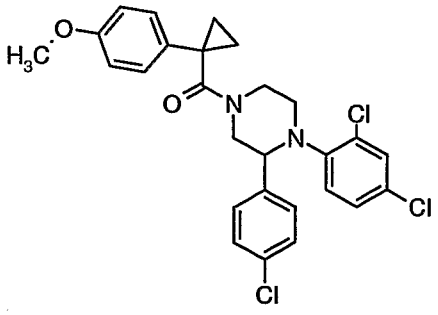
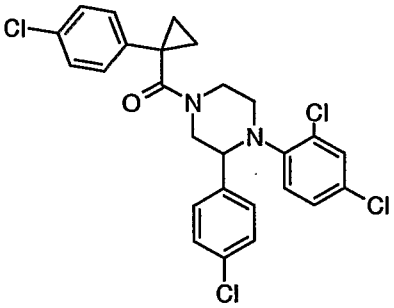
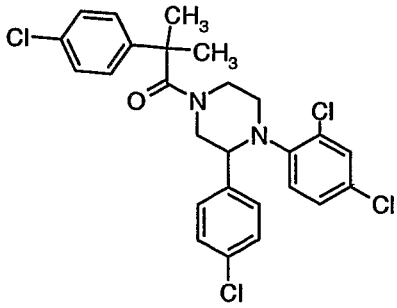
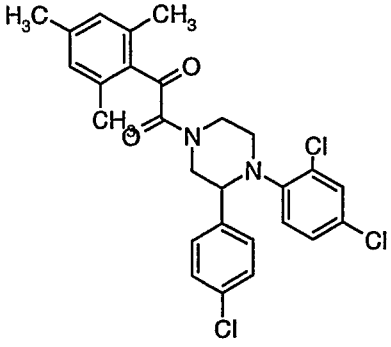
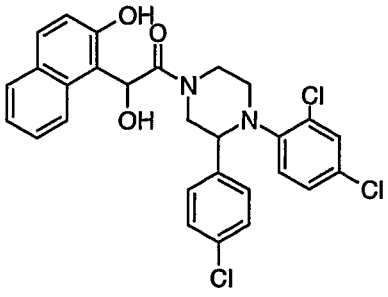

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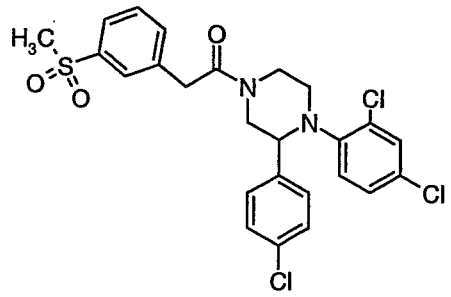
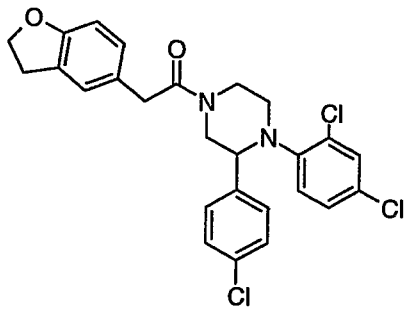
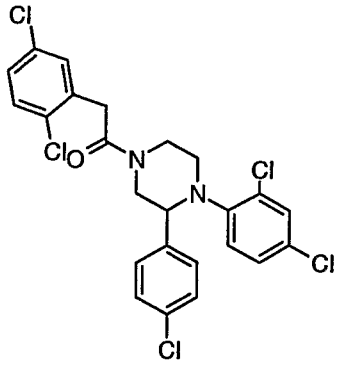
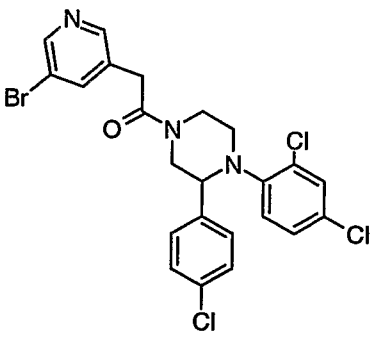
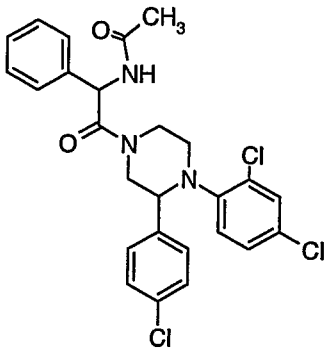
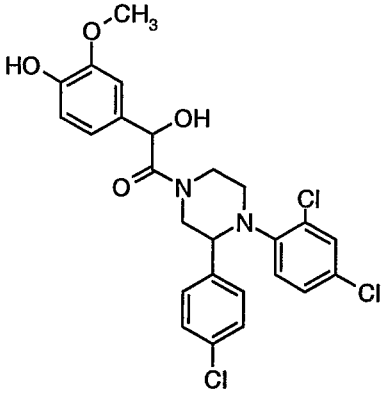
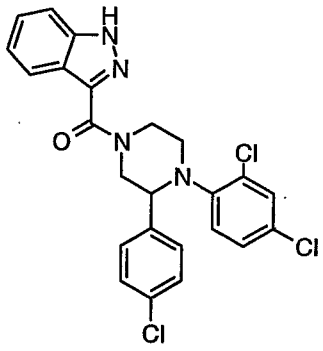
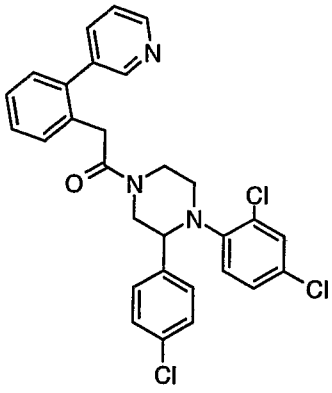
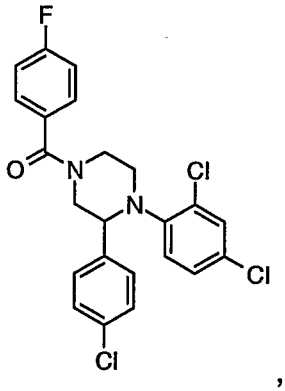
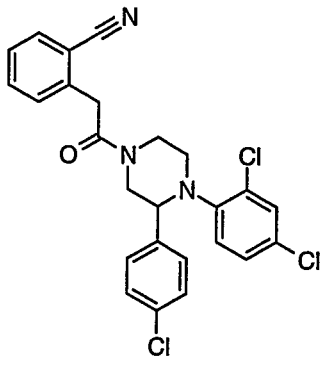
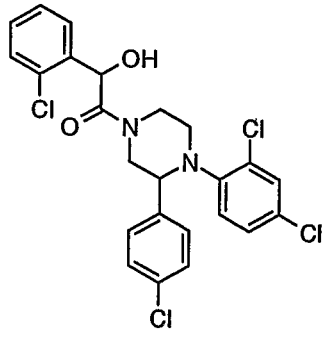

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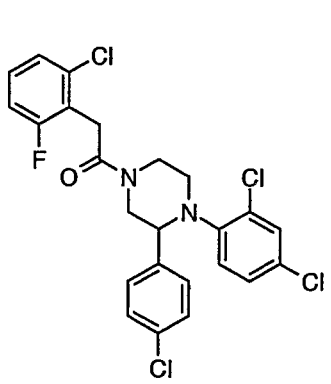
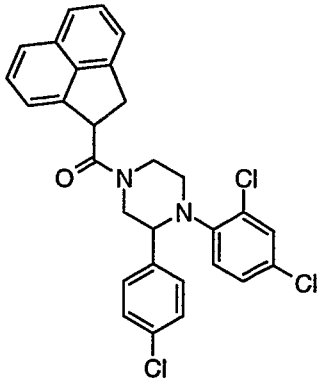
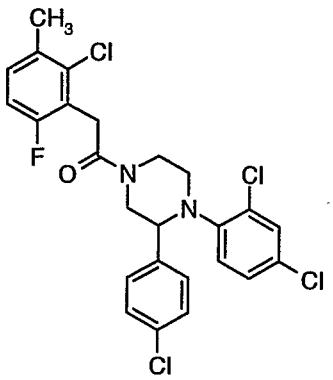
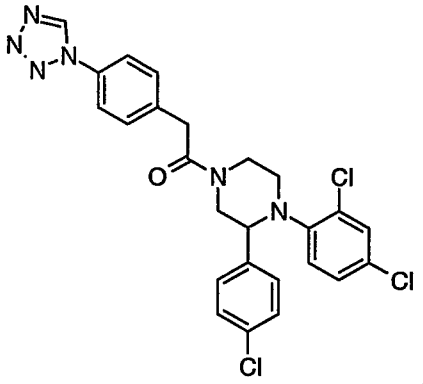
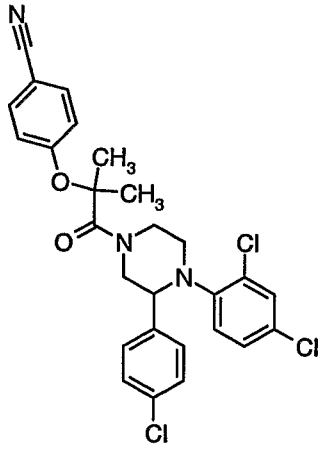
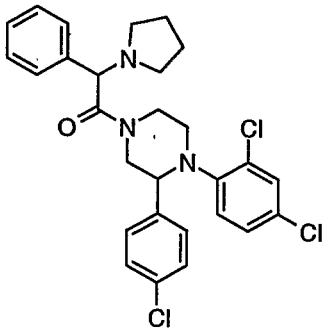
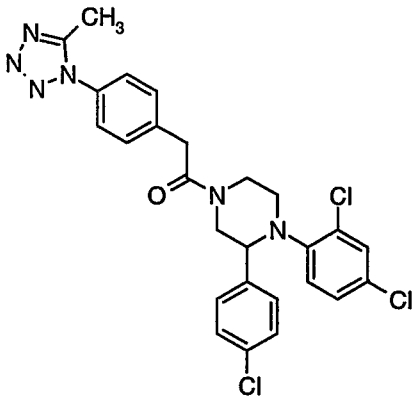
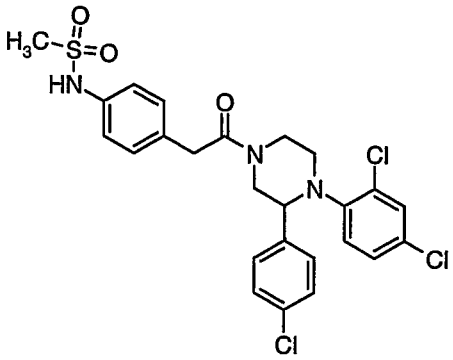
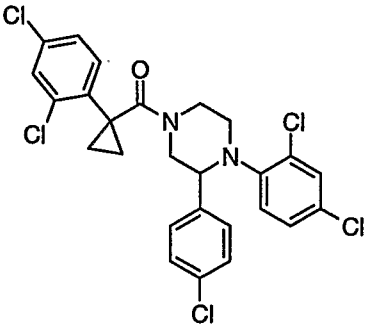
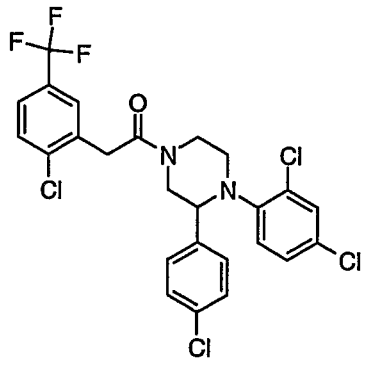
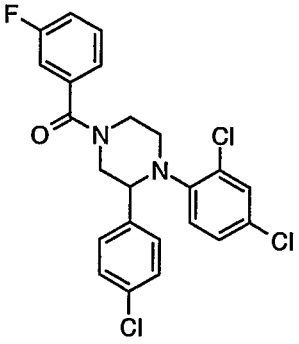

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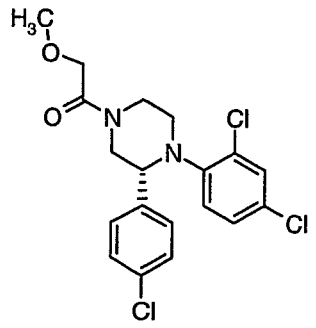
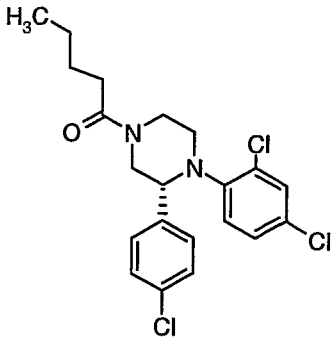
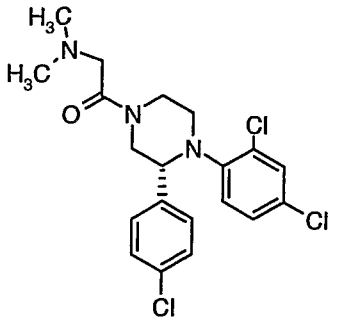
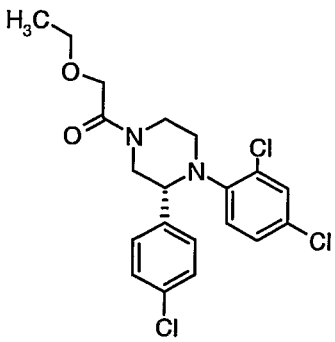
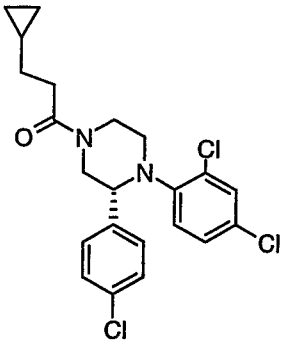
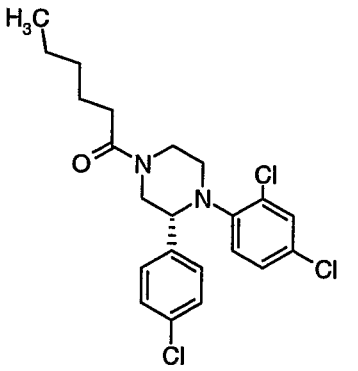
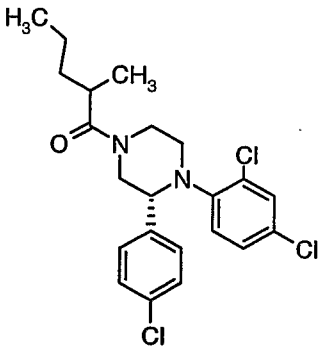
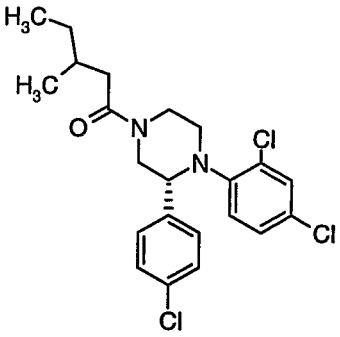
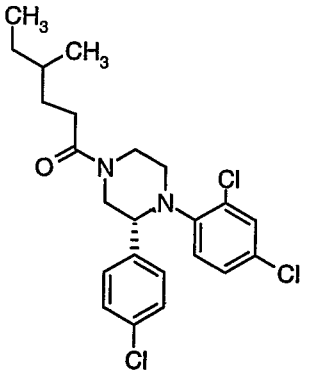
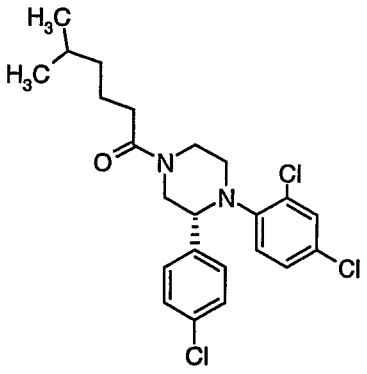
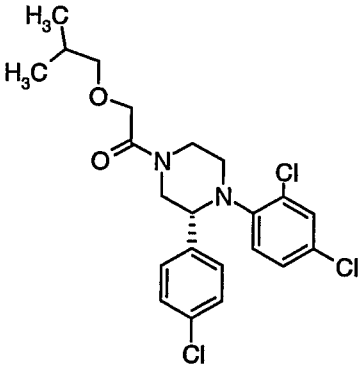
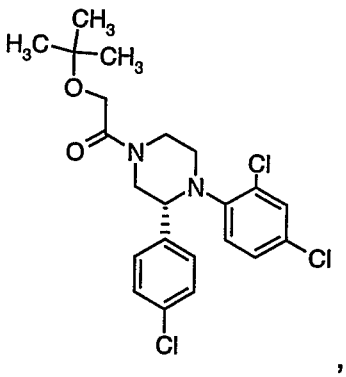

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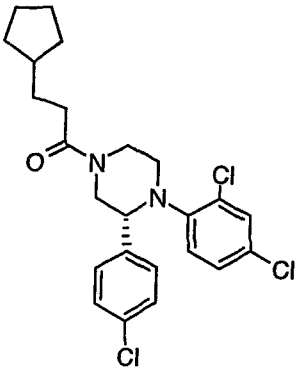
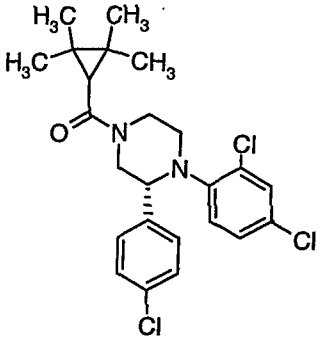
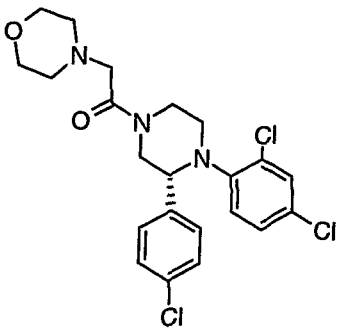
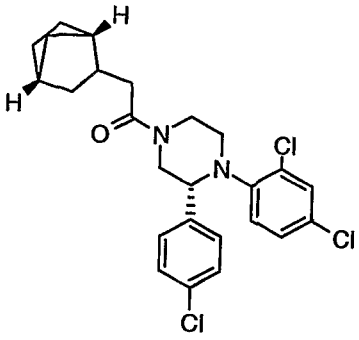
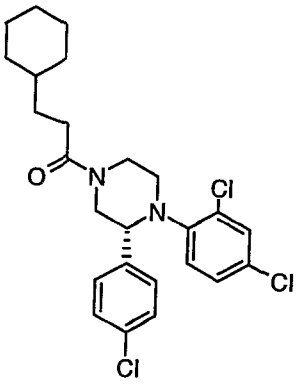
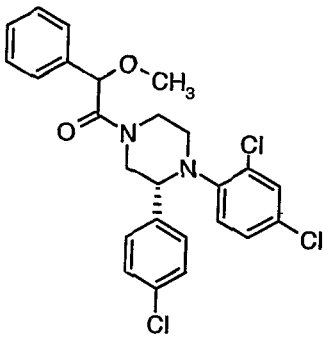
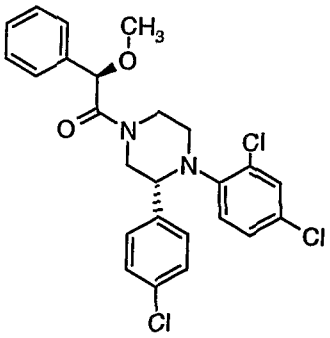
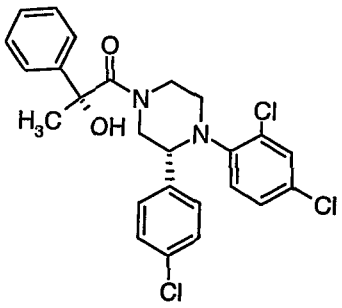
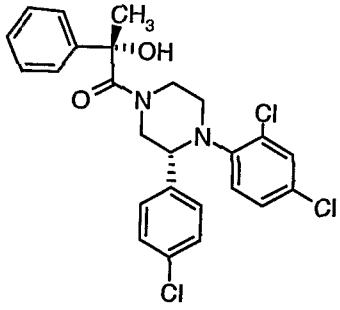
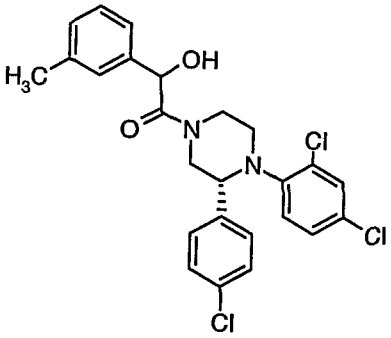
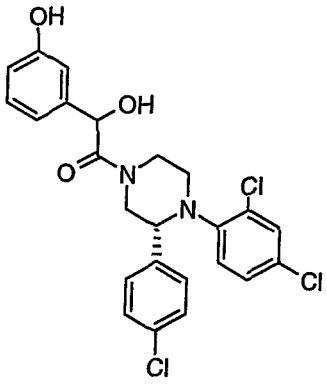
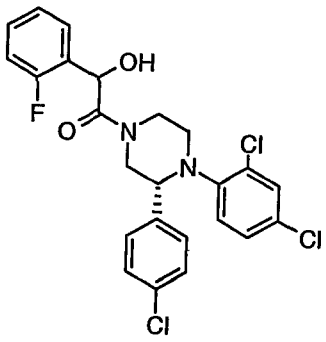

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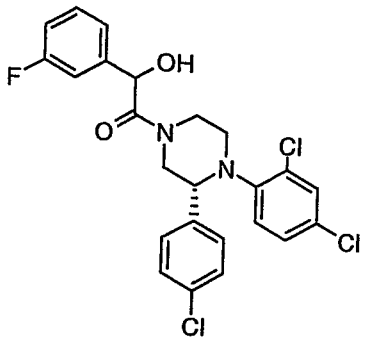
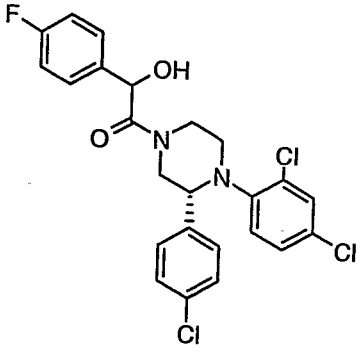
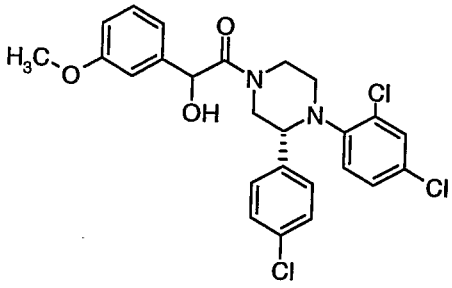
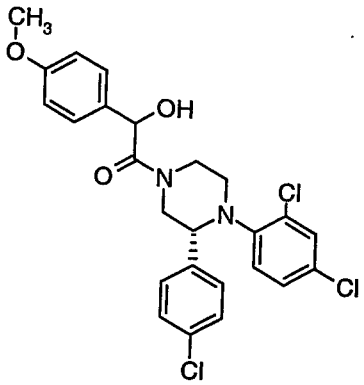
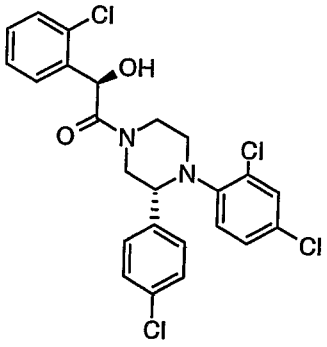
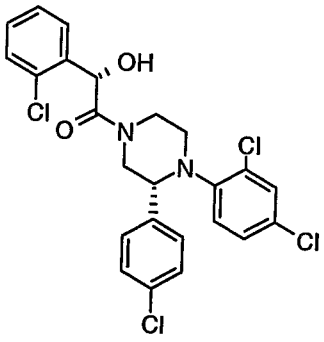
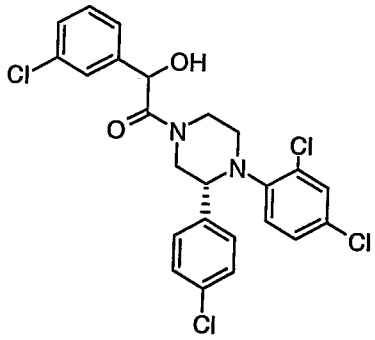
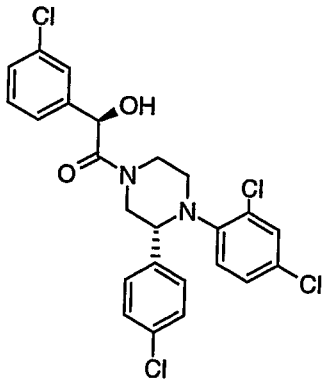
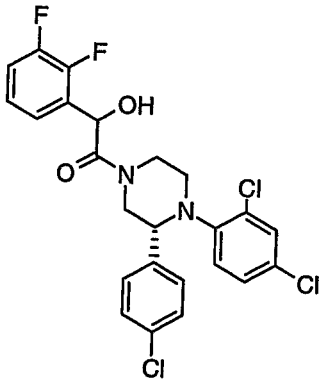
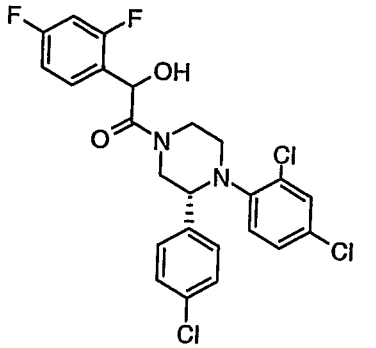

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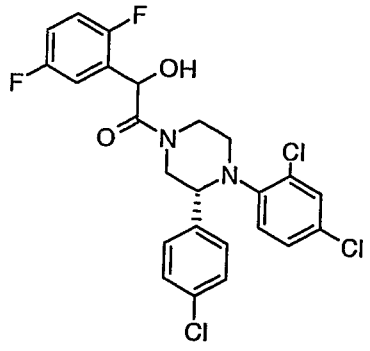
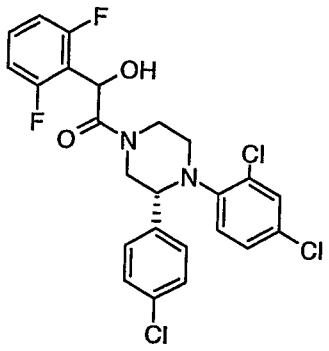
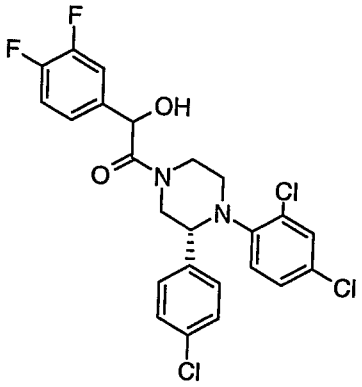
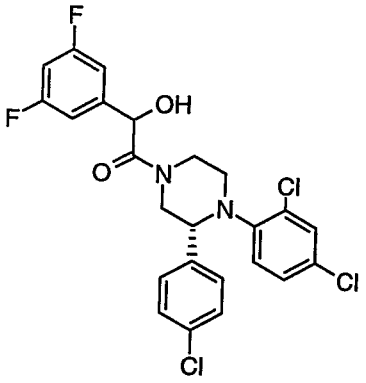
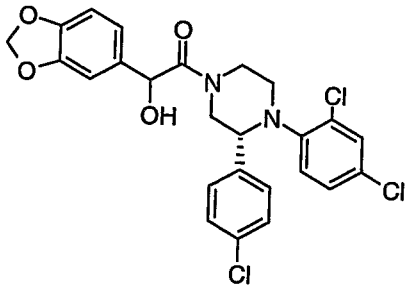
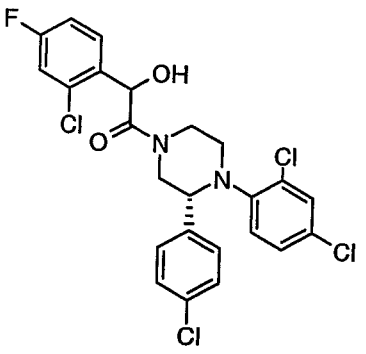
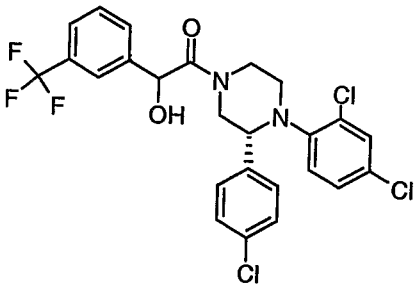
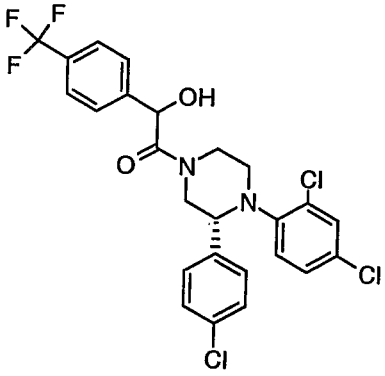
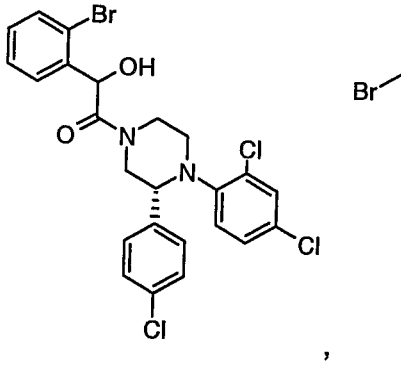
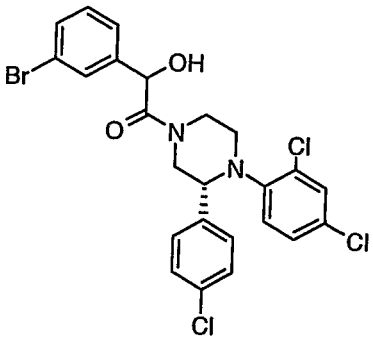

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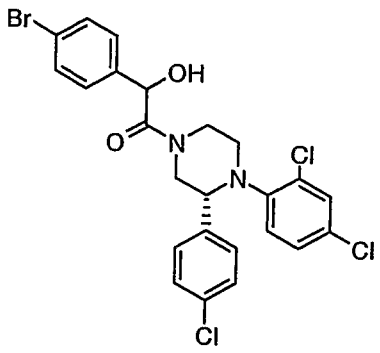
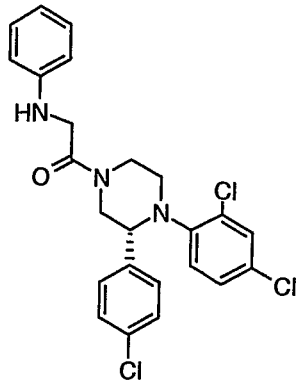
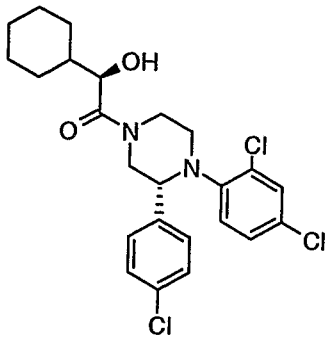
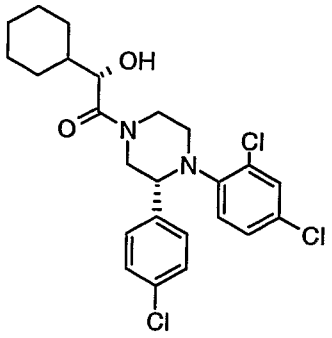
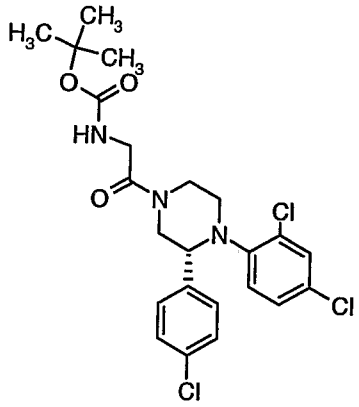
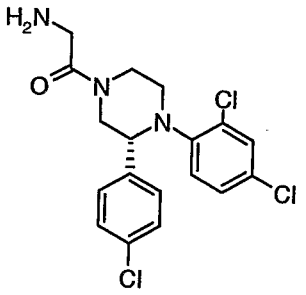
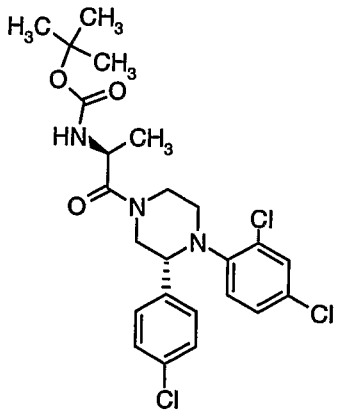
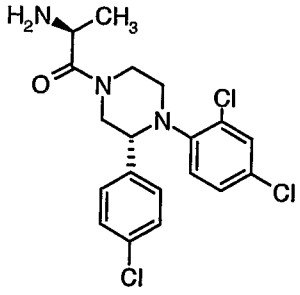
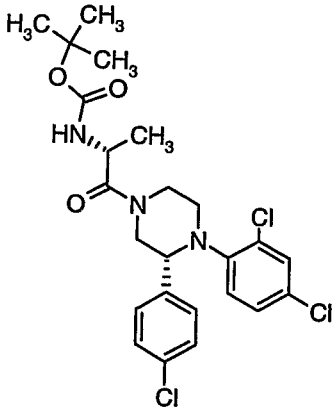
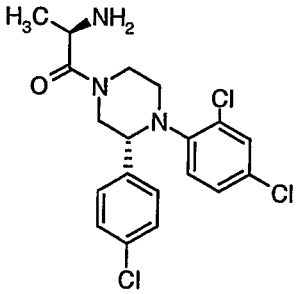
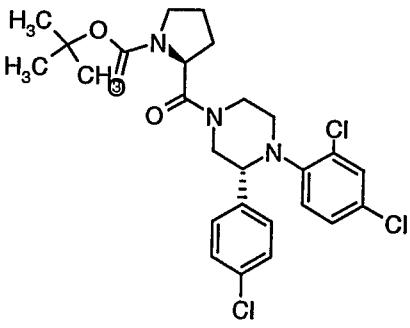
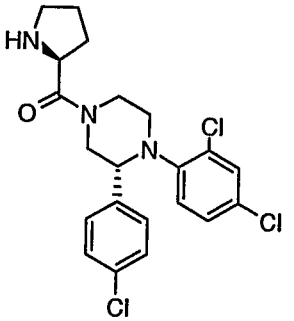

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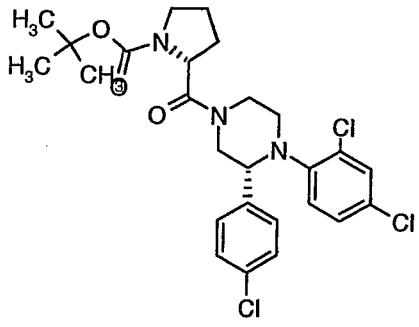
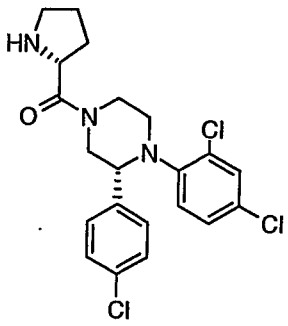
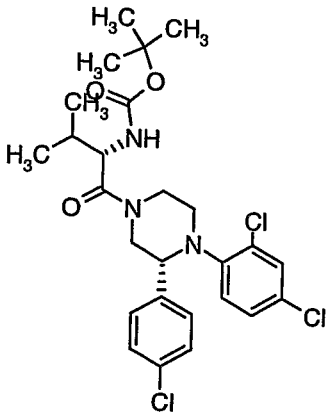
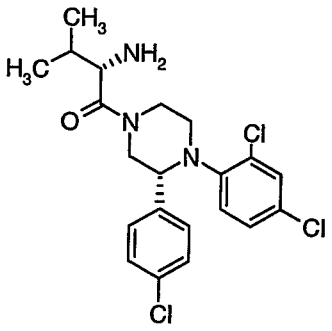
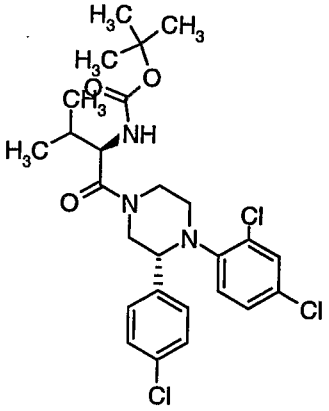
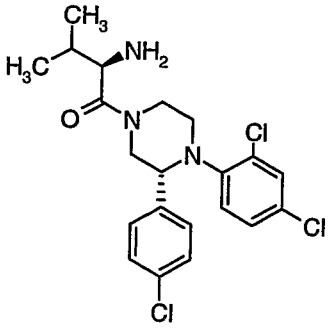
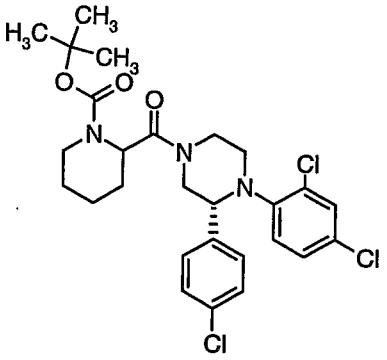
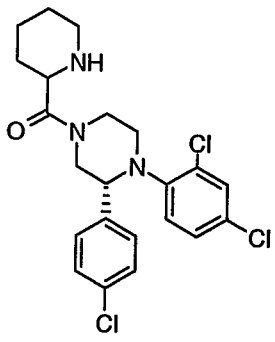
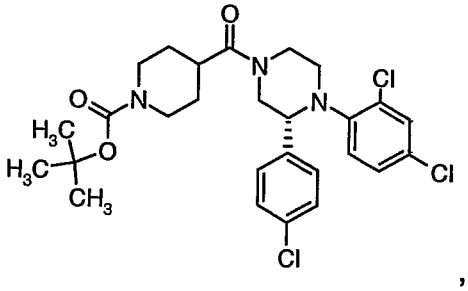
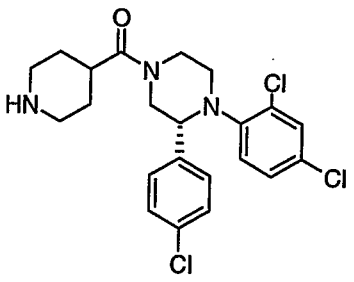

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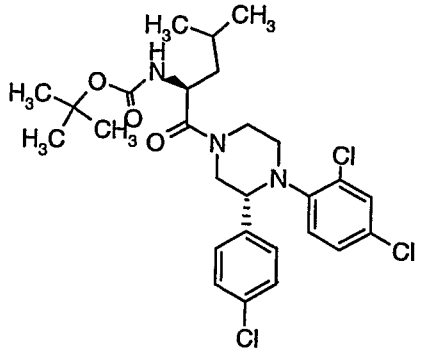
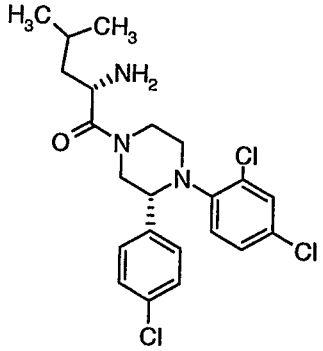
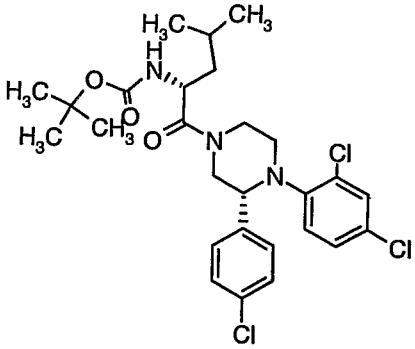
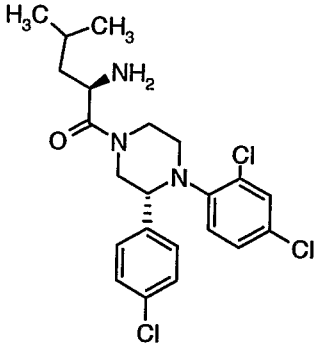
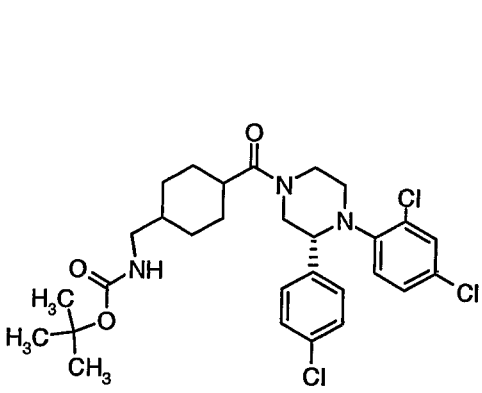
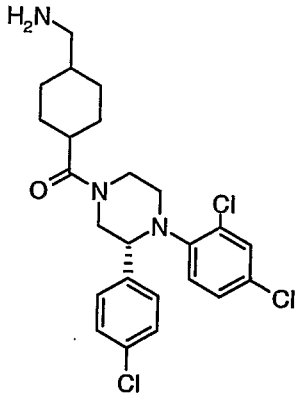
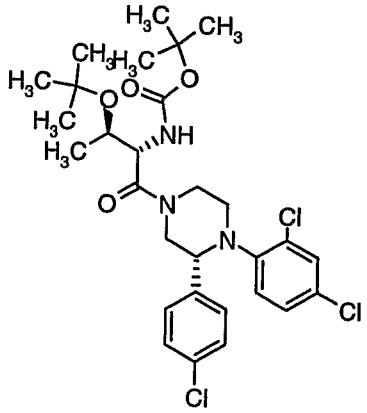
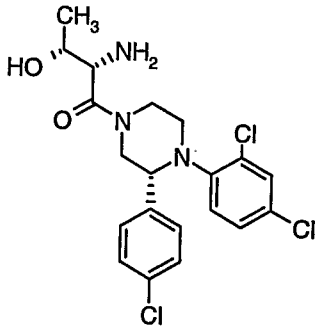
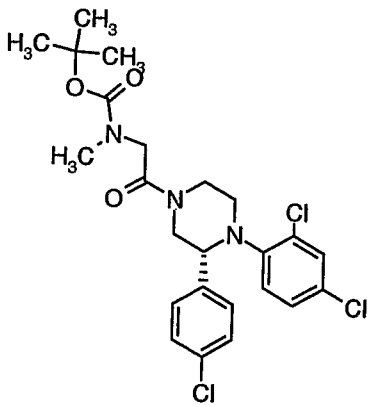

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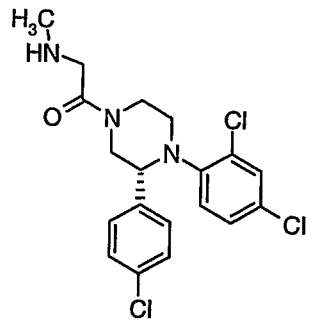
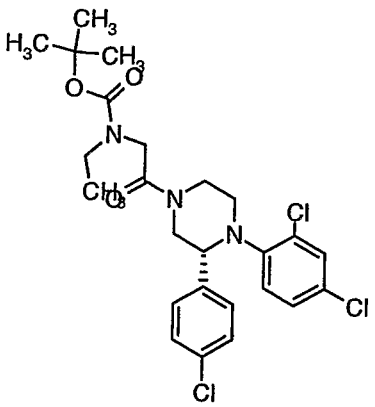
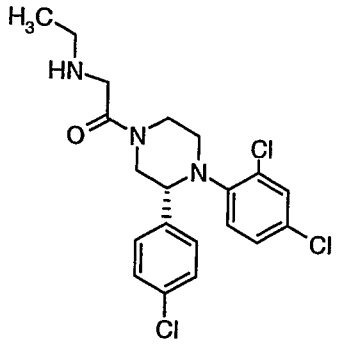
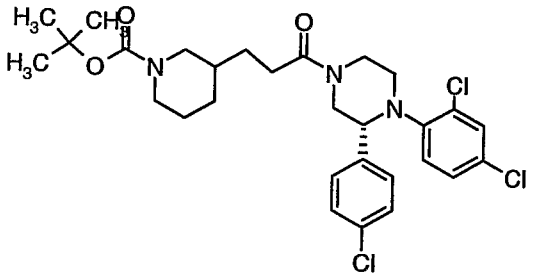
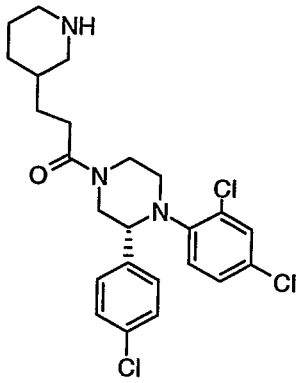
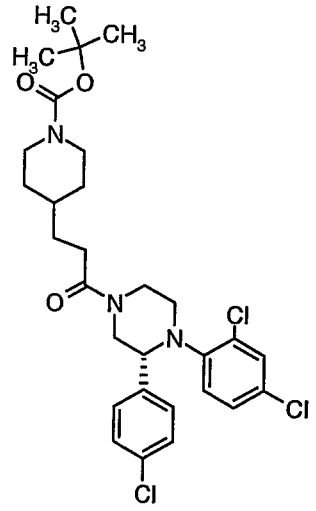
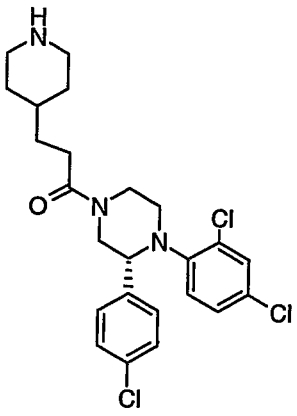
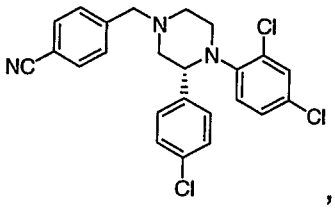
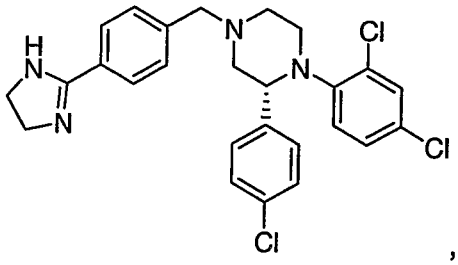
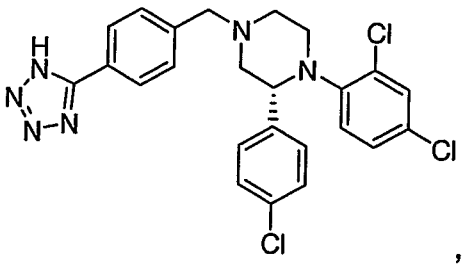

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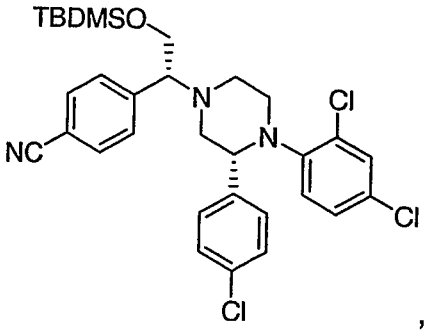

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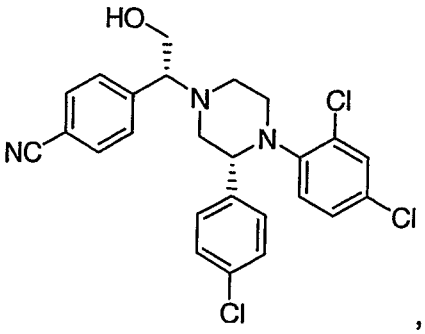

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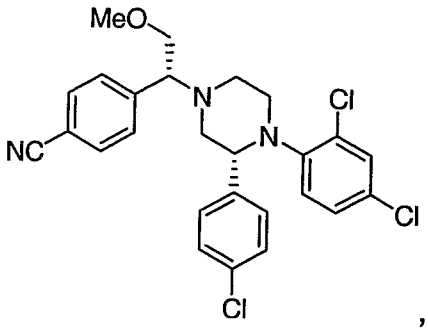

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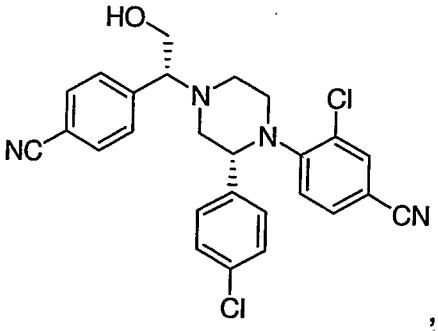
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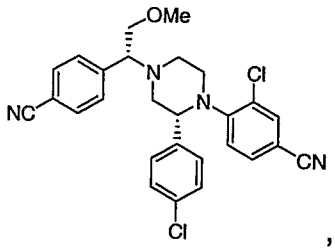
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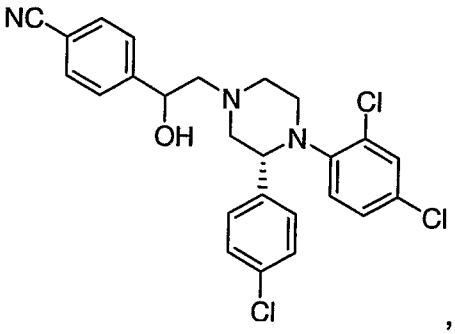
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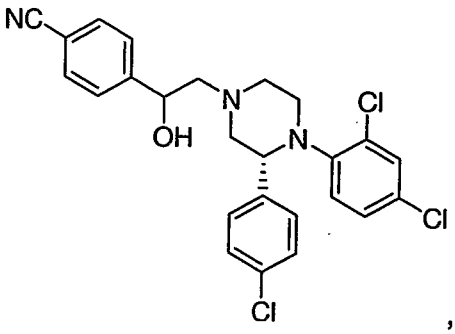
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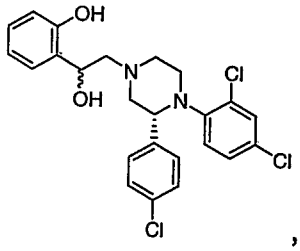
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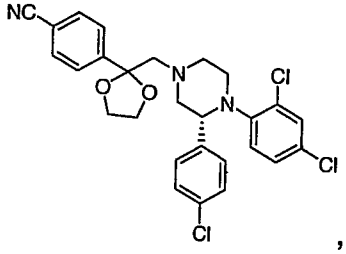
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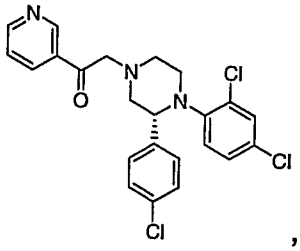
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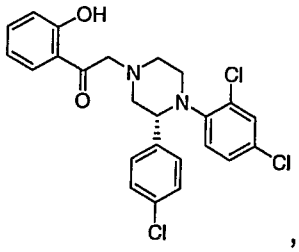
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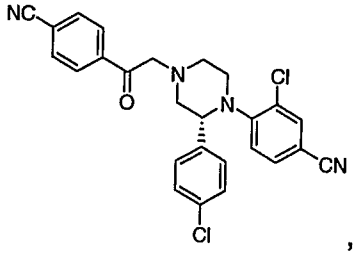
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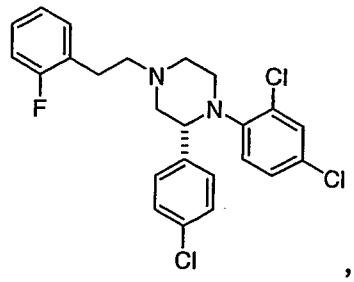
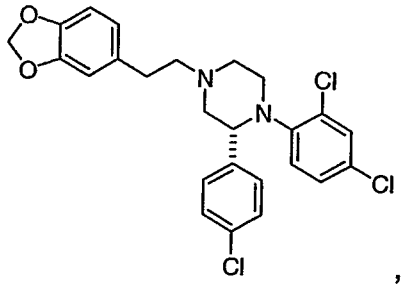
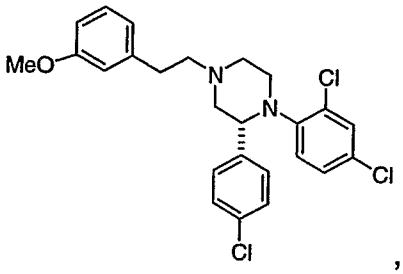
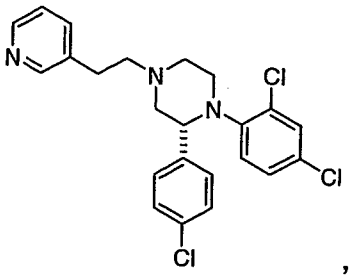
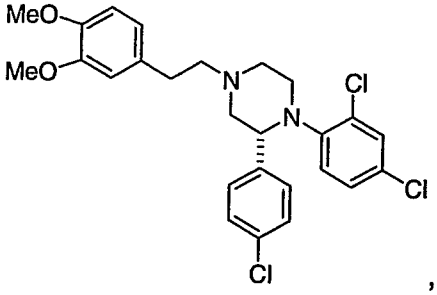
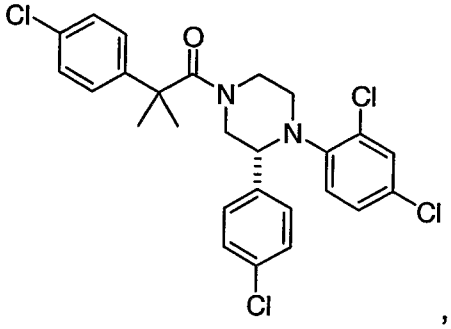
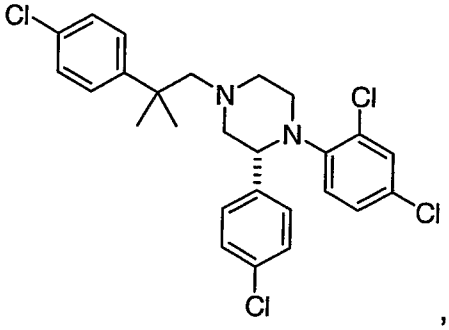
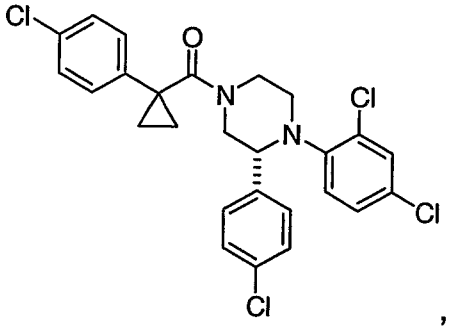
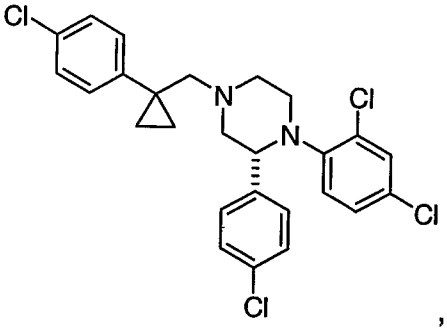
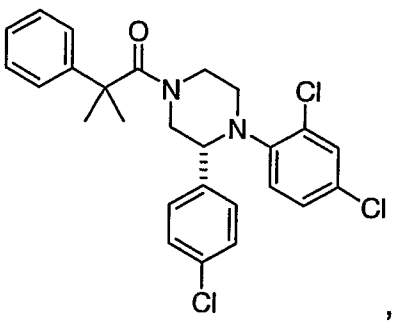
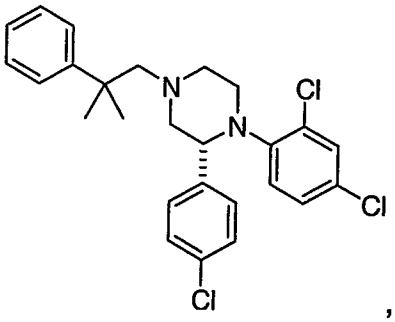

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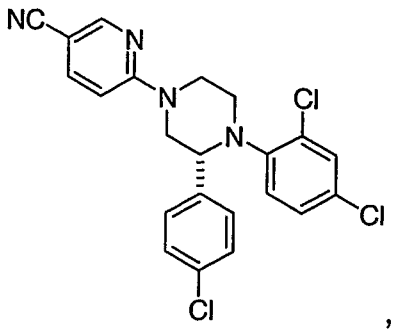
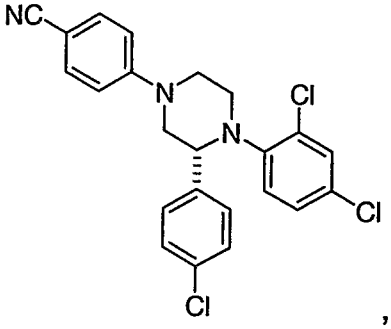
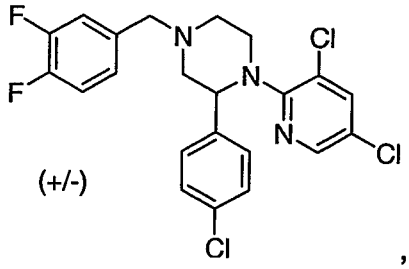
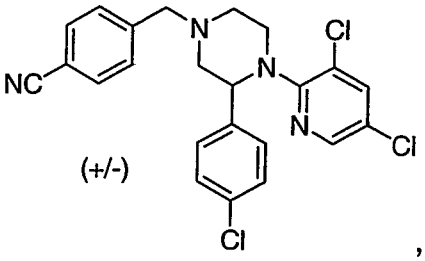
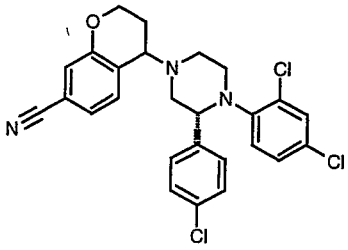
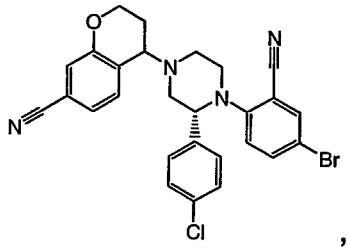
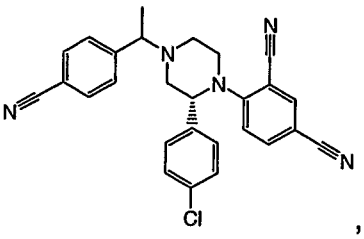
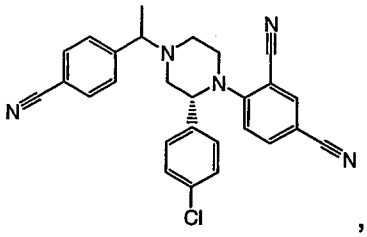
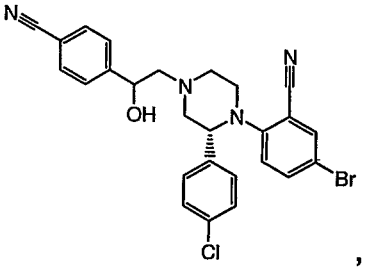
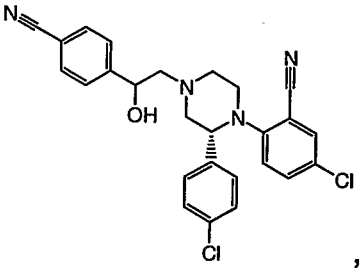
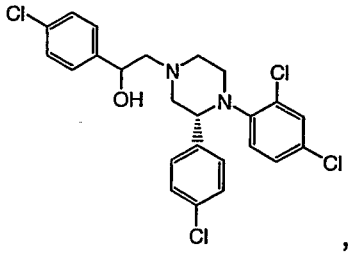
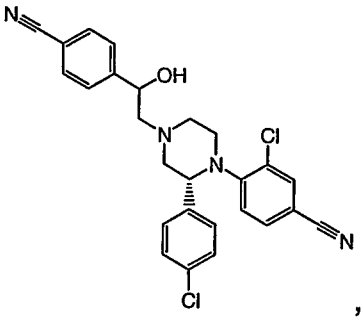
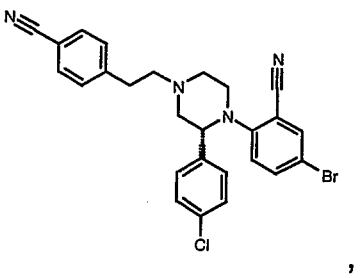

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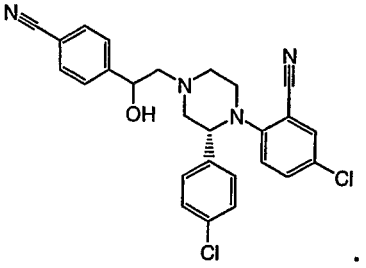
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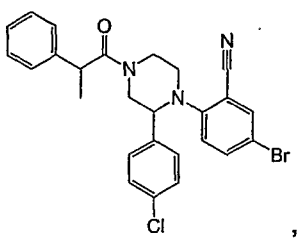
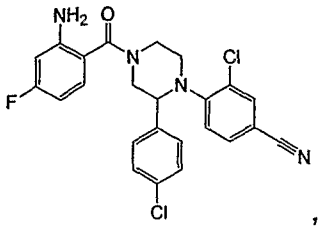
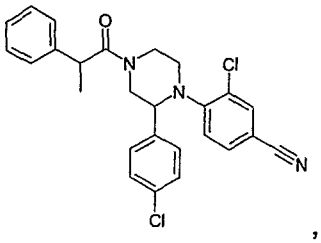
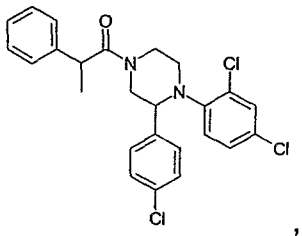
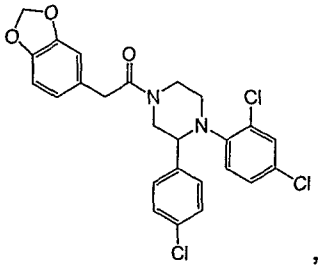
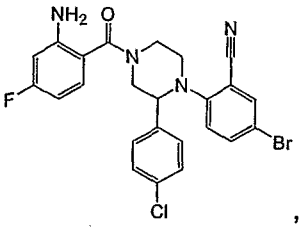
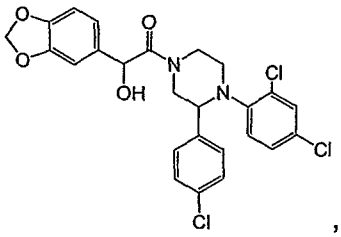
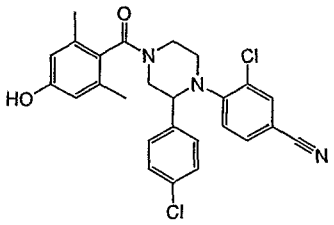
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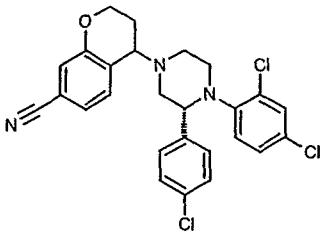
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44. A compound of Claim 1 selected from the group consisting of:


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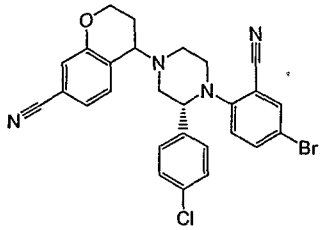
or a pharmaceutically acceptable salt, solvate, or ester thereof.

45. A compound of the following formula:



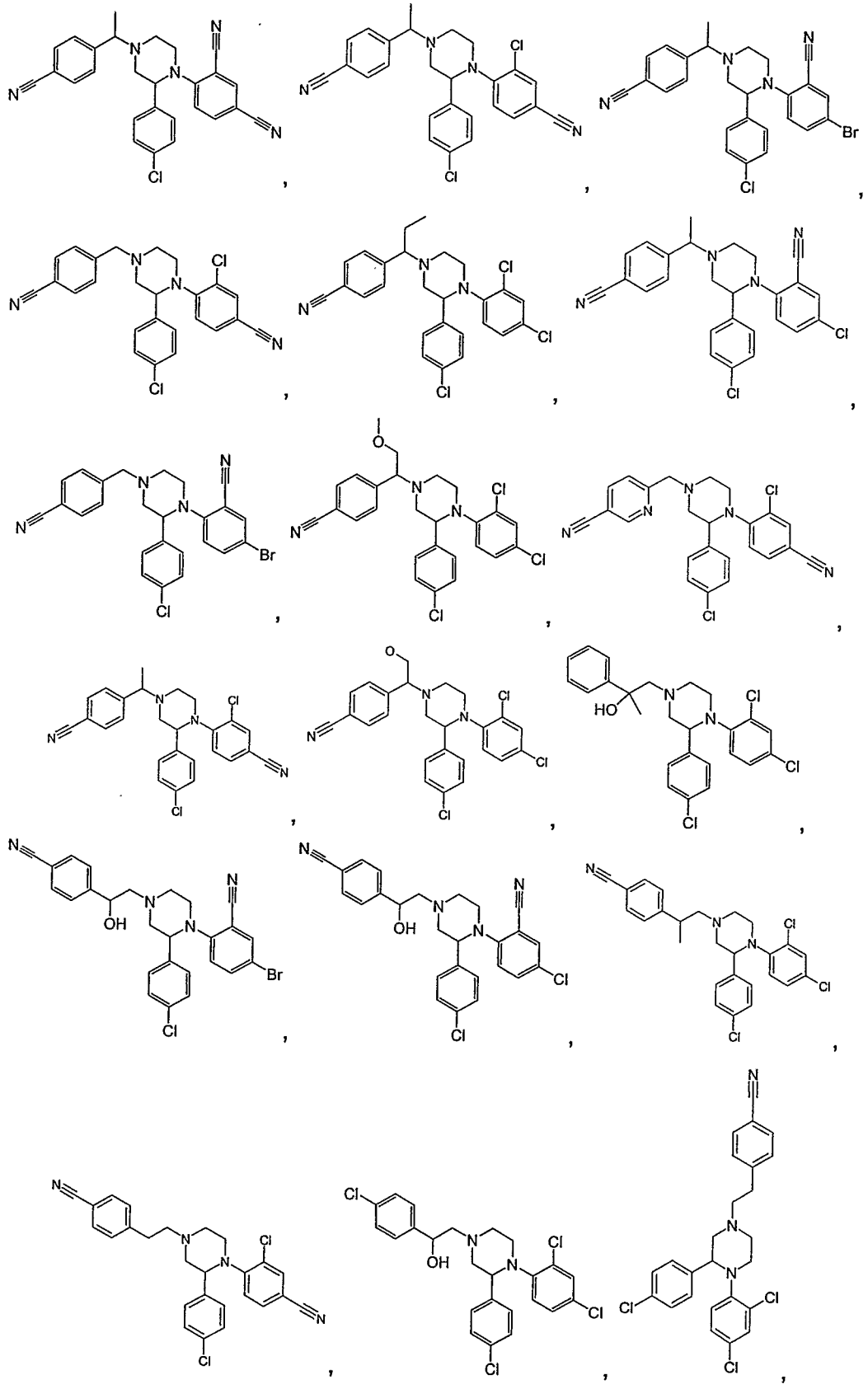
or a pharmaceutically acceptable salt, solvate, or ester thereof.

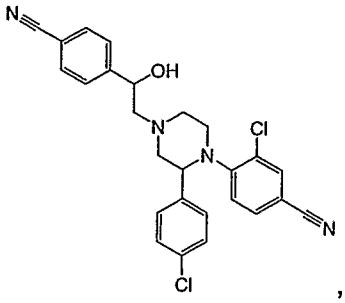
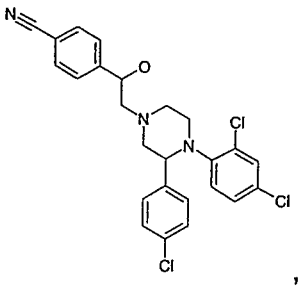
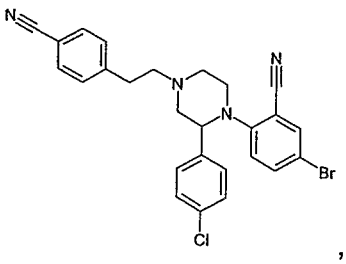
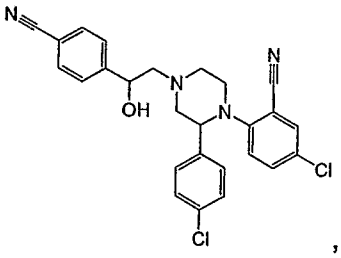
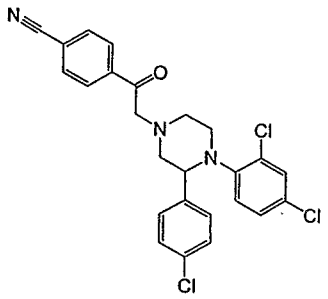
46. A compound of the following formula:



or a pharmaceutically acceptable salt, solvate, or ester thereof.

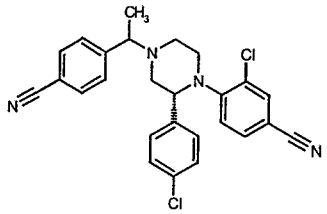
47. A compound of Claim 1 selected from the group consisting of:




,

,

,


, and

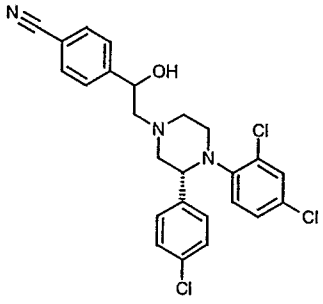
or a pharmaceutically acceptable salt, solvate, or ester thereof.

48. A compound of the following formula:



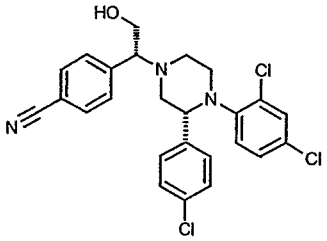
or a pharmaceutically acceptable salt, solvate, or ester thereof.

49. A compound of the following formula:



or a pharmaceutically acceptable salt, solvate, or ester thereof.

50. A compound of the following formula:



or a pharmaceutically acceptable salt, solvate, or ester thereof.

51. The compound according to Claim 1, or a pharmaceutically acceptable salt, solvate, or ester thereof, in purified form.

52. A composition comprising:
at least one compound according to Claim 1, or a pharmaceutically acceptable salt, solvate, or ester thereof; and
a pharmaceutically acceptable carrier.

53. A method of treating, reducing, or ameliorating a condition or disease selected from the group consisting of metabolic syndrome, obesity, waist circumference, lipid profile, insulin sensitivity, neuroinflammatory disorders, cognitive disorders, psychosis, addictive behavior, gastrointestinal disorders, and cardiovascular conditions, in a patient in need thereof, comprising:
administering to said patient an effective amount of at least one compound according to Claim 1, or a pharmaceutically acceptable salt, solvate, or ester thereof.

54. The method of Claim 53, wherein said condition or disease is obesity.

55. A method of treating, reducing, or ameliorating a condition or disease selected from the group consisting of metabolic syndrome, obesity, waist circumference, lipid profile, insulin sensitivity, neuroinflammatory disorders, cognitive disorders, psychosis, addictive behavior, gastrointestinal disorders, and cardiovascular conditions, in a patient in need thereof, comprising:
administering to said patient an effective amount of a composition according to Claim 52.

56. The method of Claim 55, wherein said condition or disease is obesity.

57. A composition comprising:
at least one compound of Formula (I) according to Claim 1, or a pharmaceutically acceptable salt, solvate, or ester thereof; and
at least one cholesterol lowering compound.

58. The composition of Claim 57, wherein said at least one cholesterol lowering compound is at least one sterol absorption inhibitor or at least one 5α-stanol absorption inhibitor.

59. The composition of Claim 57, wherein said at least one cholesterol lowering compound is at least one substituted azetidinone compound or substituted β-lactam compound or a pharmaceutically acceptable salt, solvate, or ester thereof.

60. The composition of Claim 59, wherein said at least one cholesterol lowering compound is ezetimibe.