SULFAMATO HYDROXAMIC ACID METALLOPROTEASE INHIBITOR

Description

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Technical Field

This invention is directed to proteinase (protease) inhibitors, and more particularly to the use of sulfamato hydroxamic acid compounds that, *inter alia*, are selective inhibitors of matrix metalloproteinases in a process for treating conditions associated with pathological matrix metalloproteinase activity, the selective inhibitors themselves, compositions of proteinase inhibitors, intermediates for the syntheses of proteinase inhibitors, and processes for the preparation of proteinase inhibitors.

Background of the Invention

Connective tissue, extracellular matrix constituents and basement membranes are required components of all mammals. These components are the biological materials that provide rigidity, differentiation, attachments and, in some cases, elasticity to biological systems including human beings and other mammals. Connective tissues components include, for example, collagen, elastin, proteoglycans, fibronectin and laminin. These biochemicals makeup, or are components of structures, such as skin, bone, teeth, tendon, cartilage, basement membrane, blood vessels, cornea and vitreous humor.

Under normal conditions, connective tissue turnover and/or repair processes are controlled and in equilibrium. The loss of this balance for whatever reason leads to a number of disease states. Inhibition of the enzymes responsible loss of equilibrium provides a control mechanism for this tissue decomposition and, therefore, a treatment for these diseases.

Degradation of connective tissue or connective tissue components is carried out by the action of proteinase enzymes released from resident tissue cells and/or invading inflammatory or tumor cells. A major class of enzymes involved in this function are the zinc metalloproteinases (metalloproteases).

The metalloprotease enzymes are divided into classes with some members having several different names in common use. Examples are: collagenase I (MMP-1, fibroblast collagenase; EC 3.4.24.3); collagenase II (MMP-8, neutrophil collagenase; EC 3.4.24.34), collagenase III (MMP-13), stromelysin 1 (MMP-3; EC 3.4.24.17), stromelysin 2 (MMP-10; EC 3.4.24.22), proteoglycanase, matrilysin (MMP-7), gelatinase A (MMP-2, 72 kDa gelatinase, basement membrane collagenase; EC 3.4.24.24), gelatinase B (MMP-9, 92 kDa gelatinase; EC 3.4.24.35), stromelysin 3 (MMP-11), metalloelastase (MMP-12, HME, human macrophage elastase) and membrane MMP (MMP-14). MMP is an abbreviation or acronym representing the term Matrix Metalloprotease with the attached numerals providing differentiation between specific members of the MMP group.

The uncontrolled breakdown of connective tissue by metalloproteases is a feature of many pathological conditions. Examples include rheumatoid arthritis, osteoarthritis, septic arthritis; corneal, epidermal or gastric ulceration; tumor metastasis, invasion or angiogenesis; periodontal disease; proteinuria; Alzheimers Disease; coronary thrombosis and bone disease. Defective injury repair processes also occur. This can produce improper wound healing leading to weak repairs, adhesions and scarring. These latter defects can lead to disfigurement and/or permanent disabilities as with post-surgical adhesions.

Metalloproteases are also involved in the biosynthesis of tumor necrosis factor (TNF), and inhibition of the production or action of TNF and related compounds is an important clinical disease treatment mechanism. TNF-α, for example, is a cytokine that at present is thought to be produced initially as a 28 kD cell-associated molecule. It is released as an active, 17 kD form that can mediate a large number of deleterious effects *in vitro* and *in vivo*. For example, TNF can cause and/or contribute to the effects of inflammation, rheumatoid arthritis, autoimmune disease, multiple sclerosis, graft rejection, fibrotic disease, cancer, infectious diseases, malaria, mycobacterial infection, meningitis, fever, psoriasis, cardiovascular/ pulmonary effects such as post-ischemic reperfusion injury, congestive heart failure, hemorrhage, coagulation, hyperoxic alveolar injury, radiation damage and acute phase responses like those seen with infections and sepsis and during shock such as septic

shock and hemodynamic shock. Chronic release of active TNF can cause cachexia and anorexia. TNF can be lethal, and TNF can help control the growth of tumor cells.

TNF-α convertase is a metalloprotease involved in the formation of soluble TNF-α. Inhibition of TNF-α convertase (TACE) inhibits production of active TNF-α. Compounds that inhibit both MMPs activity and TNF-α production have been disclosed in WIPO International Publication Nos. WO 94/24140, WO 94/02466 and WO 97/20824. Compounds that inhibit MMPs such as collagenase, stromelysin and gelatinase have been shown to inhibit the release of TNF (Gearing et al. *Nature* 376, 555-557 (1994), McGeehan et al., *Nature* 376, 558-561 (1994)). There remains a need for effective MMP inhibitors. There also remains a need for effective TNF-α convertase inhibiting agents.

MMPs are involved in other biochemical processes in mammals as well. Included is the control of ovulation, post-partum uterine involution, possibly implantation, cleavage of APP (β-Amyloid Precursor Protein) to the amyloid plaque and inactivation of α_1-protease inhibitor (α_1-PI). Inhibition of these metalloproteases permits the control of fertility and the treatment or prevention of Alzheimers Disease. In addition, increasing and maintaining the levels of an endogenous or administered serine protease inhibitor drug or biochemical such as α_1-PI supports the treatment and prevention of diseases such as emphysema, pulmonary

diseases, inflammatory diseases and diseases of aging such as loss of skin or organ stretch and resiliency.

Inhibition of selected MMPs can also be desirable in other instances. Treatment of cancer and/or inhibition of metastasis and/or inhibition of angiogenesis are examples of approaches to the treatment of diseases wherein the selective inhibition of stromelysin, gelatinase A or B, or collagenase III appear to be the relatively most important enzyme or enzymes to inhibit especially when compared with collagenase I (MMP-1). A drug that does not inhibit collagenase I can have a superior therapeutic profile. Osteoarthritis, another prevalent disease wherein it is believed that cartilage degradation of inflamed joints is at least partially caused by MMP-13 released from cells such as stimulated chrondrocytes, may be best treated by administration of drugs one of whose modes of action is inhibition of MMP-13. See, for example, Mitchell et al., *J. Clin. Invest.*, 97:761-768 (1996) and Reboul et al., *J. Clin. Invest.*, 97:2011-2019 (1996).

Inhibitors of metalloproteases are known. Examples include natural biochemicals such as tissue inhibitors of metalloproteinases (TIMPs), α_2-macroglobulin and their analogs or derivatives. These endogenous inhibitors are high molecular weight protein molecules that form inactive complexes with metalloproteases. A number of smaller peptide-like compounds that inhibit metalloproteases have been described. Mercaptoamide peptidyl derivatives have shown ACE inhibition *in vitro* and *in vivo*. Angiotensin converting enzyme (ACE) aids in the

production of angiotensin II, a potent pressor substance in mammals and inhibition of this enzyme leads to the lowering of blood pressure.

Thiol group-containing amide or peptidyl amide-based metalloprotease (MMP) inhibitors are known as is shown in, for example, WO95/12389, WO96/11209 and U.S. 4,595,700. Hydroxamate group-containing MMP inhibitors are disclosed in a number of published patent applications such as WO 95/29892, WO 97/24117, WO 97/49679 and EP 0 780 386 that disclose carbon back-boned compounds, and WO 90/05719, WO 93/20047, WO 95/09841 and WO 96/06074 that disclose hydroxamates that have a peptidyl back-bones or peptidomimetic back-bones, as does the article by Schwartz et al., *Progr. Med. Chem.*, *29:*271-334(1992) and those of Rasmussen et al., *Pharmacol. Ther.*, *75(1)*: 69-75 (1997) and Denis et al., *Invest. New Drugs, 15(3)*: 175-185 (1997). In addition, application EP 0757 984 A1 discloses aromatic sulfonamide hydroxamates in which the sulfonamido sulfonyl group is bonded on one side to a phenyl ring and the sulfonamido nitrogen is bonded to the hydroxamate group via a chain of one to four carbon atoms.

One possible problem associated with known MMP inhibitors is that such compounds often exhibit the same or similar inhibitory effects against each of the MMP enzymes. For example, the peptidomimetic hydroxamate known as batimastat is reported to exhibit IC_{50} values of about 1 to about 20 nanomolar (nM) against each of MMP-1, MMP-2, MMP-3, MMP-7, and MMP-9. Marimastat, another peptidomimetic

hydroxamate was reported to be another broad-spectrum MMP inhibitor with an enzyme inhibitory spectrum very similar to batimastat, except that marimastat exhibited an IC_{50} value against MMP-3 of 230 nM. Rasmussen et al., *Pharmacol. Ther.*, *75(1)*: 69-75 (1997).

Meta analysis of data from Phase I/II studies using marimastat in patients with advanced, rapidly progressive, treatment-refractory solid tumor cancers (colorectal, pancreatic, ovarian, prostate) indicated a dose-related reduction in the rise of cancer-specific antigens used as surrogate markers for biological activity. Although marimastat exhibited some measure of efficacy via these markers, toxic side effects were noted. The most common drug-related toxicity of marimastat in those clinical trials was musculoskeletal pain and stiffness, often commencing in the small joints in the hands, spreading to the arms and shoulder. A short dosing holiday of 1-3 weeks followed by dosage reduction permits treatment to continue. Rasmussen et al., *Pharmacol. Ther.*, *75(1)*: 69-75 (1997). It is thought that the lack of specificity of inhibitory effect among the MMPs may be the cause of that effect.

International application WO 98/38163, published on September 3, 1998 disclose a large group of hydroxamate inhibitors of MMPs and TACE. The compounds of WO 98/38163 contain one or two substituents adjacent to the hydroxamate functionality and a substituent that can be an

aromatic sulfonyl group adjacent to those one or two substituents.

International application WO 98/37877, published on September 3, 1998 discloses compounds that contain a 5- to 7-membered heterocyclic ring adjacent to the hydroxamate functionality and can contain an aromatic sulfonyl group adjacent to the heterocyclic ring.

More recently, WO 99/24399, published on 20 may, 1999, teaches hydroxamate compounds said to have activity in inhibiting MMP and TNF. Those inhibitors are exemplified by compounds having a three carbon atom chain linked to a sulfonamido group. The hydroxamate carbon is linked to a carbon that can be substituted and that carbon is linked to a methylene. The methylene is linked to a sulfonyl that is bonded to a nitrogen that is further substituted. This disclosure also lacks disclosure as to possible specificity of activity among the substrate enzymes.

Another recent disclosure is that of WO 99/29667, published on 17 June, 1999, that discloses two carbon hydroxamate containing a sulfonamido group whose nitrogen atom is in a ring that is typically bonded directly to another one or two ring group without the intermediacy of another atom. This publication suggests that some of its compounds are selective inhibitors, but provides scant data for only seven compounds.

Although many of the known MMP inhibitors such as batimastat, marimastat and the hydroxamates of WO 98/37877 and WO 98/38163 exhibit a broad spectrum of activity against MMPs, those compounds

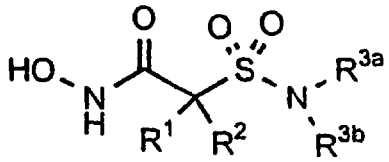
are not particularly selective in their inhibitory activity. This lack of selectivity may be the cause of the musculoskeletal pain and stiffness observed with their use. In addition, it can be therapeutically advantageous to utilize a medicament that is selective in its activity as compared to a generally active material so that treatment can be more closely tailored to the pathological condition presented by the host mammal. The disclosure that follows describes a process for treating a host mammal having a condition associated with pathological matrix metalloprotease activity that utilizes a compound that selectively inhibits one or more MMPs, while exhibiting less activity against at least MMP-1.

Summary of the Invention

The present invention is directed to a treatment process that comprises administering a contemplated sulfamato hydroxamic acid metalloprotease inhibitor in an effective amount to a host mammal having a condition associated with pathological metalloprotease activity. A contemplated molecule, *inter alia*, exhibits excellent inhibitory activity of one or more matrix metalloprotease (MMP) enzymes, such as MMP-2 and MMP-13, while exhibiting substantially less inhibition at least of MMP-1. By "substantially less" it is meant that a contemplated compound exhibits an IC_{50} value ratio against one or both of MMP-2 or MMP-13 as compared to its IC_{50} value against MMP-1, e.g., IC_{50}

MMP-2:IC_{50} MMP-1, that is less than about 1:10, preferably less than about 1:100, and most preferably less than about 1:1000 in the *in vitro* inhibition assay utilized hereinafter. The invention also contemplates particular compounds that selectively inhibit the activity of MMP-2 to a greater extent than MMP-13, as well as a composition containing such a MMP inhibitor as active ingredient and a process for using the same. A contemplated compound also exhibits inhibition of the activity of the adamalysin family of enzymes, exemplified by the enzyme ADAM 10. The invention further contemplates intermediates in the preparation of a contemplated sulfamato hydroxamic acid molecule and a process for preparing a sulfamato hydroxamic acid molecule.

Briefly, one embodiment of the present invention is directed to a treatment process that comprises administering a contemplated sulfamato hydroxamic acid metalloprotease inhibitor that selectively inhibits matrix metalloprotease and adamalysin activity as above in an effective amount to a host mammal having a condition associated with pathological metalloprotease activity. The administered enzyme inhibitor sulfamato hydroxamic acid (hydroxamate) corresponds in structure to formula I, below, or a pharmaceutically acceptable salt thereof:



I

wherein

R^1 and R^2 are preferably taken together with the carbon to which they are bonded form a cycloalkyl or more preferably a heterocyclo group either of which is optionally substituted by one, two or three R^X substituents, or R^1 and R^2 are independently selected from the group consisting of:

hydrido,

an alkyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

an alkyloxyalkyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

an alkylthioalkyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

an alkenyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

an alkynyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

an aryl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

an arylalkyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

an arylalkyloxyalkyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

an aryloxyalkyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

an arylthioalkyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

an arylalkylthioalkyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

a cycloalkyl or bicycloalkyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

a cycloalkenyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

a cycloalkylalkyl or bicycloalkylalkyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

a cycloalkyloxyalkyl or bicycloalkyloxyalkyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

a cycloalkylalkyloxyalkyl or bicycloalkyloxyalkyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

a cycloalkylthioalkyl or bicycloalkylthioalkyl group, optionally substituted with one, two or three groups independently selected from R^X;

cycloalkylalkylthioalkyl or bicycloalkylalkylthioalkyl, optionally substituted with one, two or three groups independently selected from R^X substituents,

a heterocyclo group, optionally substituted with one, two or three groups independently selected from R^X substituents,

a heterocycloalkyl group, optionally substituted with one, two or three groups independently selected from R^X substituents

a heteroaryl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

a biarylalkyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

an arylalkenyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

an arylalkynyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

a heterocycloalkylthio group, optionally substituted with one, two or three groups selected independently from R^X substituents,

a heterocycloalkyloxyalkyl group, optionally substituted with one, two or three groups selected independently from R^X substituents,

a heteroarylalkenyl group, optionally substituted with one, two or three groups independently selected from R^X substituents, and

a heteroarylalkyloxyalkyl group, optionally substituted with one, two or three groups independently selected from R^x substituents;

wherein an R^x substituent is selected from the group consisting of a hydrido, aryl, heteroaryl, heterocyclo, aroyl, alkanoyl, heteroaroyl, halogen (F, Cl, Br, I), cyano, aldehydo (CHO, formyl), hydroxy, R^cR^d-amino (-NR^cR^d), R^cR^d-aminoalkyl, nitro, nitroso, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, alkoxy, aryloxy, heteroaryloxy, alkenyloxy, alkynyloxy, alkoxyaryl, alkoxyheteroaryl, alkoxyalkyl, R^c-oxyalkyl, alkoxyalkyl, alkylenedioxy, aryloxyalkyl, perfluoroalkyl, trifluoroalkyl, alkylthio, arylthio, alkyloxycarbonyl, alkyloxycarbonyloxy, aryloxycarbonyl, arylalkyloxycarbonyl, alkyloxycarbonyl-R^c-amino, arylalkyloxycarbonyl-R^c-amino, aryloxycarbonyloxy, carboxy, R^cR^d-aminocarbonyloxy, R^cR^d-aminocarbonyl, R^cR^d-aminoalkanoyl, hydroxy-R^c-aminocarbonyl, R^cR^d-aminosulfonyl, arylsulfonyl(R^c)amino, R^cR^d-aminoalkoxy, R^cR^d-aminocarbonyl(R^c)amino, trifluoromethylsulfonyl(R^c)amino, heteroarylsulfonyl-(R^c)amino, alkylsulfonyl, arylsulfonyl(R^c)amino, arylsulfonyl(R^c)aminocarbonyl, alkylsulfonyl-(R^c)amino, arylcarbonyl(R^c)-aminosulfonyl, and an alkylsulfonyl(R^c)aminocarbonyl substituent;

wherein R^c and R^d are independently selected from the group consisting of a hydrido, alkanoyl, arylalkyl, aroyl, bisalkoxyalkyl, alkyl, haloalkyl, perfluoroalkyl, trifluoromethylalkyl,

perfluoroalkoxyalkyl, alkoxyalkyl, cycloalkyl, heterocycloalkyl, heterocycloalkylcarbonyl, aryl, heterocyclo, heteroaryl, cycloalkylalkyl, aryloxyalkyl, heteroaryloxyalkyl, heteroarylalkoxyalkyl, heteroarylthioalkyl, arylsulfonyl, alkylsulfonyl, heteroarylsulfonyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, alkyliminocarbonyl, aryliminocarbonyl, heterocycloiminocarbonyl, arylthioalkyl, alkylthioalkyl, arylthioalkenyl, alkylthioalkenyl, heteroarylalkyl, haloalkanoyl, hydroxyalkanoyl, thiolalkanoyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, aminoalkylcarbonyl, hydroxyalkyl, aminoalkyl, aminoalkylsulfonyl, aminosulfonyl wherein the amino nitrogen is (i) unsubstituted or (ii) independently substituted with one or two R^Y radicals, or the substituents on the amino group taken together with the amino nitrogen form a saturated or partially unsaturated heterocyclo group optionally substituted with one, two or three groups independently selected from R^W substituents or a heteroaryl group optionally substituted with one, two or three groups independently selected from R^V substituents;

wherein R^Y is selected from the group consisting of an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl, alkynyl, alkenyl, alkoxyalkyl, alkoxyalkyl, substituted or unsubstituted aminoalkyl, alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkanoyl, aroyl, substituted or unsubstituted aminoalkanoyl, halo alkanoyl and a hydroxyalkyl group, each of which groups is

optionally substituted by one or two groups independently selected from R^U substituents as are the substituents of the substituted aminoalkyl and substituted aminoalkanoyl groups;

wherein R^V is selected from the group consisting of a hydrido, aryl, heteroaryl, heterocyclo, aroyl, alkanoyl, heteroaroyl, halogen (F, Cl, Br, I), cyano, aldehydo (CHO, formyl), hydroxy, amino, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, alkoxy, aryloxy, heteroaryloxy, alkenyloxy, alkynyloxy, alkoxyaryl, alkoxyheteroaryl, R^YR^Z-amino, alkoxyalkyl, alkylenedioxy, aryloxyalkyl, perfluoroalkyl, trifluoroalkyl, alkylthio, arylthio, alkyloxycarbonyl, alkyloxycarbonyloxy, aryloxycarbonyl, arylalkyloxycarbonyl, arylalkyloxycarbonylamino, aryloxycarbonyloxy, carboxy, R^YR^Z-aminocarbonyloxy, R^YR^Z-aminocarbonyl, R^YR^Z-aminoalkanoyl, hydroxyaminocarbonyl, R^YR^Z-aminosulfonyl, R^YR^Z-aminocarbonyl(R^Y)amino, trifluoromethylsulfonyl(R^Y)amino, heteroarylsulfonyl-(R^Y)amino, arylsulfonyl(R^Y)amino, arylsulfonyl(R^Y)-aminocarbonyl, alkylsulfonyl(R^Y)amino, arylcarbonyl-(R^Y)aminosulfonyl, and an alkylsulfonyl(R^Y)-aminocarbonyl substituent;

wherein R^W is selected from the group consisting of a hydrido, aryl, heteroaryl, heterocyclo, aroyl, alkanoyl, heteroaroyl, halogen (F, Cl, Br, I), cyano, aldehydo (CHO, formyl), hydroxy, amino, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, alkoxy, aryloxy, heteroaryloxy, alkenyloxy, alkynyloxy, alkoxyaryl, alkoxyheteroaryl, R^YR^Z-amino,

alkoxyalkyl, alkylenedioxy, aryloxyalkyl, perfluoroalkyl, trifluoroalkyl, alkylthio, arylthio, alkyloxycarbonyl, alkyloxycarbonyloxy, aryloxycarbonyl, arylalkyloxycarbonyl, arylalkyloxycarbonylamino, aryloxycarbonyloxy, carboxy, R^YR^Z-aminocarbonyloxy, R^YR^Z-aminocarbonyl, R^YR^Z-aminoalkanoyl, hydroxyaminocarbonyl, R^YR^Z-aminosulfonyl, R^YR^Z-aminocarbonyl(R^Y)amino, trifluoromethylsulfonyl(R^Y)amino, heteroarylsulfonyl-(R^Y)amino, arylsulfonyl(R^Y)amino, arylsulfonyl(R^Y)-aminocarbonyl, alkylsulfonyl(R^Y)amino, arylcarbonyl-(R^Y)aminosulfonyl, and an alkylsulfonyl(R^Y)-aminocarbonyl substituent;

R^Z is selected from the group consisting of an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl, alkynyl, alkenyl, alkoxyalkyl, alkoxyalkylalkyl, substituted or unsubstituted aminoalkyl, alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkanoyl, aroyl, substituted or unsubstituted aminoalkanoyl, halo alkanoyl and a hydroxyalkyl group, each of which groups are optionally substituted by one or two R^U substituents;

wherein R^U is selected from the group consisting of an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl, alkynyl, alkenyl, alkoxyalkyl, alkoxyalkyl, substituted or unsubstituted aminoalkyl, alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkanoyl, aroyl, substituted or unsubstituted aminoalkanoyl, halo alkanoyl and a hydroxyalkyl group, wherein the substituents of the substituted aminoalkyl and substituted aminoalkanoyl

groups are selected from the group consisting of an alkyl, alkenyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxycarbonyl and an alkyloxycarbonyl group;

R^{3a} and R^{3b} are independently selected from the group consisting of a hydrido, alkyl, alkenyl, alkynyl, aryl, heterocyclo, heteroaryl, cycloalkyl, and an alkoxyalkyl group, each of which groups is optionally substituted by an -AREY substituent;

in that AREY substituent, A is selected from the group consisting of

(1) -O-;

(2) -S-;

(3) $-N(R^e)-$;

(4) $-CO-N(R^e)$ or $-N(R^e)-CO-$;

(5) -CO-O- or -O-CO-;

(6) -O-CO-O-;

(7) -HC=CH-;

(8) -NH-CO-NH-;

(9) -C≡C-;

(10) -NH-CO-O- or -O-CO-NH-;

(11) -N=N-;

(12) -NH-NH-;

(13) $-CS-N(R^e)-$ or $-N(R^e)-CS-$;

(14) $-CH_2-$;

(15) $-O-[(CH_2)_{1-8}]-$ or $-[(CH_2)_{1-8}]O-$; and

(16) $-S-CH_2-$ or $-CH_2-S-$; or

(17) A is absent and R is directly connected to R^{3a} or R^{3b}, or both R^{3a} and R^{3b};

the moiety R is selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl, heterocycloalkyl, cycloalkylalkyl, cycloalkoxyalkyl, heterocycloalkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, arylthioalkyl, heteroarylthioalkyl, cycloalkylthioalkyl, and a heterocycloalkylthioalkyl group wherein the aryl, heteroaryl, cycloalkyl or heterocycloalkyl substituent is (i) unsubstituted or (ii) substituted with one or two radicals selected from the group consisting of a halo, alkyl, perfluoroalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, amino, alkoxycarbonylalkyl, alkoxy, C_1-C_2-alkylene-dioxy, hydroxycarbonylalkyl, hydroxycarbonylalkylamino, nitro, hydroxy, hydroxyalkyl, alkanoylamino, and a alkoxycarbonyl group;

the group E is selected from the group consisting of

(1) $-CO(R^w)-$ or $-(R^w)CO-$;

(2) $-CON(R^e)-$ or $-(R^e)NCO-$;

(3) $-CO-$;

(4) $-SO_2-R^w$ or $-R^wSO_2-$;

(5) $-SO_2-$;

(6) $-N(R^e)-SO_2-$ or $-SO_2-N(R^e)-$; or

(7) E is absent and R is bonded directly to Y; and

Y is absent or is selected from the group consisting of a hydrido, alkyl, alkoxy, haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl, hydroxy,

nitrile, nitro, aryloxy, aralkoxy, heteroaryloxy, heteroaralkyl, R^coxyalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl, heterocycloalkyl, cycloalkyl, trifluoromethyl, alkoxycarbonyl, and a aminoalkyl group, wherein the aryl, heteroaryl or heterocycloalkyl group is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of an alkanoyl, halo, nitro, nitrile, haloalkyl, alkyl, aralkyl, aryl, alkoxy, and an amino group wherein the amino nitrogen is (i) unsubstituted or (ii) substituted with one or two groups independently selected from hydrido, alkyl, and an aralkyl group;

wherein R^e is selected from hydrido, alkyl, alkenyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxycarbonyl, alkyloxycarbonyl, R^cR^damino carbonyl, R^cR^daminosulfonyl, R^cR^daminoalkanoyl and R^cR^daminoalkysulfonyl, and R^c, R^d and R^w are as defined before; or

R^{3a} and R^{3b} taken together with the nitrogen atom to which they are bonded form a group -GAREY wherein

G is a N-heterocyclo group;

the substituent A is selected from the group consisting of

(1) -O-;

(2) -S-;

(3) $-NR^e-$;

(4) $-CO-N(R^e)$ or $-N(R^e)-CO-$;

(5) -CO-O- or -O-CO-;

(6) -O-CO-O-;

(7) -HC=CH-;

(8) -NH-CO-NH-;

(9) -C≡C-;

(10) -NH-CO-O- or -O-CO-NH-;

(11) -N=N-;

(12) -NH-NH-;

(13) -CS-N(R^e)- or -N(R^e)-CS-;

(14) -CH_2-;

(15) -O-[$(CH_2)_{1-8}$]- or -[$(CH_2)_{1-8}$]O-; and

(16) -S-CH_2- or -CH_2-S-; or

(17) A is absent and R is directly connected to G;

The moiety R is selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl, heterocycloalkyl, cycloalkylalkyl, cycloalkoxyalkyl, heterocycloalkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, arylthioalkyl, heteroarylthioalkyl, cycloalkylthioalkyl, and a heterocycloalkylthioalkyl group wherein the aryl or heteroaryl or cycloalkyl or heterocycloalkyl substituent is (i) unsubstituted or (ii) substituted with one or two radicals selected from the group consisting of a halo, alkyl, perfluoroalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, amino, alkoxycarbonylalkyl, alkoxy, C_1-C_2-alkylene-dioxy, hydroxycarbonylalkyl, hydroxycarbonylalkylamino, nitro, hydroxy, hydroxyalkyl, alkanoylamino, and a alkoxycarbonyl group;

The moiety E is selected from the group consisting of

(1) $-CO(R^W)-$ or $-(R^W)CO-$;

(2) -CONH- or -HNCO-;

(3) -CO-;

(4) $-SO_2-R^W-$ or $-R^W-SO_2-$;

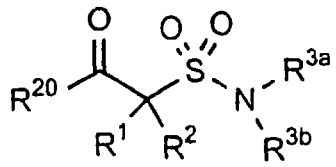
(5) $-SO_2-$;

(6) $-NH-SO_2-$ or $-SO_2-NH-$; or

(7) E is absent and Y is bonded directly to R; and

The moiety Y is absent or is selected from the group consisting of a hydrido, alkyl, alkoxy, haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl, hydroxy, aryloxy, aralkoxy, heteroaryloxy, heteroaralkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl, heterocycloalkyl, cycloalkyl, trifluoromethyl, alkoxycarbonyl, and a aminoalkyl group, wherein the aryl or heteroaryl or heterocycloalkyl group is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of an alkanoyl, halo, nitro, aralkyl, aryl, alkoxy, and an amino group wherein the amino nitrogen is (i) unsubstituted or (ii) substituted with one or two groups independently selected from hydrido, alkyl, and an aralkyl group.

More generally, a contemplated compound includes an inhibitor utilized as discussed above, as well as a pro-drug form of such a compound and also an intermediate used in the synthesis of a hydroxamate or hydroxamate pro-drug. Such a more general compound corresponds in structure to formula II, below,



II

wherein R^1, R^2, R^{3a} and R^{3b} are as before described, and

R^{20} is (a) -O-R^{21}, where R^{21} is selected from the group consisting of a hydrido, C_1-C_6-alkyl, aryl, ar-C_1-C_6-alkyl group and a pharmaceutically acceptable cation, (b) -NH-O-R^{22}, wherein R^{22} is a selectively removable protecting group such as a 2-tetrahydropyranyl, benzyl, p-methoxybenzyl (MOZ) carbonyl-C_1-C_6-alkoxy, trisubstituted silyl group or o-nitrophenyl group, peptide systhesis resin and the like, wherein trisubstituted silyl group is substituted with C_1-C_6-alkyl, aryl, or ar-C_1-C_6-alkyl, or (c) -NH-O-R^{14}, where R^{14} is hydrido, a pharmaceutically acceptable cation or C(W)R^{15} where W is O or S and R^{15} is selected from the group consisting of an C_1-C_6-alkyl, aryl, C_1-C_6-alkoxy, heteroaryl-C_1-C_6-alkyl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, aryloxy, ar-C_1-C_6-alkoxy, ar-C_1-C_6-alkyl, heteroaryl and amino C_1-C_6-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two substituents independently selected from the group consisting of an C_1-C_6-alkyl, aryl, ar-C_1-C_6-alkyl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, ar-C_1-C_6-alkoxycarbonyl, C_1-C_6-alkoxycarbonyl, and C_1-C_6-alkanoyl radical, or (iii) wherein the amino C_1-C_6-

alkyl nitrogen and two substituents attached thereto form a 5- to 8-membered heterocyclo or heteroaryl ring.

Among the several benefits and advantages of the present invention are the provision of compounds and compositions effective as inhibitors of matrix metalloproteinase activity, the provision of such compounds and compositions that are effective for the inhibition of metalloproteinases implicated in diseases and disorders involving uncontrolled breakdown of connective tissue.

More particularly, a benefit of this invention is the provision of a compound and composition effective for selectively inhibiting certain metalloproteinases, such as one or both of MMP-2 and MMP-13, associated with pathological conditions such as, for example, rheumatoid arthritis, osteoarthritis, septic arthritis, corneal, epidermal or gastric ulceration, tumor metastasis, invasion or angiogenesis, periodontal disease, proteinuria, Alzheimer's Disease, coronary thrombosis and bone disease.

An advantage of the invention is the provision of compounds, compositions and methods effective for treating such pathological conditions by selective inhibition of a metalloproteinase such as MMP-2 or MMP-13 associated with such conditions with minimal side effects resulting from inhibition of other metalloproteinases, such as MMP-1, whose activity is necessary or desirable for normal body function.

A still further benefit of the invention is that a contemplated compound exhibits greater inhibition of MMP-2 than MMP-13.

A still further advantage of the invention is that a contemplated compound exhibits inhibitory activity against the adamalysin family of enzymes.

Yet another advantage of the invention is the provision of a process for preparing such compounds.

Another benefit is the provision of a method for treating a pathological condition associated with abnormal matrix metalloproteinase activity.

A further advantage of the invention is the provision of a process for preparing such compositions.

Still further benefits and advantages of the invention will be apparent to the skilled worker from the disclosure that follows.

Detailed Description of the Invention

In accordance with the present invention, it has been discovered that certain sulfamato hydroxamic acids (hydroxamates) are effective for inhibition of matrix metalloproteinases ("MMPs") believed to be associated with uncontrolled or otherwise pathological breakdown of connective tissue. In particular, it has been found that these certain sulfamato hydroxamates are effective for inhibition of one or both of MMP-2 and MMP-13, which can be particularly destructive to tissue if present or generated in abnormal quantities or concentrations, and thus exhibit a pathological activity. Included

in that pathological activity is the assistance of tumors and tumor cells in the process of penetrating basement membrane, and developing a new or improved blood supply; i.e., angiogenesis.

Moreover, it has been discovered that these sulfamato hydroxamates are selective in the inhibition of one or both of MMP-2 and MMP-13 without excessive inhibition of other collagenases essential to normal bodily function such as tissue turnover and repair. More particularly, it has been found that a contemplated sulfamato hydroxamate of the invention, or a pharmaceutically acceptable salt thereof, is particularly active in inhibiting of one or both of MMP-2 and MMP-13 in an *in vitro* assay that is predictive of *in vivo* activity. In addition, while being selective for one or both of MMP-2 and MMP-13, a contemplated sulfamato hydroxamate, or its salt, has a limited or minimal *in vitro* inhibitory effect on MMP-1. This point is illustrated in the Inhibition Table hereinafter. Put differently, a contemplated compound can inhibit the activity of MMP-2 or MMP-13 compared to MMP-1.

The advantages of the selectivity of a contemplated compound can be appreciated, without wishing to be bound by theory, by considering the therapeutic uses the compounds. For example, inhibition of MMP-1 is suggested to be undesirable due to its role as a housekeeping enzyme, helping to maintain normal connective tissue turnover and repair. Inhibition of MMP-1 can lead to toxicities or side effects such as such as joint or connective tissue deterioration and pain. On the other hand, MMP-13 has been suggested to be intimately involved

in the destruction of joint components in diseases such as osteoarthritis. Thus, potent and selective inhibition of MMP-13 compared with inhibition MMP-1 is highly desirable because a MMP-13 inhibitor can have a positive effect on disease progression in a patient in addition to having an anti-inflammatory effect.

Inhibition of MMP-2 can be desirable for inhibition of tumor growth, metastasis, invasion and/or angiogenesis. A profile of selective inhibition of MMP-2 relative to MMP-1 can provide a therapeutic advantage. A contemplated compound not only is substantially more active in inhibiting MMP-2 than MMP-1, a contemplated compound also exhibits greater inhibition of MMP-2 than MMP-13.

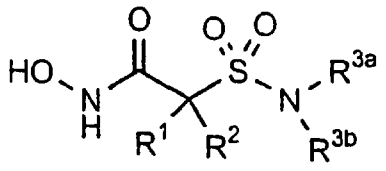
A further advantage to MMP inhibitors with selective inhibition profiles is their suitability for use in combination with other types of medicaments. For example, a patient can be treated with an MMP inhibitor compound for the inhibition of angiogenesis in combination with a second, third or fourth drug of the traditional anti-tumor type, such as taxol, cis-platinum or doxorubicin. A further advantage is that the administration of a MMP inhibitor with a selective inhibition profile can permit the reduction in dosage of the drugs being administered to the patient. This is an especially important advantage given both the toxicities and dosing limits of traditional anti-tumor drugs.

A contemplated selective MMP inhibitor compound useful in a contemplated process can be administered to by various routes and provide adequate therapeutic blood levels of enzymatically active inhibitor. A

compound can be administered, for example, by the oral (IG, PO) or intravenous (IV) routes. Oral administration is advantageous if the patient is ambulatory, not hospitalized, physically able and sufficiently responsible to take drug at the required intervals. This is true even if the person is being treated with more than one drug for one or more diseases. On the other hand, IV drug administration is an advantage in a hospital setting wherein the dose and thus the blood levels can well controlled. A contemplated inhibitor can also be formulated for IM administration if desired. This route of administration can be desirable for the administration of prodrugs or regular drug delivery to patients that are either physically weak or have a poor compliance record or require constant drug blood levels.

Thus, in one embodiment, the present invention is directed to a treatment process that comprises administering a contemplated sulfamato hydroxamic acid metalloprotease inhibitor, or a pharmaceutically acceptable salt thereof, in an effective amount to a host mammal having a condition associated with pathological matrix metalloprotease activity. A contemplated sulfamato hydroxamate inhibitor compound useful in such a process inhibits the activity of one or both of MMP-2 and MMP-13, and exhibits substantially less inhibitory activity against at least MMP-1 in the *in vitro* assay noted above and discussed in detail hereinafter. A sulfamato hydroxamate inhibitor compound for use in a contemplated process corresponds in structure to

formula I, below, or a pharmaceutically acceptable salt thereof:



I

wherein

R^1 and R^2 are preferably taken together with the carbon to which they are bonded form a cycloalkyl or more preferably a heterocyclo group either of which is optionally substituted by one, two or three R^X substituents, or R^1 and R^2 are independently selected from the group consisting of:

hydrido,

an alkyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

an alkyloxyalkyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

an alkylthioalkyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

an alkenyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

an alkynyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

an aryl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

an arylalkyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

an arylalkyloxyalkyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

an aryloxyalkyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

an arylthioalkyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

an arylalkylthioalkyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

a cycloalkyl or bicycloalkyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

a cycloalkenyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

a cycloalkylalkyl or bicycloalkylalkyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

a cycloalkyloxyalkyl or bicycloalkyloxyalkyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

a cycloalkylalkyloxyalkyl or bicycloalkyloxyalkyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

a cycloalkylthioalkyl or bicycloalkylthioalkyl group, optionally substituted with one, two or three groups independently selected from R^X;

cycloalkylalkylthioalkyl or bicycloalkylalkylthioalkyl, optionally substituted with one, two or three groups independently selected from R^X substituents,

a heterocyclo group, optionally substituted with one, two or three groups independently selected from R^X substituents,

a heterocycloalkyl group, optionally substituted with one, two or three groups independently selected from R^X substituents

a heteroaryl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

a biarylalkyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

an arylalkenyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

an arylalkynyl group, optionally substituted with one, two or three groups independently selected from R^X substituents,

a heterocycloalkylthio group, optionally substituted with one, two or three groups selected independently from R^X substituents,

a heterocycloalkyloxyalkyl group, optionally substituted with one, two or three groups selected independently from R^X substituents,

a heteroarylalkenyl group, optionally substituted with one, two or three groups independently selected from R^X substituents, and

a heteroarylalkyloxyalkyl group, optionally substituted with one, two or three groups independently selected from R^X substituents;

wherein an R^X substituent is selected from the group consisting of a hydrido, aryl, heteroaryl, heterocyclo, aroyl, alkanoyl, heteroaroyl, halogen (F, Cl, Br, I), cyano, aldehydo (CHO, formyl), hydroxy, R^CR^d-amino ($-NR^CR^d$), R^CR^d-aminoalkyl, nitro, nitroso, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, alkoxy, aryloxy, heteroaryloxy, alkenyloxy, alkynyloxy, alkoxyaryl, alkoxyheteroaryl, alkoxyalkyl, R^C-oxyalkyl, alkoxyalkyl, alkylenedioxy, aryloxyalkyl, perfluoroalkyl, trifluoroalkyl, alkylthio, arylthio, alkyloxycarbonyl, alkyloxycarbonyloxy, aryloxycarbonyl, arylalkyloxycarbonyl, alkyloxycarbonyl-R^C-amino, arylalkyloxycarbonyl-R^C-amino, aryloxycarbonyloxy, carboxy, R^CR^d-aminocarbonyloxy, R^CR^d-aminocarbonyl, R^CR^d-aminoalkanoyl, hydroxy-R^C-aminocarbonyl, R^CR^d-aminosulfonyl, arylsulfonyl(R^C)amino, R^CR^d-aminoalkoxy, R^CR^d-aminocarbonyl(R^C)amino, trifluoromethylsulfonyl(R^C)amino, heteroarylsulfonyl-

(R^c)amino, alkylsulfonyl, arylsulfonyl(R^c)amino, arylsulfonyl(R^c)aminocarbonyl, alkylsulfonyl-(R^c)amino, arylcarbonyl(R^c)-aminosulfonyl, and an alkylsulfonyl(R^c)aminocarbonyl substituent;

wherein R^c and R^d are independently selected from the group consisting of a hydrido, alkanoyl, arylalkyl, aroyl, bisalkoxyalkyl, alkyl, haloalkyl, perfluoroalkyl, trifluoromethylalkyl, perfluoroalkoxyalkyl, alkoxyalkyl, cycloalkyl, heterocycloalkyl, heterocycloalkylcarbonyl, aryl, heterocyclo, heteroaryl, cycloalkylalkyl, aryloxyalkyl, heteroaryloxyalkyl, heteroarylalkoxyalkyl, heteroarylthioalkyl, arylsulfonyl, alkylsulfonyl, heteroarylsulfonyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, alkyliminocarbonyl, aryliminocarbonyl, heterocycloiminocarbonyl, arylthioalkyl, alkylthioalkyl, arylthioalkenyl, alkylthioalkenyl, heteroarylalkyl, haloalkanoyl, hydroxyalkanoyl, thiolalkanoyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, aminoalkylcarbonyl, hydroxyalkyl, aminoalkyl, aminoalkylsulfonyl, aminosulfonyl wherein the amino nitrogen is (i) unsubstituted or (ii) independently substituted with one or two R^y radicals, or the substituents on the amino group taken together with the amino nitrogen form a saturated or partially unsaturated heterocyclo group optionally substituted with one, two or three groups independently selected from R^w substituents or a heteroaryl group optionally substituted with one,

two or three groups independently selected from R^V substituents;

wherein R^Y is selected from the group consisting of an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl, alkynyl, alkenyl, alkoxyalkyl, alkoxyalkyl, substituted or unsubstituted aminoalkyl, alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkanoyl, aroyl, substituted or unsubstituted aminoalkanoyl, halo alkanoyl and a hydroxyalkyl group, each of which groups is optionally substituted by one or two groups independently selected from R^U substituents as are the substituents of the substituted aminoalkyl and substituted aminoalkanoyl groups;

wherein R^V is selected from the group consisting of a hydrido, aryl, heteroaryl, heterocyclo, aroyl, alkanoyl, heteroaroyl, halogen (F, Cl, Br, I), cyano, aldehydo (CHO, formyl), hydroxy, amino, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, alkoxy, aryloxy, heteroaryloxy, alkenyloxy, alkynyloxy, alkoxyaryl, alkoxyheteroaryl, R^YR^Z-amino, alkoxyalkyl, alkylenedioxy, aryloxyalkyl, perfluoroalkyl, trifluoroalkyl, alkylthio, arylthio, alkyloxycarbonyl, alkyloxycarbonyloxy, aryloxycarbonyl, arylalkyloxycarbonyl, arylalkyloxycarbonylamino, aryloxycarbonyloxy, carboxy, R^YR^Z-aminocarbonyloxy, R^YR^Z-aminocarbonyl, R^YR^Z-aminoalkanoyl, hydroxyaminocarbonyl, R^YR^Z-aminosulfonyl, R^YR^Z-aminocarbonyl(R^Y)amino, trifluoromethylsulfonyl(R^Y)amino, heteroarylsulfonyl-(R^Y)amino, arylsulfonyl(R^Y)amino, arylsulfonyl(R^Y)-

aminocarbonyl, alkylsulfonyl(R^Y)amino, arylcarbonyl-(R^Y)aminosulfonyl, and an alkylsulfonyl(R^Y)-aminocarbonyl substituent;

wherein R^W is selected from the group consisting of a hydrido, aryl, heteroaryl, heterocyclo, aroyl, alkanoyl, heteroaroyl, halogen (F, Cl, Br, I), cyano, aldehydo (CHO, formyl), hydroxy, amino, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, alkoxy, aryloxy, heteroaryloxy, alkenyloxy, alkynyloxy, alkoxyaryl, alkoxyheteroaryl, R^YR^Z-amino, alkoxyalkyl, alkylenedioxy, aryloxyalkyl, perfluoroalkyl, trifluoroalkyl, alkylthio, arylthio, alkyloxycarbonyl, alkyloxycarbonyloxy, aryloxycarbonyl, arylalkyloxycarbonyl, arylalkyloxycarbonylamino, aryloxycarbonyloxy, carboxy, R^YR^Z-aminocarbonyloxy, R^YR^Z-aminocarbonyl, R^YR^Z-aminoalkanoyl, hydroxyaminocarbonyl, R^YR^Z-aminosulfonyl, R^YR^Z-aminocarbonyl(R^Y)amino, trifluoromethylsulfonyl(R^Y)amino, heteroarylsulfonyl-(R^Y)amino, arylsulfonyl(R^Y)amino, arylsulfonyl(R^Y)-aminocarbonyl, alkylsulfonyl(R^Y)amino, arylcarbonyl-(R^Y)aminosulfonyl, and an alkylsulfonyl(R^Y)-aminocarbonyl substituent;

R^Z is selected from the group consisting of an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl, alkynyl, alkenyl, alkoxyalkyl, alkoxyalkylalkyl, substituted or unsubstituted aminoalkyl, alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkanoyl, aroyl, substituted or unsubstituted aminoalkanoyl, halo alkanoyl and a

hydroxyalkyl group, each of which groups are optionally substituted by one or two R^u substituents;

wherein R^u is selected from the group consisting of an arylalkyl, aryl, heteroaryl, heterocyclo, alkyl, alkynyl, alkenyl, alkoxyalkyl, alkoxyalkyl, substituted or unsubstituted aminoalkyl, alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkanoyl, aroyl, substituted or unsubstituted aminoalkanoyl, halo alkanoyl and a hydroxyalkyl group, wherein the substituents of the substituted aminoalkyl and substituted aminoalkanoyl groups are selected from the group consisting of an alkyl, alkenyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxycarbonyl and an alkyloxycarbonyl group;

R^{3a} and R^{3b} are independently selected from the group consisting of a hydrido, alkyl, alkenyl, alkynyl, aryl, heterocyclo, heteroaryl, cycloalkyl, and an alkoxyalkyl group, each of which groups is optionally substituted by an -AREY substituent;

in that AREY substituent, A is selected from the group consisting of

(1) -O-;

(2) -S-;

(3) $-N(R^e)-$;

(4) $-CO-N(R^e)$ or $-N(R^e)-CO-$;

(5) -CO-O- or -O-CO-;

(6) -O-CO-O-;

(7) -HC=CH-;

(8) -NH-CO-NH-;

(9) -C≡C-;

(10) -NH-CO-O- or -O-CO-NH-;

(11) -N=N-;

(12) -NH-NH-;

(13) $-CS-N(R^e)-$ or $-N(R^e)-CS-$;

(14) $-CH_2-$;

(15) $-O-[(CH_2)_{1-8}]-$ or $-[(CH_2)_{1-8}]O-$; and

(16) $-S-CH_2-$ or $-CH_2-S-$; or

(17) A is absent and R is directly connected to R^{3a} or R^{3b}, or both R^{3a} and R^{3b};

the moiety R is selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl, heterocycloalkyl, cycloalkylalkyl, cycloalkoxyalkyl, heterocycloalkoxyalkyl, aryloxyalkyl, heteroaryl-oxyalkyl, arylthioalkyl, heteroarylthioalkyl, cycloalkylthioalkyl, and a heterocycloalkylthioalkyl group wherein the aryl, heteroaryl, cycloalkyl or heterocycloalkyl substituent is (i) unsubstituted or (ii) substituted with one or two radicals selected from the group consisting of a halo, alkyl, perfluoroalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, amino, alkoxycarbonylalkyl, alkoxy, C_1-C_2-alkylene-dioxy, hydroxycarbonylalkyl, hydroxycarbonylalkylamino, nitro, hydroxy, hydroxyalkyl, alkanoylamino, and a alkoxycarbonyl group;

the group E is selected from the group consisting of

(1) $-CO(R^w)-$ or $-(R^w)CO-$;

(2) $-CON(R^e)-$ or $-(R^e)NCO-$;

(3) -CO-;

(4) $-SO_2-R^w$ or $-R^wSO_2-$;

(5) $-SO_2-$;

(6) $-N(R^e)-SO_2-$ or $-SO_2-N(R^e)-$; or

(7) E is absent and R is bonded directly to Y; and

Y is absent or is selected from the group consisting of a hydrido, alkyl, alkoxy, haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl, hydroxy, nitrile, nitro, aryloxy, aralkoxy, heteroaryloxy, heteroaralkyl, R^coxyalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl, heterocycloalkyl, cycloalkyl, trifluoromethyl, alkoxycarbonyl, and a aminoalkyl group, wherein the aryl, heteroaryl or heterocycloalkyl group is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of an alkanoyl, halo, nitro, nitrile, haloalkyl, alkyl, aralkyl, aryl, alkoxy, and an amino group wherein the amino nitrogen is (i) unsubstituted or (ii) substituted with one or two groups independently selected from hydrido, alkyl, and an aralkyl group;

wherein R^e is selected from hydrido, alkyl, alkenyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxycarbonyl, alkyloxycarbonyl, R^cR^damino carbonyl, R^cR^daminosulfonyl, R^cR^daminoalkanoyl and R^cR^daminoalkysulfonyl, and R^c, R^d and R^w are as defined before; or

R^{3a} and R^{3b} taken together with the nitrogen atom to which they are bonded form a group -GAREY (R^3) wherein

G is a N-heterocyclo group;

the substituent A is selected from the group consisting of

(1) -O-;

(2) -S-;

(3) $-NR^e-$;

(4) $-CO-N(R^e)$ or $-N(R^e)-CO-$;

(5) -CO-O- or -O-CO-;

(6) -O-CO-O-;

(7) -HC=CH-;

(8) -NH-CO-NH-;

(9) -C≡C-;

(10) -NH-CO-O- or -O-CO-NH-;

(11) -N=N-;

(12) -NH-NH-;

(13) $-CS-N(R^e)-$ or $-N(R^e)-CS-$;

(14) $-CH_2-$;

(15) $-O-[(CH_2)_{1-8}]-$ or $-[(CH_2)_{1-8}]O-$; and

(16) $-S-CH_2-$ or $-CH_2-S-$; or

(17) A is absent and R is directly connected to G;

the moiety R is selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl, heterocycloalkyl, cycloalkylalkyl, cycloalkoxyalkyl, heterocycloalkoxyalkyl, aryloxyalkyl, heteroaryl-oxyalkyl, arylthioalkyl, heteroarylthioalkyl, cycloalkylthioalkyl, and a heterocycloalkylthioalkyl group wherein the aryl or heteroaryl or cycloalkyl or heterocycloalkyl substituent is (i) unsubstituted or (ii) substituted with one or two radicals selected

from the group consisting of a halo, alkyl, perfluoroalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, amino, alkoxycarbonylalkyl, alkoxy, C_1-C_2-alkylenedioxy, hydroxycarbonylalkyl, hydroxycarbonylalkylamino, nitro, hydroxy, hydroxyalkyl, alkanoylamino, and a alkoxycarbonyl group;

The moiety E is selected from the group consisting of

(1) $-CO(R^W)-$ or $-(R^W)CO-$;

(2) $-CONH-$ or $-HNCO-$;

(3) $-CO-$;

(4) $-SO_2-R^W-$ or $-R^W-SO_2-$;

(5) $-SO_2-$;

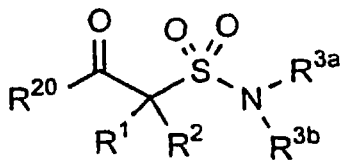
(6) $-NH-SO_2-$ or $-SO_2-NH-$; or

(7) E is absent and R is bonded directly to Y; and

The moiety Y is absent or is selected from the group consisting of a hydrido, alkyl, alkoxy, haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl, hydroxy, aryloxy, aralkoxy, heteroaryloxy, heteroaralkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl, heterocycloalkyl, cycloalkyl, trifluoromethyl, alkoxycarbonyl, and a aminoalkyl group, wherein the aryl or heteroaryl or heterocycloalkyl group is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of an alkanoyl, halo, nitro, aralkyl, aryl, alkoxy, and an amino group wherein the amino nitrogen is (i) unsubstituted or (ii) substituted with one or two groups

independently selected from hydrido, alkyl, and an aralkyl group.

More generally, a contemplated compound includes an inhibitor utilized as discussed above, as well as a pro-drug form of such a compound and also an intermediate used in the synthesis of a hydroxamate or hydroxamate pro-drug. Such a more general compound corresponds in structure to formula II, below,



II

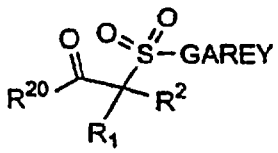
wherein R^1, R^2, R^{3a} and R^{3b} are as before described with the above preferences, and

R^{20} is (a) -O-R^{21}, where R^{21} is selected from the group consisting of a hydrido, C_1-C_6-alkyl, aryl, ar-C_1-C_6-alkyl group and a pharmaceutically acceptable cation, (b) -NH-O-R^{22}, wherein R^{22} is a selectively removable protecting group such as a 2-tetrahydropyranyl, benzyl, p-methoxybenzyl (MOZ) carbonyl-C_1-C_6-alkoxy, trisubstituted silyl group or o-nitrophenyl group, peptide systhesis resin and the like, wherein trisubstituted silyl group is substituted with C_1-C_6-alkyl, aryl, or ar-C_1-C_6-alkyl, or (c) -NH-O-R^{14}, where R^{14} is hydrido, a pharmaceutically acceptable cation or C(W)R^{15} where W is O or S and R^{15} is selected from the group consisting of an C_1-C_6-alkyl, aryl, C_1-C_6-alkoxy,

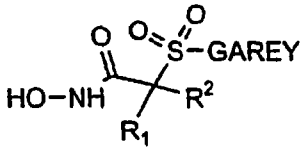
heteroaryl-C_1-C_6-alkyl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, aryloxy, ar-C_1-C_6-alkoxy, ar-C_1-C_6-alkyl, heteroaryl and amino C_1-C_6-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two substituents independently selected from the group consisting of an C_1-C_6-alkyl, aryl, ar-C_1-C_6-alkyl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, ar-C_1-C_6-alkoxycarbonyl, C_1-C_6-alkoxycarbonyl, and C_1-C_6-alkanoyl radical, or (iii) wherein the amino C_1-C_6-alkyl nitrogen and two substituents attached thereto form a 5- to 8-membered heterocyclo or heteroaryl ring.

The substituent $-NR^{3a}R^{3b}$ can also be referred to as a R^3 group. One exemplary R^3 group is $-N(CH_3)_2$, whereas another is the before-discussed substituent group -GAREY that is present in more preferred compounds as is discussed hereinbelow.

One group of more preferred compounds correspond ion structure to formula III, formula IIIA or a pharmaceutically acceptable salt thereof:



III

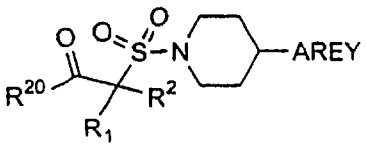


IIIA

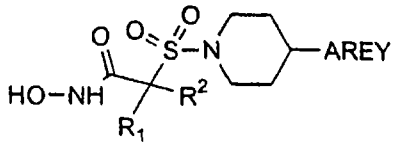
wherein substituents R^1, R^2, R^{20} and -GAREY are as discussed before, with the before-described preferences.

Yet another more preferred group of contemplated compounds correspond ion structure to formula IV,

formula IVA or a pharmaceutically acceptable salt thereof:



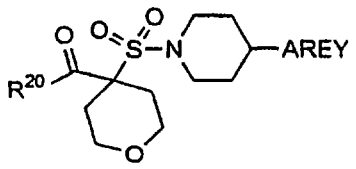
IV



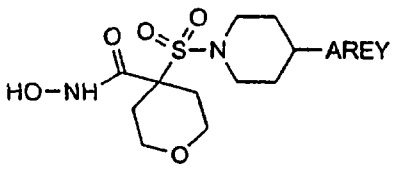
IVA

wherein substituents R^1, R^2, R^{20} and -AREY are as discussed before, with the before-described preferences.

A still more preferred group of contemplated compounds correspond ion structure to formula V, formula VA or a pharmaceutically acceptable salt thereof:



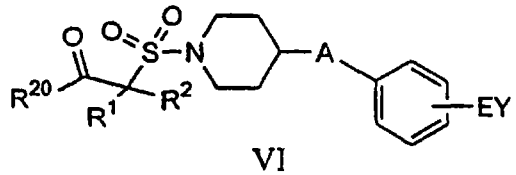
V



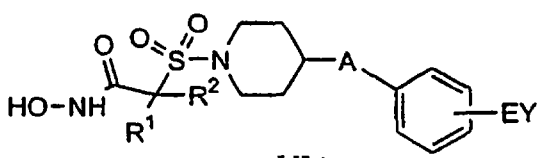
VA

wherein substituents R^{20} and -AREY are as discussed before, with the before-described preferences.

Another more preferred group of contemplated compounds correspond ion structure to formula VI, formula VIA or a pharmaceutically acceptable salt thereof:



VI

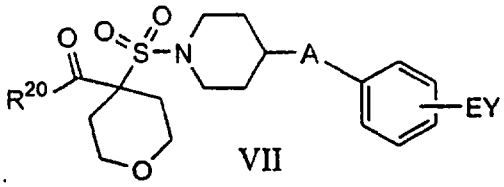


VIA

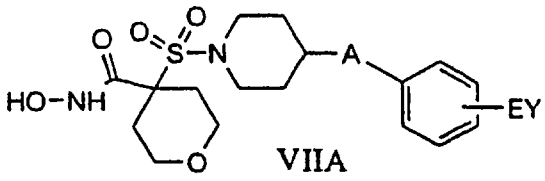
wherein substituents R^1, R^2, R^{20} and -EY are as discussed before, with the before-described

preferences, and A is $-CH_2-$, $-O-CH_2-$, $-CH_2-O-$, $-S-CH_2-$ or $-CH_2-S-$.

A still more preferred group of contemplated compounds correspond ion structure to formula VII, formula VIIA or a pharmaceutically acceptable salt thereof:



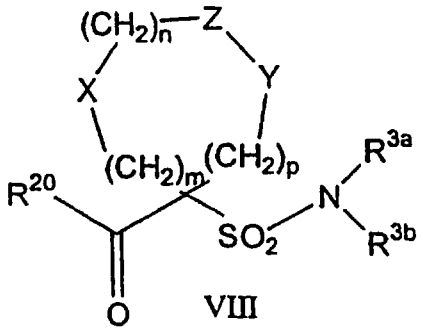
VII



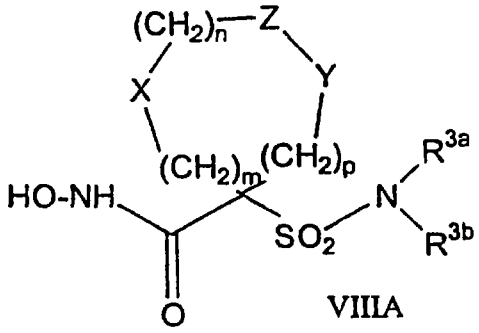
VIIA

wherein substituents R^{20} and -EY are as discussed before as part of an -AREY or -GAREY group, ,with the before-described preferences, and A is $-CH_2-$, $-O-CH_2-$, $-CH_2-O-$, $-S-CH_2-$ or $-CH_2-S-$.

Another group of preferred compounds for use in a contemplated process has a structure that corresponds to formulas VIII and VIIIA, below, or a pharmaceutically acceptable salt thereof:



VIII



VIIIA

wherein

R^{3a}, R^{3b} and R^{20} are as defined before, , with the before-described preferences; and

m is zero, 1 or 2;

n is zero, 1 or 2;

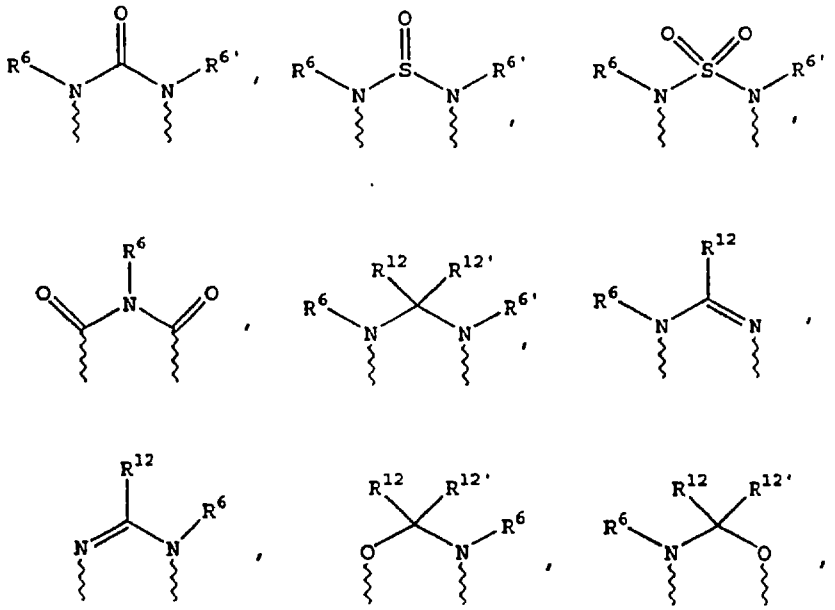
p is zero, 1 or 2;

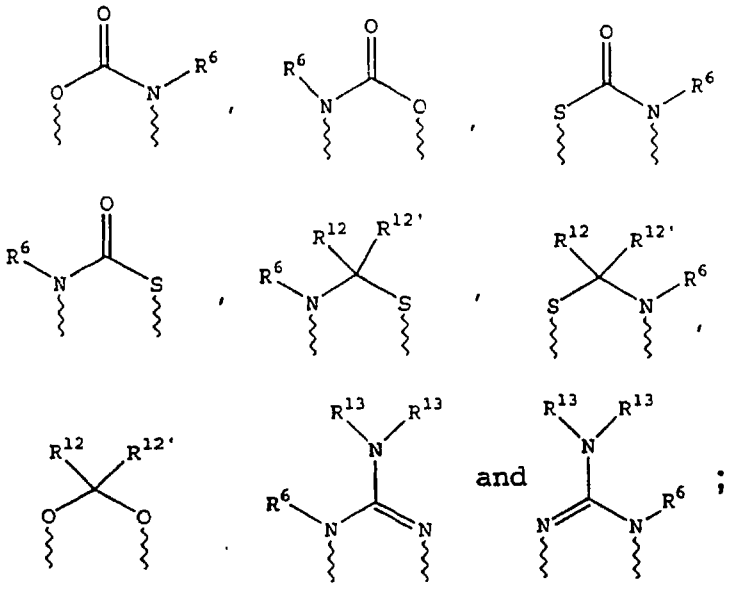
the sum of m + n + p = 1, 2, 3 or 4;

(a) one of X, Y and Z is selected from the group consisting of C(O), NR^6, O, S, S(O), $S(O)_2$ and $NS(O)_2R^7$, and the remaining two of X, Y and Z are CR^8R^9, and $CR^{10}R^{11}$, or

(b) X and Z or Z and Y together constitute a moiety that is selected from the group consisting of $NR^6C(O)$, $NR^6S(O)$, $NR^6S(O)_2$, NR^6S, NR^6O, SS, NR^6NR^6 and OC(O), with the remaining one of X, Y and Z being CR^8R^9, or

(c) n is zero and X, Y and Z together constitute a moiety selected from the group consisting of





wherein wavy lines are bonds to the atoms of the depicted ring;

R^6 and $R^{6'}$ are independently selected from the group consisting of hydrido, C_1-C_6-alkanoyl, C_6-aryl-C_1-C_6-alkyl, aroyl, bis(C_1-C_6-alkoxy-C_1-C_6-alkyl)-C_1-C_6-alkyl, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-perfluoroalkyl, C_1-C_6-trifluoromethylalkyl, C_1-C_6-perfluoroalkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_3-C_8-heterocycloalkyl, C_3-C_8-heterocycloalkylcarbonyl, C_6-aryl, C_5-C_6-heterocyclo, C_5-C_6-heteroaryl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, C_6-aryloxy-C_1-C_6-alkyl, heteroaryloxy-C_1-C_6-alkyl, heteroaryl-C_1-C_6-alkoxy-C_1-C_6-alkyl, heteroarylthio-C_1-C_6-alkyl, C_6-arylsulfonyl, C_1-C_6-alkylsulfonyl, C_5-C_6-heteroarylsulfonyl, carboxy-C_1-C_6-alkyl, C_1-C_4-alkoxycarbonyl-C_1-C_6-alkyl, aminocarbonyl, C_1-C_6-alkyliminocarbonyl, C_6-aryliminocarbonyl, C_5-C_6-heterocycloiminocarbonyl,

C_6-arylthio-C_1-C_6-alkyl, C_1-C_6-alkylthio-C_1-C_6-alkyl, C_6-arylthio-C_3-C_6-alkenyl, C_1-C_4-alkylthio-C_3-C_6-alkenyl, C_5-C_6-heteroaryl-C_1-C_6-alkyl, halo-C_1-C_6-alkanoyl, hydroxy-C_1-C_6-alkanoyl, thiol-C_1-C_6-alkanoyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, C_1-C_5-alkoxycarbonyl, aryloxycarbonyl, NR^8R^9-C_1-C_5-alkylcarbonyl, hydroxy-C_1-C_5-alkyl, an aminocarbonyl wherein the aminocarbonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C_1-C_6-alkyl, ar-C_1-C_6-alkyl, C_3-C_8-cycloalkyl and a C_1-C_6-alkanoyl group, hydroxyaminocarbonyl, an aminosulfonyl group wherein the aminosulfonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C_1-C_6-alkyl, ar-C_1-C_6-alkyl, C_3-C_8-cycloalkyl and a C_1-C_6-alkanoyl group, an amino-C_1-C_6-alkylsulfonyl group wherein the amino-C_1-C_6-alkylsulfonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C_1-C_6-alkyl, ar-C_1-C_6-alkyl, C_3-C_8-cycloalkyl and a C_1-C_6-alkanoyl group and an amino-C_1-C_6-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C_1-C_6-alkyl, ar-C_1-C_6-alkyl, C_3-C_8-cycloalkyl and a C_1-C_6-alkanoyl group;

R^7 is selected from the group consisting of a arylalkyl, aryl, heteroaryl, heterocyclo, C_1-C_6-alkyl, C_3-C_6-alkynyl, C_3-C_6-alkenyl, C_1-C_6-carboxyalkyl and a C_1-C_6-hydroxyalkyl group;

R^8 and R^9 and R^{10} and R^{11} are independently selected from the group consisting of a hydrido, hydroxy, C_1-C_6-alkyl, aryl, ar-C_1-C_6-alkyl, heteroaryl, heteroar-C_1-C_6-alkyl, C_2-C_6-alkynyl, C_2-C_6-alkenyl, thiol-C_1-C_6-alkyl, C_1-C_6-alkylthio-C_1-C_6-alkyl cycloalkyl, cycloalkyl-C_1-C_6-alkyl, heterocycloalkyl-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, aralkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, hydroxycarbonyl-C_1-C_6-alkyl, hydroxycarbonylar-C_1-C_6-alkyl, aminocarbonyl-C_1-C_6-alkyl, aryloxy-C_1-C_6-alkyl, heteroaryloxy-C_1-C_6-alkyl, arylthio-C_1-C_6-alkyl, heteroarylthio-C_1-C_6-alkyl, the sulfoxide or sulfone of any said thio substituents, perfluoro-C_1-C_6-alkyl, trifluoromethyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, alkoxycarbonylamino-C_1-C_6-alkyl and an amino-C_1-C_6-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C_1-C_6-alkyl, ar-C_1-C_6-alkyl, cycloalkyl and C_1-C_6-alkanoyl, or wherein R^8 and R^9 or R^{10} and R^{11} and the carbon to which they are bonded form a carbonyl group, or wherein R^8 and R^9 or R^{10} and R^{11}, or R^8 and R^{10} together with the atoms to which they

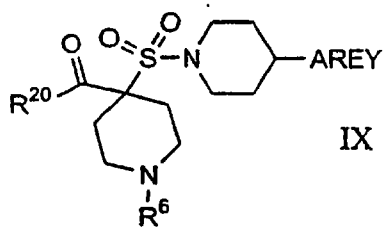
are bonded form a 5- to 8-membered carbocyclic ring, or a 5- to 8-membered heterocyclic ring containing one or two heteroatoms that are nitrogen, oxygen, or sulfur, with the proviso that only one of R^8 and R^9 or R^{10} and R^{11} is hydroxy;

R^{12} and $R^{12'}$ are independently selected from the group consisting of a hydrido, C_1-C_6-alkyl, aryl, ar-C_1-C_6-alkyl, heteroaryl, heteroaralkyl, C_2-C_6-alkynyl, C_2-C_6-alkenyl, thiol-C_1-C_6-alkyl, cycloalkyl, cycloalkyl-C_1-C_6-alkyl, heterocycloalkyl-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, aryloxy-C_1-C_6-alkyl, amino-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, hydroxycarbonyl-C_1-C_6-alkyl, hydroxycarbonylar-C_1-C_6-alkyl, aminocarbonyl-C_1-C_6-alkyl, aryloxy-C_1-C_6-alkyl, heteroaryloxy-C_1-C_6-alkyl, C_1-C_6-alkylthio-C_1-C_6-alkyl, arylthio-C_1-C_6-alkyl, heteroarylthio-C_1-C_6-alkyl, the sulfoxide or sulfone of any said thio substituents, perfluoro-C_1-C_6-alkyl, trifluoromethyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, alkoxycarbonylamino-C_1-C_6-alkyl and an amino-C_1-C_6-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C_1-C_6-alkyl, ar-C_1-C_6-alkyl, cycloalkyl and C_1-C_6-alkanoyl;

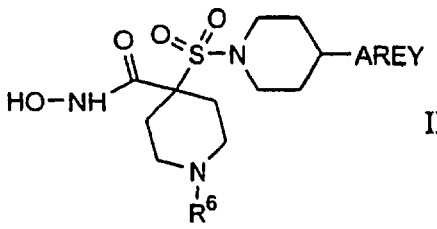
R^{13} is selected from the group consisting of a hydrido, benzyl, phenyl, C_1-C_6-alkyl, C_2-C_6-alkynyl, C_2-C_6-alkenyl and a C_1-C_6-hydroxyalkyl group.

A compound of formulas VIII and VIIIA thus includes a compound illustrated by formulas V, VA, VII and VIIA discussed above, as well as other compounds of formulas I and II.

A group of particularly preferred compounds of formula VIII and VIIIA correspond in structure to formula IX or IX, below, or a pharmaceutically acceptable salt thereof:



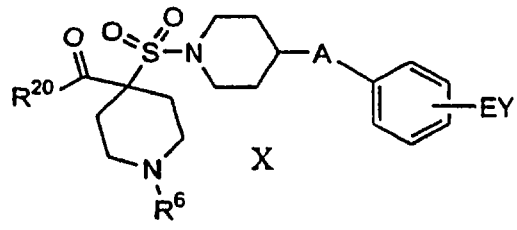
IX



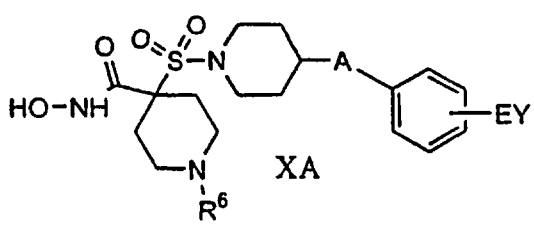
IXA

wherein R^6, R^{20} and -AREY are as described before, with the before-described preferences.

A still more preferred group of contemplated compounds correspond in structure to formula X, formula XA or a pharmaceutically acceptable salt thereof:



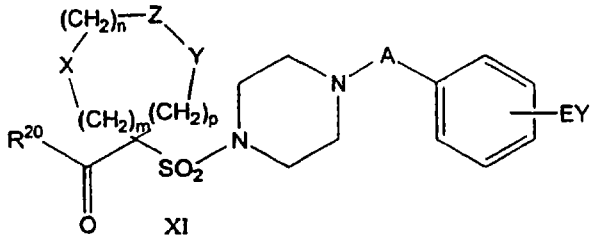
X



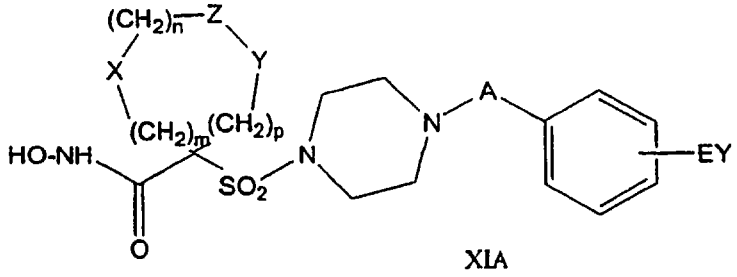
XA

wherein substituents R^6, R^{20} and -EY are as discussed before as part of an -AREY or -GAREY group, with the before-described preferences, and wherein A is $-CH_2-$, $-O-CH_2-$, $-CH_2-O-$, $-S-CH_2-$ or $-CH_2-S-$.

A group of contemplated compounds that is even still more preferred contain a $-NR^{3a}R^{3b}$ group in which R^{3a} and R^{3b} taken together with the nitrogen atom to which they are bonded form a group -GAREY where G is a disubstituted piperazinyl group correspond in structure to formula XI, formula XIA or a pharmaceutically acceptable salt thereof:



XI



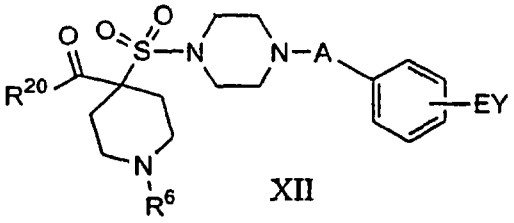
XIA

wherein the definitions for X, Y, Z, m, n, p A, E, Y and R^{20} are as before discussed, with the before-described preferences and A being absent.

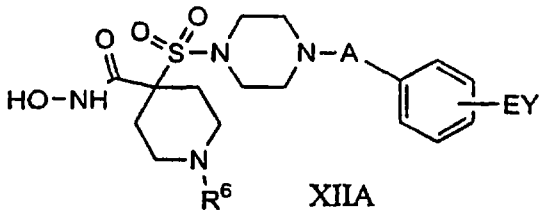
Without wishing to be bound by theory, it is believed that when substituent A is absent so that R is bonded directly to G, the bond flexibility provided by the non-sulfamido nitrogen of the piperazinyl group, -G-, to the remainder of the -AREY substituent present provides enhanced fit of an inhibitor into the binding pocket of gelatinase and MMP-13 enzymes, while not appreciably altering the binding to MMP-1. It is also believed that similar

flexibility and enhanced binding to these enzymes is achieved where $-SO_2G-$ is a substituted N-sulfonamidopiperadinyl group and substituent A is a single atom such as -O-, -S-, or $-CH_2-$ or -NH-.

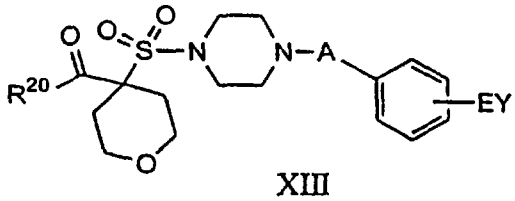
Of the compounds of formulas XI and XIA, a compound corresponding in formula to formulas XII or XII, formulas XIIA or XIIIA or a pharmaceutically acceptable salt thereof is yet more preferred,



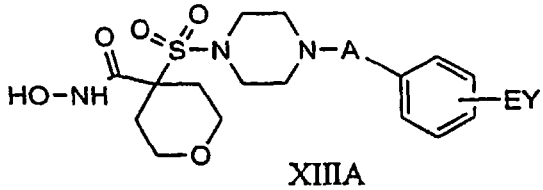
XII



XIIA



XIII



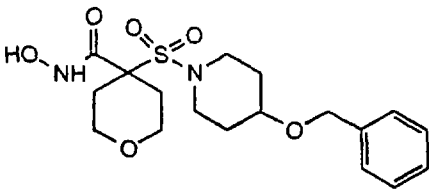
XIIIA

wherein R^6, R^{20} and -EY are as described before, with the before-described preferences.

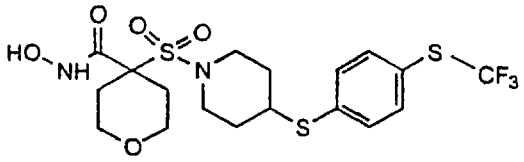
It is particularly preferred that both substituents A and E be absent in a compound of formulas XII, XIII, XIIA and XIIIA so that the substituted phenyl ring, substituent or moiety R, is bonded on one side directly to one nitrogen atom of the piperazinyl ring, and on the other side, that phenyl ring is bonded directly to the Y group.

The structures of several particularly preferred compounds of the above formulas are shown

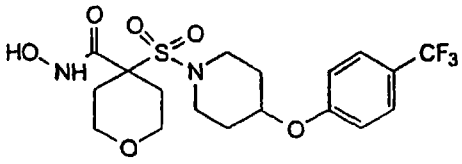
below along with the Example in which the particular compound is synthesized.



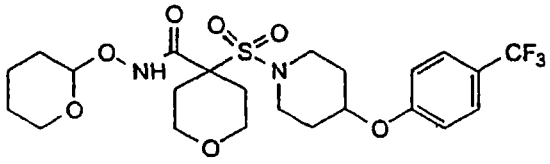
EXAMPLE 1



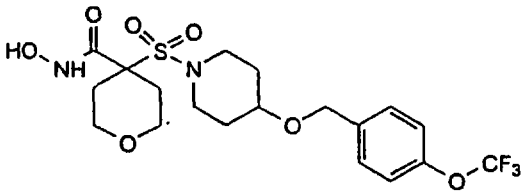
EXAMPLE 3



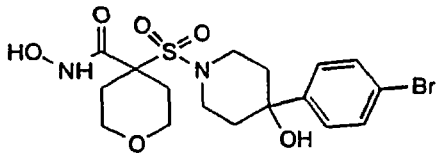
EXAMPLE 2



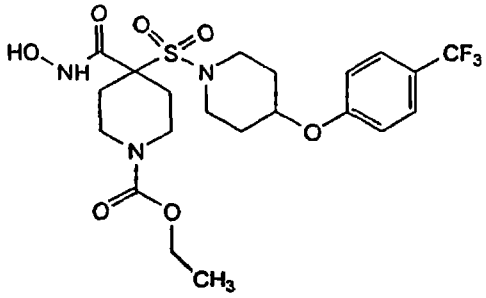
EXAMPLE 2H



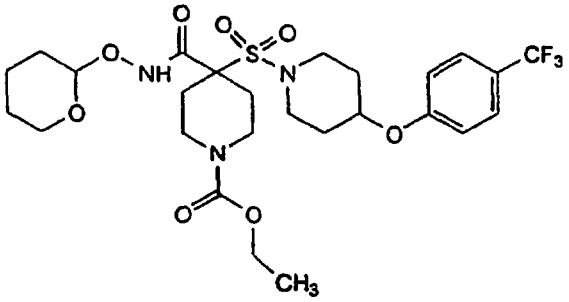
EXAMPLE 4



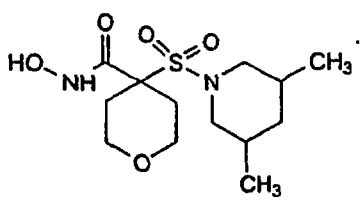
EXAMPLE 5



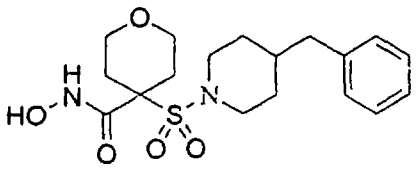
EXAMPLE 6



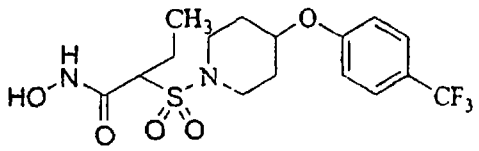
EXAMPLE 6H



EXAMPLE 7



EXAMPLE 8



EXAMPLE 9

Further particularly preferred compounds include:

4-[(hydroxyamino)-carbonyl]-4-[[4-[4-(trifluoromethyl)-phenoxy]-1-piperidinyl]sulfonyl]-1-piperidinecarboxylate;

N-hydroxy-2-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]acetamide;

N-[(tetrahydro-2H-pyran-2-yl)oxy]-2-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl] acetamide;

N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-(trifluoromethyl)-phenoxy]-1-piperidinyl)sulfonyl]-4-piperidinecarboxamide, monohydrochloride;

1-(2-Methoxyethyl)-N-[(tetrahydro-2H-pyran-2-yl)oxy]-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide;

tetrahydro-N-hydroxy-4-[[4- (4-nitrophenoxy)-1-piperidinyl]sulfonyl]-2H-pyran-4-carboxamide;

tetrahydro-N-hydroxy-4-[[4-(4-nitrophenoxy)-1-piperidinyl]sulfonyl]-2H-pyran-4-carboxamide;

N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride;

1-(phenylmethyl)-N-[(tetrahydro-2H-pyran-2-yl)oxy-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]- sulfonyl]-4-piperidinecarboxylate;

N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride;

1-(2-methoxyethyl)-N-[(tetrahydro-2H-pyran-2-yl)oxy]-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxylate;

N-hydroxy-2-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]acetamide;

N-[(tetrahydro-2H-pyran-2-yl)oxy]-2-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-acetamide;

tetrahydro-N-hydroxy-4-[[4-[4-(trifluoromethoxy)-phenoxy]-1-piperidinyl]sulfonyl]-2H-pyran-4-carboxamide;

tetrahydro-N-[(tetrahydro-2H-pyran-2-yl)oxy]-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-2H-pyran-4-carboxamide;

N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]-4-piperidinecarboxamide, monohydrochloride;

1-(phenylmethyl)-N-[(tetrahydro-2H-pyran-2-yl)oxy]-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide;

N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride;

1-(2-pyridinylmethyl)-N-[(tetrahydro-2H-pyran-2-yl)oxy]-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]-sulfonyl]-4-piperidinecarboxamide;

N-hydroxy-1-(2-pyrimidinyl)-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride;

1-(2-pyrimidinyl)-N-[(tetrahydro-2H-pyran-2-yl)oxy]-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]-4-piperidinecarboxamide;

N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-1-[4-(trifluoromethyl)-2-pyrimidinyl]-4-piperidinecarboxamide, monohydrochloride;

N-[(tetrahydro-2H-pyran-2-yl)oxy]-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-1-[4-(trifluoromethyl)-2-pyrimidinyl]-4-piperidinecarboxamide;

1-(5-ethyl-2-pyrimidinyl)-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride;

1-(5-ethyl-2-pyrimidinyl)-N-[(tetrahydro-2H-pyran-2-yl)oxy]-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide;

tetrahydro-*N*-hydroxy-4-[[4-[4-(trifluoromethoxy)-phenoxy]-1-piperidinyl]sulfonyl]-2*H*-thiopyran-4-carboxamide;

tetrahydro-*N*-hydroxy-4-[[4-[4-(trifluoromethoxy)-phenoxy]-1-piperidinyl]sulfonyl]-2*H*-thiopyran-4-carboxamide;

tetrahydro-*N*-hydroxy-4-[[4-[4-(trifluoromethoxy)-phenoxy]-1-piperidinyl]sulfonyl]-2*H*-thiopyran-4-carboxamide, 1,1-dioxide;

tetrahydro-*N*-hydroxy-4-[[4-[4-(trifluoromethoxy)-phenoxy]-1-piperidinyl]sulfonyl]-2*H*-thiopyran-4-carboxamide, 1,1-dioxide;

tetrahydro-*N*-hydroxy-4-[[4-[4-(trifluoromethyl)-phenoxy]-1-piperidinyl]sulfonyl]-2*H*-thiopyran-4-carboxamide;

tetrahydro-*N*-hydroxy-4-[[4-[4-(trifluoromethyl)-phenoxy]-1-piperidinyl]sulfonyl]-2*H*-thiopyran-4-carboxamide;

N-hydroxy-4[[1'-(*n*-pentyl)[4,4'-bipiperidin]-1-yl]sulfonyl]-tetrahydro-2*H*-pyran-4-carboxamide;

N-hydroxy-4[[1'-(4-methoxybenzoyl)[4,4'-bipiperidin]-1-yl]sulfonyl]-tetrahydro-2*H*-pyran-4-carboxamide;

N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride;

1-(2-furanylmethyl)-*N*-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide;

4-[[4-[4-[4-(trifluoromethyl)phenoxy]phenoxy]-1-piperidinyl]sulfonyl]tetrahydro-*N*-hydroxy-2*H*-pyran-4-carboxamide;

tetrahydro-N-hydroxy-4-[[4-(4-pentylphenyl)-1-piperazinyl]sulfonyl]-2H-pyran-4-carboxamide, monohydrochloride;

tetrahydro-N-hydroxy-4-[(4-phenyl-1-piperazinyl)-sulfonyl]-2H-pyran-4-carboxamide;

N-hydroxy-1-(2-methoxyethyl)-4-[[4-[[4-(trifluoromethyl)benzoyl]amino]-1-piperidinyl]-sulfonyl]-4-piperidinecarboxamide, monohydrochloride;

N-hydroxy-1-phenyl-4-[[4-[4-(trifluoromethoxy)-phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride;

N-hydroxy-1-phenyl-4-[[4-[4-(trifluoromethyl)-phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride;

4-[[4-[4-(1,1-dimethylethyl)phenyl]-1-piperazinyl]-sulfonyl]-N-hydroxy-1-(2-methoxyethyl)-4-piperidinecarboxamide, monohydrochloride;

4-[[4-(4-butoxyphenyl)-1-piperazinyl]sulfonyl]-N-hydroxy-1-(2-methoxyethyl)-4-piperidinecarboxamide, dihydrochloride;

tetrahydro-N-hydroxy-4-[[4-[[4-[(trifluoromethyl)-thio]phenyl]-thio]-1-piperidinyl]sulfonyl]-2H-pyran-4-carboxamide;

4-[[4-(4-bromophenyl)-4-fluoro-1-piperidinyl]-sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide;

4-[[4-[4-(3,5-dimethylphenoxy)phenoxy]-1-piperidinyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide;

1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride;

N-hydroxy-1-(iminophenylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride;

N-hydroxy-1-[(4-hydroxyphenyl)iminomethyl]-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride;

1-(2-furanylcarbonyl)-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide;

N-hydroxy-1-[2-(methylthio)-4-pyrimidinyl]-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride;

1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride;

N-hydroxy-4-[[1'-(2-methoxyphenyl)[4,4'-bipiperidin]-1-yl]sulfonyl]-1-(phenylmethyl)-4-piperidinecarboxamide, dihydrochloride;

4-(1,4-dioxa-8-azaspiro-[4.5]dec-8-ylsulfonyl)-tetrahydro-N-hydroxy-2H-pyran-4-carboxamide;

4-[[4-[[(3R,5R)-rel-3,5-dimethyl-1-piperidinyl]-carbonyl]-1-piperidinyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide;

4-[[4-[[(3R,5S)-rel-3,5-dimethyl-1-piperidinyl]-carbonyl]-1-piperidinyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide;

N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-(trifluoro-methyl)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride;

N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-(trifluoro-methoxy)phenoxy]-1-piperidinyl]-sulfonyl]-4-piperidinecarboxamide, monohydrochloride;

tetrahydro-N-hydroxy-4-[[4-(phenylmethyl)-1-piperazinyl]-sulfonyl]-2H-pyran-4-carboxamide, monohydrochloride;

N-hydroxy-1-(phenylmethyl)-4-[(4-phenyl-1-piperazinyl)sulfonyl]-4-piperidinecarboxamide, bis(trifluoroacetate);

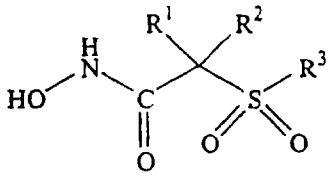
N-hydroxy-1-(phenylmethyl)-4-[(4-phenyl-1-piperazinyl)sulfonyl]-4-piperidinecarboxamide, dihydrochloride; and

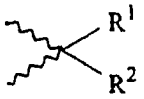
4-[[4-(4-butoxy-3-methylphenyl)-1-piperazinyl]-sulfonyl]-tetrahydro-N-hydroxy-2H-pyran-4-carboxamide.

Most preferred are compounds or their salts are those of Examples 19, 51, 47, 17, 42, 15, 12, 14, 35, 32, 23, 3, 2, 36, 43, 44, 13, 6, 46,28, 30, 10, 50, 9, 18, 31, 16, 8, 55, 11, 38, 53, 33, 41, 40, 4, 54, 34 and 5.

Table 1 through Table 221, below, illustrate several compounds useful in a process of this invention. Each group of compounds is illustrated by a generic formula, or formulae, followed by a series of preferred moieties or groups that constitute various substituents that can be attached at the position clearly shown in the generic structure. The generic symbols, e.g., R^1, R^2 and the like, are as shown in the tables and are not necessarily as defined before. This system is well known in the chemical communication arts and is widely used in scientific papers and presentations. For example in Table 1, R^1 and R^2 groups of the generic structure shown and of formula I are illustrated as being taken together with the carbon to which they are bonded illustrate structural variables that can substitute for the R^1 and R^2 groups shown in the balance of the table. There are 12 R^1 and R^2 groups shown that are used to represent, in a non-limiting manner, 12 distinct compounds that can be prepared for use in the invention.

Table 1





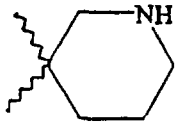
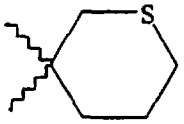
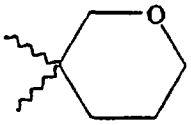
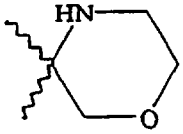
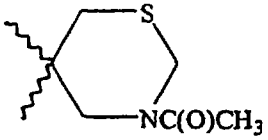
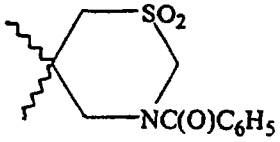
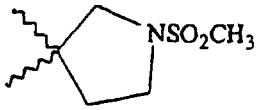
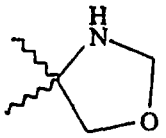
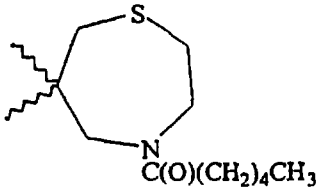
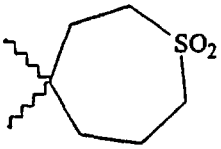
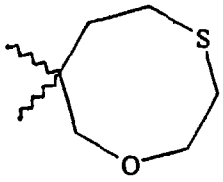
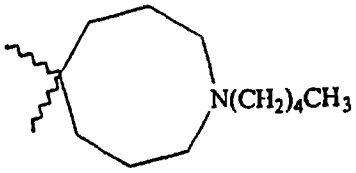
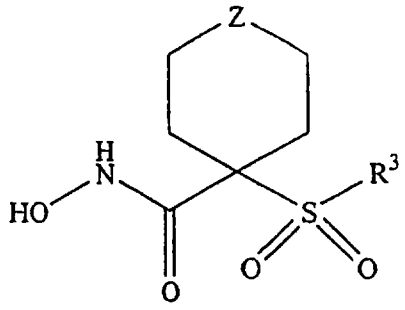
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Table 2



II

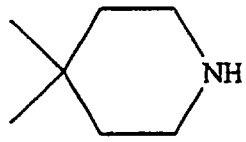
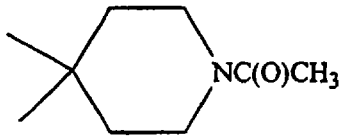
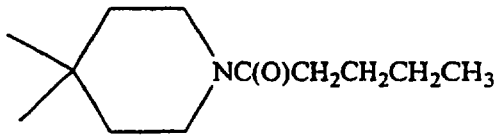
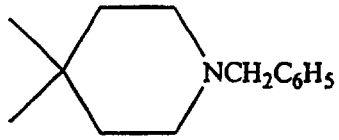
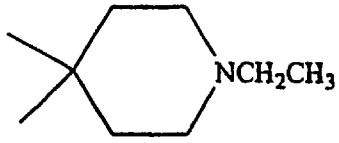
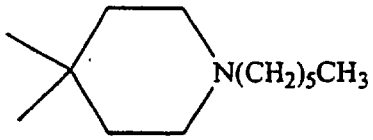
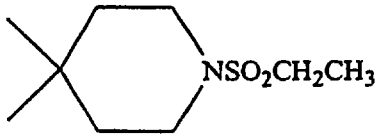
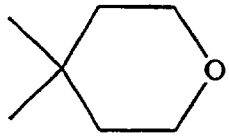
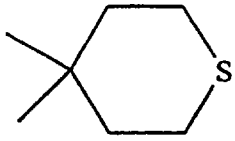
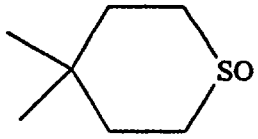
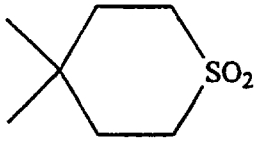
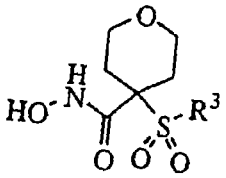
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Table 3



R^3

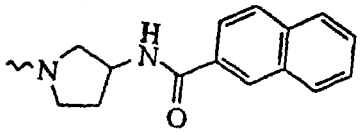
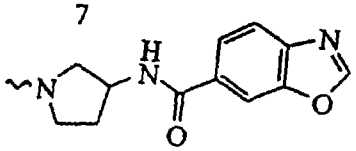
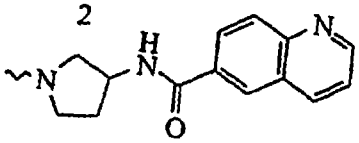
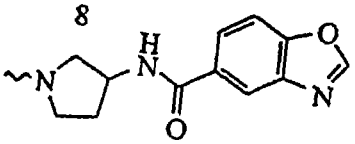
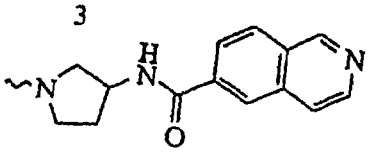
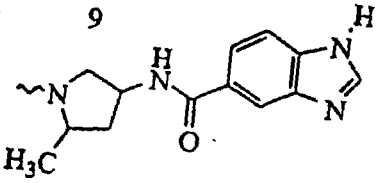
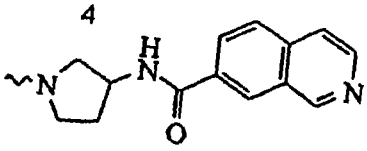
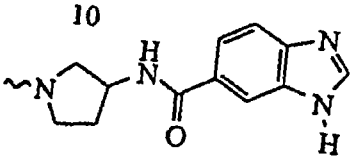
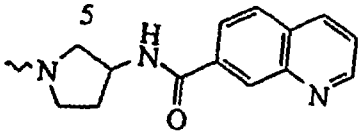
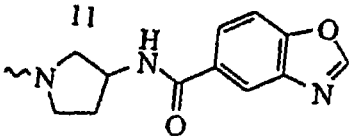
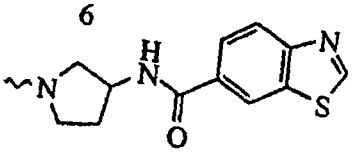
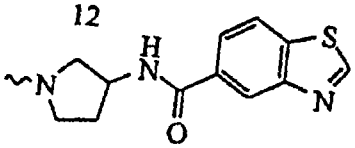
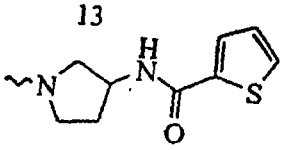
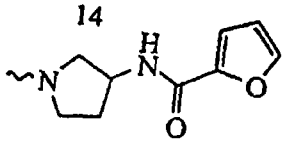
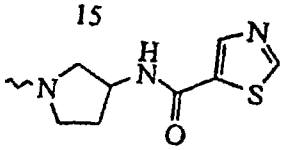
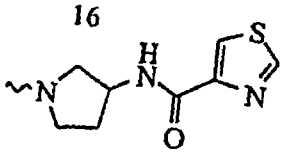
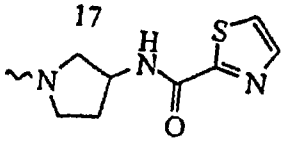
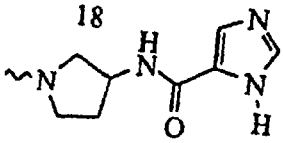
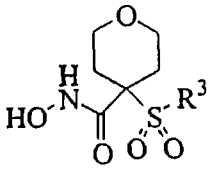
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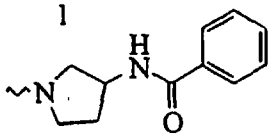
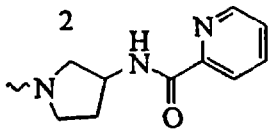
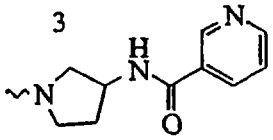
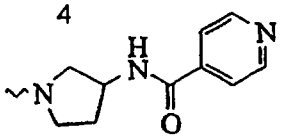
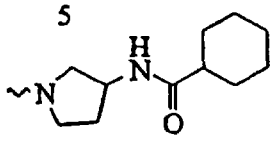
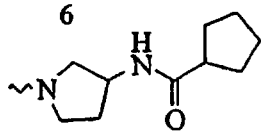
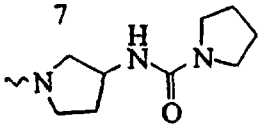
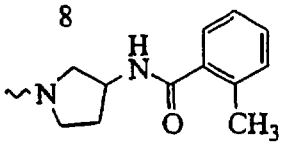
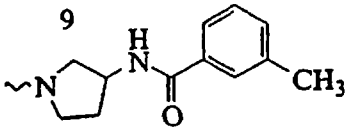
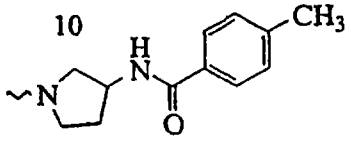
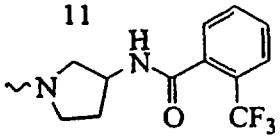
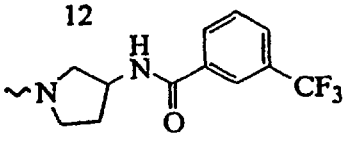
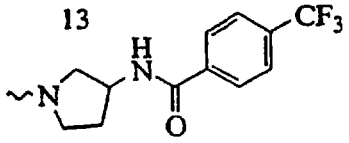
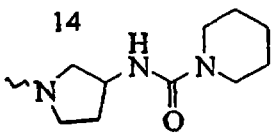
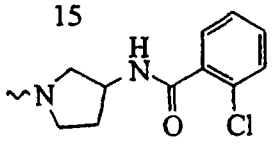
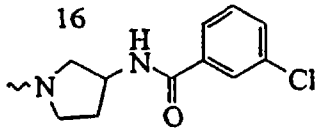
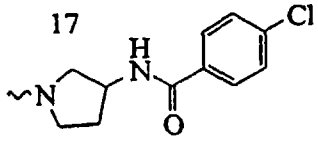
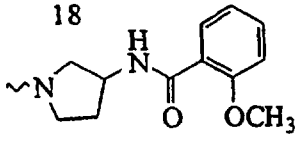
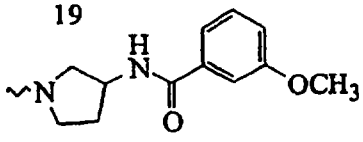
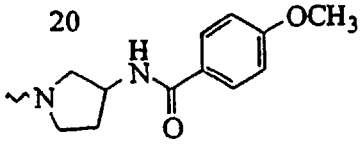
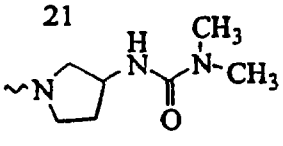
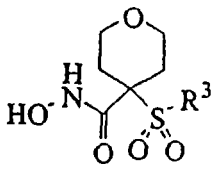
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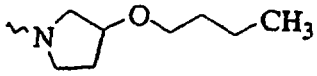
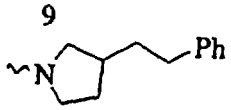
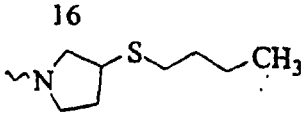
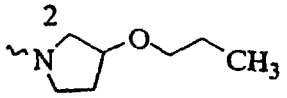
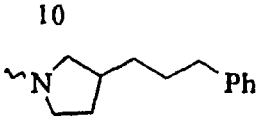
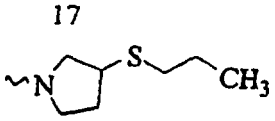
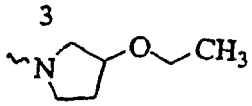
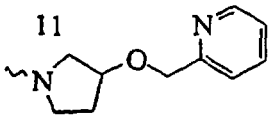
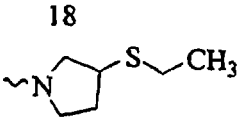
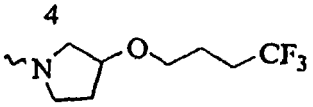
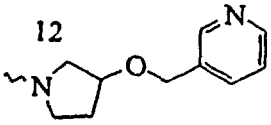
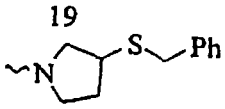
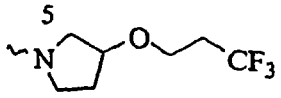
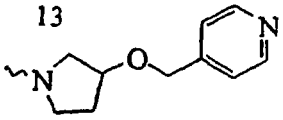
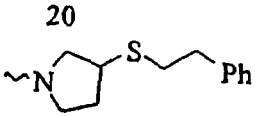
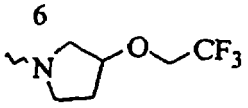
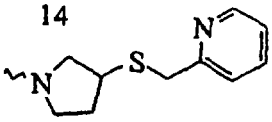
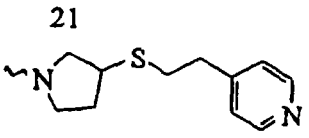
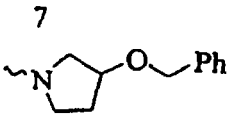
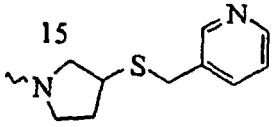
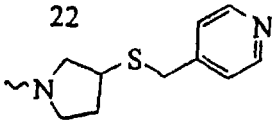
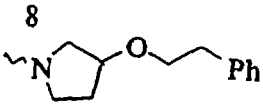
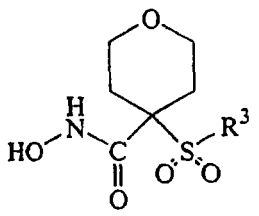
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Table 6



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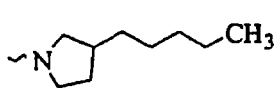
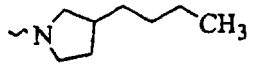
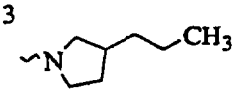
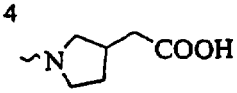
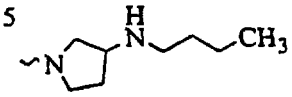
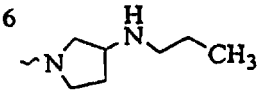
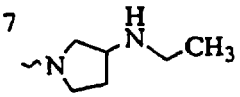
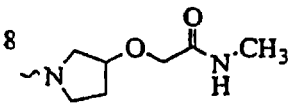
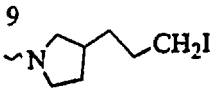
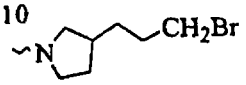
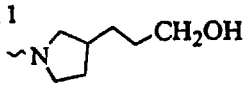
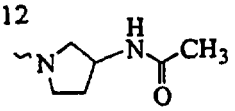
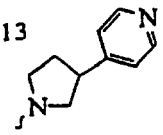
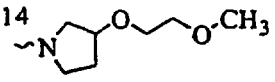
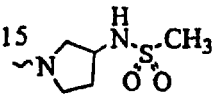
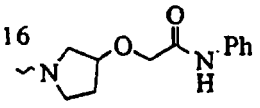
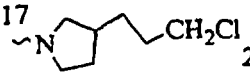
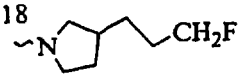
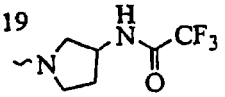
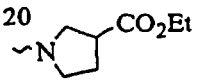
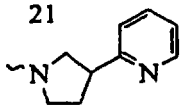
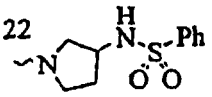
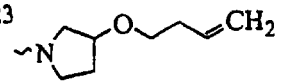
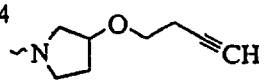
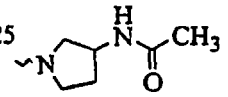
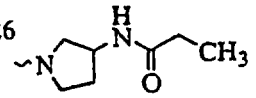
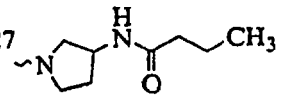
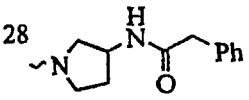
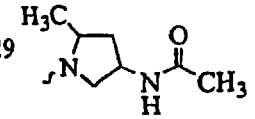
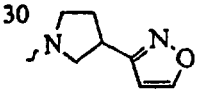
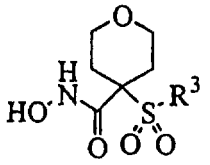
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Table 7





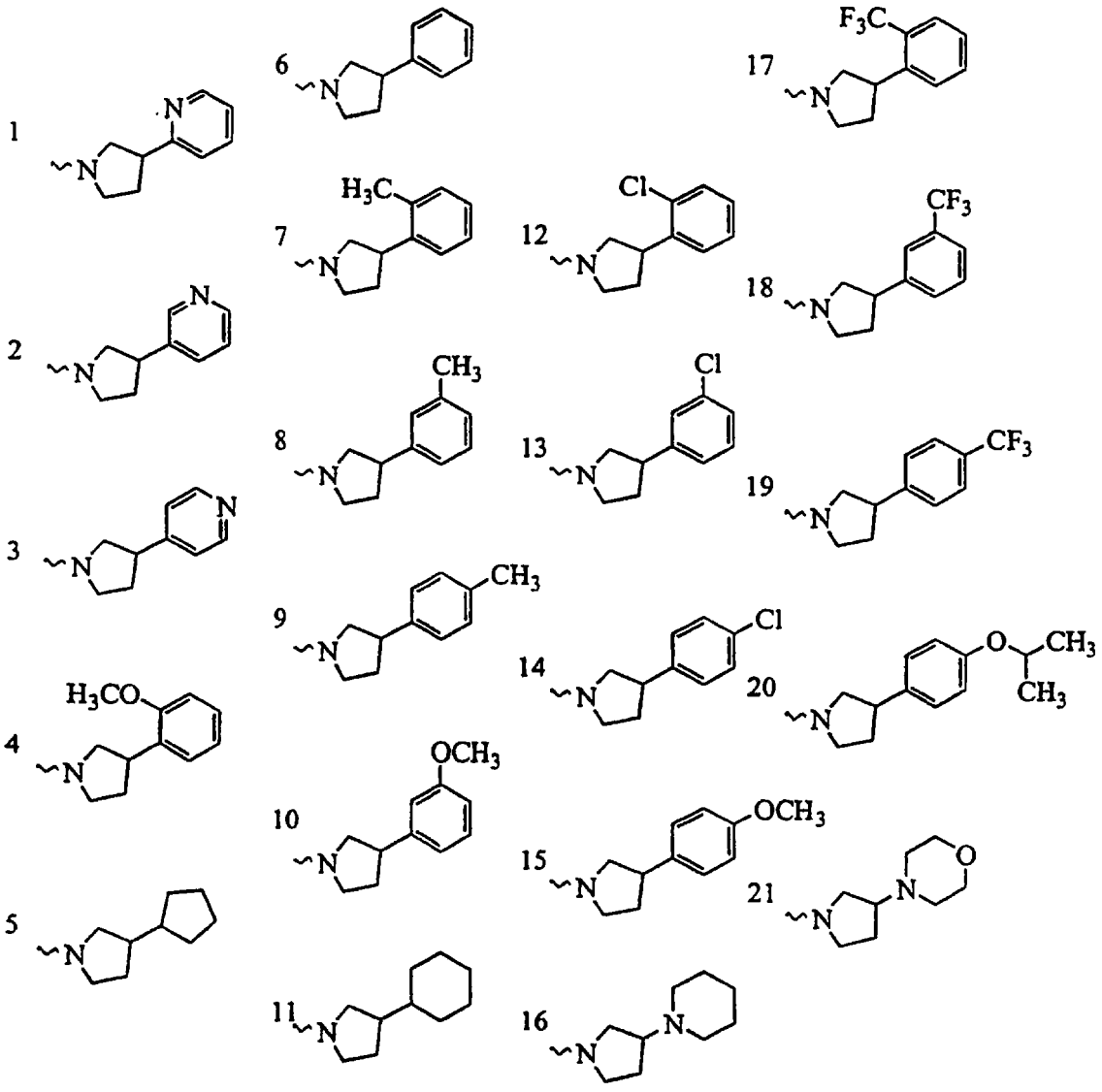
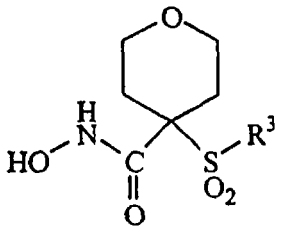

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Table 8





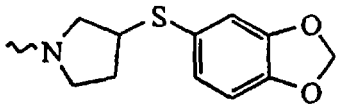
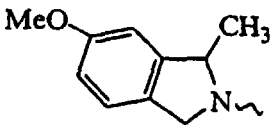
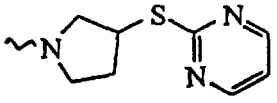
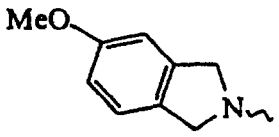
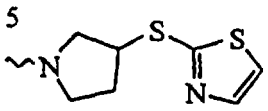
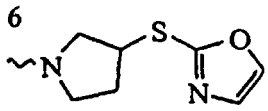
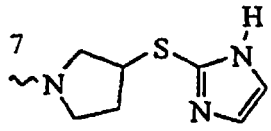
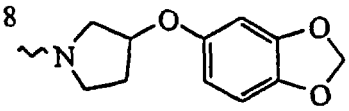
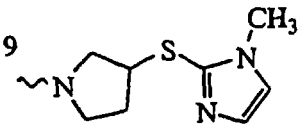
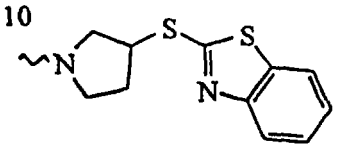
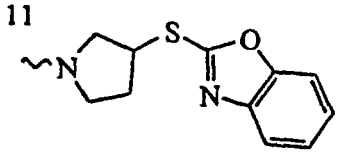
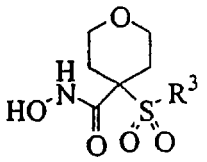
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Table 9



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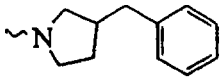
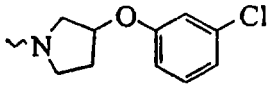
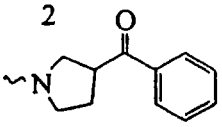
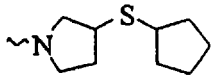
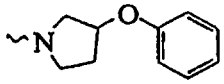
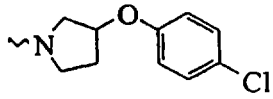
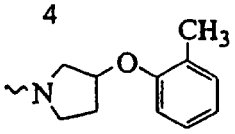
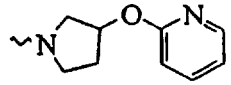
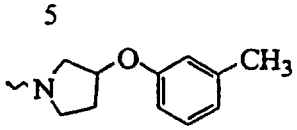
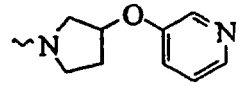
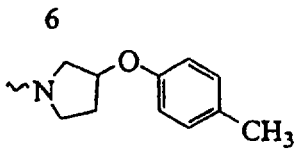
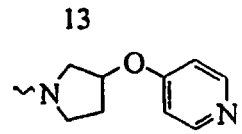
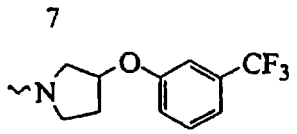
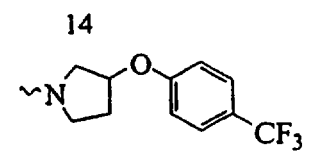
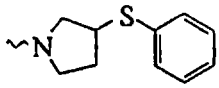
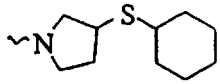
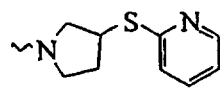
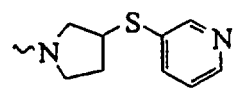
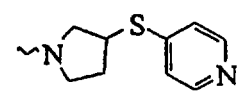
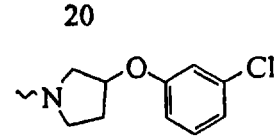
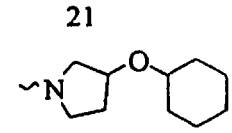
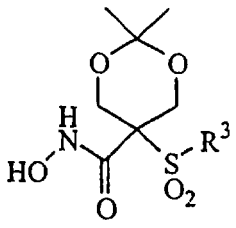
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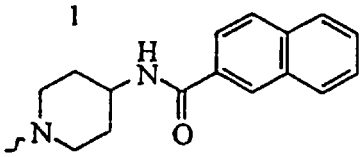
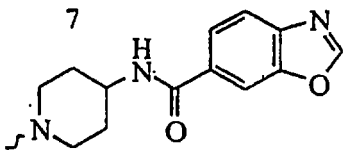
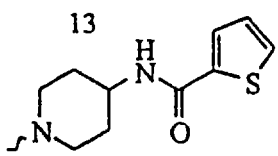
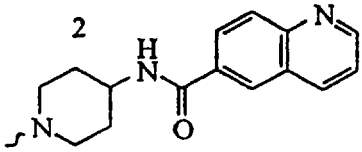
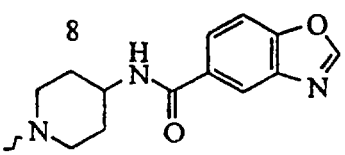
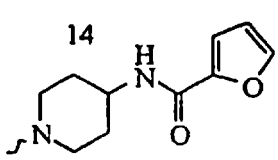
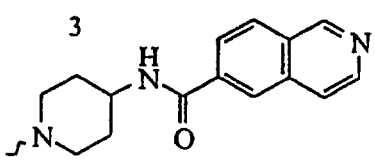
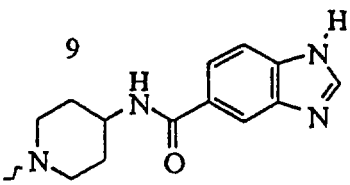
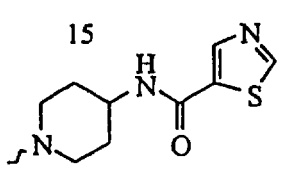
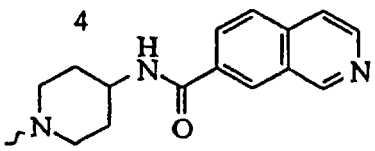
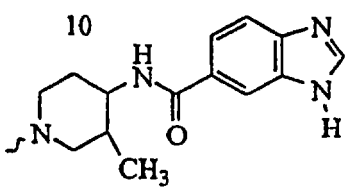
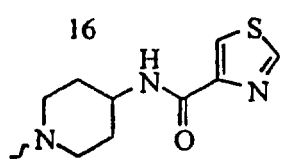
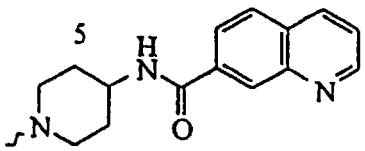
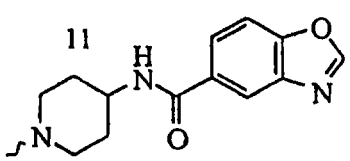
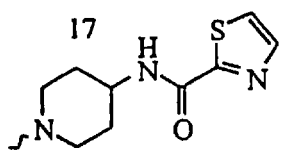
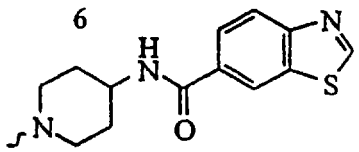
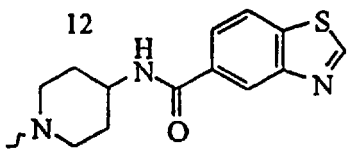
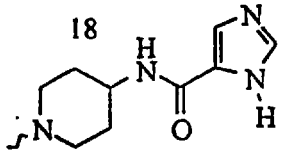
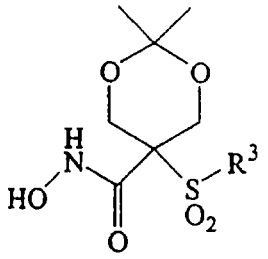
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Table 11



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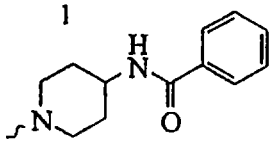
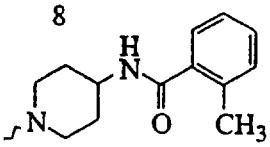
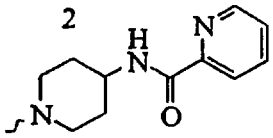
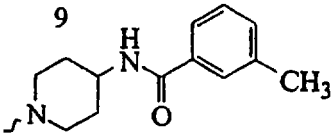
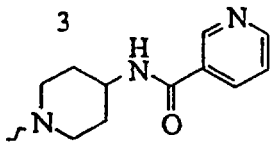
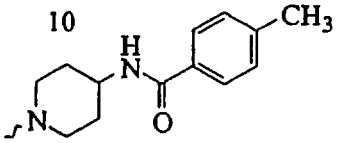
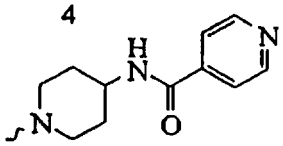
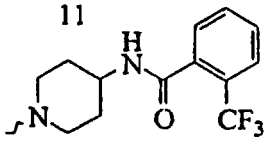
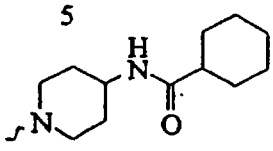
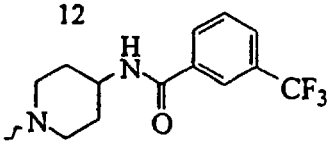
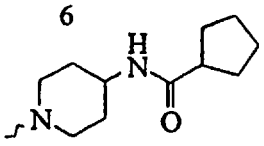
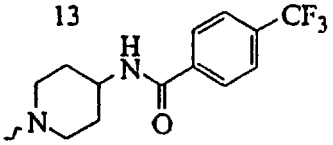
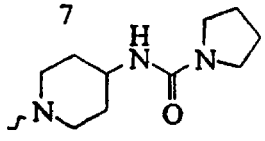
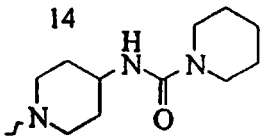
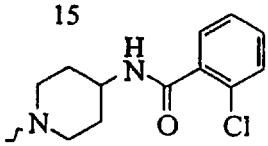
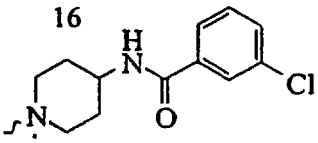
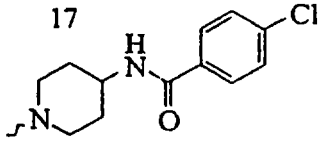
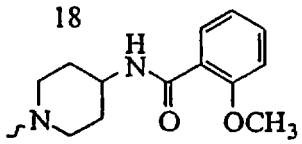
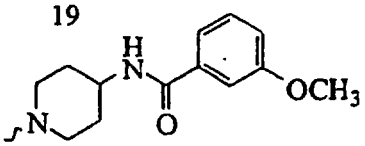
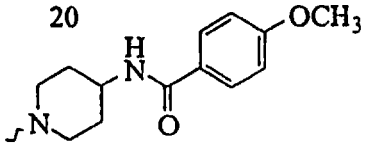
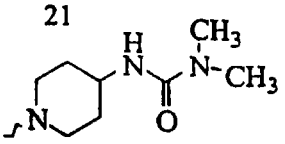
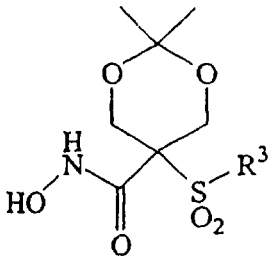
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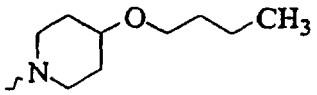
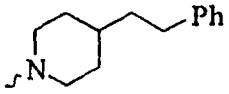
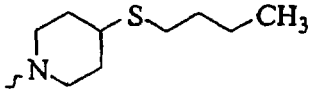
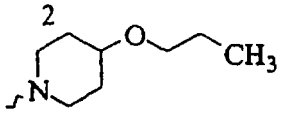
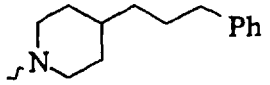
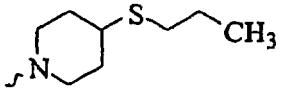
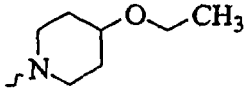
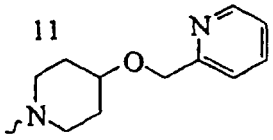
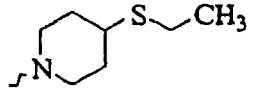
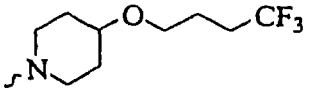
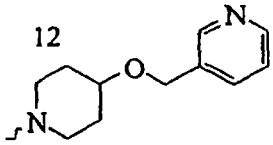
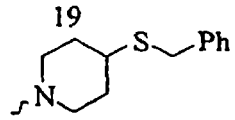
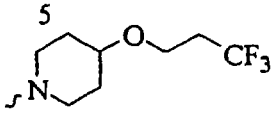
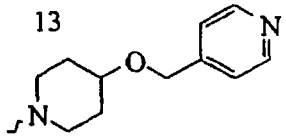
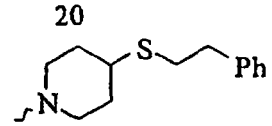
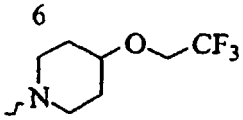
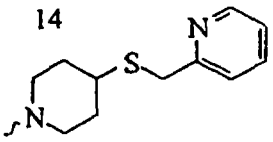
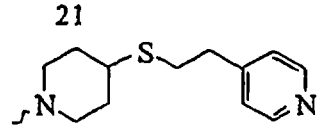
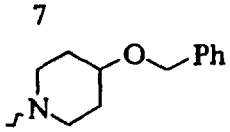
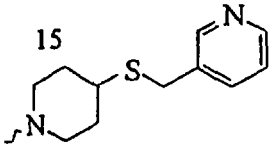
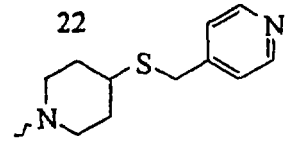
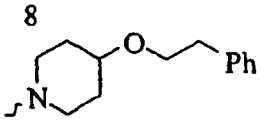
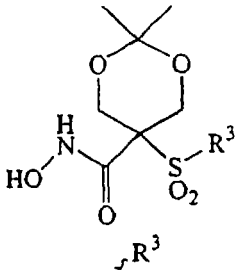
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Table 13



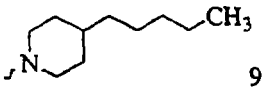
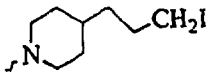
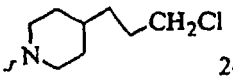
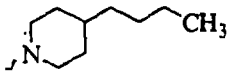
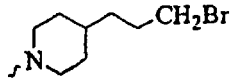
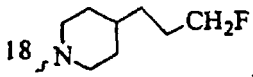
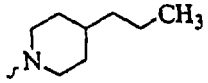
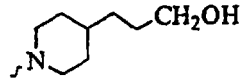
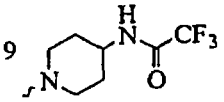
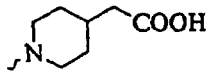
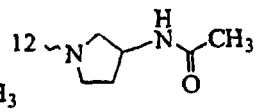
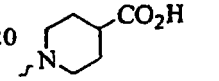
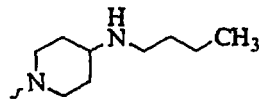
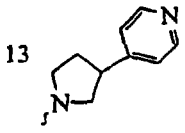
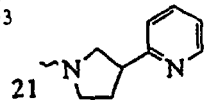
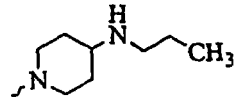
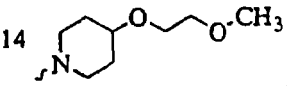
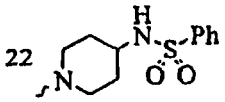
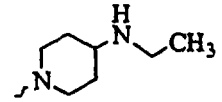
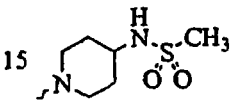
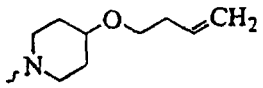
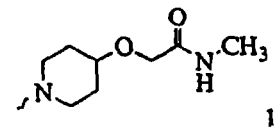
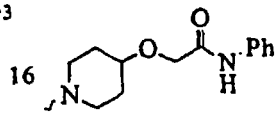
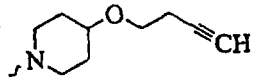
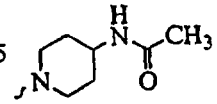
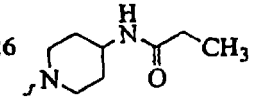
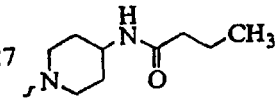
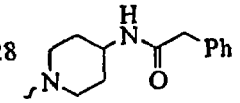
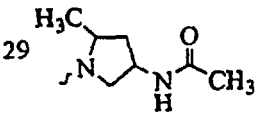
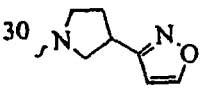
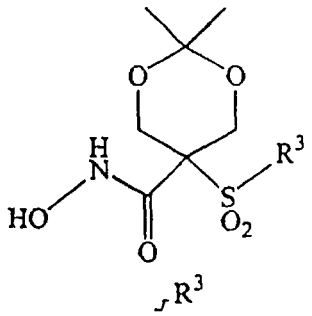
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Table 14



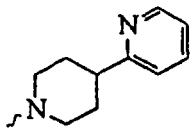
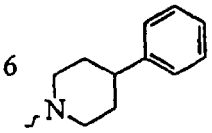
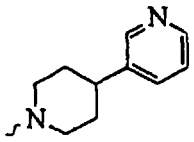
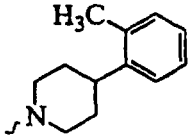
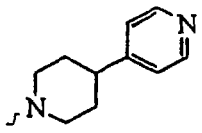
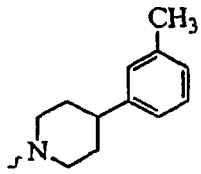
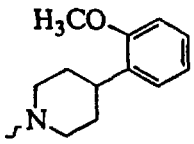
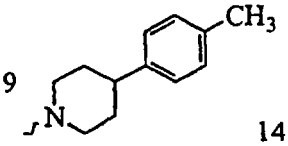
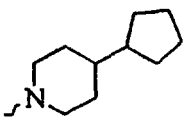
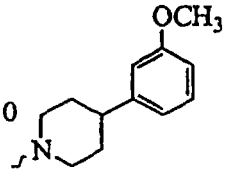
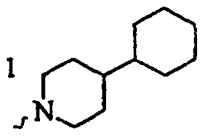
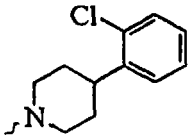
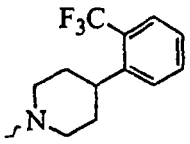
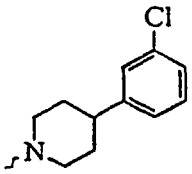
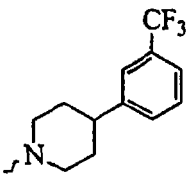
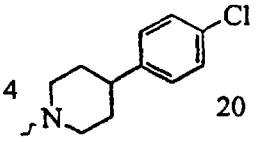
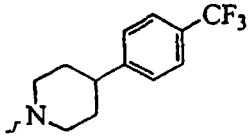
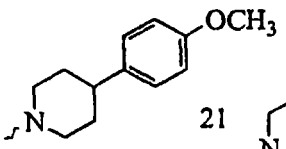
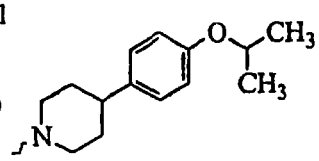
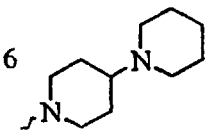
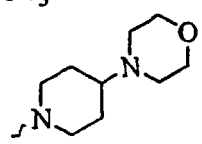
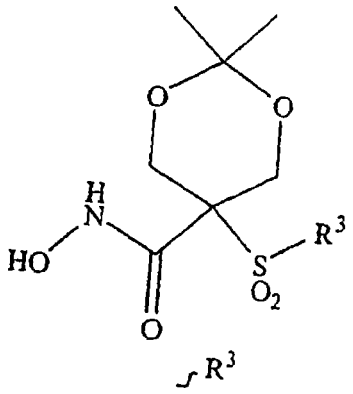
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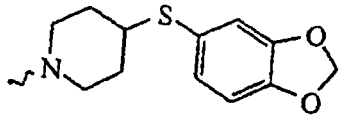
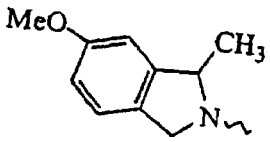
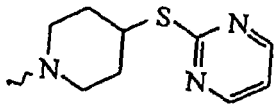
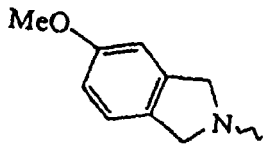
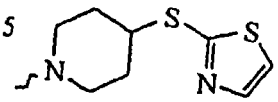
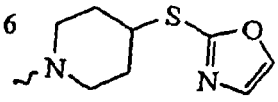
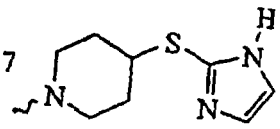
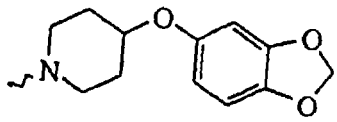
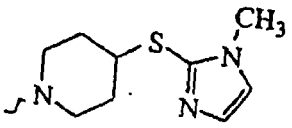
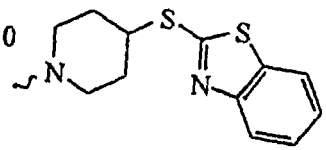
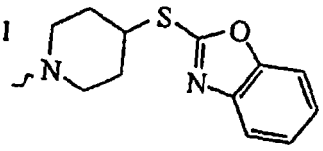
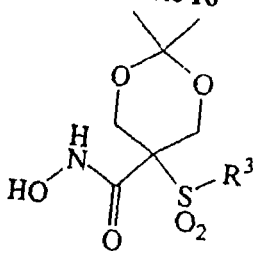
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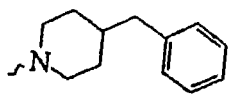
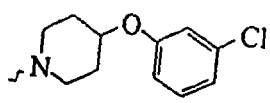
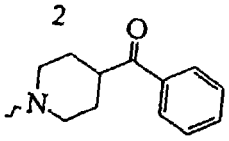
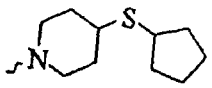
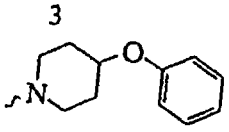
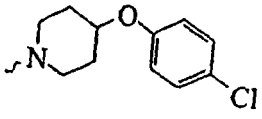
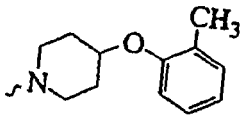
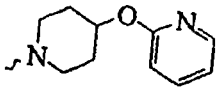
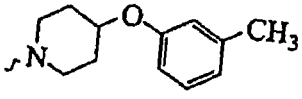
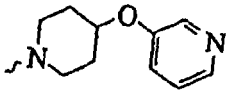
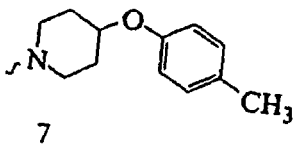
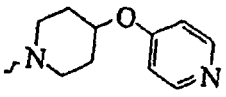
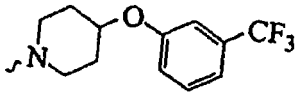
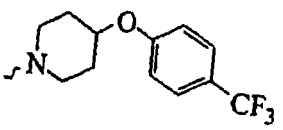
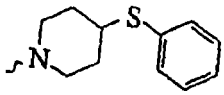
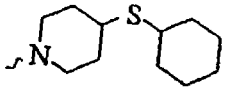
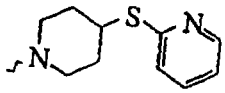
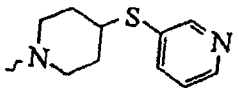
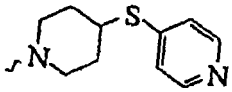
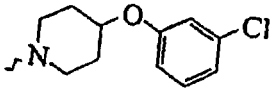
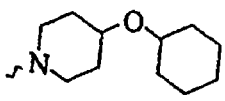
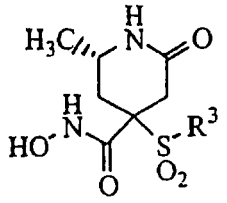
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Table 17



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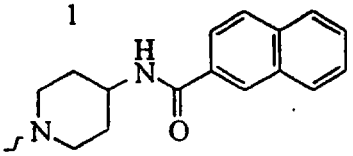
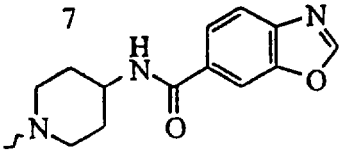
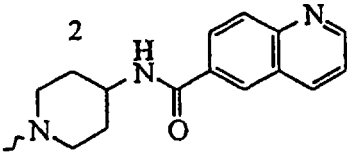
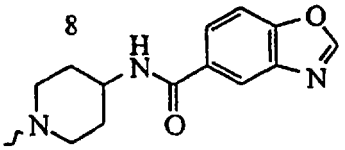
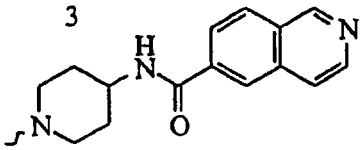
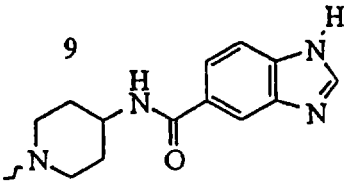
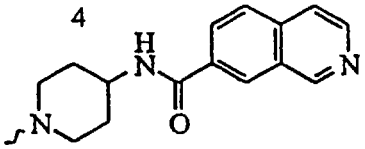
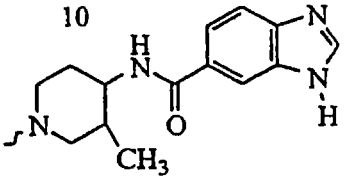
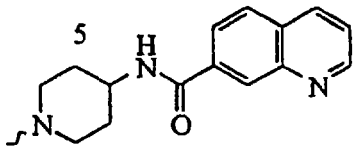
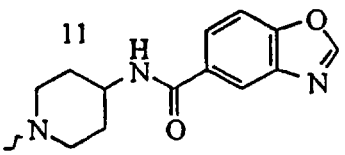
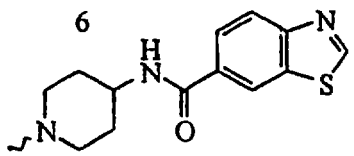
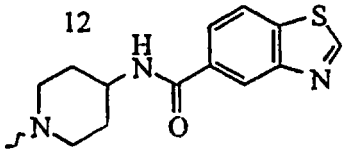
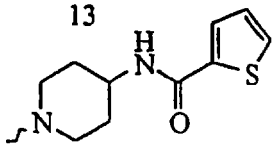
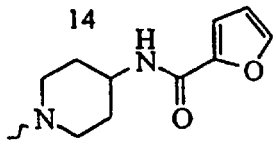
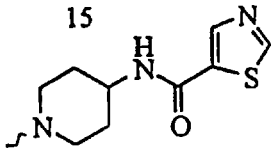
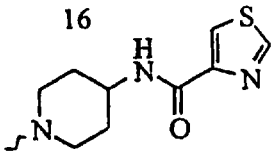
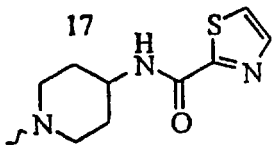
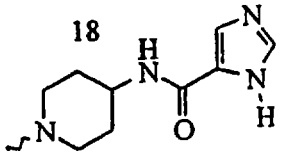
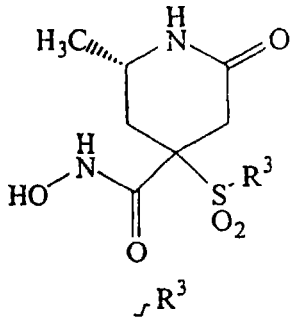
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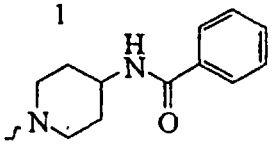
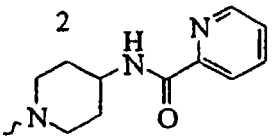
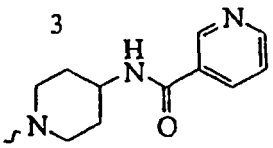
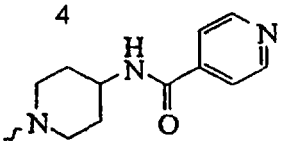
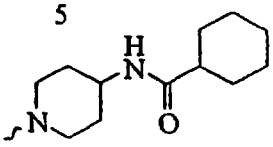
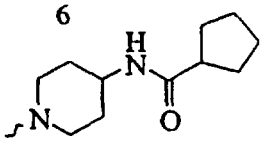
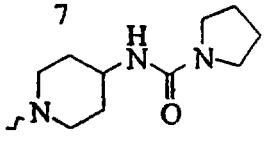
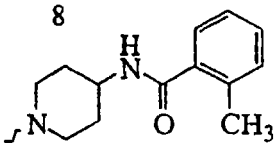
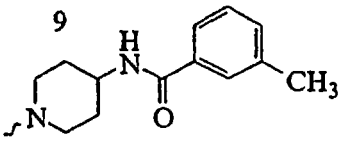
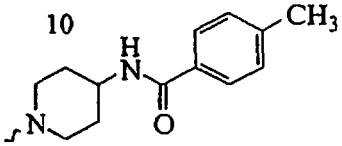
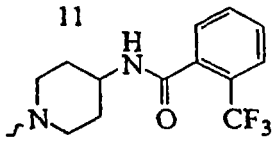
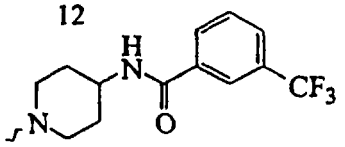
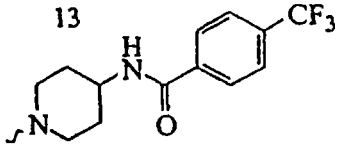
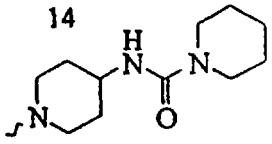
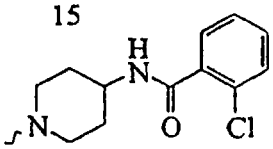
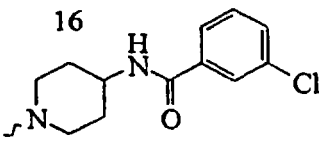
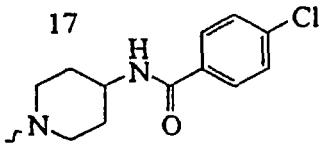
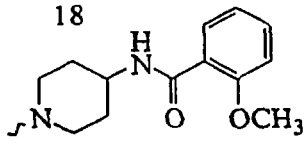
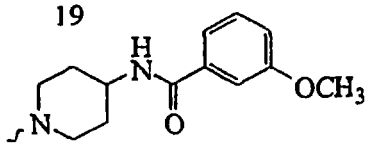
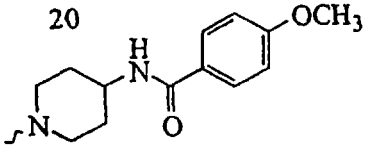
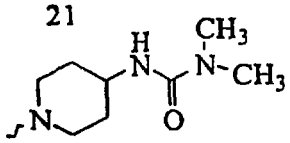
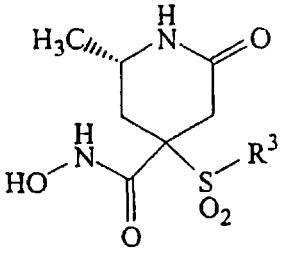
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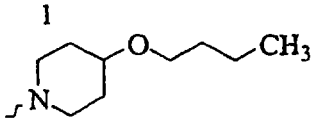
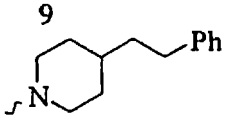
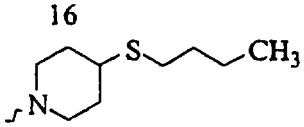
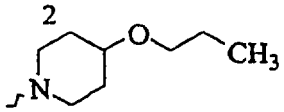
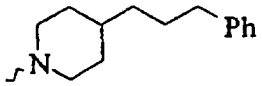
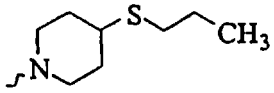
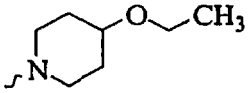
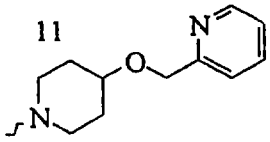
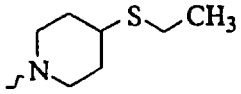
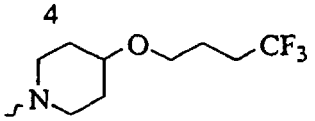
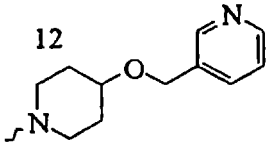
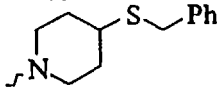
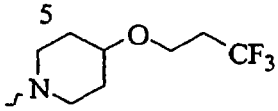
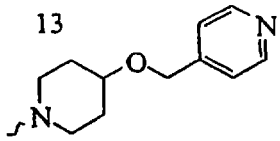
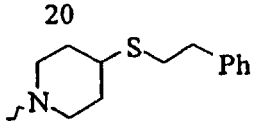
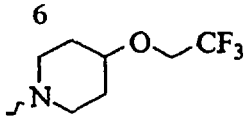
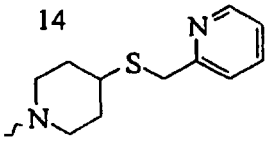
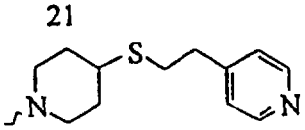
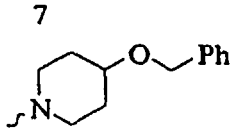
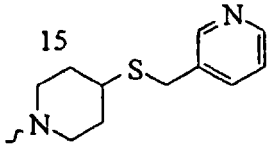
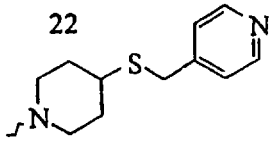
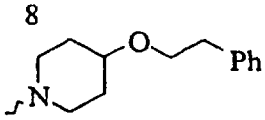
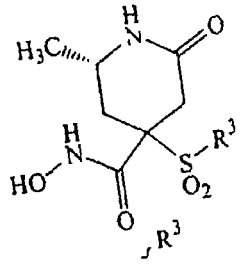
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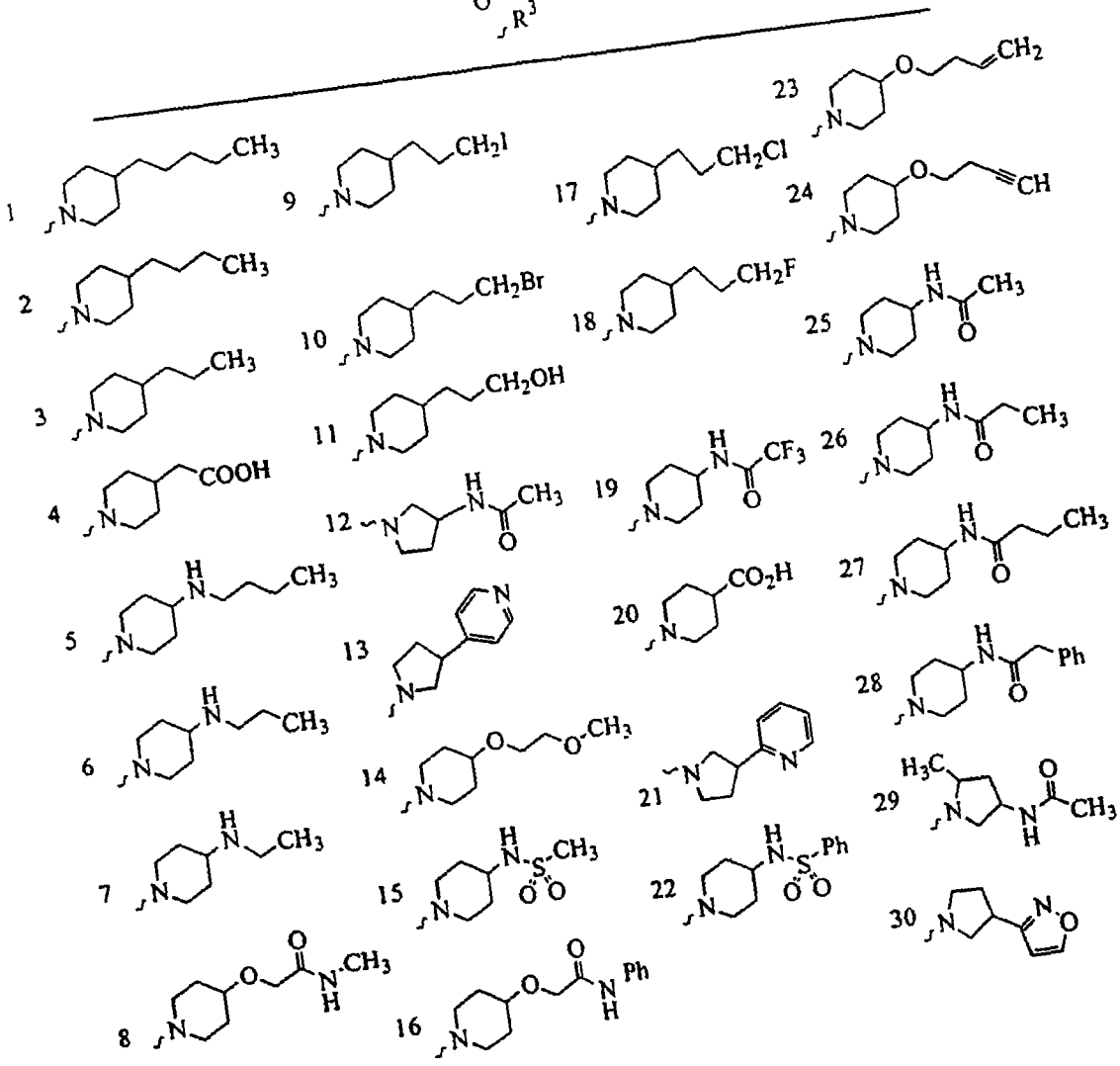
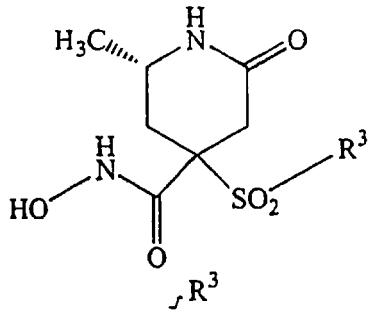
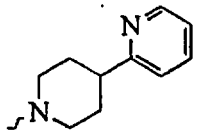
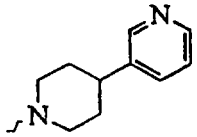
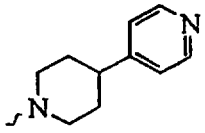

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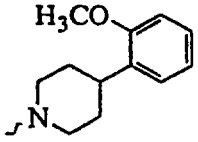
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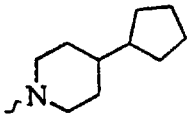


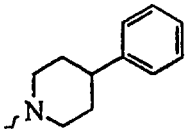
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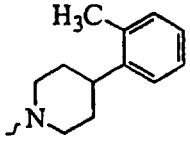
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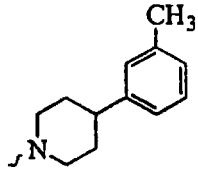
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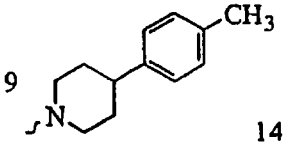
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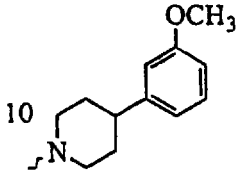
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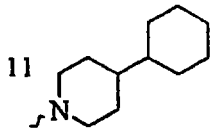
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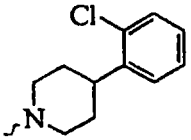
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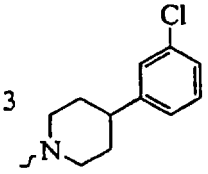
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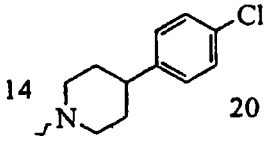
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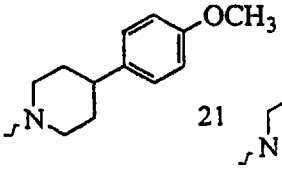
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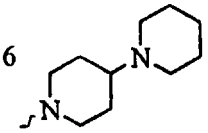
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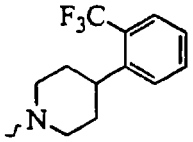
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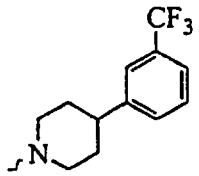
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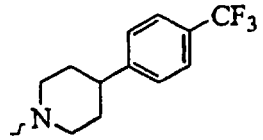
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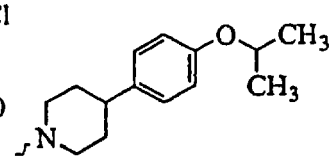
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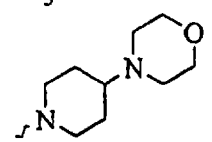
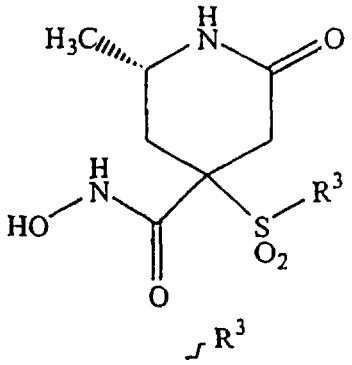
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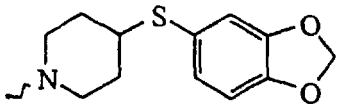
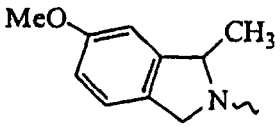
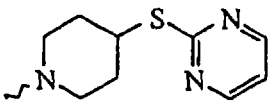
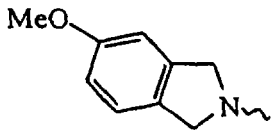
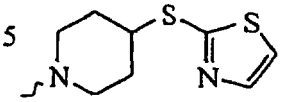
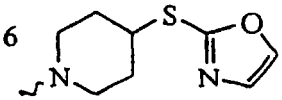
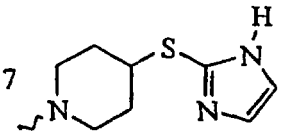
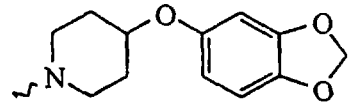
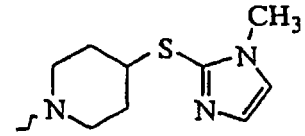
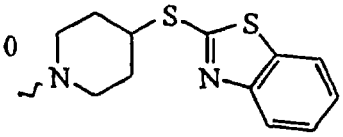
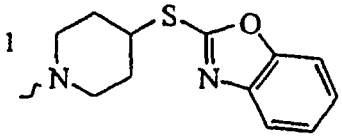
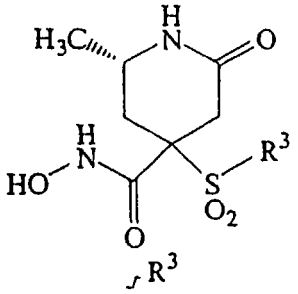
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Table 23



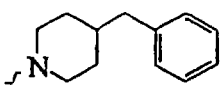
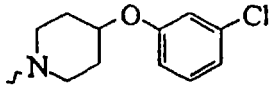
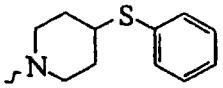
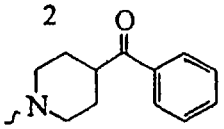
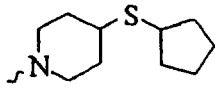
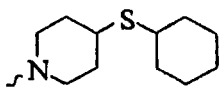
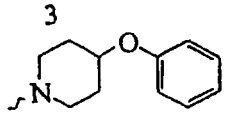
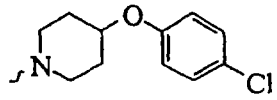
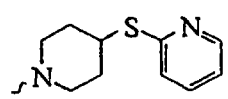
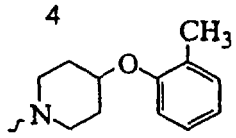
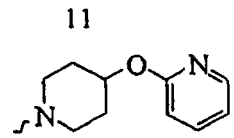
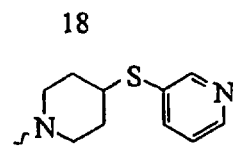
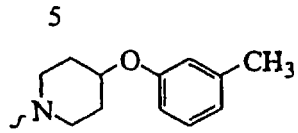
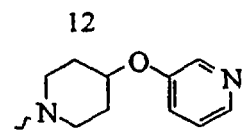
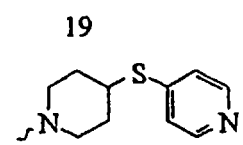
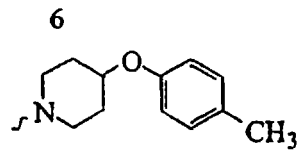
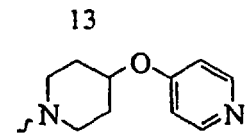
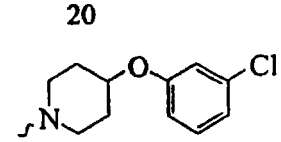
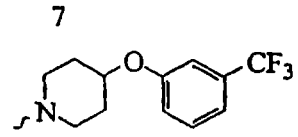
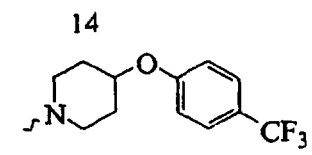
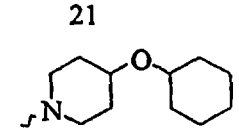
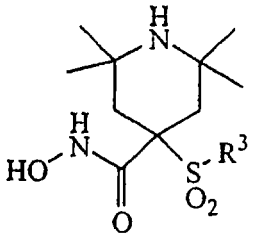
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Table 24





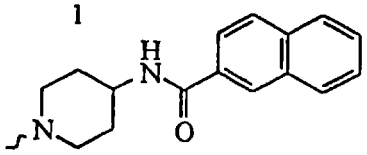
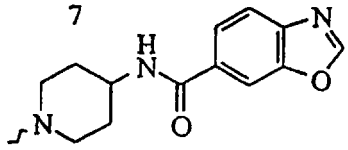
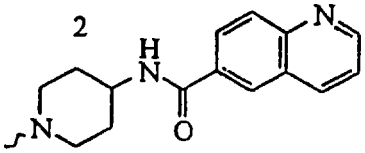
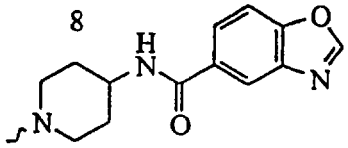
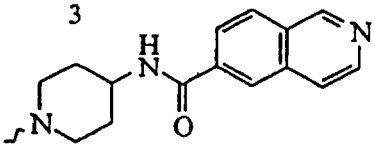
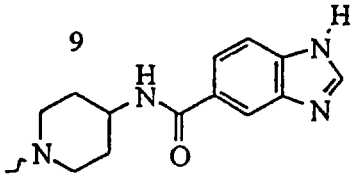
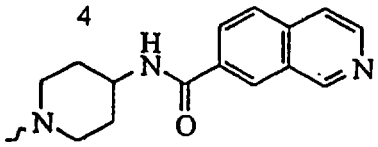
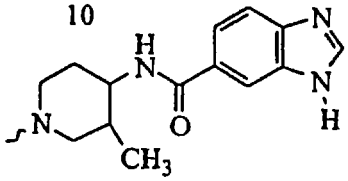
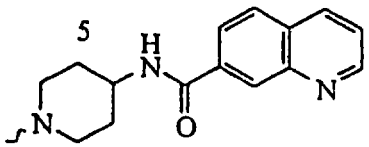
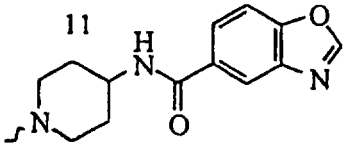
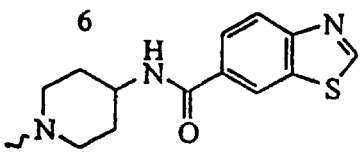
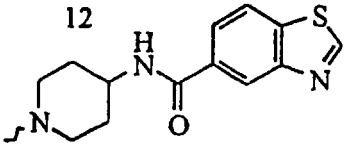
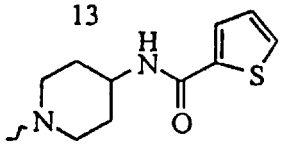
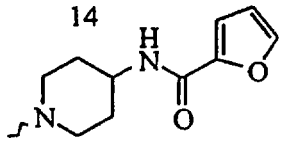
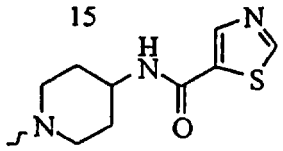
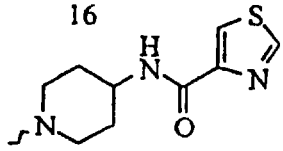
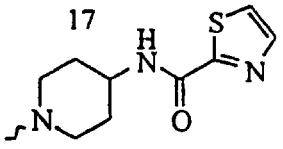
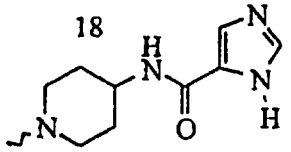
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Table 25

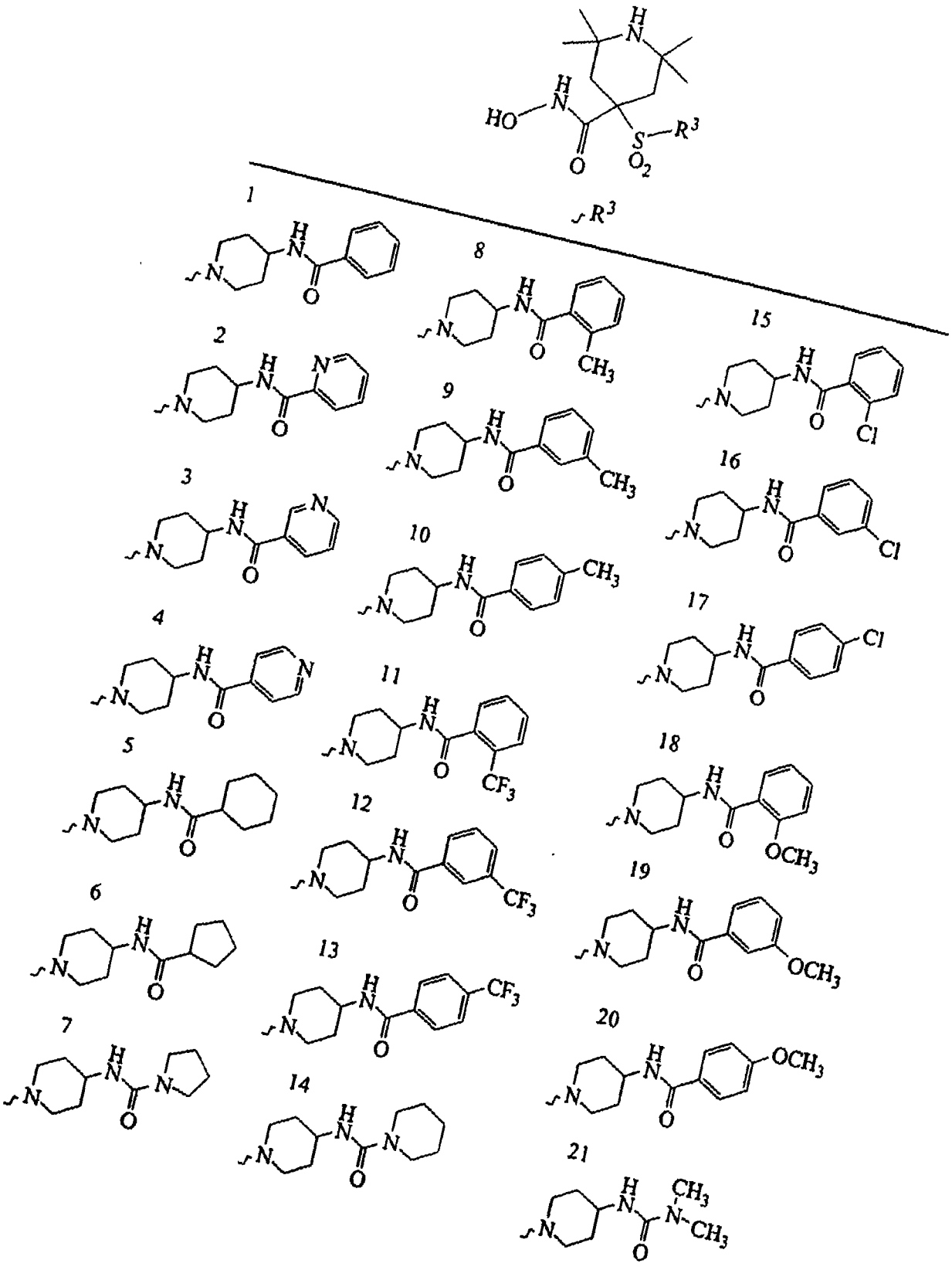
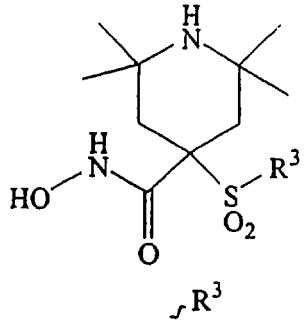


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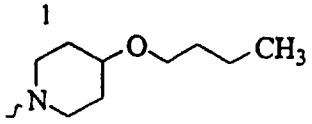
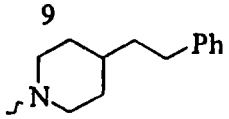
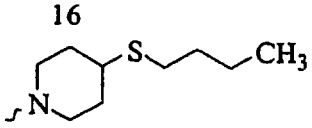
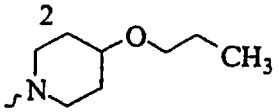
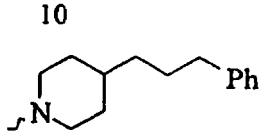
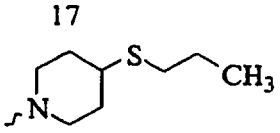
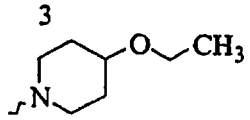
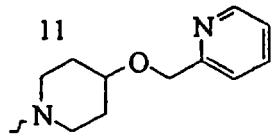
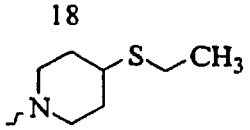
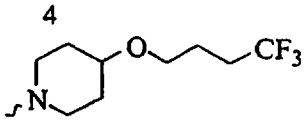
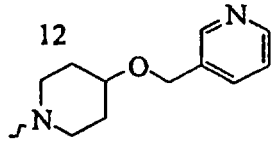
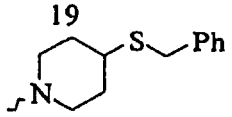
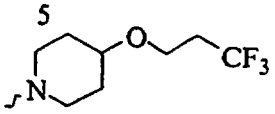
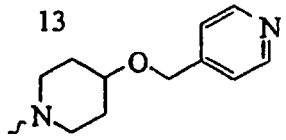
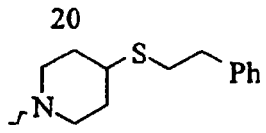
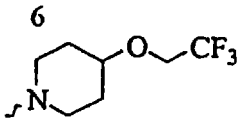
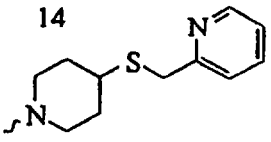
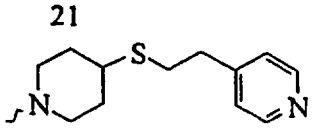
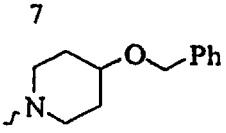
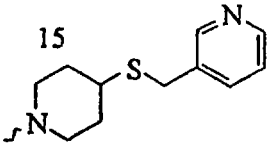
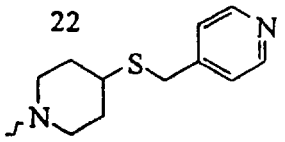
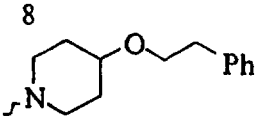
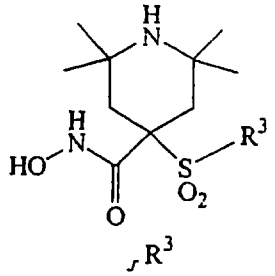
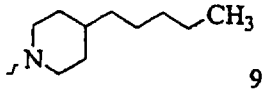
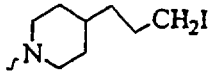
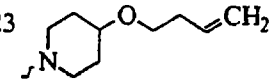
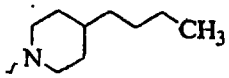
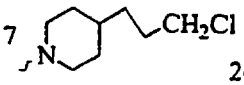
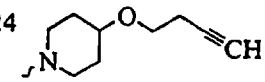
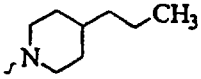
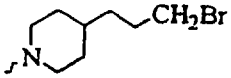
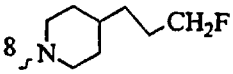
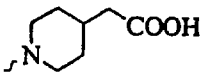
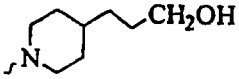
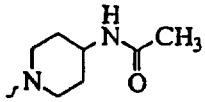
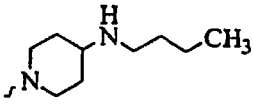
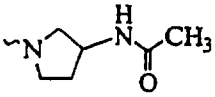
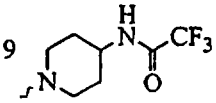
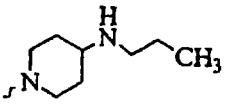
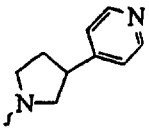
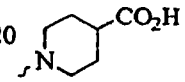
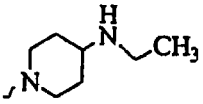
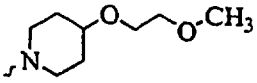
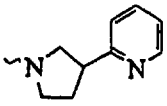
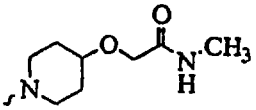
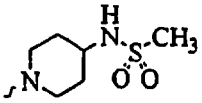
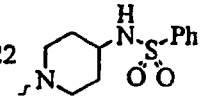
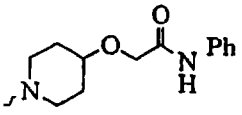
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Table 27



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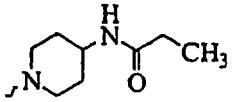
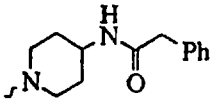
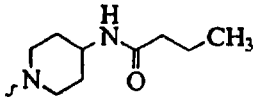
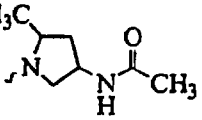
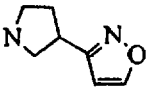
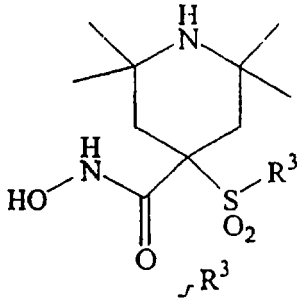
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Table 28



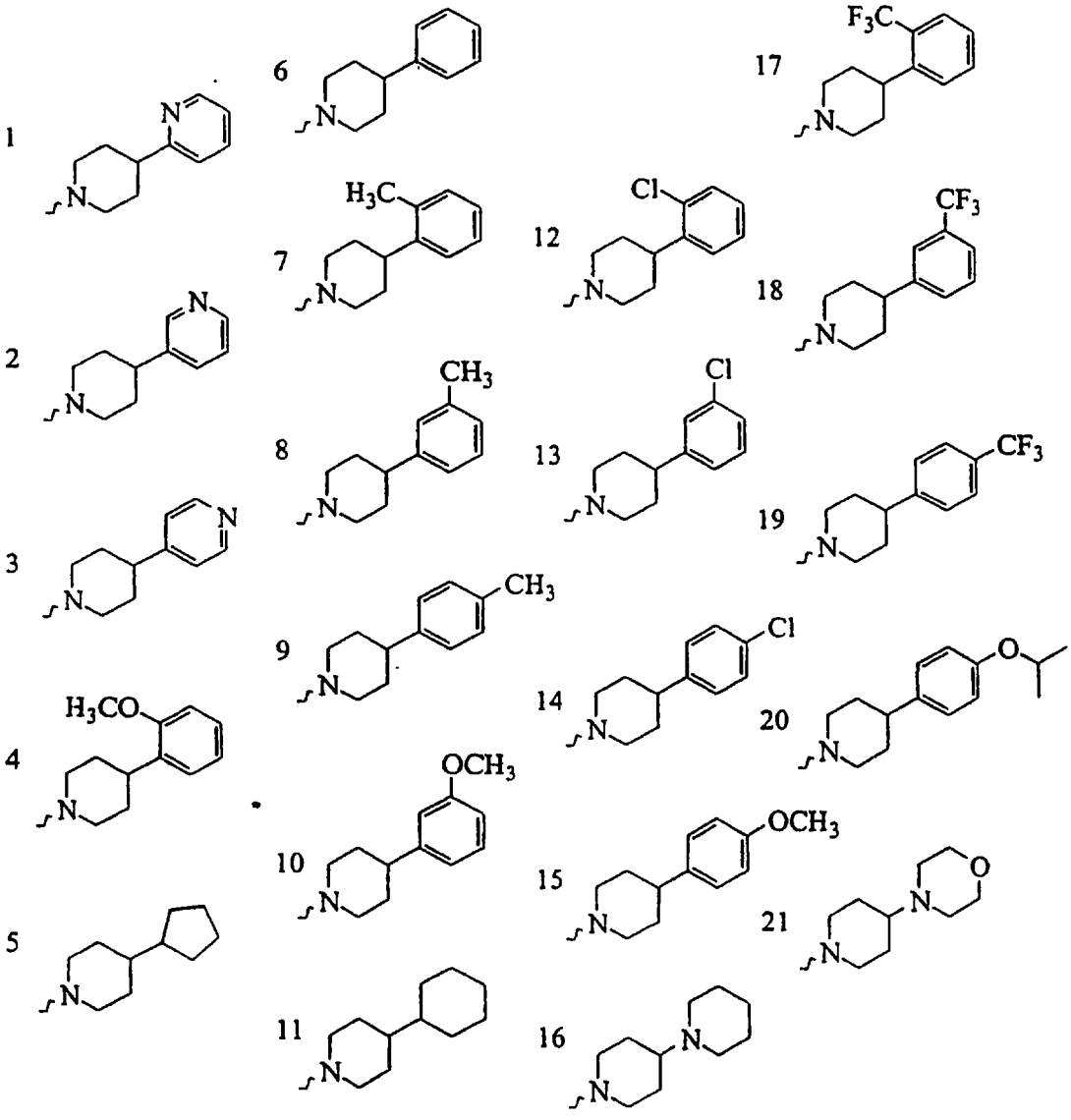
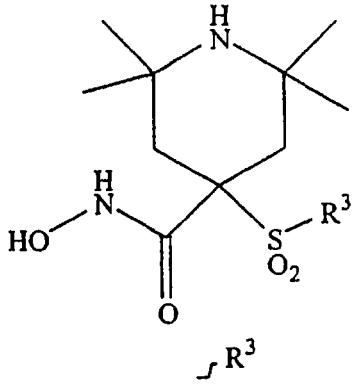


Table 29



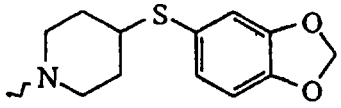
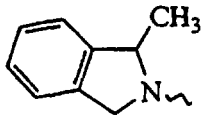
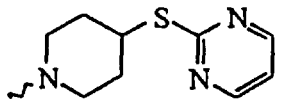
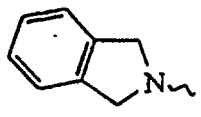
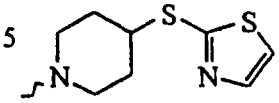
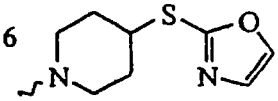
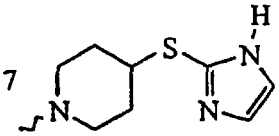
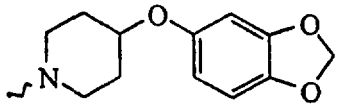
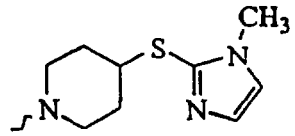
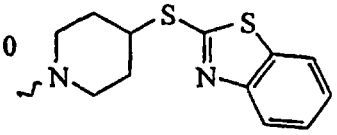
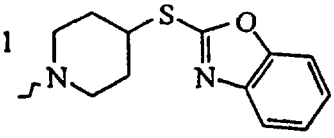
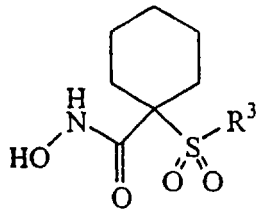
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Table 30





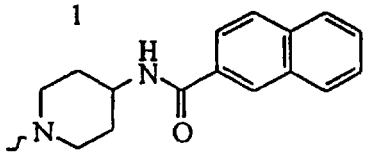
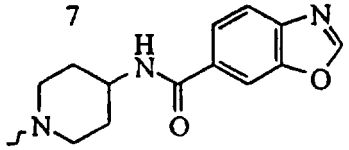
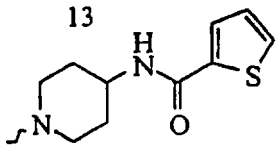
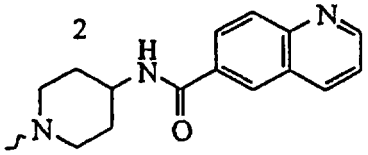
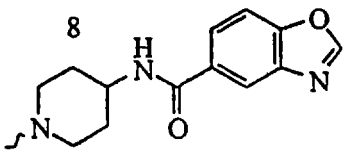
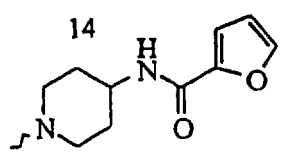
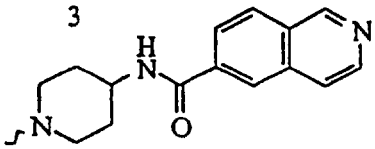
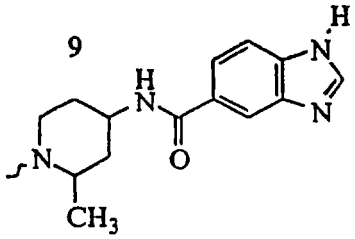
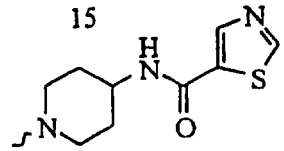
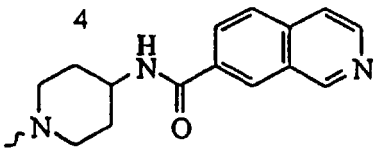
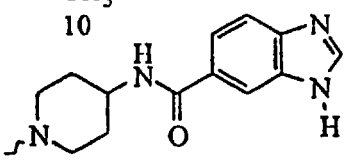
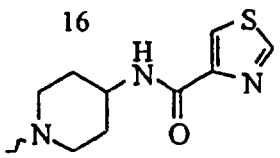
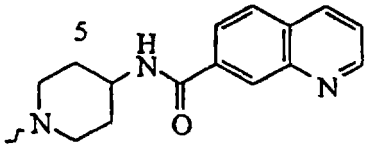
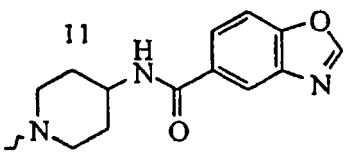
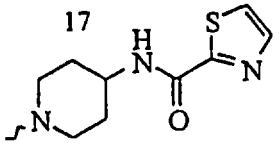
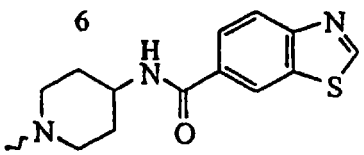
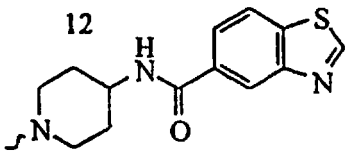
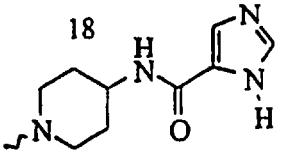
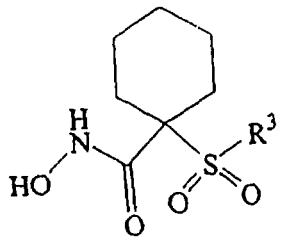
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Table 31



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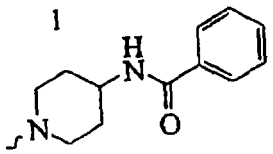
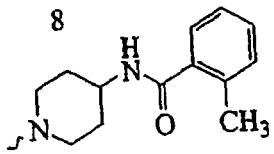
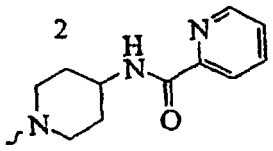
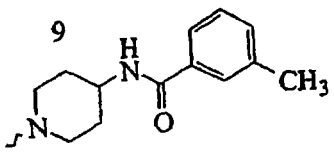
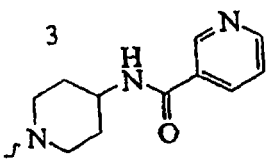
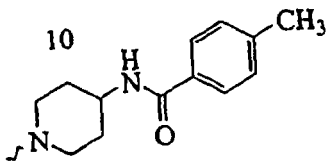
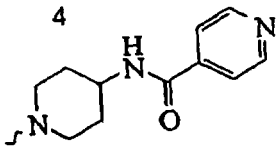
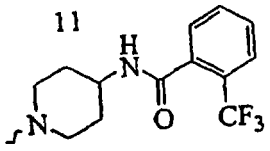
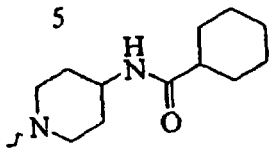
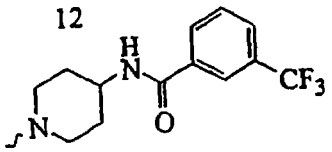
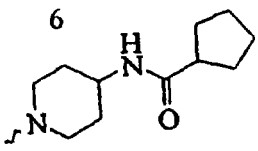
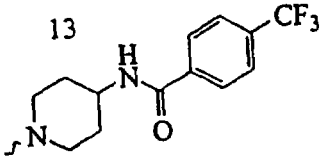
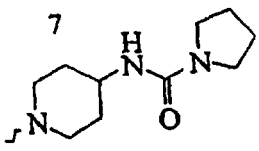
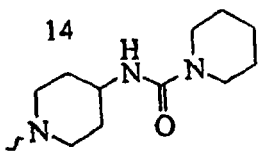
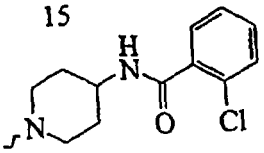
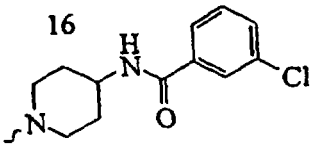
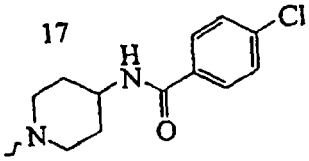
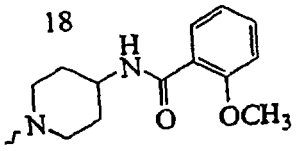
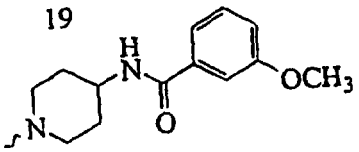
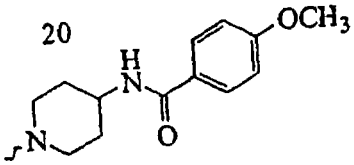
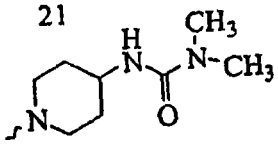
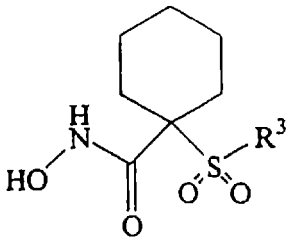
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Table 32





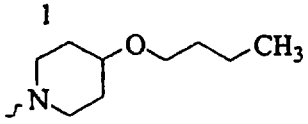
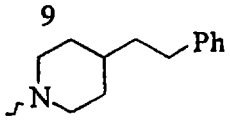
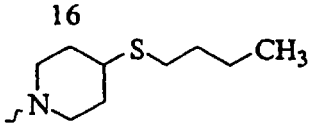
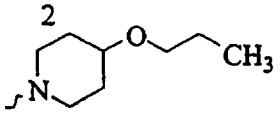
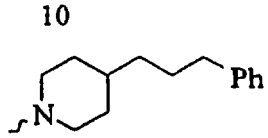
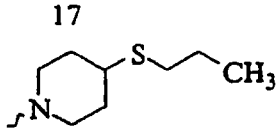
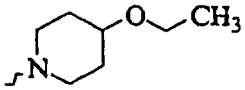
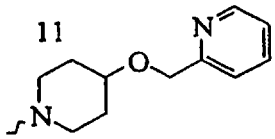
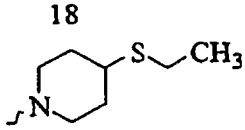
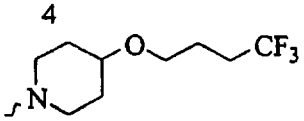
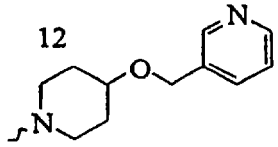
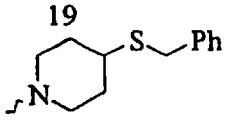
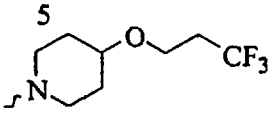
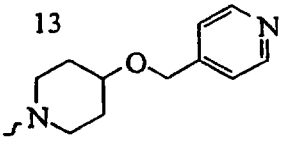
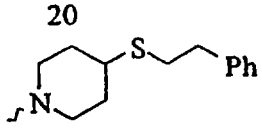
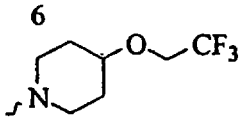
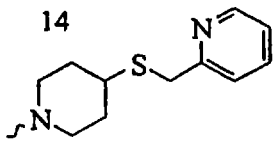
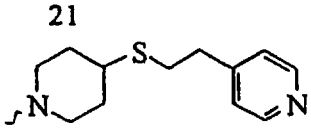
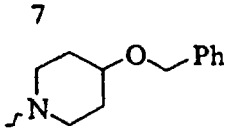
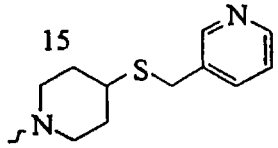
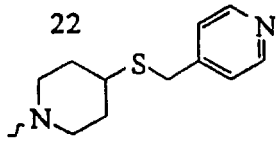
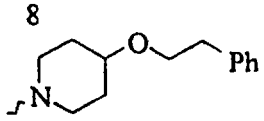
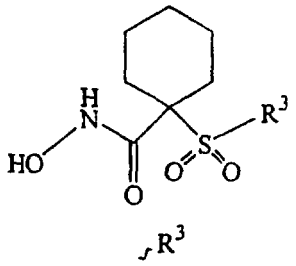
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Table 33



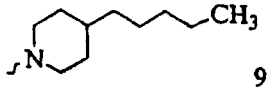
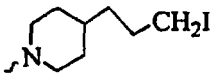
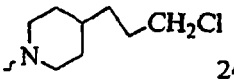
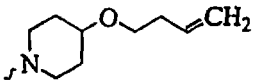
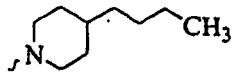
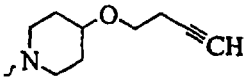
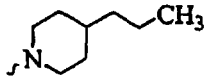
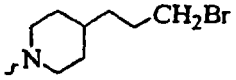
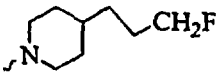
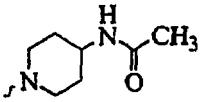
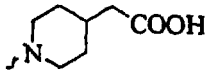
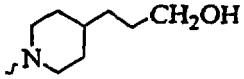
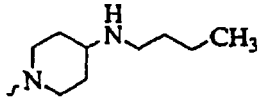
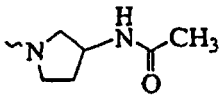
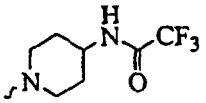
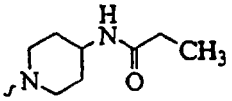
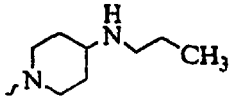
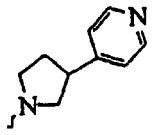
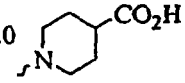
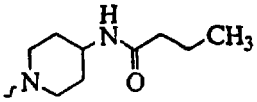
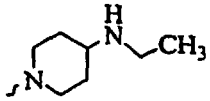
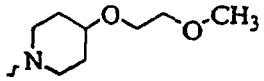
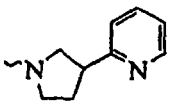
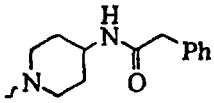
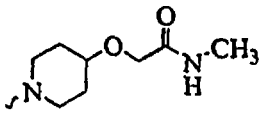
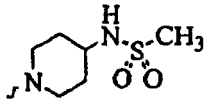
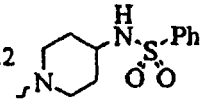
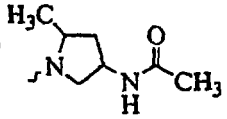
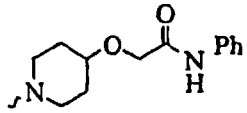
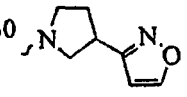
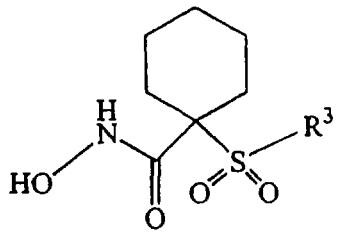
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Table 34





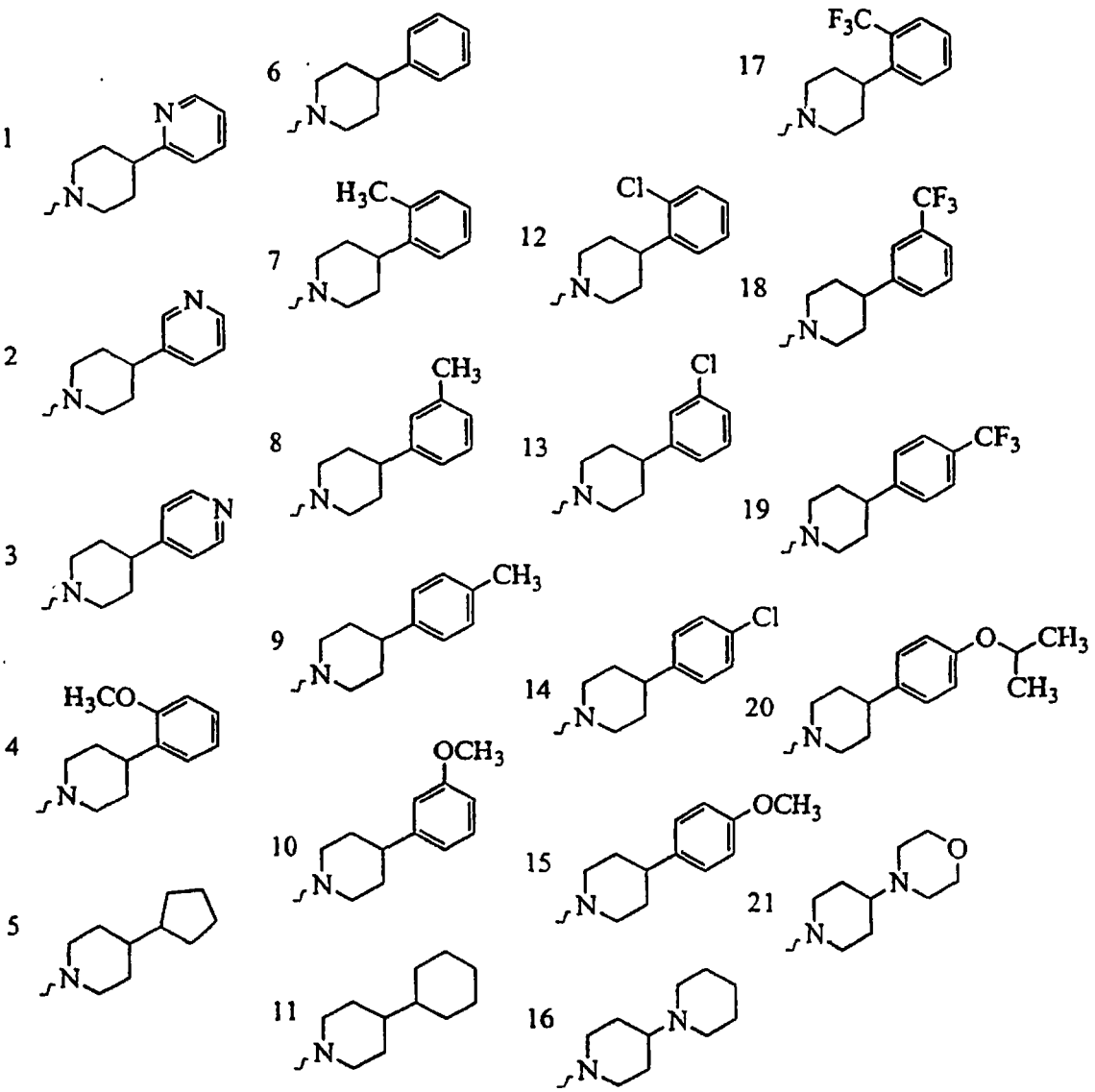
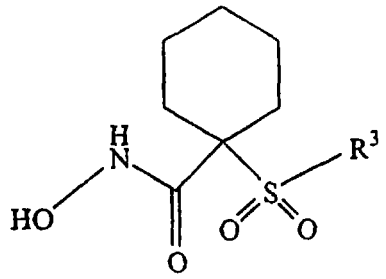


Table 35



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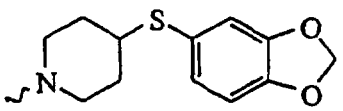
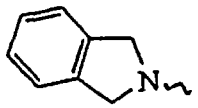
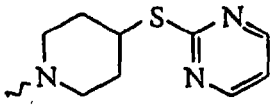
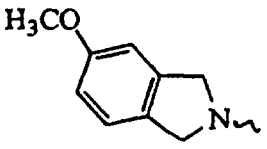
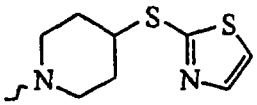
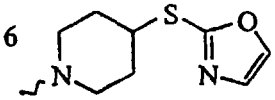
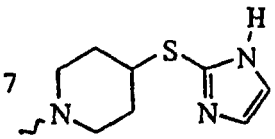
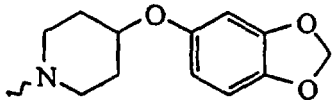
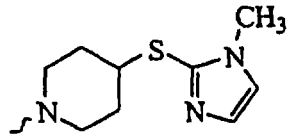
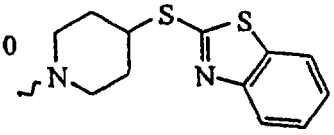
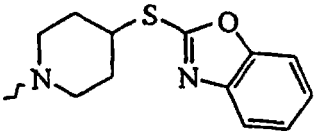
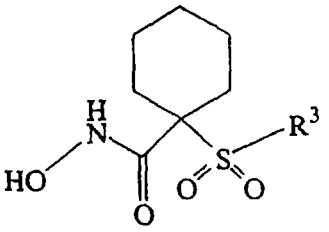
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Table 36



R^3

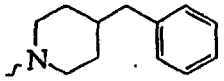
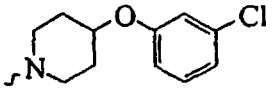
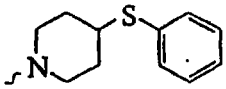
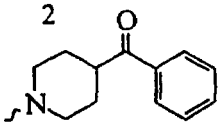
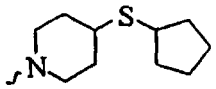
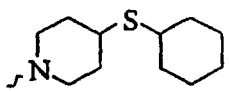
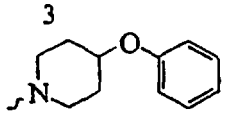
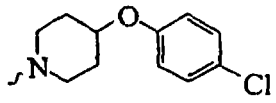
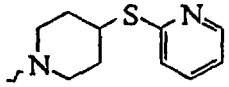
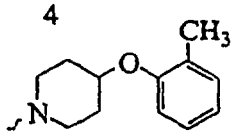
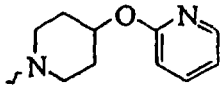
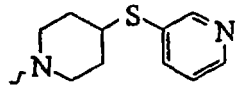
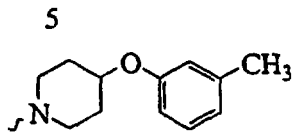
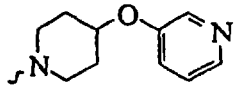
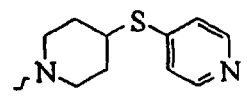
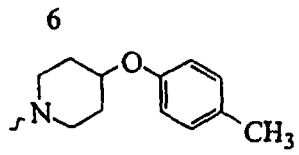
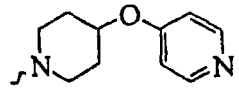
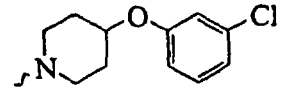
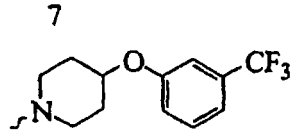
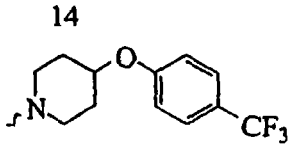
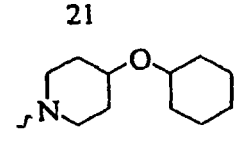
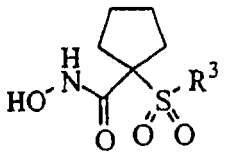
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Table 37



R^3

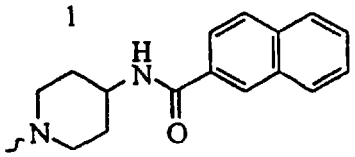
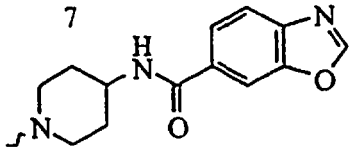
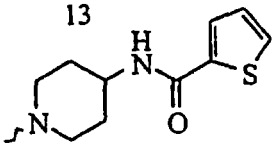
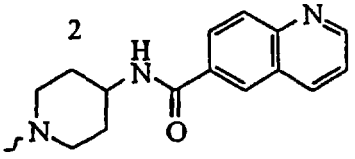
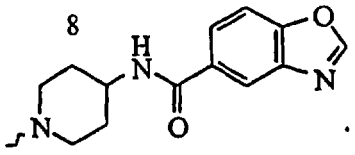
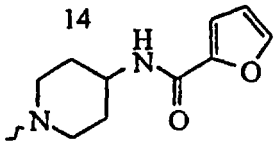
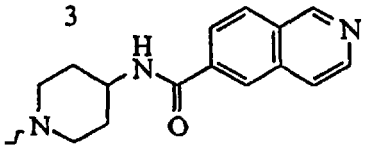
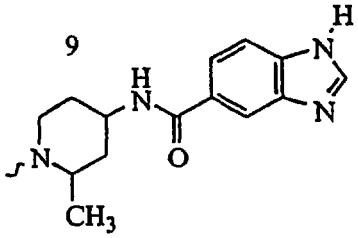
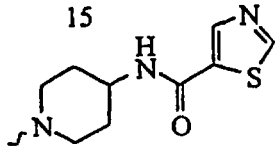
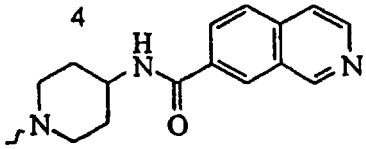
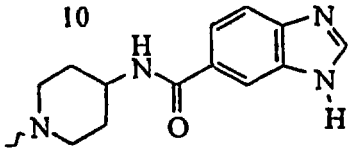
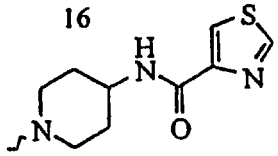
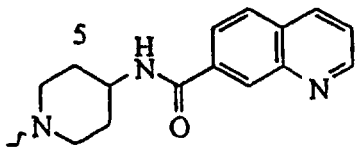
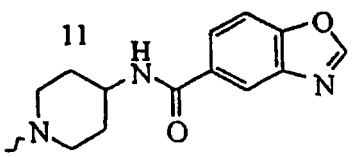
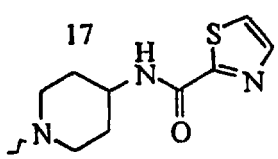
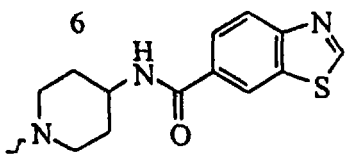
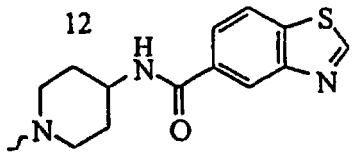
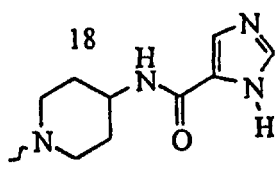
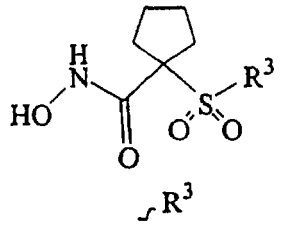
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Table 38



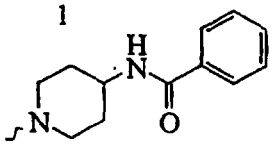
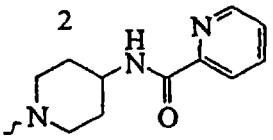
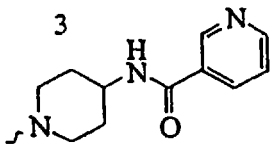
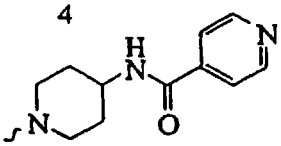
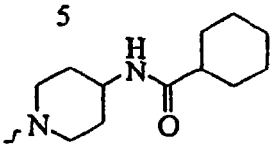
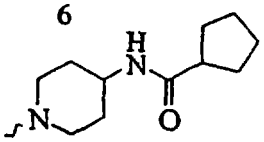
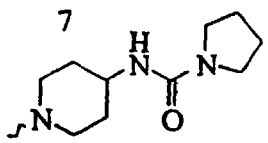
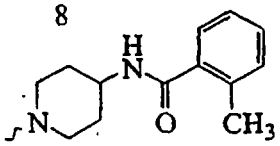
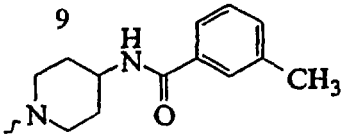
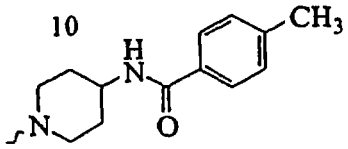
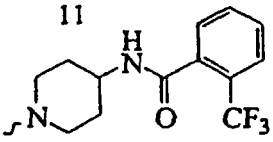
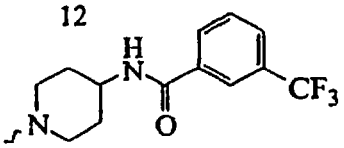
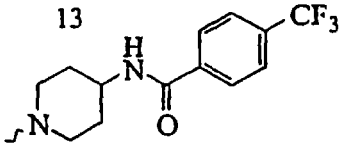
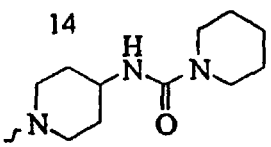
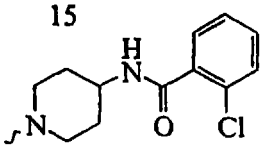
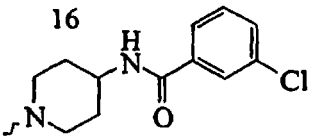
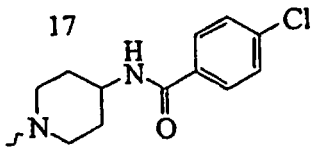
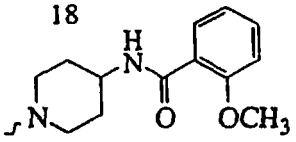
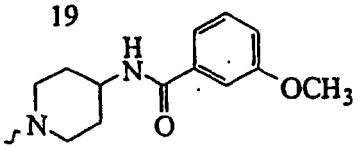
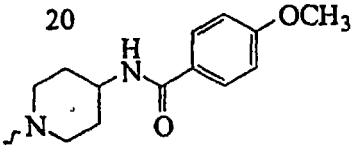
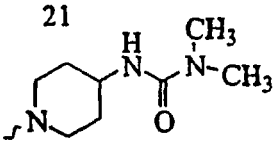
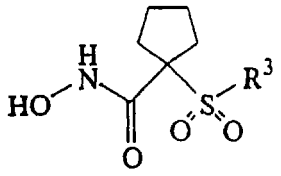
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Table 39





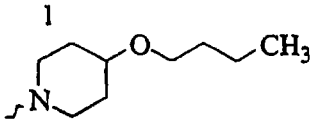
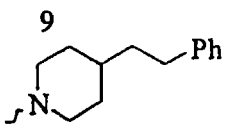
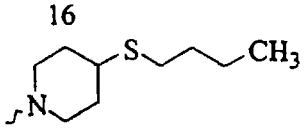
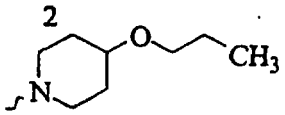
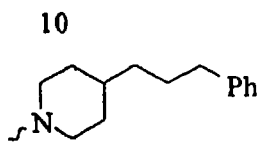
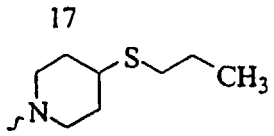
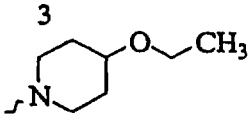
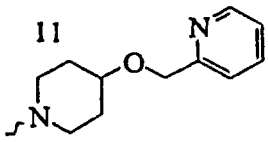
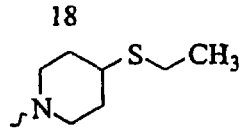
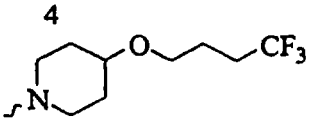
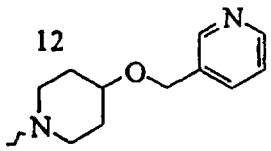
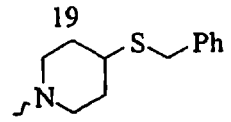
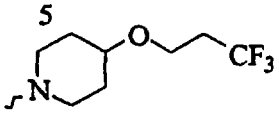
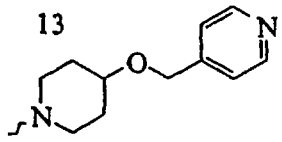
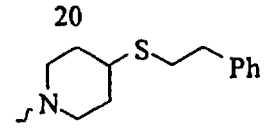
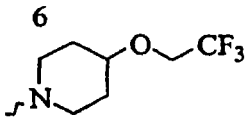
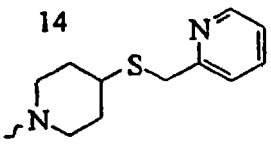
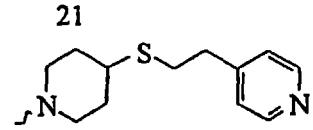
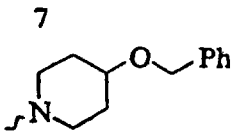
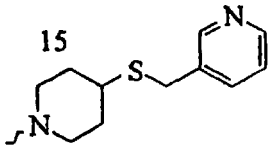
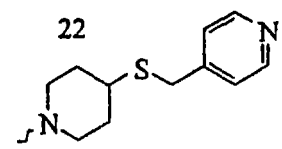
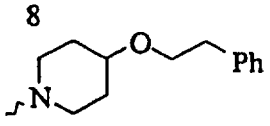
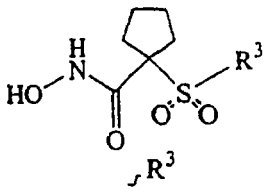
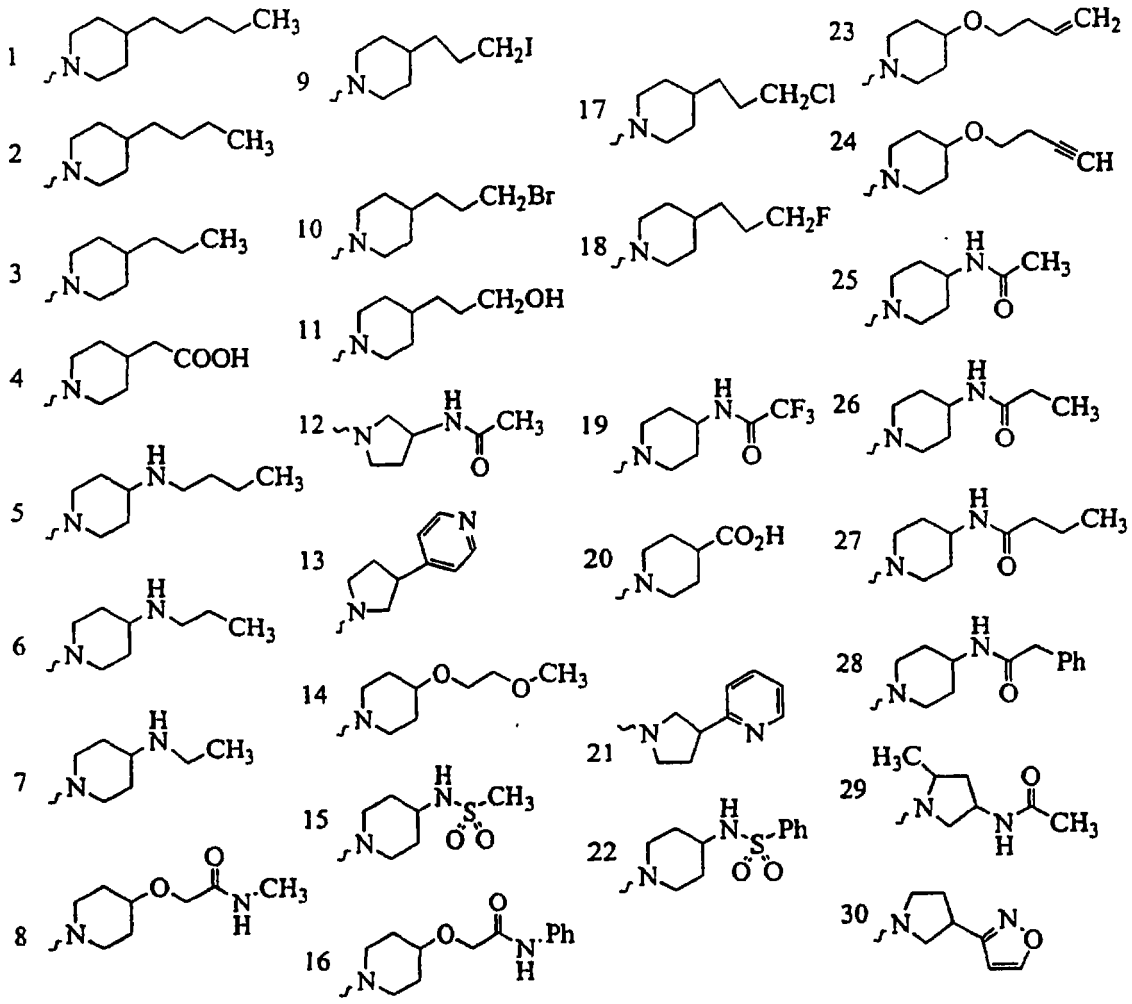
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