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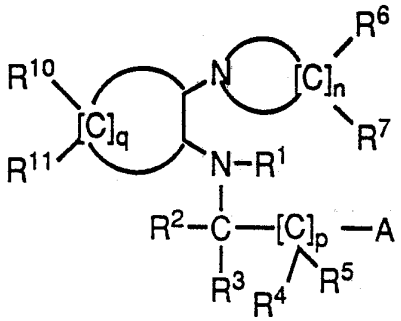
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(54) Title: NITROGEN-CONTAINING CYCLOHETERO CYCLOALKYLAMINOARYL DERIVATIVES FOR CNS DISORDERS



(I)

(57) Abstract

Certain nitrogen-containing cyclohetero cycloalkylaminoaryl compounds are described for treatment of CNS disorders such as cerebral ischemia, psychotic disorders, convulsions and parkinsonism. Compounds of particular interest are of formula (I), wherein R^1 is selected from hydrido, loweralkyl, cycloalkylalkyl of four to six carbon atoms and loweralkenylloweralkyl; wherein each of R^2 and R^3 is independently selected from hydrido and loweralkyl; wherein each of R^4 through R^7, R^{10} and R^{11} is independently selected from hydrido, hydroxy, loweralkyl, benzyl, phenoxy, benzyloxy and halologweralkyl; wherein n is a number selected from four through six; wherein p is a number selected from zero through four; wherein q is a number selected from three through five; wherein A is selected from phenyl, naphthyl and thienyl; wherein any of the foregoing A groups can be further substituted with one or more substituents independently selected from hydrido, hydroxy, loweralkyl, loweralkoxy, halo, halologweralkyl, amino, monoloweralkylamino and diloweralkylamino; or a pharmaceutically acceptable salt thereof.

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NITROGEN-CONTAINING CYCLOHETERO CYCLOALKYLAMINOARYL DERIVATIVES FOR CNS DISORDERS

Related Application

This is a continuation-in-part of U.S. Application Ser. No. 07/473,008 filed on January 31, 1990.

Field of the Invention

This invention is in the field of clinical neurology and relates specifically to a class of therapeutically useful compounds, compositions and methods for treatment of Central Nervous System (CNS) dysfunctions, neurotoxic damage, or neurodegenerative diseases. For example, these compounds are particularly useful for treating neurotoxic injury which follows periods of hypoxia, anoxia or ischemia associated with stroke, cardiac arrest or perinatal asphyxia. These compounds are also useful as antipsychotics and anticonvulsives.

Background of the Invention

Unlike other tissues which can survive extended periods of hypoxia, brain tissue is particularly sensitive to deprivation of oxygen or energy. Permanent damage to neurons can occur during brief periods of hypoxia, anoxia or ischemia. Neurotoxic injury is known to be caused or accelerated by certain excitatory amino acids (EAA) found naturally in the central nervous system (CNS). Glutamate (Glu) is an endogenous amino acid which has been characterized as a fast excitatory transmitter in the mammalian brain. Glutamate is also known as a powerful neurotoxin capable of killing CNS neurons under certain pathological conditions which accompany stroke and cardiac arrest. Normal glutamate concentrations are maintained within brain tissue by energy-consuming transport systems. Under low energy conditions which occur during conditions of hypoglycemia, hypoxia or ischemia, cells can release glutamate. Under such low energy conditions the cell is not

able to take glutamate back into the cell. Initial glutamate release stimulates further release of glutamate which results in an extracellular glutamate accumulation and a cascade of neurotoxic injury.

It has been shown that the sensitivity of central neurons to hypoxia and ischemia can be reduced by either blockage of synaptic transmission or by the specific antagonism of postsynaptic glutamate receptors [see S. M. Rothman and J. W. Olney, "Glutamate and the Pathophysiology of Hypoxia - Ischemic Brain Damage," Annals of Neurology, Vol. 19, No. 2 (1986)]. Glutamate is characterized as a broad spectrum agonist having activity at three neuronal excitatory amino acid receptor sites. These receptor sites are named after the amino acids which selectively excite them, namely: Kainate (KA), N-methyl-D-aspartate (NMDA or NMA) and quisqualate (QUIS).

Neurons which have EAA receptors on their dendritic or somal surfaces undergo acute excitotoxic degeneration when these receptors are excessively activated by glutamate. Thus, agents which selectively block or antagonize the action of glutamate at the EAA synaptic receptors of central neurons can prevent neurotoxic injury associated with hypoxia, anoxia, or ischemia caused by stroke, cardiac arrest or perinatal asphyxia.

It is known that compounds of various structures, such aminophosphonovalerate derivatives and piperidine dicarboxylate derivatives, may act as competitive antagonists at the NMDA receptor. Certain piperidineethanol derivatives, such as ifenprodil and 1-(4-chlorophenyl)-2-[1-(4-fluoro-phenyl)piperidinyl]ethanol, which are known anti-ischemic agents, have been found to be non-competitive NMDA receptor antagonists [C. Carter et al, J. Pharm Exp. Ther., 247 (3), 1222-1232 (1988)].

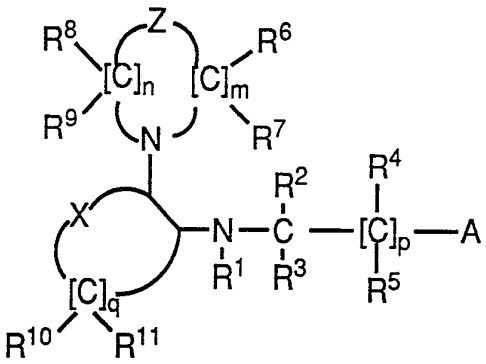
There are many classes of compunds known for treatment of psychotic disorders. For example, current therapeutic treatments for psychoses use compounds classifiable as phenothiazine-thioxanthenes, as phenylbutylpiperidines and also as certain alkaloids. An example of a phenylbutylpiperidine compound of current use in psychotic treatment therapy is haloperidol [A.F. Gilman et al, The Pharmacological Basis of Therapeutics, 7th Edn., p. 404, MacMillan (1985)].

Certain nitrogen-containing cyclohetero cycloalkylaminoaryl compounds are known for pharmaceutical purposes. For example, U.S. Patent No. 4,204,003 to Szmuszkovicz describes N-(2-aminocyclopentyl)-N-alkanoylanilides as antidepressant agents.

Certain aminocycloaliphatic benzamides have been described for various uses. For example, U.S. Patent No. 4,463,013 to Collins et al describes aminocyclohexylbenzamides for use as diuretic agents. The compound (±)-trans-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzene-acetamide has been evaluated for its selectivity as an amino acid antagonist [C.G. Parsons et al, Neuropharm., 25(2), 217-220 (1986)]. This same compound has been evaluated for its neuroprotective activity against kainate-induced toxicity [W. Lason et al, Brain Res., 482, 333-339 (1989)]. U.S. Patent No. 4,801,604 to Vonvoightlander et al describes certain cis-N-(2-aminocycloaliphatic)benzamides as anticonvulsants including, specifically, the compound cis-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzamide. These benzeneacetamide derivatives, such as trans-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-benzeneacetamide, have been described as a highly selective ligand for kappa opioid receptors. Such kappa opioid affinity is believed associated with blockade of convulsions and protection from cerebral ischemia [B.R. de Costa et al, J. Med. Chem., 32(8), 1996-2002 (1989)].

Description of the Invention

Treatment of CNS disorders and diseases such as cerebral ischemia, psychotic disorders, convulsions and parkinsonism, as well as prevention of neurotoxic damage and neurodegenerative diseases, may be accomplished by administration of a therapeutically-effective amount of a compound of Formula I:

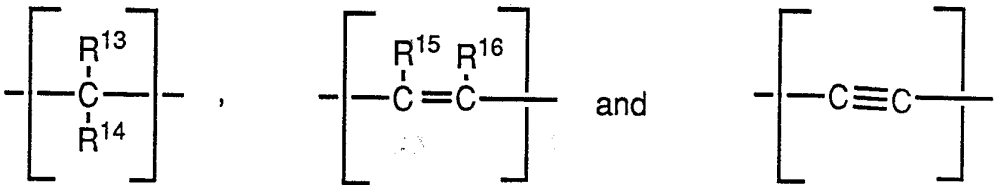


(I)

wherein R^1 is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkenylalkyl, alkynylalkyl, carboxyalkyl, alkanoyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein each of R^2 and R^3 is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkenyl, alkynyl, alkenylalkyl, alkynylalkyl, carboxyalkyl, alkanoyl, alkoxycarbonyl, carboxy, cyanoalkyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein R^2 and R^3 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of R^4 through R^{11} is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl and alkynyl; wherein R^4 and R^5 may be taken together to form oxo or to form a saturated or partially

unsaturated carbocyclic group having three to eight ring carbons; wherein R^6 and R^7 may be taken together to form oxo; wherein R^8 and R^9 may be taken together to form oxo; wherein R^{10} and R^{11} may be taken together to form oxo; wherein each of n and m is a number selected from one through four; wherein each of p and q is a number selected from zero through five; wherein each of X and Z is independently selected from

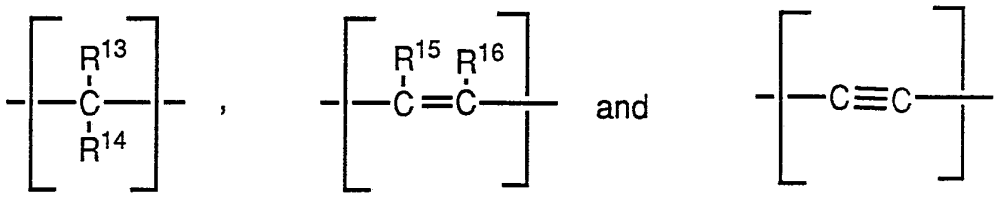
O, S, $\rangle N\text{-}R^{12}$, $\rangle SO$, $\rangle SO_2$,



wherein R^{12} may be selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, alkoxyalkyl, hydroxyalkyl, alkanoyl, aralkanoyl, aroyl, aminoalkyl, monoalkylaminoalkyl and dialkylaminoalkyl; wherein each of R^{13} through R^{16} is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; wherein A is selected from aryl, heteroaryl, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, arylamino, heteroarylamino, aralkylamino, heteroaralkylamino, arylthio, heteroarylthio, aralkylthio and heteroaralkylthio; wherein any of the foregoing A groups can be further substituted with one or more substituents independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, halo, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl and alkynyl; or a pharmaceutically-acceptable salt thereof.

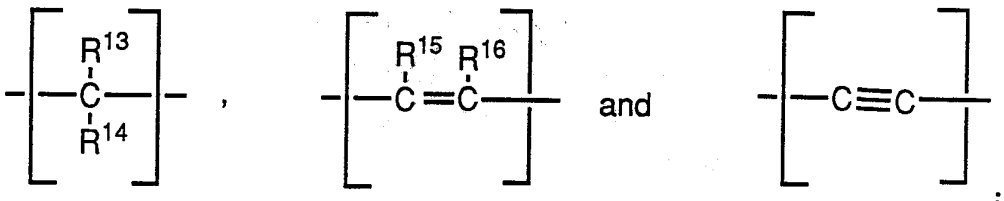
The family of compounds within Formula I is novel with the proviso that each of the compounds embraced by Formula I is a cis isomer with respect to the two nitrogen atoms of Formula I; or a pharmaceutically acceptable salt thereof.

A preferred family of compounds of Formula I consists of those compounds wherein R^1 is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkenylalkyl, alkynylalkyl and carboxyalkyl; wherein each of R^2 and R^3 is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkenyl, alkynyl, alkenylalkyl, alkynylalkyl, carboxyalkyl, alkanoyl, alkoxycarbonyl, carboxy and cyanoalkyl; wherein R^2 and R^3 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of R^4 through R^{11} is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl and alkynyl; wherein R^4 and R^5 may be taken together to form oxo or to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of n and m is a number selected from one through four; wherein each of p and q is a number selected from zero through five; wherein X is selected from



;

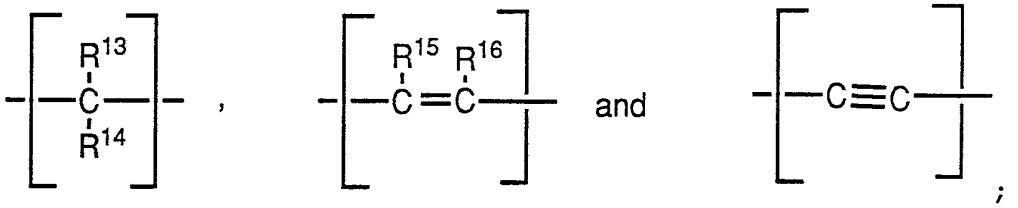
wherein Z is selected from O, , $N\text{-}R^{12}$,



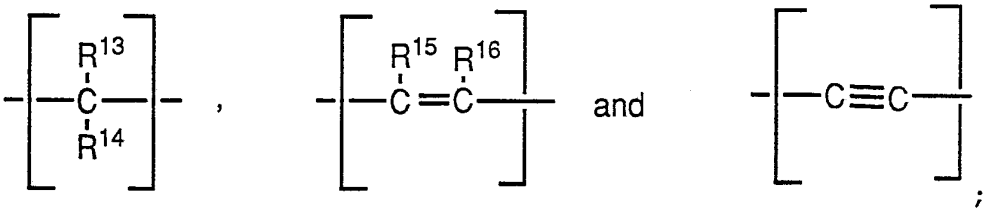
wherein R^{12} may be selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, alkoxyalkyl, hydroxyalkyl, alkanoyl, aralkanoyl, aroyl, aminoalkyl, monoalkylaminoalkyl and dialkylaminoalkyl; wherein each of R^{13} through R^{16} is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; wherein A is selected from aryl, heteroaryl, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, arylamino, heteroarylamino, aralkylamino, heteroaralkylamino, arylthio, heteroarylthio, aralkylthio and heteroaralkylthio; wherein any of the foregoing A groups can be further substituted with one or more substituents independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, halo, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl and alkynyl; or a pharmaceutically acceptable salt thereof.

A more preferred family of compounds within Formula I consists of those compounds wherein R^1 is selected from hydrido, loweralkyl, cycloalkyl of three to about eight carbon atoms, hydroxyloweralkyl, haloloweralkyl, cycloalkylalkyl of four to about eight carbon atoms, loweralkoxyloweralkyl, phenylloweralkyl, phenyl, loweralkenylloweralkyl, loweralkynylloweralkyl and carboxyloweralkyl; wherein each of R^2 and R^3 is independently selected from hydrido, loweralkyl, cycloalkyl of three to about eight carbon atoms, hydroxyloweralkyl, haloloweralkyl, cycloalkylalkyl of four to about eight carbon

atoms, loweralkoxyloweralkyl, phenylloweralkyl, phenyl, loweralkenyl, loweralkynyl, loweralkenylloweralkyl, loweralkynylloweralkyl, carboxyloweralkyl, loweralkanoyl, loweralkoxycarbonyl, carboxy and cyanoloweralkyl; wherein R^2 and R^3 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of R^4 through R^{11} is independently selected from hydrido, hydroxy, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, phenylloweralkyl, phenyl, loweralkoxy, phenoxy, phenylloweralkoxy, loweralkoxyloweralkyl, haloloweralkyl, hydroxyloweralkyl, cyano, amino, monoloweralkylamino, diloweralkylamino, carboxy, carboxyloweralkyl, loweralkanoyl, loweralkenyl and loweralkynyl; wherein R^4 and R^5 may be taken together to form oxo or to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of n and m is a number selected from one through four; wherein each of p and q is a number selected from zero through five; wherein X is selected from



wherein Z is selected from ,

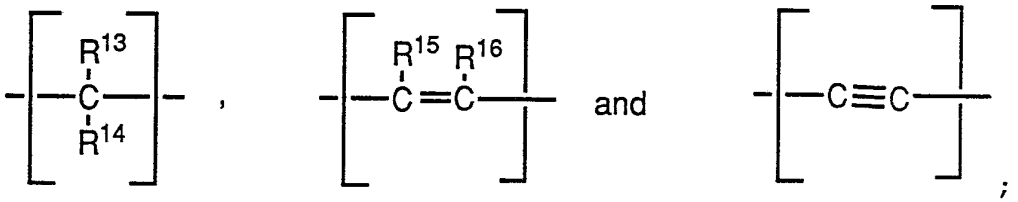


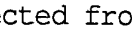
wherein R^{12} may be selected from hydrido, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, phenyl, phenylloweralkyl, heteroaryl, loweralkoxyloweralkyl,

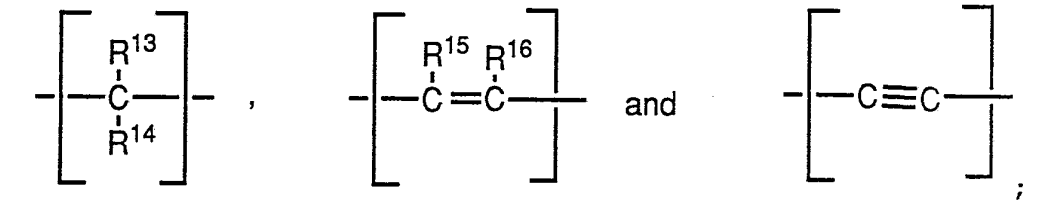
hydroxyloweralkyl, loweralkanoyl, phenylalkanoyl, benzoyl, aminoloweralkyl, monoloweralkylaminoloweralkyl and diloweralkylaminoloweralkyl; wherein each of R^{13} through R^{16} is independently selected from hydrido, hydroxy, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, phenyloweralkyl, phenyl, loweralkoxy, phenylloweralkoxy, phenoxy, loweralkoxyloweralkyl, haloloweralkyl, hydroxyloweralkyl, halo, cyano, amino, monoloweralkylamino, diloweralkylamino, carboxy, carboxyloweralkyl and loweralkanoyl; wherein A is selected from phenyl, naphthyl, heteroaryl, phenoxy, naphthyloxy, heteroaryloxy, phenylloweralkoxy, naphthylloweralkoxy, heteroarylloweralkoxy, phenylamino, naphthylamino, heteroarylamino, phenylloweralkylamino, naphthylloweralkylamino, heteroaralkylamino, phenylthio, naphthylthio, heteroarylthio, phenylloweralkylthio and heteroarylloweralkylthio; wherein any of the foregoing A groups can be further substituted with one or more substituents independently selected from hydrido, hydroxy, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, phenylloweralkyl, phenyl, loweralkoxy, phenoxy, phenyloweralkoxy, loweralkoxyloweralkyl, halo, haloloweralkyl, hydroxyloweralkyl, cyano, amino, monoloweralkylamino, diloweralkylamino, carboxy, carboxyloweralkyl, loweralkanoyl, loweralkenyl and loweralkynyl; or a pharmaceutically acceptable salt thereof.

A more highly preferred family of compounds of Formula I consists of those compounds wherein R^1 is selected from hydrido, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, benzyl, phenyl, loweralkenylloweralkyl and loweralkynylloweralkyl; wherein each of R^2 and R^3 is independently selected from hydrido, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, benzyl, phenyl, loweralkenyl,

loweralkynyl, loweralkenylloweralkyl, loweralkynylloweralkyl, loweralkanoyl and loweralkoxycarbonyl; wherein R^2 and R^3 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of R^4 through R^{11} is independently selected from hydrido, hydroxy, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, benzyl, phenyl, loweralkoxy, phenoxy, benzyloxy, loweralkoxyloweralkyl, haloloweralkyl, hydroxyloweralkyl, loweralkanoyl, loweralkenyl and loweralkynyl; wherein R^4 and R^5 may be taken together to form oxo or to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of n and m is a number selected from one through four; wherein each of p and q is a number selected from zero through five; wherein X is selected from



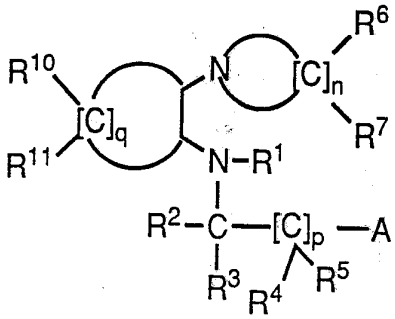
wherein Z is selected from ,



wherein R^{12} may be selected from hydrido, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, phenyl, benzyl, loweralkoxyloweralkyl and hydroxyloweralkyl; wherein each of R^{13} through R^{16} is independently selected from hydrido, hydroxy, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, benzyl, phenyl, loweralkoxy, benzyloxy, phenoxy, loweralkoxyloweralkyl, haloloweralkyl,

hydroxyloweralkyl and halo; wherein A is selected from phenyl, naphthyl, thienyl, phenoxy, benzyloxy, naphthyloxy, thiophenoxy, phenylamino, benzylamino, naphthylamino, phenylthio, benzylthio and naphthylthio; wherein any of the foregoing A groups can be further substituted with one or more substituents independently selected from hydrido, hydroxy, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, loweralkoxy, loweralkoxyloweralkyl, halo, haloloweralkyl, hydroxyloweralkyl, amino, monoloweralkylamino, diloweralkylamino, loweralkanoyl, loweralkenyl and loweralkynyl; or a pharmaceutically acceptable salt thereof.

A family of compounds of particular interest within Formula I are compounds embraced by Formula II:



(II)

wherein R^1 is selected from hydrido, loweralkyl, cycloalkylalkyl of four to six carbon atoms and loweralkenylloweralkyl; wherein each of R^2 and R^3 is independently selected from hydrido and loweralkyl; wherein each of R^4 through R^7, R^{10} and R^{11} is independently selected from hydrido, hydroxy, loweralkyl, benzyl, phenoxy, benzyloxy and haloloweralkyl; wherein n is a number selected from four through six; wherein p is a number selected from zero through four; wherein q is a number selected from three through five; wherein A is selected from phenyl, naphthyl and thienyl; wherein any of the foregoing A groups can be further substituted with one or more substituents independently selected from hydrido, hydroxy, loweralkyl, loweralkoxy,

halo, haloloweralkyl, amino, monoloweralkylamino and diloweralkylamino; or a pharmaceutically acceptable salt thereof.

A more preferred family of compounds within Formula II consists of compounds wherein R^1 is selected from hydrido, methyl, ethyl, propyl, cyclopropylmethyl, allyl and dimethylallyl; wherein each of R^2 and R^3 is independently selected from hydrido, methyl, ethyl and propyl; wherein each of R^4 through R^7, R^{10} and R^{11} is independently selected from hydrido, hydroxy, methyl, ethyl, propyl, benzyl, phenoxy, benzyloxy and haloloweralkyl; wherein n is a number selected from four or five; wherein p is a number selected from zero through two; wherein q is a number selected from three or four; wherein A is phenyl or naphthyl; wherein any of the foregoing A groups can be further substituted with one or more substituents independently selected from hydroxy, methyl, ethyl, propyl, methoxy, ethoxy, methylenedioxy, halo, trifluoromethyl, amino, methylamino and dimethylamino; or a pharmaceutically acceptable salt thereof.

Of highest interest are the following specific compounds:

(±)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)-cyclohexylamine;

1S,2R-(+)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexylamine;

1R,2S-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexylamine;

(±)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(1-pyrrolidinyl)cyclohexylamine;

1S,2R-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(1-pyrrolidinyl)cyclohexylamine;

1R,2S-(+)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(1-pyrrolidinyl)cyclohexylamine;

(±)-cis-N-methyl-N-(2-phenylethyl)-2-(1-pyrrolidinyl)-cyclohexylamine;

(±)-cis-N-methyl-N-[2-(ß-naphthyl)ethyl]-2-(1-pyrrolidinyl)-cyclohexylamine;

1S,2R-(-)-cis-N-methyl-N-[2-(3,4-methylenedioxyphenyl)-ethyl]-2-(1-pyrrolidinyl)cyclohexylamine;

1R,2S-(+)-cis-N-methyl-N-[2-(3,4-methylenedioxyphenyl)-ethyl]-2-(1-pyrrolidinyl)cyclohexylamine;

1R,2S-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-ethyl-2-(1-pyrrolidinyl)cyclohexylamine;

1R,2S-(-)-cis-N-cyclopropylmethyl-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexylamine;

1R,2S-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-(1-propyl)-2-(1-pyrrolidinyl)cyclohexylamine;

1S,2R-(+)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexylamine;

1S,2R-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-ethyl-2-(1-pyrrolidinyl)cyclohexylamine;

1S,2R-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-cyclopropyl-methyl-2-(1-pyrrolidinyl)cyclohexylamine;

1S,2R-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-(1-propyl)-2-(1-pyrrolidinyl)cyclohexylamine; and

(±)-cis-N-[2-(3,4-dichlorophenyl)methyl]-N-methyl-2-(1-pyrrolidinyl)cyclohexylamine.

The term "hydrido" denotes a single hydrogen atom (H). This hydrido group may be attached, for example, to an oxygen atom to form a hydroxyl group; or as another example, two hydrido groups may be attached to a carbon atom to form a divalent $-CH_2-$ group, that is, a "methylene" group; or as another example, one hydrido group may be attached to a carbon atom to form a trivalent $-CH<$ group. Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "hydroxyalkyl", the term "alkyl" embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about ten carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about five carbon atoms. The term "cycloalkyl" embraces cyclic radicals having three to about six carbon atoms, such as cyclopropyl and cyclobutyl. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with one or more halo groups, preferable selected from bromo, chloro and fluoro. Specifically embraced by the term "haloalkyl" are monohaloalkyl, dihaloalkyl and polyhaloalkyl groups. A monohaloalkyl group, for example, may have either a bromo, a chloro, or a fluoro atom within the group. Dihaloalkyl and polyhaloalkyl groups may be substituted with two or more of the same halo groups, or may have a combination of different halo groups. A dihaloalkyl group, for example, may have two bromo atoms, such as a dibromomethyl group, or two chloro atoms, such as a dichloromethyl group, or one bromo atom and one chloro atom, such as a bromochloromethyl group. An example of a polyhaloalkyl is a trifluoromethyl group. The terms "alkylol" and "hydroxyalkyl" embrace linear or branched alkyl groups having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl groups. The term "alkenyl" embraces linear or branched radicals having two to about twenty carbon atoms,

preferable two to about ten carbon atoms, and containing at least one carbon-carbon triple bond. The terms "cycloalkenyl" and "cycloalkynyl" embrace cyclic radicals having three to about ten ring carbon atoms including, respectively, one or more double or triple bonds involving adjacent ring carbons. The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy group. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy or haloalkoxyalkyl groups. The term "heteroaryl" embraces aromatic ring systems containing one or two hetero atoms selected from oxygen, nitrogen and sulfur in a ring system having five or six ring members, examples of which are thienyl, furanyl, pyridinyl, thiazolyl, pyrimidyl and isoxazolyl. The term "alkylene chain" describes a chain of two to six methylene ($-CH_2-$) groups which may form a cyclic structure with or without a hetero atom in the cyclic structure.

Specific examples of alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, iso-pentyl, methyl-butyl, dimethylbutyl and neopentyl. Typical alkenyl and alkynyl groups may have one unsaturated bond, such as an allyl group, or may have a plurality of unsaturated bonds, with such plurality of bonds either adjacent, such as allene-type structures, or in conjugation, or separated by several saturated carbons.

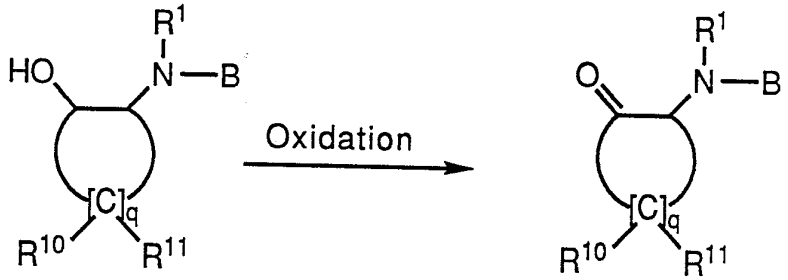
Included within the family of compounds of Formulas I-II are the tautomeric forms of the described compounds, isomeric forms including diastereoisomers, and the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. Since the compounds of Formulas I-II contain basic nitrogen atoms, such salts are typically

acid addition salts. The phrase "pharmaceutically-acceptable salts" is not intended to embrace quaternary ammonium salts. The nature of the salt is not critical, provided that it is pharmaceutically acceptable, and acids which may be employed to form salts are, of course, well known to those skilled in this art. Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulfuric acid and phosphoric acid, and such organic acids as maleic acid, succinic acid and citric acid. Other pharmaceutically acceptable salts include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium and magnesium, or with organic bases, such as dicyclohexylamine. All of these salts may be prepared by conventional means by reacting, for example, the appropriate acid or base with the corresponding compound of Formulas I-II.

General Synthetic Procedures

Compounds of Formulas I and II may be prepared in accordance with the following generic procedures, within which specific schemes are shown for Formula II type compounds.

Step 1

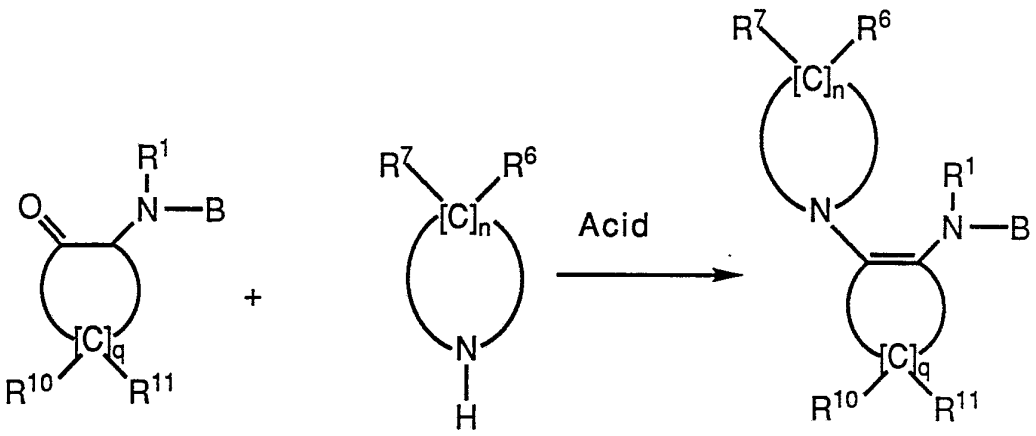


1 2

wherein R^1, R^{10}, R^{11}, and q are as defined previously; and wherein B represents a protecting group such as acetyl, benzoyl, t-butyloxy-carbonyl or benzyloxycarbonyl.

A process for preparing the compounds of the invention starts with protected hydroxyamines of general structure 1 where R^1, R^{10}, R^{11}, and q have the value assigned previously; and where B represents a protecting group such as acetyl, benzoyl or t.-butyloxycarbonyl. The alcohol is oxidized to the ketone 2 employing oxidizing agents such as pyridinium chlorochromate, chromium trioxide, potassium dichromate, or other oxidizing agents familiar to those skilled in the art. This oxidation can be achieved in either aqueous or organic solvents, depending on the oxidizing agent of choice, and at temperatures ranging from -60° to reflux of the reaction mixture.

Step 2

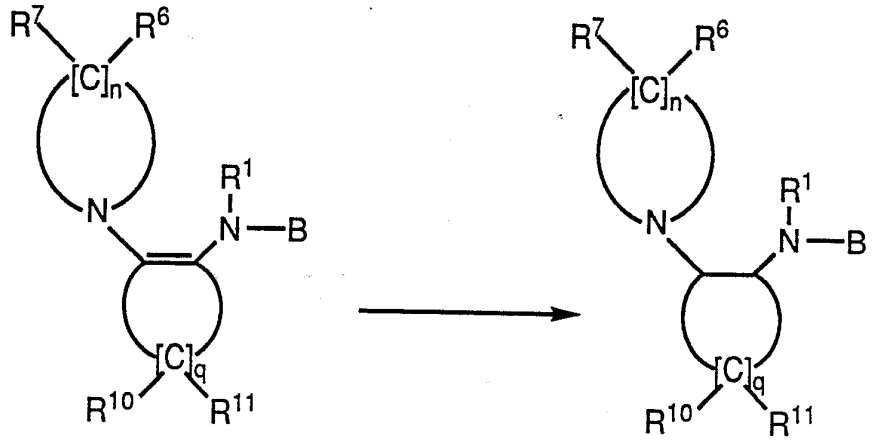


2 3 4

wherein B, R^1, R^6, R^7, R^{10}, R^{11}, n, and q are as defined previously.

In the second step of the process, ketones of general structure 2 are converted to enamines of general structure 4 by mixing 2 with amines of general structure 3 where B, R^1, R^6, R^7, R^{10}, R^{11}, n, and q are as defined previously. The compounds can be combined neat or in a variety of solvents such as toluene, xylene, or chloroform and with an acid such as p-toluenesulfonic acid, acetic acid, or trifluoroacetic acid. The temperature of the reaction can vary from room temperature to reflux of the reaction mixture.

Step 3

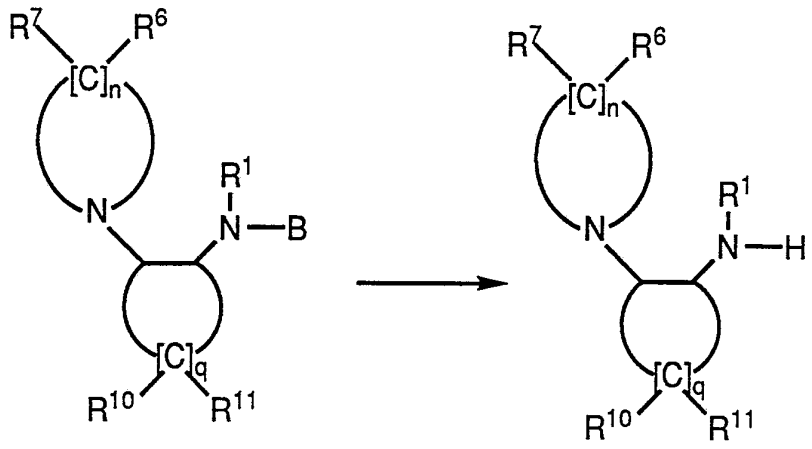


4 5

wherein B, R^1, R^6, R^7, R^{10}, R^{11}, n, and q are as defined previously.

In the third step of the process, enamines of general structure 4 are reduced to amines of general structure 5 by employing reducing agents such as lithium aluminum hydride, sodium borohydride, sodium cyanoborohydride, catalytic hydrogenation, or other reducing agents familiar to those skilled in the art. This reduction can be accomplished in either protic or aprotic solvents, depending on the reducing agent of choice, and at temperatures ranging from room temperature to reflux of the reaction mixture.

Step 4(a)



5 6

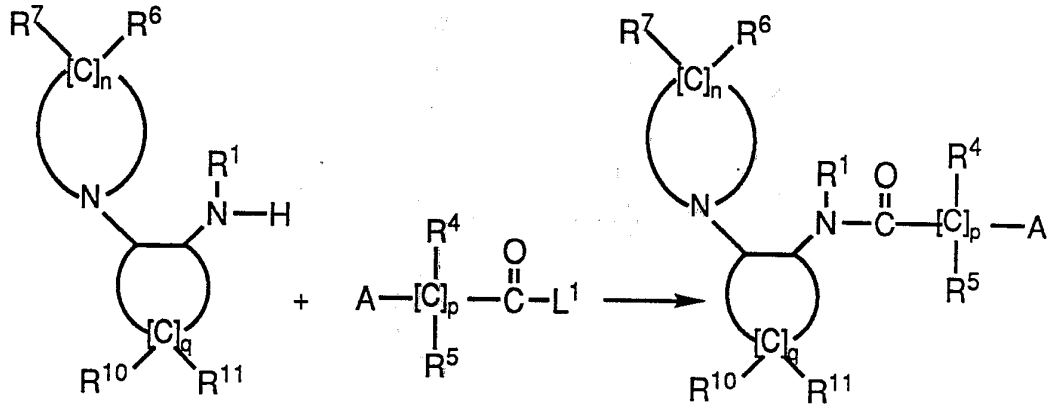
wherein B, R^1, R^6, R^7, R^{10}, R^{11}, n, and q are as defined previously.

In the fourth step of the process, amines of general structure 5 are converted to amines of general structure 6 by removal of the blocking group B. The conversion is best achieved by mixing 5 with a base such as sodium hydroxide, potassium hydroxide or other bases familiar to those skilled in the art. The reagents are combined in a protic solvent such as water, ethylene glycol, or methanol. The temperature of the reaction can vary from room temperature to reflux of the reaction mixture.

Step 4(b)

Alternately, amines of general structure 6 can be prepared from amines of general structure 5 by removal of the blocking group B by mixing 5 with an acid such as hydrochloric acid, sulfuric acid, trifluoroacetic acid or other acids familiar to those skilled in the art. The reagents are combined in a protic solvent such as water, ethylene glycol, or methanol. The temperature of the reaction can vary from room temperature to reflux of the reaction mixture.

Step 5(a)

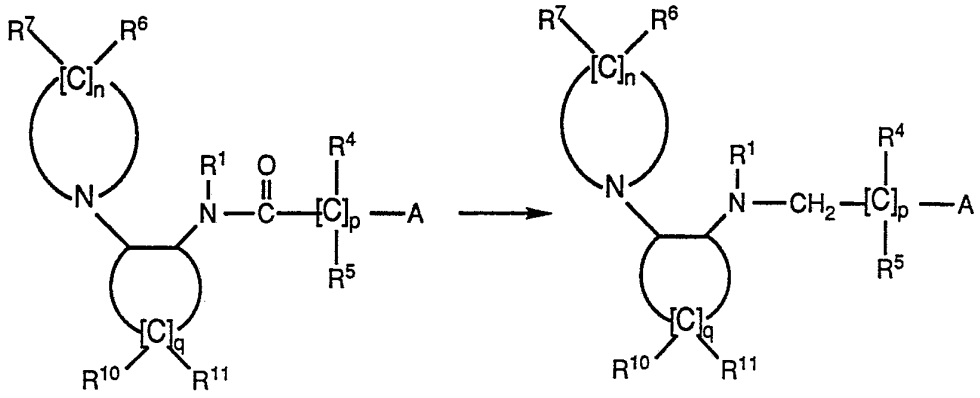


6 7 8

wherein A, R^1, R^4 through R^7, R^{10}, R^{11}, n, p, and q are as defined previously; and wherein L^1 is a good leaving group such as chloro, bromo, acyloxy, or hydroxy.

In the fifth step of the process, amines of general structure 6 are converted to amides of general structure 8 where A, R^4, and R^5 have the value assigned previously and L^1 is a good leaving group such as chloro, bromo, acyloxy, or hydroxy. The conversion can be best achieved by mixing the reagents neat or in an aprotic solvent such as tetrahydrofuran, methylene chloride, or ether. The reaction can be run in the absence or presence of an activating agent such as dicyclohexylcarbodiimide or phosphorus oxychloride, depending on the leaving group of choice. The temperature of the reaction can vary from 0° to reflux of the reaction mixture.

Step 6(a)



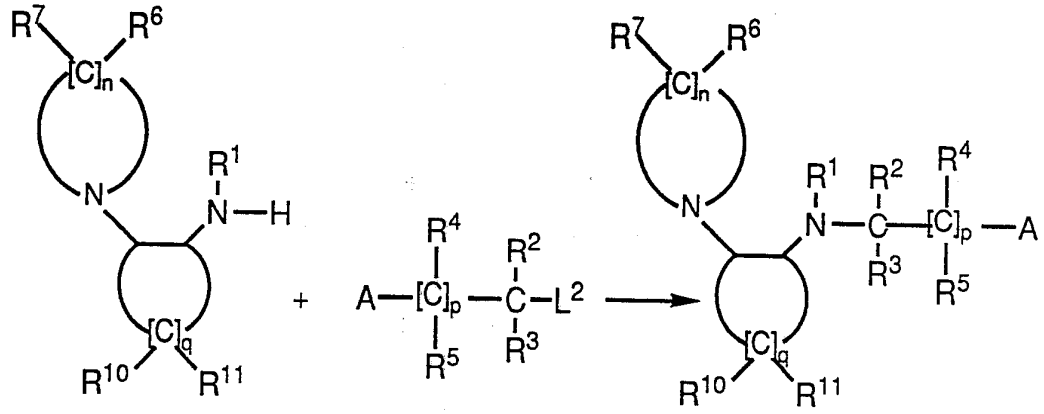
8 9

wherein A, R^1, R^4 through R^7, R^{10}, R^{11}, n, p, and q are as defined previously.

In the sixth step of the process, amides of general structure 8 are converted to amines of general structure 9 by employing reducing agents such as lithium aluminum hydride, sodium borohydride, sodium cyanoborohydride, or other reducing agents familiar to those skilled in the art. This reduction can be accomplished in either protic or aprotic solvents, depending on the reducing agent of choice, and at temperatures ranging from room temperature to reflux of the reaction mixture.

Step 5(b) [Alternate to Steps 5(a) and 5(b)]

Alternately, amines of general structure 11 can be prepared according to the following generic procedure.



6 10 11

wherein A, R^1 through R^7, R^{10}, R^{11}, n, p, and q are as defined previously; and wherein L^2 is a good leaving group such as halogen, tosylate, mesylate, brosylate or OH.

Amines of general structure 11 can be alternately prepared by combining amines of general structure 6 with compounds of general structure 10 where A, R^1 through R^7, R^{10}, R^{11}, n, p, and q have the values assigned previously and where L^2 is a good leaving group such as halogen, tosylate, mesylate, brosylate or OH. The compounds can be combined in a variety of solvents such as toluene, xylenes, dimethylformamide, hexamethylphosphoramide, or ethanol. The temperature of the reaction can vary from room temperature to reflux of the reaction mixture.

The following Examples 1 to 6 are detailed descriptions of the methods of preparation of compounds of Formula I. These detailed preparations fall within the scope of, and serve to exemplify, the above described Generic Procedures which form part of the invention. These Examples 1 to 6 are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention. All parts are by weight unless otherwise indicated. Most of the commercially available starting materials were obtained from Aldrich Chemical Company, Milwaukee, Wisconsin. Abbreviated terms used in Examples 1 to 6 are explained below:

MeOH	=	methanol
EtOH	=	ethanol
DMSO	=	dimethylsulfoxide
EtOAc	=	ethyl acetate
TLC	=	thin layer chromatography
Et_2O	=	ethyl ether
Ac_2O	=	acetic anhydride
Et_3N	=	triethylamine
THF	=	tetrahydrofuran

Example I

Step (a): Preparation of (±)-trans-2-benzamidocyclohexanol

(±)-trans-2-Aminocyclohexanol (241 gm) was combined with chloroform (2000 ml), water (2000 ml) and sodium bicarbonate (352 gm) and stirred. Benzoyl chloride (352 gm) was added dropwise to the stirred solution and stirring was continued for 1 hr. The product was filtered and washed with water. The white solid was dried at 80°C to provide the product (mp 172-173°C).

Step (b): Preparation of (±)-2-benzamidocyclohexanone

A solution of Jones reagent (1135 ml) was prepared by combining CrO_3 (140 gm) and H_2SO_4 (122 ml) with water. The Jones reagent was added dropwise to a cooled, stirred mixture of (±)-trans-2-benzamidocyclohexanol (260 gm) and acetone (3000 ml) and the stirring continued 1 hr. A 20% solution of K_2CO_3 in water was added to the reaction solution until the evolution of carbon dioxide subsided. The resulting layers were separated and the bottom layer extracted with ethyl acetate. The ethyl acetate was combined with the material from the upper layer and the resulting solution washed with water and saturated sodium chloride solution. The organic solution was concentrated on a rotary evaporator and the residue was recrystallized from aqueous 2-propanol to provide the product (mp 126-127°C).

Step (c): Preparation of (±)-cis-2-(1-pyrrolidinyl)-N-benzoylcyclohexylamine hydrochloride

(±)-2-Benzamidocyclohexanone (213 gm) was combined with pyrrolidine (103 ml), p-toluenesulfonic acid (9.3 gm) and benzene (3300 ml) and heated to reflux for 23 hours. Additional pyrrolidine (103 ml) was added to the reaction mixture and the heating continued for 24 hours. The solvent was removed on a rotary evaporator to provide a crude enamine mixture. The crude material was dissolved in ethyl acetate (100 gm/200 ml) and hydrogenated over 10% Pd on carbon at 50 psi for 1.5 hours. The mixture was filtered through celite and the filtrate was concentrated on a rotary evaporator. The residue was combined with citric acid monohydrate (306 gm), water (1300 ml) and methylene chloride (500 ml) and shaken until all solid material had dissolved. The layers were separated and the aqueous layer was washed with additional methylene chloride. Excess concentrated aqueous ammonia was added to the aqueous solution and the mixture extracted with methylene chloride. The combined organic extracts were dried

(Na_2SO_4) and the solvent removed on a rotary evaporator. The crude material was dissolved in methanol (200 ml) and treated with an excess of a solution of anhydrous hydrogen chloride in methanol. The solution was adjusted to a final volume of 700 ml by the addition of 2-propanol and the methanol was removed by distillation while maintaining a constant volume of 700 ml by the slow addition of 2-propanol. The crude product crystallized upon slow cooling and was filtered. The material was recrystallzed from 2-propanol to provide the product (mp 276-277°C).

Step (d): Preparation of (±)-cis-2-(1-pyrrolidinyl)-cyclohexylamine

(±)-cis-2-(1-Pyrrolidinyl)-N-benzoylcyclohexylamine hydrochloride (10 gm) was combined with ethylene glycol (50 ml) and potassium hydroxide (10 gm) and the solution was heated to reflux for 48 hours. The solution was diluted with water (200 ml) and extracted with ether. The ether was removed on a rotary evaporator and the residue was distilled (94°C at 0.05 mm Hg) to provide the product.

Step (e): Preparation of (-)-cis-2-(1-pyrrolidinyl)-cyclohexylamine

(±)-cis-2-(1-pyrrolidinyl)cyclohexylamine (10 gm) was combined with ethanol (10 ml) and 2-propanol (40 ml) and warmed to 60°C. A solution of R-(-)-mandelic acid (18 gm) in ethanol (50 ml) and 2-propanol (200 ml) was warmed to 60°C and added to the amine solution. The solution was allowed to cool slowly to room temperature and the resulting crystals were filtered. The crystals were washed with 20% ethanol in 2-propanol, followed by ether and dried under vacuum. The crystals were recrystallized from 20% ethanol in 2-propanol to provide the mandelate salt. The salt was partitioned between 30% NaOH and chloroform and the layers separated. The

chloroform was removed on a rotary evaporator to provide the product as a colorless oil which solidified upon standing (bp 86°C at 0.1 mm Hg, $[a]_D$ (MeOH) = -2.95°).

Step (f): Preparation of (+)-cis-2-(1-pyrrolidinyl)-cyclohexylamine

The mother liquors from Step (e) of Example 1 were concentrated on a rotary evaporator. The residue was partitioned between 30% NaOH and chloroform and the layers separated. The chloroform was removed on a rotary evaporator and the residue was distilled under high vacuum. The distillate was combined with ethanol (10 ml) and 2-propanol (40 ml) and warmed to 60°C. A solution of R-(-)-mandelic acid (18 gm) in ethanol (50 ml) and 2-propanol (200 ml) was warmed to 60°C and added to the amine solution. The solution was allowed to cool slowly to room termperature and the resulting crystals were filtered. The crystals were washed with 20% ethanol in 2-propanol, followed by ether and dried under vacuum. The crystals were recrystallized from 20% ethanol in 2-propanol to provide the mandelate salt. The salt was partitioned between 30% NaOH and chloroform and the layers separated. The chloroform was removed on a rotary evaporator to provide the product as a colorless oil which solidified upon standing (bp 86°C at 0.1 mm Hg, $[a]_D$ (MeOH) = +2.21°).

Step (g): Preparation of 1R,2S-(-)-cis-2-(1-pyrrolidinyl)-N-methylcyclohexylamine

(-)-cis-2-(1-pyrrolidinyl)cyclohexylamine (2 gm) was combined with ethyl formate (20 ml) and heated to reflux 10 minutes. The solvent was removed on a rotary evaporator. The residue was combined with anhydrous tetrahydrofuran (10 ml) and treated with 1 M lithium aluminum hydride in tetrahydrofuran (16 ml). The mixture was heated to reflux 1 hour and cooled in an ice bath. The mixture was treated with

water (2.4 ml) and 15% NaOH (0.6 ml), filtered, and the solvent removed on a rotary evaporator. The residue was distilled under high vacuum to provide the product as a colorless oil (bp 76°C at 1.1 mm Hg, $[a]_D$ (MeOH) = -31.7°).

Step (h): Preparation of (±)-2-(N-t-butyloxycarbonyl-N-methylamino) cyclohexanone

(±)-trans-N-methyl-2-aminocyclohexanol (142 gm) was combined with t-butyldicarbonate (240 gm), potassium bicarbonate (458 gm), and water (1000 ml) and stirred overnight. The aqueous mixture was extracted with methylene chloride and the organic extract was dried (Na_2SO_4) and concentrated on a rotary evaporator. The residue was recrystallized from isooctane to provide a white solid (mp 82-83°C). The solid was dissolved in methylene chloride (500 ml) and added dropwise to a stirred solution of pyridinium chlorochromate (334 gm) in methylene chloride (1000 ml). After the addition, stirring was continued for 3 hours. The mixture was diluted with ether (1500 ml) and filtered through florisil. The solvent was removed on a rotary evaporator and the residue was distilled (115°C at 0.9 mm Hg) to provide a colorless oil.

Step (i): Preparation of (±)-cis-2-[1-pyrrolidinyl]-N-methylcyclohexylamine

(±)-cis-2-Pyrrolidinyl-N-t-butyloxycarbonyl-N-methylcyclohexylamine (247 gm) was slowly added to 6 M hydrochloric acid at 60°C with vigorous stirring. The solution was stirred an additional 5 minutes at 60°C and poured onto ice (200 gm). Excess concentrated aqueous ammonia was added and the mixture was extracted with methylene chloride. The combined extracts were dried (Na_2SO_4) and the solvent removed on a rotary evaporator. The residue was

distilled (78°C at 0.3 mm Hg) to give the product as a colorless oil.

Step (j): Preparation of (±)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(1-pyrrolidinyl)cyclohexylamine (Compound No. 1).

(±)-cis-2-Pyrrolidinyl-N-methylcyclohexylamine (3 gm) was combined with anhydrous dimethylformamide (70 ml) and warmed to 60°C. 2-(3,4-dichlorophenyl)ethyl methanesulfonate (14 gm) was added to the warm amine solution over 3 days. The reaction mixture was diluted to 500 ml with water and extracted with chloroform. The combined extracts were washed with water and treated with a solution of hydrogen bromide in methanol. The solution was concentrated on a rotary evaporator and the residual dimethylformamide removed by distillation under high vacuum. The residue was triturated with 2-propanol to provide a white solid. The solid was recrystallized from 2-propanol. Analytical data are reported in Table I.

Example 2

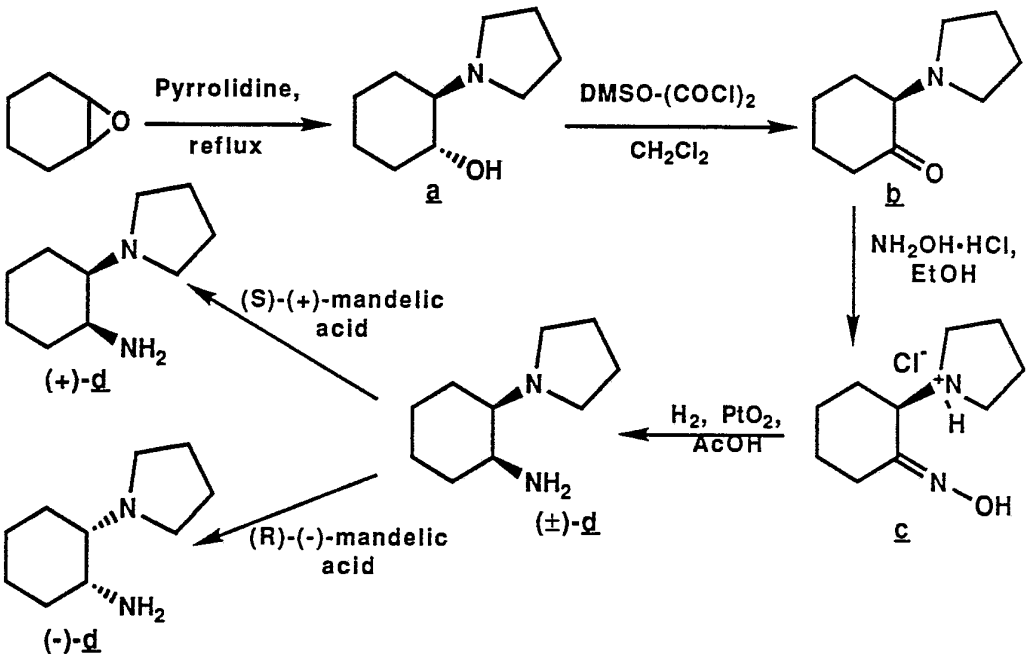
Preparation of (±)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidnyl)-cyclohexylamine

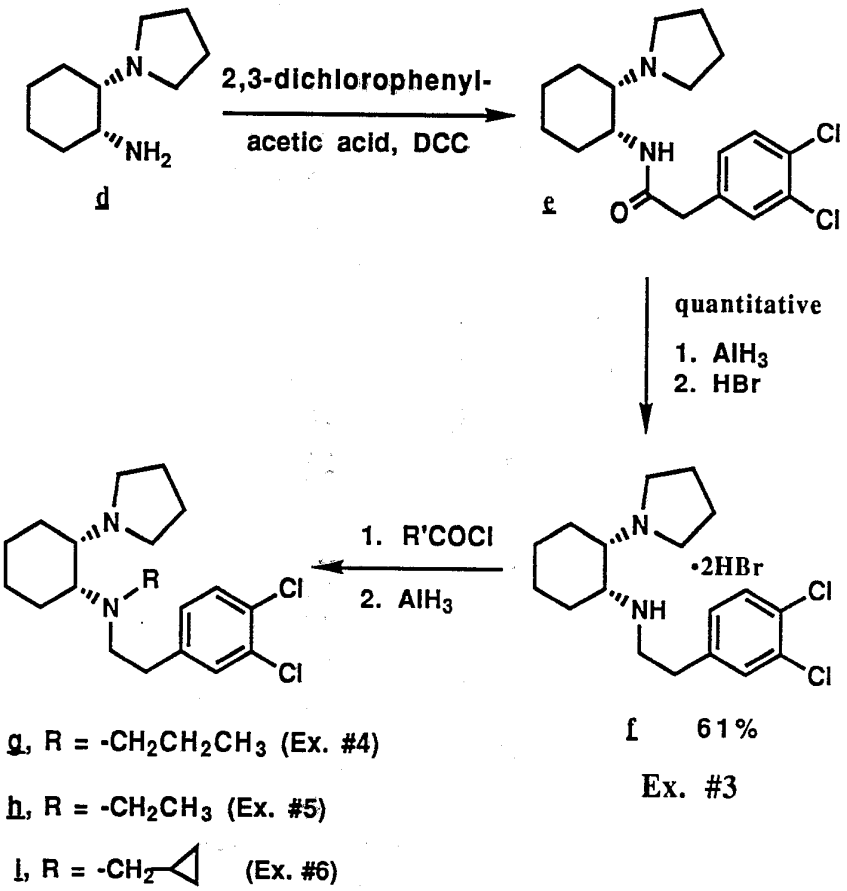
(±)-cis-2-(1-pyrrolidinyl)cyclohexylamine (5 gm) was combined with pyridine (1.2 gm), chloroform (200 ml), 3,4-dichlorophenylacetic acid (9.15 gm), and dicyclohexyl-carbodiimide (12.3 gm) and the mixture was stirred for 12 hr at room temperature. The mixture was filtered, the precipitate was washed with ether (100 ml) and the filtrate and ether wash were combined. The organic solution was diluted with ether (200 ml) and extracted with 10% citric acid in water (300 ml). The acid layer was washed with ether (2X200 ml), then treated with excess concentrated aqueous ammonia until basic. The resulting mixture was extracted with

methylene chloride (2X200 ml) and the combined organic extracts were washed with water (2X50 ml) and concentrated on a rotary evaporator. The resulting white solid was combined with tetrahydrofuran (25 ml) and added dropwise to a solution of AlH_3 in tetrahydrofuran (76.2 ml of a 0.665 M solution) at room temperature. After the addition, the mixture was poured into 15% NaOH and the resulting mixture was extracted with ether (3X100 ml). The ether was removed on a rotary evaporator and the residue was dissolved in ethanol (100 ml). The ethanol was removed on a rotary evaporator and the residue was converted to the hydrogen bromide salt which was recrystallized from ethanol. Analytical data are reported in Table I.

The overall synthon for preparing compounds of Examples 3 to 6 is shown below, which is explained in more detail in the detailed description of Examples 3 to 6 which follows the synthon.

Synthon for Ex. #3 to Ex. #6





Example 3

Preparation of 1R, 2S-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexylamine

Step (a): Preparation of 2-(1-pyrrolidinyl)cyclohexanone (b).

A solution of oxalyl chloride (50 mL, 0.5732 mol) in 200 mL of freshly distilled CH_2Cl_2 was cooled down to -70°C and DMSO (80 mL, 1.1274 mol) was carefully added dropwise. After 15 min., 2-(1-pyrrolidinyl)cyclohexanol (a) (70 g, 0.4142 mol) was added to the reaction mixture, followed by Et_3N (350 mL). The cold bath was then removed, and the mixture was stirred at room temperature for two and a half hours. Progress of the reaction was followed by gas chromatography. The solvent was partially removed in vacuo

and ethyl ether (200 mL) was added. This organic layer was washed with brine (3x100 mL), dried (Na_2SO_4), and the solvent removed in vacuo. The crude product was distilled under high vacuum (BP: 84°C/0.5 mmHg) to yield 49.5 g of the ketone (b) as a colorless oil (72%). R_f: 0.49 ($CHCl_3$:MeOH:NH_4OH = 92:7:1); B.P : 84 °C (0.5 mmHg); IR (neat) 2940, 2860, 2800, 1715, 1440 cm^{-1}; ^{1}H-NMR ($CDCl_3$) d 1.53-1.63 (m, 1H), 1.72 (m, 4H), 1.76-1.93 (m, 4H), 1.94-2.04 (m, 1H), 2.21 (m, 1H), 2.52 (m, 5H), 2.83 (dd, 1H, J_1=8.6, J_2=4.5 Hz); Mass Spectrum Calcd. for $C_{10}H_{17}NO$: 167.1310, Found: 167.1310.

Step (b): Preparation of 2-(1-pyrrolidinyl)cyclohexanone oxime (c).

2-(1-Pyrrolidinyl)cyclohexanone (b) (46.15 g, 0.276 mol) was dissolved in EtOH (175 mL) and NH_2OH•HCl (23.4 g, 0.337 mol) was added. Reaction progress was followed by gas chromatography. The solvent was removed in vacuo, the residue was dissolved in MeOH, and the solution was poured into an Erlenmeyer flask. EtOAc was added to replace the MeOH while the mixture was boiling. In this way, crystallization of the hydrochloride of the oxime occurred, and 53.06 g of salt was obtained (88%). R_f: 0.44 ($CHCl_3$:MeOH:NH_4OH = 90:9:1); M.P. (HCl salt): 170-171°C; IR (neat) 3400, 2960, 1640, 1450 cm^{-1}; ^{1}H-NMR ($CDCl_3$) d 1.36-1.58 (m, 3H), 1.73 (m, 4H), 1.79-1.88 (m, 2H), 2.02-2.15 (m, 2H), 2.46-2.54 (m, 2H), 2.69 (m, 1H), 3.02 (bd, 1H, J=13.4 Hz), 8.35 (bs, 1H); Mass Spectrum (70 eV, m/e (rel. int.)) 182 (15, M^+), 166 (100), 148 (29), 136 (27), 124 (29), 110 (100), 97 (100), 70 (60). Elemental Analysis: Calcd. for $C_{10}H_{19}ClN_2O$: C: 54.92, H: 8.70, N: 12.81, Cl: 16.25. Found: C: 54.81, H: 8.71, N: 12.78, Cl: 16.30.

Step (c): Preparation of (±) cis-2-(1-pyrrolidinyl)cyclohexylamine ((±)-d).

2-(1-pyrrolidinyl)cyclohexanone oxime (c) (22.95 g, 0.105 mol) was dissolved in glacial acetic acid (120 mL), PtO_2 (1g) was added and the mixture was hydrogenated at 45 psi for

96 hours. During this time, the catalyst was filtered and renewed every 24 hours. The reaction was followed by gas chromatography. The PtO_2 was removed by filtration of the reaction mixture through celite and excess concentrated HCl was added. The solvent was removed in vacuo at 40-50°C and the resulting hydrochloride salt was dissolved in 100 mL of water. This aqueous solution was carefully basified to 30% w/v with pellets of NaOH and extracted with $CHCl_3$ (5x50 mL). The organic layer was dried (Na_2SO_4), and the solvent was removed in vacuo. The crude amine was distilled under high vacuum to yield 13.7 g of (±)-d (78%) as a colorless unstable oil. bp: 94°C/0.05 mmHg. Ir (film): 3380, 3300, 2940, 1590, 1440, 1125, 835 cm^{-1}. (±)-d·HCl crystallized slowly from 2-propanol as small conglomerates: mp 263-265°C. ^{1}H-NMR (free base) ($CDCl_3$): d 1.00-1.18 (m, 1H), 1.20-1.40 (m, 5H), 1.50-1.68 (m, 6H), 1.74 (t, J=3.5 Hz, 1H), 1.78 (t, J=3.5 Hz, 1H), 2.30-2.48 (m, 4H), 3.08 (br s, 2H). EIms (m/z, rel. int.): 168 (31, M^+), 110 (100), 97 (42), 84 (92), 70 (33). Anal. Calcd. for $C_{10}H_{22}N_2Cl_2$: C 49.79, H 9.19, N 11.62; Found: C 49.82, H 9.19, N 11.67.

Step (d): Preparation of (1R,2S)-(-)-cis-3,4-dichloro-phenyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]acetamide [(-)-e].

3,4-Dichlorophenylacetic acid (7.3 g, 0.357 mol) was dissolved in CH_2Cl_2 (50 mL) and dicyclohexylcarbodiimide (7.4 g, 0.0357 mol) was added. The mixture was stirred at room temperature for half an hour. (-)-cis-2-(1-Pyrrolidinyl) cyclohexylamine ((-)-d) (3.0 g, 0.0179 mol) and pyridine (0.7 mL) were then added. After 5 minutes, the dicyclohexyl urea was filtered off, and the solvent was concentrated in vacuo. The residue was diluted with Et_2O (200 mL), and the resulting organic layer extracted with 5% citric acid (4x50 mL). The aqueous layer was washed with Et_2O (4x50 mL), basified with concentrated NH_4OH and extracted with CH_2Cl_2 (3x80 mL). The organic layer was washed with brine (50 mL), dried (Na_2SO_4) and the solvent removed in vacuo. 6.30 g (99%) of crude crystalline product was obtained. The amide was

recrystallized as its fumarate salt from EtOAc to yield 7.70 g (92%) of pure (-)-e•fumarate•hemihydrate. R_f: 0.27 ($CHCl_3$:MeOH:NH_4OH = 95:4.5:0.5); M.P. (free base): 110-111 °C; M.P. (fumarate salt): 159-160 °C; $[a]_D$ (fumarate salt) -12.7° (0.11, MeOH); ^{1}H-NMR ($CDCl_3$) d 1.16-1.35 (m, 4H), 1.43 (m, 1H), 1.70 (m, 5H), 1.85 (m, 1H), 2.11 (m, 1H), 2.29 (bd, 1H, J=13.4 Hz), 2.41-2.49 (m, 4H), 3.51 (s, 2H), 4.01 (s, 1H), 6.28 (bs, 1H), 7.15 (dd, 1H, J_1=8.3, J_2=2.0 Hz), 7.39 (d, 1H, J=8.3 Hz), 7.41 (d, 1H, J=2.0 Hz); Mass Spectrum: CI (NH_3) 355 (M^+); Elemental Analysis: Calcd. for $C_{18}H_{24}Cl_2N_2O$ (free base): C: 60.85, H: 6.76, N: 7.89, Cl: 20.00. Found: C: 60.75, H: 6.82, N: 7.84, Cl: 20.07. Elemental Analysis: Calcd. for $C_{22}H_{28}Cl_2N_2O_5$•1/2H_2O (fumarate salt): C: 55.00, H: 6.04, N: 5.83, Cl: 14.79. Found: C: 55.22, H: 6.06, N: 5.84, Cl: 14.86

Step (e): Preparation of (1R,2S)-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexylamine [(-)-f; Compound #3].

Aluminum Hydride solution in THF (0.67 mmol/mL) (80 mL, 0.0531 mol) [prepared by procedures described in a publication of B. R. de Costa et al, J. Med. Chem., 33, 3100-3110 (1990)] was stirred at room temperature under argon and (1R,2S)-(-)-cis-3,4-dichlorophenyl-N-[2-(1-pyrrolidinyl)cyclohexyl]acetamide [(-)-e] (3.77 g, 0.0106 mol) in THF (30 mL) was added slowly. After 5 minutes the mixture was poured into ice-cooled 15% NaOH solution (100 mL). An oily compound separated from this aqueous layer, which was extracted with Et_2O (3x100 mL). The organic layers were combined, washed with brine (2x50 mL), dried (Na_2SO_4) and the solvent removed in vacuo. A yellowish oil was obtained, which was purified by crystallization with HBr in EtOH to yield 3.24 g (61%) of (-)-f•HBr. R_f: 0.27 ($CHCl_3$:MeOH:NH_4OH = 90:9:1); M.P. (HBr salt): 274-275 °C; $[a]_D$ -11.1° (0.32, MeOH); ^{1}H-NMR ($CDCl_3$) d 1.11-1.28 (m, 4H), 1.45-1.77 (m, 8H), 1.81-1.95 (m, 2H), 2.28-2.44 (m, 4H), 2.58-2.69 (m, 1H), 2.71-2.80 (m, 3H), 2.89-2.97 (m, 1H), 7.07 (dd, 1H, J_1=8.2, J_2=2.0 Hz), 7.32 (d, 1H,

J=8.2 Hz), 7.33 (d, 1H, J=2 Hz); Mass Spectrum: CI (NH_3) 341 (M^+); Elemental Analysis: Calcd. for $C_{18}H_{28}Br_2Cl_2N_2$ (HBr salt): C: 42.97, H: 5.61, N: 5.57, total halogen as Cl: 28.23, total halogen as Br: 63.56. Found: C: 43.06, H: 5.62, N: 5.55, total halogen as Cl: 28.13, total halogen as Br: 63.40. Calcd. for $C_{18}H_{26}Cl_2N_2$ (free base): C: 63.34, H: 7.62, N: 8.21, Cl: 20.82. Found: C: 63.24, H: 7.68, N: 8.16, Cl: 20.86.

Example 4

Preparation of (1R,2S)-(-)-cis-N-[2-(3,4-dichlorophenyl)-ethyl]-N-(n-propyl)-2-(1-pyrrolidinyl)cyclohexylamine [(-)g; Compound #4].

(1R,2S)-(-)-cis-N-[2-(3,4-dichlorophenyl) ethyl]-2-(1-pyrrolidinyl)cyclohexylamine [(-)-f] (1.0 g, 0.00293 mol), prepared by procedures of Step (d) of Example 3, was dissolved in $CHCl_3$ (10 mL) and stirred in the presence of anhydrous K_2CO_3 (2.0 g, 0.0147 mol). Propionyl chloride (0.54 g, 0.00587 mol) was then added and reaction progress was followed by TLC. After completion of the reaction, the mixture was diluted with $CHCl_3$ (10 mL) and extracted with 10% NaOH (10x10 mL). The organic layer was dried and the solvent was removed in vacuo to give 1.1 g of crude product, which was not further purified. R_f: 0.51 ($CHCl_3$:MeOH:NH_4OH = 90:9:1). The crude amide (0.2 g) was reduced following procedures of Step (e) of Example 3 to give 0.18 g of product, which contained 10% of diamine f as an impurity. The entire mixture was acylated with Ac_2O and then the desired diamine g was purified by crystallization with fumaric acid in EtOAc. R_f: 0.44 ($CHCl_3$:MeOH:NH_4OH = 90:9:1); MP: 168-169 °C; $[a]_D$ -11.1° (0.38, MeOH); Elemental Analysis: Calcd. for $C_{25}H_{36}Cl_2N_2O_4 \cdot H_2O$ (fumarate salt): C: 58.03, H: 7.35, N: 5.41. Found: C: 58.03, H: 7.06, N: 5.66.

Example 5

Preparation of (1R,2S)-(-)-cis-N-ethyl-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexylamine [(-)-h; Compound #5].

The title compound was prepared following the procedures of Example 4, except that Ac_2O was used instead of propionyl chloride to obtain the amide. Diamine h was purified as the HI salt and recrystallized from MeOH. R_f: 0.42 ($CHCl_3$:MeOH:NH_4OH = 90:9:1); MP: 215.5-216.5 °C; $[a]_D$ -8.2° (0.09, MeOH); Elemental Analysis: Calcd. for $C_{20}H_{32}Cl_2I_2N_2$ (HI salt): C: 38.40, H: 5.12, N: 4.48, Cl: 11.36. Found: C: 38.42, H: 5.24, N: 4.47, Cl: 11.24.

Example 6

Preparation of (1R,2S)-(-)-cis-N-[2-(3,4-dichlorophenyl)-ethyl]-N-cyclopropylmethyl-2-(1-pyrrolidinyl)cyclohexylamine [(-)-i; Compound #6].

The title compound (-)-i was prepared following the procedures of Example 4, purified as the fumarate salt and recrystallized from EtOAc. R_f: 0.47 ($CHCl_3$:MeOH:NH_4OH = 90:9:1); MP: 183-184 °C; $[a]_D$ -28.3° (0.30, MeOH); Elemental Analysis: Calcd. for $C_{26}H_{36}Cl_2N_2O_4$ (fumarate salt): C: 61.05, H: 7.09, N: 5.48. Found: C: 61.11, H: 7.13, N: 5.45.

Table I is a list of 17 specific compounds of most interest within Formula I. These compounds may be prepared by the methods described in the "General Synthetic Procedures" as well as by the more detailed methods contained in the specific preparations of Examples 1 to 6, above.

TABLE I

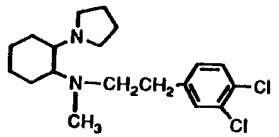
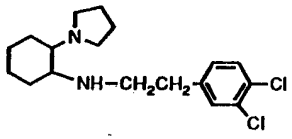
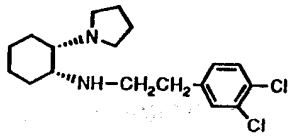
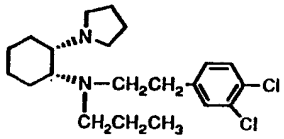
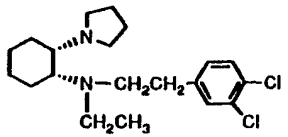
Compound No.	Name	Structure	Elemental Analysis Theor.	Found	Melting Point	Specific Rotation $[\alpha]_D$	Mass Spectral Analysis
1	(±)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(1-pyrrolidinyl)cyclohexylamine		C 56.63 H 6.79 N 6.29	56.43 6.91 6.33	120-125°C oxalate salt	-	-
2	(±)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)-cyclohexylamine		C 42.96 H 5.57 N 5.57	43.04 5.65 5.54	274-275°C HBr salt	-	-
3	1R,2S-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexylamine		C 42.96 H 5.57 N 5.57	43.03 5.61 5.57	274-275°C HBr salt	-11.1° (0.32,MeOH)	-
4	1R,2S-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-(n-propyl)-2-(1-pyrrolidinyl)cyclohexylamine		C 58.03 H 7.35 N 5.41	58.03 7.06 5.66	168-169°C fumarate salt	-11.1° (0.38,MeOH)	-
5	1R,2S-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-ethyl-2-(1-pyrrolidinyl)cyclohexylamine		C 38.40 H 5.12 N 4.48	38.47 5.22 4.51	215.5-216.5°C HI salt	-8.2° (0.09,MeOH)	-

TABLE I (Cont'd.)

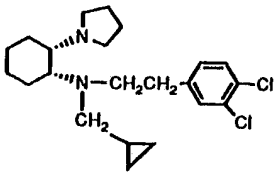
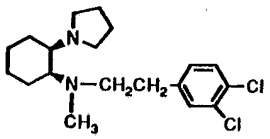
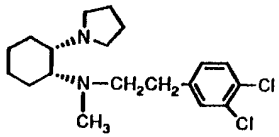
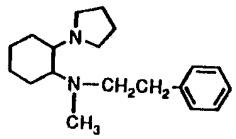
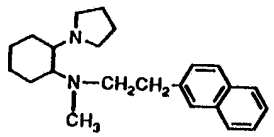
Compound No.	Name	Structure	Elemental Analysis Theor.	Found	Melting Point	Specific Rotation $[\alpha]_D$	Mass Spectral Analysis
6	1R,2S-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-cyclopropylmethyl-2-(1-pyrrolidinyl)cyclohexylamine		C 61.05 H 7.09 N 5.48	61.11 7.13 5.45	183-184°C fumarate salt	-28.3° (0.30,MeOH)	-
7	1S,2R-(-)-cis-N-[2-(3,4-dichlorophenyl)-ethyl]-N-methyl-2-(1-pyrrolidinyl)cyclohexylamine		C 44.12 H 5.85 N 5.42	44.07 5.88 5.44	215-217°C HBr salt	-8.6° (0.84, MeOH)	—
8	1R,2S-(+)-cis-N-[2-(3,4-dichlorophenyl)-ethyl]-N-methyl-2-(1-pyrrolidinyl)cyclohexylamine		C 44.12 H 5.85 N 5.42	44.21 5.91 5.40	217-218°C HBr salt	+8.0° (0.57, MeOH)	-
9	(±)-cis-N-methyl-N-(2-phenylethyl)-2-(1-pyrrolidinyl)cyclohexylamine		-	-	oil		M^+ (found) 286.242 Requires 286.241
10	(±)-cis-N-methyl-N-[2-(2-naphthyl)ethyl]-2-(1-pyrrolidinyl)cyclohexylamine		-	-	oil		M^+ (found) 336.256 Requires 336.257

TABLE I (Cont'd.)

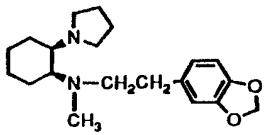
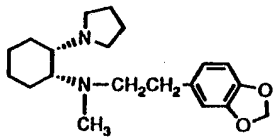
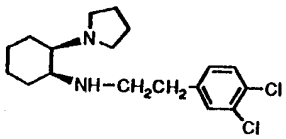
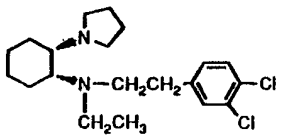
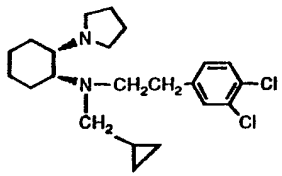
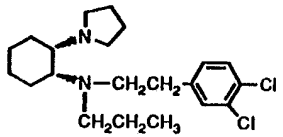
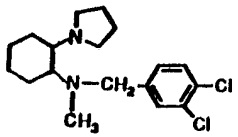
Compound No.	Name	Structure	Elemental Analysis Theor.	Found	Melting Point	Specific Rotation $[\alpha]_D$	Mass Spectral Analysis
11	1S,2R-(-)-cis-N-methyl-N-[2-(3,4-methylenedioxyphenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexylamine		C 48.79 H 6.55 N 5.69	48.68 6.59 5.68	248-249°C HBr salt	-13.0° (3.99,H_2O)	-
12	1R,2S-(+)-cis-N-methyl-N-[2-(3,4-methylenedioxyphenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexylamine		C 48.79 H 6.55 N 5.69	48.64 6.60 5.62	248-249°C HBr salt	+15.2° (2.16,H_2O)	-
13	1S,2R-(+)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexylamine		C 42.96 H 5.57 N 5.57	43.03 5.62 5.59	274-275°C HBr salt	+11.5° (0.57,MeOH)	-
14	1S,2R-(+)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-ethyl-2-(1-pyrrolidinyl)cyclohexylamine		C 38.47 H 5.22 N 4.51	38.50 5.15 4.43	215-215.5°C HI salt	+7.8° (0.32,MeOH)	-
15	1S,2R-(+)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-cyclopropylmethyl-2-(1-pyrrolidinyl)cyclohexylamine		C 61.05 H 7.09 N 5.48	61.09 7.10 5.47	183-184°C fumarate salt	+29.9° (0.35,MeOH)	-

TABLE I (Cont'd.)

Compound No.	Name	Structure	Elemental Analysis Theor.	Found	Melting Point	Specific Rotation $[\alpha]_D$	Mass Spectral Analysis
16	1S,2R-(+)-cis-N-[2-(3,4-dichlorophenyl) ethyl]-N-(1-propyl)-2-(1-pyrrolidinyl) cyclohexylamine		C 60.12 H 7.26 N 5.61	6.03 7.26 5.52	168-169°C fumarate salt	-15.0° (0.31,MeOH)	-
17	(±)-cis-N-[2-(3,4-dichlorophenyl)-methyl]-N-methyl-2-(1-pyrrolidinyl) cyclohexylamine		C 42.97 H 5.61 N 5.57	43.12 5.78 5.20	215-217°C HBr salt	-8.6° (0.84,MeOH)	-

Biological Evaluation

Radioreceptor Assay in Rat Brain Homogenate

Compounds #1, #7 and #8 were compared against di-o-tolylguanidine (DTG) [E. Weber et al, Proc. Nat'l. Acad. Sci., 83, 8784-8788, 1986] to determine the relative potency of the compounds interacting with the sigma receptor. To determine the effects of the compounds in a sigma receptor assay, crude membrane preparations were prepared as follows. Brains from male Sprague-Dawley rats were homogenized in 10 volumes (wt/vol) of 0.32 M sucrose, using a Polytron grinder. The homogenate was centrifuged at 900 X G for 10 minutes at 4°C. The supernatant was collected and centrifuged at 22,000 X g for 20 minutes at 4°C. The pellet was resuspended in 10 volumes of 50 mM Tris/HCl buffer (pH 7.4) and centrifuged at 22,000 X g for 20 minutes at 4°C. The pellet was resuspended in 5 mM Tris/HCl buffer (pH 7.4) to give a final concentration of 250 mg/ml of the crude material. Incubation tubes were prepared in triplicate and contained 0.1 ml of tissue suspension, 2 nM of [^{3}H]-(+)-1-propyl-3-(3-hydroxyphenyl)piperidine {[^{3}H]-3-(+)-PPP}, and varying concentrations of the displacing ligand (0.1-1000 nM) in a final volume of 0.5 ml. After a 1 hr incubation at room temperature, the contents of the test tubes were filtered through GS filter paper which had been presoaked for at least 2 hours in 0.05% polyethyleneamine. The test tubes were rinsed three times with Tris/HCl buffer. Radioactivity on the filters was determined and IC_{50} values were calculated from inhibition curves using the method of Cheng and Prusoff [Biochem. Pharmacol., 22, 3099-3108, 1973]. Results are shown in Table II.

Table II

Test Compound	Ki apparent (nM) (units ± SEM)
DTG	47 ± 5
Compound No. 1	230 ± 70
Compound No. 7	30 ± 10
Compound No. 8	20 ± 1

Radioreceptor Assay in Guinea Pig Brain Homogenate

Receptor binding assays were performed using the crude synaptosomal (P_2) membrane fraction of guinea pig brain for sigma receptors. Crude P_2 membrane fractions were prepared from frozen (-80°C) guinea pig brains (Pel-Freeze, Rogers, AK), minus cerebellum. After removal of cerebella, brains were allowed to thaw slowly on ice and placed on ice-cold 10 mM Tris-HCl, pH 7.4 containing 320 mM sucrose (Tris-sucrose buffer). Brains were then homogenized in a Potter-Elvehjem homogenizer by 10 strokes of a motor driven Teflon pestle in a volume of 10 mL/gm tissue wet weight. The homogenate was centrifuged at 1,000 x g for 10 min. at 4°C and the supernatants saved. The pellets were re-suspended by vortexing in 2 ml/g ice-cold TRIS-sucrose and centrifuged again at 1000 x g for 10 minutes. The combined 1000 x g supernatants were centrifuged at 31,000 x g for 15 minutes at 4°C. The pellets were resuspended by vortexing in 3 mL/gm of 10 mM Tris-HCl, pH 7.4 and the suspension allowed to incubate at 25°C for 15 min. Following centrifugation at 31,000 x g for 15 min., the pellets were resuspended by gentle Potter-Elvehjem homogenization to a final volume of 1.53 mL/gm in 10 mM Tris-HCl pH 7.4. Aliquots were stored at -80°C until use. Protein concentration was determined by the method of Lowry et al using bovine serum albumen as standard. The sigma receptors were labelled with [^{3}H]-(+)-3-PPP (98.9 Ci/mmol). Incubations were carried out in 50 mM TRIS-HCl, pH 8.0, for 120 min. at 25°C in a volume of 0.5 mL with 500 µg of membrane

protein and 3 nM [^{3}H]-(+)-3-PPP. Nonspecific binding was determined in the presence of 1 μM haloperidol. Assays were terminated by the addition of 5 mL of ice-cold 10 mM TRIS-HCl, pH 8.0, and filtration through glass fiber filters (Schleicher and Schuell), which were soaked in 0.5% poly(ethylenimine) for at least 30 min. at 25°C prior to use. Filters were then washed twice with 5 mL of ice-cold TRIS-HCl buffer. In order to obtain an initial estimate of the binding affinity of the compounds, each compound was initially tested at 3 concentrations in the sigma assay (100, 1000, 10000 nM). If a compound elicited greater than 30% inhibition of binding of the test ligand ([^{3}H]-(+)-3-PPP) at 10000 nM, a twelve point curve using unlabeled test ligand concentrations ranging from 0.05-10000 nM (0.005-1000 nM for the most potent compounds) was conducted. The CDATA (EMF Software, Inc., Baltimore, MD) iterative curve fitting program was used to analyze the results. These results were obtained from two, or in some cases three, experiments (± SEM), each carried out in duplicate. Results are shown in Table III.

Table III

Test Compound No.	K_i (nM) (units + SEM)
1	1.8 ± 0.4
2	NT
3	0.49 ± 0.04
4	56 ± 9.9
5	3.5 ± 1.0
6	38 ± 13
7	1.3 ± 0.3
8	6.0 ± 3
9	113 ± 8
10	33 ± 5
11	90 ± 20
12	31 ± 0.05
13	2.4 ± 0.8
14	3.1 ± 0.55
15	412 ± 69
16	140 ± 17
17	1.2 ± 0.03

NT = Not Tested

Blockage of Apomorphine-induced Climbing

Compounds of the invention were evaluated for their ability to block apomorphine-induced climbing. The evaluation of the compounds followed the method outlined by Protais [Psychopharmacol., 50, 1-6, 1976]. Swiss-Webster mice, weighing 20-25 g, are pretreated with the compounds of the invention by i.p. or s.c. adiminstration at various times before 2 mg/kg apomorphine is administered s.c. in a volume of 1 ml/kg. All test compounds are administered in a volume of 10 ml/kg. Mice are rated at 10 and 20 minutes after

apomorphine administration using the following rating scale: (0) forepaws on the floor, (1) forefeet holding the bars, and (2) four paws holding bars. Dose-response curves are analyzed by a computerized Finney assay [Statistical Methods in Biological Assays, 2nd Edn., Hatner Pub. Co., New York (1964)]. Compound No. 8 completely blocked apomorphine-induced climbing at a dose of 10 mg/kg.

Forebrain Ischemia Assay

Male Mongolian gerbils, 50-70 gm, were used as subjects. Compound No. 8 (50 mg/kg) was injected i.p. 30 minutes prior to carotid occlusion into 6 gerbils. In preparation for surgical procedures, the animals were lightly anesthetized with halothane and placed upside down on a heated pad with their snout within a nosecone. Nitrous oxide (70%): oxygen (30%) plus 0.5% halothane was circulated through the nosecone to provide continuous anesthesia throughout the surgical procedure. A midline incision was made in the neck and the carotid arteries were exposed. A length of suture thread was placed under each carotid. The thread was then tightened around each carotid and pressure applied to the thread to insure flow as occluded. Flow was occluded for 15 minutes and then the thread was removed. The carotids were visually inspected to confirm that reflow had occurred. The wound was then closed with autoclips and the gerbils allowed to recover. Following surgery, the gerbils were kept alive for 7 days. They were anesthetized with 100 mg/kg sodium pentobarbital and perfused transcardially with saline (with heparin) followed by buffered formalin. The brain was removed, trimmed and prepared for histological processing. Sections (10 microns) were stained with thionin. At 7 days following the ischemic insult, damaged neurons have been cleared away by glia and the extent of damage can be ascertained within the vulnerable CA1 region of the hippocampus. The degree of lesion in the CA1 region of the hippocampus was quantified by counting the pyramidal cell bodies in a 0.5 mm length of CA1 on the section corresponding

to P 1.7 mm in the atlas of Loskota, Lomax and Verity [W. J. Loskota et al, A Stereotaxic Atlas of the Mongolian Gerbil Brain, Ann Arbor Science Publishers, Ann Arber, p. 77 (1974)]. The cell loss was significantly reduced in the gerbils given Compound No. 8 ($p<0.01$).

Circling Behavior Assay

In order to assess the utility of compounds of the invention in treatment of Parkinsonism, the ability of the compound to stimulate movement following microinjections in the substnatia nigra was assessed. Parkinson's disease results from the degeneration of dopamine-secreting neurons in the substantia nigra resulting in a reduced ability to generate movement. Compound #1 binds to sigma receptors, which are highly concentrated in the substantia nigra. The demonstration of increased motor activity, following compound administration in this part of the brain, would therefore suggest a stimulatory action on the substantia nigra. Such a stimulatory action would predict increased ability to generate voluntary movement in Parkinson's patients showing decreased functionality of this brain area. Current treatments of Parkinson's disease also stimulate this brain area, but show significant side effects that may n ot be present in compounds of the invention. The following experiments demonstrate the ability of compounds of the invention to stimulate motor activity following microinjections in the substantia nigra. It is expected, therefore, that compounds of the invention would have clinical utility in the treatment of Parkinson's disease and other disorders in which there is a paucity of movement.

Three to seven days before behavioral testing, each animal (245-350 g, N = 57) was anesthetized with 50 mg/kg sodium pentobarbital and mounted in a Narishige stereotaxic apparatus. A guide cannula, constructed from 24 guage thinwall stainless steel tubing, was implanted with its tip 4.0 mm above the left substantia nigra pars reticulata

(coordinates: 3.2 mm anterior; 2.2 mm lateral; 4.7 mm ventral), from lambda and the skull surface. Cannulae were secured with stainless steel screws and dental acrylic. Stainless steel stylets kept the cannulae sealed except during drug infusion. All drugs were prepared on the day of testing. Animals were gently restrained and the drugs were administered in a volume of 0.5 ul over 72 seconds through a 31 guage microneedle that was constructed to extend 4.0 mm beyond the tips of the guide cannulae. Dose studies of circling induced by Compound #1 followed the methods previously published for DTG. Animals received a single injection of saline (n=6), 1.5 nmol (n=5), 3.7 nmol (n=6), 9.3 nmol (n=7 or 14.9 nmol (n=5) in 0.5 ul 0.9% NaCl. Following injection, each animal was fitted with a harness which was connected to an optical position transducer interfaced to a compouter that derived the number and direction of half turns for 30 min. Each rat received a single injection of the test drug to minimize tissue damage. Rats were sacrificed by an overdose of sodium pentobarbital and perfused intracardially with 10% formalin. Brains were fixed in a 30% sucrose-formalin solution and coronal sections (40 um) were taken throughout the extent of the injection site. The sections were stained with cresyl violet and examined under a microscope to localize injection sites. Only subjects with histologically confirmed injection sites were used in the data analyses. For the studies of circling behavior, the number of net (contalateral-isolateral) rotations were computed for each rat and subjected to analysis of variance. Repeated measures analysis of variance revealed that Compound #1 produced significant dose-related increases in circling behavior compared to the saline control following microinjectons in the substantia nigra ($F_{4,27}=3.09$; $p=0.032$). Consistent with the increased affinity of Compound #1 for sigma receptors, this effect occurred at doses lower than those necessary to produce the effect with (+)-pentazocine published previously. Results showing contralateral circling behavior produced by intranigral microinjections of various doses of Compound #1 are reported in Table IV and illustrated in Fig. 1.

Table IV shows the effect of Compound #1 and control (saline) on locomotor activity (1/2 contralateral rotations net in 30 min.) following microinjections in the substantia nigra. Individual subjects are shown along with the average and standrd deviation of the effect. As illustrated, increasing doses of Compound #1 produce marked effects, which are statistically significant, as described above.

Table IV

Effect of Compound #1 on Locomotor Activity

Drug Treatment	Rat Number	Net Turns	Stats
Saline	57.00	1.00	Average = 3.50
	58.00	4.00	Stan Dev = 4.35
	59.00	12.00	
	62.00	0.00	
	63.00	5.00	
	64.00	1.00	
Compound #1	35.00	25.00	Average = 11.00
DOSE = 1.49 nmol	38.00	17.00	Stan Dev 18.94
	40.00	5.00	
	50.00	4.00	
	66.00	38.00	
Compound #1	10.00	13.00	Average = 18.33
DOSE = 3.72 nmol	11.00	23.00	Stan Dev = 7.87
	13.00	5.00	
	15.00	28.00	
	45.00	25.00	
	46.00	16.00	
Compound #1	1.00	28.00	Average = 38.14
DOSE = 9.3 nmol	2.00	20.00	Stan Dev 21.46
	3.00	46.00	
	4.00	87.00	
	7.00	30.00	
	51.00	22.00	
	52.00	34.00	
Compound #1	24.00	6.00	Average = 31.00
DOSE = 14.9 nmol	25.00	58.00	Stan Dev = 27.08
	26.00	13.00	
	27.00	61.00	
	29.00	7.00	
	30.00	75.00	
	32.00	24.00	
	34.00	4.00	

Also embraced within this invention is a class of pharmaceutical compositions comprising one or more compounds of Formula I in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The

compounds of the present invention may be administered by any suitable route, preferably in the form a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. Therapeutically effective doses of the compounds of the present invention required to prevent or arrest the progress of the medical condition are readily ascertained by one of ordinary skill in the art. The compounds and composition may, for example, be administered intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically.

For oral administration, the pharmaceutical compositions may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. These may with advantage contain an amount of active ingredient from about 1 to 250 mg, preferably from about 25 to 150 mg. A suitable daily dose for a mammal may very widely depending on the condition of the patient and other factors. However, a dose of from about 0.1 to 3000 mg/kg body weight, particularly from about 1 to 100 mg/kg body weight, may be appropriate.

The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier. A suitable daily dose is from about 0.1 to 100 mg/kg body weight injected per day in multiple doses depending on the disease being treated. A preferred daily dose would be from about 1 to 30 mg/kg body weight. Compounds indicated for prophylactic therapy will preferably be administered in a daily dose generally in a range from about 0.1 mg to about 100 mg per kilogram of body weight per day. A more preferred dosage will be a range from about 1 mg to about 100 mg per kilogram of body weight. Most preferred is a dosage in a range from about 1 to about 50 mg per kilogram of body weight per day. A suitable dose can be administered, in multiple sub-doses per

day. These sub-doses may be administered in unit dosage forms. Typically, a dose or sub-dose may contain from about 1 mg to about 100 mg of active compound per unit dosage form. A more preferred dosage will contain from about 2 mg to about 50 mg of active compound per unit dosage form. Most preferred is a dosage form containing from about 3 mg to about 25 mg of active compound per unit dose.

The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex and medical condition of the patient, the severity of the disease, the route of administration, and the particular compound employed, and thus may vary widely.

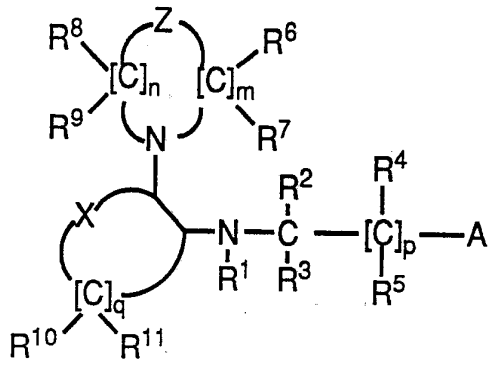
For therapeutic purposes, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes

of administration are well and widely known in the pharmaceutical art.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations. Various equivalents, changes and modifications may be made without departing from the spirit and scope of this invention, and it is understood that such equivalent embodiments are part of this invention.

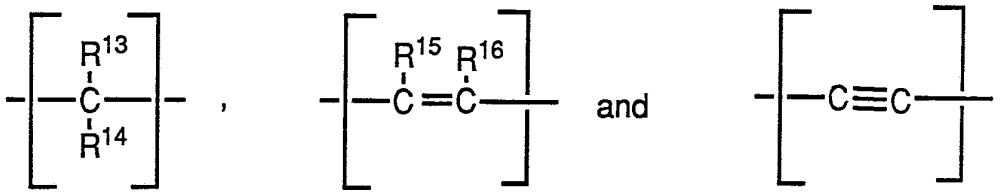
WHAT IS CLAIMED IS:

1. A compound of the formula



wherein R^1 is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkenylalkyl, alkynylalkyl, carboxyalkyl, alkanoyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein each of R^2 and R^3 is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkenyl, alkynyl, alkenylalkyl, alkynylalkyl, carboxyalkyl, alkanoyl, alkoxycarbonyl, carboxy, cyanoalkyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein R^2 and R^3 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of R^4 through R^{11} is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl and alkynyl; wherein R^4 and R^5 may be taken together to form oxo or to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein R^6 and R^7 may be taken together to form oxo; wherein R^8 and R^9 may be taken together to form oxo; wherein R^{10} and R^{11} may be taken together to form oxo; wherein each of n and m is a number selected from one through four; wherein each of p and q is a number selected

from zero through five; wherein each of X and Z is independently selected from O, S, $\rangle$N-R^{12}, $\rangle$SO, $\rangle SO_2$,

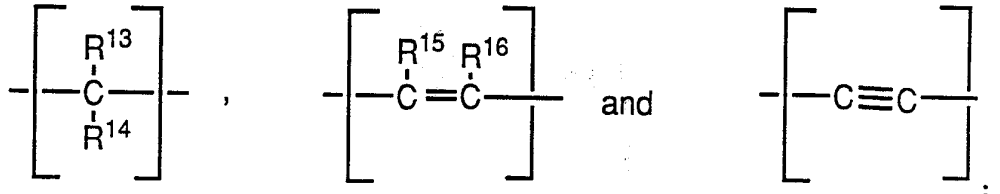


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wherein R^{12} may be selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, alkoxyalkyl, hydroxyalkyl, alkanoyl, aralkanoyl, aroyl, aminoalkyl, monoalkylaminoalkyl and dialkylaminoalkyl; wherein each of R^{13} through R^{16} is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; wherein A is selected from aryl, heteroaryl, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, arylamino, heteroarylamino, aralkylamino, heteroaralkylamino, arylthio, heteroarylthio, aralkylthio and heteroaralkylthio; wherein any of the foregoing A groups can be further substituted with one or more substituents independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, halo, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl and alkynyl; with the proviso that each of the compounds embraced by Formula I is a cis isomer with respect to the two nitrogen atoms of Formula I; or a pharmaceutically acceptable salt thereof.

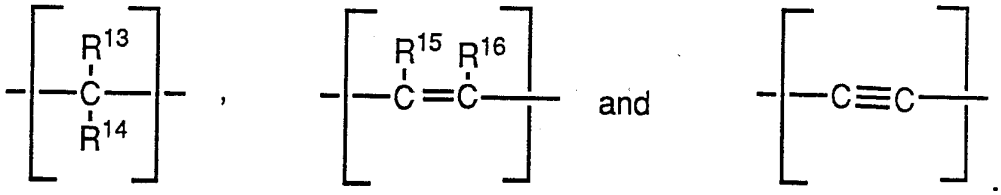
2. Compound of Claim 1 wherein R^1 is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkenylalkyl, alkynylalkyl and carboxyalkyl; wherein each of R^2 and R^3 is independently selected from hydrido, alkyl, cycloalkyl,

hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkenyl, alkynyl, alkenylalkyl, alkynylalkyl, carboxyalkyl, alkanoyl, alkoxycarbonyl, carboxy and cyanoalkyl; wherein R^2 and R^3 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of R^4 through R^{11} is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl and alkynyl; wherein R^4 and R^5 may be taken together to form oxo or to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of n and m is a number selected from one through four; wherein each of p and q is a number selected from zero through five; wherein X is selected from



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wherein Z is selected from O, , $N\text{-}R^{12}$,

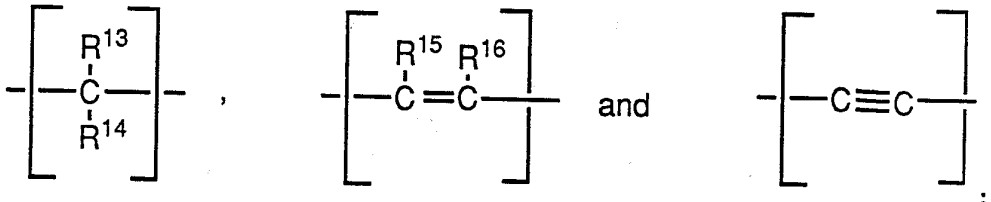


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wherein R^{12} may be selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, alkoxyalkyl, hydroxyalkyl, alkanoyl, aralkanoyl, aroyl, aminoalkyl, monoalkylaminoalkyl and dialkylaminoalkyl; wherein each of R^{13} through R^{16} is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; wherein A is selected from aryl, heteroaryl, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, arylamino, heteroarylamino, aralkylamino, heteroaralkylamino, arylthio, heteroarylthio, aralkylthio and heteroaralkylthio; wherein any of the foregoing A groups can be further substituted with one or more substituents independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, halo, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl and alkynyl; or a pharmaceutically acceptable salt thereof.

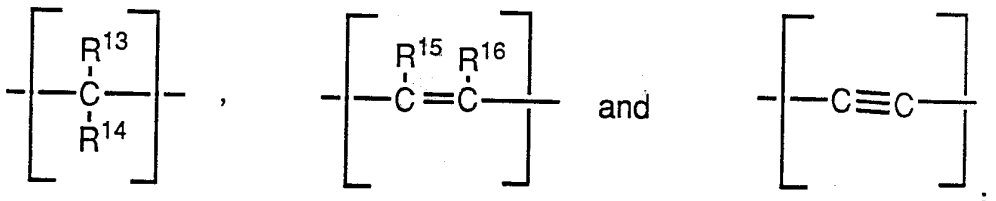
3. Compound of Claim 2 wherein R^1 is selected from hydrido, loweralkyl, cycloalkyl of three to about eight carbon atoms, hydroxyloweralkyl, haloloweralkyl, cycloalkylalkyl of four to about eight carbon atoms, loweralkoxyloweralkyl, phenylloweralkyl, phenyl, loweralkenylloweralkyl, loweralkynylloweralkyl and carboxyloweralkyl; wherein each of R^2 and R^3 is independently selected from hydrido, loweralkyl, cycloalkyl of three to about eight carbon atoms, hydroxyloweralkyl, haloloweralkyl, cycloalkylalkyl of four to about eight carbon atoms, loweralkoxyloweralkyl, phenylloweralkyl, phenyl, loweralkenyl, loweralkynyl, loweralkenylloweralkyl, loweralkynylloweralkyl, carboxyloweralkyl, loweralkanoyl, loweralkoxycarbonyl, carboxy and cyanoloweralkyl; wherein R^2 and R^3 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of R^4 through R^{11} is

independently selected from hydrido, hydroxy, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, phenylloweralkyl, phenyl, loweralkoxy, phenoxy, phenylloweralkoxy, loweralkoxyloweralkyl, haloloweralkyl, hydroxyloweralkyl, cyano, amino, monoloweralkylamino, diloweralkylamino, carboxy, carboxyloweralkyl, loweralkanoyl, loweralkenyl and loweralkynyl; wherein R^4 and R^5 may be taken together to form oxo or to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of n and m is a number selected from one through four; wherein each of p and q is a number selected from zero through five; wherein X is selected from



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wherein Z is selected from O, ,



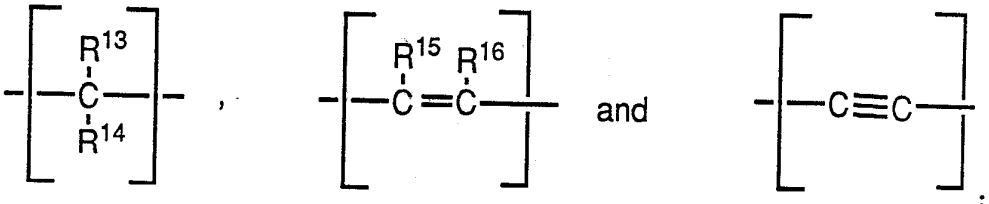
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wherein R^{12} may be selected from hydrido, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, phenyl, phenylloweralkyl, heteroaryl, loweralkoxyloweralkyl, hydroxyloweralkyl, loweralkanoyl, phenylalkanoyl, benzoyl, aminoloweralkyl, monoloweralkylaminoloweralkyl and diloweralkylaminoloweralkyl; wherein each of R^{13} through R^{16} is independently selected from hydrido, hydroxy, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms,

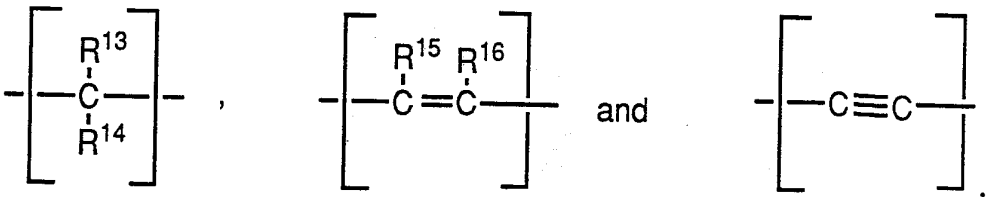
phenyloweralkyl, phenyl, loweralkoxy, phenylloweralkoxy, phenoxy, loweralkoxyloweralkyl, haloloweralkyl, hydroxyloweralkyl, halo, cyano, amino, monoloweralkylamino, diloweralkylamino, carboxy, carboxyloweralkyl and loweralkanoyl; wherein A is selected from phenyl, naphthyl, heteroaryl, phenoxy, naphthyloxy, heteroaryloxy, phenyl-loweralkoxy, naphthylloweralkoxy, heteroarylloweralkoxy, phenylamino, naphthylamino, heteroarylamino, phenylloweralkylamino, naphthylloweralkylamino, heteroaralkyl-amino, phenylthio, naphthylthio, heteroarylthio, phenylloweralkylthio and heteroarylloweralkylthio; wherein any of the foregoing A groups can be further substituted with one or more substituents independently selected from hydrido, hydroxy, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, phenylloweralkyl, phenyl, loweralkoxy, phenoxy, phenyloweralkoxy, loweralkoxyloweralkyl, halo, haloloweralkyl, hydroxyloweralkyl, cyano, amino, monoloweralkylamino, diloweralkylamino, carboxy, carboxyloweralkyl, loweralkanoyl, loweralkenyl and loweralkynyl; or a pharmaceutically acceptable salt thereof.

4. Compound of Claim 3 wherein R^1 is selected from hydrido, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, benzyl, phenyl, loweralkenylloweralkyl and loweralkynylloweralkyl; wherein each of R^2 and R^3 is independently selected from hydrido, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, benzyl, phenyl, loweralkenyl, loweralkynyl, loweralkenylloweralkyl, loweralkynylloweralkyl, loweralkanoyl and loweralkoxycarbonyl; wherein R^2 and R^3 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of R^4 through R^{11} is independently selected from hydrido, hydroxy, loweralkyl, cycloalkyl of three to

about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, benzyl, phenyl, loweralkoxy, phenoxy, benzyloxy, loweralkoxyloweralkyl, haloloweralkyl, hydroxyloweralkyl, loweralkanoyl, loweralkenyl and loweralkynyl; wherein R^4 and R^5 may be taken together to form oxo or to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of n and m is a number selected from one through four; wherein each of p and q is a number selected from zero through five; wherein X is selected from



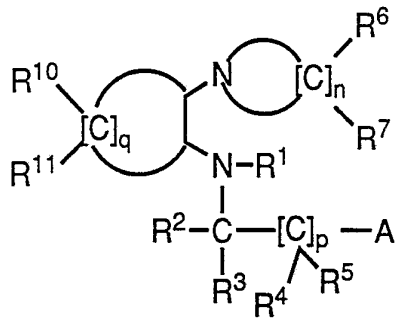
wherein Z is selected from O, ,



wherein R^{12} may be selected from hydrido, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, phenyl, benzyl, loweralkoxyloweralkyl and hydroxyloweralkyl; wherein each of R^{13} through R^{16} is independently selected from hydrido, hydroxy, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, benzyl, phenyl, loweralkoxy, benzyloxy, phenoxy, loweralkoxyloweralkyl, haloloweralkyl, hydroxyloweralkyl and halo; wherein A is selected from phenyl, naphthyl, thienyl, phenoxy, benzyloxy, naphthyloxy, thiophenoxy, phenylamino, benzylamino, naphthylamino, phenylthio, benzylthio and naphthylthio; wherein any of the foregoing A groups can be further substituted with one or more substituents independently selected from hydrido,

hydroxy, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, loweralkoxy, loweralkoxyloweralkyl, halo, haloloweralkyl, hydroxyloweralkyl, amino, monoloweralkylamino, diloweralkylamino, loweralkanoyl, loweralkenyl and loweralkynyl; or a pharmaceutically acceptable salt thereof.

5. Compound of Claim 4 of the formula



wherein R^1 is selected from hydrido, loweralkyl, cycloalkylalkyl of four to six carbon atoms and loweralkenylloweralkyl; wherein each of R^2 and R^3 is independently selected from hydrido and loweralkyl; wherein each of R^4 through R^7, R^{10} and R^{11} is independently selected from hydrido, hydroxy, loweralkyl, benzyl, phenoxy, benzyloxy and haloloweralkyl; wherein n is a number selected from four through six; wherein p is a number selected from zero through four; wherein q is a number selected from three through five; wherein A is selected from phenyl, naphthyl and thienyl; wherein any of the foregoing A groups can be further substituted with one or more substituents independently selected from hydrido, hydroxy, loweralkyl, loweralkoxy, halo, haloloweralkyl, amino, monoloweralkylamino and diloweralkylamino; or a pharmaceutically acceptable salt thereof.

6. Compound of Claim 5 wherein R^1 is selected from hydrido, methyl, ethyl, propyl, cyclopropylmethyl, allyl and dimethylallyl; wherein each of R^2 and R^3 is

independently selected from hydrido, methyl, ethyl and propyl; wherein each of R^4 through R^7, R^{10} and R^{11} is independently selected from hydrido, hydroxy, methyl, ethyl, propyl, benzyl, phenoxy, benzyloxy and halo(lower)alkyl; wherein n is a number selected from four or five; wherein p is a number selected from zero through two; wherein q is a number selected from three or four; wherein A is phenyl or naphthyl; wherein any of the foregoing A groups can be further substituted with one or more substituents independently selected from hydroxy, methyl, ethyl, propyl, methoxy, ethoxy, methylenedioxy, halo, trifluoromethyl, amino, methylamino and dimethylamino; or a pharmaceutically acceptable salt thereof.

7. Compound of Claim 6 selected from

(±)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)-cyclohexylamine;

1S,2R-(+)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexylamine;

1R,2S-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexylamine;

(±)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(1-pyrrolidinyl)cyclohexylamine;

1S,2R-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(1-pyrrolidinyl)cyclohexylamine;

1R,2S-(+)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(1-pyrrolidinyl)cyclohexylamine;

(±)-cis-N-methyl-N-(2-phenylethyl)-2-(1-pyrrolidinyl)-cyclohexylamine;

(±)-cis-N-methyl-N-[2-(ß-naphthyl)ethyl]-2-(1-pyrrolidinyl)-cyclohexylamine;

1S,2R-(-)-cis-N-methyl-N-[2-(3,4-methylenedioxy-phenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexylamine;

1R,2S-(+)-cis-N-methyl-N-[2-(3,4-methylenedioxy-phenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexylamine;

1R,2S-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-ethyl-2-(1-pyrrolidinyl)cyclohexylamine;

1R,2S-(-)-cis-N-cyclopropylmethyl-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexylamine;

1R,2S-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-(1-propyl)-2-(1-pyrrolidinyl)cyclohexylamine;

1S,2R-(+)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexylamine;

1S,2R-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-ethyl-2-(1-pyrrolidinyl)cyclohexylamine;

1S,2R-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-cyclopropyl-methyl-2-(1-pyrrolidinyl)cyclohexylamine;

1S,2R-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-(1-propyl)-2-(1-pyrrolidinyl)cyclohexylamine; and

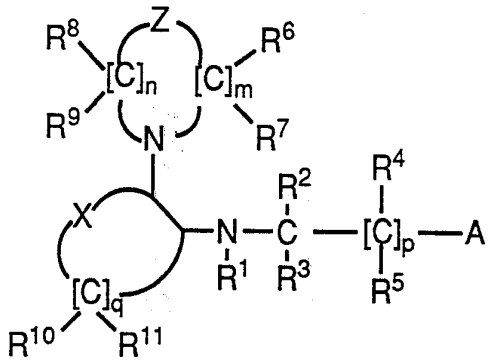
(±)-cis-N-[2-(3,4-dichlorophenyl)methyl]-N-methyl-2-(1-pyrrolidinyl)cyclohexylamine.

8. Compound of Claim 7 which is (±)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(1-pyrrolidinyl)cyclohexyl-amine•oxalate.

9. Compound of Claim 7 which is 1S,2R-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(1-pyrrolidinyl)-cyclohexylamine•2HBr.

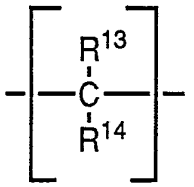
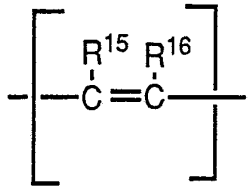
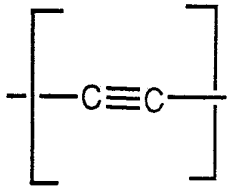
10. Compound of Claim 7 which is 1R,2S-(+)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(1-pyrrolidinyl)-cyclohexylamine•2HBr.

11. A pharmaceutical composition comprising a therapeutically-effective amount of an active compound for treating or preventing a CNS-related disorder and a pharmaceutically-acceptable carrier or diluent, said active compound selected from a family of compounds of the formula



wherein R^1 is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkenylalkyl, alkynylalkyl, carboxyalkyl, alkanoyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein each of R^2 and R^3 is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkenyl, alkynyl, alkenylalkyl, alkynylalkyl, carboxyalkyl, alkanoyl, alkoxycarbonyl, carboxy, cyanoalkyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein R^2 and R^3 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of R^4 through R^{11} is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl and alkynyl; wherein R^4 and R^5 may be

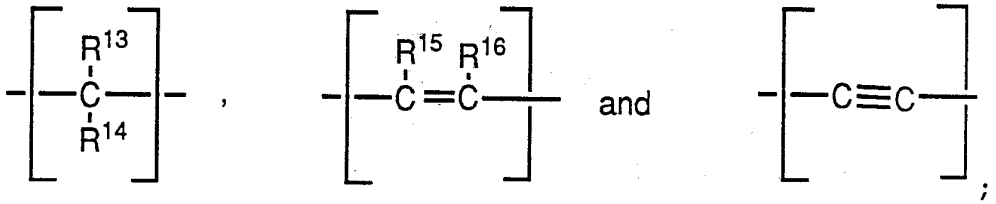
taken together to form oxo or to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein R^6 and R^7 may be taken together to form oxo; wherein R^8 and R^9 may be taken together to form oxo; wherein R^{10} and R^{11} may be taken together to form oxo; wherein each of n and m is a number selected from one through four; wherein each of p and q is a number selected from zero through five; wherein each of X and Z is independently selected from O, S, , , ,

,  and ;

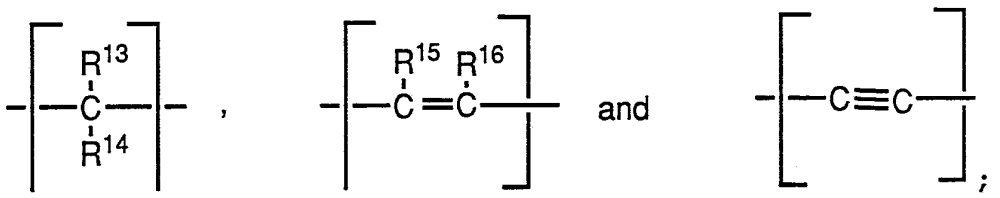
wherein R^{12} may be selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, alkoxyalkyl, hydroxyalkyl, alkanoyl, aralkanoyl, aroyl, aminoalkyl, monoalkylaminoalkyl and dialkylaminoalkyl; wherein each of R^{13} through R^{16} is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; wherein A is selected from aryl, heteroaryl, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, arylamino, heteroarylamino, aralkylamino, heteroaralkylamino, arylthio, heteroarylthio, aralkylthio and heteroaralkylthio; wherein any of the foregoing A groups can be further substituted with one or more substituents independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, halo, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl and alkynyl; with the proviso that each of the compounds embraced by

Formula I is a cis isomer with respect to the two nitrogen atoms of Formula I; or a pharmaceutically acceptable salt thereof.

12. The composition of Claim 11 wherein R^1 is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkenylalkyl, alkynylalkyl and carboxyalkyl; wherein each of R^2 and R^3 is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkenyl, alkynyl, alkenylalkyl, alkynylalkyl, carboxyalkyl, alkanoyl, alkoxycarbonyl, carboxy and cyanoalkyl; wherein R^2 and R^3 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of R^4 through R^{11} is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl and alkynyl; wherein R^4 and R^5 may be taken together to form oxo or to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of n and m is a number selected from one through four; wherein each of p and q is a number selected from zero through five; wherein X is selected from



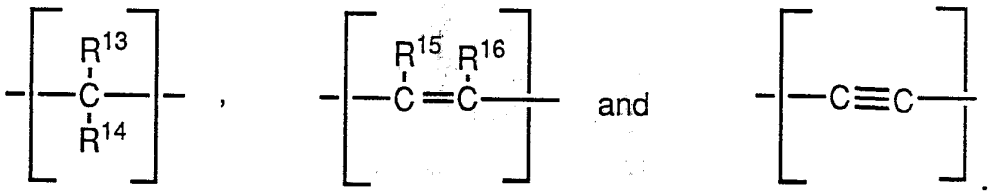
wherein Z is selected from O, .



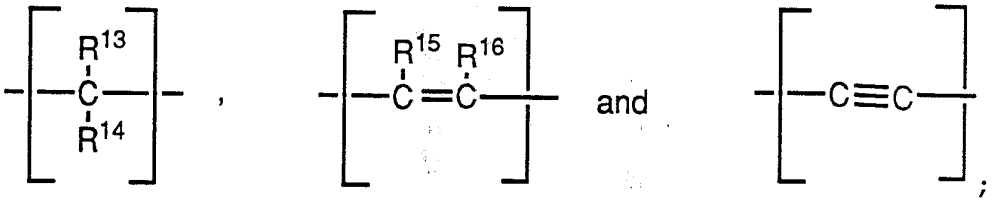
wherein R^{12} may be selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, alkoxyalkyl, hydroxyalkyl, alkanoyl, aralkanoyl, aroyl, aminoalkyl, monoalkylaminoalkyl and dialkylaminoalkyl; wherein each of R^{13} through R^{16} is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; wherein A is selected from aryl, heteroaryl, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, arylamino, heteroarylamino, aralkylamino, heteroaralkylamino, arylthio, heteroarylthio, aralkylthio and heteroaralkylthio; wherein any of the foregoing A groups can be further substituted with one or more substituents independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, halo, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl and alkynyl; or a pharmaceutically acceptable salt thereof.

13. The composition of Claim 12 wherein R^1 is selected from hydrido, loweralkyl, cycloalkyl of three to about eight carbon atoms, hydroxyloweralkyl, haloloweralkyl, cycloalkylalkyl of four to about eight carbon atoms, loweralkoxyloweralkyl, phenylloweralkyl, phenyl, loweralkenylloweralkyl, loweralkynylloweralkyl and carboxyloweralkyl; wherein each of R^2 and R^3 is independently selected from hydrido, loweralkyl, cycloalkyl of three to about eight carbon atoms, hydroxyloweralkyl, haloloweralkyl, cycloalkylalkyl of four to about eight carbon atoms, loweralkoxyloweralkyl, phenylloweralkyl, phenyl, loweralkenyl, loweralkynyl, loweralkenylloweralkyl,

loweralkynylloweralkyl, carboxyloweralkyl, loweralkanoyl, loweralkoxycarbonyl, carboxy and cyanoloweralkyl; wherein R^2 and R^3 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of R^4 through R^{11} is independently selected from hydrido, hydroxy, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, phenylloweralkyl, phenyl, loweralkoxy, phenoxy, phenylloweralkoxy, loweralkoxyloweralkyl, haloloweralkyl, hydroxyloweralkyl, cyano, amino, monoloweralkylamino, diloweralkylamino, carboxy, carboxyloweralkyl, loweralkanoyl, loweralkenyl and loweralkynyl; wherein R^4 and R^5 may be taken together to form oxo or to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of n and m is a number selected from one through four; wherein each of p and q is a number selected from zero through five; wherein X is selected from



wherein Z is selected from O, , ,

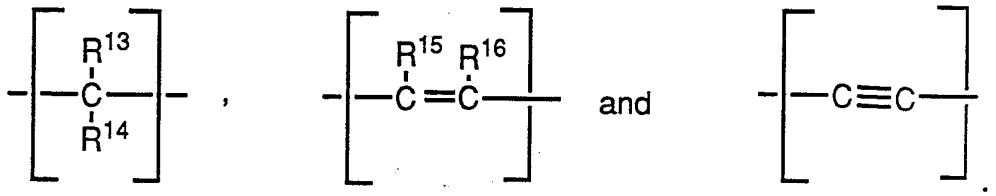


wherein R^{12} may be selected from hydrido, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, phenyl, phenylloweralkyl, heteroaryl, loweralkoxyloweralkyl, hydroxyloweralkyl, loweralkanoyl, phenylalkanoyl, benzoyl, aminoloweralkyl, monoloweralkylaminoloweralkyl and

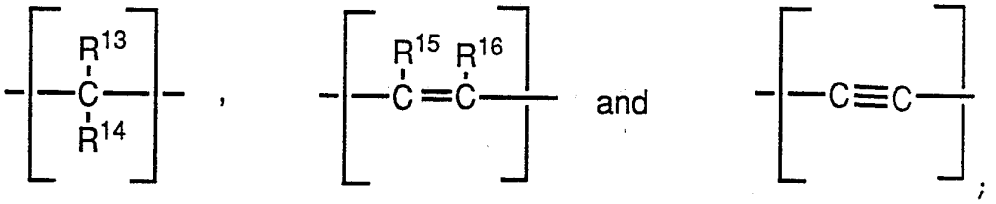
diloweralkylaminoloweralkyl; wherein each of R^{13} through R^{16} is independently selected from hydrido, hydroxy, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, phenyloweralkyl, phenyl, loweralkoxy, phenylloweralkoxy, phenoxy, loweralkoxyloweralkyl, haloloweralkyl, hydroxyloweralkyl, halo, cyano, amino, monoloweralkylamino, diloweralkylamino, carboxy, carboxyloweralkyl and loweralkanoyl; wherein A is selected from phenyl, naphthyl, heteroaryl, phenoxy, naphthyloxy, heteroaryloxy, phenylloweralkoxy, naphthylloweralkoxy, heteroarylloweralkoxy, phenylamino, naphthylamino, heteroarylamino, phenylloweralkylamino, naphthylloweralkylamino, heteroaralkylamino, phenylthio, naphthylthio, heteroarylthio, phenylloweralkylthio and heteroarylloweralkylthio; wherein any of the foregoing A groups can be further substituted with one or more substituents independently selected from hydrido, hydroxy, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, phenylloweralkyl, phenyl, loweralkoxy, phenoxy, phenyloweralkoxy, loweralkoxyloweralkyl, halo, haloloweralkyl, hydroxyloweralkyl, cyano, amino, monoloweralkylamino, diloweralkylamino, carboxy, carboxyloweralkyl, loweralkanoyl, loweralkenyl and loweralkynyl; or a pharmaceutically acceptable salt thereof.

14. The composition of Claim 13 wherein R^1 is selected from hydrido, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, benzyl, phenyl, loweralkenylloweralkyl and loweralkynylloweralkyl; wherein each of R^2 and R^3 is independently selected from hydrido, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, benzyl, phenyl, loweralkenyl, loweralkynyl, loweralkenylloweralkyl, loweralkynylloweralkyl, loweralkanoyl and loweralkoxycarbonyl; wherein R^2 and R^3 may be taken

together to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of R^4 through R^{11} is independently selected from hydrido, hydroxy, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, benzyl, phenyl, loweralkoxy, phenoxy, benzyloxy, loweralkoxyloweralkyl, haloloweralkyl, hydroxyloweralkyl, loweralkanoyl, loweralkenyl and loweralkynyl; wherein R^4 and R^5 may be taken together to form oxo or to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of n and m is a number selected from one through four; wherein each of p and q is a number selected from zero through five; wherein X is selected from



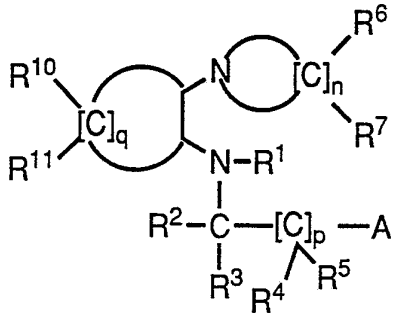
wherein Z is selected from O, .



wherein R^{12} may be selected from hydrido, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, phenyl, benzyl, loweralkoxyloweralkyl and hydroxyloweralkyl; wherein each of R^{13} through R^{16} is independently selected from hydrido, hydroxy, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, benzyl, phenyl, loweralkoxy, benzyloxy, phenoxy, loweralkoxyloweralkyl, haloloweralkyl,

hydroxyloweralkyl and halo; wherein A is selected from phenyl, naphthyl, thienyl, phenoxy, benzyloxy, naphthyloxy, thiophenoxy, phenylamino, benzylamino, naphthylamino, phenylthio, benzylthio and naphthylthio; wherein any of the foregoing A groups can be further substituted with one or more substituents independently selected from hydrido, hydroxy, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, loweralkoxy, loweralkoxyloweralkyl, halo, haloloweralkyl, hydroxyloweralkyl, amino, monoloweralkylamino, diloweralkylamino, loweralkanoyl, loweralkenyl and loweralkynyl; or a pharmaceutically acceptable salt thereof.

15. The composition of Claim 14 of the formula



wherein R^1 is selected from hydrido, loweralkyl, cycloalkylalkyl of four to six carbon atoms and loweralkenylloweralkyl; wherein each of R^2 and R^3 is independently selected from hydrido and loweralkyl; wherein each of R^4 through R^7, R^{10} and R^{11} is independently selected from hydrido, hydroxy, loweralkyl, benzyl, phenoxy, benzyloxy and haloloweralkyl; wherein n is a number selected from four through six; wherein p is a number selected from zero through four; wherein q is a number selected from three through five; wherein A is selected from phenyl, naphthyl and thienyl; wherein any of the foregoing A groups can be further substituted with one or more substituents independently selected from hydrido, hydroxy, loweralkyl, loweralkoxy, halo, haloloweralkyl, amino, monoloweralkylamino and

diloweralkylamino; or a pharmaceutically acceptable salt thereof.

16. The composition of Claim 15 wherein R^1 is selected from hydrido, methyl, ethyl, propyl, cyclopropylmethyl, allyl and dimethylallyl; wherein each of R^2 and R^3 is independently selected from hydrido, methyl, ethyl and propyl; wherein each of R^4 through R^7, R^{10} and R^{11} is independently selected from hydrido, hydroxy, methyl, ethyl, propyl, benzyl, phenoxy, benzyloxy and haloloweralkyl; wherein n is a number selected from four or five; wherein p is a number selected from zero through two; wherein q is a number selected from three or four; wherein A is phenyl or naphthyl; wherein any of the foregoing A groups can be further substituted with one or more substituents independently selected from hydroxy, methyl, ethyl, propyl, methoxy, ethoxy, methylenedioxy, halo, trifluoromethyl, amino, methylamino and dimethylamino; or a pharmaceutically acceptable salt thereof.

17. The composition of Claim 16 wherein said active compound is selected from

(±)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)-cyclohexylamine;

1S,2R-(+)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexylamine;

1R,2S-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexylamine;

(±)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(1-pyrrolidinyl)cyclohexylamine;

1S,2R-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(1-pyrrolidinyl)cyclohexylamine;

1R,2S-(+)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(1-pyrrolidinyl)cyclohexylamine;

(±)-cis-N-methyl-N-(2-phenylethyl)-2-(1-pyrrolidinyl)-cyclohexylamine;

(±)-cis-N-methyl-N-[2-(ß-naphthyl)ethyl]-2-(1-pyrrolidinyl)-cyclohexylamine;

1S,2R-(-)-cis-N-methyl-N-[2-(3,4-methylenedioxy-phenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexylamine;

1R,2S-(+)-cis-N-methyl-N-[2-(3,4-methylenedioxy-phenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexylamine;

1R,2S-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-ethyl-2-(1-pyrrolidinyl)cyclohexylamine;

1R,2S-(-)-cis-N-cyclopropylmethyl-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexylamine;

1R,2S-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-(1-propyl)-2-(1-pyrrolidinyl)cyclohexylamine;

1S,2R-(+)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexylamine;

1S,2R-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-ethyl-2-(1-pyrrolidinyl)cyclohexylamine;

1S,2R-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-cyclopropyl-methyl-2-(1-pyrrolidinyl)cyclohexylamine;

1S,2R-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-(1-propyl)-2-(1-pyrrolidinyl)cyclohexylamine; and

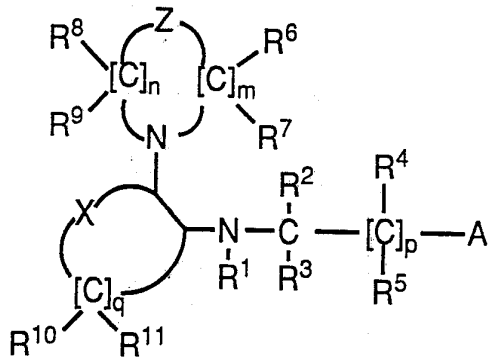
(±)-cis-N-[2-(3,4-dichlorophenyl)methyl]-N-methyl-2-(1-pyrrolidinyl)cyclohexylamine.

18. The composition of Claim 17 wherein said active compound is (±)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(1-pyrrolidinyl)cyclohexyl-amine•oxalate.

19. The composition of Claim 17 wherein said active compound is 1S,2R-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(1-pyrrolidinyl)-cyclohexylamine•2HBr.

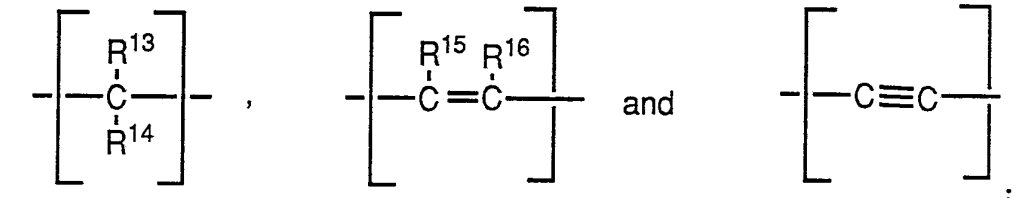
20. The composition of Claim 17 wherein said active compound is 1R,2S-(+)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(1-pyrrolidinyl)-cyclohexylamine•2HBr.

21. A method for treating a patient afflicted with or susceptible to a CNS-related disorder, which method comprises administering to the patient a therapeutically-effective amount of a compound of the formula



wherein R^1 is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkenylalkyl, alkynylalkyl, carboxyalkyl, alkanoyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein each of R^2 and R^3 is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkenyl, alkynyl, alkenylalkyl, alkynylalkyl, carboxyalkyl, alkanoyl, alkoxycarbonyl, carboxy, cyanoalkyl, alkylsulfinyl,

alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein R^2 and R^3 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of R^4 through R^{11} is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl and alkynyl; wherein R^4 and R^5 may be taken together to form oxo or to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein R^6 and R^7 may be taken together to form oxo; wherein R^8 and R^9 may be taken together to form oxo; wherein R^{10} and R^{11} may be taken together to form oxo; wherein each of n and m is a number selected from one through four; wherein each of p and q is a number selected from zero through five; wherein each of X and Z is independently selected from O, S, $\rangle N\text{-}R^{12}$, $\rangle SO$, $\rangle SO_2$,

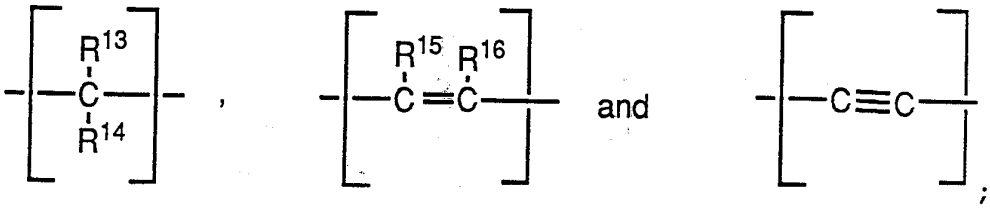


;

wherein R^{12} may be selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, alkoxyalkyl, hydroxyalkyl, alkanoyl, aralkanoyl, aroyl, aminoalkyl, monoalkylaminoalkyl and dialkylaminoalkyl; wherein each of R^{13} through R^{16} is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; wherein A is selected from aryl, heteroaryl, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, arylamino, heteroarylamino, aralkylamino, heteroaralkylamino, arylthio, heteroarylthio, aralkylthio and heteroaralkylthio; wherein any of the

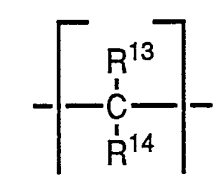
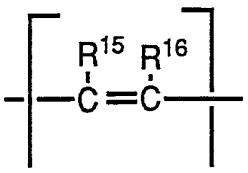
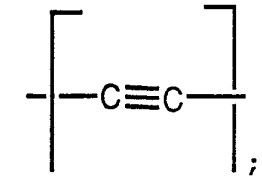
foregoing A groups can be further substituted with one or more substituents independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, halo, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl and alkynyl; with the proviso that each of the compounds embraced by Formula I is a cis isomer with respect to the two nitrogen atoms of Formula I; or a pharmaceutically acceptable salt thereof.

22. The method of Claim 21 wherein R^1 is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkenylalkyl, alkynylalkyl and carboxyalkyl; wherein each of R^2 and R^3 is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkenyl, alkynyl, alkenylalkyl, alkynylalkyl, carboxyalkyl, alkanoyl, alkoxycarbonyl, carboxy and cyanoalkyl; wherein R^2 and R^3 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of R^4 through R^{11} is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl and alkynyl; wherein R^4 and R^5 may be taken together to form oxo or to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of n and m is a number selected from one through four; wherein each of p and q is a number selected from zero through five; wherein X is selected from



;

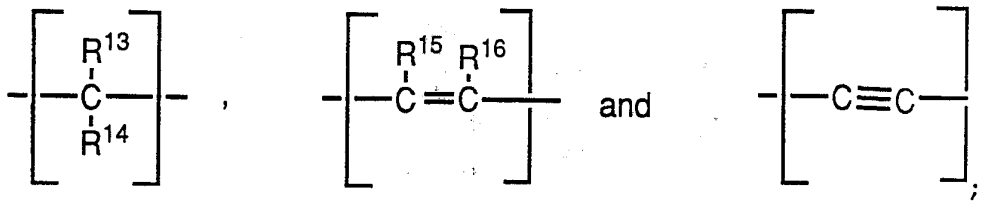
wherein Z is selected from O,  N-R^{12},

 ,  and ;

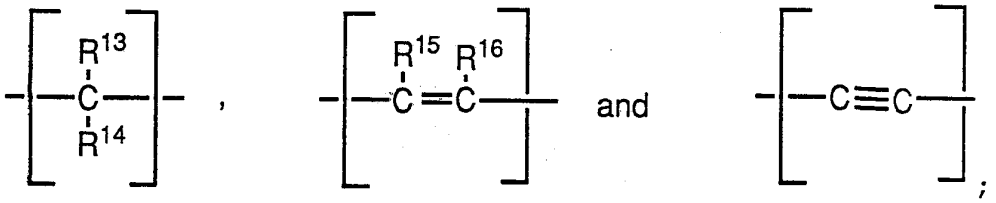
wherein R^{12} may be selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, alkoxyalkyl, hydroxyalkyl, alkanoyl, aralkanoyl, aroyl, aminoalkyl, monoalkylaminoalkyl and dialkylaminoalkyl; wherein each of R^{13} through R^{16} is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; wherein A is selected from aryl, heteroaryl, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, arylamino, heteroarylamino, aralkylamino, heteroaralkylamino, arylthio, heteroarylthio, aralkylthio and heteroaralkylthio; wherein any of the foregoing A groups can be further substituted with one or more substituents independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, halo, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl and alkynyl; or a pharmaceutically acceptable salt thereof.

23. The method of Claim 22 wherein R^1 is selected from hydrido, loweralkyl, cycloalkyl of three to about eight carbon atoms, hydroxyloweralkyl, haloloweralkyl, cycloalkylalkyl of four to about eight carbon atoms, loweralkoxyloweralkyl, phenylloweralkyl, phenyl, loweralkenylloweralkyl, loweralkynylloweralkyl and carboxyloweralkyl; wherein each of R^2 and R^3 is independently selected from hydrido, loweralkyl, cycloalkyl of three to about eight carbon atoms, hydroxyloweralkyl,

haloloweralkyl, cycloalkylalkyl of four to about eight carbon atoms, loweralkoxyloweralkyl, phenylloweralkyl, phenyl, loweralkenyl, loweralkynyl, loweralkenylloweralkyl, loweralkynyllower-alkyl, carboxyloweralkyl, loweralkanoyl, loweralkoxycarbonyl, carboxy and cyanoloweralkyl; wherein R^2 and R^3 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of R^4 through R^{11} is independently selected from hydrido, hydroxy, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, phenylloweralkyl, phenyl, loweralkoxy, phenoxy, phenylloweralkoxy, loweralkoxyloweralkyl, haloloweralkyl, hydroxyloweralkyl, cyano, amino, monoloweralkylamino, diloweralkylamino, carboxy, carboxyloweralkyl, loweralkanoyl, loweralkenyl and loweralkynyl; wherein R^4 and R^5 may be taken together to form oxo or to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of n and m is a number selected from one through four; wherein each of p and q is a number selected from zero through five; wherein X is selected from



wherein Z is selected from O, ,

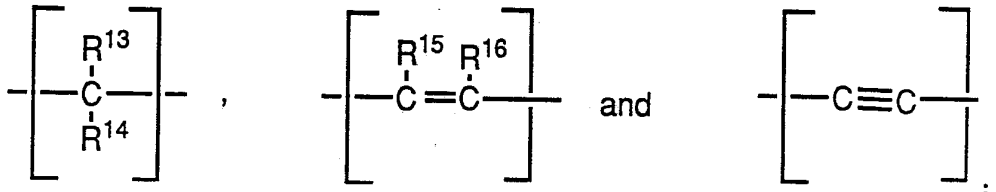


wherein R^{12} may be selected from hydrido, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, phenyl, phenylloweralkyl, heteroaryl, loweralkoxyloweralkyl,

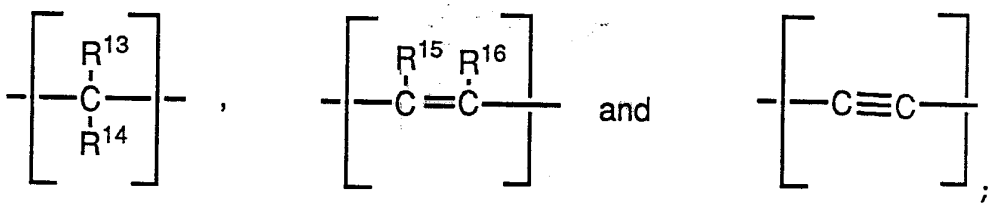
hydroxyloweralkyl, loweralkanoyl, phenylalkanoyl, benzoyl, aminoloweralkyl, monoloweralkylaminoloweralkyl and diloweralkylaminoloweralkyl; wherein each of R^{13} through R^{16} is independently selected from hydrido, hydroxy, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, phenyloweralkyl, phenyl, loweralkoxy, phenylloweralkoxy, phenoxy, loweralkoxyloweralkyl, haloloweralkyl, hydroxyloweralkyl, halo, cyano, amino, monoloweralkylamino, diloweralkylamino, carboxy, carboxyloweralkyl and loweralkanoyl; wherein A is selected from phenyl, naphthyl, heteroaryl, phenoxy, naphthyloxy, heteroaryloxy, phenylloweralkoxy, naphthylloweralkoxy, heteroarylloweralkoxy, phenylamino, naphthylamino, heteroarylamino, phenylloweralkylamino, naphthylloweralkylamino, heteroaralkylamino, phenylthio, naphthylthio, heteroarylthio, phenylloweralkylthio and heteroarylloweralkylthio; wherein any of the foregoing A groups can be further substituted with one or more substituents independently selected from hydrido, hydroxy, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, phenylloweralkyl, phenyl, loweralkoxy, phenoxy, phenyloweralkoxy, loweralkoxyloweralkyl, halo, haloloweralkyl, hydroxyloweralkyl, cyano, amino, monoloweralkylamino, diloweralkylamino, carboxy, carboxyloweralkyl, loweralkanoyl, loweralkenyl and loweralkynyl; or a pharmaceutically acceptable salt thereof.

24. The method of Claim 23 wherein R^1 is selected from hydrido, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, benzyl, phenyl, loweralkenylloweralkyl and loweralkynylloweralkyl; wherein each of R^2 and R^3 is independently selected from hydrido, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, benzyl, phenyl, loweralkenyl, loweralkynyl, loweralkenylloweralkyl, loweralkynylloweralkyl,

loweralkanoyl and loweralkoxycarbonyl; wherein R^2 and R^3 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of R^4 through R^{11} is independently selected from hydrido, hydroxy, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, benzyl, phenyl, loweralkoxy, phenoxy, benzyloxy, loweralkoxyloweralkyl, haloloweralkyl, hydroxyloweralkyl, loweralkanoyl, loweralkenyl and loweralkynyl; wherein R^4 and R^5 may be taken together to form oxo or to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of n and m is a number selected from one through four; wherein each of p and q is a number selected from zero through five; wherein X is selected from



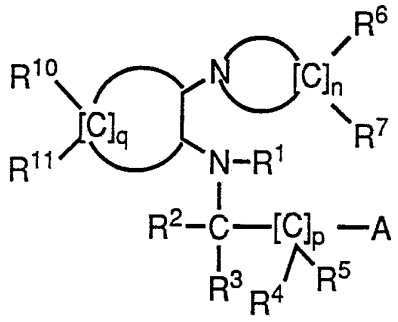
wherein Z is selected from O, ,



wherein R^{12} may be selected from hydrido, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, phenyl, benzyl, loweralkoxyloweralkyl and hydroxyloweralkyl and wherein;

each of R^{13} through R^{16} is independently selected from hydrido, hydroxy, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, benzyl, phenyl, loweralkoxy, benzyloxy, phenoxy, loweralkoxyloweralkyl, haloloweralkyl, hydroxyloweralkyl and halo; wherein A is selected from phenyl, naphthyl, thienyl, phenoxy, benzyloxy, naphthyloxy, thiophenoxy, phenylamino, benzylamino, naphthylamino, phenylthio, benzylthio and naphthylthio; wherein any of the foregoing A groups can be further substituted with one or more substituents independently selected from hydrido, hydroxy, loweralkyl, cycloalkyl of three to about eight carbon atoms, cycloalkylalkyl of four to about eight carbon atoms, loweralkoxy, loweralkoxyloweralkyl, halo, haloloweralkyl, hydroxyloweralkyl, amino, monoloweralkylamino, diloweralkylamino, loweralkanoyl, loweralkenyl and loweralkynyl; or a pharmaceutically acceptable salt thereof.

25. The method of Claim 24 of the formula



wherein R^1 is selected from hydrido, loweralkyl, cycloalkylalkyl of four to six carbon atoms and loweralkenylloweralkyl; wherein each of R^2 and R^3 is independently selected from hydrido and loweralkyl; wherein each of R^4 through R^7, R^{10} and R^{11} is independently selected from hydrido, hydroxy, loweralkyl, benzyl, phenoxy, benzyloxy and haloloweralkyl; wherein n is a number selected from four

through six; wherein p is a number selected from zero through four; wherein q is a number selected from three through five; wherein A is selected from phenyl, naphthyl and thienyl; wherein any of the foregoing A groups can be further substituted with one or more substituents independently selected from hydrido, hydroxy, loweralkyl, loweralkoxy, halo, haloloweralkyl, amino, monoloweralkylamino and diloweralkylamino; or a pharmaceutically acceptable salt thereof.

26. The method of Claim 25 wherein R^1 is selected from hydrido, methyl, ethyl, propyl, cyclopropylmethyl, allyl and dimethylallyl; wherein each of R^2 and R^3 is independently selected from hydrido, methyl, ethyl and propyl; wherein each of R^4 through R^7, R^{10} and R^{11} is independently selected from hydrido, hydroxy, methyl, ethyl, propyl, benzyl, phenoxy, benzyloxy and haloloweralkyl; wherein n is a number selected from four or five; wherein p is a number selected from zero through two; wherein q is a number selected from three or four; wherein A is phenyl or naphthyl; wherein any of the foregoing A groups can be further substituted with one or more substituents independently selected from hydroxy, methyl, ethyl, propyl, methoxy, ethoxy, methylenedioxy, halo, trifluoromethyl, amino, methylamino and dimethylamino; or a pharmaceutically acceptable salt thereof.

27. The method of Claim 26 wherein said compound is selected from

(±)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)-cyclohexylamine;

1S,2R-(+)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexylamine;

1R,2S-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexylamine;

(±)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(1-pyrrolidinyl)cyclohexylamine;

1S,2R-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(1-pyrrolidinyl)cyclohexylamine;

1R,2S-(+)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(1-pyrrolidinyl)cyclohexylamine;

(±)-cis-N-methyl-N-(2-phenylethyl)-2-(1-pyrrolidinyl)-cyclohexylamine;

(±)-cis-N-methyl-N-[2-(ß-naphthyl)ethyl]-2-(1-pyrrolidinyl)-cyclohexylamine;

1S,2R-(-)-cis-N-methyl-N-[2-(3,4-methylenedioxyphenyl)-ethyl]-2-(1-pyrrolidinyl)cyclohexylamine;

1R,2S-(+)-cis-N-methyl-N-[2-(3,4-methylenedioxyphenyl)-ethyl]-2-(1-pyrrolidinyl)cyclohexylamine;

1R,2S-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-ethyl-2-(1-pyrrolidinyl)cyclohexylamine;

1R,2S-(-)-cis-N-cyclopropylmethyl-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexylamine;

1R,2S-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-(1-propyl)-2-(1-pyrrolidinyl)cyclohexylamine;

1S,2R-(+)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexylamine;

1S,2R-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-ethyl-2-(1-pyrrolidinyl)cyclohexylamine;

1S,2R-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-cyclopropyl-methyl-2-(1-pyrrolidinyl)cyclohexylamine;

1S,2R-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-(1-propyl)-2-(1-pyrrolidinyl)cyclohexylamine; and

(±)-cis-N-[2-(3,4-dichlorophenyl)methyl]-N-methyl-2-(1-pyrrolidinyl)cyclohexylamine.

28. The method of Claim 27 wherein said compound is (±)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(1-pyrrolidinyl)cyclohexyl-amine•oxalate.

29. The method of Claim 27 wherein said compound is 1S,2R-(-)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(1-pyrrolidinyl)-cyclohexylamine•2HBr.

30. The method of Claim 27 wherein said compound is 1R,2S-(+)-cis-N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(1-pyrrolidinyl)-cyclohexylamine•2HBr.

31. The method of Claim 21 wherein said CNS-related disorder is cerebral ischemia.

32. The method of Claim 21 wherein said CNS-related disorder is a psychotic disorder.

33. The method of Claim 21 wherein said CNS-related disorder is a convulsive disorder.

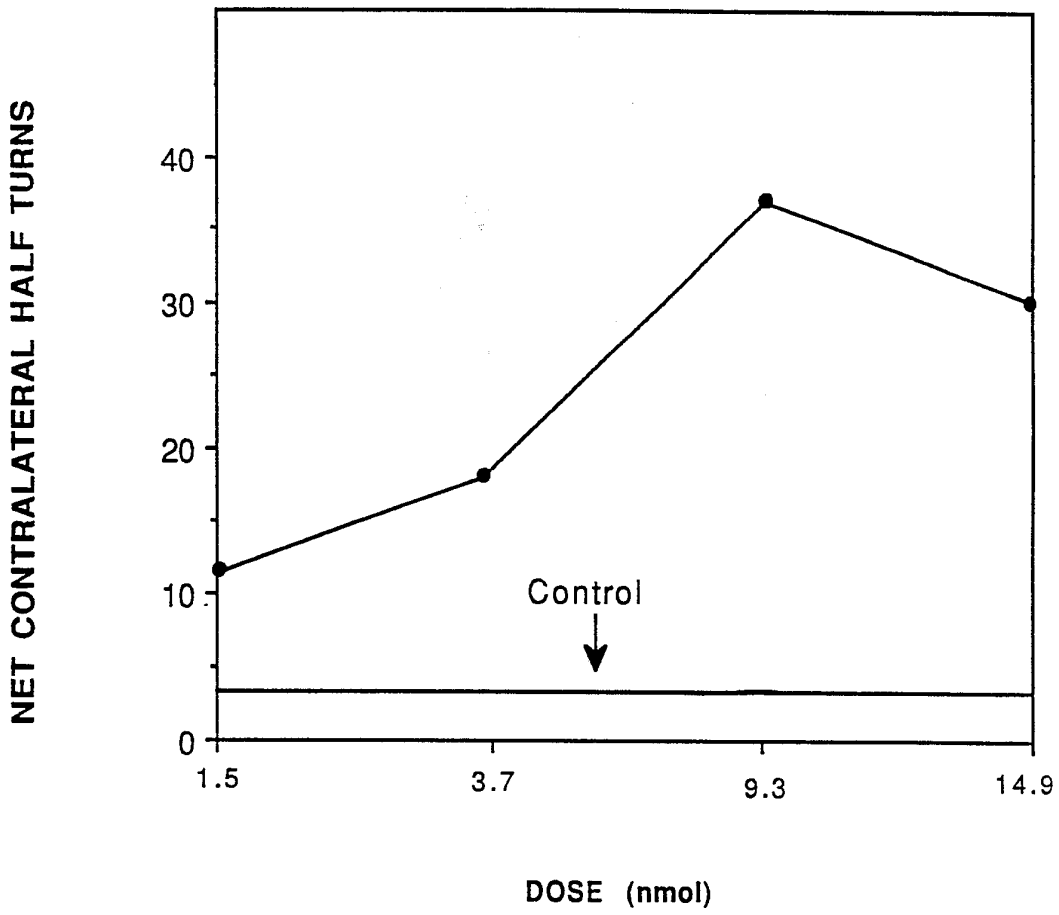

NET CONTRALATERAL HALF TURNS
40
30
20
10
0
Control
1.5
3.7
9.3
14.9
DOSE (nmol)

FIG. 1

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/00688

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): C07D 295/073 A61K 31/40
C07D 295/135

II FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols	
U.S.	548/543	514/424
	548/545	514/425
	548/578	514/429

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	US, A, 4,204,003 (SZMUSZKOVICZ) 20 MAY 1980 NOTE FORMULA "1", COLUMN 2	1-33
A	US, A, 4,463,013 (COLLINS, ET AL) 31 JULY 1984 NOTE FORMULA "1", COLUMN 2	1-33
A	US, A, 4,801,604 (VONVOIGTLANDER, ET AL) 31 JANUARY 1989, NOTE FORMULA "(1)", COLUMN 16	1-33
A	ROTHMAN ET AL, - NEUROLOGICAL PROGRESS - GLUTAMATE AND THE PATHOGHYSIOLOGY OF HYPOXIA - ISCHEMIC BRAIN DAMAGE; ANNALS OF NEUROLOGY, VOL.19, NO 2 FEBRUARY 1986. PAGES 105 TO 111. NOTE ENTIRE DOCUMENT	1-33

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
JULY 02, 1991	12 JUL 1991
International Searching Authority	**Signature of Authorized Officer**
ISA/US	for Andrew Robinson JOSEPH PAUL BRUST

Form PCT/ISA/210 (second sheet) (Rev.11-87)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	LASON, ET AL; - THE INTERACTION BETWEEN K-OPIOID AGONIST, U - 50, 488H, AND KAINIC ACID. BEHAVIORAL AND HISTOLOGICAL ASSESSMENT; BRAIN RESEARCH, 482(1989), ELSENIER, PAGES 333-339; SEE ENTIRE DOCUMENT	1-33
A	CARTER, ET AL.; IFENPRODIL AND SL 82.0715 AS CEREBRAL ANTI - ISCHEMIC AGENTS. 11. EVIDENCE FOR N-METHYL -D-ASPORTATE RECEPTOR ANTAGONIST PROPERTIES; J.PHARM. EXP. THER., 247, (3), 1988, PAGES 1222 TO 1232: SEE ENTIRE DOCUMENT	1-33
A	DE COSTA, ET AL., ALTERATIONS IN THE STEREOCHEMISTRY OF THE K-SELECTIVE, OPIOID AGONIST U 50,488 RESULT IN HIGH-AFFINITY o LIGANDS; J. MED. CHEM, 32, (1989), PAGES 1996-2002; SEE ENTIRE DOCUMENT	1-33
A	GILMAN, ET AL., THE PHARMACOLOGICAL BASIS OF THERAPEUTICS; 7TH ED., PAGE 404, MACMILLAN (1985). NOTE "HALOPERIDOL".	1-33
A	PARSONS, ET AL.; DO KAPPA OPIOIDS MIMIC SIGMA AGONISTS AS AMINO ACID ANTAGONISTS; NEUROPHORMACOLOGY 25, NO.2, (1986), PAGES 217-220.	1-33

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V ☐ **OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE** [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers because they relate to subject matter [2] not required to be searched by this Authority, namely:

2. ☐ Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [3], specifically:

3. ☐ Claim numbers_____, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ **OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING** [2]

This International Searching Authority found multiple inventions in this international application as follows:

(SEE NEXT SHEET FOR 24 WAY BREAKUP)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

- 1 TO 33 -

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

CONTINUATION

I. Compounds, compositions of said active compounds plus a carrier or diluent therefor and methods of use of said active compounds wherein the active compounds contain one heterocyclic group only and that one a pyrrolidine group, said matter being found in claims 1 to 33 and said matter being classified in class 548, subclasses, inter alia, 578,543 and 545 and class 514, subclasses, inter alia, 424,425 and 429.

II. Compounds, compositions of said active compounds plus a carrier or diluent therefor and methods of use of said active compounds wherein the active compounds contain a molecule inclusive of two heterocyclic, groups said two groups being a pyrrolidine group and a methlenedioxy group, said matter being encompassed in claims 1 to 7, 11 to 17, 21 to 27 and 31 to 33 and said matter being classified in class 548, subclass 526, and class 514, subclass 422.

III. Compounds, compositions of said active compounds plus a carrier or diluent therefor and methods of use of said active compounds wherein the active compounds contain one heterocyclic group only and that one a piperidine group, said matter being found in claims 1 to 6, 11 to 16, 21 to 26 and 31 to 33 and said matter being classified in class 546, subclass 216, 219, 220 and 229 plus and class 514, subclass 317.

IV. Compounds, composition of said active compounds plus a carrier or diluent therefor and methods of use of said active compounds wherein the active compounds (1 nitrogen and 6 carbon) said matter being classified in class 540, subclass 485, 526 and 531 and class 514, subclass 212.

V. Compounds, compositions of said active compounds plus a carrier or diluent therefor and methods of use of said active compounds contain a molecule inclusive of two heterocyclic groups said two groups being a pyrrolidine and thienyl group, said matter being encompassed in claims 1 to 5, 11 to 15, 21 to 25 and 31 to 33 and said matter being classified in class 548, subclass 527 and class 514, subclass 422.

VI. Compounds, compositions of said active compounds plus a carrier or diluent therefor and methods of use of said active compounds wherein the active compounds contain a molecule inclusive of two heterocyclic groups said two groups being a pyrrolidine group and furanyl group, said matter being encompassed in claims 1 to 3, 11 to 13, 21 to 23 and 31 to 33 and said matter being classified in class 548, subclass 517 and class 514, subclass 422.

VII. Compounds, composition of said active compounds plus a carrier or diluent therefor and methods of use of said active compounds wherein the active compounds contain a molecule inclusive of two heterocyclic groups said two groups being a pyrrolidine group and a pyridinyl group, said matter being encompassed in claims 1 to 3, 11 to 13, 21 to 23 and 31 to 33 and said matter being classified in class 514, subclass 343.

VIII. Compounds, compositions of said active compounds plus a carrier or diluent therefor and methods of use of said active compounds wherein the active compounds contain a molecule inclusive of two heterocyclic groups said two groups being a pyrrolidine group and a thiazolyl group, said matter being encompasses in claims 1 to 3, 11 to 13, 21 to 23 and 31 to 33 and said matter being classified in class 548, subclasses 200 and 205 and class 514, subclass 365.

IX. Compounds, compositions of said active compounds plus a carrier or diluent therefor and methods of use of said active compounds wherein the active compounds contain a molecule inclusive of two heterocyclic groups said two groups being a pyrrolidine group and a pyrimidyl group, said matter being encompassed in claims 1 to 3, 11 to 13, 21 to 23 and 31 to 33 and said matter being classified in class 544 subclasses 242 (plus) and class 514, subclass 256 (plus).

X. Compounds, compositions of said active compounds plus a carrier or diluent therefor and methods of use of said active compounds wherein the active compounds contain a molecule inclusive of two heterocyclic groups said two groups being a pyrrolidine group and an isoxazole group, said matter being encompassed in claims 1 to 3, 11 to 13, 21 to 23 and 31 to 33 and said matter being classified in class 548, subclasses 240 and 247 and class 514, subclass 378.

XI. Compounds, compositions of said active compounds plus a carrier or diluent therefor and methods of use of said active compounds wherein the active compounds contain a molecule inclusive of two heterocyclic group said two groups being a piperidine group and a methylenedioxy group, said matter being encompassed in claims 1 to 3, 11 to 13, 21 to 23 and 31 to 33 and said matter being classified in class 546, subclass 197 and class 514, subclass 321.

XII. Compounds, compositions of said active compounds plus a carrier or diluent therefor and methods of use of said active compounds wherein the active compounds contain a molecule inclusive of two heterocyclic groups said two groups being a seven member (1 nitrogen and 6 carbon) group and a methylenedioxy group, said matter being encompassed in claims 1 to 3, 11 to 13, 21 to 23 and 31 to 33 and said matter being classified in class 540, subclass 596, and class 514, subclass 212.

XIII. Compounds, compositions of said active compounds plus a carrier or diluent therefor and methods of use of said active compounds wherein the active compounds contain a molecule inclusive of two heterocyclic groups said two groups being a piperidine group and a thienyl group, said matter being encompassed in claims 1 to 5, 11 to 15, 21 to 25 and 31 to 33 and said matter being classified in class 546, subclass 212 and class 514, subclass 326.

XIV. Compounds, compositions of said active compounds plus a carrier or diluent therefor and methods of use of said active compounds wherein the active compounds contain a molecule inclusive of two heterocyclic groups said two groups being a piperidine group and a furanyl group, said matter being encompassed in claims 1 to 3, 11 to 13, 21 to 23 and 31 to 33 and said matter being classified in class 546, subclass 214, and class 514, subclass 326.

XV. Compounds, compositions of said active compounds plus a carrier or diluent therefor and methods of use of said active compounds wherein the active compounds contain a molecule inclusive of two heterocyclic groups said two groups being a piperidine group and a pyridine group, said matter being encompassed in claims 1 to 3, 11 to 13, 21 to 23 and 31 to 33 and said matter being classified in class 546, subclass 193 and class 514, subclass 318.

XVI. Compounds, compositions of said active compounds plus a carrier or diluent therefor and methods of use of said active compounds wherein the active compounds contain a molecule inclusive of two heterocyclic groups said two groups being a piperidine group and a pyrimidine group, said matter being encompassed in claims 1 to 3, 11 to 13, 21 to 23 and 31 to 33 and said matter being classified in class 544, subclass 242 (plus) and class 514, subclass 256 (plus).

XVII. Compounds, compositions of said active compounds plus a carrier or diluent therefor and methods use of said active compounds wherein the active compounds contain a molecule inclusive of two heterocyclic groups said two groups being a piperidine group and a thiazolyl group, said matter being encompassed in claims 1 to 3, 11 to 13, 21 to 23 and 31 to 33 and said matter being classified in class 546, subclass 209 and class 514, subclass 326.

XVIII. Compounds, compositions of said active compounds plus a carrier or diluent therefor and methods of use of said active compounds wherein the active compounds contain a molecule inclusive of two heterocyclic groups said two groups being a piperidine group and a isoxazol group, said matter being encompassed in claims 1 to 3, 11 to 13, 21 to 23 and 31 to 33 and said matter being classified in class 546, subclass 209 and class 514, subclass 326.

XIX. Compounds, compositions of said active compounds plus a carrier or diluent therefor and methods of use of said active compounds wherein the active compounds contain a molecule inclusive of two heterocyclic groups said two groups being a seven membered (1 nitrogen and 6 carbon) ring and a thienyl group, said matter being encompassed in claims 1 to 5, 11 to 15, 21 to 23 and 31 to 33 and said matter being classified in class 540, subclasses 484 and 596 and class 514, subclass 212.

XXI. Compounds, compositions of said active compounds plus a carrier or diluent therefor and methods of use of said active compounds wherein the active compounds contain a molecule inclusive of two heterocyclic groups said two groups being a seven membered (1 nitrogen and 6 carbon) ring and a pyridine group, said matter being encompassed in claims 1 to 3, 11 to 13, 21 to 23 and 31 to 33 and said matter being classified in class 540, subclass 484 and 596 and class 514, subclass 212.

XXII. Compounds, compositions of said active compounds plus a carrier or diluent therefor and methods of use of said active compounds wherein the active compounds contain a molecule inclusive of two heterocyclic groups said groups being a seven membered (1 nitrogen and 6 carbon) ring and pyrimidine group, said matter being encompassed in claims 1 to 3, 11 to 13, 21 to 23 and 31 to 33 and said matter being classified in class 540, subclass 484 and 597 and class 514, subclass 212.

XXIII. Compounds, compositions of said active compounds plus a carrier or diluent therefor and methods of use of said active compounds or diluent therefor and methods of use of said active compounds wherein the active compounds contain a molecule inclusive of two heterocyclic groups said two groups being a seven membered (1 nitrogen and 6 carbon) group and a thiazole group, said matter being encompassed in claims 1 to 3, 11 to 13, 21 to 23 and 31 to 33 and said matter being classified in class 540, subclasses 484 and 603 and class 514, subclass 212.

XXIV. Compounds, compositions of said active compounds plus a carrier or diluent therefor and methods of use of said active compounds wherein the active compounds contain a molecule inclusive of two heterocyclic groups said two groups being a seven membered (1 nitrogen and 6 carbon) group and an isoxazole group, said matter being encompassed in claims 1 to 3, 11 to 13, 21 to 23 and 31 to 33 and said matter being classified in class 540, subclasses 484 and 603 and class 514, subclass 212.

The separate inventions as grouped above are distinct and independent each from the other, as they each contain differing heterocyclic groups (as regards the active compounds, per se) either in number and/or in kind; as they have acquired a separate status in the art; as they constitute separate subjects for inventive effort; as the compounds of one group do not suggest or render obvious any of the compounds of the other group and as, for the most part, they require different searches (see NOTE, below) and are separately classified.

NOTE: Some of the above class and subclass areas are not fully extensive as, in some cases, additional search areas are involved depending on substitutions in the molecule and/or the precise attachment to some of the heterocyclic (e.g. pyrimidine, thiophene, furan, thiazole, pyridine, etc.) rings and/or as regards the nature of the substitutions on the rings.