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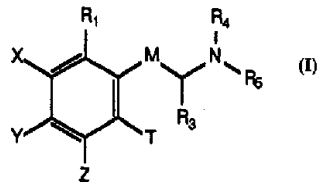
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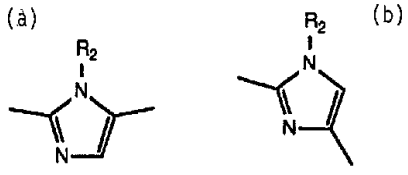
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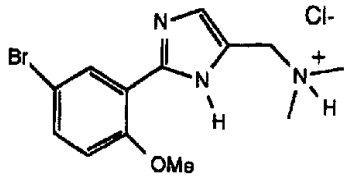
(54) Title: CERTAIN AMINOMETHYL PHENYLIMIDAZOLE DERIVATIVES; A NEW CLASS OF DOPAMINE RECEPTOR SUBTYPE SPECIFIC LIGANDS

(57) Abstract

This invention encompasses compounds of formula (I) where R_1, R_3, R_4, R_6, X, Y, and Z and T are variables; and M is (a) or (b) where R_2 is a variable; or R_1 and R_2 together may represent $-(CH_2)_{n1}$ where n1 is 1, 2 or 3. These compounds are highly selective partial agonists or antagonists at brain dopamine receptor subtypes or prodrugs thereof and are useful in the diagnosis and treatment of affective disorders such as schizophrenia and depression as well as certain movement disorders such as Parkinsonism. Furthermore, compounds of this invention may be useful in treating the extraparamidyl side effects associated with the use of conventional neuroleptic agents.







Compound 1

Certain Aminomethyl Phenylimidazole Derivatives; A New Class of Dopamine Receptor Subtype Specific Ligands

BACKGROUND OF THE INVENTION

This application is a continuation-in-part of U.S. Patent Application S.N. 08/081,317, filed November 8, 1993, which is a continuation-in-part of U.S. Patent Application S.N. 07/635,256, filed December 28, 1990, now U.S. Patent No. 5,159,083.

Field of the Invention

This invention relates to certain aminomethyl phenylimidazole derivatives which selectively bind to brain dopamine receptor subtypes. This invention also relates to pharmaceutical compositions comprising such compounds. It further relates to the use of such compounds in treating affective disorders such as schizophrenia and depression as well as certain movement disorders such as Parkinsonism. Furthermore compounds of this invention may be useful in treating the extraparamidyl side effects asssociated with the use of conventional neuroleptic agents. The interaction of aminomethyl phenylimidazole derivatives of the invention with dopamine receptor subtypes is described. This interaction results in the pharmacological activities of these compounds.

Description of the Related Art

Schizophrenia or psychosis is a term used to describe a group of illnesses of unknown origin which affect approximately 2.5 million people in the United States. These disorders of the brain are characterised by a variety of symptoms which are classified as positive symptoms (disordered thought, hallucinations and delusions) and negative symptoms (social withdrawal and unresponsiveness). These disorders have an age of onset in adolescence or early adulthood and persist for many years. The disorders tend to become more severe during the patients lifetime and can result in prolonged institutionalization. In the US today, approximately 40% of all hospitalized psychiatric patents suffer from schizophrenia.

During the 1950's physicians demonstrated that they could sucessfully treat psychotic patients with medications called neuroleptics; this classification of antipsychotic medicatin was based largely on the activating (neuroleptic) properties of the nervous system by these drugs. Subsequently, neuroleptic agents were shown to increase the concentrations of dopamine metabolites in the brain suggesting altered neuronal firing of the dopamine system. Additional evidence indicated that dopamine could increase the activity of adenylate cyclase in the corpus striatum, an effect reversed by neuroleptic agents. Thus, cumulative evidence from these and

later experiments strongly suggested that the neurotransmitter dopamine was involved in schizophrenia.

One of the major actions of antipsychotic medication is the blockade of dopamine receptors in brain. Several dopamine systems appear to exist in the brain and at least three classes of dopamine receptors appear to mediate the actions of this transmitter. These dopamine receptors differ in their pharmacological specificity and were originally classified upon these differences in the pharmacology of different chemical series. Butyrophenones, containing many potent antipsychotic drugs were quite weak at the dopamine receptor that activated adenylate cyclase (now known as a D1 dopamine receptor). In contrast, they labelled other dopamine receptors (called D2 receptors) in the subnanomolar range and a third type D3 in the nanomolar range. Phenothiazines possess nanomolar affinity for all three types of dopamine receptors. Other drugs have been developed with great specificity for the D1 subtype receptor.

Recently, a new group of drugs (such as sulpiride and clozapine) have been developed with a lesser incidence of extrapyramidal side effects than classical neuroleptics. In addition, there is some indication that they may be more beneficial in treating negative symptoms in some patients. Since all D2 blockers do not possess a similar profile, hypotheses underlying the differences have been investigated. The major differences have been in the anticholinergic actions of the neuroleptics as well as the possilility that the dopamine receptors may differ in motor areas from those in the limbic areas thought to mediate the antipsychotic responses. The existence of the D3 and other as yet undiscovered dopamine receptors may contribute to this profile. Some of the atypical compounds possess similar activity at both D2 and D3 receptors. The examples of this patent fall into this general class of molecules.

Using molecular biological techniques it has been possible to clone cDNAs coding for each of the pharmacologically defined receptors. There are at least two forms of D1, and two forms of D2 dopamine receptors. In addition, there is at least one form of D3 dopamine receptor and at least one form of D4 dopamine receptor. Examples from the aminomethyl phenylimidazole series of this patent possess differential affinities for each receptor subtype.

Schizophrenia is characterized by a variety of cognitive dysfunctions and patients perform less well than other groups on most cognitive or attentional tasks. The positive and negative symptom dimensions of schizophrenia are also associated with distinct cognitive deficits. In general, positive symptoms (disordered thought processes, hallucinations and decisions) are related to auditory processing imairments including deficits in verbal memory and language comprehenion. Negative symptoms (social withdrawal and unresponsiveness) are related more to visual/motor dysfunctions including poorer performance on visual memory, motor speed and dexterity tasks.

There disorders have an age of onset in adolescence or early adulthood and persist for many years. The interaction of frontal and septo-hippocampal brain systems, and failures of information processing and self monitoring have been theorized as the basis of positive symptoms. Negative symptoms are thought to arise from abnormalities in the interactions of frontal and striatal systems. Since cognitive disturbances are present in most of the pateitns

diagnosed as schizophrenia, it has been theorized that to understand the pathogenesis and etiology of schizophrenia we must understand the basic dysfunction of the cognitive disorder.

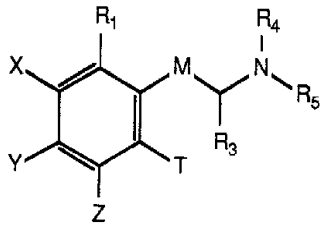
The cognitive disturbances found in schizophrenia include, but are not limited to, various verbal and visual memory deficits. There are various neurocognitive tasks for both animals and humans that have been developed to assess memory deficits, as well as memory enhancements, of various treatments. Many of the neurocognitive behavioral tasks are modulated or mediated by eural activity within the hippocampal brain system noted above.

Drug substances that interact with the hippocampus are capable of modulating memory in animals. Certain memory paradigms employed in animals have construct and predictive validity for memory assessment in humans. In animals (rodents), paradigms such as the Step-Down Passive Avoidance Task assay or the Spatial Water Maze Task assay reliably detect deficits produced by certain drugs in humans. For example, commonly prescribed benzodiazepine anxiolytics and sedative hypnotics are known to produce memory impairment in humans, including varying degrees of anterograde amnesia (depending on the exact drug). In the step-down passive avoidance paradigm, these very same drugs disrupt the memory of animals given the compounds during the information acquisition or processing period. Likewise, benzodiazepines disrupt information processing and memories in the spatial water maze task in rodents. Thus, these animal models can be used to predict the memory impairing effects of certain compounds in humans. Conversely, these same animal models can predict the memory improving or enhancing effects of compounds in humans. Although fewer in number, drugs that improve memory in humans (e.g., Nootroprice, Beta carbolines) produce memory enhancing effects in rats in these models. Therefore, the spatial water maze and step-down passive avoidance paradigms in rodents are useful in predicting memory impairing and memory enhancing effects of test compounds in humans.

SUMMARY OF THE INVENTION

This invention provides novel compounds of Formula I which interact with dopamine receptor subtypes.

The invention provides pharmaceutical compositions comprising compounds of Formula I. The invention also provides compounds useful in treating affective disorders such as schizophrenia and depression as well as certain movement disorders such as Parkinsonism. Furthermore compounds of this invention may be useful in treating the extraparamidyl side effects asssociated with the use of conventional neuroleptic agents. Accordingly, a broad embodiment of the invention is directed to a compound of Formula I:

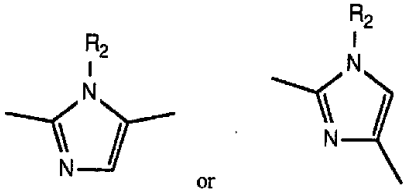


and the pharmaceutically acceptable non-toxic salts thereof wherein

R_1 and T are the same or different and represent

hydrogen, halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms;

M is



where

R_2 is

hydrogen or straight or branched chain lower alkyl having 1-6 carbon atoms, or R_1 and R_2 together may represent $-(CH_2)_{n1}$ where n_1 is 1, 2, or 3;

X and Z are the same or different and represent

hydrogen, halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, straight or branched chain lower alkoxy having 1-6 carbon atoms or SO_2R_6 where R_6 is straight or branched chain lower alkyl having 1-6 carbon atoms;

Y is

hydrogen, halogen, amino, or straight or branched chain lower alkyl having 1-6 carbon atoms;

R_3 is

hydrogen or,straight or branched chain lower alkyl having 1-6 carbon atoms, or R_3 and R_4 together may represent $-(CH_2)_{n2}-$ where n_2 is 3 or 4; and

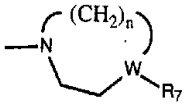
R_4 and R_5 are the same or different and represent

hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, or phenylalkyl or pyridylalkyl where each alkyl is straight or branched chain alkyl having 1-6 carbon atoms; or

R_2 and R_5 together may represent $-(CH_2)_{n3}-$ where n_3 is 2 or 3; or

NR_4R_5 represents

2-(1,2,3,4-tetrahydroisoquinolinyl), or 2-(1,2,3,4-tetrahydroiso-quinolinyl) mono or disubstituted with halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms; or



where

W is N or CH;

R_7 is

hydrogen, phenyl, pyridyl or pyrimidinyl,

hydrogen, phenyl, pyridyl or pyrimidinyl, each of which may be mono or disubstituted with halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms; or

W-R7 is oxygen or sulfur; and

n is 1, 2, or 3.

These compounds are highly selective partial agonists or antagonists at brain dopamine receptor subtypes or prodrugs thereof and are useful in the diagnosis and treatment of affective disorders such as schizophrenia and depression as well as certain movement disorders such as Parkinsonism. Furthermore compounds of this invention may be useful in treating the extraparamidyl side effects asssociated with the use of conventional neuroleptic agents.

The compounds of the invention, such as, for example, 2-Phenyl-4(5)-[(4-(2-pyrimidinyl)-piperazin-1-yl)-methyl]-imidazole dihydrochloride (compound 23), 2-Phenyl-4(5)-[(4-(2-pyridyl)-piperazin-1-yl)-methyl]-imidazole dihydrochloride (Compound 24),and 2-Phenyl-4(5)-[(4-phenyl-piperazin-1-yl)-methyl]-imidazole dihydrochloride (Compound 47), are antagonists binding to dopamine D4 receptors in both the rat and human hippocampus.

As noted above, the hippocampus is associated with both schizophrenia, and general memory processes in humans. In rodents, compound 23 produces memory enhancing effects in both the step-down passive avoidance assay as well as in the spatial water maze assay. Without being bound by a particular theory, it is believed that the D_4 receptors located in the hippocampus mediate the memory enhancing effects of the compounds of the invention. Therefore, since (1) compound 23 is active in animal models that are predictive of cognition enhancement, and specifically enhancement of memory and learning, and (2) compound 23 binds to D_4 receptors in the hippocampus, the D_4 class of dopamine antagonists, including the compounds of the invention, are useful for enhancing memory in humans.

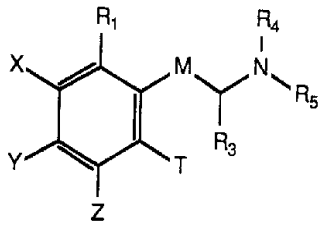
Thus, the invention further provides methods for enhancing cognition, and specifically learning and memory, in mammals. These methods comprise administering to a mammal such as a human a compound of the invention, such as, for example, a compound of formula V, VI, VII, or XII, in an amount effective to enhance cognition .

BRIEF DESCRIPTION OF THE DRAWING

Figures 1A-G show representative aminomethyl phenylimidazoles of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The novel compounds encompassed by the instant invention can be described by general formula I:

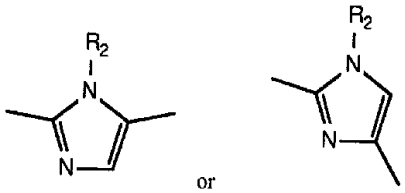


and the pharmaceutically acceptable non-toxic salts thereof wherein

R_1 and T are the same or different and represent

hydrogen, halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms;

M is



where

R_2 is

hydrogen or straight or branched chain lower alkyl having 1-6 carbon atoms, or R_1 and R_2 together may represent $-(CH_2)_{n1}$ where n_1 is 1, 2, or 3;

X and Z are the same or different and represent

hydrogen, halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, straight or branched chain lower alkoxy having 1-6 carbon atoms or SO_2R_6 where R_6 is straight or branched chain lower alkyl having 1-6 carbon atoms;

Y is

hydrogen, halogen, amino, or straight or branched chain lower alkyl having 1-6 carbon atoms;

R_3 is

hydrogen or,straight or branched chain lower alkyl having 1-6 carbon atoms, or R_3 and R_4 together may represent $-(CH_2)_{n2}-$ where n_2 is 3 or 4; and

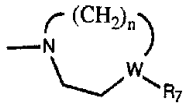
R_4 and R_5 are the same or different and represent

hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, or phenylalkyl or pyridylalkyl where each alkyl is straight or branched chain alkyl having 1-6 carbon atoms; or

R_2 and R_5 together may represent $-(CH_2)_{n3}-$ where n_3 is 2 or 3; or

NR_4R_5 represents

2-(1,2,3,4-tetrahydroisoquinolinyl), or 2-(1,2,3,4-tetrahydroiso-quinolinyl) mono or disubstituted with halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms; or



where

W is N or CH; and

R_7 is

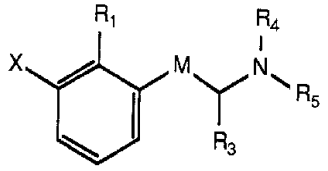
hydrogen, phenyl, pyridyl or pyrimidinyl,

hydrogen, phenyl, pyridyl or pyrimidinyl, each of which may be mono or disubstituted with halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms; or

W-R_7 is oxygen or sulfur; and

n is 1, 2, or 3.

The present invention further encompasses compounds of Formula II:



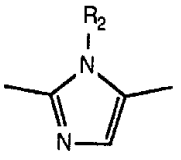
II

wherein

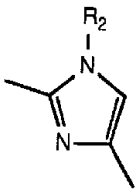
R_1 is

hydrogen, halogen,hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms;

M is



or



where

R_2 is

hydrogen or,straight or branched chain lower alkyl having 1-6 carbon atoms, or R_1 and R_2 together may represent $-(CH_2)_{n1}$ where n_1 is 1, 2, or 3;

X is

hydrogen, halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, straight or branched chain lower alkoxy having 1-6 carbon atoms or SO_2R_6 where R_6 is straight or branched chain lower alkyl having 1-6 carbon atoms;

R_3 is

hydrogen or straight or branched chain lower alkyl having 1-6 carbon atoms, or R_3 and R_4 together may represent $-(CH_2)_{n2}-$ where n_2 is 3 or 4; and

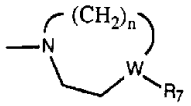
R_4 and R_5 are

the same or different and represent hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, phenylalkyl or pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1-6 carbon atoms; or

R_2 and R_5 together may represent $-(CH_2)_{n3}-$ where n3 is 2 or 3; or

NR_4R_5 represents

2-(1,2,3,4-tetrahydroisoquinolinyl) or 2-(1,2,3,4-tetrahydroiso-quinolinyl) mono or disubstituted with halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms; or



where

W is N or CH; and

R_7 is

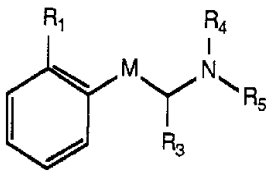
hydrogen, phenyl, pyridyl or pyrimidinyl, or

hydrogen, phenyl, pyridyl or pyrimidinyl, each of which may be mono or disubstituted with halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms; or

W-R_7 is oxygen or sulfur; and

n is 1, 2, or 3.

The present invention also encompases compounds of Formula III:



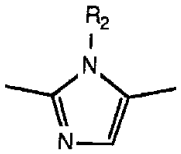
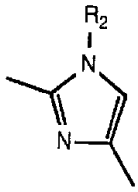
III

wherein

R_1 is

hydrogen, halogen,hydroxy, straight or branched chain lower alkyl having 1-6 carbonatoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms;

M is

or

where

R_2 is

hydrogen or,straight or branched chain lower alkyl having 1-6 carbon atoms, or R_1 and R_2 together may represent $-(CH_2)_{n_1}$ where n_1 is 1, 2, or 3;

R_3 is

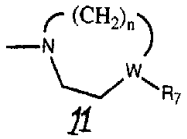
hydrogen, or straight or branched chain lower alkyl having 1-6 carbon atoms, or R_3 and R_4 together may represent $-(CH_2)_{n_2}-$ where n_2 is 3 or 4; or

R_4 and R_5 are

the same or different and represent hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, aryl straight or branched chain lower alkyl having 1-6 carbon atoms or R_2 and R_5 together may represent $-(CH_2)_{n_3}-$ where n_3 is 2 or 3; or

NR_4R_5 represents

2-(1,2,3,4-tetrahydroisoquinolinyl), or 2-(1,2,3,4-tetrahydroiso-quinolinyl) mono or disubstituted with halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms; or



where

W is N or CH; and

R_7 is

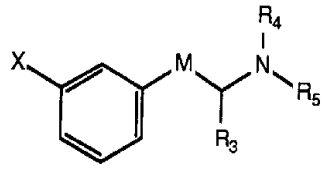
hydrogen, phenyl, pyridyl or pyrimidinyl; or

hydrogen, phenyl, pyridyl or pyrimidinyl mono or disubstituted with halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms; or

W-R_7 is oxygen or sulfur; and

n is 1, 2, or 3.

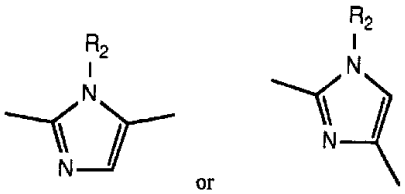
In addition, the present invention encompasses compounds of Formula IV:



IV

wherein

M is



where

R_2 is

hydrogen or,straight or branched chain lower alkyl having 1-6 carbon atoms, or R_1 and R_2 together may represent $-(CH_2)_{n1}$ where n_1 is 1, 2, or 3;

X is

hydrogen, halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, straight or branched chain lower alkoxy having 1-6 carbon atoms, or SO_2R_6 where R_6 is straight or branched chain lower alkyl having 1-6 carbon atoms;

R_3 is

hydrogen, or straight or branched chain lower alkyl having 1-6 carbon atoms, or R_3 and R_4 together may represent $-(CH_2)_{n2}-$ where n_2 is 3 or 4; and

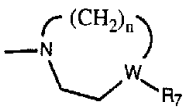
R_4 and R_5 are

the same or different and represent hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, phenylalkyl or pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1-6 carbon atoms; or

R_2 and R_5 together may represent $-(CH_2)_{n3}-$ where n_3 is 2 or 3; or

NR_4R_5 represents

2-(1,2,3,4-tetrahydroisoquinolinyl), or 2-(1,2,3,4-tetrahydroiso-quinolinyl) mono or disubstituted with halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms; or



where

W is N or CH; and

R_7 is

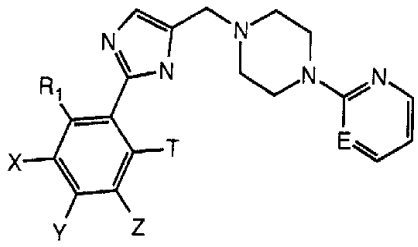
hydrogen, phenyl, pyridyl or pyrimidinyl,

hydrogen, phenyl, pyridyl or pyrimidinyl, mono or disubstituted with halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms; or

W-R_7 is oxygen or sulfur; and

n is 1, 2, or 3.

The invention also provides compounds of formula V:



V

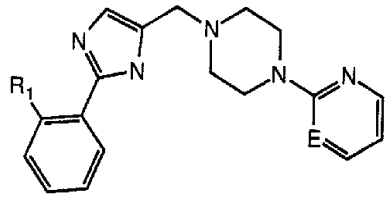
wherein:

R_1 and T independently represent hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy;

X, Y and Z independently represent hydrogen, halogen, hydroxy, lower alkyl, lower alkoxy, or $-SO_2R_6$ where R6 is lower alkyl; and

E is CH or nitrogen.

The invention also provides compounds of formula VI:



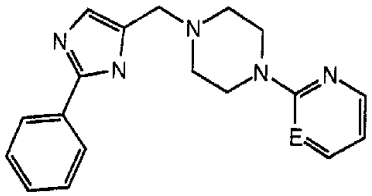
VI

wherein:

R_1 represents hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy; and

E is CH or nitrogen.

The invention provides compounds of formula VII:

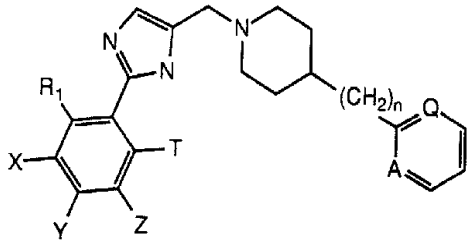


VII

wherein:

E is CH or nitrogen.

The invention also provides compounds of formula VIII:



VIII

wherein:

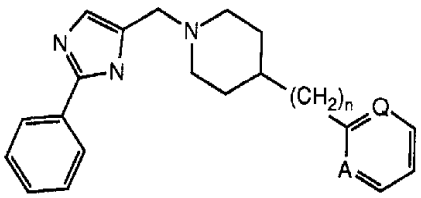
R_1 and T independently represent hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy;

X, Y and Z independently represent hydrogen, halogen, hydroxy, lower alkyl, lower alkoxy, or $-SO_2R_6$ where R6 is lower alkyl;

n is 0 or 1; and

A and Q are the same or different and represent CH or nitrogen.

The invention also provides compounds of formula IX:



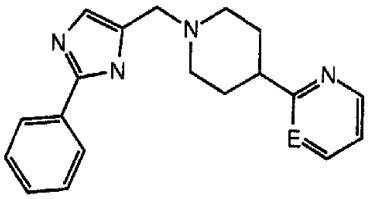
IX

wherein:

n is 0 or 1; and

A and Q are the same or different and represent CH or nitrogen.

The invention also provides compounds of formula X:

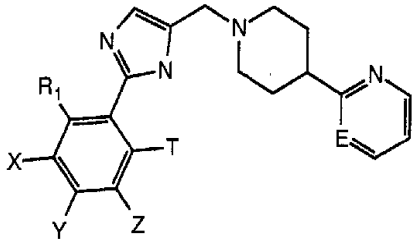


X

wherein:

E is CH or nitrogen.

The invention also provides compounds of formula XI:



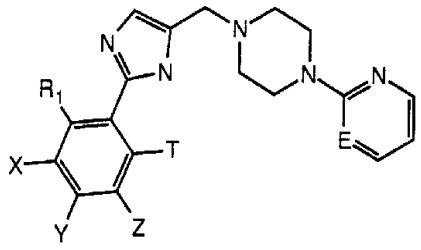
XI

wherein:

R_1, T, X, Y and Z independently represent hydrogen or lower alkyl; and

E represents CH or nitrogen.

The invention also provides compounds of formula XII:



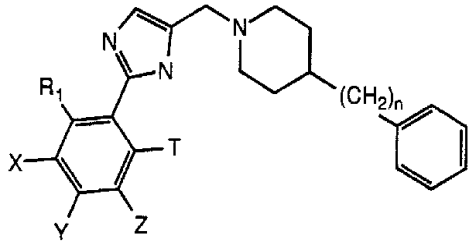
XII

wherein:

R_1, T, X, Y and Z independently represent hydrogen or lower alkyl; and

E represents CH or nitrogen.

The invention also provides compounds of formula XIII:



XIII

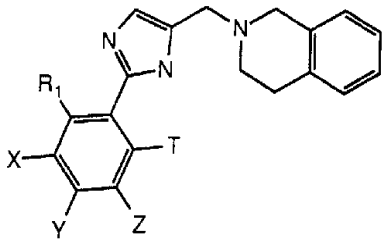
wherein

R_1 and T independently represent hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy; and

X, Y and Z independently represent hydrogen, halogen, hydroxy, lower alkyl, lower alkoxy, or $-SO_2R_6$ where R6 is lower alkyl.

n is 0 or 1.

The invention also provides compounds of formula XIV:



XIV

wherein:

R_1 and T independently represent hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy; and

X, Y and Z independently represent hydrogen, halogen, hydroxy, lower alkyl, lower alkoxy, or $-SO_2R_6$ where R6 is lower alkyl.

Non-toxic pharmaceutical salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluene sulfonic, hydroiodic, acetic and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

Representative compounds of the present invention, which are encompassed by Formula I, include, but are not limited to the compounds in Figure I and their pharmaceutically acceptable salts. The present invention also encompasses the acylated prodrugs of the compounds of Formula I. Those skilled in the art will recognize various synthetic methodologies which may be employed to prepare non-toxic pharmaceutically acceptable addition salts and acylated prodrugs of the compounds encompassed by Formula I.

By lower alkyl in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms, such as, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl.

By lower alkoxy in the present invention is meant straight or branched chain alkoxy groups having 1-6 carbon atoms, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyl, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy.

By halogen in the present invention is meant fluorine, bromine, chlorine, and iodine.

The pharmaceutical utility of compounds of this invention are indicated by the following assays for dopamine receptor subtype affinity.

<u>Assay for D2 and D3 receptor binding activity</u>

Striatial tissue is dissected from adult male Sprague Dawley rats or BHK 293 cells are harvested contianing recombinantly produced D2 or D3 receptors. The sample is homogenized in 100 volumes (w/vol) of 0.05 M Tris HCl buffer at 4o C and pH 7.4. The sample is then centrifuged at 30,000 x g and resuspended and rehomogenized. The sample is then centrifuged as described and the final tissue sample is frozen until use. The tissue is resuspended 1:20 (wt/vol) in 0.05M Tris HCl buffer containing 100 mM NaCl.

Incubations are carried out at 48°C and contain 0.5 ml of tissue sample, 0.5 nM 3H-raclopride and the compound of interest in a total incubation of 1.0 ml. Nonspecific binding is defined as that binding found in the presence of 10-4 M dopamine; without further additions, nonspecific binding is less than 20% of total binding. The binding characteristics of examples of this patent are shown in Table 1 for Rat Striatal Homogenates.

TABLE I

Compound Number[1]	IC_{50}(uM)
1	0.900
8	0.011
16	0.014
19	0.100
21	0.018
24	0.620
26	0.200

[1]Compound numbers relate to compounds shown in Figure I.

Compounds 8, 16 and 21 are particularly preferred embodiments of the present invention because of their potency in binding to dopamine receptor subtypes.

Assay for D4 receptor binding activity

Clonal cell lines expressing the human dopamine D4 receptor subtype were harvested in PBS and the cells centrifuged and the pellets stored at -80 C until used in the binding assay. The pellets were resuspended and the cells lysed at 4 C in 50 mM Tris pH 7.4 buffer containing 120mM Nacl, 1 mM EDTA and 5 mM MgCl2.. The homogenate is centrifuged at 48000xg for 10 minutes at 4 C. The resulting pellet is resuspended in fresh buffer and centrifuged again, After resuspension of the pellet in fresh buffer at 100ul aliquot is removed for protein determination. The remaining homogenate is centrifuged as above, the supernatant removed and the pellet stored

at 4 C until needed at which time it is resuspended to a final concentration of 625 ug/ml(250ug per sample) with 50 mM Tris buffer (pH 7.4) and 120 mM NaCl just prior to use.Incubations were carried out for 60 minutes at 25 C in the presence of 0.1 nM [^{3}H] YM-09151-2. The incubation was terminated by rapid filtration through Whatman GF/C filters and rinsed with 2x4 ml washes of chilled 50mM Tris (pH 7.4) and 120mM NaCl. Non-specific binding was determined with 1 uM spiperone and radioactivity determined by coiunting in an LKB beta counter. Binding parameters were determined by non-linear least squares regression analysis, from which the inhibition constant Ki could be calculated for each test compound. The binding characteristics of some compounds of this invention are shown in the examples.

The compounds of general formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition, there is provided a pharmaceutical formulation comprising a compound of general formula I and a pharmaceutically acceptable carrier. One or more compounds of general formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monosterate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example

sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monoleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitor or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For

this purpose any bland fixed oil may be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of general formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

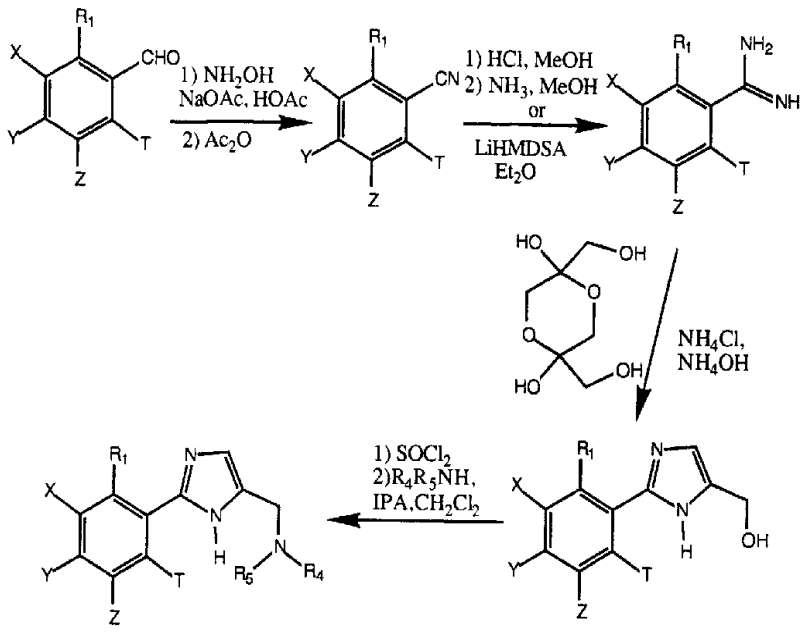
Compounds of general formula I may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anaesthetics, preservatives and buffering agents can be dissolved in the vehicle.

Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

An illustration of the preparation of compounds of the present invention is given in **Scheme I**. Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the present invention.

Scheme I

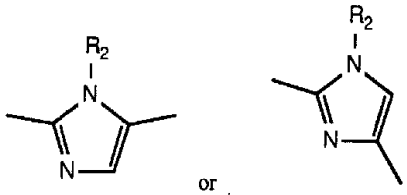


where

R_1 and T are the same or different and represent

hydrogen, halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms;

M is



or

where

R_2 is

hydrogen or straight or branched chain lower alkyl having 1-6 carbon atoms, or R_1 and R_2 together may represent $-(CH_2)_{n_1}$ where n_1 is 1, 2, or 3;

X and Z arethe same or different and represent

hydrogen, halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, straight or branched chain lower alkoxy having 1-6 carbon atoms or SO_2R_6 where R_6 is straight or branched chain lower alkyl having 1-6 carbon atoms;

Y is

hydrogen, halogen, amino, or straight or branched chain lower alkyl having 1-6 carbon atoms;

R_3 is

hydrogen or,straight or branched chain lower alkyl having 1-6 carbon atoms, or R_3 and R_4 together may represent $-(CH_2)_{n_2}-$ where n_2 is 3 or 4; and

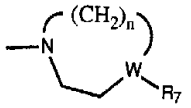
R_4 and R_5 are the same or different and represent

hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, or phenylalkyl or pyridylalkyl where each alkyl is straight or branched chain alkyl having 1-6 carbon atoms;

R_2 and R_5 together may represent $-(CH_2)_{n_3}-$ where n_3 is 2 or 3; or

NR_4R_5 represents

2-(1,2,3,4-tetrahydroisoquinolinyl), or 2-(1,2,3,4-tetrahydroiso-quinolinyl) mono or disubstituted with halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms; or



where

W is N or CH;

R_7 is

hydrogen, phenyl, pyridyl or pyrimidinyl,

hydrogen, phenyl, pyridyl or pyrimidinyl, each of which may be mono or disubstituted with halogen, hydroxy, straight or branched chain lower

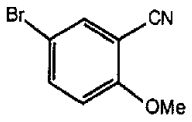
alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms; or

W-R7 is oxygen or sulfur; and

n is 1, 2, or 3.

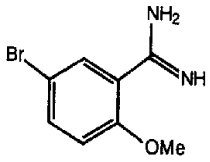
The invention is illustrated further by the following examples which are not to be construed as limiting the invention in scope or spirit to the specific procedures and compounds described in them.

Example I



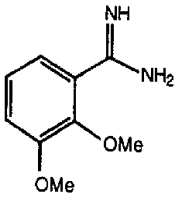
A mixture of 5-Bromo-o-anisaldehyde (6.45 g), hydroxylamine hydrochloride (2.2 g), sodium acetate (4.1 g) and acetic acid (20 mL) was heated at 100 °C with stirring for 1 h. Acetic anhydride was added (20 mL) and the mixture was refluxed for 8 h. The reaction mixture was poured onto ice water and the mixture was made basic by the careful addition of 50% sodium hydroxide. The product was extracted with ether, the ether extracts were dried over magnesium sulfate and the sovent was removed *in vacuo*. The residue was crystallized from ether/hexane to afford 5-Bromo-2-methoxy-benzonitrile.

Example II



A mixture of 5-Bromo-2-methoxy-benzonitrile (4.0 g), 3A molecular seives (5 g) and anhydrous methanol (60 mL) was saturated with HCl gas at room temperature and allowed to stand at room temperature for 24 h. The solvent was removed *in vacuo* and the residue taken up in 75 mL of anhydrous methanol and saturated with ammonia gas at room temperature. The reaction mixture was then heated at 80°C for 4 h in a sealed tube. The sovent was removed *in vacuo*, the reaction mixture was diluted with 3N HCl and washed with ethyl acetate to remove unreacted nitrile. The aqueous layer was made basic with 50% NaOH and the product was extracted three times with 10% methanol in methylene chloride. The combined organic extracts were dried over magnesium sulfate and the sovents removed *in vacuo* to afford 5-Bromo-2-methoxy-benzamidine as a glassy solid.

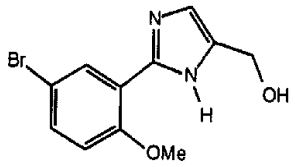
Example III



To a solution of 1,1,1,3,3,3-hexamethylsisilazane (20 g) in dry ether (150 mL) was added 2.4M n-butyllithium in hexane (5 mL). After 10 min at room temperature, 2,3-

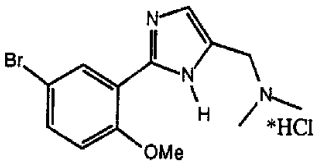
Dimethoxybenzonitrile (16.3 g) was added in one portion and the mixture was kept at room temperature for 16 h. The reaction mixture was the poured onto excess 3N HCl. The aqueous layer was separated, basified with 50% NaOH and the product was extracted three times with 10% methanol in methylene chloride. The combined organic extracts were dried over magnesium sulfate and the solvents removed *in vacuo* to afford 2,3-Dimethoxy-benzamidine as a glassy solid.

Example IV



A mixture of 5-Bromo-2-methoxy-benzamidine (1.5 g), 1,3-dihydroxy-acetone dimer (1.0 g), ammonium chloride (1.3 g), tetrahydrofuran (3 mL) and concentrated aqueous ammonium hydroxide (10 mL) was heated at 90°C for 3 h. The reaction mixture was chilled on ice and the precipitated product was collected and recrystallized from methanol to afford 2-(5-Bromo-2-methoxyphenyl)-5-hydroxymethyl-imidazole as a yellow solid.

Example V



(Compound 1)

A mixture of 2-(5-Bromo-2-methoxyphenyl)-5-hydroxymethyl-imidazole (500 mg) and thionyl chloride (1.5 mL) was heated at 80°C for 1 h. Ether (15 mL) was added and the resulting solid was collected and washed with ether. This solid was added in one portion to a mixture of dimethylamine (3 mL), isopropanol (15 mL) and methylene chloride (30 mL) and the mixture was stirred for 20 min. The solvents were removed *in vacuo* and the residue was dissolved in 2N HCl and washed two times with ethyl acetate. The aqueous layer was made basic with 50% NaOH and the product was extracted with methylene chloride. The organic

extracts were dried over magnesium sulfate, the solvents removed *in vacuo*, and the residue was treated with ethanolic HCl/ether to afford 2-(5-Bromo-2-methoxyphenyl)-4(5)-[(N,N-dimethyl)-aminomethyl]-imidazole dihydrochloride (Compound 1) , m.p. 242-243°C.

Example VI

The following compounds were prepared essentially according to the procedure described in Examples I-V:

(a) 2-Phenyl-4(5)-[(N,N-dimethyl)aminomethyl]-imidazole dihydrochloride (Compound 2), m.p. 259-260°C.

(b) 2-Phenyl-4(5)-(piperidinomethyl)-imidazole dihydrochloride (Compound 3), m.p. 245-247°C.

(c) 2-Phenyl-4(5)-[(N-methyl-N-benzyl)aminomethyl]-imidazole dihydrochloride (Compound 4), m.p. 239-240°C.

(d) 2-(2-Methoxyphenyl)-4(5)-[(N,N-dimethyl)aminomethyl]-imidazole dihydrochloride (Compound 5) melting at °C.

(e) 2-(3-Methoxyphenyl)-4(5)-[(N-methyl-N-benzyl)aminomethyl]-imidazole dihydrochloride (Compound 6), m.p. 115-117°C.

(f) 2-(2,3-Dimethoxyphenyl)-4(5)-[(N,N-dimethyl)aminomethyl]-imidazole dihydrochloride (Compound 7), m.p. 220-221°C.

(g) 2-(2,3-Dimethoxyphenyl)-4(5)-[(N-methyl-N-benzyl)aminomethyl]-imidazole dihydrochloride (Compound 8), m.p. 200-202°C.

(h) 2-(3-Methoxyphenyl)-4(5)-[(N,N-diethyl)aminomethyl]-imidazole dihydrochloride (Compound 9), m.p. 213-214°C.

(i) 2-(3-Fluorophenyl)-4(5)-[(N,N-dimethyl)aminomethyl]-imidazole dihydrochloride (Compound 10), m.p. 211-214°C.

(j) 2-(2-Fluorophenyl)-4(5)-[(N-methyl-N-benzyl)aminomethyl]-imidazole dihydrochloride (Compound 11), m.p. 241-244°C.

(k) 2-(3-Methylphenyl)-4(5)-[(N,N-dimethyl)aminomethyl]-imidazole dihydrochloride (Compound 12), m.p. 231-234°C.

(l) 2-(2-Fluorophenyl)-4(5)-[(N,N-dimethyl)aminomethyl]-imidazole dihydrochloride (Compound 13), m.p. 246-247°C.

(m) 2-(4-Fluorophenyl)-4(5)-[(N-methyl-N-benzyl)aminomethyl]-imidazole dihydrochloride (Compound 14), m.p. 237-239°C.

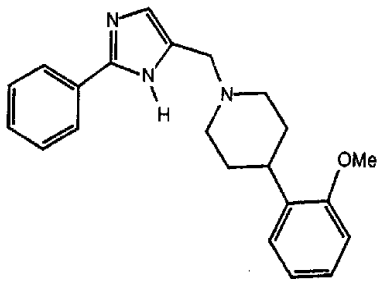
(n) 2-(2-Methoxyphenyl)-4(5)-[(N-methyl-N-benzyl)aminomethyl]-imidazole dihydrochloride (Compound 15), m.p. 239-241°C.

(o) 2-(5-Bromo-2,3-dimethoxyphenyl)-4(5)-[(N,N-dimethyl)aminomethyl]-imidazole dihydrochloride (Compound 16), m.p. 194-194°C.

(p) 2-(5-Bromo-2-methoxyphenyl)-4(5)-[(N-methyl-N-benzyl)aminomethyl]-imidazole dihydrochloride (Compound 17), m.p. 242-243°C.

(q) 2-(5-Bromo-2,3-dimethoxyphenyl)-4(5)-[(N-methyl-N-benzyl)aminomethyl]-imidazole dihydrochloride (Compound 18).

Example VII



(Compound 19)

A mixture of 2-Phenyl-5-hydroxymethyl-imidazole (350 mg) and thionyl chloride (1 mL) was heated at 80°C for 1 h. The excess thionyl chloride was removed in vacuo and the residue was dissolved in 20 mL of methylene chloride. This solution was added to a mixture of triethylamine (1 mL) and 1-(2-methoxyphenyl)-piperazine (410 mg) in methylene chloride (20 mL) and the mixture was stirred for 20 min. The solvents were removed *in vacuo* and the residue was dissolved in 2N HCl and washed two times with ethyl acetate. The aqueous layer was made basic with 50% NaOH and the product was extracted with methylene chloride. The

organic extracts were dried over magnesium sulfate, the solvents removed *in vacuo*, and the residue was crystallized from ethyl acetate to afford 2-Phenyl-4(5)-[(4-(2-methoxyphenyl)-piperazin-1-yl)-methyl]-imidazole (Compound 19), m.p. 105-107°C.

Example VIII

The following compounds were prepared essentially according to the procedure described in Example VII:

(a) 2-(4-Fluorophenyl)-4(5)-[(4-(2-methoxyphenyl)-piperazin-1-yl)-methyl]-imidazole (Compound 20), m.p. 95-97°C.

(b) 2-(2,3-Dimethoxyphenyl)-4(5)-[(4-(2-methoxyphenyl)-piperazin-1-yl)-methyl]-imidazole dihydrochloride (Compound 21), m.p. 217-218°C.

(c) 2-(3-Chlorophenyl)-4(5)-[(4-(2-methoxyphenyl)-piperazin-1-yl)-methyl]-imidazole dihydrochloride (Compound 22), m.p. 198-199°C.

(d) 2-Phenyl-4(5)-[(4-(2-pyrimidinyl)-piperazin-1-yl)-methyl]-imidazole dihydrochloride (Compound 23), m.p. 246-248°C.

(e) 2-Phenyl-4(5)-[(4-(2-pyridyl)-piperazin-1-yl)-methyl]-imidazole dihydrochloride (Compound 24), m.p. 176-177°C.

(f) 2-Phenyl-4(5)-[(4-benzyl-piperidin-1-yl)-methyl]-imidazole dihydrochloride (Compound 25), m.p. 234-236°C.

(g) 2-Phenyl-4(5)-[(4-phenyl-piperidin-1-yl)-methyl]-imidazole dihydrochloride (Compound 26), m.p. 238-240°C.

(h) 2-Phenyl-4(5)-[(1,2,3,4-tetrahydroisoquinolin)-2-yl-methyl]-imidazole dihydrochloride (Compound 27).

Example IX

The following compounds were prepared essentially according to the procedures described in Examples I-VII:

(a) 2-(2,3-Dimethoxyphenyl)-4(5)-[(1,2,3,4-tetrahydroisoquinolin)-2-yl-methyl]-imidazole dihydrochloride (Compound 28), m.p. 205-207°C.

(b) 2-(4-Methoxyphenyl)-4(5)-[(N-methyl-N-benzyl)aminomethyl]-imidazole dihydrochloride (Compound 29).

(c) 2-(3,4-Dimethoxyphenyl)-4(5)-[(N-methyl-N-benzyl)aminomethyl]-imidazole dihydrochloride (Compound 30).

(d) 2-(3-Methoxyphenyl)-4(5)-[(N-methyl)aminomethyl]-imidazole dihydrochloride (Compound 31).

(e) 2-(5-Chloro-2-methoxyphenyl)-4(5)-[(N-methyl-N-benzyl)aminomethyl]-imidazole (Compound 32), m.p. 88-89°C.

(f) 2-(5-Chloro-2-methoxyphenyl)-4(5)-[(N,N-dimethyl)aminomethyl]-imidazole dihydrochloride (Compound 33), m.p. 231-233°C.

(g) 2-(5-Chloro-2-methoxyphenyl)-4(5)-[(N-methyl)aminomethyl]-imidazole dihydrochloride (Compound 34), m.p. 225-227°C.

(h) 2-(5-Chloro-2-methoxyphenyl)-4(5)-[(N-benzyl)aminomethyl]-imidazole dihydrochloride (Compound 35), m.p. 184-186°C.

(i) 2-(5-Chloro-2-benzyloxyphenyl)-4(5)-[(N-methyl-N-benzyl)aminomethyl]-imidazole dihydrochloride (Compound 36), m.p. 118-123°C.

(j) 2-(2-Benzyloxyphenyl)-4(5)-[(N-methyl-N-benzyl)aminomethyl]-imidazole dihydrochloride (Compound 37), m.p. 199-200°C.

(l) 2-(3-Ethylphenyl)-4(5)-[(N-methyl-N-benzyl)aminomethyl]-imidazole dihydrochloride (Compound 38), m.p. 234-235°C.

(m) 2-(5-Chloro-2-methoxyphenyl)-4(5)-[(N-methyl-N-(-4-chlorobenzyl))aminomethyl]-imidazole dihydrochloride (Compound 39), m.p. 186-188°C.

(n) 2-(5-Chloro-2-hydroxyphenyl)-4(5)-[(N-methyl-N-benzyl)aminomethyl]-imidazole dihydrochloride (Compound 40), m.p. 227-228°C.

(o) 2-(5-Bromo-2-benzyloxyphenyl)-4(5)-[(N-methyl-N-benzyl)aminomethyl]-imidazole dihydrochloride (Compound 41).

(p) 2-(5-Ethyl-2-methoxyphenyl)-4(5)-[(N-methyl-N-benzyl)aminomethyl]-imidazole dihydrochloride (Compound 42), m.p. 114-115°C.

(q) 2-(5-Chloro-2-methoxyphenyl)-4(5)-[(4-(2-methoxyphenyl)-piperazin-1-yl)-methyl]-imidazole dihydrochloride (Compound 43) melting at 138-143°C.

(r) 2-(5-Chloro-2-methoxyphenyl)-4(5)-[(4-phenyl-piperidin-1-yl)-methyl]-imidazole dihydrochloride (Compound 44), m.p. 138-143°C.

(s) 2-(2,3-Dimethoxyphenyl)-4(5)-[(4-(2-methoxyphenyl)-piperidin-1-yl)-methyl]-imidazole dihydrochloride (Compound 45).

(t) 2-phenyl-4(5)-[(4-(2-pyridyl)-piperidin-1-yl)-methyl]-imidazole dihydrochloride (Compound 46).

(u) 2-phenyl-4(5)-[(4-phenyl-piperazin-1-yl)-methyl]-imidazole dihydrochloride (Compound 47).

Example X

Receptor Binding Activity (Ki, nM)

	Dopamine Receptor		
Compound No.	D2	D3	D4
47	239	169	5
23	1033	8200	2.7
24	1029	123	0.85

Example XI

Summary

The effects of 2-phenyl-4(5)-[(4-(2-pyrimidyl)-piperazin-1-yl)methyl]-imidazole dihydrochloride (Compound 23) and clozapine were evaluated in tthe following models of learning and memory: a step-down passive avoidance task assay and a modified Morris water maze assay Separate groups of male Sprague Dawley rats were pretreated with either Compound 23 or clozapine prior to training in these tasks. The control compound, clozapine, produced an

acquisition deficit in the passive avoidance task at the two highest doses tested (1.0, 2.0 mg/kg) but produced no significant deficits in retention. Clozapine produced no deficits in the water maze task at the doses tested. In the step-down passive avoidance assay animals that received the 0.25 mg/kg dose of Compound 23 showed significant improvement in memory compared to the vehicle group. Likewise in the modified Morris water maze, animals that received the 0.03, 0.25 and the 1.0 mg/kg dose of Compound 23 showed significant improvement in task retention compared to the vehicle group. These data show that Compound 23 does not impair learning, but enhances learning in animals.

Method

Non-naive male Sprague Dawley rats (SASCO St. Louis) weighing between 2000-300 grams, were housed in groups of three in a temperature and humidity controlled vivarium having a 12 hour light/dark cycle. Animals had ad lib access to food and water.

Compound 23 was dissolved in 50% Polyethylene glycol (PEG) and administered in a dose range of 0.03-1.0 mg/kg. Clozapine was dissolved in 50% PEG and administered in a dose range of from 0.25 to 2mg/kg. Both drugs were administered intravenously 5 minutes prior to training in both learning tasks

Apparatus:

Step-Down Passive Avoidance: A step-down passive avoidance platform 4 (cm)x7(cm) was placed in the center of an electrified gris floor, which was contained within a large (45 x 45 x 50 cm) white translucent plexiglas enclosure.having a closable lid. The bars of the grip were spaced 1.5 cm apart and were wired to a BRS-LVE shock generator/scrambler which was set to deliver a 2mA 6 second shock. Four passive avoidance boxes were automated by customer software (Labview) and commercial interface modules (National Instruments) connected to a computer The timing and delivery of the shock as well as the latency to steo down and the number of trials taken to reach criterion during training was under the control of the computer. All testing was done in the presence of 62db white noise.

Modified Morris Water Maze: A water maze apparatus consisted of a circular tank (120 cm in diameter and 56 cm in height) having a black interior. The tank was surrounded by external visual cues which consisted of a black and white checkered wall, a black and white striped wall, a while wall and a blue panel. The tank was filled with water (18-20°C) to a height of 52 cm and was divided into four quadrants (North, South, East and West). A black circular plexiglas platform (with black rubber top) was placed in the northeast quadrant approximately 1 cm below the surface of the water. The submerged platform was 51 cm in height and had a diameter of 9 cm. Training and testing was conducted in the presence of a 62db white noise source and under dim light conditions.

Procedure:

1. Passive Avoidance:

Acquisition Training: After pretreatment with clozapine, Compound 23 or control (vehicle), the animal was placed on the platform which automatically started a timer. When the animal stepped off the platform it automatically received the footshock. Following each shock the animal was removed from the box and placed in its cage for a one minute intertrial interval and then returned to the platform. Training was terminted when the animal remained on the platform for 120 Seconds. Immediately after training the animal was returned to its home cage in a vivarium.

Retention Testing: Testing was conduced approximately 24 hours after training. Drug-free animals were placed on the platform in the box in which they were trained and the latency to step down onto the unshocked floor was recorded for one trial. The animal was allowed to a maximum of 120 seconds to step down.

2. Modified Morris Water Maze:

Acquisition Training: Acquisition training in this task assay consisted of either four or six training trials. The four trial procedure detects cognitive enhancing effects of drugs while the six trial procedure detects drugs that produce learning deficits in this task.assay Compound 23 was tested in the water maze using a four trial procedure and clozapine using a six trial training procedure. Each animal was placed on the platform in the tank for 20 trials separated by an intertrial interval of 2 minutes. The starting position was pseudo-randomly varied but was the same order for each animal. During the ITI (intertrial interval) the animal was dried off and placed near a heat source (heat lamp). The latency to reach the submeged platform on each trial was measured and animals were allowed to remain on the platform for 10 seconds once they reach it. Since the platform was submerged just below the surface of the water, the animal was required to use the external visual cues surrounding the tank (distal cues) to locate the platform.

Retention Training: On the following day, each animal was individually tested for retention in one trial. All animals were placed in the "SOUTH" starting position and latency to find the submerged platform was recorded.

Results

Passive Avoidance: There were no significant differences for acquisition between the vehicle grup and animals treated with Compound 23. Animals that received 0.25 mg/kg dose of Compound 23 remained on the platform for a significantly longer time during retest than the vehicle animals. Animals that received the 1.0 mg/kg and 2.0 mg/kg doses of clozapine showed a significant deficit in acquisition compared to the vehicle group. There were no significant differences in retention between clozapine treated animals and the vehicle group.

Water Maze: The difference between the first trial and the retest trial (latency to locate the platform on the following day) revealed significant improvement in retention relative to controls at the 0.03 mg/kd, 0.25 mg/kg and the 1.0 mg/kg dose of Compound 23. However, the difference between the scores of trial 1 and the retest trial for animals that received clozapine revealed no significant differences.

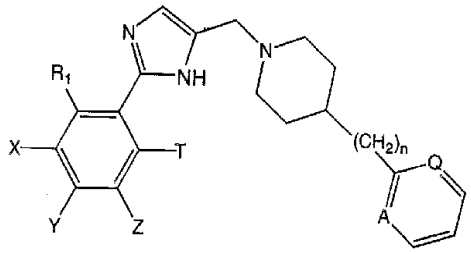
These results indicate that compound 23 improved memory in mammals. These results further show that compound 23 also enhances learning in mammals. Thus, the compounds of the invention are useful for enhancing cognition in mammals and can be used in methods for enhancing cognition, specifically learning and memory, in mammals.

The invention and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

It will be understood that the term "comprises" or its grammatical variants as used herein is equivalent to the term "includes" and is not to be taken as excluding the presence of other elements or features.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the formula:



wherein:

R_1 and T independently represent hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy;

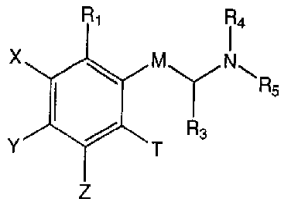
X and Z independently represent hydrogen, halogen, hydroxy, lower alkyl, lower alkoxy, or $-SO_2R_6$ where R_6 is lower alkyl;

Y is hydrogen, halogen or lower alkyl;

n is 1; and

A and Q are the same or different and represent CH or nitrogen.

2. The use of a compound of formula I in the preparation of a medicament for enhancement of memory where formula I is:



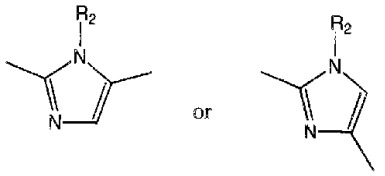
I

or the pharmaceutically acceptable non-toxic salts thereof wherein

T is benzyloxy; or

R_1 and T are the same or different and represent hydrogen, halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms;

M is



where

R_2 is hydrogen or straight or branched chain lower alkyl having 1-6 carbon atoms, or R_1 and R_2 together may represent $-(CH_2)_{n1}$ where n_1 is 1, 2, or 3;

X and Z are the same or different and represent hydrogen, halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, straight or branched chain lower alkoxy having 1-6 carbon atoms or SO_2R_6 where R_6 is straight or branched chain lower alkyl having 1-6 carbon atoms;

Y is

hydrogen, halogen, amino, methoxy, or straight or branched chain lower alkyl having 1-6 carbon atoms;

R_3 is

hydrogen or straight or branched chain lower alkyl having 1-6 carbon atoms, or R_3 and R_4 together may represent $-(CH_2)_{n2}-$ where n_2 is 3 or 4; and

R_4 is 4-chlorobenzyl; or

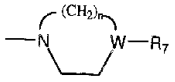
R_4 and R_5 are the same or different and represent

hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, or phenylalkyl or pyridylalkyl where each alkyl is straight or branched chain alkyl having 1-6 carbon atoms; or

R_2 and R_5 together may represent $-(CH_2)n_3-$ where n_3 is 2 or 3; or

NR_4R_5 represents

2-(1,2,3,4-tetrahydroisoquinolinyl), or 2-(1,2,3,4-tetrahydroiso-quinolinyl) mono or disubstituted with halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms; or



where

W is N or CH;

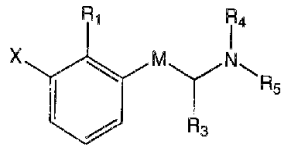
R_7 is hydrogen, phenyl, pyridyl, pyrimidinyl or benzyl, or

phenyl, pyridyl or pyrimidinyl, each of which is mono or disubstituted with halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms; or

$W-R_7$ is oxygen or sulfur; and

n is 1, 2, or 3.

3. The use according to claim 2, where formula I is:

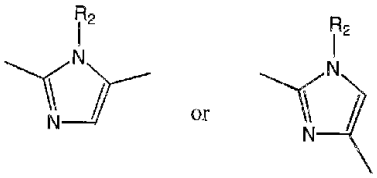


wherein

R_1 is

hydrogen, halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms;

M is



where

R_2 is

hydrogen or straight or branched chain lower alkyl having 1-6 carbon atoms, or R_1 and R_2 together may represent $-(CH_2)n_1$ where n_1 is 1, 2, or 3;

X is

hydrogen, halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, straight or branched chain lower alkoxy having 1-6 carbon atoms or SO_2R_6 where R_6 is straight or branched chain lower alkyl having 1-6 carbon atoms;

R_3 is

hydrogen or straight or branched chain lower alkyl having 1-6 carbon atoms, or R_3 and R_4 together may represent $-(CH_2)n_2-$ where n_2 is 3 or 4; and

R_4 and R_5 are

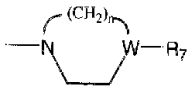
the same or different and represent hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, phenylalkyl or pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1-6 carbon atoms; or

R_2 and R_5 together may represent $-(CH_2)n_3-$ where n_3 is 2 or 3; or

NR_4R_5 represents

2-(1,2,3,4-tetrahydroisoquinolinyl) or 2-(1,2,3,4-tetrahydroiso-quinolinyl) mono or disubstituted with halogen, hydroxy, straight or branched chain

lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms; or



where

W is N or CH;

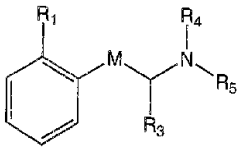
R_7 is

hydrogen, phenyl, pyridyl, or pyrimidinyl, or phenyl, pyridyl or pyrimidinyl, each of which is mono or disubstituted with halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms; or

$W-R_7$ is oxygen or sulfur; and

n is 1, 2, or 3.

4. The use according to claim 2, where formula I is:

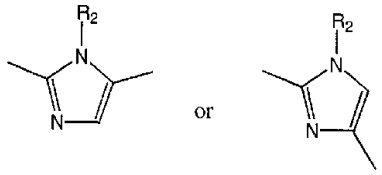


wherein

R_1 is

hydrogen, halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms;

M is



where

R_2 is

hydrogen or straight or branched chain lower alkyl having 1-6 carbon atoms, or R_1 and R_2 together may represent $-(CH_2)n_1$ where n_1 is 1, 2, or 3;

R_3 is

hydrogen, or straight or branched chain lower alkyl having 1-6 carbon atoms, or R_3 and R_4 together may represent $-(CH_2)n_2-$ where n_2 is 3 or 4; and

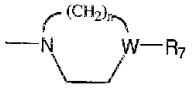
R_4 and R_5 are

the same or different and represent hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, phenyl straight or branched chain lower alkyl having 1-6 carbon atoms; or

R_2 and R_5 together may represent $-(CH_2)n_3-$ where n_3 is 2 or 3; or

NR_4R_5 represents

2-(1,2,3,4-tetrahydrosoquinolinyl), or 2-(1,2,3,4-tetrahydroiso-quinolinyl) monc or disubstituted with halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms; or



where

W is N or CH;

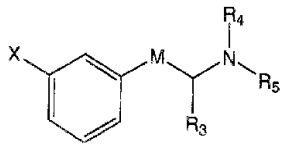
R_7 is

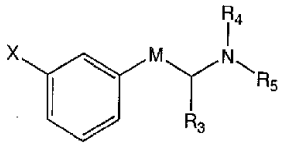
hydrogen, phenyl, pyridyl, or pyrimidinyl, or phenyl, phenyl, pyridyl or pyrimidinyl, each of which is mono or disubstituted with halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms; or

$W-R_7$ is oxygen or sulfur; and

n is 1, 2, or 3.

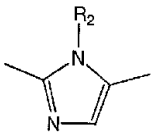
5. The use according to claim 2, where formula I is:



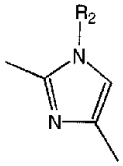


wherein

M is



or



where

R_2 is

hydrogen or straight or branched chain lower alkyl having 1-6 carbon atoms, or R_1 and R_2 together may represent $-(CH_2)n_1$ where n_1 is 1, 2, or 3;

X is

hydrogen, halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, straight or branched chain lower alkoxy having 1-6 carbon atoms, or SO_2R_6 where R_6 is straight or branched chain lower alkyl having 1-6 carbon atoms;

R_3 is

hydrogen, or straight or branched chain lower alkyl having 1-6 carbon atoms, or R_3 and R_4 together may represent $-(CH_2)n_2-$ where n_2 is 3 or 4; or

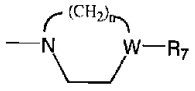
R_4 and R_5 are

The same or different and represent hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, phenylalkyl or pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1-6 carbon atoms; or

R_2 and R_5 together may represent $-(CH_2)n_3-$ where n_3 is 2 or 3; or

NR_4R_5 represents

2-(1,2,3,4-tetrahydrosoquinolinyl), or 2-(1,2,3,4-tetrahydroiso-quinolinyl) mono or disubstituted with halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms; or



where

W is N or CH;

R_7 is

hydrogen, phenyl, pyridyl, or pyrimidinyl, or phenyl, phenyl, pyridyl or pyrimidinyl, each of which is mono or disubstituted with halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms; or

$W-R_7$ is oxygen or sulfur; and

6. The use according to claim 2 wherein the compound of formula I is 2-(5-Bromo-2-methoxyphenyl)-4(5)-[(N,N-dimethyl)aminomethyl]-imidazole dihydrochloride.

7. The use according to claim 2 wherein the compound of formula I is 2-Phenyl-4(5)-[(N,N-dimethyl)aminomethyl]-imidazole dihydrochloride.

8. The use according to claim 2 wherein the compound of formula I is 2-Phenyl-4(5)-(piperidinomethyl)-imidazole dihydrochloride.

9. The use according to claim 2 wherein the compound of formula I is 2-Phenyl-4(5)-[(N-methyl-N-benzyl)aminomethyl]-imidazole dihydrochloride.

10. The use according to claim 2 wherein the compound of formula I is 2-(2-Methoxyphenyl)-4(5)-[(N,N-dimethyl)aminomethyl]-imidazole dihydrochloride.

11. The use according to claim 2 wherein the compound of formula I is 2-(3-Methoxyphenyl)-4(5)-[(N-methyl-N-benzyl)aminomethyl]-imidazole dihydrochloride.

12. The use according to claim 2 wherein the compound of formula I is 2-(2,3-Dimethoxyphenyl)-4(5)-[(N,N-dimethyl)aminomethyl]-imidazole dihydrochloride.

13. The use according to claim 2 wherein the compound of formula I is 2-(2,3-Dimethoxyphenyl)-4(5)[(N-methyl-N-benzyl)aminomethyl]-imidazole dihydrochloride.

14. The use according to claim 2 wherein the compound of formula I is 2-(3-Methoxyphenyl)-4(5)-[(N,N-diethyl)aminomethyl]-imidazole dihydrochloride.

15. The use according to claim 2 wherein the compound of formula I is 2-(3-Fluorophenyl)-4(5)-[(N,N-dimethyl)aminomethyl]-imidazole dihydrochloride.

16. The use according to claim 2 wherein the compound of formula I is 2-(2-Fluorophenyl)-4(5)-[(N-methyl-N-benzyl)aminomethyl]-imidazole dihydrochloride.

17. The use according to claim 2 wherein the compound of formula I is 2-(3-Methylphenyl)-4(5)-[(N,N-dimethyl)aminomethyl]-imidazole dihydrochloride.

18. The use according to claim 2 wherein the compound of formula I is 2-(2-Fluorophenyl)-4(5)-[(N,N-dimethyl)aminomethyl]-imidazole dihydrochloride.

19. The use according to claim 2 wherein the compound of formula I is 2-(4-Fluorophenyl)-4(5)-[(N-methyl-N-benzyl)aminomethyl]-imidazole dihydrochloride.

20. The use according to claim 2 wherein the compound of formula I is 2-(2-Methoxyphenyl)-4(5)-[(N-methyl-N-benzyl)aminomethyl]-imidazole dihydrochloride.

21. The use according to claim 2 wherein the compound of formula I is 2-(5-Bromo-2,3-dimethoxyphenyl)-4(5)-[N,N-dimethyl)aminomethyl]-imidazole dihydrochloride.

22. The use according to claim 2 wherein the compound of formula I is 2-(5-Bromo-2-methoxyphenyl)-4(5)-[(N-methyl-N-benzyl)aminomethyl]-imidazole dihydrochloride.

23. The use according to claim 2 wherein the compound of formula I is 2-(5-Bromo-2,3-dimethoxyphenyl)-4(5)-[(N-methyl-N-benzyl)aminomethyl]-imidazole dihydrochloride.

24. The use according to claim 2 wherein the compound of formula I is 2-Phenyl-4(5)-[(4-(2-methoxyphenyl)-piperazin-1-yl)-methyl]-imidazole.

25. The use according to claim 2 wherein the compound of formula I is 2-(4-Fluorophenyl)-4(5)-[(4-(2-methoxyphenyl)-piperazin-1-yl)-methyl]-imidazole.

26. The use according to claim 2 wherein the compound of formula I is 2-(2,3-Dimethoxyphenyl)-4(5)-[(4-(2-methoxyphenyl)-piperazin-1-yl)-imidazole dihydrochloride.

27. The use according to claim 2 wherein the compound of formula I is 2-(3-Chlorophenyl)-4(5)-[(4-(2-methoxyphenyl)-piperazin-1-yl)-methyl]-imidazole dihydrocloride.

28. The use according to claim 2 wherein the compound of formula I is 2-Phenyl-4(5)-[(4-(2-pyrimidinyl)-piperazin-1-yl)-methyl]-imidazole dihydrochloride.

29. The use according to claim 2 wherein the compound of formula I is 2-Phenyl-4(5)-[4-(2-pyridyl)-piperazin-1-yl)-methyl]-imidazole dihydrochloride.

30. The use according to claim 2 wherein the compound of formula I is 2-Phenyl-4(5)-[(4-benzyl-piperidin-1-yl)-methyl]-imidazole dihydrochloride.

31. The use according to claim 2 wherein the compound of formula I is 2-Phenyl-4(5)-[(4-phenyl-piperidin-1-yl)-methyl]-imidazole dihydrochloride.

32. The use according to claim 2 wherein the compound of formula I is 2-Phenyl-4(5)-[(1,2,3,4-tetrahydroisoquinolin)-2-yl-methyl]-imidazole dihydrochloride.

33. The use according to claim 2 wherein the compound of formula I is 2-(2,3-Dimethoxyphenyl)-4(5)-[(1,2,3,4-tetrahydroisoquinolin)-2-yl-methyl]-imidazole dihydrochloride.

34. The use according to claim 2 wherein the compound of formula I is 2-(4-Methoxyphenyl)-4(5)-[(N-methyl-N-benzyl)aminomethyl]-imidazole dihydrochloride.

35. The use according to claim 2 wherein the compound of formula I is 2-(3,4-Dimethoxyphenyl)-4(5)-[(N-methyl-N-benzyl)aminomethyl]-imidazole dihydrochloride.

36. The use according to claim 2 wherein the compound of formula I is 2-(3-Methoxyphenyl)-4(5)-[(N-methyl)aminomethyl]-imidazole dihydrochloride.

37. The use according to claim 2 wherein the compound of formula I is 2-(5-Chloro-2-methoxyphenyl)-4(5)H-[(N-methyl-N-benzyl)aminomethyl]-imidazole.

38. The use according to claim 2 wherein the compound of formula I is 2-(5-Chloro-2-methoxyphenyl)-4(5)-[(N,N-dimethyl)aminomethyl]-imidazole dihydrochloride.

39. The use according to claim 2 wherein the compound of formula I is 2-(5-Chloro-2-methoxyphenyl)-4(5)-[(N-methyl)aminomethyl]-imidazole dihydrochloride.

40. The use according to claim 2 wherein the compound of formula I is 2-(5-Chloro-2-methoxyphenyl)-4(5)-[(N-benzyl)aminomethyl]-imidazole dihydrochloride.

41. The use according to claim 2 wherein the compound of formula I is 2-(5-Chloro-2-benzyloxyphenyl)-4(5)-[(N-methyl-N-benzyl)aminomethyl]-imidazole dihydrochloride.

42. The use according to claim 2 wherein the compound of formula I is 2-(2-Benzyloxyphenyl)-4(5)-[(N-methyl-N-benzyl)aminomethyl]-imidazole dihydrochloride.

43. The use according to claim 2 wherein the compound of formula I is 2-(3-Ethylphenyl)-4(5)-[(N-methyl-N-benzyl)aminomethyl]-imidazole dihydrochloride.

44. The use according to claim 2 wherein the compound of formula I is 2-(5-Chloro-2-methoxyphenyl)-4(5)-[(N-methyl-N-(4-chlorobenzyl)aminomethyl]-imidazole dihydrochloride.

45. The use according to claim 2 wherein the compound of formula I is 2-(5-Chloro-2-hydroxyphenyl)-4(5)-[(N-methyl-N-benzyl)aminomethyl]-imidazole dihydrochloride.

46. The use according to claim 2 wherein the compound of formula I is 2-(5-Bromo-2-benzyloxyphenyl)-4(5)-[(N-methyl-N-benzyl)aminomethyl]-imidazole dihydrochloride.

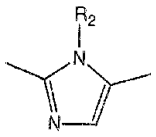
47. The use according to claim 2 wherein the compound of formula I is 2-(5-Ethyl-2-methoxyphenyl)-4(5)-[(N-methyl-N-benzyl)aminomethyl]-imidazole dihydrochloride.

48. The use according to claim 2 wherein the compound of formula I is 2-(5-Chloro-2-methoxyphenyl)-4(5)-[(4-(2-methoxyphenyl)-piperazin-1-yl)-methyl]-imidazole dihydrochloride.

49. The use according to claim 2 wherein the compound of formula I is 2-(5-Chloro-2-methoxyphenyl)-4(5)-[(4-phenyl-piperidin-1-yl)-methyl]-imidazole dihydrochloride.

50. The use according to Claim 2, wherein in the compound of formula I R_1, X, Y, Z and T are hydrogen;

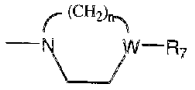
M is



where R_2 is hydrogen;

R_3 is hydrogen;

NR_4R_5 represents



where

W is N or CH;

R_7 is phenyl, pyridyl or pyrimidinyl; and

n is 2.

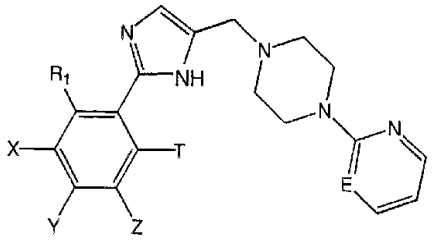
51. The use according to claim 2 wherein the compound of formula I is 2-(2,3-Dimethoxyphenyl)-4(5)-[(4-(2-methoxyphenyl)-piperidin-1-yl)-methyl]-imidazole dihydrochloride.

52. The use according to claim 2 wherein the compound of formula I is 2-phenyl-4(5)-[(4-(2-pyridyl)-piperidin-1-yl)-methyl]-imidazole dihydrochloride.

53. The use according to claim 2 wherein the compound of formula I is 2-phenyl-4(5)-[(4-phenylpiperzin-1-yl)-methyl]imidazole dihydrochloride.

54. The use according to claim 2 wherein the compound of

formula I is:



wherein:

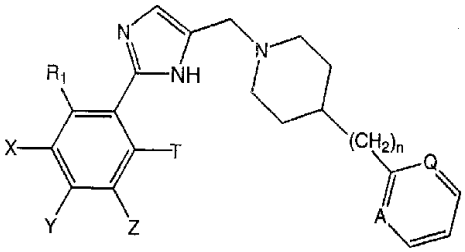
R_1 and T independently represent hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy;

X and Z independently represent hydrogen, halogen, hydroxy, lower alkyl, lower alkoxy, or $-SO_2R_6$ where R_6 is lower alkyl;

Y is hydrogen, halogen or lower alkyl; and

E is CH or nitrogen.

55. The use according to Claim 2, wherein the compound of formula I is:



wherein:

R_1 and T independently represent hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy;

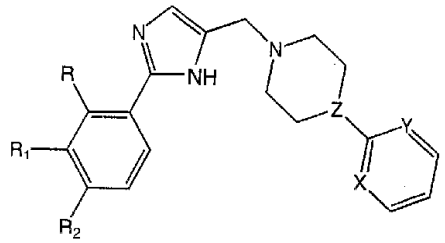
X and Z independently represent hydrogen, halogen, hydroxy, lower alkyl, lower alkoxy, or $-SO_2R_6$ where R_6 is lower alkyl;

Y is hydrogen, halogen, amino, or lower alkyl;

n is 0 or 1; and

A and Q are the same or different and represent CH or nitrogen.

56. The use according to Claim 2, wherein the compound of formula I is:



or the pharmaceutically acceptable salts thereof, wherein:

R represents hydrogen or halogen;

R_1 represents hydrogen, halogen, or straight or branched chain lower alkoxy having 1-6 carbon atoms;

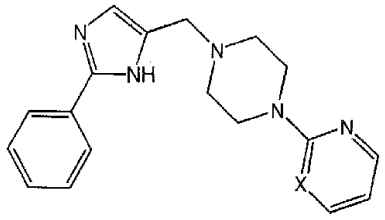
R_2 represents hydrogen or straight or branched chain lower alkoxy having 1-6 carbon atoms;

Z is nitrogen or CH;

X is nitrogen or CH; and

Y is nitrogen or CR_4 where R_4 represents hydrogen or straight or branched chain lower alkoxy having 1-6 carbon atoms.

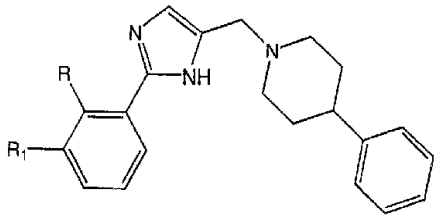
57. The use according to Claim 2, wherein the compound of formula I is:



wherein:

X is nitrogen or CH.

58. The use according to Claim 2, wherein the compound of formula I is:



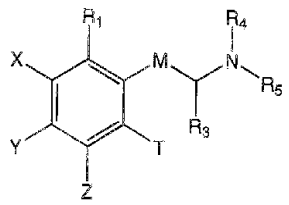
wherein:

R represents hydrogen or halogen; and

R_1 represents hydrogen, halogen, or straight or branched chain lower alkoxy having 1-6 carbon atoms.

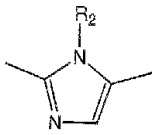
59. The use of a compound of formula I in the preparation of

a medicament for the enhancement of memory where formula I is:



wherein R1, X, Y, Z and T are hydrogen;

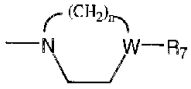
M is



where R_2 is hydrogen;

R_3 is hydrogen;

NR_4R_5 represents



where

W is N or CH;

n is 2; and

R_7 is phenyl, pyridyl, or pyrimidinyl.

60. A compound which is 2-(2,3-Dimethoxyphenyl)-4(5)-[(4-(2-methoxyphenyl)-piperidin-1-yl)-methyl]-imidazole dihydrochloride.

61. A compound which is 2-phenyl-4(5)-[(4-(2-pyridyl)-piperdin-1-yl)-methyl]-imidazole dihydrochloride.

62. A compound which is 2-phenyl-4(5)-[(4-phenyl-piperazin-1-yl)-methyl]-imidazole dihydrochloride.

63. A compound according to claim 1, substantially as hereinbefore described with reference to the examples.

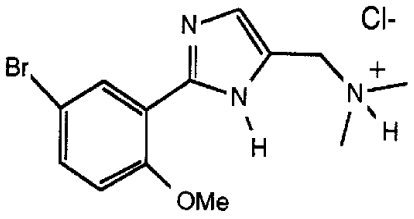
64. A use according to claim 2 substantially as hereinbefore described with reference to the examples.

Neurogen Corporation

By its Registered Patent Attorneys

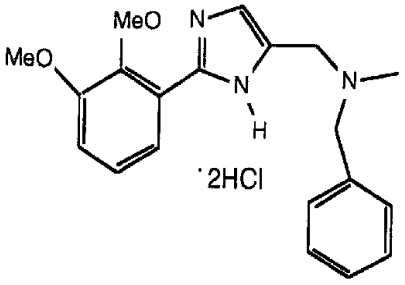
Freehills Patent Attorneys 19 March 1999

Fig. 1A



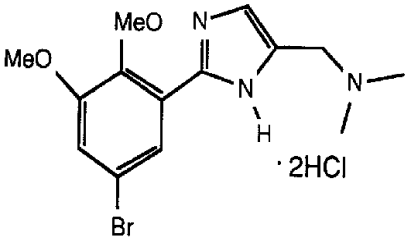
Compound 1

Fig. 1B



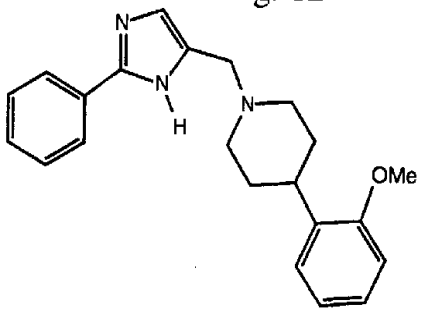
Compound 8

Fig. 1C



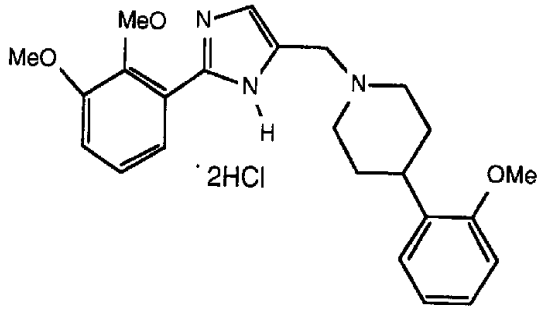
Compound 16

Fig. 1D



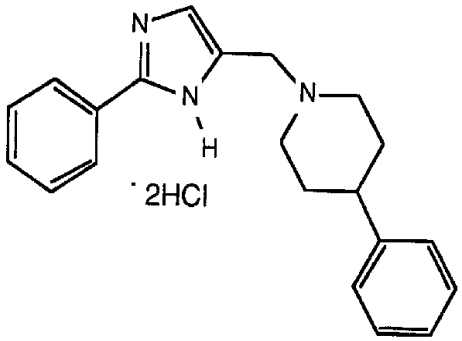
Compound 19

Fig. 1E



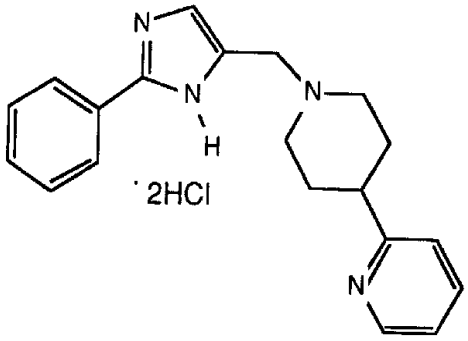
Compound 21

Fig 1F



Compound 26

Fig 1G



Compound 46