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614282

$ 515 ATTACHED
MAIL OFFICER

(1) Here insert (in full) Name or Names of Applicant or Applicants, followed by Address (es).

IXX (1) SYNTEX PHARMACEUTICALS LTD.,
We
of Syntex House, St. Ives Road,
Maidenhead, Berkshire SL6 IRD,
England.

(2) Here insert Title of Invention.

hereby apply for the grant of a Patent for an invention entitled: (2)
SUBSTITUTED IMIDAZOLYL-ALKYL-PIPERAZINE AND
DIAZEPINE DERIVATIVES.

(3) Here insert number(s) of basic application(s)

which is described in the accompanying complete specification. This application is a Convention application and is based on the application numbered (3)
042,181

(4) Here insert Name of basic Country or Countries, and basic date or dates

for a patent or similar protection made in (4) United States of America on 24th April, 1987.

LODGED AT SUB-OFFICE
22 APR 1988
Melbourne

Mx/Our address for service is Messrs. Edwd. Waters & Sons, Patent Attorneys, 50 Queen Street, Melbourne, Victoria, Australia.

DATED this 21st day of April, 1988

(5) Signature (s) of Applicant (s) or Seal of Company and Signatures of its Officers as prescribed by its Articles of Association

(5)

SYNTEX PHARMACEUTICALS LTD.

By: [signature]

IAN A. SCOTT

Registered Patent Attorney

To:

THE COMMISSIONER OF PATENTS.

Edwd. Waters & Sons, Melbourne

COMMONWEALTH OF AUSTRALIA

Patents Act 1952-1969

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT OR PATENT OF ADDITION

(1) Here insert (in full) Name of Company.

In support of the Convention Application made by[1] Syntex Pharmaceuticals Ltd

(hereinafter referred to as the applicant) for a Patent

(2) Here insert title of Invention.

for an invention entitled:[2] Substituted Imidazolyl-Alkyl-Piperazine and -Diazepine Derivatives

(3) Here insert full Name and Address, of Company official authorized to make declaration.

I,[3] Calum Brechin Macfarlane

of Syntex House, St. Ives road, Maidenhead, Berkshire SL6 1RD, England

do solemnly and sincerely declare as follows:

1. I am authorised by the applicant for the patent to make this declaration on its behalf.

(4) Here insert basic Country or Countries followed by date or dates and basic Applicant or Applicants.

2. The basic application as defined by Section 141 of the Act was made in[4] the United States of America on the 24 day of April 1987, by Jean-Claude Pascal, Chi-Ho Lee, Brian J. Alps, Henri Pinhas, and Roger L. Whiting and Serge Beranger ~~on the xxxx day of xxxxxxxx by~~

(5) Here insert (in full) Name and Address of Actual Inventor or Inventors.

3.[5] The said Jean-Claude Pascal, 23-25 Allee des Hautes Bruyeres, 94230 Cachan, France; Chi-Ho Lee, 3758 La Donna Street, Palo Alto, California 94306, U.S.A.; Brian J. Alps, 2 St. Ninians Avenue, Linlithgow, Scotland; Henri Pinhas, 39, rue Truffaut, 75017 Paris, France; Roger L. Whiting, 1848 Fallenleaf Lane, Los Altos, California 94022, U.S.A.; Serge Beranger, 12 Allee des Cedres, 91120 Bretigny-sur-Orge, France

~~is~~/are the actual inventor s of the invention and the facts upon which the applicant is entitled to make the application are as follow:

The applicant is the assignee of Jean-Claude Pascal, Chi-Ho Lee, Brian J. Alps, Henri Pinhas, and Roger L. Whiting and Serge Beranger

4. The basic application referred to in paragraph 2 of this Declaration was the first application made in a Convention country in respect of the invention the subject of the application.

DECLARED at Edinburgh

this FOURTEENTH day of APRIL 1988

(6) Signature.

(6) C.B. Macfarlane

To: THE COMMISSIONER OF PATENTS.

DR. C. B. MACFARLANE
Director
Syntex Pharmaceuticals Ltd.

Edwd. Waters & Sons, Melbourne.

(12) PATENT ABRIDGMENT (11) Document No. AU-B-15102/88
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 614282

(54) Title
SUBSTITUTED IMIDAZOLYL-ALKYL-PIPERAZINE AND DIAZEPINE DERIVATIVES

International Patent Classification(s)
(51)[4] C07D 233/64 A61K 031/55 C07D 403/06 A61K 031/495

(21) Application No. : 15102/88 (22) Application Date : 22.04.88

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(31) Number (32) Date (33) Country
042181 24.04.87 US UNITED STATES OF AMERICA

(43) Publication Date : 27.10.88

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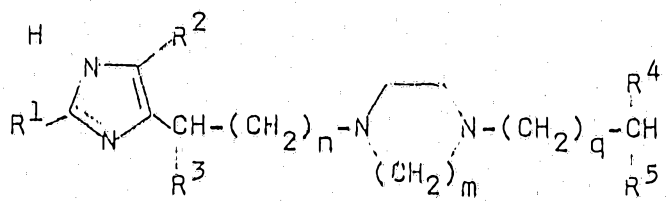
(71) Applicant(s)
SYNTEX PHARMACEUTICALS LTD.

(72) Inventor(s)
JEAN-CLAUDE PASCAL; CHI-HO LEE; BRIAN J. ALPS; HENRI PINHAS; ROGER L. WHITING; SERGE BERANGER

(74) Attorney or Agent
WATERMARK PATENT & TRADEMARK ATTORNEYS , Locked Bag 5, HAWTHORN VIC 3122

(57) Claim

1. A compound having the structure represented by the formula:



wherein:

R^1 is aryl;

R^2 is aryl, lower alkyl, or hydrogen;

R^3 is lower alkyl, hydroxy, or hydrogen;

R^4 is aryl;

R^5 is aryl;

m is two or three;

n is zero, one or two,

provided that when R^3 is hydroxy, n is one or two; and

q is zero, one, two, or three;

or a pharmaceutically acceptable salt thereof.

.../2

14. A method of treating a mammal for a disease state requiring protective activity against deleterious effects resultant upon cerebral ischemia including stroke, epilepsy or epileptic psychotic symptoms, hypertension, angina, migraine, arrhythmia, thrombosis, ambolism, acute cardiac failure, irritable bowel syndrome, neurodegenerative diseases such as Alzheimer's or Huntington's chorea, diuresis, ischemia such as focal and global ischemia or cerebrovascular ischemia induced by cocaine abuse, or spinal injury, said method comprising administering a therapeutically effective amount of the compound of Claim 1 to the mammal.

614282

Form 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-69

COMPLETE SPECIFICATION

(ORIGINAL)

Class Int. Class

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority :

Related Art :

Name of Applicant : SYNTEX PHARMACEUTICALS LTD.

Address of Applicant : Syntex House, St. Ives Road, Maidenhead, Berkshire SL6 IRD England.

Actual Inventor: JEAN-CLAUDE PASCAL, CHI-HO LEE, BRIAN J. ALPS, HENRI PINHAS and ROGER L. WHITING. SERGE BERANGER

Address for Service : EDWD. WATERS & SONS,
50 QUEEN STREET, MELBOURNE, AUSTRALIA, 3000.

Complete Specification for the invention entitled:

SUBSTITUTED IMADAZOLYL-ALKYL-PIPERAZINE AND -DIAZEPINE DERIVATIVES

The following statement is a full description of this invention, including the best method of performing it known to :- US

SUBSTITUTED IMIDAZOLYL-ALKYL-PIPERAZINE AND -DIAZEPINE DERIVATIVES

BACKGROUND OF THE INVENTION

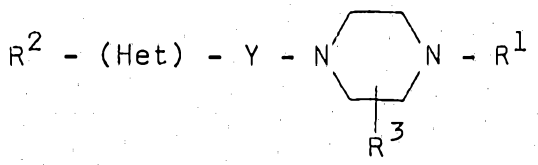
Field of the Invention

This invention relates to substituted imidazolyl-alkyl-piperazine and diazepine derivatives, the pharmaceutically acceptable salts thereof, methods of making these compounds, and pharmaceutical compositions containing these compounds. The compounds of this invention are calcium entry blockers having selectivity for cerebral blood vessels, and have protective activity against some of the deleterious effects resultant upon cerebral ischemia. The compounds of this invention are, therefore, useful for treating mammals having a variety of disease states, such as stroke, epilepsy or epileptic psychotic symptoms, hypertension, angina, migraine, arrhythmia, thrombosis, embolism, acute cardiac failure, irritable bowel syndrome, neurodegenerative diseases such as Alzheimer's or Huntington's chorea, diuresis, ischemia such as focal and global ischemia or cerebrovascular ischemia induced by cocaine abuse, and also for treatment of spinal injuries.

Background Information and Related Art

Substituted piperazines have been described as having a variety of pharmaceutical activities.

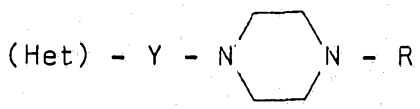
For example, U.S. Patent No. 3,362,956 and its CIP 3,491,098, disclose a series of substituted piperazines to be useful as tranquilizers, sedatives, adrenolytic agents, hypothermic agents, anti-convulsants, hypotensive agents and cardiovascular agents. For example, in the '956 patent, compounds of the formula



wherein R^1 is a lower-alkyl, hydroxy-lower alkyl, phenyl or substituted-phenyl, phenyl-lower-alkyl, or substituted-phenyl-lower-alkyl, benzhydryl or substituted benzhydryl, phenyl-lower-alkenyl or substituted-phenyl-lower-alkenyl, or pyridyl radical; R^2 is hydrogen or from one to two lower-alkyl radicals; Y is lower-alkylene of from one to six carbon atoms; and Het is a heterocyclic radical selected from the group consisting of bicyclic aromatic nitrogen heterocyclic radicals having fused five and six membered rings and containing from two to three ring nitrogen atoms which can be in any position of the two rings, for example, radicals derived from indazole (e.g. 2-azaindole, 4-azaindole, 5-azaindole, 6-azaindole, 7-azaindole), pyrrolo[2,3-d]-pyrimidine, benzimidazole and pyrido[2,1-c]-s-triazole; a benz[g]-3-indolyl radical; a 4(5)-imidazolyl radical; a 3-thianaphthenyl radical; a 3-quinolyl radical; a 3,4-dihydro-1-isoquinolyl radical; or 1,2,3,4-tetrahydro-1-isoquinolyl radical or such heterocyclic radicals substituted in any available

position by from one to three substituents, defined hereinafter as R^2, for example, methyl, ethyl, propyl, and isobutyl; lower-alkoxy, for example, methoxy, ethoxy, propoxy, and butoxy; halogen, including fluorine, chlorine, bromine, and iodine; lower-alkylmercapto, for example, methylmercapto, ethylmercapto, propylmercapto, and isobutylmercapto; lower-alkylsulfinyl, for example, methylsulfinyl, ethylsulfinyl, propylsulfinyl, and isobutylsulfinyl; lower-alkylsulfonyl, for example, methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl; trifluoromethyl; hydroxy; methylenedioxy; or ethylenedioxy, wherein the lower-alkyl moiety of the said substituents contain from one to four carbon atoms; are disclosed.

In the '098 patent compounds of the formula



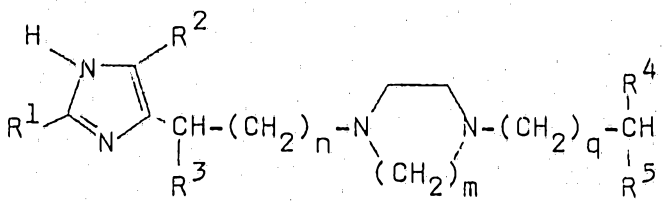
wherein R is hydrogen or a lower-alkyl, hydroxy-lower-alkyl, phenyl, phenyl-lower-alkyl, benzhydryl, phenyl-lower-alkenyl, cycloalkyl-lower-alkyl, or pyridyl radical; Y is lower-alkylene of from one to six carbon atoms; and Het is a 4(5)-imidazolyl radical; are disclosed.

None of the prior art teaches 4(5)-imdazolyl-substituted piperazine or diazepine derivatives substituted in the manner of this invention which are useful for treating mammals having a variety of disease states, such as stroke, epilepsy or epileptic psychotic symptoms, hypertension, angina, migraine, arrhythmia, thrombosis, embolism, acute cardiac failure, irritable bowel syndrome, neurodegenerative diseases such as Alzheimer's or Huntington's chorea, diuresis, ischemia

such as focal and global ischemia or cerebrovascular ischemia induced by cocaine abuse, and also for treatment of spinal injuries.

SUMMARY OF THE INVENTION

A first aspect of this invention encompasses compounds having the structures represented by Formula A:



FORMULA A

wherein:

R^1 is aryl;

R^2 is aryl, lower alkyl, or hydrogen;

R^3 is lower alkyl, hydroxy, or hydrogen;

R^4 is aryl;

R^5 is aryl;

m is two or three;

n is zero, one or two,

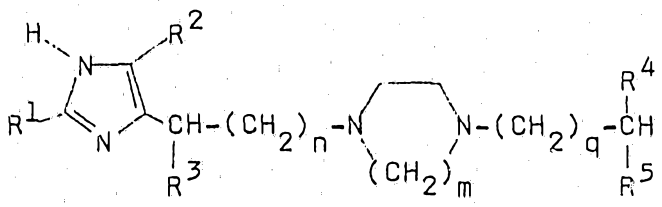
provided that when R^3 is hydroxy, n is one or two; and

q is zero, one, two, or three;

and the pharmaceutically acceptable salts thereof.

A further aspect of the present invention

encompasses methods of making compounds of Formula A



FORMULA A

wherein:

R^1 is aryl;

R^2 is aryl, lower alkyl, or hydrogen;

R^3 is lower alkyl, hydroxy, or hydrogen;

R^4 is aryl;

R^5 is aryl;

m is two or three;

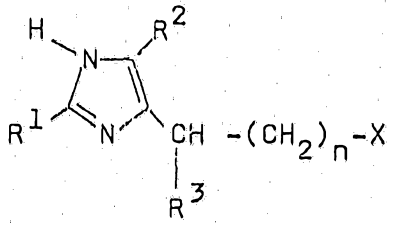
n is zero, one or two,

provided that when R^3 is hydroxy, n is one or two; and

q is zero, one, two, or three;

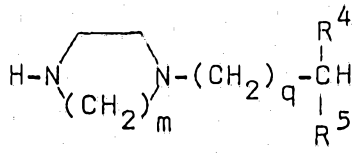
and the pharmaceutically acceptable salts thereof, which comprises

(a) condensing a compound of the formula



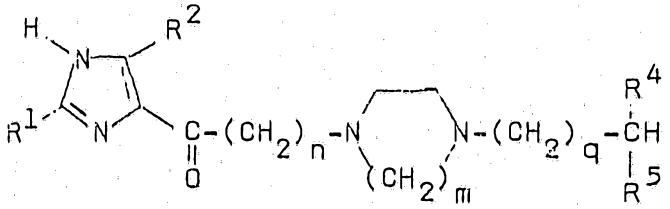
wherein n, R^1 and R^2 are as defined above, R^3 is hydrogen or lower alkyl, and X is a halogen atom,

with a compound of the formula



wherein m, q, R^4 and R^5 are as defined above; or

b) reducing a compound of the formula



wherein R^1, R^2, R^4, R^5, m, and q are as defined above and n is one or two, to form a compound of formula A wherein R^3 is hydroxy; or

c) converting a free base compound of formula A to its acid addition salt; or

d) converting an acid addition salt of a compound of formula A to a free base compound of formula A; or

e) converting an acid addition salt of a compound of formula A to another acid addition salt of a compound of formula A.

A still further aspect of the present invention encompasses methods of treating a mammals having a variety of disease states, such as stroke, epilepsy or

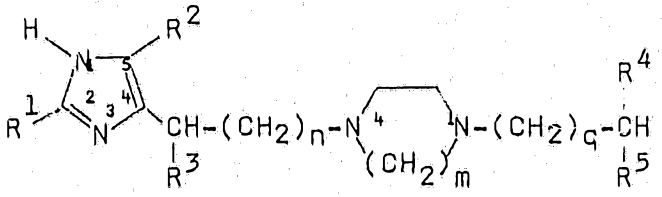
epileptic psychotic symptoms, hypertension, angina, migraine, arrhythmia, thrombosis, embolism, acute cardiac failure, irritable bowel syndrome, neurodegenerative diseases such as Alzheimer's or Huntington's chorea, diuresis, ischemia such as focal and global ischemia or cerebrovascular ischemia induced by cocaine abuse, and also for treatment of spinal injuries, comprising administering a therapeutically effective amount of compound of Formula A to a mammal.

Another aspect of the present invention encompasses pharmaceutical formulations comprising a compound of Formula A and a pharmaceutically acceptable excipient.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The numbering of the piperazines and diazepines of the present invention is as follows:



The compounds of the invention will be named using the above-shown numbering system as 1-[di-aryl]-alkyl-4-[(2- and/or 5-substituted- imidazolyl)-optionally-substituted-alkyl]-piperazines and -diazepines. Some representative compounds are named as follows:

the compound of Formula A where R^1 is 4-methylphenyl, R^2 is methyl, R^3 is hydrogen, R^4 is phenyl, R^5 is phenyl, m is 2, n is 0 and q is 0, is named "1-diphenylmethyl-4-[(2-(4-methyl-phenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine";

the compound of Formula A where R^1 is 4-methylphenyl, R^2 is hydrogen, R^3 is hydrogen, R^4 is phenyl, R^5 is phenyl, m is 2, n is 0, and q is 0, is named "1-dihpenylmethyl-4-[(2-(4-methylphenyl)-1H-imidazol-4-yl)methyl]piperazine";

the compound of Formula A where R^1 is phenyl, R^2 is methyl, R^3 is methyl, R^4 is phenyl, R^5 is phenyl, m is 2, n is 0 and q is 0, is named "1-diphenylmethyl-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine";

the compound of Formula A where R^1 is phenyl, R^2 is methyl, R^3 is hydroxy, R^4 is phenyl, R^5 is phenyl, m is 2, n is 1 and q is 0, is named "1-diphenylmethyl-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine";

the compound of Formula A where R^1 is phenyl, R^2 is methyl, R^3 is hydrogen, R^4 is 4-fluorophenyl, R^5 is 4-fluorophenyl, m is 2, n is 0 and q is 3, is named "1-[4,4-di-(4-fluorophenyl)-butyl]-4-[(2-phenyl-5-methyl-1H-imidazol-4-yl)-methyl]piperazine"; and

the compound of Formula A where R^1 is 2,4-dihydroxyphenyl, R^2 is methyl, R^3 is hydrogen, R^4 is phenyl, R^5 is phenyl, m is 3, n is 0 and q is 0, is named "1-diphenylmethyl-4-[(2-(2,4-dihydroxyphenyl)-5-methyl-1H-imidazol-4-yl)-methyl]diazepine".

Compounds of the invention where R^3 is lower alkyl or hydroxy, and/or where R^4 and R^5 are different will have one or two chiral centers and may display optical activity. The optical isomers may be separated using conventional methods. For purposes of the present invention, any compound having optical activity shall include each individual isomer as well as mixtures thereof.

As used herein, the term "alkyl" means a branched or unbranched saturated hydrocarbon radical having from 1 to 6 carbon atoms. Examples include methyl, ethyl, n-propyl, iso-propyl, n-butyl, t-butyl, n-pentyl, iso-pentyl, n-hexyl, and the like.

As used herein, the term "alkoxy" means the group -OR wherein R is alkyl as defined above. Examples include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, t-butoxy, n-pentyloxy, n-hexyloxy, and the like.

As used herein, the term "lower" modifies alkyl and alkoxy and refers to those radicals having four carbon atoms or less.

As used herein, the term "halo" means fluoro, chloro, bromo and/or iodo.

As used herein, the term "aryl" refers to phenyl and optionally mono-, di-, and tri-substituted phenyl, wherein the optional substituents are lower alkyl, lower alkoxy, hydroxy, trifluoromethyl, or halo. Examples include 3-chlorophenyl, 3-trifluoromethylphenyl, 4-methoxyphenyl, 4-chlorophenyl, 3,4-dimethoxyphenyl, 4-hydroxyphenyl, 4-methylphenyl, 3-t-butylphenyl, 4-hexylphenyl, and the like.

As used herein, the term "treatment" or "treating" means any treatment of a disease in a mammal, and includes:

(i) preventing the disease, i.e., causing the clinical symptoms of the disease not to develop;

(ii) inhibiting the disease, i.e., arresting the development of clinical symptoms; and/or

(iii) relieving the disease, i.e., causing the regression of clinical symptoms.

As used herein, the terms "pharmaceutically acceptable salts" refers to those salts that retain biological effectiveness and properties of the neutral parent compounds and which are not biologically or

otherwise undesirable. Pharmaceutically acceptable acid addition salts may be formed with inorganic acids, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, and with organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, lactic acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, para-toluenesulfonic acid, salicylic acid, and the like. The salts may be single or multiple salts of one or more anions, e.g., the mono-, di-, or tri- salts from the above-described acids.

Presently Preferred Embodiments

Presently preferred embodiments of this invention are compounds of Formula A wherein R^1 is aryl; further preferred are the compounds where R^1 is aryl, m is 2; q is 0; n is 0; R^2 is methyl; and R^3 is hydrogen. The pharmaceutically acceptable salts of these compounds are also preferred, especially the mono-, di- and trihydrochlorides, fumarates, and lactates.

Particularly preferred are those compounds where R^1 is 4-methylphenyl or phenyl and R^4 and R^5 are the same, e.g., both phenyl, i.e., 1-(diphenylmethyl)-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]-piperazine and 1-(diphenylmethyl)-4-[(2-phenyl-5-methyl-1H-imidazol-4-yl)methyl]piperazine and the trihydrochloride or trilactate salts thereof.

Other preferred compounds include those where R^1 is aryl; especially those where R^3 is lower alkyl, particularly methyl and isopropyl; m is 2; q is 0; n is 0; and R^1, R^4 and R^5 are all phenyl.

Still other preferred compounds include those where q is 3; n is 0; R^1 is phenyl; R^3 hydrogen; and R^4

and R^5 are both 4-fluorophenyl.

Another preferred compound is that wherein m is 3; q is 0; n is 0; R^1 is phenyl; R^2 [illegible]yl; R^3 is hydrogen; and R^4 and R^5 are both p[illegible]

Utility and Methods of Administration

General Utility

The compounds of this invention are useful for treating mammals having a variety of vascular disease states, and have protective activity against some of the deleterious effects resultant upon cerebral ischemia. Disease states that may be treated include stroke, migraine, epilepsy or epileptic psychotic symptoms, hypertension, angina, arrhythmia, thrombosis, embolism, acute cardiac failure, irritable bowel syndrome, neurodegenerative diseases such as Alzheimer's or Huntington'a chorea, diuresis, ischemia such as focal and global ischemia or cerebrovascular ischemia induced by cocaine abuse. The compounds of this invention are also useful for treating spinal injuries, and are particularly useful for treating cerebrovascular disease states, for example, stroke.

Generally, vascular disease states are found in mammals, including: domestic commercial animals such as horses, cattle, sheep and pigs; domestic house animals such as dogs, cats, and the like; and particularly humans.

Activity Testing

Activity testing for treating stroke, migraine, epilepsy or epileptic psychotic symptoms, hypertension, angina, arrhythmia, thrombosis, embolism, acute cardiac failure, irritable bowel syndrome, neurodegenerative diseases such as Alzheimer's or Huntington'a chorea, diuresis, ischemia such as focal and global ischemia, cerebrovascular ischemia induced by cocaine abuse, or spinal injuries can be undertaken in vitro and/or in vivo

using assay procedures known in the literature. The following are examples of such assay procedures.

Activity for treating vascular disease states can be determined *in vitro* by determining selective vascular relaxant activity, and *in vivo* by determining general cardiovascular activity.

In vitro calcium antagonistic activity of the compounds of this invention is determined by an assay using rat aortic strip, which is a modification of that described by R. Kent, et al., Federation Proceedings, 40, 724 (1981). Cerebrovascular selectivity of action is determined by comparing potencies on rabbit basilar artery and rabbit ear artery using a modification of the procedure described by R. Towart, et al., Arzneim. Forsh., 32(I), 338-346 (1982).

In vivo protective effects of the compounds of this invention against the deleterious effects of cerebral ischemia are determined by use of the standard gerbil brain ischemia model. This assay is a modification of that described by T. Kirino, Brain Res., 239, 57-69P (1982).

General Administration

The compounds of this invention are administered at a therapeutically effective dosage, i.e., a dosage sufficient to provide treatment for the disease states previously described. Administration of the active compounds and salts described herein can be via any of the accepted modes of administration for agents that serve similar utilities.

Generally, a daily dose is from 0.02 to 50 mg/kg of body weight per day of the active compound of Formula A. Most conditions respond to treatment comprising a dosage level on the order of 0.1 to 4 mg/kilogram of body weight per day. Thus, for administration to a 70 kg person, the dosage range would be about 1.4 to 3500 mg per day,

preferably about 7.0 to 280 mg per day.

Depending on the specific disease state, administration can be via any accepted systemic route, for example, via parenteral, oral, intravenous, or nasal routes, in the form of solid, semi-solid or liquid dosage forms, such as for example, tablets, suppositories, pills, capsules, powders, solutions, suspensions, aerosols, emulsions or the like, preferably in unit dosage forms suitable for simple administration of precise dosages. The compositions will include a conventional pharmaceutical carrier or excipient and an active compound of Formula A and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, etc.

If desired, the pharmaceutical composition to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate, etc.

The compounds of this invention are generally administered as a pharmaceutical composition which comprises a pharmaceutical excipient in combination with a compound of Formula A. The level of the drug in a formulation can vary within the full range employed by those skilled in the art, e.g., from about 0.01 weight percent (w%) to about 99.99 w% of the drug based on the total formulation and about 0.01 w% to 99.99 w% excipient.

Oral Administration

The preferred manner of administration, for the conditions detailed above, is oral using a convenient daily dosage regimen which can be adjusted according to the degree of affliction. For such oral administration, a pharmaceutically acceptable, non-toxic composition is formed by the incorporation of the compound of formula A

in any of the normally employed excipients, such as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccarine, talcum, cellulose, glucose, gelatin, sucrose, magnesium carbonate, and the like. Such compositions take the form of solutions, suspensions, tablets, pills, capsules, powders, sustained release formulations and the like. Such compositions may contain between 0.01 wt/% and 99.99 wt/% of the compound of Formula A, but preferably such compositions will contain between 25 wt/% and about 80 wt/%.

Preferably the compositions will take the form of a pill or tablet and thus the composition will contain, along with the active ingredient, a diluent such as lactose, sucrose, dicalcium phosphate, and the like; a disintegrant such as starch or derivatives thereof; a lubricant such as magnesium stearate and the like; and a binder such as a starch, polyvinylpyrrolidone, gum acacia, gelatin, cellulose and derivatives thereof, and the like.

Suppositories

For systemic administration via suppository, traditional binders and carriers include, for example, polyalkaline glycol or triglycerides [e.g., PEG 1000 (96%) and PEG 4000 (4%)]. Such suppositories may be formed from mixtures containing active ingredients in the range of from about 0.5 wt/% to about 10 wt/%; preferably from about 1 wt/% to about 2 wt/%.

Liquids

Liquid pharmaceutically administerable compositions can, for example, be prepared by dissolving, dispersing, etc. an active compound (about 0.5% to about 20%), as described above, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like, to thereby form

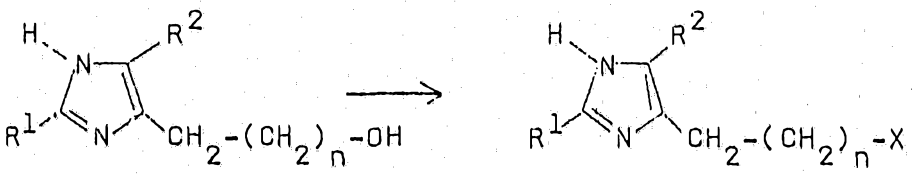
a solution or suspension.

Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania, 16th Ed., 1980. The composition to be administered will, in any event, contain a quantity of the active compound(s) in a pharmaceutically effective amount for relief of the particular condition being treated in accordance with the teachings of this invention.

Methods of Preparation

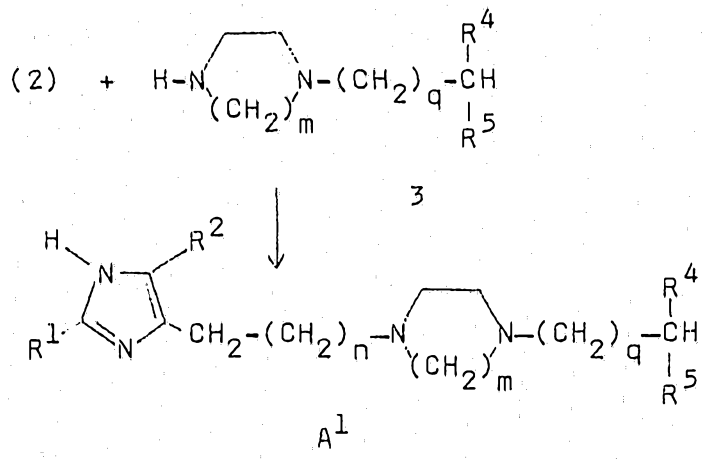
The compounds of this invention can be made as shown in Reaction Schemes I to VI, wherein R^1, R^2, R^3, R^4, and R^5 have the same meaning as set forth above in the Summary Of The Invention, and X is halo.

REACTION SCHEME I



1 2

Step I-A



Step I-B

I. Preparation of Formula A Where R^3 is Hydrogen

Referring to Reaction Scheme I, in Step I-A a mixture of a compound of Formula 1 with an inert hydrocarbon solvent (for example, benzene, toluene, chloroform and the like) is refluxed with a slight excess of a halogenating agent, for example, a thionyl halide (such as thionyl chloride), to produce the corresponding alkyl halide derivative, compound of Formula 2. Compounds of Formula 1 are obtained by reacting the appropriate amidine with the appropriate dione using the procedures of Dziuron and Schunack [Arch. Pharm., 306, 347 (1973) and Arch. Pharm., 307, 46 (1973)] Imbach, et al Bull. Soc. Chim. France, 3 1059 (1971), Cornforth and Huang, J. Chem. Soc., (1948) 731-735, Ewins, J. Chem. Soc., 99 2052 (1911), or U.S. patent 4,107,307. The reaction is conducted at a temperature from about 0°C to the reflux temperature of the solvent, but preferably between about 40°C and 65°C.

In Step I-B, the compound of Formula 2 is condensed with a compound of Formula 3, for example, at a temperature from about 25° to 80°C, preferably at the reflux temperature of the solvent system used.

The 1-substituted piperazines of Formula 3 are commercially available or can be made by the procedures of Hamlin, et al., J. Am. Chem. Soc., 71, 2731 (1949) or Cheeseman, J. Chem Soc., (1975), 115-123. Diazepine analogs (i.e., those compounds where m is 3) can be made by this method using diazepine as the starting material instead of piperazine. An alkaline solution is made by dissolving a compound of Formula 3 in a polar solvent (for example, methanol, ethanol, or a mixture such as ethanol and water, methanol and water, acetone in water, dimethylformamide in water, isopropanol in water, tetrahydrofuran in water; the ratio of from about 10:90 to about 90:10, preferably about 60:40), and adding a base (such as sodium hydroxide, potassium hydroxide, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, and the like). The alkaline solution is heated to reflux.

A solution of the compound of Formula 2 dissolved in the same polar solvent is added dropwise to the refluxing solution of the compound of Formula 3. After about 1 to 24 hours, preferably about 2 to 5 hours, the condensed product of Formula A^1 is separated from the reaction mixture either by precipitation or evaporation under reduced pressure. The reaction mixture is allowed to stand at room temperature, for example, for about 8 to 24 hours, preferably overnight. If the product precipitated, the resulting crystals are removed by filtration and recrystallized in an alcohol, preferably methanol or ethanol giving the free base of Formula A^1. If the product is an oil, the oil is washed with water and dissolved in diethyl ether. Acid is added and the product is precipitated as the acid addition salt using ethanol.

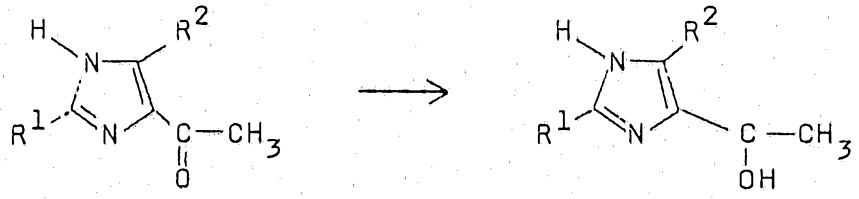
The free base can be converted to the salt by dissolving the free base in a suitable organic solvent,

such as ethanol or ether, and extracting with acidic aqueous solution. The use of heat may be required to dissolve the free base, depending upon the acid chosen.

The salt can be converted back to the free base by suspending it, for example in ether, and adding an excess of a dilute aqueous base, such as potassium carbonate, until the salt dissolves. The organic layer is separated, washed with water, dried and evaporated to yield the free base.

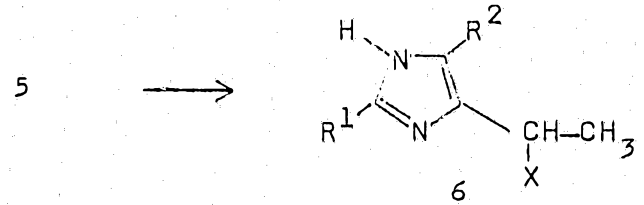
The salt of a compound of formula A can be converted to another salt by methods known in the art for interconversion of salts.

REACTION SCHEME II



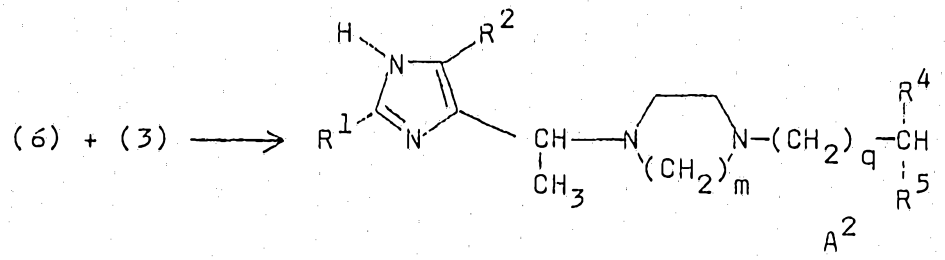
4 5

Step II-A



5 6

Step II-B



Step II-C

II. Preparation of Formula A Where R^3 is Methyl and n is 0

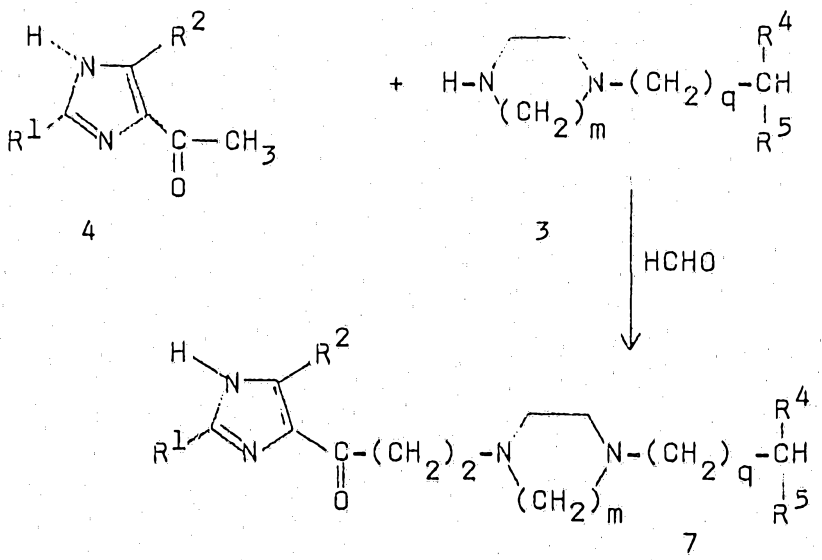
Referring to Reaction Scheme II, in Step II-A a compound of Formula 4 [obtained using the procedure of Vecchio, et al., Chim. Ind. (Milan), 58(6), 451 (1976) or of Haruki, et al., Nippon Kagaku Zasshiu, 86(9), 942-946 (1965) (Japan)] is reduced by contacting it with a reducing agent, such as a hydride (for example, potassium borohydride, or lithium aluminum hydride) in an alcoholic solution (for example, methanol, ethanol, isopropanol, and the like). The solution is stirred for about 2 to 16 hours, e.g., overnight, and the resulting solid material, of Formula 5, is removed by filtration (using reduced pressure if necessary), washed, dried and used in the next step without further purification.

In Step II-B, the crude compound of Formula 5 is dissolved in an inert solvent (for example, chloroform, dichloromethane, benzene, toluene, and the like). A halogenating agent, such as thionyl chloride, is added to the solution and the resulting mixture is heated at reflux for a period of time between 1 and 10 hours, preferably between about 4 and 6 hours. After cooling, the solvent is removed under reduced pressure and the residue is triturated in acetone to give a compound of Formula 6.

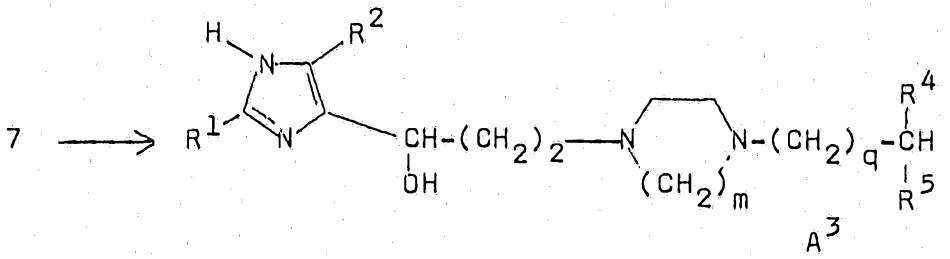
In Step II-C, the compound of Formula 6 and a compound of Formula 3 are reacted together under the

conditions described in Step I-B to give a compound according to Formula A^2. An oil product may be separated, dissolved in ether, and acidified to precipitate. The reaction time is about 1 to 24 hours, preferably about 4 to 5 hours.

REACTION SCHEME III



Step III-A



Step III-B

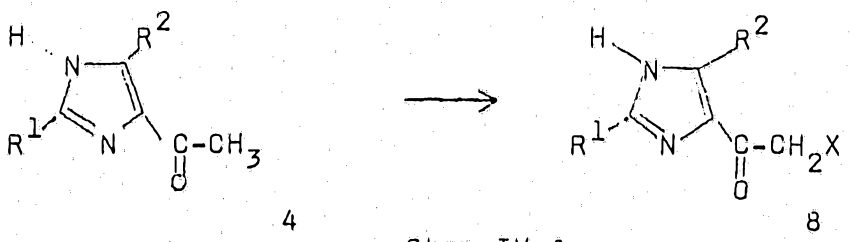
III. Preparation of Formula A Where R^3 is Hydroxyl and n is 2

Referring to Reaction Scheme III, in Step III-A a methyl ketone, such as a compound of Formula 4, an amine, such as a compound of Formula 3, and formaldehyde are reacted together under the conditions typically used for

a Mannich reaction, to give a compound of Formula 7. Thus, the ketone of Formula 7 is dissolved in a solvent such as water, methanol, ethanol, or acetic acid and formaldehyde is introduced. The amine is then added and the reaction mixture is refluxed. If necessary a small amount of an acid such as hydrochloric acid, may be introduced to assure that the reaction mixture is not basic.

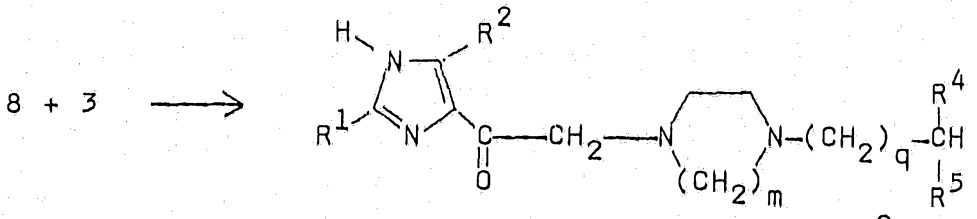
In Step III-B, the compound of Formula 7 is reduced under conditions similar to those described in Step II-A, to give a compound of Formula A^3.

REACTION SCHEME IV



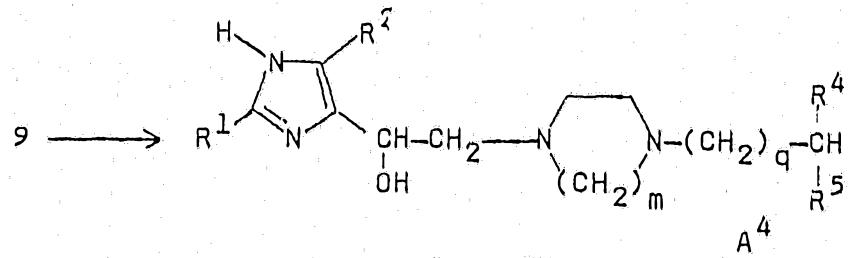
4 8

Step IV-A



9

Step IV-B



A^4

Step IV-C

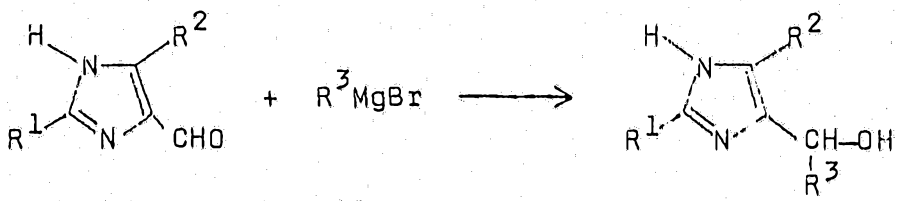
IV. Preparation of Formula A Where R^3 is Hydroxyl and n is 1

Referring to Reaction Scheme IV, in Step IV-A a compound of Formula 4 is halogenated, by contacting it with a halogenating agent, for example, thionyl halide, under conditions similar to those described in Step I-A, to give a compound of the Formula 8.

In Step IV-B, a compound of Formula 8 and a compound of Formula 3 are condensed by contacting them under conditions similar to those described for Step I-B, to give a compound of Formula 9.

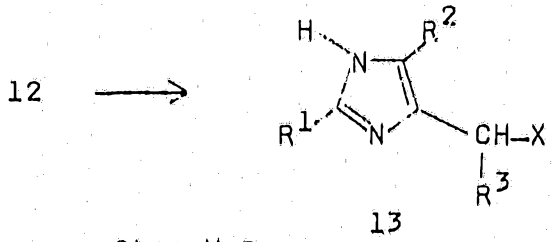
In Step IV-C, a compound of Formula 9 is reduced, by contacting it with a reducing agent under conditions similar to those described for Step II-A to give a compound of Formula A^4.

REACTION SCHEME V



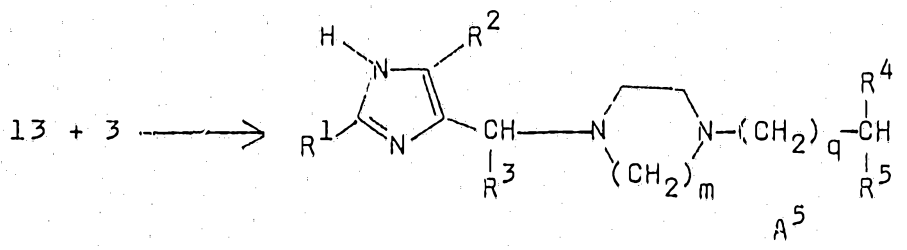
10 11 12

Step V-A



13

Step V-B



Step V-C

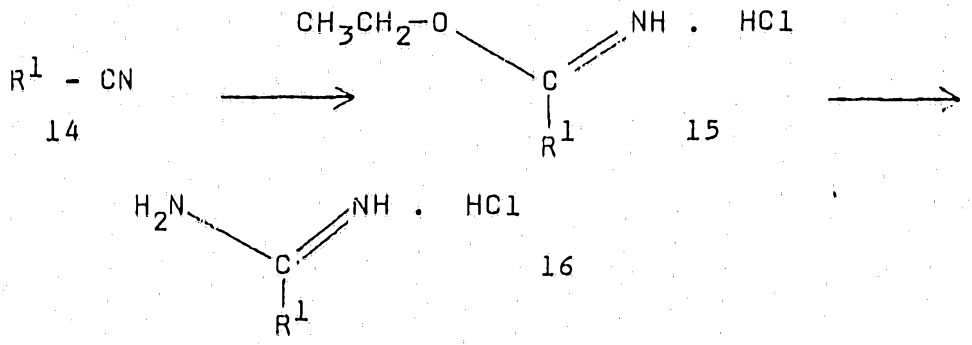
V. Preparation of Formula A Where R^3 is Lower Alkyl

Referring to Reaction Scheme V, in Step V-A, the Grignard reagent of a lower alkyl halide, the compound of Formula 11, is contacted with an imidazole compound of Formula 10 [obtained using the procedure of Cornforth and Huang, J. Chem. Soc., (1948), 731-735] in a neutral solvent (for example, diethyl ether, tetrahydrofuran, tetrahydropyran, and the like) and refluxed for between 15 minutes and 2 hours, preferably between 20 minutes and 40 minutes, and is then cooled and poured into ice water. The aqueous layer is extracted with a suitable organic solvent, such as diethyl ether. When the solvent is removed under reduced pressure, a residue is formed that can be recrystallized in ethanol yielding a compound of Formula 12.

In Step V-B, a compound of Formula 12 is halogenated under conditions similar to those described for Step I-A, to give a compound of Formula 13.

In Step V-C, a compound of Formula 13 and a compound of Formula 3 are contacted under conditions similar to those described for Step I-B, to give a compound of Formula A^5.

REACTION SCHEME VI



Referring to Reaction Scheme VI, the nitrile of Formula 14 is dissolved in alcohol, preferably methanol or ethanol, more preferably 99% ethanol, the solution is saturated with dry HCl gas and stirred at room temperature for from 1 to 24 hours, preferably overnight. The precipitate (compound of Formula 15) is filtered, washed and dried. A second crop of precipitate is collected by placing the mother liquors in a freezer overnight, and the precipitate is washed and dried.

Compound of Formula 15 is added slowly with stirring to an alcohol, preferably methanol, which is saturated with ammonia. Once the compound is dissolved, it is stirred at room temperature for from 1 to 24 hours, preferably overnight. The solution is reduced by 2/3 volume under vacuum, then diluted with 3 times its volume with isopropylacetate. The precipitate formed (compound of Formula 16) is filtered and dried.

Compound of Formula 16 is then dissolved in alcohol, preferably methanol or ethanol, more preferably 99% ethanol. Compound of Formula 17 is added dropwise and

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the reaction mixture refluxed for 1 to 40 hours, preferably 15 to 25 hours, more preferably about 20 hours. The mixture is then cooled to 15 to 40°C, preferably about 30°C, compound of Formula 3 is added, then water, a base (such as sodium hydroxide, potassium hydroxide, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, and the like, preferably sodium hydroxide) and a metal hydride (such as lithium bromide, potassium bromide, preferably lithium bromide) are added. Any insoluble material is removed by filtration and the solution is refluxed for 1 to 10 hours, preferably 4 to 6 hours. The reaction mixture is cooled and stirred at room temperature for 1 to 24 hours, preferably overnight. The precipitate is filtered, then poured into an alcohol/water mixture (such as methanol/water, ethanol/water, isopropanol/water in a ratio of from 10:90 to about 90:10, preferably 60:40). The solution is warmed to 50 to 80°C, preferably about 70°C, for 15 minutes to 4 hours, preferably about 1 hour, then cooled, and the precipitate filtered and dried to yield compound of Formula A.

Preferred Processes

The compounds of the present invention can be prepared according to any of the following last steps, in which non-essential substituents are not referenced, but will be apparent from reference to the foregoing reaction schemes:

a 4-haloalkyl-1H-imidazole (or a salt thereof) is condensed with a substituted-4-piperazine to give a compound according to Formula A where m is 2;

a 4-haloalkyl-1H-imidazole (or a salt thereof) is condensed with a substituted-4-diazepine to give a compound according to Formula A where m is 3;

a 4-(1-halo-C_2-C_4-alkyl)-1H-imidazole (or a salt thereof) is condensed with a substituted-4-piperazine to give a compound according to Formula A where m is 2, and R^3 is lower alkyl;

a 4-(1-halo-C_2-C_4-alkyl)-1H-imidazole (or a salt thereof) is condensed with a substituted-4-diazepine to give a compound according to Formula A where m is 3, and R^3 is lower alkyl;

a 1-substituted-4-[(1H-imidazol-4-yl)-1-oxo-alkyl]-piperazine is reduced to give the corresponding compound according to Formula A where m is 2, and R^3 is hydroxy;

a 1-substituted-4-[(1H-imidazol-4-yl)-1-oxo-alkyl]-diazepine is reduced to give the corresponding compound according to Formula A where m is 3, and R^3 is hydroxy;

a 2-(aryl)-4-(ω-haloalkyl)-5-alkyl-1H-imidazole (or a salt thereof) is condensed with a diaryl-alkyl-4-piperazine to give a compound according to Formula A where R^1 is aryl, R^2 is alkyl, R^3 is hydrogen, R^4 and R^5 are aryl, m is 2, n is 0-2, and q is 0-3;

a substituted amidine is reacted with a substituted dione and a substituted-4-piperazine or a substituted-4-diazepine to give a compound of Formula A;

a pharmaceutically acceptable acid is reacted with a compound of Formula A to form the corresponding acid addition salt of Formula A;

a pharmaceutically acceptable acid addition salt of Formula A is converted to another pharmaceutically acceptable acid addition salt of Formula A; or

an acid addition salt of Formula A is reacted with a base to form the corresponding free base compound of Formula A.

PREPARATION 1

Preparation of Compound of Formula 1

A solution of 1 mole (117.5 g) of tolunitrile in 500 ml absolute ethanol (99%) was saturated with dry HCl gas then kept under stirring at room temperature overnight. A first crop of crystals was collected by filtration then mother liquors were concentrated and placed in a freezer (-18°C) for 16 hours. A second crop was obtained, giving an overall yield of 80%. Without further purification, the crude product (160 g) was put in 200 ml NH_3-saturated methanol, portionwise with stirring. After complete dissolution the reaction medium was left at room temperature overnight then 1/3 of the methanol was removed under reduced pressure. The resulting solution was diluted with 200 ml of isopropyl- acetate and left to crystallize at room temperature for one day. The desired toluamidine hydrochloride was recovered by filtration, dried overnight at 50°C and used without further purification in the next step (77 g of a white powder, 90% yield).

77 g of the above benzamidine hydrochloride were dissolved in 200 ml of water then one equivalent of butanedione was added. The pH was adjusted to 7 with 2N sodium hydroxide and the reaction medium was left for two hours at 0°C. The white solid formed was filtered off and washed with acetone. The crude product (93 g) was dissolved in 500 ml of 10N HCl then the solution was heated to 100°C with stirring for 6 hours. After cooling, the white solid formed was recovered by filtration and recrystallized from water to give 65 g of 2-(4-methylphenyl)-5-methyl-4-hydroxymethyl-1H-imidazole, melting point, 167-169°C.

This 4-hydroxymethyl-1H-imidazole was then reacted with a thionyl halide using the procedures set forth

above to form the 2-(4-methylphenyl)-4-chloromethyl-5-methyl-1H-imidazole hydrochloride used in Example 1.

EXAMPLES

The following examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as a limitation on the scope of the invention, but merely as being illustrative and representative thereof.

EXAMPLE 1

1-Diphenylmethyl-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine and Derivatives Thereof

1A. Formula A Where R^1 is 4-Methylphenyl; R^2 is Methyl; R^3 is Hydrogen; R^4 and R^5 are Phenyl; m is 2; n is 0; and q is 0

50 Grams (0.2 mol) of 2-(4-methylphenyl)-4-chloromethyl-5-methyl-1H-imidazole hydrochloride dissolved in 200 ml of a mixture of ethanol:water 60:40 were added dropwise to a refluxing solution of 55 grams (0.2 mol) of N-(diphenylmethyl)piperazine and 24 grams (0.6 mol) sodium hydroxide in 200 ml of a mixture of ethanol:water 60:40. After 2 to 3 hours 1-diphenylmethyl-4-[(2-(4-methyl-phenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine precipitated from the reaction mixture. After having left the crystals standing at room temperature, they were removed by filtration and recrystallized from methanol to give the free base in 70% yield which melted at 220-222°C.

The free base was converted to its acid addition salt by the process taught in Example 6.

18. Formula A Varying R^1 and R^2

Similarly, following the procedure of Part A above, but replacing 2-(4-methylphenyl)-4-chloromethyl-5-methyl-1H-imidazole hydrochloride with:

2-phenyl-4-chloromethyl-5-methyl-1H-imidazole hydrochloride;

2-(3-methylphenyl)-4-chloromethyl-5-methyl-1H-imidazole hydrochloride;

2-(2-methylphenyl)-4-chloromethyl-5-methyl-1H-imidazole hydrochloride;

2-(4-t-butylphenyl)-4-chloromethyl-5-methyl-1H-imidazole hydrochloride;

2-(3-t-butylphenyl)-4-chloromethyl-5-methyl-1H-imidazole hydrochloride;

2-(2-t-butylphenyl)-4-chloromethyl-5-methyl-1H-imidazole hydrochloride;

2-(4-chlorophenyl)-4-chloromethyl-5-methyl-1H-imidazole hydrochloride;

2-(3-chlorophenyl)-4-chloromethyl-5-methyl-1H-imidazole hydrochloride;

2-(2-chlorophenyl)-4-chloromethyl-5-methyl-1H-imidazole hydrochloride;

2-(4-methoxyphenyl)-4-chloromethyl-5-methyl-1H-imidazole hydrochloride;

2-(3-methoxyphenyl)-4-chloromethyl-5-methyl-1H-imidazole hydrochloride;

2-(2-methoxyphenyl)-4-chloromethyl-5-methyl-1H-imidazole hydrochloride;

2-(2-methylphenyl)-4-chloromethyl-5-ethyl-1H-imidazole hydrochloride;

2-(4-methylphenyl)-4-chloromethyl-5-t-butyl-1H-imidazole hydrochloride;

2-(4-methylphenyl)-4-chloromethyl-1H-imidazole hydrochloride;

2-(3,4-dimethoxyphenyl)-4-bromomethyl-5-methyl-1H-imidazole hydrochloride; and

2,5-di-(4-methylphenyl)-4-chloromethyl-1H-imidazole hydrochloride;

there is obtained:

1-diphenylmethyl-4-[(2-phenyl-5-methyl-1H-imidazol-4-yl)methyl]piperazine, the trihydrochloride salt of which has a melting point of 214°C;

1-diphenylmethyl-4-[(2-(3-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;

1-diphenylmethyl-4-[(2-(2-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;

1-diphenylmethyl-4-[(2-(4-t-butylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;

1-diphenylmethyl-4-[(2-(3-t-butylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;

1-diphenylmethyl-4-[(2-(2-t-butylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;

1-diphenylmethyl-4-[(2-(4-chlorophenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine, the trihydrochloride salt of which has a melting point of 216°C;

1-diphenylmethyl-4-[(2-(3-chlorophenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine, the trihydrochloride salt of which has a melting point of about 215°C;

1-diphenylmethyl-4-[(2-(2-chlorophenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;

1-diphenylmethyl-4-[(2-(4-methoxyphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine, the trihydrochloride salt of which has a melting point of about 225°C;

1-diphenylmethyl-4-[(2-(3-methoxyphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;

1-diphenylmethyl-4-[(2-(2-methoxyphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;

1-diphenylmethyl-4-[(2-(2-methylphenyl)-5-ethyl-1H-imidazol-4-yl)methyl]piperazine;

1-diphenylmethyl-4-[(2-(4-methylphenyl)-5-t-butyl-1H-imidazol-4-yl)methyl]piperazine;

1-diphenylmethyl-4-[(2-(4-methylphenyl)-1H-imidazol-4-yl)methyl]piperazine;

1-diphenylmethyl-4-[(2-(3,4-dimethoxyphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine, the trihydrochloride salt of which has a melting point of 230°C; and

1-diphenylmethyl-4-[(2,5-di-(4-methylphenyl)-1H-imidazol-4-yl)methyl]piperazine;

1C. Formula A Varying q, R^4 and R^5

Similarly, following the procedure of Part A above, but replacing N-(diphenylmethyl)piperazine with:

N-[di-(2-methylphenyl)methyl]piperazine;

N-[di-(3-methylphenyl)methyl]piperazine;

N-[di-(4-methylphenyl)methyl]piperazine;

N-[di-(2-t-butylphenyl)methyl]piperazine;

N-[di-(3-t-butylphenyl)methyl]piperazine;

N-[di-(4-t-butylphenyl)methyl]piperazine;

N-[di-(2-methoxyphenyl)methyl]piperazine;

N-[di-(3-methoxyphenyl)methyl]piperazine;

N-[di-(4-methoxyphenyl)methyl]piperazine;

N-[di-(2-chlorophenyl)methyl]piperazine;

N-[di-(3-chlorophenyl)methyl]piperazine;

N-[di-(4-chlorophenyl)methyl]piperazine;

N-[di-(4-fluorophenyl)methyl]piperazine;

N-[1-(4-chlorophenyl)-1-(phenyl)methyl]piperazine;

N-(2,2-diphenylethyl)piperazine;

N-[3-(phenyl)-3-(4-methoxyphenyl)propyl]piperazine; and

N-(4,4-diphenylbutyl)piperazine,
there is obtained:
1-[di-(2-methylphenyl)methyl]-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;
1-[di-(3-methylphenyl)methyl]-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;
1-[di-(4-methylphenyl)methyl]-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;
1-[di-(2-t-butylphenyl)methyl]-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;
1-[di-(3-t-butylphenyl)methyl]-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;
1-[di-(4-t-butylphenyl)methyl]-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;
1-[di-(2-methoxyphenyl)methyl]-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;
1-[di-(3-methoxyphenyl)methyl]-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;
1-[di-(4-methoxyphenyl)methyl]-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;
1-[di-(2-chlorophenyl)methyl]-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;
1-[di-(3-chlorophenyl)methyl]-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;
1-[di-(4-chlorophenyl)methyl]-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine, the trihydrochloride salt of which has a melting point of about 225°C;
1-[di-(4-fluorophenyl)methyl]-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine, the trihydrochloride salt of which has a melting point of about 210°C;
1-[1-(4-chlorophenyl)-1-(phenyl)methyl]-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;

1-(2,2-diphenylethyl)-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;

1-[3-(phenyl)-3-(4-methyoxyphenyl)propyl]-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine; and

1-(4,4-diphenylbutyl)-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine.

1D. Formula A Varying R^1; R^2; R^4; R^5 and q

Similarly, by following the procedures of Parts B and C above, other compounds of Formula A where R^3 is hydrogen, m is 2, and n is 0 are obtained, such as:

1-diphenylmethyl-4-[(2-(3-trifluoromethylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine, the trihydrochloride salt of which has a melting point of about 210°C;

1-diphenylmethyl-4-[(2-phenyl-1H-imidazol-4-yl)-methyl]piperazine, the fumarate salt of which has a melting point of 170°C;

1-[di-(4-chlorophenyl)methyl]-4-[(2-phenyl-5-methyl-1H-imidazol-4-yl)methyl]piperazine, the trihydrochloride salt of which has a melting point of 220°C; and

1-[4,4-di-(4-fluorophenyl)butyl]-4-[(2-phenyl-5-methyl-1H-imidazol-4-yl)methyl]piperazine, the trihydrochloride salt of which has a melting point of 198°C.

1E. Formula A Varying m

Similarly, by following the procedures of Parts A to D above, but replacing the piperazines there-used with the corresponding diazepines, the compounds of Formula A wherein m is 3 are obtained.

For example, substituting 2-phenyl-4-chloromethyl-5-methyl-1H-imidazole hydrochloride for 2-(4-methylphenyl)-4-chloromethyl-5-methyl-1H-imidazole hydrochloride, and

by substituting diphenylmethyl-4-diazepine for diphenylmethyl-4-piperazine, there is obtained 1-diphenylmethyl-4-[(2-phenyl-5-methyl-1H-imidazol-4-yl)methyl]diazepine, the trihydrochloride salt of which has a melting point of about 205°C.

EXAMPLE 2

1-Diphenylmethyl-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine and Derivatives Thereof

2A. Formula 5 Where R^1 is Phenyl; and R^2 is Methyl

32 Grams (0.59 mol) of potassium borohydride were added portionwise to a solution of 30 g (0.15 mol) of 2-phenyl-4-acetyl-5-methylimidazole in 1500 ml of MeOH. After stirring overnight, a solid material was removed by filtration, then the solvent was evaporated under reduced pressure to give 27 g of 2-phenyl-4-(1-hydroxyethyl)-5-methylimidazole. The crude compound thus isolated was used without further purification.

2B. Formula 6 Where R^1 is Phenyl; R^2 is Methyl; and X is Chloro

27 Grams (0.13 mol) of 2-phenyl-4-(1-hydroxyethyl)-5-methylimidazole were dissolved in 700 ml of chloroform with 44 ml (0.6 mol) of thionyl chloride and refluxed for 5 hours. After cooling, the mixture was evaporated, the residue triturated in acetone, thereby giving, in approximately stoichiometric yield, 2-phenyl-4-(1-chloroethyl)-5-methylimidazole hydrochloride, m.p. 190°C.

2C. Formula 6 Varying R^1, R^2, and the Length of Alkyl at Position 4 of the Imidazole

Similarly, following the procedures of Part A and B above, but replacing 2-phenyl-4-acetyl-5-methylimidazole with:

2-(phenyl)-4-(2-methylpropanoyl)-5-methylimidazole;
2-(3-methylphenyl)-4-acetyl-5-methylimidazole;
2-(2-methylphenyl)-4-acetyl-5-methylimidazole;
2-(4-t-butylphenyl)-4-acetyl-5-methylimidazole;
2-(3-t-butylphenyl)-4-acetyl-5-methylimidazole;
2-(2-t-butylphenyl)-4-acetyl-5-methylimidazole;
2-(4-chlorophenyl)-4-acetyl-5-methylimidazole;
2-(3-chlorophenyl)-4-acetyl-5-methylimidazole;
2-(2-chlorophenyl)-4-acetyl-5-methylimidazole;
2-(4-methoxyphenyl)-4-acetyl-5-methylimidazole;
2-(3-methoxyphenyl)-4-acetyl-5-methylimidazole;
2-(2-methoxyphenyl)-4-acetyl-5-methylimidazole;
2-(2-methylphenyl)-4-acetyl-5-ethylimidazole;
2-(4-methylphenyl)-4-acetyl-5-t-butylimidazole; and
2-(4-methylphenyl)-4-acetylimidazole,

there is obtained:

2-(phenyl)-4-(1-chloro-2-methylpropyl)-5-methyl-imidazole hydrochloride;
2-(3-methylphenyl)-4-(1-chloroethyl)-5-methyl-imidazole hydrochloride;
2-(2-methylphenyl)-4-(1-chloroethyl)-5-methyl-imidazole hydrochloride;
2-(4-t-butylphenyl)-4-(1-chloroethyl)-5-methyl-imidazole hydrochloride;
2-(3-t-butylphenyl)-4-(1-chloroethyl)-5-methyl-imidazole hydrochloride;
2-(2-t-butylphenyl)-4-(1-chloroethyl)-5-methyl-imidazole hydrochloride;
2-(4-chlorophenyl)-4-(1-chloroethyl)-5-methyl-imidazole hydrochloride;

2-(3-chlorophenyl)-4-(1-chloroethyl)-5-methyl-imidazole hydrochloride;

2-(2-chlorophenyl)-4-(1-chloroethyl)-5-methyl-imidazole hydrochloride;

2-(4-methoxyphenyl)-4-(1-chloroethyl)-5-methyl-imidazole hydrochloride;

2-(3-methoxyphenyl)-4-(1-chloroethyl)-5-methyl-imidazole hydrochloride;

2-(2-methoxyphenyl)-4-(1-chloroethyl)-5-methyl-imidazole hydrochloride;

2-(2-methylphenyl)-4-(1-chloroethyl)-5-ethyl-imidazole hydrochloride;

2-(4-methylphenyl)-4-(1-chloroethyl)-5-t-butyl-imidazole hydrochloride; and

2-(4-methylphenyl)-4-(1-chloroethyl)-imidazole hydrochloride.

20. Formula A Where R^1 is Phenyl; R^2 is Methyl; R^3 is Methyl; R^4 and R^5 are Phenyl; m is 2; n is 0; and q is 0

14 Grams (0.052 mol) of N-(diphenylmethyl)piperazine and 6 grams (0.15 mol) of sodium hydroxide were dissolved in 180 ml of a mixture of ethanol:water 60:40. The mixture was heated to reflux, then 2-phenyl-4-(1-chloroethyl)-5-methylimidazole hydrochloride in 180 milliliters of ethanol:water 60:40 were added dropwise. After 4 to 5 hours under reflux, the reaction mixture was allowed to cool to room temperature. The oil that separated was washed twice with water, then dissolved in ether and hydrochloric acid was added. The precipitate was recrystallized from ethanol to give 1-diphenylmethyl-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride (55% yield), which melted at 215°C.

2E. Formula A Where R^3 is Methyl; R^4 and R^5 are Phenyl; m is 2; n is 0; q is 0; and Varying R^1 and R^2

Similarly, following the procedure of Part D above, but replacing 2-phenyl-4-(1-chloroethyl)-5-methyl-imidazole hydrochloride with:

2-(phenyl)-4-(1-chloro-2-methylpropyl)-5-methyl-imidazole hydrochloride;

2-(phenyl)-4-(1-chloroethyl)-5-methylimidazole hydrochloride;

2-(3-methylphenyl)-4-(1-chloroethyl)-5-methyl-imidazole hydrochloride;

2-(2-methylphenyl)-4-(1-chloroethyl)-5-methyl-imidazole hydrochloride;

2-(4-t-butylphenyl)-4-(1-chloroethyl)-5-methyl-imidazole hydrochloride;

2-(3-t-butylphenyl)-4-(1-chloroethyl)-5-methyl-imidazole hydrochloride;

2-(2-t-butylphenyl)-4-(1-chloroethyl)-5-methyl-imidazole hydrochloride;

2-(4-chlorophenyl)-4-(1-chloroethyl)-5-methyl-imidazole hydrochloride;

2-(3-chlorophenyl)-4-(1-chloroethyl)-5-methyl-imidazole hydrochloride;

2-(2-chlorophenyl)-4-(1-chloroethyl)-5-methyl-imidazole hydrochloride;

2-(4-methoxyphenyl)-4-(1-chloroethyl)-5-methyl-imidazole hydrochloride;

2-(3-methoxyphenyl)-4-(1-chloroethyl)-5-methyl-imidazole hydrochloride;

2-(2-methoxyphenyl)-4-(1-chloroethyl)-5-methyl-imidazole hydrochloride;

2-(2-methylphenyl)-4-(1-chloroethyl)-5-ethyl-imidazole hydrochloride;

2-(4-methylphenyl)-4-(1-chloroethyl)-5-t-butyl-imidazole hydrochloride; and

2-(4-methylphenyl-4-(1-chloroethyl)-imidazole hydrochloride,

there is obtained:

1-diphenylmethyl-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)propyl]piperazine hydrochloride;

1-diphenylmethyl-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-(3-methylphenyl)-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-(2-methylphenyl)-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-(4-t-butylphenyl)-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-(3-t-butylphenyl)-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-(2-t-butylphenyl)-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-(4-chlorophenyl)-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-(3-chlorophenyl)-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-(2-chlorophenyl)-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-(4-methoxyphenyl)-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-(3-methoxyphenyl)-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-(2-methoxyphenyl)-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-(2-methylphenyl)-5-ethyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-(4-methylphenyl)-5-t-butyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride; and

1-diphenylmethyl-4-[1-(2-(4-methylphenyl)-1H-imidazol-4-yl)ethyl]piperazine trichydrochloride.

2F. Formula A Where R^1 is Phenyl; R^2 is Methyl; R^3 is Methyl; m is 2; n is 0; and Varying q, R^4 and R^5

Similarly, following the procedure of Part D above, but replacing N-(diphenylmethyl)piperazine with:

N-[di-(2-methylphenyl)methyl]piperazine;
N-[di-(3-methylphenyl)methyl]piperazine;
N-[di-(4-methylphenyl)methyl]piperazine;
N-[di-(2-t-butylphenyl)methyl]piperazine;
N-[di-(3-t-butylphenyl)methyl]piperazine;
N-[di-(4-t-butylphenyl)methyl]piperazine;
N-[di-(2-methoxyphenyl)methyl]piperazine;
N-[di-(3-methoxyphenyl)methyl]piperazine;
N-[di-(4-methoxyphenyl)methyl]piperazine;
N-[di-(2-chlorophenyl)methyl]piperazine;
N-[di-(3-chlorophenyl)methyl]piperazine;
N-[di-(4-chlorophenyl)methyl]piperazine;
N-[di-(4-fluorophenyl)methyl]piperazine;
N-[1-(4-chlorophenyl)-1-(phenyl)methyl]piperazine;
N-(2,2-diphenylethyl)piperazine;
N-[3-(phenyl)-3-(4-methoxyphenyl)propyl]piperazine; and
N-(4,4-diphenylbutyl)piperazine,

there is obtained:

1-[di-(2-methylphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;

1-[di-(3-methylphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;

1-[di-(4-methylphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;

1-[di-(2-t-butylphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;

1-[di-(3-t-butylphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;

1-[di-(4-t-butylphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;

1-[di-(2-methoxyphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;

1-[di-(3-methoxyphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;

1-[di-(4-methoxyphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;

1-[di-(2-chlorophenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;

1-[di-(3-chlorophenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;

1-[di-(4-chlorophenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;

1-[di-(4-fluorophenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;

1-[(4-chlorophenyl)-1-(phenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;

1-(2,2-diphenylethyl)-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;

1-[3-(phenyl)-3-(4-methoxyphenyl)propyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride; and

1-(4,4-diphenylbutyl)-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride.

2G. Formula A Where R^3 is Methyl; m is 2; n is 0; and Varying R^1; R^2; R^4; R^5 and q

Similarly, by following the procedures of Parts E and F above, other compounds of Formula A where R^3 is methyl, m is 2, and n is 0 are obtained, such as:

1-[(4-chlorophenyl)-1-(phenyl)methyl]-4-[1-(2-phenyl-5-(4-methylphenyl)-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride; and

1-[3-(phenyl)-3-(4-methoxyphenyl)propyl]-4-[1-(2-(3-methoxyphenyl)-5-propyl-1H-imidazol-4-yl)ethyl]-piperazine trihydrochloride.

2H. Formula A Where R^3 is Lower Alkyl Other Than Methyl

Similarly, following the procedure of Part D above, but replacing 2-phenyl-4-(1-chloroethyl)-5-methyl-imidazole hydrochloride with:

2-phenyl-4-(1-chloropropyl)-5-methyl-imidazole hydrochloride; and

2-phenyl-4-(1-chlorobutyl)-5-methyl-imidazole hydrochloride,

there is obtained:

1-diphenylmethyl-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)propyl]piperazine trihydrochloride; and

1-diphenylmethyl-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)butyl]piperazine trihydrochloride.

2I. Formula A Varying m

Similarly, by following the procedures of Parts A-H above, but replacing the piperazines there-used with the

corresponding diazepines, the compounds of Formula A wherein m is 3 are obtained.

EXAMPLE 3

1-Diphenylmethyl-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride and Derivatives Thereof

3A. Formula 9 Where R^1 is Phenyl; R^2 is Methyl; R^4 and R^5 are Phenyl; m is 2; and q is 0

10 Grams (0.036 mol) of 2-phenyl-4-(2-bromoethanoyl)-5-methyl-1H-imidazole and 8.5 grams (0.034 mol) of N-(diphenylmethyl)piperazine and 5 grams (0.036 mol) of potassium carbonate were added to 300 ml of ethanol. The mixture was refluxed under stirring overnight. After cooling, the salts were removed by filtration and the solvent was removed under reduced pressure. The residue was extracted by dichloromethane and washed twice with water. The organic layer was dried over sodium sulfate and evaporated. Trituration of the residue with ethanol gave a white precipitate, 1-diphenylmethyl-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-oxoethyl]piperazine, which was used in the next reaction step without further purification.

3B. TriHCl Salt of Formula A Where R^1 is Phenyl; R^2 is Methyl; R^3 is Hydroxy; R^4 and R^5 are Phenyl; m is 2; n is 1; and q is 0

6 Grams of 1-diphenylmethyl-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-oxoethyl]piperazine was dissolved in 100 ml of methanol. The reaction was cooled to 5°C and then 2 grams (0.05 mol) of sodium borohydride was added portionwise. After stirring for 2 hours at room temperature, the mixture was evaporated off. The residue was extracted with dichloromethane and washed

with water. Then the organic layer was dried over sodium sulphate and the solvent removed under reduced pressure. The crude material was then dissolved in diethyloxide and hydrochloric acid was added. The white precipitate was then removed by filtration and dried to give 1-diphenylmethyl-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride, which melted at 200°C.

3C. TriHCl Salt of Formula A Where R^3 is Hydroxy; R^4 and R^5 are Phenyl; m is 2; n is 1; q is 0; and Varying R^1 and R^2

Similarly, following the procedures of Parts A and B above, but replacing 2-phenyl-4-(2-bromo-ethanoyl)-5-methyl-1H-imidazole with:

2-(3-methylphenyl)-4-(2-bromoethanoyl)-5-methyl-1H-imidazole;

2-(2-methylphenyl)-4-(2-bromoethanoyl)-5-methyl-1H-imidazole;

2-(4-t-butylphenyl)-4-(2-bromoethanoyl)-5-methyl-1H-imidazole;

2-(3-t-butylphenyl)-4-(2-bromoethanoyl)-5-methyl-1H-imidazole;

2-(2-t-butylphenyl)-4-(2-bromoethanoyl)-5-methyl-1H-imidazole;

2-(4-chlorophenyl)-4-(2-bromoethanoyl)-5-methyl-1H-imidazole;

2-(3-chlorophenyl)-4-(2-bromoethanoyl)-5-methyl-1H-imidazole;

2-(2-chlorophenyl)-4-(2-bromoethanoyl)-5-methyl-1H-imidazole;

2-(4-methoxyphenyl)-4-(2-bromoethanoyl)-5-methyl-1H-imidazole;

2-(3-methoxyphenyl)-4-(2-bromoethanoyl)-5-methyl-1H-imidazole;

2-(2-methoxyphenyl)-4-(2-bromoethanoyl)-5-methyl-1H-imidazole;

2-(2-methylphenyl)-4-(2-bromoethanoyl)-5-ethyl-1H-imidazole;

2-(4-methylphenyl)-4-(2-bromoethanoyl)-5-t-butyl-1H-imidazole; and

2-(4-methylphenyl)-4-(2-bromoethanoyl)-1H-imidazole,

there is obtained:

1-diphenylmethyl-4-[2-(2-(3-methylphenyl)-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[2-(2-(2-methylphenyl)-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[2-(2-(4-t-butylphenyl)-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[2-(2-(3-t-butylphenyl)-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[2-(2-(2-t-butylphenyl)-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[2-(2-(4-chlorophenyl)-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[2-(2-(3-chlorophenyl)-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[2-(2-(2-chlorophenyl)-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[2-(2-(4-methoxyphenyl)-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[2-(2-(3-methoxyphenyl)-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[2-(2-(2-methoxyphenyl)-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[2-(2-(2-methylphenyl)-5-ethyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[2-(2-(4-methylphenyl)-5-t-butyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride; and

1-diphenylmethyl-4-[2-(2-(4-methylphenyl)-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride.

3D. TriHCl Salt of Formula A Where R^1 is Phenyl; R^2 is Methyl; R^3 is Hydroxy; m is 2; n is 1; q is 0; and Varying R^4 and R^5

Similarly, following the procedures of Parts A and B above, but replacing N-(diphenylmethyl)piperazine with:

N-[di-(2-methylphenyl)methyl]piperazine;
N-[di-(3-methylphenyl)methyl]piperazine;
N-[di-(4-methylphenyl)methyl]piperazine;
N-[di-(2-t-butylphenyl)methyl]piperazine;
N-[di-(3-t-butylphenyl)methyl]piperazine;
N-[di-(4-t-butylphenyl)methyl]piperazine;
N-[di-(2-methoxyphenyl)methyl]piperazine;
N-[di-(3-methoxyphenyl)methyl]piperazine;
N-[di-(4-methoxyphenyl)methyl]piperazine;
N-[di-(2-chlorophenyl)methyl]piperazine;
N-[di-(3-chlorophenyl)methyl]piperazine;
N-[di-(4-chlorophenyl)methyl]piperazine;
N-[di-(4-fluorophenyl)methyl]piperazine;
N-[1-(4-chlorophenyl)-1-(phenyl)methyl]piperazine;
N-(2,2-diphenylethyl)piperazine;

N-[3-(phenyl)-3-(4-methoxyphenyl)propyl]piperazine;
and
N-(4,4-diphenylbutyl)piperazine,
there is obtained:
1-[di-(2-methylphenyl)methyl]-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;
1-[di-(3-methylphenyl)methyl]-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;
1-[di-(4-methylphenyl)methyl]-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;
1-[di-(2-t-butylphenyl)methyl]-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;
1-[di-(3-t-butylphenyl)methyl]-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;
1-[di-(4-t-butylphenyl)methyl]-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;
1-[di-(2-methoxyphenyl)methyl]-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;
1-[di-(3-methoxyphenyl)methyl]-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;
1-[di-(4-methoxyphenyl)methyl]-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;
1-[di-(2-chlorophenyl)methyl]-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

1-[di-(3-chlorophenyl)methyl]-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

1-[di-(4-chlorophenyl)methyl]-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

1-[di-(4-fluorophenyl)methyl]-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

1-[(4-chlorophenyl)-1-(phenyl)methyl]-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

1-(2,2-diphenylethyl)-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

1-[3-(phenyl)-3-(4-methoxyphenyl)propyl]-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]-piperazine trihydrochloride; and

1-(4,4-diphenylbutyl)-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride.

3E. TriHCl Salt of Formula A Where R^3 is Hydroxy; m is 2; n is 1 or 2; and Varying R^1; R^2; R^4; R^5 and q

Similarly, by following the procedures of Parts C and D above, other compounds of Formula A where R^3 is hydroxy, m is 2, and n is 1 or 2 are obtained, such as:

1-[(4-chlorophenyl)-1-(phenyl)methyl]-4-[3-(2-phenyl-5-methyl-1H-imidazol-4-yl)-3-hydroxypropyl]piperazine trihydrochloride, by starting with 2-phenyl-4-(3-bromo-propanoyl)-5-methyl-1H-imidazole in part 3A; and

1-(2,2-diphenylethyl)-4-[2-(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

3F. Formula A Varying m

Similarly, by following the procedures of Parts A-E above, but replacing the piperazines there-used with the corresponding diazepines, the compounds of Formula A wherein m is 3 are obtained.

EXAMPLE 4

1-Diphenylmethyl-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine and Derivatives Thereof

4A. Formula 12 Where R^1 is Phenyl; R^2 is Methyl; and R^3 is Isopropyl

35 Grams (0.45 mol) of 2-chloropropane was added to 10.8 g (0.45 mol) of magnesium in 100 ml of diethyl ether. Then 55.8 g (0.3 mol) of 2-phenyl-4-formyl-5-methyl-1H-imidazole in 100 ml of THF were added. At the end of the addition, the mixture was refluxed for 30 minutes and then cooled and poured on ice water. The aqueous layer was extracted twice with 100 ml of diethyl ether. Evaporation of the solvent gave a residue which was recrystallized in ethanol to yield 40 grams (58% yield) of 2-phenyl-4-(1-hydroxy-2-methylpropyl)-5-methyl-1H-imidazole, which melted at 214°C.

4B. Formula 12 Where R^6 is Isopropyl; and Varying R^1 and R^2

Similarly, following the procedure of Part A above, but replacing 2-phenyl-4-formyl-5-methyl-1H-imidazole with:

2-(3-methylphenyl)-5-methyl-4-formyl-1H-imidazole;
2-(2-methylphenyl)-5-methyl-4-formyl-1H-imidazole;
2-(4-t-butylphenyl)-5-methyl-4-formyl-1H-imidazole;
2-(3-t-butylphenyl)-5-methyl-4-formyl-1H-imidazole;

2-(2-t-butylphenyl)-5-methyl-4-formyl-1H-imidazole;
2-(4-chlorophenyl)-5-methyl-4-formyl-1H-imidazole;
2-(3-chlorophenyl)-5-methyl-4-formyl-1H-imidazole;
2-(2-chlorophenyl)-5-methyl-4-formyl-1H-imidazole;
2-(4-methoxyphenyl)-5-methyl-4-formyl-1H-imidazole;
2-(3-methoxyphenyl)-5-methyl-4-formyl-1H-imidazole;
2-(2-methoxyphenyl)-5-methyl-4-formyl-1H-imidazole;
2-(2-methylphenyl)-5-ethyl-4-formyl-1H-imidazole;
2-(4-methylphenyl)-5-t-butyl-4-formyl-1H-imidazole;
2-(4-methylphenyl)-4-formyl-1H-imidazole;
2-(3,4-dimethoxyphenyl)-4-formyl-5-methyl-1H-imidazole; and
2,5-di-(4-methylphenyl)-4-formyl-1H-imidazole,

there is obtained:

2-(3-methylphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
2-(2-methylphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
2-(4-t-butylphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
2-(3-t-butylphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
2-(2-t-butylphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
2-(4-chlorophenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
2-(3-chlorophenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
2-(2-chlorophenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
2-(4-methoxyphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
2-(3-methoxyphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;

2-(2-methoxyphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;

2-(2-methylphenyl)-5-ethyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;

2-(4-methylphenyl)-5-t-butyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;

2-(4-methylphenyl)-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;

2-(3,4-dimethoxyphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole; and

2,5-di-(4-methylphenyl)-4-(1-hydroxy-2-methylpropyl)-1H-imidazole.

4C. Formula 13 Where R^1 is Phenyl; R^2 is Methyl; R^3 is Isopropyl; and X is Chloro

27g of 2-phenyl-4-(1-hydroxy-2-methylpropyl)-5-methyl-1H-imidazole are dissolved in 700 ml of chloroform with 44 ml of thionyl chloride ($SOCl_2$) and refluxed for 5 hours. 2-Phenyl-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride is isolated in quantitative yield.

4D. Formula 13 Where R^6 is Isopropyl; X is Chloro; and Varying R^1 and R^2

Similarly, following the procedure of Part C above, but replacing 2-phenyl-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole with:

2-(3-methylphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;

2-(2-methylphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;

2-(4-t-butylphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;

2-(3-t-butylphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;

2-(2-t-butylphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;

2-(4-chlorophenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;

2-(3-chlorophenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;

2-(2-chlorophenyl)-5-methyl-4-(1-hyaroxy-2-methylpropyl)-1H-imidazole;

2-(4-methoxyphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;

2-(3-methoxyphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;

2-(2-methoxyphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;

2-(2-methylphenyl)-5-ethyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;

2-(4-methylphenyl)-5-t-butyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole hydrochloride;

2-(-4-methylphenyl)-4-(1-hydroxy-2-methylpropyl)-1H-imidazole hydrochloride;

2-(3,4-dimethoxyphenyl)-4-(1-hydroxy-2-methylpropyl)-5-methyl-1H-imidazole; and

2,5-di-(4-methylphenyl)-4-(1-hydroxy-2-methylpropyl)-1H-imidazole,

there is obtained:

2-(3-methylphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;

2-(2-methylphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;

2-(4-t-butylphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;

2-(3-t-butylphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;

2-(2-t-butylphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;

2-(4-chlorophenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;

2-(3-chlorophenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;

2-(2-chlorophenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;

2-(4-methoxyphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;

2-(3-methoxyphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;

2-(2-methoxyphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;

2-(2-methylphenyl)-5-ethyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;

2-(4-methylphenyl)-5-t-butyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;

2-(4-methylphenyl)-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;

2-(3,4-dimethoxyphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride; and

2,5-di-(4-methylphenyl)-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride.

4E. TriHCl Salt of Formula A Where R^1 is Phenyl; R^2 is Methyl; R^3 is Isopropyl; R^4 and R^5 are Phenyl; m is 2; n is 0; and q is 0

14 Grams (0.05 mol) of diphenylmethyl-4-piperazine and 6 grams (0.15 mol) of sodium hydroxide are dissolved in 180 ml of a mixture of ethanol:water 60:40. The mixture is heated to reflux, then 2-phenyl-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride in 180 milliliters of ethanol:water 60:40 are added dropwise. After 4 to 5 hours under reflux, the reaction mixture is allowed to cool to room temperature. The oil that separated is washed twice with water, then dissolved

in ether and hydrochloric acid is added. The precipitate is recrystallized from ethanol to give 1-diphenylmethyl-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]-piperazine trihydrochloride.

4F. TriHCl Salt of Formula A Where R^3 is Isopropyl; R^4 and R^5 are Phenyl; m is 2; n is 0; q is 0; and Varying R^1 and R^2

Similarly, following the procedure of Part E above, but replacing 2-phenyl-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride with:

2-(3-methylphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;

2-(2-methylphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;

2-(4-t-butylphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;

2-(3-t-butylphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;

2-(2-t-butylphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;

2-(4-chlorophenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;

2-(3-chlorophenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;

2-(2-chlorophenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;

2-(4-methoxyphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;

2-(3-methoxyphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;

2-(2-methoxyphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;

2-(2-methylphenyl)-5-ethyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;

2-(4-methylphenyl)-5-t-butyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;

2-(4-methylphenyl)-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;

2-(3,4-dimethoxyphenyl)-4-(1-chloro-2-methylpropyl)-5-methyl-1H-imidazole hydrochloride; and

2,5-di-(4-methylphenyl)-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride,

there is obtained:

1-diphenylmethyl-4-[1-(2-(3-methylphenyl)-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-(2-methylphenyl)-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-(4-t-butylphenyl)-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-(3-t-butylphenyl)-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-(2-t-butylphenyl)-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-(4-chlorophenyl)-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-(3-chlorophenyl)-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-(2-chlorophenyl)-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-(4-methoxyphenyl)-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-(3-methoxyphenyl)-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-(2-methoxyphenyl)-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-(2-methylphenyl)-5-ethyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-(4-methylphenyl)-5-t-butyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-(4-methylphenyl)-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-(3,4-dimethoxyphenyl)-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride; and

1-diphenylmethyl-4-[1-(2,5-di-(4-methylphenyl)-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride.

4G. Formula A Where R^3 is Isopropyl, Varying q, R^4 and R^5

Similarly, following the procedure of Part E above, but replacing N-(diphenylmethyl)piperazine with:

N-[di-(2-methylphenyl)methyl]piperazine;

N-[di-(3-methylphenyl)methyl]piperazine;

N-[di-(4-methylphenyl)methyl]piperazine;

N-[di-(2-t-butylphenyl)methyl]piperazine;

N-[di-(3-t-butylphenyl)methyl]piperazine;

N-[di-(4-t-butylphenyl)methyl]piperazine;

N-[di-(2-methoxyphenyl)methyl]piperazine;

N-[di-(3-methoxyphenyl)methyl]piperazine;
N-[di-(4-methoxyphenyl)methyl]piperazine;
N-[di-(2-chlorophenyl)methyl]piperazine;
N-[di-(3-chlorophenyl)methyl]piperazine;
N-[di-(4-chlorophenyl)methyl]piperazine;
N-[di-(4-fluorophenyl)methyl]piperazine;
N-[1-(4-chlorophenyl)-1-(phenyl)methyl]piperazine;
N-(2,2-diphenylethyl)piperazine;
N-[3-(phenyl)-3-(4-methoxyphenyl)propyl]piperazine;
and
N-(4,4-diphenylbutyl)piperazine,
there is obtained:
1-[di-(2-methylphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;
1-[di-(3-methylphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;
1-[di-(4-methylphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;
1-[di-(2-t-butylphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;
1-[di-(3-t-butylphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;
1-[di-(4-t-butylphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;
1-[di-(2-methoxyphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-[di-(3-methoxyphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-[di-(4-methoxyphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-[di-(2-chlorophenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-[di-(3-chlorophenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-[di-(4-chlorophenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-[di-(4-fluorophenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-[1-(4-chlorophenyl)-1-(phenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]-piperazine trihydrochloride;

1-(2,2-diphenylethyl)-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-[3-(phenyl)-3-(4-methyoxyphenyl)propyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]-piperazine trihydrochloride; and

1-(4,4-diphenylbutyl)-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride.

4H. TriHCl Salt of Formula A Where R^3 is Lower Alkyl Other Than Isopropyl

Similarly, by following the procedures of Parts A to G above, and substituting in for 2-chloropropane in Part

A the following compounds:

1-chloroethane;

chloromethane;

2-chlorobutane,

there are obtained the corresponding compounds where R^3 is, respectively, ethyl, methyl and butyl, such as:

1-dipnenylmethyl-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)propyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylbutyl]piperazine trihydrochloride;

1-(4,4-diphenylbutyl)-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylbutyl]piperazine trihydrochloride;

1-[1-(4-chlorophenyl)-1-(phenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)propyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-(4-methylphenyl)-5-ethyl-1H-imidazol-4-yl)propyl]piperazine trihydrochloride; and

1-diphenylmethyl-4-[1-(2,5-diphenyl-1H-imidazol-4-yl)-2-methylbutyl]piperazine trihydrochloride.

4I. Formula A Varying m

Similarly, by following the procedures of Parts A-H above, but replacing the piperazines there-used with the corresponding diazepines, the compounds of Formula A wherein m is 3 are obtained.

EXAMPLE 5

1-Diphenylmethyl-4-[2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine and Derivatives Thereof

A. A solution of 4-methylbenzonitrile in 99% ethanol was saturated with 3 equivalents of dry HCl gas

and the reaction mixture was stirred overnight. The precipitate which formed was filtered and the mother liquirs were placed in a freezer at -18°C overnight. A second crop was obtained from the mother liquors. The combined crops were dried at 30°C overnight under vacuum, giving 78% yield of ethyl 4-methylbenzenecarboximidate hydrochloride (compound of Formula 15).

B. The product of step A was added portionwise with stirring to methanol which had been saturated with ammonia in the ratio of 1 liter methanol to 1 kilogram of product of step A. The product of step A dissolved slowly and the solution was stirred overnight. Two thirds of the volume was evaporated under vacuum. The remaining solution was diluted with three times its volume of isopropylacetate. The solution was filtered and dried overnight at 50°C to yield 4-methylbenzene-carboximidamide hydrochloride (compound of Formula 16) in 90% yield.

C. One mole of the product of step B was dissolved in 2 liters of 99% ethanol. 1.1 moles of butanedione were added dropwise, the solution was warmed to reflux and refluxed for 20 hours. The solution was allowed to cool to 30°C and 1 mole of powdered biphenylpiperazine was added portionwise. This was followed by the addition of 1 liter of water, 1.5 equivalents of sodium hydroxide (as 12N solution), and 1.1 equivalents of lithium bromide. The solution was filtered to remove insolubles and then refluxed for 5 hours. The solution was allowed to cool to room temperature and was stirred overnight. The precipitate which formed was filtered and the filter cake was added to an ethanol:water mixture (60:40) in the ratio of 3 liters of solvent mixture to 1 kilogram of filter cake. The solution was warmed to 70°C for one hour and then allowed to cool to room temperature. The precipitate

formed was filtered and dried overnight at 80°C under vacuum to form 1-diphenylmethyl-4-[2-(-4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine in 88% yield.

D. The trihydrochloride salt of the free base of the product of step C was formed by dissolving the free base of step C in 99% ethanol at the ratio of 1.1 liter of ethanol per mole of product. One mole of 1N HCl solution was slowly added. The solution was filtered and then warmed to 60°C. With slow addition, 250 ml of 12N HCl solution were added. The solution was slowly cooled to -10°C and the precipitate was filtered off and dried under vacuum at 100°C for 48 hours to yield 1-diphenylmethyl-4-[2-(-4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine trichydrochloride, m.p. 204-205°C.

EXAMPLE 6

Conversion of Free Compound To Salt

Trihydrochloride salt - The hydrochloride salt was obtained by addition of hydrochloric acid to the free base of a compound of Formula A dissolved in ethanol or ether. See step D of Example 5.

Monohydrochloride salt - 100 g. of 1-diphenylmethyl-4-[2-(-4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine were dissolved in 300 ml of ethanol at 95°C. To this solution 1 equivalent of 1N HCl was added with stirring. The reaction mixture was stirred at room temperature for 2 hours then the solvents were evaporated off under reduced pressure. The residue was dissolved in ether and the precipitate was filtered. The precipitate was recrystallized from isopropyl ether:acetone (1:1) to yield 1-diphenylmethyl-4-[2-(-4-methylphenyl)-5-methyl-1H-imidazol-4-yl)-

methyl]piperazine monohydrochloride, m.p. 186-188°C with decomposition.

Monomaleate salt - 5 g. (0.0115 mole) of 1-diphenylmethyl-4-[2-(-4-methylphenyl)-5-methyl-1H-imidazol-4-yl)-methyl]piperazine were dissolved in 300 ml of ethanol at 95°C. To this solution 1.34 g (0.0115 mole) of maleic acid was added with stirring. The reaction mixture was stirred at room temperature for 2 hours then the solvents were evaporated off under reduced pressure. The residue was dissolved in ether and the precipitate was filtered. The precipitate was recrystallized from isopropyl ether:acetone (1:1) to yield 1-diphenylmethyl-4-[2-(-4-methylphenyl)-5-methyl-1H-imidazol-4-yl)-methyl]piperazine monomaleate, m.p. 164-166°C with decomposition.

Trifumarate salt - To 5 g. of 1-diphenylmethyl-4-[2-(-4-methylphenyl)-5-methyl-1H-imidazol-4-yl)-methyl]piperazine (0.0115 mole) in acetone (100 ml) there was added 1.33 g. (0.0115 mole) of fumaric acid. The solution was heated to reflux, allowed to cool to room temperature, and allowed to stand at room temperature until precipitate formed. The precipitate was collected by filtration and recrystallized from ethanol to give the fumarate salt of 1-diphenylmethyl-4-[2-(-4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine, m.p. 195°C in almost quantitative yield.

In a similar manner, all compounds of Formula A in free base form can be converted to the acid addition salts by treatment with the appropriate acid, for example, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malonic acid, succinic acid, malic acid, maleic acid, tartaric acid, citric acid, lactic acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid,

p-toluene- sulfonic acid, and the like.

EXAMPLE 7

Conversion of Salt to Free Base

20 g. of 1-diphenylmethyl-4-[2-(-4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine trihydrochloride were solubilized in 200 ml of water. Sodium hydroxide (5N) was added dropwise with stirring until pH 8-9. The aqueous medium was extracted twice by 200 ml of dichloromethane. The organic phases were combined then washed with cold water until neutrality. Sodium sulfate was added to dry the organic phase, then the solvent was evaporated under reduced pressure. The resulting residue was crystallized from aqueous ethanol (90%) to give 1-diphenylmethyl-4-[2-(-4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine.

If desired, the extraction phase can be eliminated to allow direct recovery of the product followed by recrystallization.

EXAMPLE 8

Conversion of one Salt to Another Salt

5 g of 1-diphenylmethyl-4-[2-(-4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine monofumarate were dissolved in 100 ml of hot ethanol. 3 ml of commercial concentrated HCl solution (10N) were added with stirring. The solution was refluxed for 30 minutes then the solution was allowed to cool to room temperature. The solvent was evaporated off and the residue was crystallized twice from ethanol at 98°C to yield 1-diphenylmethyl-4-[2-(-4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine trihydrochloride, m.p. 202-204° with decomposition.

EXAMPLES 9-15

The following examples illustrate the preparation of representative pharmaceutical formulations containing an active compound of Formula A, e.g., 1-diphenylmethyl-4-[(2-(4-methylphenyl)-5-methylimidazol-4-yl)methyl]-piperazine trihydrochloride. Other compounds and salts of Formula A, such as those prepared in accordance with Examples 1-8, can be used as the active compound in the formulations of Examples 9-15.

EXAMPLE 9

I.V. Formulation

Active compound	0.14 g
Propylene glycol	20.0 g
POLYETHYLENE GLYCOL 400	20.0 g
TWEEN 80	1.0 g
0.9% Saline solution	100.0 ml

Other compounds of Formula A and the pharmaceutically acceptable salts thereof may be substituted therein.

EXAMPLE 10

Ingredients	Quantity per tablet, mgs.
Active compound	25
cornstarch	20
lactose, spray-dried	153
magnesium stearate	2

The above ingredients are thoroughly mixed and pressed into single scored tablets.

EXAMPLE 11

Ingredients	Quantity per capsule, mgs.
Active compound	100
lactose, spray-dried	148
magnesium stearate	2

The above ingredients are mixed and introduced into a hard-shell gelatin capsule.

EXAMPLE 12

Ingredients	Quantity per tablet, mgs.
Active compound	1
cornstarch	50
lactose	145
magnesium stearate	5

The above ingredients are mixed intimately and pressed into single scored tablets.

EXAMPLE 13

Ingredients	Quantity per capsule, mgs.
Active compound	150
lactose	92

The above ingredients are mixed and introduced into a hard-shell gelatin capsule.

EXAMPLE 14

An injectable preparation buffered to a pH of 7 is prepared having the following composition:

Ingredients

Active compound	0.2 g
KH_2PO_4 buffer (0.4 M solution)	2 ml
KOH (1 N)	q.s. to pH 7
water (distilled, sterile)	q.s. to 20 ml

EXAMPLE 15

An oral suspension is prepared having the following composition:

Ingredients

Active compound	0.1 g
fumaric acid	0.5 g
sodium chloride	2.0 g
methyl paraben	0.1 g
granulated sugar	25.5 g
sorbitol (70% solution)	12.85 g
Veegum K (Vanderbilt Co.)	1.0 g
flavoring	0.035 ml
colorings	0.5 mg
distilled water	q.s. to 100 ml

EXAMPLE 16

Ischemia (Stroke, Epilepsy)

A. Five minute model of bilateral common carotid artery occlusion in the gerbil with 72 hour survival

1) Normal animals - Using the procedure of Kirino Brain Res., 239, 57 (1982), microscopic sections (8 mm)

of brain tissue were obtained and stained with cresyl fast violet and haematoxylin-eosin. Abnormal brain cells were counted and expressed as a percentage of the total area counted using the procedure of Alps, et al, Br. J. Pharmacol. Proc. Suppl., 88, 250P (1986). The findings for 10 animals with 100 microscopic fields counted were: mean % abnormal neurones = 4.54 ±0.44%.

2) Sham-operated animals - The animals were anesthetized with a halothane-nitrous oxide-oxygen mixture. (Halothane was initially 5% then reduced to 1.5%. The gases were delivered via face mask.) Carotid arteries were surgically exposed (no ischemia) and survival time was 72 hours post-surgery. The microscopic sections were prepared and counted as in 1) above. In this case 7 animals were used and 100 microscopic fields were counted. The results were: mean % abnormal neurones = 4.61 ±0.31%.

3) Untreated ischemic controls - In this case animals were subjected to 5 minute bilateral carotid artery occlusion with 72 hour survival. The microscopic sections were prepared and counted as in 1) above. In this case 12 animals were used and 120 microscopic fields were counted. The results were: mean % abnormal neurones = 78.30 ±2.94%.

4) Parenteral, 15 minute pre-ischemia treated - The animals were given 500 mg/kg i.p. of 1-diphenylmethyl-4-[(2-(4-methylphenyl)-5-methylimidazol-4-yl)methyl]-piperazine trihydrochloride 15 minutes prior to ischaemic insult. The treatment was repeated b.i.d. for 72 hours. The microscopic sections were prepared and counted as in 1) above. In this case 10 animals were used and 100 microscopic fields were counted. The results were: mean % abnormal neurones = 26.90 ±3.30%.

5) Parenteral 15 minute pre-ischemic treated - The animals were given 250 mg/kg i.p. of 1-diphenyl-

methyl-4-[(2-(4-methylphenyl)-5-methylimidazol-4-yl)-methyl]piperazine trihydrochloride 15 minutes prior to ischaemic insult. Treatment was repeated b.i.d. for 72 hours. The microscopic sections were prepared and counted as in 1) above. In this case 6 animals were used and 60 microscopic fields were counted. The results were: mean % abnormal neurones = 27.20 ±4.30%.

6) Parenteral 15 minute post-ischemia treated - The animals were given 500 mg/kg i.p. of 1-diphenyl-methyl-4-[(2-(4-methylphenyl)-5-methylimidazol-4-yl)-methyl]piperazine trihydrochloride 15 minutes after ischaemic insult. The treatment was repeated b.i.d. for 72 hours. The microscopic sections were prepared and counted as in 1) above. In this case 9 animals were used and 90 microscopic fields were counted. The results were: mean % abnormal neurones = 41.70 ±4.60%.

7) Oral, pre-ischemia treated - The animals were given 5 mg/kg p.o. b.i.d. of 1-diphenyl-methyl-4-[(2-(4-methylphenyl)-5-methylimidazol-4-yl)-methyl]piperazine trihydrochloride for 3 days and on the 4th day at 1 hour pre-ischaemic. Treatment was repeated b.i.d. for 72 hours. The microscopic sections were prepared and counted as in 1) above. In this case 11 animals were used and 110 microscopic fields were counted. The results were: mean % abnormal neurones = 3.00 ±1.00%.

8) Oral, pre-ischemia treated - The animals were given 10 mg/kg p.o. of 1-diphenyl-methyl-4-[(2-(4-methylphenyl)-5-methylimidazol-4-yl)-methyl]piperazine trihydrochloride for 3 days and on 4th day at 1 hour pre-ischaemia. Treatment was repeated b.i.d. for 72 hours. The microscopic sections were prepared and counted as in 1) above. In this case 9 animals were used and 90 microscopic fields were counted. The results were: mean % abnormal neurones = 22.00 ±3.10%.

B. Ten minute Model of four vessel occlusion with 72 hour survival.

The procedure used was that of Alps, et al., Neurology, 37, 809 (1987). The object of this assay was to count abnormally appearing cells in 7 different areas and exymers as a percentage of the total area counted. The number of counts per structure depended upon size, e.g., cortical areas had double the number of other areas. Mean whole brain scores were also determined for percent abnormalities. Normal brains were also used to account for incidence of artifact changes attributed to the fixation process.

1) Normal animals - Under pentobarbital anesthesia samples were obtained, fixed with 10% buffered formal gab and microscopic samples were prepared as described in A above. In this case 6 animals were used with the results shown in the below table.

Brain Area	Mean % Abnormal Neurones	No. Fields Counted
Hip CA_1	1.45 ±0.40%	60
Hip CA_{2-5}	0.43 ±0.20%	60
Hip Cortex	2.90 ±0.64%	120
Striatum	5.80 ±0.54%	60
Str. Cortex	3.22 ±0.70%	120
Thalmus	4.38 ±0.92%	60
Purk. cells	5.61 ±1.88%	60
Mean Brain score	3.33 ±0.33%	540
Mean score per area	3.39 ±0.76%	7

2) Untreated (saline) ischemic controls - The animals were subjected to 10 minutes of bilateral common carotid artery occlusion (with previously surgically sealed vertebral arteries) with 72 hours survival. The microscopic sections were prepared as in 1) above. In this case 11 animals were used with the results shown in the below table.

Brain Area	Mean % Abnormal Neurones	No. Fields Counted
Hip CA_1	71.60 ±3.00%	110
Hip CA_{2-5}	23.80 ±2.70%	110
Hip. Cortex	48.50 ±2.20%	220
Striatum	45.10 ±2.60%	110
Str. Cortex	42.50 ±2.10%	220
Thalamus	35.30 ±2.00%	110
Purk. cells	32.10 ±3.40%	110
Mean score per area	42.70 ±5.80%	7

Parenteral, post-ischaemia treated - The animals were given 100 mg/kg i.a. of 1-diphenyl-methyl-4-[(2-(4-methylphenyl)-5-methylimidazol-4-yl)-methyl]piperazine trihydrochloride 5 minutes post-ischaemia plus 500 mg/kg i.p. of 1-diphenyl-methyl-4-[(2-(4-methylphenyl)-5-methylimidazol-4-yl)-methyl]piperazine trihydrochloride 15 minutes post-ischaemia. The microscopic sections were prepared according to 1) above. In this case 5 animals

were used with the results shown in the below table.

Brain Area	Mean % Abnormal Neurones	No. Fields Counted
Hip CA_1	16.76 ±4.00%	50
Hip CA_{2-5}	1.78 ±0.99%	50
Hip. Cortex	2.41 ±0.30%	100
Striatum	1.54 ±0.33%	50
Str. Cortex	2.01 ±0.29%	100
Thalamus	0.64 ±0.25%	50
Purk. cells	2.22 ±0.79%	50

C. The effect of 1-diphenyl-methyl-4-[(2-(4-methylphenyl)-5-methylimidazol-4-yl)-methyl]piperazine trihydrochloride on pentylenetetrazole-induced seizures and mortality in the mouse.

The procedure used was that described in Allely, and Alps, Br. J. Pharmacol. Proc. Suppl., 92, 605P (1987). Groups of 20 or more (see n in table) male CDI mice were predosed with 500 mg/kg i.p. of 1-diphenyl-methyl-4-[(2-(4-methylphenyl)-5-methylimidazol-4-yl)methyl]-piperazine trihydrochloride at one of three dosing schedules - A (15 minutes), B (60 minutes), or C (3 days b.i.d. plus 15 minutes on 4th day) - before challenging with 100 mg/kg of pentylenetetrazole s.c. The animals were then observed for a 30 minute period and the occurrence of clonic or tonic seizures or death noted. Statistical analysis was by a Chi squared test of association. Results compared against saline treated

animals are shown in the below table.

Predose Schedule	Predosed mg/kg i.p.	n	% clonic seizures	% tonic seizures	% death
Saline					
--	--	40	92.5	80.0	70.0
Drug					
A	500	20	85.0	85.0	50.0
B	500	25	88.0	64.0	36.0
C	500	24	66.7	41.7	45.0

In an oral dose ranging study in rats of 1-diphenyl-methyl-4-[(2-(4-methylphenyl)-5-metnylimidazol-4-yl)methyl]-piperazine trihydrochloride no death or clinical signs of toxicity were seen at up to 25 mg/kg/day.

EXAMPLE 17
Diuresis

Male normotensive rats weighing 290-380 g were divided into four groups of seven animals. All animals were fasted and deprived of water overnight. The following morning, each group of rats was hydrated with deionized water (20 mg/kg.p.o.) 45 minutes prior to the administration of vehicle (1% polysorbate 80 in deionized water) or 1-diphenyl-methyl-4-[(2-(4-methylphenyl)-5-methylimidazol-4-yl)methyl]-piperazine trihydrochloride at doses of 5, 15, or 30 mg/kg p.o. Fifteen minutes post-drug, the animals were saline loaded (30 ml/kg, p.o. 0.9% sodium chloride) and placed individually in metabolism cages. Urine was collected at 1, 3, and 6 hour intervals post-dose. Urine volumes were measured and sodium and potassium levels were determined by flame

photometry. Differences between control and treated values were evaluated by one way analysis of variance. 1-diphenyl-methyl-4-[(2-(4-methylphenyl)-5-methylimidazol-4-yl)methyl]-piperazine trihydrochloride (30 mg/kg, p.o.) produced significant ($p < .05$) diuresis which was observed at 1 hour and 6 hours post-drug. The compound (30 mg/kg, p.o.) elicited a significant natriuretic effect at the 3 and 6 hour time periods. No significant kaliuretic effects were observed following compound administration.

Urine Volume (ml)

Cumulative time	control vehicle*	5 mg/kg p.o.	15 mg/kg p.o.	30 mg/kg p.o.
1 hour	3.3 ±2.7	5.7 ±2.5	5.7 ±4.4	6.5 ±2.3
3 hours	7.3 ±3.3	9.5 ±3.6	9.8 ±3.2	10.5 ±2.5
6 hours	9.6 ±3.9	11.8 ±3.9	11.7 ±3.3	14.6 ±1.4

Sodium ion (mEq)

Cumulative time	control vehicle*	5 mg/kg p.o.	15 mg/kg p.o.	30 mg/kg p.o.
1 hour	.06 ±.08	.07 ±.06	.12 ±.16	.15 ±.12
3 hours	.28 ±.31	.39 ±.25	.44 ±.20	.79 ±.38
6 hours	.55 ±.44	.73 ±.32	.68 ±.28	1.48 ±.24

Cumulative time	Potassium ion (mEq) control vehicle*	5 mg/kg p.o.	15 mg/kg p.o.	30 mg/kg p.o.
1 hour	.03 ±.03	.04 ±.03	.04 ±.05	.04 ±.03
3 hours	.13 ±.09	.16 ±.09	.12 ±.06	.15 ±.08
6 hours	.22 ±.12	.26 ±.12	.20 ±.08	.27 ±.06

EXAMPLE 18

Irritable Bowel Syndrome

The test used is a modification of the method of Macht and Barba-Gose, J. Amer. Pharm. Assoc., 20, 558 (1931), which traces the transit of a charcoal meal through the intestine as an index of transit time. In the present model, intestinal transit in conscious mice (15-20 g) was accelerated with an oral dose of barium chloride (300 mg/kg) administered at the same time as the charcoal meal. The animals were sacrificed 10 minutes later and the distance travelled by the charcoal measured. 1-diphenyl-methyl-4-[(2-(4-methylphenyl)-5-methylimidazol-4-yl)methyl]-piperazine trihydrochloride was given as a 15 minute oral pre-treatment and its effect on non-stimulated or barium-stimulated intestinal transit of the charcoal meal was calculated. The results were expressed as inhibition percentage of the total transit induced by Ba^{+2}, and not as the inhibition percentage of the portion representing the Ba^{+2} effect

and are shown in the below table.

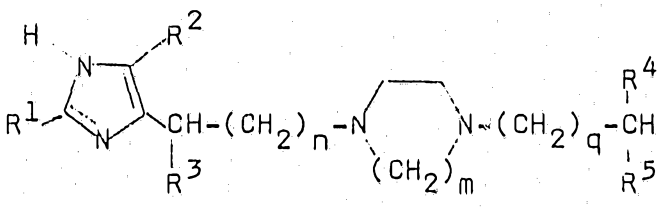
Dose 15 min mg/kg p.o.	% Change Ba^{+2}	% Inhibition of Ba^{+2} effect	% Inhibition Normal Transit
5	+ 93 %	+ 14 %	- 19.3 %
25	+ 93 %	- 30.4 %	- 28.7 %
60	+ 93 %	- 31.7 %	- 16.1 %

While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

~~WHAT IS CLAIMED IS~~:

1. A compound having the structure represented by the formula:



wherein:

R^1 is aryl;

R^2 is aryl, lower alkyl, or hydrogen;

R^3 is lower alkyl, hydroxy, or hydrogen;

R^4 is aryl;

R^5 is aryl;

m is two or three;

n is zero, one or two,

provided that when R^3 is hydroxy, n is one or two; and

q is zero, one, two, or three;

or a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1 wherein m is two, q is zero, n is zero, and R^2 is methyl.

3. The compound of Claim 2 wherein R^3 is hydrogen.

4. The compound of Claim 1 wherein R^3 is lower alkyl.

5. The compound of Claim 1 wherein R^3 is hydroxy.

6. The compound of Claim 3 wherein R^1 is 4-methylphenyl.

7. The compound of Claim 6 wherein R^4 and R^5 are phenyl, namely 1-diphenylmethyl-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine or its pharmaceutically acceptable acid addition salts.

8. The compound of Claim 6 wherein R^4 and R^5 are 4-chlorophenyl or 4-fluorophenyl.

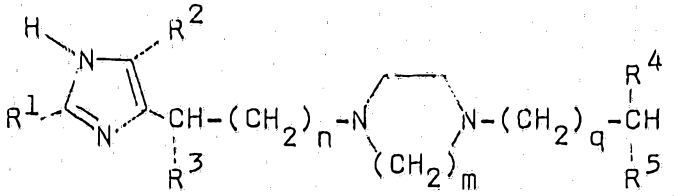
9. The compound of Claim 1 wherein R^2 is hydrogen, m is 2, q is 0, n is 0, and R^1, R^4, and R^5 are each phenyl, namely 1-diphenylmethyl-4-[2-phenyl-1H-imidazol-4-yl)methyl]piperazine or its pharmaceutically acceptable acid addition salts.

10. The compound of Claim 2 wherein R^1, R^4, and R^5 are each phenyl, namely 1-diphenylmethyl-4-[2-phenyl-5-methyl-1H-imidazol-4-yl)methyl]piperazine or its pharmaceutically acceptable acid addition salts.

11. The compound of Claim 2 wherein R^1 is 3-trifluoromethylphenyl, 4-methoxyphenyl, 4-chlorophenyl, 3,4-dimethoxyphenyl, 3-chlorophenyl, or phenyl.

12. The compound of Claim 1 wherein m is 3.

13. A compound having the structure represented by the formula:



wherein:

R^1 is aryl;

R^2 is aryl or lower alkyl;

R^3 is lower alkyl, hydroxy, or hydrogen;

R^4 is aryl;

R^5 is aryl;

m is two or three;

n is zero, one or two,

provided that when R^3 is hydroxy, n is one or two; and

q is zero, one, two, or three;

or a pharmaceutically acceptable salt thereof.

~~14. A method of treating a mammal for a disease~~ state, including stroke, epilepsy or epileptic psychotic symptoms, hypertension, angina, migraine, arrhythmia, thrombosis, embolism, acute cardiac failure, irritable bowel syndrome, neurodegenerative diseases such as Alzheimer's or Huntington's chorea, diuresis, ischemia such as focal and global ischemia or cerebrovascular ischemia induced by cocaine abuse, or spinal injury, said method comprising administering a therapeutically ~~effective amount of the compound of Claim 1 to the mammal~~.

14. A method of treating a mammal for a disease state requiring protective activity against deleterious effects resultant upon cerebral ischemia including stroke, epilepsy or epileptic psychotic symptoms, hypertension, angina, migraine, arrhythmia, thrombosis, ambolism, acute cardiac failure, irritable bowel syndrome, neurodegenerative diseases such as Alzheimer's or Huntington's chorea, diuresis, ischemia such as focal and global ischemia or cerebrovascular ischemia induced by cocaine abuse, or spinal injury, said method comprising administering a therapeutically effective amount of the compound of Claim 1 to the mammal.

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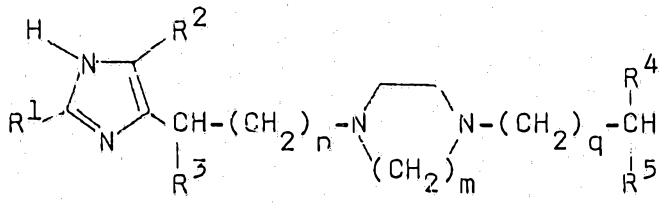
15. A pharmaceutical formulation comprising a compound of Claim 1 and a pharmaceutically acceptable excipient.

16. A process for the preparation of a compound of formula A



FORMULA A

wherein:

R^1 is aryl;

R^2 is aryl, lower alkyl, or hydrogen;

R^3 is lower alkyl, hydroxy, or hydrogen;

R^4 is aryl;

R^5 is aryl;

m is two or three;

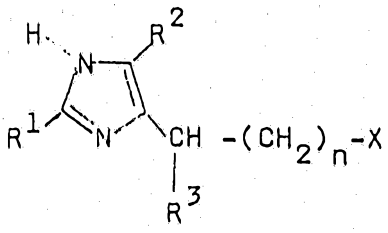
n is zero, one or two,

provided that when R^3 is hydroxy, n is one or two; and

q is zero, one, two, or three;

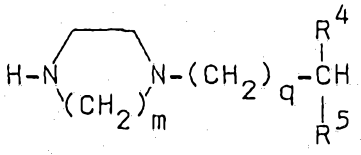
and the pharmaceutically acceptable salts thereof, which comprises

(a) condensing a compound of the formula



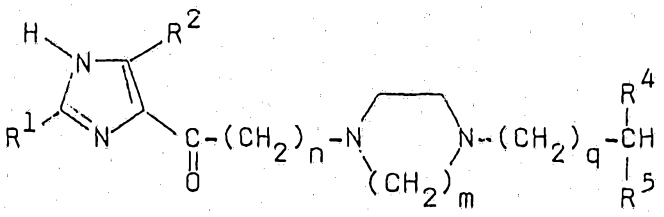
wherein n, R^1 and R^2 are as defined above, R^3

is hydrogen or lower alkyl, and X is a halogen atom, with a compound of the formula



wherein m, q, R^4 and R^5 are as defined above; or

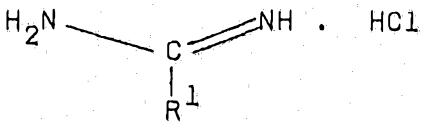
b) reducing a compound of the formula



wherein R^1, R^2, R^4, R^5, m, and q are as defined above and n is one or two,

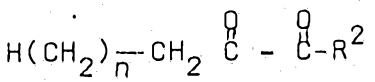
to form a compound of formula A wherein R^3 is hydroxy; or

c) reacting a compound of the formula

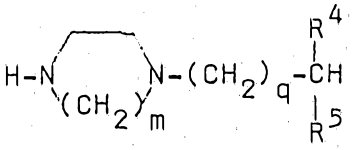


wherein R^1 is as defined above, with a compound of the

formula



wherein n and R^2 are as defined above, and a compound of the formula



wherein m, q, R^4 and R^5 are as defined above, to form a compound of Formula A wherein R^3 is hydrogen; or

d) converting a free base compound of formula A to its acid addition salt; or

e) converting an acid addition salt of a compound of formula A to a free base compound of formula A; or

f) converting an acid addition salt of a compound of formula A to another acid addition salt of a compound of formula A.

DATED THIS 21st day of April, 1988

SYNTEX PHARMACEUTICALS LTD.

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