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(54) Title: MUSCARINIC AGENTS AND USE THEREOF TO TREAT GLAUCOMA, MYOPIA AND VARIOUS OTHER CONDITIONS

A new group of compounds having muscarinic activity is disclosed (l) wherein m and n are independently 0 or 1; o and p are independently 1 or 2; —— represents a double or single bond; X is C(R)2, O, S(O)2, NR, C=O, CHOR, C=NOR, NC(O)OR, NC(O)N(R)2, NC(O)R, CHC(O)OR, CHC(O)N(R)2, CHC(O)R, NS(O)2C(R)3, (a) or (b) wherein q is 0, 1 or 2; R is H, lower alkyl, alkoxyl, arylalkyl, alkyln, alkyl or cycloalkyl; D is CH or N; E is C=O, S(O)2, S(O)2C=O, S=O or C=S; J is O, CR, C(R)2, NR or NRC (O); R¹, R² and R³ are independently H, lower alkyl, halogen, lower alkoxy, OH, HOCH₂, aryI, arylalkyl, SR or N(R)₂, and A is selected from the group consisting of (c), (d), (e) and (f). The use of the compounds and pharmaceutically acceptable salts thereof to treat glaucoma, myopia, psychosis and various other conditions involving muscarinic receptors is also disclosed.
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MUSCARINIC AGENTS AND USE THEREOF TO TREAT GLAUCOMA, MYOPIA AND VARIOUS OTHER CONDITIONS

Background of Invention:

The present invention relates to new compounds having muscarinic activity. The compounds are useful in treating glaucoma, myopia, various other medical conditions that directly or indirectly involve muscarinic receptors within the human body. The invention is particularly directed to the treatment of glaucoma by controlling the principal symptom of that disease, elevated intraocular pressure. More specifically, the invention relates to the use of particular muscarinic compounds to control intraocular pressure ("IOP") and thereby prevent or at least forestall progressive field of vision loss and other manifestations of glaucoma.

Glaucoma is a progressive disease which leads to optic nerve damage (i.e., glaucomatous optic neuropathy), and ultimately, partial or total loss of vision. The loss of visual field is secondary to the degeneration of optic nerve fibers which comprise the optic nerve. The causes of this disease have been the subject of extensive studies for many years, but are still not fully understood. However, it is known that a major risk factor for glaucomatous optic neuropathy is abnormally high IOP.

The usual reason for elevated IOP is an impairment of the outflow of fluid (i.e., aqueous humor) from the eye. Although hypersecretion of aqueous humor is not considered to be a common factor for elevated IOP, the pressure may be reduced by inhibiting the production (i.e., inflow, secretion or formation) of aqueous humor by the ciliary processes of the eye. Beta adrenoceptor blockers and carbonic anhydrase inhibitors are examples of drug classes that lower intraocular pressure by inhibiting the inflow of aqueous humor. Other classes of drugs reduce IOP by increasing the outflow of aqueous humor from the eye. Examples of these drug classes include miotics, such as pilocarpine and carbachol, and adrenergics or sympathomimetics, such as epinephrine.
While the use of the drug classes stated above is common practice in the medical therapy of glaucoma, it is not without side effects. Each class suffers from causing a particular set of side effects, locally and/or systemically, that is related to the pharmacological actions of that class. For example, beta blockers, by blocking beta adrenoceptors in the heart, can cause bradycardia or slow heart rate, and by blocking beta adrenoceptors in the bronchi can cause bronchoconstriction. Systemic carbonic anhydrase inhibitors can cause malaise, headache, and other subjective symptoms which discourage their use by the patient. Muscarinic agents, such as pilocarpine, may be used to reduce IOP by increasing the outflow of aqueous humor, but the use of these agents frequently produces side effects such as miosis, impaired accommodation and/or browache.

Miosis is caused by the contractile effect of the muscarinic agents on the iris sphincter. Muscarinic agents also have a contractile effect on the ciliary muscle. This effect is believed to be responsible for impairment of accommodation, as well as the browache experienced by some patients.

Thus, the agents used in glaucoma therapy show multiple pharmacological effects, some beneficial and some not. Since glaucoma medication must be taken over the patient's lifetime, it is advantageous to minimize the above-discussed side effects, so as to promote patients' compliance with the prescribed drug therapy, while maintaining the beneficial effect on intraocular pressure.

It has been estimated that one of every four persons suffers from myopia. About half or more of these cases are the result of elongation of the eye along the visual axis. At birth, the human eye is two-thirds the adult size. Throughout life the eye grows under the control of a finely tuned regulatory process. Abnormal regulation of this mechanism can result in a lengthening of the eye, which results in the plane of focus being in front of the retina. This growth process is believed to be regulated by neural out-put from the retina. Although atropine, a muscarinic antagonist, has been used to retard the development of myopia, it use causes profound dilation of the pupil and impairs the ability to focus. The compounds of this invention
have minimal effects on pupil dilation and therefore offer an advantage over atropine or other compounds having muscarinic activity that have been suggested as therapeutics for myopia.

Studies of muscarinic receptors have shown that there are multiple subtypes of muscarinic receptors, and that these receptor subtypes may be localized in different tissues, or may otherwise mediate different pharmacological effects. While some non-selective muscarinic agents may interact with multiple receptors and cause multiple effects, other muscarinic agents may interact more selectively with one or a combination of muscarinic receptor subtypes such that the beneficial effects are increased while the detrimental side-effects are reduced. For example, PCT International Publication Number WO 97/16196 indicates that certain 1-[cycloalkylpiperidin-4-yl]-2H benzimidazolones are selective muscarinic agonists of the m2 subtype with low activity at the m3 subtype, and when utilized for glaucoma therapy have fewer side effects than pilocarpine therapy.

The present invention is based on the discovery of new muscarinic compounds and the use of these compounds to treat glaucoma, myopia and other medical conditions. The following publications may be referred to for further background information regarding medical uses of compounds having at least some structural similarities to the compounds of the present invention:

(1) PCT International Publication Number WO 97/24324 discloses 1-(1,2-disubstituted piperidinyl)-4-substituted piperidine derivatives as tachykinin receptor antagonists for treating pain;

(2) PCT International Publication Number WO 97/16440 discloses 1-(1,2-disubstituted piperidinyl)-4-substituted piperazine derivatives as tachykinin receptor antagonists for treating pain;

(3) PCT International Publication Number WO 97/16187 discloses 1,3-dihydro-1-[1-(1-heteroarylpiperazin-4-yl)cyclohex-4-yl]-2H-benzimidazol-ones as muscarinic antagonists for treating and/or preventing myopia;
(4) United States Patent No. 5,574,044 discloses 1,3-dihydro-1-\{1-\{piperidin-4-yl\}piperidin-4-yl\}-2H-benzimidazol-2-ones and 1,3-dihydro-1-\{4-amino-1-cyclohexyl\}-2H-benzimidazol-2-ones as muscarinic antagonists for treating and/or preventing myopia;

(5) United States Patent No. 5,691,323 discloses 1,3-dihydro-1-\{1-\{piperidin-4-yl\}piperidin-4-yl\}-2H-benzimidazol-2-ones and 1,3-dihydro-1-\{4-amino-1-cyclohexyl\}-2H-benzimidazol-2-ones as muscarinic antagonists for treating and/or preventing myopia;

(6) United States Patent No. 5,718,912 discloses the use of 1-cycloalkylpiperidin-4-yl]-2H benzimidazolones to treat glaucoma;

(7) United States Patent No. 5,461,052 discloses the use of tricyclic compounds to prevent myopia;

(8) United States Patent No. 5,122,522 discloses the use of pirenzepine and other muscarinic antagonists in the treatment of myopia; and

(9) United States Patent No. 5,637,604 discloses the use of muscarinic antagonists in the treatment and control of ocular development.

**Summary of the Invention:**

The present invention is directed to a new group of compounds and to the use of these compounds to treat various conditions that directly or indirectly involve muscarinic receptors. The compounds may also be used to treat the symptoms of other types of conditions or injuries, based on the action of the compounds on muscarinic receptors. Examples of conditions that may be treated with the compounds of the present invention include glaucoma, myopia, dry eye and dry mouth (xerostoma). The compounds may also be utilized to treat conditions of the central nervous system, such as psychosis and Alzheimer's disease. The compounds have analgesic properties, and may therefore be used to treat various types of pain.
As indicated above, the compounds of the present invention are particularly useful in the treatment of glaucoma, based on the ability of the compounds to regulate intraocular pressure or "IOP". Like pilocarpine, the compounds of the present invention are believed to control IOP via an action on muscarinic receptors. However, they are more potent than pilocarpine in lowering IOP, and, at a dose that causes an equal reduction in IOP, demonstrate a reduced level of miosis. The production of miosis (i.e., pupil constriction) has been a very troublesome side effect of pilocarpine therapy. The compounds of the present invention are also believed to be relatively free of the other major side effects associated with pilocarpine therapy, namely, impairment of accommodation and browache.

Detailed Description of the Invention:

The compounds of the present invention have the following formula:

\[ \text{(I)} \]

wherein:

m and n are independently 0 or 1;
o and p are independently 1 or 2;
\begin{eqnarray*} \end{eqnarray*} represents a double or single bond;
X is C(R)₂, O, S(O)₂, NR, C(=O), CHOR, C=NOR, NC(=O)OR, NC(=O)N(R)₂,
NC(=O)R, CHC(=O)OR, CHC(=O)N(R)₂, CHC(=O)R, NS(O)₂C(R)₃,

wherein:

q is 0, 1 or 2;
R is H, lower alkyl, arylalkyl, alkenyl, alkynyl or cycloalkyl;
D is CH or N;
E is C=O, S(=O), S(=O)₂, C=S or C=NR; and
J is O, CR, C(R)₂, NR or NRC(=O);

R₁, R₂ and R₃ are independently H, lower alkyl, halogen, lower alkoxy, OH, HOCH₂,
aryl, arylalkyl, SR or N(R)₂; and
A is selected from the group consisting of:

wherein:

G and G’ are independently H, lower alkyl, arylalkyl, alkynyl, alkenyl,
cycloalkyl, aryl or heteroaryl;
J² is O, CR, C(R)₂, NR or NRC(=O);
Y is H, lower alkyl, halogen, lower alkoxy, OH, HOCH₂, SR, N(R)₂, C(O)OR
or OC(O)R; and
a, b, c and d are selected from the group consisting of CH and N such that no
more than two of a, b, c and d are N, with the proviso that a,b,c and d are not
CH when: m, n, o and p are 1; J is NR where R is H; E is C=O; D is N; and X is
C(R)₂, NR, C(=O), CHOR, NC(=O)OR, NC(=O)N(R)₂, NC(=O)R,
CHC(=O)OR, CHC(=O)N(R)₂ or CHC(=O)R, where R is alkyl, alkoxy,
arylalkyl or cycloalkyl.

In the foregoing description of the compounds of formula (I), terms utilized to describe
certain substituents (e.g., “alkyl”) have the following meaning:
The term “alkyl” includes straight or branched chain aliphatic hydrocarbon groups that are saturated and have 1 to 15 carbon atoms (C₁ to C₁₅). The alkyl groups may be substituted with other groups, such as halogen, hydroxyl or alkoxy. Preferred straight or branched alkyl groups include methyl, ethyl, propyl, isopropyl, butyl and i-butyl.

The term “cycloalkyl” includes straight or branched chain, saturated or unsaturated aliphatic hydrocarbon groups which connect to form one or more rings, which can be fused or isolated. The rings may be substituted with other groups, such as halogen, hydroxyl or lower alkyl. Preferred cycloalkyl groups include cyclopropyl, cyclobutyl, cylopentyl and cyclohexyl.

The term “alkenyl” includes straight or branched chain hydrocarbon groups having 1 to 15 carbon atoms (C₁ to C₁₅) with at least one carbon-carbon double bond. The chain hydrogens may be substituted with other groups, such as halogen. Preferred straight or branched alkenyl groups include, allyl, 1-butenyl, 1-methyl-2-propenyl and 4-pentenyl.

The term “alkynyl” includes straight or branched chain hydrocarbon groups having 1 to 15 carbon atoms (C₁ to C₁₅) with at least one carbon-carbon triple bond. The chain hydrogens may be substituted with other groups, such as halogen. Preferred straight or branched alkynyl groups include, 2-propynyl, 2-butylnyl, 3-butylnyl, 1-methyl-2-propynyl and 2-pentynyl.

The term “alkoxy” represents an alkyl group attached through an oxygen linkage.

The term “lower alkyl” represents alkyl groups containing 1 to 6 carbons (C₁ to C₆).

The term “lower alkoxy” represents alkoxy groups containing 1 to 6 carbons (C₁ to C₆).

The term “halogen” represents fluoro, chloro, bromo, or iodo.

The term “aryl” refers to carbon-based rings which are aromatic. Aromatic rings have alternating double and single bonds between an even number of atoms forming a system which
is said to ‘resonate’. The rings may be isolated, such as phenyl, or fused, such as naphthyl. The ring hydrogens may be substituted with other groups, such as lower alkyl, or halogen.

The term “heteroaryl” refers to aromatic or semiaromatic hydrocarbon rings which contain at least one heteroatom, such as O, S, or N. The heteroatoms are located in the ring adjacent to another C or N ring member. Heteroaryl rings may be isolated, with 5 to 6 ring atoms, or fused, with 8 to 10 atoms. The heteroaryl ring(s) hydrogens or heteroatoms with open valency may be substituted with other groups, such as lower alkyl or halogen. Examples of heteroaryls include pyridine, indole, quinoline, furan, thiophene and pyrrole.

The preferred compounds of formula (I) are those wherein: m is 1; p is 1; and X is CHOR, C=NOR, NC(=O)OR, NC(=O)ON(R), NC(=O)R, CHC(=O)OR, CHC(=O)N(R), CHC(=O)R, NS(O)₂C(R). Among these preferred compounds, the most preferred compounds are those wherein m, n, o and p are 1; X is CHOR, C=NOR, NC(=O)OR, NC(=O)ON(R), NC(=O)R, CHC(=O)OR, CHC(=O)N(R), NS(O)₂C(R); R is H, lower alkyl; alkenyl, alkenyl, or cycloalkyl; R¹, R² and R³ are H, lower alkyl, lower alkoxy, OH or HOCH₂; and A is

Pharmaceutically acceptable salts of the compounds formula (I) may also be utilized in the present invention. Examples of such salts include inorganic and organic acid addition salts such as hydrochloride, hydrobromide, sulphate, phosphate, acetate, fumarate, maleate, citrate, lactate, tartrate, oxalate, or similar pharmaceutically acceptable inorganic or organic acid addition salts.

The compounds of the present invention may be prepared by the method illustrated in scheme 1 below:
Compound (3) is prepared by combining compounds (1), (2) and a reducing agent such as sodium cyanoborohydride or sodium triacetoxyborohydride at a temperature of 20°C to 40°C and a pH in the range of 2-7.

The starting materials (1) and (2) are either commercially available or can be obtained by conventional procedures. The use of certain protecting groups and deprotecting steps may be necessary, as will be appreciated by those skilled in the art. Compounds of the formula (3) may exist as mixtures of stereoisomers. The preparation of individual stereoisomers may be effected by the chromatographic separation of the stereoisomers or by the selective control of the reaction conditions.

The compounds of formula (1) are utilized to treat glaucoma, myopia and dry eye by topically applying a solution or other suitable ophthalmic composition containing the compound to the eye. The establishment of a specific dosage regimen for each individual patient is left to the discretion of clinicians. The amount of the compound applied to the eye with each dose may vary, depending on the severity of the condition being treated, the drug release characteristics of the compositions in which the compound is contained, and various other factors familiar to those skilled in the art. The amount of compound administered topically to the eye will generally be in the range of from about 0.3 to about 300 micrograms per dose, preferably from about 2 to about 100 micrograms per dose.
The compounds may be administered by topically applying one to two drops of a solution or comparable amount of a microemulsion, suspension, solid, or semi-solid dosage form to the affected eye(s) one to four times per day. The concentration of the compounds of formula (I) in such compositions will vary, depending on the type of composition utilized. For example, it may be possible to use a relatively lower concentration of the compound when compositions which provide for sustained release of the compounds or compositions which include a penetration enhancer are utilized. The concentrations generally will be in the range of from about 0.001 to about 1 percent by weight, based on the total weight of the composition ("wt.%"), preferably from about 0.01 to about 0.3 wt.%. 

The compounds of formula (I) may be included in various types of ophthalmic compositions. Since the compounds are relatively stable and soluble in water, the compositions will generally be aqueous in nature. Aqueous solutions are generally preferred, based on ease of formulation, as well as patients' ability to easily administer such compositions by means of instilling one to two drops of the solutions in the affected eyes. However, the compounds may also be readily incorporated into other types of aqueous compositions, such as viscous or semi-viscous gels or other types of solid or semi-solid compositions.

In addition to the compounds of formula (I) and the aqueous vehicles described above, the compositions of the present invention may also include one or more ancillary ingredients, such as preservatives, co-solvents and viscosity building agents.

Ophthalmic products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use. Suitable preservatives include: benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, polyquaternium 1, or other agents known to those skilled in the art. Such preservatives are typically employed at a level of from 0.001% to 1.0% by weight.

In order to enhance the aqueous solubility of the compounds of formula (I), a surfactant or other appropriate co-solvent may be included in the compositions. Such co-solvents include: polyethoxylated castor oils, such as those manufactured by BASF under the Cremophor® brand;
Polysorbate 20, 60 and 80; nonionic surfactants, such as the following Pluronic® brand surfactants of BASF: Pluronic® F-68, F-84 and P-103; cyclodextrin; or other agents known to those skilled in the art. Such co-solvents are typically employed at a level of from 0.01% to 2% by weight.

Viscosity greater than that of simple aqueous solutions may be desirable to increase ocular absorption of the compound, to decrease variability in dispensing the formulations, to decrease physical separation of components of a suspension or emulsion of formulation and/or otherwise to improve the ophthalmic formulation. Such viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose or other agents known to those skilled in the art. Such agents are typically employed at a level of from 0.01% to 2% by weight.

An appropriate buffer system (e.g., sodium phosphate or sodium acetate or sodium borate) may be added to prevent pH drift under storage conditions.

The compounds of formula (I) may also be utilized to treat psychosis, Alzheimer’s disease, dry mouth, pain and various other conditions. The compounds may be administered by any convenient method, for example, by oral, parenteral, buccal, rectal or transdermal administration. The compounds may be administered via conventional pharmaceutical compositions adapted for such administration. The compositions are generally provided in unit dose form (e.g., tablets), comprising 0.5 - 100 mg of one or more compounds of formula (I) in a pharmaceutically acceptable carrier, per each unit dose. The dosage of the compounds is 1 - 300 mg/day, preferably 10 - 100 mg/day, when administered to patients, e.g. humans, as a drug. The compounds may be administered one to four times a day.

The methods for synthesizing the compounds of formula (I) and the pharmaceutical compositions of the present invention are further illustrated by the following examples. The term “Compound” in Examples 9 and 10 is intended to represent a compound of formula (I) or a pharmaceutically acceptable salt thereof.
Example 1

Preparation of 1,3-dihydro-4-phenyl-1-(1-ethoxycarbonylpiperidine-4-yl)piperidine-4-yl-4-imidazol-2-one:

Step 1
Preparation of ethyl 4-[(2-acetophenyl)]amino-1-piperidinecarboxylate.

To a stirred solution of 2-bromoacetophenone (3.00 g, 15.0 mmol) in EtOH (20 mL) was added ethyl 4-amino-1-piperidinecarboxylate (2.59 mL, 15.0 mmol). The resulting mixture was heated at 60°C for 1 h. The solution was cooled to ambient temperature, and a solid formed. The solid was removed by filtration and the filtrate was concentrated under reduced pressure. The residue triturated with ether and the solid that formed was collected by filtration. The solids were combined and dried under reduced pressure to give the title compound (3.20 g, 74%). This was treated with ethanolic HCl to form the title compound as a white solid. m.p. 210°C; 1H NMR(CDCl3) δ 9.12(2H, brs, -NH-), 8.04(2H,m,phenyl H), 7.88(1H,t,J=7.4 Hz, phenyl H), 7.62(2H,m,phenyl H), 4.87(2H,s), 4.66(1H,m), 4.14(5H, m,COOCH2CH3), 3.39(2H,m-), 2.82(2H,t, J=30.6 Hz), 2.18 (2H,m), 1.56 (2H,m), 1.67(2H,m), 1.14 (3H,t,J=8.0 Hz, -COOCH2CH3); MS m/z 291(M+1).

Step 2
Preparation of 1,3-dihydro-4-phenyl-1-(4-ethylpiperidine carboxyl)-imidazol-2-one.

To a stirred solution of ethyl 4-[(2-acetophenyl)]amino-1-piperidinecarboxylate (1.66 g, 5.1 mmol) in water (10 mL) was added KOCN and the resulting suspension was heated at reflux for 4 hours ("h"). The solution was cooled to room temperature, and the solid that formed was collected by filtration. The solid was washed with water (2 x 20 mL) and dried to give the title compound (1.20 g, 75%) as a white solid. m.p. 187-189°C; 1H NMR(CDCl3) δ 10.79(1H, brs, -NHCO-), 7.41(5H,m,phenyl H), 6.52(1H,s,CH=), 5.05(2H,s), 4.66(1H,m), 4.34(2H, m), 4.22(2H,q, J= 8.0 Hz -COOCH2CH3), 2.60(3H,m), 2.98(2H, t, J= 12.0 Hz), 1.96(2H,m), 1.67(2H,m), 1.29(3H,t,J=8.0 Hz, -COOCH2CH3); MS m/z 316(M+1).
Step 3
Preparation of 1,3-dihydro-4-phenyl-1-piperidinyl-imidazol-2-one.

A mixture of 1,3-dihydro-4-phenyl-1-(4-ethylpiperidine carboxyl)-imidazol-2-one (0.94 g, 2.9 mmol) in 2N sodium hydroxide (30 mL) was heated at 90°C for 16 h. The solution was cooled to room temperature and sodium ammonium chloride was added (3.0 g, 56 mmol). After 30 min the mixture was extracted with chloroform (4 x 25 mL). The combined extracts were washed with brine (30 mL), dried (magnesium sulfate) and evaporated under reduced pressure. The crude residue was purified by chromatography using silica gel (methylene chloride/methanol, 8:2) to give 0.39 g of the title compound as a tan solid.; ¹H NMR(CDCl₃) d 10.79(1H, brs, -NHCO-), 7.78-7.01 (5H, m, phenyl H), 6.52 (1H, s, C-CHN-), 4.26 (1H, m), 3.15, (2H, m), 2.70 (3H, m), 2.98-1.96 (2H, m), 1.67 (2H, m); MS m/z 244 (M+1).

Step 4
Preparation of 1,3-dihydro-4-phenyl-1-(1-ethoxycarbonylpiperidine-4-yl)piperidine-4-yl-4-imidazol-2-one hydrochloride.

To a stirred solution of 1,3-dihydro-4-phenyl-1-piperidinyl-imidazol-2-one (0.39, g 1.59 mmol) in a mixture of 1,2 dichloroethane (20.0 mL) and acetic acid (0.10 mL) was added sodium triacetoxyborohydride (0.58 g, 2.54 mmol) and 1-carboxy-4-piperidone (0.41 g, 2.38 mmol). The resulting solution was stirred at room temperature for 72 h. The solution was then poured into chloroform (100 mL) and the organic layer was washed with a saturated aqueous solution of sodium bicarbonate (50 mL), brine (50 mL), dried (magnesium sulfate) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (methylene chloride/methanol, 95:5) to give 0.36 g of the free base of the title compound. The free base was dissolved in ethanol and the resulting solution was treated with ethanolic HCl. The solid that formed was recrystallized from 2-propanol to provide the title compound as a white solid. mp 247-250°C, ¹H NMR(DMSO-d₆) d 10.82(2H, brs, -NHCO- and -NH-), 7.52(1H, m, phenyl H), 7.35(2H, m , phenyl H), 7.22(1H, m phenyl H), 6.94(1H, s, C=CH-N-), 4.14(5H, m), 3.54-3.19(6H, m), 1.61(2H, m), 1.19(3H, t, J=4.8 Hz, -COOCH₂CH₃); MS m/z 399 (M+1); Analyzed for C₂₃H₂₄N₂O₅ Cl; 0.8M H₂O: Calculated C, 58.80; H, 7.31; N, 12.47; Found C, 58.85; H, 7.32; N, 12.08.
Example 2
Preparation of 1,3-dihydro-1-[1-((ethoxycarbonyl)piperidin-4-yl)piperidin-4-yl]-2H-benzimidazol-2-thione:

A solution of N-(2-aminophenyl) [1-((ethoxycarbonyl)piperidin-4-yl)piperidin-4-yl] amine (0.2 g, 0.58 mmol) (W.J. Thompson, et al, U.S. Patent 5,574,044) in ethyl acetate (10 ml) was cooled in an ice bath. The solution was treated with aqueous saturated potassium carbonate (10 ml) and thiophosgene (0.044 ml, 0.58 mmol) and stirred for 30 minutes. Then the ice bath was removed and the reaction was stirred overnight at room temperature. The reaction mixture was diluted with dichloromethane (100 ml) and washed with brine (100 ml). The organic layer was dried over magnesium sulfate and concentrated in vacuo to give a yellow foamy solid, 0.15 g. This residue was purified by chromatography using silica gel and ethyl acetate to give the title compound as a yellow solid, 80 mg (36%), mp 100-3 °C, MS (M + H+) = 398 m/e.

Example 3
Preparation of 1,3-dihydro-1-[1-[1-ethoxycarbonylpiperidin-3-yl]piperidin-4-yl]-2H-benzimidazol-2-one:

Step 1
Preparation of 1-ethoxycarbonylpiperidin-3-ol.

To a solution of 3-hydroxypiperidine HCl (5.0 g, 36.3 mmol) and sodium carbonate (7.70 g, 72.6 mmol) in water (50 mL) at 0°C was added ethyl chloroformate (4.16 mL, 43.6 mmol). The suspension was stirred for 30 min, and then extracted with EtOAc (100 mL x 3). The volatiles were evaporated to give the title compounds as an oil (6.30 g, 98%): 1H NMR (CDCl3) 4.13 (q, J = 6.0 Hz, CH2Me, 2 H), 3.65 (m, 2H), 3.56 (m, 1H), 3.19 (m, 2H), 2.0-1.7 (m, 3 H), 1.50 (m, 2 H), 1.26 (t, J = 6.0 Hz, 3 H).

Step 2
Preparation of 1-ethoxycarbonylpiperidin-3-one.
To a solution of 1-ethoxycarbonylpiperidin-3-ol (6.15 g, 35.5 mmol) in methylene chloride (150 mL) maintained at room temperature was added DCC (15.32 g, 71.0 mmol). The suspension was stirred overnight. Ether (100 mL) was added to the reaction mixture and the suspension was stirred for 10 min. The resulting mixture was filtered through celite and the filtrate was concentrated in vacuo. The residue was washed with brine (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel (50% EtOAc/Hexane) to give 1.54 g (25%) of the title compound as a liquid: MS(Cl) 172 (M+H); $^1$H NMR (CDCl$_3$) 4.18 (q, J = 6.0 Hz, CH$_2$Me, 2 H), 4.05 (s, NCH$_2$O, 2 H), 3.64 (t, J = 6.0 Hz, CH$_2$, 2H), 2.48 (t, J = 6.0 Hz, CH$_2$, 2 H), 2.00 (m, CH$_2$, 2H), 1.27 (t, J = 6.0 Hz, 3 H).

Step 3

Preparation of 1,3-dihydro-1-[1-ethoxycarbonylpiperidin-3-yl]piperidin-4-yl]-2H-benzimidazol-2-one.

To a mixture of 4-(2-keto-1-benzimidazoliny1)piperidine (0.434 g, 2.0 mmol), 1-ethoxycarbonylpiperidin-3-one (0.512 g, 3.0 mmol), and glacial acetic acid (0.127g, 2.12 mmol) in methylene chloride (10 mL) at ambient temperature was added sodium triacetoxyborohydride (0.695 g, 3.28 mmol). The mixture was stirred for 2h; during this period a precipitate formed. A saturated aqueous solution of sodium bicarbonate (30 mL) was added and the resulting mixture was extracted with methylene chloride (50 mL x 3). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated in vacuo. Crystallization of the residue from EtOAc (5 mL) gave 0.153 g of a solid that was collected by filtration. Concentration of the filtrate and purification of the residue by chromatography on silica (methanol/methylene chloride 20:1) gave an additional 0.213 g of solid. The combined yield of the title compound was 49%. mp 186-189°C; MS(Cl) 373 (M+H); $^1$H NMR (CDCl$_3$) $\delta$ 9.24 (s, NHCO, 1H), 7.26 (m, ar, 1H), 7.10 (m, ar,3H), 4.35 (m, 2 H), 4.13 (q, J = 6.0 Hz, CH$_2$Me, 2 H), 4.05 (m, 1H), 3.11 (m, 2 H), 2.71 (m, 2H), 2.43 (m, 4H), 2.0-1.7 (m, 6 H), 1.46 (m, 2H), 1.27 (t, J = 6.0 Hz, Me, 3H).
Example 4
Preparation of 1,3-dihydro-1-[(1-ethoxycarbonylpiperidine-4-yl) 1, 2, 3, 6-tetrahydro-4-piperidinyl]-2H-benzimidazole-2-one:

To a stirred solution of 1,3-dihydro-1-(1, 2, 3, 6-tetrahydro-4-pyridinyl)-2H-benzimidazole-2-one (1.02 g, 4.7 mmol) in 1, 2-dichloroethane (15.0 mL) was added in sequence: acetic acid (0.28 mL, 4.98 mmol), sodium triacetoxyborohydride (1.60 g, 7.50 mmol), and 1-carboethoxy-4-piperidone (1.21 g, 7.1 mmol). The reaction mixture was then stirred at ambient temperature for 72 h. The reaction mixture was poured into methylene chloride (100 mL) and the resulting mixture washed with a saturated sodium bicarbonate solution (50 mL) and brine (50 mL). The organic layer was dried with magnesium sulfate and concentrated in vacuo to give a solid which was purified by recrystallization (ethyl acetate) to give 0.36 g (21%) of the title compound as a white solid. mp 155-157°C; 'H NMR (DMSO-d6) δ 10.06 (1H, brs, -NHCO), 7.08 (4H, m, phenyl H), 5.97 (1H, d, J=2.0 Hz, -C=CH-CH3), 4.23 (1H, m), 4.15 (2H, q, J=4.8 Hz, -COOCH2CH3), 3.40 (2H, d, J=2.0 Hz, -C=CH-CH3), 2.92 (2H, m) 2.86 (2H, m), 1.96 (4H, m), 1.55 (2H, m), 1.27 (3H, t, J=4.8 Hz, -COOCH2CH3); MS m/z 371 (M + 1); Analyzed for C29H36N3O4 0.2M H2O: Calculated: C, 64.22; H, 7.11; N, 14.98; Found: C, 64.10; H, 6.95; N, 14.95.

Example 5
Preparation of 1,3-dihydro-1-[(1-ethoxyethylcarbonylpiperidin-4-yl)piperidin-4-yl]-2H-benzoxazolin-2-one hydrochloride:

Step 1
Preparation of 1-benzyl-4-(2-methoxyphenyl)aminopiperidine.

To a mixture of N-benzyl-4-piperidone (12.3 g, 65 mmol) and 2-methoxyaniline, (5.43 g, 43.38 mmol) in 100 mL of methylene chloride was added 0.74 mL of acetic acid glacial followed by sodium triacetoxyborohydride (14.9 g, 70.5 mmol). The reaction mixture was stirred at room temperature for 48 h and then poured into a mixture of 200 mL of CHCl3 and 200 mL of saturated aqueous Na2CO3. The layers were separated. The aqueous layer was extracted with CHCl3 (2 x 100 mL) and the combined organic extracts dried (MgSO4) and
concentrated under reduced pressure to give the title compound as an oil. MS (ES) m/e 297 (M+H)+. 1H NMR (CDCl3) δ 1.48 (m, 2H), 2.01 (m, 4H), 2.74 (d, 2H), 3.29 (m, 1H), 3.52 (s, 2H), 3.82 (s, 3H), 4.08 (m, 1H), 6.58-6.88 (m, 4H), 7.27 (m, 5H).

Step 2
Preparation of 1,3-dihydro-1-(1-benzylpiperidin-4-yl)-2H-benzoxazolin-2-one.

1-Benzyl-4-(2-methoxyphenyl)aminopiperidine (5 g, 16.85 mmol) was dissolved in HBr 47% (20 mL) and warmed at reflux for 4 h. The reaction mixture was cooled to room temperature and the volatiles were removed under reduced pressure. To the residue was added dichloromethane (100 mL), triethylamine (6.8 g, 67.4 mmol) and 4-nitrophenyl chloroformate (6.8 g, 33.7 mmol). The reaction mixture was stirred at room temperature for 3 h and then washed with 1N NaOH (20 mL). The organic layer was dried (Na2SO4), and the solvent evaporated under vacuum to give 2 g (42%) of the title compound as an oil. MS(ES)309 (M+1). 1H NMR (CDCl3) δ 1.75 (m, 2H), 2.01 (m, 4H), 3.00 (d, 2H), 3.50 (s, 2H), 4.14 (m, 1H), 7.04-7.29 (m, 9H).

Step 3
Preparation of 1,3-dihydro-1-(piperidine-4-yl)-2H-benzoxazolin-2-one hydrochloride.

1,3-Dihydro-1-(1-benzylpiperidin-4-yl)-2H-benzoxazolin-2-one (2 g, 6.49 mmol) was dissolved in tetrahydrofuran (50 mL) and ammonium formate was added (0.82 g, 12.97 mmol) followed by 1 g of 10% Pd/C. The mixture was stirred at room temperature overnight. The reaction mixture was filtered and the filtrate concentrated in vacuo. The residue was dissolved in ether and transformed to the hydrochloride salt providing the title compound as a white solid. MS(ES) 219 (M+1). 1HNMR (CDCl3) δ 1.77 (m, 2H), 2.11 (m, 4H), 3.02 (m, 2H), 3.55 (m, 1H), 4.13 (m, 1H).
Step 4
Preparation of 1,3-dihydro-1-[1-(1-ethoxy carbonyl piperidin-4-yl)piperidin-4-yl]-2H-benzoxazolin-2-one hydrochloride.

From 1-ethoxycarbonyl piperidine and 1,3-dihydro-1-(piperidine-4-yl)-2H-benzoxazolin-2-one hydrochloride using the procedures described for Example 4, there was obtained the title compound as a white solid. mp> 270 °C. MS(ES) 375 (M+1). \(^1\)H NMR (DMSO, \(d_6\)) \(d\) 1.28 (t, 3H), 1.67 (m, 2H), 2.16 (m, 4H), 2.93 (m, 4H), 3.25-3.75 (m, 5H), 4.10 (m, 4H), 4.68 (m, 1H), 7.14-7.95 (3 sets, 4H), 11.46 (m, 1H). Analyzed for C\(_{20}\)H\(_{27}\)N\(_3\)O\(_4\) 0.2 H\(_2\)O. Calculated: C: 58.09; H: 6.92; N: 9.85, Found: C: 58.07; H: 7.04; N: 10.16.

Example 6
Preparation of 3-[1-(1-ethoxycarbonyl-4-piperidin-4-yl)piperidin-4-yl]-2-indolinone hydrochloride:

Step 1
Preparation of 3-(1-tert-butoxycarbonyl-4-piperidylidene)-2-indolinone.

Anhydrous ammonia was bubbled into a solution of 2-indolone (5.88 g, 44.16 mmol) and 1-tert-butoxycarbonyl-4-piperidone (8.96 g, 44.96 mmol) in ethanol (100 mL) until the solution was saturated with ammonia. The reaction mixture was then heated in a sealed tube at 80 °C for 4h. The reaction mixture was cooled to ambient temperature. The yellow solid that formed was collected by filtration and dried to give 10 g (72 %) of the title compound. mp 208-210 °C. MS(ES): 315 (M+1) \(^1\)H NMR (DMSO, \(d_6\)) \(d\) 1.29 (s, 9H), 2.81 (m, 2H), 3.29 (m, 4H), 3.47 (m, 2H), 6.66 (d, 1H), 6.81 (t, 1H), 7.05 (t, 1H), 7.41 (d, 1H), 10.36 (s, 1H).

Step 2
Preparation of 3-(1-tert-butoxycarbonyl-4-piperidyl)-2-indolinone.

To a solution of 3-(1-tert-butoxycarbonyl-4-piperidylidene)-2-indolinone (6 g, 19.11 mmol) in methanol was added 2 g of 10 % Pd/C in methanol. The resulting slurry was hydrogenated using a Parr Apparatus. After 2 h the reaction mixture was filtered, and the filtrate
concentrated under reduced pressure to provide the title compound as a white solid. mp 180-
182 °C. \(^1\)H NMR (DMSO, \(d_6\)) d 1.47 (s, 13H), 2.25 (m, 1H), 2.75 (m, 2H), 3.51 (d, 2H), 4.06 (m, 1H), 6.90 (d, 1H), 6.94 (t, 1H), 7.29 (m, 2H), 10.49 (s, 1H).

**Step 3**
Preparation of 3-(4-piperidyl)-2-indolinone.

A suspension of 3-(1-tert-butoxycarbonyl-4-piperidyl)-2-indolinone (5 g, 24.15 mmol) in 100 mL of 1 M aqueous HCl was warmed at reflux overnight. The homogenous solution that formed was cooled to room temperature and neutralized by adding a saturated solution of bicarbonate. Addition of methylene chloride and brine resulted in the formation of a solid which was collected by filtration. mp, decomposition starting at 220 °C. \(^1\)H NMR (DMSO, d6) d 1.47 (m, 4H), 2.11 (m, 1H), 2.52 (m, 2H), 3.46 (d, 1H), 3.73 (m, 2H), 6.81 (d, 1H), 6.94 (t, 1H), 7.21 (m, 2H), 10.48 (s, 1H).

**Step 4**
Preparation of 3-[1-(1-ethoxycarbonyl-4-piperidin-4-yl)piperidin-4-yl]-2-indolinone hydrochloride.

From 3-(4-piperidyl)-2-indolinone and 1-ethoxycarbonyl-4-piperidone using the procedures described for Example 4, there was obtained the title compound. MS(ES): 372 (M+1) \(^1\)H NMR (DMSO, \(d_6\)) d 1.19 (t, 3H), 1.44 (m, 3H), 1.80 (m, 2H), 2.03 (m, 3H), 2.35 (m, 1H), 2.75 (m, 2H), 2.95 (m, 2H), 3.2-3.6 (m, 4H), 4.01 (m, 4H), 6.80-7.30 (m, 4H), 10.45 (m, 2H). Analyzed for C\(_{31}\)H\(_{29}\)N\(_3\)O\(_3\)HCl 0.1H\(_2\)O Calculated: C 59.22; H 7.57; N 9.86; Found: C 58.46; H 7.40; N 9.81.

**Example 7**
Preparation of 1,3-dihydro-1-[1-(3-propargyloxycarbonyl)piperidine-4-yl]piperidin-4-yl]-2H-benzimidazol-2-one:
Step 1
Preparation of 1,3-dihydro-1-[1-[1-(tert-butyloxycarbonyl)piperidine-4-yl]piperidin-4-yl]-2H-benzimidazol-2-one.

To a mixture of N-tert-butyloxycarbonyl-4-piperidone (6.86 g, 34.4 mmol) and 4-(2-oxo-1-benzimidazoliny1) piperidine (5 g, 23 mmol) in 100 mL of CH₂Cl₂ was added 1.4 mL of acetic acid glacial followed by sodium triacetoxyborohydride (8 g, 37.7 mmol). The reaction mixture was stirred at room temperature for 24 h and then poured into 200 mL of CHCl₃ and 200 mL of saturated aqueous Na₂CO₃. The layers were separated and the aqueous layer was extracted with CHCl₃ (2 x 100 mL). The combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure. Recrystallization of the crude residue from 100 mL of ethyl acetate gave 7 g (76%) of the title compound in two crops. MS (Cl) m/e 401 (M+H). Analyzed for C₂₅H₃₀N₄O₃. 0.2 H₂O. Calculated: C: 65.39; H: 8.08; N: 13.86. Found: C: 65.29; H: 8.01; N: 13.87.

Step 2
Preparation of 1,3-dihydro-1-[1-(1-piperidine-4-yl)piperidin-4-yl]-2H-benzimidazol-2-one dihydrochloride.

A suspension of 1,3-dihydro-1-[1-[1-(tert-butyloxycarbonyl)piperidine-4-yl]piperidin-4-yl]-2H-benzimidazol-2-one (7.0g, 17.5 mmol) in 150 mL of 1N HCl was warmed at reflux for 4 h, cooled to room temperature and concentrated under reduced pressure. The residue was dried overnight under vacuum, to provide 7 g (100%) of the title compound as a white solid. MS (Cl) m/e 301 (M+H). Analyzed for C₁₂H₁₃N₄O. 2HCl .0.2 H₂O. Calculated: C: 50.13; H: 6.93; N: 13.75 Found: C: 50.31; H: 7.21; N: 13.77.

Step 3
Preparation of propargyl-4-nitrophenyl carbonate.

To a solution of 4-nitrophenyl chloroformate (1.0 g, 5.3 mmol) in CHCl₃ (50 mL) was added pyridine (0.42 g, 5.3 mmol) followed by propargyl alcohol (.29 g, 5.3 mmol). The reaction mixture was stirred at room temperature for 3 h and then washed with 1N NaOH (20 mL), the
organic layer was separated, dried (Na$_2$SO$_4$), and the solvent evaporated under reduced pressure to give 1 g (72%) of the title compound as a yellow-white solid which was purified by re-crystallization (ethyl acetate-hexane (2-8)). mp 100-102 °C, $^1$H NMR (DMSO, d$_6$) d 2.63 (m, 1H), 4.86 (m, 2H), 7.42 (d, 2H), 8.28 (d, 2H).

Step 4
Preparation of 1,3-dihydro-1-[1-[1-(3-propargyloxycarbonyl)piperidine-4-yl]piperidin-4-yl]-2H-benzimidazol-2-one.

A mixture of 1,3-dihydro-1-[1-(1-piperidine-4-yl)piperidin-4-yl]-2H-benzimidazol-2-one dihydrochloride (0.50 g, 1.35 mmol), propargyl-4-nitrophenyl carbonate (0.32 g, 1.35 mmol) and 1.1 mL of triethylamine in 20 mL of tetrahydrofuran was stirred for 12 h. The mixture was diluted with 100 mL of chloroform, washed with 20 mL of NaOH, dried (MgSO$_4$) and concentrated under reduced pressure. Drying under reduced pressure afforded a white solid which was recrystallized twice from ethyl acetate to give 0.2 g of the title compounds as a white solid. Mp: 202-205 °C. Analyzed for C$_{23}$H$_{26}$N$_4$O$_3$. 0.2 H$_2$O Calculated: C: 65.33; H: 6.98; N,14.51 Found: C, 65.24; H: 6.81; N: 14.37.

Example 8
Preparation of 1, 3-dihydro-1-[1-(1-methanesulfonylpiperidine-4-yl)piperidin-4-yl]-2H-benzimidazol-2-one hydrochloride.

From 1,3-dihydro-1-[1-(1-piperidine-4-yl)piperidin-4-yl]-2H-benzimidazol-2-one dihydrochloride and methanesulfonyl chloride using the procedure in step 5 of Example 7, there was obtained the title compound as a white solid. mp >280 °C. MS (Cl) m/e 379 (M+H)$^+$. $^1$HNMR (CDCl$_3$) d 1.28 (m, 2H), 1.87(m, 6H), 2.11 (s, 3H), 2.33-2.62 (m, 5H), 2.99 (m, 2H), 3.86 (m, 1H), 4.33 (m, 1H), 4.72 (m, 1H), 7.02-7.31 (m, 4H), 9.62(s, 1H). Analyzed for C$_{25}$H$_{26}$N$_4$O$_3$S, 1HCl 0.5 H$_2$O Calculated: C: 51.00; H: 6.66; N: 13.22 Found: C: 51.14; H: 6.63; N: 13.02.
Example 9

The following formulation further illustrates the topical ophthalmic pharmaceutical compositions of the present invention.

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<th>Ingredient</th>
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<td>Benzalkonium chloride</td>
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</tr>
<tr>
<td>Edetate sodium</td>
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</tr>
<tr>
<td>Sodium chloride</td>
<td>q.s. to render isosmotic</td>
</tr>
<tr>
<td>Hydrochloric acid and/or</td>
<td>q.s. to adjust pH</td>
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<tr>
<td>Sodium Hydroxide</td>
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</tr>
<tr>
<td>Purified water</td>
<td>q.s. to 100% of volume</td>
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</table>

Example 10

The following formulation further illustrates the systemic pharmaceutical compositions of the present invention, particularly oral tablet compositions.

<table>
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</thead>
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<tr>
<td>Lactose</td>
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<tr>
<td>Avicel™</td>
<td>31.5 mg</td>
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</tr>
<tr>
<td>Magnesium Stearate</td>
<td>0.25 g</td>
</tr>
</tbody>
</table>
What is claimed is:

1. A compound of the following formula:

\[
\begin{array}{c}
\text{A} \quad \text{R}^1 \quad \text{R}^2 \\
\text{X} \quad \text{R}^3 \\
\end{array}
\]

wherein:

- \( m \) and \( n \) are independently 0 or 1;
- \( o \) and \( p \) are independently 1 or 2;
- \( \cdots \) represents a double or single bond;
- \( X \) is \( C(R)_2 \), \( O \), \( S(O)_q \), \( NR \), \( C(=O) \), \( CHOR \), \( C=NR \), \( NC(=O)OR \), \( NC(=O)N(R)_2 \), \( NC(=O)R \), \( CHC(=O)OR \), \( CHC(=O)N(R)_2 \), \( CHC(=O)R \), \( NS(O)_2C(R)_3 \);

\[
\begin{array}{c}
\text{oxygen} \\
\text{or} \\
\text{benzene} \\
\end{array}
\]

wherein:

- \( q \) is 0, 1 or 2;
- \( R \) is \( H \), lower alkyl, alkoxy, arylalkyl, alkynyl, alkenyl or cycloalkyl;
- \( D \) is \( CH \) or \( N \);
- \( E \) is \( C=O \), \( S(=O)_2 \), \( C=S \) or \( C=NR \);
- \( J \) is \( O \), \( CR \), \( C(R)_2 \), \( NR \) or \( NRC(=O) \);
- \( R^1 \), \( R^2 \) and \( R^3 \) are independently \( H \), lower alkyl, halogen, lower alkoxy, \( OH \), \( HOCH_2 \), aryl, arylalkyl, \( SR \) or \( N(R)_2 \); and
A is selected from the group consisting of:

wherein:

G and G' are independently H, lower alkyl, arylalkyl, alkynyl, alkenyl, cycloalkyl, aryI or heteroaryl;

J is O, CR, C(R)₂, NR or NRC(=O);

Y is H, lower alkyl, halogen, lower alkoxyI, OH, HOCH₂, SR, N(R)₂, C(O)OR or OC(O)R; and

a, b, c and d are selected from the group consisting of CH and N such that no more than two of a, b, c and d are N, with the proviso that a, b, c and d are not CH when: m, n, o and p are 1; J is NR where R is H; E is C=O; D is N; and X is C(R)₂, NR, C(=O), CHOR, NC(=O)OR, NC(=O)N(R)₂, NC(=O)R, CHC(=O)OR, CHC(=O)N(R)₂ or CHC(=O)R, where R is alkyl, alkoxyI, arylalkyl or cycloalkyl;

or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition for treating conditions involving muscarinic receptors, comprising a pharmacologically effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier therefor.

3. A method of controlling intraocular pressure which comprises topically applying to the affected eye a topical ophthalmic pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 1 and a pharmaceutically acceptable vehicle thereof.

- 24 -
4. A method of treating myopia which comprises topically applying to the affected eye a topical ophthalmic pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 1 and a pharmaceutically acceptable vehicle thereof.

5. A method of treating dry eye which comprises topically applying to the affected eye a topical ophthalmic pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 1 and a pharmaceutically acceptable vehicle thereof.

6. A method of treating psychosis which comprises administering to the patient a composition according to claim 2.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Category</th>
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Further documents are listed in the continuation of box C.

* Special categories of cited documents:
  *"A" document defining the general state of the art which is not considered to be of particular relevance
  *"E" earlier document published on or after the international filing date
  *"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  *"O" document referring to an oral disclosure, use, exhibition or other means
  *"P" document published prior to the international filing date but later than the priority date claimed

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

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

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

*"A" document member of the same patent family

Date of the actual completion of the international search: 28 April 1999

Date of mailing of the international search report: 26.05.99

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel: (+31-70) 340-2040, Tx: 31 651 epc nl.
Fax: (+31-70) 340-3016

Authorized officer

Fink, D
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INTERNATIONAL SEARCH REPORT

Box I  Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [x] Claims Nos.: 1-6 (partly)
   because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
   see FURTHER INFORMATION sheet PCT/ISA/210

2. [x] Claims Nos.: 1-6 (partly)
   because they relate to subject matter not required to be searched by this Authority, namely:
   Although claims 3-6 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

3. [ ] Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II  Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)
Claims Nos.: 1-6 (partly)

The definitions of the variables A, X, m, n, o, p and R1-R3 in the present compound claim 1 are such that a comprehensive novelty-search was not possible.
It appears from the description (cf. the present working examples and the passage on page 8, lines 13-22) that the 1-(piperidin-4-yl/piperidin-3-yl/cyclohexyl)-piperidine/1,2,3,6-tetrahydropyridine group is an essential structural feature of the present compounds.
Therefore, the present search - as far as the question of novelty is concerned - has been limited to those (six-membered ring) compounds of the formula (I) of the present claim 1 wherein either (i) the variables m, n, o and p are all 1 or (ii) wherein the variables n and o are 1, m is 0 and p is 2.
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