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Daugan

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[54] **USE OF CGMP-PHOSPHODIESTERASE INHIBITORS IN METHODS AND COMPOSITIONS TO TREAT IMPOTENCE**

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[52] **U.S. Cl.** **514/250**

[58] **Field of Search** 514/250

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[57] **ABSTRACT**

The use of (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione, (3S 6R,12aR)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-6-(3,4-methylenedioxyhenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione, and physiologically acceptable salts and solvates thereof, in methods and compositions for the treatment of impotence.

21 Claims, No Drawings

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USE OF CGMP-PHOSPHODIESTERASE INHIBITORS IN METHODS AND COMPOSITIONS TO TREAT IMPOTENCE

This application is a 371 of PCT/EP96/03024, filed Jul. 11, 1996.

This invention relates to the use of tetracyclic derivatives which are potent and selective inhibitors of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase (cGMP specific PDE) in the treatment of impotence.

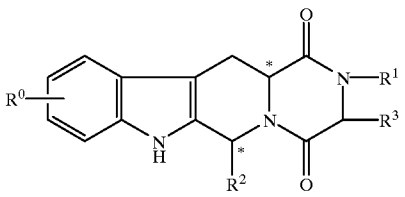
Impotence can be defined as a lack of power, in the male, to copulate and may involve an inability to achieve penile erection or ejaculation, or both. More specifically, erectile impotence or dysfunction may be defined as an inability to obtain or sustain an erection adequate for intercourse. Its prevalence is claimed to be between 2 and 7% of the human male population, increasing with age, up to 50 years, and between 18 and 75% between 55 and 80 years of age.

Reports of well-controlled clinical trials in man are few and the efficacy of orally administered drugs is low. Although many different drugs have been shown to induce penile erection, they are only effective after direct injection into the penis, e.g. intraurethrally or intracavernosally (i.c.), and are not approved for erectile dysfunction. Current medical treatment is based on the i.c. injection of vasoactive substances and good results have been claimed with phenoxybenzamine, phentolamine, papaverine and prostaglandin E_1, either alone or in combination; however, pain, priapism and fibrosis of the penis are associated with the i.c. administration of some of these agents. Potassium channel openers (KCO) and vasoactive intestinal polypeptide (VIP) have also been shown to be active i.c., but cost and stability issues could limit development of the latter. An alternative to the i.c. route is the use of glyceryl trinitrate (GTN) patches applied to the penis, which has been shown to be effective but produces side-effects in both patient and partner.

As a general alternative to pharmacological intervention, a variety of penile prostheses has been used to assist achievement of an erection. The short term success rate is good, but problems with infection and ischaemia, especially in diabetic men, make this type of treatment a final option rather than first-line therapy.

The compounds of the invention are potent inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs). GB 9514464.8, which is the priority document for the present application describes the syntheses of the compounds of the invention and their utility in impotence. WO95/19978, which was unpublished at the priority date of the present application, also describes the syntheses of the compounds of the invention and their utility in other diseases associated with inhibition of cGMP PDEs. The compounds may be represented by the following general formula (I):

(I)

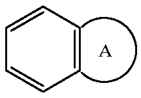


and salts and solvates (e.g. hydrates) thereof, in which:

R^0 represents hydrogen, halogen or C_{1-6} alkyl;

R^1 represents hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-3}alkyl, arylC_{1-3}alkyl or heteroarylC_{1-3}alkyl;

R^2 represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan and pyridine or an optionally substituted bicyclic ring



attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring A is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur and nitrogen; and

R^3 represents hydrogen or C_{1-3}alkyl, or R^1 and R^3 together represent a 3- or 4-membered alkyl or alkenyl chain.

Suitable individual compounds of the invention for use in the treatment of erectile dysfunction include:

Cis-2,3,6,7,12,12a-hexahydro-2-(4-pyridylmethyl)-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

Cis-2,3,6,7,12,12--hexahydro-6-(2,3-dihydrobenzo[b]furan-5-yl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

Cis-2,3,6,7,12,12a-hexahydro-6-(5-bromo-2-thienyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-methylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-isopropyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopentyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopropylmethyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3-chloro-4-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(5aR,12R,14aS)-1,2,3,5,6,11,12,14a-Octahydro-12-(3,4-methylenedioxyphenyl)-pyrrolo[1",2":4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indole-5-1,4-dione;

Cis-2,3,6,7,12,12a-hexahydro-2-cyclopropyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(3S,6R,12aR)-2,3,6,7,12,12a-hexahydro-3-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

The specific compounds of the invention are:

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione(Compound A); and

(3S,6R,12aR)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (Compound B);

and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

Unexpectedly, it has now been found that compounds of formula (I), and in particular compounds A and B, are useful in the treatment of erectile dysfunction. Furthermore the compounds may be administered orally, thereby obviating the disadvantages associated with i.c. administration. Thus the present invention concerns the use of compounds of formula (I), and in particular compounds A and B, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.

The pharmaceutically acceptable salts of the compounds of formula (I), and in particular compounds A and B which contain a basic centre are acid addition salts formed with pharmaceutically acceptable acids. Examples include the hydrochloride, hydrobromide, sulphate or bisulphate, phosphate or hydrogen phosphate, acetate, benzoate, succinate, fumarate, maleate, lactate, citrate, tartrate, gluconate, methanesulphonate, benzenesulphonate and p-toluenesulphonate salts. Compounds of formula (I), and in particular compounds A and B can also provide pharmaceutically acceptable metal salts, in particular alkali metal salts, with bases. Examples include the sodium and potassium salts.

It has been shown that compounds of the present invention are potent and selective inhibitors of cGMP specific PDE. It has now been surprisingly found that human corpus cavernosum contains three distinct PDE enzymes. The predominant PDE has further surprisingly been found to be cGMP PDE. As a consequence of the selective PDE V inhibition exhibited by compounds of the present invention, the subject compounds can elevate cGMP levels, which in turn can mediate relaxation of the corpus cavernosum tissue and consequent penile erection.

Although the compounds of the invention are envisaged primarily for the treatment of erectile dysfunction or male sexual dysfunction, they may also be useful for the treatment of female sexual dysfunction including orgasmic dysfunction related to clitoral disturbances.

Generally, in man, oral administration of the compounds of the invention is the preferred route, being the most convenient and avoiding the disadvantages associated with i.c. administration. In circumstances where the recipient suffers from a swallowing disorder or from impairment of drug absorption after oral administration, the drug may be administered parenterally, e.g. sublingually or buccally.

For administration to man in the curative or prophylactic treatment of the disorders identified above, oral dosages of a compound of formula (I), and in particular compounds A and B will generally be in the range of from 0.5–800 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules contain from 0.2–400 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier, for administration in single or multiple doses, once or several times per day. Dosages for buccal or sublingual administration will typically be within the range of from 0.1–400 mg per single dose as required. In practice the physical will determine the actual dosing regiment which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can be individual instances in which higher or lower dosage ranges may be merited, and such are within the scope of this invention.

For human use, compounds of formula (I), and in particular compounds A and B can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, the compound may be administered orally, buccally or sublingually, in the form of tablets containing excipients such as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. Such liquid preparations may be prepared with pharmaceutically acceptable additives such as suspending agents (e.g. methylcellulose, a semi-synthetic glyceride such as witepsol or mixtures of glycerides such as a mixture of apricot kernel oil and PEG-6 esters or mixtures of PEG-8 and caprylic/capric glycerides).

For veterinary use, a compound of formula (I), and in particular compound A or B or a non-toxic salt thereof is administered as a suitably acceptable formulation in accordance with normal veterinary practice and the veterinary surgeon will determine the dosing regiment and route of administration which will be most appropriate for a particular male animal.

Thus the invention includes a pharmaceutical composition for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man, comprising a compound of formula (I), and in particular compound A or B, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

There is further provided a process for the preparation of a pharmaceutical composition for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man, comprising formulating a compound of formula (I), and in particular compound A or B, or a pharmaceutically acceptable salt thereof, with a pharmaceutically acceptable diluent or carrier.

The invention also provides a method of treating a male animal, including man, to cure or prevent erectile dysfunction which comprises treating said male animal with an effective amount of a compound of formula (I), and in particular compound A or B, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity.

Moreover, the invention includes the use of a compound of formula (I), and in particular compound A or B, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.

A compound of formula (I), and in particular compound A or B, may also be used in combination with other therapeutical agents which may be useful in the treatment of erectile dysfunction substantially as hereinbefore described. The invention thus provides, in another aspect, a combination of a compound of formula (I), and in particular compound A or B together with another therapeutically active agent.

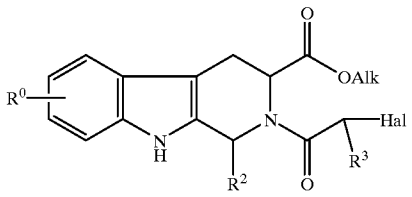
The combination referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical compositions comprising a combination as defined above together with a pharmaceutically acceptable diluent or carrier comprise a further aspect of the invention.

The individual components of such a combination may also be administered either sequentially or simultaneously in separate pharmaceutical formulations.

Appropriate doses of known therapeutic agents for use in combination with a compound of the invention will be readily appreciated by those skilled in the art.

The compounds of the invention may be prepared by any suitable method known in the art or by the following process which forms part of the present invention. The process has been previously substantially described in the priority document of the present invention GB9514464.8, and in WO95/19978. Thus, a process for preparing a compound of formula (I) comprises treating a compound of formula (I)

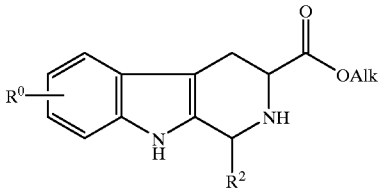
(II)



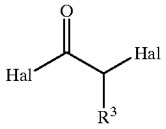
(in which Alk represents C_{1-6}alkyl, e.g. methyl or ethyl and Hal is a halogen atom, e.g. chlorine) with a primary amine R^1NH_2 in a suitable solvent such as an alcohol (e.g. methanol or ethanol) or a mixture of solvents, conveniently at a temperature of from 20° C. to reflux (e.g. at about 50° C.).

A compound of formula (II) may conveniently be prepared by treating a compound of formula (III) with a compound of formula (IV)

(III)



(IV)



in a suitable solvent such as a halogenated hydrocarbon (e.g. trichloromethane or dichloromethane), or an ether (e.g. tetrahydrofuran), preferably in the presence of a base such as an organic amine (e.g. a trialkylamine such as triethylamine) or an alkali metal carbonate or bicarbonate (e.g. $NaHCO_3$). The reaction may conveniently be effected at a temperature of from −20° C. to +20° C. (e.g. at about 0° C.).

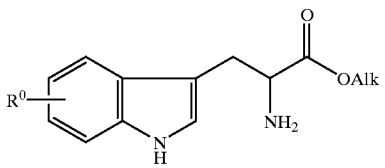
A compound of formula (I) may also be prepared from a compound of formula (III) in a two-step procedure via a compound of formula (II) isolated without purification.

Compounds of formula (I) may be prepared as individual enantiomeres in two steps for the appropriate enantiomer of formula (III) or as mixtures (e.g. racemates) of either pairs of cis or trans isomers from the correspondong mixtures of either pairs of cis or trans isomers of formula (III).

Individual enantiomers of the compounds of the invention may be prepared form racemates by resolution using methods known in the art for the separation of racemic mixtures into their constituent enantiomers, for example using HPLC (high performance liquid chromatography) on a chiral column such as Hypersil naphthylurea.

A compound of formula (III) may conveniently be prepared form a tryptophan alkyl ester of formula (V)

(V)



(where Alk is as previously defined) or a salt thereof (e.g. the hydrochloride salt) with an aldehyde R^2CHO. The reaction may conveniently be effected in a suitable solvent such as a halogenated hydrocarbon (e.g. dichloromethane) or an aromatic hydrocarbon (e.g. toluene) in the presence of an acid such as trifluoroacetic acid. The reaction may conveniently be carried out at a temperature of from −20° C. to reflux to provide a compound of formula (III) in one step. The reaction may also be carried out in a solvent such as an aromatic hydrocarbon (e.g. benzene or toluene) under reflux, optionally using a Dean-Stark apparatus to trap the water produced.

The reaction provides a mixture of cis and trans isomers which may be either individual enantiomers or racemates of pairs of cis or trans isomers depending upon whether racemic or enantiomerically pure tryptophan alkyl ester was used as the starting material. Individual cis or trans enantiomers may conveniently be separated from pictures thereof by fractional crystallisation or by chromatography (e.g. flash column chromatography) using appropriate solvents and eluents. Similarly, pairs of cis and trans isomers may be separated by chromatography (e.g. flash column chromatography) using appropriate eluants. An optically pure trans isomer may also be converted to an optically pure cis isomer using suitable epimerisation procedures. One such procedure comprises treating the trans isomer or a mixture (e.g. 1:1 mixture) of cis and trans isomers with methanolic or aqueous hydrogen chloride at a temperature of from 0° C. to the refluxing temperature of the solution. The mixture may then be subjected to chromatography (e.g. flash column chromatography) to separate the resulting diastereoisomers, or in the procedure utilising aqueous hydrogen chloride the desired cis isomer precipitates out as the hydrochloride salt which may then be isolated by filtration.

The pharmaceutically acceptable acid addition salts of a compound of formula (I), and in particular compound A or B which contain a basic centre may be prepared in a conventional manner. For example, a solution of the free base may be treated with a suitable acid, either neat or in a suitable solution, and the resulting salt isolated either by filtration or by evaporation under vacuum of the reaction solvent. Pharmaceutically acceptable base addition salts may be obtained in an analogous manner by treating a solution of compound A or B with a suitable base. Both types of salt may be formed or interconverted using ion-exchange resin techniques.

Compounds of the invention may be isolate din associated with solvent molecules by crystallisation from or evaporation of an appropriate solvent.

The syntheses of compounds A and B and of the intermediates for use therein are illustrated by the following examples. The examples have been previously described in the priority document of the instant invention GB9514464.8, and the corresponding Intermediate or Example numbers therein are shown in parentheses next to the current Intermediate or Example number.

In the Examples section hereinafter the following abbreviations are used:

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