



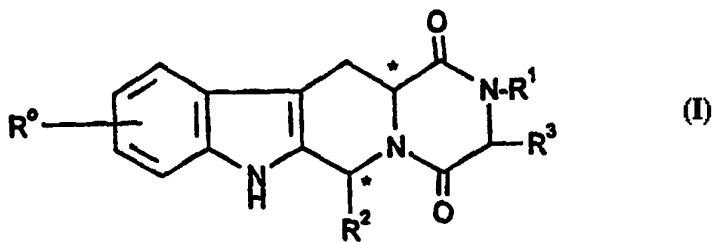
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<p>(21) International Application Number: PCT/EP96/03024 (22) International Filing Date: 11 July 1996 (11.07.96) (30) Priority Data: 9514464.8 14 July 1995 (14.07.95) GB (71) Applicant (for all designated States except US): LABORATOIRE GLAXO WELLCOME S.A. [FR/FR]; 43, rue Vineuse, F-75116 Paris (FR). (72) Inventor; and (75) Inventor/Applicant (for US only): DAUGAN, Alain, Claude-Marie [FR/FR]; Laboratoire Glaxo Wellcome S.A., Centre de Recherches, Z.A. de Courtaboeuf, 25, avenue de Quebec, F-91940 Les Ulis (FR). (74) Agents: FILLER, Wendy, Anne et al.; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 ONN (GB).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p>

(54) Title: USE OF CGMP-PHOSPHODIESTERASE INHIBITORS TO TREAT IMPOTENCE

(57) Abstract

The use of compounds of formula (I) (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-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione, and physiologically acceptable salts and solvates thereof, in the treatment of impotence.



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USE OF CGMP-PHOSPHODIESTERASE INHIBITORS TO TREAT IMPOTENCE

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.

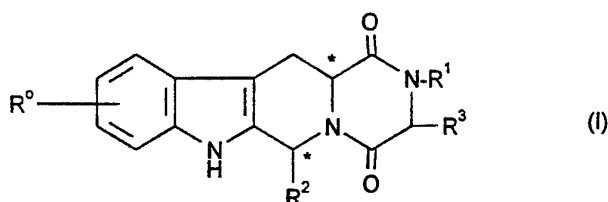
Reports of well-controlled clinical trials in man are few and the efficacy of orally administered drugs is low. Although many different drugs have been shown to induce penile erection, they are only effective after direct injection into the penis, e.g. intraurethrally or intracavernosally (i.c.), and 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 E₁, 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):

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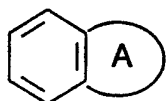


and salts and solvates (e.g. hydrates) thereof, in which:

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

10 R^1 represents hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl C_{1-3} alkyl, aryl C_{1-3} alkyl or heteroaryl C_{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

15

20 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;

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Cis-2,3,6,7,12,12a-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;

5 (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-

10 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;

15 (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;

20 (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:

25 (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.

30 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

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