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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 471/14, A61K 31/395, C07D 471/04, 209/14 // (C07D 471/14, 241:00, 221:00, 209:00)

A1

(11) International Publication Number: WO 95/19978

(43) International Publication Date: 27 July 1995 (27.07.95)

(21) International Application Number: PCT/EP95/00183

(22) International Filing Date: 19 January 1995 (19.01.95)

(30) Priority Data:
9401090.7 21 January 1994 (21.01.94) GB

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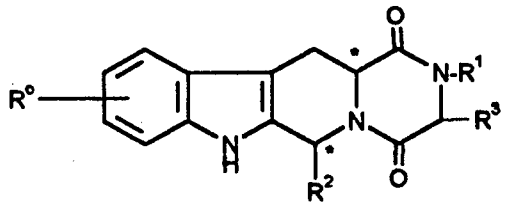
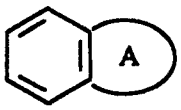
(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: TETRACYCLIC DERIVATIVES, PROCESS OF PREPARATION AND USE



(I)



(a)

(57) Abstract

A compound of formula (I) and salts and solvates 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 (a) 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. A compound of formula (I) is a potent and selective inhibitor of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase (cGMP specific PDE) having a utility in a variety of therapeutic areas where such inhibition is beneficial, including the treatment of cardiovascular disorders.

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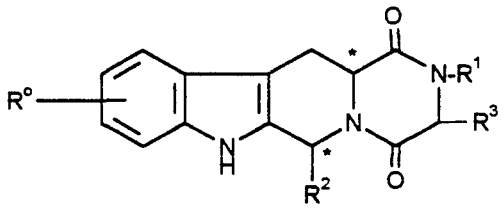
TETRACYCLIC DERIVATIVES, PROCESS OF PREPARATION AND USE

This invention relates to a series of tetracyclic derivatives, to processes for their preparation, pharmaceutical compositions containing them, and their use as therapeutic agents. In particular, the invention relates to tetracyclic derivatives which are potent and selective inhibitors of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase (cGMP specific PDE) having utility in a variety of therapeutic areas where such inhibition is thought to be beneficial, including the treatment of cardiovascular disorders.

Thus, according to a first aspect, the present invention provides compounds of formula (I)

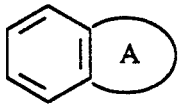


(I)

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

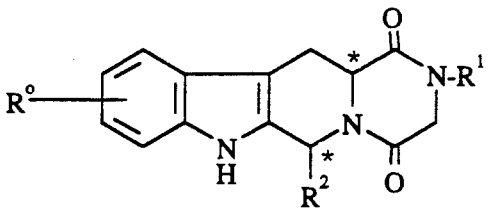
R^o represents hydrogen, halogen or C_{1-6} alkyl;

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.

There is further provided by the present invention a subgroup of compounds of formula (I), the subgroup comprising compounds of formula (Ia)

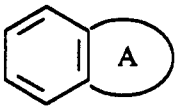


(Ia)

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

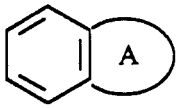
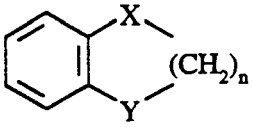
R^o represents hydrogen, halogen or C_{1-6} alkyl;

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

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.

Within R^1 above, the term "aryl" as part of an arylC_{1-3}alkyl group means phenyl or phenyl substituted by one or more (e.g. 1, 2 or 3) substituents selected from halogen, C_{1-6}alkyl, C_{1-6}alkoxy and methylenedioxy. The term "heteroaryl" as part of a heteroarylC_{1-3}alkyl group means thienyl, furyl or pyridyl each optionally substituted by one or more (e.g. 1, 2 or 3) substituents selected from halogen, C_{1-6} alkyl and C_{1-6}alkoxy. The term "C_{3-8}cycloalkyl" as a group or part of a C_{3-8}cycloalkylC_{1-3}alkyl group means a monocyclic ring comprising three to eight carbon atoms. Examples of suitable cycloalkyl rings include the C_{3-6}cycloalkyl rings cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

Within R^2 above, optional benzene ring substituents are selected from one or more (e.g. 1, 2 or 3) atoms or groups comprising halogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, $-CO_2R^b$, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, cyano, nitro and NR^aR^b, where R^a and R^b are each hydrogen or C_{1-6}alkyl, or R^a may also represent C_{2-7}alkanoyl or C_{1-6}alkylsulphonyl. Optional substituents for the remaining ring systems are selected from one or more (e.g. 1, 2 or 3) atoms or groups comprising halogen, C_{1-6}alkyl, C_{1-6}alkoxy and arylC_{1-3}alkyl as defined above.

The bicyclic ring  may, for example, represent naphthalene, a heterocycle such as benzoxazole, benzothiazole, benzisoxazole, benzimidazole, quinoline, indole, benzothiophene or benzofuran or  (where n is an integer 1 or 2 and X and Y may each represent CH_2, O, S or NH).

In the above definitions, the term "alkyl" as a group or part of a group means a straight chain or, where available, a branched chain alkyl moiety. For example, it may represent a C_{1-4}alkyl function as represented by methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl and t-butyl. The term 'alkenyl' as used herein includes straight-chained and branched alkenyl groups, such as vinyl and allyl groups. The term 'alkynyl' as used herein includes straight-chained and branched alkynyl groups, suitably acetylene. The term "halogen" herein means a fluorine, chlorine, bromine or iodine atom. The term "haloC_{1-6}alkyl" means an alkyl group as defined above comprising one to six carbon atoms substituted at one or more carbon atoms by one or more (e.g. 1, 2 or 3) halogen atoms. Similarly, a haloC_{1-6}alkoxy group is a haloC_{1-6}alkyl group as defined above linked to the R^2 benzene ring via an oxygen atom. Examples of haloC_{1-6}alkyl groups include trifluoromethyl and 2,2,2-trifluoroethyl. An example of a haloC_{1-6}alkoxy group is trifluoromethoxy. The term "C_{2-7}alkanoyl" means a C_{1-6}alkylcarbonyl group where the C_{1-6}alkyl portion is as defined above. An example of a suitable C_{2-7}alkanoyl group is the C_2alkanoyl group acetyl.

It will be appreciated that when R^o is a halogen atom or a C_{1-6}alkyl group this substituent may be sited at any available position on the phenyl portion of the tetracyclic ring. However, a particular site of attachment is the ring 10-position.

The compounds of formula (I) may contain two or more asymmetric centres and thus can exist as enantiomers or diastereoisomers. In particular, in formula (I) above two ring chiral centres are denoted with asterisks. It is to be understood that the invention includes both mixtures and separate individual isomers of the compounds of formula (I).

The compounds of formula (I) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers thereof.

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