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(54) Title: CGMP-PDE INHIBITORS FOR THE TREATMENT OF ERECTILE DYSFUNCTION

(57) Abrégé/Abstract:
Compounds which are selective inhibitors of cGMP PDE are useful in the treatment of erectile dysfunction (impotence) in male animals, including man.

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(57) Abstract

Compounds which are selective inhibitors of cGMP PDE are useful in the treatment of erectile dysfunction (impotence) in male animals, including man.

cGMP-PDE INHIBITORS FOR THE TREATMENT OF ERECTILE DYSFUNCTION

This invention relates to the use of compounds which are selective inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs) in the treatment of erectile dysfunction (impotence) in male animals, including man.

Impotence can be defined literally 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. In the USA alone, for example, it has been estimated that there are up to 10 million impotent males, with the majority suffering from problems of organic rather than of psychogenic origin.

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.

According to the specification of our International patent application no PCT/EP94/01580, (publication no WO94/28902), we describe and claim the use of a series of pyrazolo [4,3-d]pyrimidin-7-ones for the treatment of impotence. The compounds are potent and selective inhibitors of cGMP PDE in contrast to their inhibition of cyclic adenosine 3',5'-monophosphate phosphodiesterases (cAMP PDEs). This selective enzyme inhibition leads to elevated cGMP levels which, in turn, provides the basis for the utilities previously disclosed for the compounds in the treatment of stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency, peripheral vascular disease, stroke, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, and diseases characterised by disorders of gut motility, e.g. irritable bowel syndrome. The specification goes on to describe investigations which identified three PDE isoenzymes in human corpus cavenosum tissue, relaxation of which leads to penile erection. The predominant enzyme was found to be the cGMP-specific PDE_v, while cGMP-stimulated cAMP PDE_{II} and cGMP-inhibited cAMP PDE_{III}, were also present. The compounds described were found to be potent and selective inhibitors of the PDE_V enzyme but demonstrated only weak inhibitory activity against the PDE_{II} and PDE_{III} enzymes. This activity is believed to be responsible for the action of the compounds in the treatment of erectile dysfunction.

A number of cGMP-PDE inhibitors have previously been described in the literature for a variety of utilities, these include use in treating obstructive lung diseases such as asthma and brochitis, in combatting allergic diseases such as allergic asthma, allergic rhinitis, urticaria, and irritable bowel syndrome; and in combatting angina, hypertension and congestive heart failure. Utility has also been claimed as diuretics, as antiinflammatory agents, in the treatment of baldness, for conditions of reduced blood vessel patency, and in glaucoma. However there has not previously been any suggestion that any of these compounds would be of utility in the treatment of erectile dysfunction.

Thus the present invention provides the use of a compound which is a selective cGMP PDE inhibitor for the manufacture of a medicament for the treatment of erectile dysfunction in a male animal, including man, wherein said compound is:

i a 5-substituted pyrazolo [4,3-d]pyrimidine-7-one as disclosed in European patent application 0201188;

ii a griseolic acid derivative as disclosed in European patent applications nos 0214708 and 0319050;

iii a 2-phenylpurinone derivative as disclosed in European patent application 0293063;

iv a phenylpyridone derivative as disclosed in European patent application 0347027;

v a fused pyrimidine derivative as disclosed in European patent application 0347146;

vi a condensed pyrimidine derivative as disclosed in European patent application 0349239;

vii a pyrimidopyrimidine derivative as disclosed in European patent application 0351058;

viii a purine compound as disclosed in European patent application 0352960;

ix a quinazolinone derivative as disclosed in European patent application 0371731;

x a phenylpyrimidone derivative as disclosed in European patent application 0395328;

xi an imidazoquinoxalinone derivative or its aza analogue as disclosed in European patent application 0400583;

xii a phenylpyrimidone derivative as disclosed in European patent application 0400799;

xiii a phenylpyridone derivative as disclosed in European patent application 0428268;

xiv a pyrimidopyrimidine derivative as disclosed in European patent 0442204;

xv a 4-aminoquinazoline derivative as disclosed in European patent application 0579496;

xvi a 4,5-dihydro-4-oxo-pyrrolo[1,2-a]quinoxaline derivative or its aza analogue as disclosed in European patent application 0584487;

xvii a polycyclic guanine derivative as disclosed in International patent application WO91/19717;

xviii a nitrogenous heterocyclic compound as disclosed in International patent application WO93/07124;

xix a 2-benzyl-polycyclic guanine derivative as disclosed in International patent application WO94/19351;

xx a quinazoline derivative as disclosed in US patent 4060615;

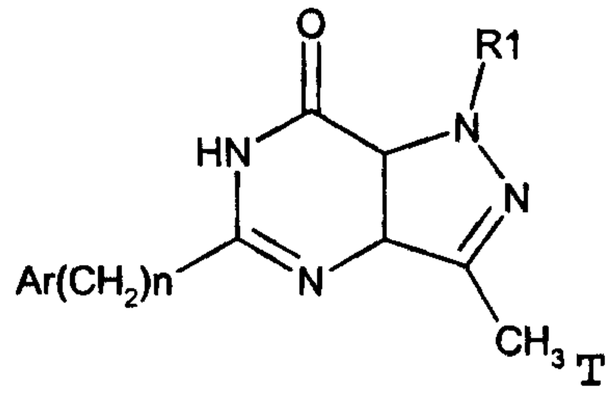
xxi a 6-heterocyclyl pyrazolo [3,4-d]pyrimidin-4-one as disclosed in US patent 5294612;

xxii a benzimidazole as disclosed in Japanese patent application 5-222000; or

xxiii a cycloheptimidazole as disclosed in European Journal of Pharmacology, 251, (1994), 1.

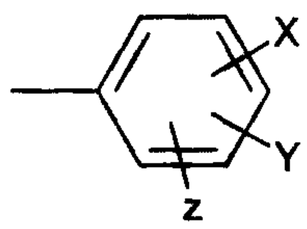
xxiv a N-containing heterocycle as disclosed in International patent application WO94/22855.

More specifically, the present invention provides the use of a compound which is a selective cGMP PDE inhibitor for the manufacture of a medicament for the treatment of erectile dysfunction in male animals, including man, wherein the compound is selected from:

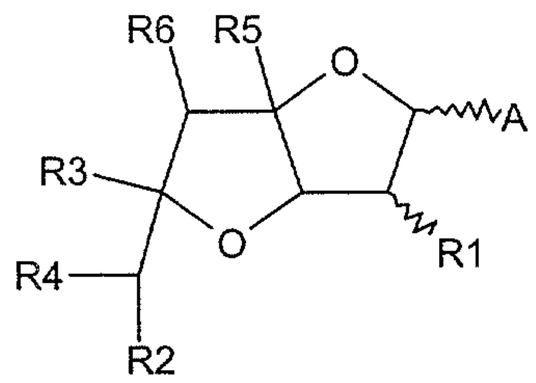


and the pharmaceutically acceptable salts thereof,

in which: R' is a lower alkyl of from one to six carbon atoms, a lower alkenyl of from one to six carbon atoms, a lower hydroxyalkyl of from one to six carbon atoms, a lower hydroxyalkenyl of from two to six or 2, 3 or 4-pyridyl; and Ar represents a group of formula:

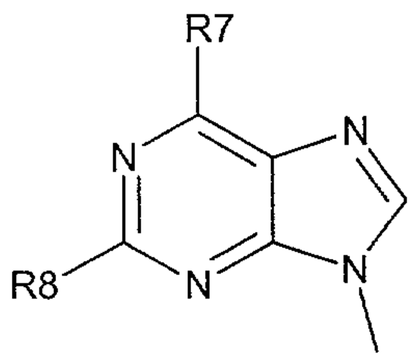


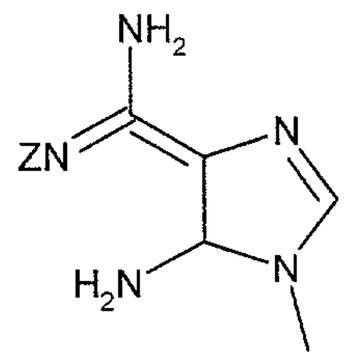
in which X, Y and Z are, independently, (1) hydrogen; (2) lower alkyl of from one to six carbon atoms; (3) halogen, (4) hydroxyl; (5) lower alkoxy of from one to six carbon atoms; (6) nitro; (7) amino; (8) NR'R" wherein R' and R" are each, independently, (a) hydrogen or (b) lower alkyl of from one to six carbon atoms optionally substituted by (i) amino, (ii) morpholino or (iii) cycloalkyl of from, five to seven carbon atoms; (9) sulfonyl; or (10) -SO_2NR'R" wherein R' and R" are as defined above; with the proviso that not all of X, Y and Z can be nitro, amino, or NR'R'' at once;

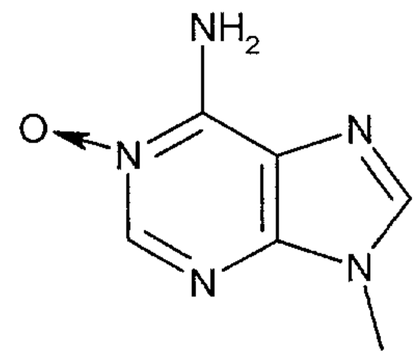


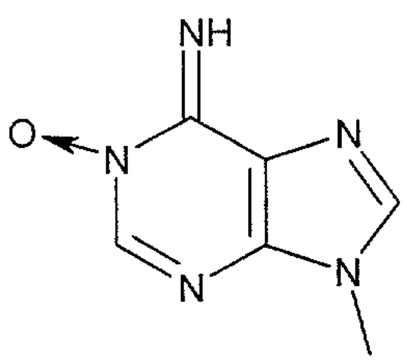
and the pharmaceutically acceptable salts thereof,

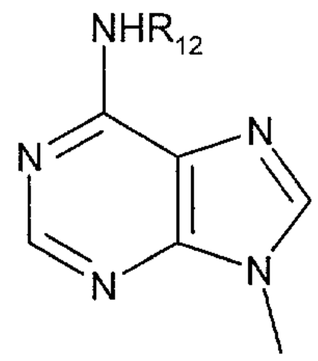
in which: A represents a group of formula:

(a) 

(b) 

(c) 

(d) 

(e) 

R^1 and R^2 are the same or different and each represents a hydrogen atom, a halogen atom or a group of formula $-OR^9$;

R^3 and R^4 are the same or different and each represents a carbamoyl group or a carboxy group;

R^5 and R^6 both represent hydrogen atoms or together they represent an extra carbon-carbon bond between the carbon atoms to which they are attached;

R^7 represents a hydrogen atom, a halogen atom or a group of formula $-OR^9$, $-NR^{10}R^{11}$ or $-SR^9$;

R^8 represents a halogen atom or a group of formula $-OR^9$, $-NR-^{10}R^{11}$ or $-SR^9$;

R^9 represents a hydrogen atom, a C_1-C_6 alkyl group, an alkylsulphonyl group, a haloalkylsulphonyl group, an arylsulphonyl group or a hydroxy protecting group;

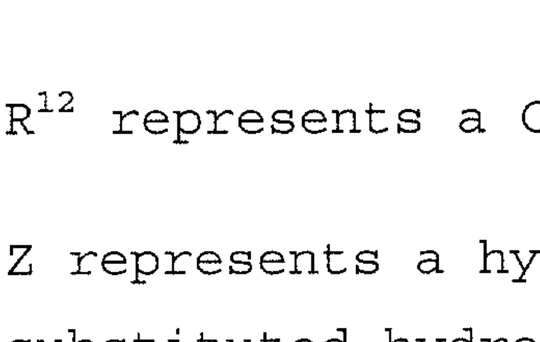
R^{10} and R^{11} are the same or different and each represents a hydrogen atom, a hydroxy group, a C_1-C_6 alkyl group, a C_1-C_6 hydroxyalkyl group, a C_1-C_6 aminoalkyl group, an aralkyl group, an aryl group, a C_1-C_6 alkoxy group, an aralkyloxy group, an amino group, a C_1-C_{20} aliphatic acyl group or an aromatic acyl group; or R^{10} and R^{11} together represent a substituted methylene group, or R^{10} and R^{11}, together with nitrogen atom to which they are attached, represent a heterocyclic group having 5 or 6 ring atoms, of which, in addition to the nitrogen atom shown, 0 or 1 are additional oxygen, nitrogen or sulphur hetero-atoms, said heterocyclic group being unsubstituted or having from 1 to 3 C_1-C_4 alkyl and/or C_1-C_4 alkoxy substituents;

R^{12} represents a C_1-C_6 alkyl group;

Z represents a hydrogen atom, a hydroxy group or a substituted hydroxy group; and

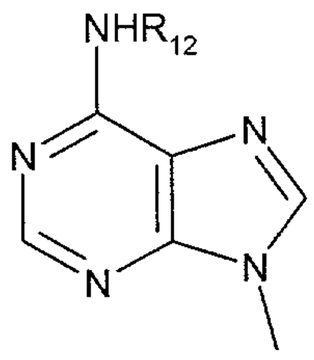
W represents an alkoxy group or an aralkoxy group;

provided that, when A represents said group of formula (e), R^5 and R^6 both represent hydrogen atoms;



and the pharmaceutically acceptable salts and esters thereof,

in which A represents a group of formula:



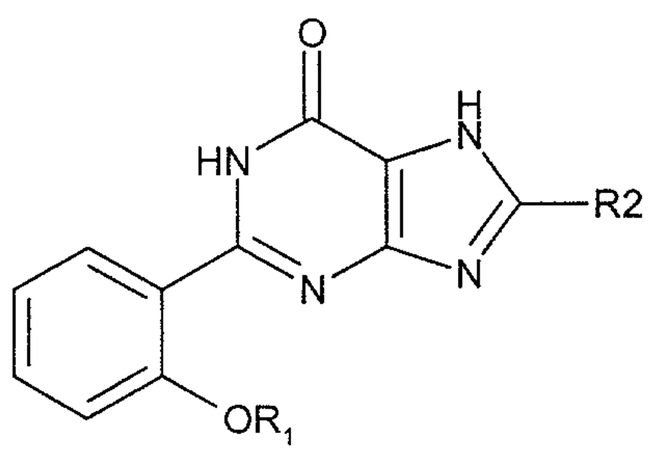
R^1 and R^2 are the same or different and each represents a hydrogen atom, a halogen atom or a group of formula $-OR^9$;

R^3 and R^4 are the same or different and each represents a carbamoyl group or a carboxy group;

R^5 and R^6 both represent hydrogen atoms;

R^9 represents a hydrogen atom, a C_1-C_6 alkyl group, an alkylsulphonyl group, a haloalkylsulphonyl group, an arylsulphonyl group or a hydroxy-protecting group;

R^{12} represents a C_1-C_6 alkyl group;



and pharmaceutically acceptable salts thereof, wherein

R^1 is C_{1-6} alkyl or C_{2-6} alkenyl, and

R^2 is hydrogen or hydroxy;

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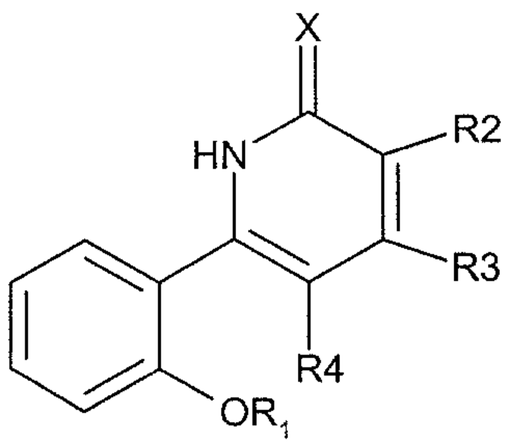


or a pharmaceutically acceptable salt thereof, wherein

X is O or S;

R^1 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-5} cycloalkylC_{1-4} alkyl, or C_{1-4} alkyl substituted by 1 to 6 fluoro groups;

R^2 is hydrogen, -CN, $-CONR^5R^6$, $-CO_2R^7$, 5-tetrazolyl, $-NO_2$, $-NH_2$ or

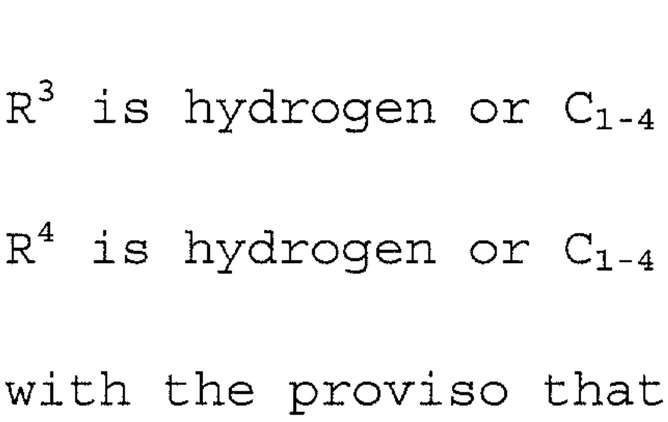
$-NHCOR^8$ wherein R^5, R^6, R^7 and R^8 are independently hydrogen or C_{1-4} alkyl;

R^3 is hydrogen or C_{1-4} alkyl; and

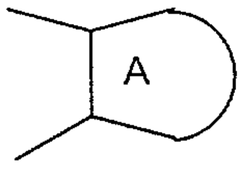
R^4 is hydrogen or C_{1-4} alkyl;

with the proviso that R^1 is not methyl when R^2 is $-CO_2H$, $-CO_2CH_2CH_3$ or

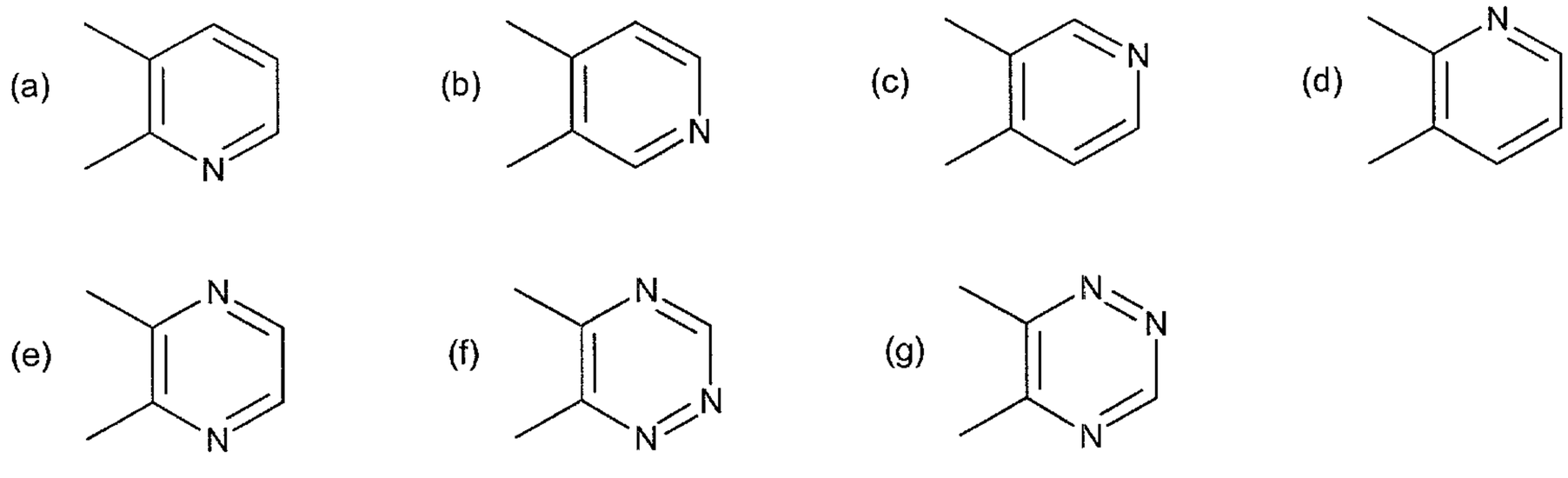
-CN, X is O, R^3 is hydrogen and R^4 is hydrogen or methyl;



and pharmaceutically acceptable salts thereof, wherein

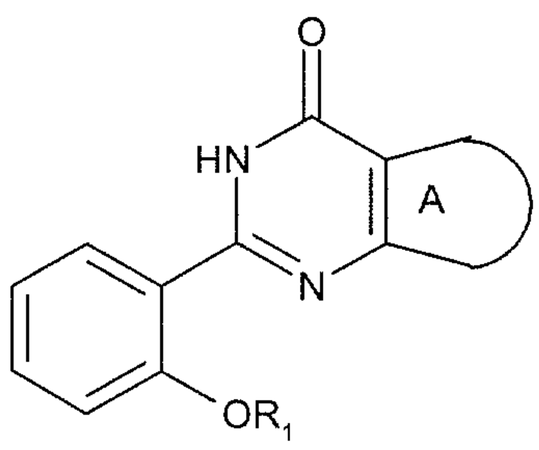


is a ring of sub-formula (a), (b), (c), (d), (e), (f) or (g):

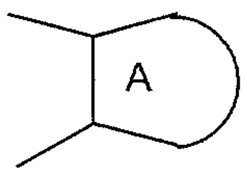


R^1 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-5} cycloalkylC_{1-6} alkyl, or C_{1-6} alkyl substituted by 1 to 6 fluoro groups; R^2 is C_{1-6} alkythio, C_{1-6} alkylsulphonyl, C_{1-6} alkoxy, hydroxy, hydrogen, hydrazino, C_{1-6} alkyl, phenyl, $-NHCOR^3$ wherein R^3 is hydrogen or C_{1-6} alkyl, or $-NR^4R^5$, wherein R^4 and R^5 together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, hexahydroazepino, morpholino or piperazino ring, or R^4 and R^5 are independently hydrogen, C_{3-5} cycloalkyl or C_{1-6} alkyl which is optionally substistuted by $-CF_3$, phenyl, $-S(O)_nC_{1-6}$ alkyl wherein n is 0, 1 or 2, $-OR^6$, $-CO_2R^7$ or $-NR^8R^9$ wherein R^6 to R^9 are independently hydrogen or C_{1-6} alkyl, provided that the carbon atom adjacent to the nitrogen atom is not substituted by said $-S(O)_nC_{1-6}$ alkyl, $-OR^6$ or $-NR^8R^9$ groups; and

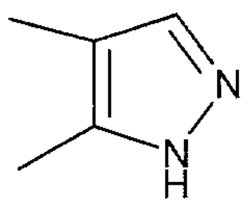
R is hydrogen and can also be hydroxy when R^2 is hydroxy;



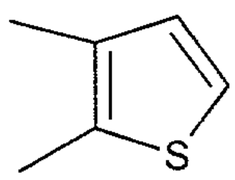
and pharmaceutically acceptable salts thereof, wherein



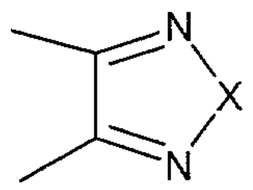
is a ring of sub-formula (a), (b) or (c):



(a)



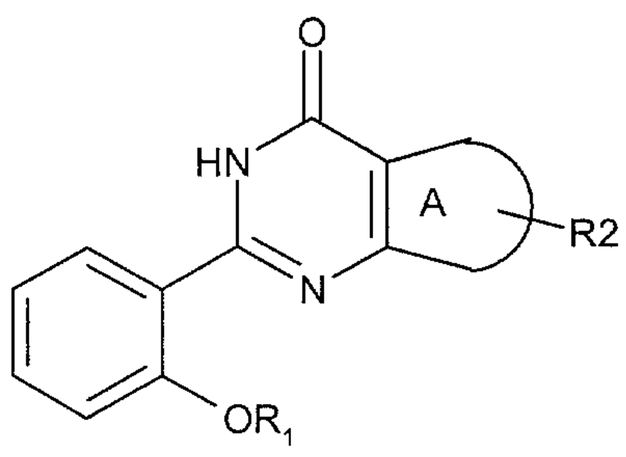
(b)



(c)

X is oxygen or sulphur, and

R^1 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-5} cycloalkyl C_{1-4} alkyl, or C_{1-4} alkyl substituted by 1 to 6 fluoro groups;

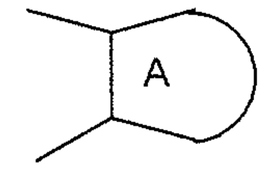


and pharmaceutically acceptable salts thereof, wherein

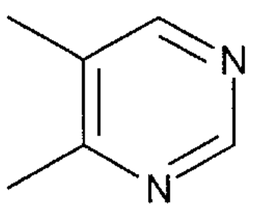
R^1 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-5} cycloalkyl C_{1-6} alkyl, or C_{1-6} alkyl substituted by 1 to 6 fluoro groups;

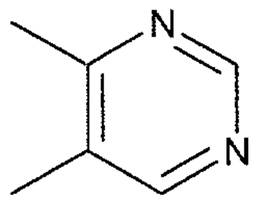
R^2 is C_{1-6} alkythio, C_{1-6} alkylsulphonyl, C_{1-6} alkoxy, hydroxy, hydrogen, hydrazino, C_{1-6} alkyl, phenyl, $-NHCOR^3$ wherein R^3 is hydrogen or C_{1-6} alkyl, or $-NR^4R^5$, wherein R^4 and R^5 together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, hexahydroazepino, morpholino or piperazino ring, or R^4 and R^5 are independently hydrogen, C_{3-5} cycloalkyl or C_{1-6} alkyl which is optionally substituted by $-CF_3$, phenyl, $-S(O)_nC_{1-6}$ alkyl wherein n is 0, 1 or 2, $-OR^6$,

$-CO_2R^7$ or $-NR^8R^9$ wherein R^6 to R^9 are independently hydrogen or C_{1-6} alkyl, provided that the carbon atom adjacent to the nitrogen atom is not substituted by said $-S(O)_nC_{1-6}$ alkyl, $-OR^6$ or NR^8R^9 groups; and

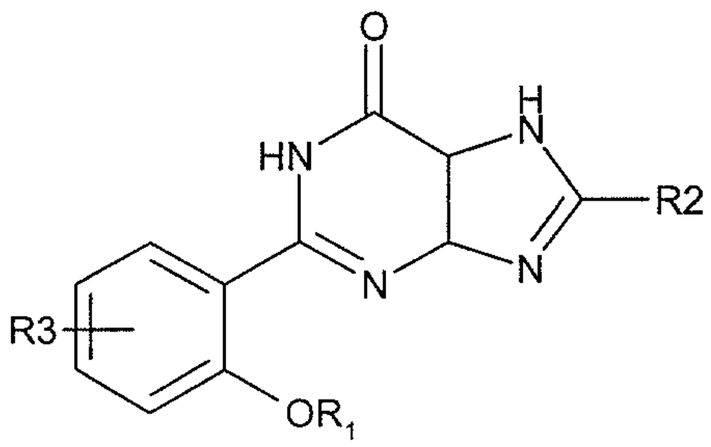


is a ring of sub-formula (a) or (b):

(a) 

(b) 

;



and pharmaceutically acceptable salts thereof, wherein

R^1 is C_{1-6} alkyl, C_{2-5} alkenyl, C_{3-5} cycloalkyl C_{1-6} alkyl, phenyl C_{1-4} alkyl, or C_{1-4} alkyl substituted by 1 to 6 fluoro groups;

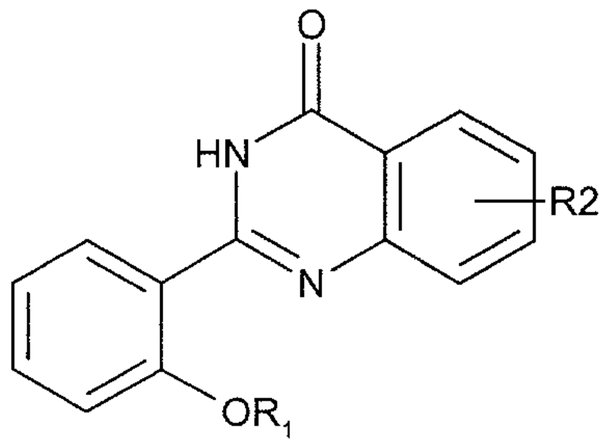
R^2 is hydrogen, hydroxy, C_{1-4} alkyl, phenyl, mercapto, C_{1-4} alkylthio, CF_3 or amino;

R^3 is hydrogen, nitro, amino, C_{1-4} alkanoylamino, C_{1-6} alkoxy, C_{1-4} alkyl, halo, $SO_2NR^4R^5$, $CONR^4R^5$, cyano or C_{1-4} alkyl S(O)n;

R^4 and R^5 are independently hydrogen or C_{1-6} alkyl; and

n is 0, 1 or 2;

provided that R^3 is not hydrogen when R^1 is C_{1-6} alkyl or C_{2-6} alkenyl and R^2 is not hydrogen or hydroxy;

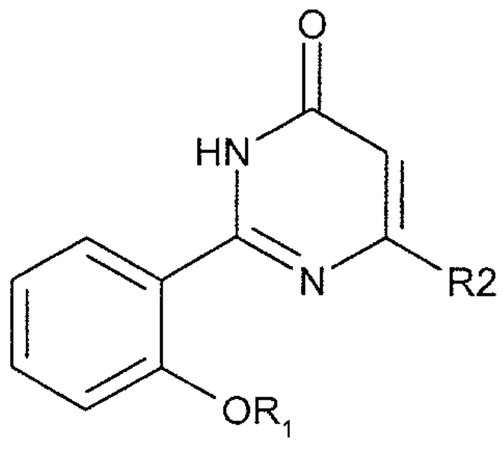


and pharmaceutically acceptable salts thereof, wherein

R^1 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-5} cycloalkyl C_{1-4}alkyl, phenyl C_{1-4} alkyl or C_{1-4} alkyl substituted by 1 to 6 fluoro groups;

R^2 is hydrogen, C_{1-6} alkyl, C_{1-6} alkythio, C_{1-6} alkoxy, nitro or $-NR^3R^4$ and

R^3 and R^4 are independently hydrogen or C_{1-4} alkyl substituted by hydroxy provided that the carbon atom adjacent to the nitrogen atom is not substituted by hydroxy; with the proviso that R^1 is not methyl or ethyl when R^2 is hydrogen;

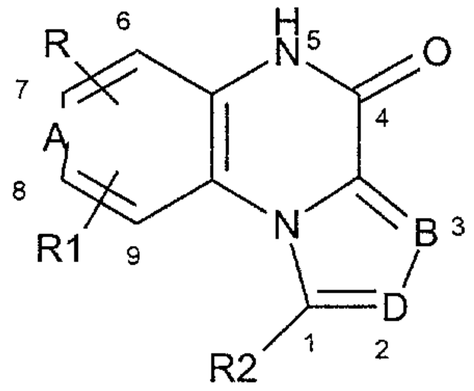


and pharmaceutically acceptable salts thereof, wherein

R^1 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-5} cycloalkyl C_{1-6} alkyl, phenyl C_{1-6} alkyl or C_{1-6} alkyl substituted by 1 to 6 fluoro groups; and

R^2 is C_{1-6} alkyl, phenyl, hydroxy, C_{1-6} alkoxy, halo, $-NHCOR^3$,

-NHCONHR^4, 5-tetrazolyl, -CO_2R^5, cyano, -$CONR^6R^7$, or -NR^8R^9 wherein R^3 to R^7 are independently hydrogen or C_{1-6} alkyl and R^8 and R^9 are independently hydrogen or C_{1-6} alkyl optionally substituted by hydroxy provided that the carbon atom adjacent to the nitrogen atom is not substituted by hydroxy;



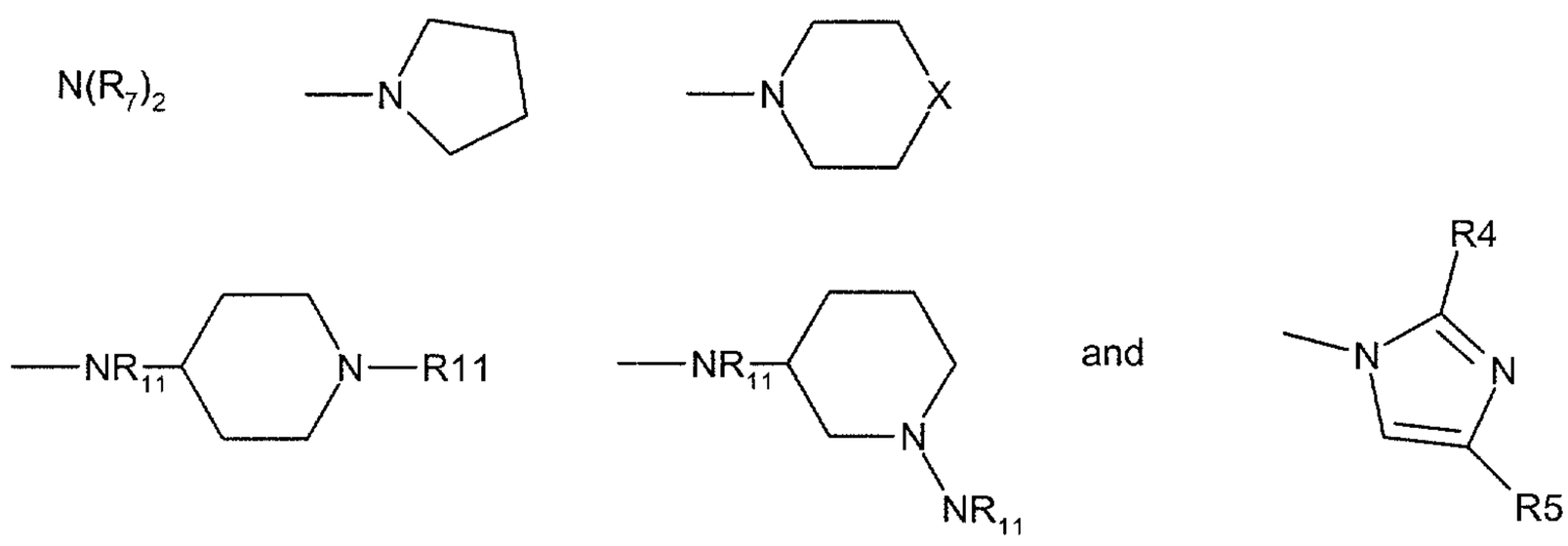
and pharmaceutically acceptable salts thereof, wherein

A is N or CH;

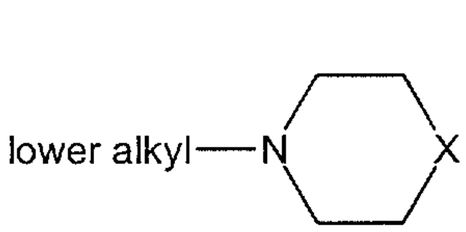
B is N CR_3;

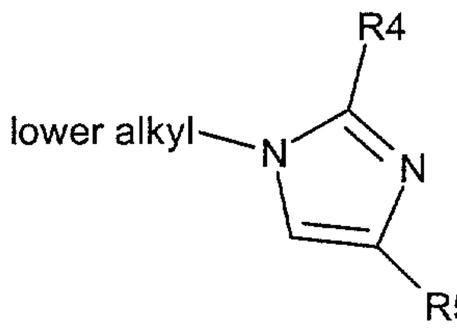
D is N or CR_2;

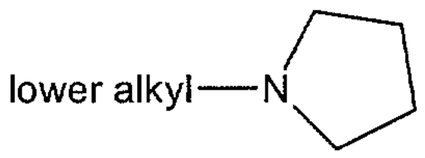
R, R_1 are the same or independently hydrogen, hydroxy, lower alkyl, lower alkoxy, phenyloxy, R_6 $S(O)_n$-, W-ALK-Q-,



R_2 is hydrogen, lower alkyl, phenyl which may be substituted by up to three methoxy groups, lower alkyl substituted by phenyl which may be substituted by up to three methoxy groups, - lower alkyl -$N(R_8)_2$,







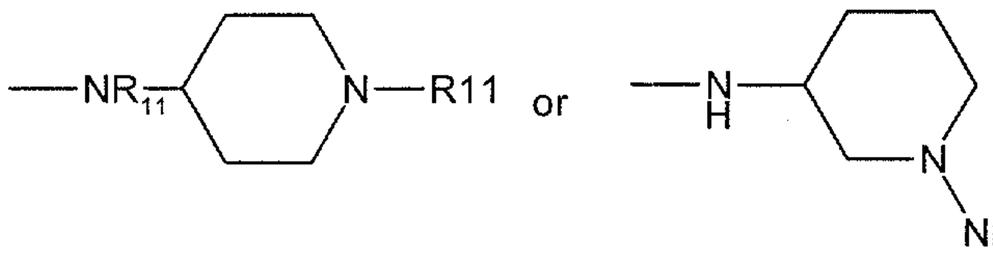
pyridinyl or lower-alkyl pyridinyl;

R_3 is hydrogen, lower alkyl, phenyl, lower alkylphenyl, pyridinyl or loweralkyl pyridinyl;

R_4, R_5 are the same or independently hydrogen or lower alkyl;

R_6 is lower alkyl, phenyl, lower alkylphenyl or pyridinyl;

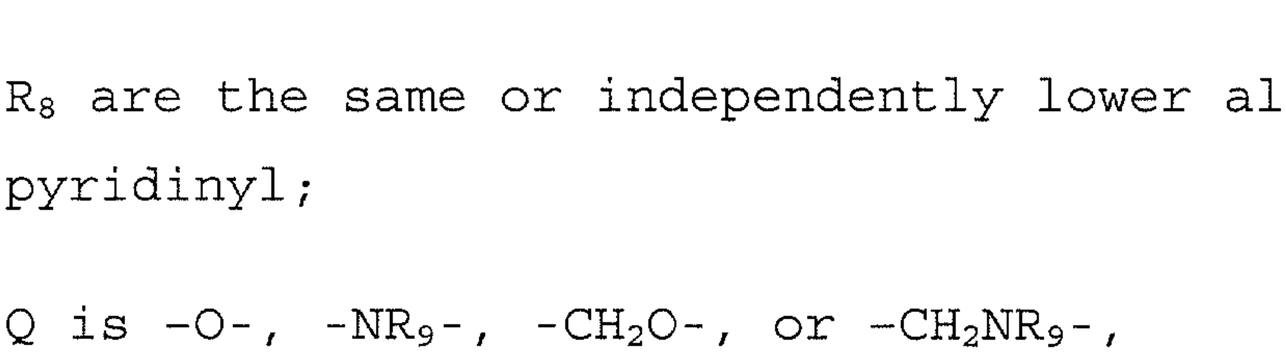
R_7 are the same or independently hydrogen, loweralkyl, phenyl, pyridinyl,



R_8 are the same or independently lower alkyl, phenyl or pyridinyl;

Q is $-O-$, $-NR_9-$, $-CH_2O-$, or $-CH_2NR_9-$,

W is hydroxy, lower alkoxy, phenoxy, $-N(R_{10})_2$,



ALK is a C_1-C_4 straight or branched chain alkyl;

R_9 is hydrogen, lower alkyl or phenyl;

R_{10} are the same or independently hydrogen, lower alkyl or phenyl;

R_{11} are the same or independently hydrogen or lower alkyl;

X is $-CH_2-$, $-O-$ $S(O)_n$, $-NR_{10}$;

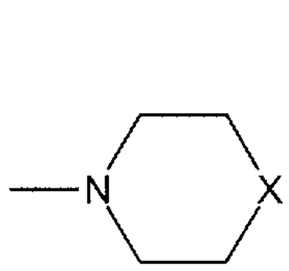
n is the integer 0, 1 or 2 and

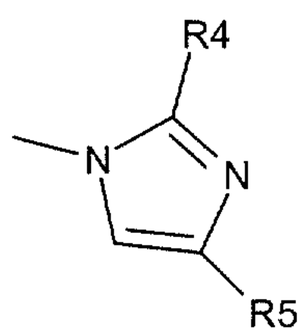
p is the integer 0 or 1,

with the provisos that:

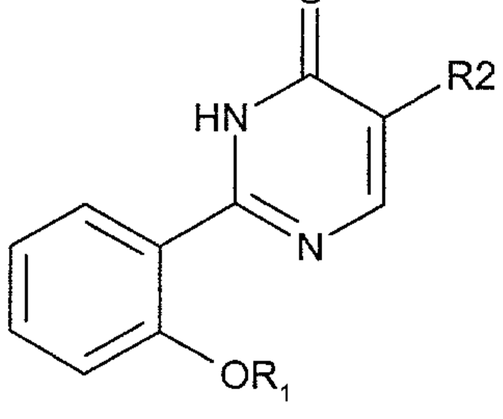
one and only one of B or D must be N;

when A is CH, when D is N, when B is CR_3 where R_3 is H, when R_2 is hydrogen, lower alkyl or phenyl then R and/or R_1 must be





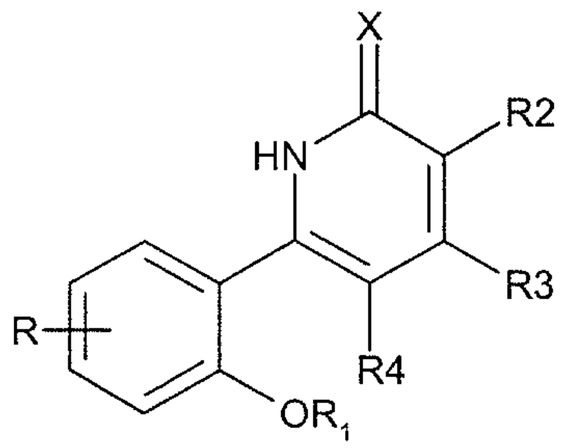
or W-ALK-Q;



and pharmaceutically acceptable salts thereof, wherein

R^1 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-5} cycloalkyl C_{1-6} alkyl, phenyl C_{1-6} alkyl or C_{1-6} alkyl substituted by 1 to 6 fluoro groups; and

R^2 is hydrogen, amino, -$NHCOR^3$, or $CONR^4R^5$, wherein R^3 is C_{1-6} alkyl, R^4 is C_{1-6} alkyl and R^5 is hydrogen or C_{1-6} alkyl;



and pharmaceutically salts thereof, wherein

X is O or S:

R^1 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-5} cycloalkyl C_{1-4} alkyl, or C_{1-4} alkyl substituted by 1 to 3 fluoro groups;

R^2 is hydrogen, -CN, $-CONR^5R^6$, $-CO_2R^7$, 5-tetrazolyl, $-NO_2$ or -$NHCOR^8$ wherein R^5 to R^8 are independently hydrogen or C_{1-4} alkyl;

R^3 is hydrogen or C_{1-4} alkyl;

R^4 is hydrogen or C_{1-4} alkyl; and

R is halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, $-CONR^9R^{10}$, $-CO_2R^{11}$, $-S(O)_nC_{1-4}$ alkyl, $-NO_2$, - NH_2, $-NHCOR^{12}$, or $-SO_2NR^{13}R^{14}$ wherein n is 0, 1 or 2 and R^9 to R^{14} are independently hydrogen or C_{1-4} alkyl; with the proviso that R^1 is not methyl when R^2 is $-CO_2H$, $-CO_2CH_2CH_3$ or –CN, X is O, R^3 is hydrogen, R^4 is hydrogen or methyl and R is 6-methoxy;

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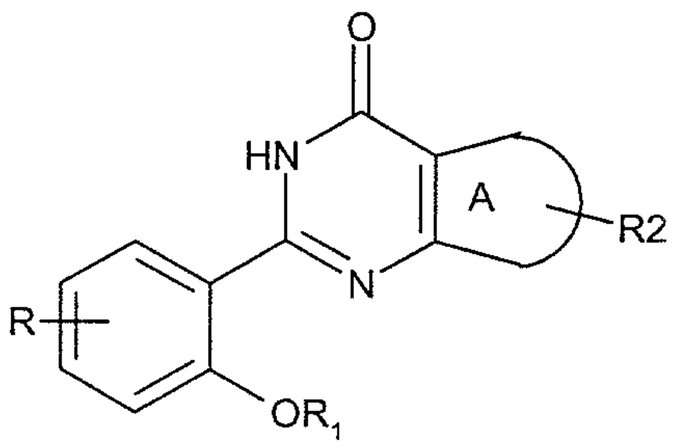


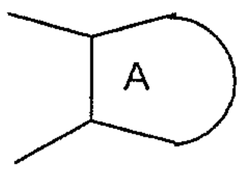
and pharmaceutically acceptable salts thereof, wherein

R^1 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-5} cycloalkyl C_{1-6} alkyl, or C_{1-6} alkyl substituted by 1 to 6 fluoro groups;

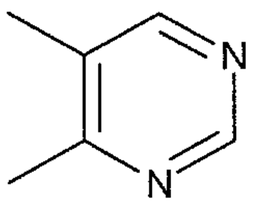
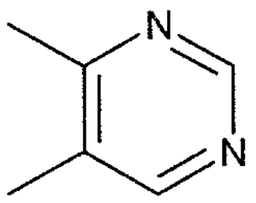
R^2 is C_{1-6} alkythio, C_{1-6} alkylsulphonyl, C_{1-6} alkoxy, hydroxy, hydrogen, hydrazino, C_{1-6} alkyl, phenyl, $-NHCOR^3$ wherein R^3 is hydrogen or C_{1-6} alkyl, or $-NR^4R^5$, wherein R^4 and R^5 together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, hexahydroazepino, morpholino or piperazino ring, or R^4 and R^5 are independently hydrogen, C_{3-5} cycloalkyl or C_{1-6} alkyl which is optionally substituted by $-CF_3$, phenyl, $-S(O)_nC_{1-6}$ alkyl wherein

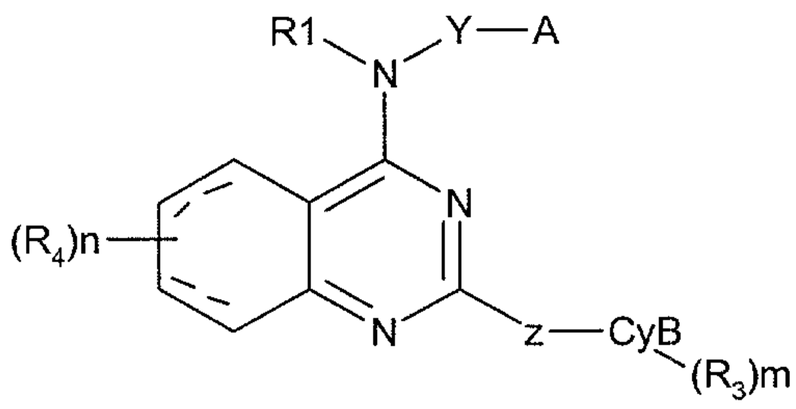
n is 0, 1 or 2, $-OR^6$, $-CO_2R^7$ or $-NR^8R^9$ wherein R^6 to R^9 are independently hydrogen or C_{1-6} alkyl, provided that the carbon atom adjacent to the nitrogen atom is not substituted by said $-S(O)_n$ C_{1-6} alkyl, or $-OR^6$ or $-NR^8R^9$ atoms;

R is halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, $-CONR^{10}R^{11}$, CO_2R^{12}, C_{1-4} alkyl $S(O)_n$, $-NO_2$, $-NH_2$, $-NHCOR^{13}$ or $SO_2NR^{14}R^{15}$ wherein n is 0, 1 or 2 and R^{10} to R^{15} are independently hydrogen or C_{1-4} alkyl; and



a is a ring of sub-formula (a) or (b):

(a)  (b) 



and pharmaceutically acceptable salts thereof,

wherein --- represents a single or double bond;

R^1 is hydrogen or C_{1-4} alkyl;

Y is a single bond or C_{1-6} alkylene;

A is

$-CyA-(R^2)_1$,

$-O-R^0$ or $-S(O)_p-R^o$, or

$-NR^{16}R^{17}$

in which R^0 is hydrogen, C_{1-4} alkyl, hydroxy C_{1-4} alkyl or $CyA-(R^2)_1$;

R^{16} and R^{17} independently are hydrogen or C_{1-4} alkyl;

p is 0-2;

CyA is

a 3-7 membered, saturated or unsaturated carbocycle,

a 4-7 membered, unsaturated or partially saturated heterocycle containing one nitrogen atom

a 4-7 membered, unsaturated or partially saturated heterocycle containing one nitrogen atom and one oxygen atom,

a 4-7 membered, unsaturated or partially saturated heterocycle containing one nitrogen atom and two oxygen atoms,

a 4-7 membered, unsaturated or partially saturated heterocycle containing two nitrogen atoms and one oxygen atom

a 4-7 membered, unsaturated or partially saturated heterocyle containing one or two sulfur atoms,

a 4-7 membered, unsaturated, partially saturated or fully saturated heterocycle containing one or two oxygen atoms,

R^2 is (1) hydrogen, (2) C_{1-4} alkyl, (3) C_{1-4} alkoxy, (4) $-COOR^5$, in which R^5 is hydrogen or C_{1-4} alkyl, (5) $-NR^6R^7$, in which R^6 and R^7 independently are hydrogen or C_{1-4} alkyl, (6) $-SO_2NR^6R^7$, in which R^6 and R^7 are as hereinbefore defined, (7) halogen, (8) trifluoromethyl, (9) nitro or (10) trifluoromethoxy;

Z is a single bond, methylene, ethylene, vinylene or ethynylene;

CyB is a 4-7 membered, unsaturated or partially saturated heterocycle containing one nitrogen atom,

a 4-7 membered, unsaturated or partially saturated heterocycle containing two nitrogen atmos,

a 4-7 membered, unsaturated or partially saturated heterocycle containing three nitrogen atoms,

a 4-7 membered, unsaturated or partially saturated heterocycle containing one or two oxygen atoms,

a 4-7 membered, unsaturated or partially saturated heterocycle containing one or two sulfur atoms,

R^3 is hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, halogen or trifluoromethyl;

R^4 is (1) hydrogen, (2) C_{1-4} alkyl, (3) C_{1-4} alkoxy, (4) $-COOR^8$, in which R^8 is hydrogen or C_{1-4} alkyl, (5) $-NR^9R^{10}$, in which R^9 is hydrogen, C_{1-4} alkyl or phenyl (C_{1-4} alkyl) and R^{10} is hydrogen or C_{1-4} alkyl, (6) $-NHCOR^{11}$, in which R^{11} is C_{1-4} alkyl, (7) $-NHSO_2R^{11}$, in which R^{11} is as hereinbefore defined, (8) $SO_2NR^9R^{10}$ in which R^9 and R^{10} are as hereinbefore defined, (9) $-OCOR^{11}$, in which R^{11} is as hereinbefore defined, (10) halogen, (11) trifluoromethyl, (12) hydroxy, (13) nitro, (14) cyano,

(15) $-SO_2N=CHNR^{12}R^{13}$ in which R^{12} is hydrogen or C_{1-4} alkyl and R^{13} is C_{1-4} alkyl, (16) $-CONR^{14}R^{15}$ in which R^{14} is hydrogen or C_{1-4} alkyl or phenyl (C_{1-4} alkyl) and R^{15} is C_{1-4} alkyl or (17) C_{1-4} alkylthio, (18) C_{1-4} alkylsulfinyl, (19) C_{1-4} alkylsulfonyl, (20) ethynyl, (21) hydroxymethyl, (22) tri(C_{1-4} alkyl) silylethynyl or (23) acetyl; and l, m and n independently are 1 or 2;

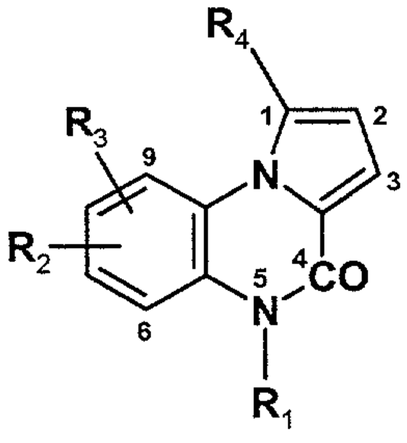
with the proviso that

$CyA-(R^2)_1$ does not represent cyclopentyl or trifluoromethylphenyl when Y is a single bond,

CyB does not bond to Z through a nitrogen atom when Z is vinylene or ethynylene,

CyB is not pyridine or thiophene when CyA is a 4-7 membered unsaturated, partially saturated or fully saturated heterocycle containing one or two oxygen atoms, and

Y is not a single bond when A is (ii) $-O-R^0$ or (iii) $-NR^{16}R^{17}$;



I

and pharmaceutically acceptable salts thereof,

wherein the phenyl ring either in position 6, 7, 8 or 9 may contain a nitrogen atom instead of a CH-moiety and the residues R_1, R_2, R_3 and R_4 have the following meanings:

R_1: C_2-C_6-alkenyl, C_2-C_6-alkynyl, hydroxy, C_1-C_6-alkoxy, C_3-C_6-alkenyloxy, C_3-C_6-alkynyloxy, C_2-C_6-alkanoyloxy, benzoyloxy, morpholinocarbonyloxy, C_1-C_6-alkyloxycarbonyloxy, C_1-C_6-alkylaminocarbonyloxy, C_1-C_6-dialkylaminocarbonyloxy or the moiety

-Alk-A

wherein Alk is: C_1-C_6-alkyl, C_2-C_6-hydroxy-alkyl or C_3-C_6-cycloalkyl and the symbol A means:

(1) hydrogen, halogen, hydroxy, C_1-C_6-alkoxy, C_2-C_6-alkanoyloxy, phenyl;

(2) $-NHR_5$, $-NR_5R_6$, $NR_5R_6R_7$, pyridylamino, imidazolyl, pyrrolidinyl, N-C_1-C_6-alkylpyrrolidinyl, piperidylamino, N-(phenyl-C_1-C_4-alkyl)-piperidylamino, wherein R_5 and R_6 are identical or different and mean hydrogen, C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-hydroxycycloalkyl, morpholino-C_1-C_6-alkyl,

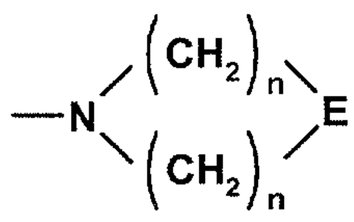
phenyl, phenyl-C_1-C_6-alkyl or phenyl-C_2-C_6-oxyalkyl, wherein the phenyl residues also may be substituted with halogen and R_7 is hydrogen or C_1-C_6-alkyl;

(3) The moiety

-CO-D

wherein D is phenyl, C_1-C_6-alkyl, C_3-C_7-cycloalkyl, hydroxy, C_1-C_6-alkoxy, C_3-C_7-cycloalkyloxy, morpholino, pyrrolidino, piperidino, homopiperidino, piperazino, $-NHR_5$ or $-NR_5R_6$ and R_5 and R_6 have the given meaning;

(4) The moiety



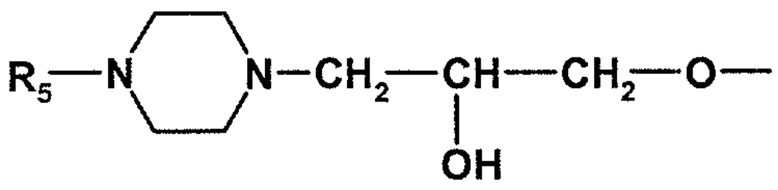
wherein n may be an integer of 1-3 and E means CH_2, oxygen, sulphur, NH, CHOH, CH-C_1-C_6-alkyloxy, CH-C_2-C_6-alkanoyloxy, CHC_6H_5, CHCOD, CH-$CN_2C_6H_5$, N-C_1-C_6-alkyl, N-C_1-C_6-hydroxyalkyl, N-C_6H_5, N-$CH_2C_6H_5$, N-$CH(C_6H_5)_2$, N-$(CH_2)_2$-OH, N-$(CH_2)_3$-OH or NCOD and die phenyl residues (C_6H_5) may also be substituted with halogen, C_1-C_6-alkoxy, trifluormethyl, C_1-C_6-alkyl, methylenedioxy, cyan and D has the above given meaning;

R_2 and R_3, which may be identical or different:

hydrogen, halogen, hydroxy, C_1-C_6-alkyl, trifluormethyl, -CN, C_1-C_6-alkoxy, C_3-C_6-alkenyloxy, C_3-C_6-alkynyloxy, $-NHR_5$, $-NR_5R_6$, $NR_5R_6R_7$ (meanings R_5, R_6, R_7 as given), or the moiety -G-Alk-A, wherein Alk and A have the given meanings and G is oxygen, sulphur, NH or NR_5;

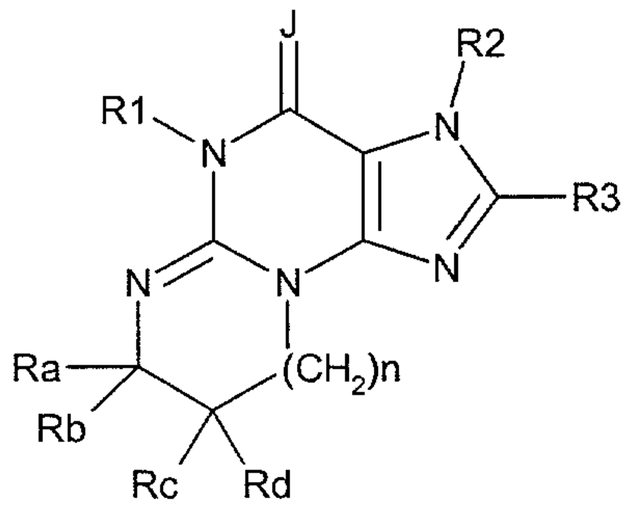
R_4: hydrogen or halogen,

wherein R_1 also may be hydrogen, if R_2 is the moiety

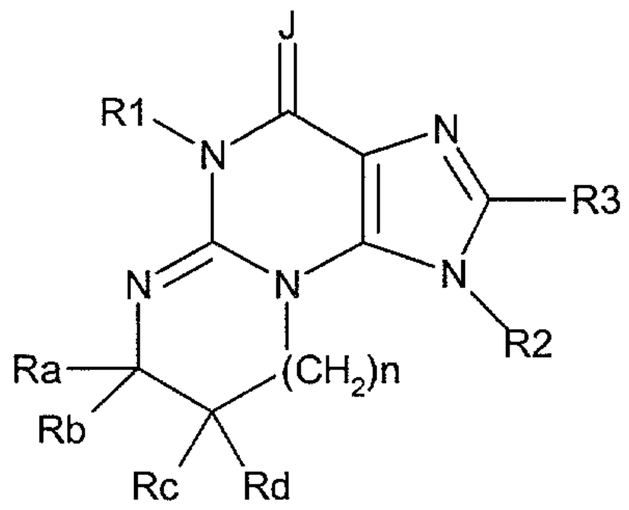


and R_5 means phenyl, C_1-C_4-alkoxy-phenyl or diphenylmethyl and R_3 und R_4 are hydrogen,

and the physiologically acceptable acid addition salts and quarternary ammonia salts thereof, excluding the compounds of formula I wherein R_1 is methyl, dimethylamino-propyl, dimethylamino-ethyl, morpholino-ethyl or pyrrolidino-ethyl, R_2, R_3 and R_4 are hydrogen and the phenyl ring does not contain a nitrogen atom;



and



and pharmaceutically acceptable salts thereof,

wherein J is oxygen or sulfur,

R^1 is hydrogen, alkyl or alkyl substituted with aryl or hydroxy;

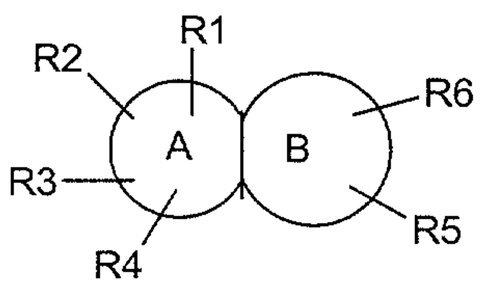
R^2 is hydrogen, aryl, heteroaryl, cycloalkyl, alkyl or alkyl substituted with aryl, heteroaryl, hydroxy, alkoxy, amino, monoalkyl amino or dialkylamino, or $-(CH_2)_m$ $TCOR^{20}$ wherein m is an integer from 1 to 6, T is oxygen or -NH- and R^{20} is hydrogen, aryl, heteroaryl, alkyl or alkyl substituted with aryl or heteroaryl;

R^3 is hydrogen, halo, trifluromethyl, alkoxy, alkylthio, alkyl, cycloalkyl, aryl, aminosulfonyl, amino,

monoalkylamino, dialkylamino, hydroxyalkylamino, aminoalkylamino, carboxy, alkoxycarbonyl or aminocarbonyl or alkyl substituted with aryl, hydroxy, alkoxy, amino, monalkylamino or dialkylamino;

R^a, R^b, R^c and R^d independently represent hydrogen, alkyl, cycloalkyl or aryl; or (R^a and R^b) or (R^c and R^d) or (R^b and R^c) can complete a saturated ring of 5- to 7-carbon atoms, or (R^a and R^b) taken together and (R^b and R^c) taken together, each complete a saturated ring of 5- to 7-carbon atoms, wherein each ring optionally can contain a sulfur or oxygen atom and whose carbon atoms may be optionally substituted with one or more of the following: alkenyl, alkynyl, hydroxy, carboxy, alkoxycarbonyl, alkyl or alkyl substituted with hydroxy, carboxy or alkoxycarbonyl; or such saturated ring can have two adjacent carbon atoms which are shared with an adjoining aryl ring; and

n is zero or one;

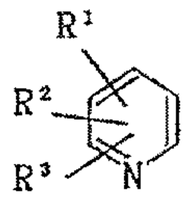


and pharmaceutically acceptable salts thereof,

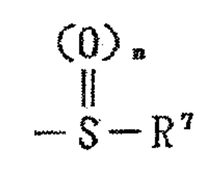
wherein, ring A signifies a benzene ring, pyridine ring or cyclohexane ring, ring B signifies a pyridine ring, pyrimidine ring or imidazol ring,

rings A and B are bonded by sharing two atoms, and the atoms that are shared may be either carbon or nitrogen atoms,

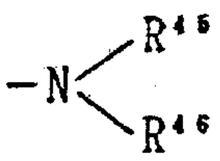
except for the event that ring A is a pyridine ring and ring B shares a nitrogen atom of this pyridine ring for bonding, ring A shall be as shown by the formula



wherein, R^1, R^2, R^3 and R^4 may be identical or different hydrogen atoms, halogen atoms, possibly halogen-substituted low alkyl radicals, possibly substituted cycloalkyl radicals, low alcoxy radicals, hydroxyalkyl radicals, nitro radicals, amino radicals, acyl-amino radicals, possibly protected carboxyl radicals, radicals represented by the formula



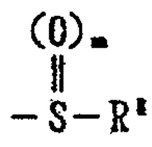
(where R^7 in this formula signifies a low alkyl radicals and n may be 0 or be an integer with a value of 1 - 2), or a radical represented by the formula



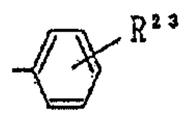
where R^{45} (where $R^{45}$and R^{46} in this formula signify identical or different hydrogen atoms or low alkyl radicals, R^{45} and R^{46} may unite with the nitrogen atom to which they are bonded to form a ring possibly containing different nitrogen and/or oxygen atoms, or, alternatively, this ring may also be substituted,

further, two of the R^1, R^2, R^3, and R^4 radicals may combine to form a methylene dioxy, ethylene dioxy or phenyl ring,

R^5 signifies a hydrogen atom, halogen atom, hydroxyl group, hydrazino radical, a possibly substituted cycloalkyl radical, a low alcoxy radical, a low alkenyl radical, a possibly protected carboxyalkyl radical, a possibly protected carboxyalkenyl radical, a hydroxy alkyl radical, a possibly protected carboxyl radical, a radical represented by the formula



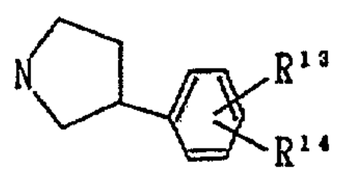
(where R^3 in this formula signifies a low alkyl radical and m may be either 0 or an integer with a value from 1 - 2), a radical represented by the formula -O-R^9 (where R^9 in this formula signifies a possibly protected hydroxyalkyl radical, a possibly protected carboxyalkyl radical or a possibly substituted benzyl radical), a radical represented by the formula



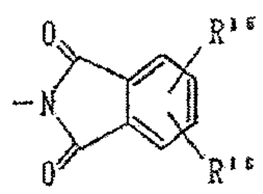
(where R^{23} in this formula signifies a hydroxyl group, a low alkyl radical, a hydroxyalkyl radical or a hydroxyalkyl oxy radical), a possibly substituted heteroaryl radical, a possibly substituted 1,3 benzodioxolyl radical, a possibly substituted 1,4 benzodioxyl radical, a possibly substituted 1,3 benzodioxolyl alkyl resin, a possibly substituted 1,4 benzodioxyl alkyl radical radical represented by the formula $C(R^{24})=X$ (where X in this formula signifies an oxygen atom, a sulphur atom or a radical represented by the formula =N-R^{10} (where R^{10} in this formula signifies a hydroxyl group or a

possibly protected carboxyalkyloxy radical) and (R^{24} signifies a hydrogen atom or a low alkyl radical), or a radical represented by the formula $-NR^{11}R^{12}$ (where R^{11} and R^{12} in this formula signify identical or different hydrogen atoms, low alkyl radicals, hydroxyalkyl radicals, aminoalkyl radicals, possibly protected carboxyalkyl radicals, alkyl carbamoyl radicals, possibly protected carboxy alkyl carbamoyl radicals, possibly substituted heteroaryl alkyl radicals, 1,3 benzoxolyl alkyl radicals or 1,4 benzodioxyl alkyl radicals, and where, furthermore, R^{11} and R^{22} may unite with the nitrogen atom to which they are bonded to form a ring possibly containing different nitrogen and/or oxygen atoms, or, alternatively, this ring may also be substituted),

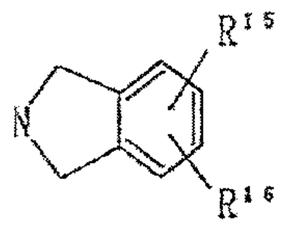
R^6 signifies a hydrogen atom, a halogen atom, hydroxyl group, amino group, low alkyl radical, low alcoxy radical, low alkenyl radical, a 1,3-benzodioxolyl alkyloxy radical, 1,4-benzodioxyl alkyloxy radical, a possibly substituted phenyl alkyloxy radical, a radical represented by the formula



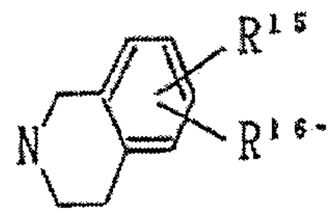
(where R^{13}, R^{14} in this formula signify identical or different hydrogen atoms, low alkyl radicals or alcoxy radicals, furthermore, R13 and R14 may combine to form methylene dioxy or ethylene dioxy), a radical represented by the formula



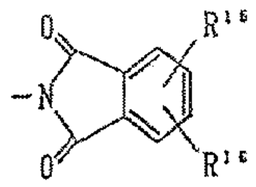
a radical represented by the formula



a radical represented by the formula

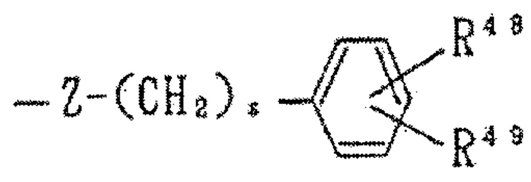


a radical represented by the formula

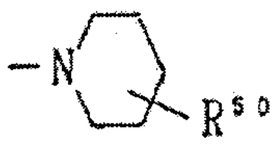


(where R^{15} and ^{16} used in these formulae signify identical or different hydrogen atoms, low alkyl radical or low alkoxy radical,

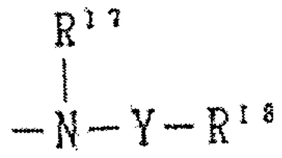
furthermore, R^{15} and R^{16} may combine to form methylene dioxy or ethylene dioxy), a piperidine-4-spiro-2'-dioxane-1-yl radical, a radical represented by the formula



(where R^{48} and R^{49} in this formula signify identical or different hydrogen atoms, low alkyl radicals or low alcoxy radicals, furthermore, R^{48} and R^{49} may combine to form methylene dioxy or ethylene dioxy, Z signifies a sulphur atom or an oxygen atom), a radical represented by the formula

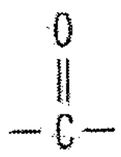


(where R^{50} in this formula signifies s hydroxyl group, a halogen atom, a low alkyl radical, a low alcoxy radical, a possibly protected carboxyl radical, a cyano radical, a hydroxyalkyl radical or a carboxyalkyl radical), a radical represented by the formula



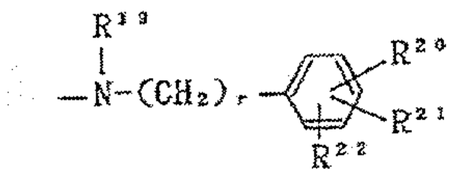
(where R^{17} in this formula stands for a hydrogen atom, low alkyl radical, acyl radical, low alcoxyalkyl radical, a possibly protected carboxyalkyl radical or a hydroxyalkyl radical, Y stands for a radical represented by the formula

(where q in this formula signifies 0 or an integer from 1 - 8), or a radical represented by the formula

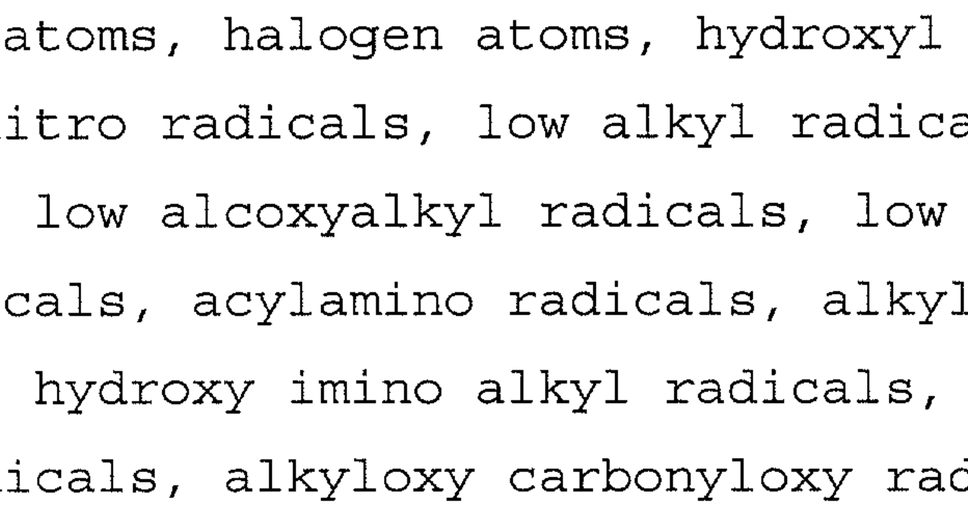


furthermore, when q in the radical represented by the formula

has the value of an integer from 1 - 8, the respective carbon atoms may also possess 1 - 2 substituted radicals, R^{18} signifies a hydrogen atom, hydroxyl group, a possibly protected carboxylradical, a cyano radical, an acyl radical, a possibly substituted heteroaryl radical, or a possibly substituted cycloalkyl radical), or a radical represented by the formula



(where R^{19} in this formula stands for a hydrogen atom, low alkyl radical, low alkoxyalkyl radical, acyl radical, a possibly protected carboxyalkyl radical or a hydroxyalkyl radical R^{20}, R^{21}, and R^{22} signify identical or different hydrogen atoms, halogen atoms, hydroxyl groups, amino groups, nitro radicals, low alkyl radicals, low alkoxy radicals, low alcoxyalkyl radicals, low alkenyl radicals, acyl radicals, acylamino radicals, alkyl sulphonyl amino radicals, hydroxy imino alkyl radicals, alkyloxy carbonyl amino radicals, alkyloxy carbonyloxy radicals or possibly substituted heteroaryl radicals, furthermore, any two of R^{20}, R^{21}, and R^{22} may also combine to form a saturated or unsaturated ring that may contain nitrogen, sulphur or oxygen atoms, R signifies 0 or an integer from 1 to 8;

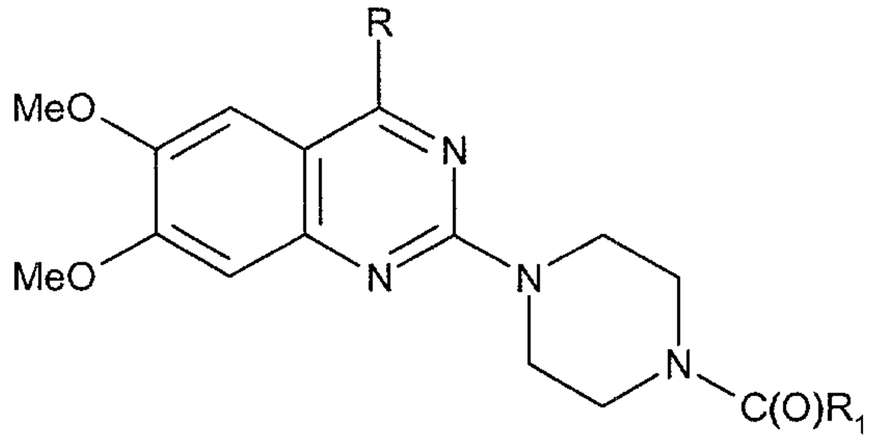


and pharmaceutically acceptable salts thereof, wherein:

R_1, R_2 and R_3 are independently selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, halogeno, hydroxy, (di-lower alkyl) amino, 4-morpholinyl, 1-pyrrolidinyl, 1-pyrrolyl, $-CF_3$, $-OCF_3$, phenyl and methoxphenyl; or R_1 and R_2 together are methylenedioxy; or R_1

and R_2 together with the carbon atoms to which they are attached form a benzene ring; and

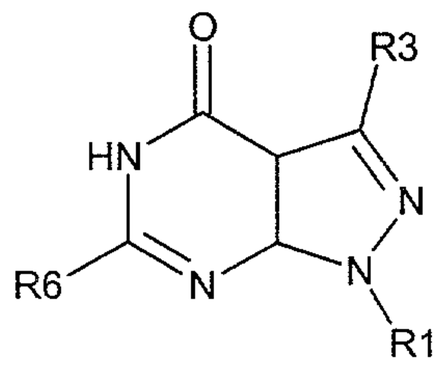
R^a is hydrogen and R^b and R^c, together with the carbon atoms to which they are attached, form a saturated ring of 5 carbons; or R^a is lower alkyl, R^b is hydrogen or lower alkyl, and R^c is hydrogen; or R^a, R^b and the carbon atom to which they are attached form a saturated ring of 5-7 carbons, and R^c is hydrogen; or R^a is hydrogen, and R^b, R^c and the carbon atoms to which they are attached form a tetrahydrofuran ring; or R^a and R^b, together with the carbon atom to which they are attached, and R^b and R^c, together with the carbon atoms to which they are attached, each form a saturated ring of 5-7 carbons;



and pharmaceutically acceptable salts thereof, wherein:

R is amino or hydrazino;

R_1 is cycloalkyl having 3 to 8 ring carbon atoms inclusive and cycloalkenyl having 4 to 8 ring carbon atoms inclusive;



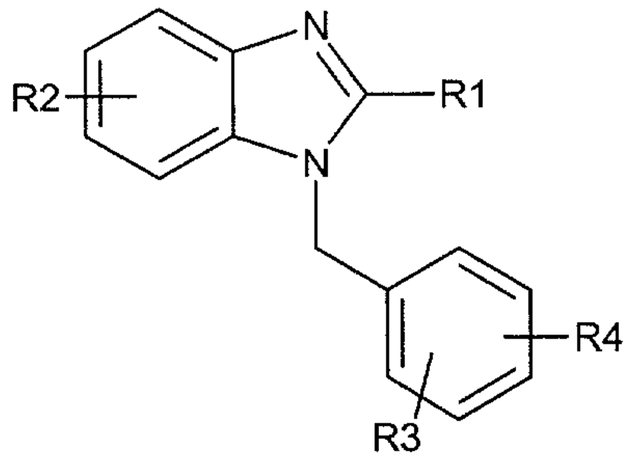
and pharmaceutically acceptable addition salts thereof,

wherein

R^1 is hydrogen, alkyl, C_4 to C_7 cycloalkyl, C_4 to C_7 cycloalkyl, substituted by C_1 to C_{10} alkyl or hydroxyl, 2- or 3-tetrahydrothienyl, 1,1, -dioxide, C_4 to C_7 cycloalkyl-C_1 to C_{10} alkyl, carboxy-C_1 to C_{10} alkyl, carbo-C_1 to C_4 lower alkoxy C_1 to C_{10} alkyl, dialkylamino C_1 to C_{10} alkyl, phenyl-C_1 to C_4 lower-alkyl, phenyl-C_1 to C_4 lower-alkyl in which the phenyl ring is substituted in the 2, 3 or 4 position by one or two substituents, the same or different, selected from the group consisting of amino, halogen, C_1 to C_{10} alkyl, carboxyl, carbo-C_1 to C_4 lower-alkoxy, carbamoyl, $NHSO_2$ (quinolinyl), nitro and cyano;

R^3 is C_1 to C_4 lower alkyl, phenyl C_1 to C_4 lower alkyl, lower-alkoxyphenyl-C_1 to C_4 lower-alkyl, diC_1 to C_4 lower-alkoxy-phenyl-C_1 to C_4 lower alkyl, pyridyl-C_1 to C_4 lower alkyl, C_4 to C_7 cycloalkyl-C_1 to C_4 lower-alkyl, phenylamino, diC_1 to C_{1-} alkylamino, halogen, trifluoromethyl, C_1 to C_4 lower-alkylthio, cyano or nitro; and

R^6 is a nine or ten membered bicyclic ring having carbon and from one or two nitrogen atoms, and the heterocycle is made up of fused 5 or 6 membered rings or such ring substituted at any available carbon atom by one or two substituents, the same or different, selected from the group consisting of C_1 to C_4 lower-alkyl, halogen, C_1 to C_4 lower-alkoxy, C_4 to C_7 cycloalkyloxy, 4-morpholinyl, $C_1$to C_4 lower-alkoxy-C_1 to C_4 lower-alkoxy, hydroxy, imidazolyl, oxo and 4-morpholinyl-C_1 to C_4 lower-alkoxy, or at any time available nitrogen atom by C_1 to C_4 lower-alkyl, C_2 to C_4 lower-alkanoyl, or trifluoroacetyl;

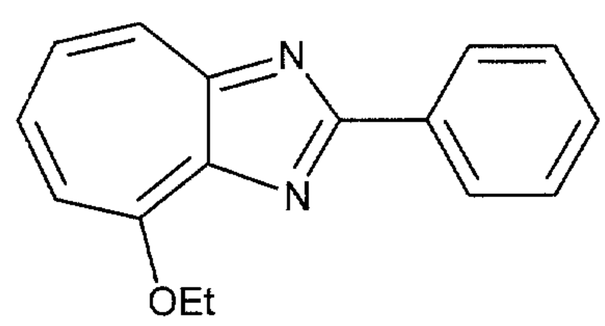


and pharmaceutically acceptable salts thereof,

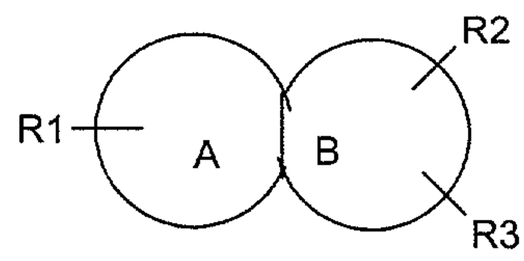
where R^1 stands for a low alkyl radical or (low) cycloalkyl;

R^2 for a carboxy radical, esterified carboxy radical or an amidized carboxy radical; and

R^3 and R^4 each stand for hydrogen, halogen atoms, carboxy radicals, esterified carboxy radicals or low alkyl radicals that may possess 1 - 3 halogen atoms, respectively;



(2-phenyl-8-ethoxycycloheptimidazole);

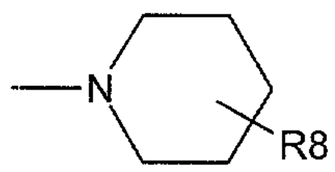


and pharmacologically acceptable salts thereof,

in which ring A represents a benzene, pyridine or cyclohexane ring and B represents a pyridine, imidazole or pyrimidine ring, with the proviso that rings A and B are bonded to each other with two atoms being shared by the, and the shared atoms may be any of carbon and nitrogen atoms:

R^1 represents a group represented by the formula: $-NR^4R^5$ (wherein R^4 and R^5 may be the same or different from each other and each represent a hydrogen atom, a lower alkyl or acyl group or a carboxyl group which may be protected, or alternatively R^4 and R^5 may form a ring together with the nitrogen atom to which they are bonded, provided that the ring may be substituted), or a heteroaryl group which has one or two nitrogen atoms and may be substituted;

R^2 represents a hydrogen atom, a group represented by the formula:

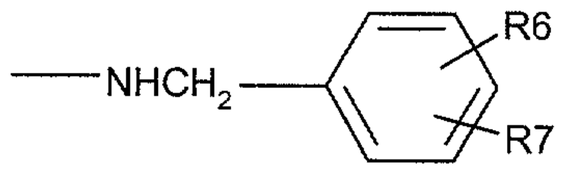


(wherein R^8 represents a carboxyl or tetrazolyl group which may be protected),

or a halogen atom:

and

R^3 represents a hydrogen atom or a group represented by the formula:



(wherein R^6 and R^7 each represent a hydrogen or halogen atom or a lower alkoxy group, or alternatively R^6 and R^7 may together form a methylenedioxy or ethylenedioxy group);

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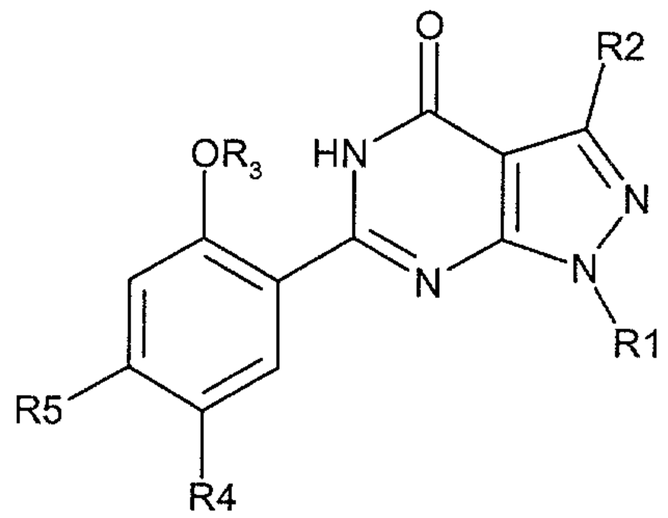


and pharmaceutically acceptable salts and solvates (eg. hydrates) thereof, in which:

R^1 represents arylmethyl or C_{1-6} alkyl optionally substituted by one or more fluorine atoms;

R^2 represents methyl;

R^3 represents C_{2-4} alkyl;

R^4 represents nitro, cyano, C_{1-6} alkoxy, $C(=X)NR^6R^7$, NR^8R^9, $(CH_2)_mNR^{10}C(=Y)R^{11}$ or a 5-membered heterocyclic ring selected from thienyl, thiazolyl and 1,2,4-triazolyl each ring optionally substituted by a

C_{1-4} alkyl or aryl group; or when R^1 is arylmethyl or C_{1-6} alkyl substituted by one or more fluorine atoms then R^4 may also represent hydrogen;

R^5 represents hydrogen or C_{1-6} alkyl;

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

R^7 represents hydrogen, amino, hydroxyl, C_{1-6} alkyl, aryl or arylC_{1-4} alkyl;

R^8 represents hydrogen or C_{1-6} alkyl;

R^9 represents hydrogen, C_{1-6} alkyl, SO_2R^{12}, CO_2R^{12}, $C(=NCN)SR^{12}$ or $C(=NCN)NR^{13}R^{14}$;

R^{10} represents hydrogen or C_{1-6} alkyl;

R^{11} represents C_{1-6} alkyl optionally substituted by one or more halogen atoms, or R^{11} represents aryl, aryl C_{1-4} alkyl, thienyl, $NR^{15}R^{16}$, $CH_2NR^{17}R^{18}$ or R^{10} and R^{11} together represent $-A(CH_2)_n-$;

R^{12} represents C_{1-6} alkyl, aryl or arylC_{1-4}alkyl;

R^{13} represents hydrogen or C_{1-6} alkyl;

R^{14} represents hydrogen, C_{1-6} alkyl, aryl, aryl C_{1-4} alkyl or R^{13} and R^{14} together with the nitrogen atom to which they are attached form a morpholine, piperazine or N-C_{1-4} alkylpiperazine ring;

R^{15} represents hydrogen or C_{1-6} alkyl or R^{10} and R^{15} together represent $-A(CH_2)_n-$;

R^{16} represents hydrogen, C_{1-6} alkyl, aryl, aryl C_{1-4} alkyl, CO_2R^{12}, $CH_2CO_2R^{12}$ or R^{15} and R^{16} together with the nitrogen atom to which they are attached form a morpholine, piperazine or N-C_{1-4}alkyl-piperazine ring;

R^{17} represents hydrogen or C_{1-6} alkyl;

R^{18} represents hydrogen, C_{1-6} alkyl, aryl, aryl C_{1-4} alkyl, COR^{12} or R^{17} and R^{18} together with the nitrogen atom to which they are attached form a morpholine, piperazine, or N-C_{1-4} alkylpiperazine ring;

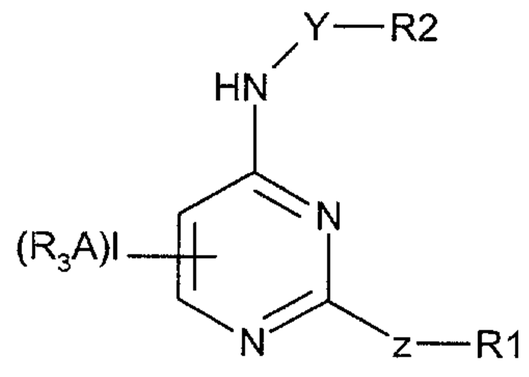
A represents CH_2 or C = O;

m represents zero or 1;

n represents 1,2 or 3;

X represents S or NH, or when R^7 represents amino then X may also represent O;

Y represents O or S;



and pharmaceutically acceptable salts thereof,

wherein A is a bond, C1-4 alkylene or C1-4 oxyalkylene;

Y is a bond, C1-4 alkylene, C1-4 alkyleneoxy, C1-4 alkoxyphenylene or phenyl (C1-4) alkylene;

Z is a bond or vinylene;

R1 is a 4-15 membered heterocyclic ring containing one or two nitrogen atoms optionally substituted by one or two groups chosen from C1-4 alkyl, C1-4 alkoxy, halogen, trifluoromethyl, and nitro;

R2 is

(i) 4-15 membered heterocyclic ring containing one or two hetero atoms chosen from nitrogen, oxygen and sulphur, not more than one hetero atom being sulphur, optionally substituted by one or two groups chosen from C1-4 alkyl, C1-4 alkoxy, halogen, trifluoromethyl, nitro and groups of formula: - COOR10

wherein R10 is hydrogen or C1-4 alkyl,

C4-15 carbocyclic ring,

C1-4 alkoxy,

hydroxy(C1-4 alkoxy) or

hydroxy

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R^3 is

4-15 membered heterocyclic ring containing one or two hetero atoms chosen from nitrogen, oxygen and sulphur, not more than one hetero atom being oxygen or sulphur, optionally substituted by one or two groups chosen from C1-4 alkyl, C1-4 alkoxy, halogen, trifluoromethyl, nitro, cyano, ethynyl and groups of formula: - SONR7R8

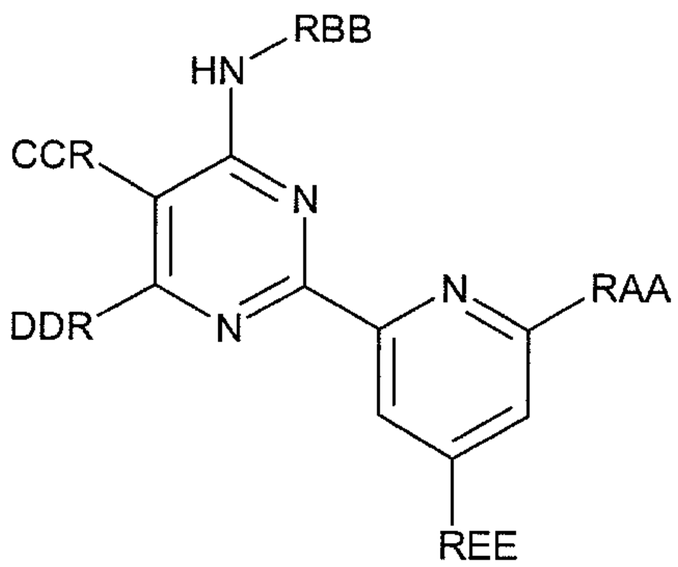
wherein R7 and R8 are independently hydrogen or C1-4 alkyl.

C4-15 carbocyclic ring,

a group of formula:CH2 = CH(X)- wherein X is halogen, or hydrogen

and l is 1 or 2;

provided that R2 is not hydroxy when Y is a bond: R1 is not bonded through its nitrogen atom when Z is vinylene; and excluding compounds of the formula:



wherein R^{AA} is methyl or n-propyl;

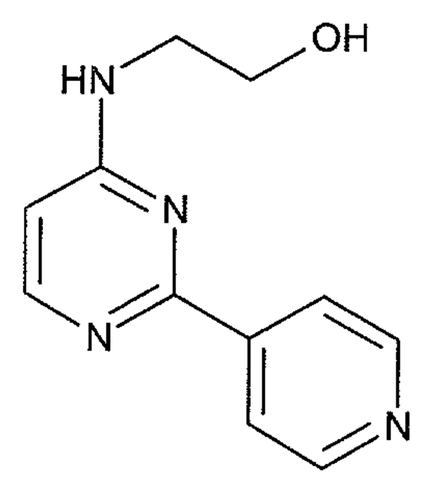
R^{BB} is cyclopentyl, cyclohexyl, 2-hydroxyethyl, methoxyethyl, 2-(1-piperindinyl)ethyl or phenyl or benzyl which may be substituted by 1 or 2 of methyl, methoxy, chloro, nitro and trifluoromethyl;

R^{CC} is hydrogen or methyl;

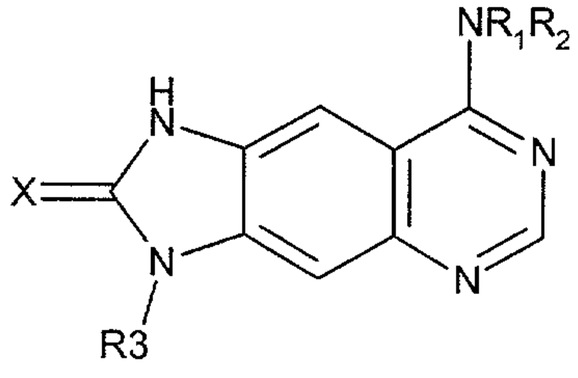
R^{DD} is methyl or n-propyl, isopropyl or benzyl; and

R^{EE} is hydrogen or methyl;

and the compound of formula:



;



and pharmaceutically acceptable salts thereof,

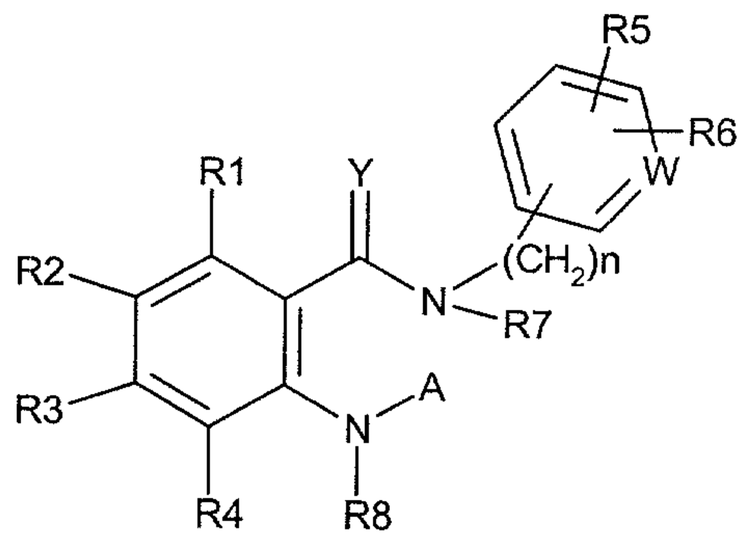
where R^1 and R^2 may stand for identical or different hydrogen atoms, low alkyl radicals (the respective alkyls may be cycloalkyl with a substitution number of 1 - 3, either identical or different, hydroxy, low alkoxy, carboxy, low alcoxycarbonyl, amino, monoalkyl-substituted amino, dialkyl-substituted amino, nitro, halogen or alicyclic heterocyclic radical (the respective alicyclic heterocyclic radical may be substituted by identical or different low alkyls with a substitution number of 1 - 3, aralkyl, aryl possibly substituted by a low alcoxy radical with a substitution number from 1 - 3 or an aromatic heterocyclic radical), a cycloalkyl, di-cycloalkyl, benzocycloalkyl (the respective benzoalkyl may be substituted by identical or different low alkyls with a substitution number of 1 - 3, hydroxy, low alcoxy, carboxy, low alcoxycarbonyl, amino, aminoalkyl-substituted amino, dialkyl-substituted amino,

nitro, sulphonamide, halogen, or trifluoromethyl), low alkenyl, aryl (the respective aryl may be subsituted by identical or different low alkyls with a substitution number of 1 - 3, hydroxy, low alcoxy, carboxy, low alcoxycarbonyl, amino, monoalkyl-substituted amino, di-alkyl substituted amino, nitro, sulphonamide, halogen or trifluoromethyl), aromatic heterocyclic radical-substituted alkyl (the respective aromatic heterocyclic radical-substituted part may be substituted by identical or different low alkyls with a substitution number of 1 - 3, hydroxy, low alcoxy, carboxy, low alcoxycarbonyl, amino, monoalkyl-substituted amino, di-alkyl substituted amino, nitro, sulphonamide, halogen, or trifluoromethyl, or the alkyl part may be substituted by aryl), aromatic heterocyclic radical (the respective aromatic heterocyclic radical may be substituted by identical or different low alkyls with a substitution number of 1 - 3, hydroxy, low alcoxy, carboxy, low alcoxycarbonyl, amino, monoalkyl-substituted amino, di-alkyl substituted amino, nitro, sulphonamide, halogen or trifluoromethyl), or aralkyl (the aryl part of the respective aralkyl may be substituted by identical or different low alkyls with a substitution number of 1 - 3, low alcoxy, di-alcoxy-substituted amino, halogen or trifluoromethyl); and, furthermore,

R^1 and R^2 may stand for heterocyclic radicals formed by R^1 and R^2 combining with the inclusion of nitrogen (N) (the respective heterocyclic radical may be substituted by identical or different alkyls with a substitution number of 1 - 3, aryl, or aralkyl);

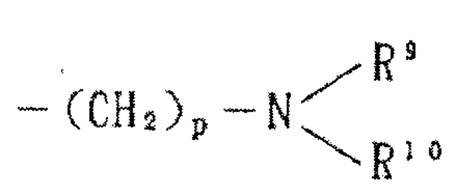
R3 stands for hydrogen, low alkyl (the respective low alkyl may be substituted by identical or different cycloalkyls with a substitution number of 1 - 3, hydroxy, low alcoxy, carboxy, low alcoxycarbonyl, amino, monoalkyl-substituted

amino, di-alkyl-substituted amino, nitro, halogen, or alicyclic heterocyclic radical (the respective alicyclic heterocyclic radical may be substituted by identical or different low alkyls with a substitution number of 1 - 3, aralkyl, aryl possibly substituted by a low alcoxy radical with a substitution number from 1 - 3 or an aromatic heterocyclic radical.)), cycloalkyl, low alkenyl, aryl (the respective aryl may be subsituted by identical or different low alkyls with a substitution number of 1 - 3, hydroxy, low alkoxy, carboxy, low alcoxycarbonyl, amino, monoalkyl-substituted amino, di-alkyl substituted amino, nitro, sulphonamide, halogen or trifluoromethyl.), aromatic heterocyclic radical-substituted alkyl (the respective aromatic heterocyclic radical-substituted part may be substituted by identical or different low alkyls with a substitution number of 1 - 3, hydroxy, low alcoxy, carboxy, low alcoxycarbonyl, amino, monoalkyl-substituted amino, di-alkyl substituted amino, nitro, sulphonamide, halogen, or trifluoromethyl, or the alkyl part may be substituted by aryl), aromatic heterocyclic radical (the respective aromatic heterocyclic radical may be substitued by identical or different low alkyls with a substitution number of 1 - 3, hydroxy, low alcoxy, carboxy, low alcoxycarbonyl, amino, monoalkyl-substituted amino, di-alkyl substituted amino, nitro, sulphonamide, halogen or trifluoromethyl), or aralkyl (the aryl part of the respective aralkyl may be substituted by identical or different low alkyls with a substitution number of 1 - 3, low alcoxy, di-alcoxy-substituted amino, halogen or trifluoromethyl.); and X stands for O (oxygen) or S (sulphur);



and pharmaceutically acceptable salts thereof,

where R^1, R^2, R^3 and R^4 signify identical or different hydrogen atoms, halogen atoms, hydroxyl groups, possibly halogen-substituted low alkyl radicals, possible halogen-substituted low alcoxy radicals, nitro radicals, hydroxyalkyl radicals, cyano radicals, radicals represented by the formula



where R^9 and R^{10} stand for identical or different hydrogen atoms, possibly halogen-substituted low alkyl radicals, aryl-alkyl radicals, heteroaryl-alkyl radicals, acyl radical, possibly protected carboxyl radicals,

and, where furthermore R^9 and R^{10} may combine with the nitrogen to which they are bonded to form a ring,

and where, moreover, this ring may also possess a substitute radical,

P stands for 0 or an integer having a value from 1 - 6.), a carbamoyl radical which may have a substitute radical, a pyrazolyl radical which may have a substitute radical, an imidazolyl radical which may have a substitute radical, or a radical represented by the formula

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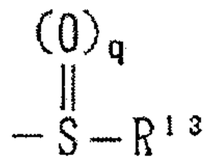


where R^{13} signifies a hydrogen atom or a possibly halogen-substituted low alkyl radical. And, where q is 0 or an integer with a value of 1 - 2,

furthermore, the two mutually adjacent substitute radicals selected from R^1, R^2, R^3, and R^4 may combine with the carbon atom to which they are bonded to form a ring,

R^5 and R^6 stand for hydrogen atoms, halogen atoms, hydroxyl groups, cyano radicals, possibly halogen-substituted low alkyl radicals, or possibly halogen-substituted low alcoxy radicals, furthermore, R^5 and R^6 may combine with the carbon atom to which they are bonded to form an oxolane ring, a 1,3-di-oxolane ring or a 1,4 di-oxane ring,

W signifies the radical represented by the formula -N= or a radical represented by the formula -CH=. R^7 and R^8 stand for identical or different hydrogen atoms, possibly halogen-substituted low alkyl radicals,

furthermore, R^1 and R^7 may combine with the carbon atom to which they are bonded to form rings that may also contain nitrogen, oxygen, or sulphur atoms. Furthermore, this ring may also possess substitute radicals,

A stands for a hydrogen atom, a possibly halogen-substituted low alkyl radical, or a radical represented by the formula -X-(CH2)m-Z (where x stands for a radical represented by the formula -CO-, a radical represented by the formula -CS-, a radical represented by the formula -CH2-, or a radical represented by the formula -C(O)2,

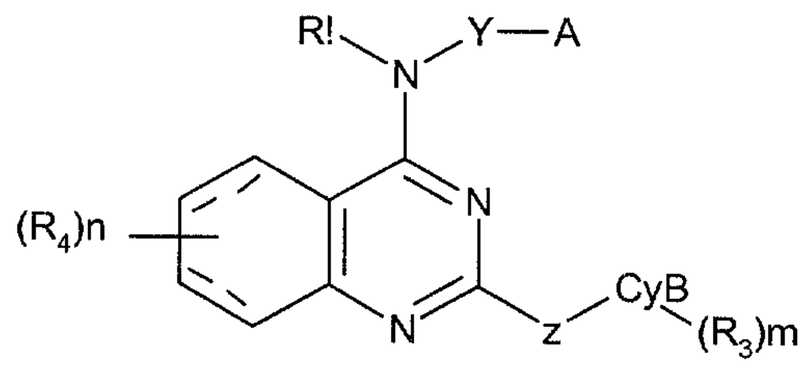
Z signifies the hydroxyl group, a possibly halogen-substituted low alcoxy radical, a cyano radical, a halogen atom, a possibly protected carbamoyl radical, an aryl radical which may possess substitute radicals, an aryloxy radical which may possess substitute radicals, a heteroaryl radical which may possess substitute radicals, a hetero aryl alkyloxy radical which may possess substitute radicals, a radical represented by the formula $-NR^{11}R^{12}$ (where R^{11} and R^{12} signify identical or different hydrogen atoms, possibly halogen-substituted low alkyl radicals, aryl-alkyl radicals which may possess substitute radicals, heteroaryl-alkyl radicals which may possess substitute radicals, acyl radicals, possibly protected carboxy radicals, or carbamoyl radicals which may possess substitute radicals,

furthermore, R^{11} and R^{12} may combine with the nitrogen atom to which they are bonded to form a ring, moreover, this ring may have substitute radicals.), or a cycloalkyl radical which may possess substitute radicals,

m may be either 0 or an integer with a value from 1 - 6,

Y stands for an oxygen or sulphur atom,

N signifies either 0 or an integer with a value from 1 - 6;



and pharmaceutically acceptable salts, addition salts or hydrates thereof,

wherein R^1 is hydrogen or C1-4 alkyl;

Y is a single bond or C1-6 alkylene;

A is

$-CyA-(R^2)_l$,

$-O-R^0$ or $-S(O)_p - R^0$,

in which R^0 is R^{0A} or R^{0B},

R^{0A} is $-CyA-(R^2)l$;

R^{0B} is hydrogen or C1-4 alkyl;

p is 0-2;

CyA is

(1) 3-7 membered, saturated or unsaturated, monocyclic carbocyclic ring,

(2) 7-membered, unsaturated or partially saturated, monocyclic hetero ring containing as hetero atoms, one nitrogen atom, one nitrogen and one oxygen atoms, two nitrogen and one oxygen atoms, or one nitrogen and two oxygen atoms,

(3) 6-membered, unsaturated or partially saturated, monocyclic hetero ring containing as hetero atoms, one nitrogen and one oxygen atoms, two nitrogen and one oxygen atoms, or one nitrogen and two oxygen atoms,

(4) 6-membered, unsaturated or partially saturated, monocyclic hetero ring containing as a hetero atom, one nitrogen atom,

(5) 4- or 5-membered, unsaturated or partially saturated, monocyclic hetero ring containing as hetero atoms, one nitrogen atom, one nitrogen and one oxygen atoms, two nitrogen and one oxygen atoms, or one nitrogen and two oxygen atoms,

(6) 4-7 membered, unsaturated or partially saturated, monocyclic hetero ring containing as hetero atoms, one or two sulfur atoms or

(7) 4-7 membered, unsaturated or partially or fully saturated, monocyclic hetero ring containing as hetero atoms, one or two oxygen atoms;

R^2 is R^{2A} or R^2B;

R^{2A} is (1) $-NR^6AR^{7A}$, in which R^{6A} and R^{7A} independently are hydrogen or C1-4 alkyl (with the proviso that $R-^{6A}$ and R^{7A-} are not hydrogen at same time), (2)$-SO_2NR^6R^7$, in which R^6 and R^7 independently are hydrogen or C1-4 alkyl, (3) trifluoromethyl or (4) trifluoromethoxy;

R^{2B} is (1) hydrogen (2) C1-4 alkyl, (3) C1-4 alkoxy, (4) $-COOR^5$ in which R^5 is hydrogen or C1-4 alkyl, (5) halogen, (6) nitro or

(7) $-NRGBR^{7B}$, in which R^{6B} and R^{7B} are hydrogen;

Z is Z^A or Z^B

Z^A is methylene, ethylene, vinylene or ethnylene;

Z^B is single bond;

CyB is

(1) 7-membered, unsaturated or partially saturated monocyclic hetero ring containing as hetero atoms, one, two or three nitrogen atoms,

(2) 6-membered, unsaturated or partially saturated monocyclic hetero ring containing as hetero atoms, two or three nitrogen atoms,

(3) 6-membered, unsaturated or partially saturated, monocylic hetero ring containing as a hetero atom, one nitrogen atom,

(4) 4- or 5- membered, unsaturated or partially saturated, monocyclic, hetero ring containing as hetero atoms, one, two or three nitrogen atoms, or

(5) 4-7 membered, unsaturated or partially saturated, monocyclic hetero ring containing as hetero atoms, one or two oxygen atoms, or one or two sulfur atoms;

R^3 is hydrogen, C1-4 alkyl, C1-4 alkoxy, halogen or trifluoromethyl;

R^4 is R^{4A} or R^{4B};

R^{4A} is (1) $-NHSO_2R^{11}$ in which R^{11} is C1-4 alkyl, (2) $SO_2NR^9R^{10}$, in which

R^9 is hydrogen, C1-4 alkyl or phenyl (C1-4 alkyl) and R^{10} is hydrogen or C1-4 alkyl, (3) $-OCOR^{11}$, in which R^{11} is as hereinbefore defined, (4) hydroxy, (5) $-SO_2N=CHNR^{12}R^{13}$ in which R^{12} is hydrogen or C1-4 alkyl and R^{13} is C1-4 alkyl, (6) $-CONR^{14}R^{15}$ in which R^{14} is hydrogen or C1-4 alkyl and R^{15} is C1-4 alkyl or phenyl (C1-4alkyl), (7) ethynyl, (8) tri(C1-4 alkyl) silylethynyl or (9) acetyl;

R^{4B} is (1) hydrogen, (2) C1-4 alkyl, (3) C1-4 alkoxy,

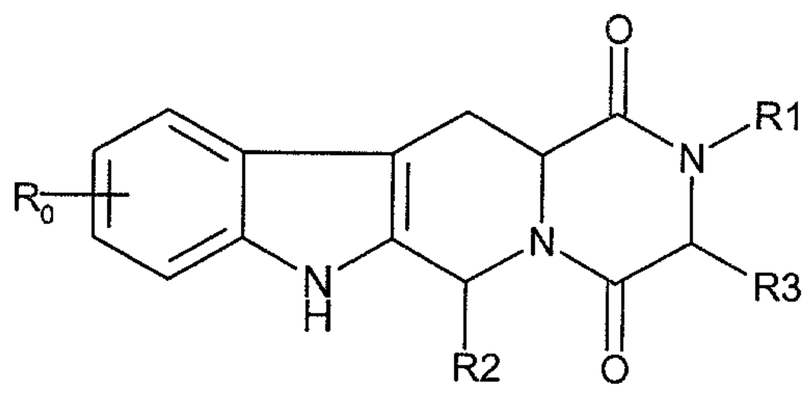
(4) $-COOR^8$, in which R^8 is hydrogen or C1-4 alkyl,

(5) $-NR^9R^{10}$, in which R^9 and R^{10} are as hereinbefore defined,

(6) $-NHCOR^{11}$, in which R^{11} is as hereinbefore defined,

(7) halogen, (8) trifluoromethyl, (9) nitro, (10) cyano, (11) C1-4 alkyl-thio, (12) C1-4 alkylsulfinyl, (13) C1-4 alkylsulfonyl, (14) hydroxymethyl, and l, m and n independently are 1 or 2; with the proviso that the group of the formula: $-CyA-(R^2)$, does not represent a cyclopentyl and

trifluoromethylphenyl group when Y is a single bond, that a CyB ring does not bond to Z through a nitrogen atom in the CyB ring when Z is vinylene or ethynylene, that a CyB ring is not pyridine or thiopene when CyA is a ring of CyA is a ring of CyA - (7) that Y is not a single bond, when A is (ii) $-O-R^0$ or $-S(O)_p-R^0$ and that A is not -CyA - $(R^2B)1$ and OR^{0B}, when Z is Z^B and R^4 is R^{4B};



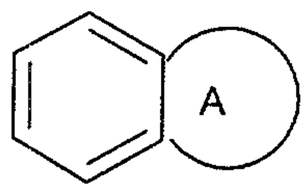
and pharmaceutically acceptable salts and solvates thereof,

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, 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;

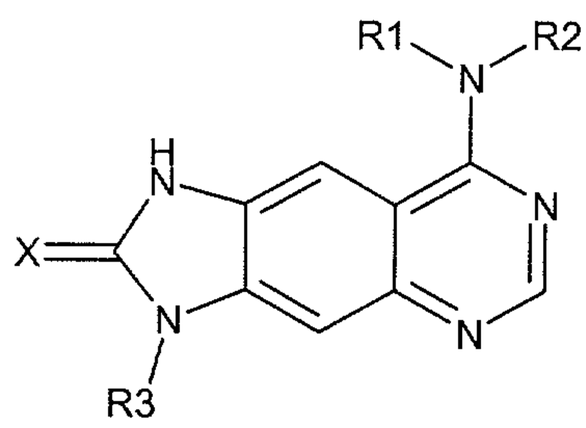
R^2 represents an optionally substituted monocyclic aromatic ring selected from benzene, thiopene, furan and pyridine or an optionally substituted bicyclic ring



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;

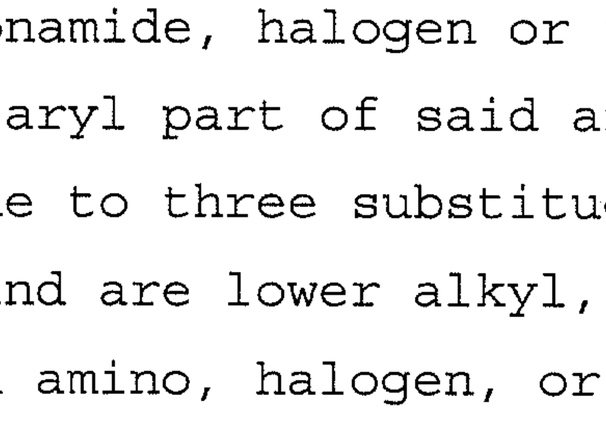


and pharmaceutically acceptable salts thereof,

wherein R^1 and R^2 are the same or different and represent hydrogen, lower alkyl (which is optionally substituted with one to three substituents which are the same or different and are cycloalkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, dialkyl-substituted amino, nitro, halogen, alicyclic heterocycle group (which is optionally substituted with one to three substituents which are the same or different and are lower alkyl, aralkyl, aryl optionally substituted with one to three substituents which are the same or different and are lower alkoxy, or aromatic heterocycle group) cycloalkyl, bicycloalkyl, benzocycloalkyl (which is optionally substituted with one to three substituents which are the same or different and are lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monalkyl-substituted amino, dialkyl-substituted amino, nitro, sulfonamide, halogen, or trifluormethyl) lower alkenyl, aryl (which is optionally substituted with one to three substituents which are the same or different and are lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, dialkyl-substituted

amino, nitro, sulfonamide, halogen, or trifluoromethyl) aromatic heterocycle group-substituted alkyl (which is optionally substituted with one to three substituents which are the same or different and are lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monalkyl-substituted amino, dialkyl-substituted amino, nitro, sulfonamide, halogen or trifluoromethyl and where said alkyl part is optionally substituted with aryl), aromatic heterocycle group (which is optionally substituted with one to three substituents which are the same or different and are lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monalkyl substituted amino, dialkyl-substituted amino, nitro, sulfonamide, halogen or trifluoromethyl), or aralkyl (where the aryl part of the said aralkyl is optionally substituted with one to three substituents which are the same or different and are lower alkyl, lower alkoxy, dialkyl substituted amino, halogen or trifluoromethyl), or R^1 and R^2 are taken together to represent heterocycle group containing nitrogen atom (which is optionally substituted with one to three substituents which are the same or different and are lower alkyl, aryl or aralkyl), R^3 represents hydrogen, lower alkyl (which is optionally substituted with one to three substituents which are the same or different and are cycloalkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monalkyl-substituted amino, dialkyl substituted amino, nitro, halogen, or alicyclic heterocycle group (which is optionally substituted with one to three substituents which are the same or different and are lower alkyl, aralkyl, aryl optionally substituted with one to three substituents which are the same or different and are lower alkoxy, or aromatic heterocyle group), cycloalkyl, lower alkenyl, aryl (which is optionally substituted with one to three substituents which are the same or different

and are lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, dialkyl-substituted amino, nitro, sulfonamide, halogen or trifluoromethyl), aromatic heterocycle group-substituted alkyl (where said aromatic heterocycle group part is optionally substituted with one to three substituents which are the same or different and are lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl amino, monoalkyl-substituted amino, dialkyl-substituted amino, nitro, sulfonamide, halogen or trifluoromethyl, and where the alkyl part is optionally substituted with aryl), aromatic heterocycle group (where said aromatic heterocycle group is optionally substituted with one to three substituents which are the same or different and are lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, dialkyl-substituted amino, nitro, sulfonamide, halogen or trifluoromethyl), or aralkyl (where the aryl part of said aralkyl is optionally substituted with one to three substituents which are the same or different and are lower alkyl, lower alkoxy, dialkyl-substituted amino, halogen, or trifluoromethyl), or aralkyl (where the aryl part of said aralkyl is optionally substituted with one to three substituents which are the same or different and are lower alkyl, lower alkoxy, dialkyl substituted amino, halogen, or trifluoromethyl), and X represents oxygen atom or sulfur atom; and



and pharmacologically acceptable salts thereof

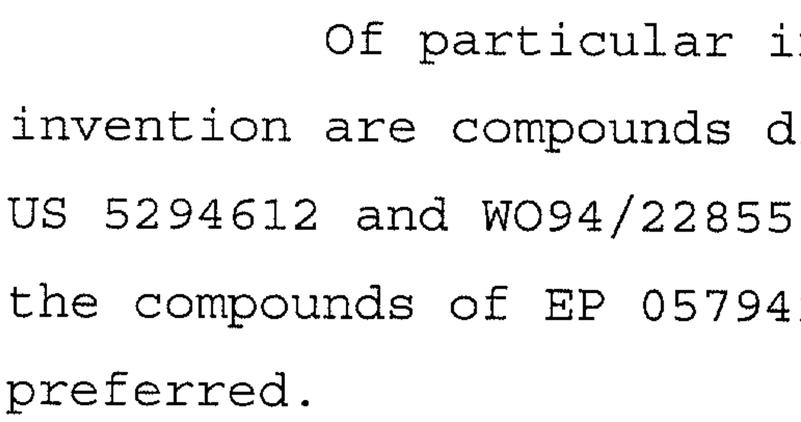
(wherein R^1, R^2, R^3, R^4 and R^5 may be the same or different from each other and each represents a hydrogen atom, a halogen atom, a lower alkyl group or a lower alkoxy group; and

R^6 and R^7 may be the same or different from each other and each represents a hydrogen atom, a lower alkyl group, a hydroxyalkyl group, a lower alkoxyalkyl group, a cyanoalkyl group, a heteroarylalkyl group, a cycloalkyl group, a cycloalkylalkyl group or a carboxyl alkyl group which may be protected, or alternatively R^6 and R^7 may form a ring together with the nitrogen atom to which they are bonded, this ring optionally having a substituent.

The invention includes the use of any compound within the scope of the claims of the patents listed above as well as the particular individual compounds disclosed therein.

Of particular interest for use in the present invention are compounds disclosed in EP 0579496, WO93/07124, US 5294612 and WO94/22855 (xv, xviii, xxi and xxiv above); the compounds of EP 0579496 and WO94/22855 being especially preferred.

More specifically, the present invention provides the use of a compound as described herein, wherein the compound which is a selective cGMP PDE inhibitor is selected from:



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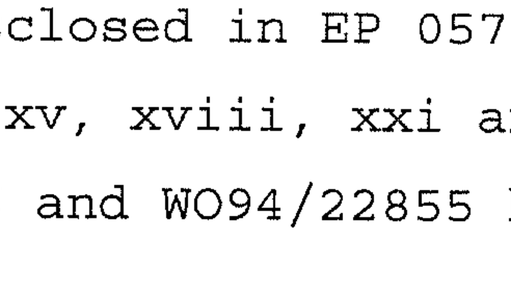

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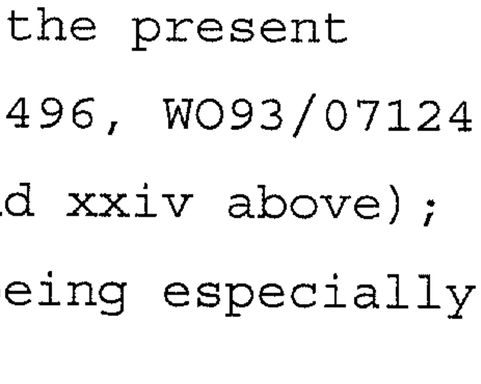
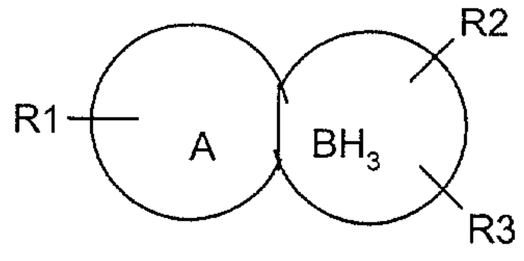


and



as described herein.

Examples of particular and preferred compounds from these patents and publications for use in the present invention include:

1,3-dimethyl-5-benzylpyrazolo[4,3-d]pyrimidine-7-one (preparation as described in European patent application 201188, Example 1),

2-(2-propoxyphenyl)-6-purinone (preparation as described in European patent application 0293063, Example 1),

6-(2-propoxyphenyl)-1,2-dihydro-2-oxopyridine-3-carboxamide (preparation as described in European patent application 0347027, Example 2),

2-(2-propoxyphenyl)pyrido[2,3-d]pyrimid-4(3H)-one (preparation as described in European patent application 0347146, Example 1),

7-methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (preparation as described in European patent application 0351058, Example 1),

6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide (preparation as described in European patent application 0395328, Example 15),

1-ethyl-3-methylimidazo[1,5a]quinoxalin-4(5H)-one (preparation as described in European patent application 0400583),

4-phenylmethylamino-6-chloro-2-(1-imidazoloyl)-quinazoline (preparation as described in European patent application 0579496, Example 5(c)),

5-ethyl-8-[3-(N-cyclohexyl-N-methylcarbamoyl)-propyloxy]-4,5-dihydro-4-oxopyrido[3,2-e]pyrrolo[1,2-a]pyrazine (preparation as described in European patent application 0584487, Example 1),

5'-methyl-3'-(phenylmethyl)-spiro[cyclopentane-1,7'(8'H)-(3'H)-imidazo[2,1-b]purin]4'(5'H)-one (preparation as described in International patent application WO91/19717, Example 9A3),

1-[6-chloro-4-(3,4-methylenedioxybenzyl)aminoquinazolin-2-yl)piperidine-4-carboxylic acid (preparation as described in International patent application WO93/07124),

(6aR,9aS)-2-(4-trifluoromethylphenyl)methyl-5-methyl-3,4,5,6a,7,8,9,9a-octahydrocyclopent[4,5]imidazo[2,1-b]purin-4-one (preparation as described in International Patent application WO94/19351, Example 14),

1-tert-butyl-3-phenylmethyl-6-(4-pyridyl)pyrazolo[3,4-d]pyrimid-4-one (preparation as described in US patent 5294612, Example 90),

1-cyclopentyl-3-methyl-6-(4-pyridyl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimid-4-one (preparation as described in US patent 5294612, Example 83),

2-butyl-1-(2-chlorobenzyl)6-ethoxycarbonylbenzimidazole (preparation described in Japanese patent application 5-222000),

2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-nitroquinazoline (preparation as described in International patent application WO94/22855, Example 11),

and 2-phenyl-8-ethoxycycloheptimidazole (KT2-734).

Of particular interest for use in the present invention are the compounds:

4-phenylmethylamino-6-chloro-2-(1-imidazoloyl)quinazoline (preparation as described in European patent application 0579496, Example 5(c)),

1-[6-chloro-4-(3,4-methylenedioxybenzyl)aminoquinazolin-2-yl)piperidine-4-carboxylic acid (preparation as described in International patent application WO93/07124),
(6aR,9aS)-2-(4-trifluoromethylphenyl)methyl-5-methyl-3,4,5,6a,7,8,9,9a-octahydrocyclopent[4,5]imidazo[2,1-b]purin-4-one (preparation as described in International Patent application WO94/19351, Example 14),
1-tert-butyl-3-phenylmethyl-6-(4-pyridyl)pyrazolo[3,4-d]pyrimid-4-one (preparation as described in US patent 5294612, Example 90),
1-cyclopentyl-3-methyl-6-(4-pyridyl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimid-4-one, (preparation as described in US patent 5294612, Example 83), or
2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-nitroquinazoline (preparation as described in International patent application WO94/22855, Example 11).

Further cGMP PDE inhibitors for use in the treatment of erectile dysfunction are:

xxv a pyrazolopyrimidine derivative as disclosed in European patent application 0636626;

xxvi a 4-aminopyrimidine derivative as disclosed in European patent application 0640599;

xxvii a imidazoquinazoline derivative as disclosed in International patent application WO95/06648;

xxviii an anthranilic acid derivative as disclosed in International patent application WO95/18097;

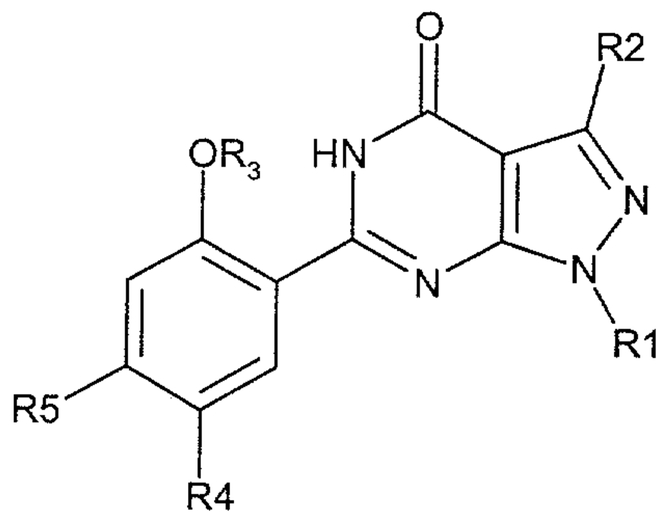
xxix a 4-aminoquinazoline derivative as disclosed in US patent 5436233;

xxx a tetracyclic derivative as disclosed in International patent application WO95/19978;

xxxi an imidazoquinazoline derivative as disclosed in European patent application 0668280; or

xxxii a quinazoline compound as disclosed in European patent application 0669324.

More specifically, the present invention provides the use of a compound which is a selective cGMP PDE inhibitor for the manufacture of a medicament for the treatment of erectile dysfunction in a male animal, including man, wherein said compound is selected from:



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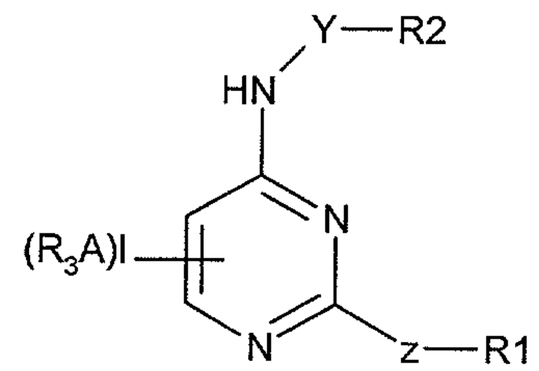

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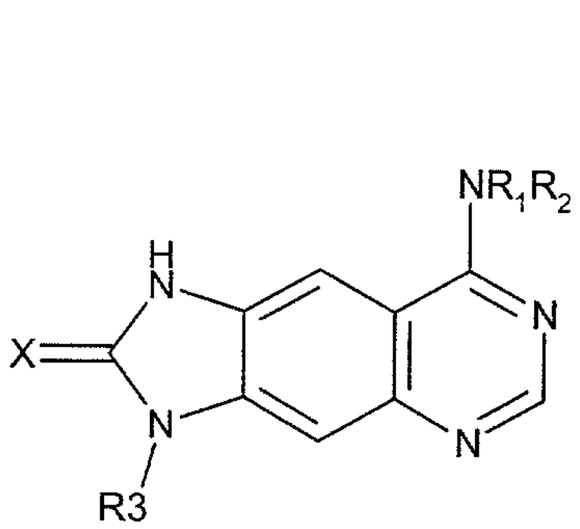

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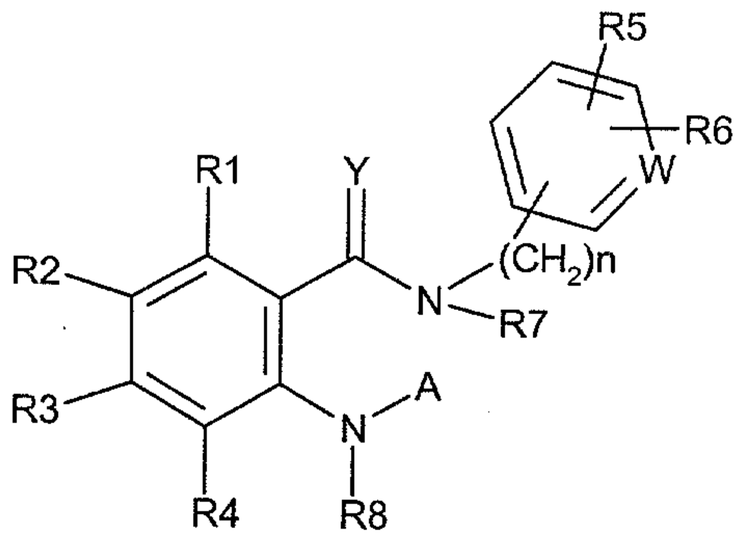

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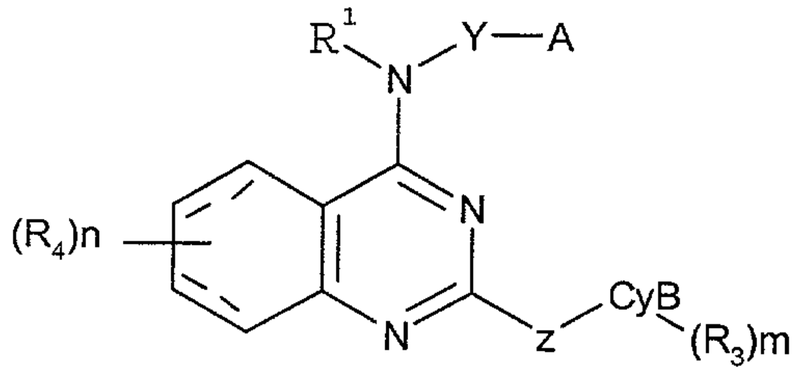

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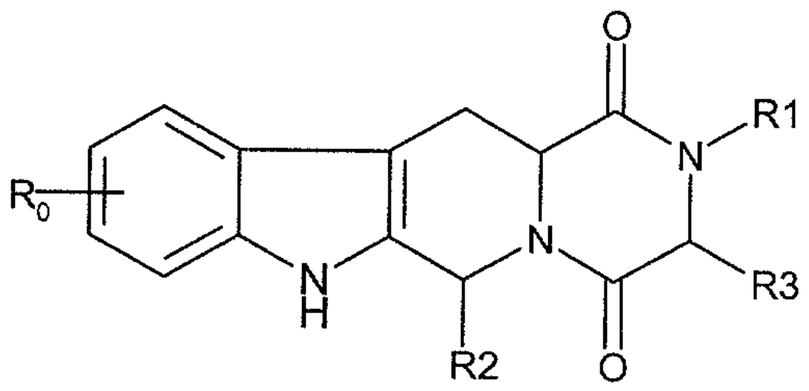

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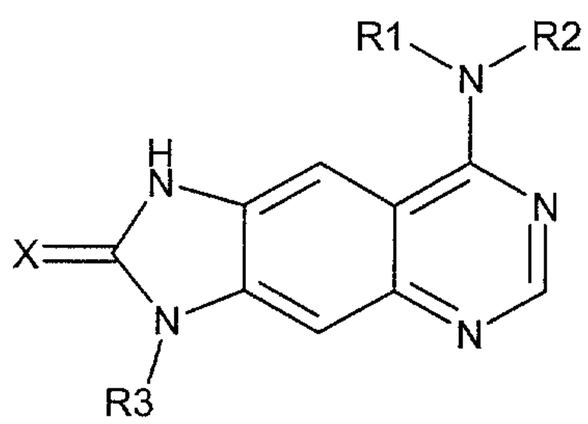
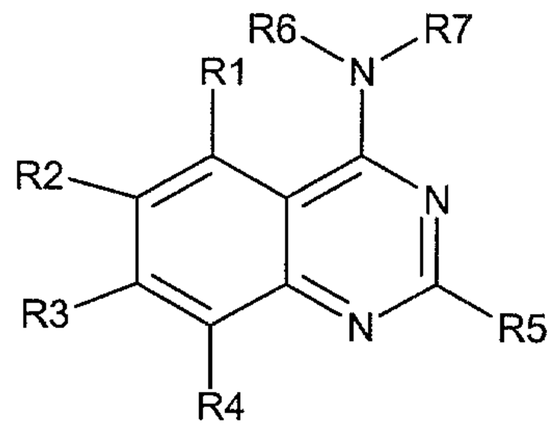


, and



as mentioned above.

The compounds may be evaluated as selective inhibitors of cGMP-PDE using any of the methods previously described but in particular their activity against cGMP-PDE_v may be assessed as described in our International patent application PCT/EP94/01580, (WO94/28902).

Generally, in man, oral administration is the preferred route, being the most convenient and avoiding the disadvantages associated with i.c. administration. A preferred dosing regimen for a typical man is 5 to 75 mg of compound daily, however the dosage may be increased depending on the potency of the compound being administered and higher dosages are within the scope of the invention. Alternative dosage regimes are also possible depending upon the individual patients circumstances such as the frequency of sexual intercourse. 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 veterinary use, a compound of the invention 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 regimen and route of administration which will be most appropriate for a particular male animal.

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

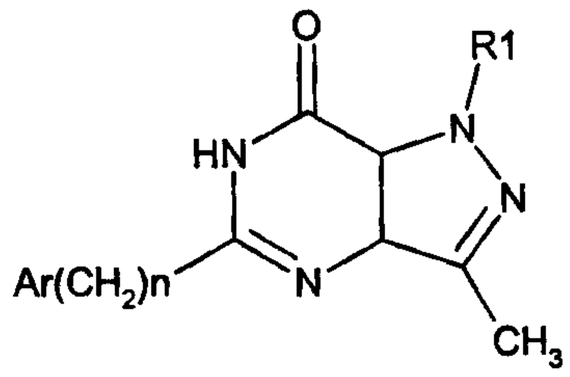
The invention also provides a method of treating erectile dysfunction in a male animal which comprises administering an effective amount of a compound which is a selective cGMP-PDE inhibitor as defined above.

The invention also provides a medicine for treating erectile dysfunction in a male animal, or female sexual dysfunction, premature labour or dysmenorrhea, comprising an effective amount of the compound which is a selective cGMP-PDE inhibitor, as mentioned above, and a pharmaceutically acceptable diluent or carrier.

The invention further provides a commercial package which comprises the above-mentioned medicine and a written matter providing instructions for treating the disorder described hereinbefore.

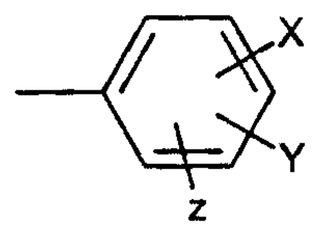
CLAIMS:

1. The use of a compound which is a selective cGMP PDE inhibitor for the manufacture of a medicament for the treatment of erectile dysfunction in a male animal, including man, wherein the compound is selected from:

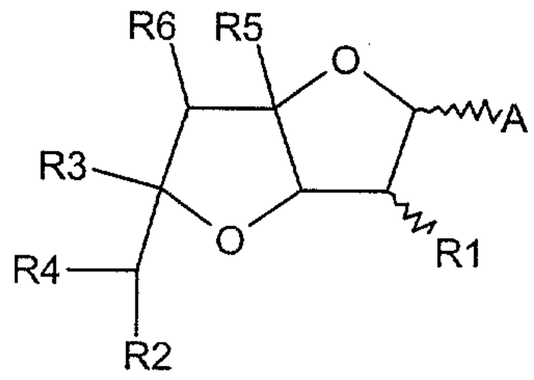


and the pharmaceutically acceptable salts thereof,

in which: R^1 is a lower alkyl of from one to six carbon atoms, a lower alkenyl of from one to six carbon atoms, a lower hydroxyalkyl of from one to six carbon atoms, a lower hydroxyalkenyl of from two to six or 2, 3 or 4-pyridyl; and Ar represents a group of formula:

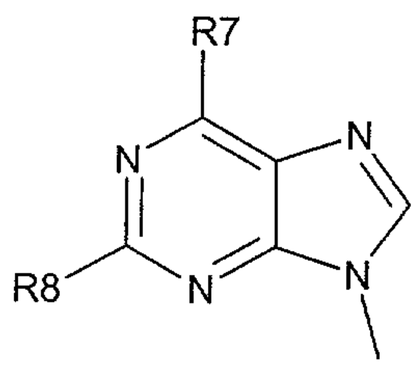


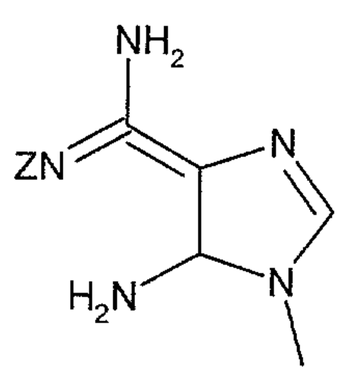
in which X, Y and Z are, independently, (1) hydrogen; (2) lower alkyl of from one to six carbon atoms; (3) halogen, (4) hydroxyl; (5) lower alkoxy of from one to six carbon atoms; (6) nitro; (7) amino; (8) NR'R" wherein R' and R" are each, independently, (a) hydrogen or (b) lower alkyl of from one to six carbon atoms optionally substituted by (i) amino, (ii) morpholino or (iii) cycloalkyl of from, five to seven carbon atoms; (9) sulfonyl; or (10) $-SO_2NR'R"$ wherein R' and R" are as defined above; with the proviso that not all of X, Y and Z can be nitro, amino, or NR'R'' at once;

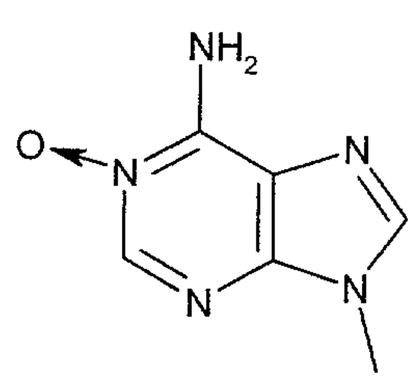


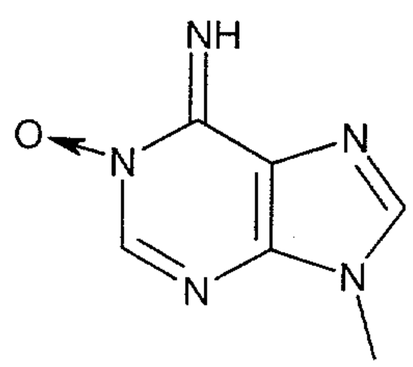
and the pharmaceutically acceptable salts thereof,

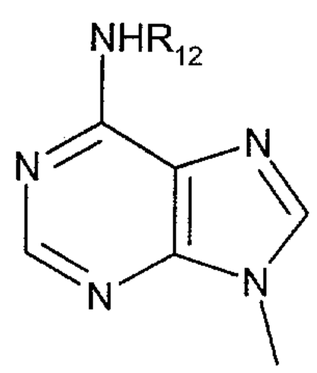
in which: A represents a group of formula:

(a) 

(b) 

(c) 

(d) 

(e) 

R^1 and R^2 are the same or different and each represents a hydrogen atom, a halogen atom or a group of formula $-OR^9$;

R^3 and R^4 are the same or different and each represents a carbamoyl group or a carboxy group;

R^5 and R^6 both represent hydrogen atoms or together they represent an extra carbon-carbon bond between the carbon atoms to which they are attached;

R^7 represents a hydrogen atom, a halogen atom or a group of formula- OR^9, $-NR^{10}R^{11}$ or $-SR^9$;

R^8 represents a halogen atom or a group of formula $-OR^9$, $-NR-^{10}R^{11}$ or $-SR^9$;

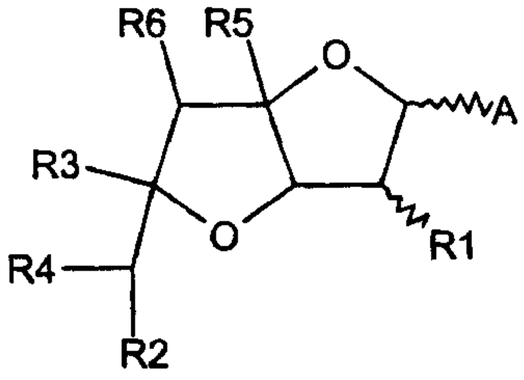
R^9 represents a hydrogen atom, a C_1-C_6 alkyl group, an alkylsulphonyl group, a haloalkylsulphonyl group, an arylsulphonyl group or a hydroxy protecting group;

R^{10} and R^{11} are the same or different and each represents a hydrogen atom, a hydroxy group, a C_1-C_6 alkyl group, a C_1-C_6 hydroxyalkyl group, a C_1-C_6, aminoalkyl group, an aralkyl group, an aryl group, a C_1-C_6 alkoxy group, an aralkyloxy group, an amino group, a C_1-C_{20} aliphatic acyl group or an aromatic acyl group; or R^{10} and R^{11} together represent a substituted methylene group, or R^{10} and R^{11}, together with the nitrogen atom to which they are attached, represent a heterocyclic group having 5 or 6 ring atoms, of which, in addition to the nitrogen atom shown, 0 or 1 are additional oxygen, nitrogen or sulphur hetero-atoms, said heterocyclic group being unsubstituted or having from 1 to 3 C_1-C_4 alkyl and/or C_1-C_4 alkoxy substituents;

R^{12} represents a C_1-C_6 alkyl group; and

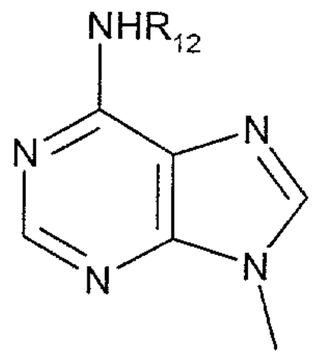
Z represents a hydrogen atom, a hydroxy group or a substituted hydroxy group;

provided that, when A represents the group of formula (e), R^5 and R^6 both represent hydrogen atoms;



and the pharmaceutically acceptable salts and esters thereof,

in which A represents a group of formula:



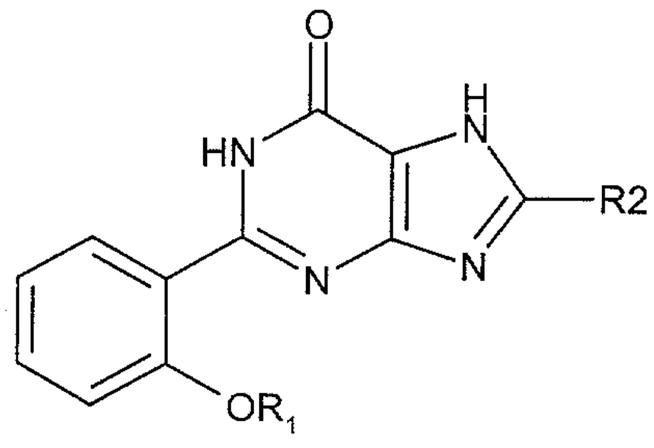
R^1 and R^2 are the same or different and each represents a hydrogen atom, a halogen atom or a group of formula $-OR^9$;

R^3 and R^4 are the same or different and each represents a carbamoyl group or a carboxy group;

R^5 and R^6 both represent hydrogen atoms;

R^9 represents a hydrogen atom, a C_1-C_6 alkyl group, an alkylsulphonyl group, a haloalkylsulphonyl group, an arylsulphonyl group or a hydroxy-protecting group;

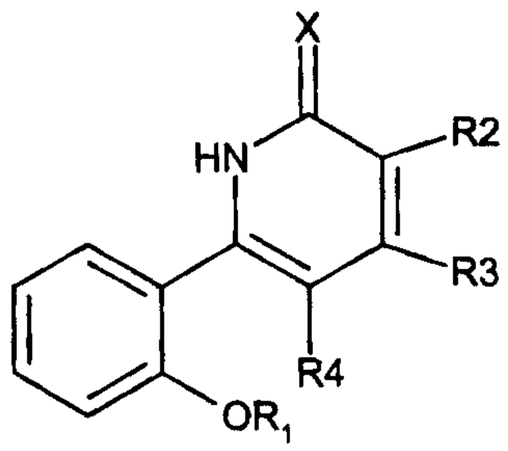
R^{12} represents a C_1-C_6 alkyl group;



and pharmaceutically acceptable salts thereof, wherein

R^1 is C_{1-6} alkyl or C_{2-6} alkenyl, and

R^2 is hydrogen or hydroxy;



or a pharmaceutically acceptable salt thereof, wherein

X is O or S;

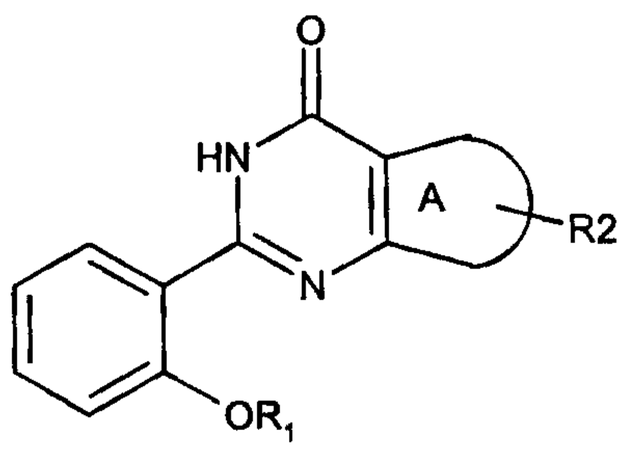
R^1 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-5} cycloalkylC_{1-4} alkyl, or C_{1-4} alkyl substituted by 1 to 6 fluoro groups;

R^2 is hydrogen, -CN, $-CONR^5R^6$, $-CO_2R^7$, 5-tetrazolyl, $-NO_2$, $-NH_2$ or $-NHCOR^8$ wherein R^5, R^6, R^7 and R^8 are independently hydrogen or C_{1-4} alkyl;

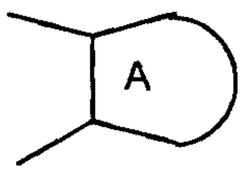
R^3 is hydrogen or C_{1-4} alkyl; and

R^4 is hydrogen or C_{1-4} alkyl;

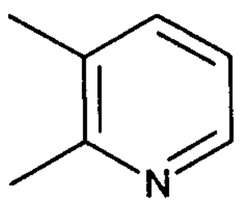
with the proviso that R^1 is not methyl when R^2 is $-CO_2H$, $-CO_2CH_2CH_3$ or -CN, X is O, R^3 is hydrogen and R^4 is hydrogen or methyl;

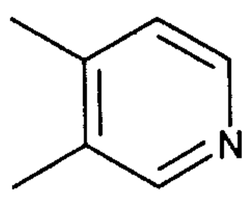


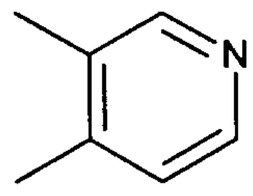
and pharmaceutically acceptable salts thereof, wherein

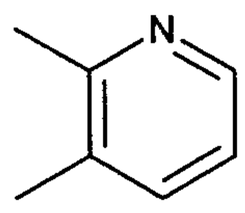


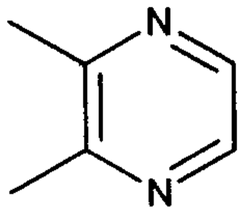
is a ring of sub-formula (a), (b), (c), (d), (e), (f) or (g):

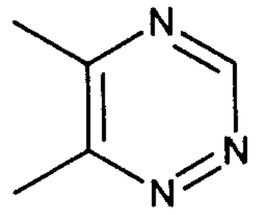
(a) 

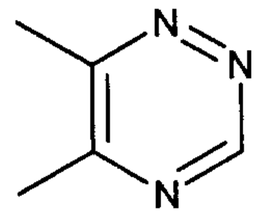
(b) 

(c) 

(d) 

(e) 

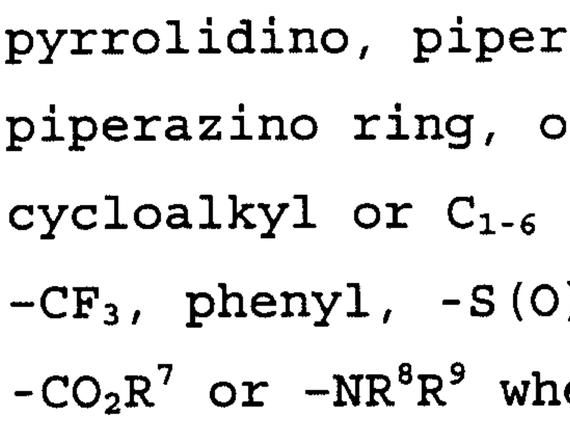
(f) 

(g) 

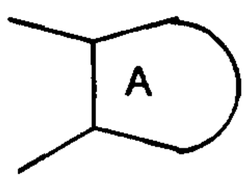
R^1 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-5} cycloalkyl C_{1-6} alkyl, or C_{1-6} alkyl substituted by 1 to 6 fluoro groups;

R^2 is C_{1-6} alkythio, C_{1-6} alkylsulphonyl, C_{1-6} alkoxy, hydroxy, hydrogen, hydrazino, C_{1-6} alkyl, phenyl, $-NHCOR^3$ wherein R^3 is hydrogen or C_{1-6} alkyl, or $-NR^4R^5$, wherein R^4 and R^5 together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, hexahydroazepino, morpholino or piperazino ring, or R^4 and R^5 are independently hydrogen, C_{3-5} cycloalkyl or C_{1-6} alkyl which is optionally substistuted by $-CF_3$, phenyl, $-S(O)_nC_{1-6}$ alkyl wherein n is 0, 1 or 2, $-OR^6$, $-CO_2R^7$ or $-NR^8R^9$ wherein R^6 to R^9 are independently hydrogen or C_{1-6} alkyl, provided that the carbon atom adjacent to the nitrogen atom is not substituted by said $-S(O)_nC_{1-6}$ alkyl, $-OR^6$ or $-NR^8R^9$ groups; and

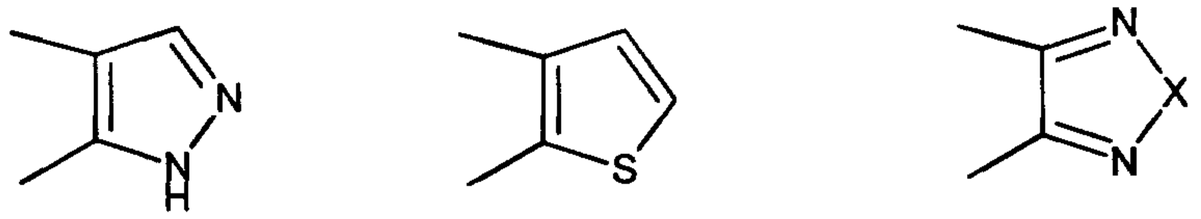
R^1 can be hydrogen or hydroxy when R^2 is hydroxy;



and pharmaceutically acceptable salts thereof, wherein



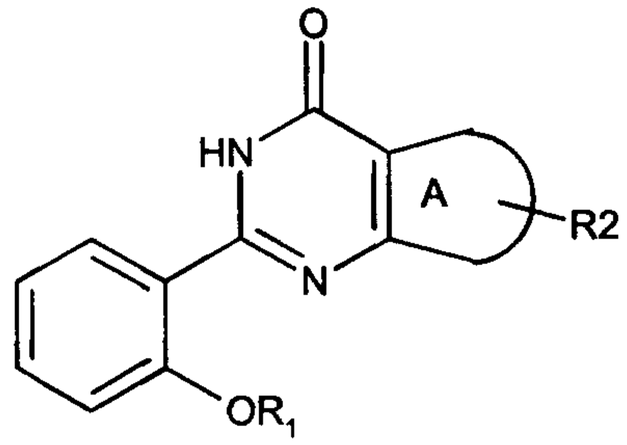
is a ring of sub-formula (a), (b) or (c):



(a) (b) (c)

X is oxygen or sulphur, and

R^1 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-5} cycloalkyl C_{1-4} alkyl, or C_{1-4} alkyl substituted by 1 to 6 fluoro groups;

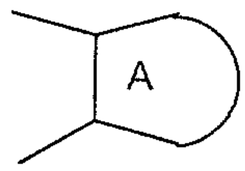


and pharmaceutically acceptable salts thereof, wherein

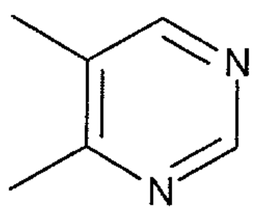
R^1 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-5} cycloalkyl C_{1-6} alkyl, or C_{1-6} alkyl substituted by 1 to 6 fluoro groups;

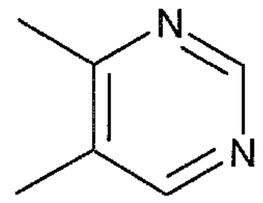
R^2 is C_{1-6} alkythio, C_{1-6} alkylsulphonyl, C_{1-6} alkoxy, hydroxy, hydrogen, hydrazino, C_{1-6} alkyl, phenyl, $-NHCOR^3$ wherein R^3 is hydrogen or C_{1-6} alkyl, or $-NR^4R^5$, wherein R^4 and R^5 together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, hexahydroazepino, morpholino or piperazino ring, or R^4 and R^5 are independently hydrogen, C_{3-5} cycloalkyl or C_{1-6} alkyl which is optionally substituted by $-CF_3$, phenyl, $-S(O)_nC_{1-6}$ alkyl wherein n is 0, 1 or 2, $-OR^6$,

$-CO_2R^7$ or $-NR^8R^9$ wherein R^6 to R^9 are independently hydrogen or C_{1-6} alkyl, provided that the carbon atom adjacent to the nitrogen atom is not substituted by said $-S(O)_nC_{1-6}$ alkyl, $-OR^6$ or NR^8R^9 groups; and



is a ring of sub-formula (a) or (b):

(a) 

(b) 

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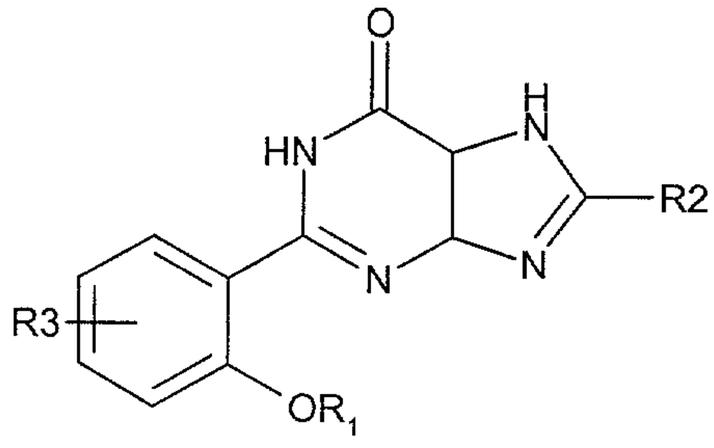


and pharmaceutically acceptable salts thereof, wherein

R^1 is C_{1-6} alkyl, C_{2-5} alkenyl, C_{3-5} cycloalkyl C_{1-6} alkyl, phenyl C_{1-4} alkyl, or C_{1-4} alkyl substituted by 1 to 6 fluoro groups;

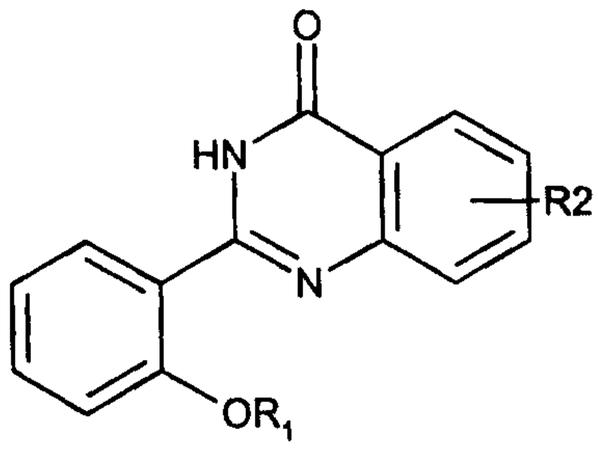
R^2 is hydrogen, hydroxy, C_{1-4} alkyl, phenyl, mercapto, C_{1-4} alkylthio, CF_3 or amino;

R^3 is hydrogen, nitro, amino, C_{1-4} alkanoylamino, C_{1-6} alkoxy, C_{1-4} alkyl, halo, $SO_2NR^4R^5$, $CONR^4R^5$, cyano or C_{1-4} alkyl S(O)n;

R^4 and R^5 are independently hydrogen or C_{1-6} alkyl; and

n is 0, 1 or 2;

provided that R^3 is not hydrogen when R^1 is C_{1-6} alkyl or C_{2-6} alkenyl and R^2 is other than hydrogen or hydroxy;

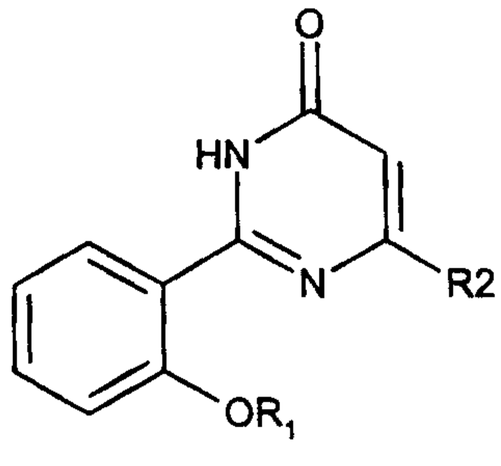


and pharmaceutically acceptable salts thereof, wherein

R^1 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-5} cycloalkyl C_{1-4}alkyl, phenyl C_{1-4} alkyl or C_{1-4} alkyl substituted by 1 to 6 fluoro groups;

R^2 is hydrogen, C_{1-6} alkyl, C_{1-6} alkythio, C_{1-6} alkoxy, nitro or $-NR^3R^4$ and

R^3 and R^4 are independently hydrogen or C_{1-4} alkyl substituted by hydroxy provided that the carbon atom adjacent to the nitrogen atom is not substituted by hydroxy; with the proviso that R^1 is not methyl or ethyl when R^2 is hydrogen;

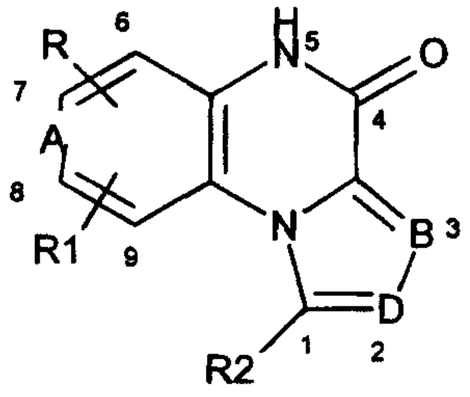


and pharmaceutically acceptable salts thereof, wherein

R^1 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-5} cycloalkyl C_{1-6} alkyl, phenyl C_{1-6} alkyl or C_{1-6} alkyl substituted by 1 to 6 fluoro groups; and

R^2 is C_{1-6} alkyl, phenyl, hydroxy, C_{1-6} alkoxy, halo, $-NHCOR^3$,

-NHCONHR^4, 5-tetrazolyl, -CO_2R^5, cyano, -$CONR^6R^7$, or -NR^8R^9 wherein R^3 to R^7 are independently hydrogen or C_{1-6} alkyl and R^8 and R^9 are independently hydrogen or C_{1-6} alkyl optionally substituted by hydroxy provided that the carbon atom adjacent to the nitrogen atom is not substituted by hydroxy;



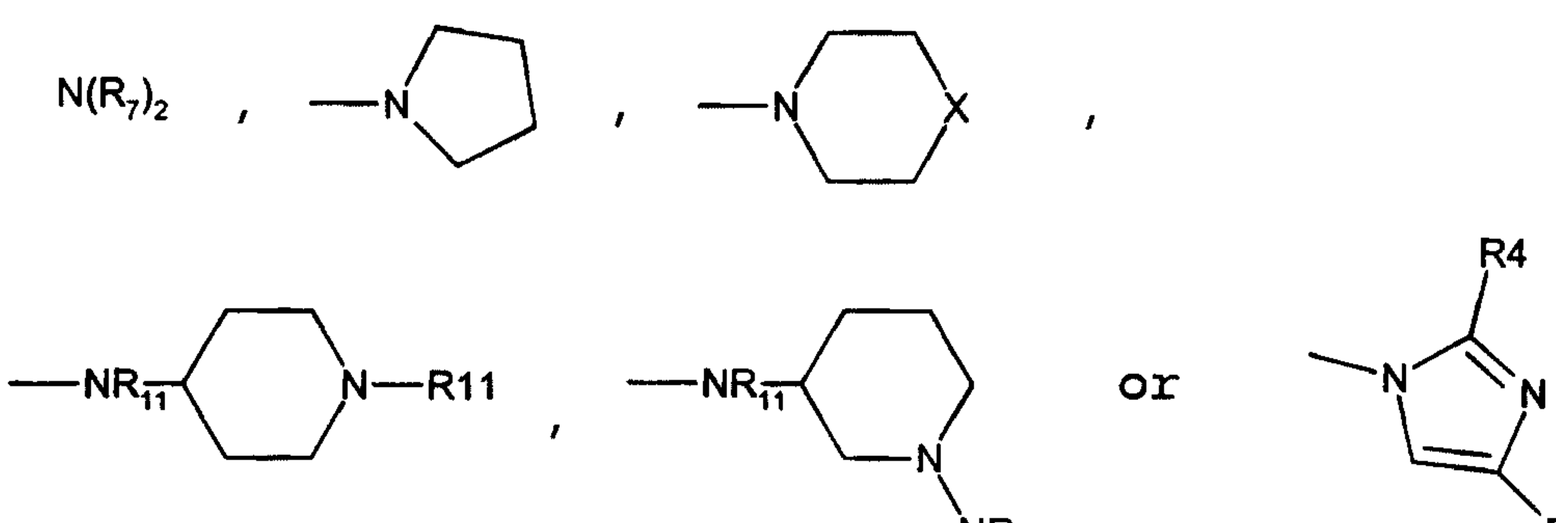
and pharmaceutically acceptable salts thereof, wherein

A is N or CH;

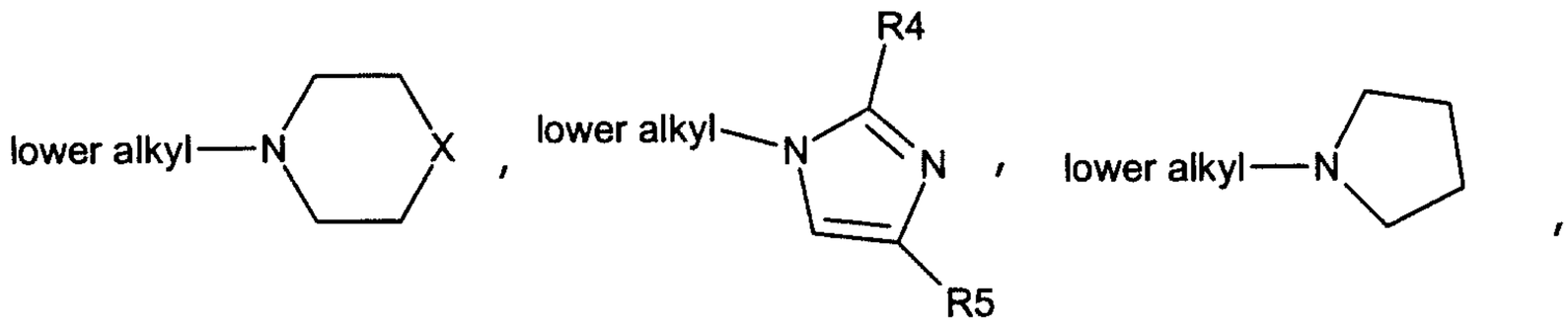
B is N or CR_3;

D is N or CR_2;

R and R_1 are independently hydrogen, hydroxy, lower alkyl, lower alkoxy, phenyloxy, R_6 -$S(O)_n$-, W-ALK-Q-,



R_2 is hydrogen, lower alkyl, phenyl which may be substituted by up to three methoxy groups, lower alkyl substituted by phenyl which may be substituted by up to three methoxy groups, - lower alkyl -$N(R_8)_2$,



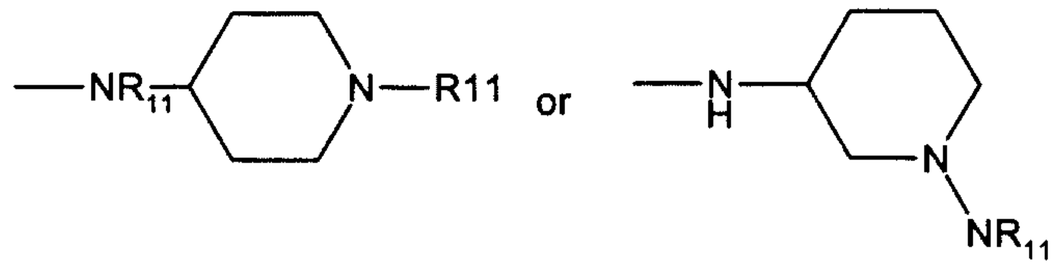
pyridinyl or lower-alkyl pyridinyl;

R_3 is hydrogen , lower alkyl, phenyl, lower alkylphenyl, pyridinyl or loweralkyl pyridinyl;

R_4 and R_5 are independently hydrogen or lower alkyl;

R_6 is lower alkyl, phenyl, lower alkylphenyl or pyridinyl;

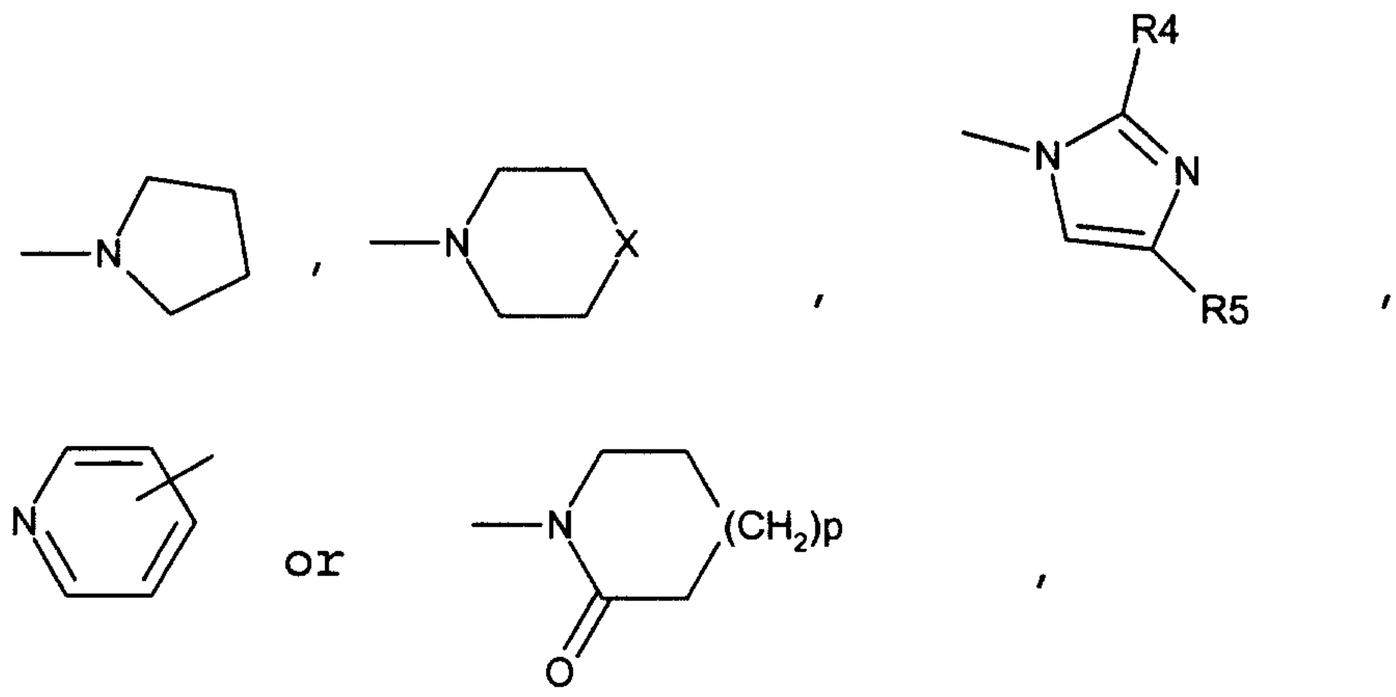
each R_7 is independently hydrogen, lower alkyl, phenyl, pyridinyl,



each R_8 is independently lower alkyl, phenyl or pyridinyl;

Q is -O-, $-NR_9-$, $-CH_2O-$, or $-CH_2NR_9-$,

W is hydroxy, lower alkoxy, phenoxy, $-N(R_{10})_2$,



ALK is a C_1-C_4 straight or branched chain alkyl;

R_9 is hydrogen, lower alkyl or phenyl;

each R_{10} is independently hydrogen, lower alkyl or phenyl;

each R_{11} is independently hydrogen or lower alkyl;

X is $-CH_2-$, $-O-$, $-S(O)^-_n$, $-NR_{10}$;

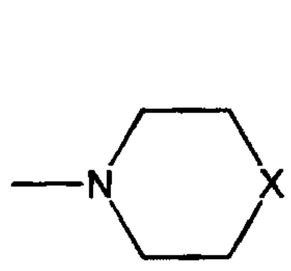
n is the integer 0, 1 or 2 and

p is the integer 0 or 1,

with the provisos that:

one and only one of B or D must be N;

when A is CH, when D is N, when B is CR_3 where R_3 is H, when R_2 is hydrogen, lower alkyl or phenyl then one or both of R and R_1 must be



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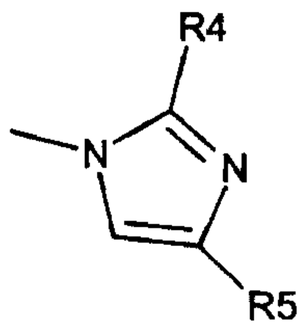
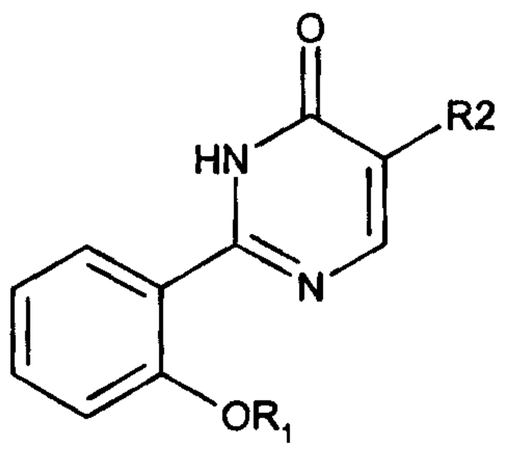


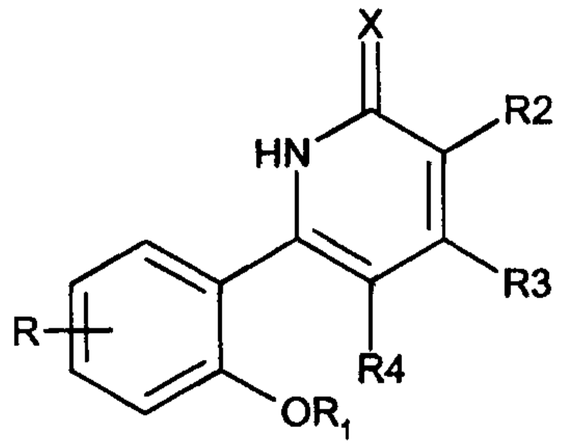
or W-ALK-Q;



and pharmaceutically acceptable salts thereof, wherein

R^1 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-5} cycloalkyl C_{1-6} alkyl, phenyl C_{1-6} alkyl or C_{1-6} alkyl substituted by 1 to 6 fluoro groups; and

R^2 is hydrogen, amino, -$NHCOR^3$, or $CONR^4R^5$, wherein R^3 is C_{1-6} alkyl, R^4 is C_{1-6} alkyl and R^5 is hydrogen or C_{1-6} alkyl;



and pharmaceutically salts thereof, wherein

X is O or S:

R^1 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-5} cycloalkyl C_{1-4} alkyl, or C_{1-4} alkyl substituted by 1 to 3 fluoro groups;

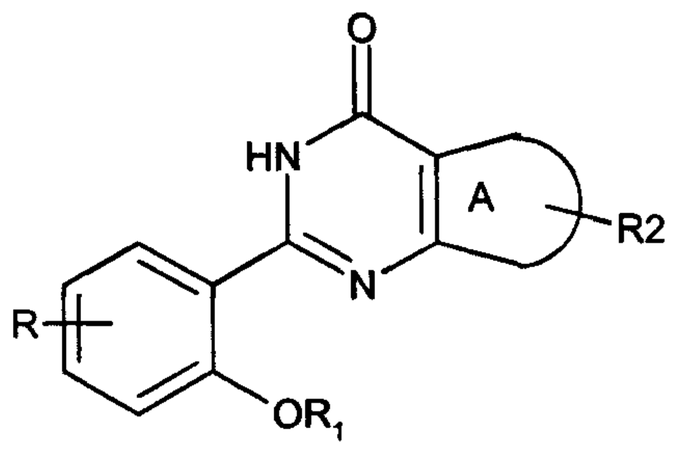
R^2 is hydrogen, -CN, -$CONR^5R^6$, -CO_2R^7, 5-tetrazolyl, -NO_2 or -$NHCOR^8$ wherein R^5 to R^8 are independently hydrogen or C_{1-4} alkyl;

R^3 is hydrogen or C_{1-4} alkyl;

R^4 is hydrogen or C_{1-4} alkyl; and

R is halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, -$CONR^9R^{10}$, -CO_2R^{11}, -$S(O)_nC_{1-4}$ alkyl, -NO_2, - NH_2, -$NHCOR^{12}$, or -$SO_2NR^{13}R^{14}$ wherein n is 0, 1 or 2 and R^9 to R^{14} are independently hydrogen or C_{1-4} alkyl;

with the proviso that R^1 is not methyl when R^2 is -CO_2H, -$CO_2CH_2CH_3$ or -CN, X is O, R^3 is hydrogen, R^4 is hydrogen or methyl and R is 6-methoxy;

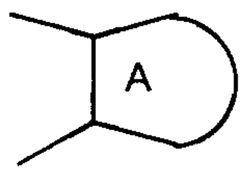


and pharmaceutically acceptable salts thereof, wherein

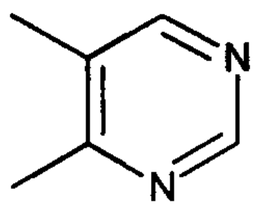
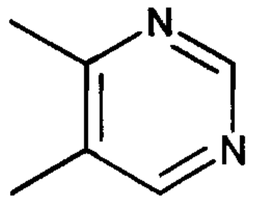
R^1 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-5} cycloalkyl C_{1-6} alkyl, or C_{1-6} alkyl substituted by 1 to 6 fluoro groups;

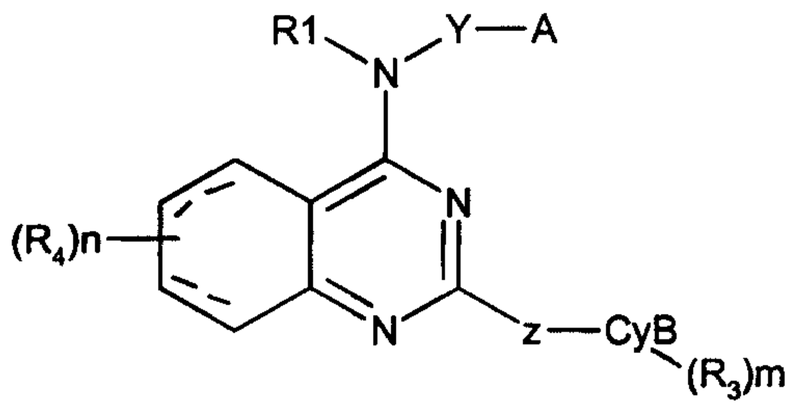
R^2 is C_{1-6} alkythio, C_{1-6} alkylsulphonyl, C_{1-6} alkoxy, hydroxy, hydrogen, hydrazino, C_{1-6} alkyl, phenyl, $-NHCOR^3$ wherein R^3 is hydrogen or C_{1-6} alkyl, or $-NR^4R^5$, wherein R^4 and R^5 together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, hexahydroazepino, morpholino or piperazino ring, or R^4 and R^5 are independently hydrogen, C_{3-5} cycloalkyl or C_{1-6} alkyl which is optionally substituted by $-CF_3$, phenyl, $-S(O)_nC_{1-6}$ alkyl wherein n is 0, 1 or 2, $-OR^6$, $-CO_2R^7$ or $-NR^8R^9$ wherein R^6 to R^9 are independently hydrogen or C_{1-6} alkyl, provided that the carbon atom adjacent to the nitrogen atom is not substituted by $-S(O)_n$ C_{1-6} alkyl, $-OR^6$ or $-NR^8R^9$;

R is halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, $-CONR^{10}R^{11}$, CO_2R^{12}, C_{1-4} alkyl $S(O)_n$, $-NO_2$, $-NH_2$, $-NHCOR^{13}$ or $SO_2NR^{14}R^{15}$ wherein n is 0, 1 or 2 and R^{10} to R^{15} are independently hydrogen or C_{1-4} alkyl; and



is a ring of sub-formula (a) or (b):

(a)  (b)  ;



and pharmaceutically acceptable salts thereof,

wherein --- represents a single or double bond;

R^1 is hydrogen or C_{1-4} alkyl;

Y is a single bond or C_{1-6} alkylene;

A is

-CyA-$(R^2)_1$,

$-O-R^0$ or $-S(O)_p-R^0$, or

$-NR^{16}R^{17}$

in which R^0 is hydrogen, C_{1-4} alkyl, hydroxy C_{1-4} alkyl or CyA-$(R^2)_1$;

R^{16} and R^{17} independently are hydrogen or C_{1-4} alkyl;

p is 0-2;

CyA is

a 3-7 membered, saturated or unsaturated carbocycle,

a 4-7 membered, unsaturated or partially saturated heterocycle containing one nitrogen atom

a 4-7 membered, unsaturated or partially saturated heterocycle containing one nitrogen atom and one oxygen atom,

a 4-7 membered, unsaturated or partially saturated heterocycle containing one nitrogen atom and two oxygen atoms,

a 4-7 membered, unsaturated or partially saturated heterocycle containing two nitrogen atoms and one oxygen atom

a 4-7 membered, unsaturated or partially saturated heterocyle containing one or two sulfur atoms,

a 4-7 membered, unsaturated, partially saturated or fully saturated heterocycle containing one or two oxygen atoms,

R^2 is (1) hydrogen, (2) C_{1-4} alkyl, (3) C_{1-4} alkoxy, (4) $-COOR^5$, in which R^5 is hydrogen or C_{1-4} alkyl, (5) $-NR^6R^7$, in which R^6 and R^7 independently are hydrogen or C_{1-4} alkyl, (6) $-SO_2NR^6R^7$, in which R^6 and R^7 are as hereinbefore defined, (7) halogen, (8) trifluoromethyl, (9) nitro or (10) trifluoromethoxy;

Z is a single bond, methylene, ethylene, vinylene or ethynylene;

CyB is a 4-7 membered, unsaturated or partially saturated heterocycle containing one nitrogen atom,

a 4-7 membered, unsaturated or partially saturated heterocycle containing two nitrogen atmos,

a 4-7 membered, unsaturated or partially saturated heterocycle containing three nitrogen atoms,

a 4-7 membered, unsaturated or partially saturated heterocycle containing one or two oxygen atoms,

a 4-7 membered, unsaturated or partially saturated heterocycle containing one or two sulfur atoms,

R^3 is hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, halogen or trifluoromethyl;

R^4 is (1) hydrogen, (2) C_{1-4} alkyl, (3) C_{1-4} alkoxy, (4) $-COOR^8$, in which R^8 is hydrogen or C_{1-4} alkyl, (5) $-NR^9R^{10}$, in which R^9 is hydrogen, C_{1-4} alkyl or phenyl (C_{1-4} alkyl) and R^{10} is hydrogen or C_{1-4} alkyl, (6) $-NHCOR^{11}$, in which R^{11} is C_{1-4} alkyl, (7) $-NHSO_2R^{11}$, in which R^{11} is as hereinbefore defined, (8) $SO_2NR^9R^{10}$ in which R^9 and R^{10} are as hereinbefore defined, (9) $-OCOR^{11}$, in which R^{11} is as hereinbefore defined, (10) halogen, (11) trifluoromethyl, (12) hydroxy, (13) nitro, (14) cyano, (15) $-SO_2N=CHNR^{12}R^{13}$ in which R^{12} is hydrogen or C_{1-4} alkyl and R^{13} is C_{1-4} alkyl, (16) $-CONR^{14}R^{15}$ in which R^{14} is hydrogen or C_{1-4} alkyl or phenyl (C_{1-4} alkyl) and R^{15} is C_{1-4} alky, (17) C_{1-4} alkylthio, (18) C_{1-4} alkylsulfinyl, (19) C_{1-4} alkylsulfonyl, (20) ethynyl, (21) hydroxymethyl, (22) tri(C_{1-4} alkyl) silylethynyl or (23) acetyl; and

l, m and n independently are 1 or 2;

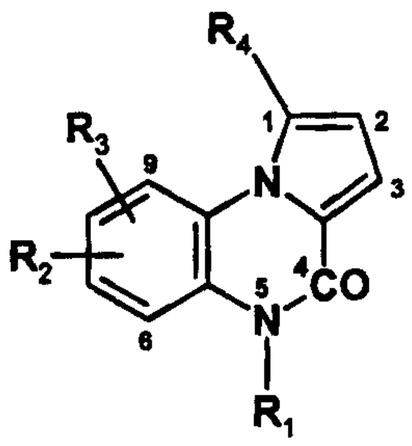
with the proviso that

CyA-$(R^2)_1$ does not represent cyclopentyl or trifluoromethylphenyl when Y is a single bond,

CyB does not bond to Z through a nitrogen atom when Z is vinylene or ethynylene,

CyB is not pyridine or thiophene when CyA is a 4-7 membered unsaturated, partially saturated or fully saturated heterocycle containing one or two oxygen atoms, and

Y is not a single bond when A is $-O-R^0$ or $-NR^{16}R^{17}$;



I

and pharmaceutically acceptable salts thereof,

wherein the phenyl ring either in position 6, 7, 8 or 9 may contain a nitrogen atom instead of a CH-moiety and the residues R_1, R_2, R_3 and R_4 have the following meanings:

R_1: C_2-C_6-alkenyl, C_2-C_6-alkynyl, hydroxy, C_1-C_6-alkoxy, C_3-C_6-alkenyloxy, C_3-C_6-alkynyloxy, C_2-C_6-alkanoyloxy, benzoyloxy, morpholinocarbonyloxy, C_1-C_6-alkyloxycarbonyloxy, C_1-C_6-alkylaminocarbonyloxy, C_1-C_6-dialkylaminocarbonyloxy or the moiety

-Alk-A

wherein Alk is: C_1-C_6-alkyl, C_2-C_6-hydroxy-alkyl or C_3-C_6-cycloalkyl and the symbol A means:

(1) hydrogen, halogen, hydroxy, C_1-C_6-alkoxy, C_2-C_6-alkanoyloxy, phenyl;

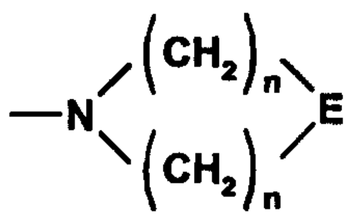
(2) $-NHR_5$, $-NR_5R_6$, $NR_5R_6R_7$, pyridylamino, imidazolyl, pyrrolidinyl, N-C_1-C_6-alkylpyrrolidinyl, piperidylamino, N-(phenyl-C_1-C_4-alkyl)-piperidylamino, wherein R_5 and R_6 are identical or different and mean hydrogen, C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-hydroxycycloalkyl, morpholino-C_1-C_6-alkyl, phenyl, phenyl-C_1-C_6-alkyl or phenyl-C_2-C_6-oxyalkyl, wherein the phenyl residues also may be substituted with halogen and R_7 is hydrogen or C_1-C_6-alkyl;

(3) The moiety

-CO-D

wherein D is phenyl, C_1-C_6-alkyl, C_3-C_7-cycloalkyl, hydroxy, C_1-C_6-alkoxy, C_3-C_7-cycloalkyloxy, morpholino, pyrrolidino, piperidino, homopiperidino, piperazino, -NHR_5 or -NR_5R_6 and R_5 and R_6 have the above given meanings;

(4) The moiety



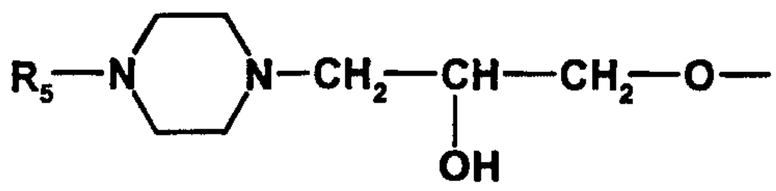
wherein n may be an integer of 1-3 and E means CH_2, oxygen, sulphur, NH, CHOH, CH-C_1-C_6-alkyloxy, CH-C_2-C_6-alkanoyloxy, CHC_6H_5, CHCOD, CH-$CN_2C_6H_5$, N-C_1-C_6-alkyl, N-C_1-C_6-hydroxyalkyl, N-C_6H_5, N-$CH_2C_6H_5$, N-$CH(C_6H_5)_2$, N-$(CH_2)_2$-OH, N-$(CH_2)_3$-OH or NCOD and phenyl residues (C_6H_5) may also be substituted with halogen, C_1-C_6-alkoxy, trifluoromethyl, C_1-C_6-alkyl, methylenedioxy or cyano and D has the above given meaning;

R_2 and R_3, which may be identical or different:

hydrogen, halogen, hydroxy, C_1-C_6-alkyl, trifluoromethyl, -CN, C_1-C_6-alkoxy, C_3-C_6-alkenyloxy, C_3-C_6-alkynyloxy, -NHR_5, -NR_5R_6, $NR_5R_6R_7$ (R_5, R_6, R_7 have the meanings as given above), or the moiety -G-Alk-A, wherein Alk and A have the above given meanings and G is oxygen, sulphur, NH or NR_5;

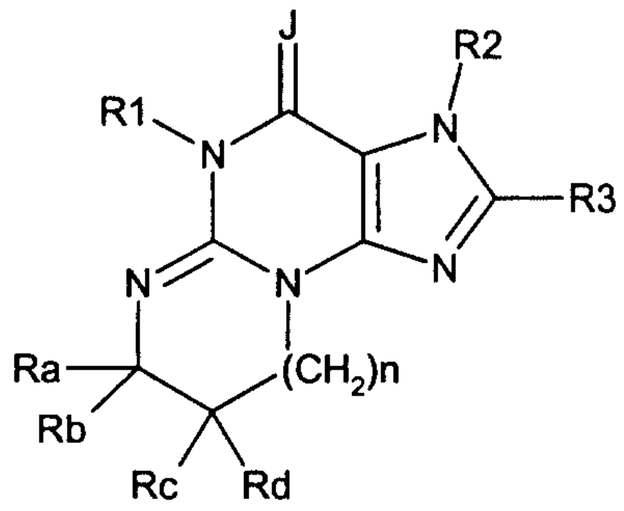
R_4: hydrogen or halogen,

wherein R_1 also may be hydrogen, if R_2 is the moiety

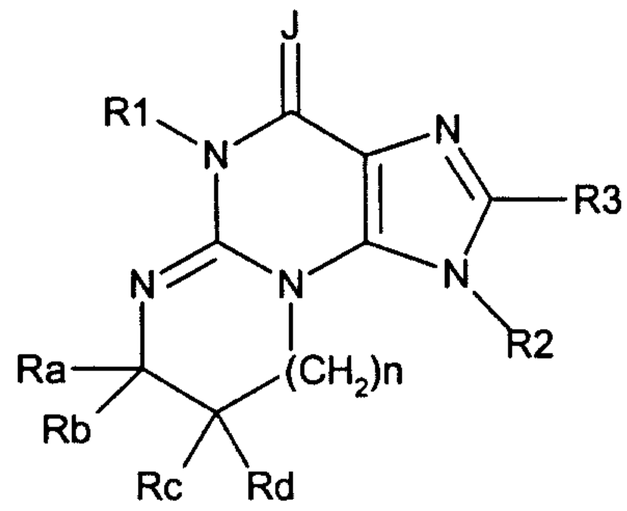


and R_5 means phenyl, C_1-C_4-alkoxy-phenyl or diphenylmethyl and R_3 and R_4 are hydrogen,

and the physiologically acceptable acid addition salts and quarternary ammonia salts thereof, excluding the compounds of formula I wherein R_1 is methyl, dimethylamino-propyl, dimethylamino-ethyl, morpholino-ethyl or pyrrolidino-ethyl, R_2, R_3 and R_4 are hydrogen and the phenyl ring does not contain a nitrogen atom;



and



and pharmaceutically acceptable salts thereof,

wherein J is oxygen or sulfur,

R^1 is hydrogen, alkyl or alkyl substituted with aryl or hydroxy;

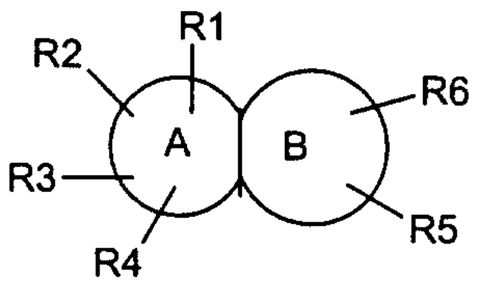
R^2 is hydrogen, aryl, heteroaryl, cycloalkyl, alkyl or alkyl substituted with aryl, heteroaryl, hydroxy, alkoxy, amino, monoalkylamino, dialkylamino, or $-(CH_2)_m$ $TCOR^{20}$ wherein m is an integer from 1 to 6, T is oxygen or -NH- and R^{20} is hydrogen, aryl, heteroaryl, alkyl or alkyl substituted with aryl or heteroaryl;

R^3 is hydrogen, halo, trifluoromethyl, alkoxy, alkylthio, alkyl, cycloalkyl, aryl, aminosulfonyl, amino, monoalkylamino, dialkylamino, hydroxyalkylamino, aminoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl or

alkyl substituted with aryl, hydroxy, alkoxy, amino, monalkylamino or dialkylamino;

R^a, R^b, R^c and R^d independently represent hydrogen, alkyl, cycloalkyl or aryl; or (R^a and R^b) or (R^c and R^d) or (R^b and R^c) can complete a saturated ring of 5- to 7-carbon atoms, or (R^a and R^b) taken together and (R^b and R^c) taken together, each complete a saturated ring of 5- to 7-carbon atoms, wherein each ring optionally can contain a sulfur or oxygen atom and whose carbon atoms may be optionally substituted with one or more of the following: alkenyl, alkynyl, hydroxy, carboxy, alkoxycarbonyl, alkyl or alkyl substituted with hydroxy, carboxy or alkoxycarbonyl; or such saturated ring can have two adjacent carbon atoms which are shared with an adjoining aryl ring; and

n is zero or one;

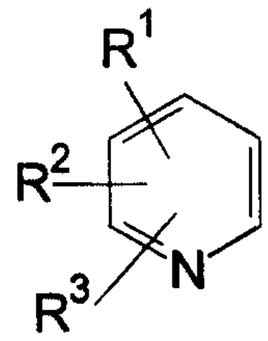


and pharmaceutically acceptable salts thereof,

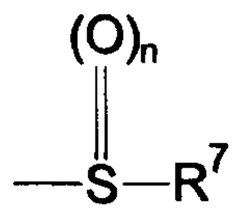
wherein, ring A signifies a benzene ring, pyridine ring or cyclohexane ring, ring B signifies a pyridine ring, pyrimidine ring or imidazole ring,

rings A and B are bonded by sharing two atoms, and the atoms that are shared may be either carbon or nitrogen atoms,

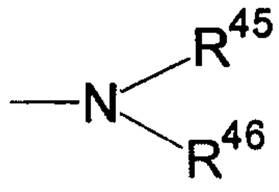
except for the event that ring A is a pyridine ring and ring B shares a nitrogen atom of this pyridine ring for bonding, ring A shall be as shown by the formula



wherein, R^1, R^2, R^3 and R^4 independently represent a hydrogen atom, a halogen atom, an optionally halogen-substituted lower alkyl radical, an optionally substituted cycloalkyl radical, a lower alkoxy radical, a hydroxyalkyl radical, a nitro radical, an amino radical, an acyl-amino radical, an optionally protected carboxyl radical, a radical represented by the formula



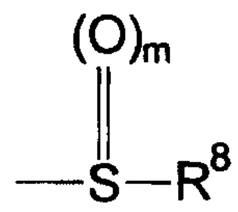
(where R^7 in this formula signifies a lower alkyl radical and n may be 0 or an integer with a value of 1 - 2), or a radical represented by the formula



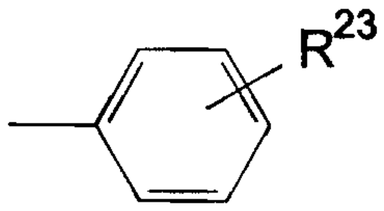
(where $R^{45}$and R^{46} in this formula independently represent a hydrogen atom or a lower alkyl radical, or R^{45} and R^{46} may unite with the nitrogen atom to which they are bonded to form a ring optionally containing one or more heteroatoms in addition to the nitrogen atom to which R^{45} and R^{46} are bonded selected from nitrogen and oxygen, and this ring may be substituted),

further, two of the R^1, R^2, R^3, and R^4 radicals may combine to form a methylenedioxy, ethylenedioxy or phenyl ring,

R^5 signifies a hydrogen atom, a halogen atom, a hydroxyl group, a hydrazino radical, an optionally substituted cycloalkyl radical, a lower alkoxy radical, a lower alkenyl radical, an optionally protected carboxyalkyl radical, an optionally protected carboxyalkenyl radical, a hydroxy alkyl radical, an optionally protected carboxyl radical, a radical represented by the formula



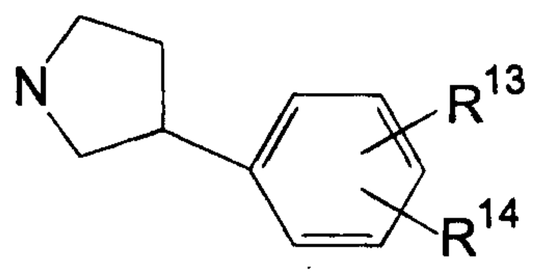
(where R^3 in this formula signifies a lower alkyl radical and m may be either 0 or an integer with a value from 1 - 2), a radical represented by the formula -O-R^9 (where R^9 in this formula signifies an optionally protected hydroxyalkyl radical, an optionally protected carboxyalkyl radical or an optionally substituted benzyl radical), a radical represented by the formula



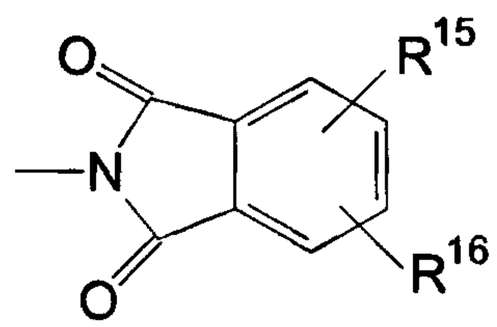
(where R^{23} in this formula signifies a hydroxyl group, a lower alkyl radical, a hydroxyalkyl radical or a hydroxyalkyloxy radical), an optionally substituted heteroaryl radical, an optionally substituted 1,3 benzodioxolyl radical, an optionally substituted 1,4 benzodioxyl radical, an optionally substituted 1,3 benzodioxolyl alkyl radical, an optionally substituted 1,4 benzodioxyl alkyl radical, a radical represented by the formula C(R^{24})=X (where X in this formula signifies an oxygen atom, a sulphur atom or a radical represented by the formula =N-R^{10} (where R^{10} in this formula signifies a hydroxyl group or an optionally protected carboxyalkyloxy radical) and R^{24}

signifies a hydrogen atom or a lower alkyl radical), or a radical represented by the formula $-NR^{11}R^{12}$ (where R^{11} and R^{12} in this formula independently represent a hydrogen atom, a lower alkyl radical, a hydroxyalkyl radical, an aminoalkyl radical, an optionally protected carboxyalkyl radical, an alkyl carbamoyl radical, an optionally protected carboxyalkylcarbamoyl radical, an optionally substituted heteroaryl alkyl radical, a 1,3 benzoxolyl alkyl radical or a 1,4 benzodioxyl alkyl radical, and where, furthermore, R^{11} and R^{22} may unite with the nitrogen atom to which they are bonded to form a ring optionally containing one or more heteroatoms in addition to the nitrogen atom to which R^{11} and R^{12} are bonded selected from nitrogen and oxygen, and this ring may also be substituted),

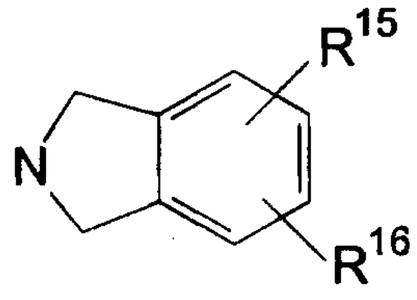
R^6 signifies a hydrogen atom, a halogen atom, a hydroxyl group, an amino group, a lower alkyl radical, a lower alkoxy radical, a lower alkenyl radical, a 1,3-benzodioxolyl alkyloxy radical, a 1,4-benzodioxyl alkyloxy radical, an optionally substituted phenyl alkyloxy radical, a radical represented by the formula



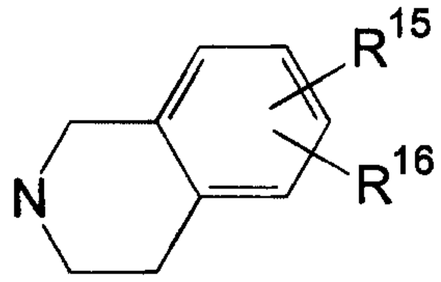
(where R^{13} and R^{14} in this formula independently represent a hydrogen atom, a lower alkyl radical or an alkoxy radical, furthermore, R13 and R14 may combine to form methylenedioxy or ethylenedioxy), a radical represented by the formula



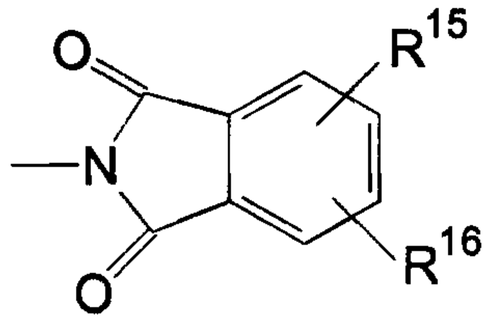
a radical represented by the formula



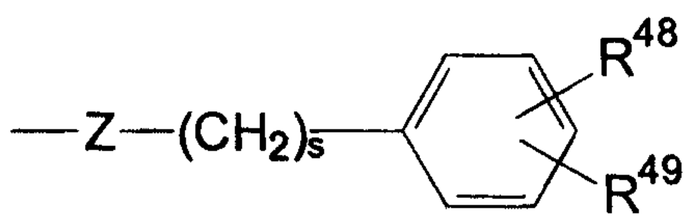
a radical represented by the formula



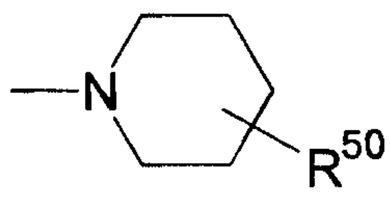
a radical represented by the formula



(where R^{15} and ^{16} used in these formulae independently represent a hydrogen atom, a lower alkyl radical or a lower alkoxy radical, furthermore, R^{15} and R^{16} may combine to form methylenedioxy or ethylenedioxy), a piperidine-4-spiro-2'-dioxane-1-yl radical, a radical represented by the formula

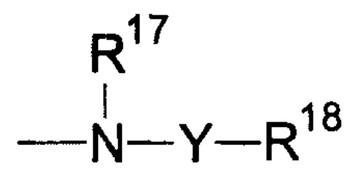


(where R^{48} and R^{49} in this formula independently represent a hydrogen atom, a lower alkyl radical or a lower alkoxy radical, furthermore, R^{48} and R^{49} may combine to form methylenedioxy or ethylenedioxy, Z signifies a sulphur atom or an oxygen atom), a radical represented by the formula

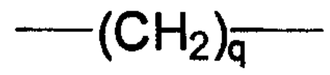


(where R^{50} in this formula signifies a hydroxyl group, a halogen atom, a lower alkyl radical, a lower alkoxy radical,

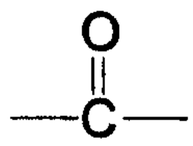
an optionally protected carboxyl radical, a cyano radical, a hydroxyalkyl radical or a carboxyalkyl radical), a radical represented by the formula



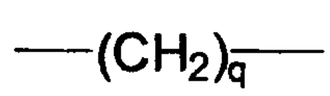
(where R^{17} in this formula stands for a hydrogen atom, a lower alkyl radical, an acyl radical, a lower alcoxyalkyl radical, an optionally protected carboxyalkyl radical or a hydroxyalkyl radical, Y stands for a radical represented by the formula



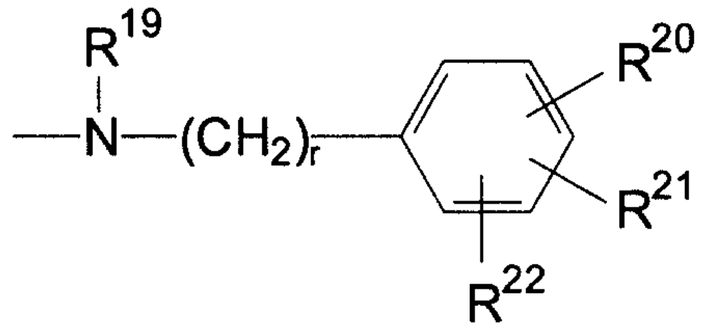
(where q in this formula signifies 0 or an integer from 1 - 8), or a radical represented by the formula



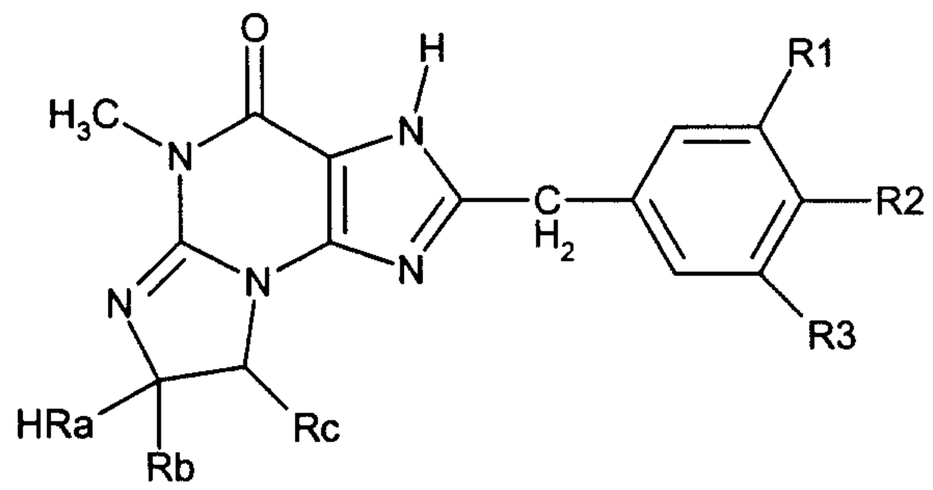
furthermore, when q in the radical represented by the formula



has the value of an integer from 1 - 8, the respective carbon atoms may also possess 1 - 2 substitutuents, R^{18} signifies a hydrogen atom, a hydroxyl group, an optionally protected carboxyl radical, a cyano radical, an acyl radical, an optionally substituted heteroaryl radical, or an optionally substituted cycloalkyl radical), or a radical represented by the formula



(where R^{19} in this formula stands for a hydrogen atom, a lower alkyl radical, a lower alkoxyalkyl radical, an acyl radical, an optionally protected carboxyalkyl radical or a hydroxyalkyl radical R^{20}, R^{21}, and R^{22} independently represent a hydrogen atom, a halogen atom, a hydroxyl group, an amino group, a nitro radical, a lower alkyl radical, a lower alkoxy radical, a lower alkoxyalkyl radical, a lower alkenyl radical, an acyl radical, an acylamino radical, an alkylsulphonylamino radical, a hydroxyiminoalkyl radical, a alkyloxycarbonylamino radical, an alkyloxycarbonyloxy radical or an optionally substituted heteroaryl radical, furthermore, any two of R^{20}, R^{21}, and R^{22} may combine to form a saturated or unsaturated ring that may contain one or more heteroatoms selected from nitrogen, sulphur and oxygen, and r signifies 0 or an integer from 1 to 8);

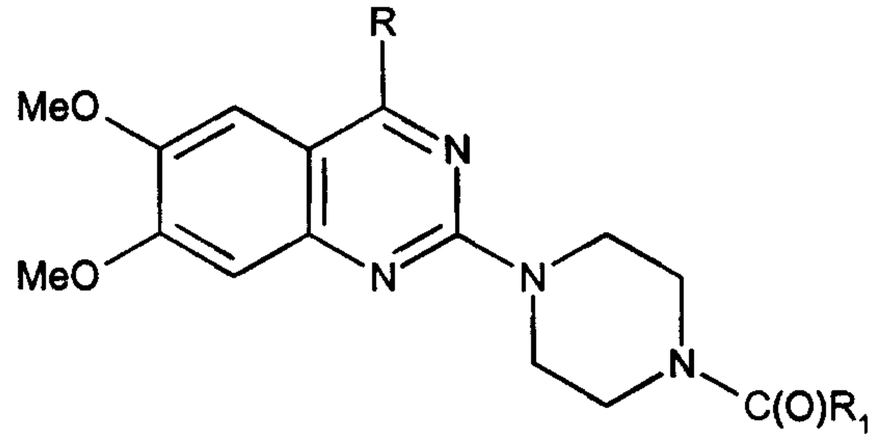


and pharmaceutically acceptable salts thereof, wherein:

R_1, R_2 and R_3 are independently selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, halogeno, hydroxy, (di-lower alkyl) amino, 4-morpholinyl, 1-pyrrolidinyl, 1-pyrrolyl, $-CF_3$, $-OCF_3$, phenyl and methoxphenyl; or R_1 and R_2 together are methylenedioxy; or R_1

and R_2 together with the carbon atoms to which they are attached form a benzene ring; and

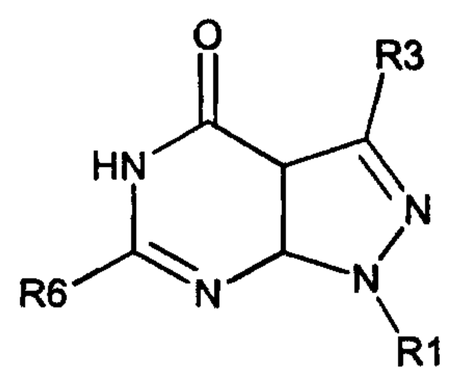
R^a is hydrogen and R^b and R^c, together with the carbon atoms to which they are attached, form a saturated ring of 5 carbons; or R^a is lower alkyl, R^b is hydrogen or lower alkyl, and R^c is hydrogen; or R^a, R^b and the carbon atom to which they are attached form a saturated ring of 5-7 carbons, and R^c is hydrogen; or R^a is hydrogen, and R^b, R^c and the carbon atoms to which they are attached form a tetrahydrofuran ring; or R^a and R^b, together with the carbon atom to which they are attached, and R^b and R^c, together with the carbon atoms to which they are attached, each form a saturated ring of 5-7 carbons;



and pharmaceutically acceptable salts thereof, wherein:

R is amino or hydrazino;

R_1 is cycloalkyl having 3 to 8 ring carbon atoms inclusive or cycloalkenyl having 4 to 8 ring carbon atoms inclusive;



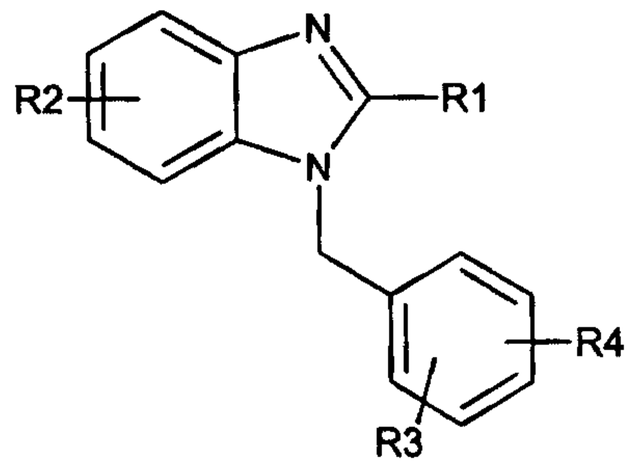
and pharmaceutically acceptable addition salts thereof,

wherein

R^1 is hydrogen, alkyl, C_4 to C_7 cycloalkyl, C_4 to C_7 cycloalkyl substituted by C_1 to C_{10} alkyl or hydroxyl, 2- or 3-tetrahydrothienyl, 1,1, -dioxide, C_4 to C_7 cycloalkyl-C_1 to C_{10} alkyl, carboxy-C_1 to C_{10} alkyl, carbo-C_1 to C_4 lower alkoxy C_1 to C_{10} alkyl, dialkylamino C_1 to C_{10} alkyl, phenyl-C_1 to C_4 lower-alkyl, phenyl-C_1 to C_4 lower-alkyl in which the phenyl ring is substituted in the 2, 3 or 4 position by one or two substituents, the same or different, selected from the group consisting of amino, halogen, C_1 to C_{10} alkyl, carboxyl, carbo-C_1 to C_4 lower-alkoxy, carbamoyl, $NHSO_2$ (quinolinyl), nitro and cyano;

R^3 is C_1 to C_4 lower alkyl, phenyl C_1 to C_4 lower alkyl, lower-alkoxyphenyl-C_1 to C_4 lower-alkyl, di-C_1 to C_4 lower-alkoxy-phenyl-C_1 to C_4 lower alkyl, pyridyl-C_1 to C_4 lower alkyl, C_4 to C_7 cycloalkyl-C_1 to C_4 lower-alkyl, phenylamino, di-C_1 to C_{1-4} alkylamino, halogen, trifluoromethyl, C_1 to C_4 lower-alkylthio, cyano or nitro; and

R^6 is a nine or ten membered bicyclic ring containing carbon and from one to two nitrogen atoms, and the ring is made up of fused 5 or 6 membered rings, optionally substituted at any available carbon atom by one or two substituents, the same or different, selected from the group consisting of C_1 to C_4 lower-alkyl, halogen, C_1 to C_4 lower-alkoxy, C_4 to C_7 cycloalkyloxy, 4-morpholinyl, C_1 to C_4 lower-alkoxy-C_1 to C_4 lower-alkoxy, hydroxy, imidazolyl, oxo and 4-morpholinyl-C_1 to C_4 lower-alkoxy, or optionally substituted at any available nitrogen atom at any time by C_1 to C_4 lower-alkyl, C_2 to C_4 lower-alkanoyl, or trifluoroacetyl;

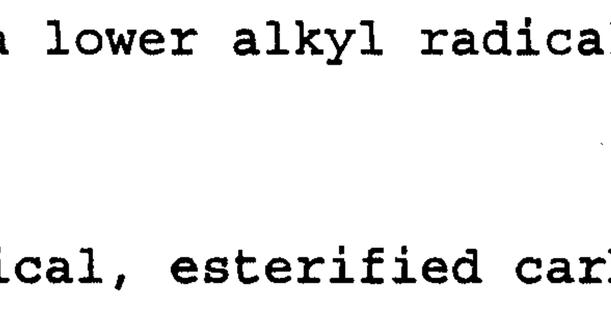


and pharmaceutically acceptable salts thereof,

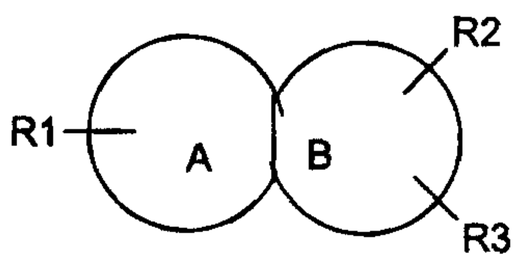
where R^1 stands for a lower alkyl radical or a lower cycloalkyl radical;

R^2 for a carboxy radical, esterified carboxy radical or an amidized carboxy radical; and

R^3 and R^4 each stand for a hydrogen atom, a halogen atom, a carboxy radical, an esterified carboxy radical or a lower alkyl radical optionally substituted by 1 - 3 halogen atoms, respectively;



(2-phenyl-8-ethoxycycloheptimidazole);



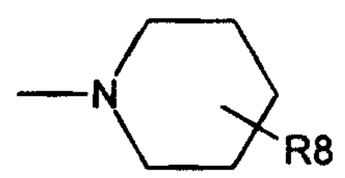
and pharmacologically acceptable salts thereof,

in which ring A represents a benzene, pyridine or cyclohexane ring and B represents a pyridine, imidazole or pyrimidine ring, with the proviso that rings A and B are bonded to each other with two atoms being shared by the

rings, and the shared atoms may be any of carbon and nitrogen atoms;

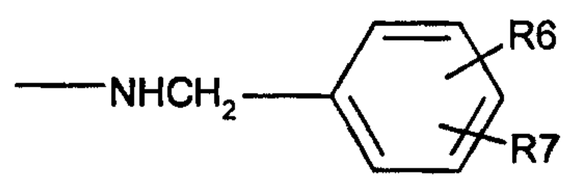
R^1 represents a group represented by the formula: $-NR^4R^5$ (wherein R^4 and R^5 may be the same or different from each other and each represents a hydrogen atom, a lower alkyl or acyl group or a carboxyl group which may be protected, or alternatively R^4 and R^5 may form a ring together with the nitrogen atom to which they are bonded, wherein the ring may be substituted), or a heteroaryl group which has one or two nitrogen atoms and may be substituted;

R^2 represents a hydrogen atom, a group represented by the formula:

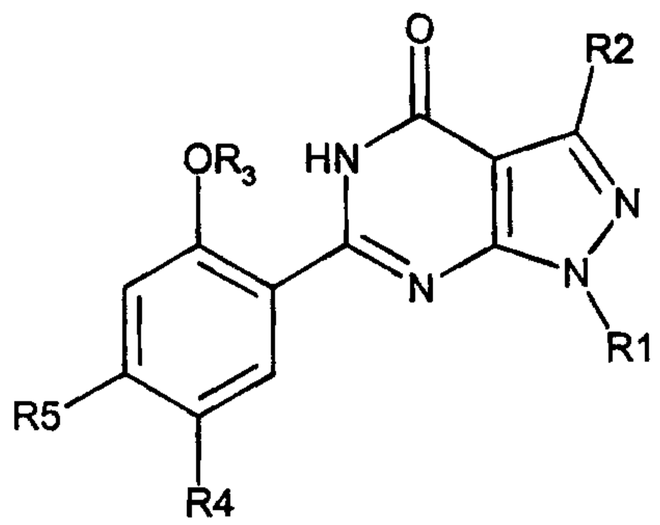


(wherein R^8 represents a carboxyl or tetrazolyl group which may be protected), or a halogen atom; and

R^3 represents a hydrogen atom or a group represented by the formula:



(wherein R^6 and R^7 each represent a hydrogen or halogen atom or a lower alkoxy group, or alternatively R^6 and R^7 may together form a methylenedioxy or ethylenedioxy group);



and pharmaceutically acceptable salts and solvates thereof, in which:

R^1 represents arylmethyl or C_{1-6} alkyl optionally substituted by one or more fluorine atoms;

R^2 represents methyl;

R^3 represents C_{2-4} alkyl;

R^4 represents nitro, cyano, C_{1-6} alkoxy, $C(=X)NR^6R^7$, NR^8R^9, $(CH_2)_mNR^{10}C(=Y)R^{11}$ or a 5-membered heterocyclic ring selected from thienyl, thiazolyl and 1,2,4-triazolyl each ring optionally substituted by a C_{1-4} alkyl or aryl group; or when R^1 is arylmethyl or C_{1-6} alkyl substituted by one or more fluorine atoms then R^4 may also represent hydrogen;

R^5 represents hydrogen or C_{1-6} alkyl;

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

R^7 represents hydrogen, amino, hydroxyl, C_{1-6} alkyl, aryl or arylC_{1-4} alkyl;

R^8 represents hydrogen or C_{1-6} alkyl;

R^9 represents hydrogen, C_{1-6} alkyl, SO_2R^{12}, CO_2R^{12}, $C(=NCN)SR^{12}$ or $C(=NCN)NR^{13}R^{14}$;

R^{10} represents hydrogen or C_{1-6} alkyl;

R^{11} represents C_{1-6} alkyl optionally substituted by one or more halogen atoms, or R^{11} represents aryl, aryl C_{1-4} alkyl, thienyl, $NR^{15}R^{16}$, $CH_2NR^{17}R^{18}$ or R^{10} and R^{11} together represent $-A(CH_2)_n-$;

R^{12} represents C_{1-6} alkyl, aryl or arylC_{1-4}alkyl;

R^{13} represents hydrogen or C_{1-6} alkyl;

R^{14} represents hydrogen, C_{1-6} alkyl, aryl, aryl C_{1-4} alkyl or R^{13} and R^{14} together with the nitrogen atom to which they are attached form a morpholino, piperazino or N-C_{1-4} alkylpiperazino ring;

R^{15} represents hydrogen or C_{1-6} alkyl or R^{10} and R^{15} together represent $-A(CH_2)_n-$;

R^{16} represents hydrogen, C_{1-6} alkyl, aryl, aryl C_{1-4} alkyl, CO_2R^{12}, $CH_2CO_2R^{12}$ or R^{15} and R^{16} together with the nitrogen atom to which they are attached form a morpholino, piperazino or N-C_{1-4}alkyl-piperazino ring;

R^{17} represents hydrogen or C_{1-6} alkyl;

R^{18} represents hydrogen, C_{1-6} alkyl, aryl, aryl C_{1-4} alkyl, COR^{12} or R^{17} and R^{18} together with the nitrogen atom to which they are attached form a morpholino, piperazino, or N-C_{1-4} alkylpiperazino ring;

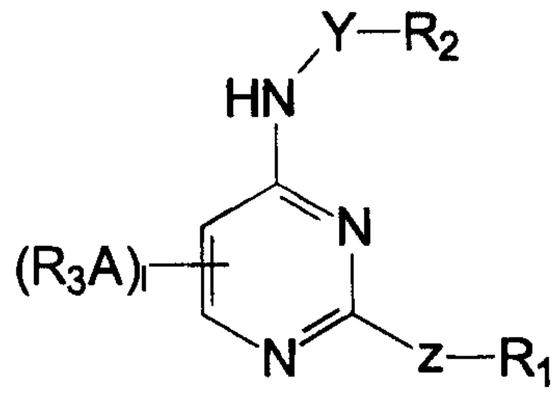
A represents CH_2 or C = O;

m represents zero or 1;

n represents 1,2 or 3;

X represents S or NH, or when R^7 represents amino then X may also represent O;

Y represents O or S;



and pharmaceutically acceptable salts thereof,

wherein A is a bond, C1-4 alkylene or C1-4 oxyalkylene;

Y is a bond, C1-4 alkylene, C1-4 alkyleneoxy, C1-4 alkoxyphenylene or phenyl (C1-4) alkylene;

Z is a bond or vinylene;

R1 is a 4-15 membered heterocyclic ring containing one or two nitrogen atoms optionally substituted by one or two groups chosen from C1-4 alkyl, C1-4 alkoxy, halogen, trifluoromethyl, and nitro;

R2 is

(i) 4-15 membered heterocyclic ring containing one or two heteroatoms chosen from nitrogen, oxygen and sulphur, not more than one heteroatom being sulphur, optionally substituted by one or two groups chosen from C1-4 alkyl, C1-4 alkoxy, halogen, trifluoromethyl, nitro and groups of formula: - COOR10, wherein R10 is hydrogen or C1-4 alkyl,

(ii) C4-15 carbocyclic ring,

(iii) C1-4 alkoxy,

(iv) hydroxy(C1-4 alkoxy) or

(v) hydroxy,

R^3 is

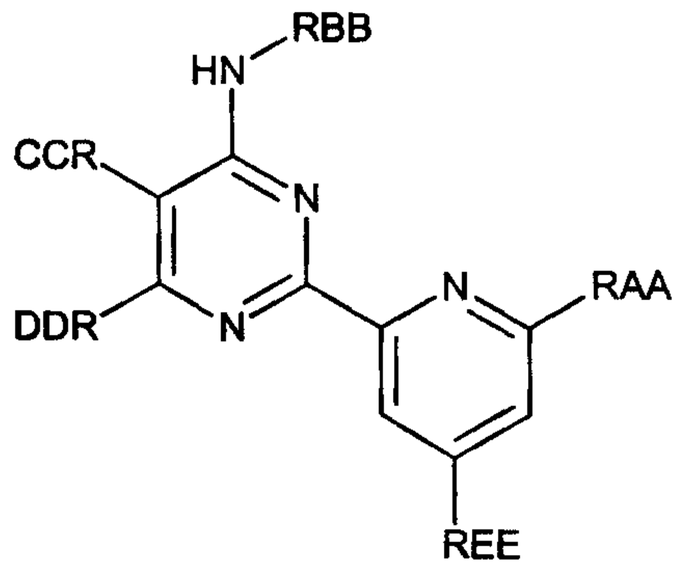
4-15 membered heterocyclic ring containing one or two heteroatoms chosen from nitrogen, oxygen and sulphur, not more than one heteroatom being oxygen or sulphur, optionally substituted by one or two groups chosen from C1-4 alkyl, C1-4 alkoxy, halogen, trifluoromethyl, nitro, cyano, ethynyl and groups of formula: - SONR7R8, wherein R7 and R8 are independently hydrogen or C1-4 alkyl,

C4-15 carbocyclic ring,

a group of formula:CH2 = CH(X)- wherein X is halogen, or hydrogen;

and l is 1 or 2;

provided that R2 is not hydroxy when Y is a bond; R1 is not bonded through its nitrogen atom when Z is vinylene; and excluding compounds of the formula:



wherein R^{AA} is methyl or n-propyl;

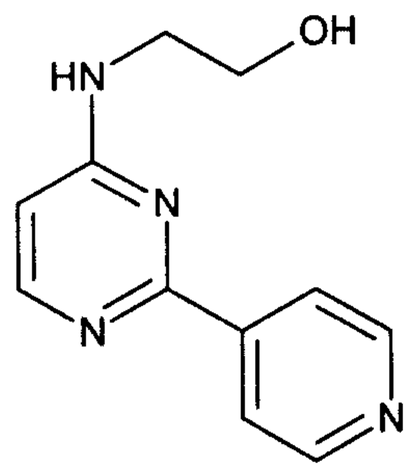
R^{BB} is cyclopentyl, cyclohexyl, 2-hydroxyethyl, methoxyethyl, 2-(1-piperindinyl)ethyl, phenyl or benzyl which may be substituted by 1 or 2 of methyl, methoxy, chloro, nitro and trifluoromethyl;

R^{CC} is hydrogen or methyl;

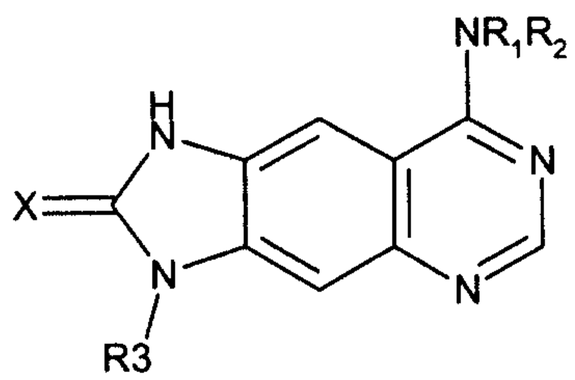
R^{DD} is methyl, n-propyl, isopropyl or benzyl; and

R^{EE} is hydrogen or methyl;

and the compound of formula:



;



and pharmaceutically acceptable salts thereof,

where R^1 and R^2 independently represent hydrogen, lower alkyl (the respective alkyls may be cycloalkyl with a substitution number of 1 - 3, either identical or different), hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, dialkyl-substituted amino, nitro, halogen, an alicyclic heterocyclic radical (the respective alicyclic heterocyclic radicals may be independently substituted by lower alkyl with a substitution number of 1 - 3, aralkyl, aryl optionally substituted by a lower alkoxy radical with a substitution number from 1 - 3 or an aromatic heterocyclic radical), cycloalkyl, di-cycloalkyl, benzocycloalkyl (the respective benzoalkyls may be independently substituted by lower alkyl with a substitution number of 1 - 3, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, aminoalkyl-substituted amino, dialkyl-substituted amino, nitro, sulphonamide,

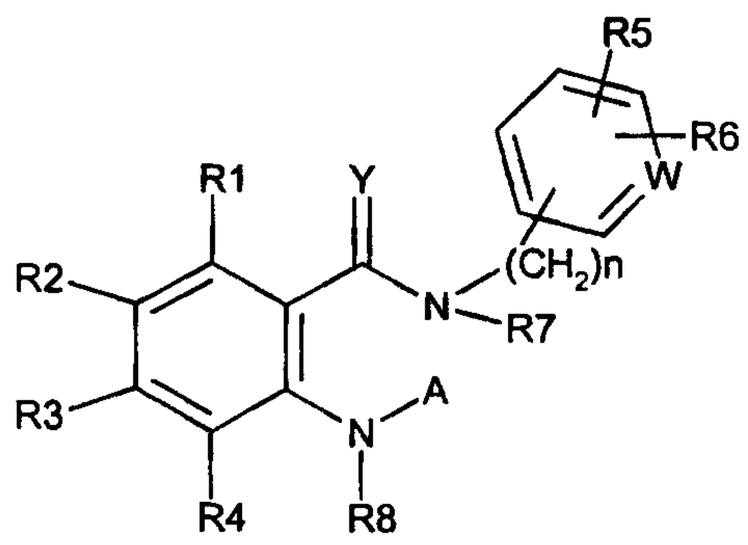
halogen, or trifluoromethyl), lower alkenyl, aryl (the respective aryls may be independently substituted by lower alkyl with a substitution number of 1 - 3, hydroxy, lower alkoxy, carboxy, low alkoxycarbonyl, amino, monoalkyl-substituted amino, di-alkyl substituted amino, nitro, sulphonamide, halogen or trifluoromethyl), aromatic heterocyclic radical-substituted alkyl (the respective aromatic heterocyclic radical-substituted parts may be independently substituted by lower alkyl with a substitution number of 1 - 3, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, di-alkyl substituted amino, nitro, sulphonamide, halogen, or trifluoromethyl, or the respective alkyl parts may be substituted by aryl), aromatic heterocyclic radicals (the respective aromatic heterocyclic radicals may be independently substituted by lower alkyl with a substitution number of 1 - 3, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, di-alkyl substituted amino, nitro, sulphonamide, halogen or trifluoromethyl), or aralkyl (the aryl parts of the respective aralkyls may be independently substituted by lower alkyl with a substitution number of 1 - 3, lower alkoxy, di-alkoxy-substituted amino, halogen or trifluoromethyl); and, furthermore,

R^1 and R^2 may stand for a heterocyclic radical formed by R^1 and R^2 combining with the nitrogen (N) atom to which they are bonded (the heterocyclic radical may be substituted by alkyl with a substitution number of 1 - 3, aryl, or aralkyl);

R3 stands for hydrogen, lower alkyl (the lower alkyl may be substituted by cycloalkyl with a substitution number of 1 - 3, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, di-alkyl-substituted amino, nitro, halogen, or alicyclic heterocyclic radical

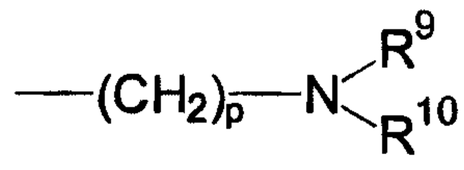
(the alicyclic heterocyclic radical may be substituted by lower alkyl with a substitution number of 1 - 3, aralkyl, aryl optionally substituted by a lower alkoxy radical with a substitution number from 1 - 3 or an aromatic heterocyclic radical.)), cycloalkyl, lower alkenyl, aryl (the aryl may be subsituted by lower alkyl with a substitution number of 1 - 3, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, di-alkyl substituted amino, nitro, sulphonamide, halogen or trifluoromethyl), aromatic heterocyclic radical-substituted alkyl (the aromatic heterocyclic radical-substituted part may be substituted by lower alkyl with a substitution number of 1 - 3, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, di-alkyl substituted amino, nitro, sulphonamide, halogen, or trifluoromethyl, or the alkyl part may be substituted by aryl), aromatic heterocyclic radical (the aromatic heterocyclic radical may be substituted by lower alkyl with a substitution number of 1 - 3, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, di-alkyl substituted amino, nitro, sulphonamide, halogen or trifluoromethyl), or aralkyl (the aryl part of the aralkyl may be substituted by lower alkyl with a substitution number of 1 - 3, lower alkoxy, di-alkoxy-substituted amino, halogen or trifluoromethyl.); and

X stands for oxygen or sulphur;

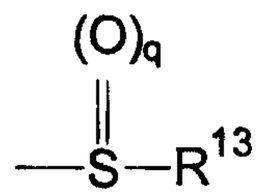


and pharmaceutically acceptable salts thereof,

where R^1, R^2, R^3 and R^4 independently represent a hydrogen atom, a halogen atom, a hydroxyl group, an optionally halogen-substituted lower alkyl radical, an optionally halogen-substituted lower alkoxy radical, a nitro radical, a hydroxyalkyl radical, a cyano radical, a radical represented by the formula



(where R^9 and R^{10} independently represent a hydrogen atom, an optionally halogen-substituted lower alkyl radical, an aryl-alkyl radical, a heteroaryl-alkyl radical, an acyl radical, an optionally protected carboxyl radical, and, where furthermore R^9 and R^{10} may combine with the nitrogen to which they are bonded to form a ring, and where, moreover, this ring may be substituted, p stands for 0 or an integer having a value from 1 - 6), a carbamoyl radical which may be substituted, a pyrazolyl radical which may be substituted, an imidazolyl radical which may be substituted, or a radical represented by the formula



where R^{13} signifies a hydrogen atom or an optionally halogen-substituted lower alkyl radical; and, where q is 0 or an integer with a value of 1 - 2,

furthermore, R^1 and R^2, R^2 and R^3 or R^3 and R^4 may combine with the carbon atoms to which they are bonded to form a ring,

R^5 and R^6 stand for a hydrogen atom, a halogen atom, a hydroxyl group, a cyano radical, an optionally halogen-substituted lower alkyl radical, or an optionally halogen-substituted lower alkoxy radical, furthermore, R^5 and R^6 may combine with the carbon atoms to which they are bonded to form an oxolane ring, a 1,3-di-oxolane ring or a 1,4 di-oxane ring,

W signifies the radical represented by the formula -N= or a radical represented by the formula -CH=,

R^7 and R^8 independently represent a hydrogen atom, an optionally halogen-substituted lower alkyl radical,

furthermore, R^1 and R^7 may combine with the carbon and nitrogen atoms to which they are bonded to form a ring that may contain one or more heteroatoms in addition to the nitrogen atom to which R^7 is bonded selected from nitrogen, oxygen and sulphur, and this ring may be substituted,

A stands for a hydrogen atom, an optionally halogen-substituted lower alkyl radical, or a radical represented by the formula -X-(CH2)m-Z (where X stands for a radical represented by the formula -CO-, a radical represented by the formula -CS-, a radical represented by the formula -CH2-, or a radical represented by the formula -C(O)2,

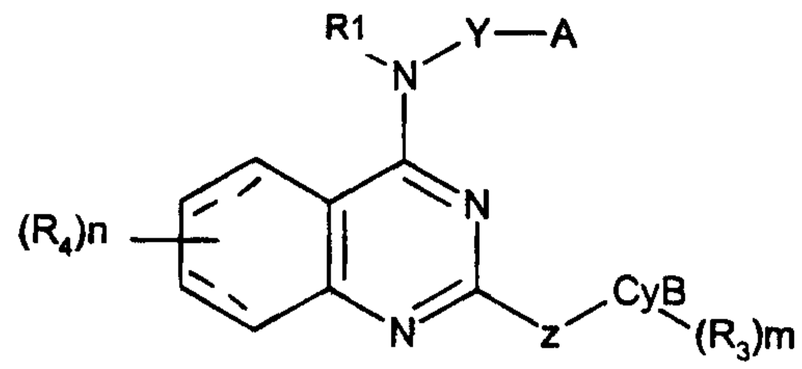
Z signifies a hydroxyl group, an optionally halogen-substituted lower alkoxy radical, a cyano radical, a halogen atom, an optionally protected carbamoyl radical, an optionally substituted aryl radical, an optionally substituted aryloxy radical, an optionally substituted heteroaryl radical, an optionally substituted heteroaryl alkyloxy radical, a radical represented by the formula $-NR^{11}R^{12}$ (where R^{11} and R^{12} independently represent a hydrogen atom, an optionally halogen-substituted lower alkyl

radicals, an optionally substituted aryl-alkyl radical, an optionally substituted heteroaryl-alkyl radical, an acyl radical, an optionally protected carboxy radical, or an optionally substituted carbamoyl radical, furthermore, R^{11} and R^{12} may combine with the nitrogen atom to which they are bonded to form a ring, which may be substituted), or a cycloalkyl radical which may be substituted,

m may be either 0 or an integer with a value from 1 - 6,

Y stands for an oxygen or sulphur atom,

n signifies either 0 or an integer with a value from 1 - 6;



and pharmaceutically acceptable salts, addition salts or hydrates thereof,

wherein R^1 is hydrogen or C1-4 alkyl;

Y is a single bond or C1-6 alkylene;

A is

$-CyA-(R^2)_1$,

$-O-R^0$ or $-S(O)_p - R^0$,

in which R^0 is R^{0A} or R^{0B},

R^{0A} is $-CyA-(R^2)_1$;

R^{0B} is hydrogen or C1-4 alkyl;

p is 0-2;

CyA is

(1) 3-7 membered, saturated or unsaturated, monocyclic carbocyclic ring,

(2) 7-membered, unsaturated or partially saturated, monocyclic hetero ring containing as heteroatoms, one nitrogen atom, one nitrogen and one oxygen atoms, two nitrogen and one oxygen atoms, or one nitrogen and two oxygen atoms,

(3) 6-membered, unsaturated or partially saturated, monocyclic hetero ring containing as heteroatoms, one nitrogen and one oxygen atoms, two nitrogen and one oxygen atoms, or one nitrogen and two oxygen atoms,

(4) 6-membered, unsaturated or partially saturated, monocyclic hetero ring containing as a heteroatom, one nitrogen atom,

(5) 4- or 5-membered, unsaturated or partially saturated, monocyclic hetero ring containing as heteroatoms, one nitrogen atom, one nitrogen and one oxygen atoms, two nitrogen and one oxygen atoms, or one nitrogen and two oxygen atoms,

(6) 4-7 membered, unsaturated or partially saturated, monocyclic hetero ring containing as heteroatoms, one or two sulfur atoms or

(7) 4-7 membered, unsaturated or partially or fully saturated, monocyclic hetero ring containing as heteroatoms, one or two oxygen atoms;

R^2 is R^{2A} or R^{2B};

R^{2A} is (1) - $NR^{6A}AR^{7A}$, in which R^{6A} and R^{7A} independently are hydrogen or C1-4 alkyl (with the proviso that R^{6A} and R^{7A} are

not both hydrogen at the same time), (2)-$SO_2NR^6R^7$, in which R^6 and R^7 independently are hydrogen or C1-4 alkyl, (3) trifluoromethyl or (4) trifluoromethoxy;

R^{2B} is (1) hydrogen (2) C1-4 alkyl, (3) C1-4 alkoxy, (4) $-COOR^5$ in which R^5 is hydrogen or C1-4 alkyl, (5) halogen, (6) nitro or (7) $-NR^{6B}GBR^{7B}$, in which R^{6B} and R^{7B} are hydrogen;

Z is Z^A or Z^B

Z^A is methylene, ethylene, vinylene or ethylene;

Z^B is single bond;

CyB is

(1) 7-membered, unsaturated or partially saturated monocyclic hetero ring containing as heteroatoms, one, two or three nitrogen atoms,

(2) 6-membered, unsaturated or partially saturated monocyclic hetero ring containing as heteroatoms, two or three nitrogen atoms,

(3) 6-membered, unsaturated or partially saturated, monocylic hetero ring containing as a heteroatom, one nitrogen atom,

(4) 4- or 5- membered, unsaturated or partially saturated, monocyclic, hetero ring containing as heteroatoms, one, two or three nitrogen atoms, or

(5) 4-7 membered, unsaturated or partially saturated, monocyclic hetero ring containing as heteroatoms, one or two oxygen atoms, or one or two sulfur atoms;

R^3 is hydrogen, C1-4 alkyl, C1-4 alkoxy, halogen or trifluoromethyl;

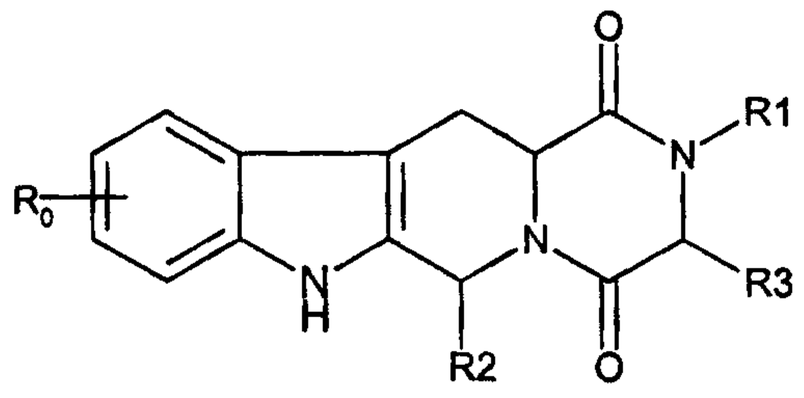
R^4 is R^{4A} or R^{4B};

R^{4A} is (1) $-NHSO_2R^{11}$ in which R^{11} is C1-4 alkyl, (2) $SO_2NR^9R^{10}$, in which R^9 is hydrogen, C1-4 alkyl or phenyl (C1-4 alkyl) and R^{10} is hydrogen or C1-4 alkyl, (3) $-OCOR^{11}$, in which R^{11} is as hereinbefore defined, (4) hydroxy, (5) $-SO_2N=CHNR^{12}R^{13}$ in which R^{12} is hydrogen or C1-4 alkyl and R^{13} is C1-4 alkyl, (6) $-CONR^{14}R^{15}$ in which R^{14} is hydrogen or C1-4 alkyl and R^{15} is C1-4 alkyl or phenyl (C1-4alkyl), (7) ethynyl, (8) tri(C1-4 alkyl) silylethynyl or (9) acetyl;

R^{4B} is (1) hydrogen, (2) C1-4 alkyl, (3) C1-4 alkoxy, (4) $-COOR^8$, in which R^8 is hydrogen or C1-4 alkyl, (5) $-NR^9R^{10}$, in which R^9 and R^{10} are as hereinbefore defined, (6) $-NHCOR^{11}$, in which R^{11} is as hereinbefore defined, (7) halogen, (8) trifluoromethyl, (9) nitro, (10) cyano, (11) C1-4 alkylthio, (12) C1-4 alkylsulfinyl, (13) C1-4 alkylsulfonyl, (14) hydroxymethyl, and

l, m and n independently are 1 or 2;

with the proviso that the group of the formula: $-CyA-(R^2)$, does not represent a cyclopentyl and trifluoromethylphenyl group when Y is a single bond, that a CyB ring does not bond to Z through a nitrogen atom in the CyB ring when Z is vinylene or ethynylene, that a CyB ring is not pyridine or thiophene when CyA is a 4-7 membered, unsaturated or paritally or fully saturated, monocyclic hetero ring, containing as heteroatoms, one or two oxygen atoms, that Y is not a single bond, when A is $-O-R^0$ or $-S(O)_p-R^0$ and that A is not $-CyA-(R^{2B})_1$ and OR^{0B}, when Z is Z^B and R^4 is R^{4B};



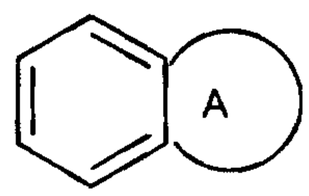
and pharmaceutically acceptable salts and solvates thereof,

in which:

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

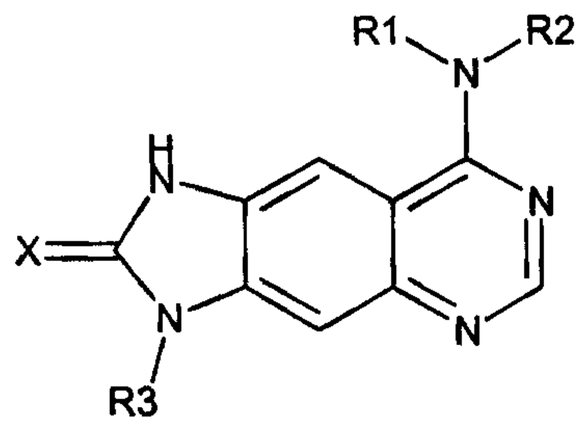
R^1 represents hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl C_{1-3} alkyl, aryl C_{1-3} alkyl or heteroaryl C_{1-3} alkyl;

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

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;



and pharmaceutically acceptable salts thereof,

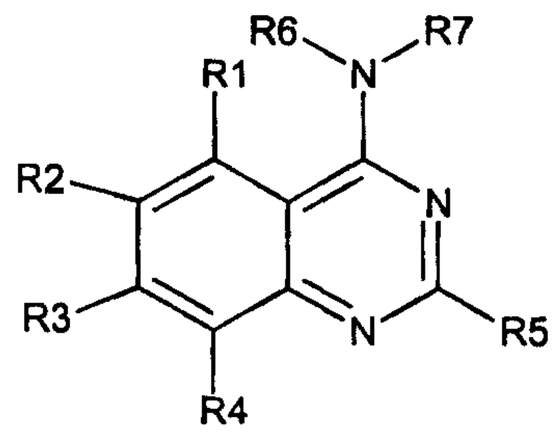
wherein R^1 and R^2 are the same or different and represent hydrogen, lower alkyl (which is optionally substituted with one to three substituents which are the same or different and are cycloalkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, dialkyl-substituted amino, nitro or halogen), alicyclic heterocycle group (which is optionally substituted with one to three substituents which are the same or different and are lower alkyl, aralkyl, aryl optionally substituted with one to three substituents which are the same or different and are lower alkoxy, or aromatic heterocycle group), cycloalkyl, bicycloalkyl, benzocycloalkyl (which is optionally substituted with one to three substituents which are the same or different and are lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, dialkyl-substituted amino, nitro, sulfonamide, halogen, or trifluormethyl), lower alkenyl, aryl (which is optionally substituted with one to three substituents which are the same or different and are lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, dialkyl-substituted amino, nitro, sulfonamide, halogen, or trifluoromethyl) aromatic heterocycle group-substituted alkyl (where the aromatic heterocycle group part is optionally substituted with one to three substituents which are the same or different and are lower alkyl, hydroxy, lower alkoxy,

carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, dialkyl-substituted amino, nitro, sulfonamide, halogen or trifluoromethyl and where the alkyl part is optionally substituted with aryl), aromatic heterocycle group (which is optionally substituted with one to three substituents which are the same or different and are lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl substituted amino, dialkyl-substituted amino, nitro, sulfonamide, halogen or trifluoromethyl), or aralkyl (where the aryl part of the aralkyl is optionally substituted with one to three substituents which are the same or different and are lower alkyl, lower alkoxy, dialkyl substituted amino, halogen or trifluoromethyl), or R^1 and R^2 are taken together with the nitrogen atom to which they are bonded to form a heterocycle group containing nitrogen atom (which heterocycle group is optionally substituted with one to three substituents which are the same or different and are lower alkyl, aryl or aralkyl),

R^3 represents hydrogen, lower alkyl (which is optionally substituted with one to three substituents which are the same or different and are cycloalkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, dialkyl substituted amino, nitro or halogen) alicyclic heterocycle group (which is optionally substituted with one to three substituents which are the same or different and are lower alkyl, aralkyl, aryl optionally substituted with one to three substituents which are the same or different and are lower alkoxy, or aromatic heterocyle group), cycloalkyl, lower alkenyl, aryl (which is optionally substituted with one to three substituents which are the same or different and are lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, dialkyl-substituted amino,

nitro, sulfonamide, halogen or trifluoromethyl), aromatic heterocycle group-substituted alkyl (where the aromatic heterocycle group part is optionally substituted with one to three substituents which are the same or different and are lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonylamino, monoalkyl-substituted amino, dialkyl-substituted amino, nitro, sulfonamide, halogen or trifluoromethyl, and where the alkyl part is optionally substituted with aryl), aromatic heterocycle group (where the aromatic heterocycle group is optionally substituted with one to three substituents which are the same or different and are lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, dialkyl-substituted amino, nitro, sulfonamide, halogen or trifluoromethyl), or aralkyl (where the aryl part of the aralkyl is optionally substituted with one to three substituents which are the same or different and are lower alkyl, lower alkoxy, dialkyl-substituted amino, halogen, or trifluoromethyl), and

X represents oxygen atom or sulfur atom; and

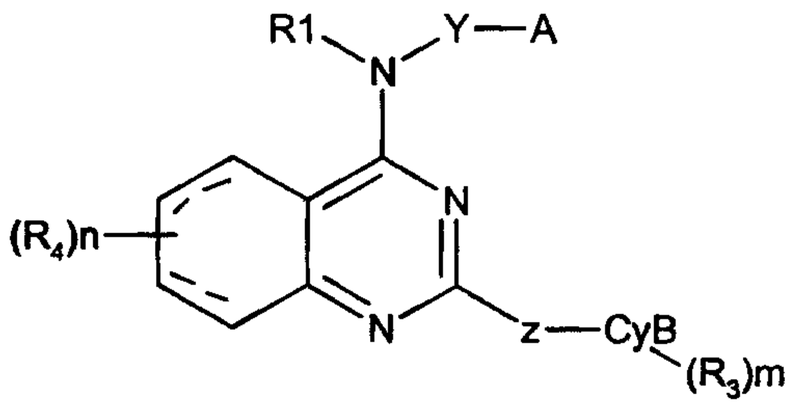


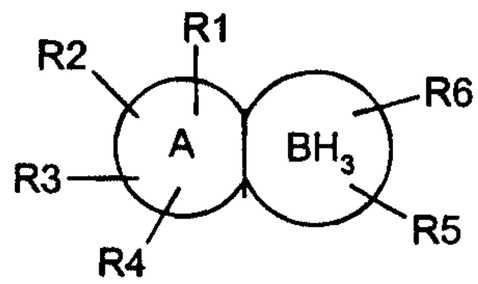
and pharmacologically acceptable salts thereof

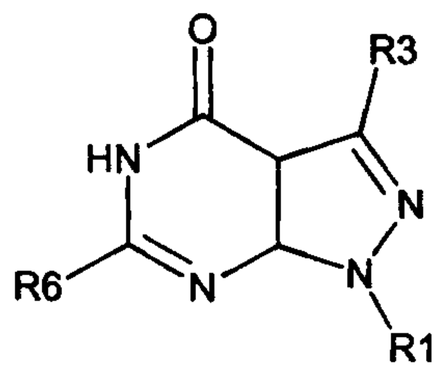
(wherein R^1, R^2, R^3, R^4 and R^5 may be the same or different from each other and each represents a hydrogen atom, a halogen atom, a lower alkyl group or a lower alkoxy group; and

R^6 and R^7 may be the same or different from each other and each represents a hydrogen atom, a lower alkyl group, a hydroxyalkyl group, a lower alkoxyalkyl group, a cyanoalkyl group, a heteroarylalkyl group, a cycloalkyl group, a cycloalkylalkyl group or a carboxyl alkyl group which may be protected, or alternatively R^6 and R^7 may form a ring together with the nitrogen atom to which they are bonded, this ring optionally having a substituent).

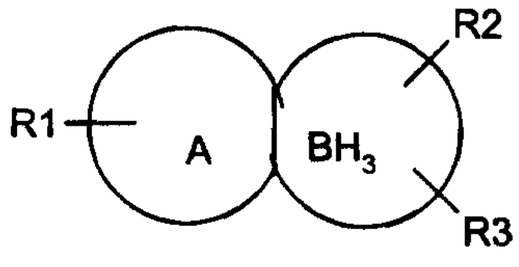
2. The use of a compound as claimed in claim 1 wherein the compound which is a selective cGMP PDE inhibitor is selected from:







and



as defined in claim 1.

3. The use of a compound as claimed in claim 1 wherein said compound is:

1,3-dimethyl-5-benzylpyrazolo[4,3-d]pyrimidine-7-one;

2-(2-propoxyphenyl)-6-purinone;

6-(2-propoxyphenyl)-1,2-dihydro-2-oxopyridine-3-carboxamide;

2-(2-propoxyphenyl)pyrido[2,3-d]pyrimid-4(3H)-one;

7-methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine;

6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide;

1-ethyl-3-methylimidazo[1,5a]quinoxalin-4(5H)-one;

4-phenylmethylamino-6-chloro-2-(1-imidazoloyl)quinazoline;

5-ethyl-8-[3-(N-cyclohexyl-N-methylcarbamoyl)-propyloxy]-4,5-dihydro-4-oxo-pyrido[3,2-e]pyrrolo[1,2-a]pyrazine;

5'methyl-3'-(phenylmethyl)-spiro[cyclopentane-1,7'(8'H)-(3'H)-imidazo[2,1-b]purin]4'(5'H)-one

1-[6-chloro-4-(3,4-methylenedioxybenzyl)aminoquinazolin-2-yl)piperidine-4-carboxylic acid;

(6aR,9aS)-2-(4-trifluoromethylphenyl)methyl-5-methyl-3,4,5,6a,7,8,9,9a-octahydrocyclopent[4,5]imidazo[2,1-b]purin-4-one;

1-tert-butyl-3-phenylmethyl-6-(4-pyridyl)pyrazolo[3,4-d]pyrimid-4-one;

1-cyclopentyl-3-methyl-6-(4-pyridyl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimid-4-one;

2-butyl-1-(2-chlorobenzyl)6-ethoxycarbonylbenzimidazole;

2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-nitroquinazoline;

or 2-phenyl-8-ethoxycycloheptimidazole.

4. The use of a compound as claimed in claim 3 where said compound is:

4-phenylmethylamino-6-chloro-2-(1-imidazoloyl)quinazoline;

1-[6-chloro-4-(3,4-methylenedioxybenzyl)aminoquinazolin-2-yl)piperidine-4-carboxylic acid;

(6aR,9aS)-2-(4-trifluoromethylphenyl)methyl-5-methyl-3,4,5,6a,7,8,9,9a-octahydrocyclopent[4,5]imidazo[2,1-b]purin-4-one;

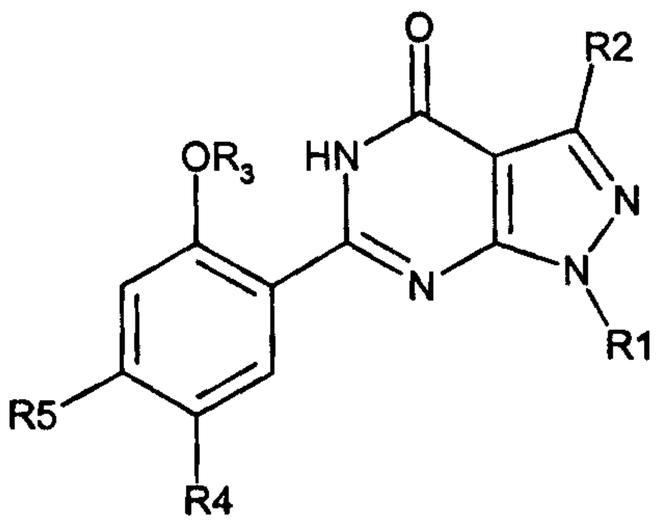
1-tert-butyl-3-phenylmethyl-6-(4-pyridyl)pyrazolo[3,4-d]pyrimid-4-one;

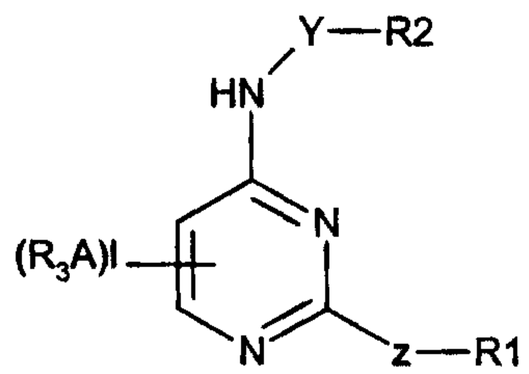
1-cyclopentyl-3-methyl-6-(4-pyridyl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimid-4-one;

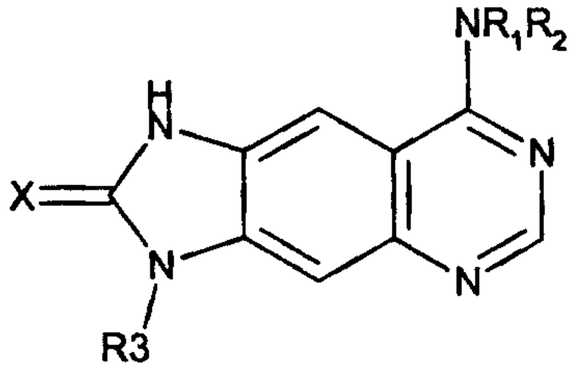
or

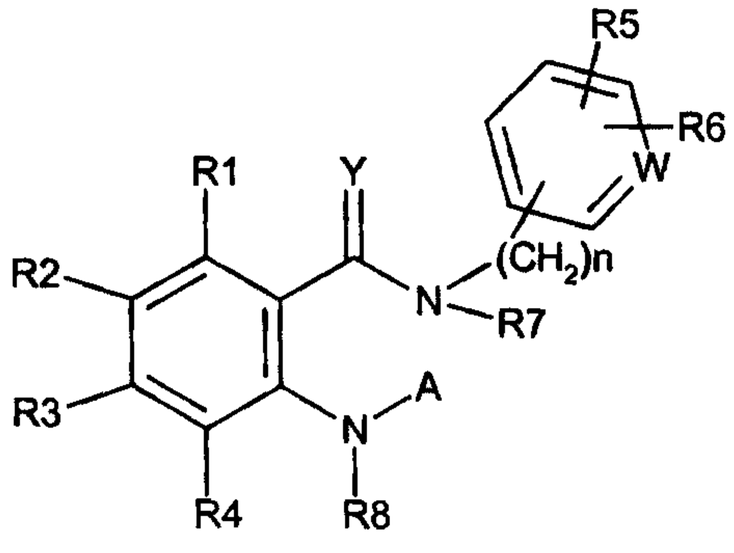
2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-nitroquinazoline;

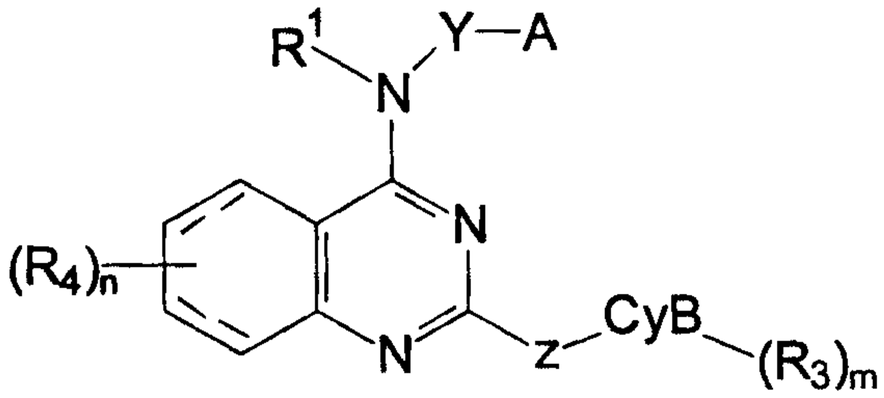
5. The use of a compound which is a selective cGMP PDE inhibitor for the manufacture of a medicament for the treatment of erectile dysfunction in a male animal, including man, wherein said compound is selected from:

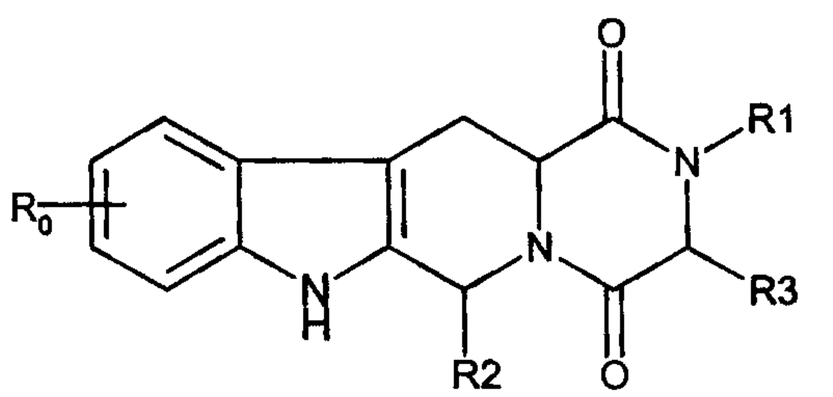


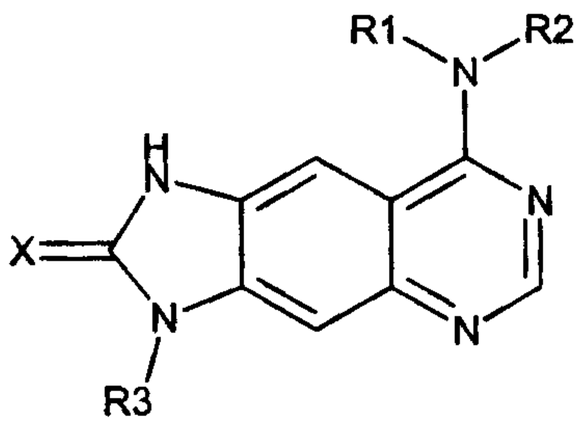


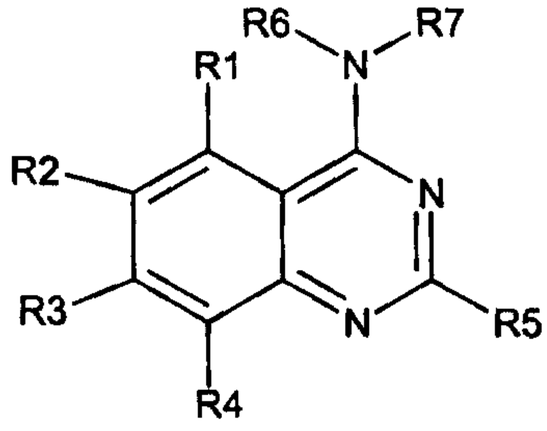












, and

as defined in claim 1.

6. The use of a compound which is a selective cGMP PDE inhibitor for the manufacture of a medicament for the curative or prophylactic treatment of female sexual dysfunction, premature labour or dysmenorrhea, wherein the compound is a compound as defined in any one of claims 1

to 5 for use in the treatment of erectile dysfunction in a male animal.

7. Use of a selective cGMP PDE inhibitor as defined in any one of claims 1 to 5 for the treatment of erectile dysfunction in a male animal or female sexual dysfunction, premature labour or dysmenorrhea.

8. The use according to any one of claims 1 to 7, wherein the male animal is a male human.

9. A medicine for treating erectile dysfunction in a male animal, or female sexual dysfunction, premature labour or dysmenorrhea, comprising an effective amount of the compound which is a selective cGMP-PDE inhibitor, as defined in claim 1, 2 or 5, and a pharmaceutically acceptable diluent or carrier.

10 A medicine for treating erectile dysfunction in a male human, which comprises a pharmaceutically acceptable diluent or carrier, and an effective amount of a compound that is:

1,3-dimethyl-5-benzylpyrazolo[4,3-d]pyrimidine-7-one;

2-(2-propoxyphenyl)6-purinone;

6-(2-propoxyphenyl)-1,2-dihydro-2-oxopyridine-3-carboxamide;

2-(2-propoxyphenyl)pyrido[2,3-d]pyrimid-4(3H)-one;

7-methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine;

6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide;

1-ethyl-3-methylimidazo[1,5a]quinoxalin-4(5H)-one;

4-phenylmethylamino-6-chloro-2-(1-imidazoloyl)quinazoline;

5-ethyl-8-[3-(N-cyclohexyl-N-methylcabamoyl)-propyloxy]-4,5-dihydro-4-oxo-pyrido[3,2-e]pyrrolo[1,2-a]pyrazine;

5'-methyl-3'-(phenylmethyl)-spiro[cyclopentane-1,7'(8'H)-(3'H)-imidazo[2,1-b]purin]4'(5'H)-one

1-[6-chloro-4-(3,4-methylenedioxybenzyl)aminoquinazolin-2-yl)piperidine-4-carboxylic acid;

(6aR,9aS)-2-(4-trifluoromethylphenyl)methyl-5-methyl-3,4,5,6a,7,8,9,9a-octahydrocyclopent[4,5]imidazo[2,1-b]purin-4-one;

1-tert-butyl-3-phenylmethyl-6-(4-pyridyl)pyrazolo[3,4-d]pyrimid-4-one;

1-cyclopentyl-3-methyl-6-(4-pyridyl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimid-4-one ;

2-butyl-1-(2-chlorobenzyl)6-ethoxycarbonylbenzimidazole;

2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-nitroquinazoline; or

2-phenyl-8-ethoxycycloheptimidazole.

11. A medicine for treating erectile dysfunction in a male human, which comprises a pharmaceutically acceptable diluent or carrier, and an effective amount of a compound that is:

4-phenylmethylamino-6-chloro-2-(1-imidazoloyl)quinazoline;

1-[6-chloro-4-(3,4-methylenedioxybenzyl)aminoquinazolin-2-yl)piperidine-4-carboxylic acid;

(6aR,9aS)-2-(4-trifluoromethylphenyl)methyl-5-methyl-3,4,5,6a,7,8,9,9a-octahydrocyclopent[4,5]imidazo[2,1-b]purin-4-one;

1-tert-butyl-3-phenylmethyl-6-(4-pyridyl)pyrazolo[3,4-d]pyrimid-4-one;

1-cyclopentyl-3-methyl-6-(4-pyridyl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimid-4-one ; or

2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-nitroquinazoline.

12. A commercial package comprising the medicine of claim 9, together with a written matter providing instructions for treating erectile dysfunction in a male animal, or female sexual dysfunction, premature labour or dysmenorrhea.

13. A commercial package comprising the medicine of claim 10 or 11, together with a written matter providing instructions for treating erectile dysfunction in a male human.

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