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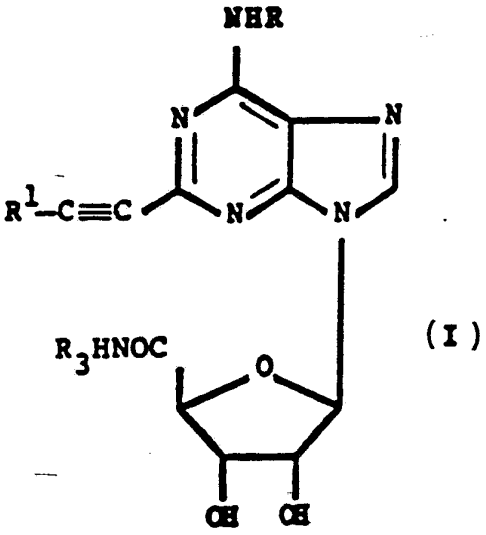
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(54) Title: ADENOSINE DERIVATIVES HAVING A_2 AGONIST ACTIVITY



(I)

(57) Abstract

Adenosine derivatives having A_2 agonist activity of formula (I), a process for the preparation thereof and pharmaceutical compositions containing them. The compounds of the invention are useful for the treatment of cardiovascular pathologies and nervous system diseases.

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ADENOSINE DERIVATIVES HAVING A_2 AGONIST ACTIVITY

The present invention relates to adenosine derivatives having A_2 agonist activity and the use thereof in therapy.

Adenosine is known to modulate a number of physiological functions. At the cardiovascular system level, adenosine is a strong vasodilator and a cardiac depressor. On central nervous system, adenosine induces sedative, anxiolytic and antiepileptic effects. At the kidney level, it exerts a diphasic action, inducing vasoconstriction at low concentrations and vasodilatation at high doses. Adenosine acts as a lipolysis inhibitor on fat cells and as an antiaggregant on platelets (Stone T.W., Purine receptors and their pharmacological roles. In: Advances in drug research. Academic Press Limited, 1989, 18, 291-429; Progress Cardiovasc. Dis. 1989, 32, 73-97).

A number of studies showed adenosine actions are mediated by two subtypes of receptors which are located on the cell membrane: an high-affinity one, inhibiting the activity of the enzyme adenylate cyclase (A_1 receptor), and a low-affinity one, stimulating the activity of the same enzyme (A_2 receptor). (J. Med. Chem. 1982, 25, 197-207. Physiol. Rev. 1990, 70(3), 761-845. J. Med. Chem. 1992, 35, 407-422). Both receptors are widely spread in the different systems of the organism. In some tissues, however, only one of said receptors is mainly present. For example, A_1 receptor is prevailing at the cardiac level, whereas the A_2 receptor is present mainly at the vascular level and

on platelets.

Therefore, it is clear that compounds capable of interacting selectively with the A_2 receptor could have an interesting pharmacological pattern. In fact, the vasodilating activity, together with the antiaggregating action, can lead to useful therapeutical applications in the treatment of severe cardiovascular pathologies , such as ischemic cardiopathy, hypertension and atherosclerosis.

Moreover, due to the actions on central nervous system, the use of A_2 selective medicaments can be envisaged in the treatment of cerebrovascular ischemia, epilepsy and various emotional disorders, such as anxiety and psychosis.

The prototypical compound having activity on the A_2 receptor is adenosine-5'-N-ethyluronamide or NECA (Mol. Pharmacol., 1986, 25, 331-336). On the other hand, NECA is also active on the A_1 receptor and therefore it lacks selectivity for the adenosine receptors. Being the only available compound having A_2 affinity, NECA was used for pharmacological tests for the receptor binding. Only recently, the use of NECA as a prototypical A_2 agonist has been gradually quit since compounds were found having a certain A_2 receptor selectivity. Said compounds are NECA derivatives which are substituted at the C2-position with phenylamino groups. For example, compound 2-(p-(carboxyethyl)phenylethylamino)-5'-N-ethyluronamide, named CGS 21680 (J. Pharmacol Exp. Ther., 1989, 251, 888-893) has become the reference compound for the pharmacological studies on A_2 receptor.

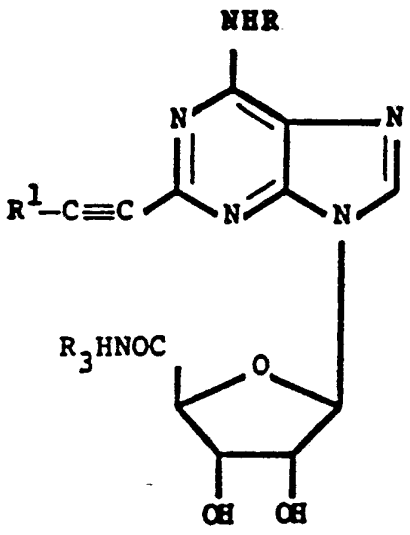
Purine derivatives having a selective A_2 agonist activity are disclosed, for example, in GB-A-2203149, EP-A-0309112, EP-A-0267878, EP-A-0277917, EP-A-0323807.

Particularly, substitution at the 2-position of the purine group has been considered promising to give the desired selectivity (J. Med. Chem. 1992, 35, 407-422).

2-Alkynylpurine derivatives have been disclosed in EP-A-0219876.

Now it has been found that 2-alkynyladenosine derivatives substituted at the ethyne position with aryl, heterocyclic or hydroxyalkyl groups and in which the riboside residue is substituted by the N-alkyl- (or cycloalkyl)-uronamido, have surprisingly advantageous properties compared with the known compounds.

The compounds of the invention have the following general formula:



I

wherein

R is hydrogen, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl C_1-C_3 alkyl;

R_1 has one of the following meanings:

a) phenyl or naphthyl optionally substituted with one to three halogen atoms (chlorine, fluorine and bromine), C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_2-C_6 alkoxycarbonyl, C_2-C_6 alkoxyalkyl, C_1-C_6 alkylthio, thio, CHO, cyanomethyl, nitro, cyano, hydroxy, carboxy, C_2-C_6 acyl, amino, C_1-C_3 monoalkylamino, C_2-C_6 dialkylamino, methylenedioxy; aminocarbonyl;

b) a group of formula $-(CH_2)_m$-Het wherein m is 0 or an integer from 1 to 3 and Het is 5 or 6 membered heterocyclic aromatic or non aromatic ring, optionally benzocondensed, containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur, linked through a carbon atom or through a nitrogen atom;

c) C_3-C_7 cycloalkyl optionally containing insaturations or C_2-C_4 alkenyl;

d) $-(CH_2)_n-\underset{\displaystyle R_4}{\overset{\displaystyle R_5}{\overset{|}{\underset{|}{C}}}}-R_2$

R_2 is hydrogen, methyl or phenyl;

R_5 is hydrogen, C_1-C_6 linear or branched alkyl, C_5-C_6 cycloalkyl or C_3-C_7 cycloalkenyl, phenyl-C_1-C_2-alkyl or R_2 and R_5, taken together, form a 5 or 6-membered carbocyclic ring or R_3 is hydrogen and R_2 and R_4, taken together, form an oxo group or a corresponding acetalic derivative;

when R is different from hydrogen and/or R_3 is different from ethyl, R_1 can also be C_1-C_6 linear or

branched alkyl;

R_4 is OH, NH_2, dialkylamino, halogen, cyano;

n is 0 or 1 to 4;

Within the scope of the definitions given for formula I, the following meanings are preferred:

- for C_1-C_6 alkyl: methyl or ethyl;
- for C_3-C_7 cycloalkyl: cyclopropyl, cyclopentyl, cyclohexyl or cyclohexenyl;
- for phenyl-C_1-C_2 alkyl: benzyl or phenylethyl;
- for C_1-C_6 haloalkyl: trifluoromethyl;
- for halogen: chlorine;
- for C_1-C_6 alkoxy: methoxy or ethoxy;
- for C_1-C_6 haloalkoxy: trifluoromethoxy or difluoromethoxy;
- for C_2-C_6 alkoxycarbonyl: methoxycarbonyl or ethoxycarbonyl;
- for C_2-C_6 alkoxyalkyl: methoxymethyl, methoxyethyl or ethoxymethyl;
- for C_1-C_6 alkylthio: methylthio;
- for C_2-C_6 acyl: acetyl;
- for C_1-C_3 monoalkylamino: methylamino, ethylamino, isopropylamino;
- for C_2-C_6 dialkylamino: dimethylamino, diethylamino, methylethylamino, methylisopropylamino, diisopropylamino;
- for heterocyclic aromatic or non aromatic ring containing 1 to 3 N, S, O atoms: pyridyl, thienyl, furyl, imidazolyl, thiazolyl, pyrazolyl, triazolyl.
- for acetalic derivative: diethylacetal.

Preferred compounds of formula I are:

1. Compounds in which R is hydrogen;

2. Compounds in which R is C_3-C_7 cycloalkyl; (R) or (S)-phenylisopropyl;

3. Compounds in which R_1 is phenyl or naphthyl optionally monosubstituted with one of the substituents in point a);

4. Compounds in which R_1 is phenyl optionally substituted with one of the substituents in point a);

5. Compounds in which R_1 is phenyl, 2-, 3- or 4-nitrophenyl, 2-, 3- or 4-aminophenyl, 2-, 3- or 4-methylphenyl, 2-, 3- or 4-acetylphenyl, 4-cyanomethylphenyl, 4-formylphenyl, 2-, 3- or 4-trifluoromethylphenyl, 2-, 3- or 4-fluorophenyl, 2-, 3- or 4-methoxyphenyl, 2-, 3- or 4-carbomethoxyphenyl, 2-, 3- or 4-carbethoxyphenyl;

6. Compounds in which R_1 is cyclohexyl or 1-cyclohexenyl;

7. Compounds in which R_1 is 2-thienyl, 2-pyridyl, 4-pyridyl, 4-pyrazolyl, 2-furyl, 3-furyl, 2-thiazolyl, 1-imidazolyl-methyl, 1-triazolylmethyl.

8. Compounds in which R_1 is $-(CH_2)_n-\underset{\displaystyle R_4}{\overset{\displaystyle R_5}{\overset{|}{\underset{|}{C}}}}-R_2$ group

wherein R_2 is hydrogen or methyl, R_5 is hydrogen or C_1-C_6 alkyl, R_4 is hydroxy or amino.

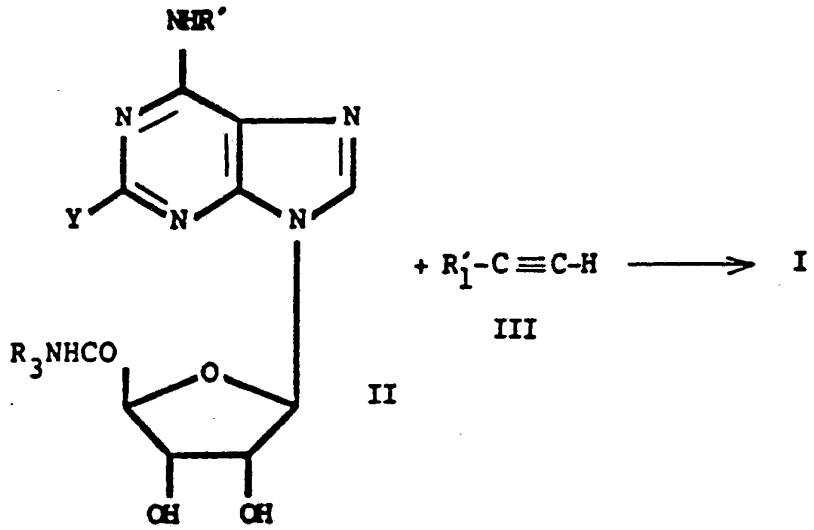
9. Compounds in which R is hydrogen and R_1 has the meanings according to points 2-7 above.

The claimed compounds can be used as anhydrous bases, solvates or pharmaceutically acceptable acid salts.

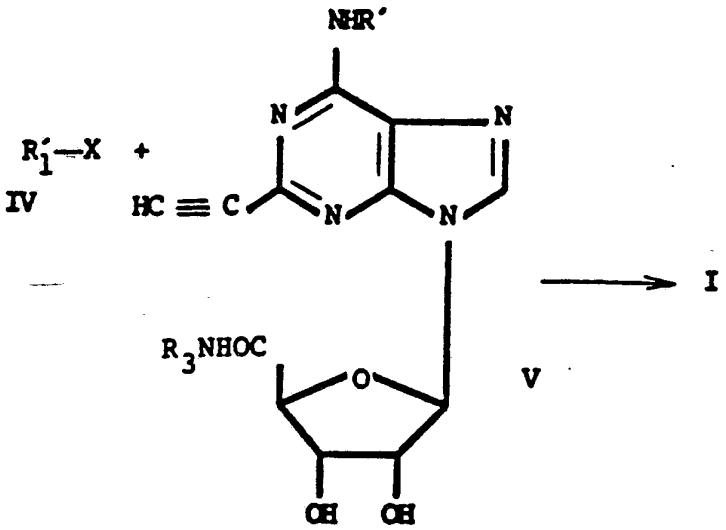
Compounds I can be prepared according to the

following general schemes:

Scheme I



Scheme II



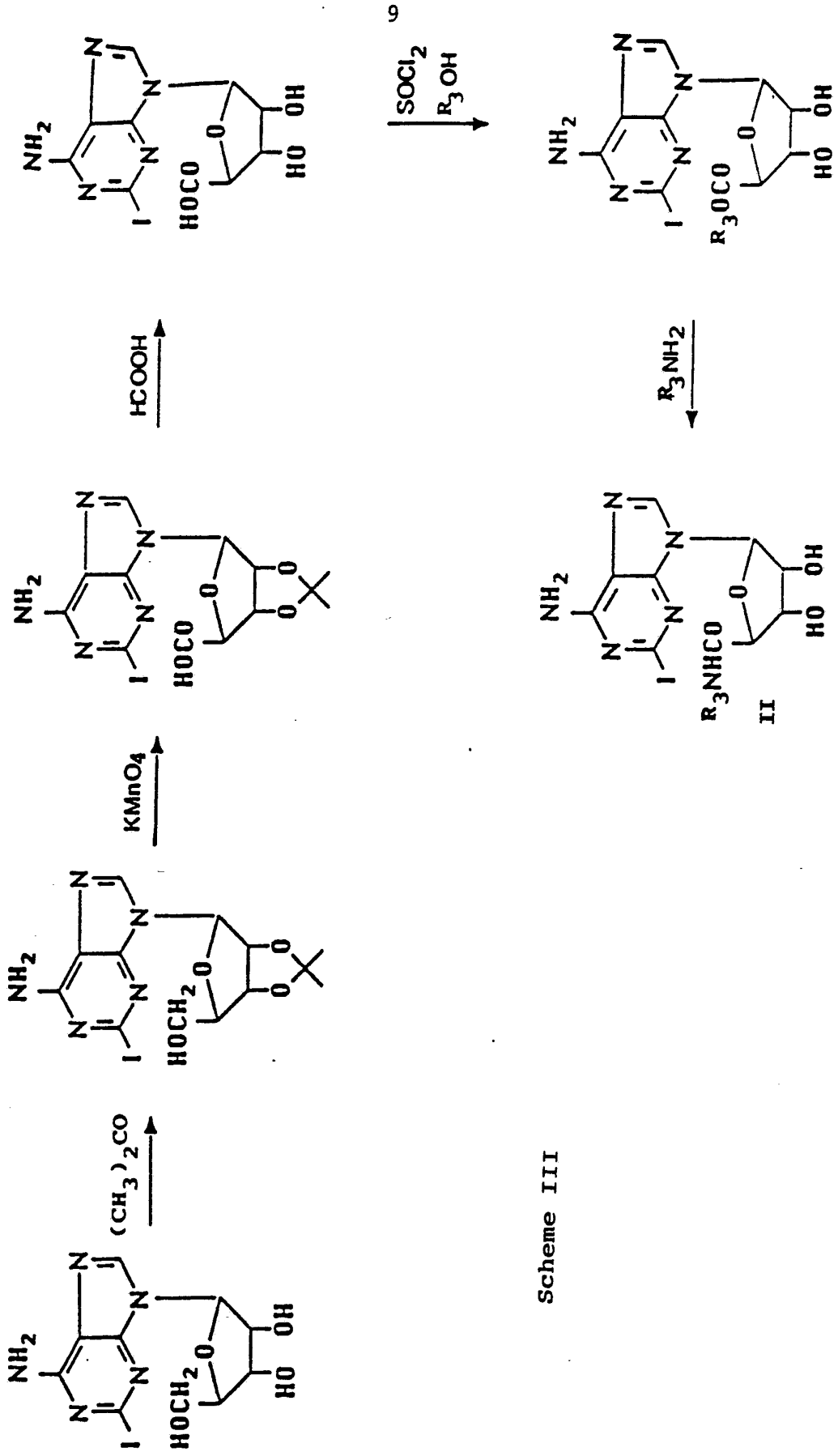
In schemes I and II, R' and R'_1 have the same meanings as R and R_1 or they are groups which can be converted into R and R_1, respectively, for example by removing any protecting groups which can be present in R' and R'_1 compatible with the reaction conditions; Y is Br or I and X is chlorine, bromine or iodine.

Preferably Y is iodine and X is bromine or iodine.

The reactions reported in schemes I and II are carried out in the presence of catalysts (for example: bis(triphenylphosphine) palladium dichloride and a cuprous halide) and of a suitable acid-binding agent, such as an organic base (for example: triethylamine, diisopropylethylamine or pyridine).

As the solvent, a substituted amide (such as dimethylformamide), an ether (such as dioxane or tetrahydrofuran), acetonitrile or optionally a mixture of two or more of said solvents, are preferably used.

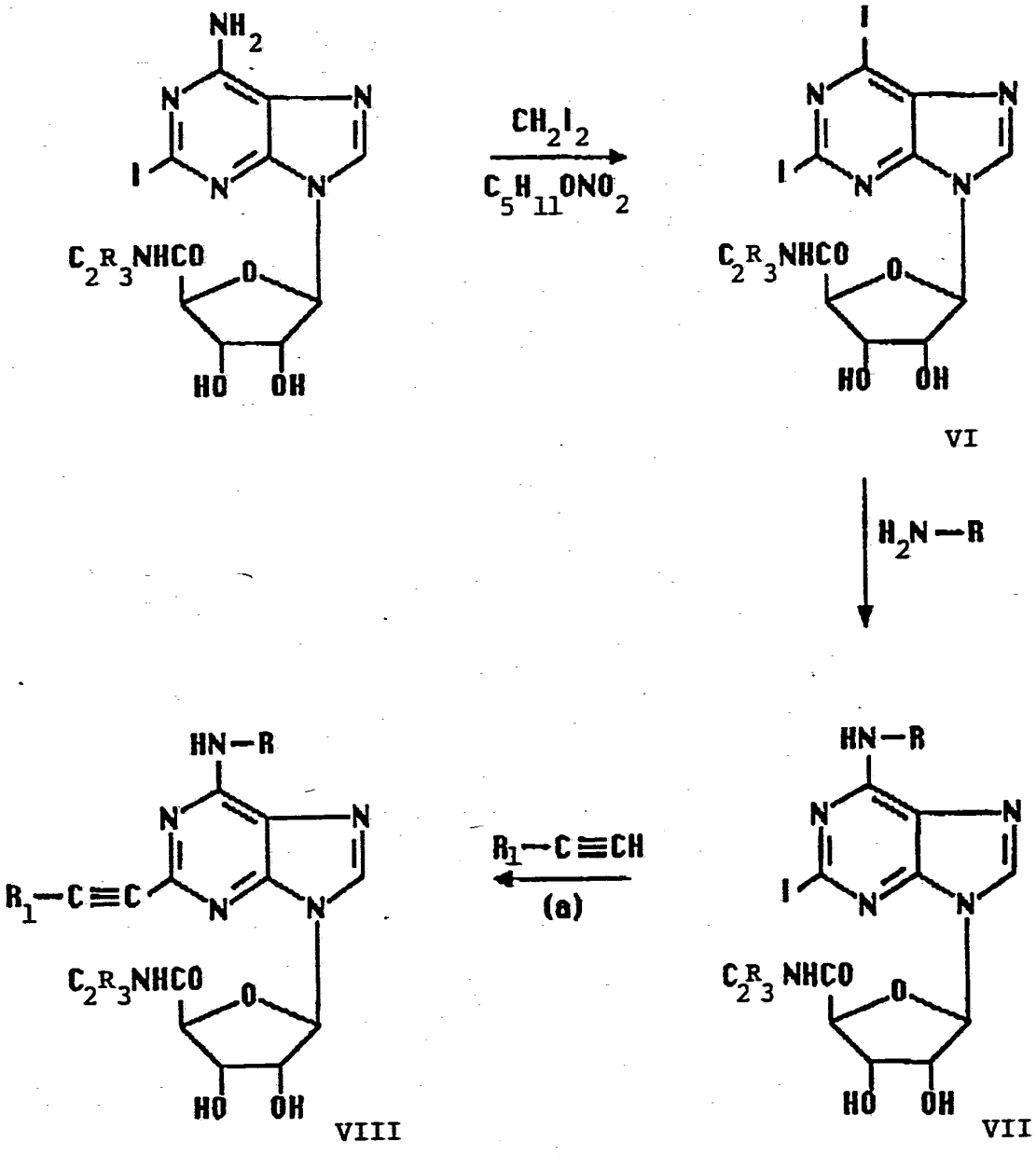
The compounds of formula II, in which Y is iodine and R' is hydrogen, can be prepared from 2-iodioadenosine (Synthesis, 1982, 670-672) according to the following scheme III


NH2
HOCO
HO OH
HCOOH
SOCl2
R3OH
R3OCO
R3NH2
R3NHCO
II
KMnO4
HOCH2
(CH3)2CO

Scheme III

The compounds of formula II, in which Y is iodine and R' is different from hydrogen can be prepared according to the following Scheme IV

Scheme IV



(a) = $(Ph_3P)PdCl_2$; CuI ; Et_3N

In the above scheme IV, R, R_1 and R_3 are as above defined.

The compounds of formula VI are novel and they are a further object of the invention, as intermediates.

The compounds of formula V are prepared by reaction of compounds II with an acetylene derivative, for example 1-trimethylsilylethynyle, under the conditions reported for the reaction between compounds II and III. Compounds V are novel and they are a further object of the invention, as intermediates.

Compounds III and IV are known or they can be prepared according to well-known methods.

Compounds I have a strong A_2 agonist selectivity and therefore they are useful for the treatment of cardiovascular pathologies such as cardiac ischemia, hypertension and atherosclerosis and of diseases of central nervous system such as cerebrovascular ischemia, epilepsy and emotional disorders (anxiety and psychosis).

Pharmacological activity

The pharmacological properties of the disclosed compounds can be shown in the most suitable experimental models both in vitro and in vivo.

Adenosine A_2 receptor affinity was tested by means of receptor binding techniques on rat (Wistar strain) brain striatum, which is a tissue rich in A_2 receptors. Compound ^{3}H-CGS 21680 (J. Pharm. Exp. Ther. 1989, 251, 888-893) was used as the radioligand.

The A_1 receptor affinity was tested with receptor binding techniques on rat (Wistar strain) cerebellar cortex membranes, which are tissues rich in A_1 recep-

tors. ^{3}H-Cyclohexyl-adenosine, ^{3}H-CHA (Proc. Natl. Acad. Sci. - USA - 1980, 77, 5547-5551) was used as the radioligand. The affinity for the A_1 or A_2 receptor shown by each compound was compared to evaluate selectivity for the A_2 receptor. A number of experimental proofs evidence a marked relationship between the affinity found with binding techniques in brain tissues and the physiological effects modulated by adenosine receptors.

In order to evaluate the functional response of specific tissues to the disclosed compounds, the isolated organs models were used. Particularly, the vasodilatation response, which is modulated by A_2 receptors, was studied to the tested compounds (Eur. J. Pharmacol 1990, 176, 207-212) on rat aorta in which a contraction had been induced by a prostaglandin compound ($PGF_{2\alpha}$). Any chronotropic negative effects of the various compounds (Br. J. Pharmacol 1983, 78, 207-212) were tested on rat isolated heart atria, whose rate is known to be modulated by A_1 receptors. From the comparison of the activities shown by each compound for the functional responses of the A_2 type (vasodilatation) or the A_1 type (reduction in the heart rate), the potential anti-ischemic and antihypertensive activities of the tested compounds can be evaluated, as well as the absence of undesired effects on the heart rate.

In order to evaluate the potential anti-atherosclerosis and anti-ischemic activities, the inhibiting effect of various compounds on platelet aggregation induced by aggregation agents such as adenosine diphosphate (ADP) (J. Physiol. 1963, 168, 178-195) was

studied. The test is particularly important as only the A_2 receptor is present on the platelet cell membrane.

The in vivo activity was evaluated in Swiss mice and spontaneously hypertensive rats (SHR). The behaviour response to a treatment with various doses of the tested compounds administered parenterally was evaluated. To test the antiepileptic action, the property of the novel compounds to antagonize the convulsions induced by pentylenetetrazole was evaluated in the mouse.

The antihypertensive activity was tested measuring the systolic arterial pressure by means of the "tail-cuff" technique (Arch. Int. Pharmacodyn., 1987, 286, 546-254) in SHR rats conditioned to the experimental environment.

The tested compounds were administered parenterally at increasing doses and arterial pressure and heart rate were measured at various times from the treatment.

The compounds of formula I showed a marked A_2 affinity with Ki ranging from 7 to 200 nM. The A_2 selectivity for some compounds is higher than 100 and anyhow it turned out to be markedly higher than that of the prototypical compound NECA. In the platelet aggregation test, said compounds proved to be effective anti-platelet aggregation agents, with IC_{50}s of 0,1-10 µM. The vasodilatation activity is clear, as evidenced by ED_{50}s of 0,1-10 µM, whereas the same concentrations did not change the heart rate of isolated atria. In the in vivo models, the tested compounds showed a depressing activity on central nervous system, they antagoni-

zed the convulsions induced by pentylenetetrazole and reduced the arterial pressure without changing significantly the heart rate. The compounds turned out to be active at doses from 0.001 to 3 mg/kg intraperitoneally.

For the envisaged therapeutical uses, compounds I will be formulated as suitable pharmaceutical compositions, which can be administered, for example, by the oral or parenteral routes, using known techniques and excipients, as described for example in Remington's Pharmaceutical Sciences Handbook, Mack Pub. Co., NY, USA, XVII ed. The daily dosage will depend, of course, on many factors (severity of the pathology to treat, patient conditions, toxicology and pharmacokinetic of the selected compound) but generally it will range from 0,01 to 10 mg/kg of body weight, preferably from 0,1 to 1 mg/kg, optionally subdivided in more administrations. Examples of pharmaceutical compositions comprise capsules, tablets, solutions, syrups, vials, controlled-release forms and the like.

The following examples illustrate the invention.

EXAMPLE 1

N-ethyl-1'-deoxy-1'-(6-amino-2-iodo-9H-purin-9-yl)-ß-D-ribofuranuronamide.

a) A solution of 2 g (5.08 mmoles) of 2-iodoadenosine in 100 ml of acetone was added with 9.6 g of p-toluenesulfonic acid. The reaction mixture was stirred at room temperature for 1 h, then, after addition of 15 g of $NaHCO_3$, it was stirred again for 3 h. The solid was removed and washed 2 times with ethyl acetate and the filtrate was concentrated to dryness. The residue was

flash chromatographed on a silica gel column eluting with $CHCl_3$-MeOH (99:1) to give 1.62 g (74%) of 6-amino-2-iodo-9-(2',3'-O-isopropylidene-ß-D-ribofuranosyl)-9H-purine as a solid:

m.p. 185-187°C;

^1H NMR (Me_2SO-d_6) δ 1.33 and 1.54 (s, 3H each, $C(\underline{CH_3})_2$, 3.53 (m, 2H, CH_2-5'), 4.19 (m, 1H, H-4'), 5.07 (t, 1H, OH), 4.93 (m, 1H, H-3'), 5.27 (m, 1H, H-2'), 6.05 (d, J=2.5 Hz, 1H, H-1'), 7.76 (s, 2H, NH_2), 8.28 (s, 1H, H-8). Anal. ($C_{13}H_{16}IN_5O_4$) C, H, N.

b) A stirred solution of 1.6 g (3.7 mmoles) of the product obtained in a) in 200 ml of H_2O was added with 0.60 g of KOH and, dropwise, with a solution of 1.70 g (10.8 mmoles) of $KMnO_4$ in 50 ml of H_2O. The mixture was left aside in the dark at room temperature for 20 h. The reaction mixture was cooled to 5-10°C and then decolorized with a solution of 4 ml of 30% H_2O_2 in 16 ml of water, keeping the temperature under 10°C with an ice-salt bath. The mixture was filtered through Celite and the filtrate was concentrated under vacuum to about 15 ml and then acidified to pH 4 con 2N HCl. The resulting precipitate was filtered, and subsequently washed with water, acetone and ether to give 1.25 g (76%) of 1'-deoxy-1'-(6-amino-2-iodo-9H-purin-9-yl)-2',3'-O-isopropylidene-ß-D-ribofuranuronic acid as a white solid:

m.p. 187-190°C;

IR ν max 1590, 1640 cm^{-1} (COOH); ^1H NMR (Me_2SO-d_6) δ 1.33 and 1.49 (s, 3H each, $C(\underline{CH_3})_2$, 4.64 (s, 1H, H-4'), 5.35 (d, $J_{3',2'}$=5.6 Hz, 1H, H-3'), 5.41 (d, $J_{2',3'}$=5.6 Hz, 1H, H-2'), 6.23 (s, 1H, H-1'), 7.53 (s, 1H, COOH), 7.67 (s, 2H, NH_2), 8.17 (s, 1H, H-8). Anal.

($C_{13}H_{14}IN_5O_5$) C, H, N.

c) A solution of 1.72 g (3.85 mmoles) of the product obtained in b) in 80 ml of 50% formic acid was stirred at 80°C for 1.5 h. The reaction mixture was evaporated under vacuum and the residue was dissolved in water, and the solution was evaporated. This process was repeated several times, until there was no more odor of formic acid in the residue. Recrystallization from water yielded 1.33 g (85%) of 1'-deoxy-1'-(6-amino-2-iodo-9H-purin-9-yl)-ß-D-ribofuranuronic acid as a white solid:

m.p. 217-220°C (dec.)

^1H NMR (Me_2SO-d_6) δ 4.28 (m, 1H, H-3'), 4.41 (d, J=2.1 Hz, 1H, H-4'), 4.81 (m, 1H, H-2'), 5.95 (d, J=6.7 Hz, 1H, H-1'), 7.78 (s, 2H, NH_2), 8.38 (s, 1H, H-8), 12.98 (br s, 1H, COOH). Anal. ($C_{10}H_{10}IN_5O_5$) C, H, N.

d) A cooled (5°C) and stirred solution of 1.29 g (3.17 mmoles) of the product obtained in c) in 150 ml of absolute ethanol was added dropwise with 1.15 ml of ice-cooled $SOCl_2$. The mixture was stirred at room temperature overnight and then brought to pH 8 with saturated aqueous sodium bicarbonate. The mixture was filtered and the filtrate was concentrated under vacuum. The recrystallization of the residue from water-ethanol (1:1) gave 900 mg (65%) of ethyl 1'-deoxy-1'-(6-amino-2-iodo-9H-purin-9-yl)-ß-D-ribofuranuronate as a white solid:

m.p. 221-223°C (dec.)

IR ν max 1728 cm^{-1} (COOEt); ^1H NMR (Me_2SO-D_6) δ 1.21 (t, 3H, $-CH_2\underline{CH_3}$), 4.18 (q, 2H, $-\underline{CH_2}CH_3$), 4.34 (m, 1H, H-3'), 4.47 (s, 1H, H-4'), 4.58 (m, 1H, H-2'), 5.96 (d,

J=6.7 Hz, 1H, H-1'), 7.74 (s, 2H, NH_2), 8.33 (s, 1H, H-8). Anal. ($C_{12}H_{14}IN_5O_5$) C, H, N.

e) A mixture of 620 mg of the product obtained in the step d) and 18 ml of dry ethylamine was stirred at -20°C for 3 h and then at room temperature overnight. The reaction mixture was diluted with absolute ethanol and the precipitated product was filtered and washed with dry ether to give 530 mg (85%) of N-ethyl-1'-deoxy-1'-(6-amino-2-iodo-9H-purin-9-yl)-ß-D-ribofuranuronamide as a pure solid:

m.p. 232-234°C

IR ν max 1637, 1560 cm^{-1} (C=O, amide); ^1H NMR (Me_2SO-d_6) δ 1.06 (t, 3H, $-CH_2\underline{CH_3}$), 3.28 (m, 2H, $-\underline{CH_2}CH_3$), 4.16 (m, 1H, H-3'), 4.31 (d, J=2,1 Hz, 1H, H-4'), 4.58 (m, 1H, H-2'), 5.91 (d, 1H, J=7.3 Hz, H-1'), 7.79 (s, 2H, NH_2), 8.15 (t, 1H, NH), 8.40 (s, 1H, H-8). Anal. ($C_{12}H_{15}IN_6O_4$) C, H, N.

EXAMPLE 2

A solution of 250 mg (0.58 mmole) of the product of Example 1 in 10 ml of dry acetonitrile, 5 ml of DMF and 2.5 ml of triethylamine under nitrogen was added with 8.1 mg (0.0115 mmole) of bis(triphenylphosphine)palladium dichloride and 0.58 mg (0.003 mmole) of cuprous iodide. The mixture was added with 2.9 mmoles of phenylacetylene and the reaction mixture was stirred under nitrogen atmosphere at room temperature for 2 h. The solvent was evaporated off under vacuum and the residue was chromatographed on a silica gel column, eluting with a chloroform-benzene-methanol 78:10:12 mixture, to give N-ethyl-1'-deoxy-1'-(6-amino-2-phenylethynyl-9H-purin-9-yl)-ß-D-ribofuranuronamide

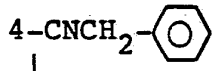
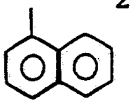
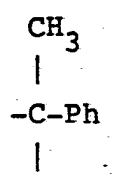
(yield: 60%):

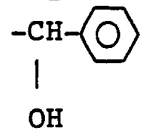
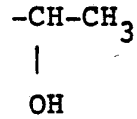
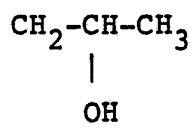
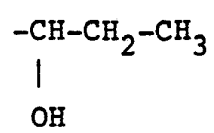
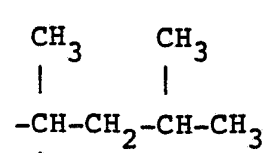
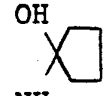
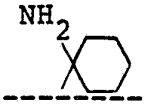
m.p. 175-178°C (dec)

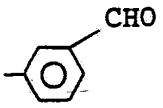
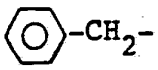
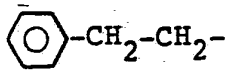
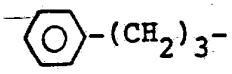
^{1}H NMR (Me_2SO-d_6) δ 1.02 (t, 3H, $-CH_2\underline{CH_3}$), 3.28 (m, 2H, $-\underline{CH_2}CH_3$), 4.15 (m, 1H, H-3'), 4.31 (d, J=1.2 Hz, 1H, H-4'), 4.62 (m, 1H, H-2'), 5.97 (d, 1H, J=7.5 Hz, H-1'), 7.58 (d, J=7.8 Hz, 2H, H-Ph), 7.46 (m, 2H, H-Ph), 7.66 (s, 2H, NH_2), 8.49 (s, 1H, H-8), 8.60 (t, 1H, NH). Anal. ($C_{20}H_{20}N_6O_4 \cdot H_2O$) C, H, N.

EXAMPLES 3-35

By the same method of Example 2, the following compounds I, wherein R_3 is ethyl and R is hydrogen, were prepared.

Ex.	R_1	m.p. (°C)	Yield (%)	Reaction time (h)
3	4-NO_2-Ph	180-183 (dec)	80	4
4	4-NH_2-Ph	225-228 (dec)	60	4
5	4-NH_2-CO-Ph	240-243 (dec)	55	16
6	4-CH_3-Ph	210-213 (dec)	50	3
7	4-CHO-Ph	210-213 (dec)	80	6
8	4-CH_3-CO-Ph	185-188 (dec)	60	20
9	4-$CNCH_2$-	230-232 (dec)	55	20
10		225-228 (dec)	45	20
11		203-205 (dec)	75	20
12	$HO(CH_2)_4$	245-247	69	24

Ex.	R_1	m.p. (°C)	Yield (%)	Reaction time (h)
13		200-203 (dec)	68	6
14		210-213 (dec)	75	3
15	$(CH_3)_3Si$	208-211 (dec)	95	16
16	$(CH_2)_3Cl$	156-158	52	20
17	$(CH_2)_3CN$	131-134	65	48
18	CH_2OH	173-175 (dec)	52	3
19		150-152 (dec)	67	20
20	CH_2CH_2OH	245-248 (dec)	70	20
21		211-214 (dec)	52	20
22	$(CH_2)_3OH$	230-232	57	20
23		232-234 (dec)	39	5
24		148-150 (dec)	37	5
25		135-137	41	5
26		153-155	30	20
27		211-213	76	30

Ex.	R_1	m.p. (°C)	Yield (%)	Reaction time (h)
28	CH_2NH_2	-	52	36
29	$CH_2CH_2N(CH_3)_2$	227-230 (dec)	61	20
30	$-C(CH_3)=CH_2$	175-177 (dec)	65	20
31		164-165 (dec)	50	36
32	$-CH(OC_2H_5)_2$	184-187	56	48
33		124-126	53	4
34		143-145	53	16
35		128-130	53	16

Anal. (CHN) and ^{1}H-NMR in agreement with the given formulas.

EXAMPLE 36

a) N-ethyl-1'-deoxy-1'-[6-amino-2-ethynyl-9H-purin-9-yl]-ß-D-ribofuranuronamide.

1.6 mg (3.96 mmoles) of the product obtained in Example 15 in 30 ml of methanol were added with 0.32 g of KOH in 10 ml of methanol. The reaction mixture was stirred at room temperature for 1 h

and then the solvent was removed under vacuum. The residue was partitioned between ethyl acetate and water and the combined organic layers were dried (Na_2SO_4) and evaporated to give 1.0 g (81%) of the title compound as a chromatographically pure solid:

m.p.: 245-248°C (dec)

^1H NMR (Me_2SO-d_6) δ 1.04 (t, 3H, $-CH_2\underline{CH_3}$), 3.26 (m, 2H, $-\underline{CH_2}CH_3$), 4.10 (s, 1H, -C≡CH), 4.12 (m, 1H, H-3'), 4.29 (d, J=1.5, 1H, H-4'), 4.55 (m, 1H, H-2'), 5.92 (d, 1H, J=7.5 Hz, H-1'), 7.62 (s, 2H, NH_2), 8.46 (s, 1H, H-8), 8.63 (t, 1H, NH). Anal. ($C_{14}H_{16}N_6O_4 \cdot H_2O$) C, H, N.

b) N-ethyl-1'-deoxy-1'-{6-amino-2-(4-trifluoromethyl)phenyl]ethynyl-9h-purin-9-yl}-ß-D-ribofuranuronamide.

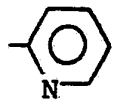
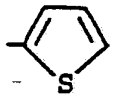
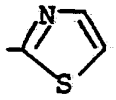
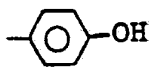
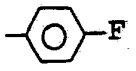
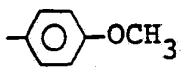
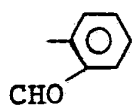
A solution of 200 mg (0.66 mmole) of the compound of step a) in 10 ml of dry acetonitrile, 5 ml of DMF and 2.6 ml of triethylamine under nitrogen atmosphere, was added with 9.24 mg (0.013 mmole) of bis(triphenylphosphine)palladium dichloride and 0.66 mg (0.0035 mmole) of cuprous iodide. The mixture was added with 3.3 mmoles of 4-trifluoromethyl-iodobenzene and the reaction mixture was stirred under nitrogen atmosphere for 1 h at 50°C. The solvent was evaporated under vacuum and the residue was chromatographed on a silica gel column, eluting with chloroform-benzene-methanol (80:10:10). The title product was obtained in a 65% yield.

m.p.: 224-227°C (dec)

^{1}H NMR (Me_2SO-d_6) δ 1.01 (t, 3H, $-CH_2\underline{CH_3}$), 3.26 (m, 2H, $-\underline{CH_2}CH_3$), 4.14 (m, 1H, H-3'), 4.31 (s, 1H, H-4'), 4.61 (m, 1H, H-2'), 5.97 (d, 1H, J=7.5 Hz, H-1'), 7.71 (s, 2H, NH_2), 7.81 (s, 4H, H-Ph), 8.52 (s, 1H, H-8), 8.58 (t, 1H, NH). Anal. ($C_{21}H_{19}F_3N_6O_4 \cdot H_2O$) C, H, N.

EXAMPLES 37-43

By the same method of Example 36, the following compounds I, wherein R is hydrogen and R_3 is ethyl, were prepared.

Ex.	R_1	m.p. (°C)	Yield (%)	Reaction time (h)
37		213-215 (dec)	88	20
38		245-248 (dec)	82	16
39		210-213 (dec)	67	5
40		200-202	63	16
41		184-185 (dec)	55	16
42		151-154 (dec)	49	3
43		189-191	23	5

EXAMPLES 44-46

By reacting the compound of Example 1d with an amine selected from:

- cyclopentylamine;
- benzylamine;
- aniline;

at room temperature for 20 hours, the following compounds as chromatographically pure oils were obtained after the usual work-up (solution concentrated to dryness and the residue chromatographed on a silica gel column eluting with a suitable mixture of solvents):

N-cyclopentyl-1'-deoxy-1'-(6-amino-2-iodo-9H-purin-9-yl)-ß-D-ribofuranuronamide (IIa)

^{1}H NMR (Me_2SO-d_6) δ 1.33-1.98 (m, 8H, H-cyclopentyl), 4.06 (m, 1H, H-cyclopentyl), 4.19 (m, 1H, H-3'), 4.35 (d, 1H, J = 2.4 Hz, H-4'), 4.58 (m, 1H, H-2'), 5.93 (d, 1H, J = 6.4 Hz, H-1'), 7.77 (s, 2H, NH_2), 8.08 (d, 1H, J = 7.5 Hz, NH), 8.50 (s, 1H, H-8). Anal. ($C_{15}H_{19}IH_6O_4$) C, H, N.

N-benzyl-1'-deoxy-1'-(6-amino-2-iodo-9H-purin-9-yl)-ß-D-ribofuranuronamide (IIb)

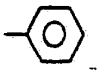
^{1}H NMR (Me_2SO-d_6) δ 4.22 (m, 1H, H-3'), 4.42 (d, 1H, J = 1.5 Hz, H-4'), 4.46 (m, 2H, CH_2), 4.59 (m, 1H, H-2'), 5.94 (d, 1H, J = 7.2 Hz, H-1'), 7.28 (m, 5H, H-Ph), 7.81 (s, 2H, NH_2), 8.40 (s, 1H, H-8), 8.74 (t, 1H, HN). Anal. ($C_{17}H_{17}IN_6O_4$) C, H, N.

N-phenyl-1'-deoxy-1'-(6-amino-2-iodo-9H-purin-9-yl)-ß-D-ribofuranuronamide (IIc)

^{1}H NMR (Me_2SO-d_6) δ 4.35 (m, 1H, H-3'), 4.58 (d, J = 1.5 Hz, 1H, H-4'), 4.66 (m, 1H, H-2'), 6.01 (d, 1H, J =

6.6 Hz, H-1'), 7.11 (t, 1H, H-Ph), 7.34 (t, 2H, H-Ph), 7.65 (d, 2H, H-Ph), 7.78 (s, 2H, NH_2), 8.52 (s, 1H, H-8), 10.16 (s, 1H, NH). Anal. ($C_{16}H_{15}IN_6O_4$) C, H, N.

Said compounds were reacted with 1-hexyne according to the procedure of Example 2 to give the compounds of formula I reported in the following Table.

Ex.	R	R_1	R_3	m.p. (°C)	Yield (%)	Reaction time (h)
44	H	$-(CH_2)_3-CH_3$		145-147	48	40
45	H	$-(CH_2)_3-CH_3$	$-CH_2-$	128-130	37	40
46	H	$-(CH_2)_3-CH_3$		-	35	40

Anal. (CHN) and ^{1}H-NMR in agreement with the given formulas.

EXAMPLE 47

a) N-ethyl-1'-deoxy-1'-(2,6-diiodo-9H-purin-9-yl)-ß-D-ribofuranuronamide (VI)

To 0.5 g (1.16 mmol) in 10 ml of DMF was added 1.7 ml of isopentyl nitrite and 5.6 ml of diiodometane and the mixture was heated at 85°C under a N_2 atmosphere for 2 h. The solvent was removed under pressure (oil pomp) and the residue was chromatographed on a flash silica gel column eluting with a gradient from $CHCl_3$ to $CHCl_3$-MeOH (98:2) to give 285 mg (45%) of the title compound as a chromatographically pure oil.

^{1}H NMR (Me_2SO-d_6) δ 1.04 (t, 3H, $CH_2\underline{CH_3}$), 3.19 (m, 2H, $\underline{CH_2}CH_3$), 4.28 (m, 1H, H-3'), 4.36 (s, 1H, H-4'), 4.70 (m, 1H, H-2'), 6.03 (d, 1H, J = 6.4 Hz, H-1'), 8.15 (t, 1H, NH), 8.98 (s, 1H, H-8). Anal. ($C_{12}H_{13}I_2N_5O_4$) C, H, N.

b) N-ethyl-1'-deoxy-1'-(6-cyclopentylamino-2-iodo-9H-purin-9-yl)-ß-D-ribofuranuronamide (VII)

To 240 mg (0.44 mmol) of N-ethyl-1'-deoxy-1'-(2,6-diiodo-9H-purin-9-yl)-ß-D-ribofuranuronamide was added 10 ml of cyclopentylamine and the mixture was stirred at room temperature for 4 h. The solution was concentrated to dryness and the residue was chromatographed on a silica gel column eluting with $CHCl_3$-MeOH (96:4) to give 160 mg (72%) of the title compound as a chromatographically pure oil.

^{1}H NMR (Me_2SO-d_6) δ 1.07 (t, 3H, $CH_2\underline{CH_3}$), 1.48-2.08 (m, 8H, H-cyclopentyl), 3.23 (m, 2H, $\underline{CH_2}CH_3$), 4.18 (m, 1H, H-3'), 4.32 (d, 1H, J = 1.7 Hz, H-4'), 4.44 (m, 1H, H-cyclopentyl), 4.60 (m, 1H, H-2'), 5.92 (d, 1H, J = 7.2 Hz, H-1'), 8.16 (t, 1H, $\underline{NH}CH_2$), 8,29 (d, 1H, J = 7.7 Hz, NH), 8.41 (s, 1H, H-8). Anal. ($C_{17}H_{23}IN_6O_4$) C, H, N.

c) N-ethyl-1'-deoxy-1'-[6-cyclopentylamino-2-(1-hexyn-1-yl)-9H-purin-9-yl]-ß-D-ribofuranuronamide (VIII)

The title compound was prepared according to Example 2.

Reaction time: 16 h.

Chromatographical system: chloroform-methanol (95:5)

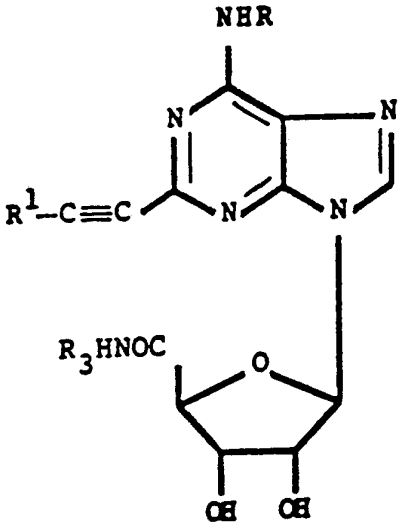
Yield: 57%

m.p.: 120-122 °C.

^{1}H NMR (Me_2SO-d_6) δ 0.92 (t, 3H, $CH_2\underline{CH_3}$), 1.08 (t, 3H, $NCH_2\underline{CH_3}$), 1.35-2.07 (m, 12H, H-cyclopentyl and $\underline{CH_2CH_2}$), 2.44 (m, 2H, $\underline{CH_2}C = C$), 3.31 (m, 2H, $N\underline{CH_2}CH_3$), 4.12 (m, 1H, H-3'), 4.31 (s, 1H, H-4'), 4.60 (m, 2H, H-2' and H-cyclopentyl), 5.94 (d, 1H, J = 7.7 Hz, H-1'), 8.03 (d, 1H, NH), 8.43 (s, 1H, H-8), 8.76 (t, 1H, $\underline{NH}CH_2$). Anal. ($C_{23}H_{32}N_6O_4 \cdot H_2O$) C, H, N.

CLAIMS

1. Compounds of formula I



I

wherein

R is hydrogen, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl C_1-C_3 alkyl;

R_1 has one of the following meanings:

a) phenyl or naphthyl optionally substituted with one to three halogen atoms (chlorine, fluorine and bromine), C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_2-C_6 alkoxycarbonyl, C_2-C_6 alkoxyalkyl, C_1-C_6 alkylthio, thio, CHO, cyanomethyl, nitro, cyano, hydroxy, carboxy, C_2-C_6 acyl, amino, C_1-C_3 monoalkylamino, C_2-C_6 dialkylamino, methylenedioxy; aminocarbonyl;

b) a group of formula $-(CH_2)_m$-Het wherein m is 0 or an integer from 1 to 3 and Het is 5 or 6 membered heterocyclic aromatic or non aromatic ring, optionally benzocondensed, containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur, linked through a carbon atom or through a

nitrogen atom;

c) C_3-C_7 cycloalkyl optionally containing insaturations or C_2-C_4 alkenyl;

d) $-(CH_2)_n-\underset{\displaystyle R_4}{\overset{\displaystyle R_5}{\overset{|}{C}}}-R_2$

R_2 is hydrogen, methyl or phenyl;

R_5 is hydrogen, C_1-C_6 linear or branched alkyl, C_5-C_6 cycloalkyl or C_3-C_7 cycloalkenyl, phenyl-C_1-C_2-alkyl or R_2 and R_5, taken together, form a 5 or 6-membered carbocyclic ring or R_5 is hydrogen and R_2 and R_4, taken together, form an oxo group or a corresponding acetalic derivative;

when R is different from hydrogen and/or R_3 is different from ethyl, R_1 can also be C_1-C_6 linear or branched alkyl;

R_4 is OH, NH_2, dialkylamino halogen, cyano;

n is 0 or 1 to 4.

2. Compounds according to claim 1 in which R is hydrogen or cyclopentyl.

3. Compounds according to claim 1 or 2 in which R_1 is phenyl, 2-, 3- or 4-nitrophenyl, 2-, 3- or 4-aminophenyl, 2-, 3- or 4-methylphenyl, 2-, 3- or 4-acetylphenyl, 4-cyanomethylphenyl, 4-formylphenyl, 2-, 3- or 4-trifluoromethylphenyl, 2-, 3- or 4-fluorophenyl, 2-, 3- or 4-methoxyphenyl, 2-, 3- or 4-carbomethoxyphenyl, 2-, 3- or 4-carbethoxyphenyl, cyclohexyl or 1-cyclohexenyl, hydroxyphenyl.

4. Compounds according to claim 1 or 2 in which R_1 is 2-thienyl, 2-pyridyl, 4-pyridyl, 4-pyrazolyl, 2-furyl,

3-furyl, 2-thiazolyl.

5. Compounds according to claim 1 or 2 in which R_1 is a group

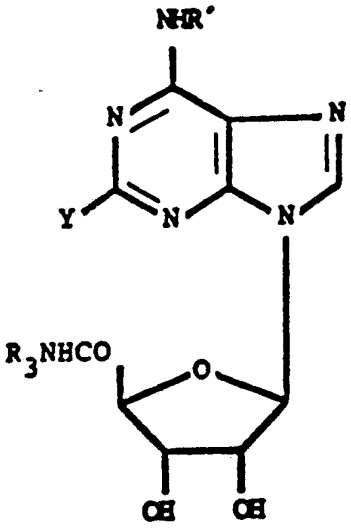
$-(CH_2)_n-\underset{\underset{OH}{|}}{\overset{\overset{R_5}{|}}{C}}-R_2$ wherein R_2 and R_5 are hydrogen and n is an integer 1 to 4 or

R_2 is phenyl, R_5 is hydrogen and n is zero.

6. A compound according to anyone of the preceding claims, wherein R_3 is cyclopentyl, benzyl or phenyl.

7. A compound according to claim 6, wherein R_1 is n-butyl.

8. A process for the preparation of compounds of formula I which comprises the reaction of a compound of formula II



II

wherein Y is Br or I and R' has the same meanings as R or is a group which can be converted into R, with a compound of formula III

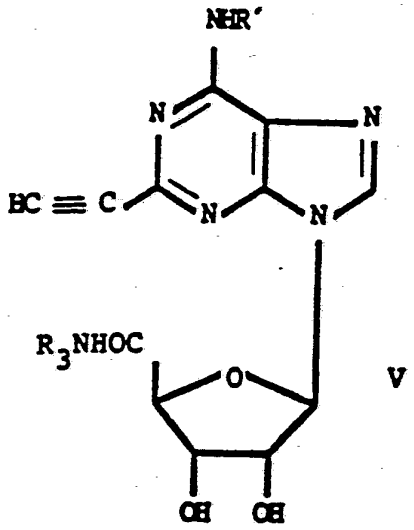
R'_1-C≡≡C-H III

wherein R'_1 has the same meanings as R_1 or is a group which can be converted into R_1.

9. A process for the preparation of compounds of formula I which comprises the reaction of a compound of formula IV

R'_1--X IV

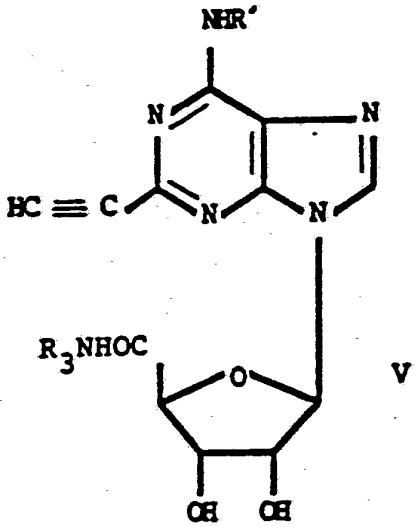
wherein R'_1 is as defined in claim 8, with a compound of formula V



V

wherein R' is as defined in the claim 8.

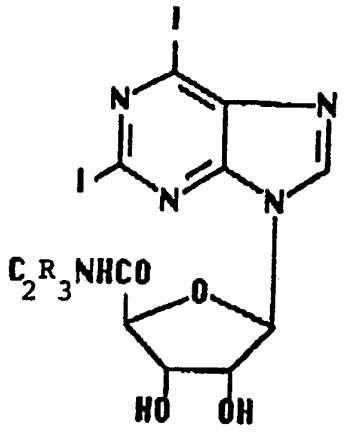
10. Compounds of formula V



V

wherein R' is as defined in claims 8 and 9, as intermediate compounds.

11. Compounds of formula VI



VI

wherein R_3 is as defined in claim 1, as intermediate compound.

12. Pharmaceutical compositions containing a compound of claims 1-7 in admixture with a suitable carrier.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 93/00972

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07H19/167

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07H ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
O,X	International Symposium on Pharmacology of Purinergic Receptors-IUPHAR Satellite Symposium, Nordwijk, NL, 6-8 July 1990. Presentation on 2-Alkynyl derivatives of Adenosine by G. Cristalli	1,2,5,7, 8,12
L	JOURNAL OF MEDICINAL CHEMISTRY. vol. 35, no. 13, June 1992, WASHINGTON US pages 2363 - 2368 CRISTALLI G. ET AL '2-Alkynyl Derivatives of Adenosine and Adenosine-5'-N-ethyluronamide as Selective Agonists at A2 Adenosine Receptors' See page 2363, footnote 1, Cited in support of above 'O' document	1,2,5,7, 8,12
P,X	see page 2363 - page 2365	1,2,5,7, 8,12

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° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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

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

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

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
27 AUGUST 1993	15.09.93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	DAY G.J.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	JOURNAL OF MEDICINAL CHEMISTRY. vol. 35, no. 2, 24 January 1992, WASHINGTON US pages 241 - 252 MATSUDA A. ET AL 'Nucleosides and Nucleotides. 103. 2_Alkynyladenosines: A Novel Class of Selective Adenosine A2 Receptor Agonists with Potent Antihypertensive Effects' See Scheme 1	1,12
A	CHEMICAL AND PHARMACEUTICAL BULLETIN. vol. 33, no. 4, 1985, TOKYO JP pages 1766 - 1769 SHINOZAKI ET AL 'Palladium-catalyzed cross-coupling of 2-Iodoadenosine with terminal alkynes: Synthesis and biological activities of 2-alkynyladenosines' see the whole document	1,12
A	EUROPEAN JOURNAL OF PHARMACOLOGY vol. 196, no. 1, 10 April 1991, AMSTERDAM, NL pages 69 - 76 ABIRU T. ET AL 'The antihypertensive effect of 2-Alkynyladenosines and their selective affinity for Adenosine A2 receptors' see abstract	1,12
A	EP,A,0 277 917 (CIBA-GEIGY AG) 10 August 1988 see page 6	1,12

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

EP 9300972
SA 73390

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 27/08/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0277917	10-08-88	AU-A- 1123388	18-08-88
		JP-A- 63201196	19-08-88
		US-A- 4968697	06-11-90