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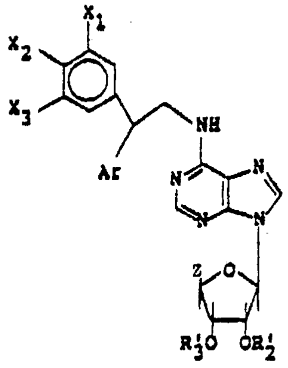

(I)

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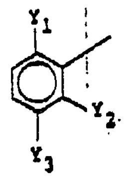

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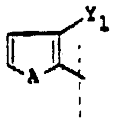

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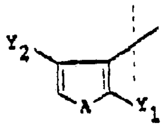

(57) Abstract

Adenosines of formula (I), wherein Ar is (II), (III) or (IV), wherein A is oxygen or sulfur. The adenosines have highly selective A$_2$ receptor binding activity and useful properties advantageous in treating cardiovascular diseases, such as hypertension, angina or myocardial ischemia, pain, insomnia and psychosis. Also a novel preparation of selected adenosines.

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SELECTED N^6-SUBSTITUTED ADENOSINES HAVING SELECTIVE A_2 BINDING ACTIVITY

This is a continuation-in-part of US Application Serial Number 925,185 filed October 31, 1986.

BACKGROUND OF THE INVENTION

The compounds of the present invention are related to the N^6-substituted adenosines of copending application U.S. Serial Number 756,922 filed June 17, 1985 which is a continuation of U.S. Serial Number 621,943 filed June 22, 1984 now abandoned, which is a continuation in part of U.S. Serial Number 519,284, filed August 1, 1983 now abandoned.

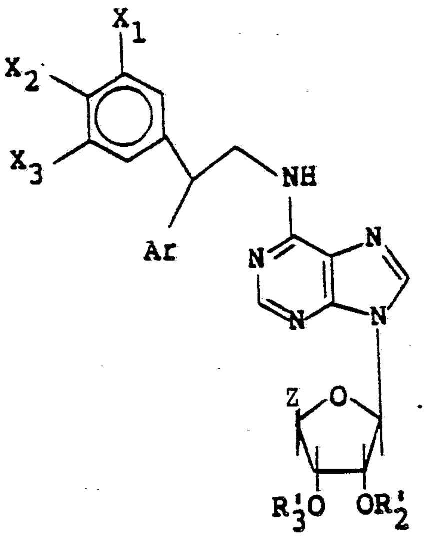
The instant compounds have a surprisingly greater affinity for A_2 receptors than A_1 receptors. The compounds have highly desirable central nervous system and cardiovascular activities, such as analgesic, antipsychotic, sedative, antihypertensive, and cardiotonic activity, especially, antianginal and vasodilator effects.

Thus, the above noted copending application and references therein provide a background for the present invention including descriptions of literature assays in which the compounds of the present invention have been found to possess activity as described herein. Therefore, copending application U.S. Serial Number 756,922 is incorporated by reference.

References related to the novel process of the present invention include European Application 222330A, J. Med. Chem., Vol. 29, No. 9, pp. 1683-89 (1986) or WO8600310, and J. Med. Chem., Vol. 23, pp. 313-9 (1986) or U.S. Patent No. 3,852,268. None of these references show the preparation of a 5' uronamide from inosine isopropylidene of the present novel process having unexpected advantages.

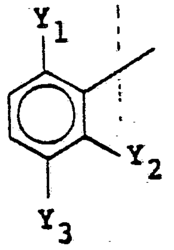
SUMMARY OF THE INVENTION

The present invention relates to a compound of the formula (I)



I

or a pharmaceutically acceptable acid addition salt thereof; wherein Ar is



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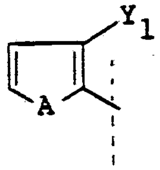
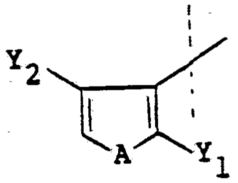


or

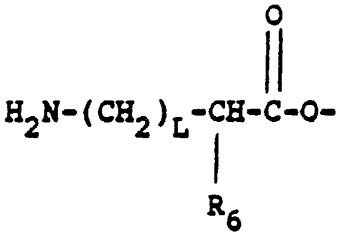


wherein X_1, X_2, X_3, Y_1, Y_2 and Y_3 may be independently selected from hydrogen, halogen, lower alkyl, lower alkylthio or alkoxy, and X_1, X_2, X_3 may also be trifluoromethyl with the proviso that Y_2 or Y_3 must be hydrogen except when Y_1 is hydrogen and

Y_2 and Y_3 taken together are $-(CH)-_4$ with the further overall proviso that at least two of X_1, X_2, X_3, Y_1, Y_2 and Y_3 are not hydrogen.

R_2' and R_3' are each independently hydrogen, alkanoyl having two to twelve carbon atoms in a straight or branched alkyl chain which may be substituted by amino, benzoyl or benzoyl substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; additionally, R_2' and R_3' may be linked together to form either a five-membered alkylidene ring having a total of up to twenty carbons such as, for example, isopropylidene, or a cyclic phosphate diester and R_5' may be a phosphate, hydrogen or dihydrogen phosphate, or an alkali metal or ammonium or dialkali or diammonium salt thereof, such as, for example, PO_3Na_2;

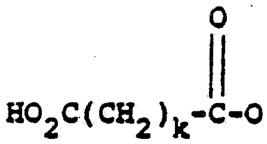
Z is $-(CH_2)-Q$ wherein Q is selected from the group consisting of hydrogen; hydroxy; halogen; cyano; azido; amino; lower alkoxy; lower acyloxy; lower thioalkyl; lower sulfonylalkyl;



$$H_2N-(CH_2)_L-\underset{\displaystyle R_6}{\underset{|}{CH}}-\overset{\displaystyle O}{\overset{||}{C}}-O-$$

wherein L is 0-4; and

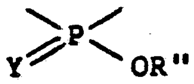
R_6 is hydrogen or when L is 0 then R_6 may also be a side chain of a naturally occurring amino acid, such as, benzyl as found in a phenylalanine ester, or isopropyl as found in a valinyl ester or



$$HO_2C(CH_2)_k-\overset{O}{\overset{\|}{C}}-O$$

wherein k is 0-4;

$-P(=Y)(OR")_2$, $-P(=Y)(OR")(OR'")$ and taken together with R^3 is



wherein Y is oxygen or sulfur and R" and R'" are independently hydrogen or lower alkyl; or (2)

$$\begin{array}{c}TC\\ \|\\ J\end{array}$$

wherein J is O, S, NR_7 wherein R_7 is hydrogen, lower alkyl or cycloalkyl of from 3 to 7 carbons such as cyclopropyl, cyclobutyl, cyclopentyl and the like or 1- or 2-methylcyclopropyl, 1-, or 2-ethylcyclobutyl and the like; and

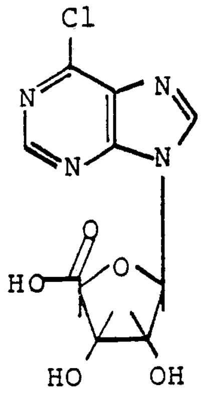
T is (a) NR_4R_5 wherein R_4 is straight chain lower alkyl having 1-4 carbon atoms; hydroxy, lower alkoxy or halogen substituted straight chain lower alkyl having 1-4 carbon atoms; cyclopropyl; secondary alkyl having 3-6 carbon atoms; hydroxy, lower alkoxy or halogen substituted secondary alkyl having 3-6 carbon atoms; alkenyl having 3 to 6 carbon atoms; aralkyl having 1 to 4 carbons in the alkyl chain and optionally substituted in the aryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups; and heteroarylalkyl having 1 to 4 carbons in the alkyl chain and optionally substituted in the heteroaryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups, and

R_5 is hydrogen or straight chain lower alkyl having 1 to 4 carbons; or

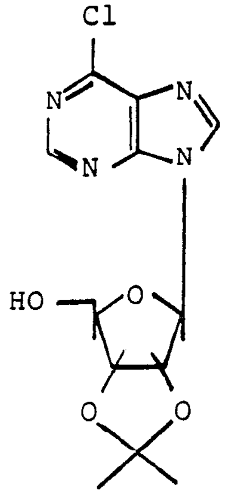
(b) OR_4 wherein R_4 is as defined above.

The present invention also relates to a pharmaceutical composition comprising a therapeutically effective amount of a compound of the above formula I with a pharmaceutically acceptable carrier, and to a method of treating mammals by administering to such mammals a dosage form of a compound of the formula I as defined above.

Finally, the present invention is a novel process for preparing a compound of the formula



which comprises treating a compound of the formula



with H_2CrO_4 in acetone.

In the compounds of the formula I, the term "lower alkyl" is meant to include a straight or branched alkyl group having from 1 to 6 carbon atoms such as, for example, methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, tert-butyl, amyl, isoamyl, neopentyl, hexyl, and the like.

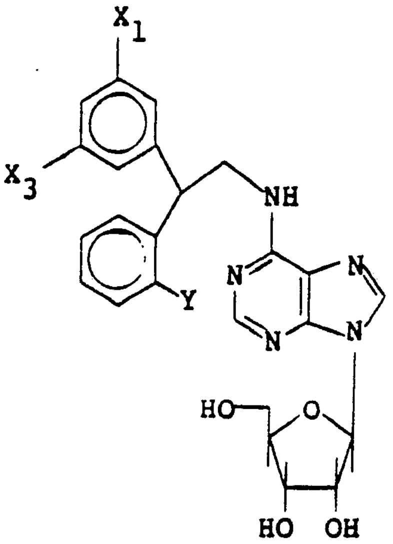
Halogen includes particularly chlorine or bromine.

Lower alkoxy and thioalkoxy are O-alkyl or S-alkyl of from 1 to 6 carbon atoms as defined above for "lower alkyl".

The compounds of formula I are useful both in the free base form and in the form of acid addition salts. Both forms are within the scope of the invention. In practice, use of the salt form amounts to use of the base form. Appropriate pharmaceutically acceptable salts within the scope of the invention are those derived from mineral acids such as hydrochloric acid and sulfuric acid; and organic acids such as ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, and the like, giving the hydrochloride, sulfamate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, and the like, respectively. (See for example, "Pharmaceutical Salts", J. Pharm. Sci. (1977) 66(1):1-19.)

The acid addition salts of said basic compounds are prepared either by dissolving the free base in aqueous or aqueous alcohol solution or other suitable solvents containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and acid in an organic solvent, in which case the salt separates directly or can be obtained by concentration of the solution.

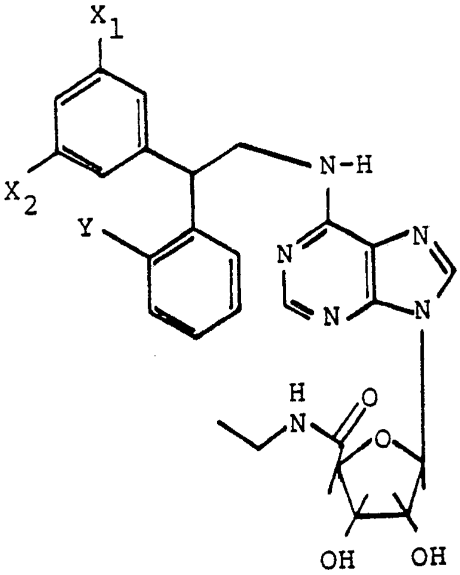
Preferred compounds of formula I are



I_1

wherein X_1 and X_3 are as defined above and Y is Y_1 when Y_1 is not hydrogen.

Another group of preferred compounds of formula I is



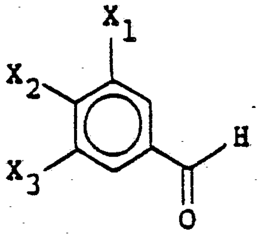
I_2

wherein X_1, X_2 and Y are as defined above.

The most preferred compound of the present invention is of the formula I_1 wherein X_1 and X_3 are methoxy and Y is methyl.

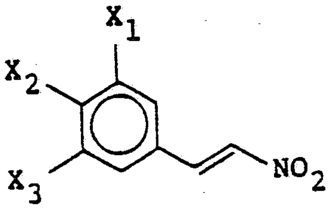
The present invention is also novel processes for the preparation of a compound of formula I as follows:

Generally, the compounds of formula I may be synthesized by conversion of an aryl aldehyde of formula (V)



V

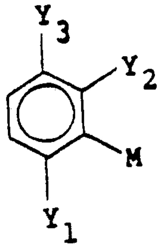
wherein X_1, X_2 and X_3 are as defined above; to the corresponding w-nitrostyrene of the formula (IV)



IV

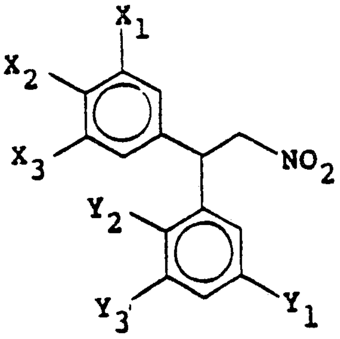
wherein X_1, X_2 and X_3 are as defined above. The conversion is accomplished by (1) treating with nitromethane in basic medium, i.e. in a solvent such as methanol, ethanol, or aqueous methenyl in the presence of NaOH, and (2) chlorosulfonylmethane in the presence of about two equivalents of triethylamine in an aprotic solvent such as dichloromethane.

The w-nitrostyrene of the formula IV is then treated with an organometallic compound of the formula IVa



IVa

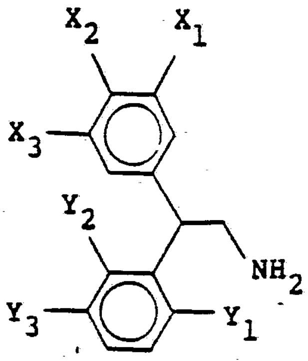
wherein Y_1, Y_2 and Y_3 are as defined above and M is a moiety preferably such that IVa is a Grignard or lithium derivative in an aprotic solvent system (preferably toluene-ether) at a low temperature (preferably from -10° to -40°C) using reaction conditions known by an ordinarily skilled artisan to be required by the Grignard or lithium derivative. Treatment with the organometallic compound gives a compound of formula (III)



III

wherein X_1, X_2, X_3, Y_1, Y_2, and Y_3 are as defined above.

The compound of formula III is then reduced by treatment with, for example, lithium aluminum hydride using conditions within the skill of an ordinarily skilled artisan to give a compound of the formula (II)

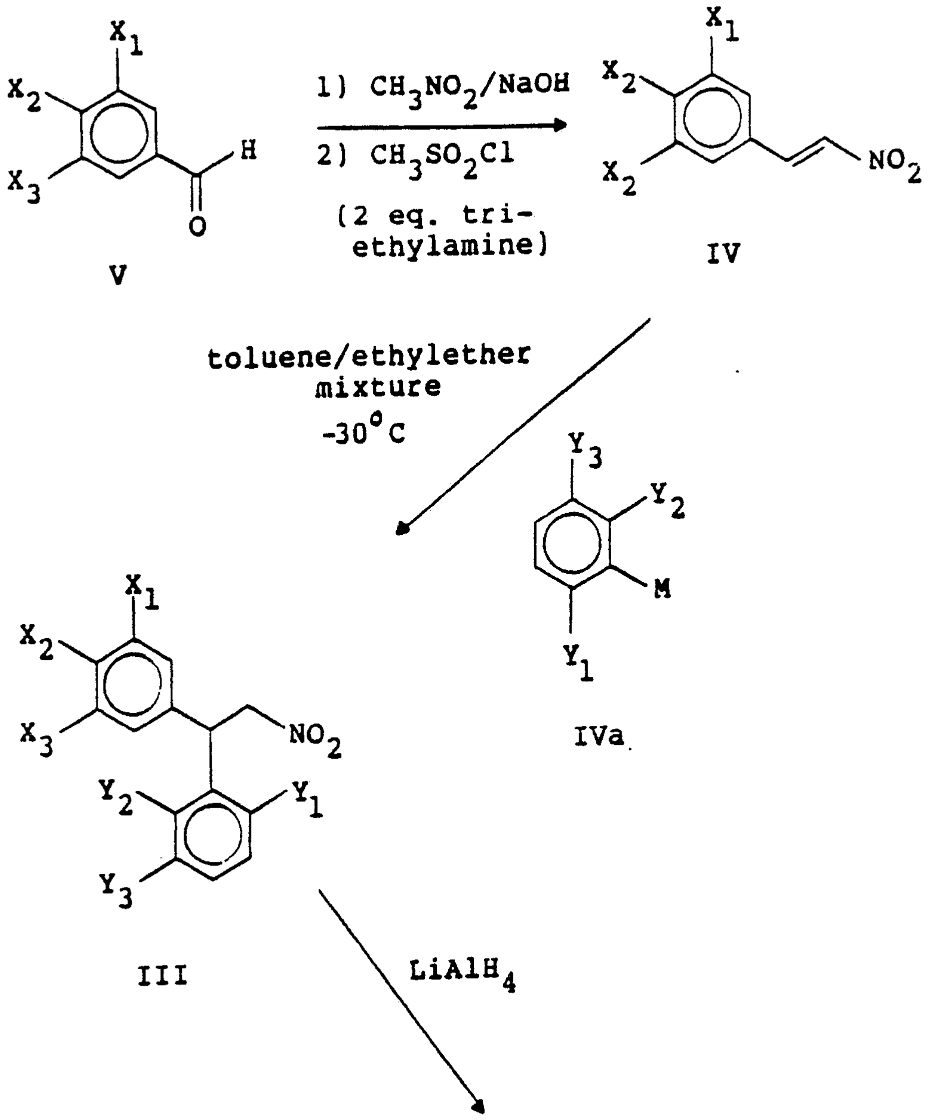


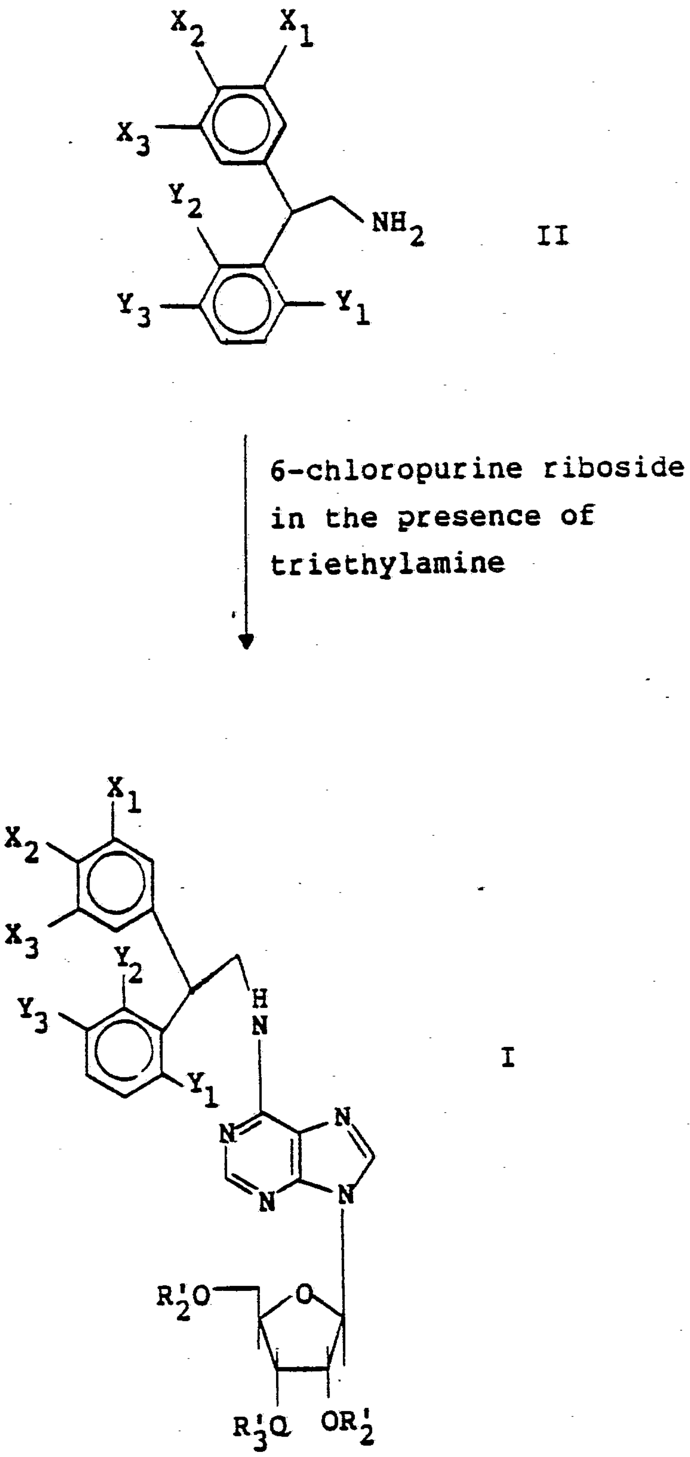
II

wherein X_1, X_2, X_3, Y_1, Y_2 and Y_3 are as defined above.

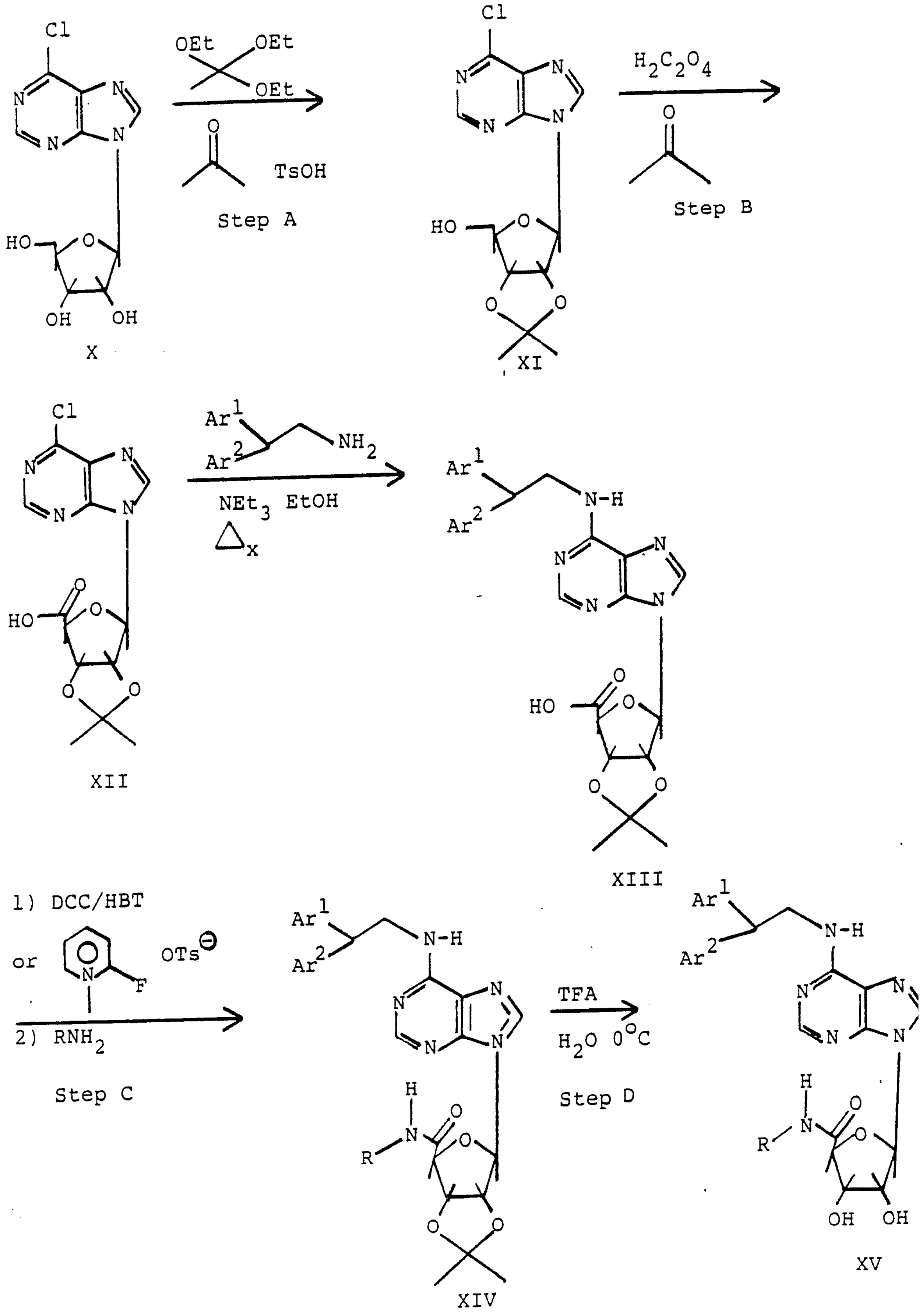
Finally, the compound of formula II is coupled with 6-chloropurine riboside in the presence of triethylamine according to the procedure as described in application U.S. Serial Number 756,922 to obtain a compound of formula I as defined above.

The above described process can be shown as follows:


X1
X2
X3
H
O
V
1) CH3NO2/NaOH
2) CH3SO2Cl
(2 eq. triethylamine)
X1
X2
X2
NO2
IV
toluene/ethylether mixture
-30°C
Y3
Y2
M
Y1
IVa
X1
X2
X3
NO2
Y2
Y1
Y3
III
LiAlH4



Although the N^6 sidechain is made as described above, a particularly preferred novel process to make the uronamide portion of the molecule of the compound I is also the present invention. It is shown as follows:


Cl
OEt
OEt
OEt
TsOH
Step A
HO
OH
OH
X
$H_2C_2O_4$
Step B
XI
Ar^1
Ar^2
NH_2
NEt_3 EtOH
XII
N-H
XIII
1) DCC/HBT
or
$OTs^{\ominus}$
F
2) RNH_2
Step C
H
R
XIV
TFA
H_2O 0°C
Step D
XV

The novel process shown above to make the uronamide portions on the compound of formula I is generally carried out by treating the compound of formula X with ethyl orthoformate and tosic acid in acetone, to give isopropylidene XI in 80-90% yields. Oxidation of XI with chromic acid in acetone gives the uronic acid XII in 53-60% yield. This can be converted to acid XIII in 80% yield by treatment with an appropriate 2,2-diarylethylamine and triethylamine in ethanol, and then amidated with an appropriate primary amine and a condensing agent such as dicyclohexylcarbodiimide/1-hydroxybenzotriazole or N-methyl-2-fluoropyridinium tosylate/triethylamine, to give the protected nucleoside XIV, which on acid hydrolysis, preferably with aqueous TFA at 0°C gives the desired nucleoside XV. Alternatively compound XIV can be generated from uronic acid XII, by amidation of the uronic acid moiety as described to give XIV followed by displacement of the C6-Cl under the same conditions as described previously.

Although this process is related to those previously claimed in World Appl. 8600310 following the procedure of J. Med. Chem., Vol. 23, pp. 313-9 (1986) it has several distinct advantages. In the present process the isopropylidenation of inosine is physically awkward whereas the X to XI transformation is operationally very simple. Furthermore the oxidation of inosine isopropylidene to the corresponding uronic acid according to previously known processes is also tedious, and in our hands never gave the claimed yields (≈65%) but consistently lower yields (20-25%). The conversion of XI to XII was found to be reproducible in 50-60% yield, and the entire reaction can be carried out in 2-4 hours, a major savings in time. We were unsuccessful in several attempts to convert inosine isopropylidene-5'-uronic acid into intermediate XIV, under conditions claimed previously, whereas our procedures reproducibly allowed for XV (or XIV) to be produced from the corresponding uronic acids in 60-95% yields. Therefore, the present process unexpectedly provides a process overall operationally much simpler than previously claimed processes, and that the complete process X to XV can be carried out on a laboratory scale in 20-30% overall yield in 3 working days.

The starting materials in the above described processes to prepare the compounds of the formula I are generally known, commercially available or can be prepared by methods either known or analogous to those known.

Variations in the processes of the present invention are within the skill of an ordinary artisan. The products of the processes are isolated by conventional means such as extraction, distillation, chromatography and the like.

The compounds of formula I are now found to possess surprising and unexpected preference in binding A_2 adenosine receptors.

By molecular modeling the compounds of the present invention can be said to preferably bind to A_2 receptors. Such A_2 binding indicates a different mechanism of action from that previously indicated for adenosine derivatives known for common utilities. Such utilities in view of the novel A_2 binding preference is unexpected compared to the differing affinities for the A_1 and A_2 receptors indicated in the above cited U.S. Serial Number 756,922. Thus, the compounds of the present invention represent a novel mechanism of action which cannot be predicted from previously disclosed data. Further the demonstrated difference between A_2 and A_1 receptor binding is in the range of 1.5 to 35 fold. Additionally, activity in the animal tests of the present compounds exceeds that expected based on the measured A_1 receptor binding of these compounds and, therefore, is also surprising. Further among the present compounds, the effect of the compound of Example 19 is not reversed in the MAST test by an A_1 selective antagonist unlike selected compounds of examples from SN 756,922 noted above. Also, the compound of Example 19 is now found to have a different effect on dopamine receptors from selected compounds of the examples in USSN 756,922 again as noted above.

These compounds of formula I are active in animal tests which are predictive of neuroleptic activity for the treatment of major psychoses such as schizophrenia. The compounds of the invention also have sedative/hypnotic properties and as such, are useful in the treatment of pain.

Additionally, the compounds of the present invention are useful in the treatment of congestive heart failure. Particularly, the compounds of formula I are now found to possess vasodilator properties with a marked selectivity for coronary over peripheral vasculature and a positive inotropic effect which increases blood flow useful in the treatment of angina and congestive heart failure. For a similar effect with an adenosine see patent application PD-3545.

The biological data from assays corresponding to those described in U.S. Serial Number 756,922 for the compounds in the present invention are summarized in the following tables for the noted examples described hereinafter.

Accordingly, the present invention also includes a pharmaceutical composition for treating psychoses, sleep disorders, pain, or cardiovascular diseases comprising a corresponding antipsychotic, sedative, analgesic, or cardiovascular disease effective amount of a compound of the formula I as defined above with a pharmaceutically acceptable carrier.

Treatment of cardiovascular diseases means usefulness as antihypertensive agents for the treatment of high blood pressure. Also the treatment increases coronary blood flow, for example, as a vasodilator and therefore is useful in the treatment of angina and congestive heart failure as well.

Table 1. Adenosine Receptor Binding - A_1 and A_2 Receptor Affinity (RBA1 and RBA2)

Example	RBA1 IC_{50} (nM)	RBA2 IC_{50} (nM)
1	380	62
2	1300	150
3	40	9
4	68	17
5	400	230
6	100	27
7	33	9
8	20	10
9	130	27
10	10	6
11	53	9
12	280	47
13	3800	1600
14	51	7.7
15	46	17
16	63	44
17	78	13
18	2500	890
19	207	6.7
20	356	34
21	50	10
22	57	7.8
23	74	5.3
24	280	8.2
25	84	7.4
26	160	16
27	500	19
28	260	16
29	170	4.5
30	220	8.7

Example	RBA1 IC_{50} (nM)	RBA2 IC_{50} (nM)
31	3300	200
32	>100,000	3830
33	1540	41
34	1930	58
35	330	6.7
36	574	13.6

Table 2. MAST Values

Example	Dose (IP[1]) mg/kg	% IMA[2]	% SFO[3]
1	3	10	0
	10	41	0
	30	67	0
2	3	22	0
	10	50	0
	30	52	0
3	1	27	0
	3	67	0
	10	73	0
4	3	30	0
	10	59	0
	30	58	0
5	3	4	0
	10	26	0
	30	26	0

Example	Dose (IP[1]) mg/kg	% IMA[2]	% SFO[3]
6	3	44	0
	10	87	0
	30	90	11
7	1.0	11	0
	3.0	56	0
	10	79	0
	30	88	0
8	3	47	0
	10	63	0
	30	73	0
9	3	35	0
	10	51	0
	30	81	0
10	1	57	0
	3	61	0
	10	78	0
11	0.1	8	0
	0.3	14	0
	1.0	58	0
	3.0	71	0
	10	80	0
	30	83	0
12	3	28	0
	10	46	0
	30	78	0

Example	Dose (IP[1]) mg/kg	% IMA[2]	% SFO[3]
14	0.3	-2	0
	1	39	0
	3	60	0
	10	89	0
	30	84	0
15	3	46	0
	10	84	0
	30	81	0
16	3	1	0
	10	52	0
	30	70	0
17	1	25	0
	3	64	0
	10	77	0
19	1	32	0
	3	58	0
	10	81	0
	30	83	0
20	3	8	0
	10	44	0
	30	61	0
21	3	51	0
	10	60	0
	30	65	0

Example	Dose (IP[1]) mg/kg	% IMA[2]	% SFO[3]
22	1	48	0
	3	68	0
	10	88	0
	30	82	0
23	0.3	14	0
	1	53	0
	3	74	0
	10	80	0
	30	79	11
24	3	51	0
	10	71	0
	30	78	0
25	0.3	29	0
	1	48	0
	3	78	0
	10	90	0
	30	91	0
26	3	11	0
	10	63	0
	30	65	0
27	3	26	0
	10	41	0
	30	53	0
28	3	17	0
	10	34	0
	30	58	0

Example	Dose (IP[1]) mg/kg	% IMA[2]	% SFO[3]
33	3	11	0
	10	30	0
	30	49	0
34	3	38	0
	10	64	0
	30	66	0
35	0.3	10	0
	1.0	52	0
	3	68	0
	10	82	22
	30	90	0
36	3	44	0
	10	68	0
	30	77	0

[1] Intraperitoneal

[2] Inhibition of mouse activity

[3] Screen fall off (% inhibition of screen test failure)

Table 3. Sidman Rat ED_{50}s

Example 11	2.1 mg/kg
Example 19	3.2 mg/kg
Example 22	5.0 mg/kg
Example 23	3.5 mg/kg
Example 24	8.5 mg/kg

Table 4. AHP3 Data

Example	Dose mg/kg	Max BP↓
1	10	21%
2	10	20%
3	10	17%
4	10	13%
6	10	33%
7	3	13%
8	10	22%
9	10	43%
11	10	29%
17	10	23%
19	10	22%
20	10	32%
21	10	14%
22	10	13%
23	10	40%
24	10	34%
26	10	16%
27	10	12%

Accordingly, the present invention further includes a method for treating psychoses, sleep disorders, pain, or cardiovascular diseases in mammals suffering therefrom comprising administering to such mammals either orally or parenterally a corresponding pharmaceutical composition having a compound of the formula I as defined above in appropriate dosage form.

The compositions and methods of administration are as understood by the present state of the art, for example, as disclosed in U.S. Serial Number 756,922.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from 1 mg to 500 mg preferably to 5 to 100 mg according to the particular application and the potency of the active ingredient. The compositions can, if desired, also contain other compatible therapeutic agents.

In therapeutic use as described above, the mammalian dosage range for a 70 kg subject is from 0.01 to 100 mg/kg of body weight per day or preferably 0.1 to 50 mg/kg of body weight per day. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is with the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The following Examples further illustrate the invention.

EXAMPLE 1

N,6-(2-(2,6-Dimethylphenyl)-2-phenylethyl)adenosine

a) E,2-(2,6-Dimethylphenyl)nitroethene

Aqueous sodium hydroxide (2.5 M, 20 ml) was added dropwise over 15 min to a solution of 2,6-dimethylbenzaldehyde (6.7 g, 50 mmol) and nitromethane (3.1 g, 50 mmol) in methanol (25 ml) stirred under N_2 at 0°C. After a further 15 mins the reaction mixture was quenched by pouring onto dilute hydrochloric acid (0.5 M, 100 ml) and extracting with ether (3x25 ml). The combined extracts were washed with water (2x25 ml) and saturated brine (25 ml) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residual yellow oil was dissolved in CH_2Cl_2 (150 ml) and stirred under N_2 at 0°C. Mesyl chloride (5.7 g, 50 mmol) in CH_2Cl_2 (25 ml) and then triethylamine (10.1 g, 100 mmol) in CH_2Cl_2 (25 ml) were added sequentially to the solution. After 1.5 hr the reaction mixture was poured onto dilute hydrochloric acid (0.5 M, 200 ml). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (50 ml). The combined organic phases were washed with water (2x50 ml), saturated brine (50 ml), and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the nitrostyrene (8.33 g, 96%) as a light brown oil. Nmr ($CDCl_3$) δ 8.22 (1H, d, J=14 Hz), 6.9-7.4 (4H, m), 2.41 (6H, s).

b) 2-(2,6-Dimethylphenyl)-2-phenylethylamine

Phenylmagnesium bromide (2.9 M in ether, 5 ml, 14.5 mmol), was added dropwise over 10 min to a solution of E,2-(2,6-dimethylphenyl)nitroethene (1.77 g, 10 mmol) in toluene (50 ml) stirred under N_2 at -30°. The solution reddened, and after a further 15 min at -30° the reaction was quenched by addition of dilute hydrochloric acid (0.4 M, 50 ml). The layers were separated, and the aqueous layer was extracted with toluene (25 ml). The combined organic phases were washed with water (25 ml, emulsions usual at this step), saturated brine (25 ml), and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude diarylnitroethane (2.05 g) as a yellow oil. This was dissolved in ether (25 ml) and added dropwise over 20 min to a suspension of $LiAlH_4$ (1.11 g, 30 mmol) in ether (100 ml) stirred under N_2 at 25°. Vigorous gas evolution and mild exotherm! After 3 hr the reaction was quenched by cautious, sequential, dropwise addition of water (1 ml), aqueous sodium hydroxide solution (10% w/v, 1 ml) and water (3 ml). Vigorous gas evolution and exotherm! The mixture was vacuum filtered, and the residue was washed with ether (100 ml). The combined filtrates were extracted with dilute hydrochloric acid (0.1 M, 2x100 ml). The aqueous layer was washed with ether (2x50 ml), made basic with NaOH pellets (1.0 g, 25 mmol) and extracted with ether (3x25 ml). The combined extracts were washed with water (2x25 ml, (frequent emulsions)), saturated brine (25 ml), and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the desired amine (1.00 g, 44%) as a pale yellow oil.

Nmr ($CDCl_3$) δ 7.1-7.3 (5H, m), 6.9-7.1 (3H, m), 4.56 (1H, d of d, J=6,8 Hz), 3.61-3.35 (2H, ABq of ds, J_{AB} = 12.5 Hz, Jd=6,8 Hz), 2.18 (6H, s), 1.16 (2H, br s).

c) N,6-(2-(2,6-Dimethylphenyl)-2-phenethyl)adenosine

6-Chloropurine riboside (1.28 g, 4.4 mmol), 2-(2,6-dimethylphenyl)-2-phenylethylamine (1.00 g, 4.4 mmol) and triethylamine (0.89 g, 8.8 mmol) were refluxed in ethanol (40 ml) under N_2 with stirring for 15 h. The solvent was removed under reduced pressure to give a pale brown solid foam, which was added to ethyl acetate (50 ml), washed with water (2x25 ml, emulsion!), saturated brine (25 ml), and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residual solid foam was purified by silica gel chromatography eluting with 5% CH_3OH in $CHCl_3$. The solvent was removed under reduced pressure to give the desired nucleoside (1.44 g, 67%) as an offwhite solid foam, mp 112-124°C.

Calcd. for $C_{26}H_{29}N_5O_4 \cdot 0.13\ CHCl_3$
C, 63.91; H, 5.93; N, 14.27; Cl, 2.82
Found C, 63.42; H, 6.05; N, 14.26; Cl, 2.83.

EXAMPLE 2

N,6-(2-(2,6-Dimethylphenyl)-2-(4-methylphenyl)ethyl)adenosine

2-(2,6-Dimethylphenyl)-2-(4-methylphenyl)ethylamine (0.92 g, 38%) was prepared from E,2-(2,6-dimethylphenyl) nitroethene (1.77 g, 10 mmol, see Example 1), 4-bromotoluene (2.56 g, 15 mmol) and Mg (0.36 g, 15 mmol), followed by $LiAlH_4$ reduction (1.11 g, 30 mmol) as described in Example 1.

The nucleoside (1.20 g, 62%) was prepared from the amine (0.92 g, 3.8 mmol) 6-chloropurine riboside (1.11 g, 3.8 mmol) and triethylamine (0.81 g, 8 mmol) as a pale yellow solid foam, mp 113-22°C as described in Example 1.

EXAMPLE 3

N,6-(2-(3,5-Dimethylphenyl)-2-phenethyl)adenosine

The nitrostyrene (2.25 g, 79%) was prepared from 3,5-dimethylbenzaldehyde (2.1 g, 0.16 mole) and nitromethane (0.9 g, .016 mole) as described in Example 1.

The amine (0.57 g, 21%) was prepared from E,2-(3,5-dimethylphenyl)nitroethene (2.25 g, .012 mole), phenylmagnesium bromide (6.3 ml, .019 mole), followed by $LiAlH_4$ reduction (1.38 g, .036 mole) as described in Example 1.

The nucleoside (0.62 g, 47%) was prepared from the amine (0.57 g, .0025 mole), 6-chloropurine riboside (0.66 g, .0023 mole) and triethylamine (0.3 ml, .0025 mole) as a solid, mp 94-97°C as described in Example 1.

EXAMPLE 4

N,6-(2-Naphth-1-yl-2-phenethyl)adenosine

The nitrostyrene (19.38 g, 97%) was prepared from 1-naphthaldehyde (15.62 g, 100 mmol) and nitromethane (6.1 g, 100 mmol) as described in Example 1.

The amine (3.78 g, 59%) was prepared from E,2-naphth-1-ylnitroethene (4.88 g, 25 mmol), and phenylmagnesium bromide (27 mmol), followed by $LiAlH_4$ reduction (2.22 g, 60 mmol) as described in Example 1.

The nucleoside (3.43 g, 67%) was prepared from 2-napth-1-yl-2-phenethylamine (2.56 g, 10 mmol), 6-chloropurine riboside (2.87 g, 10 mmol) and triethylamine (2.0 g, 20 mmol) as a white powder, mp 120-8°C as described in Example 1.

EXAMPLE 5

N,6-(2-(3,5-Dichlorophenyl)-2-(2,6-dimethylphenyl)ethyl) adenosine

The nitrostyrene (8.48 g, 97%) was prepared from 3,5-dichlorobenzaldehyde (7.00 g, 40 mmol) and nitromethane (2.44 g, 40 mmol) as described in Example 1.

The amine (1.39 g, 47%) was prepared from E,2-(3,5-dichlorophenyl)nitroethene (2.18 g, 10 mmol), 2,6-dimethylbromobenzene (2.78 g, 15 mmol) and Mg (0.36 g, 15 mmol) followed by $LiAlH_4$ reduction (1.11 g, 30 mmol) as described in Example 1.

The nucleoside (2.05 g, 77%) was prepared from 2-(3,5-dichlorophenyl)-2-(2,6-dimethylphenyl) ethylamine (1.39 g, 4.7 mmol), 6-chloropurine riboside (1.35 g, 4.7 mmol) and triethylamine (0.95 g, 9.4 mmol) as a white solid foam, mp 125-35°C as described in Example 1.

EXAMPLE 6

N,6-(2-(2,6-Dichlorophenyl)-2-phenethyl)adenosine

The nitrostyrene (10.18 g, 93.4%) was prepared from 2,6-dichlorobenzaldehyde (8.75 g, 50 mmol) and nitromethane (3.05 g, 50 mmol) as described in Example 1.

The amine (1.95 g, 45%) was prepared from E,2-(2,6-dichlorophenyl)nitroethene (3.27 g, 15 mmol) and phenylmagnesium bromide (18 mmol) followed by $LiAlH_4$ reduction (2.22 g, 60 mmol) as described in Example 1.

The nucleoside (1.55 g, 61%) was prepared from the amine (1.48 g, .0056 mole), 6-chloropurine riboside (1.40 g, .0049 mole) and triethylamine (1.4 ml, .01 mole) as a solid, mp 102-12°C as described in Example 1.

EXAMPLE 7

N,6-(2-(3,5-Dichlorophenyl)-2-phenethyl)adenosine

The amine (1.09 g, 41%) was prepared from E,2-(3,5-dichlorophenyl)nitroethene (2.18 g, see Example 5) and phenylmagnesium bromide (15 mmol), followed by $LiAlH_4$ reduction (1.11 g, 30 mmol) as described in Example 1.

The nucleoside (1.63 g, 77%) was prepared from 2-(3,5-dichlorophenyl)-2-phenethylamine (1.09 g, 4.1 mmol) 6-chloropurine riboside (1.08 g, 4.1 mmol) and triethylamine (0.81 g, 8 mmol) as an offwhite solid foam, mp 110-115°C as described in Example 1.

EXAMPLE 8

N,6-(2-(3-Chlorophenyl)-2-(3,5-dichlorophenyl)ethyl)adenosine

The amine (1.08 g, 36%) was prepared from E,2-(3,5-dichlorophenyl)nitroethene (2.18 g, 10 mmol, see Example 5) 3-bromochlorobenzene (3.83 g, 20 mmol) and Mg (0.36 g, 15 mmol), followed by $LiAlH_4$ reduction (1.11 g, 30 mmol) as described in Example 1.

The nucleoside (1.53 g, 77%) was prepared from 2-(3-chlorophenyl)-2-(3,5-dichlorophenyl)ethylamine (1.08 g, 3.6 mmol), 6-chloropurine riboside (1.05 g, 3.6 mmol) and triethylamine (0.71 g, 7 mmol) as a white solid foam, mp 107-23°C as described in Example 1.

EXAMPLE 9

N,6-(2-(3-Chlorophenyl)-2-(2,6-dichlorophenyl)ethyl)adenosine

The amine (1.21 g, 40%) was prepared from E,2-(2,6-dichlorophenyl)nitroethene (2.18 g, 10 mmol, see Example 6), 3-bromochlorobenzene (3.83 g, 20 mmol) and Mg (0.36 g, 15 mmol) followed by $LiAlH_4$ reduction (1.11 g, 30 mmol) as described in Example 1.

The nucleoside (0.84 g, 38%) was prepared from 2-(3-chlorophenyl)-2-(2,6-dichlorophenyl)ethylamine (1.21 g, 4 mmol), 6-chloropurine riboside (1.15 g, 4 mmol) and triethylamine (0.81 g, 8 mmol) as a pale yellow solid foam, mp 113-25°C as described in Example 1.

EXAMPLE 10

N,6-(2-(3-Chlorophenyl)-2-(3,5-dimethoxyphenyl)ethyl)adenosine

The nitrostyrene (14.41 g, 97%) was prepared from 3,5-dimethoxybenzaldehyde (12.2 g, 73 mmol) and nitromethane (4.6 g, 75 mmol) as described in Example 1.

The amine (0.46 g, 26%) was prepared from E,2-(3,5-dimethoxyphenyl)nitroethene (1.25 g, .006 mole), 3-chlorobromobenzene (2.9 ml, .025 mole), magnesium (0.48 g, .02 mole), followed by $LiAlH_4$ reduction (1.40 g, .037 mole) as described in Example 1.

The nucleoside (0.36 g, 44%) was prepared from the amine (0.40 g, .0014 mole), 6-chloropurine riboside (0.40 g, .0014 mole) and triethylamine (0.2 ml, .0015 mole) as an offwhite solid, mp 81-86°C as described in Example 1.

EXAMPLE 11

N,6-(2-(3,5-Dimethoxyphenyl)-2-phenethyl)adenosine

The amine (10.4 g, 59%) was prepared from E,2-(3,5-dimethoxyphenyl)nitroethene (14.41 g, 68 mmol, see Example 10) and phenylmagnesium bromide (100 mmol), followed by $LiAlH_4$ reduction (7.77 g, 210 mmol) as described in Example 1.

The nucleoside (17.14 g, 83%) was prepared from the amine (10.4 g, 40 mmol), 6-chloropurine riboside (11.5 g, .40 mmol), and triethylamine (8.08 g, 80 mmol) as an offwhite solid foam, mp 97-105°C as described in Example 1.

EXAMPLE 12

N,6-(2-(2,5-Dimethoxyphenyl)-2-phenethyl)adenosine

The nitrostyrene (7.65 g, 49%) was prepared from 2,5-dimethoxybenzaldehyde (12.5 g, .075 mole) and nitromethane (4.58 g, .075 mole) as described in Example 1.

The amine (1.04 g, 21%) was prepared from E,2-(2,5-dimethoxyphenyl)nitroethene (7.0 g, .033 mole), phenylmagnesium bromide (15.8 ml, .047 mole), followed by $LiAlH_4$ reduction (2.90 g, .076 mole) as described in Example 1.

The nucleoside (0.43 g, 23%) was prepared from the amine (1.04 g, .004 mole), 6-chloropurine riboside (1.03 g, .0036 mole) and triethylamine (0.5 ml, .004 mole) as a solid, mp 96-100°C as described in Example 1.

EXAMPLE 13

N,6-(2-(2,6-Dimethoxyphenyl)-2-phenethyl)adenosine

The nitrostyrene (6.87 g, 82%) was prepared from 2,6-dimethoxybenzaldehyde (6.5 g, 37 mmol) and nitromethane (2.29 g, 37 mmol) as described in Example 1.

The amine (0.49 g) was prepared in very impure form from E,2-(2,6-dimethoxyphenyl)nitroethene (2.09 g, 10 mmol) and phenyl lithium (15 mmol in ether/cyclohexane), followed by $LiAlH_4$ (1.11 g, 30 mmol) as described in Example 1.

The nucleoside (0.29 g, 6% based on nitrostyrene) was prepared from crude 2-(2,6-dimethoxyphenyl)-2-phenethylamine (0.49 g), 6-chloropurine riboside (0.58 g, 2 mmol) and triethylamine (0.40 g, 4 mmol), as described in Example 1, except for an additional purification on preparative silica gel chromatography plates, eluting twice with 8% CH_3OH in $CHCl_3$, as a yellow brown solid foam, mp 112-21°C.

EXAMPLE 14

N,6-(2-(2-Methoxyphenyl)-2-(3-methoxyphenyl)ethyl)adenosine

The nitrostyrene (32.5 g, 91%) was prepared from 2-methoxybenzaldehyde (27.2 g, 0.2 mole) and nitromethane (12.2 g, 0.2 mole) as described in Example 1.

The amine (1.81 g, 28%) was prepared from E,2-(2-methoxyphenyl)nitroethene (4.48 g, .025 mole), 3-methoxybromobenzene (6.3 ml, .05 mole), magnesium (0.97 g, .04 mole), followed by $LiAlH_4$ reduction (2.43 g, .064 mole) as described in Example 1.

The nucleoside (1.20 g, 37%) was prepared from the amine (1.80 g, .007 mole), 6-chloropurine riboside (1.72 g, .006 mole) and triethylamine (0.9 ml, .0066 mole) as a beige foam, mp 103-05°C as described in Example 1.

EXAMPLE 15

N,6-(2-(3,4-Dimethoxyphenyl)-2-phenethyl)adenosine

The nitrostyrene (12.23 g, 39%) was prepared from 3,4-dimethoxybenzaldehyde (24.9 g, .15 mole) and nitromethane (9.15 g, .15 mole) as described in Example 1.

The amine (1.18 g, 12%) was prepared from E,2-(3,4-dimethoxyphenyl)nitroethene (8.82 g, .042 mole), phenylmagnesium bromide (20.7 ml, .06 mole), followed by $LiAlH_4$ reduction (2.55 g, .067 mole) as described in Example 1.

The nucleoside (1.24 g, 59%) was prepared from the amine (1.16 g, .0045 mole), 6-chloropurine riboside (1.09 g, .0038 mole) and triethylamine (0.6 mole, .0042 mole) as a solid, mp 96-104°C as described in Example 1.

EXAMPLE 16

N,6-(2-(3,5-Diethoxyphenyl)-2-phenethyl)adenosine

The nitrostyrene (2.73 g, 88%) was prepared from 3,5-diethoxybenzaldehyde (2.68 g, .014 mole) and nitromethane (0.86 g, .014 mole) as described in Example 1.

The amine (1.25 g, 37%) was prepared from E,2-(3,5-diethoxyphenyl)nitroethene (2.73 g, .012 mole), phenylmagnesium bromide (6.3 ml, .019 mole), followed by $LiAlH_4$ reduction (1.17 g, .031 mole) as described in Example 1.

The nucleoside (1.62 g, 74%) was prepared from the amine (1.23 g, .004 mole), 6-chloropurine riboside (1.15 g, .004 mole) and triethylamine (0.6 ml, .0044 mole) as a white foam, mp 88-93°C as described in Example 1.

EXAMPLE 17

N,6-(2-(3,5-Dimethoxyphenyl)-2-thien-2-yl)ethyl)adenosine

The amine (1.60 g, 27%) was prepared from E,2-(3,5-dimethoxyphenyl)nitroethene (5.23 g, .025 mole, see Example 10), 2-bromothiophene (5.2 ml, .05 mole) and magnesium (0.96 g, .04 mole), followed by $LiAlH_4$ reduction (3.80 g, .10 mole) as described in Example 1.

The nucleoside (1.61 g, 59%) was prepared from the amine (1.38 g, .0052 mole), 6-chloropurine riboside (1.35 g, .0047 mole), and triethylamine (0.7 ml, .0052 mole) as a solid, mp 80-83°C as described in Example 1.

EXAMPLE 18

N,6-(2-(3,5-Dimethoxyphenyl)-2-naphth-1-ylethyl)adenosine

The amine (0.48 g, 14%) was prepared from E,2-(3,5-dimethoxyphenyl)nitroethene (2.22 g, .011 mole, see

Example 10), 1-bromonaphthalene (3.1 ml, .022 mole), and magnesium (0.43 g, .018 mole), followed by $LiAlH_4$ reduction (0.90 g, .024 mole) as described in Example 1.

The nucleoside (0.22 g, 25%) was prepared from the amine (0.48 g, .0016 mole), 6-chloropurine riboside (0.40 g, .0014 mole) and triethylamine (0.2 ml, .0015 mole) as a solid, mp 114-118.5°C as described in Example 1.

EXAMPLE 19

N,6-(2-(3,5-Dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine

The amine (1.90 g, 67%) was prepared from E,2-(3,5-dimethoxy)nitroethene (2.09 g, 10 mmol, see Example 10), 2-bromotoluene (2.57 g, 15 mmol) and magnesium (0.36 g, 15 mmol), followed by $LiAlH_4$ reduction (1.11 g, 30 mmol) as described in Example 1.

The nucleoside (2.85 g, 79%) was prepared from 2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethylamine (1.90 g, 6.7 mmol), 6-chloropurine riboside (1.94 g, 6.7 mmol) and triethyl amine (1.31 g, 13 mmol) as an offwhite solid foam, mp 105-12°C as described in Example 1.

EXAMPLE 20

N,6-(2-(3,5-Dimethoxyphenyl)-2-(2,6-dimethylphenyl)ethyl)adenosine

The amine (2.05 g, 71%) was prepared from E,2-(3,5-dimethoxyphenyl)nitroethene (2.09 g, 10 mmol, see Example 10), 2,6-dimethylbromobenzene (2.78 g, 15 mmol) and magnesium (0.36 g, 15 mmol), followed by $LiAlH_4$ reduction (1.11 g, 30 mmol) as described in Example 1.

The nucleoside (2.23 g, 79%) was prepared from 2-(3,5-dimethoxyphenyl)-2-(2,6-dimethylphenyl) ethylamine (2.05 g, 7 mmol), 6-chloropurine riboside (2.05 g, 7 mmol) and triethylamine (1.41 g, 14 mmol) as a white solid foam, mp 107-17°C as described in Example 1.

EXAMPLE 21

N,6-(2-(3,5-Dimethoxyphenyl)-2-(3-methoxyphenyl)ethyl)adenosine

The amine (1.70 g, 59%) was prepared from E,2-(3,5-dimethoxyphenyl)nitroethene (2.09 g, 10 mmol, see Example 10), 3-bromoanisole (2.80 g, 15 mmol) and magnesium (0.48 g, 20 mmol) followed by $LiAlH_4$ reduction (1.11 g, 30 mmol) as described in Example 1.

The nucleoside (2.42 g, 76%) was prepared from 2-(3,5-dimethoxyphenyl)-2-(3-methoxyphenyl)ethylamine (1.70 g, 6 mmol), 6-chloropurine riboside (1.72 g, 6 mmol) and triethylamine (1.21 g, 12 mmol) as a beige solid foam, mp 90-101°C as described in Example 1.

EXAMPLE 22

N,6-(2-(3,4,5-Trimethoxyphenyl)-2-phenethyl)adenosine

The nitrostyrene (31.21 g, 63%) was prepared from 3,4,5-trimethoxybenzaldehyde (40.8 g, .21 mole) and nitromethane (12.4 g, .20 mole) as described in Example 1.

The amine (0.84 g, 4%) was prepared from E,2-(3,4,5-trimethoxyphenyl)nitroethene (15.72 g, .066 mole), phenylmagnesium bromide (29.6 ml, .089 mole), followed by $LiAlH_4$ reduction (1.83 g, .048 mole) as described in Example 1.

The nucleoside (1.25 g, 85%) was prepared from the amine (0.82 g, .0029 mole), 6-chloropurine riboside (0.75 g, .0026 mole), and triethylamine (0.4 ml, .0029 mole) as a solid, mp 95-99°C as described in Example 1.

EXAMPLE 23

N,6-(2-(3,5-Dimethoxyphenyl)-2-(2-methoxyphenyl)ethyl)adenosine

The amine (5.26 g, 46%) was prepared from E,2-(3,5-dimethoxyphenyl)nitroethene (8.36 g, .04 mole, see Example 10), 2-methoxybromobenzene (10.2 ml, .08 mole), and magnesium (1.57 g, .064 mole), followed by $LiAlH_4$ reduction (5.98 g, .16 mole) as described in Example 1.

The nucleoside (5.15 g, 90%) was prepared from the amine (3.16 g, .011 mole), 6-chloropurine riboside (2.86 g, .01 mole) and triethylamine (1.4 ml, .011 mole) as a solid, mp 93-97°C as described in Example 1.

EXAMPLE 24

N,6-(2-(3,4,5-Trimethoxyphenyl)-2-(methylphenyl)ethyl)adenosine

The amine (1.01 g, 31%) was prepared from E,2-(3,4,5-trimethoxyphenyl)nitroethene (2.39 g, 10 mmol, see Example 22), 2-bromotoluene (2.57 g, 15 mmol), and magnesium (0.36 g, 15 mmol) followed by $LiAlH_4$ reduction (1.11 g, 30 mmol) as described in Example 1.

The nucleoside (1.16 g, 66%) was prepared from 2-(3,4,5-trimethoxyphenyl)-2-(2-methylphenyl ethylamine (1.01 g, 3 mmol), 6-chloropurine riboside (0.89 g, 3 mmol) and triethylamine (0.61 g, 6 mmol) as a white solid foam, mp 107-15°C as described in Example 1.

EXAMPLE 25

N,6-(2-(2-Methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethyl) adenosine

The amine (0.70 g, 9%) was prepared from E,2-(3,4,5-trimethoxyphenyl)nitroethene (5.98 g, .025 mole, see Example 22), 2-methoxybromobenzene (6.4 ml, .05 mole), magnesium (0.97 g, .04 mole), followed by $LiAlH_4$ reduction (2.43 g, .064 mole) as described in Example 1.

The nucleoside (0.67 g, 54%) was prepared from the amine (0.70 g, .0022 mole), 6-chloropurine riboside (0.57 g, .002 mole), and triethylamine (0.3 ml, .0022 mole) as a grey foam, mp 99-104°C as described in Example 1.

EXAMPLE 26

N,6-(2-(2-Methoxyphenyl)-2-(3-(trifluoromethyl)phenyl)ethyl) adenosine

The nitrostyrene (9.84 g, 91%) was prepared from 3-(trifluoromethyl)benzaldehyde (8.7 g, 50 mmol) and nitromethane (3.1 g, 50 mmol) as described in Example 1.

The amine (1.72 g, 57%) was prepared from E,2-(3-(trifluoromethyl)phenyl)nitroethene (2.17 g, 10 mmol), 2-bromoanisole (2.81 g, 15 mmol) and magnesium (0.36 g, 15 mmol) as described in Example 1.

The nucleoside (2.22 g, 71%) was prepared from 2-(2-methoxyphenyl)-2-(3-(trifluoromethyl)phenyl) ethylamine (1.72 g, 5.7 mmol), 6-chloropurine riboside (1.78 g, 6.2 mmol) and triethylamine (1.2 g, 12 mmol) as a pale yellow solid foam, mp 100-108°C as described in Example 1.

EXAMPLE 27

N,6-(2-(2-Methoxyphenyl)-2-(3,5-bis(trifluoromethyl)phenyl) ethyl)adenosine

The nitrostyrene (5.48 g, 87%) was prepared from 3,5-bis(trifluoromethyl)benzaldehyde (5.77 g, 22 mmol) and nitromethane (2.69 g, 44 mmol) as described in Example 1.

The amine (0.76 g, 42%) was prepared from E,2-(3,5-bis(trifluoromethyl)phenyl)nitroethene (1.43 g, 5 mmol), 2-bromoanisole (1.39 g, 7.5 mmol), and magnesium (0.18 g, 7.5 mmol) followed by $LiAlH_4$ reduction (0.55 g, 15 mmol) as described in Example 1.

The nucleoside (0.97 g, 75%) was prepared from 2-(2-methoxyphenyl)-2-(3,5-bis(trifluoromethyl) phenyl)ethylamine (0.76 g, 2.1 mmol), 6-chloropurine riboside (0.61 g, 2.1 mmol), and triethylamine (0.40 g, 4 mmol) as a white solid foam, mp 105-12°C as described in Example 1.

EXAMPLE 28

N,6-(2-(3,5-Bis(trifluoromethyl)phenyl-2-phenethyl)adenosine

The amine (0.92 g, 27%) was prepared from E,2-(3,5-bis(trifluoromethyl)phenyl)nitroethene (2.85 g, 10 mmol, see Example 27) and phenylmagnesium bromide (15 mmol) followed by $LiAlH_4$ reduction (1.11 g, 30 mmol) as described in Example 1.

The nucleoside (1.20 g, 75%) was prepared from 2-(3,5-bis(trifluoromethyl)phenyl)-2-phenethylamine (0.92 g, 2.7 mmol), 6-chloropurine riboside (0.80 g, 2.7 mmol) and triethylamine (0.60 g, 6 mmol) as a pale yellow solid foam, mp 99-105°C as described in Example 1.

EXAMPLE 29

N^6-((-)-2-(3,5-Dimethoxyphenyl)-2-(2-methylphenyl)ethyl) adenosine

(±) 2-(3,5-Dimethoxyphenyl)-2-(2-methylphenyl)ethylamine (40.65 g, 0.15 mol) and [2R,3R]dibenzoyl tartaric acid monohydrate (56.4 g, 0.15 mol) were dissolved in refluxing EtOH (≈700 ml) and then recrystallized 5 times, seeding with crystals of optically enriched salt (produced in 94% EE by recrystallizing a small sample 10 times) to give 5.78 g of salt, EE = 93.4%, mp 175.5-177°C, $[\alpha]_D^{23}$ (MeOH) -93.5°. The ammonium salt (5.00 g) was partitioned between dilute NaOH solution (1N, 30 ml) and ether (50 ml). The layers were separated and the aqueous layer was extracted with further ether (25 ml). The combined organic phases were washed with water (2x25 ml), saturated brine (25 ml) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give (-)-2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethylamine (2.08 g) as a cloudy pale yellow oil $[\alpha]_D^{23}$ (MeOH) -57.4°, EE = 93.4%.

The nucleoside (3.53 g, 90%) was prepared from (-)-2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethylamine (2.02 g, 7.45 mmol), 6-chloropurine riboside (2.16 g, 7.5 mmol) and NEt_3 (1.51 g, 15 mmol) in ethanol (70 ml) at reflux stirred under N_2 for 18 hours. On cooling the desired nucleoside crystallized out (3.53 g, 90%) as white microscopic needles, mp 195-197°C. Rotation $[\alpha]_D^{23}$ (DMSO) -78.1°. Diastereoisomeric excess ≥ 90%.

EXAMPLE 30

$\underline{N}^6$-((+)-2-(3,5-Dimethoxyphenyl)-2-(2-methylphenyl)ethyl) adenosine

The mother liquors, from the first crystallization of (±) 2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl ammonium di-o-benzoyl[2R,3R]tartrate, described in Example 29, were evaporated to dryness. It was then stirred with dilute NaOH solution (0.4 M, 500 ml) and ether (100 ml) until all solid had dissolved. The layers were separated and the aqueous layer was extracted with further ether (2x100 ml). The combined ethereal extracts were washed with NaOH solution (0.25 M, 100 ml), water (100 ml), saturated brine (100 ml), and dried ($MgSO_4$). The solvent was removed under reduced pressure to give 2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethylamine (17.2 g) 2:1 enriched in the (+) enantiomer. This was combined with D-dibenzoyltartrate•H_2O (23.88 g, 63.5 mmol) and recrystallized three times from ethanol, seeding with crystals of optically enriched salt, to give 6.60 g of salt. EE = 91%, mp 169-71°C, $[\alpha]_D^{23}$ (MeOH) +96°. The salt (5.00 g) was partitioned between NaOH solution (1 M, 30 ml) and ether (50 ml). The layers were separated, and the ethereal layer was extracted with further ether (25 ml). The combined organic phase was washed with water (2x25 ml), saturated brine (25 ml), and dried ($MgSO_4$). The solvent was removed under reduced pressure to give (+)-2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethylamine (2.09 g) as a cloudy pale yellow oil. $[\alpha]_D^{23}$ (MeOH) +53.3°, EE = 87% (estimated).

The nucleoside was prepared from (+)-2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethylamine (2.03 g, 7.5 mmol) 6-chloropurine riboside (2.16 g, 7.5 mmol) and NEt_3 (1.51 g, 15 mmol) in ethanol at reflux stirring under N_2 for 18 hours. The solvent was removed under reduced pressure, the residue added to water (50 ml) and extracted with ethyl acetate (2x25 ml). The combined organic phases were washed with water (25 ml), saturated brine (25 ml), and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was recrystallized from EtOH (25 ml) at 0°C to give N^6-((+)-2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl) adenosine (2.86 g, 74%) as white needles, mp 168-169°C. Rotation $[\alpha]_D^{23}$ (DMSO) -5.5°. Diastereoisomeric excess 80%.

EXAMPLE 31

5'-Bromo-5'-deoxy-N^6-(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine

A solution of 5'-bromo-5'-deoxy-S-phenylthioinosine-S,S-dioxide-2',3'-di-o-isopropylidene (3.0 g, 6 mmol), 2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethylamine (1.83 g, 6 mmol) and NEt_3 (1.21 g, 12 mmol) was stirred in $CHCl_3$ (30 ml) under N_2 at 25°C for 40 hours. The mixture was poured onto NaH_2PO_4 solution (0.4 M, 50 ml), the layers separated, and the aqueous layer extracted with further $CHCl_3$ (30 ml). The organic extracts were washed with water (2x30 ml), saturated brine (30 ml), and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residual solid foam was added to 10% aqueous TFA (10 ml) and stirred under N_2 at 0°C for 45 minutes. The reaction mixture was poured onto Na_2CO_3 solution (1 M, 200 ml) and extracted with EtOAc (3x50 ml). The combined extracts were washed with water (2x25 ml), saturated brine (25 ml), and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (225 g) eluting with 5% MeOH in $CHCl_3$ to give 5'-bromo-5'-deoxy-N^6-(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine (2.07 g, 56%) as a pale yellow solid foam, mp 76-91°C.

EXAMPLE 32

$\underline{N}^6$-(2-(3,5-Dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine 5'-uronic acid

6-Chloropurine riboside-2',3'-di-o-isopropylidene

Triethyl orthoformate (59.2 g, 0.4 mol) was added to a suspension of 6-chloropurine riboside (28.75 g, 0.10 mol) and tosic acid monohydrate (18 g, 0.095 mol) in acetone (1 L) stirred under N_2 at 25°. After 3 hours the now clear solution was concentrated under reduced pressure, and the residue was poured onto K_2HPO_4 solution (26.1 g in 800 ml) and extracted with ethyl acetate (2x200 ml). The combined extracts were washed with water (2x100 ml), saturated brine (100 ml), and dried ($MgSO_4$). The solvent was removed under reduced pressure to give 6-chloropurine riboside-2',3'-di-o-isopropylidene (28.5 g, 87%) as a light yellow crystalline solid, mp 155-158°C.

6-Chloropurine riboside-2',3'-di-o-isopropylidene-5'-uronic acid

A solution of chromic acid (2 M) in aqueous sulfuric acid (3 M, 100 ml) was added over 1 hour to a partial solution of 6-chloropurine riboside-2',3'-di-o-isopropylidene (32.65 g, 100 mmol) in acetone (500 ml) stirred under N_2 at 25° without cooling. After a further 15 minutes the mixture was celite filtered, and the residue was rinsed with EtOAc (2x250 ml). The combined filtrates were washed with $Na_2S_2O_5$ solution (0.5 M, 50 ml) and water (3x50 ml). The organic phase was extracted with NaOH solution (0.5 M, 250 ml). The basic extract was washed with EtOAc (200 ml) and acidified with concentrated HCl. The yellow oil was extracted with ethyl acetate (3x100 ml), and the organic phase was washed with water (100 ml), saturated brine (100 ml), and dried ($MgSO_4$). The solvent was removed under reduced pressure to give 6-chloropurine riboside-2',3'-di-o-isopropylidene-5'-uronic acid (20.3 g, 57%) as a light orange solid, mp 135-152°C.

Analytical sample recrystallized from aqueous MeOH, mp 180-210° (dec).

N^6-(2-(3,5-Dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-2',3'-di-o-isopropylidene-5'-uronic acid

A solution of 6-chloropurine riboside-2',3'-di-o-isopropylidene-5'-uronic acid (3.41 g, 10 mmol), 2-(3,5-dimethoxyphenyl)-2-(methylphenyl)ethylamine (2.71 g, 10 mmol) and NEt_3 (3.03 g, 30 mmol) were refluxed in EtOH (100 ml) stirring under N_2 for 18 hours. The solvent was removed under reduced pressure, and the residue was dissolved in NaOH solution (0.25 M, 50 ml), washed with EtOAc (2x25 ml), acidified with concentrated HCl, and then extracted with EtOAc (3x30 ml). The combined organic extracts were washed with water (2x25 ml), saturated brine (25 ml), and dried ($MgSO_4$). The solvent was removed under reduced pressure to give N^6-(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-2',3'-di-o-isopropylidene-5'-uronic acid (4.94 g, 82%) as a light yellow solid foam, mp 113-121°C.

N^6-(2-(3,5-Dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-5'-uronic acid

N^6-(2-(3,5-Dimethoxyphenyl)-2-(2-methylphenyl)ethyl) adenosine-2',3'-di-o-isopropylidene-5'-uronic acid (1.50 g, 2.6 mmol) was stirred in aqueous TFA (10 ml, 1:9) under N_2 at 0°C for 4 hours. The reaction mixture was quenched by pouring onto EtOAc (50 ml), and most of the TFA was washed out with NaOH solution (2.2 M, 50 ml) and NaH_2PO_4 solution (0.2 M, 50 ml). The organic phase was washed with saturated brine (50 ml), dried ($MgSO_4$), and the solution concentrated under reduced pressure before residual volatiles were azeotroped three times with toluene. The residual solid foam was dissolved in EtOH (24 ml) and triturated with ether to give N^6-(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-5'-uronic acid (0.71 g, 51%) as a white powder, mp 129-139°C.

EXAMPLE 33

$\underline{N}^6$-(2-(3,5-Dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-5'-uronamide

Dicyclohexylcarbodiimide (0.55 g, 2.7 mmol) was added to a suspension of 1-hydroxybenzotriazole (0.32 g, 2.4 mmol) in CH_2Cl_2 (20 ml) containing $\underline{N}^6$-(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-2',3'-di-$\underline{o}$-isopropylidene-5'-uronic acid (Example 32, 1.15 g, 2 mmol) stirred under N_2 at 0°. After 10 minutes NH_3 was bubbled through the mixture for 15 minutes at 0°C, and then the mixture was allowed to warm up to 25°C. It was then vacuum filtered, the residue rinsed with CH_2Cl_2 (10 ml) and the solvent removed from the combined filtrates under reduced pressure. The residual glassy solid was dissolved in aqueous TFA (10 ml, 1:9) and stirred under N_2 at 0°C for 2.5 hours. The reaction mixture was poured onto NaOH solution (125 ml, 1 M) and was extracted with EtOAc (100 ml). The organic layer was washed with water (50 ml), saturated brine (50 ml), and dried (MgSO4). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica (150 g) eluting with 5% MeOH in $CHCl_3$ to give $\underline{N}^6$-(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl) ethyl)adenosine-5'-uronamide (0.71 g, 61%) as a white crystalline solid, mp 181-184°C.

EXAMPLE 34

$\underline{N}^{5'}$-Methyl-$\underline{N}^6$-(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl) adenosine-5'-uronamide

Triethylamine (0.61 g, 6 mmol) and methylamine hydrochloride (0.27 g, 4 mmol) were added sequentially 1 minute apart to a suspension of $\underline{N}$-methyl-2-fluoropyridinium tosylate (0.42 g, 1.5 mmol) and N^6-(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-2',3'-di-$\underline{o}$-isopropylidene-5'-uronic acid (Example 32, 0.58 g, 1 mmol) in CH_2Cl_2 (5 ml) stirred under N_2 at 0°C. After 1 hour the reaction mixture was diluted with EtOAc (25 ml) and washed with dilute HCl (1 M, 10 ml), water (10 ml), saturated brine (10 ml), and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residual solid foam was dissolved in aqueous TFA (5 ml, 1:9 at 0°C) and stirred under N_2 for 2 hours. The reaction was quenched by addition of EtOAc (50 ml), and washing with NaOH solution (1 M, 50 ml) dilute Na_2CO_3 solution (50 ml), and saturated brine (25 ml), and drying ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by preparative TLC (silica) eluting with 10% MeOH in $CHCl_3$ to give $\underline{N}^{5'}$-methyl-$\underline{N}^{6}$-(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl) ethyl)adenosine-5'-uronamide (0.36 g, 64%) as a white glassy foam, mp 122-127°C.

EXAMPLE 35

$\underline{N}^{5'}$-Ethyl-$\underline{N}^{6}$-(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl) adenosine-5'-uronamide

Dicyclohexylcarbodiimide (0.52 g, 2.5 mmol) was added to a suspension of 1-hydroxybenzotriazole (0.27 g, 2 mmol) in CH_2Cl_2 (20 ml) containing $\underline{N}^{6}$-(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-2',3'-di-$\underline{o}$-isopropylidene-5'-uronic acid (Example 32, 1.15 g, 2 mmol) stirred under N_2 at 0°C. After 10 minutes ethylamine (0.27 ml, 4 mmol) was added. After 16 hours the reaction mixture was filtered, and the residue was rinsed with CH_2Cl_2 (10 ml). The solvent was removed from the combined filtrates under reduced pressure and the residual light yellow solid foam was dissolved in aqueous TFA (10 ml, 1:9) at 0°C and stirred under N_2 for 75 minutes. The reaction mixture was quenched with EtOAc (100 ml) and washed with NaOH solution (1 M, 100 ml), saturated Na_2CO_3 solution (50 ml), saturated brine (50 ml), and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (100 g) eluting with 5% MeOH in $CHCl_3$ to give $\underline{N}^{5'}$-ethyl-$\underline{N}^{6}$-(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-5'-uronamide (0.86 g, 72%) contaminated with ≈10 mol% dicyclohexylurea, as a pale yellow solid foam, mp 103-112°C.

EXAMPLE 36

$\underline{N}^{5'}$-Cyclopropyl-$\underline{N}^{6}$-(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-5'-uronamide

Triethylamine (0.20 g, 2 mmol) and cyclopropylamine (0.11 g, 2 mmol) were added sequentially 2 minutes apart to a mixture of N-methyl-2-fluoropyridinium tosylate (0.42 g, 1.5 mmol) and $\underline{N}^{6}$-(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-2',3'-di-o-isopropylidene-5'-uronic acid (Example 32, 0.58 g, 1.0 mmol) stirred in CH_2Cl_2 (5 ml) under N_2 at 25°C. After 15 minutes the reaction mixture was diluted with EtOAc (25 ml), and washed with dilute HCl (0.5 M, 10 ml), water (10 ml), saturated brine (10 ml), and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residual solid foam was stirred in aqueous TFA (5 ml, 1:9) under N_2 at 0°C for 2 hours. The reaction mixture was quenched with EtOAc (50 ml), and washed with NaOH solution (1 M, 50 ml), dilute Na_2CO_3 solution (50 ml), saturated brine (25 ml), and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by preparative TLC, eluting with 10% MeOH in CH_2Cl_2, to give $\underline{N}^{5'}$-cyclopropyl-$\underline{N}^{6}$-(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-5'-uronamide (0.39 g, 67%) as a white glass, mp 117-126°C.

EXAMPLE 37

$\underline{N}^{5'}$-Ethyl-$\underline{N}^{6}$-((-)-2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-5'-uronamide

N-Ethyl-6-chloropurine-ribofuranuronamide-2',3'-di-o-isopropylidene

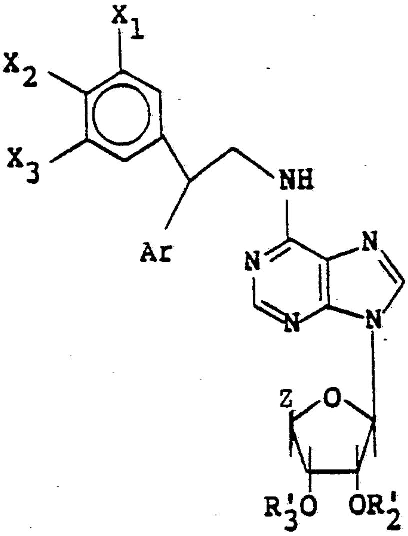
Triethylamine (1.01 g, 10 mmol) was added to a suspension of 6-chloropurine ribofuranuronic acid-2',3'-di-o-isopropylidene (1.70 g, prepared in Example 32) and N-methyl-2-fluoropyridinium tosylate (2.12 g, 7.5 mmol) stirred in CH_2Cl_2 (25 mL) under N_2 at 0°C. After 15 minutes ethylamine (1 mL, ≈15 mmol) was added. After a further 1 hour the reaction mixture was poured onto dilute HCl, (1N, 25 mL), the layers separated, and the aqueous layer extracted with CH_2Cl_2 (25 mL). The combined organic phases were washed with water (25 mL), saturated brine (25 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel, eluting with hexane/EtOAc to give N-ethyl-6-chloropurine-ribofuranuronamide-2',3'-di-o-isopropylidene (1.20 g, 65%) as an offwhite solid foam; mp 73-80°C.

$N^{5'}$-Ethyl-N^6-((-)-2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl) ethyl)adenosine-5'-uronamide

(-)-2-(3,5-Dimethoxyphenyl)-2-(2-methylphenyl)ethylamine (0.17 g, 0.6 mmol, prepared as in Example 29), N-ethyl-6-chloropurine-ribofuranuronamide-2',3'-di-o-isopropylidene (0.22 g, 0.6 mmol) and triethylamine (0.12 g, 1.2 mmol) were refluxed in EtOH (6 mL) under N_2 for 20 hours. The volatiles were removed under reduced pressure and the residual glass was stirred in aqueous TFA (1:9, 5 mL) under N_2 at 0°C for 2 hours. The mixture was diluted with EtOAc (50 mL) and washed with dilute NaOH (1M, 50 mL), dilute Na_2CO_3 solution (50 mL), saturated brine (50 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by preparative tlc (10% MeOH in $CHCl_3$, rf 0.28) to give $N^{5'}$-ethyl-N^6-((-)-2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-5-uronamide (0.28 g, 83%) as a white glass; mp 110-120°C.

CLAIMS

1. A compound of the formula



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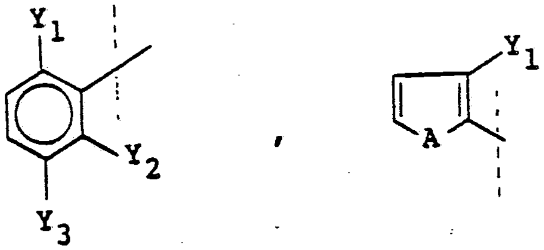
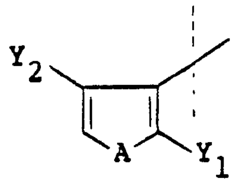
or a pharmaceutically acceptable acid addition salt thereof; wherein Ar is



or

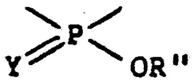


wherein A is oxygen or sulfur and wherein X_1, X_2, X_3, Y_1, Y_2 and Y_3 may be independently selected from hydrogen, halogen, lower alkyl, lower alkylthio or alkoxy, and X_1, X_2, X_3 may also be trifluoromethyl with the proviso that Y_2 or Y_3 must be hydrogen and Y_2 and Y_3 taken together are $-(CH)-_4$ with the further overall proviso that at least two of X_1, X_2, X_3, Y_1, Y_2 and Y_3 are not hydrogen.

R_2' and R_3' are each independently hydrogen, alkanoyl having two to twelve carbon atoms in a straight or branched alkyl chain which may be substituted by amino, benzoyl or benzoyl substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; additionally, R_2' and R_3' may be linked together to form either a five-membered alkylidene ring having a total of up to twenty carbons such as, for example, isopropylidene, or a cyclic phosphate diester and R_5' may be a phosphate, hydrogen or dihydrogen phosphate, or an alkali metal or ammonium or dialkali or diammonium salt thereof; and

Z is $-(CH_2)-Q$ wherein Q is selected from the group consisting of hydrogen, hydroxy, halogen, cyano, azido, amino, lower alkoxy, lower acyloxy, lower thioalkyl, lower sulfonylalkyl,

$-P(=Y)(OR")_2$, $-P(=Y)(OR")(OR'")$ and taken together with R^3 is



wherein Y is oxygen or sulfur and R" and R'" are independently hydrogen or lower alkyl; or (2)

$$\begin{array}{c}\mathrm{TC}\\ \|\\ \mathrm{J}\end{array}$$

wherein J is O, S, NR_7 wherein R_7 is hydrogen, lower alkyl or cycloalkyl of from 3 to 7 carbons such as cyclopropyl, cyclobutyl, cyclopentyl and the like or 1- or 2-methylcyclopropyl, 1-, or 2-ethylcyclobutyl and the like; and

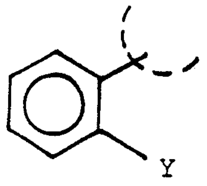
T is (a) NR_4R_5 wherein R_4 is straight chain lower alkyl having 1-4 carbon atoms; hydroxy, lower alkoxy or halogen substituted straight chain lower alkyl having 1-4 carbon atoms; cyclopropyl; secondary alkyl having 3-6 carbon atoms; hydroxy, lower alkoxy or halogen substituted secondary alkyl having 3-6 carbon atoms; alkenyl having 3 to 6 carbon atoms; aralkyl having 1 to 4 carbons in the alkyl chain and optionally substituted in the aryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups; and heteroarylalkyl having 1 to 4 carbons in the alkyl chain and optionally substituted in the heteroaryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups, and

R_5 is hydrogen or straight chain lower alkyl having 1 to 4 carbons; or

(b) OR_4 wherein R_4 is as defined above.

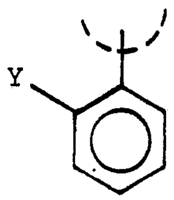
2. A compound of Claim 1 wherein Z is -(CH_2)-Q wherein Q is OH.

3. A compound of Claim 2 wherein R_2' and R_3' are OH, and Ar is



wherein Z is as defined above, Y is Y_1 as defined above when Y_1 is not hydrogen.

4. A compound of Claim 2 wherein X_1, X_2, wherein Ar is



wherein Y is as defined above, and Z is -C(O)N(H)C_2H_4.

5. A compound of Claim 1 and being N,6-(2-(2,6-dimethylphenyl)-2-phenethyl)adenosine.

6. A compound of Claim 1 and being N,6-(2-(2,6-dimethylphenyl)-2-(4-methylphenyl)ethyl)adenosine.

7. A compound of Claim 1 and being N,6-(2-(3,5-dimethylphenyl)-2-phenethyl)adenosine.

8. A compound of Claim 1 and being N,6-(2-naphth-1-yl-2-phenethyl)adenosine.

9. A compound of Claim 1 and being N,6-(2-(3,5-dichlorophenyl)-2-(2,6-dimethylphenyl)ethyl)adenosine.

10. A compound of Claim 1 and being N,6-(2-(2,6-dichlorophenyl)-2-(phenethyl)adenosine.

11. A compound of Claim 1 and being N,6-(2-(3,5-dichlorophenyl)-2-phenethyl)adenosine.

12. A compound of Claim 1 and being N,6-(2-(3-chlorophenyl)-2-(3,5-dichlorophenyl)ethyl)adenosine.

13. A compound of Claim 1 and being N,6-(2-(3-chlorophenyl)-2-(2,6-dichlorophenyl)ethyl)adenosine.

14. A compound of Claim 1 and being N,6-(2-(3-chlorophenyl)-2-(3,5-dimethoxyphenyl)ethyl)adenosine.

15. A compound of Claim 1 and being N,6-(2-(3,5-dimethoxyphenyl)-2-phenethyl)adenosine.

16. A compound of Claim 1 and being N,6-(2-(2,5-dimethoxyphenyl)-2-phenethyl)adenosine.

17. A compound of Claim 1 and being N,6-(2-(2,6-dimethoxyphenyl)-2-phenethyl)adenosine.

18. A compound of Claim 1 and being N,6-(2-(2-methoxyphenyl)-2-(3-methoxyphenyl)ethyl)adenosine.

19. A compound of Claim 1 and being N,6-(2-(3,4-dimethoxyphenyl)-2-phenethyl)adenosine.

20. A compound of Claim 1 and being N,6-(2-(3,5-diethoxyphenyl)-2-phenethyl)adenosine.

21. A compound of Claim 1 and being N,6-(2-(3,5-dimethoxyphenyl)-2-thien-2-yl)ethyl)adenosine.

22. A compound of Claim 1 and being N,6-(2-(3,5-dimethoxyphenyl)-2-naphth-1-ylethyl)adenosine.

23. A compound of Claim 1 and being N,6-(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine.

24. A compound of Claim 1 and being N,6-(2-(3,5-dimethoxyphenyl)-2-(2,6-dimethylphenyl)ethyl)adenosine.

25. A compound of Claim 1 and being N,6-(2-(3,5-dimethoxyphenyl)-2-(3-methoxyphenyl)ethyl)adenosine.

26. A compound of Claim 1 and being N,6-(2-(3,4,5-trimethoxyphenyl)-2-phenethyl)adenosine.

27. A compound of Claim 1 and being N,6-(2-(3,5-dimethoxyphenyl)-2-(2-methoxyphenyl)ethyl)adenosine.

28. A compound of Claim 1 and being N,6-(2-(3,4,5-trimethoxyphenyl)-2-(methylphenyl)ethyl)adenosine.

29. A compound of Claim 1 and being N,6-(2-(2-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethyl)adenosine.

30. A compound of Claim 1 and being N,6-(2-(2-methoxyphenyl)-2-(3-trifluoromethylphenyl)ethyl)adenosine.

31. A compound of Claim 1 and being N,6-(2-(2-methoxyphenyl)-2-(3,5-bis(trifluoromethyl)phenyl)ethyl) adenosine.

32. A compound of Claim 1 and being N^6-((-)-2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine.

33. A compound of Claim 1 and being N^6-((+)-2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine.

34. A compound of Claim 1 and being 5'-bromo-5'-deoxy-N^6-(2-3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine.

35. A compound of Claim 1 and being N^6-(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-5'-uronic acid.

36. A compound of Claim 1 and being N^6-(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-5'-uronamide.

37. A compound of Claim 1 and being N$^{5'}$-methyl-N^6-(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-5'-uronamide.

38. A compound of Claim 1 and being N$^{5'}$-ethyl-N^6-(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-5'-uronamide.

39. A compound of Claim 1 and being N$^{5'}$-cyclopropyl-N^6-(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl) adenosine-5'-uronamide.

40. A compound of Claim 1 and being N,6-(2-(3,5-bis (trifluoromethyl)phenyl)-2-phenethyl)adenosine.

41. A compound of Claim 1 and being N$^{5'}$-ethyl-N^6-((-)-2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-5'-uronamide.

42. A pharmaceutical composition for treating psychoses, pain, angina or congestive heart failure comprising an antipsychoses, analgesic, antianginal or anticongestive heart failure effective amount of a compound of Claim 1 and a pharmacologically acceptable carrier.

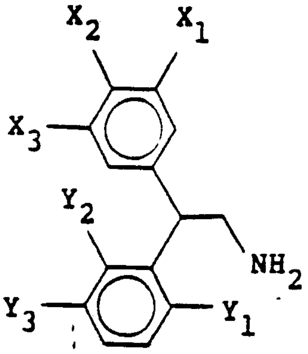
43. A method of treating psychoses in mammals suffering therefrom comprising administering to said mammals a compound of Claim 1 in unit dosage form.

44. A method of treating pain in mammals suffering therefrom comprising administering to said mammals a compound of Claim 1 in unit dosage form.

45. A method of treating angina in mammals suffering therefrom comprising administering to said mammals a compound of Claim 1 in unit dosage form.

46. A method of treating congestive heart failure in mammals suffering therefrom comprising administering to said mammals a compound of Claim 1 in unit dosage form.

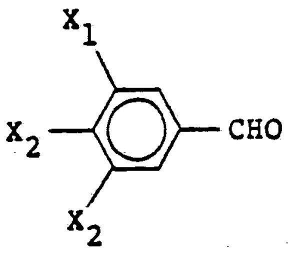
47. A process for preparing a compound of Claim 1 which comprises coupling a compound of the formula



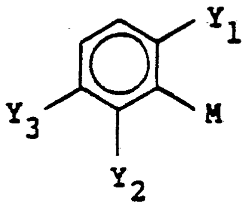
II

with 6-chloropurine riboside in the presence of triethyleneamine to obtain the compound of Claim 1.

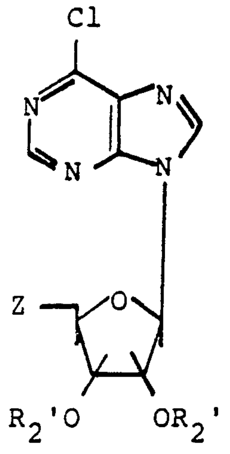
48. A process for the preparation of a compound of Claim 1 which comprises A) treating a compound of the formula



wherein X_1, X_2 and X_3 are as defined above; with 1) CH_3NO_2 in the presence of NaOH and 2) CH_3SO_2Cl in the presence of triethylamine; B) treating the product of A) with a compound of the formula

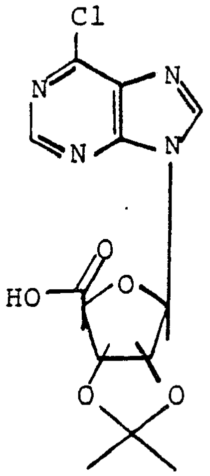


wherein Y_1, Y_2 and Y_3 are as defined above, and M is a Grignard or lithium moiety; in an aprotic solvent; then C) reducing the product of B) by treating with $LiAlH_4$ and finally D) coupling the product of C) with 6-chloropurine riboside of the formula

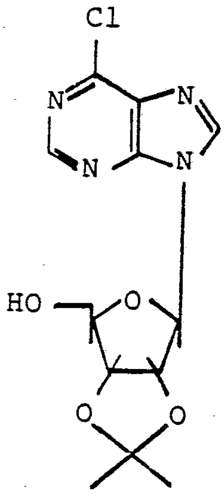


wherein Z is as defined above in the presence of triethylamine to obtain the compound of Claim 1.

49. A method for preparing a compound of the formula

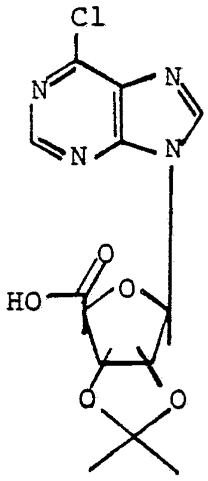


which comprises treating a compound of the formula

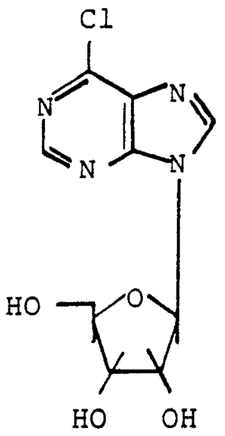


with H_2CrO_4 in acetone.

50. A process for the preparation of the compound of the formula



which comprises (1) treating a compound of the formula



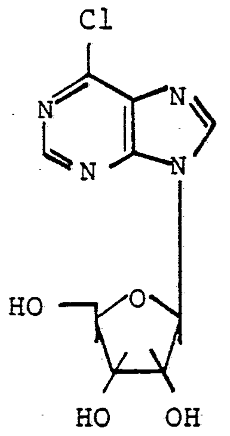
with ethyl orthoformate and tosic acid in acetone; and then (2) treating the product of step (1) with H_2CrO_4 in acetone.

51. A process for the preparation of a compound of Claim 1 wherein Z is

$$\begin{matrix} TC \\ \| \\ J \end{matrix}$$

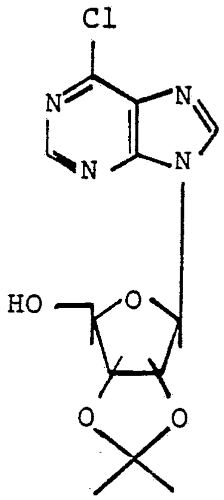
wherein J is O and T is NR_4R_5 when R_4 and R_5 are as defined above which comprises

(1) reacting a compound of the formula



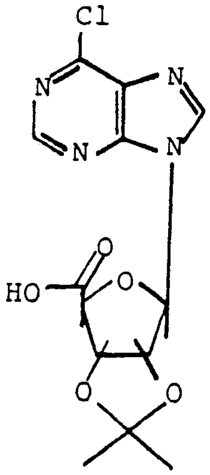
X

with ethyl formate and tosic acid in acetone; to obtain the compound of the formula



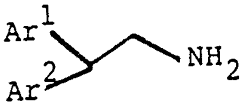
XI

(2) treating the compound of the formula XI of step (1) with H_2CrO_4 in acetone; to obtain the compound of the formula

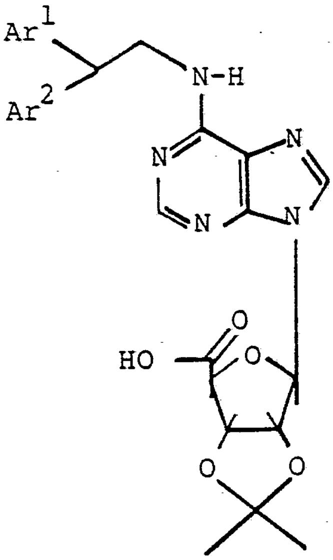


XII

then (3)(a) treating the compound of the formula XII of step (2) with

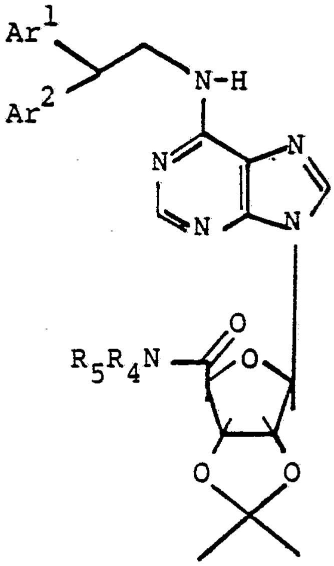


wherein Ar^1 and Ar^2 are as defined above in the presence of triethylamine; to obtain the compound of formula



XIII

and then treating the compound of formula XIII with HNR_4R_5 in the presence of a coupling agent, to obtain



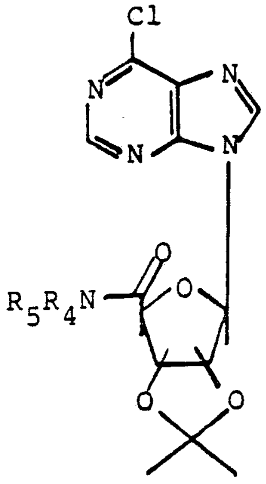
XIV

and alternatively further treating the compound of the formula XIV to obtain the compound of formula I wherein Z is

$$\begin{array}{c}TC\\ \|\\ J\end{array}$$

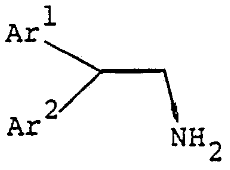
wherein J is O and T is NR_4R_5 wherein R_4 and R_5 are as defined above and R_2' and R_3' are other than propylidene; or

then (3)(b) treating the compound of formula XII of step (2) with HNR_4R_5 to obtain the compound of formula

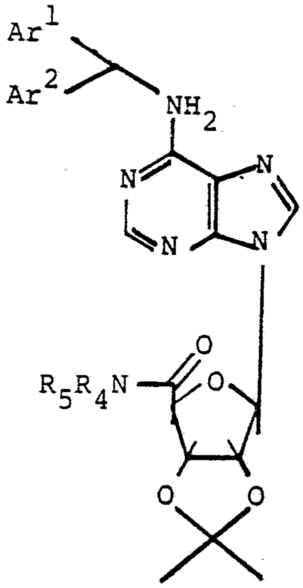


XVI

and then treating the compound of formula XVI with



to obtain the compound of the formula



XIV

and alternatively, further teaching the compound of the formula XIV to obtain the compound of formula I wherein Z is

$$\begin{array}{c} TC \\ \| \\ J \end{array}$$

wherein J is O and T is NR_4R_5 wherein R_4 and R_5 are as defined above and R_2' and R_3' are other than propylidene.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 87/02719

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

IPC^4: C 07 H 19/167; A 61 K 31/70

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC^4	C 07 H 19/00

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]
Y	EP, A, 0181129 (WARNER-LAMBERT CO.) 14 May 1986 see examples 1,6 --	1,42
Y	EP, A, 0152944 (BOEHRINGER MANNHEIM GmbH) 28 August 1985 see the whole document --	1,42
Y	EP, A, 0139358 (WARNER-LAMBERT CO.) 2 May 1985 --	1,42
A	US, A, 3781273 (BOEHRINGER MANNHEIM GmbH) 25 December 1973 see the whole document --	1,42
A	FR, A, 2195434 (BOEHRINGER MANNHEIM GmbH) 8 March 1974 see the whole document --------	1,42

* 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 15th February 1988	Date of Mailing of this International Search Report 11 APR 1988
International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer M. VAN MOL

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 8702719

SA 19648

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 23/03/88
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