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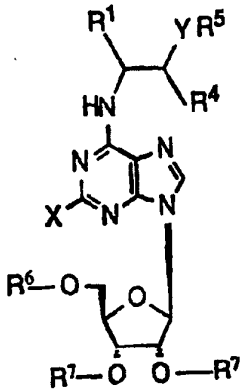

(I)

(57) Abstract

A compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein X is halogen, trifluoromethyl, cyano, C_{1-6}-alkoxy, C_{1-6}-alkylthio, C_{1-6}-alkylamino or C_{1-6}-dialkylamino; R^1 and R^4 are H or straight or branched C_{1-6}-alkyl or trifluoromethyl or R^1 and R^4 together form a cycloalkyl ring; Y is O, S, SO_2, NH or N-alkyl; R^5 is selected from optionally substituted heterocycles; R^6 and R^7 are hydrogen, benzoyl or C_{1-6}-alkanoyl. The compounds have been found useful for treating central nervous system and cardiovascular ailments.

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Purine derivatives

The present invention relates to therapeutically active *N*-substituted adenosine derivatives which are substituted at the purine 2-position and pharmaceutically acceptable addition salts thereof, processes for their preparation as well as methods for alleviation of diseases treatable *via* adenosine receptors, to compounds for use in such a method and to pharmaceutical compositions containing the said compounds.

Background of the Invention

Adenosine is a naturally occurring purine nucleoside, from which is derived a range of agonists at adenosine receptors having considerable potential in the treatment of human disease (Life Sciences, 1991, 49, 1435-1453; Journal of Medicinal Chemistry, 1992, 35, 407-422; Annual Reports in Medicinal Chemistry, 1993, 28, 295-304).

Adenosine has been shown to have a number of significant effects on the mammalian central nervous system (CNS) (Annual Reports in Medicinal Chemistry, 1988, 23, 39-48; Adenosine in the Nervous System, T.W. Stone, Ed., Academic Press Ltd., London 1991) especially under conditions of neuronal stress where the compound appears to act as an endogenous neuroprotectant (Progress in Neurobiology, 1988, 31, 85-108, Trends in Pharmacological Sciences, 1992, 11, 439-445). For example, the concentration of adenosine has been demonstrated to rise greatly in certain brain regions following epileptic seizures or conditions of neuronal ischaemia/anoxia (Brain Research, 1990, 516, 248-256).

It has been established for some years now that centrally acting adenosine receptor agonists or compounds which increase extracellular adenosine levels can exhibit what is termed neuromodulator activity (Trends in Neurosciences, 1984, 164-168). Such substances influence the release of neurotransmitters in regions of the central nervous system (Annual Review of Neuroscience, 1985, 8, 103-124; Trends in Neurosciences, 1984, 164-168), with particular inhibitory effects on the release of the excitatory amino acid glutamic acid (glutamate) in the CNS (Nature, 1985, 316, 148-150) especially under ischaemic conditions (Journal of Neurochemistry, 1992, 58, 1683-1690).

There are therefore several CNS ailments for which this adenosine receptor mediated neuromodulator activity could be of clear therapeutic benefit. Examples of these would include the treatment of convulsive disorders (European Journal of Pharmacology, 1991, 195, 261-265; Journal of Pharmacology and Experimental Therapeutics, 1982, 220, 70-76; European Journal of Pharmacology, 1993, 242, 221-228), prevention of neurodegeneration under conditions of brain anoxia/ischaemia (Neuroscience Letters, 1987, 83, 287-293; Stroke, 1988, 19, 1133-1139; Neuroscience, 1989, 30, 451-462; Pharmacology of Cerebral Ischaemia 1990, (Kriegelstein, J. and Oberpichler, H., Eds., Wissenschaftliche Verlagsgesellschaft mbH: Stuttgart, 1990, pp 439-448; Trends in Pharmacological Sciences 1992, 11, 439-445) or the use of a purinergic agent in the treatment of pain (European Journal of Pharmacology, 1989, 162, 365-369; Neuroscience Letters, 1991, 121, 267-270).

Adenosine receptors represent a subclass (P_1) of the group of purine nucleotide and nucleoside receptors known as purinoreceptors. This subclass has been further classified into two distinct receptor types which have become known as A_1 and A_2. Extensive research has been carried

out in a quest to identify selective ligands at these sites. Selective ligands exist for A_1 and A_2 adenosine receptors and the structure-activity relationships of the various reference ligands have been reviewed (Biochemical Pharmacology, 1986, 35, 2467-2481; Comprehensive Medicinal Chemistry, Volume 3, (Hansch, C., Sammes, P.G. and Taylor, J.B., Eds., Pergamon Press PLC: 1990, pp 601-642). Among the known adenosine receptor agonists most selective for the A_1 receptor over the A_2 receptor are the examples where the adenine nucleus is substituted with a cycloalkyl group on the amino function, for example *N*-cyclopentyladenosine (CPA) and *N*-cyclohexyladenosine (CHA) (Journal of Medicinal Chemistry, 1985, 28, 1383-1384) or 2-chloro-*N*-cyclopentyladenosine (CCPA) (Naunyn-Schmiedeberg's Arch. Pharmacol. 1988, 337, 687-689).

Various examples of *N*-heteroarylalkyl substituted A_1 selective adenosine analogues have been reported in the literature. It should be noted that some of these are named as N-6 or N^6-substituted adenosine derivatives, but this is equivalent to the American Chemical Society suggested nomenclature where compounds substituted on adenosine's 6-amino position are referred to as *N*-substituted adenosine derivatives.

There is evidence for further subdivision of adenosine receptors into the subtypes A_{2a}, A_{2b} (of high and low affinity), A_3 and A_4. The latest status of these subtypes has been reviewed (Journal of Biological Chemistry, 1992, 267, 6451-6454; Drug Development Research, 1993, 28, 207-213; Trends in Pharmacological Sciences 1993, 290-291). The A_3 receptor (Proceedings of the National Academy of Sciences of the USA, 1992, 89, 7432-7436) appears to be responsible for some of the cardiovascular effects of reference ligands (British Journal of Pharmacology, 1993, 109, 3-5).

The synthesis and pharmacological properties of *N*-thienylalkyl and *N*-pyridylalkyl adenosine derivatives has been published in the scientific literature (e.g. Nucleosides and Nucleotides, 1992, 11, 1077-1088; Nucleosides and Nucleotides, 1991, 10, 1563-1572; Canadian Journal of Pharmacology, 1986, 333, 313-322). Furthermore, 2-substituted *N*-piperidinyladenosine derivatives have been described recently (Bioorganic and Medicinal Chemistry Letters, 1993, 3, 2661-2666).

Certain *N*-imidazolylalkyl and *N*-indolylalkyl adenosine derivatives have also been described (Life Sciences, 1987, 41, 2295-3202; Justus Liebigs Annalen der Chemie 1976, 4, 745-761; Chemical & Pharmaceutical Bulletin, 1974, 22, 1410-13, Biochemical Pharmacology, 1974, 23, 2883-2889).

Various studies of the 6-amino subregion of adenosines which include *N*-heteroarylalkyl substituents have been published (Journal of Medicinal Chemistry 1986, 29, 989-996; Naunyn-Schmiedeberg's Archives of Pharmacology, 1986, 333, 313-322; Biochemical Pharmacology, 1986, 35, 2467-2481).

Examples of modified adenosine derivatives containing a range of *N*-heteroarylalkyl substituents have been claimed in several patents and patent applications. For example EP 0 232 813 A2 includes *N*-heteroarylcycloalkylmethyl adenosines which are apparently useful as analgesics, antipsychotics, sedatives, antihypertensives and antianginals.

US 4,600,707 discloses *N*-benzothienyl adenosines and the corresponding *N*-oxide and *S*-dioxides as antipsychotics.

In WO 8504882 *N*-heteroarylethyl adenosines are claimed as cardiac vasodilators. Some similar analogues containing *N*-heteroarylalkyl

adenosine compounds are included in Ger. Offen. DE 2147314, Ger. Offen. DE 2139107, EP 0 423 776 A2, EP 0 423 777 A2, US 4,340,7-30 and US 1,164,580 without any mention being made of their potential pharmacological effects on the CNS.

PCT-publication WO 9205177 and USP 3,901,876 discloses *N*-substituted adenosine derivatives with hypotensive properties, none of them being further substituted at the purine 2-position.

Utility of adenosine receptor agonists as cerebral neuroprotectants is claimed in the following patents and patent publications: WO 90/05526, EP 0490818A1, US 5,187,162, EP 526866A1, US 5,219,839, WO 93/08206, WO 93/23417 and WO 93/23418.

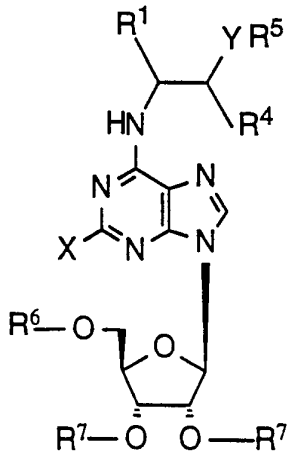
The present invention relates to new adenosine analogues having potent binding *in vitro* to the adenosine A_1 receptor and at the same time showing selectivity for A_1 receptor binding *in vitro* over that of the A_2 receptor subtype (for method description, see European Journal of Pharmacology, 1993, 242, 221-228). In addition, the compounds contained in this invention have a relatively high lipophilicity, especially when compared to adenosine analogues which are not substituted on the 6-amino group or at the purine 2-position. This latter property makes these compounds suitable for passage across the blood brain barrier, and supports the suggestion that the compounds may be candidate drugs for the CNS and other ailments mentioned within this invention.

The possibility that some of the compounds may be substrates for nucleoside-specific active transport systems across the blood brain barrier is, however, not excluded. These useful properties support the suggestion that the compounds may be candidate drugs for the CNS ailments mentioned above in humans. There are however instances where it has been demonstrated that co-administration of a peripherally

active adenosine receptor antagonist can lower the expected dose related side effects on the cardiovascular system when an adenosine agonist is used as a neuroprotectant in animal models (Journal of Molecular Neuroscience, 1990, 2, 53-59). This method of lowering potential side-effects is also applicable during the therapeutic use of the adenosine receptor agonists covered by the present invention.

The invention also covers the potential prodrugs of the adenosine derivatives described above. Adenosine sugar moiety esters which can find utility as prodrugs are exemplified in this patent.

The compounds of the invention are purine derivatives of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein

X is halogen, amino, trifluoromethyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, cyano, C_{1-6}-alkylamino or di-C_{1-6}-alkylamino;

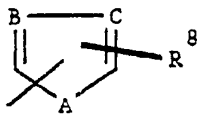
R^1 is H or straight or branched C_{1-6}-alkyl or trifluoromethyl;

R^4 is H or straight or branched C_{1-6}-alkyl;

or R^1 and R^4 together form a cyclobutyl, cyclopentyl or cyclohexyl ring;

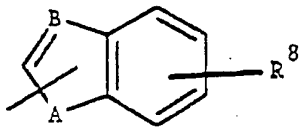
Y is O, S, SO_2, N-H or N-alkyl;

R^5 is a group of formula (XI) or (XII):



(XI)

or



(XII)

wherein A is -NH-, -O- or -S-;

B is -CH- or -N-;

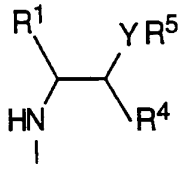
C is -CH- or -N-;

which may be optionally substituted with R^8 which is H, phenyl, C_{1-6}-alkyl, tri-fluoromethyl, amino, hydroxy, C_{1-6}-alkoxy, cyano or halogen;

R^6 is hydrogen, benzoyl or C_{1-6}-alkanoyl and

R^7 is hydrogen, benzoyl or C_{1-6}-alkanoyl.

In certain examples, the group



can contain one or more asymmetric carbon atoms in addition to those asymmetric centres already present in the ribose moiety of these adenosine agonists. The invention includes all resulting diastereoisomers and mixtures thereof.

The compounds according to the invention includes various salts which can be considered physiologically acceptable. These include addition salts derived from inorganic or organic acids, for example, acetates, fumarates, glutarates, glutaconates, hydrochlorides, lactates, maleates, methanesulphonates, phosphates, salicylates, succinates, sulphates, sulphamates, tartrates and *para*-toluenesulphonates. In some cases,

solvates of either the free nucleosides or the acid addition salts can be isolated and these solvates may, for example, be hydrates or alcoholates.

Compounds accordimg to the invention are for instance:

[1S,trans]-*N*-[2-[(2-Benzothiazolyl)thio]cyclobutyl]-2-chloroadenosine,
[1R,trans]-*N*-[2-[(2-Benzothiazolyl)thio]cyclobutyl]-2-chloroadenosine,
[1S,cis]-*N*-[2-[(2-Benzothiazolyl)thio]cyclobutyl]-2-chloroadenosine,
[1R,cis]-*N*-[2-[(2-Benzothiazolyl)thio]cyclobutyl]-2-chloroadenosine,
[1S,trans]-*N*-[2-[(2-Benzothiazolyl)thio]cyclohexyl]-2-chloroadenosine,
[1R,trans]-*N*-[2-[(2-Benzothiazolyl)thio]cyclohexyl]-2-chloroadenosine,
[1S,cis]-*N*-[2-[(2-Benzothiazolyl)thio]cyclohexyl]-2-chloroadenosine,
[1R,cis]-*N*-[2-[(2-Benzothiazolyl)thio]cyclohexyl]-2-chloroadenosine,
N-[(R)-1-(2-Benzothiazolyl)thio-2-propyl]-2-methoxyadenosine,
N-[(R)-1-(2-Benzothiazolyl)oxy-2-propyl]-2-chloroadenosine or
2-Chloro-*N*-[(R)-1-(6-hydroxy-2-benzothiazolyl)thio-2-propyl]adenosine.

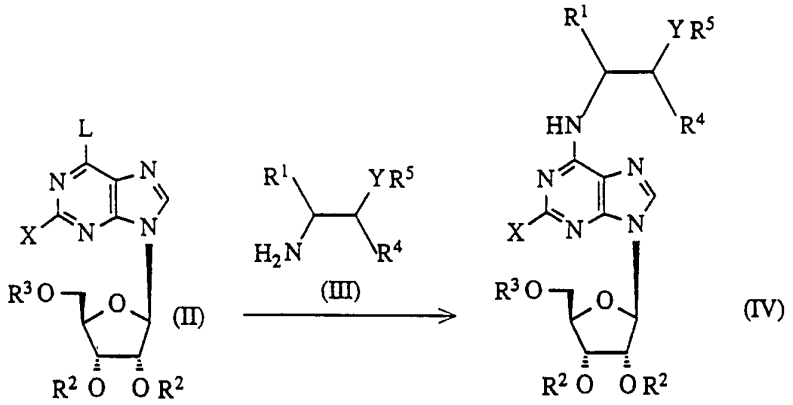
Compounds of formula (I), which act as adenosine receptor agonists, are expected from observations in animal models to be useful in the treatment of central nervous system conditions such as anxiety, neuronal ischaemia/anoxia, convulsive disorders (f. inst. epilepsy) and neurodegeneration (including Parkinson's disease) in humans. This includes treating disorders where the blood flow to regions of the brain is interrupted, for example during traumatic head injury, cardiac arrest and stroke.

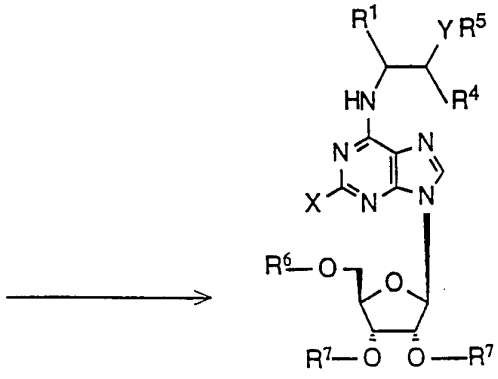
Further, the compounds of formula (I) are expected to be useful as analgesic agents, in lowering plasma free fatty acid levels or as cardiovascular agents, e.g. for the treatment of myocardial ischaemia.

The invention also relates to methods of preparing the above mentioned compounds. These methods comprise:

Method A

A compound of formula (I) may be prepared by reacting a substance of formula (II), wherein L represents a leaving group such as a halogen atom (e.g. a chlorine or bromine atom) or a trimethylsilyloxy group, R^2 and R^3 are the same or different and represent hydrogen or a protecting group such as benzoyl-, p-toluoyl-, C_{1-6}-alkanoyl- (e.g. acetyl-), a 2,3-*O*-(1-methyl)- ethylidene group or a substituted silyl group (e.g. a trimethylsilyl or t-butyldimethylsilyl group) (for descriptions see Nucleic Acid Chemistry, Townsend L.B. and Tipson, R.S., eds., John Wiley and Sons Inc., 1986, 3. and earlier volumes) with an amine derivative of general formula (III), synthesised according to methods known in the art (see for example WO 93/08206 and WO 93/23418)

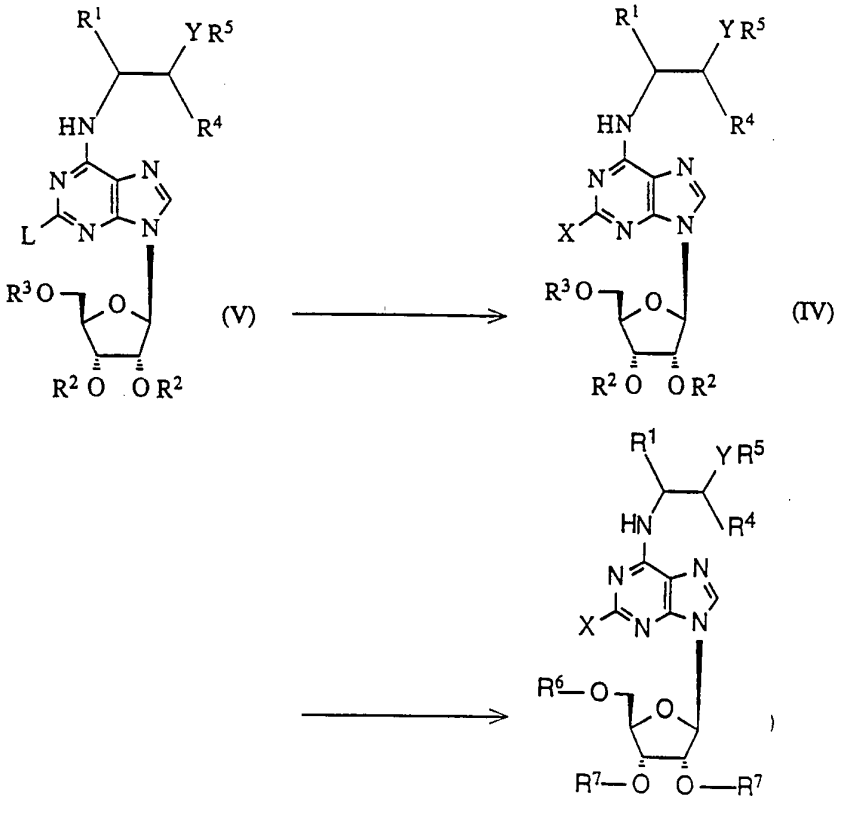




giving the compound of formula (IV) as the reaction product. In cases where R^2 and R^3 are not hydrogen an additional step will be required to remove protecting groups from a compound of formula (IV); in cases where the groups R^2 and R^3 are for example C_{1-6}-alkanoyl- or benzoyl-, suitable conditions for deprotection include methanolic ammonia, an alkali metal carbonate in methanol, an alkali metal alkoxide in the corresponding alcohol. Where the protecting groups are for example alkylsilicon or arylsilicon derivatives, suitable deprotection methods include for example treatment with tetraalkylammonium fluorides or aqueous hydrolysis in the presence of acid or base.

Method B

A compound of formula (I) wherein X represents -NH-R^9, S-R^9 or -O-R^9, where R^9 is C_{1-6}-alkyl may be prepared by reacting a substance of general formula (V)

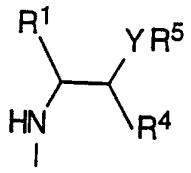


(V) (IV)

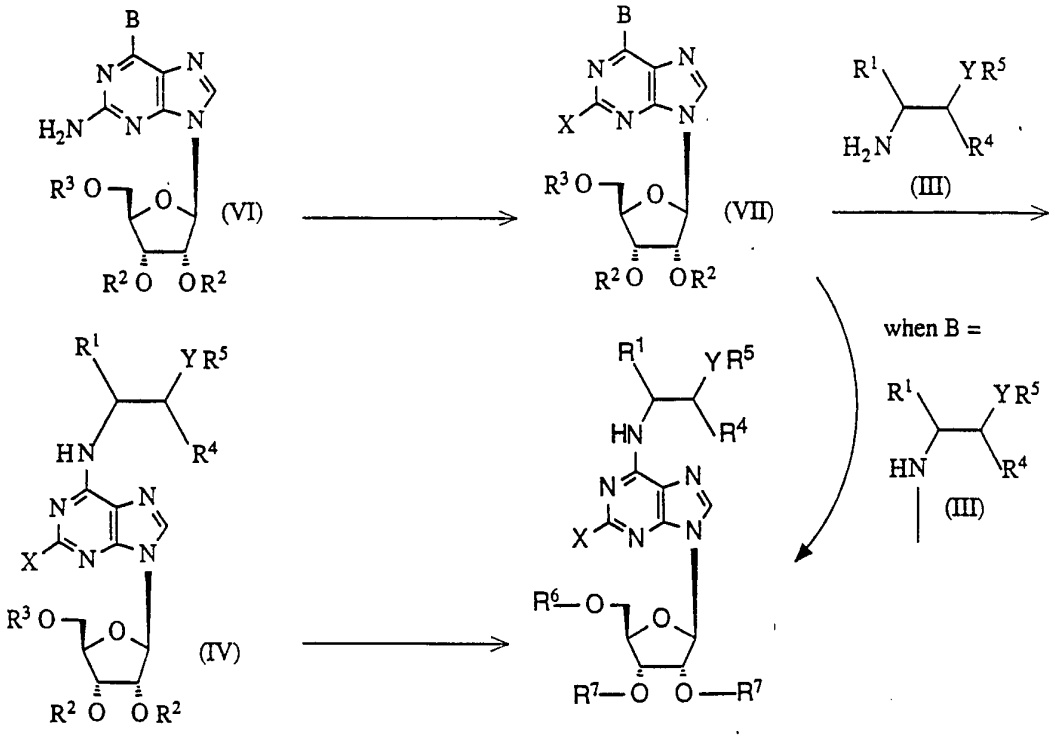
(where L is a leaving group as defined in method (A)) with a nucleophile, for example C_{1-6}-alkylamino (optionally in the presence of a suitable base) or with the anion (C_{1-6}-alkoxide or C_{1-6}-thioalkoxide) to afford (IV). In cases where R^2 and R^3 are hydrogen, a compound of formula (I) can be obtained directly. However, in cases where R^2 and R^3 are not hydrogen an additional step will be involved to remove protecting groups such as C_{1-6}-alkanoyl- or benzoyl- from a compound of formula (IV); examples of conditions for removal of protecting groups are given in process (A). In some reactions involving nucleophilic substitution of a compound of formula (V) with the anion (C_{1-6}-alkoxide or C_{1-6}-thioalkoxide), where R^2 and R^3 are for example C_{1-6}-alkanoyl- or benzoyl- partial or full deprotection may take place. In cases where only partial deprotection has taken place, deprotection can be completed under conditions exemplified in method (A).

Method C

A compound of formula (I) may be prepared by reacting a substance of the general formula (VI) (where B represents



or L as defined previously) with a diazotising agent (such as, for example, 3-methylbutyl nitrite) to form a diazo-intermediate which can be reacted further with a variety of substrates (for example chloroform, tetrachloroethane, trimethylsilylchloride, bromoform or fluoroboric acid) as exemplified below in order to introduce the group -X into a compound of formula (VII).



In the case where B represents a leaving group L, a further displacement reaction with for example a compound of formula (III) will be required in order to obtain a compound of formula (IV). In cases where the groups R^2 and R^3 are not hydrogen, or not all hydrogen, another step will be required to remove protecting groups from a compound of formula (IV); conditions for removing protecting groups are described in method A.

Compounds of formula (I) in which R^6 and R^7 are C_{1-6}-alkanoyl- or benzoyl-, may be prepared according to methods A-C as compounds of formula (IV) and (VII) in which R^2 and R^3 are represented by C_{1-6}-alkanoyl- or benzoyl-. In cases where R^2 and R^3 are different from R^6 and R^7, R^2 and R^3 can be replaced with hydrogen, C_{1-6}-alkanoyl- or benzoyl- according to methods known in the art.

Methods for assessing adenosine receptor binding *in vitro* have been reviewed [Adenosine Receptors, (Cooper, D.M.F. and Londos, C., eds.) Alan R. Liss, Inc., New York, 1988, 43-62].

Evaluation of these compounds in established animal models has indicated that the compounds according to the invention possess desirable central nervous system properties. For example, they act as anticonvulsant agents, are effective in animal paradigms of pain, and show cerebroprotective effects in laboratory test animals subjected to simulated cerebral ischaemia. In addition, the compounds may have efficacy as neuroprotective agents in cases of cerebral oedema and traumatic head injury, and as protectants in myocardial ischaemia.

Evaluation of *in vitro* binding to adenosine A_1 and A_2 receptors

The affinity of the novel compounds described in this invention for the adenosine A_1 receptor was determined essentially as described in the literature using [^{3}H]-(R)-PIA [*N*-(R)-(1-phenyl-2-propyl)adenosine] as a radioligand (Naunyn-Schmiedeberg's Archives of Pharmacology, 1980, 313, 179-187). Affinity for the A_2 receptor was measured using the radioligand [^{3}H]-CGS 21680 (European Journal of Pharmacology, 1989, 168, 243-246), and the values for representative compounds (single determinations only) are given in the table below. *In vitro* receptor binding values obtained for the reference standards CPA and (R)-PIA are included for comparison. The methods used are described fully in European Journal of Pharmacology, 1993, 242, 221-228.

DMCM INDUCED SEIZURES IN MICE, I.P.30 min

DMCM (methyl 6,7-dimethoxy-4-ethyl-β-carboline-3-carboxylate) is an inverse agonist at the benzodiazepine receptor, presumably producing seizures by decreasing the potency of inhibition of the GABA receptor/benzodiazepine receptor/chloride ionophore complex.

METHODS

18 mg/kg of DMCM dissolved in 0.02 N HCl (1 mg/ml) is administered i.p. in a volume of 300 μl to male NMRI mice weighing 20 $\pm$ 2 g. This induces two different responses: a) some animals manifest a brief loss of righting reflexes or take up an upright position in which they have a mild short clonus of the upper extremities, b) other animals manifest intense clonic and tonic convulsions of all extremities often followed by death. DMCM is administered 30 min after an intraperitoneal injection of a test compound. The latency time for the presence of intense clonic and tonic convulsions and death is noted until 15 min after administration of DMCM. At least 5 doses of each test compound are tested with 8 mice per dose. This method is described in more detail in European Journal of Pharmacology, 1993, 242, 221-228.

Test results obtained by testing compounds of the invention are presented in table I.

TABLE I

Adenosine agonist tested (Example No.)	A_1 receptor binding (K_i, nM)	A_2 receptor binding (K_i, nM)	Ratio A_2/A_1
13	3.4	2570	756
23	4.5	170	38
15	7	950	136
3	9	990	110
22	10	1000	100
27	14	4970	355
CPA	1.2	192	160
(R)-PIA	1.9	116	61

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, and if desired in the form of a pharmaceutically acceptable acid addition salt thereof, may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets of filled capsules, or liquids, such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral use (including subcutaneous administration and infusion). Such pharmaceutical compositions and unit dosage forms thereof may comprise con-

ventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the adenosine receptor agonist commensurate with the intended daily dosage range to be employed. Tablets containing ten (10) milligrams of active ingredient or, more broadly, ten (10) to hundred (100) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

The compounds of this invention can thus be used for the formulation of pharmaceutical preparation, e.g. for oral and parenteral administration to mammals including humans, in accordance with conventional methods of galenic pharmacy.

Conventional excipients are such pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral or enteral application which do not deleteriously react with the active compounds.

Examples of such carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose and polyvinylpyrrolidone.

The pharmaceutical preparations can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or colouring substances and the like, which do not deleteriously react with the active compounds.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Ampoules are convenient unit dosage forms.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like, the carrier preferably being lactose and/or corn starch and/or potato starch, are particularly suitable for oral application. A syrup, elixir or the like can be used in cases where a sweetened vehicle can be employed.

Generally, the compounds of this invention are dispensed in unit form comprising 0.05-100 mg in a pharmaceutically acceptable carrier per unit dosage.

The dosage of the compounds according to this invention is 0.1-300 mg/day, preferably 10-100 mg/day, when administered to patients, e.g. humans, as a drug.

A typical tablet which may be prepared by conventional tabletting techniques contains:

Active compound	5.0 mg
Lactosum	67.0 mg Ph.Eur.
Avicel™	31.4 mg
Amberlite™IRP 88	1.0 mg
Magnesii stearas	0.25 mg Ph.Eur.

As a result of their activity against pain or convulsive disorders and prevention of neurodegeneration under conditions of anoxia/ischaemia the compounds of the invention are extremely useful in the treatment of related symptoms in mammals, when administered in an amount effective for agonist activity of compounds of the invention. The compounds of the invention may accordingly be administered to a subject, e.g., a

living animal body, including a human, in need of adenosine receptor agonist, and if desired in the form of a pharmaceutically acceptable acid addition salt thereof (such as the hydrobromide, hydrochloride, or sulphate, in any event prepared in the usual or conventional manner, e.g., evaporation to dryness of the free base in solution together with the acid), ordinarily concurrently, simultaneously, or together with a pharmaceutically acceptable carrier or diluent, especially and preferably in the form of a pharmaceutical composition thereof, whether by oral, rectal, or parenteral (including subcutaneous) route, in an effective amount of adenosine receptor agonist, and in any event an amount which is effective for the treatment of anoxia, traumatic injury, ischaemia, migraine or other pain symptoms, epilepsy, or neurodegenerative diseases owing to their adenosine receptor agonist activity. Suitable dosage ranges are 1-200 milligrams daily, 10-100 milligrams daily, and especially 5-25 milligrams daily, depending as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and the preference and experience of the physician or veterinarian in charge.

The preparation of compounds of formula (I) is further illustrated in the following examples.

Hereinafter, TLC is thin layer chromatography, THF is tetrahydrofuran, TFA is trifluoracetic acid and m.p. is melting point. Where melting points are given, these are uncorrected. The structures of the compounds are confirmed by assignment of 400 MHz NMR spectra (from which representative peaks are quoted) and by microanalysis where appropriate. Compounds used as starting materials are either known compounds or compounds which can be prepared by methods known per se. Column chromatography was carried out using the technique described by Still,

W.C. *et al.*, Journal of Organic Chemistry, 1978, 43, 2923 on Merck silica gel 60 (Art 9385). HPLC was carried out on a Waters model 510 chromatograph interfaced via a system module to a Waters 490 multi-wavelength detector to a reversed phase C_{18} column (250 x 4 mm, 5μm, 100Å; eluent flow rate 1 ml/min). Retention times are given in minutes.

EXAMPLE 1

2-Chloro-*N*-[(R)-1-(2-thiazolyl)thio-2-propyl]adenosine

The title compound was prepared according to general method A.

2',3',5'-Tri-*O*-benzoyl-2-chloro-*N*-[(R)-1-(thiazolyl)thio-2-propyl]adenosine

To a suspension of 2-[(R)-*N*-*tert*-butyloxycarbonyl]amino-1-propanol (4.0 g, 23 mmol), 2-mercaptothiazole (2.9 g, 25 mmol) and triphenylphosphine (7.3 g, 28 mmol) in dry toluene (50 ml) under nitrogen, a solution of diisopropylazocarboxylate (4.9 g, 28 mmol) in dry toluene (30 ml) was added dropwise. The reaction mixture was stirred for 40 h at 20°C and filtered. The filtrate was evaporated to an oil prior to purification by "flash" chromatography. Elution with a mixture of heptane and ethyl acetate (3:2) provided 2-[2-(R)-*tert*-butyloxycarbonylamino-1-propylthio]-thiazole (3.0 g, 48%) as an oil, TLC R_f 0.33 [heptane/ethyl acetate (3:2)].

2-[2-(R)-*tert*-butyloxycarbonylamino-1-propylthio]thiazole (3.0 g, 11 mmol) was dissolved in ethyl acetate (30 ml) and a 6N solution of hydrochloric acid in dry ethyl acetate (15 ml) was added. After 20 h at room temperature the reaction mixture was filtered to provide crude 2-[(R)-2-aminopropyl-1-propylthio]thiazole as a hygroscopic, apparent dihydrochloride salt (2.3 g).

To a solution of 9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2,6-dichloro-9H-purine (1.5 g, 2.4 mmol) in dry dioxan (50 ml), the above 2-[(R)-2-aminopropyl-1-propylthio]thiazole dihydrochloride (1.5 g, 7.1 mmol) and triethylamine (0.78 g, 7.7 mmol) were introduced at 20°C. After stirring at 50°C for 40 h the reaction mixture was concentrated to a yellow oil, which was purified by flash chromatography eluting with a mixture of heptane and ethyl acetate (1:1), to afford the title 2',3',5'-tri-*O*-benzoyl-2-chloro-*N*-[(R)-1-(2-thiazolyl)thio-2-propyl]adenosine (1.2 g, 63%) as a foam, TLC R_f 0.19 [SiO_2; heptane/ethyl acetate (1:1)].

2-Chloro-*N*-[(R)-1-(2-thiazolyl)thio-2-propyl)]adenosine

2',3',5'-Tri-*O*-benzoyl-2-chloro-*N*-[(R)-1-(2-thiazolyl)thio-2-propyl]adenosine (1.2 g, 1.5 mmol) was dissolved in methanolic ammonia (25 ml) (previously saturated at -10°C) and stirred at 20°C for 40 h. The reaction mixture was concentrated to an oil at reduced pressure and purified by flash chromatography eluting with a mixture of dichloromethane, ethanol and ammonia (90:10:1), to provide the title 2-chloro-*N*-[(R)-1-(2-thiazolyl)thio-2-propyl)]adenosine (0.32 g, 46%) as a foam, ^{1}H NMR (DMSO-d_6) δ 1.31 (3H, d, CHC$\underline{H}_3$), 3.95 (1H, q, H-4'), 4.12 (1H, q, H-3'), 4.51 (1H, q, H-2'), 5.07 (1H, t, 5'-OH), 5.22, 5.50 (2H, 2d, 2'-and 3'-OH), 5.82 (1H, d, H-1'), 7.63 (1H, d, Ar-H), 7.72 (1H, d, Ar-H), 8.41 (1H, s, H-8), 8.48 (1H, d, N-H).

$C_{16}H_{19}ClN_6O_4S_2 . H_2O$ requires C, 41.1; H, 4.3; N, 18.0. Found: C, 41.2; H, 4.3; N, 17.4%.

EXAMPLE 2

2-Chloro-*N*-[(R)-1-(1-methyl-2-imidazolyl)thio-2-propyl]adenosine

The title compound was prepared according to method A as described above in Example 1 by reacting (R)-1-(1-methyl-2-imidazolyl)thio-2-propylamine hydrochloride [prepared using the same method as described in Example 1 from 2-mercapto-1-methylimidazole (3.31 g, 29 mmol) and 2-[(R)-*N*-*tert*-butyloxycarbonyl]amino-1-propanol (5.08 g, 29 mmol) followed by acidic hydrolysis] (2.30 g, 11.1 mmol) with 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-dichloro-9H-purine (2.46 g, 5.5 mmol), followed by debenzoylation of the purified product using methanolic ammonia. This provided the title 2-chloro-*N*[(R)-1-(1-methyl-2-imidazolyl)-thio-2-propyl]adenosine (1.1 g, 43%) as a foam after column chromatography. ^{1}H NMR (DMSO-d_6) δ 1.28 (3H, d, -CHC$\underline{H}_3$), 3.53 - 3.60 (1H, m, H-5'$_a$), 3.63 -3.70 (1H, m, H-5'$_b$), 3.95 (1H, q, H-4'), 4.13 (1H, q, H-3'), 4.51 (1H, q, H-2'), 5.07 (1H, t, 5'-OH), 5.22, 5.50 (2H, 2d, 2'-and 3'-OH), 5.82 (1H, d, H-1'), 6.92 (1H, s, Ar-H) 7.20 (1H, s, Ar-H), 8.40 (1H, s, H-8), 8.55 (1H, s, N-H). HPLC retention time 19.3 min [gradient elution, 20 - 80% acetonitrile/water (containing 0.1% TFA)].

$C_{17}H_{22}ClN_7O_4S$. 1.0 H_2O requires C, 43.1; H, 5.1; N, 20.7. Found: C, 43.4; H, 5.0; N, 20.7%.

EXAMPLE 3

2-Chloro-*N*-{(R)-1-[5-methyl-(1,3,4-thiadiazol-2-yl)]thio-2-propyl}-adenosine

The title compound was prepared according to method A as described above in Example 1 by reacting 2-[(R)-2-amino-1-propylthio]-5-methyl-

[1,3,4]-thiadiazole hydrochloride [prepared by alkylation of 2-mercapto-5-methyl-(1,3,4)-thiadiazole (1.32 g, 10 mmol) using methanesulphonic acid, 2-[(R)-*N*-*tert*-butyloxycarbonylamino]-1-propyl ester (3.04 g, 12 mmol) followed by acidic hydrolysis] (1.01 g, 4.47 mmol) with 9-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)-2,6-dichloro-9H-purine (2.36 g, 3.73 mmol), followed by debenzoylation of the purified product using methanolic ammonia. This provided the title 2-chloro-*N*{(R)-1-[5-methyl-(1,3,4-thiadiazol-2-yl)]thio-2-propyl}adenosine (0.94 g, 53%) as a foam after column chromatography. ^{1}H NMR (DMSO-d_6)δ 1.35 (3H, d, -CHC$\underline{H}_3$), 2.67 (3H, s, -CH_3), 3.53-3.61 (2H, m, H-5'$_a$ and H-5'$_b$), 3.96 (1H, q, H-4), 4.14 (1H, q, H-3'), 4.52 (1H, q, H-2'), 5.07 (1H, t, 5'-OH), 5.22, 5.50 (2H, 2d, 2'- and 3'-OH), 5.83 (1H, d, H-1'), 8.33-8.46 (2H, m, H-8 and -NH). HPLC retention time 9.9 min [gradient elution, 20-80% acetonitrile/water (containing 0.1% TFA)].

EXAMPLE 4

N-[(R)-1-(2-Benzoxazolyl)thio-2-propyl]-2-chloroadenosine

The title compound was prepared essentially according to method A as described above in Example 1 by reacting 2-[(R)-2-amino-1-propylthio]-benzoxazole hydrochloride [prepared by alkylation of 2-mercaptobenz-oxazole (3.5 g, 23 mmol) using methanesulphonic acid, 2-[(R)-*N*-*tert*--butyloxycarbonylamino]-1-propyl ester (7.2 g, 30 mmol) followed by acidic hydrolysis] (1.7 g, 6 mmol) with 9-(2,3,5-tri-*O*-acetyl-*β*-D-ribo-furanosyl)-2,6-dichloro-9H-purine (2.7 g, 6.0 mmol), followed by deacylation of the purified product using sodium methoxide in methanol. This provided the title *N*-[(R)-1-(2-benzoxazolyl)thio2-propyl]--2-chloroadenosine (0.37 g, 28%) as a foam after column chromatog-raphy. ^{1}H NMR (DMSO-d_6)δ 1.38 (3H, d, -CHC$\underline{H}_3$), 3.40 - 3.75 (4H, m, H-5'$_a$ and H-5'$_b$ and -CH_2-), 3.94 (1H, q, H-4), 4.12 (1H, q, H-3'), 4.52

(1H, m, H-2'), 5.06 (1H, t, 5'-OH), 5.22, 5.49 (2H, 2d, 2'- and 3'-OH), 5.82 (1H, d, H-1'), 7.26 - 7.35 (2H, m, Ar-H), 7.53 - 7.64 (2H, m, Ar-H), 8.39 (1H, s, H-8), 8.48 (1H, d, -NH).

$C_{20}H_{21}ClN_6O_5S$. 0.25 EtOH requires C, 48.8; H, 4.5; N, 16.6. Found: C, 48.6; H, 4.5; N, 16.5%.

EXAMPLE 5

N-[(R)-1-(2-Benzothiazolyl)thio-2-propyl]-2-chloroadenosine

The title compound was prepared according to general method A as described above in Example 1 by reacting 2-[(R)-2-amino-1-propylthio]benzothiazole hydrochloride [prepared by a Mitsunobu reaction as described in Example 1 using 2-[(R)-*N*-tert-butyloxycarbonyl]amino-1-propanol (2.5 g, 14 mmol) and 2-mercaptobenzothiazole (2.3 g, 14 mmol) followed by acidic hydrolysis] (1.7 g, 5.7 mmol) with 9-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)-2,6-dichloro-9H-purine (2.8 g, 4.5 mmol), followed by debenzoylation of the purified 2',3',5'-tri-*O*-benzoyl-2-chloro-*N*-[(R)-1-(2-benzothiazolyl)thio-2-propyl]adenosine in methanolic ammonia (200 ml) (previously saturated at -10°C) to provide the title 2-chloro-*N*-[(R)-1-(2-benzothiazolyl)thio-2-propyl]adenosine (1.05 g, 24%) (following column chromatography), ^{1}H NMR (DMSO-d_6) δ 1.38 (3H, d, -CHC$\underline{H_3}$), 3.50 - 3.68 (4H, m, H-5'$_a$ and H-5'$_b$ and -CH_2-), 3.95 (1H, d, H-4'), 4.12 (1H, d, H-3'), 4.51 (1H, q, H-2'), 5.07 (1H, t, 5'-OH), 5.22, 5.50 (2H, 2d, 2'-and 3'-OH), 5.83 (1H, d, H-1'), 7.34, 7.45 (2H, 2t, Ar-H), 7.85, 7.98 (2H, 2d, Ar-H), 8.40 (1H, s, H-8), 8.53 (1H, d, N-H). HPLC retention time 16.6 min [gradient elution, 20 - 80% acetonitrile/water (containing 0.1% TFA)].

$C_{20}H_{21}ClN_6O_4S_2$. 0.5 EtOH requires C, 47.4; H, 4.5; N, 15.8. Found: C,

47.3; H, 4.5; N, 15.8%.

EXAMPLE 6

N-[(S)-1-(2-Benzothiazolyl)thio-2-propyl]-2-chloroadenosine

The title compound was prepared according to general method A as described above in Example 1 by reacting 2-[(S)-2-amino-1-propylthio]benzothiazole hydrochloride [prepared by a Mitsunobu reaction as laid out in Example 1 using 2-[(S)-*N*-*tert*-butyloxycarbonyl]amino-1-propanol (3.5 g, 20 mmol) and 2-mercaptobenzothiazole (3.35 g, 20 mmol) followed by acidic hydrolysis] (1.1 g, 4.2 mmol) with 9-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)-2,6-dichloro-9H-purine (2.8 g, 4.5 mmol), followed by debenzoylation of the purified 2',3',5'-tri-*O*-benzoyl-2-chloro-*N*-[(S)-1-(2-benzothiazolyl)thio-2-propyl]adenosine using sodium methoxide in methanol to provide the title 2-chloro-*N*-[(S)-1-(2-benzothiazolyl)thio-2-propyl]adenosine (0.88 g, 49%) (following column chromatography), ^{1}H NMR (DMSO-d_6) δ 1.38 (3H, d, -CHC$\underline{H}_3$), 3.50 - 3.68 (4H, m, H-5'$_a$ and H-5'$_b$ and -CH_2-), 3.95 (1H, d, H-4'), 4.12 (1H, d, H-3'), 4.51 (1H, q, H-2'), 5.07 (1H, t, 5'-OH), 5.22, 5.50 (2H, 2d, 2'-and 3'-OH), 5.83 (1H, d, H-1'), 7.34, 7.45 (2H, 2t, Ar-H), 7.85, 7.98 (2H, 2d, Ar-H), 8.40 (1H, s, H-8), 8.52 (1H, s, N-H). HPLC retention time 20.1 min [gradient elution, 20 - 80% acetonitrile/water (containing 0.1% TFA)].

$C_{20}H_{21}ClN_6O_4S_2$. 1.5 H_2O requires C, 44.8 ; H, 4.5; N, 15.7. Found: C, 44.9; H, 4.1; N, 15.2%.

EXAMPLE 7

N-[(R)-1-(2-Benzothiazolyl)thio-2-propyl]-2-bromoadenosine

The title compound was prepared according to general method A as described above in Example 1 by reacting 2-[(R)-2-amino-1-propylthio]benzothiazole hydrochloride (prepared as indicated in Example 5) (1.07 g, 3.6 mmol) with 2-bromo-9-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)-6-chloro--9H-purine (see WO 93/08206; Bioorganic and Medicinal Chemistry Letters, 1993, 3, 2661-2666) (1.48 g, 3.0 mmol) followed by deacylation of the purified 2',3',5'-tri-*O*-acetyl-2-bromo-*N*-[(R)-1-(2-benzothiazolyl)thio-2-propyl]adenosine using sodium methoxide in methanol to provide the title *N*-[(R)-1-(2-benzothiazolyl)thio-2-propyl]-2-bromoadenosine (0.20 g, 14%) as a foam (following column chromatography), ^{1}H NMR (DMSO-d_6) δ 1.38 (3H, d, -CHC<u>H</u>$_3$), 3.50 - 3.77 (4H, m, H-5'$_a$ and H-5'$_b$ and -CH_2-), 3.94 (1H, d, H-4'), 4.12 (1H, d, H-3'), 4.51 (1H, q, H-2'), 4.70 1H, m, -C<u>H</u>CH_3), 5.05 (1H, t, 5'-OH), 5.22, 5.49 (2H, 2d, 2'-and 3'-OH), 5.83 (1H, d, H-1'), 7.36, 7.46 (2H, 2t, Ar-H), 7.86, 7.99 (2H, 2d, Ar-H), 8.40 (1H, s, H-8). HPLC retention time 6.74 min [gradient elution, 20 - 80% acetonitrile/water (containing 0.1% TFA)].

$C_{20}H_{21}N_6BrO_4S_2$. 0.1 H_2O requires C, 43.3; H, 3.8; N, 15.1. Found: C, 43.7; H, 4.3; N, 14.7%.

EXAMPLE 8

N-[(R)-1-(2-Benzothiazolyl)thio-2-propyl]-2-methyladenosine

The title compound was prepared according to general method A as des-

cribed above in Example 1 by reacting 2-[(R)-2-amino-1-propylthio]benzothiazole hydrochloride (prepared as described in Example 5) (0.89 g, 3.0 mmol) with 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-6-chloro-2-methyl-9H-purine (1.07 g, 2.5 mmol) [prepared from 2-methylinosine (Journal of Organic Chemistry, 1967, 32, 3258-3260) by standard acylation and chlorination steps]. Deacylation of the purified 2',3',5'-tri-*O*-acetyl-*N*-[(R)-1-(2-benzothiazolyl)thio-2-propyl]-2-methyladenosine using sodium methoxide in methanol to provide the desired *N*-[(R)-1-(2-benzothiazolyl)thio-2-propyl]-2-methyladenosine (0.28 g, 11%) (following column chromatography), ^{1}H NMR (DMSO-d_6) δ 1.40 (3H, d, -CHC<u>H</u>$_3$), 2.30 (3H, s, -CH_3), 3.50 - 3.77 (4H, m, H-5'$_a$ and H-5'$_b$ and -CH_2-), 3.98 (1H, d, H-4'), 4.13 (1H, d, H-3'), 4.63 (1H, q, H-2'), 4.86 (1H, br, -C<u>H</u>CH$_3$), 5.19, 5.42 (2H, 2d, 2'-and 3'-OH), 5.70 (1H, t, 5'-OH), 5.85 (1H, d, H-1'), 7.36, 7.47 (2H, 2t, Ar-H), 7.80 - 7.96 (2H, m, Ar-H), 8.0 (1H, s, N-H), 8.26 (1H, s, H-8), 8.52 (1H, s, N-H). HPLC retention time 22.4 min [gradient elution, 20 - 80% acetonitrile/water (containing 0.1% TFA)].

$C_{21}H_{24}N_6O_4S_2$. H_2O requires C, 49.8 ; H, 4.8; N, 16.6. Found: C, 49.9; H, 5.1; N, 16.4%.

EXAMPLE 9

N-[(R)-1-(2-benzothiazolyl)thio-2-propyl]-2-methylthioadenosine

The title compound was prepared according to general method A. 9-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-2-amino-6-chloro-9H-purine (Nucleic Acid Chemistry, Townsend L.B. and Tipson, R.S., eds., John Wiley and Sons Inc., 1986, 3, 144) (4.0 g, 9.3 mmol) was dissolved in acetonitrile (100 ml). Isoamylnitrite (10.84 g, 93 mmol) was introduced followed by methyl disulphide (4.14 ml, 46 mmol) and the reaction

mixture was heated at an oil bath temperature of 100°C for 2h. The evolved gas was oxidised using a hypochlorite scrubber. The reaction mixture was cooled, evaporated and purified by flash chromatography on silica gel. Elution initially with dichloromethane, followed by dichloromethane/methanol (100:1) provided 9-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)-6-chloro-2-methylthio-9H-purine (3.1 g, 72%) as a foam, ^{1}H NMR ($CDCl_3$)δ 2.12, 2.14, 2.18 (9H, 3s, 2', 3' and 5'-O-acetyl CH_3), 2.66 (3H, s, -SCH_3), 4.28 - 4.51 (3H, m, H-5'$_a$, H-5'$_b$ and H-4'), 5.66 (1H, t, H-3'), 6.0 (1H, t, H-2'), 6.13 (1H, d, H-1'), 8.11 (1H, s, H-8).

The above 9-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)-6-chloro-2-methylthio-9H-purine (0.5 g, 1.1 mmol) was reacted with 2-[(R)-2-amino-1-propylthio]benzothiazole hydrochloride (0.5 g, 1.5 mmol) (by the procedure described in Example 5) followed by deacylation of the purified 2',3',5'-tri-*O*-acetyl-*N*-[(R)-1-(2-benzothiazolyl)thio-2-propyl]-2-methylthio-adenosine using methanolic ammonia (200 ml) (previously saturated at -10°C) to provide the title compound *N*-[(R)-1-(2-benzothiazolyl)thio-2-propyl]-2methylthioadenosine (0.085 g, 16%) as a foam (following column chromatography), ^{1}H NMR (DMSO-d_6) δ 1.39 (3H, d, -CHC$\underline{H_3}$), 2.31 (3H, s, -SC$\underline{H_3}$), 3.46 - 3.71 (4H, m, H-5'$_a$ and H-5'$_b$ and -CH_2), 3.92 (1H, q, H-4'), 4.14 (1H, q, H-3'), 4.60 (1H, q, H-2'), 4.70 - 4.91 (1H, m, -CH), 5.05 (1H, t, 5'-OH), 5.22, 5.45 (2H, 2d, 2'-and 3'-OH), 5.83 (1H, d, H-1'), 7.31 - 7.53 (2H, m, Ar-H), 7.84, 8.0 (2H, 2d, Ar-H), 8.10 (1H, d, N-H), 8.25 (1H, s, H-8).

EXAMPLE 10

N-[(R)-1-(2-Benzothiazolyl)thio-2-propyl]-2-(dimethylamino)adenosine

The title compound was prepared according to general method B by

reaction of *N*-[(R)-1-(2-benzothiazolyl)thio-2-propyl]-2-chloroadenosine (1.02 g, 2.0 mmol) (Example 5) in dimethylformamide (10 ml) to provide the desired *N*-[(R)-1-(2-benzothiazolyl)thio-2-propyl]-2-(dimethylamino)-adenosine (0.12 g, 12%) as a foam (following column chromatography), ^{1}H NMR (DMSO-d_6) δ 1.38 (3H, d, -CHC<u>H</u>$_3$), 2.92 (6H, s, -N(C<u>H</u>$_3$)$_2$), 3.40 - 3.72 (4H, m, H-5'$_a$ and H-5'$_b$ and -CH_2-), 3.88 (1H, q, H-4'), 4.15 (1H, q, H-3'), 4.65 (1H, q, H-2'), 4.72 - 4.85 (1H, m, -CH-), 4.89 (1H, t, 5'-OH), 5.14, 5.36 (2H, 2d, 2'-and 3'-OH), 5.75 (1H, d, H-1'), 7.35, 7.46 (2H, 2 t, Ar-H), 7.50 (1H, d, N-H), 7.84, 7.99 (2H, 2d, Ar-H), 7.94 (1H, s, H-8). HPLC retention time 16.8 min [gradient elution, 20 - 80% acetonitrile/water (containing 0.1% TFA)].

$C_{22}H_{26}N_7O_4S_2$. 0.5 H_2O requires C, 50.2 ; H, 5.2; N, 18.6. Found: C, 50.5; H, 5.7; N, 18.2%.

EXAMPLE 11

N-[(R)-1-(2-Benzothiazolyl)thio-2-propyl]-2-(ethylamino)adenosine

The title compound was prepared according to general method B by reaction of *N*-[(R)-1-(2-benzothiazolyl)thio-2-propyl]-2-bromoadenosine (Example 7) (0.24 g, 0.35 mmol) with 70% w/w aqueous ethylamine (0.23 g) in dioxan (10ml) in a sealed vessel at 100°C to provide the desired *N*-[(R)-1-(2-benzo thiazolyl)thio-2-propyl]-2-(ethylamino)adenosine as a foam (following column chromatography), ^{1}H NMR (DMSO-d_6) δ 1.04 (3H, br t, -NCH$_2$C<u>H</u>$_3$), 1.42 (3H, d, -CHC<u>H</u>$_3$), 3.20 (3H, br m, -NC<u>H</u>$_2$CH$_3$), 3.55 - 3.80 (4H, m, H-5'$_a$ and H-5'$_b$ and -CH_2-), 3.95 (1H, q, H-4'), 4.15 (1H, q, H-3'), 5.16, 5.41 (2H, 2d, 2'-and 3'-OH), 5.79 (1H, d, H-1'), 6.22 (1H, t, -N<u>H</u>CH$_2$CH$_3$), 7.43, 7.54 (2H, 2 t, Ar-H), 7.98 (1H, s, H-8). HPLC retention time 17.0 min [gradient elution, 20 - 80% acetonitrile/water (containing 0.1% TFA)].

EXAMPLE 12

2-Amino-*N*-[(R)-1-(2-benzothiazolyl)thio-2-propyl]adenosine

The title compound was prepared according to general method A as described above in Example 1 by reacting 2-[(R)-2-amino-1-propylthio]benzothiazole hydrochloride (prepared as described in Example 5) (7.13 g, 24 mmol) with 2-amino-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-6-chloro-9H-purine (Nucleic Acid Chemistry, Townsend L.B. and Tipson, R.S., eds., John Wiley and Sons Inc., 1986, 3, 144) (8.56 g, 20 mmol) followed by deacylation of a portion of the purified 2',3',5'-tri-*O*-acetyl-2-amino-*N*-[(R)-1-(2-benzothiazolyl)thio-2-propyl]adenosine using sodium methoxide in methanol to provide the title 2-amino-*N*-[(R)-1-(2-benzothiazolyl)thio2--propyl]adenosine (0.71 g, 19%) as a foam (following column chromatography) ^{1}H NMR (DMSO-d_6) δ 1.34 (3H, d, -CHC$\underline{H}_3$), 3.50 - 3.73 (4H, m, H-5'$_a$ and H-5'$_b$ and -CH_2-), 3.90 (1H, q, H-4'), 4.10 (1H, d, H-3'), 4.51 (1H, q, H-2'), 5.11, 5.37 (2H, 2d, 2'-and 3'-OH), 5.40 (1H, t, 5'-OH), 5.73 (1H, d, H-1'), 5.79 (1H, br, -NH_2), 7.36, 7.47 (2H, 2t, Ar-H), 7.92 (1H, s, H-8), 8.0 (1H, d, N-H). HPLC retention time 13.5 min [gradient elution, 20 - 80% acetonitrile/water (containing 0.1% TFA)].

EXAMPLE 13

N-[(R)-1-(2-Benzothiazolyl)thio-2-propyl]-2-fluoroadenosine

The title compound was prepared according to general method C by reacting 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2-amino-6-chloro-9H-purine (see Example 9) (0.45 g, 0.73 mmol) using the diazotisation/fluoroboric acid method described previously (see WO 93/08206; Bioorganic and Medicinal Chemistry Letters, 1993, 3, 2661-2666) to provide 2',3',5'-tri-*O*-acetyl-*N*-[(R)-1-(2-benzothiazolyl)thio-2-propyl]-2-

fluoroadenosine (0.19 g, 43%), followed by deacylation using sodium methoxide in methanol to provide the title *N*-[(R)-1-(2-benzothiazolyl)thio-2-propyl]-2-fluoroadenosine (0.088 g) (following column chromatography), ^{1}H NMR (DMSO-d_6) δ 1.37 (3H, d, -CHC<u>H</u>$_3$, 3.50 - 3.79 (4H, m, H-5'$_a$ and H-5'$_b$ and -C<u>H</u>$_2$-), 3.95 (1H, d, H-4'), 4.13 (1H, m, H-3'), 4.51 (1H, q, H-2'), 4.67 (1H, br, -C<u>H</u>CH$_3$), 5.07 (1H, t, 5'-OH), 5.23, 5.50 (2H, 2d, 2'-and 3'-OH), 5.79 (1H, d, H-1'), 7.37, 7.48 (2H, 2t, Ar-H), 7.85, 7.79 (2H, 2d, Ar-H), 8.36 (1H, s, H-8), 8.58 (1H, d, N-H). HPLC retention time 18.9 min [gradient elution, 20 - 80% acetonitrile/water (containing 0.1% TFA)].

$C_{20}H_{21}FN_6O_4S_2$. 1.25 H_2O requires C, 46.6 ; H, 4.1; N, 16.3. Found: C, 46.5; H, 4.5; N, 16.3%.

EXAMPLE 14

N-[(S)-2-(2-Benzothiazolyl)thio-1-propyl]-2-chloroadenosine

(S)-(2-Benzothiazolyl)thio-1-propylamine (1.5 g, 5.0 mmol) (prepared by the method described in Example 1 from (S)-2-hydroxypropylamine) was reacted with 9-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)-2,6-dichloro-9H-purine (1.49 g, 2.4 mmol) in dioxan (20 ml) in the presence of triethylamine (2.77 ml, 20 mmol) to provide 2',3',5'-tri-*O*-acetyl-*N*-[(S)-2-(2-benzothiazolyl)thio-1-propyl]-2-chloroadenosine, which was deacylated using methanolic ammonia (previously saturated at -10°C) to provide the title *N*-[(S)-2-(2-benzothiazolyl)thio-1-propyl]-2-chloroadenosine (0.78 g, 47%) as a foam (following column chromatography), ^{1}H NMR (DMSO-d_6)δ 1.52 (3H, d, -CH$_3$), 3.56 (1H, ABX, H-5'$_a$), 3.68 (1H, m, H-5'$_b$), 3.73 - 3.91 (1H, m, -C-H), 3.84 - 3.92 (1H, m, -C-H), 3.96 (1H, q, H-4'), 4.15 (1H, m, H-3'), 4.53 (1H, dd, H-2'), 5.08 (1H. t, 5'-OH), 5.23, 5.50 (3H, 3 br, 2' and 3'-OH), 5.84 (1H, d,

H-1'), 7.36, 7.47 (2H, 2, Ar-H), 7.83, 7.99 (2H, 2d, Ar-H), 8.40 (1H, s, H-8), 8.72 (1H, t, N-H). HPLC retention time 17.8 min [gradient elution, 20 - 80% acetonitrile/water (containing 0.1% TFA)].

$C_{20}H_{21}ClN_6O_4S_2$. 0.5 H_2O. 0.1 EtOAc requires C, 46.5 ; H, 4.4; N, 16.0. Found: C, 46.6; H, 4.4; N, 15.8%.

EXAMPLE 15

N-[(R)-1-(2-Benzothiazolyl)thio-2-butyl]-2-chloroadenosine

The title compound was prepared according to general method A as described above in Example 1 by reacting 2-[(R)-2-amino-1-butylthio]benzothiazole hydrochloride (1.16 g, 4.2 mmol) with 9-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)-2,6-dichloro-9H-purine (1.57 g, 3.5 mmol), followed by deacylation of the purified 2',3',5'-tri-*O*-acetyl-2-chloro-*N*-[(R)-1-(2-benzothiazolyl)thio-2-propyl]adenosine using sodium methoxide in methanol. This provided the title *N*-[(R)-1-(2-benzothiazolyl)thio-2-butyl]-2-chloroadenosine (0.93 g, 51%) (following column chromatography), ^1H NMR (DMSO-d_6) δ 1.38 (3H, d, $-CH_2C\underline{H}_3$), 1.65 - 1.86 (2H, m, $-C\underline{H}_2CH_3$), 3.95 (1H, q, H-4'), 4.14 (1H, d, H-3'), 4.48 - 4.62 (2H, m, H-2' and $-C\underline{H}CH_2H_3$), 5.07 (1H, t, 5'-OH), 5.22, 5.50 (2H, 2d, 2'-and 3'-OH), 5.83 (1H, d, H-1'), 7.34, 7.45 (2H, 2t, Ar-H), 7.84, 8.0 (2H, 2d, Ar-H). HPLC retention time 21.8 min [gradient elution, 20 - 80% acetonitrile/water (containing 0.1% TFA)].

$C_{21}H_{23}ClN_6O_4S_2$. requires C, 48.2 ; H, 4.4; N, 16.1. Found: C, 47.9; H, 4.5; N, 15.7%.

EXAMPLE 16

N-[1-(2-Benzothiazolyl)thio-3-methyl-2-butyl]-2-chloroadenosine

The title compound was prepared according to general method A as described above in Example 1 by reacting 2-[2-amino-3-methyl-1-butylthio]-benzothiazole hydrochloride (1.37 g, 4.2 mmol) with 9-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)-2,6-dichloro-9H-purine (1.57 g, 3.5 mmol), followed by deacylation of the purified 2',3',5'-tri-*O*-acetyl-2-chloro-*N*-[1-(2-benzothiazolyl)thio-2-propyl]adenosine using sodium methoxide in methanol. This provided the title *N*-[1-(2-benzothiazolyl)thio-3-methyl-2-butyl]-2-chloroadenosine (0.69 g, 37%) as a foam (mixture of diastereoisomers) (following column chromatography), ^{1}H NMR (DMSO-d_6) δ 0.97 - 1.05 [6H, m, -CH(C$\underline{H}_3$)$_2$], 2.0 - 2.13 [1H, m, -C$\underline{H}$(CH$_3$)$_2$], 3.50 - 3.70 (3H, m, H-5'$_a$ and H-5'$_b$ and -CH-), 3.88 - 3.97 (2H, m, H-4' and -CH-), 5.02, 5.06 (1H, 2t, 5'-OH), 5.21, 5.50 (2H, 2d, 2'-and 3'-OH), 5.32 (1H, dd, H-1'), 7.36, 7.46 (2H, 2t, Ar-H). HPLC retention time 23.8 min [gradient elution, 20 - 80% acetonitrile/water (containing 0.1% TFA)].

$C_{22}H_{25}ClN_6O_4S_2$. requires C, 49.2 ; H, 4.7; N, 15.7. Found: C, 49.3; H, 5.0; N, 15.4%.

EXAMPLE 17

N-[3-(2-Benzothiazolyl)thio-1,1,1-trifluoro-2-propyl]-2-chloroadenosine

The title compound was prepared according to method A. 2-(*N*-tert-butyloxycarbonyl)amino-1,1,1-trifluoro-3-propanol was prepared by reaction of 2-hydroxymethyl-3,3,3-trifluoropropionic acid (3.16 g, 20 mmol) with diphenylphosphoryl azide (5.50 g, 20 mmol) in *tert*-butanol. The resultant 4-(trifluoromethyl)oxazolidin-2-one was treated with hydro-

chloric acid to afford 2-amino-3,3,3-trifluoropropanol. This amine was *N*-Boc protected under standard conditions (see Example 18) to provide 2-(*N*-tert-butyloxycarbonyl)amino-1,1,1-trifluoro-3-propanol (0.65 g), TLC R_f 0.37 [SiO_2; ethyl acetate/ cyclohexane (1:1)].

N-[3-(2-Benzothiazolyl)thio-1,1,1-trifluoro-2-propyl]-2-chloroadenosine was prepared according to general method A as described in Example 1 by reacting 2-[(R)-2-amino-1,1,1 trifluoro-3-propylthio]benzothiazole hydrochloride [prepared by a Mitsunobu reaction as described in Example 1 using the above 2-(*N*-tert-butyloxycarbonyl)amino-1,1,1-trifluoro-3-propanol and 2-mercaptobenzothiazole followed by acidic hydrolysis] (0.13 g, 0.47 mmol) with 9-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)-2,6-dichloro-9H-purine (0.21 g, 0.45 mmol). Debenzoylation of the purified 2',3',5'-tri-*O*-acetyl-*N*-[3-(2-benzothiazolyl)thio-1,1,1-trifluoro-2-propyl]-2-chloroadenosine in methanolic ammonia (20 ml) (previously saturated at -10°C) provided the title *N*-[3-(2-benzothiazolyl)thio-1,1,1-trifluoro-2-propyl]-2-chloroadenosine (0.12 g, 45%) (following column chromatography) [a mixture of (R)- & (S)- diastereoisomers]; ^{1}H NMR (DMSO-d_6) δ 3.39 - 3.49 (1H, m, -CH), 3.58, 3.68 (2H, ABX, H-5'$_a$ and H-5'$_b$), 3.98 (1H, q, H-4'), 4.11 - 4.18 (2H, m, H-3' and -CH-), 4.47 - 4.56 (1H, m, H-2'), 5.08 (1H, m, 5'-OH), 5.18 - 5.28 (1H, m, -C<u>H</u>CH$_2$-), 5.27, 5.57 (2H, 2d, 2'-and 3'-OH), 5.94 (1H, d, H-1'), 7.08, 7.22, 7.30 (3H, 3 t, Ar-H), 7.71 (1H, d, Ar-H), 8.75 (1H, s, H-8), 8.79 (1H, d, N-H).

EXAMPLE 18

trans-*N*-[2-[(2-Benzothiazolyl)thio]cyclopentyl]-2-chloroadenosine

trans-*N*-(*tert*-Butyloxycarbonyl)-2-hydroxycyclopentylamine (see WO 93/23418) was prepared as a mixture of enantiomers by reaction of cyclopentene epoxide (8.0 g, 95.1 mmol) with a 25% aqueous ammonia

solution (35 ml) in a sealed glass vessel at 110°C for 1.5 h. The reaction mixture was cooled and evaporated to half its original volume before 1N sodium hydroxide solution (95 ml) and THF (100 ml) were introduced at 0°C. A solution of di-*tert*-butyl dicarbonate (21.8 g, 99.6 mmol) in THF (50 ml) was added dropwise and the reaction mixture stirred at room temperature for 18 h. The phases were separated and the aqueous phase was washed with ethyl acetate (100 ml). The organic phases were combined and washed with saturated brine (100 ml), dried ($MgSO_4$) and evaporated. The solid residue was recrystallised from a 10:1 mixture of heptane and ethyl acetate (55 ml) to provide an analytical sample of trans-*N*-(*tert*-butyloxycarbonyl)-2-hydroxycyclopentylamine (4.06 g, 21%), mp 103-105°C.

$C_{10}H_{19}NO_3$ requires C, 59.7; H, 9.5; N, 7.0. Found: C, 59.6; H, 9.8; N, 7.0%.

The above trans-*N*-(*tert*-butyloxycarbonyl)-2-hydroxycyclopentylamine (24.7 g, 123 mmol) (prepared as described in Example 11) was dissolved in THF (500 ml) and 4-nitrobenzoic acid (20.51 g, 123 mmol) was added, followed by triphenylphosphine (48.28 g, 184 mmol). A solution of diethylazodicarboxylate (32.06 g, 184 mmol) in THF (250 ml) was introduced dropwise. The reaction mixture was stirred for 18 h at room temperature, evaporated and purified by flash chromatography eluting with a mixture of cycohexane and ethyl acetate (4:1) to provide the intermediate 4-nitrobenzoyl ester as a solid (25.5 g), TLC R_f 0.52 [SiO_2: cyclohexane/ ethyl acetate (1:1)]. This ester was suspended in a mixture of a mixture of methanol (180 ml) and 25% aqueous ammonia solution (20 ml) and the mixture was stirred at room temperature for 70 h before evaporation to a residue. Purification by flash chromatography eluting with a mixture of cycohexane and ethyl acetate (4:1) provided fractions containing the title compound which crystallised on evaporation to afford

cis-*N*-(*tert*-butyloxycarbonyl)-2-hydroxycyclopentylamine as a solid (11.0 g, 44%), mp 64 - 65°C.

trans-*N*-[2-[(2-Benzothiazolyl)thio]cyclopentyl]-2-chloroadenosine

The above cis-*N*-(*tert*-butyloxycarbonyl)-2-hydroxycyclopentylamine was converted into trans-2-(2-benzothiazolyl)cyclopentylamine hydrochloride by the sequence of reactions described in Example 1 (i.e. thioether formation by the Mitsunobu procedure resulting in inversion at the 2-position, followed by acidic hydrolysis of the *N*-Boc- group).

This trans-2-(2-benzothiazolyl)cyclopentylamine hydrochloride (1.0 g, 3.0 mmol) was combined with 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-dichloro-9H-purine (1.34 g, 3 mmol) and triethylamine (1.66 ml) and reacted using the procedure described in Example 1. Deacylation of the purified [trans]-2',3',5'-tri-*O*-acetyl-*N*-[2-[(2-benzothiazolyl)thio]-cyclopentyl]-2-chloroadenosine was carried out using methanolic ammonia (200 ml) (previously saturated at -10°C) which provided the title product as a ca. 1:1 mixture of diastereoisomers, HPLC retention time 24.1 and 24.82 min [isocratic elution, 35% acetonitrile/ 65% water (containing 0.1% TFA)]. A single diastereoisomer of trans-*N*-[2-[(2benzothiazolyl)thio]cyclopentyl]-2-chloroadenosine (0.11 g, 7%) was obtained as a foam (following short path column chromatography), ^{1}H NMR (DMSO-d_6)δ 1.65 - 2.62 (6H, 5m, -$CH_2CH_2CH_2$-), 3.51 - 3.58 and 3.62 - 3.69 (2H, ABX, H-5'$_a$ and H-5'$_b$), 3.94 (1H, br q, H-4'), 4.13 (1H, br q, H-3'), 4.28 (1H, q, -CH-), 4.49 (1H, q, H-2'), 4.68 (1H, m, -CH-), 4.62 (1H, q, H-2'), 5.07 (1H, t, 5'-OH), 5.22, 5.50 (2H, 2d, 2'-and 3'-OH), 5.82 (1H, d, H-1'), 7.35, 7.45 (2H, 2t, Ar-H), 7.79, 7.98 (2H, 2d, Ar-H), 8.40 (1H, s, H-8), 8.71 (1H, d, N-H). HPLC retention time 24.82 min [gradient elution, 20 - 80% acetonitrile/water (containing 0.1% TFA)].

$C_{22}H_{23}ClN_6O_4S_2$. 0.5 EtOH requires C, 49.5 ; H, 4.7 ; N, 15.1 . Found: C, 49.1; H, 4.8; N, 14.9%.

EXAMPLE 19

cis-*N*-[2-[(2-Benzothiazolyl)thio]cyclopentyl]-2-chloroadenosine

trans-*N*-(*tert*-Butyloxycarbonyl)-2-hydroxycyclopentylamine (see Example 16) was converted into cis-2-(2-benzothiazolyl)cyclopentylamine hydrochloride by the sequence of reactions described in Example 1 (i.e. thioether formation by the Mitsunobu procedure resulting in inversion at the cyclopentane 2-position, followed by acidic hydrolysis of the Boc-group) (see also WO 93/23418).

The above cis-2-(2-benzothiazolyl)cyclopentylamine hydrochloride (1.5 g, 4.6 mmol) was combined with 9-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)-2,6-dichloro-9H-purine (2.0 g, 4.5 mmol) and triethylamine (2.49 ml) and reacted by the method described in Example 1. Deacylation of the purified cis-2',3',5'-tri-*O*-acetyl-*N*-[2-[(2-benzothiazolyl)thio]-cyclopentyl]-2-chloroadenosine using sodium methoxide in methanol provided the title cis-*N*-[2-[(2-benzothiazolyl)thio]cyclopentyl]-2-chloroadenosine (0.89 g, 38%) as a foam (following column chromatography) (a ca. 2:1 mixture of diastereoisomers), ^{1}H NMR (DMSO-d_6)δ 1.62 - 2.45 (6H, 5m, -$CH_2CH_2CH_2$-), 3.52 - 3.60 (1H, m, H-5'$_a$), 3.64 - 3.70 (1H, m, H-5'$_b$), 3.94 (1H, br q, H-4'), 4.11 (1H, br q, H-3'), 4.62 (1H, q, H-2'), 5.75 - 5.83 (1H, 2m, H-1'), 7.26 - 7.94 (4H, 4m, Ar-H).

EXAMPLE 20

N-[(R)-1-(6-Amino-2-benzothiazolyl)thio-2-propyl]-2-chloroadenosine

The title compound was prepared according to general method A as described above in Example 1 by reacting 6-amino-2-[(R)-2-aminopropyl-1-propylthio]benzothiazole hydrochloride [prepared by a Mitsunobu reaction as described in Example 1 using 2-[(R)-*N*-*tert*-butyloxycarbonyl]amino-1-propanol (13.1 g, 75 mmol) and 6-amino-2-mercaptobenzothiazole (13.7 g, 75 mmol) followed by acidic hydrolysis]) (2.51 g, 7.2 mmol) with 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-dichloro-9H-purine (2.68 g, 6.0 mmol), followed by deacylation of the purified 2',3',5'-tri-*O*-acetyl-*N*-[(R)-1-(6-amino-2-benzothiazolyl)thio-2-propyl]-2-chloroadenosine in methanolic ammonia (200 ml) (previously saturated at -10°C) to provide the title *N*-[(R)-1-(6-amino2-benzothiazolyl)thio-2-propyl]-2-chloroadenosine (1.97 g, 63%) as a foam (following column chromatography), ^{1}H NMR (DMSO-d_6) δ 1.36 (3H, d, -CHC$\underline{H}_3$), 3.50 - 3.71 (4H, m, H-5'$_a$ and H-5'$_b$ and -CH_2-), 3.95 (1H, d, H-4'), 4.14 (1H, d, H-3'), 4.53 (1H, q, H-2'), 4.63 (1H, m, -CH), 5.08 (1H, t, 5'-OH), 5.22, 5.50 (2H, 2d, 2'-and 3'-OH), 5.83 (1H, d, H-1'), 6.71, 6.99, 7.53 (3H, 3d, Ar-H), 8.41 (1H, s, H-8), 8.52 (1H, d, N-H). HPLC retention time 10.29 min [gradient elution, 20 - 80% acetonitrile/water (containing 0.1% TFA)].

EXAMPLE 21

2-Chloro-*N*-[(R)-1-(6-ethoxy-2-benzothiazolyl)thio-2-propyl]adenosine

The title compound was prepared according to general method A as described above in Example 1 by reacting 2-[(R)-2-amino-1-propylthio]-6-ethoxybenzothiazole hydrochloride [prepared by a Mitsunobu reaction as described in Example 1 using 2-[(R)-*N*-*tert*-butyloxycarbonyl]amino-1-propanol (3.5 g, 20 mmol) and 6-ethoxy-2-mercaptobenzothiazole (4.23 g, 20 mmol) followed by acidic hydrolysis] (3.8 g, 11.1 mmol) with 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-dichloro-9H-purine (1.1 g, 2.5 mmol), followed by deacylation of the purified 2',3',5'-tri-*O*-acetyl-2-

chloro-*N*-[(R)-1-(6-ethoxy-2-benzothiazolyl)thio-2-propyl]adenosine using sodium methoxide in methanol to provide the title *N*[(R)-1-(6-ethoxy-2-benzothiazolyl)thio-2-propyl]-2-chloroadenosine (0.22 g, 17%) as a foam (following column chromatography), ^{1}H NMR (DMSO-d_6) δ 1.32 - 1.40 (6H, m, -$CH_2C\underline{H}_3$ and -$CHC\underline{H}_3$), 3.44 - 3.81 (4H, m, H-5'$_a$ and H-5'$_b$ and -CH_2-), 3.97 (1H, d, H-4'), 4.08 (2H, q, -$C\underline{H}_2CH_3$), 4.14 (1H, d, H-3'), 4.53 (1H, q, H-2'), 4.68 (1H, m, -CH), 5.09 (1H, t, 5'-OH), 5.23, 5.51 (2H, 2d, 2'-and 3'-OH), 5.83 (1H, d, H-1'), 7.06, 7.57, 7.74 (3H, 3d, Ar-H), 8.42 (1H, s, H-8), 8.53 (1H, d, N-H). HPLC retention time 22.4 min [gradient elution, 20 - 80% acetonitrile/water (containing 0.1% TFA)].

$C_{22}H_{25}ClN_6O_5S_2$. 0.5 H_2O. 0.2 EtOAc requires C, 47.2 ; H, 4.8; N, 14.5. Found: C, 47.3; H, 4.9; N, 14.3%.

EXAMPLE 22

2-Chloro-*N*-[(R)-1-(5-chloro-2-benzothiazolyl)thio-2-propyl]adenosine

The title compound was prepared according to general method A as described above in Example 1 by reacting 2-[(R)-2-amino-1-propylthio]-5-chlorobenzothiazole hydrochloride [prepared by a Mitsunobu reaction as described in Example 1] with 2-[(R)-*N*-*tert*-butyloxycarbonyl]amino-1-propanol (1.75 g, 10 mmol) and 5-chloro-2-mercaptobenzothiazole (2.02 g, 10 mmol) followed by acidic hydrolysis] (0.5 g, 1.5 mmol) with 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-dichloro-9H-purine (0.54 g, 1.2 mmol), followed by deacylation of the purified 2',3',5'-tri-*O*-acetyl-2-chloro-*N*-[(R)-1-(5-chloro-2-benzothiazolyl)thio-2-propyl]adenosine using sodium methoxide in methanol to provide the title *N*-[(R)-1-(5-chloro-2-benzothiazolyl)thio-2-propyl]2-chloroadenosine (0.30 g, 46%) as a solid, mp 145°C (following column chromatography), ^{1}H NMR (DMSO-

d_6) δ 1.39 (3H, d, -CHC<u>H</u>$_3$), 3.45 - 3.78 (4H, m, H-5'$_a$ and H-5'$_b$ and -CH_2-), 3.96 (1H, q, H-4'), 4.14 (1H, t, H-3'), 4.52 (1H, t, H-2'), 4.72 (1H, m, -CH), 5.84 (1H, d, H-1'), 7.41 (1H, dd, Ar-H), 7.94 (1H, s, Ar-H), 8.02 (1H, dd, Ar-H), 8.42 (1H, s, H-8), 8.52 (1H, d, N-H). HPLC retention time 23.58 min [gradient elution, 20 - 80% acetonitrile/water (containing 0.1% TFA)].

$C_{20}H_{20}Cl_2N_6O_4S_2$. 1.0 H_2O requires C, 42.8; H, 3.9; N, 15.0. Found: C, 42.9; H, 3.8; N, 14.8%.

EXAMPLE 23

2-Chloro-*N*-[(R)-1-(2-thienyl)thio-2-propyl]adenosine

The title compound was prepared according to method A as described in Example 1 by reacting 2-[(R)-2-amino-1-propylthio]thiophene hydrochloride [prepared by a Mitsunobu reaction as described in Example 1 using 2-[(R)-*N*-*tert*-butyloxycarbonyl]amino-1-propanol (7.53 g, 43 mmol) and 2-mercaptothiophene (5.00 g, 43 mmol) followed by acidic hydrolysis] (0.63 g, 3.0 mmol) with 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-dichloro-9H-purine (1.12 g, 2.5 mmol), followed by deacylation of the purified 2',3',5'-tri-*O*-acetyl-2-chloro-*N*-[(R)-1-(2-thienyl)thio-2-propyl]adenosine using sodium methoxide in methanol to provide the title 2-chloro-*N*-[(R)-1-(2-thienyl)thio-2-propyl]adenosine (0.95 g, 82%) as a foam after column chromatography. ^{1}H NMR (DMSO-d_6)δ 1.26 (3H, d, -CHC<u>H</u>$_3$), 2.95 - 3.18 (2H, ABX, -CH_2-S-), 3.55 and 3.61 (2H, ABX, H-5'$_a$ and H-5'$_b$), 3.95 (1H, q, H-4), 4.14 (1H, t, H-3'), 4.44 (1H, m, -C<u>H</u>-CH_3), 4.54 (1H, t, H-2'), 5.84 (1H, d, H-1'), 7.03 (1H, t, Ar-H), 7.23, 7.61 (2H, 2d, Ar-H), 8.38 (1H, d, -NH), 8.42 (1H, s, H-2). HPLC retention time 19.5 min [gradient elution, 20-80% acetonitrile/water (containing 0.1% TFA)].

$C_{17}H_{20}ClN_5O_4S_2$ requires C, 44.6; H, 4.4 ; N, 15.3. Found: C, 44.2; H, 4.5; N, 15.0%.

EXAMPLE 24

2-Chloro-*N*-[(R)-1-(4-methyl-1,2,4-triazol-3-yl)thio-2-propyl]adenosine

The title compound was prepared according to method A as described in Example 1 by reacting 3-[(R)-2-amino-1-propylthio]-4-methyl-1,2,4-triazole hydrochloride [prepared by a Mitsunobu reaction as described in Example 1 using 2-[(R)-*N*-*tert*-butyloxycarbonyl]amino-1-propanol (3.5 g, 20 mmol) and 3-mercapto-4-methyl-1,2,4-triazole (2.3 g, 20 mmol) followed by acidic hydrolysis] (0.56 g, 2.2 mmol) with 9-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)-2,6-dichloro-9H-purine (1.0 g, 2.2 mmol), followed by deacylation of the purified 2',3',5'-tri-*O*-acetyl-2-chloro-*N*-[(R)-1-(4-methyl-1,2,4-triazol-3-yl)thio-2-propyl]adenosine using sodium methoxide in methanol to provide the title 2-chloro-*N*[(R)-1-(4-methyl-1,2,4-triazol-3-yl)thio-2-propyl]adenosine (0.17 g, 17%) as a foam after column chromatography. ^{1}H NMR (DMSO-d_6)δ 1.24 (3H, d, -CHC<u>H</u>$_3$), 3.56, 3.67 (2H, ABX, 5'$_a$ and H-5'$_b$), 3.95 (1H, q, H-4), 4.14 (1H, br q, H-3'), 4.15 - 4.42 (2H, m, -CH_2S-), 4.52 (1H, br q, H-2'), 4.80 (1H, m, -C<u>H</u>CH_3), 5.07 (1H, br, 5'-OH), 5.22, 5.50 (2H, 2 br, 2'-and 3'-OH), 5.82 (1H, d, H-1'), 8.33 (1H, d, -NH), 8.39, 8.41 (2H, 2s, H-2 and Ar-H). HPLC retention time 7.79 min [gradient elution, 20-80% acetonitrile/water (containing 0.1% TFA)].

EXAMPLE 25

N-[(R)-1-(2-Benzimidazolyl)thio-2-propyl]-2-chloroadenosine

The title compound was prepared according to method A as described in

Example 1 by reacting 2-[(R)-2-amino-1-propylthio]benzimidazole hydrochloride [prepared by a Mitsunobu reaction as described in Example 1 using 2-[(R)-*N*-*tert*-butyloxycarbonyl]amino-1-propanol (1.75 g, 10 mmol) and 2-mercaptobenzimidazole (1.5 g, 10 mmol) followed by acidic hydrolysis] (0.63 g, 2.20 mmol) with 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-dichloro-9H-purine (1.0 g, 2.2 mmol), followed by deacylation of the purified 2',3',5'-tri-*O*-acetyl-*N*-[(R)-1-(2-benzimidazolyl)thio-2-propyl]-2-chloroadenosine in methanolic ammonia (200 ml) (previously saturated at -10°C) to provide the title *N*-[(R)-1-(2-benzimidazolyl)thio-2-propyl]-2-chloroadenosine (0.52 g, 51%) mp 213-215°C after column chromatography and trituration with dichloromethane; ^{1}H NMR (DMSO-d_6)δ 1.38 (3H, d, -CHC<u>H</u>$_3$), 3.95 (1H, q, H-4), 4.12 (1H, br q, H-3'), 4.42 - 4.70 (2H, m, -C<u>H</u>CH$_3$ and H-2'), 5.07 (1H, br, 5'-OH), 5.22, 5.50 (2H, 2 br, 2'-and 3'-OH), 5.82 (1H, d, H-1'), 7.04 - 7.57 (4H, 2m, Ar-H) 8.42 (1H, s, H-2), 8.73 (1H, d, -NH). HPLC retention time 13.7 min [gradient elution, 20-80% acetonitrile/water (containing 0.1% TFA)].

EXAMPLE 26

2-Chloro-*N*-[(R)-1-(4-phenyl-2-thiazolyl)thio-2-propyl]adenosine

The title compound was prepared according to method A as described in Example 1 by reacting 2-[(R)-2-amino-1-propylthio]-4-phenylthiazole hydrochloride [prepared by a Mitsunobu reaction as described in Example 1 using 2-[(R)-*N*-*tert*-butyloxycarbonyl]amino-1-propanol (2.72 g, 15.5 mmol) and 2-mercapto-4-phenylthiazole (3.0 g, 15.5 mmol) followed by acidic hydrolysis] (1.15 g, 4.0 mmol) with 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-dichloro-9H-purine (1.5 g, 3.35 mmol), followed by deacylation of the purified 2',3',5'-tri-*O*-acetyl-2-chloro-*N*-[(R)-1-(4-phenyl-2-thiazolyl)thio-2-propyl]adenosine using sodium methoxide in methanol to provide the title 2-chloro-*N*-[(R)-1-(4-phenyl-

2-thiazolyl)thio-2-propyl]adenosine (0.36 g, 20%) as a foam after column chromatography. ^{1}H NMR (DMSO-d_6)δ 1.37 (3H, d, -CHC<u>H</u>$_3$), 3.4 - 3.73 (2H, m, 5'$_a$ and H-5'$_b$ and -CH_2-S-), 3.94 (1H, q, H-4), 4.13 (1H, q, H-3'), 4.52 (1H, q, H-2'), 4.71 (1H, m, -C<u>H</u>CH$_3$), 5.06 (1H, t, 5'-OH), 5.22, 5.50 (2H, 2d, 2'-and 3'-OH), 5.83 (1H, d, H-1'), 7.33, 7.42 (3H, dt, Ar-H), 7.91 (2H, d, Ar-H), 8.41 (1H, s, H-2), 8.47 (1H, d, -NH). HPLC retention time 18.99 min [gradient elution, 20-80% acetonitrile/water (containing 0.1% TFA)].

EXAMPLE 27

2-Chloro-*N*-{(R)-1-[5-phenyl-(1,2,4-triazol-3-yl)]thio-2-propyl}adenosine

The title compound was prepared according to method A as described in Example 1 by reacting 3-[(R)-2-amino-1-propylthio]-5-phenyl-1,2,4-triazole hydrochloride [prepared by a Mitsunobu reaction as described in Example 1 using 2-[(R)-*N*-*tert*-butyloxycarbonyl]amino-1-propanol (2.0 g, 11.4 mmol) and 3-mercapto-5-phenyl-1,2,4-triazole (2.0 g, 11 mmol) followed by acidic hydrolysis] (0.50 g, 1.8 mmol) with 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-dichloro-9H-purine (0.75 g, 1.7 mmol), followed by deacylation of the purified 2',3',5'-tri-*O*-acetyl-2-chloro-*N*-{(R)-1-[5-phenyl-(1,2,4-triazol-3-yl)]thio-2-propyl}adenosine using sodium methoxide in methanol to provide the title 2-chloro-*N*-{(R)-1-[5-phenyl-(1,2,4-triazol-3-yl)]thio-2-propyl}adenosine (0.21 g, 24%) as a foam after column chromatography. ^{1}H NMR (DMSO-d_6)δ 1.34 (3H, d, -CHC<u>H</u>$_3$), 3.37 - 3.70 (4H, m, -CH_2-, H-5'$_a$ and H-5'$_b$), 3.95 (1H, q, H-4), 4.13 (1H, t, H-3'), 4.53 (1H, t, H-2'), 4.59 - 4.69 (1H, m, -C<u>H</u>CH$_3$), 5.07 (1H, t, 5'-OH), 5.22, 5.50 (2H, 2d, 2'-and 3'-OH), 5.83 (1H, d, H-1'), 7.43 - 7.54 (3H, m, Ar-H), 7.90, 8.0 (2H, m, Ar-H), 8.40 (1H, s, H-2). 8.42 (1H, d, -NH), HPLC retention time 14.5 min [gradient elution, 20-80% acetonitrile/water (containing 0.1% TFA)].

$C_{21}H_{23}ClN_8O_4S$. 1.0 H_2O .0.15 C_7H_{16} requires C, 48.0; H, 5.0 ; N, 20.3. Found: C, 48.2; H, 4.8; N, 20.2%.

EXAMPLE 28

N-[(R)-2-(2-Benzothiazolylthio)-1-ethyl]-2-chloroadenosine

2-(2-Benzothiazolylthio)ethylamine dihydrochloride was prepared by standard synthetic steps with a by Mitsunobu reaction between *N*-(2-hydroxyethyl)phthalimide and 2-mercaptobenzothiazole, followed by reaction with hydrazine hydrate. This amine dihydrochloride (0.52 g, 2.11 mmol) was reacted with 9-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)--2,6-dichloro-9H-purine (0.79 g, 1.7 mmol), followed by deacylation of the purified 2',3',5'-tri-*O*-acetyl-*N*-[(R)-2(2-benzothiazolylthio)-1-ethyl]-2-chloroadenosine using sodium methoxide in methanol to provide the title *N*-[(R)-2-(2-benzothiazolylthio)-1-ethyl]-2-chloroadenosine as a foam after column chromatography, ^{1}H NMR (DMSO-d_6) δ 3.54 - 3.60 and 3.64 - 3.71 (4H, m, H-5'$_a$ and H-5'$_b$ and -CH_2-), 3.42, (2H, q, -CH_2-), 3.96 (1H, d, H-4'), 4.15 (1H, q, H-3'), 4.52 (1H, q, H-2'), 5.08 (1H, t, 5'-OH), 5.22, 5.51 (2H, 2d, 2'-and 3'-OH), 5.85 (1H, d, H-1'), 7.38, 7.48 (2H, 2t, Ar-H), 7.85, 8.02 (2H, 2d, Ar-H), 8.43 (1H, s, H-8), 8.68 (1H, t, N-H). HPLC retention time 18.5 min [gradient elution, 20 - 80% acetonitrile/water (containing 0.1% TFA)].

EXAMPLE 29

N-[(R)-1-(2-Benzothiazolyl)amino-2-propyl]-2-chloroadenosine

2-[(R)-*N*-*tert*-butyloxycarbonylamino]-1-propylamine was prepared by standard synthetic steps from (R)-2-(*N*-*tert*-butyloxycarbonylamino)-1-propanol by Mitsunobu reaction with phthalimide followed by reaction

with hydrazine hydrate. This amine (0.52 g, 3.0 mmol) and 2-chlorobenzothiazole (0.76 g, 4.5 mmol) were dissolved in dioxan (20 ml) and triethylamine (0.83 ml, 6.0 mmol) was introduced. The reaction mixture was heated at 50°C for 18 h, evaporated and purified by "flash" column chromatography, eluting with heptane/ethyl acetate (10:3) to provide the 2-[(R)-2-(*N-tert*-butyloxycarbonylamino)-1-propylamino]-benzothiazole (0.09 g, 10%) as an oil, TLC R_f 0.31 [SiO_2; hexane/ethyl acetate (10:3)].

2-[(R)-(2-Amino-1-propyl)amino]benzothiazole trihydrochloride (0.065 g, 70%), m.p. 226-226°C, was subsequently obtained by hydrolysis in a mixture of 6N hydrochloric acid and ethyl acetate (2 ml), the procedure described in Example 1. This 2-[(R)-(2-amino-1-propyl)amino]-benzothiazole trihydrochloride (0.06 g, 0.19 mmol) was reacted with 9-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)-2,6-di-chloro-9H-purine (0.127 g, 1.2 mmol), followed by deacylation of the purified 2',3',5'-tri-*O*-acetyl-*N*-[(R)-1-(2-benzothiazolyl)amino-2-propyl]-2-chloroadenosine using sodium methoxide in methanol (to remove the 2' and 3'-acetyl groups) followed by ethylamine in ethanol, which provided the title *N*-[(R)-1-(2-benzothiazolyl)amino-2-propyl]-2-chloroadenosine (0.027 g, 29%) as a foam (following column chromatography), ^{1}H NMR (DMSO-d_6) δ 1.25 (3H, d, -CHC<u>H</u>$_3$), 3.52 - 3.70 (4H, m, H-5'$_a$, H-5'$_b$ and -CH_2-), 3.94 (1H, q, H-4'), 4.12 (1H, q, H-3'), 4.52 (1H, q, H-2'), 4.53 - 4.62 (1H, m, -C<u>H</u>CH_3), 5.07 (1H, t, 5'-OH), 5.22, 5.48 (2H, 2d, 2'-and 3'-OH), 5.84 (1H, d, H-1'), 7.01, 7.22 (2H, 2t, Ar-H), 7.43, 7.66 (2H, 2d, Ar-H), 8.14 (1H, t, N-H), 8.41 (1H, s, H-8), 8.44 (1H, d, N-H). HPLC retention time 10.7 min [gradient elution, 20 - 80% acetonitrile/water (containing 0.1% TFA)].

EXAMPLE 30

N-[(R)-1-(2-Benzothiazolylsulphonyl)-2-propyl]-2-chloroadenosine

2-[(R)-2-(*N-tert*-Butyloxycarbonylamino)-1-propylsulphonyl]benzothiazole was prepared by oxidation of 2-[(R)-2-(*N-tert*-butyloxycarbonylamino)-1-propylthio]benzothiazole (see Example 5) (0.55 g, 1.7 mmol) with "Oxone" on a Montmorillionite support. A mixture of the sulphonyl and sulphinyl derivatives was obtained, and the 2-[(R)-2-(*N-tert*-butyloxycarbonylamino)-1-propylsulphonyl]benzothiazole was isolated following column chromatography. Deprotection was performed under standard conditions with hydrogen chloride in ethyl acetate. The resultant 2-[(R)-2-aminopropyl-1-propylsulphonyl]benzothiazole hydrochloride (0.088 g, 0.4 mmol) was reacted with 9-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)-2,6-dichloro-9H-purine (0.18 g, 0.4 mmol), followed by deacylation of the purified 2',3',5'-tri-*O*-acetyl-*N*-[(R)-1-(2-benzothiazolyl)sulphonyl-2-propyl]-2-chloroadenosine using sodium methoxide in methanol provided the title *N*-[(R)-1-(2-benzothiazolyl)sulphonyl-2-propyl]-2-chloroadenosine as a foam (following column chromatography); ^{1}H NMR (DMSO-d_6) δ 1.83 (3H, d, -CHC$\underline{H}_3$), 3.55, 3.66 (2H, ABX, H-5'$_a$ and H-5'$_b$), 3.96 (1H, q, H-4'), 4.17 (1H, q, H-3'), 4.59 (1H, q, H-2'), 5.08 (1H, t, 5'-OH), 5.24, 5.68 (2H, 2d, 2'-and 3'-OH), 5.95 (1H, d, H-1'), 7.34, 7.47 (2H, 2t, Ar-H), 7.84, 8.01 (2H, 2d, Ar-H), 8.14 (1H, t, N-H), 8.71 (1H, s, H-8). HPLC retention time 13.5 min [gradient elution, 20 - 80% acetonitrile/water (containing 0.1% TFA)].

EXAMPLE 31

5'-*O*-Acetyl-2-chloro-*N*-[(R)-1-(6-ethoxy-2-benzothiazolyl)thio-2-propyl]-adenosine

Partial deacylation of the purified 2',3',5'-tri-*O*-acetyl-2-chloro-*N*-[(R)-1-(6-ethoxy-2-benzothiazolyl)thio-2-propyl]adenosine (described in Example 19) using sodium methoxide in methanol provided the title 5'-*O*-acetyl-*N*--[(R)-1-(6ethoxy2-benzothiazolyl)thio-2-propyl]-2-chloroadenosine (0.070 g, 18%) as a foam (following column chromatography), ^{1}H NMR (DMSO-d_6) δ 1.34 - 1.41 (6H, m, -$CH_2C\underline{H}_3$ and -$CHC\underline{H}_3$), 2.03 (3H, s, -$COCH_3$), 4.60 (1H, q, H-2'), 4.68 (1H, m, -$C\underline{H}CH_3$), 5.42, 5.62 (2H, 2d, 2'-and 3'-OH), 5.86 (1H, d, H-1'), 7.04 (1H, dd, Ar-H), 7.57, 7.72 (2H, 2d, Ar-H), 8.38 (1H, s, H-8), 8.52 (1H, d, N-H). HPLC retention time 25.6 min [gradient elution, 20 - 80% acetonitrile/water (containing 0.1% TFA)].

$C_{24}H_{27}ClN6_8O_6S_2$. 0.5 H_2O .0.2 C_7H_{14} requires C, 48.9; H, 5.0 ; N, 13.5. Found: C, 48.7; H, 4.9; N, 13.4%.

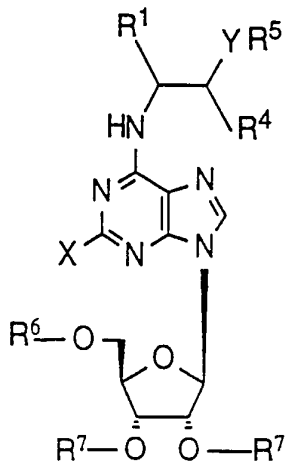
EXAMPLE 32

5'-*O*-Acetyl-2-chloro-*N*-{(R)-1-[5-phenyl-(1,2,4-triazol-3-yl)]thio-2-propyl}-adenosine

Partial deacylation of the purified 2',3',5' Tri-*O*-acetyl-2-chloro-*N*-{(R)-1-[5-phenyl-(1,2,4-triazol-3-yl)]thio-2-propyl}adenosine (described in Example 27) using sodium methoxide in methanol to provide the title 5'-*O*-acetyl-2-chloro-*N*-{(R)-1-[5-phenyl-(1,2,4-triazol-3yl)]thio-2-propyl}-adenosine (0.035 g, 8%) as a foam after column chromatography. ^{1}H NMR (DMSO-d_6)δ 1.34 (3H, d, -$CHC\underline{H}_3$), 2.02 (3H, s, -$COCH_3$), 4.53 - 4.68 (2H, q, H-2' and -$C\underline{H}CH_3$), 5.40, 5.61 (2H, 2d, 2'-and 3'-OH), 5.86 (1H, d, H-1'), 7.38 - 8.01 (5H, 3m, Ar-H), 8.37 (1H, s, H-2). HPLC retention time 16.9 min [gradient elution, 20 - 80% acetonitrile/water (containing 0.1% TFA)].

CLAIMS

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein

X is halogen, amino, trifluoromethyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, cyano, C_{1-6}-alkylamino or di-C_{1-6}-alkylamino;

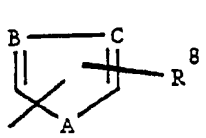
R^1 is H or straight or branched C_{1-6}-alkyl or trifluoromethyl;

R^4 is H or straight or branched C_{1-6}-alkyl;

or R^1 and R^4 together form a cyclobutyl, cyclopentyl or cyclohexyl ring;

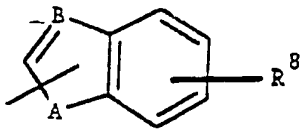
Y is O, S, SO_2, N-H or N-alkyl;

R^5 is a group of formula (XI) or (XII):



(XI)

or



(XII)

wherein A is -NH-, -O- or -S-;

B is -CH- or -N-;

C is -CH- or -N-;
which may be optionally substituted with R^8 which is H, phenyl, C_{1-6}-alkyl, tri-fluoromethyl, amino, hydroxy, C_{1-6}-alkoxy, cyano or halogen;

R^6 is hydrogen, benzoyl or C_{1-6}-alkanoyl and
R^7 is hydrogen, benzoyl or C_{1-6}-alkanoyl.

2. A compound according to claim 1, wherein R^5 is a group of formula (XI).

3. A compound according to claim 1, wherein R^5 is a group of formula (XII).

4. A compound according to claim 1, wherein B is -N-.

5. A compound according to claim 4, wherein A is -S-.

6. A compound according to claim 1, wherein A is -S- and X is halogen.

7. A compound according to claim 6, wherein Y is -S-, R^6 is hydrogen and R^7 is hydrogen.

8. A compound according to claim 7, wherein X is Cl.

9. A compound according to claim 1 selected from:

2-Chloro-*N*-[(R)-1-(2-thiazolyl)thio-2-propyl]adenosine,
2-Chloro-*N*-[(R)-1-(1-methyl-2-imidazolyl)thio-2-propyl)adenosine,
2-Chloro-*N*-{(R)-1-[5-methyl-(1,3,4-thiadiazol-2-yl)]thio-2-propyl}adenosine,
N-[(R)-1-(2-Benzoxazolyl)thio-2-propyl]-2-chloroadenosine,
N-[(R)-1-(2-Benzothiazolyl)thio-2-propyl]-2-chloroadenosine,
N-[(S)-1-(2-Benzothiazolyl)thio-2-propyl]-2-chloroadenosine,
N-[(R)-1-(2-Benzothiazolyl)thio-2-propyl]-2-bromoadenosine,
N-[(R)-1-(2-benzothiazolyl)thio-2-propyl]-2-methyladenosine,
N-[(R)-1-(2-Benzothiazolyl)thio-2-propyl]-2-methylthioadenosine,
N-[(R)-1-(2-Benzothiazolyl)thio-2-propyl]-2-(dimethylamino)adenosine,
N-[(R)-1-(2-Benzothiazolyl)thio-2-propyl]-2-(ethylamino)adenosine,
2-Amino-*N*-[(R)-1-(2-benzothiazolyl)thio-2-propyl]adenosine,
N-[(R)-1-(2-Benzothiazolyl)thio-2-propyl]-2-fluoroadenosine,
N-[(S)-1-(2-Benzothiazolyl)thio-1-propyl]-2-chloroadenosine,
N-[(R)-1-(2-Benzothiazolyl)thio-2-butyl]-2-chloroadenosine,
N-[(R)-1-(2-Benzothiazolyl)thio-3-methyl-2-butyl]-2-chloroadenosine,
N-[3-(2-Benzothiazolyl)thio-1,1,1-trifluoro-2-propyl]-2-chloroadenosine,
trans-*N*-[2-[(2-Benzothiazolyl)thio]cyclopentyl]-2-chloroadenosine,
cis-*N*-[2-[(2-Benzothiazolyl)thio]cyclopentyl]-2-chloroadenosine,
N-[(R)-1-(6-Amino-2-benzothiazolyl)thio-2-propyl]-2-chloroadenosine,
2-Chloro-*N*-[(R)-1-(6-ethoxy-2-benzothiazolyl)thio-2-propyl]adenosine,
2-Chloro-*N*-[(R)-1-(5-chloro-2-benzothiazolyl)thio-2-propyl]adenosine,
2-Chloro-*N*-[(R)-1-(2-thienyl)thio-2-propyl]adenosine,
2-Chloro-*N*-[(R)-1-(4-methyl-1,2,4-triazol-3-yl)thio-2-propyl]adenosine,
N-[(R)-1-(2-Benzimidazolyl)thio-2-propyl]-2-chloroadenosine,
2-Chloro-*N*-[(R)-1-(4-phenyl-2-thiazolyl)thio-2-propyl]adenosine,
2-Chloro-*N*-{(R)-1-[5-phenyl-(1,2,4-triazol-3-yl)thio-2-propyl]}adenosine,
N-[2-Benzothiazolyl)thio-1-ethyl]-2-chloroadenosine,
N-[(R)-1-(2-Benzothiazolyl)amino-2-propyl]-2-chloroadenosine,
N-[(R)-1-(2-Benzothiazolyl)sulphonyl-2-propyl]-2-chloroadenosine,

5'-*O*-Acetyl-2-chloro-*N*-[(R)-1-(6-ethoxy-2-benzothiazolyl)thio-2-propyl]-adenosine,

5'-*O*-Acetyl-2-chloro-*N*-{(R)-1-[5-phenyl-(1,2,4-triazol-3-yl)]thio-2-propyl}-adenosine,

[1S,trans]-*N*-[2-[(2-Benzothiazolyl)thio]cyclobutyl]-2-chloroadenosine,

[1R,trans]-*N*-[2-[(2-Benzothiazolyl)thio]cyclobutyl]-2-chloroadenosine,

[1S,cis]-*N*-[2-[(2-Benzothiazolyl)thio]cyclobutyl]-2-chloroadenosine,

[1R,cis]-*N*-[2-[(2-Benzothiazolyl)thio]cyclobutyl]-2-chloroadenosine,

[1S,trans]-*N*-[2-[(2-Benzothiazolyl)thio]cyclohexyl]-2-chloroadenosine,

[1R,trans]-*N*-[2-[(2-Benzothiazolyl)thio]cyclohexyl]-2-chloroadenosine,

[1S,cis]-*N*-[2-[(2-Benzothiazolyl)thio]cyclohexyl]-2-chloroadenosine,

[1R,cis]-*N*-[2-[(2-Benzothiazolyl)thio]cyclohexyl]-2-chloroadenosine,

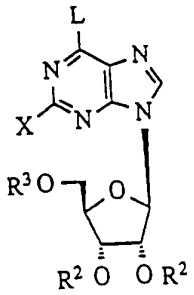
N-[(R)-1-(2-Benzothiazolyl)thio-2-propyl]-2-methoxyadenosine,

N-[(R)-1-(2-Benzothiazolyl)oxy-2-propyl]-2-chloroadenosine or

2-Chloro-*N*-[(R)-1-(6-hydroxy-2-benzothiazolyl)thio-2-propyl]adenosine or a pharmaceutically acceptable salt thereof.

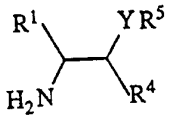
10. A method for the preparation of a compound of formula (I) CHARACTERIZED in:

a) reacting a compound of formula (II)



(II)

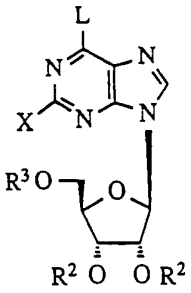
wherein X has the meaning set forth above, wherein L is a leaving group and wherein R^2 and R^3 are the same or different and represent hydrogen, benzoyl-, C_{1-6}-alkanoyl-, with an amine derivative of the general formula (III)



(III)

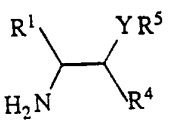
wherein R^1, R^4 and R^5 have the meaning set forth above, to form a compound of the invention, wherein R^6 and R^7 in formula (I) are the same or different and represent hydrogen, benzoyl-, C_{1-6}-alkanoyl- or

b) reacting a compound of formula (II)



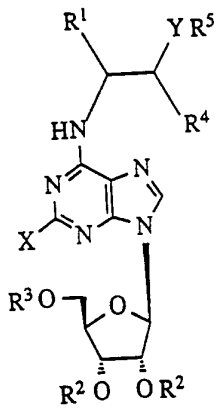
(II)

wherein X has the meaning set forth above, wherein L is a leaving group and wherein R^2 and R^3 are the same or different and represent hydrogen or benzoyl-, p-toluoyl-, C_{1-6}-alkanoyl, trimethylsilyl or t-butyldimethylsilyl, with an amine derivative of the general formula (III)



(III)

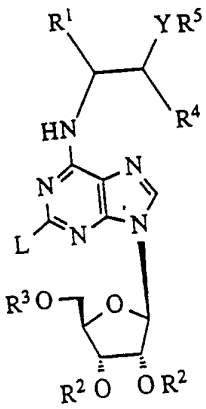
wherein R^1, R^4 and R^5 have the meaning set forth above, to form a compound of formula (IV)



(IV)

wherein X, R^1, R^2, R^3, R^4 and R^5 have the meaning set forth above, and reacting the compound of formula (IV) with suitable deprotecting agents such as methanolic ammonia, an alkali metal carbonate in alcohol or tetraalkylammonium fluoride to form a compound of the invention wherein R^6 and R^7 in formula (I) are hydrogen, or

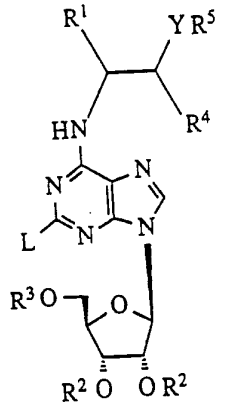
c) reacting a compound of formula (V)



(V)

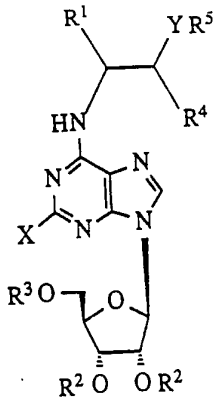
wherein L, R^1, R^4 and R^5 have the meanings set forth above and R^2 and R^3 are independently hydrogen, benzoyl- or C_{1-6}-alkanoyl- with a nucleophile XH, wherein X is C_{1-6}-alkylamino, C_{1-6}-dialkylamino or C_{1-6}-alkoxy, to form a compound of the invention, or

d) reacting a compound of formula (V)



(V)

wherein L, R^1, R^2, R^3, R^4 and R^5 have the meanings set forth above with a nucleophile XH, wherein X is C_{1-6}-alkylamino or C_{1-6}-alkoxy, to form a compound of formula (IV)

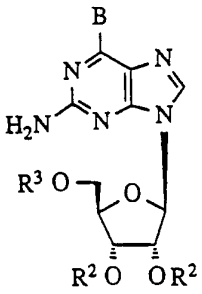


(IV)

wherein R^1, R^2, R^3, R^4 and R^5 have the meaning set forth above, and wherein X is C_{1-6}-alkylamino or C_{1-6}-alkoxy, and reacting the compound of formula (IV) with suitable deprotecting agents such as methanolic

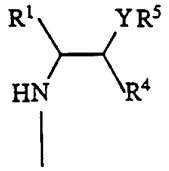
ammonia, an alkali metal carbonate in alcohol or tetraalkylammonium fluoride to form a compound of the invention wherein R^6 and R^7 in formula (I) are hydrogen or

e) reacting a compound of formula (VI)



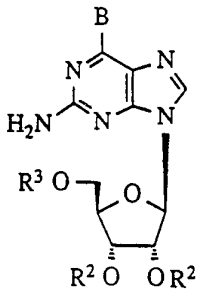
(VI)

wherein B is



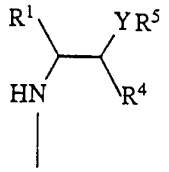
wherein Y, R^1, R^4 and R^5 have the meaning set forth above, and wherein R^2 and R^3 are hydrogen, benzoyl- or C_{1-6}-alkanoyl-, with a diazotising agent such as 3-methylbutyl nitrite, to form an diazo-intermediate which can be reacted further with chloroform, tetrachloroethane, trimethylsilylchloride, bromoform or fluoroboric acid in order to introduce the group -X into the compound of the invention, or

f) reacting a compound of formula (VI) wherein R^2 and R^3 have the meaning set forth above

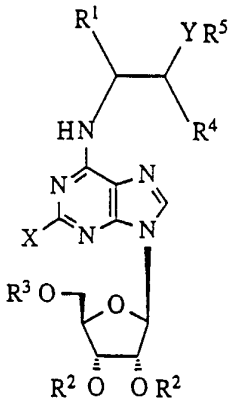


(VI)

and B is



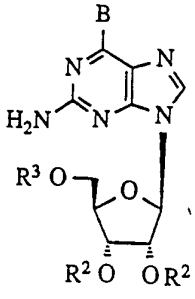
wherein Y, R^1, R^4 and R^5 have the meaning set forth above, with a diazotising agent such as 3-methylbutyl nitrite, to form a compound of formula (IV)



(IV)

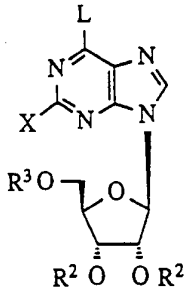
wherein X, R^1, R^2, R^3, R^4 and R^5 have the meaning set forth above, and reacting the compound of formula (IV) with suitable deprotecting agents such as methanolic ammonia, an alkali metal carbonate in alcohol or tetraalkylammonium fluoride to form a compound of the invention wherein R^6 and R^7 in formula (I) are hydrogen or

g) reacting a compound of formula (VI)



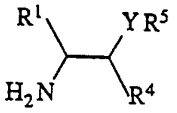
(VI)

wherein B is a leaving group L with the meaning as set forth above, and wherein R^2 and R^3 are hydrogen, benzoyl- or C_{1-6}-alkanoyl-, with a diazotising agent such as 3-methylbutyl nitrite, to form an intermediate which can be reacted further with chloroform, tetrachloroethane, trimethylsilylchloride, bromoform or fluoroboric acid in order to introduce the group -X into the compound of formula (II)



(II)

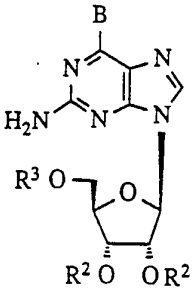
wherein X, L, R^2 and R^3 have the meaning set forth above, and reacting the compound of formula (II) with an amine derivative of the general formula (III)



(III)

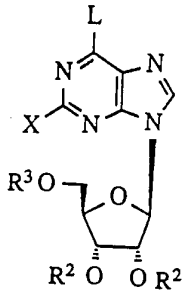
wherein R^1, R^4 and R^5 have the meaning set forth above, to form a compound of the invention, or

h) reacting a compound of formula (VI)



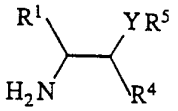
(VI)

wherein B is a leaving group L with the meaning as set forth above, and wherein R^2 and R^3 have the meaning set forth above, with a diazotising agent such as 3-methylbutyl nitrite, to form an intermediate which can be reacted further with chloroform, tetrachloroethane, trimethylsilyl-chloride, bromoform or fluoroboric acid in order to introduce the group -X into the compound of formula (II)



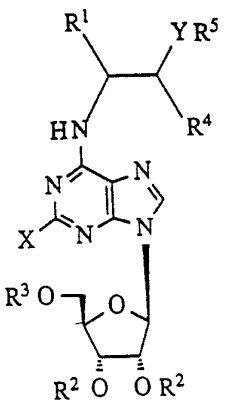
(II)

wherein X, L, R^2 and R^3 have the meaning set forth above, and reacting the compound of formula (II) with an amine derivative of the general formula (III)



(III)

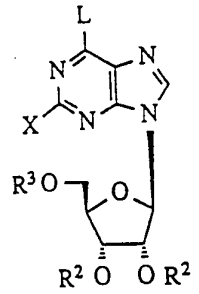
wherein R^1, R^4 and R^5 have the meaning set forth above, to form a compound of formula (IV)



(IV)

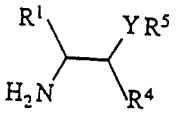
wherein X, R^1, R^2, R^3, R^4 and R^5 have the meaning set forth above, and reacting the compound of formula (IV) with suitable deprotecting agents such as methanolic ammonia, an alkali metal carbonate in alcohol or tetraalkylammonium fluoride to form a compound of the invention wherein R^6 and R^7 in formula (I) are hydrogen, or

i) reacting a compound of formula (II)



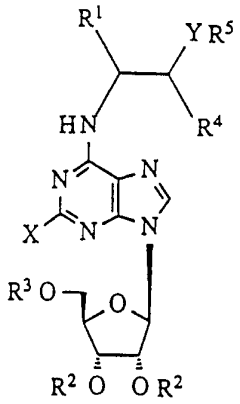
(II)

wherein X has the meaning set forth above, wherein L is a leaving group and wherein R^2 and R^3 are the same or different and represent benzoyl- or C_{1-6}-alkanoyl, with an amine derivative of the general formula (III)



(III)

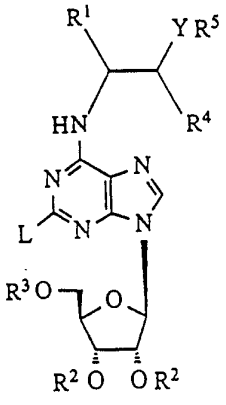
wherein R^1, R^4 and R^5 have the meaning set forth above, to form a compound of formula (IV)



(IV)

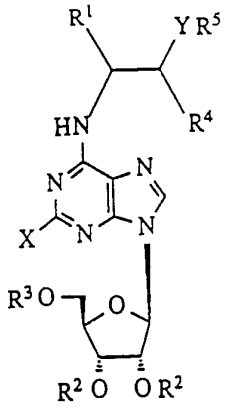
wherein X, R^1, R^2, R^3, R^4 and R^5 have the meaning set forth above, and deprotecting the compound of formula (IV) with agents such as methanolic ammonia, an alkali metal carbonate in alcohol, alkali metal alkoxide in alcohols or tetraalkylammonium fluoride to form a compound of the invention wherein R^6 in formula (I) is benzoyl or C_{1-6}-alkanoyl, or

j) reacting a compound of formula (V)



(V)

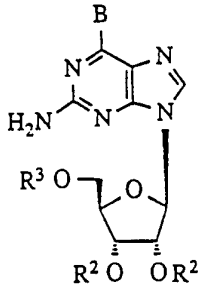
wherein L, R^1, R^4 and R^5 have the meanings set forth above and wherein R^2 and R^3 are the same or different and represent benzoyl or C_{1-6}-alkanoyl with a nucleophile XH, wherein X is C_{1-6}-alkylamino or C_{1-6}-alkoxy, to form a compound of formula (IV)



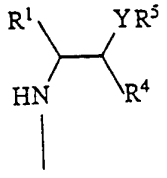
(IV)

wherein R^1, R^2, R^3, R^4 and R^5 have the meaning set forth above, and wherein X is C_{1-6}-alkylamino or C_{1-6}-alkoxy, and deprotecting the compound of formula (IV) with agents such as methanolic ammonia, an alkali metal carbonate in alcohol, alkali metal alkoxide in alcohols or tetraalkylammonium fluoride to form a compound of the invention wherein R^6 in formula (I) is benzoyl- or C_{1-6}-alkanoyl- or

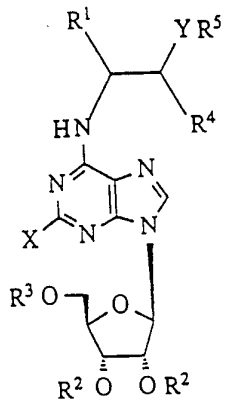
k) reacting a compound of formula (VI) wherein R^2 and R^3 are the same or different and represent benzoyl or C_{1-6}-alkanoyl



(VI)

and B is 

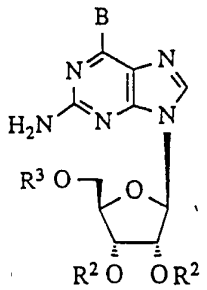
wherein Y, R^1, R^4 and R^5 have the meaning set forth above, with a diazotising agent such as 3-methylbutyl nitrite, to form a compound of formula (IV)



(IV)

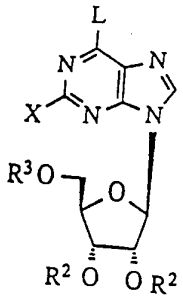
wherein X, R^1, R^2, R^3, R^4 and R^5 have the meaning set forth above, and deprotecting the compound of formula (IV) with agents such as methanolic ammonia, an alkali metal carbonate in alcohol, alkali metal alkoxide in alcohols or tetraalkylammonium fluoride to form a compound of the invention wherein R^6 is benzoyl- or C_{1-6}-alkanoyl or

l) reacting a compound of formula (VI)



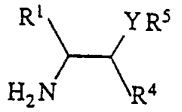
(VI)

wherein B is a leaving group L with the meaning as set forth above, and wherein R^2 and R^3 are the same or different and represent benzoyl or C_{1-6}-alkanoyl, with a diazotising agent such as 3-methylbutyl nitrite, to form an intermediate which can be reacted further with chloroform, tetrachloroethane, trimethylsilylchloride, bromoform or fluoroboric acid in order to introduce the group -X into the compound of formula (II)



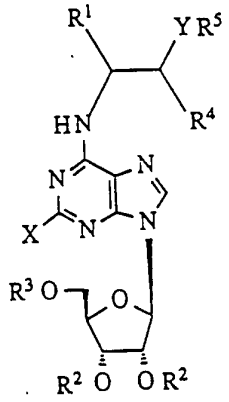
(II)

wherein X, L, R^2 and R^3 have the meaning set forth above, and reacting the compound of formula (II) with an amine derivative of the general formula (III)



(III)

wherein R^1, R^4 and R^5 have the meaning set forth above, to form a compound of formula (IV)



(IV)

wherein X, R^1, R^2, R^3, R^4 and R^5 have the meaning set forth above, and deprotecting the compound of formula (IV) with agents such as methanolic ammonia, an alkali metal carbonate in alcohol, alkali metal alkoxide in alcohols or tetraalkylammonium fluoride to form a compound of the invention wherein R^6 is benzoyl or C_{1-6}-alkanoyl.

11. A pharmaceutical composition comprising as active component a compound according to claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

12. A pharmaceutical composition suitable for use in the treatment of a central nervous system ailment, which comprises as active component a compound according to claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

13. A pharmaceutical composition according to claim 11 or 12 in the form of an oral dosage unit containing about 1-200 mg of the active compound.

14. A method of treating a central nervous system ailment in a person in need of such treatment characterized in administering to said person an amount of a compound of claim 1 effective in alleviation of such an ailment.

15. A method of treating a central nervous system ailment in a subject in need of such treatment comprising the step of administering to said subject an amount of a compound of claim 1 which is effective for the alleviation of such ailment in the form of a pharmaceutical composition thereof, in which it is present together with a pharmaceutically acceptable carrier or diluent.

16. The use of a compound according to claim 1 for preparing a medicinal product for alleviation of central nervous system diseases treatable *via* adenosine receptors.

17. The use of a compound according to claim 1 for preparing a medicinal product for treatment of diseases of the cardiovascular system.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 93/00434

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: C07H 19/16, C07H 19/167, A61K 31/70
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: C07H, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO, A1, 9205177 (RHONE-POULENC RORER INTERNATIONAL (HOLDINGS) INC.), 2 April 1992 (02.04.92) --	1-13,16-17
A	EP, A2, 0423776 (G.D. SEARLE & CO.), 24 April 1991 (24.04.91) --	1-13,16-17
A	WO, A1, 8504882 (NELSON RESEARCH AND DEVELOPMENT COMPANY), 7 November 1985 (07.11.85) --	1-13,16-17
A	DE, A, 2147314 (SCHERING AG), 19 April 1973 (19.04.73) --	1-13,16-17

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier 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 when the document is taken alone
"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

Date of the actual completion of the international search	Date of mailing of the international search report
29 March 1994	31 -03- 1994
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Eva Johansson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 93/00434

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO, A1, 9323418 (NOVO NORDISK A/S), 25 November 1993 (25.11.93) --	1-13,16-17

INTERNATIONAL SEARCH REPORT

In ational application No.

PCT/DK 93/00434

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 14-15
because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

26/02/94

International application No.
PCT/DK 93/00434

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A1- 9205177	02/04/92	AU-A- 8726691	15/04/92
		CA-A- 2092305	26/03/92
		EP-A- 0550631	14/07/93
EP-A2- 0423776	24/04/91	CA-A- 2027999	20/04/91
		JP-A- 3133995	07/06/91
		US-A- 5055569	08/10/91
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		AU-A- 4219585	15/11/85
		CA-A- 1293721	31/12/91
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		CA-A- 1305135	14/07/92
		DE-D- 3587717	00/00/00
		EP-A,B- 0180614	14/05/86
		SE-T3- 0180614	
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		BE-A- 788958	19/03/73
		CA-A- 983922	17/02/76
		CH-A- 582197	30/11/76
		FR-A,B- 2154527	11/05/73
		GB-A- 1407083	24/09/75
		NL-A- 7212592	20/03/73
		SE-B,C- 393383	09/05/77
		US-A- 3901876	26/08/75
WO-A1- 9323418	25/11/93	NONE	