Novel substituted adenosine derivatives of formula (I), or a pharmaceutically acceptable salt thereof, wherein X represents hydrogen, halogen, amino, perhalomethyl, acetamido, cyano, C₁₋₅-alkyl, C₁₋₅-alkoxy, C₁₋₅-alkylthio or C₁₋₅-alkylamino; R¹ is -NR²R³, -YR⁴, wherein Y is oxygen or sulphur; R² is C₁₋₅-alkyl; R³ is phenyl or C₁₋₅-alkyl, which may be substituted with phenyl or phenoxy; R⁴ is naphthyl; partly saturated naphthyl; C₁₋₅-alkyl, which may be substituted with phenoxy or phenyl, which may be substituted with nitro, halogen or amino; or C₃₋₅-cycloalkyl, which may be substituted with phenyl or phenoxy, which have been found useful for treating central nervous system ailments.
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**Novel adenosine derivatives**

The present invention relates to modified adenosine derivatives having a substituent at the 6-position containing sulphur, oxygen or nitrogen, further substituted at the purine 2-position as well as pharmaceutically acceptable addition salts thereof having central nervous system (CNS) properties. Also covered are processes for preparation of the above derivatives and their pharmaceutical compositions as well as methods for using the compounds and compositions as drugs primarily for CNS ailments.

**Background of the Invention**

Adenosine can be considered to be a hormone which has been shown to have a number of significant effects on the mammalian central nervous system [Annual Reports in Medicinal Chemistry, 1988, 23, 39-48; International Review of Neurobiology (Smythies, J.R. and Bradley, R.J., eds.) Academic Press Inc., 1985, 27, 63-139], 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, 1988, 9, 193-194). 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. Such substances


Adenosine receptors represent a subclass (P1) 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 A1 and A2. Extensive research has been carried out in a quest to identify selective ligands at these sites [see, for example, Comprehensive Medicinal Chemistry, Volume 3, (Hansch, C., Sammes, P.G. and Taylor, J.B., Eds., Pergamon Press PLC: 1990, pp 601-642)]. Selective ligands exist for A1 and A2 adenosine receptors and the structure-activity relationships of the various reference ligands have been reviewed (Biochemical Pharmacology, 1986, 35, 2487-2481) together with their therapeutic potential (Journal of Medicinal Chemistry, 1992, 35, 407-422). Among the
known adenosine receptor agonists most selective for the A1 receptor over the A2 receptor are the examples where the adenine nucleus is substituted with a cycloalkyl group on the amino function, for example N-cyclopentyl-
adenosine and N-cyclohexyladenosine (Journal of Medicinal Chemistry, 1985, 28, 1383-1384) or 2-chloro-N-cyclopentyladenosine (Naunyn-Schmiedeberg’s Arch pharmacol. 1988, 337, 687-689).

Examples of adenosine derivatives in the chemical literature with the heteroatoms, oxygen or nitrogen bonded directly to the 6-amino substituent are summarised below.


In the above scientific articles, no mention is made of any pharmacological effects of the compounds concerned on the central nervous system.
In US 3,819,613, substituted adenosine analogues with hydrazone derivatives on the 6-amino function are disclosed as hypotensive agents. In GB 1,351,501, adenosine and 2-aminoadenosine derivatives having a -NH-R_2 group joined to the 6-amino function are disclosed as coronary dilators and platelet aggregation inhibitors. In EP A 152,944, a series of 2-, 6- and 8-substituted adenosine derivatives are described having activity as anti-allergy agents. In EP A 253,962, adenosine and 2-haloadenosine analogues having an alkyl, cycloalkyl or an aralkyl group attached to the 6-amino function are described with activity as anti-dementia agents. In EP 402,752A, derivatives of adenosine unsubstituted in the 2-position are described which have a substituted heteroaromatic 1-pyrrolyl moiety attached to the 6-amino group. In WO 91/04032, methods of preventing neural tissue damage in neurodegenerative diseases by increasing extracellular concentrations of adenosine are described. Examples are given of prodrug esters of AICA riboside (5-amino-1-β-D-ribofuranosyl)imidazo-4-carboxamide) which are claimed to be centrally acting neuroprotective agents. In WO 92/02214, analogs of AICA riboside are revealed for the treatment of myocardial and cerebral ischaemias. In WO 90/05526, 2-(alkyl-alkynyl)adenosine derivatives are described for treatment of ischaemic disease of the heart and brain.

The present invention relates to new adenosine analogues having potent binding in vitro to the adenosine A1 receptor, and at the same time showing selectivity for A1 receptor binding in vitro over that to the A2 receptor subtype. In addition, many of the novel compounds contained in this invention have a relatively high lipophilicity, especially when compared to adenosine analogues and adenosine itself which are not substituted on the 6-amino group or the purine 2-position. This latter property may make these compounds suitable for passage across the blood brain barrier.

The possibility that some of the compounds may be substrates for nucleosi-
de-specific active transport systems into the CNS across the blood barrier is, however, not excluded. These useful properties support the notion that some of the examples may have potential as candidate drugs for treatment of the CNS ailments mentioned within this invention in humans.

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

\[
\begin{array}{c}
\text{HN} \\
\text{X} \\
\text{HO} \\
\end{array}
\]

wherein
X represents hydrogen, halogen, amino, perhalomethyl, acetamido, cyano, \(C_{1-6}\)-alkyl, \(C_{1-6}\)-alkoxy, \(C_{1-6}\)-alkylthio or \(C_{1-6}\)-alkylamino;
\(R^1\) is \(-NR_2R_3\), \(-YR_4\);
\(Y\) is oxygen or sulphur;
\(R^2\) is \(C_{1-6}\)-alkyl;
\(R^3\) is phenyl or \(C_{1-6}\)-alkyl, which may be substituted with phenyl or phenoxy;
\(R^4\) is naphthyl;
partly saturated naphthyl;
\(C_{1-6}\)-alkyl, which may be substituted with phenoxy or phenyl, which may be substituted with nitro, halogen or amino;
or \(C_{3-8}\)-cycloalkyl, which may be substituted with phenyl or phenoxy;

In certain examples, the group \(R^1\) can contain one or more asymmetric carbon atoms in addition to those asymmetric centres already present in the molecule. In examples where this is the case, this invention includes all
resulting diastereoisomers and mixtures thereof.

Various salts of compounds of formula (I) can be prepared which can be considered physiologically acceptable. These include addition salts derived from inorganic or organic acids, for example, acetates, fumarates, glutarates, glutaconates, lactates, maleates, methanesulphonates, phosphates, salicylates, succinates, sulphates, sulphamates, tartrates and paratoluene-sulphonates. 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 of formula (I), which act as adenosine receptor agonists, are found to be useful in the treatment of central nervous system conditions such as anxiety, neuronal ischaemia/anoxia, convulsive disorders (epilepsy) and neurodegeneration (including Parkinson's disease).

Further, the compounds of formula (I) are found to be useful as analgesic agents, in lowering plasma free fatty acid (FFA) levels or as cardiovascular agents and also have application to 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, P¹, P² and P³ are the same or different and represent hydrogen or a protecting group
such as benzoyl-, p-toluoyl-, lower alkanoyl- (e.g. acetyl-), a substituted silyl group (e.g. a trimethylsilyl or t-butyldimethylsilyl group) or in the case of P₃, a triaryl methyl group, or in the case of P¹ and P², a 2',3'-O-(1-methyl)ethylidene derivative, with an O-alkylated hydroxylamine or a functionalised hydrazine derivative of general formula (III)

General process (A)

\[
\begin{align*}
\text{L} & \quad \text{H}_2\text{N} \quad \text{R}^1 \\
\text{X} & \quad \text{P}^3 \text{O} \quad \text{O} \quad \text{P}^1 \\
\text{P}^2 \text{O} & \quad \text{O} \quad \text{P}^1
\end{align*}
\]

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{X} & \quad \text{P}^3 \text{O} \quad \text{O} \quad \text{P}^1 \\
\text{P}^2 \text{O} & \quad \text{O} \quad \text{P}^1
\end{align*}
\]

\[
\begin{align*}
\text{N} \quad \text{N} \\
\text{N} \quad \text{N} \\
\text{X} \quad \text{P}^3 \text{O} \quad \text{O} \quad \text{P}^1 \\
\text{P}^2 \text{O} \quad \text{O} \quad \text{P}^1
\end{align*}
\]

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{X} \quad \text{P}^3 \text{O} \quad \text{O} \quad \text{P}^1 \\
\text{P}^2 \text{O} & \quad \text{O} \quad \text{P}^1
\end{align*}
\]

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{R}^1 \\
\text{HO} & \quad \text{HO} \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{X} \quad \text{P}^3 \text{O} \quad \text{O} \quad \text{P}^1 \\
\text{P}^2 \text{O} & \quad \text{O} \quad \text{P}^1
\end{align*}
\]

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{R}^1 \\
\text{HO} & \quad \text{HO} \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{X} \quad \text{P}^3 \text{O} \quad \text{O} \quad \text{P}^1 \\
\text{P}^2 \text{O} & \quad \text{O} \quad \text{P}^1
\end{align*}
\]

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{R}^1 \\
\text{HO} & \quad \text{HO} \quad \text{OH}
\end{align*}
\]

giving the compound of formula (IV) as the reaction product. In cases where P¹, P² and P³ are not hydrogen an additional step will be required to remove protecting groups from (IV); in cases where the groups P¹, P² and P³ are, for example, acetyl 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 methods for deprotection include for example treatment with tetraalkylammonium fluorides or aqueous hydrolysis in the presence of acid or base. Where the $P^1$ and $P^2$ groups comprise a $2',3'-O$-(1-methyl)ethyldene group, or $P^3$ comprises a triaryl methyl group, suitable conditions for deprotection include, for example, hydrolysis with aqueous mineral acid.

**Method B**

A compound of formula (I) (wherein X represents $-NH_2$, $-NH-C_{1-6}$-alkyl, or $-O-C_{1-6}$-alkyl, or $S-C_{1-6}$-alkyl) may be prepared by reacting a substance of general formula (V).

![Diagram](image-url)
(where L is a leaving group as defined in method (A)) with a nucleophile, for example C_{1-3}-alkylamino (optionally in the presence of a suitable base) or with the anion (C_{4-8}-alkoxide or C_{1-8}-thioalkoxide) to afford the product (IV). In cases where P^1, P^2 and P^3 are hydrogen, compound (I) can be obtained directly. However, in cases where P_2 and P_3 are not hydrogen an additional step will be involved to remove protecting groups from (IV); examples of conditions for removal of protecting groups are given in process (A). In some reactions involving (V) with the anion C_{1-8}-alkoxide or C_{1-8}-thioalkoxide, where P^1,P^2 and P^3 are for example acetyl- or benzoyl-, partial or full deprotection may take place. In cases where only partial deprotection has taken place, deprotection can be completed under conditions described in method (A).

15 Method C

A compound of formula (I) may be prepared by reacting a substance of general formula (VI) (where B represents -NH-R^1 or L as defined previously) with a diazotising agent (such as, for example, 3-methylbutyl nitrite) to form an intermediate species which can be reacted further with a variety of substrates as exemplified below in order to introduce the group -X into the product (VII).
In the case where B represents a leaving group L, a further displacement reaction with for example (III) will be required in order to obtain the product (IV). In cases where the groups P¹, P² and P³ are not hydrogen, or not all hydrogen, another step will be required to remove protecting groups from (IV); conditions for removing protecting groups are described in method A. Alternatively, where B represents HN-R¹, direct deprotection of intermediate (VII) can be carried out to provide (I).

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 models 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.
Evaluation of \textit{in vitro} binding to adenosine A1 and A2 receptors

The affinity of the novel compounds described in this invention for the adenosine A1 receptor was determined essentially as described in the literature using $[^3\text{H}]$-R-PIA as a radioligand (Naunyn-Schmiedeberg's Archives of Pharmacology, 1980, 313, 179-187). Affinity for the A2 receptor was measured using the radioligand $[^3\text{H}]$-CGS 21680 (European Journal of Pharmacology, 1989, 168, 243-246), and the values for representative compounds is given in the table below.

Test results obtained by testing some compounds employed in the present invention are included in table I.

\begin{center}
\begin{tabular}{|l|c|c|c|}
\hline
Adenosine agonist tested & A1 receptor binding ($K_{i_{50}}$, nM) & A2 receptor binding ($K_{i_{50}}$, nM) & Ratio A2/A1 \\
\hline
Example 3 & 18 & 1659 & 92 \\
Example 7 & 6.7 & 2876 & 429 \\
Example 8 & 21 & 1154 & 55 \\
\hline
\end{tabular}
\end{center}

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 conventional 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, polyhyroxethoxylated castor oil, gelatine, lactose amyllose, 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 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 tableting techniques contains:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active compound</td>
<td>5.0 mg</td>
</tr>
<tr>
<td>Lactosum</td>
<td>67.0 mg Ph.Eur.</td>
</tr>
<tr>
<td>Avicel™</td>
<td>31.4 mg</td>
</tr>
<tr>
<td>Amberlite™IRP 88</td>
<td>1.0 mg</td>
</tr>
<tr>
<td>Magnesii stearas</td>
<td>0.25 mg Ph.Eur.</td>
</tr>
</tbody>
</table>

Owing to 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 sulfate, 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, ischemia, 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 30-70 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 the invention is further illustrated in the following examples.

Hereinafter, TLC is thin layer chromatography, THF is tetrahydrofuran, TFA is trifluoroacetic acid and mp is melting point. Where melting points are given, these are uncorrected. The structures of the compounds are confirmed by assignment of 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 on Merck silica gel 60 (Art 9385). HPLC was carried out on a Waters or Merck chromatograph with a multiwavelength detector and a reversed phase C18 column (250 x 4 mm, 5μm, 100Å; eluent flow rate 1 mL/min at 35°C). Retention times are given in minutes.

EXAMPLE 1 (Method A)

2-Chloro-N-(N-methyl-N-(2-phenylethyl)amino)adenosine.

N-Methyl-2-phenylethylamine hydrochloride.

Phenylacetaldehyde (24.0 g, 0.20 mol), a 33% solution of methylamine in ethanol (42.35 g, 0.41 mol) and methylamine hydrochloride (10.13 g, 14.8 mmol) were dissolved in methanol (200 ml). Sodium cyanoborohydride (3.77 g, 60 mmol) was introduced and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was evaporated in vacuo to ca. 50 ml, concentrated hydrochloric acid (40 ml) was added and once the exotherm had subsided the reaction mixture was stirred for 2 h. Water (200 ml) was introduced followed by potassium hydroxide (27g, 0.48 mol) and the cooled solution was extracted with dichloromethane (7 x 100 ml). The combined dichloromethane extracts were extracted with 2 N hydrochloric acid solution (200 ml) and 0.2 N hydrochloric acid solution (200 ml). The combined acidic extracts were washed with dichloromethane (2 x 50 ml) and the aqueous phase was basified with 4 N sodium hydroxide solution before being extracted with dichloromethane (2 x 100 ml). The combined extracts were dried (MgSO₄) and evaporated to a residue (9.2 g) which was dissolved in toluene (200 ml) with methanol (5 ml) present.

Chlorotrimethylsilane (8.63 ml) dissolved in toluene (300 ml) was added and the hydrochloride salt of N-methyl-2-phenylethylamine precipitated. After
cooling the suspension, the solid was collected by filtration and dried in vacuo; $^1$H NMR (DMSO-d$_6$) $\delta$ 2.54 (3H, s, -CH$_3$), 2.92-3.07 (4H, m, -CH$_2$CH$_2$-), 7.20 -7.40 (5H, m, Ar-H).

N-Methyl-N-nitroso-2-phenylethylamine

A sample of N-methyl-2-phenylethylamine hydrochloride (6.4 g, 37.3 mmol) was dissolved in water (18 ml), ethanol (11 ml) and 2 N hydrochloric acid (4 ml) were introduced and the solution was heated to 70°C. A solution of sodium nitrite (2.6g, 37.7 mmol) in water (11 ml) was added dropwise to the reaction mixture over 30 min. During the addition the reaction mixture was acidified with 2 N hydrochloric acid (4 ml). Cooling was followed by extraction with n-heptane (4 x 100 ml); the combined extracts were dried (MgSO$_4$) and evaporated in vacuo to provide the N-methyl-N-nitroso-2-phenylethylamine as an oil (5.0 g, 81%) (a ca. 65:35 mixture of apparent geometric isomers), $^1$H NMR (DMSO-d$_6$) $\delta$ 2.98 (3H, s, -CH$_3$), 3.05 (2H, t, PhCH$_2$-), 4.37 (2H, t, -CH$_2$-N-), 7.13-7.36 (5H, m, Ar-H) (major isomer); 2.78 (2H, t, PhCH$_2$-), 2.98 (3H, s, -CH$_3$), 3.77 (2H, t, -CH$_2$-N-), 7.13-7.36 (5H, m, Ar-H) (minor isomer).

1-Methyl-1-(2-phenylethyl)hydrazine.

The above nitrosamine (5.0 g, 30.4 mmol) was dissolved in dry THF (100 ml) and a 1 M solution of lithium aluminium hydride in THF was added dropwise. On heating to 55°C reaction commenced, the mixture was heated at reflux for 30 min. and cooled to room temperature. The reaction mixture was kept cool using a 23°C water bath and water (50 ml) was carefully introduced dropwise with rapid stirring, followed by 1 N sodium hydroxide solution (4 ml). The precipitate was removed by filtration and the filtrate was extracted with dichloromethane (3 x 50 ml). The combined extracts were dried (MgSO$_4$) and evaporated to a residue (4.08 g) which was dissolved in
toluene (100 ml) with methanol (2 ml) present. Chlorotrimethylsilane (3.46 ml) dissolved in toluene (200 ml) was introduced and the hydrochloride salt of 1-methyl-1-(2-phenylethyl)hydrazine was separated as a gum, $^1$H NMR (CDCl$_3$) $\delta$ 2.44 (3H, s, -CH$_3$), 2.56 (2H, t, -CH$_2$), 2.76 (2H, t, -CH$_2$), 3.36 (2H, br s, -NH$_2$), 7.13 - 7.32 (5H, m, Ar-H).

9-(2,3,5-Tri-O-benzoyl-$\beta$-D-ribofuranosyl)-2,6-dichloro-9H-purine

2,6-dichloro-9(H)-purine (5.8 g, 30.7 mmol) and 1-acetyl-2,3,5-tri-O-benzoyl-D-ribofuranose (16.26 g, 32.2 mmol) were thoroughly mixed (as powdery solids) and fused together at 145-150°C under oil pump vacuum. The resultant oily mixture was stirred gently for 0.75 h (during which time the acetic acid by-product evaporated) and cooled to ca. 50°C before being dissolved in dichloromethane (100 ml) with stirring. This solution was applied directly to a column of silica gel (6 x 22 cm) and eluted initially with cyclohexane/dichloromethane (1/1), then with dichloromethane and finally with cyclohexane/ethyl acetate (1/1) to provide 9-(2,3,5-tri-O-benzoyl-$\beta$-D-ribofuranosyl)-2,6-dichloro-9H-purine (16.6 g, 87%) as a colourless foam, TLC $R_f$ 0.50 [SiO$_2$, cyclohexane/ethyl acetate (1/1)]. $^1$H NMR (DMSO-d$_6$) $\delta$

4.72 (1H, dd, H-5'$_a$), 4.88 (1H, q, H-4'), 4.93 (1H, dd, H-5'$_b$), 6.15 (2H, m, H-2' & H-3'), 6.50 (1H, d, H-1'), 7.34 - 7.65 (9H, m, m- & p-ArH), 7.90 - 8.13 (6H, m, o-ArH), 8.28 (1H, s, H-8). (This method of preparation is a modification of that described by Imai, K-i. et al, Chemical and Pharmaceutical Bulletin, 1966, 14, 1377-1381, but without the use of a catalyst).

2',3',5'-Tri-O-benzoyl-2-chloro-N-(N-methyl-N-(2-phenylethyl)amino)adenosine

The above hydrochloride salt of 1-methyl-1-(2-phenylethyl)hydrazine (0.67 g, 1.05 mmol), 9-(2,3,5-tri-O-benzoyl-$\beta$-D-ribofuranosyl)-2,6-dichloro-9H-purine (1.90 g, 3 mmol) and triethylamine (1.24 ml, 9 mmol) were dissolved in 1,4-
dioxan (20 ml). The solution was stirred at ambient temperature for 20 h. The cooled reaction mixture was evaporated to a gum and purified by flash chromatography on silica gel. Elution with cyclohexane/ethyl acetate (4/1) initially and then with a 1/1 mixture of these solvents provided 2',3',5'-tri-O-benzoyl-2-chloro-N-(N-methyl-N-(2-phenylethyl)amino)adenosine (1.28 g, 60%) as a foam, $^1$H NMR (DMSO-d$_6$) $\delta$ 2.63 (3H, s, -CH$_3$), 4.66 (1H, dd, H-5$_2$), 4.77 (1H, dd, H-5$_3$), 4.86 (1H, q, H-4''), 6.23 (1H, t, H-3''), 6.36 (1H, t, H-2''), 6.54 (1H, d, H-1''), 7.11 - 7.98 (20H, m, Ar-H), 8.44 (1H, s, H-8), 9.40 (1H, br s, N-H).

2',3',5'-tri-O-benzoyl-2-chloro-N-(N-methyl-N-(2-phenylethyl)amino)adenosine (1.24 g, 1.74 mmol) was dissolved in methanolic ammonia (50 ml) and allowed to stand at ambient temperature for 20 h. The reaction mixture was evaporated and the residue was purified by flash chromatography on silica gel. Elution with dichloromethane/methanol (19/1) initially, then increasing the polarity of the eluent to a 9/1 mixture of dichloromethane/methanol provided the title compound (0.57 g, 78%) as semi-solid foam, TLC $r_f$ 0.25 [SiO$_2$, dichloromethane/ ethanol 25% aqueous ammonia solution (60/10/1)], $^1$H NMR (DMSO-d$_6$) $\delta$ 2.65 (3H, s, -CH$_3$), 3.53 - 3.60 (1H, m, H-5$_2$), 3.63 - 3.70 (1H, m, H-5$_3$), 4.05 (1H, q, H-4''), 4.15 (1H, q, H-3''), 4.55 (1H, q, H-2''), 5.08 (1H, t, 5'-OH), 5.22, 5.50 (2H, 2d, 2'-and 3'-OH), 5.56 (1H, d, H-1''), 7.11 - 7.28 (5H, m, Ar-H), 8.42 (1H, s, H-8), 9.33 (1H, br s, N-H).

C$_{29}$H$_{22}$ClN$_6$O$_4$. 0.6 H$_2$O requires C, 51.2 ; H, 5.5 ; N, 18.9.

Found: C, 51.3 ; H 5.4 ; N 18.7%.

EXAMPLE 2

2-Chloro-N-[(N-methyl-N-phenyl)amino]adenosine.

The title compound was prepared according to method A described in
Example 1 by reacting 1-methyl-1-phenylhydrazine (1.29 g, 11 mmol) with 9-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2,6-dichloro-9H-purine (1.58 g, 2.5 mmol) and debenzoylating the purified product using potassium carbonate in methanol to provide the title 2-chloro-N-[(N-methyl-N-phenyl)amino]adenosine (0.70 g, 69%) (after column chromatography) as a colourless foam, TLC r, 0.50 [SiO₂, THF], 1H NMR (DMSO-d₆) δ 3.23 (3H, 2s, CH₃), 3.50 - 3.72 (2H, br, -CH₂), 5.06 (1H, br, 5'-OH), 5.24, 5.52 (2H, 2d, 2'- and 3'-OH), 5.86 (1H, br, H-1'), 6.70 - 6.84 (3H, m, Ar-H), 7.15 - 7.24 (2H, t, Ar-H).

C₁₁H₁₉N₆O₄. 0.66 H₂O requires C, 48.7; H, 4.9; N, 20.0. Found: C, 49.1; H 4.9; N 19.6%

EXAMPLE 3

2-Chloro-N-(N,N-dimethylamino)adenosine

The title compound was prepared according to method A described in Example 1 by reacting 1,1-dimethylhydrazine (0.15 g, 2.52 mmol) with 9-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2,6-dichloro-9H-purine (1.45 g, 2.29 mmol) and debenzoylating the purified product using methanolic ammonia to provide the title 2-chloro-N-(N,N-dimethylamino)adenosine (0.140 g, 29%) (after column chromatography) as a colourless foam, 1H NMR (DMSO-d₆) δ 2.58 (6H, s, 2 x -CH₃), 3.52 - 3.57 (1H, m, H-5'), 3.62-3.68 (1H, m, H-5'ₜ), 3.93 (1H, q, H-4'), 4.11 (1H, q, H-3'), 4.50 (1H, q, H-2'), 5.06 (1H, t, 5'-OH), 5.22, 5.48 (2H, 2d, 2'-and 3'-OH), 5.82 (1H, d, H-1'), 8.38 (1H, s, H-8), 9.34 (1H, br s, N-H).

C₁₂H₁₇N₆O₄. 0.5 EtOH. 0.5 H₂O requires C, 41.5; H, 5.6; N, 22.3. Found: C, 41.5; H, 5.5; N, 22.1%.
EXAMPLE 4

2-Chloro-N-(phenylmethoxy) adenosine.

2',3',5'-Tri-O-benzoyl-2-chloro-N-(phenylmethoxy) adenosine

(This example was also prepared by general method A). 9-(2,3,5-Tri-O-benzoyl-\(\alpha\)-D-ribofuranosyl)-2,6-dichloro-9H-purine (2.0 g, 3.2 mmol), \(\beta\)-(p-phenylmethyl)hydroxylamine hydrochloride (0.77 g, 4.8 mmol) and diisopropylethylamine (1.03 g, 8.0 mmol) were dissolved in dioxan (50 ml). The reaction mixture was heated at reflux for 20 h, filtered and evaporated in vacuo. The crude product was coevaporated with dichloromethane and crystallised from a mixture of dichloromethane and methanol to provide the title compound (1.0 g, 43%), as white crystals, mp 115 - 119\(^\circ\)C, \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 3.52 - 3.70 (2H, m, H-5\(_a\) and H-5\(_b\)), 3.95 (1H, d, H-4'\(_a\)), 4.15 (1H, dd, H-3'), 4.52 (1H, dd, H-2'), 5.00 (2H, s, CH2), 5.88 (1H, d, H-1'), 8.52 (1H, s, H-8).

C\(_{96}\)H\(_{29}\)ClN\(_5\)O\(_8\) requires C, 63.4%; H, 4.1%; N, 9.7%; Cl, 4.9.
Found C, 63.5%; H, 4.3%; N, 9.5%; Cl, 5.2%.

2',3',5'-Tri-O-benzoyl-2-chloro-N-(phenylmethoxy) adenosine (0.80 g, 1.1 mmol) was suspended in methanolic ammonia (50 ml). The reaction mixture was stirred at room temperature for 72 h. The solvent was evaporated in vacuo and the crude product was purified by flash chromatography (2 x 40 cm) eluting with dichloromethane/ethanol/aqueous ammonia solution (90/10/1) to give the title 2-chloro-N-(phenylmethoxy) adenosine as a foam (0.40 g, 89%), \(^1\)H NMR (DMSO-d\(_6\)) \(\delta\) 3.52 - 3.70 (2H, m, H-5\(_a\) and H-5\(_b\)), 3.95 (1H, d, H-4'\(_a\)), 4.15 (1H, dd, H-3'), 4.52 (1H, dd, H-2'), 5.00 (2H, s,
N-[(4-Nitrophenyl)methoxy]adenosine

The title compound was prepared according to Method A described above (R², R³ = H) by reacting O-[(4-nitrophenyl)methyl]hydroxylamine hydrochloride (1.43 g, 7 mmol) with 6-chloropurine riboside (i.e. 9-β-D-ribofuranosyl-6-chloro-9H-purine) (1.0 g, 3.5 mmol) in DMF (40 ml) at 110°C for 2 h with diisopropylethylamine (1.80 g, 14 mmol) present. The reaction mixture was evaporated and to the resultant residue was added saturated sodium bicarbonate solution (20 ml) and water (20 ml). Methanol was gradually added until the residue dissolved, and the solid which gradually precipitated was removed by filtration. The filtrate was concentrated to a residue which was purified by flash chromatography on silica gel. Elution with ethyl acetate/ethanol (30/1) initially, followed by a (8/1) mixture of these solvents provided a solid which was recrystallised from ethanol. The first crop of material was discarded, but the second crop was confirmed as the title compound (70 mg, 7%) mp 115-117°C. TLC rₖ 0.20 [SiO₂, ethyl acetate/methanol (9/1)]; ¹H NMR (DMSO-d₆) δ 3.46 - 3.57 (2H, m, H-5'ₐ and H-5'ₗ), 3.90 (1H, q, H-4'), 4.08 (1H, q, H-3'), 4.43 (1H, q, H-2'), 5.07 (1H, t, 5'-OH), 5.44, 5.74 (2H, 2d, 2' and 3'-OH), 5.82 (1H, d, H-1'), 7.67 (2H, d, Ar-H), 8.08 (1H, s, H-8), 8.22 (2H, d, Ar-H), 9.34 (1H, br s, N-H).

C₁₇H₁₈N₆O₇. 0.75 H₂O requires C, 47.3 ; H, 4.6 ; N, 19.45. Found: C, 48.8; H, 4.55; N, 19.45%.
EXAMPLE 6 (Method A)

2-Chloro-N-(2-phenylethoxy)adnosine.

N-(2-Phenylethoxy)phthalimide

N-Hydroxypthalimide (15.0 g, 92 mmol) and sodium acetate (7.5 g, 92 mmol) were stirred in dimethylsulfoxide (70 ml) at ambient temperature for 3h. 2-Chloroethylbenzene (12.5 g, 89 mmol) was added and the reaction mixture was heated at reflux for 2 h. After cooling and standing overnight the reaction mixture was filtered and the filtrate was poured onto ice/water (300 ml). The mixture was extracted with dichloromethane (4 x 100 ml), the combined extracts were dried (MgSO₄) and evaporated in vacuo to a residue. Purification by flash chromatography on a silica gel column eluting with heptane/ethyl acetate (1/1) afforded the title compound as a colourless foam (15.7 g, 33%); ¹H NMR (DMSO-d₆) δ 3.05 (2H, t, -OCH₂-), 4.39 (2H, t, -CH₂Ph), 7.20-7.35 (5H, m, Ar-H), 7.85 (4H, s, Ar-H).

O-(2-Phenylethyl)hydroxylamine hydrochloride.

N-(2-Phenylethoxy)phthalimide (11.3 g, 42 mmol) was dissolved in hot 96% ethanol (100 ml). Hydrazine hydrate (2.5 g, 50 mmol) was introduced and the reaction mixture was heated at reflux with mechanical stirring for 1.5h. The reaction mixture was stored at 4°C for 72 h, filtered and the filtrate was evaporated in vacuo. The crude white residue was suspended in toluene and stored at 4°C for 16h and filtered. The filtrate was treated with a solution of chlorotrimethylsilane (4.34 g) in toluene (200 ml) with methanol (1.05 g) present and the title compound precipitated. The suspension was allowed to cool and the product was collected and dried in vacuo, giving a white hygroscopic solid product (5.84g, 84%). ¹H NMR (DMSO-d₆) δ 2.95
(2H, t, -OCH₂), 4.25 (2H, t, -CH₂Ph), 7.20 - 7.35 (5H, m, Ar-H).

2',3',5'-Tri-O-benzoyl-2-chloro-N-(2-phenylethoxy)adenosine.

9-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-2,6-dichloro-9H-purine (2.0 g, 3.2 mmol), O-(2-phenylethyl)hydroxylamine hydrochloride (0.70 g, 4.0 mmol) and diisopropylethylamine (0.95 g, 7.4 mmol) were dissolved in 1,4-dioxan (40ml) and heated at reflux for 3 days. After cooling the reaction mixture was diluted with dichloromethane (50 ml) and washed with water (2 x 30 ml). The organic phase was dried (MgSO₄). Flash chromatography on a silica gel column, eluting with heptane/ethyl acetate (1/1) gave the desired product as a foam (1.54 g, 66%). ¹H NMR (DMSO-d₆) δ 3.05 (2H, t, -OCH₂), 4.19 (2H, t, -CH₂Ph), 4.70 (1H, dd, H-5'ₐ), 4.80 (1H, dd, H-5'ₐ), 4.90 (1H, dd, H-4'), 5.22 (1H, t, H-3'), 6.39 (1H, t, H-2'), 6.59 (1H, d, H-1'), 8.51 (1H, s, H-8).

C₃₉H₂₃ClN₅O₆ requires C, 63.8; H, 4.4; N, 9.5. Found C, 63.7; H, 4.5; N, 9.4%.

2',3',5'-Tri-O-benzoyl-2-chloro-N-(2-phenylethoxy)adenosine (1.54 g, 2.0mmol) was suspended in a solution of methanolic ammonia and stirred at room temperature for 2 days. The reaction mixture was concentrated in vacuo and the crude product was purified by flash chromatography eluting with dichloromethane/ethanol/aqueous ammonia solution (90/10/1), providing the product as a foam (0.48 g, 57%). ¹H NMR (DMSO-d₆) δ 3.00 (2H, t, -CH₂O), 3.55 - 3.70 (2H, m, H-5'ₐ and H-5'ₐ), 3.99 (1H, d, H-4'), 4.15 - 4.20 (3H, m, -CH₂Ph and H-3'), 4.52 (1H, dd, H-2'), 5.88 (1H, d, H-1'), 8.51 (1H, s, H-8). HPLC retention time 13.64 min (gradient elution over 30 min; 20-80% acetonitrile/0.1% trifluoroacetic acid in water; 99.0% purity/254nm).

C₁₈H₂₀ClN₅O₅·0.75 H₂O requires C, 49.7; H, 5.0; N, 16.1. Found C, 49.9; H,
4.9; N, 15.8%.

Example 7 (Method A)

5 2-Chloro-N-cyclopentylxoyadenosine

The title compound was prepared according to method A as described in example 6 by reacting O-cyclopentylhydroxylamine (prepared by the overall procedure described in example 5) (0.78 g, 5.67 mmol) with 9-(2,3,5-tri-O-benzoyl-D-ribofuranosyl)-2,6-dichloro-9H-purine (3.0 g, 4.74 mmol), followed by debenzoylation of the purified product using methanolic ammonia to provide the title 2-chloro-N-cyclopentoxadenosine (0.11 g) (after column chromatography) as a solid, mp 116-119°C, 1H NMR (DMSO-d6) δ 1.50 - 1.80 (8H, m, -CH2CH2CH2CH2), 3.52 - 3.58 (1H, m, H-5'a), 3.63 - 3.70 (1H, m, H-5'b), 3.94 (1H, q, H-4'), 4.13 (1H, q, H-3'), 4.51 (1H, q, H-2'), 4.57 (1H, br m, -OCH-), 5.06 (1H, t, 5'-OH), 5.22, 5.50 (2H, 2d, 2'-and 3'-OH), 5.86 (1H, d, H-1'), 8.46 (1H, s, H-8), 11.40 (1H, s, N-H).

Example 8 (Method A)

2-Chloro-N-methoxyadenosine

The title compound was prepared according to method A as described in example 4 by reacting O-methylhydroxylamine (0.20 g, 2.0 mmol) with 9-(2,3,5-tri-O-benzoyl-D-ribofuranosyl)-2,6-dichloro-9H-purine (1.27 g, 2.0 mmol) and debenzoylating the purified product using methanolic ammonia to provide the title 2-chloro-N-methoxyadenosine (0.40 g, 45%) (after column chromatography) as a colourless foam which became crystalline on trituration with dichloromethane, providing 0.20 g of a white solid, mp 123 - 125°C. 1H NMR (DMSO-d6) δ 3.52 -3.59 (1H, m, H-5'a), 3.63 - 3.70 (1H, m, H-5'b), 3.78 (3H, s, -OCH3), 3.96 (1H, q, H-4'), 4.14 (1H, q, H-3'), 4.52 (1H,
- 26 -

q, H-2'), 5.06 (1H, t, 5'-OH), 5.22, 5.51 (2H, 2d, 2'-and 3'-OH), 5.87 (1H, d, H-1'), 8.50 (1H, s, H-8), 11.60 (1H, s, N-H).

C_{11}H_{14}ClN_{5}O_{5}. 1.33 H_2O requires C, 37.1 ; H, 4.7 ; N, 19.7. Found: C, 37.4; H, 4.4; N, 19.3%.

**EXAMPLE 9 (Method A)**

2-Chloro-N-[2-(phenoxy)ethoxy]adenosine.

The title compound was prepared according to method A as described in examples 4 and 5 by reacting O-[2-(phenoxy)ethyl]hydroxylamine (prepared by the procedure described in example 6) (0.94 g, 5.0 mmol) with 9-(2,3,5-tri-O-benzoyl-8-D-ribofuranosyl)-2,6-dichloro-9H-purine (2.0 g, 3.16 mmol), followed by debenzylation of the purified product using methanolic ammonia to provide the title 2-chloro-N-[2-(phenoxy)ethoxy]adenosine (0.44 g, 32%) (after column chromatography) as a colourless foam, ^1H NMR (DMSO-d_6) δ 3.52 - 3.59 (1H, m, H-5'a), 3.63 - 3.70 (1H, m, H-5'',a), 3.94 (1H, q, H-4'), 4.11 (1H, q, H-3'), 4.32 (4H, dt, -OCH_2CH_2O-), 4.50 (1H, q, H-2'), 5.06 (1H, t, 5'-OH), 5.22, 5.50 (2H, 2d, 2'-and 3'-OH), 5.86 (1H, d, H-1'), 6.92 - 6.97 (3H, m, Ar-H), 7.26 - 7.33 (2H, dd, Ar-H), 8.51 (1H, s, H-8), 11.64 (1H, br, N-H).

C_{18}H_{26}ClN_5O_4. 0.66 H_2O requires C, 48.1 ; H, 4.8 ; N, 15.6. Found: C, 48.1; H, 4.7; N, 15.4%.

**EXAMPLE 10 (Method A)**

2-Chloro-N-(1,2,3,4-tetrahydroanaphth-1-vloyx)adenosine.

The title compound was prepared according to method B as described in
examples 4 and 5 by reacting O-[1,2,3,4-tetrahydronaphth-1-yl]hydroxylamine (prepared by the procedure described in example 6) (0.35 g, 2.0 mmol) with 9-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2,6-dichloro-9H-purine (1.0 g, 1.58 mmol) and debenzoylating the purified product using methanolic ammonia to provide the title 2-chloro-N -(1,2,3,4-tetrahydronaphth-1-yl)oxy)adenosine (0.10 g, 15%) (after column chromatography) as a colourless foam (a mixture of diastereoisomers), 

1H NMR (DMSO-d$_6$) δ 1.65 - 2.85 (6H, m, -CH$_2$CH$_2$CH$_2$-), 3.53 -3.61 (1H, m, H-5'), 3.64 - 3.70 (1H, m, H-5''), 3.94 (1H, br d, H-4'), 4.16 (1H, br d, H-3'), 4.53 (1H, q, H-2'), 5.07 (2H, m, 5'-OH and -OCH-), 5.26, 5.53 (2H, 2d, 2'-and 3'-OH), 5.88 (1H, d, H-1'), 7.13 - 7.30 (3H, m, Ar-H), 7.88 - 7.96 (1H, m, Ar-H), 8.52 (1H, s, H-8), 11.60 (1H, br s, N-H). HPLC retention time 20.71 and 20.95 min (gradient elution over 25 min.; 25-45% acetonitrile/ 0.1M).

EXAMPLE 11 (Method B)

2,N-Dimethoxyadenosine.

2-Chloro-N-methoxyadenosine (Example 8) (0.20 g, 0.60 mmol) was added to a mixture of sodium hydride (40% oil dispersion) (0.12 g, 3.0 mmol) methanol (0.24 ml) and DMF (5 ml) which had been stirred under nitrogen at room temperature for 1 h. The reaction mixture was heated at 80°C for 16 h, cooled and evaporated. Flash chromatography provided the title

2,N-dimethoxyadenosine, still however containing some starting 2-chloro-N-methoxyadenosine. 

1H NMR (DMSO-d$_6$) δ 3.52 -3.59 (1H, m, H-5'), 3.63 - 3.70 (1H, m, H-5''), 3.77 (3H, s, -OCH$_3$), 3.97 (1H, q, H-4'), 4.14 (1H, q, H-3'), 4.60 (1H, q, H-2'), 5.09 (1H, t, 5'-OH), 5.18, 5.44 (2H, 2d, 2'-and 3'-OH), 5.83 (1H, d, H-1'), 8.24 (1H, s, H-8), 11.04 (1H, s, N-H) (desired product only quoted).
EXAMPLE 12 (Method C)

2-Methylthio-N-[2-(phenoxy)ethoxy]adenosine.

9-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-6-chloro-2-methylthio-9H-purine (0.50 g, 1.1 mmol) (prepared by Method C, using the procedure described in PCT Publication No. WO 93/08206, O-[2-(phenoxy)ethoxy]hydroxylamine hydrochloride (0.41 g, 2.16 mmol) (see Example 9) and triethylamine (0.45 g, 4.4 mmol) were stirred at 100°C in dioxan (20 ml) for 6 h, and at ca. 95°C for 65 h. The product, after column chromatography, was deprotected using methanolic ammonia, to provide the title 2-methylthio-N-[2-(phenoxy)ethoxy]adenosine (0.09 g, 18%), (after column chromatography) as a colourless foam. tlc Rf 0.26 [(SiO2, dichloromethane/methanol (9/1)]. ¹H NMR (DMSO-d6) δ 2.51 (3H, s, -SCH3), 3.52 - 3.60 (1H, m, H-5'a), 3.62 - 3.69 (1H, m, H-5'b), 3.94 (1H, q, H-4'), 4.16 (1H, q, H-3'), 4.30 (4H, br d, -OCH2CH2O-), 4.61 (1H, q, H-2'), 5.04 (1H, t, 5'-OH), 5.23, 5.50 (2H, 2d, 2'-and 3'-OH), 5.90 (1H, d, H-1'), 6.92 - 7.01 (3H, m, Ar-H), 7.32 (2H, dd, Ar-H), 8.36 (1H, s, H-8), 11.20 (1H, s, N-H).

EXAMPLE 13 (Method A)

2-Amino-N-(dimethylamino)adenosine.

The title compound was prepared according to method A as described in example 4 by reacting 1,1-dimethylhydrazine (0.79 g, 13.1 mmol) with 9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-2-amino-6-chloro-9H-purine (4.0 g, 9.35 mmol) and debenzoylating the purified product using methanolic ammonia to provide the title 2-amino-N-(dimethylamino)adenosine (after column chromatography) as an amorphous foam (0.56 g, 45%). ¹H NMR (DMSO-d6) δ 2.54 (6H, s, 2 x -CH3), 3.50 - 3.57 (1H, m, H-5'a), 3.61 - 3.68 (1H, m, H-5'b), 3.93 (1H, q, H-4'), 4.12 (1H, q, H-3'), 4.51 (1H, q, H-2'), 5.12,
5.38 (2H, 2d, 2'-and 3'-OH), 5.42 (1H, t, 5'-OH), 5.76 (1H, d, H-1'), 5.95 (2H, s, -NH₂), 7.93 (1H, s, H-8), 8.20 (1H, s, N-H).

**EXAMPLE 14 (Method A)**

2-Chloro-N-(N-methyl-N-(2-phenoxyethyl)amino)adenosine

The title compound was prepared according to method A by reacting 1-methyl-1-(2-phenoxyethyl)hydrazine (prepared by the general method described in example 1) (0.80 g, 4 mmol) and 9-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2,6-dichloro-9H-purine (2.53 g, 4 mmol) and triethylamine (1.11 ml, 8 mmol) in dioxan (25 ml), followed by debenzoylation of the purified product using methanolic ammonia to provide the title 2-chloro-N-(N-methyl-N-(2-phenoxyethyl)amino)adenosine (0.84 g, 47%) (after column chromatography) obtained as a solid, mp 166-8°C, ¹H NMR (DMSO-d₆) δ 2.70 (3H, s, -CH₃), 3.22 (2H, br t, -CH₂-), 3.51 - 3.58 (1H, m, H-5'), 3.62 - 3.69 (1H, m, H-5'ₗ), 3.95 (1H, q, H-4'), 4.05 - 4.15 (3H, m, -CH₂- and H-3'), 4.50 (1H, q, H-2'), 5.06 (1H, t, 5'-OH), 5.21, 5.49 (2H, 2d, 2'-and 3'-OH), 5.81 (1H, d, H-1'), 6.79 - 7.25 (5H, m, Ar-H), 8.41 (1H, s, H-8), 9.41 (1H, br s, N-H).

**EXAMPLE 15 (Method A)**

N-Cyclopentoxy-2-methyladenosine

Q-Cyclopentylhydroxylamine hydrochloride (0.52 g, 3.75 mmol) was reacted with 9-(2,3,5-triO-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] in dioxan (40 ml) in the presence of triethylamine (0.63 g, 6.25 mmol). The reaction mixture was heated at 100°C for 70 h, before being filtered and
evaporated. The product (after purification by chromatography), followed by 
debenzylation using methanolic ammonia to provide the title N-cyclopen-
toxy-2-methyladenosine (after column chromatography) as a foam. $^1$H NMR 
(DMSO-d$_6$) $\delta$ 1.47 - 1.93 (8H, m, -CH$_2$CH$_2$CH$_2$CH$_2$-), 2.32 (3H, s, -CH$_3$), 4.59 
(1H, br m, -O-CH-), 5.88 (1H, d, H-1').
CLAIMS

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

\[
\begin{align*}
\text{HN} & \quad \text{R}^1 \\
\text{X} & \quad \text{N} \quad \text{N} \\
\text{HO} & \quad \text{O} \\
\text{HO} & \quad \text{OH}
\end{align*}
\]

wherein

X represents hydrogen, halogen, amino, perhalomethyl, acetamido, cyano, 
C$_{1,6}$-alkyl, C$_{1,6}$-alkoxy, C$_{1,6}$-alkylthio or C$_{1,6}$-alkylamino;

R$^1$ is -NR$_2$R$^3$, -YR$^4$,

wherein Y is oxygen or sulphur;

R$^2$ is C$_{1,6}$-alkyl;

R$^3$ is phenyl or C$_{1,6}$-alkyl, which may be substituted with phenyl or phenoxy;

R$^4$ is naphthyl;

partly saturated naphthyl;

C$_{1,6}$-alkyl, which may be substituted with phenoxy or phenyl, which may be

substituted with nitro, halogen or amino;
or C$_{3,8}$-cycloalkyl, which may be substituted with phenyl or phenoxy.

2. A compound according to claim 1 wherein X is halogen or C$_{1,6}$-alkoxy.

3. A compound selected from
2-chloro-N-(N-methyl-N-(2-phenylethyl)amino)adenosine,
2-chloro-N-[(N-methyl-N-phenyl)amino]adenosine,
2-chloro-N-(N,N-dimethylamino)adenosine,
2-chloro-N-(phenylmethoxy)adenosine,
N-[(4-Nitrophenyl)methoxy]adenosine,
2-chloro-N-(2-phenylethoxy)adenosine,
2-chloro-N-cyclopent oxyadenosine,
2-chloro-N-methoxyadenosine,
2-chloro-N-[2-(phenoxy)ethoxy]adenosine,
2-chloro-N-(1,2,3,4-tetrahydronaphth-1-yloxy)adenosine,
2,N-dimethoxyadenosine,
2-methylthio-N-[2-(phenoxy)ethoxy]adenosine,
2-amino-N-(dimethylamino)adenosine,
2-chloro-N-(N-methyl-N-(2-phenoxyethyl)amino)adenosine,
N-cyclopent oxy-2-methyladenosine or a pharmaceutically acceptable salt thereof.

4. A pharmaceutical composition comprising as active component a compound according to claim 1-3 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

5. A pharmaceutical composition suitable for use in the treatment of a central nervous system ailment comprising as active component a compound according to claim 1-3 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

6. A pharmaceutical composition suitable for use in the treatment of myocardial ischaemia comprising as active component a compound according to claim 1-3 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.
7. A pharmaceutical composition suitable for use in the treatment of conditions related to high plasma FFA levels comprising as active component a compound according to claim 1-3 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

8. A pharmaceutical composition according to claim 4-7 in the form of an oral dosage unit containing about 1-200 mg of the active compound.

9. 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 1-3 effective in alleviation of such an ailment.

10. A method of treating myocardial ischaemia in a person in need of such treatment characterized in administering to said person an amount of a compound of claim 1-3 effective in alleviation of such an ailment.

11. A method of treating conditions related to high plasma FFA levels in a person in need of such treatment characterized in administering to said person an amount of a compound of claim 1-3 effective in alleviation of such an ailment.

12. 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 1-3 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.

13. A method of treating myocardial ischaemia in a subject in need of such treatment comprising the step of administering to said subject an amount of
a compound of claim 1-3 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.

14. A method of treating conditions related to high plasma FFA levels in a subject in need of such treatment comprising the step of administering to said subject an amount of a compound of claim 1-3 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.
**A. CLASSIFICATION OF SUBJECT MATTER**

IPCS: 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)

IPCS: 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)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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Further documents are listed in the continuation of Box C.

See patent family annex.

**Date of the actual completion of the international search**

19 August 1993

Date of mailing of the international search report

23-08-1993

Name and mailing address of the ISA/Swedish Patent Office

Box 5055, S-102 42 STOCKHOLM

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Authorized officer

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Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)
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<td>DE, A, 2131938 (TAKEDA CHEMICAL INDUSTRIES LTD.), 5 January 1972 (05.01.72)</td>
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INTERNATIONAL SEARCH REPORT

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.: 9–14 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.
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