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(54) Title: PROCESS FOR PREPARING IMMUCILLINS HAVING A METHYLENE LINK

(57) Abstract: The invention relates to a process for preparing compounds that are inhibitors of nucleoside phosphorylases and nucleosidases, in particular, compounds that have a methylene link between a nucleoside base analogue moiety of the molecule and a sugar analogue moiety, via an amino nitrogen of the sugar analogue moiety.



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PROCESS FOR PREPARING IMMUCILLINS HAVING A METHYLENE LINK**TECHNICAL FIELD**

5 This invention relates to a process for the preparation of nucleosidase and phosphorylase inhibitors known as Immucillins. In particular, the invention relates to a process for preparing DAD-Me-Immucillins, and related compounds, having a methylene link between the two parts of the Immucillin molecule, namely the nucleoside base analogue moiety and the sugar analogue moiety, via an amino nitrogen of the
10 sugar analogue moiety.

BACKGROUND

Purine nucleoside phosphorylase (PNP), purine phosphoribosyltransferase (PPRT) and
15 nucleoside hydrolase (NH) are enzymes that can be inhibited by members of a class of compounds known as the Immucillins, some of which are potent inhibitors of one or more of the above enzymes. Immucillins are nucleoside analogues where the "sugar" part of the molecule has been replaced with an "imino sugar" moiety or with an hydroxylated aminoalkyl moiety.

20 PNP catalyses the phosphorolytic cleavage of the ribo- and deoxyribonucleosides of guanine and hypoxanthine to give the corresponding sugar-1-phosphate and guanine, hypoxanthine, or other purine bases. Humans deficient in PNP suffer a specific T-cell immunodeficiency due to an accumulation of dGTP which prevents stimulation of T
25 lymphocytes. Inhibitors of PNP are therefore immunosuppressive, and are active against T-cell malignancies and T-cell proliferative disorders.

NH enzymes catalyse the hydrolysis of nucleosides. They are not found in mammals, but are required for nucleoside salvage in some protozoan parasites. Certain protozoan
30 parasites use nucleoside phosphorylases instead of, or as well as, nucleoside hydrolases for this purpose. Inhibitors of nucleoside hydrolases and phosphorylases can be expected to interfere with the metabolism of the parasite and therefore be usefully employed against protozoan parasites.

35 US 5,985,848, US 6,066,722, US 6,228,741 and US 7,109,331 describe Immucillins that are inhibitors of PNP and PPRT. These Immucillins are useful for treating parasitic

infections, T-cell malignancies, autoimmune diseases and inflammatory disorders. They are also useful for immunosuppression in organ transplantation. US 6,693,193 and US 7,022,852 describe a process for preparing certain Immucillin compounds.

5 The imino sugar part of an Immucillin molecule has the nitrogen atom located between C-1 and C-4 so as to form a 1,4-dideoxy-1,4-imino-D-ribitol compound. The location of the nitrogen atom in the ribitol ring may be important for binding to enzymes. In addition, the location of the link between the imino sugar moiety and the nucleoside base analogue may be critical for enzyme inhibitory activity. The compounds described
10 above have that link at C-1 of the imino sugar ring.

Two sub-classes of the Immucillins are known as the DAD-Me-Immucillins and their acyclic amine analogues. Another sub-class has an azetidine ring linked to the base moiety. The location of the nitrogen atom in the imino sugar ring of the DAD-Me-
15 Immucillins is varied. In these sub-classes, the imino sugar moiety or the acyclic amine is linked to the nucleoside base analogue via a methylene bridge. DAD-Me-Immucillins are described in US 2006/0160765 and WO 2004/018496. Their acyclic amine analogues are described in WO 2008/030119. The azetidine analogues are described in WO 2008/079028.

20 The synthesis of DAD-Me-Immucillins and acyclic amine analogues using a pathway based on a Mannich coupling between a 9-deazapurine or derivative thereof, formaldehyde and an amine is described in US 2006/0217551 and WO 2004/069856. An alternative route is the reductive amination of a fully protected 9-deaza-9-
25 formylpurine derivative with an amine.

The Mannich route is the more efficient method, but it has limitations and product yields vary considerably depending on the particular substrate. In particular, where the amine is a primary amine the yield is often low. This is because reaction products are able to
30 undergo further reaction and mixtures are therefore commonly obtained. The reductive amination route also has serious limitations. The route is multi-step and lengthy, and requires the use of low temperature and air sensitive reagents which adds to the cost of manufacture.

35 Known syntheses of the fully protected 9-deaza-9-formylpurine derivatives utilize the synthesis and lithiation of 9-deaza-9-halo-purine derivatives and their coupling with

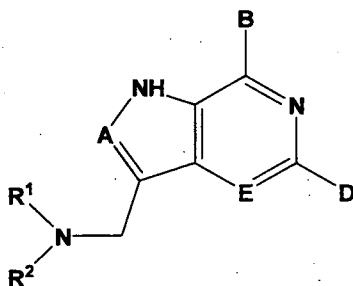
formyl equivalents such as dimethylformamide. The lithiation requires protection at N-7. The route is multi-step and lengthy, and requires the use of low temperature and air sensitive reagents which adds to the cost of manufacture.

There is therefore a need for alternative synthesis routes to DAD-Me-Immucillins and related compounds. The applicants have now found such an alternative which is applicable to the synthesis of DAD-Me-Immucillins and any related or similar compound having a methylene link between the nucleoside base analogue moiety and the amino nitrogen of the sugar analogue moiety.

It is therefore an object of the invention to provide a process for the preparation of nucleoside phosphorylase and nucleosidase inhibitors which overcomes at least in part disadvantages with known processes, or to at least provide a useful choice.

STATEMENTS OF INVENTION

In a first aspect the invention provides a process for preparing a compound of formula (1):



(1)

where:

R¹ and R² together with the nitrogen to which they are attached form a 4-6 membered azacarbocyclic ring which is substituted by at least one halogen, SQ, OQ, or Q; or

R¹ and R² together with the nitrogen to which they are attached form a 4-6 membered azacarbocyclic ring which is substituted by at least one CH₂Z and at least one halogen, SQ or OQ; or

R¹ and R² are independently selected from H and alkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl and aryl each of which is optionally substituted with one or more hydroxy, alkoxy, thiol, alkylthio, arylthio, aralkylthio, cycloalkylthio, halogen, carboxylic acid, carboxylate, carboxamide, alkyl ester or nitro groups, where each

alkylthio, arylthio, cycloalkylthio and aralkylthio group is optionally substituted with one or more alkyl, halogen, amino, hydroxy, or alkoxy groups;

provided that R^1 and R^2 are not both H;

Q is hydrogen or an alkyl, aralkyl, cycloalkyl or aryl group each of which may be substituted with one or more substituents selected from hydroxy, halogen, alkoxy, amino, and carboxy;

Z is halogen, SQ, OQ or Q;

A is selected from N, CH and CR^3 , where R^3 is selected from hydroxy, halogen, alkoxy, alkyl, aralkyl, cycloalkyl, aryl, NHR^4 , NR^4R^5 and SR^6 , where R^4 , R^5 and R^6 are each alkyl, aralkyl or aryl groups optionally substituted with hydroxy or halogen, and where R^3 is optionally substituted with hydroxy or halogen when R^3 is alkyl, aralkyl or aryl;

B is OQ, NH_2 or NHR^8 , where R^8 is selected from alkyl, aralkyl, cycloalkyl and aryl, each of which may be substituted with one or more substituents selected from hydroxy and halogen;

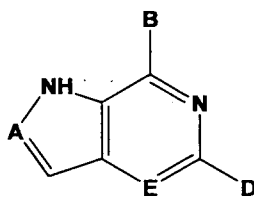
D is selected from H, hydroxy, NH_2 , and NHR^7 , where R^7 is an alkyl, aralkyl, cycloalkyl or aryl group optionally substituted with hydroxy or halogen;

E is selected from N and CH;

or a tautomer thereof, or a pharmaceutically acceptable salt thereof, or an ester thereof, or a prodrug thereof;

comprising the combination of steps (i) then (ii) or (i) then (iii) where these steps are:

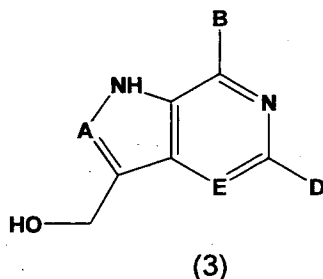
(i) hydroxymethylation of a compound of formula (2)



(2)

where A, B, D and E are as defined above or are equivalents thereof which have been protected by one or more protecting groups;

to give a compound of formula (3)



where A, B, D and E are as defined above or are equivalents thereof which have been protected by one or more protecting groups;

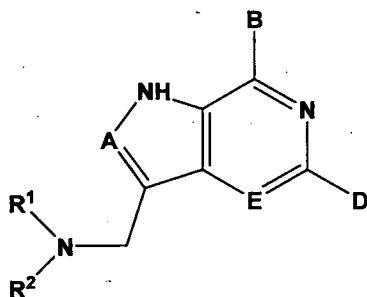
(ii) forming the compound of formula (1) by:

- a. oxidation of the hydroxymethylene group of the compound of formula (3) to an aldehyde;
- b. reductive amination of the aldehyde with a primary or secondary amine; and
- c. removal of any of the one or more protecting groups to give the compound of formula (1); or

(iii) forming the compound of formula (1) by:

- a. conversion of the OH of the hydroxymethylene group of the compound of formula (3) to OL, where OL is alkylsulfonyloxy or arylsulfonyloxy, each of which is optionally substituted with one or more alkyl, halogen or alkoxy groups;
- b. reaction with a primary or secondary amine to displace the OL group; and
- c. removal of any of the one or more protecting groups to give the compound of formula (1).

In a second aspect, the invention provides process for preparing a compound of formula (1'):



where:

R¹ and R² together with the nitrogen to which they are attached form a 4-6 membered azacarbocyclic ring which is substituted by at least one SQ or OQ,

where Q is hydrogen or an alkyl, aralkyl or aryl group each of which may be substituted with one or more substituents selected from hydroxy, halogen, alkoxy, amino, and carboxy; or

R^1 and R^2 are H or alkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl each of which is optionally substituted with one or more hydroxy, alkoxy, thiol, alkylthio, arylthio, aralkylthio, halogen, carboxylic acid, carboxylate alkyl ester, or nitro groups, where each alkylthio, arylthio and aralkylthio group is optionally substituted with one or more alkyl, halogen, amino, hydroxy, or alkoxy groups;

provided that R^1 and R^2 are not both H;

A is selected from N, CH and CR^3 , where R^3 is selected from hydroxy, halogen, alkoxy, alkyl, aralkyl, aryl, NH_2 , NHR^4 , NR^4R^5 and SR^6 , where R^4 , R^5 and R^6 are each alkyl, aralkyl or aryl groups optionally substituted with hydroxy or halogen, and where R^3 is optionally substituted with hydroxy or halogen when R^3 is alkyl, aralkyl or aryl;

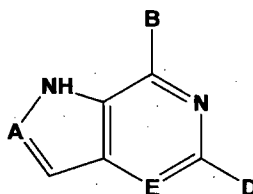
B is OQ where Q is hydrogen or an alkyl, aralkyl or aryl group each of which may be substituted with one or more substituents selected from hydroxy, halogen, alkoxy, amino, and carboxy;

D is selected from H, hydroxy, NH_2 , and NHR^7 , where R^7 is an alkyl, aralkyl or aryl group optionally substituted with hydroxy or halogen;

E is selected from N and CH;
or a tautomer thereof, or a pharmaceutically acceptable salt thereof, or an ester thereof, or a prodrug thereof;

comprising the combination of steps (i) then (ii) or (i) then (iii) wherein these steps are:

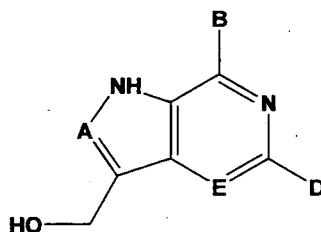
(i) hydroxymethylation of a compound of formula (2')



(2')

where A, B, D and E are as defined above or are equivalents thereof which have been protected by one or more protecting groups;

to give a compound of formula (3')



(3')

where A, B, D and E are as defined above or are equivalents thereof which have been protected by one or more protecting groups;

(ii) forming the compound of formula (1') by:

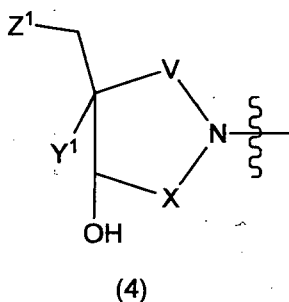
- a. oxidation of the hydroxymethylene group of the compound of formula (3) to an aldehyde;
- b. reductive amination of the aldehyde with a primary or secondary amine; and
- c. removal of any of the one or more protecting groups to give the compound of formula (1'); or

(iii) forming the compound of formula (1') by:

- a. conversion of the OH of the hydroxymethylene group of the compound of formula (3) to OL, where OL is an alkylsulfonyloxy or arylsulfonyloxy;
- b. reaction with a primary or secondary amine to displace the leaving group; and
- c. removal of any of the one or more protecting groups to give the compound of formula (1').

Preferably R_1 and R_2 together with the nitrogen to which they are attached form a 4-6 membered azacarbocyclic ring which is substituted by at least one SQ or OQ, where Q is hydrogen or an alkyl, cycloalkyl, aralkyl or aryl group each of which may be substituted with one or more substituents selected from hydroxy, halogen, alkoxy, amino, and carboxy; and preferably B is OQ where Q is hydrogen or an alkyl, aralkyl or aryl group each of which may be substituted with one or more substituents selected from hydroxy, halogen, alkoxy, amino, and carboxy.

Alternatively, preferably R_1 and R_2 together with the nitrogen to which they are attached form a radical of formula (4):



where:

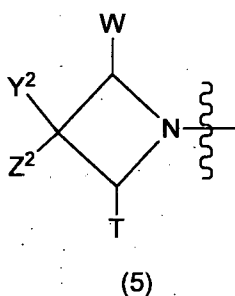
V is CH_2 or NH ;

Y^1 is H, halogen or hydroxy; provided that when V is NH then Y is H;

X is CH_2 or CHOH in the R- or S-configuration; and

Z^1 is halogen, SQ, OQ or Q, where Q is as defined above.

Alternatively, preferably R^1 and R^2 together with the nitrogen to which they are attached form a radical of formula (5):



where:

W and T are each independently selected from the group consisting of hydrogen, CH_2OH , CH_2OQ and CH_2SQ ; and

Y^2 and Z^2 are each independently selected from the group consisting of halogen, CH_2OH , CH_2OQ and CH_2SQ , SQ, OQ and Q; provided that at least one of W, T, Y^2 and Z^2 is not hydrogen;

where Q is as defined above.

Preferably Z is hydrogen, SQ or OQ.

Preferably Q is alkyl or cycloalkyl e.g. methyl, ethyl, n-propyl, n-butyl, cyclobutyl, cyclopentyl, cyclohexyl or cyclohexyl; aryl e.g. phenyl, 4-chlorophenyl, 4-fluorophenyl or 3-chlorophenyl or 4-pyridyl; or aralkyl, e.g. benzyl or 4-chlorobenzyl.

Preferably V is CH₂. It is also preferred that X is CH₂. Preferably Y¹ is hydrogen or hydroxy. More preferably Y¹ is hydrogen.

5 Preferably Z¹ is OH, SQ or OQ, and Q is alkyl e.g. methyl, ethyl, n-propyl, n-butyl, cyclobutyl, cyclopentyl, cyclohexyl or cyclohexyl, aryl e.g. phenyl, 4-chlorophenyl, 4-fluorophenyl or 3-chlorophenyl or 4-pyridyl, or aralkyl, e.g. benzyl or 4-chlorobenzyl. Alternatively, it is preferred that Z¹ is Q, where Q is hydrogen or lower alkyl e.g. methyl, ethyl, n-propyl or n-butyl.

10 Preferably Z² is selected from hydrogen, halogen, CH₂OH, CH₂OQ and CH₂SQ. More preferably Z² is CH₂OH. Alternatively it is preferred that Z₂ is CH₂SQ. In another preferred embodiment, Z² is Q.

15 Preferably one of Y² and Z² is CH₂OQ and the other is hydrogen. Alternatively preferably one of Y₂ and Z₂ is CH₂SQ and the other is hydrogen. Preferably where Y² or Z² is CH₂SQ, then Q is alkyl, e.g. methyl. Alternatively preferably one of Y² and Z² is CH₂OH.

20 Preferably W is H or CH₂OH. Preferably T is H or CH₂OH. Preferably W and T are both H. Alternatively, it is preferred that W and T are both CH₂OH. Alternatively, it is preferred that one of W and T is H and the other is CH₂OH.

25 Alternatively preferably R¹ and R² in the compound of formula (1) or (1') are independently selected from H and alkyl, cycloalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl and aryl, each of which is optionally substituted.

When R¹ or R² in the compound of formula (1) or (1') is an optionally substituted alkyl group, the alkyl group is preferably substituted with one or more hydroxyl groups, e.g.

30 R¹ or R² may be hydroxymethyl, hydroxyethyl, hydroxypropyl, dihydroxypropyl, hydroxybutyl, dihydroxybutyl, trihydroxybutyl, hydroxypentyl, dihydroxypentyl, or trihydroxypentyl. R¹ or R² may also be alkyl substituted by one or more hydroxy groups and/or one or more optionally substituted thiol, alkylthio, arylthio, or aralkylthio groups. For example, R¹ or R² may be methylthiomethyl, methylthioethyl, methylthiopropyl, methylthiohydroxypropyl, methylthiodihydroxypropyl, methylthiobutyl, methylthiohydroxybutyl, methylthiodihydroxybutyl, methylthiotrihydroxybutyl,

methylthiopentyl, methylthiohydroxypentyl, methylthiodihydroxypentyl, methylthiotrihydroxypentyl, or methylthiotetrahydroxypentyl.

In the compound of formula (1) or (1'): preferably B is hydroxy. Alternatively it is preferred that B is NH₂. Preferably A is CH. Preferably D is H or NH₂. Preferably E is N. Preferably B is hydroxy, A is CH, E is N and D is H. Alternatively preferably B is NH₂, A is CH, E is N and D is H. Alternatively preferably B is hydroxy, A is CH, E is N and D is NH₂.

Preferably B is hydroxy, A is CH, E is N, D is H and R¹ and R² together with the nitrogen to which they are attached form a radical of formula (4).

Alternatively preferably B is NH₂, A is CH, E is N, D is H and R¹ and R² together with the nitrogen to which they are attached form a radical of formula (4).

Alternatively preferably B is hydroxy, A is CH, E is N, D is NH₂ and R¹ and R² together with the nitrogen to which they are attached form a radical of formula (4).

Alternatively preferably B is hydroxy, A is CH, E is N, D is H and R¹ and R² together with the nitrogen to which they are attached form a radical of formula (5).

Alternatively preferably B is NH₂, A is CH, E is N, D is H and R¹ and R² together with the nitrogen to which they are attached form a radical of formula (5).

Alternatively preferably B is hydroxy, A is CH, E is N, D is NH₂ and R¹ and R² together with the nitrogen to which they are attached form a radical of formula (5).

Preferably B is hydroxy, A is CH, E is N, D is H and R¹ and R² are independently selected from H and alkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl and aryl each of which is optionally substituted with one or more hydroxy, alkoxy, thiol, alkylthio, arylthio, aralkylthio, cycloalkylthio, halogen, carboxylic acid, carboxylate, carboxamide, alkyl ester or nitro groups, where each alkylthio, arylthio, cycloalkylthio and aralkylthio group is optionally substituted with one or more alkyl, halogen, amino, hydroxy, or alkoxy groups; provided that R¹ and R² are not both H.

Alternatively preferably B is NH₂, A is CH, E is N, D is H and R¹ and R² are independently selected from H and alkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl and aryl each of which is optionally substituted with one or more hydroxy, alkoxy, thiol, alkylthio, arylthio, aralkylthio, cycloalkylthio, halogen, carboxylic acid, carboxylate, carboxamide, alkyl ester or nitro groups, where each alkylthio, arylthio, cycloalkylthio and aralkylthio group is optionally substituted with one or more alkyl, halogen, amino, hydroxy, or alkoxy groups; provided that R¹ and R² are not both H.

Alternatively preferably B is hydroxy, A is CH, E is N, D is NH₂ and R¹ and R² are independently selected from H and alkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl and aryl each of which is optionally substituted with one or more hydroxy, alkoxy, thiol, alkylthio, arylthio, aralkylthio, cycloalkylthio, halogen, carboxylic acid, carboxylate, carboxamide, alkyl ester or nitro groups, where each alkylthio, arylthio, cycloalkylthio and aralkylthio group is optionally substituted with one or more alkyl, halogen, amino, hydroxy, or alkoxy groups; provided that R¹ and R² are not both H.

Preferably any halogen in the compound of formula (1) or (1') is fluorine or chlorine.

It is preferred that the hydroxymethylation of the compound of formula (2) or (2') in step (i) is carried by reaction using formaldehyde in the presence of a base, e.g. a mild inorganic or organic base, e.g. potassium carbonate. Alternatively preferably, the hydroxymethylation of the compound of formula (2) or (2') in step (i) is carried out by reaction using paraformaldehyde in the presence of a base, e.g. a mild inorganic or organic base, e.g. potassium carbonate. It is also preferred that the solvent is an aqueous organic solvent, e.g. aqueous dioxane.

It is also preferred that the oxidation of the hydroxymethylene group of the compound of formula (3) or (3') in step (ii) a. is carried out using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or Dess-Martin periodinane. Preferably the oxidation with Dess-Martin periodinane is carried out in acetic acid solution.

The reductive amination of step (ii) b. is preferably carried out using sodium borohydride to reduce an imine adduct formed between the aldehyde and the primary or secondary amine. Alternatively preferably, the reductive amination of step (ii) b. is carried out using sodium cyanoborohydride can be used directly on a mixture of the aldehyde and the primary or secondary amine without prior formation of an imine.

Preferably the OL group in step (iii) a. is selected from the group comprising methanesulfonyloxy, p-toluenesulfonyloxy, 2,4,6-trimethylbenzenesulfonyloxy, 4-bromobenzenesulfonyloxy and trifluoromethanesulfonyloxy.

In another aspect, the invention provides a compound of formula (1) or (1') when prepared by a process of the first or second aspect of the invention.

DETAILED DESCRIPTION

Definitions

The term "alkyl" is intended to include straight- and branched-chain groups. The non-aromatic moiety of an aralkyl radical is intended to include straight- and branched-chain alkyl groups. Examples of alkyl groups include, but are not limited to: methyl group, ethyl group, *n*-propyl group, *iso*-propyl group, *n*-butyl group, *iso*-butyl group, *sec*-butyl group, *t*-butyl group, *n*-pentyl group, 1,1-dimethylpropyl group, 1,2-dimethylpropyl group, 2,2-dimethylpropyl group, 1-ethylpropyl group, 2-ethylpropyl group, *n*-hexyl group, 1-methyl-2-ethylpropyl cyclobutyl group, cyclopentyl group and cyclohexyl group.

The term "alkenyl" means any hydrocarbon radical having at least one double bond, and having up to 30 carbon atoms, and includes any C₂-C₂₅, C₂-C₂₀, C₂-C₁₅, C₂-C₁₀, or C₂-C₆ alkenyl group, and is intended to include both straight- and branched-chain alkenyl groups. The same terminology applies to the non-aromatic moiety of an aralkenyl radical. Examples of alkenyl groups include, but are not limited to: ethenyl group, *n*-propenyl group, *iso*-propenyl group, *n*-butenyl group, *iso*-butenyl group, *sec*-butenyl group, *t*-butenyl group, *n*-pentenyl group, 1,1-dimethylpropenyl group, 1,2-dimethylpropenyl group, 2,2-dimethylpropenyl group, 1-ethylpropenyl group, 2-ethylpropenyl group, *n*-hexenyl group and 1-methyl-2-ethylpropenyl group.

The term "alkynyl" means any hydrocarbon radical having at least one triple bond, and having up to 30 carbon atoms, and includes any C₂-C₂₅, C₂-C₂₀, C₂-C₁₅, C₂-C₁₀, or C₂-C₆ alkynyl group, and is intended to include both straight- and branched-chain alkynyl groups. The same terminology applies to the non-aromatic moiety of an aralkynyl radical. Examples of alkynyl groups include, but are not limited to: ethynyl group, *n*-propynyl group, *iso*-propynyl group, *n*-butynyl group, *iso*-butynyl group, *sec*-butynyl

group, *t*-butynyl group, *n*-pentynyl group, 1,1-dimethylpropynyl group, 1,2-dimethylpropynyl group, 2,2-dimethylpropynyl group, 1-ethylpropynyl group, 2-ethylpropynyl group, *n*-hexynyl group and 1-methyl-2-ethylpropynyl group.

5 The term "cycloalkyl" means a saturated or partially saturated non-aromatic carbocyclic group, preferably comprising from 3 to 8 carbon atoms. Examples of cycloalkyl groups include, but are not limited to: cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group and cyclooctyl group. Preferred cycloalkyl groups are 3-, 4- or 5-membered rings, e.g. cyclopropyl group, cyclobutyl group or cyclopentyl
10 group.

The term "aryl" means an aromatic radical having 4 to 18 carbon atoms and includes heteroaromatic radicals. Examples include monocyclic groups, as well as fused groups such as bicyclic groups and tricyclic groups. Some examples include, but are not
15 limited to: phenyl group, indenyl group, 1-naphthyl group, 2-naphthyl group, azulenyl group, heptalenyl group, biphenyl group, indacenyl group, acenaphthyl group, fluorenyl group, phenalenyl group, phenanthrenyl group, anthracenyl group, cyclopentacyclooctenyl group, and benzocyclooctenyl group, pyridyl group, pyrrolyl group, pyridazinyl group, pyrimidinyl group, pyrazinyl group, triazolyl group, tetrazolyl
20 group, benzotriazolyl group, pyrazolyl group, imidazolyl group, benzimidazolyl group, indolyl group, isoindolyl group, indolizynyl group, purinyl group, indazolyl group, furyl group, pyranyl group, benzofuryl group, isobenzofuryl group, thienyl group, thiazolyl group, isothiazolyl group, benzothiazolyl group, oxazolyl group, and isoxazolyl group.

25 The term "aralkyl" means an alkyl radical having an aryl substituent.

The term "alkoxy" means an hydroxy group with the hydrogen replaced by an alkyl group.

30 The term "halogen" includes fluorine, chlorine, bromine and iodine.

The term "prodrug" as used herein means a pharmacologically acceptable derivative of a compound, such that an *in vivo* biotransformation of the derivative gives the compound. Prodrugs of compounds of formula (1) or (1') may be prepared by modifying
35 functional groups present in the compounds in such a way that the modifications are

cleaved *in vivo* to give the compounds. Examples of suitable prodrugs include, but are not limited to, esters and acetals.

The term "pharmaceutically acceptable salts" is intended to apply to non-toxic salts derived from inorganic or organic acids, including, for example, the following acid salts: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, *p*-toluenesulfonate, salicylate, succinate, sulfate, tartrate, thiocyanate, and undecanoate.

The term "leaving group" means a group that is capable of being displaced by another group, typically by way of a nucleophilic substitution reaction. Examples of leaving groups include, but are not limited to, halogen atoms and alkyl or aryl sulfonates such as methanesulfonates and benzenesulfonates, or substituted forms thereof such as bromobenzenesulfonates, trifluoromethanesulfonates, *p*-toluenesulfonates, nitrobenzenesulfonates, nonafluorobutanesulfonates, 2,2,2-trifluoroethanesulfonates, fluorosulfonates, or perchlorates.

The term "protecting group" means a group that selectively protects an organic functional group, temporarily masking the chemistry of that functional group and allowing other sites in the molecule to be manipulated without affecting the functional group. Suitable protecting groups are known to those skilled in the art and are described, for example, in *Protective Groups in Organic Synthesis* (3rd Ed.), T. W. Greene and P. G. M. Wuts, John Wiley & Sons Inc (1999). Examples of protecting groups include, but are not limited to: benzyl group, benzyl group substituted with one or more substituents e.g. halogen or alkyl or alkoxy (e.g. methoxy), trialkyl(aryl)silyl, alkylorthoester, alkylacetal, ester, O-methyl, O-benzyloxymethyl, O-methoxymethyl, trialkylsilyl, e.g. tert-butyldimethylsilyl, alkyl diarylsilyl, e.g. tert-butyldiphenylsilyl, trityl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, e.g. methoxycarbonyl, aryloxycarbonyl, and aralkyloxycarbonyl, e.g. benzyloxycarbonyl. For example, suitable O-protecting groups that can be used in the process of the invention include, but are not limited to, (i), alkyl ethers such as methyl, ethyl, tert-butyl, allyl, allyloxycarbonyl, *p*-methoxybenzyl,

3,4-dimethoxybenzyl or (ii) silyl ethers, e.g. trimethylsilyl, tert butyldimethylsilyl, tert-butyl diphenylsilyl or triisopropylsilyl. Suitable N-protecting groups that can be used in the process of the invention include, but are not limited to, (i) N-acyl derivatives such as tert-butoxycarbonyl, benzyloxycarbonyl, trifluoroacetamide, allyloxycarbonyl, 9-fluorenylmethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, acetate, benzoate, pivaloate, or (ii) N,O-acetal derivatives such as benzyloxymethyl, methyloxymethyl, tert-butoxymethyl, methoxyethoxyethyl, or (iii) N-alkyl such as p-methoxybenzyl, allyl, trityl.

10 **Synthesis of Compounds**

The invention provides a new way, in the synthesis of compounds of formula (1) or (1'), of introducing the methylene group that links their 9-deazapurine base and their cyclic or acyclic amine moieties.

15 The process involves two steps. In the first step, direct substitution of the 9-hydrogen atom by a 9-hydroxymethyl substituent is a novel and efficient approach. The reagent of choice is formaldehyde, and the reaction can be suitably promoted by use of a mild inorganic or organic base in an aqueous organic solvent. Potassium carbonate has proven to be an effective mild inorganic base, and aqueous dioxane a useful solvent.
20 Other bases include, but are not limited to, sodium bicarbonate or triethylamine in aqueous THF.

The 9-deazapurine substrate can be unprotected or protected. Examples of deazapurine substrates that can be used in the process of the invention include, but are not limited to, 9-deazahypoxanthine, 4-(benzyloxy)-5H-pyrrolo[3,2-d]pyrimidine, N-(4-methoxybenzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine or N-benzyl-5H-pyrrolo[3,2-d]pyrimidin-4-amine. Thus, the base 9-deazahypoxanthine itself undergoes the reaction, as does the protected base 6-benzyloxy-9-deazapurine. The use of such a 6-O-protected 9-deazahypoxanthine derivative can be advantageous for the easier removal
30 of unwanted impurities from the final product due to its better crystallinity and/or chromatographic purification.

The first step of the process is preferably carried out by heating the reaction mixture, e.g. the 9-deazapurine substrate and aqueous formaldehyde. The reaction mixture can be heated at a temperature of up to about 100 °C, preferably about 80-100 °C, more preferably about 90-100°C. Work-up of the reaction mixture is preferably via
35

chromatography on silica gel. The work-up also preferably involves treatment with methanolic ammonia.

For the second step of the process, there are two options.

In one alternative, the 9-hydroxymethyl substituent in the product from the first step is oxidized to a 9-formyl substituent, then subjected to a reductive amination reaction with the desired cyclic or acyclic amine, or a protected version thereof.

The oxidation can be achieved with a variety of oxidants. DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) in an organic solvent or Dess-Martin periodinane in acetic acid have proved effective. Other possible oxidants include, but are not limited to, dimethyl sulfoxide in a Swern type reaction, chromium oxidants e.g. chromium trioxide, pyridinium dichromate or pyridinium chlorochromate, TEMPO/BA IB, TEMPO/sodium hypochlorite. Suitable solvents include chloroform, dichloromethane or acetic acid.

The reductive amination can be effected by a number of hydride reducing agents. In the case of primary amines it is convenient to first form the imine-adduct between the amine and the aldehyde and then apply a reducing agent. Sodium borohydride in an organic solvent has proven effective. Other possible reducing agents include, but are not limited to, sodium cyanoborohydride, lithium aluminium hydride, borane and its complexes with ethers or amines, sodium triacetoxyborohydride, or hydrogen and a palladium catalyst. Sodium cyanoborohydride can be used directly on a mixture of aldehyde and amine without prior formation of the imine.

In another alternative, the 9-hydroxymethyl substituent in the product from the first step is converted into a sulfonate leaving group, and this is then displaced with the desired cyclic or acyclic amine, or a protected version thereof.

Suitable sulfonylation reagents include methanesulfonyl chloride, p-toluenesulfonyl chloride, 2,4,6-trimethylbenzenesulfonyl chloride, 4-bromobenzenesulfonyl chloride, trifluoromethanesulfonyl chloride and a base. Suitable bases include, but are not limited to, pyridine, diisopropylethylamine, 2,6-lutidine and triethylamine. The displacement of the leaving group occurs following addition of the amine to the reaction mixture.

The amine moiety that is linked to the base substrate via the methylene link can be a cyclic or an acyclic amine. Where the amine is a cyclic amine, it is preferably a 5-membered azacarbocycle, such as pyrrolidine, or a four membered azacarbocycle, such as azetidine. The azacarbocycle is substituted with one or more substituents such as halogen, hydroxy, alkoxy (e.g. methoxy), alkylthio, thiol, CH₂OH, CH₂(alkoxy), CH₂(alkylthio) or alkyl. These substituents may optionally be protected by one or more protecting groups.

Where protecting groups have been employed in the process of the invention, they are removed using the appropriate deprotection conditions to give the compounds of formula (1). For example, benzyl and O-methyl protecting groups may be removed by treatment with a suitable acid, e.g. HCl.

General Aspects

The compounds of formula (1) or (1') prepared according to the invention are useful as pharmaceuticals. The compounds are useful in both free base form and in the form of salts.

It will be appreciated that the compounds of formula (1) or (1'), e.g. where B and/or D is hydroxy or NH₂ group, can exist as tautomers. For example, the representation of a compound of formula (1) or (1') where B and/or D is hydroxy group is of the enol-type tautomeric form of a corresponding amide, and this will largely exist in the amide form. The use of the enol-type tautomeric representation is simply to allow fewer structural formulae to represent the compounds of the invention. The scope of this invention is intended to encompass all possible tautomeric forms.

It will also be appreciated that the compounds of formula (1) or (1') can exist in the form of optical isomers, diastereomers or racemates. The scope of this invention is intended to encompass all possible such isomeric forms that the compounds of formula (1) or (1') may possess. For example, asymmetric carbons may have the R- or S-configuration.

Products Prepared by the Process

The compounds preferably prepared by the process of the invention include, but are not limited to, the compounds of the following list:

rac-(2*R*,3*S*)-3-((4-hydroxy-3*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)methylamino)butane-1,2,4-triol;

7-(((2,4-dihydroxybutyl)(methyl)amino)methyl)-3*H*-pyrrolo[3,2-*d*]pyrimidin-4(5*H*)-one;

5 (R) 3-((4-hydroxy-5*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)methylamino)-propane-1,2-diol hydrochloride;

(2*R*,3*R*)-3-((4-hydroxy-5*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)methylamino)butane-1,2,4-triol hydrochloride;

2-amino-7-(2,3-dihydroxy-1-(2-hydroxyethylamino)propyl)-3*H*-pyrrolo[3,2-*d*]pyrimidin-4(5*H*)-one;

10 7-(2,3-dihydroxy-1-(2-hydroxyethylamino)propyl)-3*H*-pyrrolo[3,2-*d*]pyrimidin-4(5*H*)-one;

2-amino-7-(1-amino-2,3,5-trihydroxypentyl)-3*H*-pyrrolo[3,2-*d*]pyrimidin-4(5*H*)-one;

7-(1-amino-2,3,5-trihydroxypentyl)-3*H*-pyrrolo[3,2-*d*]pyrimidin-4(5*H*)-one;

15 2-amino-7-(4-amino-2,3,5-trihydroxypentyl)-3*H*-pyrrolo[3,2-*d*]pyrimidin-4(5*H*)-one;

7-(4-amino-2,3,5-trihydroxypentyl)-3*H*-pyrrolo[3,2-*d*]pyrimidin-4(5*H*)-one;

2-amino-7-(1-(1,3-dihydroxypropan-2-ylamino)-2-hydroxyethyl)-3*H*-pyrrolo[3,2-*d*]pyrimidin-4(5*H*)-one;

7-(1-(1,3-dihydroxypropan-2-ylamino)-2-hydroxyethyl)-3*H*-pyrrolo[3,2-*d*]pyrimidin-4(5*H*)-one;

20 2-amino-7-(((2,4-dihydroxybutyl)(methyl)amino)methyl)-3*H*-pyrrolo[3,2-*d*]pyrimidin-4(5*H*)-one;

2-amino-7-((2,4-dihydroxybutylamino)methyl)-3*H*-pyrrolo[3,2-*d*]pyrimidin-4(5*H*)-one;

25 7-((2,4-dihydroxybutylamino)methyl)-3*H*-pyrrolo[3,2-*d*]pyrimidin-4(5*H*)-one;

2-amino-7-(((3,4-dihydroxy-2-(hydroxymethyl)butylamino)methyl)-3*H*-pyrrolo[3,2-*d*]pyrimidin-4(5*H*)-one;

7-((3,4-dihydroxy-2-(hydroxymethyl)butylamino)methyl)-3*H*-pyrrolo[3,2-*d*]pyrimidin-4(5*H*)-one;

30 2-amino-7-((3-hydroxy-2-(hydroxymethyl)propylamino)methyl)-3*H*-pyrrolo[3,2-*d*]pyrimidin-4(5*H*)-one;

7-((3-hydroxy-2-(hydroxymethyl)propylamino)methyl)-3*H*-pyrrolo[3,2-*d*]pyrimidin-4(5*H*)-one;

2-amino-7-(((3-hydroxy-2-(hydroxymethyl)propyl)(methyl)amino)methyl)-3*H*-pyrrolo[3,2-*d*]pyrimidin-4(5*H*)-one;

35 7-(((3-hydroxy-2-(hydroxymethyl)propyl)(methyl)amino)methyl)-3*H*-pyrrolo[3,2-*d*]pyrimidin-4(5*H*)-one;

2-amino-7-(3,4-dihydroxy-5-(methylthiomethyl)pyrrolidin-2-yl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-(3,4-dihydroxy-5-(methylthiomethyl)pyrrolidin-2-yl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

5 2-amino-7-(2,3-dihydroxy-1-(2-(methylthio)ethylamino)propyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-(2,3-dihydroxy-1-(2-(methylthio)ethylamino)propyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

10 2-amino-7-(1-amino-2,3-dihydroxy-5-(methylthio)pentyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-(1-amino-2,3-dihydroxy-5-(methylthio)pentyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-(2-hydroxy-1-(1-hydroxy-3-(methylthio)propan-2-ylamino)ethyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

15 7-(2-hydroxy-1-(1-hydroxy-3-(methylthio)propan-2-ylamino)ethyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-((3,4-dihydroxy-1-(methylthio)butan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

20 7-(((3,4-dihydroxy-1-(methylthio)butan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-(((2-hydroxy-4-(methylthio)butyl)(methyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-(((2-hydroxy-4-(methylthio)butyl)(methyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

25 2-amino-7-((2-hydroxy-4-(methylthio)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-((2-hydroxy-4-(methylthio)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-((3,4-dihydroxy-2-(methylthiomethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

30 7-(((3,4-dihydroxy-2-(methylthiomethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-((3-hydroxy-2-(methylthiomethyl)propylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

35 7-((3-hydroxy-2-(methylthiomethyl)propylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-(((3-hydroxy-2-(methylthiomethyl)propyl)(methyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-(((3-hydroxy-2-(methylthiomethyl)propyl)(methyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

5 7-(((2R,3R)-1,3,4-trihydroxybutan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-(((2S,3S)-1,3,4-trihydroxybutan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-(((2R,3S)-1,3,4-trihydroxybutan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

10 7-(((2S,3R)-1,3,4-trihydroxybutan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-(((2R,3R)-1,3,4-trihydroxybutan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

15 2-amino-7-(((2S,3S)-1,3,4-trihydroxybutan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-(((2R,3S)-1,3,4-trihydroxybutan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-(((2S,3R)-1,3,4-trihydroxybutan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-((1,3-dihydroxy-2-(hydroxymethyl)propan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-((1,3-dihydroxy-2-(hydroxymethyl)propan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

25 7-((4-hydroxybutylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-((4-hydroxybutylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-((2-hydroxyethylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-((2-hydroxyethylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-((3-hydroxy-2-(hydroxymethyl)propylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-((3-hydroxy-2-(hydroxymethyl)propylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-(((3-hydroxy-2-(hydroxymethyl)propyl)(methyl)-amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

35 2-amino-7-(((3-hydroxy-2-(hydroxymethyl)propyl)(methyl)-amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

3-(((1,3-dihydroxypropan-2-yl)(methyl)amino)methyl)-1H-pyrazolo[4,3-d]pyrimidin-7(6H)-one;

7-(((3-hydroxy-2-(hydroxymethyl)propylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-(((3-hydroxy-2-(hydroxymethyl)propylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-(((3-hydroxy-2-(hydroxymethyl)propyl)(methyl)-amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-(((3-hydroxy-2-(hydroxymethyl)propyl)(methyl)-amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-(((3-hydroxy-2-(hydroxymethyl)propyl)(hydroxymethyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-(((3-hydroxy-2-(hydroxymethyl)propyl)(hydroxymethyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-(((1,3-dihydroxy-2-(methylthiomethyl)propan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-(((1,3-dihydroxy-2-(methylthiomethyl)propan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-(((2R,3R)-2,3,4-trihydroxybutylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-(((2S,3S)-2,3,4-trihydroxybutylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-(((2R,3S)-2,3,4-trihydroxybutylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-(((2S,3R)-2,3,4-trihydroxybutylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-(((2R,3R)-2,3,4-trihydroxybutylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-(((2S,3S)-2,3,4-trihydroxybutylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-(((2R,3S)-2,3,4-trihydroxybutylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-(((2S,3R)-2,3,4-trihydroxybutylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-((benzyl((2R,3R)-3,4-dihydroxy-2-(methylthiomethyl)butyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-((benzyl((2S,3S)-3,4-dihydroxy-2-(methylthiomethyl)butyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-((benzyl((2R,3S)-3,4-dihydroxy-2-(methylthiomethyl)butyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-((benzyl((2S,3R)-3,4-dihydroxy-2-(methylthiomethyl)butyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-((benzyl((2R,3R)-3,4-dihydroxy-2-(methylthiomethyl)butyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

5 2-amino-7-((benzyl((2S,3S)-3,4-dihydroxy-2-(methylthiomethyl)butyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-((benzyl((2R,3S)-3,4-dihydroxy-2-(methylthiomethyl)butyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

10 2-amino-7-((benzyl((2S,3R)-3,4-dihydroxy-2-(methylthiomethyl)butyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(S)-7-(1-(1,3-dihydroxypropan-2-ylamino)-2-hydroxyethyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(R)-7-(1-(1,3-dihydroxypropan-2-ylamino)-2-hydroxyethyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

15 (S)-2-amino-7-(1-(1,3-dihydroxypropan-2-ylamino)-2-hydroxyethyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(R)-2-amino-7-(1-(1,3-dihydroxypropan-2-ylamino)-2-hydroxyethyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

20 7-(((2R,3R)-2,3-dihydroxy-4-(methylthio)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-(((2S,3S)-2,3-dihydroxy-4-(methylthio)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-(((2R,3S)-2,3-dihydroxy-4-(methylthio)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

25 7-(((2S,3R)-2,3-dihydroxy-4-(methylthio)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-(((2R,3R)-2,3-dihydroxy-4-(methylthio)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

30 2-amino-7-(((2S,3S)-2,3-dihydroxy-4-(methylthio)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-(((2R,3S)-2,3-dihydroxy-4-(methylthio)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-(((2S,3R)-2,3-dihydroxy-4-(methylthio)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

35 (R)-7-((benzyl(2,3-dihydroxypropyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(S)-7-((benzyl(2,3-dihydroxypropyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(R)-2-amino-7-((benzyl(2,3-dihydroxypropyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(S)-2-amino-7-((benzyl(2,3-dihydroxypropyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

5 (R)-3-((2,3-dihydroxypropylamino)methyl)-1H-pyrazolo[4,3-d]pyrimidin-7(6H)-one;

(S)-3-((2,3-dihydroxypropylamino)methyl)-1H-pyrazolo[4,3-d]pyrimidin-7(6H)-one;

(R)-7-(((2,3-dihydroxypropyl)(2-hydroxyethyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

10 (S)-7-(((2,3-dihydroxypropyl)(2-hydroxyethyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(R)-2-amino-7-(((2,3-dihydroxypropyl)(2-hydroxyethyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(S)-2-amino-7-(((2,3-dihydroxypropyl)(2-hydroxyethyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

15 (2R,3R)-7-((3,4-dihydroxy-2-(hydroxymethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(2S,3S)-7-((3,4-dihydroxy-2-(hydroxymethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

20 (2R,3S)-7-((3,4-dihydroxy-2-(hydroxymethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(2S,3R)-7-((3,4-dihydroxy-2-(hydroxymethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(2R,3R)-2-amino-7-((3,4-dihydroxy-2-(hydroxymethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

25 (2S,3S)-2-amino-7-((3,4-dihydroxy-2-(hydroxymethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(2R,3S)-2-amino-7-((3,4-dihydroxy-2-(hydroxymethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

30 (2S,3R)-2-amino-7-((3,4-dihydroxy-2-(hydroxymethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-(((2R,3R)-3,4-dihydroxy-1-(methylthio)butan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-(((2S,3S)-3,4-dihydroxy-1-(methylthio)butan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

35 7-(((2R,3S)-3,4-dihydroxy-1-(methylthio)butan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

- 7-(((2S,3R)-3,4-dihydroxy-1-(methylthio)butan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
- 2-amino-7-(((2R,3R)-3,4-dihydroxy-1-(methylthio)butan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
- 5 2-amino-7-(((2S,3S)-3,4-dihydroxy-1-(methylthio)butan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
- 2-amino-7-(((2R,3S)-3,4-dihydroxy-1-(methylthio)butan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
- 2-amino-7-(((2S,3R)-3,4-dihydroxy-1-(methylthio)butan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
- 10 2-amino-7-(((2R,3R)-3,4-dihydroxy-2-(methylthiomethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
- 2-amino-7-(((2S,3S)-3,4-dihydroxy-2-(methylthiomethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
- 15 2-amino-7-(((2R,3S)-3,4-dihydroxy-2-(methylthiomethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
- 2-amino-7-(((2S,3R)-3,4-dihydroxy-2-(methylthiomethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
- 7-(((2R,3R)-3,4-dihydroxy-2-(methylthiomethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
- 20 7-(((2S,3S)-3,4-dihydroxy-2-(methylthiomethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
- 7-(((2R,3S)-3,4-dihydroxy-2-(methylthiomethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
- 25 7-(((2S,3R)-3,4-dihydroxy-2-(methylthiomethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
- (3R,4R)-1-[(9-deazahypoxanthin-9-yl)methyl]-3-hydroxy-4-(hydroxymethyl)pyrrolidine;
- (3S,4R)-1-[(9-deazahypoxanthin-9-yl)methyl]-3,4-dihydroxy-4-methylthiomethylpyrrolidine;
- 30 (3S,4S)-1-[(9-deazahypoxanthin-9-yl)methyl]-3,4-dihydroxy-4-hydroxymethylpyrrolidine;
- (3R,4S)-1-[(9-deazahypoxanthin-9-yl)methyl]-3-hydroxy-4-(methylthiomethyl)pyrrolidine;
- N-(9-deazahypoxanthin-9-yl)methyl-1,4-dideoxy-1,4-imino-D-ribitol;
- (3R,4R)-3-hydroxy-4-hydroxymethyl-1-(hypoxanthin-9-yl)pyrrolidine;
- (3S,4S)-1-[(9-deazahypoxanthin-9-yl)methyl]-3-hydroxy-4-methylpyrrolidine;
- 35 (3R,4R)-1-[(9-deazaguanin-9-yl)methyl]-3-hydroxy-4-(hydroxymethyl)pyrrolidine;
- (3S,4S)-1-[(9-deazahypoxanthin-9-yl)methyl]-3-hydroxy-4-methylpyrrolidine;

(3S,4S)-1-[(9-deaza-8-fluoro-hypoxanthin-9-yl)methyl]-3-hydroxy-4-(hydroxymethyl)-pyrrolidine;

(3S,4S)-1-[(9-deazaguanin-9-yl)methyl]-3-hydroxy-4-methyl-pyrrolidine;

(3R,4R)-1-[(8-aza-9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(hydroxymethyl)pyrrolidine;

5 (3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(2-phenylethyl)pyrrolidine;

(3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(benzylthiomethyl)pyrrolidine;

(3R,4S)-1-[(8-aza-9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(benzylthiomethyl)pyrrolidine;

(3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(4-chlorophenylthiomethyl)pyrrolidine;

10 (3R,4R)-1-[(9-deazaadenin-9-yl)methyl]-3-acetoxy-4-(acetoxymethyl)pyrrolidine;

(3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(*n*-butylthiomethyl)pyrrolidine;

(3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(4-fluorophenylthiomethyl)pyrrolidine;

15 (3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(*n*-propylthiomethyl)pyrrolidine;

(3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(cyclohexylthiomethyl)pyrrolidine;

(3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(3-chlorophenylthiomethyl)pyrrolidine;

(3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(ethylthiomethyl)pyrrolidine;

20 (3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(phenylthiomethyl)pyrrolidine;

(3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(4-pyridylthiomethyl)pyrrolidine;

(3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-*n*-propylpyrrolidine;

(3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(homocysteinylmethyl)pyrrolidine;

(3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(benzyloxymethyl)pyrrolidine;

25 (3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(*i*-propylthiomethyl)pyrrolidine;

(3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(methoxymethyl)pyrrolidine;

(3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(cyclohexylmethylthiomethyl)pyrrolidine;

(3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(cycloheptylthiomethyl)pyrrolidine;

30 (3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(cyclopentylthiomethyl)pyrrolidine;

(3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(cyclobutylthiomethyl)pyrrolidine;

2-amino-7-((3,4-dihydroxy-1-(methylthio)butan-2-ylamino)methyl)-4-amino-5H-pyrrolo[3,2-*d*]pyrimidine;

7-((3,4-dihydroxy-1-(methylthio)butan-2-ylamino)methyl)-4-amino-5H-pyrrolo[3,2-*d*]pyrimidine;

35

2-amino-7-(((2-hydroxy-4-(methylthio)butyl)(methyl)amino)methyl)- 4-amino-5H-pyrrolo[3,2-d]pyrimidine;

7-(((2-hydroxy-4-(methylthio)butyl)(methyl)amino)methyl)- 4-amino-5H-pyrrolo[3,2-d]pyrimidine;

5 2-amino-7-((2-hydroxy-4-(methylthio)butylamino)methyl)- 4-amino-5H-pyrrolo[3,2-d]pyrimidine;

7-((2-hydroxy-4-(methylthio)butylamino)methyl)- 4-amino-5H-pyrrolo[3,2-d]pyrimidine;

10 2-amino-7-((3,4-dihydroxy-2-(methylthiomethyl)butylamino)methyl)- 4-amino-5H-pyrrolo[3,2-d]pyrimidine;

7-((3,4-dihydroxy-2-(methylthiomethyl)butylamino)methyl)- 4-amino-5H-pyrrolo[3,2-d]pyrimidine;

2-amino-7-((3-hydroxy-2-(methylthiomethyl)propylamino)methyl)- 4-amino-5H-pyrrolo[3,2-d]pyrimidine;

15 7-((3-hydroxy-2-(methylthiomethyl)propylamino)methyl)- 4-amino-5H-pyrrolo[3,2-d]pyrimidine;

7-(((3-hydroxy-2-(methylthiomethyl)propyl)(methyl)amino)methyl)- 4-amino-5H-pyrrolo[3,2-d]pyrimidine;

20 2-amino-7-(((3-hydroxy-2-(methylthiomethyl)propyl)(methyl)amino)methyl)- 4-amino-5H-pyrrolo[3,2-d]pyrimidine;

2-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino)-2-(methylthiomethyl)propane-1,3-diol;

(S)-1-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino)-3-(methylthio)propan-2-ol;

(R)-4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino)-3-(methylthio)propan-2-ol;

25 (2R,3S)-4-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino)-3-(methylthiomethyl)butane-1,2-diol;

(2S,3S)-4-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino)-3-(methylthiomethyl)butane-1,2-diol;

(2R,3S)-4-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino)-3-

30 (methylthiomethyl)butane-1,2-diol;

(2R,3S)-4-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino)-3-(methylthiomethyl)butane-1,2-diol;

(2R,3R)-4-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)(methyl)amino)-3-(methylthiomethyl)butane-1,2-diol;

35 (2S,3S)-4-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)(methyl)amino)-3-(methylthiomethyl)butane-1,2-diol;

(2R,3S)-4-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)(methyl)amino)-3-(methylthiomethyl)butane-1,2-diol;

(2S,3R)-4-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)(methyl)amino)-3-(methylthiomethyl)butane-1,2-diol;

5 (2R,3R)-2-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino)-4-(methylthio)butane-1,3-diol;

(2S,3S)-2-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino)-4-(methylthio)butane-1,3-diol;

10 (2R,3S)-2-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino)-4-(methylthio)butane-1,3-diol;

(2S,3R)-2-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino)-4-(methylthio)butane-1,3-diol;

(2R,3R)-2-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)(methyl)amino)-4-(methylthio)butane-1,3-diol;

15 (2S,3S)-2-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)(methyl)amino)-4-(methylthio)butane-1,3-diol;

(2R,3S)-2-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)(methyl)amino)-4-(methylthio)butane-1,3-diol;

20 (2S,3R)-2-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)(methyl)amino)-4-(methylthio)butane-1,3-diol;

(2R,3R)-2-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino)methyl)-4-(methylthio)butane-1,3-diol;

(2S,3S)-2-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino)methyl)-4-(methylthio)butane-1,3-diol;

25 (2R,3S)-2-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino)methyl)-4-(methylthio)butane-1,3-diol;

(2S,3R)-2-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino)methyl)-4-(methylthio)butane-1,3-diol;

30 (2R,3R)-1-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)(methyl)amino)-4-(methylthio)butane-2,3-diol;

(2S,3S)-1-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)(methyl)amino)-4-(methylthio)butane-2,3-diol;

(2R,3S)-1-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)(methyl)amino)-4-(methylthio)butane-2,3-diol;

35 (2S,3R)-1-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)(methyl)amino)-4-(methylthio)butane-2,3-diol;

(R)-2-((R)-1-(4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-2-hydroxyethylamino)-3-(methylthio)propan-1-ol;
(S)-2-((S)-1-(4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-2-hydroxyethylamino)-3-(methylthio)propan-1-ol;
5 (R)-2-((S)-1-(4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-2-hydroxyethylamino)-3-(methylthio)propan-1-ol;
(S)-2-((R)-1-(4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-2-hydroxyethylamino)-3-(methylthio)propan-1-ol;
meso-7-((2,4-*cis*-2,4-bis(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-
10 4(5H)-one;
(±) 7-((2,4-*trans*-2,4-bis(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
(+) 7-((2,4-*trans*-2,4-bis(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
15 (-) 7-((2,4-*trans*-2,4-bis(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
7-((3,3-bis(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
(±) 7-((2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
7-(((2*R*)-2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
20 7-(((2*S*)-2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
7-((3-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
7-((3-hydroxy-3-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
(±) 7-((2,3-*cis*-3-hydroxy-2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-
25 d]pyrimidin-4(5H)-one;
(+) 7-((2,3-*cis*-3-hydroxy-2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
(-) 7-((2,3-*cis*-3-hydroxy-2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
30 (±) 7-((2,3-*trans*-3-hydroxy-2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
(+) 7-((2,3-*trans*-3-hydroxy-2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
(-) 7-((2,3-*trans*-3-hydroxy-2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-
35 d]pyrimidin-4(5H)-one;

meso-2-amino-7-((2,4-*cis*-2,4-bis(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(±) 2-amino-7-((2,4-*trans*-2,4-bis(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

5 (+) 2-amino-7-((2,4-*trans*-2,4-bis(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(-) 2-amino-7-((2,4-*trans*-2,4-bis(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-((3,3-bis(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(±) 2-amino-7-((2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-(((2*R*)-2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

15 2-amino-7-(((2*S*)-2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-((3-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-((3-hydroxy-3-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(±) 2-amino-7-((2,3-*trans*-3-hydroxy-2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(-) 2-amino-7-((2,3-*trans*-3-hydroxy-2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

25 (+) 2-amino-7-((2,3-*trans*-3-hydroxy-2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(±) 2-amino-7-((2,3-*cis*-3-hydroxy-2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(+) 2-amino-7-((2,3-*cis*-3-hydroxy-2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(-) 2-amino-7-((2,3-*cis*-3-hydroxy-2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(1-((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-3-(methylthiomethyl)azetidin-3-yl)methanol;

35 1-((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-3-(methylthiomethyl)azetidin-3-ol;

(±)-(2,4-*trans*-1-((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-4-(methylthiomethyl)azetidin-2-yl)methanol;
 (+)-(2,4-*trans*-1-((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-4-(methylthiomethyl)azetidin-2-yl)methanol;
 5 (-)-(2,4-*trans*-1-((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-4-(methylthiomethyl)azetidin-2-yl)methanol;
meso-(2,4-*cis*-1-((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-4-(methylthiomethyl)azetidin-2-yl)methanol;
 7-(((2*RS*)-2-(methylthiomethyl)azetidin-1-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 10 7-(((2*R*)-2-(methylthiomethyl)azetidin-1-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 7-(((2*S*)-2-(methylthiomethyl)azetidin-1-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 7-(((3-(methylthiomethyl)azetidin-1-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 (±) 2,3-*trans*-1-((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-2-(methylthiomethyl)azetidin-3-ol;
 15 (+) 2,3-*trans*-1-((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-2-(methylthiomethyl)azetidin-3-ol;
 (-) 2,3-*trans*-1-((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-2-(methylthiomethyl)azetidin-3-ol;
 (±) 2,3-*cis*-1-((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-2-(methylthiomethyl)azetidin-3-ol;
 20 (+) 2,3-*cis*-1-((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-2-(methylthiomethyl)azetidin-3-ol; and
 (-) 2,3-*cis*-1-((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-2-(methylthiomethyl)azetidin-3-ol.

ABBREVIATIONS

DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMSO	Dimethylsulfoxide
30 THF	Tetrahydrofuran
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
TMS	Tetramethylsilane
t.l.c	Thin layer chromatography
HRMS	High resolution mass spectrometry
35 ES	Electrospray

EXAMPLES

The following examples further illustrate the invention. It is to be appreciated that the invention is not limited to these examples.

General

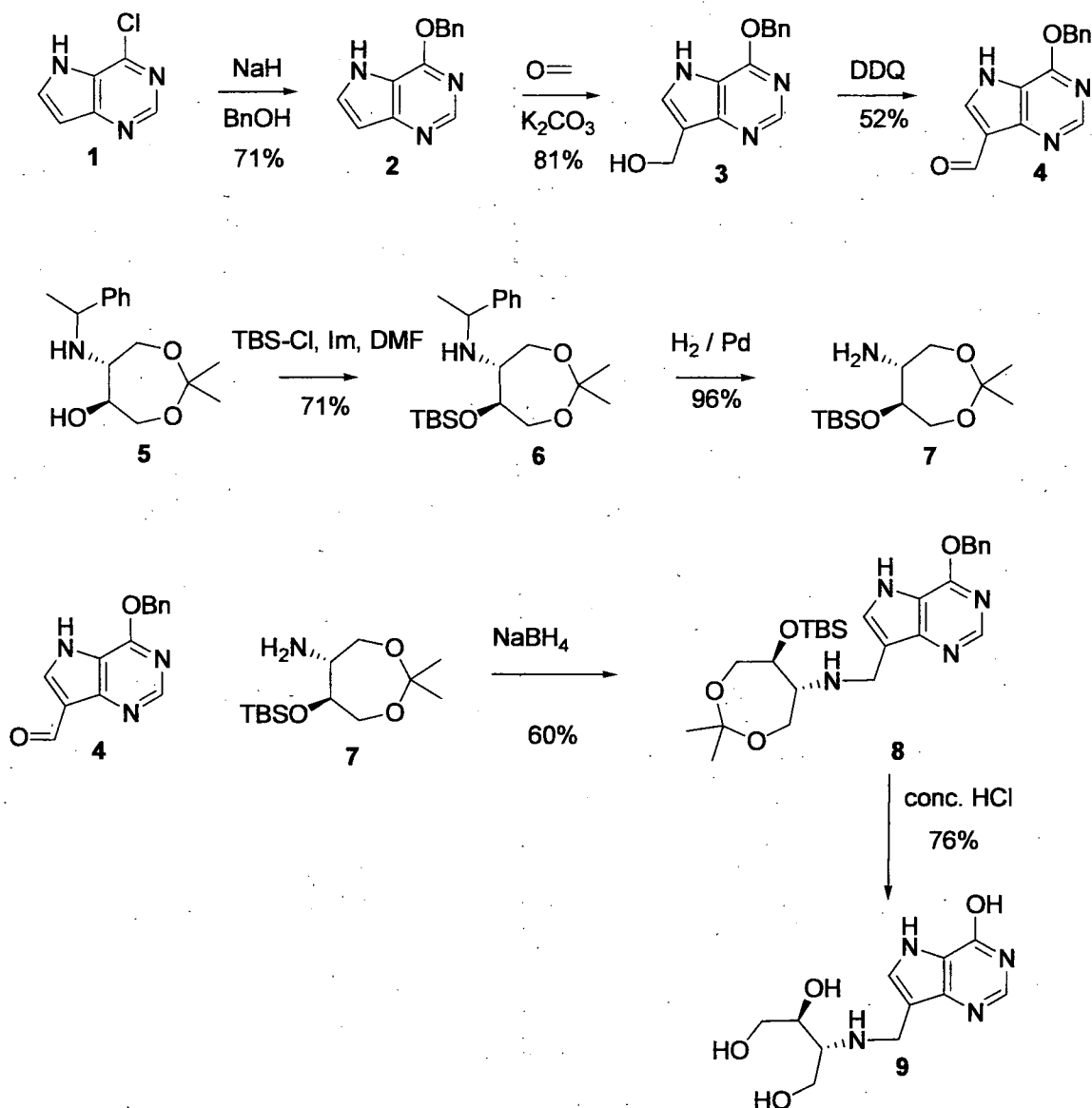
All reagents were used as supplied; anhydrous solvents were obtained commercially.

Air sensitive reactions were carried out under argon unless otherwise stated. Organic solutions were dried over MgSO_4 and the solvents were evaporated under reduced pressure. Chromatography solvents were distilled prior to use. Thin layer chromatography (t.l.c.) was performed on glass or aluminium sheets coated with 60 F₂₅₄ silica. Organic compounds were visualised under UV light or by use of a spray or dip of cerium(IV) sulfate (0.2%, w/v) and ammonium molybdate (5%) in sulfuric acid (2M), one of I_2 (0.2%) and KI (7%) in H_2SO_4 (10%) or, for nitrogen-containing compounds, *p*-(*N,N*-dimethylamino)benzaldehyde (1%) in HCl (37%)-MeOH, 1:3 (100 mL) (Erich reagent). Flash column chromatography was performed on Sorbsil C60 40/60 silica, Scharlau or Merck silica gel 60 (40-60 μm). Melting points were recorded on a Reichert hot stage microscope and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a path length of 1 dm and are in units of $10^{-1}\text{deg cm}^2 \text{g}^{-1}$; concentrations are in g/100 mL.

NMR spectra were recorded on Bruker 300 and 500 MHz spectrometers.

High resolution mass spectra, ES data were collected on a Waters Q-ToF Premier Mass Spectrometer with LockSpray equipped with an electrospray ionization probe. Microanalyses were carried out by the Campbell Microanalytical Laboratory, University of Otago.

Example 1 – Synthesis of (2S,3R)-3-[(4-hydroxy-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl-amino]butane-1,2,4-triol hydrochloride (9)



4-(Benzyloxy)-5H-pyrrolo[3,2-d]pyrimidine (2). To benzyl alcohol (5 mL) stirred under Ar and cooled with a water bath was added sodium hydride (250 mg, 60% in mineral oil, 6.25 mmol). After all sodium hydride had reacted, 4-chloro-5H-pyrrolo[3,2-d]pyrimidine (1) (720 mg, 4.68 mmol) was added and the mixture heated to 90 °C overnight then the majority of the benzyl alcohol removed by distillation (bath temp 90 °C, 0.1 mmHg). The brown residue was diluted with water and then extracted with ethyl acetate (2x). The ethyl acetate extracts were washed with brine, dried and then concentrated under reduced pressure. Purification of the residue by flash chromatography, eluting with ethyl acetate/petroleum ether 1:1, afforded title compound 2 as a colourless crystalline solid (744 mg, 71%). mp 159-160 °C. ¹H NMR (300 MHz, CDCl₃, TMS) δ 9.41 (br s, 1H), 8.57 (s, 1H), 7.48-7.28 (m, 6H), 6.67 (dd, *J* = 3.1, 2.2 Hz, 1H), 5.58 (s, 2H). ¹³C NMR (75

MHz, CDCl_3 , solvent centre line δ 77.0) δ 155.4, 150.5, 150.0, 136.2, 128.6, 128.5, 128.4, 128.3, 115.1, 103.2, 67.8. +ESI-MS calcd for $[\text{M}+\text{H}]^+$ $\text{C}_{13}\text{H}_{12}\text{N}_3\text{O}_1$: 226.0980; Found: 226.0975. Anal. calcd. for $\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}_1$: C, 69.32; H, 4.92; N, 18.66; Found: C, 69.05; H, 5.01; N, 18.86.

5 **(4-(Benzyloxy)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methanol (3).** A solution of deazapurine **2** (685 mg, 3.04 mmol), potassium carbonate (841 mg, 6.08 mmol) and formaldehyde solution (37%, 2.44 mL, 30 mmol) in water/dioxane (1:1, 10 mL) was heated to 90 °C for 16 hours. The mixture was cooled and then concentrated under
10 reduced pressure then dissolved in methanol/ CH_2Cl_2 (1:1) and 7N ammonia in methanol (5 mL) added. The mixture was stirred for 30 minutes then silica gel (5 g) was added and the volatiles were removed under reduced pressure. Purification by flash silica-gel chromatography, eluting with a gradient of methanol/ CH_2Cl_2 1:99 to 1:19 afforded a mixture of title compound **3** and its 7-N-hydroxymethyl derivative. The mixture was
15 dissolved in CH_2Cl_2 /methanol (1:1, 10 mL) and 7N ammonia in methanol (5 mL) added. After 45 minutes the volatiles were removed under reduced pressure affording the title compound **3** as a colourless crystalline solid (630 mg, 81%). mp 177-179 °C. ^1H NMR (300 MHz, 5:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$, TMS) δ 8.83 (s, 1H), 7.52-7.34 (m, 6H), 5.58 (s, 2H), 4.80 (s, 2H); ^{13}C NMR (75 MHz, CDCl_3 , solvent centre line δ 77.0) δ 155.4, 149.0, 147.8, 135.9, 128.4, 128.2, 115.8, 115.4, 67.9, 54.2. +ESI-MS calcd for $[\text{M}+\text{Na}]^+$ $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_2\text{Na}_1$: 278.0905; Found: 278.0908. Anal calcd for $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_2$: C, 65.87; H, 5.13; N, 16.46; Found C, 65.87; H, 5.24; N, 16.67.

25 **4-(Benzyloxy)-5H-pyrrolo[3,2-d]pyrimidine-7-carbaldehyde (4).** A solution of alcohol **3** (184 mg, 721 μmol) and DDQ (245 mg, 1081 μmol) in CHCl_3 (20 mL) were heated to reflux for 16 hours. The mixture was concentrated under reduced pressure and then diluted with 1:1 water/sat. sodium carbonate (20 mL). The precipitate was collected and then washed once with 1:1 water/sat. sodium carbonate (10 mL) then water (10 mL) and then dried under high vacuum. The cream coloured solid (140 mg) was suspended in
30 ethyl acetate (50 mL), the mixture heated to reflux then cooled and the precipitate of the title compound **4** was collected (95 mg, 52%). mp 235 °C (decomposed). ^1H NMR (300 MHz, d_6 -DMSO, TMS) δ 10.03 (1H, s), 8.47 (s, 3H), 8.03 (s, 3H), 7.56-7.34 (m, 5H), 5.59 (s, 2H). ^{13}C NMR (75 MHz, d_6 -DMSO, solvent δ 39.7) δ 183.2, 156.5, 150.5, 140.4, 137.0, 128.7, 128.4, 128.3, 119.3, 117.1, 67.3. +ESI-MS calcd for $[\text{MH}]^+$ $\text{C}_{14}\text{H}_{12}\text{N}_3\text{O}_2$: 254.0931; found: 254.0930.
35

(5R,6S)-6-(tert-Butyldimethylsilyloxy)-2,2-dimethyl-N-((S)-1-phenylethyl)-1,3-

dioxepan-5-amine (6). Imidazole (1.283 g, 18.84 mmol) and then *tert*-butyldimethylsilyl chloride (1.704 g, 11.31 mmol) were added to a solution of (5S,6R)-2,2-dimethyl-6-((S)-1-phenylethylamino)-1,3-dioxepan-5-ol (see *J. Org. Chem.* 1998, 63, 7582-7583 and *J. Org. Chem.* 1999, 64, 4962-4965; 1.0 g, 3.77 mmol) in dry *N,N*-dimethylformamide (20 mL) and the solution was heated at 80 °C for 3 h. The solution was concentrated to dryness. The residue was dissolved in toluene and the solution was washed with water, dried and concentrated to dryness. Chromatography (EtOAc/pet ether 1:5) gave the title compound **6** as a syrup (1.37 g, 3.61 mmol, 96%). ¹H NMR (CDCl₃, TMS) δ 7.31-7.26 (5H, m), 3.88 (1H, dd, *J* = 13.2, 6.6 Hz), 3.74 (1H, dd, *J* = 12.2, 2.4 Hz), 3.57-3.41 (4H, m), 2.34-2.29 (1H, m), 1.82 (1H, br s), 1.34 (3H, d, *J* = 6.5 Hz), 1.30 and 1.28 (3H each, s), 0.84 (9H, s), 0.02 and -0.03 (3H each, s).

(5R,6S)-6-[(tert-Butyldimethylsilyl)oxy]-2,2-dimethyl-1,3-dioxepan-5-amine (7). To a solution of methylbenzylamine derivative **6** (861 mg, 2.26 mmol) in ethyl acetate (10 mL) was added 10% Pd/C (250 mg) and a balloon of hydrogen fitted. The reaction mixture was stirred for 16 hours and then the hydrogen replaced with Ar and the suspension filtered through celite and the celite washed well with ethyl acetate. The filtrate was concentrated under reduced pressure and then dried under high vacuum affording a colourless oil (600 mg, 96%). ¹H NMR (300 MHz, CDCl₃, TMS) 3.63-3.45 (m, 4H), 3.35 (ddd, *J* = 8.0, 7.1, 3.4 Hz, 1H), 2.74 (ddd, *J* = 8.4, 7.1, 3.6 Hz, 1H), 1.32 (s, 3H), 1.31 (s, 3H), 0.91 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 100.8, 76.6, 62.9, 62.4, 57.2, 25.7, 24.6, 24.4, 17.9, -4.3, -4.6. Anal calcd for C₁₃H₂₉NO₃Si: C, 56.68; H, 10.61; N, 5.08; Found: C, 57.06; H, 10.44; N, 5.15.

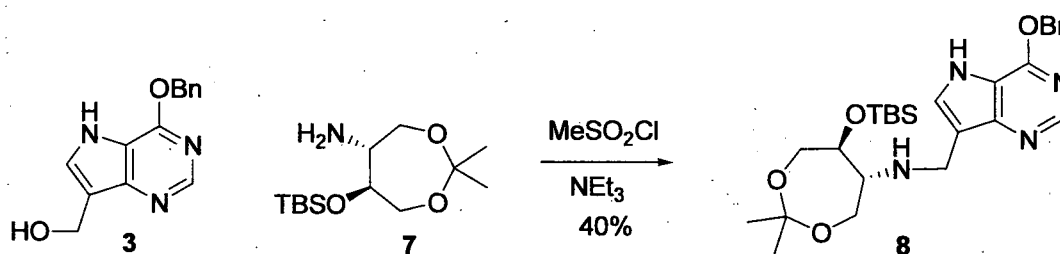
(5R,6S)-N-[(4-(benzyloxy)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl]-6-[(tert-butyldimethylsilyl)oxy]-2,2-dimethyl-1,3-dioxepan-5-amine (8). A suspension of amine **7** (39 mg, 0.14 mmol) and aldehyde **5** (45 mg, 0.14 mmol) in ethanol (3 mL) was heated to 70°C for 45 minutes after which time another portion of amine **7** (15 mg, 0.05 mmol) was added giving a homogenous solution. The mixture was cooled and then sodium borohydride (32 mg, 0.84 mmol) was added and the reaction stirred for 30 minutes then the mixture absorbed onto silica and purified by flash chromatography, eluting with 99:1 CHCl₃/7N ammonia in methanol to give clean fractions of the title compound **8** as a colourless crystalline solid (44 mg, 60%). mp 131-132 °C. [α]_D²² -34 (c 0.49, CHCl₃). ¹H NMR (300 MHz, CDCl₃, TMS) δ 9.24 (br s, 1H), 8.56 (s, 1H), 7.50-7.33 (m, 5H), 7.25 (br d, *J* = 2.6 Hz, 1H), 5.63-5.55 (m, 2H), 4.10 (d, *J* = 13.6 Hz, 1H), 4.01

(d, $J = 13.6$ Hz, 1H), 3.81 (dd, $J = 12.3, 2.7$ Hz, 1H), 3.60-3.51 (m, 4H), 2.69-2.58 (m, 1H), 1.31 (s, 3H), 1.29 (s, 3H), 0.83 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3 , solvent centre line δ 77.0) δ 155.1, 149.7, 149.1, 136.2, 128.5, 128.4, 128.3, 126.8, 115.6, 115.3, 100.9, 73.8, 67.8, 63.2, 62.8, 59.5, 41.2, 25.6, 24.7, 24.5, 17.8, -4.3, -4.7. +ESI-MS calcd for $[\text{MH}]^+$ $\text{C}_{27}\text{H}_{41}\text{N}_4\text{O}_4\text{Si}$: 513.2897; found: 513.2888. Anal calcd for $\text{C}_{27}\text{H}_{40}\text{N}_4\text{O}_4\text{Si}$: C, 63.25; H, 7.86; N, 10.93; Found: C, 63.28; H, 7.83; N, 10.80.

(2S,3R)-3-[(4-hydroxy-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino]butane-1,2,4-

triol hydrochloride (9). A stirred solution of heterocycle **8** (5 mg, 9.75 μmol) in conc. HCl (1.0 mL) was heated to 60 $^\circ\text{C}$ for 40 minutes. The mixture was cooled and concentrated under reduced pressure and the residue obtained concentrated from water to remove residual hydrochloric acid to give the title compound **9** as a colourless gum (2 mg, 76%). ^1H NMR (300 MHz, D_2O) δ 8.34 (s, 1H), 7.74 (s, 1H), 4.58 (d, $J = 13.9$ Hz, 1H), 4.49 (d, $J = 13.9$ Hz, 1H), 3.98 (dd, $J = 13.0, 4.2$ Hz, 1H), 3.94 (ddd, $J = 7.7, 4.4, 3.4$ Hz, 1H), 3.85 (dd, $J = 13.0, 4.9$ Hz, 1H), 3.72 (dd, $J = 12.2, 3.5$ Hz, 1H), 3.60 (dd, $J = 12.2, 4.4$ Hz, 1H), 3.44-3.36 (m, 1H).

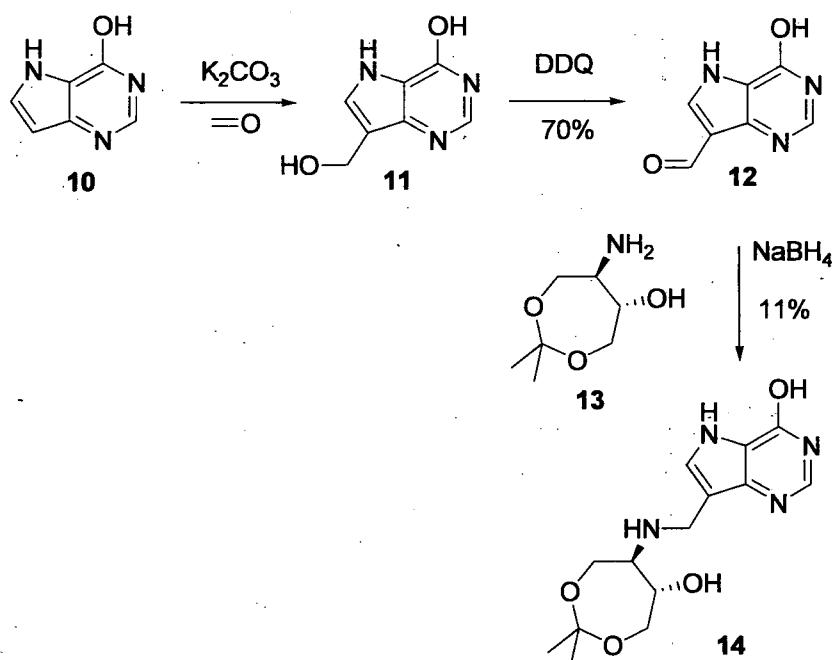
Example 2 – Synthesis of (5R,6S)-N-[(4-(benzyloxy)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl]-6-[(tert-butyldimethyl-silyl)oxy]-2,2-dimethyl-1,3-dioxepan-5-amine (8)



(5R,6S)-N-[(4-(benzyloxy)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl]-6-[(tert-

butyldimethyl-silyl)oxy]-2,2-dimethyl-1,3-dioxepan-5-amine (8). To a stirred solution of alcohol **3** (32 mg, 125 μmol) and triethylamine (35.2 μL , 251 μmol) in CH_2Cl_2 (3 mL) was added methanesulfonyl chloride (9.77 μL , 125 μmol). The reaction mixture was allowed to stir for 45 minutes and then amine **7** (49 mg) was added. The reaction mixture was allowed to stir overnight then the mixture absorbed onto silica-gel and purified by flash chromatography, eluting with a gradient of CHCl_3 /7N methanolic ammonia 99:1 to 97:3 to give the title compound **8** as a colourless solid (26 mg, 40%) with spectral data identical to above, and recovered alcohol **7** (7 mg, 22%).

Example 3 – Synthesis of 7-[[[(5R,6S)-6-hydroxy-2,2-dimethyl-1,3-dioxepan-5-ylamino]-methyl]-5H-pyrrolo[3,2-d]pyrimidin-4-ol (14)

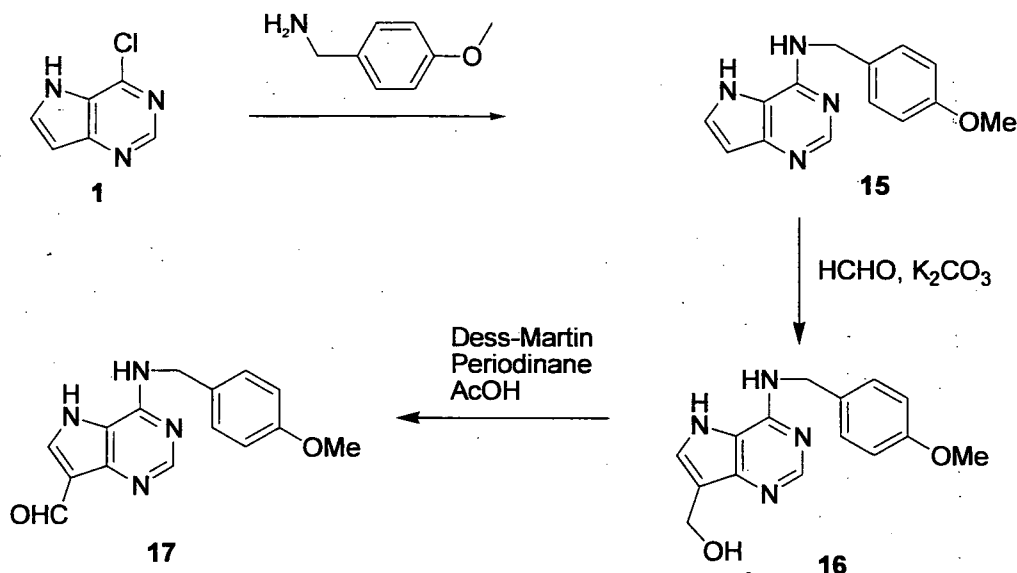


7-(Hydroxymethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-ol (11). To a stirred suspension of 9-deazahypoxanthine (10) (820 mg, 6.07 mmol) and potassium carbonate (700 mg, 5.07 mmol) in 1:1 dioxane/water (20 mL) was added 37% formaldehyde (4.0 mL, 49 mmol). The resulting mixture was heated to 100 °C for 3 hours then cooled and concentrated under reduced pressure. The resulting mixture was taken up in methanol (5 mL) and 7N methanolic ammonia (10 mL) added. The mixture was stirred at ambient temperature for 20 minutes and then concentrated under reduced pressure. The mixture was diluted with methanol (10 mL), then left to stand for 72 hours at 4 °C before the precipitate was collected and washed with a small amount of methanol then water. The mother liquor was concentrated under reduced pressure, diluted with water and the solid obtained was collected and combined with the previous precipitate to give the title compound 11 as a white solid after drying (combined yield 779 mg, 78%). 1H NMR (300 MHz, d_6 -DMSO, TMS) δ 11.8 (br s, 2H), 7.77 (s, 1H), 7.27 (s, 1H), 4.70 (br s, 1H), 4.54 (s, 2H). ^{13}C NMR (75 MHz, d_6 -DMSO) δ 154.0, 142.6, 141.5, 126.1, 118.3, 118.0, 54.0; +ESI-MS calcd for $[MH]^+$ $C_7H_8N_3O_2$: 166.0617; Found: 166.0612. Anal calcd for $[1 \cdot (0.3H_2O)]$: C, 49.12; H, 4.51; N, 24.55; Found: C, 49.57; H, 4.19; N, 24.09.

4-Hydroxy-5H-pyrrolo[3,2-d]pyrimidine-7-carbaldehyde (12). A suspension of alcohol **11** (294 mg, 1.9 mmol) and DDQ (606 mg, 2.66 mmol) was stirred at ambient temperature for 72 hours. The suspension was diluted with CHCl_3 (5 mL) and the precipitated solid collected. This solid was resuspended in acetic acid (1 mL) and allowed to react with an additional portion of DDQ (200 mg, 0.88 mmol). The solid obtained as above was dried under vacuum to remove all acetic acid and then washed with CH_2Cl_2 (10 mL) followed by acetone (10 mL) and further dried to give the title compound **12** as a cream coloured solid (203 mg, 70%). ^1H NMR (300 MHz, d_6 -DMSO, TMS) δ 13.06 (br s, 1H), 12.22 (br s, 1H), 10.05 (s, 1H), 8.07 (d, $J = 3.3$ Hz, 1H), 7.98 (s, 1H). ^{13}C NMR (75 MHz, d_6 -DMSO) δ 183.7, 154.5, 144.5, 132.7, 134.3, 121.2, 117.8.

7-[[[(5R,6S)-6-hydroxy-2,2-dimethyl-1,3-dioxepan-5-ylamino]methyl]-5H-pyrrolo[3,2-d]pyrimidin-4-ol (14). A suspension of amine **13** (119 mg, 736 μmol) and aldehyde **12** (100 mg, 613 μmol) in dioxane/methanol (2 mL, 1:1) was heated to 60 $^\circ\text{C}$, when all material had dissolved, the mixture was cooled and sodium borohydride (21.67 μL , 613 μmol) was added and then the mixture left to stir overnight. The volatiles were removed under reduce pressure and the residue purified by flash chromatography to give the title compound **14** as a colourless solid (20 mg, 11%). ^1H NMR (300 MHz, CD_3OD , TMS) δ 7.87 (s, 1H), 7.41 (s, 1H), 4.02 (d, $J = 13.7$ Hz, 1H), 3.95 (d, $J = 13.7$ Hz, 1H), 3.82 (dd, $J = 12.5, 2.7$ Hz, 1H), 3.66 (dd, $J = 12.4, 2.8$ Hz, 1H), 3.64-3.50 (m, 2H), 3.45 (ddd, $J = 6.6, 6.6, 2.7$ Hz, 1H), 2.56 (ddd, $J = 7.0, 7.0, 2.5$ Hz, 1H), 1.29 (s, 3H), 1.29 (s, 3H).

Example 4 – Synthesis of 4-(4-Methoxybenzylamino)-5H-pyrrolo[3,2-d]pyrimidine-7-carbaldehyde (17)



***N*-(4-Methoxybenzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine (15)**

4-Chloro-5H-pyrrolo[3,2-d]pyrimidine (4.68 g, 30.5 mmol) and 4-methoxybenzylamine (11.94 mL, 91 mmol) were heated at 60 °C in EtOH (50 mL) for 16 h. The solvent was evaporated and the residue chromatographed on silica gel (CH₂Cl₂-MeOH, 97:3 → 95:5) to give the crude product as an oily solid which was triturated with Et₂O and the resulting solid filtered off and dried (~5 g). Recrystallization from MeOH-water gave *N*-(4-methoxybenzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine as a tan coloured solid (3.37 g, 44%). An analytical sample was obtained by recrystallization once more from MeOH.

¹H NMR (300 MHz, *d*₆-DMSO, TMS) δ 10.90 (br.s, 1H), 8.20 (s, 1H), 7.48 (d, *J* = 2.8 Hz, 1H), 7.36-7.29 (m, 3H), 6.92 (d, *J* = 8.6 Hz, 2H), 6.37 (d, *J* = 2.8 Hz, 1H), 4.66 (d, *J* = 5.4 Hz, 2H), 3.73 (s, 3H). ¹³C NMR (75.5 MHz, *d*₆-DMSO, solvent δ 39.7) δ 158.6 (C), 150.4 (CH), 149.4 (C), 146.8 (C), 131.7 (C), 129.2 (CH), 127.6 (CH), 114.0 (CH), 113.9 (C), 101.6 (CH), 55.3 (CH₃), 43.0 (CH₂). +ESI-MS Calc. for C₁₄H₁₅N₄O [M+H]⁺ 255.1246 found 255.1240.

(4-(4-Methoxybenzylamino)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methanol (16)

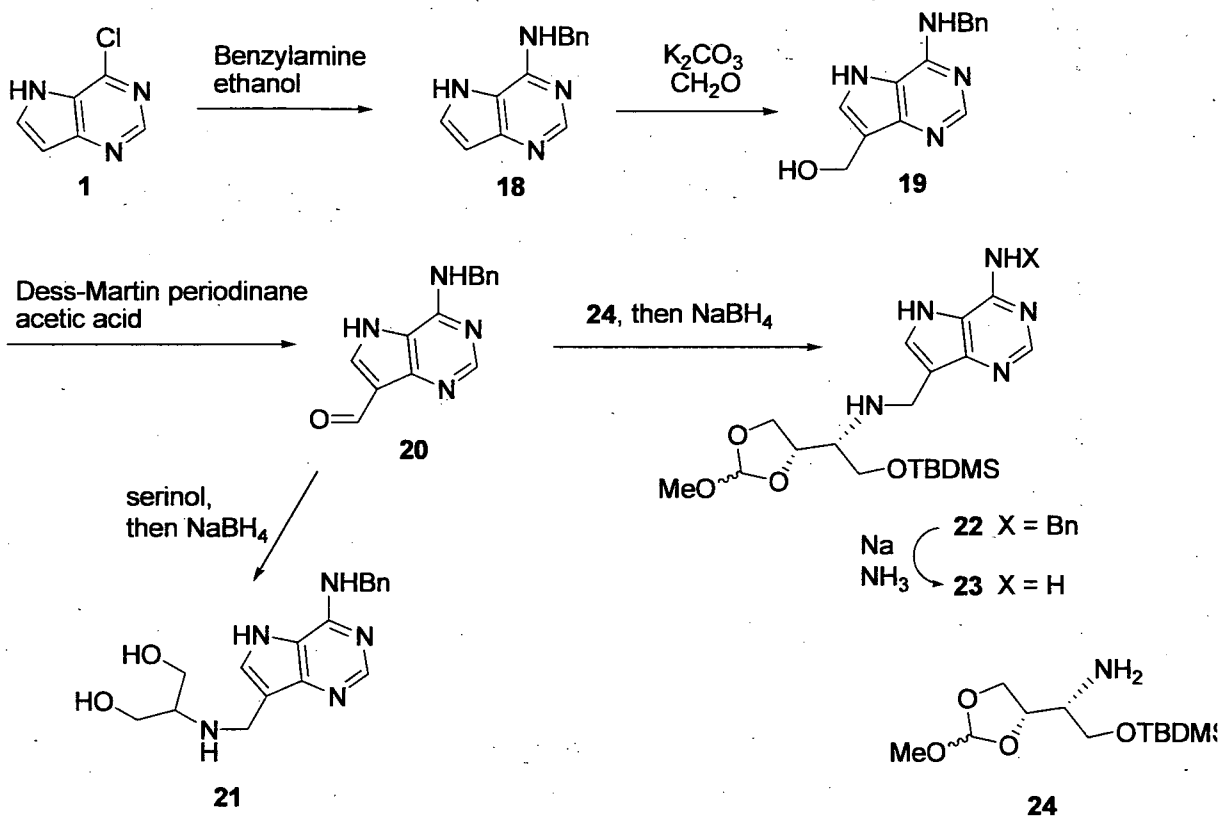
N-(4-Methoxybenzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine (0.1 g, 0.393 mmol), formaldehyde solution (37% aq., 0.912 mL, 11.80 mmol) and K₂CO₃ (0.136 g, 0.983

mmol) were heated to 90 °C in a 4:1 mixture of 1,4-dioxane and H₂O (5 mL) for 15 min. The solvent was evaporated and the residue chromatographed on silica gel (CH₂Cl₂-MeOH-28% aq. NH₄OH, 95:5:0.05) to give 4-(4-methoxybenzylamino)-5H-pyrrolo[3,2-*d*]pyrimidin-7-yl)methanol (100 mg, 89%) as a colourless solid. ¹H NMR (300 MHz, *d*₆-DMSO, TMS) δ 10.73 (s, 1H), 8.17 (s, 1H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.34-7.27 (m, 3H), 6.90 (d, *J* = 8.7 Hz, 2H), 4.70 (t, *J* = 5.3 Hz, 1H), 4.64 (d, *J* = 5.5 Hz, 2H), 4.60 (d, *J* = 5.1 Hz, 2H), 3.30 (s, 3H).

4-(4-Methoxybenzylamino)-5H-pyrrolo[3,2-*d*]pyrimidine-7-carbaldehyde (17)

(4-(4-methoxybenzylamino)-5H-pyrrolo[3,2-*d*]pyrimidin-7-yl)methanol (0.1 g, 0.352 mmol) was dissolved in AcOH (1 mL) and Dess-Martin periodinane (0.149 g, 0.352 mmol) added. The mixture became reddish in colour. After about 30 min, silica gel was added and the solvent evaporated. The residue was chromatographed on silica gel (CH₂Cl₂-MeOH-28% aq. NH₄OH, 95:5:0.05) to give 4-(4-methoxybenzylamino)-5H-pyrrolo[3,2-*d*]pyrimidine-7-carbaldehyde as a yellow solid. (0.083 g, 84 %). ¹H NMR (300 MHz, *d*₆-DMSO, TMS) δ 11.58 (br.s, 1H), 10.10 (s, 1H), 8.33 (s, 1H), 8.20 (s, 1H), 7.63 (t, *J* = 5.2 Hz, 1H), 7.33 (d, *J* = 8.6 Hz, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 4.65 (d, *J* = 5.3 Hz, 2H), 3.74 (s, 3H). ¹³C NMR (75.5 MHz, *d*₆-DMSO, centre line δ 39.7) δ 184.3 (C), 158.7 (C), 152.6 (CH), 149.7 (C), 145.5 (C), 133.6 (CH), 131.1 (C), 129.3 (CH), 117.0 (C), 114.8 (C), 114.0 (CH), 55.3 (CH₃), 43.0 (CH₂). +ESI-MS calc. for C₁₅H₁₅N₄O₂ [M+H]⁺, 283.1195, found 283.1186.

Example 5 – Synthesis of 2-((4-(Benzylamino)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino)propane-1,3-diol (21) and 7-(((1R)-2-(tert-Butyldimethylsiloxy)-1-((4S)-2-methoxy-1,3-dioxolan-4-yl)ethylamino)methyl)-5H-pyrrolo[3, 2]pyrimidin-4-amine (23)



N-Benzyl-5H-pyrrolo[3,2-d]pyrimidin-4-amine (18)

A solution of chloride 1 (4.6 g, 30.0 mmole) and benzylamine (12.84 g, 120 mmol, 4 eq) in ethanol (50 mL) was heated at reflux for 6 h. The ethanol was removed under reduced pressure and the residue taken up in acetonitrile and filtered. The filtrate was concentrated under reduced pressure and then most of the benzylamine removed by heating at 150 °C under vacuum (15 mm Hg). The residue was further purified by elution through a column of silica gel with dichloromethane-methanolic ammonia (3.5 M), 19:1 and 9:1 and then crystallised from acetonitrile to give benzyldeazaadenine 18 (P. Capek, M. Otmar, M. Masojdkova, I. Votruba and A. Holy, *Collect. Czech. Chem. Commun.*, 2003, 68, 779-791) (4.2 g, 18.7 mmol, 63%) as an off-white solid. 1H NMR (300 MHz, DMSO- d_6 , TMS) δ 10.93 (s, 1H), 8.16 (s, 1H), 7.6-7.2 (m, 7H), 6.37 (s, 1H), 4.72 (m, 2H). ^{13}C NMR (75.5 MHz, DMSO- d_6 , solvent δ 39.8 ppm) δ 150.5, 149.6, 146.9, 140.0, 128.8, 127.9, 127.9, 127.3, 114.0, 101.8, 43.6.

(4-(Benzylamino)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methanol (19)

A solution of benzyldeazaadenine **18** (5 g, 22.3 mmol), potassium carbonate (7.70 g, 55.7 mmol, 2.5 eq) and formaldehyde (37% aqueous, 50 mL, 622 mmol, 30 eq) in water (100 mL) and dioxane (400 mL) was heated at 90 °C for 1 h. After cooling, the solvents were removed under reduced pressure and the residue was taken up in methanol containing a little ammonia and evaporated onto silica gel. This silica was applied to the top of a short silica column. Elution with dichloromethane-methanol, 19:1-6:1 gave the title compound (4.4 g, 17.3, 78%) as an off-white solid. NMR spectra are in agreement with data reported in P. Capek, M. Otmar, M. Masojdkova, I. Votruba and A. Holy, *Collect. Czech. Chem. Commun.*, 2003, 68, 779-791.

4-(Benzylamino)-5H-pyrrolo[3,2-d]pyrimidine-7-carbaldehyde (20)

A solution of pyrimidine **19** (4.4 g, 17.3 mmol) and Dess-Martin periodinane (9.84 g, 22.5 mmol, 1.3 eq) in acetic acid (200 mL) was stirred at room temperature for 15 h. The solvent was evaporated under reduced pressure and the residue was taken up in methanol (100 mL) and basified with sodium hydrogen carbonate solution (10% aqueous). Upon addition of sodium thiosulfate solution (0.5 M, 100 mL), a white precipitate formed which was isolated by filtration. This solid was suspended in hot methanol and filtered again. The off-white solid comprised the title compound **20** (2.3 g, 80% purity, 7.29 mmol, 42% yield) contaminated with iodobenzoic acid. It was used without further purification. Chromatography gave a pure sample. ¹H NMR (300 MHz, DMSO-*d*₆, TMS) δ 12 (bs, 1H), 10.11 (s, 1H), 8.34 (s, 1H), 8.23 (s, 1H), 7.71 (s, 1H), 7.5-7.2 (m, 5H), 4.74 (s, 2H). ¹³C NMR (75.5 MHz, DMSO-*d*₆, solvent δ 39.8 ppm) δ 184.7, 152.6, 150.0, 145.3, 139.4, 134.2, 128.8, 128.0, 127.5, 117.1, 115.0, 43.7. +ESI-MS C₁₄H₁₃N₄O [M+H]⁺ calcd 253.1089, found 253.1080.

2-((4-(Benzylamino)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino)propane-1,3-diol (21)

Aldehyde **20** (528 mg, 1.7 mmol) was suspended in a stirred solution of serinol (153 mg, 1.7 mmol, 1 eq) in methanol (50 mL). After 90 min at room temperature, sodium borohydride (69.7 mg, 1.8 mol, 1.1 eq) was added to the resulting solution and stirring continued for a further 30 min. The solution was evaporated onto silica gel and applied to the top of a column of silica gel. Elution with 10% methanolic ammonia (3.5 M) in dichloromethane gave the title compound **21** (400 mg, 1.2 mmol, 73%) as a colourless glass. ¹H NMR (500 MHz, CD₃OD, TMS) δ 8.25 (s, 1H), 7.46 (s, 1H), 7.39 (m, 2H), 7.34 (m, 2H), 7.27 (m, 1H), 4.76 (s, 2H), 4.09 (s, 2H), 3.70 (dd, *J* = 5.3, 11.5 Hz, 2H),

3.60 (dd, $J = 5.8, 11.5$ Hz, 2H), 2.89 (m, 1H). ^{13}C NMR (125.7 MHz, CD_3OD , TMS) δ 151.2, 145.8, 140.4, 140.1, 129.7, 128.9, 128.6, 128.5, 115.8, 113.6, 62.1, 61.2, 45.5, 41.4.

5 ***N*-Benzyl-7-(((1*R*)-2-(*tert*-butyldimethylsiloxy)-1-((4*S*)-2-methoxy-1,3-dioxolan-4-yl)ethylamino)methyl)-5*H*-pyrrolo[3, 2]pyrimidin-4-amine (22)**

A solution of aldehyde **20** (182 mg, 0.72 mmol) and (1*R*)-2-(*tert*-butyldimethylsiloxy)-1-((4*S*)-2-methoxy-1,3-dioxolan-4-yl)ethanamine **24** (200 mg, 0.72 mmol, 1 eq, as a 1:1 mixture of anomers) in methanol (25 mL) was stirred at room temperature overnight.

10 Sodium borohydride (164 mg, 4.3 mmol, 6 eq) was then added. After 30 min, the mixture was concentrated under reduced pressure and then partitioned between dichloromethane and water. Chromatography on a column of silica gel eluted with 5-10% methanol in dichloromethane gave the target compound **22** (280 mg, 0.54 mmol, 76%, 1:1 mixture of anomers) as a colourless foam. ^1H NMR (300 MHz, CD_3OD , TMS) δ 8.23 (m, 1H), 7.5-7.2 (m, 6H), 5.68 (m, 1H), 4.76 (s, 2H), 4.31 (dd, $J = 6.4, 13.2$ Hz, 0.5H), 4.06 (m, 3.5H), 3.79 (m, 1H), 3.66 (m, 1H), 3.54 (m, 1H), 3.27 (s, 1.5H), 3.18 (s, 1.5 H), 2.70 (m, 1H), 0.84 (s, 9H), 0.00 (s, 6H). ^{13}C NMR (75.5 MHz, CD_3OD , solvent centre line 49.0 ppm) δ 151.1, 145.8, 143.7, 140.1, 129.6, 128.9, 128.4, 128.2, 116.9, 115.8, 114.8, (79.8, 77.7), (67.7, 67.3), (63.8, 63.4), (61.3, 60.8), 51.6, 45.4, (42.1, 42.0), 26.3, 19.6, -5.5. +ESI-MS $\text{C}_{26}\text{H}_{40}\text{N}_5\text{O}_4\text{Si}$ $[\text{M}+\text{H}]^+$ calc. 514.2850 found 514.2862.

7-(((1*R*)-2-(*tert*-Butyldimethylsiloxy)-1-((4*S*)-2-methoxy-1,3-dioxolan-4-yl)ethylamino)methyl)-5*H*-pyrrolo[3, 2]pyrimidin-4-amine (23)

25 A solution of benzyl amine **22** (520 mg, 0.10 mmol) in THF (12 mL) was added slowly to a solution of sodium ammonia cooled in a dry ice-acetone bath. Fragments of sodium were added over 1 h as necessary to maintain a deep blue colour. The reaction was quenched with water, brought to room temperature and partitioned between water and dichloromethane. Chromatography on a column of silica gel eluted with 20% methanol in dichloromethane gave the colourless, glassy title compound **23** (292 mg, 0.068 mmol, 68%) as a mixture of anomers. ^1H NMR (500 MHz, CD_3Cl_3 , TMS) δ 10.82 (bs, 1H), 8.20 (s, 0.5H), 8.19 (m, 0.5H), 7.23 (s, 1H), 6.07 (bs, 2H), 5.69 (m, 0.5H), 5.68 (m, 0.5H), 4.35 (dd, $J = 6.8, 12.9$ Hz, 0.5H), 4.16 (m, 0.5H), 4.11-4.01 (m, 2H), 3.95 (m, 1H), 3.84 (m, 2H), 3.70 (m, 1H), 3.60 (m, 1H), 3.26 (s, 1.5H), 3.25 (s, 1.5H), 2.88 (m, 0.5H), 2.78 (m, 0.5H), 1.30 (bm, 1H) 0.84 (s, 9H), 0.00 (s, 6H). ^{13}C NMR (75.5 MHz, CD_3Cl_3 , solvent centre line 77.4 ppm) δ 151.1, (149.9, 149.7), (145.2, 144.9), 127.5, (116.2, 115.9),

115.0, (113.7, 113.4), (78.9, 76.8), (67.1, 66.7), (62.4, 62.3), (61.7, 61.0), (52.3, 52.0)
42.3, 26.2, 18.6, -5.2. +ESI-MS $C_{19}H_{34}N_5O_4Si$ $[M+H]^+$ calc. 424.2380 found 424.2375.

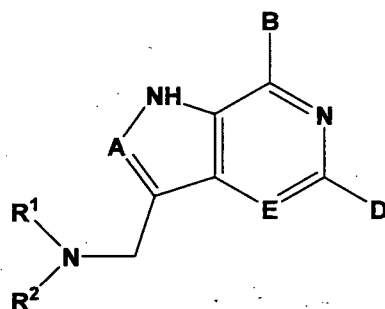
5 Although the invention has been described by way of example, it should be appreciated that variations or modifications may be made without departing from the scope of the invention. Furthermore, when known equivalents exist to specific features, such equivalents are incorporated as if specifically referred to in the specification.

10 INDUSTRIAL APPLICABILITY

The process of the invention provides an alternative to known processes for preparing compounds that are inhibitors of nucleoside phosphorylases and nucleosidases, which compounds may be useful for the treatment of diseases such as cancer, bacterial infection, protozoal infection (including malaria), and T-cell mediated diseases.

CLAIMS

1. A process for preparing a compound of formula (1):



(1)

where:

R^1 and R^2 together with the nitrogen to which they are attached form a 4-6 membered azacarbocyclic ring which is substituted by at least one halogen, SQ, OQ, or Q; or

R^1 and R^2 together with the nitrogen to which they are attached form a 4-6 membered azacarbocyclic ring which is substituted by at least one CH_2Z and at least one halogen, SQ or OQ; or

R^1 and R^2 are independently selected from H and alkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl and aryl each of which is optionally substituted with one or more hydroxy, alkoxy, thiol, alkylthio, arylthio, aralkylthio, cycloalkylthio, halogen, carboxylic acid, carboxylate, carboxamide, alkyl ester or nitro groups, where each alkylthio, arylthio, cycloalkylthio and aralkylthio group is optionally substituted with one or more alkyl, halogen, amino, hydroxy, or alkoxy groups;

provided that R^1 and R^2 are not both H;

Q is hydrogen or an alkyl, aralkyl, cycloalkyl or aryl group each of which may be substituted with one or more substituents selected from hydroxy, halogen, alkoxy, amino, and carboxy;

Z is halogen, SQ, OQ or Q;

A is selected from N, CH and CR^3 , where R^3 is selected from hydroxy, halogen, alkoxy, alkyl, aralkyl, cycloalkyl, aryl, NH_2 , NHR^4 , NR^4R^5 and SR^6 , where R^4 , R^5 and R^6 are each alkyl, aralkyl or aryl groups optionally substituted with hydroxy or halogen, and where R^3 is optionally substituted with hydroxy or halogen when R^3 is alkyl, cycloalkyl, aralkyl or aryl;

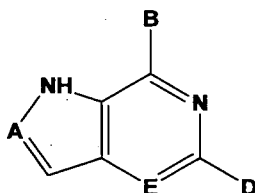
B is OQ, NH₂ or NHR⁸, where R⁸ is selected from alkyl, aralkyl, cycloalkyl and aryl, each of which may be substituted with one or more substituents selected from hydroxy and halogen;

D is selected from H, hydroxy, NH₂, and NHR⁷, where R⁷ is an alkyl, aralkyl, cycloalkyl or aryl group optionally substituted with hydroxy or halogen;

E is selected from N and CH;
or a tautomer thereof, or a pharmaceutically acceptable salt thereof, or an ester thereof, or a prodrug thereof;

comprising the combination of steps (i) then (ii) or (i) then (iii) where these steps are:

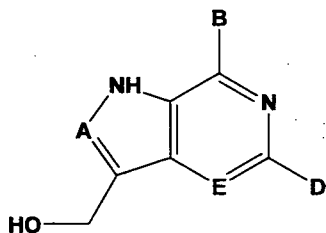
(i) hydroxymethylation of a compound of formula (2)



(2)

where A, B, D and E are as defined above or are equivalents thereof which have been protected by one or more protecting groups;

to give a compound of formula (3)



(3)

where A, B, D and E are as defined above or are equivalents thereof which have been protected by one or more protecting groups;

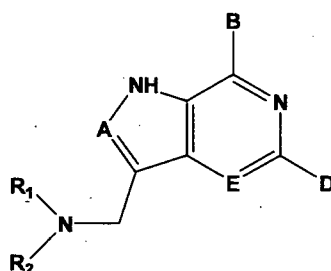
(ii) forming the compound of formula (1) by:

- a. oxidation of the hydroxymethylene group of the compound of formula (3) to an aldehyde;
- b. reductive amination of the aldehyde with a primary or secondary amine; and
- c. removal of any of the one or more protecting groups to give the compound of formula (1); or

(iii) forming the compound of formula (1) by:

- a. conversion of the OH of the hydroxymethylene group of the compound of formula (3) to OL, where OL is alkylsulfonyloxy or arylsulfonyloxy, each of which is optionally substituted with one or more alkyl, halogen or alkoxy groups;
- b. reaction with a primary or secondary amine to displace the OL group; and
- c. removal of any of the one or more protecting groups to give the compound of formula (1).

2. A process for preparing a compound of formula (1'):



(1')

where:

R¹ and R² together with the nitrogen to which they are attached form a 4-6 membered azacarbocyclic ring which is substituted by at least one SQ or OQ, where Q is hydrogen or an alkyl, aralkyl or aryl group each of which may be substituted with one or more substituents selected from hydroxy, halogen, alkoxy, amino, and carboxy; or

R¹ and R² are H or alkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl each of which is optionally substituted with one or more hydroxy, alkoxy, thiol, alkylthio, arylthio, aralkylthio, halogen, carboxylic acid, carboxylate alkyl ester, or nitro groups, where each alkylthio, arylthio and aralkylthio group is optionally substituted with one or more alkyl, halogen, amino, hydroxy, or alkoxy groups;

provided that R^1 and R^2 are not both H;

A is selected from N, CH and CR^3 , where R^3 is selected from hydroxy, halogen, alkoxy, alkyl, aralkyl, aryl, NHR^4 , NR^4R^5 and SR^6 , where R^4 , R^5 and R^6 are each alkyl, aralkyl or aryl groups optionally substituted with hydroxy or halogen, and where R^3 is optionally substituted with hydroxy or halogen when R^3 is alkyl, aralkyl or aryl;

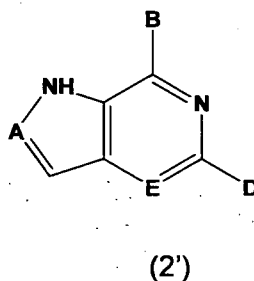
B is OQ where Q is hydrogen or an alkyl, aralkyl or aryl group each of which may be substituted with one or more substituents selected from hydroxy, halogen, alkoxy, amino, and carboxy;

D is selected from H, hydroxy, NH_2 , and NHR^7 , where R^7 is an alkyl, aralkyl or aryl group optionally substituted with hydroxy or halogen;

E is selected from N and CH;
or a tautomer thereof, or a pharmaceutically acceptable salt thereof, or an ester thereof, or a prodrug thereof;

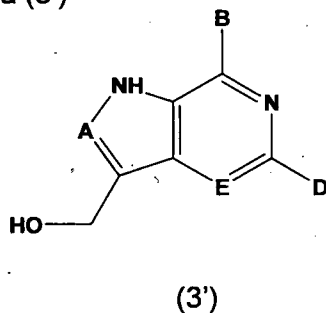
comprising the combination of steps (i) then (ii) or (i) then (iii) wherein these steps are:

(i) hydroxymethylation of a compound of formula (2')



where A, B, D and E are as defined above or are equivalents thereof which have been protected by one or more protecting groups;

to give a compound of formula (3')



where A, B, D and E are as defined above or are equivalents thereof which have been protected by one or more protecting groups;

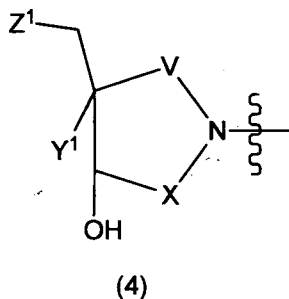
(ii) forming the compound of formula (1') by:

- a. oxidation of the hydroxymethylene group of the compound of formula (3) to an aldehyde;
- b. reductive amination of the aldehyde with a primary or secondary amine; and
- c. removal of any of the one or more protecting groups to give the compound of formula (1'); or

(iii) forming the compound of formula (1') by:

- a. conversion of the OH of the hydroxymethylene group of the compound of formula (3') to OL, where OL is a alkylsulfonyloxy or arylsulfonyloxy;
- b. reaction with a primary or secondary amine to displace the leaving group; and
- c. removal of any of the one or more protecting groups to give the compound of formula (1').

3. A process as claimed in claim 1 where R^1 and R^2 together with the nitrogen to which they are attached form a radical of formula (4):



where:

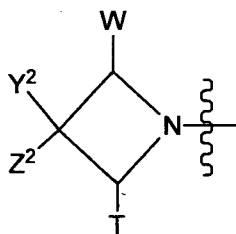
V is CH_2 or NH ;

Y^1 is H, halogen or hydroxy; provided that when V is NH then Y is H;

X is CH_2 or CHOH in the R- or S-configuration; and

Z^1 is halogen, SQ, OQ or Q, where Q is as defined in claim 1.

4. A process as claimed in claim 1 where R^1 and R^2 together with the nitrogen to which they are attached form a radical of formula (5):



(5)

where:

W and T are each independently selected from the group consisting of hydrogen, CH₂OH, CH₂OQ and CH₂SQ; and

Y² and Z² are each independently selected from the group consisting of halogen, CH₂OH, CH₂OQ and CH₂SQ, SQ, OQ and Q; provided that at least one of W, T, Y² and Z² is not hydrogen;

where Q is as defined in claim 1.

5. A process as claimed in claim 1 where R¹ and R² are H or alkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, or aryl each of which is optionally substituted with one or more hydroxy, alkoxy, thiol, alkylthio, arylthio, cycloalkylthio, aralkylthio, halogen, carboxylic acid, carboxylate alkyl ester, or nitro groups, where each alkylthio, arylthio and aralkylthio group is optionally substituted with one or more alkyl, halogen, amino, hydroxy, or alkoxy groups; provided that R¹ and R² are not both H.

6. A process as claimed in claim 3 where Z₁ is Q, SQ or OQ and V is CH₂.

7. A process as claimed in any one of claims 1 to 6 where B is hydroxy.

8. A process as claimed in any one of claims 1 to 7 where A is CH.

9. A process as claimed in any one of claims 1 to 8 where D is H.

10. A process as claimed in any one of claims 1 to 9 where E is N.

11. A process as claimed in any one of claims 1 to 10 where the hydroxymethylation of the compound of formula (2) or (2') in step (i) is carried by reaction using formaldehyde in the presence of a base.

12. A process as claimed in any one of claims 1 to 11 where the oxidation of the hydroxymethylene group of the compound of formula (3) or (3') in step (ii) a. is carried out using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or Dess-Martin periodinane.

13. A process as claimed in any one of claims 1 to 12 where the reductive amination of step (ii) b. is carried out using sodium borohydride to reduce an imine adduct formed between the aldehyde and the primary or secondary amine; or using sodium cyanoborohydride directly on a mixture of the aldehyde and the primary or secondary amine without prior formation of an imine.

14. A process as claimed in any one of claims 1 to 13 where the OL group in step (iii) a. is selected from the group comprising methanesulfonyloxy, p-toluenesulfonyloxy, 2,4,6-trimethylbenzene-sulfonyloxy, 4-bromobenzenesulfonyloxy and trifluoromethanesulfonyloxy.

15. A process as claimed in claim 1 where the compound of formula (1) is selected from the group comprising:

rac-(2*R*,3*S*)-3-((4-hydroxy-3*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)methylamino)butane-1,2,4-triol;

7-(((2,4-dihydroxybutyl)(methyl)amino)methyl)-3*H*-pyrrolo[3,2-*d*]pyrimidin-4(5*H*)-one;

(*R*) 3-((4-hydroxy-5*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)methylamino)-propane-1,2-diol hydrochloride;

(2*R*,3*R*)-3-((4-hydroxy-5*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)methylamino)butane-1,2,4-triol hydrochloride;

2-amino-7-(2,3-dihydroxy-1-(2-hydroxyethylamino)propyl)-3*H*-pyrrolo[3,2-*d*]pyrimidin-4(5*H*)-one;

7-(2,3-dihydroxy-1-(2-hydroxyethylamino)propyl)-3*H*-pyrrolo[3,2-*d*]pyrimidin-4(5*H*)-one;

2-amino-7-(1-amino-2,3,5-trihydroxypentyl)-3*H*-pyrrolo[3,2-*d*]pyrimidin-4(5*H*)-one;

7-(1-amino-2,3,5-trihydroxypentyl)-3*H*-pyrrolo[3,2-*d*]pyrimidin-4(5*H*)-one;

2-amino-7-(4-amino-2,3,5-trihydroxypentyl)-3*H*-pyrrolo[3,2-*d*]pyrimidin-4(5*H*)-one;

7-(4-amino-2,3,5-trihydroxypentyl)-3*H*-pyrrolo[3,2-*d*]pyrimidin-4(5*H*)-one;

2-amino-7-(1-(1,3-dihydroxypropan-2-ylamino)-2-hydroxyethyl)-3*H*-pyrrolo[3,2-*d*]pyrimidin-4(5*H*)-one;

7-(1-(1,3-dihydroxypropan-2-ylamino)-2-hydroxyethyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
2-amino-7-(((2,4-dihydroxybutyl)(methyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
5 2-amino-7-((2,4-dihydroxybutylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
7-((2,4-dihydroxybutylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
2-amino-7-((3,4-dihydroxy-2-(hydroxymethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
10 7-((3,4-dihydroxy-2-(hydroxymethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
2-amino-7-((3-hydroxy-2-(hydroxymethyl)propylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
7-((3-hydroxy-2-(hydroxymethyl)propylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
15 2-amino-7-(((3-hydroxy-2-(hydroxymethyl)propyl)(methyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
7-(((3-hydroxy-2-(hydroxymethyl)propyl)(methyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
20 2-amino-7-(3,4-dihydroxy-5-(methylthiomethyl)pyrrolidin-2-yl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
7-(3,4-dihydroxy-5-(methylthiomethyl)pyrrolidin-2-yl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
2-amino-7-(2,3-dihydroxy-1-(2-(methylthio)ethylamino)propyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
25 7-(2,3-dihydroxy-1-(2-(methylthio)ethylamino)propyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
2-amino-7-(1-amino-2,3-dihydroxy-5-(methylthio)pentyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
30 7-(1-amino-2,3-dihydroxy-5-(methylthio)pentyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
2-amino-7-(2-hydroxy-1-(1-hydroxy-3-(methylthio)propan-2-ylamino)ethyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
7-(2-hydroxy-1-(1-hydroxy-3-(methylthio)propan-2-ylamino)ethyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
35

2-amino-7-((3,4-dihydroxy-1-(methylthio)butan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-((3,4-dihydroxy-1-(methylthio)butan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

5 2-amino-7-(((2-hydroxy-4-(methylthio)butyl)(methyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-(((2-hydroxy-4-(methylthio)butyl)(methyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

10 2-amino-7-((2-hydroxy-4-(methylthio)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-((2-hydroxy-4-(methylthio)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-((3,4-dihydroxy-2-(methylthiomethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

15 7-((3,4-dihydroxy-2-(methylthiomethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-((3-hydroxy-2-(methylthiomethyl)propylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-((3-hydroxy-2-(methylthiomethyl)propylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

20 7-(((3-hydroxy-2-(methylthiomethyl)propyl)(methyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-(((3-hydroxy-2-(methylthiomethyl)propyl)(methyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

25 7-(((2R,3R)-1,3,4-trihydroxybutan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-(((2S,3S)-1,3,4-trihydroxybutan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-(((2R,3S)-1,3,4-trihydroxybutan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

30 7-(((2S,3R)-1,3,4-trihydroxybutan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-(((2R,3R)-1,3,4-trihydroxybutan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

35 2-amino-7-(((2S,3S)-1,3,4-trihydroxybutan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-(((2R,3S)-1,3,4-trihydroxybutan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-(((2S,3R)-1,3,4-trihydroxybutan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

5 7-(((1,3-dihydroxy-2-(hydroxymethyl)propan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-(((1,3-dihydroxy-2-(hydroxymethyl)propan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-((4-hydroxybutylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

10 2-amino-7-((4-hydroxybutylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-((2-hydroxyethylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-((2-hydroxyethylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-(((3-hydroxy-2-(hydroxymethyl)propylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

15 2-amino-7-(((3-hydroxy-2-(hydroxymethyl)propylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-(((3-hydroxy-2-(hydroxymethyl)propyl)(methyl)-amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

20 2-amino-7-(((3-hydroxy-2-(hydroxymethyl)propyl)(methyl)-amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

3-(((1,3-dihydroxypropan-2-yl)(methyl)amino)methyl)-1H-pyrazolo[4,3-d]pyrimidin-7(6H)-one;

7-(((3-hydroxy-2-(hydroxymethyl)propylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

25 2-amino-7-(((3-hydroxy-2-(hydroxymethyl)propylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-(((3-hydroxy-2-(hydroxymethyl)propyl)(methyl)-amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

30 2-amino-7-(((3-hydroxy-2-(hydroxymethyl)propyl)(methyl)-amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-(((3-hydroxy-2-(hydroxymethyl)propyl)(hydroxymethyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-(((3-hydroxy-2-(hydroxymethyl)propyl)(hydroxymethyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

35 7-(((1,3-dihydroxy-2-(methylthiomethyl)propan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-((1,3-dihydroxy-2-(methylthiomethyl)propan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
7-(((2R,3R)-2,3,4-trihydroxybutylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
7-(((2S,3S)-2,3,4-trihydroxybutylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
5 7-(((2R,3S)-2,3,4-trihydroxybutylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
7-(((2S,3R)-2,3,4-trihydroxybutylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
2-amino-7-(((2R,3R)-2,3,4-trihydroxybutylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
2-amino-7-(((2S,3S)-2,3,4-trihydroxybutylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
10 2-amino-7-(((2R,3S)-2,3,4-trihydroxybutylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
2-amino-7-(((2S,3R)-2,3,4-trihydroxybutylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
2-amino-7-(((2S,3R)-2,3,4-trihydroxybutylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
15 7-((benzyl((2R,3R)-3,4-dihydroxy-2-(methylthiomethyl)butyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
7-((benzyl((2S,3S)-3,4-dihydroxy-2-(methylthiomethyl)butyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
7-((benzyl((2R,3S)-3,4-dihydroxy-2-(methylthiomethyl)butyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
20 7-((benzyl((2S,3R)-3,4-dihydroxy-2-(methylthiomethyl)butyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
2-amino-7-((benzyl((2R,3R)-3,4-dihydroxy-2-(methylthiomethyl)butyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
25 2-amino-7-((benzyl((2S,3S)-3,4-dihydroxy-2-(methylthiomethyl)butyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
2-amino-7-((benzyl((2R,3S)-3,4-dihydroxy-2-(methylthiomethyl)butyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
2-amino-7-((benzyl((2S,3R)-3,4-dihydroxy-2-(methylthiomethyl)butyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
30 2-amino-7-((benzyl((2S,3R)-3,4-dihydroxy-2-(methylthiomethyl)butyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
(S)-7-(1-(1,3-dihydroxypropan-2-ylamino)-2-hydroxyethyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
(R)-7-(1-(1,3-dihydroxypropan-2-ylamino)-2-hydroxyethyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
35 (S)-2-amino-7-(1-(1,3-dihydroxypropan-2-ylamino)-2-hydroxyethyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(R)-2-amino-7-(1-(1,3-dihydroxypropan-2-ylamino)-2-hydroxyethyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-(((2R,3R)-2,3-dihydroxy-4-(methylthio)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

5 7-(((2S,3S)-2,3-dihydroxy-4-(methylthio)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-(((2R,3S)-2,3-dihydroxy-4-(methylthio)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

10 7-(((2S,3R)-2,3-dihydroxy-4-(methylthio)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-(((2R,3R)-2,3-dihydroxy-4-(methylthio)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-(((2S,3S)-2,3-dihydroxy-4-(methylthio)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

15 2-amino-7-(((2R,3S)-2,3-dihydroxy-4-(methylthio)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-(((2S,3R)-2,3-dihydroxy-4-(methylthio)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(R)-7-((benzyl(2,3-dihydroxypropyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

20 (S)-7-((benzyl(2,3-dihydroxypropyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(R)-2-amino-7-((benzyl(2,3-dihydroxypropyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(S)-2-amino-7-((benzyl(2,3-dihydroxypropyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

25 (R)-3-((2,3-dihydroxypropylamino)methyl)-1H-pyrazolo[4,3-d]pyrimidin-7(6H)-one;

(S)-3-((2,3-dihydroxypropylamino)methyl)-1H-pyrazolo[4,3-d]pyrimidin-7(6H)-one;

(R)-7-(((2,3-dihydroxypropyl)(2-hydroxyethyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

30 (S)-7-(((2,3-dihydroxypropyl)(2-hydroxyethyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(R)-2-amino-7-(((2,3-dihydroxypropyl)(2-hydroxyethyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(S)-2-amino-7-(((2,3-dihydroxypropyl)(2-hydroxyethyl)amino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

35 (2R,3R)-7-((3,4-dihydroxy-2-(hydroxymethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(2S,3S)-7-((3,4-dihydroxy-2-(hydroxymethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(2R,3S)-7-((3,4-dihydroxy-2-(hydroxymethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

5 (2S,3R)-7-((3,4-dihydroxy-2-(hydroxymethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(2R,3R)-2-amino-7-((3,4-dihydroxy-2-(hydroxymethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

10 (2S,3S)-2-amino-7-((3,4-dihydroxy-2-(hydroxymethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(2R,3S)-2-amino-7-((3,4-dihydroxy-2-(hydroxymethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(2S,3R)-2-amino-7-((3,4-dihydroxy-2-(hydroxymethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

15 7-(((2R,3R)-3,4-dihydroxy-1-(methylthio)butan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-(((2S,3S)-3,4-dihydroxy-1-(methylthio)butan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

20 7-(((2R,3S)-3,4-dihydroxy-1-(methylthio)butan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-(((2S,3R)-3,4-dihydroxy-1-(methylthio)butan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-(((2R,3R)-3,4-dihydroxy-1-(methylthio)butan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

25 2-amino-7-(((2S,3S)-3,4-dihydroxy-1-(methylthio)butan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-(((2R,3S)-3,4-dihydroxy-1-(methylthio)butan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

30 2-amino-7-(((2S,3R)-3,4-dihydroxy-1-(methylthio)butan-2-ylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-(((2R,3R)-3,4-dihydroxy-2-(methylthiomethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-(((2S,3S)-3,4-dihydroxy-2-(methylthiomethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

35 2-amino-7-(((2R,3S)-3,4-dihydroxy-2-(methylthiomethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-(((2S,3R)-3,4-dihydroxy-2-(methylthiomethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-(((2R,3R)-3,4-dihydroxy-2-(methylthiomethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

5 7-(((2S,3S)-3,4-dihydroxy-2-(methylthiomethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

7-(((2R,3S)-3,4-dihydroxy-2-(methylthiomethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one; and

10 7-(((2S,3R)-3,4-dihydroxy-2-(methylthiomethyl)butylamino)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one.

(3R,4R)-1-[(9-deazahypoxanthin-9-yl)methyl]-3-hydroxy-4-(hydroxymethyl)pyrrolidine;

(3S,4R)-1-[(9-deazahypoxanthin-9-yl)methyl]-3,4-dihydroxy-4-methylthiomethylpyrrolidine;

(3S,4S)-1-[(9-deazahypoxanthin-9-yl)methyl]-3,4-dihydroxy-4-hydroxymethylpyrrolidine;

15 (3R,4S)-1-[(9-deazahypoxanthin-9-yl)methyl]-3-hydroxy-4-(methylthiomethyl)pyrrolidine;

N-(9-deazahypoxanthin-9-yl)methyl-1,4-dideoxy-1,4-imino-D-ribitol;

(3R,4R)-3-hydroxy-4-hydroxymethyl-1-(hypoxanthin-9-yl)pyrrolidine;

(3S,4S)-1-[(9-deazahypoxanthin-9-yl)methyl]-3-hydroxy-4-methyl-pyrrolidine;

(3R,4R)-1-[(9-deazaguanin-9-yl)methyl]-3-hydroxy-4-(hydroxymethyl)pyrrolidine;

20 (3S,4S)-1-[(9-deazahypoxanthin-9-yl)methyl]-3-hydroxy-4-methyl-pyrrolidine;

(3S,4S)-1-[(9-deaza-8-fluoro-hypoxanthin-9-yl)methyl]-3-hydroxy-4-(hydroxymethyl)-pyrrolidine;

(3S,4S)-1-[(9-deazaguanin-9-yl)methyl]-3-hydroxy-4-methyl-pyrrolidine;

(3R,4R)-1-[(8-aza-9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(hydroxymethyl)pyrrolidine;

25 (3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(2-phenylethyl)pyrrolidine;

(3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(benzylthiomethyl)pyrrolidine;

(3R,4S)-1-[(8-aza-9-deazaadenin-9-yl)methyl]-3-hydroxy-4-

(benzylthiomethyl)pyrrolidine;

(3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(4-

30 chlorophenylthiomethyl)pyrrolidine;

(3R,4R)-1-[(9-deazaadenin-9-yl)methyl]-3-acetoxy-4-(acetoxymethyl)pyrrolidine;

(3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(*n*-butylthiomethyl)pyrrolidine;

(3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(4-

fluorophenylthiomethyl)pyrrolidine;

35 (3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(*n*-propylthiomethyl)pyrrolidine;

(3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(cyclohexylthiomethyl)pyrrolidine;

(3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(3-chlorophenylthiomethyl)pyrrolidine;
 (3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(ethylthiomethyl)pyrrolidine;
 (3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(phenylthiomethyl)pyrrolidine;
 5 (3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(4-pyridylthiomethyl)pyrrolidine;
 (3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-*n*-propylpyrrolidine;
 (3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(homocysteinylmethyl)pyrrolidine;
 (3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(benzyloxymethyl)pyrrolidine;
 (3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(*i*-propylthiomethyl)pyrrolidine;
 10 (3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(methoxymethyl)pyrrolidine;
 (3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(cyclohexylmethylthiomethyl)pyrrolidine;
 (3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(cycloheptylthiomethyl)pyrrolidine;
 (3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(cyclopentylthiomethyl)pyrrolidine;
 15 and
 (3R,4S)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxy-4-(cyclobutylthiomethyl)pyrrolidine;
 2-amino-7-((3,4-dihydroxy-1-(methylthio)butan-2-ylamino)methyl)-4-amino-5H-pyrrolo[3,2-d]pyrimidine;
 7-((3,4-dihydroxy-1-(methylthio)butan-2-ylamino)methyl)-4-amino-5H-pyrrolo[3,2-
 20 d]pyrimidine;
 2-amino-7-(((2-hydroxy-4-(methylthio)butyl)(methyl)amino)methyl)-4-amino-5H-pyrrolo[3,2-d]pyrimidine;
 7-(((2-hydroxy-4-(methylthio)butyl)(methyl)amino)methyl)-4-amino-5H-pyrrolo[3,2-d]pyrimidine;
 25 2-amino-7-((2-hydroxy-4-(methylthio)butylamino)methyl)-4-amino-5H-pyrrolo[3,2-d]pyrimidine;
 7-((2-hydroxy-4-(methylthio)butylamino)methyl)-4-amino-5H-pyrrolo[3,2-d]pyrimidine;
 2-amino-7-((3,4-dihydroxy-2-(methylthiomethyl)butylamino)methyl)-4-amino-5H-pyrrolo[3,2-d]pyrimidine;
 30 7-((3,4-dihydroxy-2-(methylthiomethyl)butylamino)methyl)-4-amino-5H-pyrrolo[3,2-d]pyrimidine;
 2-amino-7-((3-hydroxy-2-(methylthiomethyl)propylamino)methyl)-4-amino-5H-pyrrolo[3,2-d]pyrimidine;
 35 7-((3-hydroxy-2-(methylthiomethyl)propylamino)methyl)-4-amino-5H-pyrrolo[3,2-d]pyrimidine;

7-(((3-hydroxy-2-(methylthiomethyl)propyl)(methyl)amino)methyl)- 4-amino-5H-pyrrolo[3,2-d]pyrimidine;

2-amino-7-(((3-hydroxy-2-(methylthiomethyl)propyl)(methyl)amino)methyl)- 4-amino-5H-pyrrolo[3,2-d]pyrimidine.;

2-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino)-2-(methylthiomethyl)propane-1,3-diol;

(S)-1-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino)-3-(methylthio)propan-2-ol;

(R)-4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino)-3-(methylthio)propan-2-ol;

(2R,3S)-4-[(4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino]-3-

(methylthiomethyl)butane-1,2-diol;

(2S,3S)-4-[(4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino]-3-

(methylthiomethyl)butane-1,2-diol;

(2R,3S)-4-[(4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino]-3-

(methylthiomethyl)butane-1,2-diol;

(2R,3S)-4-[(4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino]-3-

(methylthiomethyl)butane-1,2-diol;

(2R,3R)-4-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)(methyl)amino)-3-

(methylthiomethyl)butane-1,2-diol;

(2S,3S)-4-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)(methyl)amino)-3-

(methylthiomethyl)butane-1,2-diol;

(2R,3S)-4-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)(methyl)amino)-3-

(methylthiomethyl)butane-1,2-diol;

(2S,3R)-4-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)(methyl)amino)-3-

(methylthiomethyl)butane-1,2-diol;

(2R,3R)-2-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino)-4-(methylthio)butane-1,3-diol;

(2S,3S)-2-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino)-4-(methylthio)butane-1,3-diol;

(2R,3S)-2-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino)-4-(methylthio)butane-1,3-diol;

(2S,3R)-2-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino)-4-(methylthio)butane-1,3-diol;

(2R,3R)-2-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)(methyl)amino)-4-(methylthio)butane-1,3-diol;

(2S,3S)-2-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)(methyl)amino)-4-(methylthio)butane-1,3-diol;

- (2R,3S)-2-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)(methyl)amino)-4-(methylthio)butane-1,3-diol;
- (2S,3R)-2-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)(methyl)amino)-4-(methylthio)butane-1,3-diol;
- 5 (2R,3R)-2-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino)methyl)-4-(methylthio)butane-1,3-diol;
- (2S,3S)-2-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino)methyl)-4-(methylthio)butane-1,3-diol;
- (2R,3S)-2-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino)methyl)-4-
- 10 (methylthio)butane-1,3-diol;
- (2S,3R)-2-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methylamino)methyl)-4-(methylthio)butane-1,3-diol;
- (2R,3R)-1-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)(methyl)amino)-4-(methylthio)butane-2,3-diol;
- 15 (2S,3S)-1-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)(methyl)amino)-4-(methylthio)butane-2,3-diol;
- (2R,3S)-1-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)(methyl)amino)-4-(methylthio)butane-2,3-diol;
- (2S,3R)-1-(((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)(methyl)amino)-4-
- 20 (methylthio)butane-2,3-diol;
- (R)-2-((R)-1-(4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-2-hydroxyethylamino)-3-(methylthio)propan-1-ol;
- (S)-2-((S)-1-(4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-2-hydroxyethylamino)-3-(methylthio)propan-1-ol;
- 25 (R)-2-((S)-1-(4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-2-hydroxyethylamino)-3-(methylthio)propan-1-ol;
- (S)-2-((R)-1-(4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-2-hydroxyethylamino)-3-(methylthio)propan-1-ol;
- meso*-7-((2,4-*cis*-2,4-bis(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-
- 30 4(5H)-one;
- (±) 7-((2,4-*trans*-2,4-bis(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
- (+) 7-((2,4-*trans*-2,4-bis(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
- 35 (-) 7-((2,4-*trans*-2,4-bis(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

- 7-((3,3-bis(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
(±) 7-((2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
7-(((2*R*)-2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
7-(((2*S*)-2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
5 7-((3-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
7-((3-hydroxy-3-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
(±) 7-((2,3-*cis*-3-hydroxy-2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
10 (+) 7-((2,3-*cis*-3-hydroxy-2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
(-) 7-((2,3-*cis*-3-hydroxy-2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
(±) 7-((2,3-*trans*-3-hydroxy-2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
15 (+) 7-((2,3-*trans*-3-hydroxy-2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
(-) 7-((2,3-*trans*-3-hydroxy-2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
20 *meso*-2-amino-7-((2,4-*cis*-2,4-bis(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
(±) 2-amino-7-((2,4-*trans*-2,4-bis(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
(+) 2-amino-7-((2,4-*trans*-2,4-bis(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
25 (-) 2-amino-7-((2,4-*trans*-2,4-bis(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
2-amino-7-((3,3-bis(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
30 (±) 2-amino-7-((2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
2-amino-7-(((2*R*)-2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
2-amino-7-(((2*S*)-2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;
35 4(5H)-one;

2-amino-7-((3-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

2-amino-7-((3-hydroxy-3-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

5 (±) 2-amino-7-((2,3-*trans*-3-hydroxy-2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(-) 2-amino-7-((2,3-*trans*-3-hydroxy-2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(+) 2-amino-7-((2,3-*trans*-3-hydroxy-2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

10 (±) 2-amino-7-((2,3-*cis*-3-hydroxy-2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(+) 2-amino-7-((2,3-*cis*-3-hydroxy-2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

15 (-) 2-amino-7-((2,3-*cis*-3-hydroxy-2-(hydroxymethyl)azetidin-1-yl)methyl)-3H-pyrrolo[3,2-d]pyrimidin-4(5H)-one;

(1-((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-3-(methylthiomethyl)azetidin-3-yl)methanol;

1-((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-3-(methylthiomethyl)azetidin-3-ol;

20 (±)-(2,4-*trans*-1-((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-4-(methylthiomethyl)azetidin-2-yl)methanol;

(+)-(2,4-*trans*-1-((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-4-(methylthiomethyl)azetidin-2-yl)methanol;

(-)-(2,4-*trans*-1-((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-4-(methylthiomethyl)azetidin-2-yl)methanol;

25 *meso*-(2,4-*cis*-1-((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-4-(methylthiomethyl)azetidin-2-yl)methanol;

7-(((2*RS*)-2-(methylthiomethyl)azetidin-1-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;

7-(((2*R*)-2-(methylthiomethyl)azetidin-1-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;

30 7-(((2*S*)-2-(methylthiomethyl)azetidin-1-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;

7-((3-(methylthiomethyl)azetidin-1-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;

(±) 2,3-*trans*-1-((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-2-(methylthiomethyl)azetidin-3-ol;

(+) 2,3-*trans*-1-((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-2-(methylthiomethyl)azetidin-3-ol;

(-) 2,3-*trans*-1-((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-2-(methylthiomethyl)azetidin-3-ol;

(±) 2,3-*cis*-1-((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-2-(methylthiomethyl)azetidin-3-ol;

5 (+) 2,3-*cis*-1-((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-2-(methylthiomethyl)azetidin-3-ol; and

(-) 2,3-*cis*-1-((4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)-2-(methylthiomethyl)azetidin-3-ol.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/NZ2008/000348

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.

C07D 487/04 (2006.01)

C07D 471/04 (2006.01)

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)

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

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

STN (Registry, CAPlus): Substructure search based upon formula I. Google search based upon keywords such as 9-hydroxymethyl, purine, oxidation, aldehyde, dess-martin, hydroxymethylation, formaldehyde, (mesyl or tosyl), nucleophilic, amine

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO2004/018496 A1 (ALBERT EINSTEIN COLLEGE OF MEDICINE OF YESHIVA UNIVERSITY & INDUSTRIAL RESEARCH LIMITED) 4 th March 2004. The whole document, in particular schemes 3 and 5	1-15
Y	Čapek, P. <i>et al</i> "A Facile Synthesis of 9-Deaza Analogue of Olomoucine", Collect. Czech. Chem. Commun., 2003, Vol. 68, No. 4, Pages 779-791. ISSN: 0010-0765 Scheme 1 (step vii) and compound 11 on page 781	1-15
Y	Hocek, M., <u>Title Unknown</u> , DSc Thesis, Academy of Sciences of the Czech Republic (published on 16 th November 2006). Retrieved from the Internet on 28 th May 2009: <URL: http://www.avcr.cz/data/vzdelavani/dsc/udeleni/hocek_teze_dsc.pdf >. Scheme 7 on page 11	1-15
Y	Biamonte, M. A. <i>et al</i> "Orally Active Purine-Based Inhibitors of Heat Shock Protein 90", J. Med. Chem., 2006, Vol. 49, No. 2, Pages 817-828. ISSN: 0022-2623 Scheme 4, route A (step c) on page 820	1-15



Further documents are listed in the continuation of Box C



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	"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	
"E" earlier application or patent but published on or after the international filing date	"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	
"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)	"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	
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family	
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
01 June 2009

Date of mailing of the international search report

09 JUN 2009

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/NZ2008/000348

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member	
WO 2004/018496	AU 2003258911	BR 0313664	CA 2496698
	CN 1692120	EP 1539783	HK 1085219
	KR 20050093756	NZ 538368	RU 2005107714
	US 2006160765		

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX