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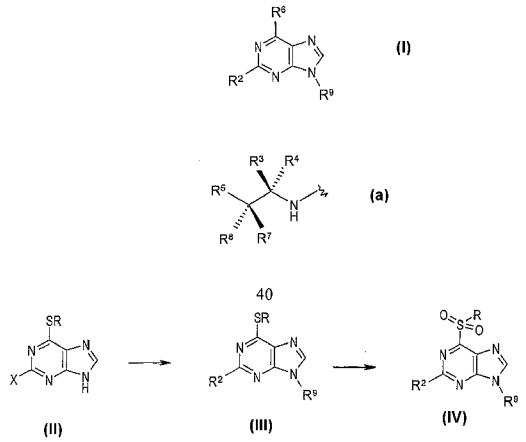
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(54) Title: PROCESS



(57) **Abstract:** The present invention relates to a process for preparing a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^2 is (a) where R^3, R^4, R^7 and R^8 are each independently selected from H, alkyl, aryl and aralkyl, said alkyl, aryl and aralkyl groups each being optionally substituted with one or more R^{12} groups, and wherein at least one of R^3, R^4, R^7 and R^8 is other than H; R^5 is OH, O-alkyl, NH_2, H, alkyl, aryl or aralkyl, said alkyl, aryl and aralkyl groups each being optionally substituted with one or more R^{12} groups; R^6 is $NR^{10}R^{11}$, wherein R^{10} and R^{11} are each independently H or hydrocarbyl; R^9 is hydrocarbyl; and each R^{12} is independently selected from OR^{13}, halo, alkyl, $COOR^{14}$, $CONR^{15}R^{16}$, $SO_2NR^{17}R^{18}$, NO_2, CN, $NR^{19}R^{20}SR^{21}$ and CF_3, where $R^{13\text{-}21}$ are each independently H, alkyl or aryl; said process comprising the steps of (II) (III) (IV) (i) converting a compound of formula (II) to a compound of formula (III), wherein X is halo and R is aryl, alkyl, cycloalkyl, aralkyl, heteroaryl or alkyl-heteroaryl; (ii) converting said compound of formula (III) to a compound of formula (IV); and (iii) converting said compound of formula (IV) to a compound of formula (I).

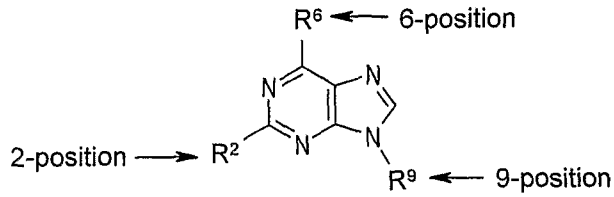
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PROCESS

The present invention relates to a new process for preparing substituted purine derivatives. More specifically, the process of the invention relates to the synthesis of 2,6,9-trisubstituted purines which are useful in the treatment of proliferative disorders such as cancer, leukemia, psoriasis and the like.

BACKGROUND

2,6,9-Trisubstituted purine derivatives are known to have antiproliferative and other therapeutic properties by virtue of their ability to inhibit protein kinases, in particular, cyclin dependent kinases.



2,6,9-trisubstituted purine

Initiation, progression, and completion of the mammalian cell cycle are regulated by various cyclin-dependent kinase (CDK) complexes, which are critical for cell growth. These complexes comprise at least a catalytic (the CDK itself) and a regulatory (cyclin) subunit. Some of the more important complexes for cell cycle regulation include cyclin A (CDK1 – also known as cdc2, and CDK2), cyclin B1-B3 (CDK1), cyclin D1-D3 (CDK2, CDK4, CDK5, CDK6), cyclin E (CDK2). Each of these complexes is involved in a particular phase of the cell cycle. Not all members of the CDK family are involved exclusively in cell cycle control, however. Thus, CDKs 7, 8, and 9 are implicated in the regulation of transcription, and CDK5 plays a role in neuronal and secretory cell function.

The activity of CDKs is regulated post-translationally, by transitory associations with other proteins, and by alterations of their intracellular localisation. Tumour development is closely associated with genetic alteration and deregulation of CDKs and their regulators, suggesting that inhibitors of CDKs may be useful anti-cancer

therapeutics. Indeed, early results suggest that transformed and normal cells differ in their requirement for e.g. cyclin A/CDK2 and that it may be possible to develop novel antineoplastic agents devoid of the general host toxicity observed with conventional cytotoxic and cytostatic drugs. While inhibition of cell cycle-related CDKs is clearly relevant in e.g. oncology applications, this may not be the case for the inhibition of RNA polymerase-regulating CDKs. On the other hand, inhibition of CDK9/cyclin T function was recently linked to prevention of HIV replication and the discovery of new CDK biology thus continues to open up new therapeutic indications for CDK inhibitors (Sausville, E.A. Trends Molec. Med. 2002, 8,S32-S37).

The function of CDKs is to phosphorylate and thus activate or deactivate certain proteins, including e.g. retinoblastoma proteins, lamins, histone H1, and components of the mitotic spindle. The catalytic step mediated by CDKs involves a phospho-transfer reaction from ATP to the macromolecular enzyme substrate. Several groups of compounds (reviewed in e.g. Fischer, P.M. Curr. Opin. Drug Discovery Dev. 2001, 4, 623-634) have been found to possess anti-proliferative properties by virtue of CDK-specific ATP antagonism.

By way of example, WO 98/05335 (CV Therapeutics Inc) discloses 2,6,9-trisubstituted purine derivatives that are selective inhibitors of cell cycle kinases. Such compounds are useful in the treatment of autoimmune disorders, e.g. rheumatoid arthritis, lupus, type I diabetes, multiple sclerosis, treating cancer, cardiovascular disease, such as restenosis, host v graft disease, gout, polycystic kidney disease and other proliferative diseases whose pathogenesis involves abnormal cell proliferation.

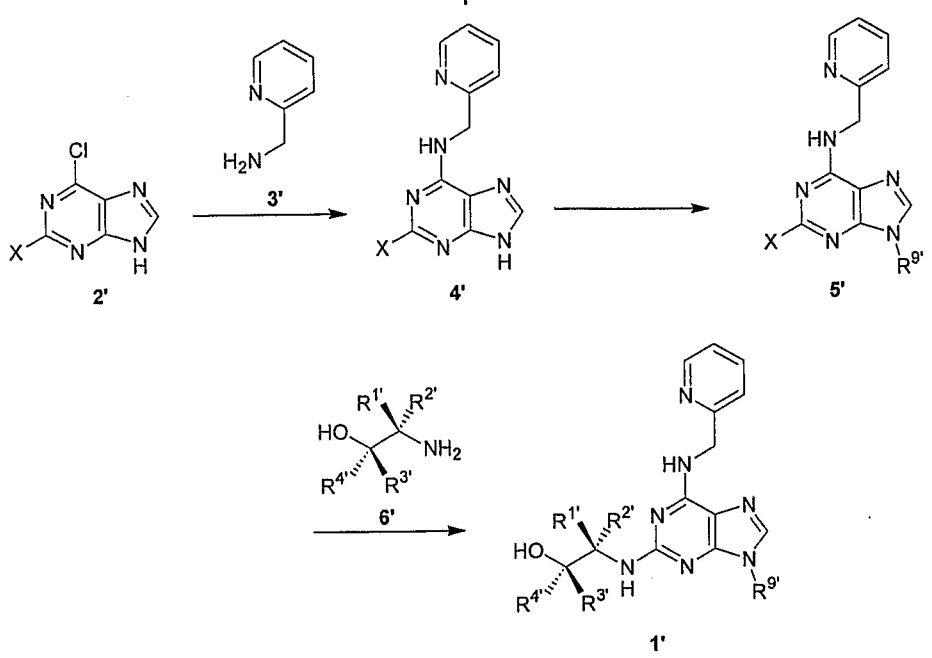
WO 99/07705 (The Regents of the University of California) discloses purine analogues that inhibit inter alia protein kinases, G-proteins and polymerases. More specifically, WO 99/07705 relates to methods of using such purine analogues to treat cellular proliferative disorders and neurodegenerative diseases.

WO 97/20842 (CNRS) also discloses purine derivatives displaying antiproliferative properties which are useful in treating cancer, psoriasis, and neurodegenerative

disorders. WO 03/002565 (Cyclacel Limited) discloses similar such derivatives, whereas WO 04/016613 and WO 04/016612 (also in the name of Cyclacel Limited), disclose purine derivatives substituted in the 6-position by a pyridinylmethylamino group.

To date, prior art methods of preparing 2,6,9-trisubstituted purines typically involve introducing the 6-substituent, followed by the 9-substituent, and finally the 2-substituent. By way of example, WO 97/20842 describes the synthesis of roscovitine by preparing 6-benzylamino-2-chloropurine and subsequently converting to 6-benzylamino-2-chloro-9-isopropylpurine by treatment with isopropyl bromide/potassium carbonate in DMSO. The 6-benzylamino-2-chloro-9-isopropylpurine is then treated with R(-)-2-amino-1-butanol to form 6-benzylamino-2-R-(1-ethyl-2-hydroxyethylamino)-9-isopropylpurine in racemic form.

Likewise, WO 04/016613 and WO 04/016612 disclose the synthesis of 2,6,9-trisubstituted purines in which the 6-substitutuent is a pyridinylmethylamino group. By way of example, compounds of general structure **1'** can be prepared by the synthetic route shown below in Scheme 1, starting with commercially available 2,6-dichloropurine (**2'**, X = Cl) or 2-amino-6-chloropurine (**2'**, X = NH_2). In the latter case, the amino group is transformed to provide the particularly suitable 6-chloro-2-fluoro-purine starting material (**2'**, X = F; Gray, N. S., Kwon, S., and Schultz, P. G. *Tetrahedron Lett.* 1997, 38, 1161-1164.). Selective amination at the more reactive C-6 position with the appropriate pyridylmethylamine **3'** then affords intermediate **4'**. This is alkylated at the N-9 position, e.g. by nucleophilic substitution using the appropriate alkyl halide $R^{9'}$-X. Intermediate **5'** is finally aminated with an aminoalcohol **6'** at elevated temperature to form the desired 2,6,9-trisubstituted purine.



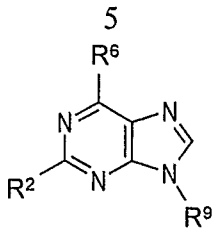
Scheme 1

The above-described prior art methods are however often associated with poor yields and difficult purification steps, particularly where the 2-substituent contains one or more chiral centres. Moreover, the prior art methods usually require the use of a large excess of aminoalcohol **6'**, in order to introduce the 2-substituent.

The present invention therefore seeks to provide an alternative synthetic route for preparing 2,6,9-trisubstituted purines. More preferably, the invention seeks to alleviate one or more of the problems associated with prior art synthetic routes, and in particular, seeks to provide a process which enables easier purification (i.e. cleaner reactions), and/or the use of reduced amounts of reagents, and/or improved yields.

STATEMENT OF INVENTION

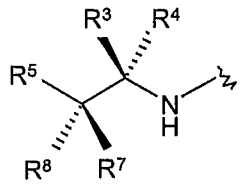
A first aspect of the invention relates to a process for preparing a compound of formula I, or a pharmaceutically acceptable salt thereof,



I

wherein

R^2 is



where

R^3, R^4, R^7 and R^8 are each independently selected from H, alkyl, aryl and aralkyl, said alkyl, aryl and aralkyl groups each being optionally substituted with one or more R^{12} groups, and wherein at least one of R^3, R^4, R^7 and R^8 is other than H;

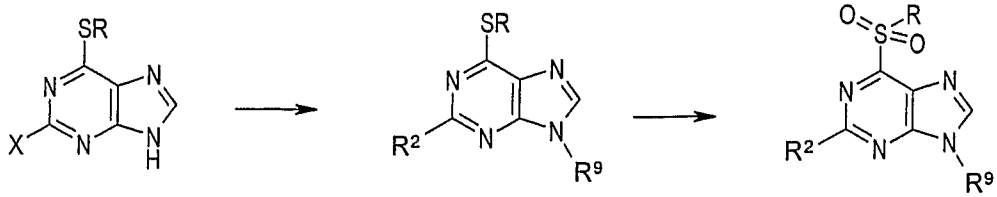
R^5 is OH, O-alkyl, H, alkyl, aryl or aralkyl, said alkyl, aryl and aralkyl groups each being optionally substituted with one or more R^{12} groups;

R^6 is $NR^{10}R^{11}$, wherein R^{10} and R^{11} are each independently H or hydrocarbyl;

R^9 is hydrocarbyl; and

each R^{12} is independently selected from OR^{13}, halo, alkyl, $COOR^{14}$, $CONR^{15}R^{16}$, $SO_2NR^{17}R^{18}$, NO_2, CN, $NR^{19}R^{20}SR^{21}$ and CF_3, where $R^{13\text{-}20}$ are each independently H, alkyl or aryl;

said process comprising the steps of:



II III IV

(i) converting a compound of formula II to a compound of formula III, wherein X is halo and R is aryl, alkyl, cycloalkyl, aralkyl, heteroaryl or alkyl-heteroaryl;

(ii) converting said compound of formula III to a compound of formula IV; and

(iii) converting said compound of formula IV to a compound of formula I.

A second aspect of the invention relates to the use of a process as set forth above in the preparation of a 2,6,9-trisubstituted purine.

A third aspect of the invention relates to the use of a process as set forth above in the preparation of a CDK inhibitor.

Advantageously, the process of the present invention enables the synthesis of 2,6,9-trisubstituted purine derivatives in high yields. One particular advantage is that the inventive process allows for the use of reduced amounts of reagent in the amination step, i.e. in the introduction of the R^2 substituent. Overall, the reaction is cleaner, higher yielding, requires less amine and can be performed under milder conditions.

Moreover, the SR group introduced in the 6-position is subsequently activated by oxidation to form the corresponding SO_2R derivative. The SO_2R group is a labile leaving group that can readily be replaced by the desired R^6 group (NHR^8) in the final step of the process.

DETAILED DESCRIPTION

As used herein, the term "hydrocarbyl" refers to a group comprising at least carbon and hydrogen. If the hydrocarbyl group comprises more than one carbon then those carbons need not necessarily be linked to each other. For example, at least two of the carbons may be linked *via* a suitable element or group. Thus, the hydrocarbyl group may contain heteroatoms. Suitable heteroatoms will be apparent to those skilled in the art and include, for instance, sulphur, nitrogen, oxygen, phosphorus and silicon. Where the hydrocarbyl group contains one or more heteroatoms, the group may be linked via a carbon atom or via a heteroatom to another group, i.e. the linker atom may be a carbon or a heteroatom. Preferably, the hydrocarbyl group is an aryl, heteroaryl, alkyl, cycloalkyl, aralkyl, heterocycloalkyl, or alkenyl group. More preferably, the hydrocarbyl group is an aryl, heteroaryl, alkyl, cycloalkyl, aralkyl or alkenyl group.

The hydrocarbyl group may be optionally substituted by one or more R^{12} groups, where each R^{12} is independently selected from OR^{13}, halo, alkyl, $COOR^{14}$, $CONR^{15}R^{16}$, $SO_2NR^{17}R^{18}$, NO_2, CN, $NR^{19}R^{20}SR^{21}$ and CF_3, where R^{13-21} are each independently H, alkyl or aryl.

As used herein, the term "alkyl" includes both saturated straight chain and branched alkyl groups which may be substituted (mono- or poly-) or unsubstituted. Preferably, the alkyl group is a C_{1-20} alkyl group, more preferably a C_{1-15}, more preferably still a C_{1-12} alkyl group, more preferably still, a C_{1-6} alkyl group, more preferably a C_{1-3} alkyl group. Particularly preferred alkyl groups include, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl and hexyl. Suitable substituents include, for example, one or more R^{12} groups as defined above. Preferably, the alkyl group is unsubstituted.

As used herein, the term "alkenyl" refers to a group containing one or more carbon-carbon double bonds, which may be branched or unbranched, substituted (mono- or poly-) or unsubstituted. Preferably the alkenyl group is a C_{2-20} alkenyl group, more preferably a C_{2-15} alkenyl group, more preferably still a C_{2-12} alkenyl group, or preferably a C_{2-6} alkenyl group, more preferably a C_{2-3} alkenyl group. Suitable substituents include, for example, one or more R^{12} groups as defined abovc.

As used herein, the term "aryl" refers to a C_{6-12} aromatic group which may be substituted (mono- or poly-) or unsubstituted. Typical examples include phenyl and naphthyl etc. Suitable substituents include, for example, one or more R^{12} groups as defined above.

As used herein, the term "heteroaryl" refers to a C_{2-12} aromatic, substituted (mono- or poly-) or unsubstituted group, which comprises one or more heteroatoms. Preferably, the heteroaryl group is a C_{4-12} aromatic group comprising one or more heteroatoms selected from N, O and S. Suitable heteroaryl groups include pyrrole, pyrazole, pyrimidine, pyrazine, pyridine, quinoline, thiophene, 1,2,3-triazole, 1,2,4-triazole,

thiazole, oxazole, iso-thiazole, iso-oxazole, imidazole, furan and the like. Again, suitable substituents include, for example, one or more R^{12} groups as defined above.

As used herein, the term "cycloalkyl" refers to a cyclic alkyl group which may be substituted (mono- or poly-) or unsubstituted. Preferably, the cycloalkyl group is a C_{3-12} cycloalkyl group. Suitable substituents include, for example, one or more R^{12} groups as defined above.

As used herein, the term "aralkyl" refers to a group having both aryl and alkyl functionalities. By way of example, the term includes groups in which one of the hydrogen atoms of the alkyl group is replaced by an aryl group, e.g. a phenyl group optionally having one or more R^{12} substituents, such as halo, alkyl, alkoxy, hydroxy, and the like. Preferred aralkyl groups include benzyl, phenethyl and the like.

Likewise, the term "alkyl-heteroaryl" refers to a group having both heteroaryl and alkyl functionalities. By way of example, the term includes groups in which one of the hydrogen atoms of the alkyl group is replaced by a heteroaryl group, e.g. a pyridinyl group optionally having one or more R^{12} substituents, such as halo, alkyl, alkoxy, hydroxy, and the like. Preferred alkyl-heteroaryl groups include CH_2-pyridinyl and the like.

In one preferred embodiment, one of R^3 and R^4 is alkyl, aryl or aralkyl, and the other is H.

In another preferred embodiment, one of R^7 and R^8 is alkyl, aryl or aralkyl, and the other is H.

In another preferred embodiment, one of R^3 and R^4 is alkyl, and the other is H.

In another preferred embodiment, one of R^7 and R^8 is alkyl, and the other is H.

In another preferred embodiment, one of R^3 and R^4 is methyl, ethyl or isopropyl, and the other is H.

In a more preferred embodiment,
one of R^3 and R^4 is alkyl, and the other is H; and
one of R^7 and R^8 is alkyl, and the other is H.

In an even more preferred embodiment,
one of R^3 and R^4 is H and the other is methyl, ethyl or iso-propyl;
one of R^7 and R^8 is H, and the other is methyl, ethyl, iso-propyl or tert-butyl.

In one preferred embodiment of the invention, R^5 is OH.

In one especially preferred embodiment, R^3 is ethyl, R^4 is H, R^5 is OH and R^7 and R^8 are both H.

In one preferred embodiment, R^9 is alkyl or cycloalkyl, each of which may be optionally substituted by one or more R^{12} groups.

In one highly preferred embodiment, R^9 is isopropyl or cyclopentyl.

In one highly preferred embodiment, R^{10} is H.

In one preferred embodiment, R^{11} is aryl, heteroaryl, aralkyl, alkyl-heteroaryl, alkyl, alkenyl or cycloalkyl, each of which may be optionally substituted with one or more R^{12} groups.

In a preferred embodiment, R^{11} is aryl, aralkyl, heteroaryl or alkyl-heteroaryl, each of which may be optionally substituted with one or more R^{12} groups.

More preferably, R^{11} is phenyl, benzyl, pyridinyl or CH_2-pyridinyl, each of which may be optionally substituted with one or more R^{12} groups.

In one particularly preferred embodiment, each R^{12} is independently selected from OH, alkoxy, halo, alkyl, COOH, COOMe, $CONH_2$, SO_2NH_2, NO_2, CN, NHMe, NH_2, NMe and CF_3.

Even more preferably, R^{11} is selected from phenyl, benzyl, CH_2-pyridin-2-yl, CH_2-pyridin-3-yl and CH_2-pyridin-4-yl, each of which may be optionally substituted by one or more halo, OH, OMe and/or NO_2 groups.

The process of the present invention is suitable for preparing a wide range of substituted purine derivatives. By way of example, the process is suitable for preparing substituted purines such as those described in WO 97/20842 (CNRS), and WO 03/002565, WO 04/016613 and WO 04/016612 (all in the name of Cyclacel Limited), the teachings of which are hereby incorporated by reference.

In one especially preferred embodiment of the invention, the process of the invention is suitable for preparing compounds of formula I selected from the following:

(2*S*3*R*)-3-{9-Isopropyl-6-[(pyridin-2-ylmethyl)-amino]-9H-purin-2-ylamino}-pentan-2-ol;

(2*R*3*S*)-3-{9-Isopropyl-6-[(pyridin-2-ylmethyl)-amino]-9H-purin-2-ylamino}-pentan-2-ol;

(3*RS*,4*R*)-4-{9-Isopropyl-6-[(pyridin-2-ylmethyl)-amino]-9H-purin-2-ylamino}-hexan-3-ol;

(3*RS*,4*S*)-4-{9-Isopropyl-6-[(pyridin-2-ylmethyl)-amino]-9H-purin-2-ylamino}-hexan-3-ol;

(3*RS*,4*R*)-4-{9-Isopropyl-6-[(pyridin-2-ylmethyl)-amino]-9H-purin-2-ylamino}-2-methyl-hexan-3-ol;

(3*RS*,4*S*)-4-{9-Isopropyl-6-[(pyridin-2-ylmethyl)-amino]-9H-purin-2-ylamino}-2-methyl-hexan-3-ol;

(3*RS*,4*R*)-4-{9-Isopropyl-6-[(pyridin-2-ylmethyl)-amino]-9H-purin-2-ylamino}-2,2-dimethyl-hexan-3-ol;

(3*RS*,4*S*)-4-{9-Isopropyl-6-[(pyridin-2-ylmethyl)-amino]-9H-purin-2-ylamino}-2,2-dimethyl-hexan-3-ol;

(3*R*)-3-{9-Isopropyl-6-[(pyridin-2-ylmethyl)-amino]-9H-purin-2-ylamino}-2-methyl-pentan-2-ol;

(3*S*)-3-{9-Isopropyl-6-[(pyridin-2-ylmethyl)-amino]-9H-purin-2-ylamino}-2-methyl-pentan-2-ol;

(2*S*3*R*)-3-{9-Isopropyl-6-[(pyridin-3-ylmethyl)-amino]-9H-purin-2-ylamino}-pentan-2-ol;

(2*R*3*S*)-3-{9-Isopropyl-6-[(pyridin-3-ylmethyl)-amino]-9H-purin-2-ylamino}-pentan-2-ol;

(3*RS*,4*R*)-4-{9-Isopropyl-6-[(pyridin-3-ylmethyl)-amino]-9H-purin-2-ylamino}-hexan-3-ol;

(3*RS*,4*S*)-4-{9-Isopropyl-6-[(pyridin-3-ylmethyl)-amino]-9H-purin-2-ylamino}-hexan-3-ol;

(3*RS*,4*R*)-4-{9-Isopropyl-6-[(pyridin-3-ylmethyl)-amino]-9H-purin-2-ylamino}-2-methyl-hexan-3-ol;

(3*RS*,4S)-4-{9-Isopropyl-6-[(pyridin-3-ylmethyl)-amino]-9H-purin-2-ylamino}-2-methyl-hexan-3-ol;

(3*RS*,4*R*)-4-{9-Isopropyl-6-[(pyridin-3-ylmethyl)-amino]-9H-purin-2-ylamino}-2,2-dimethyl-hexan-3-ol;

(3*RS*,4*S*)-4-{9-Isopropyl-6-[(pyridin-3-ylmethyl)-amino]-9H-purin-2-ylamino}-2,2-dimethyl-hexan-3-ol;

(3*R*)-3-{9-Isopropyl-6-[(pyridin-3-ylmethyl)-amino]-9H-purin-2-ylamino}-2-methyl-pentan-2-ol;

(3*S*)-3-{9-Isopropyl-6-[(pyridin-3-ylmethyl)-amino]-9H-purin-2-ylamino}-2-methyl-pentan-2-ol;

(3S)-3-{9-Isopropyl-6-[(pyridin-3-ylmethyl)-amino]-9H-purin-2-ylamino}-2-methyl-pentan-2-ol; and

(3R)-3-{9-Isopropyl-6-[(pyridin-3-ylmethyl)-amino]-9H-purin-2-ylamino}-2-methyl-pentan-2-ol;

(2*RS*,3*R*)-3-(6-Benzylamino-9-isopropyl-9*H*-purin-2-ylamino)-pentan-2-ol;

R-2-{9-Isopropyl-6-[(pyridin-2-ylmethyl)-amino]-9H-purin-2-ylamino}-butan-1-ol;

R-2-{9-Isopropyl-6-[(pyridin-4-ylmethyl)-amino]-9H-purin-2-ylamino}-butan-1-ol;

(2*S*,3*R*)-3-(6-Benzylamino-9-isopropyl-9*H*-purin-2-ylamino)-pentan-2-ol;

(2*R*,3S)-3-(6-Benzylamino-9-isopropyl-9*H*-purin-2-ylamino)-pentan-2-ol;

(3*RS*,4*R*)-4-(6-Benzylamino-9-isopropyl-9*H*-purin-2-ylamino)-hexan-3-ol;

(3*RS*,4*S*)-4-(6-Benzylamino-9-isopropyl-9*H*-purin-2-ylamino)-hexan-3-ol;

(3*RS*,4*R*)-4-(6-Benzylamino-9-isopropyl-9*H*-purin-2-ylamino)-2-methyl-hexan-3-ol;

(3*RS*,4*S*)-4-(6-Benzylamino-9-isopropyl-9*H*-purin-2-ylamino)-2-methyl-hexan-3-ol;

(3*RS*,4*R*)-4-(6-Benzylamino-9-isopropyl-9*H*-purin-2-ylamino)-2,2-dimethyl-hexan-3-ol;

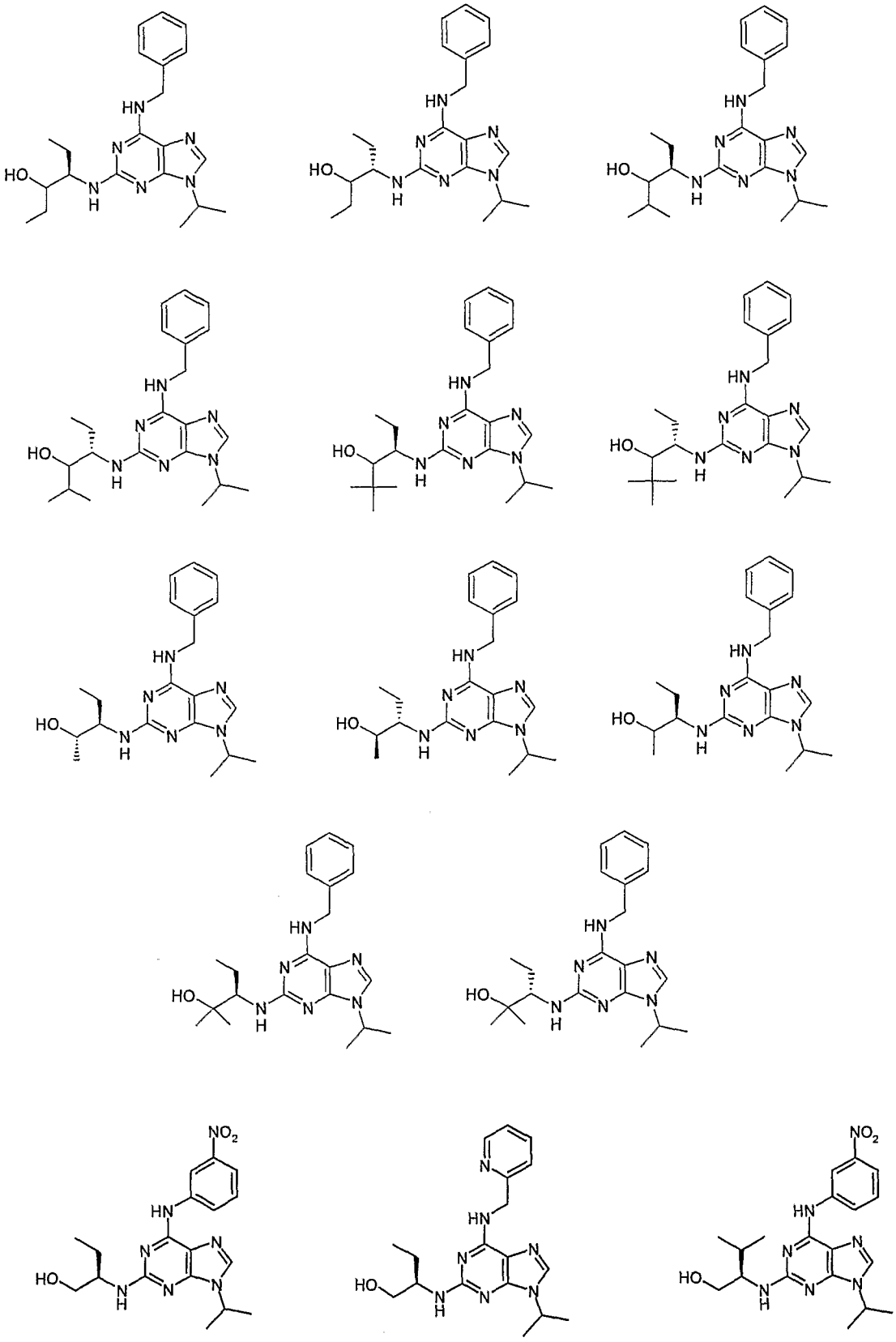
(3*RS*,4*S*)-4-(6-Benzylamino-9-isopropyl-9*H*-purin-2-ylamino)-2,2-dimethyl-hexan-3-ol;

(*R*)-3-(6-Benzylamino-9-isopropyl-9*H*-purin-2-ylamino)-2-methyl-pentan-2-ol;

(*S*)-3-(6-Benzylamino-9-isopropyl-9*H*-purin-2-ylamino)-2-methyl-pentan-2-ol;

and pharmaceutically acceptable salts thereof.

In another preferred embodiment of the invention, the process of the invention is suitable for preparing compounds of formula I selected from the following:



and pharmaceutically acceptable salts thereof.

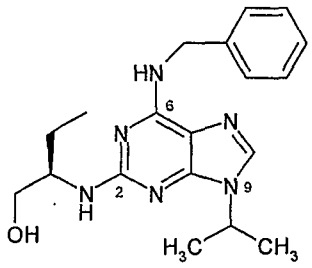
In one especially preferred embodiment of the invention, the compound of formula I is 2-(1-D,L-hydroxymethylpropylamino)-6-benzylamine-9-isopropylpurine, otherwise known as "roscovitine", or 2-[(1-ethyl-2-hydroxyethyl)amino]-6-benzylamine-9-isopropylpurine.

As used herein, the term "roscovitine" encompasses the resolved R and S enantiomers, mixtures thereof, and the racemate thereof.

Roscovitine has been shown to be a potent inhibitor of cyclin dependent kinase enzymes, particularly CDK2. CDK inhibitors are understood to block passage of cells from the G1/S and the G2/M phase of the cell cycle. The pure R-enantiomer of Roscovitine, "CYC202" (R-Roscovitine) has recently emerged as a potent inducer of apoptosis in a variety of tumour cells (McClue SJ, Blake D, Clarke R, et al. *In vitro* and *in vivo* antitumor properties of the cyclin dependent kinase inhibitor CYC202 (R-Roscovitine), Int J Cancer. 2002; 102: 463-468) and is already in clinical trials to treat breast cancer and non-small cell lung cancer (Fischer PM and Gianella-Borradori A.; CDK inhibitors in clinical development for the treatment of cancer; Expert Opin Investig Drugs, 2003; 12: 955-970). Roscovitine has also been shown to be an inhibitor of retinoblastoma phosphorylation and therefore implicated as acting more potently on Rb positive tumors.

More recently, it has now been observed that roscovitine has therapeutic applications in the treatment of certain proliferative disorders that have to date been particularly difficult to treat, for example, multiple myeloma, B-cell chronic lymphocytic leukemia (B-CLL) and mantle cell lymphoma (WO 2005/044275, WO 2005/002584 and WO 2005/044274, all in the name of Cyclacel Limited).

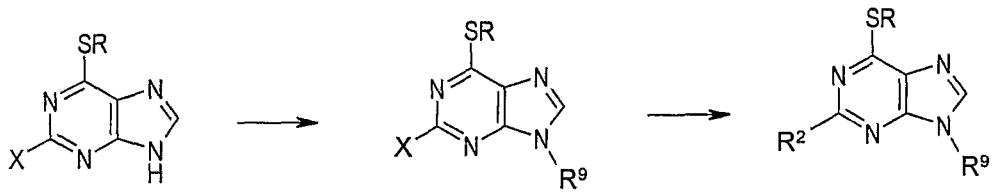
In one particularly preferred embodiment of the invention, the compound of formula I is the R enantiomer of roscovitine, namely 2-(1-R-hydroxymethylpropylamino)-6-benzylamino-9-isopropylpurine or "CYC202", the structure of which is shown below.



In one preferred embodiment, the process of the invention comprises the steps of:

(ia) converting said compound of formula II to a compound of formula IIa; and

(ib) converting said compound of formula IIa to a compound of formula III



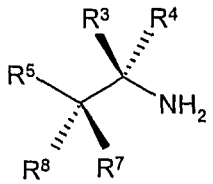
II IIa III

In a more preferred embodiment, step (ia) comprises treating said compound of formula II with R^9-OH, where R^9 is as defined above.

In an even more preferred embodiment, step (ia) comprises reacting said compound of formula II with R^9-OH in the presence of PPh_3 and diisopropyl azodicarboxylate (DIAD).

In one preferred embodiment, the solvent in step (ia) is THF.

In one preferred embodiment, step (ib) of the process comprises reacting said compound of formula IIa with an amine of formula VII,



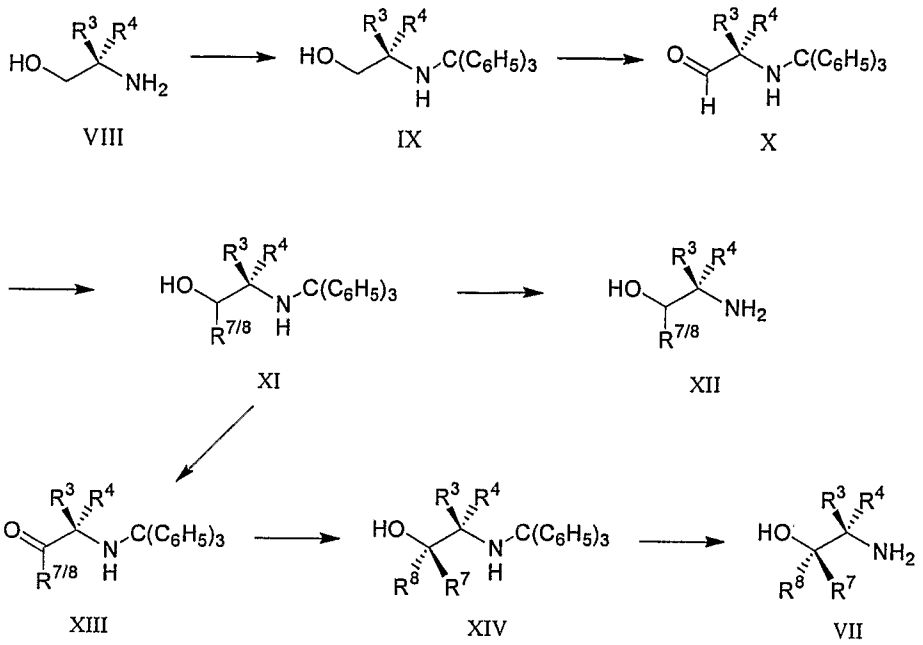
VII

Preferably, step (ib) is carried out in the presence of a tertiary amine and an alcohol.

Even more preferably, step (ib) is carried out in the presence of $^{n}Pr_3N$ and n-butanol.

In one particularly preferred embodiment, said compound of formula IIa, said amine of formula VIII, $^{n}Pr_3N$ and n-butanol are heated at reflux temperature.

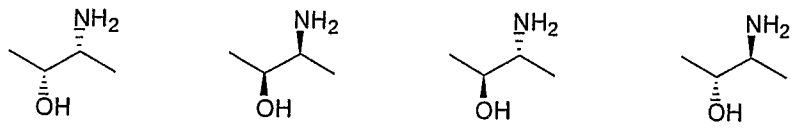
Substituted amino alcohols VII (R^3 or R^4 <> H) can be synthesized from α-amino alcohols VIII (R^3 or R^4 <> H) as shown in Scheme 2 below. Many of the latter are available commercially; alternatively, they can be prepared readily by reduction of the corresponding α-amino acids. The initial reaction in the synthetic methodology adopted was trityl protection of the amino function to afford intermediate IX (R^3 or R^4 <> H; Evans, P. A., Holmes, A. B., and Russell, K. *J. Chem. Soc., Perkin Trans. 1*, 1994, 3397-3409). This was subjected to Swern oxidation to the corresponding aldehyde X (R^3 or R^4 <> H; Takayama, H., Ichikawa, T., Kuwajima, T., Kitajima, M., Seki, H., Aimi, N., and Nonato, M. G. *J. Am. Chem. Soc.* 2000, 122, 8635-8639). Introduction of the substituent R^7 (if R^4 <> H) or R^8 (if R^3 <> H) was accomplished *via* chelation-controlled alkylation (Reetz, M. T., Roelfing, K., and Griebenow, N. *Tetrahedron Lett.* 1994, 35, 1969-1972) using the appropriate alkyllithium reagent and a copper bromide / dimethyl sulfide complex catalyst in diethyl ether. Depending on the substituent to be introduced, this procedure afforded intermediates XI in diastereomeric excess (*de*) of 50-80 %. Alternatively, achiral methods can be used, optionally followed by separation / resolution of the optical isomers. For production of amino alcohols where both R^7 and R^8 are other than H, intermediate XI was subjected to another Swern oxidation reaction to the respective ketone XIII, followed by introduction of the second substituent through alkylation. The final step in the synthesis for all the amino alcohols was removal of the trityl group using trifluoroacetic acid to afford VII or XII.



Scheme 2

In those cases where amino alcohols contain two identical substituents at the carbinol C (VII, R^3 or R^4 <> H; $R^7 = R^8$, not H), these can be obtained directly from a suitable corresponding α-amino acid ester, *e.g.* by double Grignard alkylation (Guenther, B. R., and Kirmse, W. *Liebigs Ann. Chem.* 1980, 518-532).

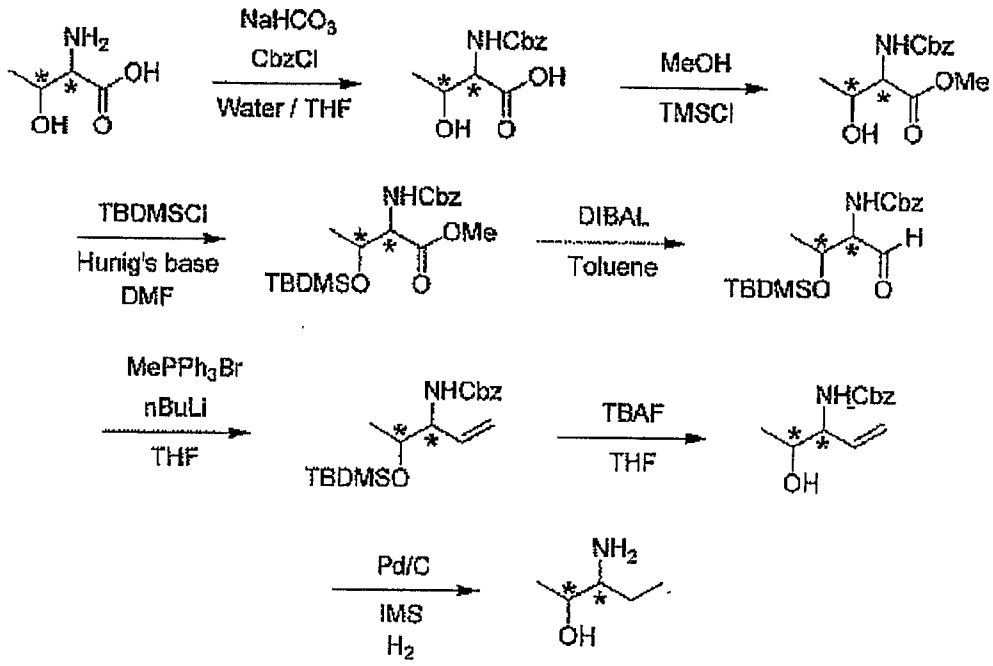
In one preferred embodiment of the invention, the amino alcohol of formula VII is 3-amino-pentan-2-ol, i.e. is an enantiomer selected from the following:



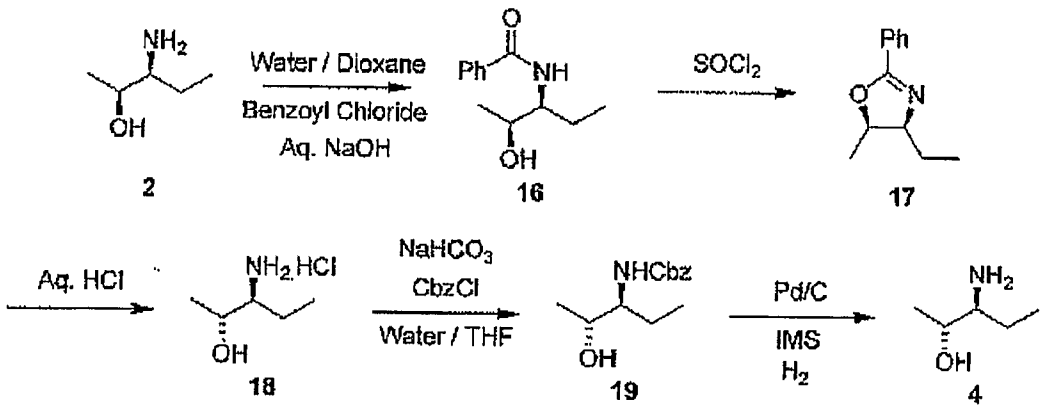
1a 2a 3a 4a

Development of the synthetic route to 3-amino-pentan-2-ol from threonine (Scheme 3) was carried out using L-threonine as this was the least expensive of the starting materials available. The L-threonine was also commercially available as the cbz protected methyl ester, which allowed quicker access to the more critical later stages of the synthesis. The synthesis of (2R,3R)-3-amino-pentan-2-ol I from cbz protected L-threonine methyl ester was successfully achieved without encountering any major

problems. The syntheses of (2S,3S)-3-amino-pentan-2-ol 2 and (2S,3R)-3-amino-pentan-2-ol **3** from D-threonine and L-allo-threonine respectively were then carried out after initial development of the cbz protection and methyl ester formation steps. The synthesis of (2R,3S)-3-amino-pentan-2-ol **4** was achieved by inversion of the stereocentre at position 2 (OH) of compound **2** (Scheme 4).

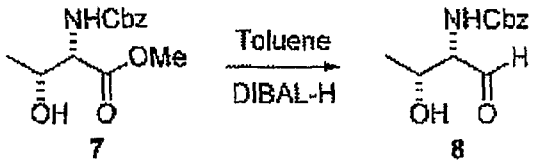


Scheme 3



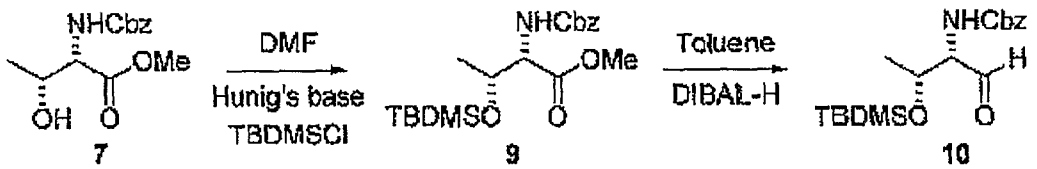
Scheme 4

It was thought that the DIBAL reduction of the commercially available Z--(L)-threonine methyl ester 7 without protection of the OH group would reduce the number of steps required and hence increase the overall yield of the synthesis.



Scheme 5

Attempts at the reduction only gave partial conversion to the desired product **8** (maximum conversion approximately 30%). This was thought to be partially due to complexation of DIBAL to the free OH of the starting material. Some elimination product was also evident in ^{1}H NMR spectra of the crude material obtained. It was therefore deemed necessary to protect the OH group before the synthesis could proceed. Benzyl protection of the OH group was unsuccessful giving only elimination products. TBDMS protection was more successful giving the desired product **9** in greater than quantitative yield due to an impurity which was inseparable by column chromatography.



Scheme 6

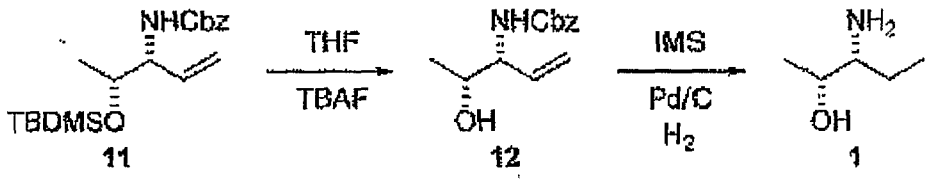
The subsequent DIBAL reduction furnished the aldehyde **10** in 46% yield over 2 steps after purification. This was improved to 62% upon scale-up. A small scale Wittig reaction gave complete conversion to the alkene **11** after 1 hour at room temperature. Purification by column chromatography gave the desired product in approximately 50% yield. However, the presence of a TBDMS impurity which was inseparable by column

chromatography was-noted in the ^{1}H NMR spectrum. The yield was improved to 64% upon scale-up.



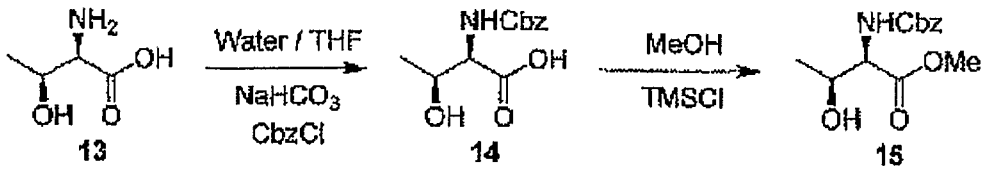
Scheme 7

A small scale deprotection of the OH group using TBAF was successful giving compound **12** in 55% yield after purification. The yield was again improved upon scale-up to 80%. Hydrogenation of compound **12** gave the desired aminoalcohol 1 in 85% yield. The product was found to be >95% pure by ^{1}H NMR spectroscopy. Chiral HPLC analysis of the product after trityl protection gave a chiral purity of 98.6%. A total of 0.53 g of (2R,3R)-3-amino-pentan-2-ol 1 is available for use.



Scheme 8

As D-threonine, L-allo-threonine and D-allo-threonine are not commercially available as the analogous cbz protected methyl esters, cbz protection of threonine and subsequent methyl ester formation were required. Cbz protection of D-threonine **13** was carried out using sodium bicarbonate and benzyl chloroformate in aqueous THF giving the desired product **14** in quantitative yield. ^{1}H NMR spectroscopy confirmed the crude product was of sufficient purity to use in the next stage without purification. Reaction of compound **14** with TMSCI in methanol gave the methyl ester **15** in 79% yield. Again, ^{1}H NMR spectroscopy confirmed the crude product was of sufficient purity to use in the next stage without purification.

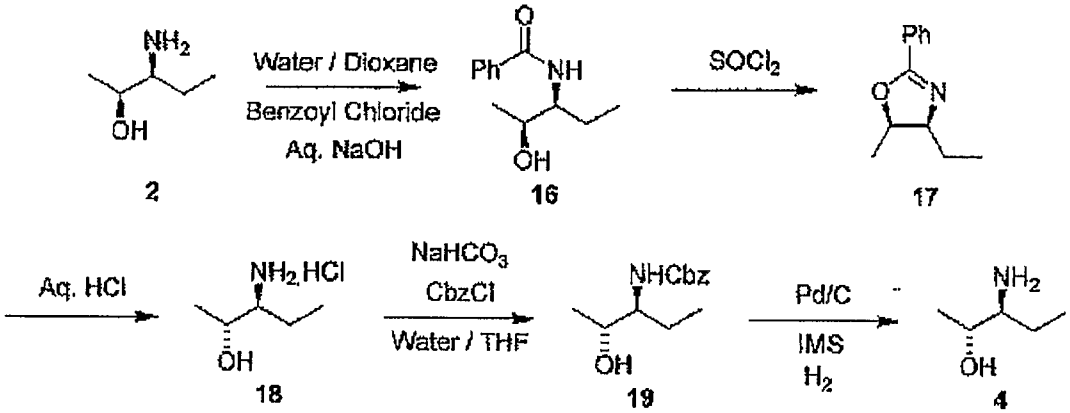


Scheme 9

The cbz protected threonine methyl ester **15** was successfully converted to (2S,3S)-3-amino-pentan-2-ol **2** using the methodology already developed. The product was found to be >95% pure by ^{1}H NMR spectroscopy. Chiral HPLC analysis of the product after trityl protection gave a chiral purity of 98.7%. A total of 2.5 g of (2S,3S)-3-amino-pentan-2-ol **2** is available for use.

(2S,3R)-3-Amino-pentan-2-ol **3** was synthesised from L-allo-threonine using the above methodology. The product was found to be >90% pure by ^{1}H NMR spectroscopy. Chiral HPLC analysis of the product after trityl protection gave a chiral purity of 93.7%. A total of 0.4 g of (2S,3R)-3-amino-pentan-2-ol **3** is available for use.

Due to the high cost of D-allo-threonine, an alternative route was devised for the synthesis of (2R,3S)-3-amino-pentan-2-ol **4**. This route relied on the complete inversion of the stereocenter at position 2 (OH) of compound **2**.



Scheme 10

Compound **2** was N-benzoyl protected using standard conditions. The crude product **16** was then treated with thionyl chloride to give the oxazoline 17 in 90% yield. Hydrolysis with aqueous HCl yielded the hydrochloride salt of (2R,3S)-3-amino-pentan-2-ol **18**. In order to isolate and purify the final product, the salt was cbz protected giving compound **19**. This was purified by column chromatography and then hydrogenated to give the desired (2R,3S)-3-amino-pentan-2-ol **4** in 35% yield over 3 steps. The product was found to be >90% pure by ^{1}H NMR spectroscopy. Chiral HPLC analysis of the product after trityl protection gave a chiral purity of 95.1%.

In one embodiment of the invention, step (ii) comprises treating said compound of formula III with potassium peroxymonosulfate, $KHSO_5$, to form said compound of formula IV.

In one particularly preferred embodiment, step (ii) comprises treating said compound of formula III with $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (Oxone®) to form said compound of formula IV.

The active ingredient of Oxone® is potassium peroxymonosulfate, $KHSO_5$ (CAS-RN *10058-23-8*), commonly known as potassium monopersulfate, which is present as a component of a triple salt with the formula $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (potassium hydrogen peroxymonosulfate sulfate (5:3:2:2), CAS-RN *70693-62-8;* commercially available from DuPont). The oxidation potential of Oxone® is derived from its peracid chemistry; it is the first neutralization salt of peroxymonosulfuric acid H_2SO_5 (also known as Caro's acid).

$K^+ {}^-O\text{-}S(=O)_2(\text{-}OOH)$

Potassium Monopersulfate

Preferably, step (ii) is carried out in a water/methanol solvent mixture.

The activated SO_2R derivative produced in the oxidation step is readily converted to the corresponding amine by amination with a compound of formula $HNR^{10}R^{11}$.

Thus, in one embodiment of the invention, step (iii) comprises reacting said compound of formula IV with an amine of formula $NHR^{10}R^{11}$, where R^{10} and R^{11} are as defined above.

Preferably, step (iii) is carried out in an alcohol solvent. More preferably, the solvent is ethanol.

In one particularly preferred embodiment of the invention, said compound of formula IV, said amine of formula $NHR^{10}R^{11}$ and the solvent are heated at reflux temperature.

In one preferred embodiment, said compound of formula II is prepared by reacting a compound of formula V with a compound of formula RSH,



V II

where Y is halo, and X and R are as defined above.

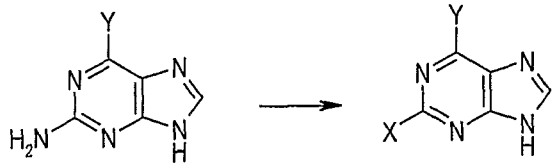
More preferably, Y is chloro and X is fluoro.

In one preferred embodiment, said compound of formula V and said compound of formula RSH are reacted in the presence of a base. More preferably, the base is NEt_3.

Preferably, said compound of formula V and said compound of formula RSH are reacted in an alcohol solvent. More preferably, the solvent is ethanol.

In one preferred embodiment of the invention, R is aryl or aralkyl, more preferably, phenyl or benzyl. Even more preferably, R is benzyl.

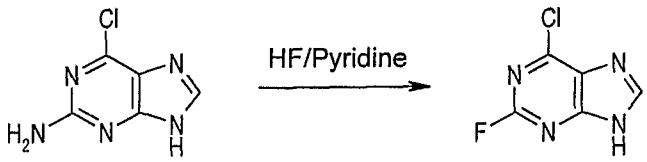
In one preferred embodiment, said compound of formula V is prepared from a compound of formula VI



VI V

wherein X and Y are as defined above,

Even more preferably, X is fluoro and Y is chloro, and said compound of formula V is prepared by treating 2-amino-6-chloropurine with HF/pyridine.



SALTS/ESTERS

The compounds prepared by the process of the invention can be in the form of salts or esters, in particular pharmaceutically and veterinarily acceptable salts or esters.

Pharmaceutically acceptable salts of the compounds prepared by the process of the invention include suitable acid addition or base salts thereof. A review of suitable pharmaceutical salts may be found in Berge et al, J Pharm Sci, 66, 1-19 (1977). Salts are formed, for example with strong inorganic acids such as mineral acids, e.g. hydrohalic acids such as hydrochloride, hydrobromide and hydroiodide, sulphuric acid, phosphoric acid sulphate, bisulphate, hemisulphate, thiocyanate, persulphate and sulphonic acids; with strong organic carboxylic acids, such as alkanecarboxylic acids of 1 to 4 carbon atoms which are unsubstituted or substituted (e.g., by halogen), such as acetic acid; with saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or tetraphthalic; with hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid; with aminoacids, for example aspartic or glutamic acid; with benzoic acid; or with organic

sulfonic acids, such as (C_1-C_4)-alkyl- or aryl-sulfonic acids which are unsubstituted or substituted (for example, by a halogen) such as methane- or p-toluene sulfonic acid. Salts which are not pharmaceutically or veterinarily acceptable may still be valuable as intermediates.

Preferred salts include, for example, acetate, trifluoroacetate, lactate, gluconate, citrate, tartrate, maleate, malate, pantothenate, adipate, alginate, aspartate, benzoate, butyrate, digluconate, cyclopentanate, glucoheptanate, glycerophosphate, oxalate, heptanoate, hexanoate, fumarate, nicotinate, palmoate, pectinate, 3-phenylpropionate, picrate, pivalate, proprionate, tartrate, lactobionate, pivolate, camphorate, undecanoate and succinate, organic sulphonic acids such as methanesulphonate, ethanesulphonate, 2-hydroxyethane sulphonate, camphorsulphonate, 2-naphthalenesulphonate, benzenesulphonate, p-chlorobenzenesulphonate and p-toluenesulphonate; and inorganic acids such as hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, hemisulphate, thiocyanate, persulphate, phosphoric and sulphonic acids.

Esters are formed either using organic acids or alcohols/hydroxides, depending on the functional group being esterified. Organic acids include carboxylic acids, such as alkanecarboxylic acids of 1 to 12 carbon atoms which are unsubstituted or substituted (e.g., by halogen), such as acetic acid; with saturated or unsaturated dicarboxylic acid, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or tetraphthalic; with hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid; with aminoacids, for example aspartic or glutamic acid; with benzoic acid; or with organic sulfonic acids, such as (C_1-C_4)-alkyl- or aryl-sulfonic acids which are unsubstituted or substituted (for example, by a halogen) such as methane- or p-toluene sulfonic acid. Suitable hydroxides include inorganic hydroxides, such as sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminium hydroxide. Alcohols include alkanealcohols of 1-12 carbon atoms which may be unsubstituted or substituted, e.g. by a halogen).

ENANTIOMERS/TAUTOMERS

The invention includes, where appropriate all enantiomers, diastereoisomers and tautomers of the compounds prepared by the process of the invention. The person skilled in the art will recognise compounds that possess optical properties (one or more chiral carbon atoms) or tautomeric characteristics. The corresponding enantiomers and/or tautomers may be isolated/prepared by methods known in the art.

Compounds prepared by the process of the invention containing a chiral centre may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone.

STEREO AND GEOMETRIC ISOMERS

Some of the compounds prepared by the process of the invention may exist as stereoisomers and/or geometric isomers, e.g. they may possess one or more asymmetric and/or geometric centres and so may exist in two or more stereoisomeric and/or geometric forms. The present invention contemplates the preparation of all the individual stereoisomers and geometric isomers of those inhibitor agents, and mixtures thereof. The terms used in the claims encompass these forms.

The present invention also includes all suitable isotopic variations of the compounds prepared by the inventive process, or a pharmaceutically acceptable salts thereof. An isotopic variation of compound of the present invention or a pharmaceutically acceptable salt thereof is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Examples of isotopes that can be incorporated into the agent and pharmaceutically acceptable salts thereof include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulphur, fluorine and chlorine such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F and ^{36}Cl, respectively. Certain isotopic variations of the agent and pharmaceutically acceptable salts thereof, for example, those in which a radioactive isotope such as ^{3}H or ^{14}C is incorporated, are useful in drug and/or substrate tissue distribution studies. Tritiated, i.e., ^{3}H, and carbon-14, i.e.,

^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium, i.e., ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements and hence may be preferred in some circumstances. Isotopic variations of the agent of the present invention and pharmaceutically acceptable salts thereof of this invention can generally be prepared by conventional procedures using appropriate isotopic variations of suitable reagents.

The present invention is further described by way of the following non-limiting Examples.

EXAMPLES

General

The following apparatus was used:

NMR - Varian INOVA-500; DMSO-d6 solvent;

UV - Diode array from hplc;

IR - Jasco FT/IR-460; Condensed phase (ATR);

MS - Waters ZQ quadrupole with electrospray ionisation;

HPLC - Phenomenex Synergi 4u MAX-RP 80A; linear gradient H_2O/MeCN (containing 0.1% TFA) - flow rate 1ml/min; 0-60% H_2O over 20 min. Purity assessed by integration of chromatograms (wavelength = 254nm);

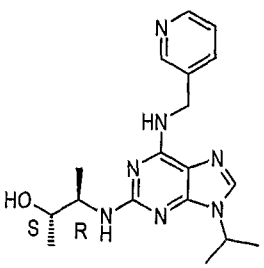
Silica: Kieselgel 60 (40-63um), Merck;

Preparative Chiral HPLC - a) CHIRALPAK ASH; CO2:MeOH 90%:10%; b) CHIRALCEL OK 20 um; n-heptane:ethanol 90%:10%;

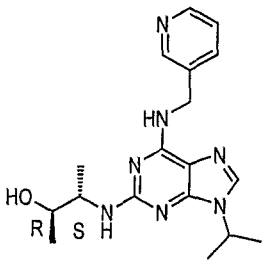
Analytical Chiral HPLC - CHIRALPAK AD-H; n-heptane:ethanol 70%:30% (0.1% diethylamine)

Synthesis of Compounds

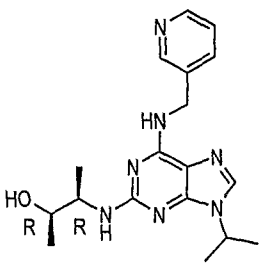
Compounds I.1 to I.4 were prepared from 2-amino-6-chloropurine as outlined below in Scheme 11.



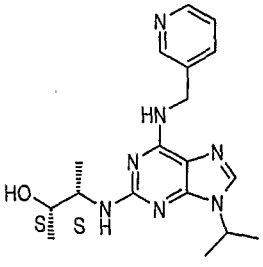
I.1



I.2

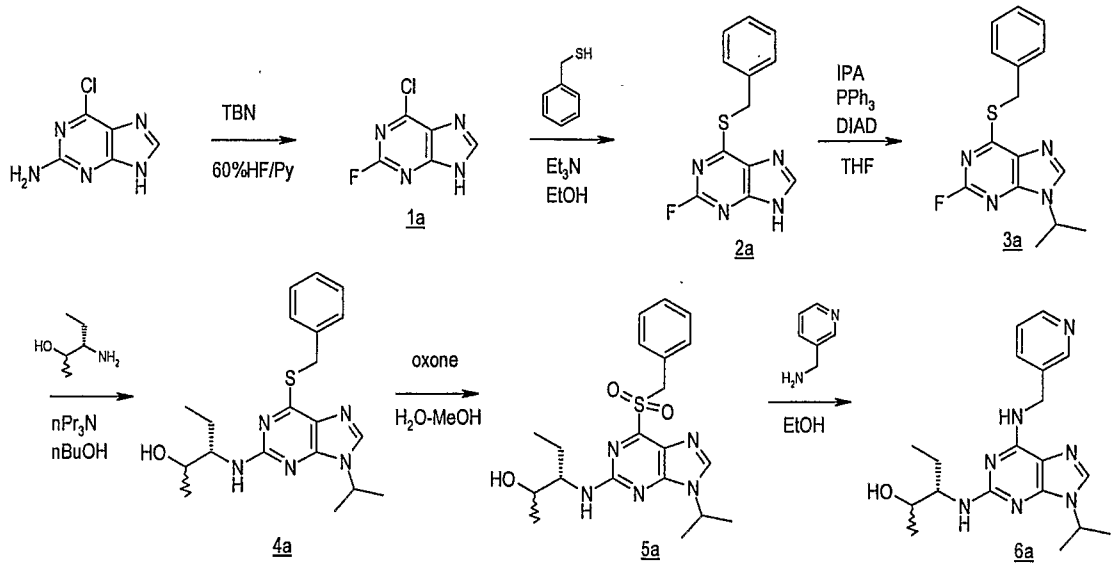


I.3

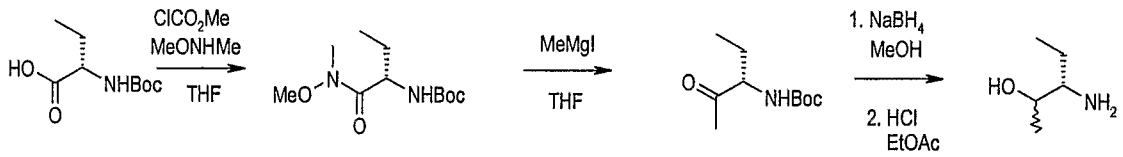


I.4

The 3-aminopentan-2-ol intermediates were prepared by UFC from both the R- and S-amino acids (Scheme 12) as a mixture of stereoisomers at the C-2 position of the aminopentanols. Once incorporated into the purine nucleus, the two diastereomeric pairs were separated into chirally pure final products by Chiral Technologies by means of preparative HPLC.



Scheme 11



Scheme 12

Example 1

Prepared in a manner similar to Kim *et al*, *J. Med. Chem.*, 46, 4987 (2003), but with modified conditions:

Compound 1a

A 500ml PFA flask fitted with PTFE-coated thermometer, nitrogen inlet and septum was charged with 70% hydrogen fluoride-pyridine (92ml) and cooled to –50°C in a cardice-IPA bath. The solution was carefully diluted with pyridine (17.5ml) to obtain a 60% HF-pyridine mixture. 2-Amino-6-chloropurine (30.0g, 0.177M) was added in small portions, maintaining the internal temperature below –30°C. Once the addition was complete, the cardice cooling bath was replaced with ice-methanol. Once the internal temperature had risen to ca. –25°C, *tert*-butyl nitrite (90% w/w, 30ml, 0.228M) was added in 0.1ml portions over a period of 1h, with swirling to assist mixing.

Foaming and an exotherm ensued. The internal temperature was maintained ≤ 5°C by the rate of addition. Once the addition was complete, the cooling bath was removed and the mixture was stirred 1h at room temperature. Some residual solid was present and the mixture was warmed to 22°C to obtain a homogeneous solution. The mixture was poured into ice-water (800ml) and neutralized with solid potassium hydrogen carbonate. The aqueous solution was extracted with ethyl acetate (3x600ml). The combined organics were washed successively with 10% citric acid (2x150ml) and brine (200ml) then dried ($MgSO_4$), filtered and evaporated to give an off-white solid. ^{1}H-nmr shows this to be a 2:1 complex of the title compound and pyridine (=81% w/w product). 31.91g (85%) obtained.

Compound 2a

Prepared in a manner similar to Ding, *et al*, *J. Org. Chem.*, 66, 8273 (2001), but with modified conditions:

Compound 1a (81% w/w, 84.97g, 0.399M) was partially dissolved in ethanol (700ml) and benzylmercaptan (56ml, 0.459M) added dropwise. Triethylamine (67ml, 0.479M) was added in a steady stream, producing a mild exotherm to 25°C. The mixture was heated at reflux for 2h, then cooled to room temperature. Ethanol evaporated *in vacuo*. The residue treated with water (800ml) and extracted with ethyl acetate (3x500ml). The combined organics were washed (brine, 300ml), dried ($MgSO_4$), filtered and evaporated to a yellow solid. This was triturated with heptane and filtered. The collected solid was washed successively with heptane (3x300ml) and light petroleum ether (3x300ml). Dried under vacuum at room temperature. 93.78g (90%) obtained.

Compound 3a

A dry, nitrogen-flushed flask was charged with compound 2a (45.84g, 0.176M) and triphenylphosphine (83.14g, 0.317M). THF (1L) added, followed by propan-2-ol (20.2ml, 0.264M). The mixture was cooled to –40°C and diisopropyl azodicarboxylate (47.4ml, 0.229M) added dropwise over a period of 1h, keeping the internal temperature ≤-40°C. The mixture was stirred at room temperature 18h. The mixture was evaporated and the last traces of THF removed on high vacuum at 35°C for 3h. The resulting

yellow syrup was dissolved in ether (160ml) with trituration and diluted with light petroleum ether (80ml). The resulting mixture was filtered and the collected triphenylphosphine oxide washed with 1:1 ether-light petroleum ether (400ml). The filtrate was evaporated and the residue purified by chromatography (400g SiO_2 eluted with a light petroleum ether-ether gradient). 24.57g product obtained pure and a further 19.84g which also contained varying amounts of dihydro-diisopropyl azodicarboxylate. Combined yield 83%.

Compound 4a

Compound 3a (94% w/w, 5.67g, 17.64 mmol) was dissolved in n-butanol (100ml) together with 3'(S)-Aminopentan-2(R,S)-ol (2.73g, 26.46mmol) and tripropylamine (10.1ml, 52.93mmol) added in a steady stream. The vessel was flushed with argon and the mixture heated at reflux 18h. The mixture was cooled to room temperature and n-butanol removed *in vacuo*. The residue was purified by chromatography (150g SiO_2 eluted with a heptane – ethyl acetate gradient). 4.49g (66%) obtained as a white solid.

Compound 5a

Oxone (12.89g, 20.96mmol) was partially dissolved in water (40ml) and cooled to –2°C. Compound 4a (4.49g, 11.65mmol) was dissolved in methanol (40ml) and added dropwise to the cooled aqueous solution over a period of 35 min. The mixture was stirred 5 min with cooling, then 2.5 h at room temperature. The mixture was concentrated to 2/3 its volume *in vacuo* and diluted with water (200ml). Extracted with ethyl acetate (3x150ml). The combined organics were washed (brine), dried ($MgSO_4$), filtered and evaporated to a pale yellow solid. 4.09g (84%) obtained.

Compound 6a

Compound 5a (3.86g, 9.25 mmol) dissolved in ethanol (350ml) and 3-(aminomethyl)pyridine (2.82ml, 27.74 mmol) added in a steady stream. The apparatus was flushed with argon and the mixture heated at reflux 18h. The mixture was cooled and ethanol removed *in vacuo*. The residue was purified by chromatography (75g SiO_2 eluted with an ethyl acetate – methanol gradient) to give 2.57g (75%) of the product as a white solid.

Compound No.	I.1	I.2	I.3	I.4
Batch	387-124-1	387-125-1	387-124-2	387-125-2

Spectral Data for Compounds I.1 to I.4

^{1}H-NMR Data

387-124-1	**387-124-2**	**387-125-1**	**387-125-2**
0.95 (t, 3H, J=7.3)	0.96 (t, 3H, J=7.8)	1.02 (t, 3H, J=7.8)	0.96 (t, 3H, J=7.3)
1.06 (d, 3H, J=6.3)	1.22 (d, 3H, J=6.3)	1.14 (d, 3H, J=6.4)	1.21 (d, 3H, J=5.9)
1.40 (m, 1H)	1.54 (d, 6H, J=6.8)	1.47 (m, 1H)	1.53 (d, 6H, J=6.8)
1.47 (d, 6H, J=6.8)	1.58 (m, 1H)	1.54 (d, 6H, J=6.8)	1.58 (m, 1H)
1.54 (m, 1H)	1.71 (m, 1H)	1.58 (m, 1H)	1.71 (m, 1H)
3.84-3.90 (m, 2H)	3.65 (m, 1H)	3.92-3.98 (m, 2H)	3.66 (m, 1H)
4.53 (sept, 1H, J=6.8)	3.82 (pen, 1H, J=6.4)	4.61 (sept, 1H, J=6.8)	3.82 (pen, 1H, J=5.8)
	4.61 (sept, 1H, J=6.8)		4.61 (sept, 1H, J=6.8)
4.66, (d, 1H, J=5.8)	4.78 (bs, 2H)	4.74, (d, 1H, J=5.8)	4.78 (bs, 2H)
4.71 (bs, 2H)	4.88, (d, 1H, J=7.8)	4.79 (bs, 2H)	4.89, (d, 1H, J=7.8)
5.98 (bs, 1H)	6.08 (bs, 1H)	6.07 (bs, 1H)	6.15 (bs, 1H)
7.18 (dd, 1H, J=4.9, 7.8)	7.24 (dd, 1H, J=3.9, 7.8)	7.25 (dd, 1H, J=4.9, 7.8)	7.24 (dd, 1H, J=4.9, 7.8)
7.42 (s, 1H)	7.50 (s, 1H)	7.50 (s, 1H)	7.50 (s, 1H)
7.63 (d, 1H, J=7.8)	7.71 (d, 1H, J=7.6)	7.70 (d, 1H, J=7.8)	7.70 (d, 1H, J=7.8)
8.45 (dd, 1H, J=1.5, 4.9)	8.51 (d, 1H, J=3.9)	8.52 (dd, 1H, J=1.5, 4.9)	8.51 (d, 1H, J=4.4)
8.57 (d, 1H, J=1.9)	8.65 (s, 1H)	8.64 (d, 1H, J=1.9)	8.64 (s, 1H)

IR Data

	387-124-1	**387-124-2**	**387-125-**	**387-125-2**

ν_{OH} str	3429	3458	3425	3416
ν_{NH} str1	3247	3248	3247	3246
ν_{NH} str2	3197	3197	3196	3200

MS Data

	387-124-1	**387-124-2**	**387-125-1**	**387-125-2**
m/z	370.46	370.59	370.52	370.52

$C_{19}H_{27}N_7O$ = 369.46. MH^+ requires 370.47

HPLC Data

C-18 0-60% ACN in water (0.1% TFA) over 20 min

	387-124-1	**387-124-2**	**387-125-1**	**387-125-2**
Ret. Time (min)	10.37	10.50	10.31	10.45
Rel. Area (%)	100	100	100	100

UV Data

	387-124-1	**387-124-2**	**387-125-1**	**387-125-2**
Principal maxima (nm)	213.8, 236.0, 291.9	214.7, 235.9, 291.9	214.9, 236.2, 292.0	215.5, 236.1, 291.9

Synthesis of 3-amino-pentan-2-ol (Compounds 1-4)

Cbz protection

A solution of benzyl chloroformate (6.3 mL) in THF (74 mL) was added dropwise to a stirred suspension of D-threonine (5.0 g) and sodium bicarbonate (7.1 g) in water (74 mL) at room temperature under nitrogen. The resulting solution was stirred overnight. The THF was then removed in vacuo and the remaining aqueous solution washed with ethyl acetate (100 mL) before the pH was adjusted to 3 by the addition of 10% acetic acid (40 mL). The resulting aqueous suspension was then extracted with ethyl acetate (3 x 100 mL) and the combined organic phase was washed with saturated aqueous sodium chloride (100 mL), dried over $MgSO_4$, filtered and stripped to give the desired

product **14** as a clear colourless oil (11.1 g, quantitative). ^{1}H NMR spectroscopy confirmed the identity of the product and showed it to be of sufficient purity for use in the next stage without purification.

Methyl ester formation

Trimethylsilyl chloride (10.7 mL) was added dropwise to a solution of cbz protected D-threonine **14** (10.7 g) in methanol (100 mL) at 0 to 5°C under nitrogen. The resulting solution was stirred at room temperature overnight after which time the solvent was removed in vacuo. The resulting residue was dissolved in DCM (200 mL), washed with water (2 x 200 mL), dried over $MgSO_4$, filtered and stripped to give the desired product **15** as a white solid (8.9 g, 79%). ^{1}H NMR spectroscopy confirmed the identity of the product and showed it to be of sufficient purity for use in the next stage without purification.

TBDMS protection

Hunig's base (17.6 mL) and TBDMSCI (10.7 g) were added to a solution of Z-(L)-threonine methyl ester 7 (6.0 g) in DMF (120 mL) at room temperature under nitrogen. The resulting solution was stirred at room temperature overnight. Water (300 mL) and ethyl acetate (300 mL) were added and the phases separated. The aqueous phase was extracted with ethyl acetate (2 x 200 mL) and the combined organic phase washed with water (200 mL), saturated aqueous sodium chloride (200 mL), dried over $MgSO_4$, filtered and stripped to give a dark orange oil (16.6 g). Purification by column chromatography (eluent graduated from 100% hexane to 40% ethyl acetate in hexane) yielded the desired product **9** as a light yellow oil (11.1 g). ^{1}H NMR spectroscopy confirmed the identity of the product but also confirmed the presence of an impurity that was inseparable by column chromatography. This accounts for the greater than quantitative yield (130%).

DIBAL reduction

DIBAL (1M in toluene, 57.7 mL) was added dropwise to a solution of compound **9** in toluene at <-65°C under nitrogen. The resulting solution was stirred at <-65°C for 1 hour. Tlc showed the reaction was incomplete. DIBAL (1 M in toluene, 29.0 mL) was

added dropwise to the reaction solution maintaining the temperature below -65°C. The resulting solution was stirred at <-65°C for a further hour after which time tic showed the reaction was still incomplete. DIBAL (1M in toluene, 14.4 mL) was added dropwise to the reaction solution maintaining the temperature below -65°C. After a further 30 minutes at <-65°C, the reaction was found to be complete by tic. A solution of acetic acid (19 mL) in toluene (47 mL) was added dropwise maintaining the temperature below -60°C. The resulting solution was allowed to warm to room temperature before pouring into a solution of citric acid (25 g) in water (233 mL). The product was extracted into 50:50 ethyl acetate I hexane (200 mL then 2 x 100 mL) and the combined organic phase was washed with water (100 mL), saturated aqueous sodium chloride (200 mL), dried over $MgSO_4$, filtered and stripped to give the crude product as a dark yellow oil (9.3 g). Purification by flash column chromatography (eluent 10% ethyl acetate in hexane) yielded the desired aldehyde **10** as a light yellow oil (4.9 g, 62% over 2 steps, JCCA296C). ^1H NMR spectroscopy confirmed the identity of the product and showed it to be of sufficient purity for use in the next stage.

Wittig

n-Butyllithium (1.6M in hexanes, 17.9 mL) was added dropwise to a suspension of methyl triphenylphosphonium bromide (10.2 g) in THF (160 mL) at <-65°C under nitrogen. The resulting yellow suspension was stirred at room temperature for 30 minutes before cooling back to <-65°C. The aldehyde **10** (4.9 g) in THF (50 mL) was then added dropwise maintaining the temperature below -65°C. The resulting reaction mixture was stirred at room temperature for 1 hour. Water (250 mL) and Et_20 (250 mL) were added and the phases separated. The aqueous phase was extracted with Et_20 (2 x 250 mL) and the combined organic phase was washed with saturated aqueous sodium chloride (250 mL), dried over $MgSO_4$, filtered and stripped to give the crude product as a yellow oil (8.0 g). Purification by flash column chromatography (eluent 10% ethyl acetate in hexane) yielded the desired alkene 11 as a light yellow oil (3.1 g, 64%, JCCA306B). ^1H NMR spectroscopy confirmed the identity of the product and showed it to be of sufficient purity for use in the next stage.

TBDMS deprotection

TBAF (1M in THF, 13.3 mL) was added dropwise to a solution of the alkene **11** (3.1 g) in THF (100 mL) at 0 to 5°C under nitrogen. The resulting solution was stirred at 0 to 5°C for 2 hours. Tlc showed the reaction was incomplete so TBAF (1M in THF, 4.4 mL) was added at 0 to 5°C. After a further 1 hour the reaction was complete by tic. Water (100 mL) and Et_2O (100 mL) were added and the phases separated. The aqueous phase was extracted with Et_2O (2 x 50 mL) and the combined organic phase was washed with water (100 mL), saturated aqueous sodium chloride (100 mL), dried over $MgSO_4$, filtered and stripped to give the crude product as a light yellow oil (3.7 g). Purification by flash column chromatography (eluent 40% ethyl acetate in hexane) yielded the desired product **12** as a light yellow oil (1.8 g, 80%, JCCA308B). ^1H NMR spectroscopy confirmed the identity of the product and showed it to be of sufficient purity for use in the next stage.

Hydrogenation

5% Pd/C (60% water wet, 0.45 g) was charged to a flask under nitrogen and washed in with IMS (5 mL). A solution of compound **12** (1.8 g) in IMS (15 mL) was added to the flask which was then flushed with hydrogen. The reaction was stirred at room temperature under hydrogen (atmospheric) for 1 hour. Tlc indicated the reaction was incomplete and 5% PdIC (60% water wet, 0.45 g) was charged to the reaction mixture. After a further hour, tic indicated the reaction was complete. The reaction mixture was filtered through Celite (30 g) and the filter cake washed with IMS (2 x 50 mL). The filtrate was stripped to dryness. The product was dissolved in DCM (10 mL) and the solvent removed in vacuo to give the product **1** as an off-white solid (0.6254 g, 85%, JCCA310B). ^1H NMR spectroscopy confirmed the presence of only one diastereomer gave a purity of > 95%.

N-Benzoyl protected (2S,3S)-3-amino pentan-2-o1 **16**

(2S,3S)-3-Amino-pentan-2-ol 2 (1.0 g) was dissolved in 2:1 water I dioxane (15 mL) at room temperature under nitrogen. A dual dropwise addition of benzoyl chloride (1.4 mL) and 5M aqueous NaOH (3.7 mL) was carried out maintaining the pH of the reaction solution at 8 to 9. The resulting solution was stirred at room temperature for 1

hour then stripped to dryness. The residue was dissolved in water (25 mL) and ethyl acetate (25 mL) and the phases separated. The aqueous phase was extracted with ethyl acetate (2 x 25 mL) and the combined organic phase was washed with saturated aqueous sodium chloride (25 mL), dried over $MgSO_4$, filtered and stripped to give the desired product **16** as a white solid (1.6 g, 80%). ^1H NMR spectroscopy confirmed the identity of the product and showed it to be of sufficient purity for use in the next stage.

Oxazoline 17

Compound 16 (1.1 g) was added to thionyl chloride (20 mL) at -5 to 0°C under nitrogen and the resulting solution stirred at -5 to 0°C for 1 hour. The reaction was stripped to dryness and the residue dissolved in DCM (40 mL) and the resulting solution poured into 10% sodium carbonate (200 rmL) with stirring and whilst ensuring the pH remained >8. The phases were separated and the aqueous phase extracted with DCM (40 mL). The combined organic phase was washed with water (40 mL), dried over $MgSO_4$, filtered and stripped to give the crude product as a brown oil (1.7 g). The crude product was combined with the crude product from a previous small scale reaction (0.47 g, JCCA320A). Purification by flash column chromatography (euent graduated 100% hexane to 10% ethyl acetate in hexane) yielded the desired oxazoline 17 as a yellow solid (1.3 g, 89% from total of 1.6 g 16 in 2 reactions). ^1H NMR spectroscopy confirmed the identity of The product and showed it to be of sufficient purity for use in the next stage.

(2R,3S)-3-Amino-pentan-2-ol hydrochloride salt **18**

A solution of the oxazoline 17 (1.3 g) and 50:50 HCI I water (40 mL) under nitrogen was heated at reflux for 3 hours and 30 minutes. The reaction was cooled to room temperature and washed with Et_20 (3 x 40 mL). The aqueous phase was then stripped to dryness to give the product **18** as a tan coloured oil (1.0 g). ^1H NMR spectroscopy confirmed the identity of the product.

Cbz protected (2R,3S)-3-amino pentan-2-o1 **19**

A solution of benzyl chloroformate (1.07 mL) in THF (15 mL) was added dropwise to a stirred suspension of compound 18 (1.0 g) and sodium bicarbonate (1.8 g) in water

(15 mL) at room temperature under nitrogen. The resulting solution was stirred for 5 hours. The THF was then removed in vacuo and DCM (50 mL) added to the remaining aqueous solution. The phases were separated and the aqueous phase extracted with DCM (2 x 50 mL). The combined organic phase was washed with water (50 mL), saturated aqueous sodium chloride (50 mL), dried over $MgSO_4$, filtered and stripped to give the crude product as a clear colourless oil (1.4 g). Purification by flash column chromatography (eluent graduated 20% to 60% ethyl acetate in hexane) yielded the desired product 19 as white solid (0.8 g, 47% over 2 steps, JCCA325B). ^1H NMR spectroscopy confirmed the identity of the product and showed it to be of sufficient purity for use in the next stage.

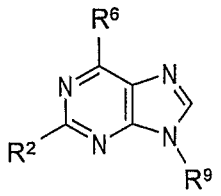
(2R, 3S)-3-Amino-pentan-2-ol **14**

5% Pd/C (60% water wet, 0.2 g) was charged to a flask under nitrogen and washed in with IMS (5 mL). A solution of compound 19 (0.8 g) in IMS (15 mL) was added to the flask which was then flushed with hydrogen. The reaction was stirred at room temperature under hydrogen (atmospheric) for 30 minutes. TIc indicated the reaction was incomplete and 5% Pd/C (60% water wet, 0.2 g) was charged to the reaction mixture. After a further 30 minutes, tic indicated the reaction was complete. The reaction mixture was filtered through Celite (20 g) and the filter cake washed with IMS (3 x 20 mL). The filtrate was stripped to dryness. The product was dissolved in DCM (5 mL) and the solvent removed in vacuo to give the product 4 as a light yellow oil (0.25 g, 72%, JCCA326A). ^1H NMR spectroscopy confirmed the presence of only one diastereoisomer in a purity of >90%.

Various modifications and variations of the described aspects of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes of carrying out the invention which are obvious to those skilled in the relevant fields are intended to be within the scope of the following claims.

CLAIMS

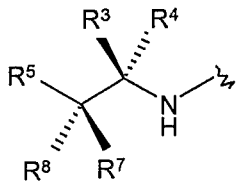
1. A process for preparing a compound of formula I, or a pharmaceutically acceptable salt thereof,



I

wherein

R^2 is



where

R^3, R^4, R^7 and R^8 are each independently selected from H, alkyl, aryl and aralkyl, said alkyl, aryl and aralkyl groups each being optionally substituted with one or more R^{12} groups, and wherein at least one of R^3, R^4, R^7 and R^8 is other than H;

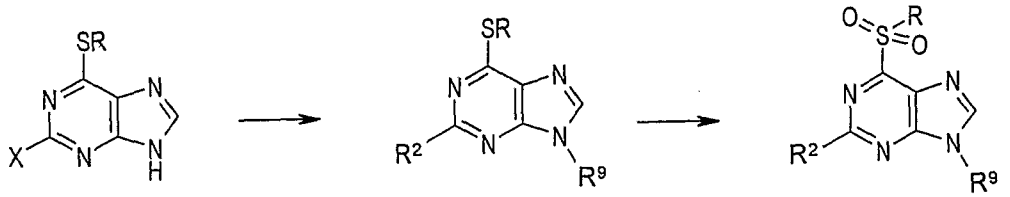
R^5 is OH, O-alkyl, H, alkyl, aryl or aralkyl, said alkyl, aryl and aralkyl groups each being optionally substituted with one or more R^{12} groups;

R^6 is $NR^{10}R^{11}$, wherein R^{10} and R^{11} are each independently H or hydrocarbyl;

R^9 is hydrocarbyl; and

each R^{12} is independently selected from OR^{13}, halo, alkyl, $COOR^{14}$, $CONR^{15}R^{16}$, $SO_2NR^{17}R^{18}$, NO_2, CN, $NR^{19}R^{20}SR^{21}$ and CF_3, where $R^{13\text{-}21}$ are each independently H, alkyl or aryl;

said process comprising the steps of:



II III IV

(i) converting a compound of formula II to a compound of formula III, wherein X is halo and R is aryl, alkyl, cycloalkyl, aralkyl, heteroaryl or alkyl-heteroaryl;

(ii) converting said compound of formula III to a compound of formula IV; and

(iii) converting said compound of formula IV to a compound of formula I.

2. A process according to claim 1 wherein one of R^3 and R^4 is alkyl, aryl or aralkyl, and the other is H.

3. A process according to any preceding claim wherein one of R^7 and R^8 is alkyl, aryl or aralkyl, and the other is H.

4. A process according to any preceding claim wherein one of R^3 and R^4 is alkyl, and the other is H.

5. A process according to any preceding claim wherein one of R^7 and R^8 is alkyl, and the other is H.

6. A process according to any preceding claim wherein one of R^3 and R^4 is methyl, ethyl or isopropyl, and the other is H.

7. A process according to any preceding claim wherein:
one of R^3 and R^4 is alkyl, and the other is H; and
one of R^7 and R^8 is alkyl, and the other is H.

8. A process according to any preceding claim wherein:
one of R^3 and R^4 is H and the other is methyl, ethyl or iso-propyl;

one of R^7 and R^8 is H, and the other is methyl, ethyl, iso-propyl or tert-butyl.

9. A process according to any preceding claim wherein R^{10} is H and R^{11} is aryl, heteroaryl, aralkyl, alkyl-heteroaryl, alkyl, alkenyl or cycloalkyl, each of which may be optionally substituted with one or more R^{12} groups.

10. A process according to any preceding claim wherein R^9 is alkyl or cycloalkyl, each of which may be optionally substituted by one or more R^{12} groups.

11. A process according to any preceding claim wherein each R^{12} is independently selected from OH, alkoxy, halo, alkyl, COOH, COOMe, $CONH_2$, SO_2NH_2, NO_2, CN, NHMe, NH_2, NMe and CF_3.

12. A process according to any preceding claim wherein R^9 is isopropyl or cyclopentyl.

13. A process according to any preceding claim wherein R^{11} is aryl, aralkyl, heteroaryl or alkyl-heteroaryl, each of which may be optionally substituted with one or more R^{12} groups.

14. A process according to any preceding claim wherein R^{11} is phenyl, benzyl, pyridinyl or CH_2-pyridinyl, each of which may be optionally substituted with one or more R^{12} groups.

15. A process according to any preceding claim wherein R^{11} is selected from phenyl, benzyl, CH_2-pyridin-2-yl, CH_2-pyridin-3-yl and CH_2-pyridin-4-yl, each of which may be optionally substituted by one or more halo, OH, OMe or NO_2 groups.

16. A process according to any preceding claim wherein said compound of formula I is selected from the following:

(2*S*3*R*)-3-{9-Isopropyl-6-[(pyridin-2-ylmethyl)-amino]-9H-purin-2-ylamino}-pentan-2-ol;

(2*R*3*S*)-3-{9-Isopropyl-6-[(pyridin-2-ylmethyl)-amino]-9H-purin-2-ylamino}-pentan-2-ol;

(3*RS*,4*R*)-4-{9-Isopropyl-6-[(pyridin-2-ylmethyl)-amino]-9H-purin-2-ylamino}-hexan-3-ol;

(3*RS*,4*S*)-4-{9-Isopropyl-6-[(pyridin-2-ylmethyl)-amino]-9H-purin-2-ylamino}-hexan-3-ol;

(3*RS*,4*R*)-4-{9-Isopropyl-6-[(pyridin-2-ylmethyl)-amino]-9H-purin-2-ylamino}-2-methyl-hexan-3-ol;

(3*RS*,4*S*)-4-{9-Isopropyl-6-[(pyridin-2-ylmethyl)-amino]-9H-purin-2-ylamino}-2-methyl-hexan-3-ol;

(3*RS*,4*R*)-4-{9-Isopropyl-6-[(pyridin-2-ylmethyl)-amino]-9H-purin-2-ylamino}-2,2-dimethyl-hexan-3-ol;

(3*RS*,4*S*)-4-{9-Isopropyl-6-[(pyridin-2-ylmethyl)-amino]-9H-purin-2-ylamino}-2,2-dimethyl-hexan-3-ol;

(3*R*)-3-{9-Isopropyl-6-[(pyridin-2-ylmethyl)-amino]-9H-purin-2-ylamino}-2-methyl-pentan-2-ol;

(3*S*)-3-{9-Isopropyl-6-[(pyridin-2-ylmethyl)-amino]-9H-purin-2-ylamino}-2-methyl-pentan-2-ol;

(2*S*3*R*)-3-{9-Isopropyl-6-[(pyridin-3-ylmethyl)-amino]-9H-purin-2-ylamino}-pentan-2-ol;

(2*R*3*S*)-3-{9-Isopropyl-6-[(pyridin-3-ylmethyl)-amino]-9H-purin-2-ylamino}-pentan-2-ol;

(3*RS*,4*R*)-4-{9-Isopropyl-6-[(pyridin-3-ylmethyl)-amino]-9H-purin-2-ylamino}-hexan-3-ol;

(3*RS*,4*S*)-4-{9-Isopropyl-6-[(pyridin-3-ylmethyl)-amino]-9H-purin-2-ylamino}-hexan-3-ol;

(3*RS*,4*R*)-4-{9-Isopropyl-6-[(pyridin-3-ylmethyl)-amino]-9H-purin-2-ylamino}-2-methyl-hexan-3-ol;

(3*RS*,4S)-4-{9-Isopropyl-6-[(pyridin-3-ylmethyl)-amino]-9H-purin-2-ylamino}-2-methyl-hexan-3-ol;

(3*RS*,4*R*)-4-{9-Isopropyl-6-[(pyridin-3-ylmethyl)-amino]-9H-purin-2-ylamino}-2,2-dimethyl-hexan-3-ol;

(3*RS*,4*S*)-4-{9-Isopropyl-6-[(pyridin-3-ylmethyl)-amino]-9H-purin-2-ylamino}-2,2-dimethyl-hexan-3-ol;

(3*R*)-3-{9-Isopropyl-6-[(pyridin-3-ylmethyl)-amino]-9H-purin-2-ylamino}-2-methyl-pentan-2-ol;

(3*S*)-3-{9-Isopropyl-6-[(pyridin-3-ylmethyl)-amino]-9H-purin-2-ylamino}-2-methyl-pentan-2-ol;

(3S)-3-{9-Isopropyl-6-[(pyridin-3-ylmethyl)-amino]-9H-purin-2-ylamino}-2-methyl-pentan-2-ol; and

(3R)-3-{9-Isopropyl-6-[(pyridin-3-ylmethyl)-amino]-9H-purin-2-ylamino}-2-methyl-pentan-2-ol;

(2*RS*,3*R*)-3-(6-Benzylamino-9-isopropyl-9*H*-purin-2-ylamino)-pentan-2-ol;

R-2-{9-Isopropyl-6-[(pyridin-2-ylmethyl)-amino]-9H-purin-2-ylamino}-butan-1-ol;

R-2-{9-Isopropyl-6-[(pyridin-4-ylmethyl)-amino]-9H-purin-2-ylamino}-butan-1-ol;

(2*S*,3*R*)-3-(6-Benzylamino-9-isopropyl-9*H*-purin-2-ylamino)-pentan-2-ol;

(2*R*,3S)-3-(6-Benzylamino-9-isopropyl-9*H*-purin-2-ylamino)-pentan-2-ol;

(3*RS*,4*R*)-4-(6-Benzylamino-9-isopropyl-9*H*-purin-2-ylamino)-hexan-3-ol;

(3*RS*,4*S*)-4-(6-Benzylamino-9-isopropyl-9*H*-purin-2-ylamino)-hexan-3-ol;

(3*RS*,4*R*)-4-(6-Benzylamino-9-isopropyl-9*H*-purin-2-ylamino)-2-methyl-hexan-3-ol;

(3*RS*,4*S*)-4-(6-Benzylamino-9-isopropyl-9*H*-purin-2-ylamino)-2-methyl-hexan-3-ol;

(3*RS*,4*R*)-4-(6-Benzylamino-9-isopropyl-9*H*-purin-2-ylamino)-2,2-dimethyl-hexan-3-ol;

(3*RS*,4*S*)-4-(6-Benzylamino-9-isopropyl-9*H*-purin-2-ylamino)-2,2-dimethyl-hexan-3-ol;

(*R*)-3-(6-Benzylamino-9-isopropyl-9*H*-purin-2-ylamino)-2-methyl-pentan-2-ol;

(*S*)-3-(6-Benzylamino-9-isopropyl-9*H*-purin-2-ylamino)-2-methyl-pentan-2-ol;

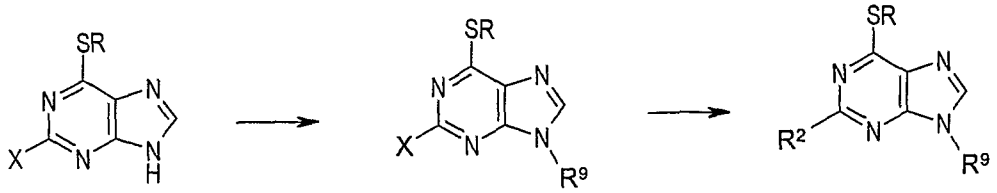
and pharmaceutically acceptable salts thereof.

17. A process according to any one of claims 1 to 16 wherein said compound of formula I is 2-(1-D,L-hydroxymethylpropylamino)-6-benzylamine-9-isopropylpurine or 2-(1-R-hydroxymethylpropylamino)-6-benzylamino-9-isopropylpurine.

18. A process according to any preceding claim which comprises the steps of:

(ia) converting said compound of formula II to a compound of formula IIa; and

(ib) converting said compound of formula IIa to a compound of formula III



II IIa III

19. A process according to claim 18 wherein step (ia) comprises treating said compound of formula II with R^9-OH, where R^9 is as defined in claim 1.

20. A process according to claim 19 which comprises reacting said compound of formula II with R^9-OH in the presence of PPh_3 and DIAD.

21. A process according to claim 20 wherein the solvent is THF.

22. A process according to any one of claims 20 to 21 wherein step (ib) comprises reacting said compound of formula IIa with an amine of formula R^2NH_2, where R^2 is as defined in claim 1.

23. A process according to claim 22 wherein step (ib) is carried out in the presence of a tertiary amine and an alcohol.

24. A process according to claim 23 wherein step (ib) is carried out in the presence of $^nPr_3N$ and n-butanol.

25. A process according to claim 24 wherein said compound of formula IIa, said amine of formula R^2NH_2, $^nPr_3N$ and n-butanol are heated at reflux temperature.

26. A process according to any preceding claim wherein step (ii) comprises treating said compound of formula III with potassium peroxymonosulfate, $KHSO_5$, to form said compound of formula IV.

27. A process according to claim 26 wherein step (ii) comprises treating said compound of formula III with $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (Oxone®) to form said compound of formula IV.

28. A process according to claim 26 wherein step (ii) is carried out in a water/methanol solvent mixture.

29. A process according to any preceding claim wherein step (iii) comprises reacting said compound of formula IV with an amine of formula $NHR^{10}R^{11}$, where R^{10} and R^{11} are as defined in claim 1.

30. A process according to claim 29 wherein step (iii) is carried out in an alcohol solvent.

31. A process according to claim 30 wherein the solvent is ethanol.

32. A process according to claim 30 wherein said compound of formula IV, said amine of formula $NHR^{10}R^{11}$ and the solvent are heated at reflux temperature.

33. A process according to any preceding claim wherein said compound of formula II is prepared by reacting a compound of formula V with a compound of formula RSH,



V II

where Y is halo, and X and R are as defined in claim 1.

34. A process according to claim 33 wherein Y is chloro and X is fluoro.

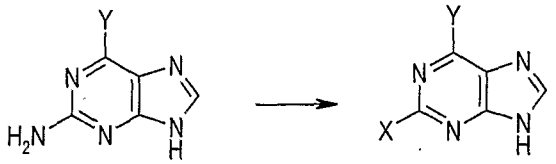
35. A process according to claim 33 or claim 34 wherein said compound of formula V and said compound of formula RSH are reacted in the presence of a base.

36. A process according to claim 35 wherein the base is NEt_3.

37. A process according to any one of claims 33 to 36 wherein said compound of formula V and said compound of formula RSH are reacted in an alcohol solvent.

38. A process according to claim 37 wherein the solvent is ethanol.

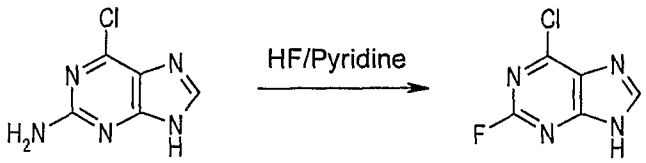
39. A process according to any one of claims 33 to 38 wherein said compound of formula V is prepared from a compound of formula VI



VI V

wherein X and Y are as defined in claim 33.

40. A process according to claim 39, where X is fluoro and Y is chloro, which comprises treating 2-amino-6-chloropurine with HF/pyridine



41. A process according to any one of claims 33 to 40 wherein R is aryl or aralkyl.

42. A process according to claim 41 wherein R is phenyl or benzyl.

43. Use of a process according to any one of claims 1 to 42 in the preparation of a 2,6,9-trisubstituted purine.

44. Use of a process according to any one of claims 1 to 42 in the preparation of a CDK inhibitor.