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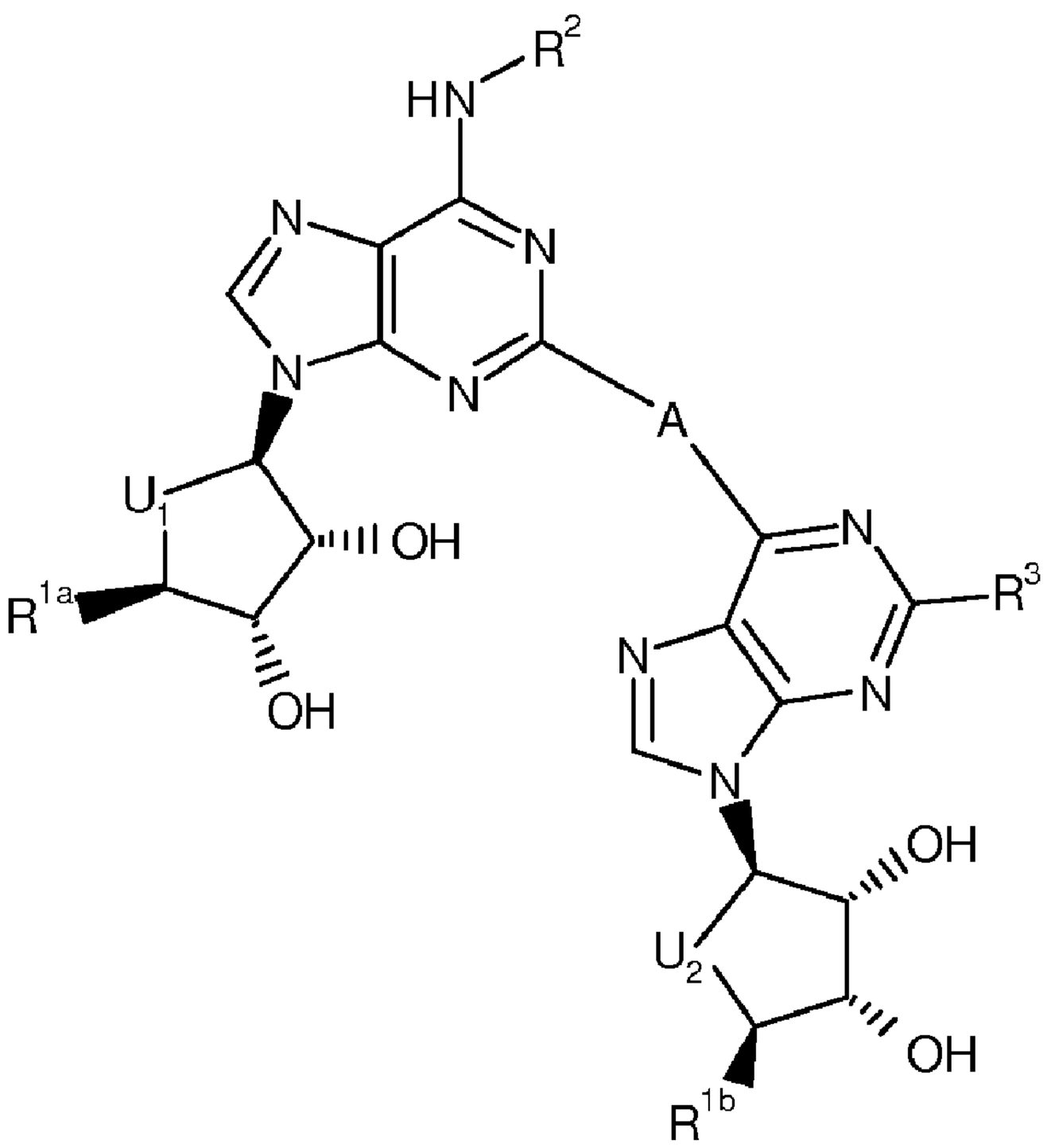
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(54) Titre : UTILISATION DE DERIVES DE L'ADENOSINE EN TANT QU'AGONISTES DU RECEPTEURS A2A
(54) Title: ADENOSINE DERIVATIVES AS A2A RECEPTOR AGONISTS



(I)

(57) Abrégé/Abstract:
A compound of formula (I), or stereoisomers or pharmaceutically acceptable salts thereof, formula (1), or stereoisomers or pharmaceutically acceptable salts thereof, wherein A, U^1, U^2, R^{1a}, R^{1b}, R^2 and R^3 have the meanings as indicated in the

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(57) Abrégé(suite)/Abstract(continued):
specification, are useful for treating conditions mediated by activation of the adenosine A_{2A} receptor, especially inflammatory or obstructive airways diseases. Pharmaceutical compositions that contain the compounds and a process for preparing the compounds are also described.

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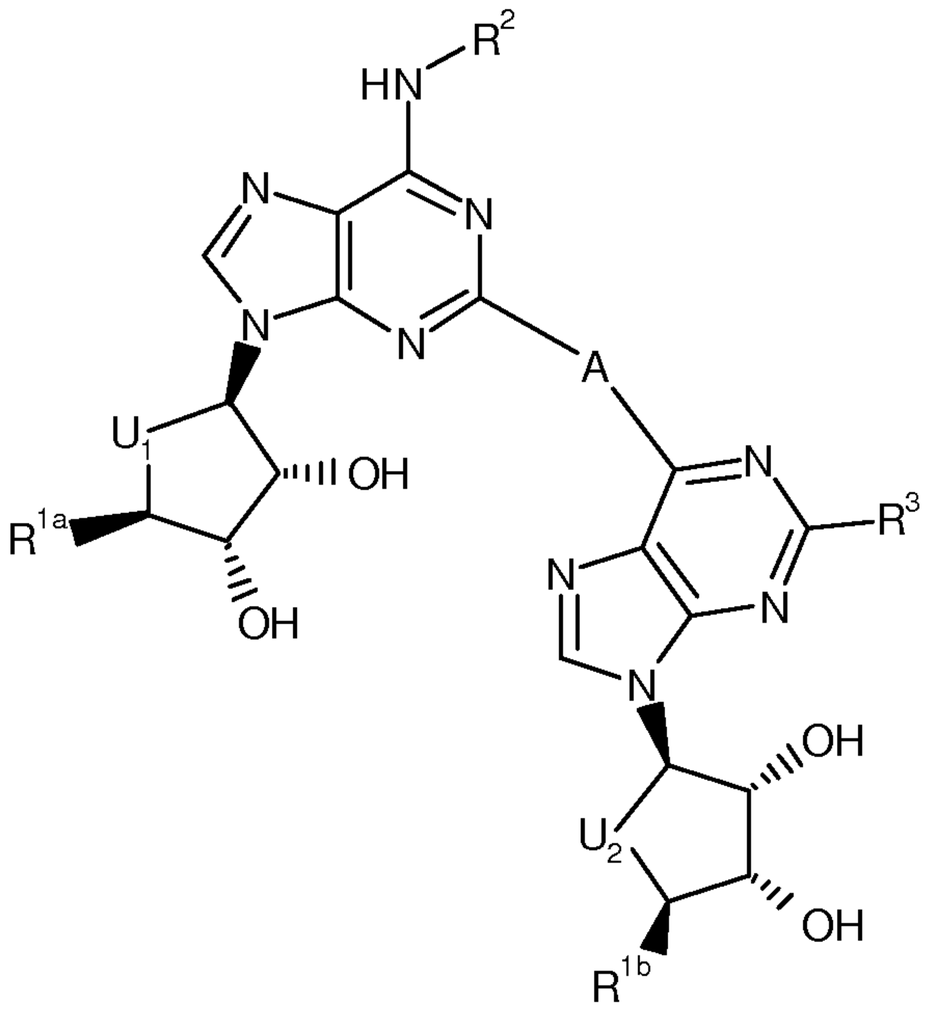
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(54) Title: ADENOSINE DERIVATIVES AS A2A RECEPTOR AGONISTS



(I)

(57) Abstract: A compound of formula (I), or stereoisomers or pharmaceutically acceptable salts thereof, formula (1), or stereoisomers or pharmaceutically acceptable salts thereof, wherein A, U^1, U^2, R^{1a}, R^{1b}, R^2 and R^3 have the meanings as indicated in the specification, are useful for treating conditions mediated by activation of the adenosine A_{2A} receptor, especially inflammatory or obstructive airways diseases. Pharmaceutical compositions that contain the compounds and a process for preparing the compounds are also described.

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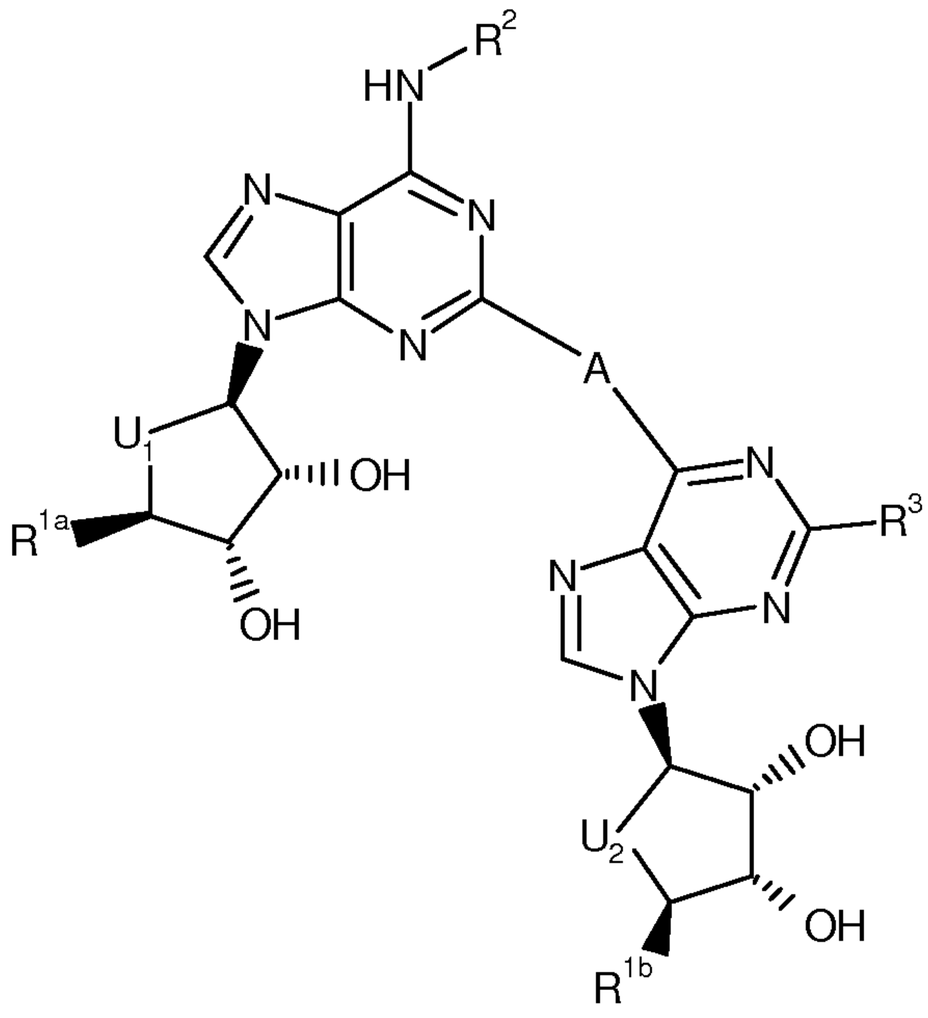
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ADENOSINE DERIVATIVES AS A2A RECEPTOR AGONISTS

This invention relates to organic compounds, their preparation and use as pharmaceuticals.

An aspect of the invention provides compounds of formula (I), or stereoisomers or pharmaceutically acceptable salts thereof,



(I)

,

wherein

U_1 and U_2 are independently selected from CH_2 and O with the proviso that when U_1 is O then R^{1a} is not a N-bonded substituent, and when U_2 is O then R^{1b} is not a N-bonded substituent;

R^1 and R^{1b} are independently selected from a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, that group being optionally substituted by oxo, O-C_1-C_8-alkyl, C_6-C_{10}-aryl, R^{1c} or by C_1-C_8-alkyl optionally substituted by OH, or

R^1 and R^{1b} are independently selected from -NR^4R^4, -NR^5-C_1-C_8-alkylcarbonyl, -NR^5-C_3-C_8-cycloalkylcarbonyl, -NR^5SO_2-C_1-C_8-alkyl, -NR^5-C_7-C_{14}-aralkylcarbonyl and -$NR^5C(=O)$-$C(=O)$-NR^5-C_1-C_8-alkyl optionally substituted by R^{1c}, or

R^{1a} and R^{1b} are independently selected from NR^4-C_1-C_8-alkyl, $NR^5C(O)C_1$-C_8-hydroxyalkyl, $NR^5CO_2C_1$-C_8-alkyl, and $NR^5CO_2C_2$-C_8-hydroxyalkyl, or

R^{1a} and R^{1b} are independently selected from C_1-C_8-hydroxyalkyl, CH_2-O-C_1-C_8-alkyl, C(O)-O-C_1-C_8-alkyl, $C(O)NR^5R^5$ and C(O)-NH-C_1-C_8-alkyl;

R^{1c} is a 3- or 12-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, said 3- or 12-membered heterocyclic ring being optionally substituted by halo, cyano, oxo, OH, carboxy, amino, nitro, C_1-C_8-alkyl, C_1-C_8-alkylsulfonyl, aminocarbonyl, C_1-C_8-alkylcarbonyl or O-C_1-C_8-alkyl optionally substituted by aminocarbonyl;

R^2 is C_1-C_8-alkyl optionally substituted by OH; halogen; C_6-C_{10}-aryl optionally substituted by OH, SO_2R^{10}, SC_1-C_8-alkyl, CN, halogen, O-C_7-C_{14}-aralkyl or O-C_1-C_8-alkyl; a C_3-C_{15}-carbocyclic group optionally substituted by O-C_7-C_{14} aralkyl, C_3-C_{15}-carbocyclic group, O-C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl or C_1-C_8-alkyl; O-C_1-C_8-alkyl; -SO_2-C_1-C_8-alkyl; a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, that group being optionally substituted by a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, C_7-C_{14}-aralkyl or C_6-C_{14}-aryl optionally substituted by O-C_7-C_{14}-aralkyl; or

R^2 is C_3-C_{15}-carbocyclic group optionally substituted by O-C_7-C_{14}-aralkyl, C_3-C_{15}-carbocyclic group, O-C_1-C_8-alkyl, or C_1-C_8-alkyl; or

R^2 is a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, that group being optionally substituted by 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, C_7-C_{14}-aralkyl, or C_6-C_{14}-aryl optionally substituted by O-C_7-C_{14}-aralkyl;

R^3 is hydrogen, halo, C_2-C_8-alkenyl, C_2-C_8-alkynyl or C_1-C_8-alkoxycarbonyl, or

R^3 is amino optionally substituted by C_3-C_8-cycloalkyl optionally substituted by amino, hydroxy, C_7-C_{14}-aralkyloxy, -SO_2-C_6-C_{10}-aryl or -NH-C(=O)-NH-R^{3c}, or

R^3 is amino substituted by R^{3a}, -R^{3a}-C_7-C_{14}-aralkyl or a C_5-C_{15}-carbocyclic group optionally substituted by OH, C_1-C_8-alkyl or C_1-C_8-alkoxycarbonyl, or

R^3 is aminocarbonyl optionally substituted by R^{3b}, or

R^3 is C_1-C_8-alkylamino optionally substituted by OH, R^{3b}, amino, di(C_1-C_8-alkyl)amino, -NH-C(=O)-C_1-C_8-alkyl, -NH-SO_2-C_1-C_8-alkyl, -NH-C(=O)-NH-R^{3c}, -NH-C(=O)-NH-C_1-C_8-alkyl-R^{3b} , a C_5-C_{15}-carbocyclic group or by C_6-C_{10}-aryl optionally substituted by C_6-C_{10}-aryloxy, or

R^3 is C_1-C_8-alkylaminocarbonyl or C_3-C_8-cycloalkylamino-carbonyl optionally substituted by amino, C_1-C_8-alkylamino, di(C_1-C_8-alkyl)amino or -NH-C(=O)-NH-R^{3d}, or

R^3 is a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, that group being optionally substituted by 0-3R^4;

R^{3a} and R^{3b} are each independently a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur; optionally substituted by halo, cyano, oxo, OH, carboxy, nitro, C_1-C_8-alkyl, C_1-C_8-alkylcarbonyl, OH-C_1-C_8-alkyl, C_1-C_8-haloalkyl, amino-C_1-C_8-alkyl, amino(OH)C_1-C_8-alkyl or C_1-C_8-alkoxy optionally substituted by aminocarbonyl;

R^{3c} is a 5- or 6-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by a 5- or 6-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur;

R^{3d} are independently a 5- or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, said 5- or 6-membered heterocyclic ring being optionally substituted by halo, cyano, oxo, OH, carboxy, amino, nitro, C_1-C_8-alkyl, C_1-C_8-alkylsulfonyl, aminocarbonyl, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxy optionally substituted by aminocarbonyl, or a 5- or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, said ring also being optionally substituted by halo, cyano, oxo, OH, carboxy, amino, nitro, C_1-C_8-alkyl, C_1-C_8-alkylsulfonyl, aminocarbonyl, C_1-C_8-alkylcarbonyl, or C_1-C_8-alkoxy optionally substituted by aminocarbonyl;

R^4 is selected from OH, C_1-C_8-alkyl optionally substituted by OH, C_1-C_8-alkoxy, C_7-C_{14}-aralkyl optionally substituted with OH, O-C_1-C_8-alkyl, halogen C_6-C_{10}-aryl, or O-C_6-C_{10}-aryl, C_1-C_8-alkoxy, C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl or -halogen, O-C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl or -halogen, $NR^{4a}R^{4b}$, $NHC(O)R^{4c}$, $NHS(O)_2R^{4d}$, $NHS(O)_2R^{4e}$, $NR^{4f}C(O)NR^{4e}R^{4h}$, $NR^{4f}C(O)NR^{4g}R^{4h}$, $NR^{4i}C(O)OR^{4j}$, C_1-C_8-alkylcarbonyl, C_1-C_8-

alkoxycarbonyl, di(C_1-C_8-alkyl)aminocarbonyl, $COOR^{4k}$, $C(O)R^{4l}$, $NHC(O)R^{4q}$, $NHC(=NR^{4m})N(R^{4n})R^{4o}$, and a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur optionally substituted by $COOR^{4p}$;

R^{4a}, R^{4c}, R^{4f}, R^{4h} and R^{4i} are, independently, H, or C_1-C_8-alkyl;

R^{4b} is H, C_1-C_8-alkyl a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted by 0-3R^5 or C_6-C_{10}-aryl;

R^{4d}, R^{4e}, and R^{4j} are, independently, C_1-C_8-alkyl or a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted by 0-3R^5;

R^{4g} is C_1-C_8-alkyl optionally substituted by a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted with SO_2R^{10}, CN, or 0-3R^5, or

R^{4g} is a C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl, SO_2R^{10} or -halogen, or

R^{4g} is a C_7-C_{14}-aralkyl optionally substituted by OH, O-C_1-C_8-alkyl, halogen, C_6-C_{10}-aryl, SO_2R^{10}, CN, -C(=NH)NH2, or O-C_6-C_{10}-aryl, or

R^{4g} is a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted by 0-3R^5;

R^{4k} is H, C_1-C_8-alkyl, C_6-C_{10}-aryl or a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur;

R^{4l} is C_1-C_8-alkyl, C_6-C_{10}-aryl, NHR^6 or a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur;

R^{4m} is CN;

R^{4n} is H or C_1-C_8-alkyl;

R^{4o} is H, C_1-C_8-alkyl optionally substituted by OH or by a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted with SO_2R^{10}, CN, or 0-3R^5, C_1-C_8-alkoxy, C_7-C_{14}-aralkyl optionally substituted with OH, O-C_1-C_8-alkyl, halogen C_6-C_{10}-

aryl, or O-C_6-C_{10}-aryl, C_1-C_8-alkoxy, C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl SO_2R^{10} or -halogen;

R^{4p} is H, C_1-C_8-alkyl or C_7-C_{14}-aralkyl;

R^{4q} is C_6-C_{10}-aryl optionally substituted by OH, C(=NH)NH_2, or SO_2NH_2, or a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur optionally substituted by 0-3R^5 or a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted by 0-3R^5;

R^5 is selected from OH, C_1-C_8-alkyl optionally substituted by OH, CN, SO_2R^{10} or halogen, C_7-C_{14}-aralkyl optionally substituted with OH, O-C_1-C_8-alkyl, C_6-C_{10}-aryl, or O-C_6-C_{10}-aryl, C_1-C_8-alkoxy, C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl or -halogen, O-C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl optionally substituted by halogen, $NR^{5a}R^{5b}$, $NHC(O)R^{5c}$, $NHS(O)_2R^{5d}$, $NHS(O)_2R^{5e}$, $NR^{5f}C(O)NR^{5g}R^{5h}$, $NR^{5i}C(O)OR^{5j}$, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, di(C_1-C_8-alkyl)aminocarbonyl, $COOR^{5k}$, $C(O)R^{5l}$, a C(O)-C_6-C_{10}-aryl optionally substituted by OH, -COOH, C_1-C_8-alkyl, O-C_1-C_8-alkyl, -halogen, or SO_2R^{10}, $C(O)NHR^{5m}$ or a 3-12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted by 0-3R^7;

R^{5a}, R^{5b}, R^{5c}, R^{5f}, R^{5h} and R^{5i} are, independently, H, C_1-C_8-alkyl or C_6-C_{10}-aryl;

R^{5d}, R^{5e}, R^{5g}, R^{5j} and R^{5m} are, independently, C_1-C_8-alkyl or a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted by $COOR^8$;

R^{5k} is H, C_1-C_8-alkyl, C_6-C_{10}-aryl or a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur;

R^{5l} is C_1-C_8-alkyl, C_6-C_{10}-aryl or a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted by $COOR^9$;

R^6 is $COOR^{6a}$ or a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted by $COOR^{6b}$;

R^{6a}, R^{6b}, R^7, R^8 and R^9 are selected from H, C_1-C_8-alkyl and C_7-C_{14}-aralkyl; and

R^{10} is C_1-C_8-alkyl optionally substituted by halogen, C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl or -halogen, or $NR^{4a}R^{4b}$;

A is selected from -E-NR^{14}-, -E-NR^{14}-G-NR^{15}-, -E-$NR^{14}C(O)NR^{14}$-G-NR^{15}-, -E-$NR^{14}C(O)$G-NR^{15}-, -E-NR^{14}-G-NR^{14}-E^a-, -$NR^{14}C(O)$-E-$NR^{14}C(O)NR^{14}$-, -NR^{15}-G-NR^{15}-, -NR^{15}-$(CR^{16}R^{17})_n$-NR^{15}-, -NR^{15}-X3-G-X4-NR^{15}-, -$NR^{14}C(O)NR^{14}$-, $NR^{14}C(O)NR^{14}$-J-NR^{15}-, $NR^{14}C(O)$-$(CR^{16}R^{17})_n$-$C(O)NR^{14}$-, and $NR^{14}C(O)NR^{14}$-E-$NR^{14}C(O)NR14^4$-;

E is selected from C_3-C_{15}-carbocyclic group optionally substituted by HO, C_1-C_8-alkyl, C_6-C_{10}-aryl, 3- to 12-membered heterocyclic group, a C_6-C_{10}-aryl optionally substituted by HO, C_1-C_8-alkyl, O- C_1-C_8-alkyl, halogen, and -E^a-$C(O)NR^{14}$-E^b-$NR^{14}C(O)$-E^a-;

each E^a is independently selected from a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, a C_3-C_{15}-carbocyclic group, and C_6-C_{10}-aryl optionally substituted by HO, C_1-C_8-alkyl, O-C_1-C_8-alkyl, or halogen;

E^b is selected from a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, a C_3-C_{15}-carbocyclic group, and C_6-C_{10}-aryl optionally substituted by HO, C_1-C_8-alkyl, O-C_1-C_8-alkyl, or halogen;

G is selected from selected from C(O), $NR^{14}C(O)$, $C(O)NR^{14}$, C_1-C_8-alkyl optionally substituted by OH, halogen or C_6-C_{10}-aryl, a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur optionally substituted by R^{18}, a C_3-C_{15}-carbocyclic group optionally substituted by HO, C_1-C_8-alkyl, and C_6-C_{10}-aryl optionally substituted by HO, C_1-C_8-alkyl, O-C_1-C_8-alkyl, or halogen;

J is selected from C_6-C_{10}-aryl, SO_2, and C_6-C_{10}-aryl-SO_2-;

X3 and X4 are independently selected from C_1-C_8-alkyl optionally substituted by OH, halogen or C_6-C_{10}-aryl, a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected

from the group consisting of oxygen and sulfur optionally substituted by R^{18}, a C_3-C_{15}-carbocyclic group, and C_6-C_{10}-aryl;

each R^{14} is independently selected from H, C_1-C_8-alkyl, and C_6-C_{10}-aryl;

each R^{15} is independently selected from H, -CN, C_1-C_8-alkyl, and C_6-C_{10}-aryl;

each R^{16} and each R^{17} are independently selected from H, halogen, OH, C_1-C_8-alkyl, and C_6-C_{10}-aryl;

R^{18} is 3- or 12-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, said 3- or 12-membered heterocyclic ring being optionally substituted by halo, cyano, oxo, OH, carboxy, amino, nitro, C_1-C_8-alkyl, C_1-C_8-alkylsulfonyl, aminocarbonyl, C_1-C_8-alkylcarbonyl or O-C_1-C_8-alkyl optionally substituted by aminocarbonyl; and

n is an integer selected from 1-8.

Definitions

Terms used in the specification have the following meanings:

"Optionally substituted" means the group referred to can be substituted at one or more positions by any one or any combination of the radicals listed thereafter.

"Halo" or "halogen", as used herein, may be fluorine, chlorine, bromine or iodine. Preferably halo is chlorine.

"Hydroxy", as used herein, is OH.

"C_1-C_8-Alkyl", as used herein, denotes straight chain or branched alkyl having 1-8 carbon atoms. Preferably C_1-C_8-alkyl is C_1-C_4-alkyl.

"C_1-C_8-Alkoxy", or as used herein, denotes straight chain or branched alkoxy having 1-8 carbon atoms (e.g., O-C_1-C_8-alkyl). Preferably, C_1-C_8-alkoxy is C_1-C_4-alkoxy.

"C_3-C_8-Cycloalkyl", as used herein, denotes cycloalkyl having 3-8 ring carbon atoms, e.g., a monocyclic group, such as a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl, any of which can be substituted by one or more, usually one or two, C_1-C_4-alkyl groups; or a bicyclic group, such as bicycloheptyl or bicyclooctyl.

"C_1-C_8-Alkylamino" and "di(C_1-C_8-alkyl)amino", as used herein, denote amino substituted respectively by one or two C_1-C_8-alkyl groups as hereinbefore defined, which may be the same or different.

"C_1-C_8-Alkylcarbonyl" and "C_1-C_8-alkoxycarbonyl", as used herein, denote C_1-C_8-alkyl or C_1-C_8-alkoxy, respectively, as hereinbefore defined attached by a carbon atom to a carbonyl group.

"C_6-C_{10}-Aryl", as used herein, denotes a monovalent carbocyclic aromatic group that contains 6-10 carbon atoms and which may be, e.g., a monocyclic group, such as phenyl; or a bicyclic group, such as naphthyl.

"C_7-C_{14}-Aralkyl", as used herein, denotes alkyl, e.g., C_1-C_4-alkyl, as hereinbefore defined, substituted by C_6-C_{10}-aryl as hereinbefore defined. Preferably, C_7-C_{14}-aralkyl is C_7-C_{10}-aralkyl, such as phenyl-C_1-C_4-alkyl.

"C_1-C_8-Alkylaminocarbonyl" and "C_3-C_8-cycloalkylaminocarbonyl", as used herein, denote C_1-C_8-alkylamino and C_3-C_8-cycloalkylamino respectively as hereinbefore defined attached by a carbon atom to a carbonyl group. Preferably C_1-C_8-alkylaminocarbonyl and C_3-C_8-cycloalkyl-aminocarbonyl are C_1-C_4-alkylaminocarbonyl and C_3-C_8-cycloalkylaminocarbonyl, respectively.

"C_3-C_{15}-Carbocyclic group", as used herein, denotes a carbocyclic group having 3-15 ring carbon atoms, e.g., a monocyclic group, either aromatic or non-aromatic, such as a cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl or phenyl; or a bicyclic group, such as bicyclooctyl, bicyclononyl, bicyclodecyl, indanyl or indenyl, again any of which can be substituted by one or more, usually one or two, C_1-C_4-alkyl groups. Preferably the C_3-C_{15}-carbocyclic group is a C_5-C_{10}-carbocyclic group, especially phenyl, cyclohexyl or indanyl. The C_5-C_{15}-carbocyclic group can unsubstituted or substituted. Substituents on the heterocyclic ring include halo, cyano, OH, carboxy, amino, aminocarbonyl, nitro, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy and C_3-C_{10}-cycloalkyl.

"3- to 12-Membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur", as used herein, may be, e.g., furan, pyrrole, pyrrolidine, pyrazole, imidazole, triazole, isotriazole, tetrazole, thiadiazole, isothiazole, oxadiazole, pyridine, piperidine, pyrazine, oxazole, isoxazole, pyrazine, pyridazine, pyrimidine, piperazine, pyrrolidine, morpholino, triazine, oxazine or thiazole.

Preferred heterocyclic rings include piperazine, pyrrolidine, morpholino, imidazole, isotriazole, pyrazole, tetrazole, thiazole, triazole, thiadiazole, pyridine, piperidine, pyrazine, furan, oxazole, isoxazole, oxadiazole and azetidine. The 3- to-12-membered heterocyclic ring can be unsubstituted or substituted.

Throughout this specification and in the claims that follow, unless the context requires otherwise, the word "comprise", or variations, such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps. As understood by one skilled in the art only combinations of substituents that are chemically possible are embodiments of the invention.

Especially preferred specific compounds of formula (I) are those described hereinafter in the Examples.

Stereoisomers are those compounds where there is an asymmetric carbon atom. The compounds exist in individual optically active isomeric forms or as mixtures thereof, e.g., as diastereomeric mixtures. The present invention embraces both individual optically active *R* and *S* isomers, as well as mixtures thereof. Individual isomers can be separated by methods well known to those skilled in the art, e.g., chiral high performance liquid chromatography (HPLC).

Tautomers are one of two or more structural isomers that exist in equilibrium and are readily converted from one isomeric form to another.

The compounds of the invention may exist in both unsolvated and solvated forms. The term "solvate" is used herein to describe a molecular complex comprising the compound of the invention and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term "hydrate" is employed when said solvent is water.

According to formula (I), R^{1a} and R^{1b} are, independently, suitably a N-bonded 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, that group being optionally substituted by oxo, O-C_1-C_8-alkyl, C_6-C_{10}-aryl, R^{1c} or by C_1-C_8-alkyl optionally substituted by OH. The 3- to 12-membered heterocyclic groups are preferably 5- to 6-membered heterocyclic groups (e.g., tetrazole groups, pyrrole groups, pyrazole groups, pyridine groups, isoxazole groups, triazole groups, or hydantoin groups).

The R^{1a} and R^{1b} heterocyclic groups can be N-bonded where possible. The heterocyclic groups are preferably substituted by at least one group selected from C_1-C_8-alkyl optionally substituted by OH (e.g., an ethyl group, a hydroxymethyl group or a hydroxyethyl group). These substitution groups on the heterocyclic groups can be C- or N-bonded to the heterocyclic group where possible.

According to formula (I), R^{1a} and R^{1b} are also, independently, suitably -NH-C_1-C_8-alkylcarbonyl or -NH-C_3-C_8-cycloalkylcarbonyl. The -NH-C_1-C_8-alkylcarbonyl group is preferably a acetamide group or a propionamide group. The -NH-C_3-C_8-cycloalkylcarbonyl is preferably a cyclobutane carboxylic acid amide group.

According to formula (I), R^{1a} and R^{1b} are also, independently suitably C_1-C_8-hydroxy alkyl or CH_2-O-C_1-C_8-alkyl.

According to formula (I) R^{1a} and R^{1b} are also, independently, suitably NHC(O)C_1-C_8-hydroxyalkyl. R^1 is preferably NHC(O)C_1-C_2 hydroxyalkyl (e.g., a 2-hydroxy-acetamide group, a 2-hydroxy-propionamide group, or a 3-hydroxy-propionamide group).

According to formula (I), R^2 is suitably H, C_1-C_8-alkyl optionally substituted by OH, halogen or C_6-C_{10}-aryl optionally substituted by OH or O-C_1-C_8 alkyl. When substituted, suitably the C_1-C_8-alkyl is substituted by OH, phenyl, napthlene, or preferably by two phenyl groups. When the C_1-C_8-alkyl is substituted by two phenyl groups, either or both phenyl groups are preferably unsubstituted, or substituted by at least one OCH_3, one OH or one halogen.

According to formula (I), R^2 is also suitably C_1-C_8-alkyl substituted by a phenyl. This phenyl can be further substituted by a phenyl where this phenyl is substituted by CN, halogen, or C_1-C_8-alkyl.

According to formula (I), R^2 is also suitably a C_3-C_{15}-carbocyclic group (e.g., a fluorene group).

According to formula (I), R^3 is suitably selected from amino substituted by R^{3c}, -R^{3c}-C_7-C_{14}-aralkyl, C_1-C_8-alkyl optionally substituted by R^{3c}, and a C_3-C_{15}-carbocyclic group optionally substituted by OH, C_1-C_8-alkyl or C_1-C_8-alkoxycarbonyl. R^{3c} is suitably a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur (e.g., a pyrrolidine or a pyrazole) optionally

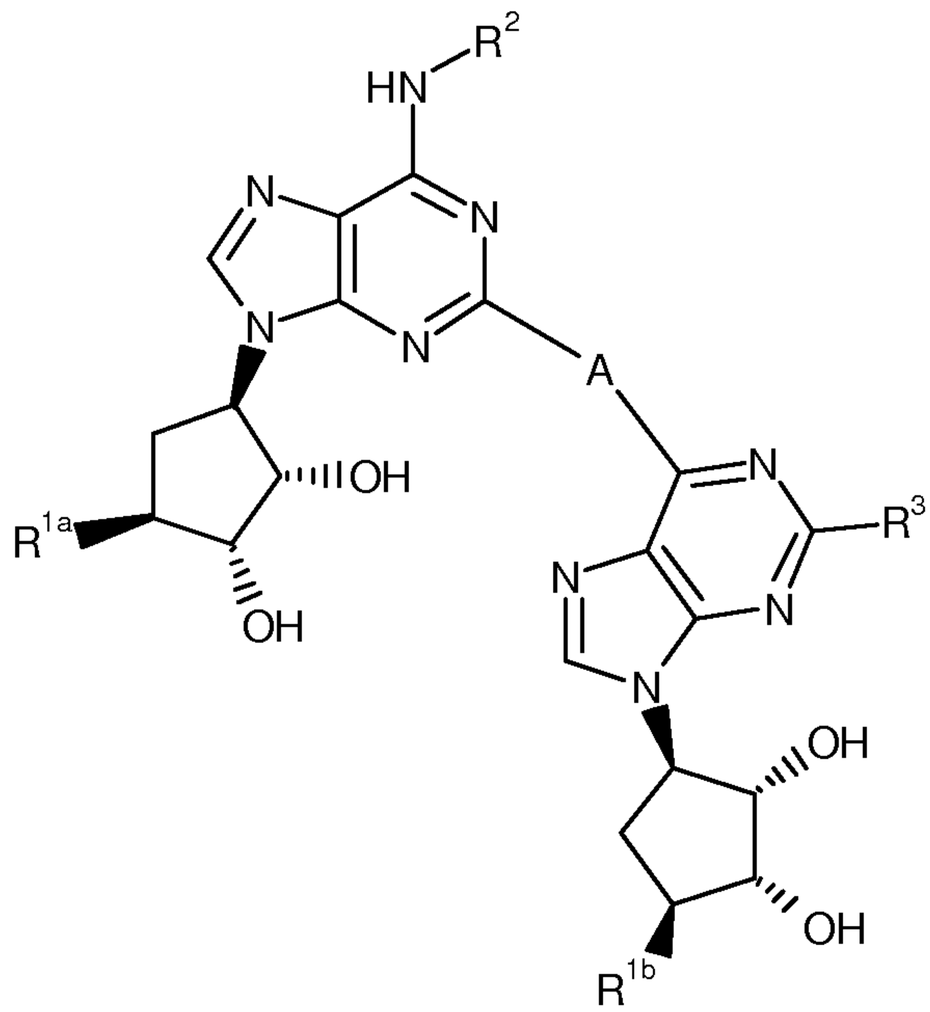
substituted by halo, cyano, oxo, OH, carboxy, nitro, C_1-C_8-alkyl, C_1-C_8-alkylcarbonyl, OH-C_1-C_8-alkyl, C_1-C_8-haloalkyl, amino-C_1-C_8-alkyl, amino(OH)C_1-C_8-alkyl and C_1-C_8-alkoxy optionally substituted by aminocarbonyl. Preferably the 3- to 12-membered heterocyclic group is substituted by at least one C_1-C_8-alkyl group.

According to formula (I), R^3 is also independently suitably a N-bonded 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur. This heterocyclic group is preferably a pyrrolidine, pyrazole, triazole, tetrazole or imidazole. The heterocyclic group is optionally substituted by $NR^{4f}C(O)NR^{4g}R^{4h}$, $NR^{4a}R^{4b}$, $NHC(O)R^{20q}$ and where R^{4a} and R^{4b} are preferably H or C_1-C_8-alkyl (e.g., methyl) and R^{4f} and R^{4h} are preferably H. R^{4g} is preferably a 3- to 12-membered heterocyclic group, such as pyridine.

According to formula (I), R^3 is also suitably C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl, SO_2R^{10} or -halogen, where R^{10} is suitably NH_2.

According to formula (I), A is suitably selected from -E-NR^{14}-, -E-NR^{14}-G-NR^{14}-, -E-$NR^{14}C(O)NR^{14}$-G-NR^{14}, -E-$NR^{14}C(O)$G-NR^{15}-, -E-NR^{14}-G-NR^{14}-E^a-, E is suitably selected from 5-6 heterocyclic group, such as pyrrolidine and piperidine. E^a is suitably C_3-C_{15}-carbocyclic group, such as cyclohexyl. Each R^{14} is independently suitably selected from H and C_1-C_8-alkyl, such as methyl. G is suitably selected a C_3-C_{15}-carbocyclic group optionally substituted by HO or C_1-C_8-alkyl or G is suitably selected from 5-6 heterocyclic group, such as pyrrolidine and piperidine. Preferably the C_3-C_{15}-carbocyclic group is unsubstituted.

Another aspect of the invention provides compounds of formula (Ia), or stereoisomers or pharmaceutically acceptable salts thereof,



(Ia)

,

wherein

R^1 and R^{1b} are independently selected from a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, that group being optionally substituted by oxo, O-C_1-C_8-alkyl, C_6-C_{10}-aryl, R^{1c} or by C_1-C_8-alkyl optionally substituted by OH, or

R^1 and R^{1b} are independently selected from -NR^4R^4, and -NR^5-C_1-C_8-alkylcarbonyl;

R^2 is C_1-C_8-alkyl optionally substituted by OH, halogen C_6-C_{10}-aryl optionally substituted by OH, SC_1-C_8-alkyl, CN, halogen, O-C_7-C_{14}-aralkyl, or O-C_1-C_8-alkyl, a C_3-C_{15}-carbocyclic group optionally substituted by O-C_7-C_{14} aralkyl, C_3-C_{15}-carbocyclic group, O-C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl or C_1-C_8-alkyl, O-C_1-C_8-alkyl, -SO_2-C_1-C_8-alkyl, a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, that group being optionally substituted by 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, C_7-C_{14}-aralkyl, or C_6-C_{14}-aryl optionally substituted by O-C_7-C_{14}-aralkyl, or

R^3 is hydrogen, halo, C_2-C_8-alkenyl, C_2-C_8-alkynyl or C_1-C_8-alkoxycarbonyl, or

R^3 is C_1-C_8-alkylamino optionally substituted by OH, R^{3b}, amino, di(C_1-C_8-alkyl)amino, -NH-C(=O)-C_1-C_8-alkyl, -NH-SO_2-C_1-C_8-alkyl, -NH-C(=O)-NH-R^{3c}, -NH-C(=O)-NH-C_1-

C_8-alkyl-R^{3b} , a C_3-C_{15}-carbocyclic group or by C_6-C_{10}-aryl optionally substituted by C_6-C_{10}-aryloxy, or

R^3 is a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, that group being optionally substituted by 0-3R^4;

R^{3a} and R^{3b} are each independently a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur; optionally substituted by halo, cyano, oxo, OH, carboxy, nitro, C_1-C_8-alkyl, C_1-C_8-alkylcarbonyl, OH-C_1-C_8-alkyl, C_1-C_8-haloalkyl, amino-C_1-C_8-alkyl, amino(OH)C_1-C_8-alkyl and C_1-C_8-alkoxy optionally substituted by aminocarbonyl;

R^{3c} is a 5- or 6-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by a 5- or 6-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur;

R^{3d} are independently a 5- or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, said 5- or 6-membered heterocyclic ring being optionally substituted by halo, cyano, oxo, OH, carboxy, amino, nitro, C_1-C_8-alkyl, C_1-C_8-alkylsulfonyl, aminocarbonyl, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxy optionally substituted by aminocarbonyl, or a 5- or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, said ring also being optionally substituted by halo, cyano, oxo, OH, carboxy, amino, nitro, C_1-C_8-alkyl, C_1-C_8-alkylsulfonyl, aminocarbonyl, C_1-C_8-alkylcarbonyl, or C_1-C_8-alkoxy optionally substituted by aminocarbonyl;

R^4 is selected from OH, C_1-C_8-alkyl optionally substituted by OH, C_1-C_8-alkoxy, C_7-C_{14}-aralkyl optionally substituted with OH, O-C_1-C_8-alkyl, halogen C_6-C_{10}-aryl, or O-C_6-C_{10}-aryl, C_1-C_8-alkoxy, C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl or -halogen, O-C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl or -halogen, $NR^{4f}C(O)NR^{4g}R^{4h}$;

R^{4f}, R^{4h} are, independently, H, or C_1-C_8-alkyl;

R^{4g} is a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur;

A is selected from -E-NR^{14}-, -E-NR^{14}-G-NR^{15}-, -E-$NR^{14}C(O)NR^{14}$-G-NR^{15}-, -E-$NR^{14}C(O)$G-NR^{15}-, -E-NR^{14}-G-NR^{14}-E^a-, and -NR^{15}-G-NR^{15}-;

E is selected from C_3-C_{15}-carbocyclic group optionally substituted by HO, C_1-C_8-alkyl, C_6-C_{10}-aryl, 3- to 12-membered heterocyclic group, a C_6-C_{10}-aryl optionally substituted by HO, C_1-C_8-alkyl, O-C_1-C_8-alkyl, halogen, or -E^a-$C(O)NR^{14}$-E^b-$NR^{14}C(O)$-E^a-;

each E^a is independently selected from a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, a C_3-C_{15}-carbocyclic group, and C_6-C_{10}-aryl optionally substituted by HO, C_1-C_8-alkyl, O-C_1-C_8-alkyl, or halogen;

E^b is selected from a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, a C_3-C_{15}-carbocyclic group, and C_6-C_{10}-aryl optionally substituted by HO, C_1-C_8-alkyl, O-C_1-C_8-alkyl, or halogen;

G is selected from selected from C(O), $NR^{14}C(O)$, $C(O)NR^{14}$, C_1-C_8-alkyl optionally substituted by OH, halogen or C_6-C_{10}-aryl, a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur optionally substituted by R^{18}, a C_3-C_{15}-carbocyclic group optionally substituted by HO, C_1-C_8-alkyl, and C_6-C_{10}-aryl optionally substituted by HO, C_1-C_8-alkyl, or O-C_1-C_8-alkyl, halogen; and

R^{18} is 3- or 12-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, said 3- or 12-membered heterocyclic ring being optionally substituted by halo, cyano, oxo, OH, carboxy, amino, nitro, C_1-C_8-alkyl, C_1-C_8-alkylsulfonyl, aminocarbonyl, C_1-C_8-alkylcarbonyl or O-C_1-C_8-alkyl optionally substituted by aminocarbonyl.

Another aspect of the invention provides compounds of formula (Ia), or stereoisomers or pharmaceutically acceptable salts thereof,

wherein

R^1 and R^{1b} are independently selected from a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, that group

being optionally substituted by oxo, O-C_1-C_8-alkyl, C_6-C_{10}-aryl, R^{1c} or by C_1-C_8-alkyl optionally substituted by OH, or

R^1 and R^{1b} are independently selected from -NR^4R^4, and -NR^5-C_1-C_8-alkylcarbonyl;

R^2 is C_1-C_8-alkyl optionally substituted by OH, halogen C_6-C_{10}-aryl optionally substituted by OH, SC_1-C_8-alkyl, CN, halogen, O-C_7-C_{14}-aralkyl, or O-C_1-C_8-alkyl, a C_3-C_{15}-carbocyclic group optionally substituted by O-C_7-C_{14} aralkyl, C_3-C_{15}-carbocyclic group, O-C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl or C_1-C_8-alkyl, O-C_1-C_8-alkyl, -SO_2-C_1-C_8-alkyl, a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, that group being optionally substituted by 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, C_7-C_{14}-aralkyl, or C_6-C_{14}-aryl optionally substituted by O-C_7-C_{14}-aralkyl, or

R^3 is hydrogen, halo, C_2-C_8-alkenyl, C_2-C_8-alkynyl or C_1-C_8-alkoxycarbonyl, or

R^3 is C_1-C_8-alkylamino optionally substituted by OH, R^{3b}, amino, di(C_1-C_8-alkyl)amino, -NH-C(=O)-C_1-C_8-alkyl, -NH-SO_2-C_1-C_8-alkyl, -NH-C(=O)-NH-R^{3c}, -NH-C(=O)-NH-C_1-C_8-alkyl-R^{3b} , a C_3-C_{15}-carbocyclic group or by C_6-C_{10}-aryl optionally substituted by C_6-C_{10}-aryloxy, or

R^3 is a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, that group being optionally substituted by 0-3R^4;

R^{3a} and R^{3b} are each independently a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur; optionally substituted by halo, cyano, oxo, OH, carboxy, nitro, C_1-C_8-alkyl, C_1-C_8-alkylcarbonyl, OH-C_1-C_8-alkyl, C_1-C_8-haloalkyl, amino-C_1-C_8-alkyl, amino(OH)C_1-C_8-alkyl or C_1-C_8-alkoxy optionally substituted by aminocarbonyl;

R^{3c} is a 5- or 6-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by a 5- or 6-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur;

R^{3d} are independently a 5- or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, said

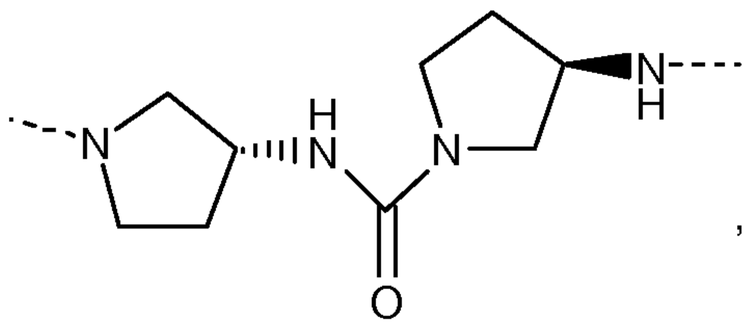
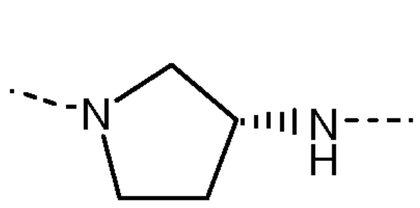
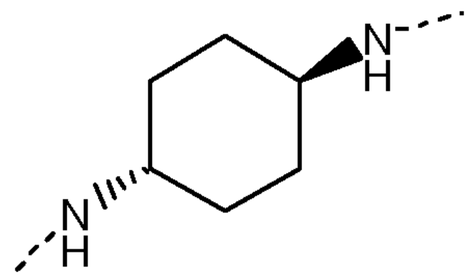
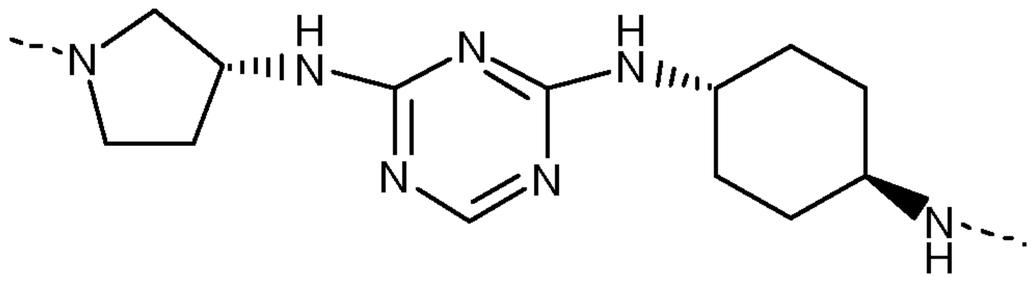
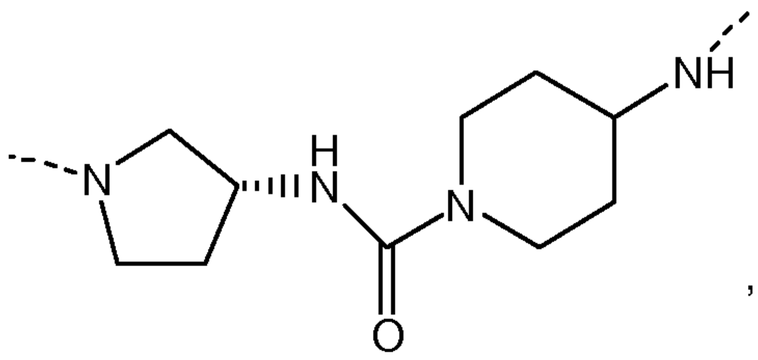
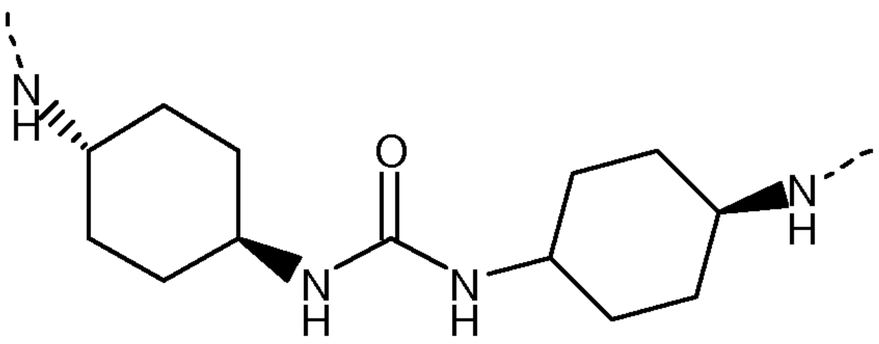
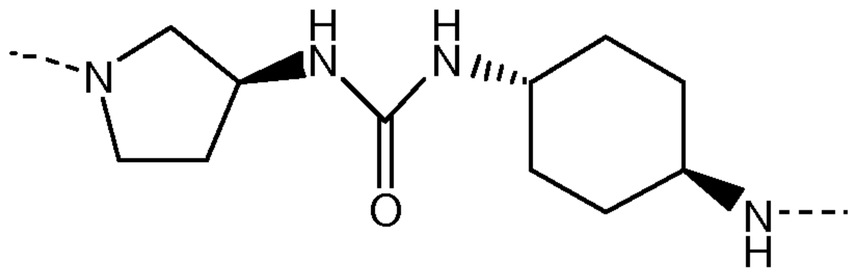
5- or 6-membered heterocyclic ring being optionally substituted by halo, cyano, oxo, OH, carboxy, amino, nitro, C_1-C_8-alkyl, C_1-C_8-alkylsulfonyl, aminocarbonyl, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxy optionally substituted by aminocarbonyl, or a 5- or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, said ring also being optionally substituted by halo, cyano, oxo, OH, carboxy, amino, nitro, C_1-C_8-alkyl, C_1-C_8-alkylsulfonyl, aminocarbonyl, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxy optionally substituted by aminocarbonyl;

R^4 is selected from OH, C_1-C_8-alkyl optionally substituted by OH, C_1-C_8-alkoxy, C_7-C_{14}-aralkyl optionally substituted with OH, O-C_1-C_8-alkyl, halogen C_6-C_{10}-aryl, or O-C_6-C_{10}-aryl, C_1-C_8-alkoxy, C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl or -halogen, O-C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl or -halogen, and $NR^{4f}C(O)NR^{4g}R^{4h}$;

R^{4f}, R^{4h} are, independently, H, or C_1-C_8-alkyl;

R^{4g} is a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur; and

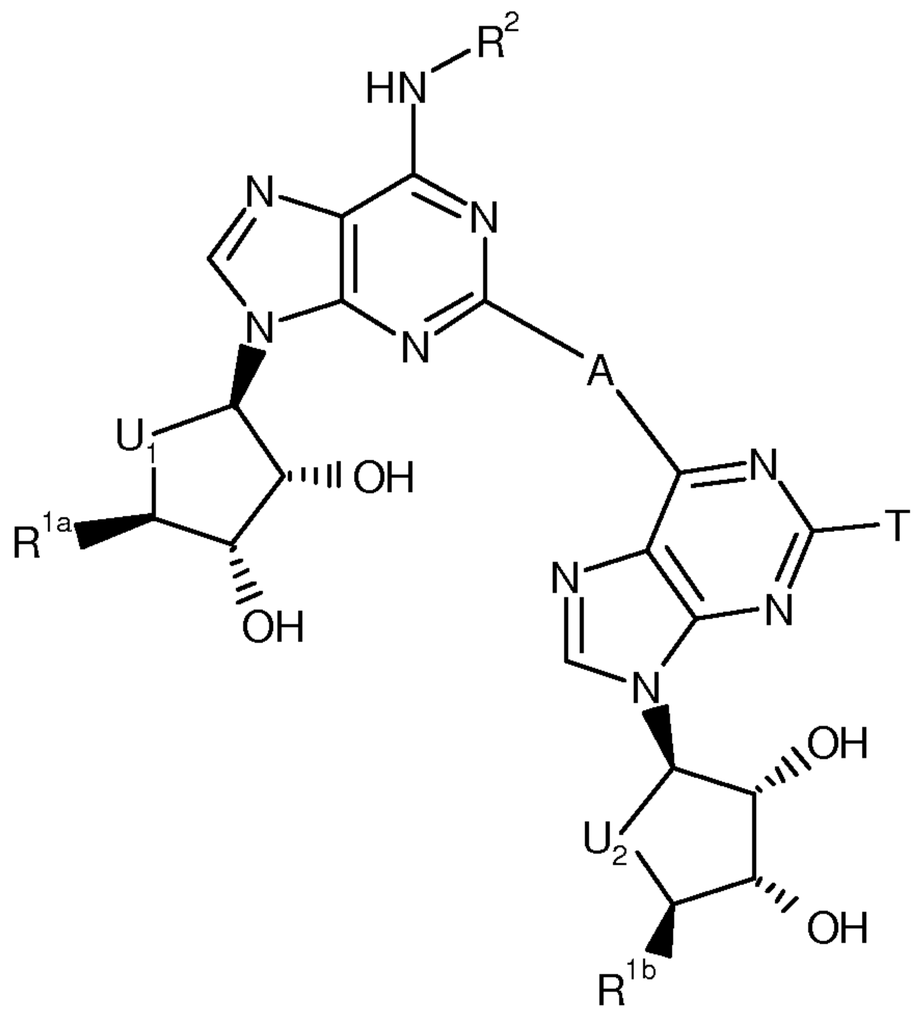
A is selected from


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,

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and

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SYNTHESIS

Another embodiment of the present invention provides a process for the preparation of compounds of formula (I), in free or pharmaceutically acceptable salt form, which comprises the steps of:

(i) reacting a compound of formula (II)



(II)

,

where

R^{1a}, R^{1b}, R^2, U_1, U_2 are as defined hereinbefore; and

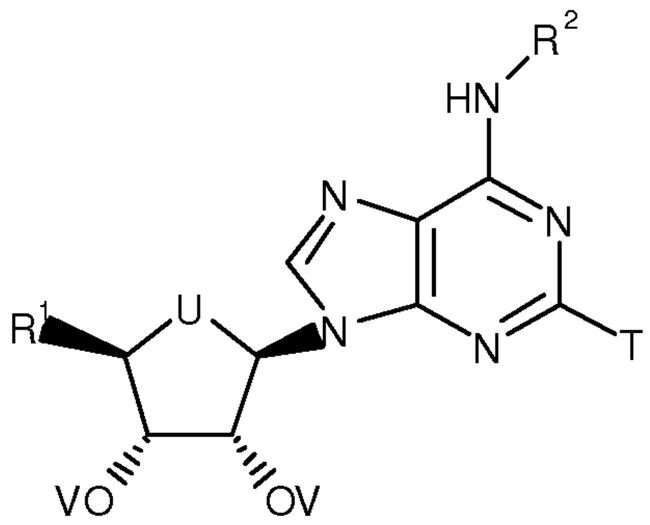
T is a leaving group with a compound of formula (III)

$$H—R^3 \qquad \textbf{(III)},$$

where R^3 is as defined hereinbefore; and

(ii) removing any protecting groups and recovering the resultant compound of formula (II), in free or pharmaceutically acceptable salt form.

The compound of formula (II) may be prepared by reacting a compound of formula (IV)



(IV)

,

wherein

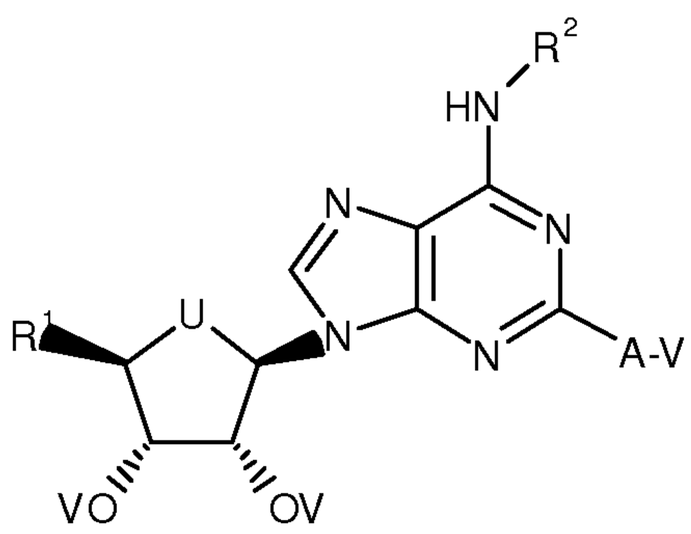
R^1 is equivalent to R^{1a} and R^{1b};

R^2 and U is equivalent to U_1 and U_2, and are as defined in claim 1;

V is H or a protecting group;

T is a leaving group, with a compound of formula H—A—V, where A is as defined hereinbefore; and

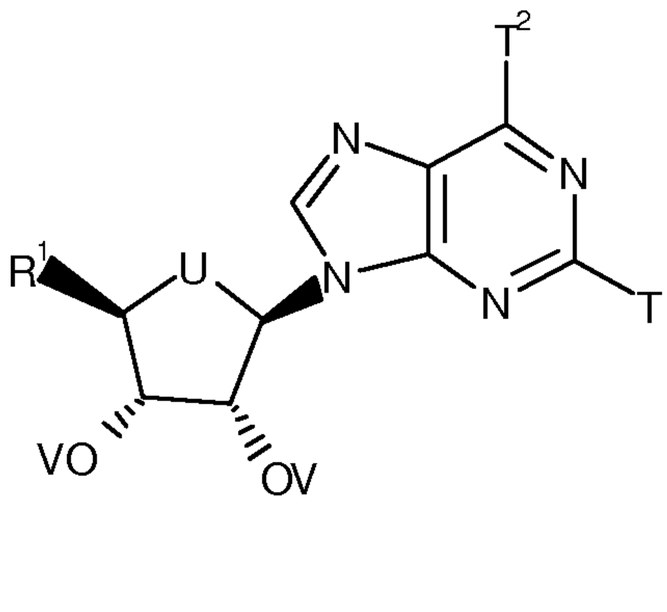
V is H or a protecting group to provide a compound of formula (VI)



(VI)

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Compound (VI) can be reacted with a compound of formula (VII)



(VII)

,

wherein

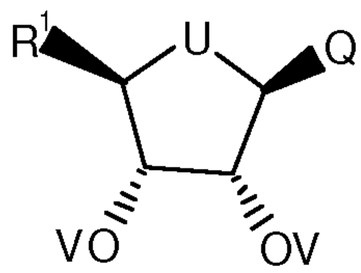
R^1 is equivalent to R^{1a} and R^{1b};

U is equivalent to U_1 and U_2;

V are defined in claim 1; and

T and T^2 are halogen.

The compound of formula (VII) may be prepared by reacting a compound of formula (VIII)



(VIII)

,

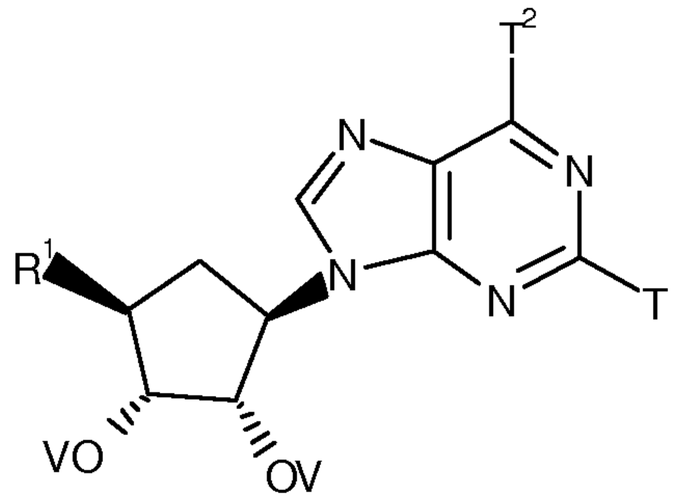
wherein

R^1 is equivalent to R^{1a} and R^{1b};

U is equivalent to U_1 and U_2;

V are as defined in claim 1; and

Q represents a leaving group or a protected derivative thereof with a 2,6-dihalopurine, e.g., 2,6-dichloropurine to provide a compound of formula (VII)



(VIII)

,

wherein

R^1 is equivalent to R^{1a} and R^{1b};

U is equivalent to U_1 and U_2;

V are defined in claim 1; and

T and T^2 are halogen.

The compounds of formula (I) can be prepared, for example, using the reactions and techniques described below and in the Examples. The compounds of formula (I) can be prepared analogously to the preparations described in Applicant's patent applications PCT/EP2005/011344, GB 0500785.1, and GB 0505219.6. The reactions may be performed in a solvent appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the

synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention.

The various substituents on the synthetic intermediates and final products shown in the following reaction schemes can be present in their fully elaborated forms, with suitable protecting groups where required as understood by one skilled in the art, or in precursor forms which can later be elaborated into their final forms by methods familiar to one skilled in the art. The substituents can also be added at various stages throughout the synthetic sequence or after completion of the synthetic sequence. In many cases, commonly used functional group manipulations can be used to transform one intermediate into another intermediate, or one compound of formula (I) into another compound of formula (I) Examples of such manipulations are conversion of an ester or a ketone to an alcohol; conversion of an ester to a ketone; interconversions of esters, acids and amides; alkylation, acylation and sulfonylation of alcohols and amines; and many others. Substituents can also be added using common reactions, such as alkylation, acylation, halogenation or oxidation. Such manipulations are well-known in the art, and many reference works summarize procedures and methods for such manipulations. Some reference works which gives examples and references to the primary literature of organic synthesis for many functional group manipulations, as well as other transformations commonly used in the art of organic synthesis are *March's Organic Chemistry*, 5th Edition, Wiley and Chichester, Eds. (2001); *Comprehensive Organic Transformations*, Larock, Ed., VCH (1989); *Comprehensive Organic Functional Group Transformations*, Katritzky et al. (series editors), Pergamon (1995); and *Comprehensive Organic Synthesis*, Trost and Fleming (series editors), Pergamon (1991). It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. Multiple protecting groups within the same molecule can be chosen such that each of these protecting groups can either be removed without removal of other protecting groups in the same molecule, or several protecting groups can be removed using the same reaction step, depending upon the outcome desired. An authoritative account describing many alternatives to the trained practitioner is Greene and Wuts, *Protective Groups In Organic Synthesis*, Wiley and Sons (1999). It is understood by those skilled in the art that only combinations of substituents that are chemically possible are embodiments of the present invention.

Compounds of formula (I) in free form may be converted into salt form, and vice versa, in a conventional manner. The compounds in free or salt form can be obtained in the form of hydrates or solvates containing a solvent used for crystallization. Compounds of formula (I) can be recovered from reaction mixtures and purified in a conventional manner. Isomers, such as stereoisomers, may be obtained in a conventional manner, e.g., by fractional crystallization or asymmetric synthesis from correspondingly asymmetrically substituted, e.g., optically active, starting materials.

Compounds of formula (I) and their pharmaceutically acceptable salts are useful as pharmaceuticals. In particular, they activate the adenosine A_{2A} receptor, i.e., they act as A_{2A} receptor agonists. Their properties as A_{2A} agonists may be demonstrated using the method described by Murphree et al., *Mol Pharmacol*, Vol. 61, pp. 455-462 (2002).

Compounds of the Examples hereinbelow have K_i values below 1.0 µM in the above assay. For example, the compound of Example 1 has a K_i value of 0.76 µM.

Having regard to their activation of the adenosine A_{2A} receptor, compounds of formula (I), in free or pharmaceutically acceptable salt form, hereinafter alternately referred to as "agents of the invention", are useful in the treatment of conditions which respond to the activation of the adenosine A_{2A} receptor, particularly inflammatory or allergic conditions. Treatment in accordance with the invention may be symptomatic or prophylactic.

Accordingly, agents of the invention are useful in the treatment of inflammatory or obstructive airways diseases, resulting, for example, in reduction of tissue damage, airways inflammation, bronchial hyperreactivity, remodelling or disease progression. Inflammatory or obstructive airways diseases and conditions to which the present invention is applicable include acute lung injury (ALI), adult/acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary, airways or lung disease (COPD, COAD or COLD), including chronic bronchitis or dyspnea associated therewith, emphysema, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular, other inhaled drug therapy. The invention is also applicable to the treatment of bronchitis of whatever type or genesis including, e.g., acute, arachidic, catarrhal, croupus, chronic or phthinoid bronchitis. Further inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by

repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis.

Other inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma, mild asthma, moderate asthma, severe asthma, bronchitic asthma, exercise-induced asthma, occupational asthma and asthma induced following bacterial infection. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g., of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics. (For convenience this particular asthmatic condition is referred to as "wheezy-infant syndrome".)

Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g., of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways hyperreactivity. It may further be evidenced by reduced requirement for other, symptomatic therapy, i.e., therapy for or intended to restrict or abort symptomatic attack when it occurs, for example, anti-inflammatory (e.g., cortico-steroid) or bronchodilatory. Prophylactic benefit in asthma may in particular be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognised asthmatic syndrome, common to a substantial percentage of asthmatics and characterised by asthma attack, e.g., between the hours of about 4-6 am, i.e., at a time normally substantially distant from any previously administered symptomatic asthma therapy.

Having regard to their anti-inflammatory activity, in particular in relation to inhibition of eosinophil activation, agents of the invention are also useful in the treatment of eosinophil related disorders, e.g., eosinophilia, in particular eosinophil related disorders of the airways (e.g., involving morbid eosinophilic infiltration of pulmonary tissues) including hypereosinophilia as it effects the airways and/or lungs as well as, for example, eosinophil-related disorders of the airways consequential or concomitant to Löffler's syndrome, eosinophilic pneumonia, parasitic (in particular, metazoan) infestation (including tropical eosinophilia), bronchopulmonary aspergillosis, polyarteritis nodosa (including Churg-Strauss syndrome), eosinophilic granuloma and eosinophil-related disorders affecting the airways occasioned by drug-reaction.

Agents of the invention are also useful in the treatment of inflammatory or allergic conditions of the skin, for example, psoriasis, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus, pemphisus, epidermolysis bullosa acquisita, and other inflammatory or allergic conditions of the skin.

Agents of the invention may also be used for the treatment of other diseases or conditions, in particular, diseases or conditions having an inflammatory component, for example, treatment of diseases and conditions of the eye, such as conjunctivitis, keratoconjunctivitis sicca, and vernal conjunctivitis, diseases affecting the nose including allergic rhinitis, and inflammatory disease in which autoimmune reactions are implicated or having an autoimmune component or aetiology, including autoimmune haematological disorders (e.g., hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (e.g., ulcerative colitis and Crohn's disease), endocrine opthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary billiary cirrhosis, uveitis (anterior and posterior), keratoconjunct-ivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis and glomerulonephritis (with and without nephrotic syndrome, e.g., including idiopathic nephrotic syndrome or minimal change nephropathy).

Further, agents of the invention may also be used for the treatment of cystic fibrosis, pulmonary hypertension, pulmonary fibrosis, inflammatory bowel syndrome, wound healing, diabetic nephropathy as described in WO 05/107463, reduction of inflammation in transplanted tissue as described in US 2005/182018, inflammatory diseases caused by pathogenic organisms as described in WO 03/086408, and cardiovascular conditions as described in WO 03/029264.

Also, the agents of the invention may be used to assess the severity of coronary artery stenosis as described in WO 00/078774 and useful in conjunction with radioactive imaging agents to image coronary activity and useful in adjunctive therapy with angioplasty as described in WO 00/78779.

Agents of the invention are also useful in combination with a protease inhibitor for prevention of organ ischemia and reperfusion injury as described in WO 05/003150, and in combination with an integrin antagonist for treating platelet aggregation as described in WO 03/090733.

Agents of the invention are also useful in promoting wound healing in bronchial epithelial cells as described in *AJP-Lung*, Vol. 290, pp. 849-855.

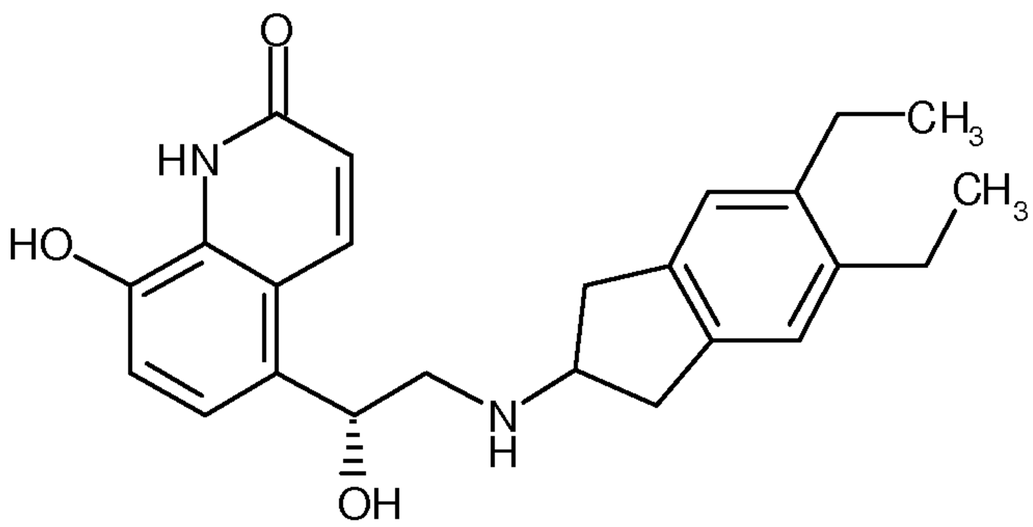
Other diseases or conditions which may be treated with agents of the invention include diabetes, e.g., diabetes mellitus type I (juvenile diabetes) and diabetes mellitus type II, diarrheal diseases, ischemia/reperfusion injuries, retinopathy, such as diabetic retinopathy or hyperbaric oxygen-induced retinopathy, conditions characterized by elevated intraocular pressure or secretion of ocular aqueous humor, such as glaucoma, ischemic tissue/organ damage from reperfusion and bedsores.

The effectiveness of an agent of the invention in inhibiting inflammatory conditions, for example, in inflammatory airways diseases, may be demonstrated in an animal model, e.g., a mouse or rat model, of airways inflammation or other inflammatory conditions, for example, as described by Szarka et al, *J Immunol Methods*, Vol. 202, pp. 49-57 (1997); Renzi et al., *Am Rev Respir Dis*, Vol. 148, pp. 932-939 (1993); Tsuyuki et al., *J Clin Invest*, Vol. 86, pp. 2924-2931 (1995); Cernadas et al., *Am J Respir Cell Mol Biol*, Vol. 20, pp. 1-8 (1999); and Fozard et al., *Eur J Pharmacol*, Vol. 438, pp. 183-188 (2002).

The agents of the invention are also useful as co-therapeutic agents for use in combination with other drug substances, such as anti-inflammatory, bronchodilatory, antihistamine or anti-tussive drug substances, particularly in the treatment of obstructive or inflammatory airways diseases such as those mentioned hereinbefore, for example, as potentiators of therapeutic activity of such drugs or as a means of reducing required dosaging or potential side effects of such drugs. An agent of the invention may be mixed with the other drug substance in a fixed pharmaceutical composition or it may be administered separately, before, simultaneously with or after the other drug substance.

Accordingly the invention includes a combination of an agent of the invention as hereinbefore described with an anti-inflammatory, bronchodilatory, antihistamine or anti-tussive drug substance, said agent of the invention and said drug substance being in the same or different pharmaceutical composition.

Suitable anti-inflammatory drugs include steroids, in particular, glucocorticosteroids such as budesonide, beclamethasone dipropionate, fluticasone propionate, ciclesonide or mometasone furoate, or steroids described in WO 02/88167, WO 02/12266, WO 02/100879, WO 02/00679 (especially those of Examples 3, 11, 14, 17, 19, 26, 34, 37, 39, 51, 60, 67, 72, 73, 90, 99 and 101), WO 03/35668, WO 03/48181, WO 03/62259, WO 03/64445, WO 03/72592, WO 04/39827 and WO 04/66920; non-steroidal glucocorticoid receptor agonists, such as those described in DE 10261874, WO 00/00531, WO 02/10143, WO 03/82280, WO 03/82787, WO 03/86294, WO 03/104195, WO 03/101932, WO 04/05229, WO 04/18429, WO 04/19935 and WO 04/26248; LTB4 antagonists, such as BIIL 284, CP-195543, DPC11870, LTB4 ethanolamide, LY 293111, LY 255283, CGS025019C, CP-195543, ONO-4057, SB 209247, SC-53228 and those described in US 5451700; LTD4 antagonists such include montelukast, pranlukast, zafirlukast, accolate, SR2640, Wy-48,252, ICI 198615, MK-571, LY-171883, Ro 24-5913 and L-648051; PDE4 inhibitors, such as cilomilast (Ariflo® GlaxoSmithKline), Roflumilast (Byk Gulden),V-11294A (Napp), BAY19-8004 (Bayer), SCH-351591 (Schering-Plough), Arofylline (Almirall Prodesfarma), PD189659 / PD168787 (Parke-Davis), AWD-12-281 (Asta Medica), CDC-801 (Celgene), SelCID(TM) CC-10004 (Celgene), VM554/UM565 (Vernalis), T-440 (Tanabe), KW-4490 (Kyowa Hakko Kogyo), and those disclosed in WO 92/19594, WO 93/19749, WO 93/19750, WO 93/19751, WO 98/18796, WO 99/16766, WO 01/13953, WO 03/104204, WO 03/104205, WO 03/39544, WO 04/000814, WO 04/000839, WO 04/005258, WO 04/018450, WO 04/018451, WO 04/018457, WO 04/018465, WO 04/018431, WO 04/018449, WO 04/018450, WO 04/018451, WO 04/018457, WO 04/018465, WO 04/019944, WO 04/019945, WO 04/045607 and WO 04/037805; adenosine A_{2B} receptor antagonists, such as those described in WO 02/42298; and beta-2 adrenoceptor agonists, such as albuterol (salbutamol), metaproterenol, terbutaline, salmeterol fenoterol, procaterol, and especially, formoterol, carmoterol and pharmaceutically acceptable salts thereof, and compounds (in free or salt or solvate form) of formula (I) of WO 00/75114, which document is incorporated herein by reference, preferably compounds of the Examples thereof, especially a compound of formula



and pharmaceutically acceptable salts thereof, as well as compounds (in free or salt or solvate form) of formula (I) of WO 04/16601, and also compounds of EP 1440966, JP 05025045, WO 93/18007, WO 99/64035, US 2002/0055651, US 2005/0133417, US 2005/5159448, WO 01/42193, WO 01/83462, WO 02/66422, WO 02/70490, WO 02/76933, WO 03/24439, WO 03/42160, WO 03/42164, WO 03/72539, WO 03/91204, WO 03/99764, WO 04/16578, WO 04/22547, WO 04/32921, WO 04/33412, WO 04/37768, WO 04/37773, WO 04/37807, WO 04/39762, WO 04/39766, WO 04/45618, WO 04/46083, WO 04/80964, EP 1460064, WO 04/087142, WO 04/089892, EP 01477167, US 2004/0242622, US 2004/0229904, WO 04/108675, WO 04/108676, WO 05/033121, WO 05/040103, WO 05/044787, WO 05/058867, WO 05/065650, WO 05/066140, WO 05/07908, WO 2007018461, WO 2007027133, WO 2006051373, WO 2006056471, and WO 2004016601.

Suitable bronchodilatory drugs include anticholinergic or antimuscarinic agents, in particular, ipratropium bromide, oxitropium bromide, tiotropium salts and CHF 4226 (Chiesi), and glycopyrrolate, but also those described in EP 424021, US 3714357, US 5171744, US 2005/171147, US 2005/182091, WO 01/04118, WO 02/00652, WO 02/51841, WO 02/53564, WO 03/00840, WO 03/33495, WO 03/53966, WO 03/87094, WO 04/018422, WO 04/05285 and WO 05/077361.

Suitable dual anti-inflammatory and bronchodilatory drugs include dual beta-2 adrenoceptor agonist/muscarinic antagonists such as those disclosed in US 2004/0167167, US 2004/0242622, US 2005/182092, WO 04/74246 and WO 04/74812.

Suitable antihistamine drug substances include cetirizine hydrochloride, acetaminophen, clemastine fumarate, promethazine, loratidine, desloratidine, diphenhydramine and fexofenadine hydrochloride, activastine, astemizole, azelastine, ebastine, epinastine, mizolastine and tefenadine, as well as those disclosed in JP 2004107299, WO 03/099807 and WO 04/026841.

Other useful combinations of agents of the invention with anti-inflammatory drugs are those with antagonists of chemokine receptors, e.g., CCR-1, CCR-2, CCR-3, CCR-4, CCR-5, CCR-6, CCR-7, CCR-8, CCR-9 and CCR10, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, particularly CCR-5 antagonists, such as Schering-Plough antagonists SC-351125, SCH-55700 and SCH-D, Takeda antagonists, such as *N*-[[4-[[[6,7-dihydro-2-(4-methylphenyl)-5*H*-benzo-cyclohepten-8-yl]carbonyl]amino]phenyl]-methyl]tetrahydro-*N,N*-dimethyl-2*H*-pyran-4-amin-ium chloride (TAK-770), and CCR-5 antagonists described in US 6166037 (particularly claims 18 and 19), WO 00/66558 (particularly claim 8), WO 00/66559 (particularly claim 9), WO 04/018425 and WO 04/026873.

In accordance with the foregoing, the invention also provides a method for the treatment of a condition responsive to activation of the adenosine A_{2A} receptor, for example, an inflammatory or allergic condition, particularly an inflammatory or obstructive airways disease, which comprises administering to a subject, particularly a human subject, in need thereof a compound of formula (I) in free form or in the form of a pharmaceutically acceptable salt. In another aspect the invention provides a compound of formula (I), in free form or in the form of a pharmaceutically acceptable salt, for use in the manufacture of a medicament for the treatment of a condition responsive to activation of the adenosine A_{2A} receptor, particularly an inflammatory or obstructive airways disease.

The agents of the invention may be administered by any appropriate route, e.g., orally, for example, in the form of a tablet or capsule; parenterally, for example, intravenously; by inhalation, for example, in the treatment of inflammatory or obstructive airways disease; intranasally, for example, in the treatment of allergic rhinitis; topically to the skin, for example, in the treatment of atopic dermatitis; or rectally, for example, in the treatment of inflammatory bowel disease.

In a further aspect, the invention also provides a pharmaceutical composition comprising a compounds of formula (I), in free form or in the form of a pharmaceutically acceptable salt, optionally together with a pharmaceutically acceptable diluent or carrier therefor. The composition may contain a co-therapeutic agent, such as an anti-inflammatory, broncho-dilatory, antihistamine or anti-tussive drug as hereinbefore described. Such compositions may be prepared using conventional diluents or excipients and techniques known in the galenic art. Thus oral dosage forms may include tablets and capsules. Formulations for topical administration may take the form of creams, ointments, gels or

transdermal delivery systems, e.g., patches. Compositions for inhalation may comprise aerosol or other atomizable formulations or dry powder formulations.

When the composition comprises an aerosol formulation, it preferably contains, for example, a hydro-fluoro-alkane (HFA) propellant, such as HFA134a or HFA227 or a mixture of these, and may contain one or more co-solvents known in the art, such as ethanol (up to 20% by weight), and/or one or more surfactants such as oleic acid or sorbitan trioleate, and/or one or more bulking agents, such as lactose. When the composition comprises a dry powder formulation, it preferably contains, for example, the compounds of formula (I) having a particle diameter up to 10 microns, optionally together with a diluent or carrier, such as lactose, of the desired particle size distribution and a compound that helps to protect against product performance deterioration due to moisture, e.g., magnesium stearate. When the composition comprises a nebulised formulation, it preferably contains, for example, the compound of formula (I) either dissolved, or suspended, in a vehicle containing water, a co-solvent, such as ethanol or propylene glycol and a stabilizer, which may be a surfactant.

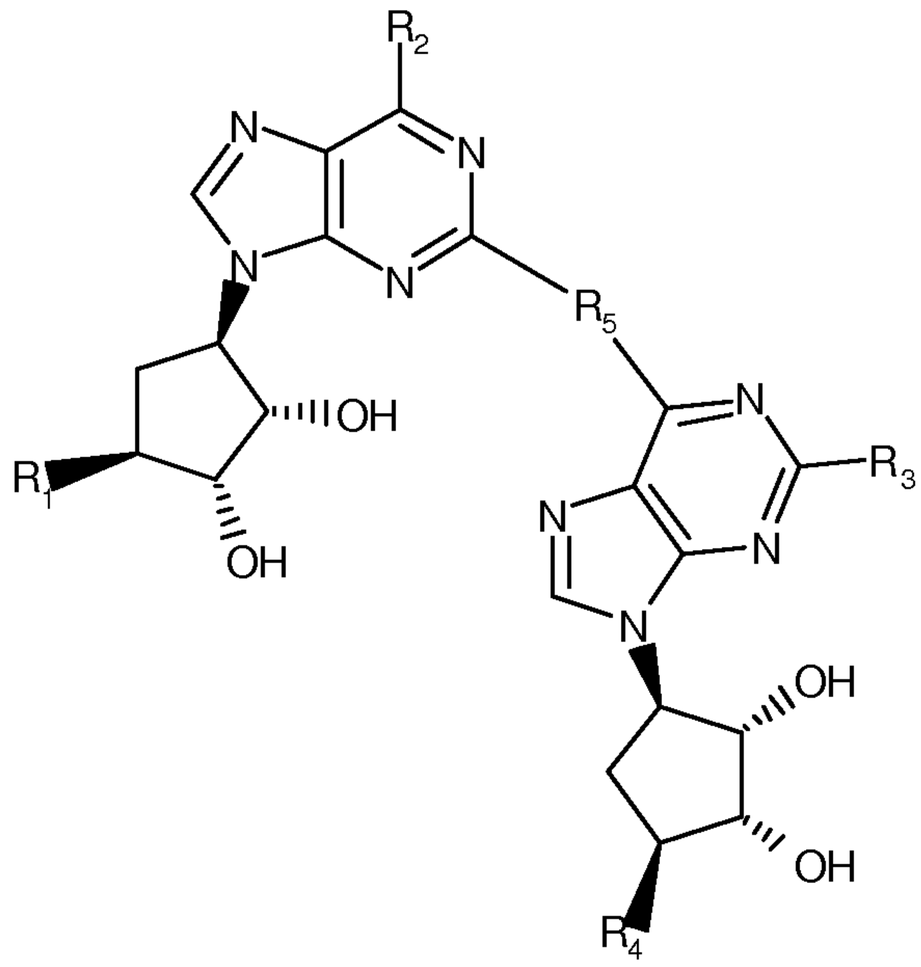
The invention includes (A) a compounds of formula (I) in inhalable form, e.g., in an aerosol or other atomisable composition or in inhalable particulate, e.g., micronised, form, (B) an inhalable medicament comprising a compounds of formula (I) in inhalable form; (C) a pharmaceutical product comprising a compounds of formula (I) in inhalable form in association with an inhalation device; and (D) an inhalation device containing a compounds of formula (I) in inhalable form.

Dosages of compounds of formula (I) employed in practising the present invention will of course vary depending, for example, on the particular condition to be treated, the effect desired and the mode of administration. In general, suitable daily dosages for administration by inhalation are of the order of 0.005-10 mg, while for oral administration suitable daily doses are of the order of 0.05-100 mg.

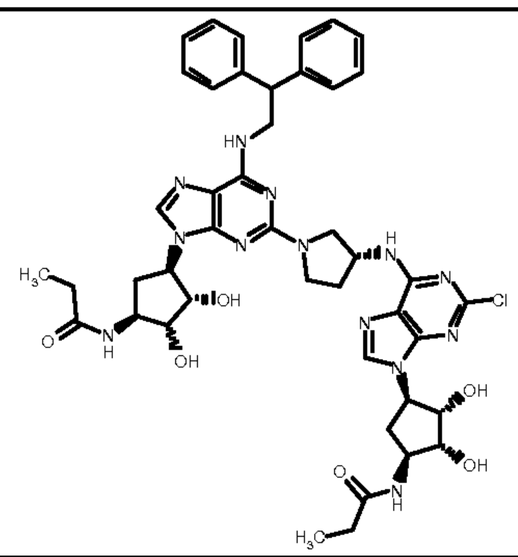
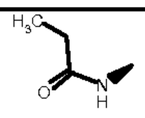
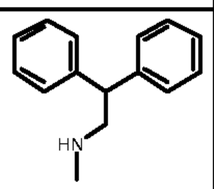
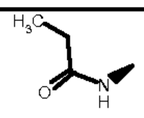
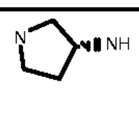
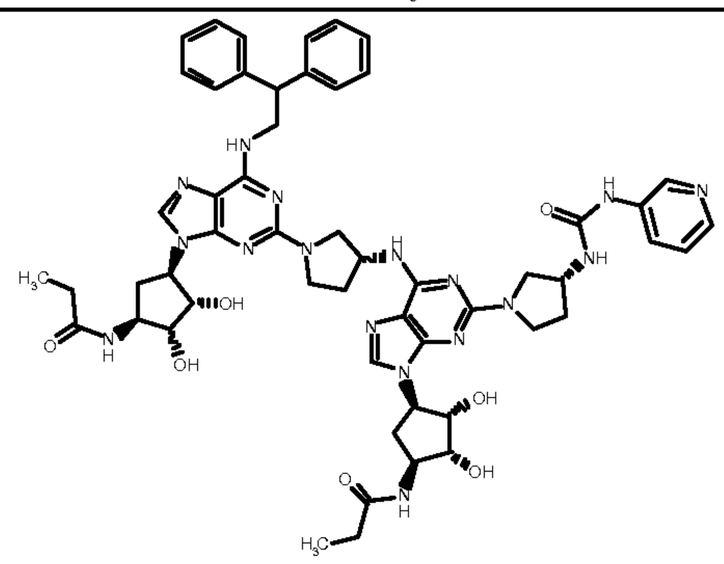
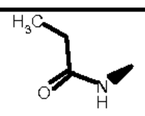
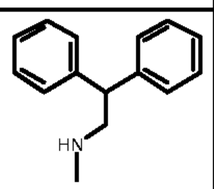
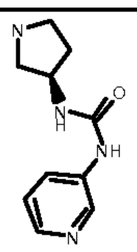
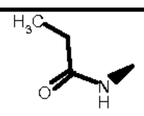
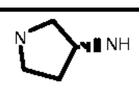
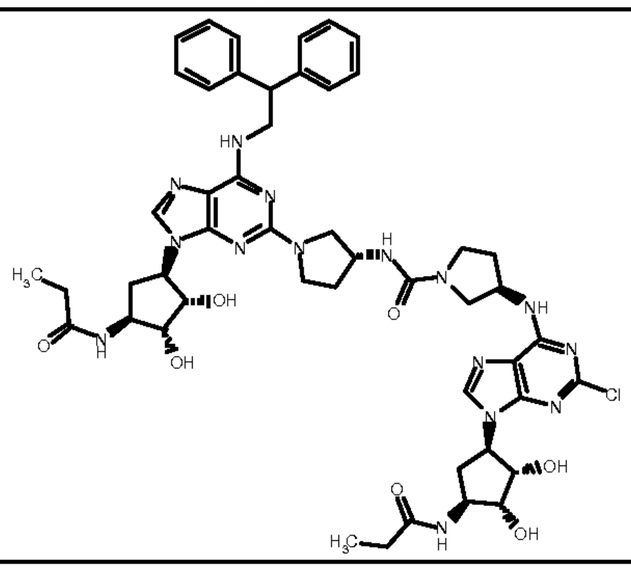
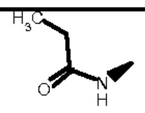
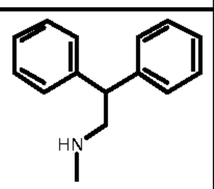
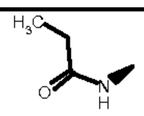
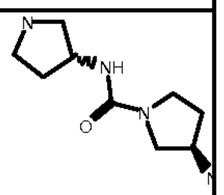
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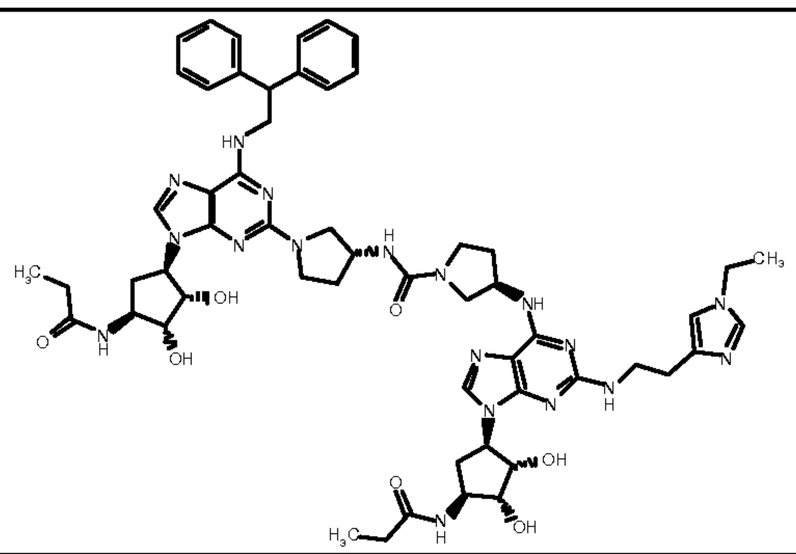
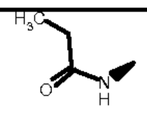
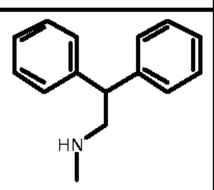
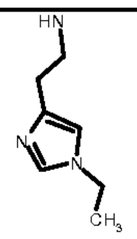
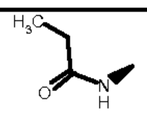
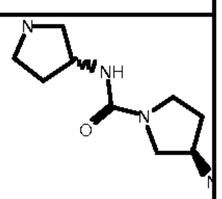
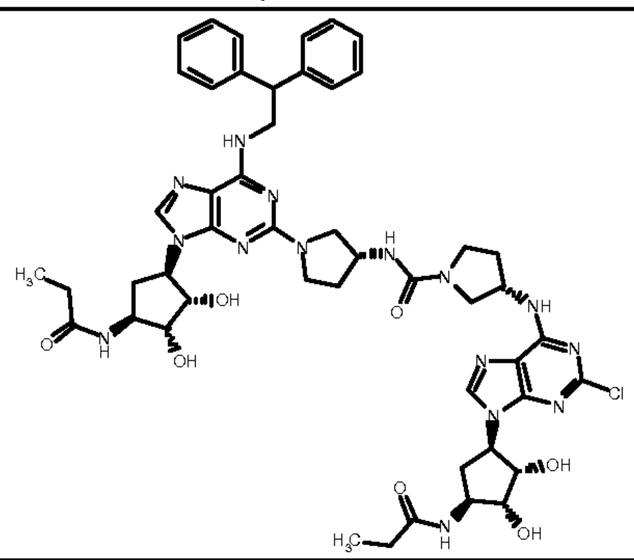
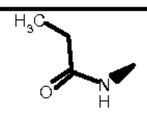
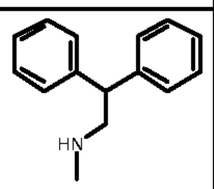
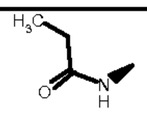
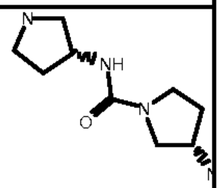
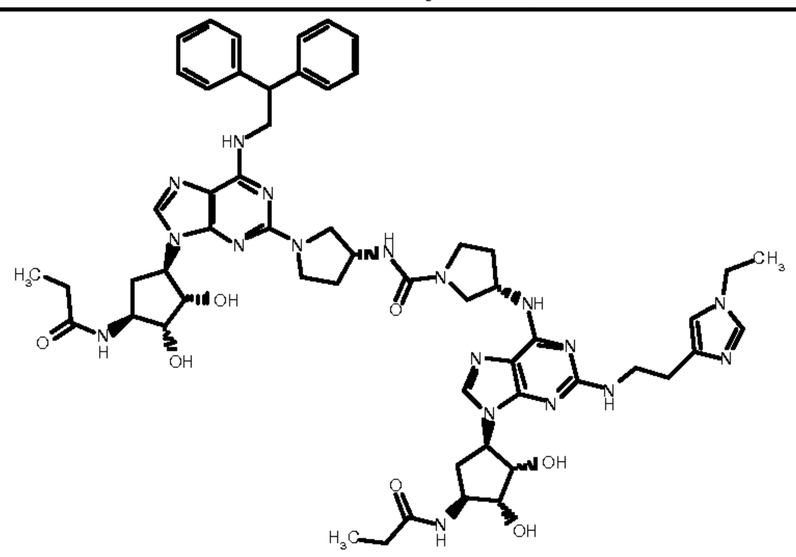
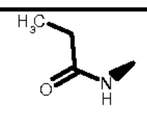
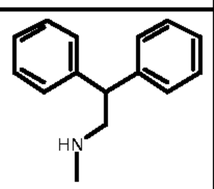
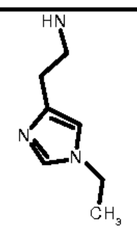
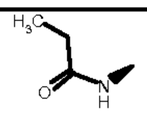
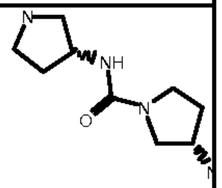
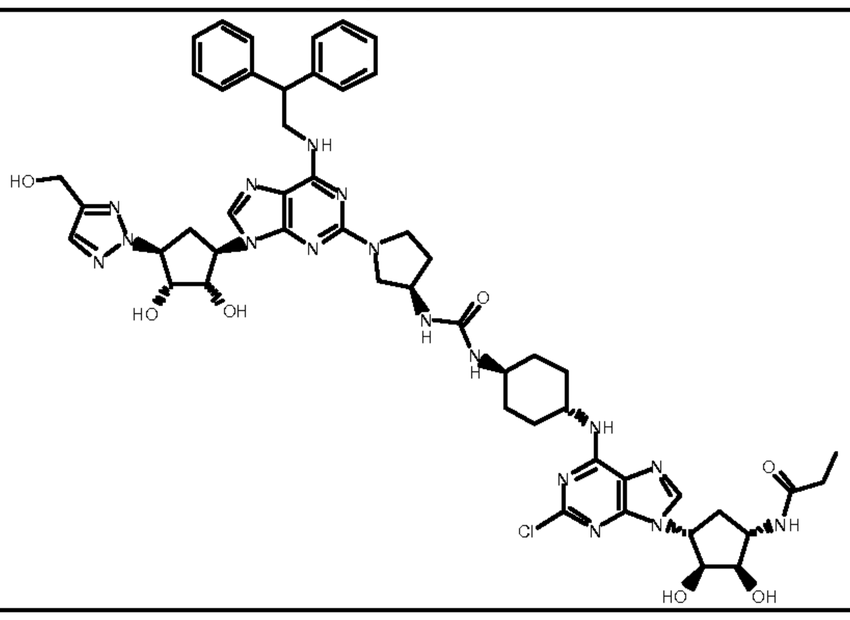
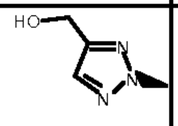
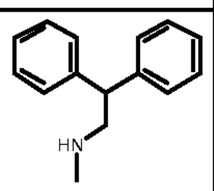
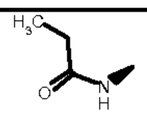
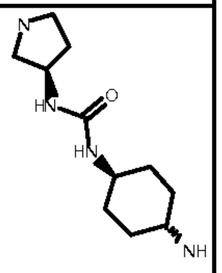
EXAMPLES

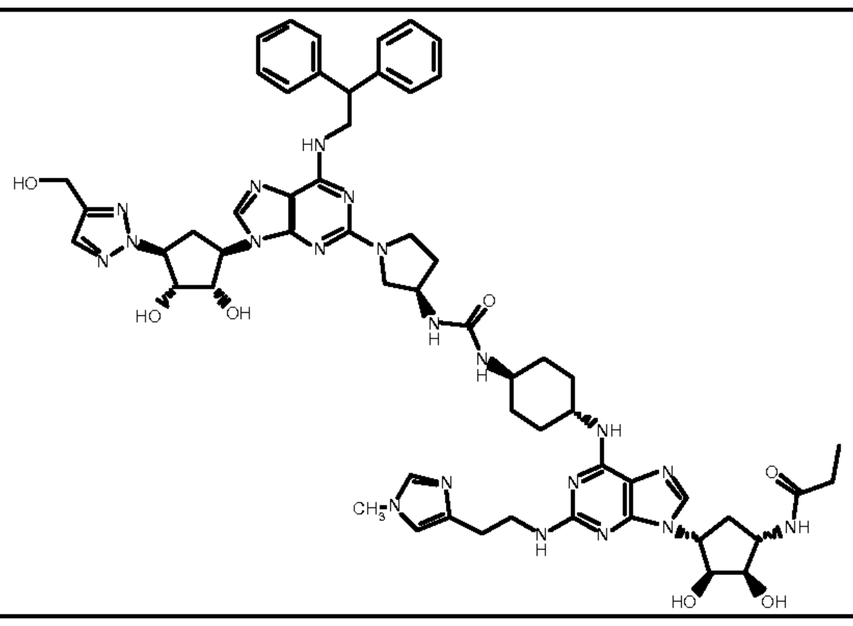
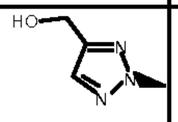
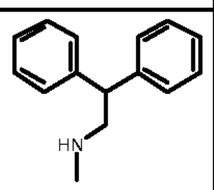
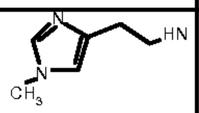
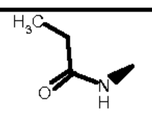
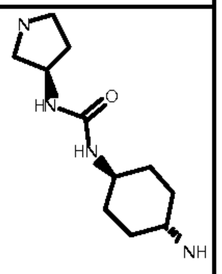
A compounds of formula **X** are shown in the following table. Methods of preparing such a compound is described hereinafter.



(X)

Ex	Structure	R_1	R_2	R_3	R_4	R_5
1				-Cl		
2						
3				-Cl		

Ex	Structure	R_1	R_2	R_3	R_4	R_5
4						
5				-Cl		
6						
7				-Cl		

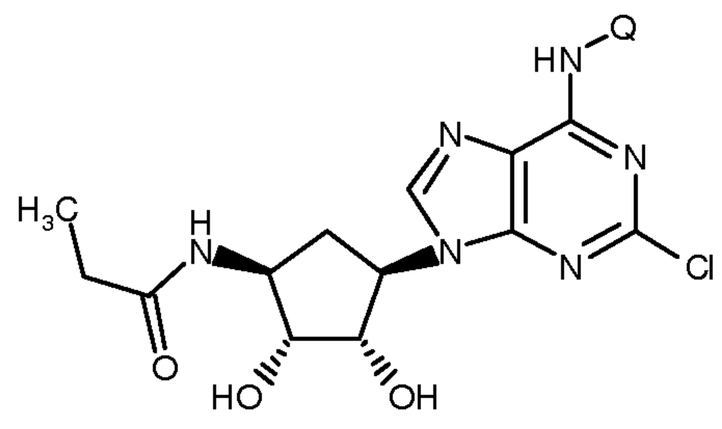
Ex	Structure	R_1	R_2	R_3	R_4	R_5
8						

Preparation of intermediates

Abbreviations used are as follows:

CDI	1,1'-Carbonyldiimidazole
DCM	Dichloromethane
DEAD	Diethyl Azodicarboxylate
DIPEA	Diisopropylethylamine
DMF	Dimethylformamide
DMSO	Dimethyl Sulfoxide
EDCI	1-Ethyl-3-(3'-dimethylaminopropyl) carbodiimide
EtOAc	Ethyl Acetate
HPLC	High Performance Liquid Chromatography
HCl	Hydrochloric Acid
LCMS	Liquid Chromatographic Mass Spectroscopy
MeOH	Methanol
NMP	*n*-Methyl Pyrrolidone
NMO	*N*-Methylmorpholine *N*-Oxide
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

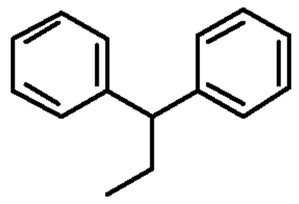
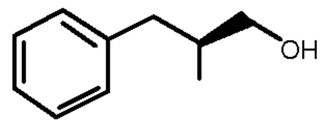
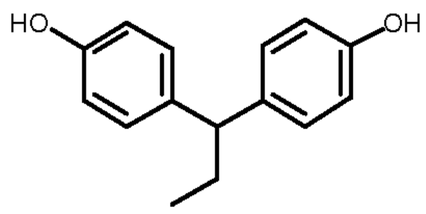
The following intermediates of formula (A)



,

are shown in Table 1 below, their method of preparation being described hereinafter.

TABLE 1

Intermediate	Q	M/s MH+
AA		521
AB		475
AC		553

Intermediate AA

***N*-{(1*S*,2*R*,3*S*,4*R*)-4-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide**

Step AA1 (1*S*,4*R*)-4-(2,6-Dichloro-purin-9-yl)-cyclopent-2-enol

2,6-Dichloropurine (10 g, 52.90 mmol), (1*S*,4*R*)-cis 4-acetoxy-2-cyclopenten-1-ol (10 g, 70.40 mmol), tris(dibenzylideneacetone)dipalladium(0) (3.20 g, 3.50 mmol) and polymer supported triphenylphosphine (3 mmol/g, 11.60 g, 35.00 mmol) are placed in an oven-dried flask under an atmosphere of argon. Dry deoxygenated THF (80 mL) is added and the reaction mixture is stirred gently for 5 minutes. TEA (20 mL) is added and the reaction mixture is stirred at 50°C. The reaction is shown to be complete by LCMS after 1 hour. The reaction mixture is allowed to cool, filtered and the solvent is removed *in vacuo*. The title compound is obtained after purification by flash column chromatography (silica, DCM/MeOH 25:1).

^{1}H NMR ($CDCl_3$, 400 MHz); 8.30 (s, 1H), 6.40 (m, 1H), 5.90 (m, 1H), 5.50 (m, 1H), 4.95 (m, 1H), 3.05 (m, 1H), 2.10 (m, 1H), MS (ES+) *m/e* 271 (MH^+).

Step AA2: Carbonic acid (1*S*,4*R*)-4-(2,6-dichloro-purin-9-yl)-cyclopent-2-enyl ester ethyl ester

(1*S*,4*R*)-4-(2,6-Dichloro-purin-9-yl)-cyclopent-2-enol (9.5 g, 35.05 mmol) is placed in an oven-dried flask under an atmosphere of argon. Dry THF (200 mL) is added followed by dry pyridine (5.54 g, 70.1 mmol). Ethyl chloroformate (15.21 g, 140.2 mmol) is added slowly so that the temperature does not rise above 40°C and the reaction mixture is stirred at room temperature. The reaction is shown to be complete by LCMS after 1 hour. The solvent is removed *in vacuo* and the residue is partitioned between DCM (200 mL) and water (200 mL). The organic layer is washed with water (150 mL) and brine (150 mL), dried over $MgSO_4$, filtered and the solvent is removed *in vacuo.* The title compound is obtained after crystallisation from MeOH.

^{1}H NMR ($CDCl_3$, 400 MHz); 8.20 (s, 1H), 6.45 (m, 1H), 6.25 (m, 1H), 5.75 (m, 1H), 5.70 (m, 1H), 4.25 (q, 2H), 3.20 (m, 1H), 2.05 (m, 1H), 1.35 (t, 3H), MS (ES+) *m/e* 343 (MH^+).

Step AA3: Di-Boc-[(1*S*,4*R*)-4-(2,6-dichloro-purin-9-yl)-cyclopent-2-enyl]-amine

Carbonic acid (1*S*,4*R*)-4-(2,6-dichloro-purin-9-yl)-cyclopent-2-enyl ester ethyl ester (2.5 g, 7.29 mmol), di-*t*-butyliminodicarboxylate (1.74 g, 8.02 mmol), and triphenylphosphine (0.29 g, 1.09 mmol) are placed in an oven-dried flask under an atmosphere of argon. Dry deoxygenated THF (30 ml) is added followed by tris(dibenzylideneacetone)dipalladium(0) (0.33 g, 0.36 mmol) and the reaction mixture is stirred at room temperature. The reaction is shown to be complete by LCMS after 3 hours. The solvent is removed *in vacuo* and the title compound is obtained after purification by flash column chromatography (silica, EtOAc/*iso*-hexane 4:1).

^{1}H NMR ($CDCl_3$, 400 MHz); 8.70 (s, 1H), 6.20 (m, 1H), 5.85 (m, 1H), 5.80 (m, 1H), 5.40 (m, 1H), 3.20 (m, 1H), 2.15 (m, 1H), 1.55 (s, 18H), MS (ES+) *m/e* 470 (MH^+).

Step AA4: (1*S*,2*R*,3*S*,5*R*)-3-(Di-Boc-amino)-5-(2,6-dichloro-purin-9-yl)-cyclopentane-1,2-diol

A mixture comprising di-Boc-[(1*S*,4*R*)-4-(2,6-dichloro-purin-9-yl)-cyclopent-2-enyl]-amine (1.30 g, 2.77 mmol) (1.49 g, 3.17 mmol), methane sulphonamide (0.30 g, 3.17 mmol) and AD-mix-α (6.75 g, 1.5 g/mmol) in *t*-butanol/water (20 mL of a 1:1 mixture) is treated with osmium tetroxide (1.5 mL, 4% w/w in water). After stirring vigorously at room temperature overnight, the reaction mixture is partitioned between EtOAc and water. The organic portion

is separated, washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo* to yield the title compound which is used in the next step without further purification.

^{1}H NMR ($CDCl_3$, 400 MHz); 8.35 (s, 1H), 4.80 (m, 1H), 4.70 (m, 1H), 4.50 (m, 1H), 3.85 (m, 1H), 3.75 (m, 1H), 3.10 (m, 1H), 2.75 (m, 1H), 2.55 (m, 1H), 1.55 (s, 18H), MS (ES+) *m/e* 504 (MH^+).

Step AA5: (1*S*,2*R*,3*S*,5*R*)-3-Amino-5-(2,6-dichloro-purin-9-yl)-cyclopentane-1,2-diol trifluoroacetate

A solution of (1*S*,2*R*,3*S*,5*R*)-3-(di-Boc-amino)-5-(2,6-dichloro-purin-9-yl)-cyclopentane-1,2-diol (0.55 g, 1.09 mmol) in DCM (4 mL) is treated with TFA (2 mL) and stirred at room temperature. After 2 hours, the solvent is removed *in vacuo* to yield the title compound which is used in the next step without further purification. MS (ES+) *m/e* 304 (MH^+).

Step AA6: N-[(1*S*,2*R*,3*S*,4*R*)-4-(2,6-Dichloro-purin-9-yl)-2,3-dihydroxy-cyclopentyl]-propionamide

A solution of (1*S*,2*R*,3*S*,5*R*)-3-amino-5-(2,6-dichloro-purin-9-yl)-cyclopentane-1,2-diol trifluoroacetate (0.304 g, 1.0 mmol) in THF (10 mL) is treated with DIPEA (0.387 g, 3.0 mmol) followed by propionyl chloride (0.093 g, 1.0 mmol). After stirring at room temperature for 2 hours, the solvent is removed *in vacuo* and the title compound is obtained after purification by reverse phase column chromatography (Isolute™ C18, 0-100% acetonitrile in water – 0.1% TFA). MS (ES+) *m/e* 360 (MH^+).

Step AA7: N-{(1*S*,2*R*,3*S*,4*R*)-4-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide

N-[(1*S*,2*R*,3*S*,4*R*)-4-(2,6-dichloro-purin-9-yl)-2,3-dihydroxy-cyclopentyl]-propionamide (160 mg, 0.44 mmol) is dissolved in THF (5 mL) under an atmosphere of argon. DIPEA (69 mg, 0.53 mmol) is added followed by 2,2-diphenylethylamine (96 mg, 0.49 mmol) and the reaction mixture is stirred at 50°C. The reaction is shown to be complete by LCMS after 2 hours. The solvent is removed *in vacuo* and the title compound is obtained after purification

by reverse phase column chromatography (Isolute™ C18, 0-100% acetonitrile in water – 0.1% TFA).

^{1}H NMR (MeOD, 400 MHz); 8.00 (s, 1H), 7.40-7.15 (m, 10H), 4.75 (m, 1H), 4.60 (m, 1H), 4.50 (m, 1H), 4.20 (m, 3H), 3.95 (m, 1H), 2.85 (m, 1H), 2.40 (q, 2H), 2.10 (m, 1H), 1.20 (t, 3H), MS (ES+) *m/e* 521 (MH^+).

Intermediate **AA** may also be prepared using the following process:

Step AAI1: {2-Chloro-9-[(1*R*,4*S*)-4-(di-Boc-amino)-cyclopent-2-enyl]-9H-purin-6-yl}-(2,2-diphenyl-ethyl)-amine

(1*S*,2*R*,3*S*,5*R*)-3-(di-Boc-amino)-5-(2,6-dichloro-purin-9-yl)-cyclopentane-1,2-diol (13.0 g, 27.66 mmol) is dissolved in THF (250 mL) under an atmosphere of argon. DIPEA (4.28 g, 33.19 mmol) is added followed by 2,2-diphenylethylamine (6.0 g, 30.43 mmol) and the reaction mixture is stirred at 50°C. The reaction is shown to be complete by LCMS after 18 hours. The solvent is removed *in vacuo* and the reaction mixture is partitioned between dichloromethane (250 mL) and 0.1 M HCl (250 mL). The organic layer is washed with water (200 mL) and brine (200 mL), dried over $MgSO_4$, filtered and the solvent is removed *in vacuo* to give the title compound.

^{1}H NMR ($CDCl_3$, 400 MHz); 8.05 (s, 1H), 7.30-7.10 (m, 10H), 6.00 (m, 1H), 5.70 (m, 2H), 5.60 (m, 1H), 5.20 (m, 1H), 4.30 (m, 1H), 4.20 (m, 1H), 3.65 (m, 1H), 3.05 (m, 1H), 2.00 (m, 1H), 1.70 (m, 1H), 1.40 (s, 18H), MS (ES+) *m/e* 631 (MH^+).

Step AAI2: (1*R*,2*S*,3*R*,5*S*)-3-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(di-Boc-amino)-cyclopentane-1,2-diol

The title compound is prepared analogously to (1*S*,2*R*,3*S*,5*R*)-3-(di-Boc-amino)-5-(2,6-dichloro-purin-9-yl)-cyclopentane-1,2-diol by replacing di-Boc-[(1*S*,4*R*)-4-(2,6-dichloro-purin-9-yl)-cyclopent-2-enyl]-amine with {2-chloro-9-[(1*R*,4*S*)-4-(di-Boc-amino)-cyclopent-2-enyl]-9*H*-purin-6-yl}-(2,2-diphenyl-ethyl)-amine.

^{1}H NMR (MeOD, 400 MHz); 8.05 (s, 1H), 7.35-7.15 (m, 10H), 4.70-4.55 (m, 4H), 4.50 (m, 1H), 4.35 (m, 1H), 4.20 (m, 2H), 2.55 (m, 1H), 2.45 (m, 1H), 1.60 (s, 18H).

Step AAI3: (1*S*,2*R*,3*S*,5*R*)-3-Amino-5-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-cyclopentane-1,2-diol trifluoroacetate

(1*R*,2*S*,3*R*,5*S*)-3-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(di-Boc-amino)-cyclopentane-1,2-diol (10.3 g, 15.50 mmol) is dissolved in DCM (50 mL). TFA (25 mL) is added and the reaction mixture is stirred at room temperature. The reaction is shown to be complete by LCMS after 2 hours. The solvent is removed *in vacuo* to give the title compound.

^{1}H NMR (MeOD, 400 MHz); 7.90 (s, 1H), 7.30-7.10 (m, 10H), 4.65 (m, 1H), 4.50 (m, 1H), 4.40 (m, 1H), 4.20 (m, 1H), 4.10 (m, 2H), 3.50 (m, 1H), 2.75 (m, 1H), 2.15 (m, 1H), MS (ES+) *m/e* 465 (MH^+).

Step AAI4: N-{(1*S*,2*R*,3*S*,4*R*)-4-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide

(1*S*,2*R*,3*S*,5*R*)-3-Amino-5-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-cyclopentane-1,2-diol TFA (9.50 g, 16.42 mmol) and DIPEA (6.36 g, 49.27 mmol) are placed in a flask with dry THF (150 mL). Propionyl chloride (1.52 g, 16.42mmol) is added dropwise and the reaction mixture is stirred at room temperature. The reaction is shown to be complete by LCMS after 1 hour. The solvent is removed *in vacuo* and the residue is partitioned between DCM (250 mL) and water (250 mL). The organic layer is washed with water (200 mL) and brine (200 mL), dried over $MgSO_4$, filtered and the solvent is removed *in vacuo.* The solid is recrystallized from 1,2-dichloroethane to give the title compound.

^{1}H NMR (MeOD, 400 MHz); 8.00 (s, 1H), 7.40-7.15 (m, 10H), 4.75 (m, 1H), 4.60 (m, 1H), 4.50 (m, 1H), 4.20 (m, 3H), 3.95 (m, 1H), 2.85 (m, 1H), 2.40 (q, 2H), 2.10 (m, 1H), 1.20 (t, 3H), MS (ES+) *m/e* 521 (MH^+).

Intermediate AB

***N*-{(1*S*,2*R*,3*S*,4*R*)-4-[2-Chloro-6-((*S*)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide trifluoroacetate**

Step AB1: [(1*S*,4*R*)-4-(2,6-Dichloro-purin-9-yl)-cyclopent-2-enyl]-propionyl-carbamic acid tert-butyl ester

The title compound is prepared analogously to di-Boc-[(1*S*,4*R*)-4-(2,6-dichloro-purin-9-yl)-cyclopent-2-enyl]-amine (by replacing di-*t*-butyliminodicarboxylate with propionyl-carbamic acid tert-butyl ester.

Step AB2: [(1*S*,2*R*,3*S*,4*R*)-4-(2,6-Dichloro-purin-9-yl)-2,3-dihydroxy-cyclopentyl]-propionyl-carbamic acid tert-butyl ester:

A mixture comprising [(1*S*,4*R*)-4-(2,6-dichloro-purin-9-yl)-cyclopent-2-enyl]-propionyl-carbamic acid tert-butyl ester (6.54 g, 15.8 mmol), methane sulphonamide (1.46 g, 15.3 mmol) and AD-mix-α (23 g, 1.5 g/mmol) in *t*-butanol/water (80 mL of a 1:1 mixture) is treated with osmium tetroxide (3.5 mL, 4% w/w in water). After stirring vigorously at room temperature for 72 hours, the reaction mixture is partitioned between EtOAc and water. The organic portion is separated, washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue is triturated with methanol to afford the title compound. MS (ES+) *m/e* 460 (MH^+).

Step AB3: *N*-{(1*S*,2*R*,3*S*,4*R*)-4-[2-Chloro-6-((*S*)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide trifluoroacetate

A solution comprising [(1*S*,2*R*,3*S*,4*R*)-4-(2,6-dichloro-purin-9-yl)-2,3-dihydroxy-cyclopentyl]-propionyl-carbamic acid tert-butyl ester (0.5 g, 1.1 mmol), DIPEA (0.227 mL, 1.3 mmol), (*S*)-2-amino-3-phenyl-propan-1-ol (0.181 mg, 1.2 mmol) in 1,2-dichloroethane (3 mL) is heated at 50°C overnight. 0.1 M HCl (10 mL) is added to the reaction mixture and following agitation, the organic portion is separated and treated with TFA (1 mL). After standing at room temperature for 2 hours, the solvent is removed *in vacuo* to yield the title compound. MS (ES+) *m/e* 475.2 (MH^+).

Intermediate AC

This compound is prepared analogously to Intermediate **AB** by replacing (*S*)-2-amino-3-phenyl-propan-1-ol with 4,4'-(2-aminoethylidene)bisphenol (prepared according to the preparation of Schelkun et al., *Bioorg Med Chem Lett*, Vol. 9, pp. 2447-2452 (1999) MS (ES+) *m/e* 553.2 (MH^+).

Intermediate B

***N*-{(1*S*,2*R*,3*S*,4*R*)-4-[2-((R)-3-Amino-pyrrolidin-1-yl)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide dihydrochloride:**

Step B1: {(*R*)-1-[9-((1*R*,2*S*,3*R*,4*S*)-2,3-Dihydroxy-4-propionylamino-cyclopentyl)-6-(2,2-diphenyl-ethylamino)-9*H*-purin-2-yl]-pyrrolidin-3-yl}-carbamic acid tert-butyl ester:

A reaction mixture comprising *N*-{(1*S*,2*R*,3*S*,4*R*)-4-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide (2.5 g, 4.80 mmol) and (3*R*)-(+)-(3-Boc-amino)pyrrolidine (2.5 g, 13.6 mmol) in DMSO (8 mL) is heated at 100°C overnight. Purification of the product by reverse phase column chromatography (Isolute™ C18, 0-20% acetonitrile in water – 0.1% TFA) yields the title compound. MS (ES+) *m/e* 521.4 (MH^+).

Step B2: *N*-{(1*S*,2*R*,3*S*,4*R*)-4-[2-((R)-3-Amino-pyrrolidin-1-yl)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide dihydrochloride:

{(*R*)-1-[9-((1*R*,2*S*,3*R*,4*S*)-2,3-Dihydroxy-4-propionylamino-cyclopentyl)-6-(2,2-diphenyl-ethylamino)-9*H*-purin-2-yl]-pyrrolidin-3-yl}-carbamic acid tert-butyl ester (ca 4.80 mmol) is dissolved in 1.25 M HCl in MeOH (60 mL). After stirring at room temperature for 3 days, the solvent is removed *in vacuo* to yield the title compound. MS (ES+) *m/e* 571.24 (MH^+).

Intermediate C

***N*-{(1*S*,2*R*,3*S*,4*R*)-4-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide**

Step C1: Acetic acid {(1*S*,2*R*,3*S*,4*R*)-4-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentylcarbamoyl}-methyl ester

A suspension of (1*S*,2*R*,3*S*,5*R*)-3-amino-5-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-cyclopentane-1,2-diol dihydrochloride (Intermediate **AAI3**) (250 mg, 0.46 mmol) in dry THF (10 mL) is treated with TEA (0.188 g, 1.86 mmol) followed by acetoxyacetylchloride

(0.064 g, 0.46 mmol) and then stirred at room temperature for 30 minutes. The solvent is removed *in vacuo* and the solvent is partitioned between DCM and 0.1 M HCl. The organic portion is separated and washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford the title product. MS (ES+) *m/e* 565.38 (MH^+).

Step C2: *N*-{(1*S*,2*R*,3*S*,4*R*)-4-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide:

To a suspension of acetic acid {(1*S*,2*R*,3*S*,4*R*)-4-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentylcarbamoyl}-methyl ester (0.2 g, 0.35 mmol) in MeOH (10 mL) is added potassium carbonate (0.098 g, 0.7 mmol) and the reaction mixture is stirred at room temperature for 1 hour. The solvent is removed *in vacuo* and the solvent is partitioned between DCM and water. The organic portion is separated, dried ($MgSO_4$) and concentrated *in vacuo* to afford the title product. MS (ES+) *m/e* 522.4/ 524.5 (MH^+).

Intermediate D

{1-[(1*S*,4*R*)-4-(2,6-Dichloro-purin-9-yl)-cyclopent-2-enyl]-1*H*-pyrazol-4-yl}-methanol

A mixture comprising carbonic acid (1*S*,4*R*)-4-(2,6-dichloro-purin-9-yl)-cyclopent-2-enyl ester ethyl ester (Intermediate **AA2**) (1.00 g, 2.92 mmol), (1*H*-pyrazol-4-yl)-methanol (preparation shown below) (0.34 g, 3.50 mmol) and triphenyl phosphine (0.115 g, 0.44 mmol) in deoxygenated THF (10 mL) under an inert atmosphere of argon is treated with *tris*(dibenzylideneacetone)dipalladium(0) (0.13 g, 0.15 mmol) and stirred at 50°C for 1 hour. The solvent is removed *in vacuo* and the crude product is purified by chromatography on silica eluting with MeOH/DCM (1:25) to yield the title compound.

Preparation of (1*H*-pyrazol-4-yl)-methanol

4-Ethylpyrazole carboxylate (10 g, 71.40 mmol) is placed in an oven-dried flask under an atmosphere of argon. Dry THF (100 mL) is added followed by the dropwise addition of lithium aluminum hydride (1 M in THF, 100 mL, 100 mmol). Once the addition is complete the reaction mixture is stirred at 50°C. The reaction is shown to be complete by NMR after 4 hours. The reaction mixture is cooled on an ice-bath and the reaction mixture is quenched with water (3.8 mL) then 15% sodium hydroxide (3.8 mL) and finally water again (11.4 mL).

The solvent is removed *in vacuo* and the solid is placed in a Soxhlet apparatus. THF is refluxed through the system for 24 hours. The solvent is removed *in vacuo* to give the title compound.

^{1}H NMR (MeOD, 400 MHz); 7.60 (s, 2H), 4.55 (s, 2H).

Intermediate E

[4-((*R*)-3-Pyrrolidin-3-ylureido)-cyclohexyl]-carbamic acid tert-butyl ester

Step E1: (4-tert-Butoxycarbonylamino-cyclohexyl)-carbamic acid phenyl ester

Phenyl chloroformate (1 eq.) is added dropwise to a solution of pyridine/DCM. The reaction mixture is cooled to 0°C and a solution of (4-amino-cyclohexyl)-carbamic acid tert-butyl ester (1 eq.) in DCM is added dropwise. The reaction mixture is stirred at room temperature for 1 hour. The reaction mixture is partitioned between (0.2 M) $HCl_{(aq)}$ and DCM. The organics are washed with water, saturated sodium hydrogen carbonate solution and brine. The combined organics are dried ($MgSO_4$), filtered and reduced in *vacuo* to yield the title compound.

Step E2: {4-[3-((*R*)-1-Benzyl-pyrrolidin-3-yl)-ureido]-cyclohexyl}-carbamic acid tert-butyl ester

A solution of (4-tert-butoxycarbonylamino-cyclohexyl)-carbamic acid phenyl ester (1 eq.) and (*R*)-1-benzyl-pyrrolidin-3-ylamine (1 eq.) in MeOH is heated using microwave radiation at 100°C for 30 minutes. The resulting solution is purified by reverse phase column chromatography (Isolute™ C18, 0-100% acetonitrile in water 0.1% HCl) to afford the title compound.

Step E3: [4-((*R*)-3-Pyrrolidin-3-ylureido)-cyclohexyl]-carbamic acid tert-butyl ester

To a solution of {4-[3-((*R*)-1-benzyl-pyrrolidin-3-yl)-ureido]-cyclohexyl}-carbamic acid tert-butyl ester in ethanol under an inert atmosphere of argon is added palladium hydroxide on carbon. The reaction mixture is purged with argon and placed under an atmosphere of hydrogen overnight. The mixture is filtered and the catalyst washed with ethanol. The organic portions are combined and concentrated *in vacuo* to yield the title compound.

Intermediate F

[(*R*)-1-((*R*)-Pyrrolidin-3-ylcarbamoyl)-pyrrolidin-3-yl]-carbamic acid tert-butyl ester

This compound is prepared analogously to Intermediate E by replacing (4-amino-cyclohexyl)-carbamic acid tert-butyl ester with (*R*)-pyrrolidin-3-yl-carbamic acid tert-butyl ester.

Intermediate F

[(*R*)-1-((*R*)-Pyrrolidin-3-ylcarbamoyl)-pyrrolidin-3-yl]-carbamic acid tert-butyl ester may also be prepared using the following process

Step F1: ((*R*)-1-Benzyl-pyrrolidin-3-yl)-carbamic acid 4-nitro-phenyl ester

4-Nitro-phenyl chloroformate (1 eq.) is added dropwise to a solution of pyridine/DCM (1:5) at 0°C. The reaction mixture is kept at 0°C and a solution of (*R*)-1-benzyl-pyrrolidin-3-ylamine (1 eq.) in DCM is added dropwise. The reaction mixture is stirred at room temperature overnight. The reaction mixture is partitioned between (0.2 M) $HCl_{(aq)}$ and DCM. The organics are washed with water, saturated sodium hydrogen carbonate solution and brine. The combined organics are dried ($MgSO_4$), filtered and reduced in *vacuo* to yield the title compound. MS (ES+) *m/e* 342.10 (MH^+).

Step F2: [(*R*)-1-((*R*)-1-Benzyl-pyrrolidin-3-ylcarbamoyl)-pyrrolidin-3-yl]-carbamic acid tert-butyl ester

A solution of ((*R*)-1-benzyl-pyrrolidin-3-yl)-carbamic acid 4-nitro-phenyl ester (1 eq.) and (3*R*)-(+)-3-(Boc-amino)pyrrolidine in MeOH is heated using microwave radiation at 100°C for 1 hour. The reaction mixture is reduced in *vacuo.* The resulting oil is dissolved in DCM and isocyanate resin (3 eq.) is added and shaken overnight. The resin was filtered off and the DCM was removed in *vacuo* to yield the title compound. MS (ES+) *m/e* 299.21 (MH^+).

Step F3: [(*R*)-1-((*R*)-Pyrrolidin-3-ylcarbamoyl)-pyrrolidin-3-yl]-carbamic acid tert-butyl ester

To a solution of [(*R*)-1-((*R*)-1-benzyl-pyrrolidin-3-ylcarbamoyl)-pyrrolidin-3-yl]-carbamic acid tert-butyl ester in ethanol under an inert atmosphere of argon is added palladium hydroxide on carbon. The reaction mixture is purged with nitrogen and placed under an atmosphere of hydrogen overnight. The mixture is filtered and the catalyst washed with ethanol. The organic portions are combined and concentrated *in vacuo*. The resulting

brown oil is purified by column chromatography (Isolute™ Si, 2% MeOH in DCM) yield the title compound. MS (ES+) *m/e* 389.25 (MH^+).

Intermediate G

{4-[3-(4-Amino-cyclohexyl)-ureido]-cyclohexyl}-carbamic acid tert-butyl ester

This compound is prepared analogously to Intermediate E by replacing (*R*)-1-benzyl-pyrrolidin-3-ylamine (Step E2) with (4-amino-cyclohexyl)-carbamic acid benzyl ester.

Intermediate H

[1-((*R*)-Pyrrolidin-3-ylcarbamoyl)-piperidin-4-yl]-carbamic acid tert-butyl ester

This compound is prepared analogously to Intermediate F by replacing (3R)-(+)-3-(BOC-amino)pyrrolidine with Piperidin-4-yl-carbamic acid tert-butyl ester in step F2.

Intermediate I

{4-[4-(Pyrrolidin-3-ylamino)-[1,3,5]triazin-2-ylamino]-cyclohexyl}-carbamic acid tert-butyl ester

Step I 1: (*R*)-3-[4-(4-tert-Butoxycarbonylamino-cyclohexylamino)-[1,3,5]triazin-2-ylamino]-pyrrolidine-1-carboxylic acid allyl ester

(*R*)-3-Amino-pyrrolidine-1-carboxylic acid allyl ester (1 eq.) is dissolved in DCM. The reaction mixture is cooled to 0°C and a solution of 2,4-dichloro-[1,3,5]triazine (1 eq.) in DCM is added dropwise. The reaction mixture is stirred at room temperature for 2 hours. The reaction mixture is re-cooled to 0°C and a solution of (4-amino-cyclohexyl)-carbamic acid tert-butyl ester (1 eq.) in DCM is added dropwise. The reaction mixture is stirred at room temperature overnight. The reaction mixture is partitioned between (0.2 M) $HCl_{(aq)}$ and DCM. The organics are washed with water, saturated $NaHCO_{3(aq)}$ and brine. The combined organics are dried ($MgSO_4$), filtered and reduced in *vacuo*, to yield the title compound.

Step I 2: {4-[4-((*R*)-Pyrrolidin-3-ylamino)-[1,3,5]triazin-2-ylamino]-cyclohexyl}-carbamic acid tert-butyl ester

Can be made from the product of Step 1 following Ref: Forns et al., *Tetrahedron Lett*, Vol. 44, No. 36, pp. 6907-6910 (2003). Using (*R*)-3-[4-(4-tert-butoxycarbonylamino-cyclohexylamino)-[1,3,5]triazin-2-ylamino]-pyrrolidine-1-carboxylic acid allyl ester instead of the resin-bound amine.

Preparation of Examples

Example 1 ***N*-{(1*S*,2*R*,3*S*,4*R*)-4-[2-{(*R*)-3-[2-Chloro-9-((1*R*,2*S*,3*R*,4*S*)-2,3-dihydroxy-4-propionylamino-cyclopentyl)-9H-purin-6-ylamino]-pyrrolidin-1-yl}-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide**

Step 1: [(1*S*,2*R*,3*S*,4*R*)-4-(2-Chloro-6-{(*R*)-1-[9-((1*R*,2*S*,3*R*,4*S*)-2,3-dihydroxy-4-propionylamino-cyclopentyl)-6-(2,2-diphenyl-ethylamino)-9*H*-purin-2-yl]-pyrrolidin-3-ylamino}-purin-9-yl)-2,3-dihydroxy-cyclopentyl]-di-carbamic acid tert-butyl ester

(1*S*,2*R*,3*S*,5*R*)-3-(di-Boc-amino)-5-(2,6-dichloro-purin-9-yl)-cyclopentane-1,2-diol (Intermediate AA4) (52 mg, 0.10 mmol) and *N*-{(1*S*,2*R*,3*S*,4*R*)-4-[2-((*R*)-3-amino-pyrrolidin-1-yl)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide (Intermediate B) (58 mg, 0.10 mmol) are suspended in ^{i}PrOH (1 mL). DIPEA (0.089 mL, 0.51 mmol) is added and the reaction mixture is heated using microwave radiation at 100°C for 1 hour. The reaction mixture is partitioned between water and EtOAc and the organic portion is dried ($MgSO_4$), filtered and reduced *in vacuo*. Purification by reverse phase column chromatography (Isolute™ C18, 0-100% acetonitrile in water) affords the title compound. (MH+ 1038/1040).

Step 2: *N*-{(1*S*,2*R*,3*S*,4*R*)-4-[2-{(*R*)-3-[9-((1*R*,2*S*,3*R*,4*S*)-4-Amino-2,3-dihydroxy-cyclopentyl)-2-chloro-9*H*-purin-6-ylamino]-pyrrolidin-1-yl}-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide

[(1*S*,2*R*,3*S*,4*R*)-4-(2-Chloro-6-{(*R*)-1-[9-((1*R*,2*S*,3*R*,4*S*)-2,3-dihydroxy-4-propionylamino-cyclopentyl)-6-(2,2-diphenyl-ethylamino)-9*H*-purin-2-yl]-pyrrolidin-3-ylamino}-purin-9-yl)-2,3-dihydroxy-cyclopentyl]-di-carbamic acid tert-butyl ester (39 mg, 0.038 mmol) is

dissolved in MeOH (1 mL) and (4 M) HCl in dioxane (1 mL) is added. The reaction mixture is stirred at room temperature overnight. The reaction mixture is reduced *in vacuo* yield the title compound. (MH+ 838).

Step 3: *N*-{(1*S*,2*R*,3*S*,4*R*)-4-[2-{(*R*)-3-[2-Chloro-9-((1*R*,2*S*,3*R*,4*S*)-2,3-dihydroxy-4-propionylamino-cyclopentyl)-9*H*-purin-6-ylamino]-pyrrolidin-1-yl}-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide

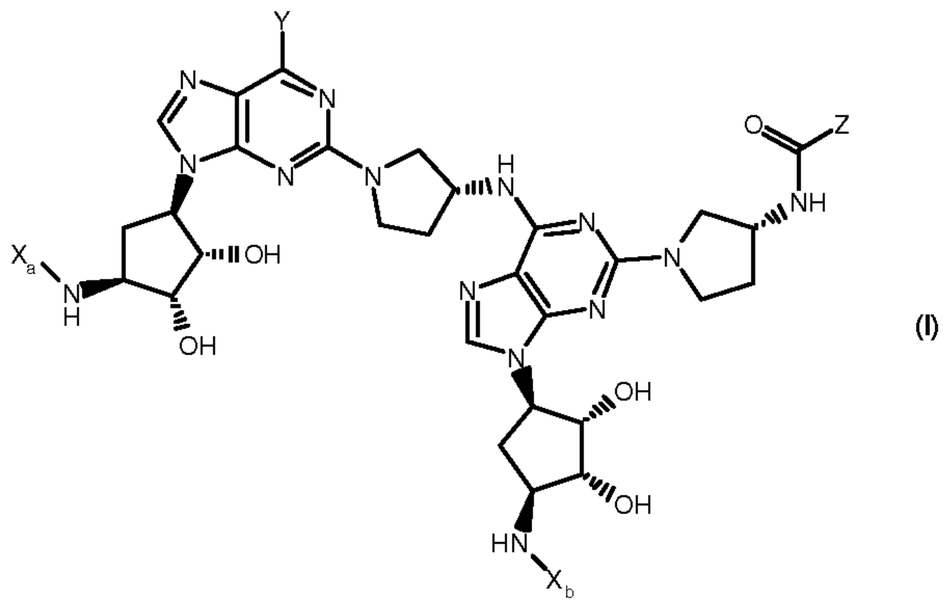
N-{(1*S*,2*R*,3*S*,4*R*)-4-[2-{(*R*)-3-[9-((1*R*,2*S*,3*R*,4*S*)-4-Amino-2,3-dihydroxy-cyclopentyl)-2-chloro-9*H*-purin-6-ylamino]-pyrrolidin-1-yl}-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide (32 mg, 0.038 mmol) and TEA (0.016 mL, 0.113 mmol) are suspended in THF (0.5 mL). MeOH (0.5 mL) is added to aid solubility. Propionic acid chloride (0.0035 mL, 0.040 mmol) is added and the reaction mixture is stirred at room temperature overnight. The reaction mixture is reduced *in vacuo* and purified by reverse phase column chromatography (Isolute™ C18, 0-100% acetonitrile in water – 0.1% TFA) to yield the title compound (MH+ 894/895).

Example 2 **N-{(1*S*,2*R*,3*S*,4*R*)-4-[2-{(*R*)-3-[2-[(*R*)-3-(3-Pyridin-3-yl-ureido)-pyrrolidin-1-yl]-9-((1*R*,2*S*,3*R*,4*S*)-2,3-dihydroxy-4-propionylamino-cyclopentyl)-9*H*-purin-6-ylamino]-pyrrolidin-1-yl}-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide**

N-{(1*S*,2*R*,3*S*,4*R*)-4-[2-{(*R*)-3-[2-Chloro-9-((1*R*,2*S*,3*R*,4*S*)-2,3-dihydroxy-4-propionylamino-cyclopentyl)-9*H*-purin-6-ylamino]-pyrrolidin-1-yl}-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide (1 eq.) and 1-pyridin-3-yl-3-(*R*)-pyrrolidin-3-yl-urea (3 eq.) are dissolved in EtOH. The reaction mixture is refluxed at room temperature for 48 hours. The reaction mixture is reduced *in vacuo* and purified by reverse phase column chromatography (Isolute™ C18, 0-100% acetonitrile in water – 0.1% TFA) to yield the title compound.

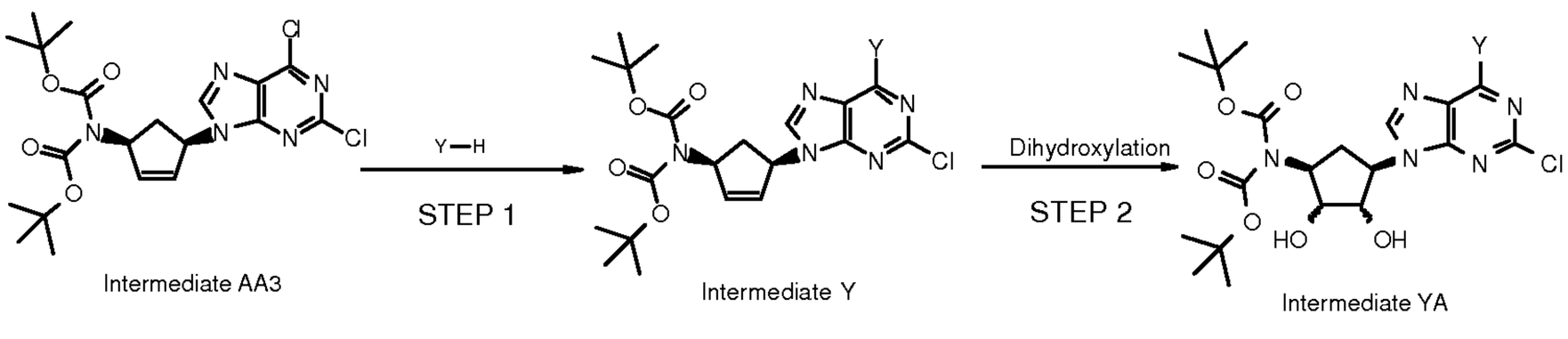
Examples 3-8 are prepared individually by the following methods described for multi-parallel synthesis.

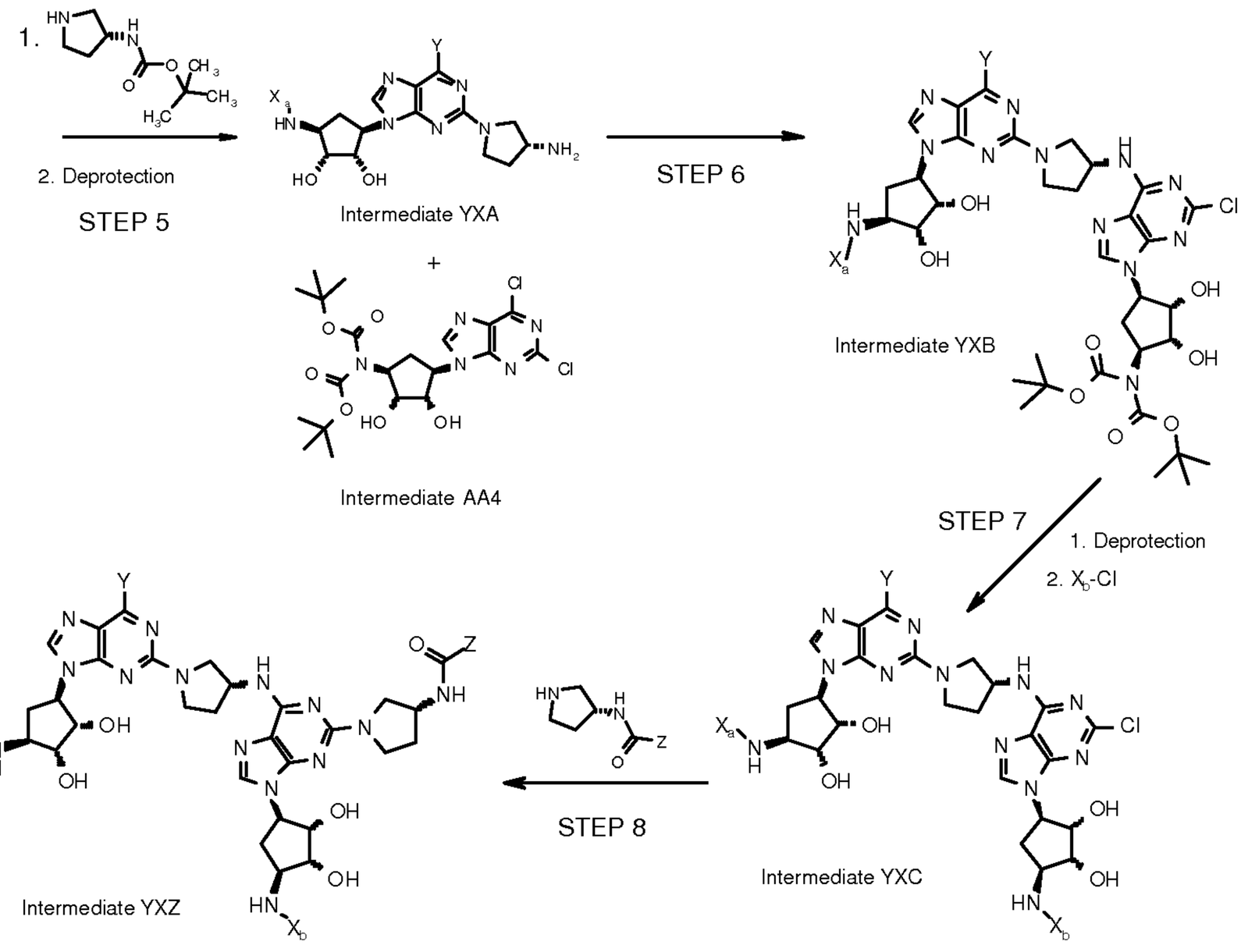
Examples of the formula (I) are prepared in a multiparallel sequence of reactions as described below.



(I)

Scheme 1

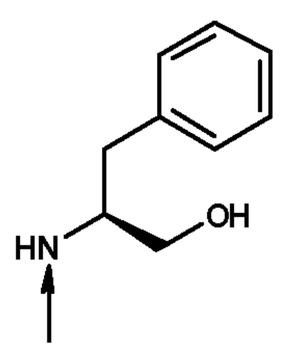

Intermediate AA3
Y—H
STEP 1
Intermediate Y
Dihydroxylation
STEP 2
Intermediate YA
Deprotection
STEP 3
Intermediate YB
X_a-Cl
STEP 4
Intermediate YX


1.
2. Deprotection
STEP 5
Intermediate YXA
+
Intermediate AA4
STEP 6
Intermediate YXB
STEP 7
1. Deprotection
2. X_b-Cl
Intermediate YXC
STEP 8
Intermediate YXZ

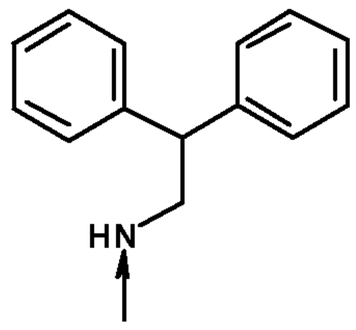
Step 1:

Reaction of Intermediate **AA3**, in an analogous manner to that used in the preparation of Intermediate **AAI1** by replacing diphenylethylamine with the appropriate amine, individually with the amines Y-H gives the Intermediate **Y**.

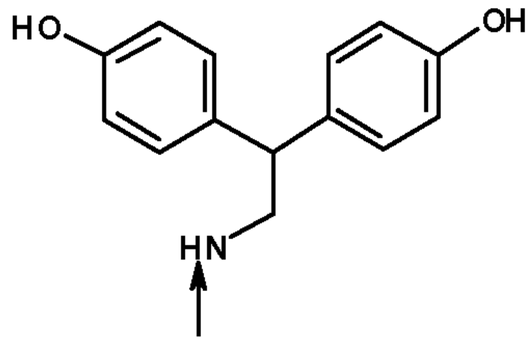
Amines Y-H



Y1



Y2



Y3

Step 2:

Reaction of Intermediates **Y** individually with either the dihydroxylating agent osmium tetroxide or ruthenium tetroxide gives the Intermediates **YA**.

Step 3:

Reaction of Intermediates **YA**, in an analogous manner to that used in the preparation of Intermediate **AAI3** gives the Intermediates **YB**.

Step 4:

Reaction of Intermediates **YB** with the appropriate acid chloride, in an analogous manner to that used in the preparation of either Intermediate **AAI4** (with propionyl chloride) or Intermediate **C** (with acetoxyacetylchloride) gives the Intermediates **YX**.

Intermediates YX

Where X_a = $CH_3CH_2C(O)$-, $CH_3OC(O)$-, $HOCH_2C(O)$-, $HOCH(CH_3)C(O)$-

Step 5:

Reaction of Intermediates **YX** with (3*R*)-(+)-(3-Boc-amino)pyrrolidine followed by deprotection in an analogous manner to that used in the preparation of Intermediate **B** gives the Intermediates **YXA**

Steps 6 and 7:

Reaction of Intermediates **YXA**, in an analogous manner to that used to prepare Example 1, individually using the appropriate acid chlorides in *Step 3* affords the Intermediates **YXC**.

Intermediates YXC

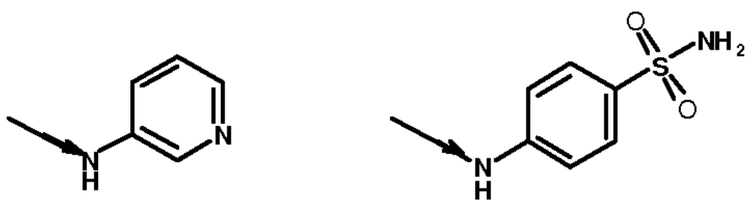
Where X_b = $CH_3CH_2C(O)$-, $CH_3OC(O)$-, $HOCH_2C(O)$-, $HOCH(CH_3)C(O)$-

Step 8:

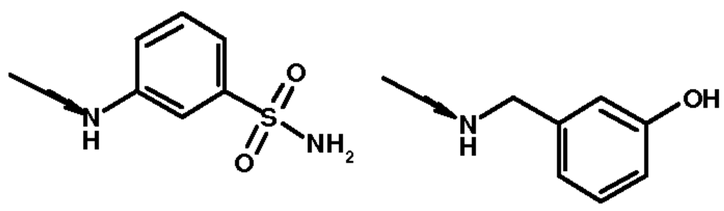
Intermediates **YXC** are reacted in ethanol at reflux, or in DMSO at 90-110°C, for 18-24 hours individually with a 3-fold excess of the appropriate Intermediate **Z**. The examples or Formula (I) are isolated following purification by mass directed reversed phase chromatography.

Intermediate Z

Where Z =

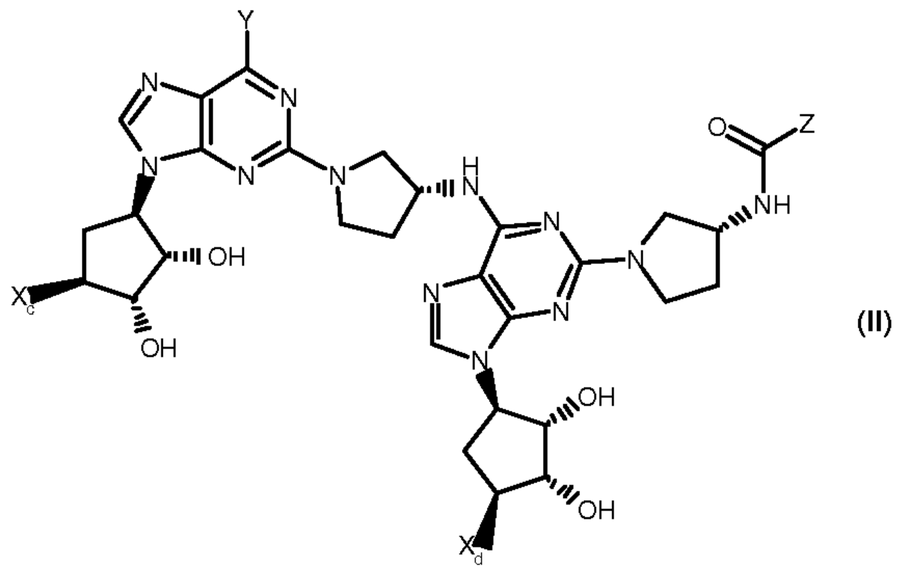


Z1 Z2



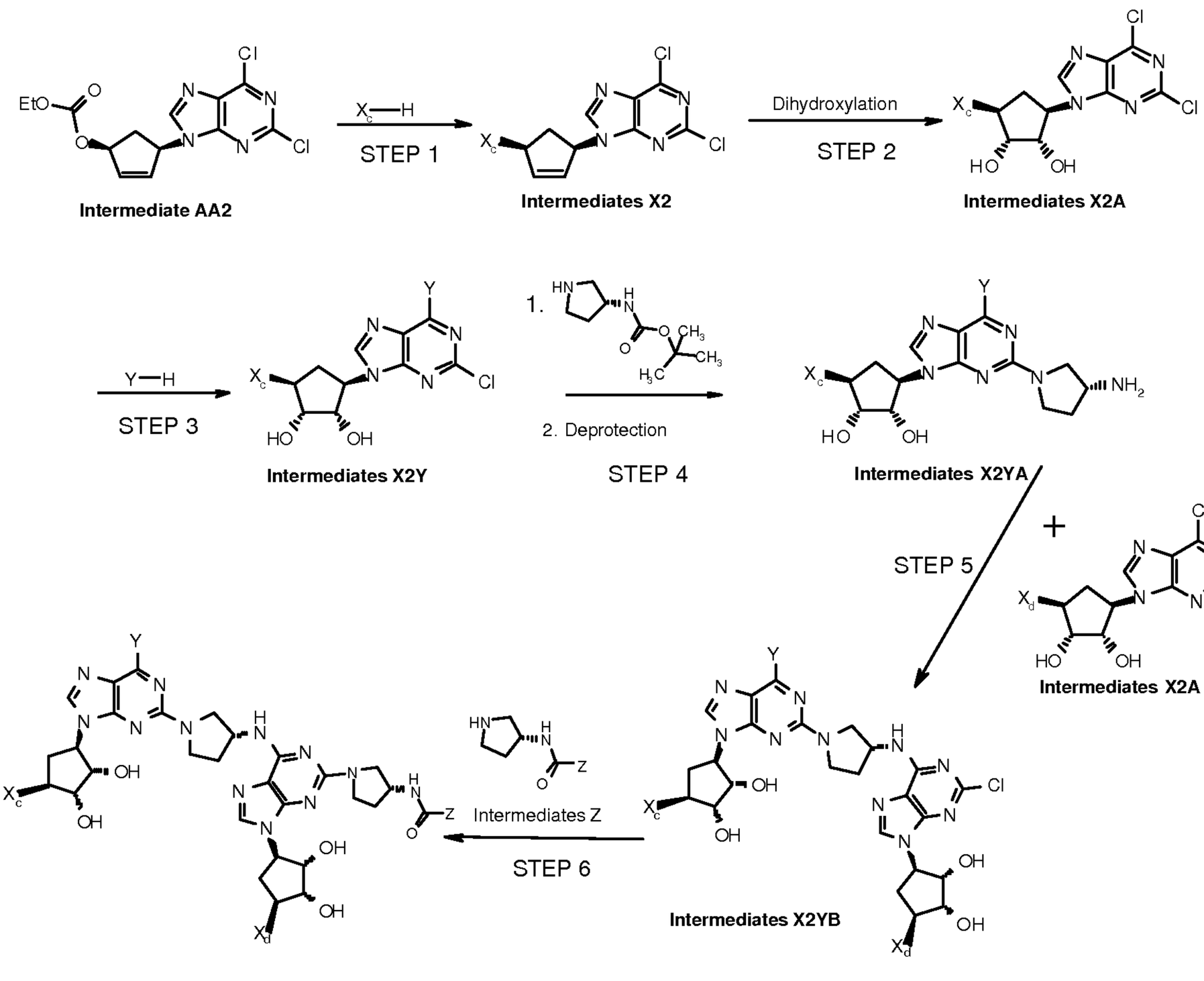
Z3 Z4

Examples of formula (II) can be prepared as described below in Scheme **2**:



(II)

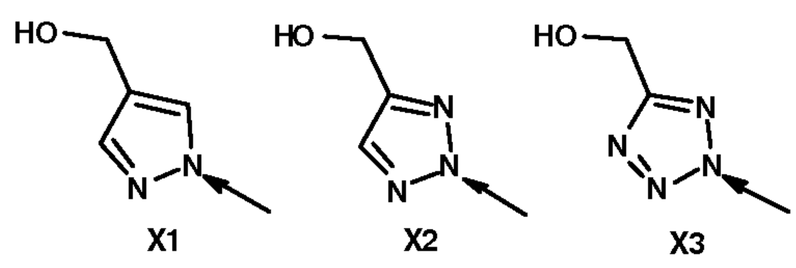
Scheme 2



Step 1:

Reaction of Intermediate **AA2**, in an analogous manner to that used in the preparation of Intermediate **D**, by replacing (1*H*-pyrazol-4-yl)-methanol with the appropriate heterocycle, individually with the heterocycles X_c-H gives the Intermediates **X2**.

Heterocycles X_c-H



Heterocycles X-H are prepared as follows:

- X1 the preparation is described with Intermediate **D**.
- X2-X3 are prepared following literature procedures.

Step 2:

Reaction of Intermediates **X2**, individually with either the dihydroxylating agent osmium tetroxide or ruthenium tetroxide gives the Intermediates **X2A**.

Step 3:

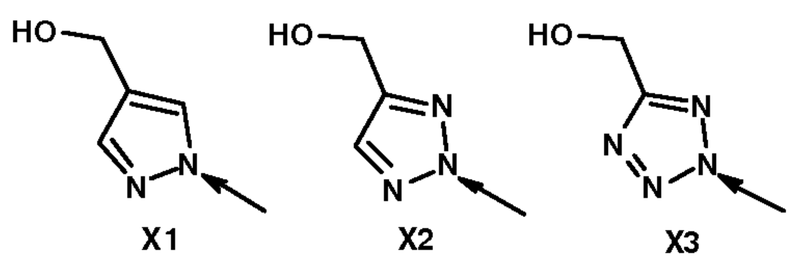
Reaction of Intermediates **X2A**, in an analogous manner to that used in the preparation of Intermediate **AB**, *Step AB3* by replacing (*S*)-2-amino-3-phenyl-propan-1-ol with the appropriate amine, individually with the amines Y-H gives the Intermediates **X2Y**.

Step 4:

Intermediates **X2Y** are reacted with (3*R*)-(+)-(3-Boc-amino)pyrrolidine followed by deprotection in an analogous manner to that used in the preparation of Intermediate **B** gives the Intermediates **Y2XA**.

Step 5:

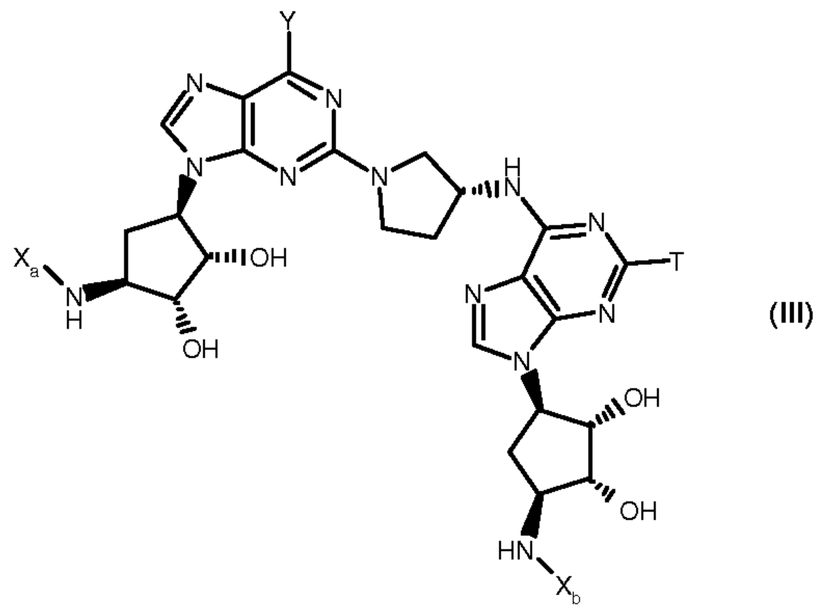
Reaction of Intermediates **Y2XA** in an analogous manner to that used to prepare [(1*S*,2*R*,3*S*,4*R*)-4-(2-chloro-6-{(*R*)-1-[9-((1*R*,2*S*,3*R*,4*S*)-2,3-dihydroxy-4-propionylamino-cyclopentyl)-6-(2,2-diphenyl-ethylamino)-9*H*-purin-2-yl]-pyrrolidin-3-ylamino}-purin-9-yl)-2,3-dihydroxy-cyclopentyl]-di-carbamic acid tert-butyl ester (Example 1, *Step 1*), individually using the corresponding Intermediate **X2A** affords the Intermediate **X2YB**.

Where X_d is selected from 

Step 6:

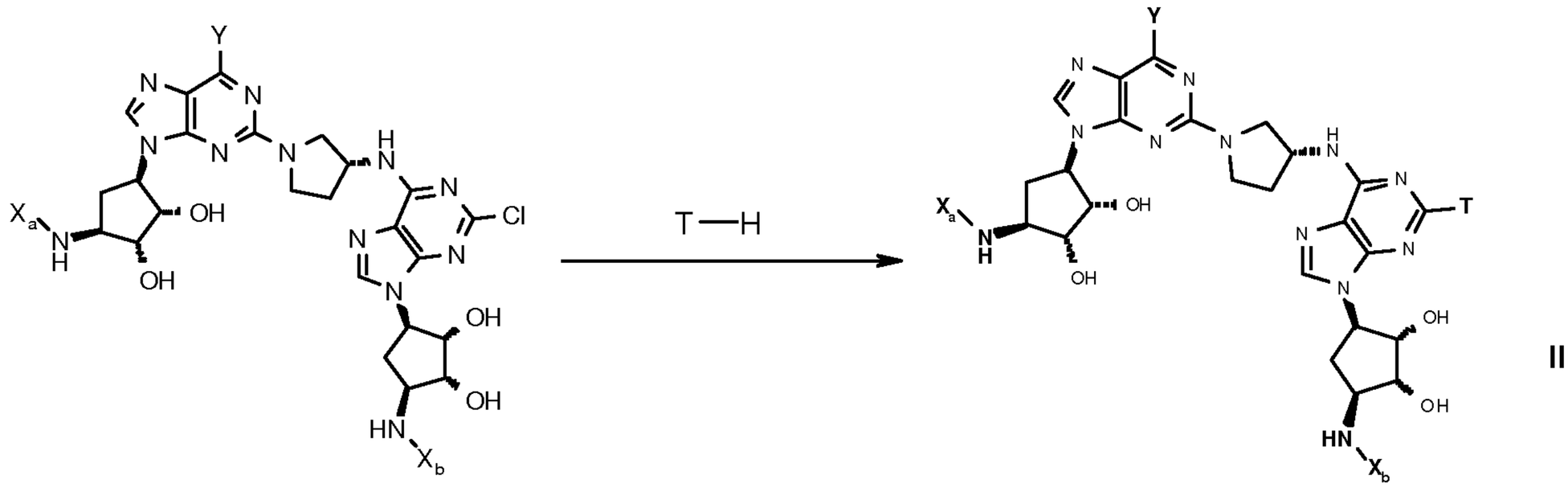
Intermediate **X2YB** are reacted in ethanol at reflux, or in DMSO at 90-110°C, for 18-24 hours individually with a 3-fold excess of the appropriate Intermediate **Z** (as described previously). The examples of formula (III) are isolated following purification by mass directed reversed phase chromatography.

Examples of the formula (III) are prepared as described below.



(III)

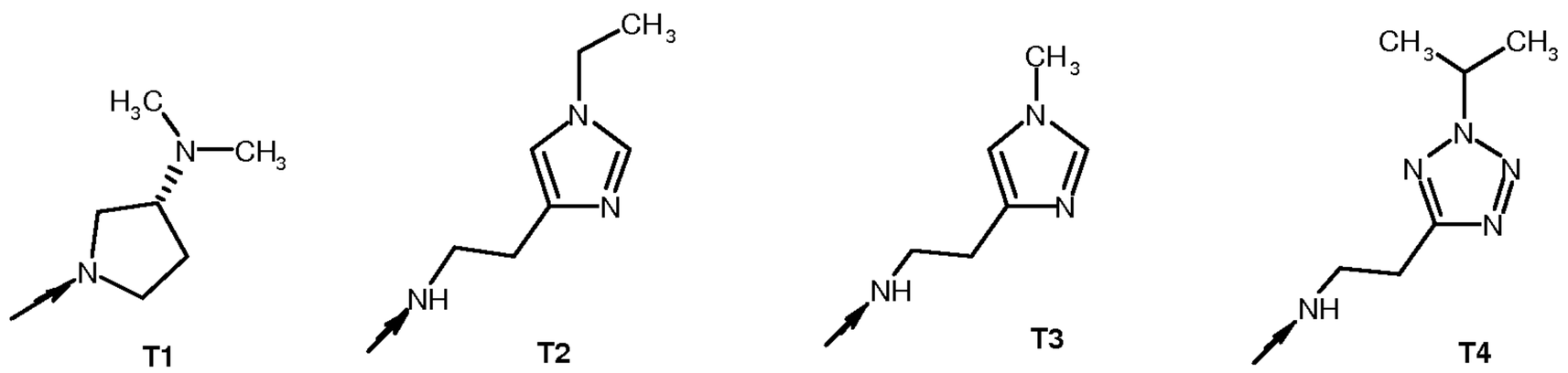
Scheme 3



III

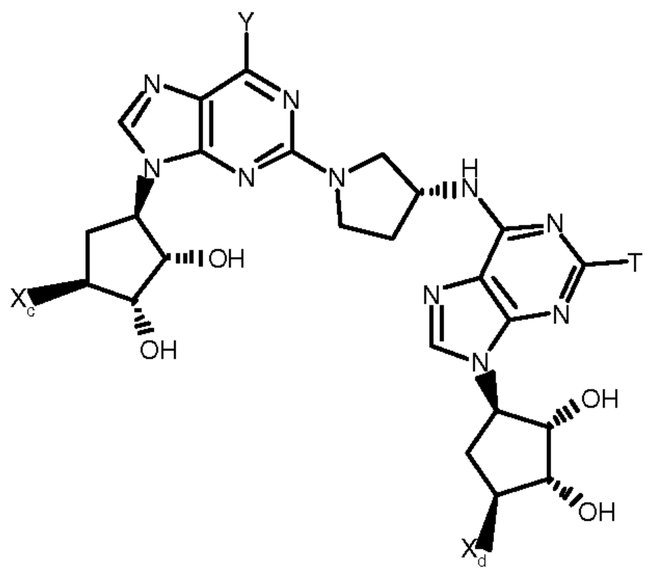
Intermediates **YXC** are reacted in acetonitrile/*N*-methyl-pyrrolidone in the presence of sodium iodide, triethylamine, individually with the amines T-H. Heating with microwave radiation at temperatures from 120-220°C gives the series of Examples of formula (III).

Amines T-H



T1 **T2** **T3** **T4**

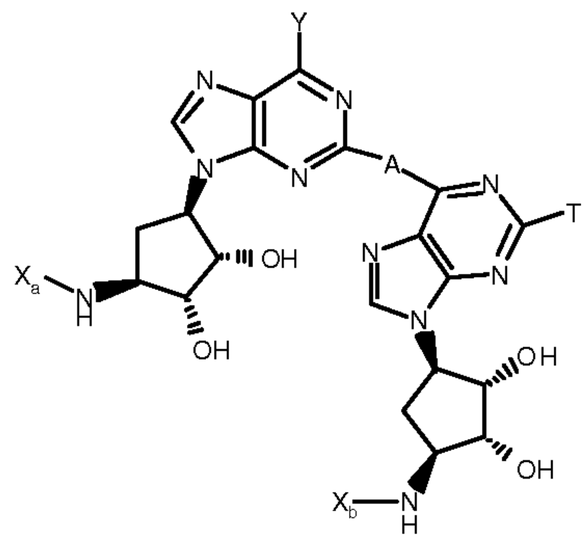
Examples of the formula (IV) are prepared as described below.



(IV)

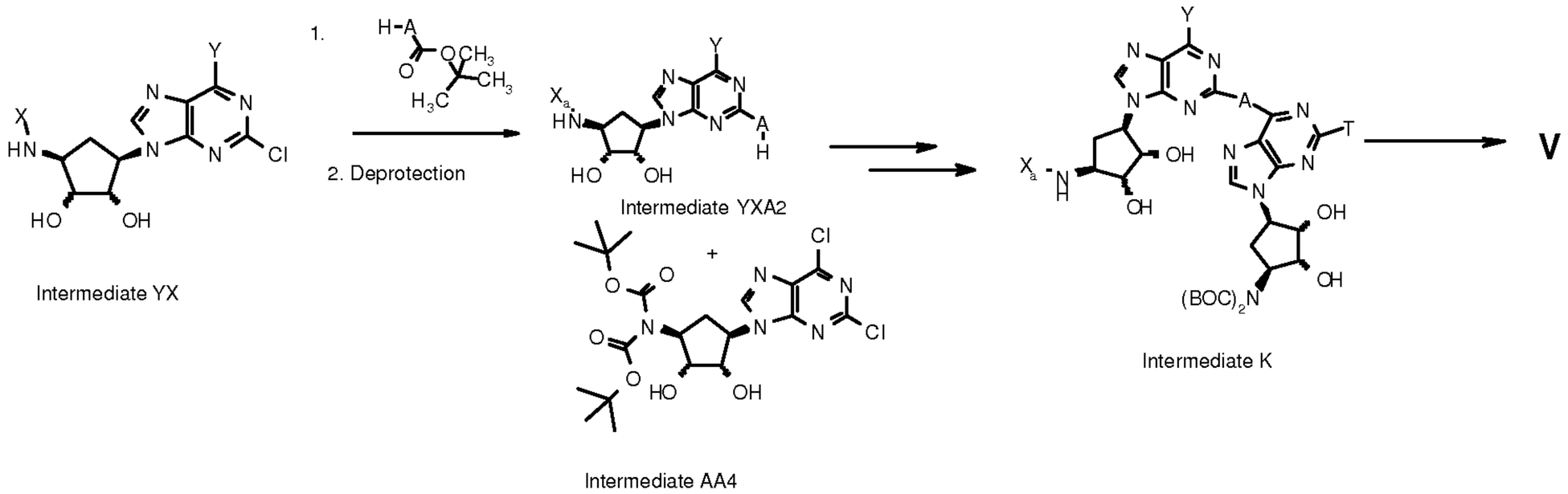
These examples are prepared from Intermediates **X2YB** in an analogous manner to that used to prepare Examples of formula (III).

Examples of the formula (V) are prepared as described below.



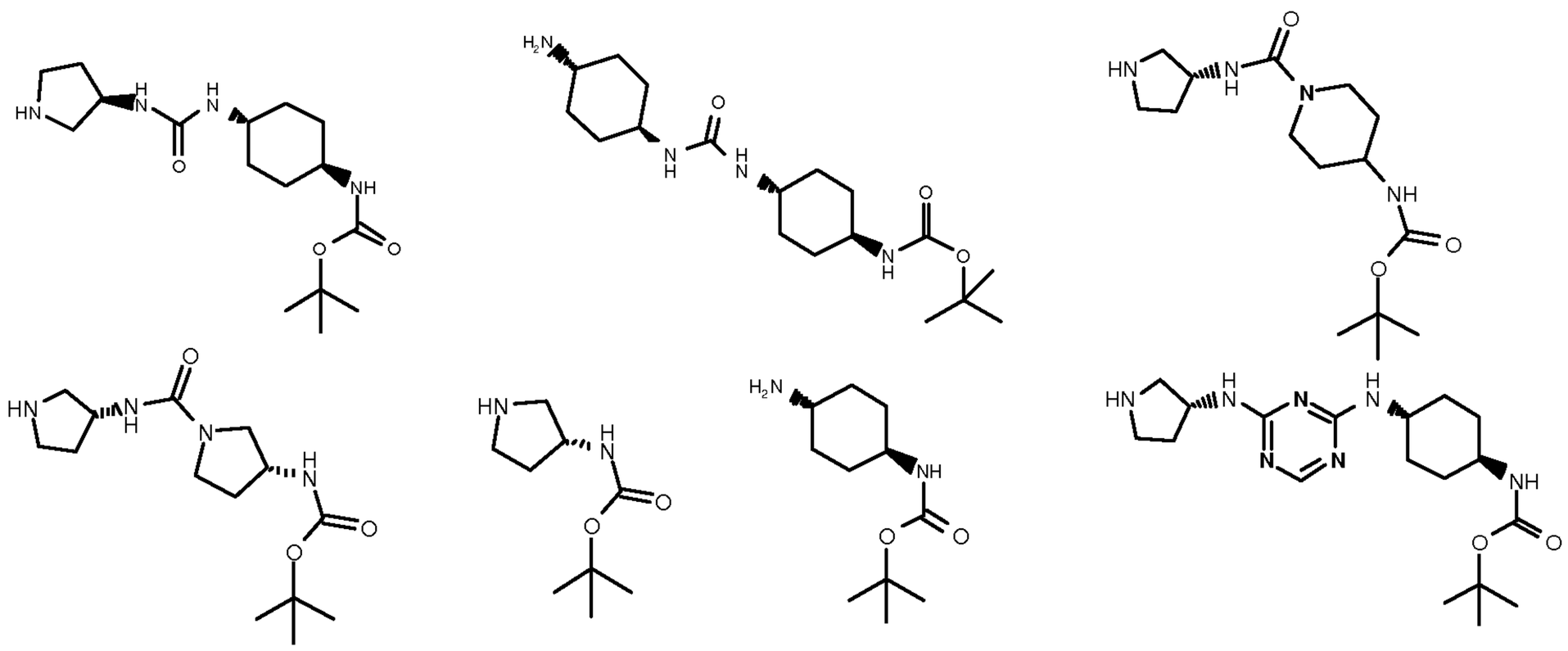
(V)

Scheme 4:

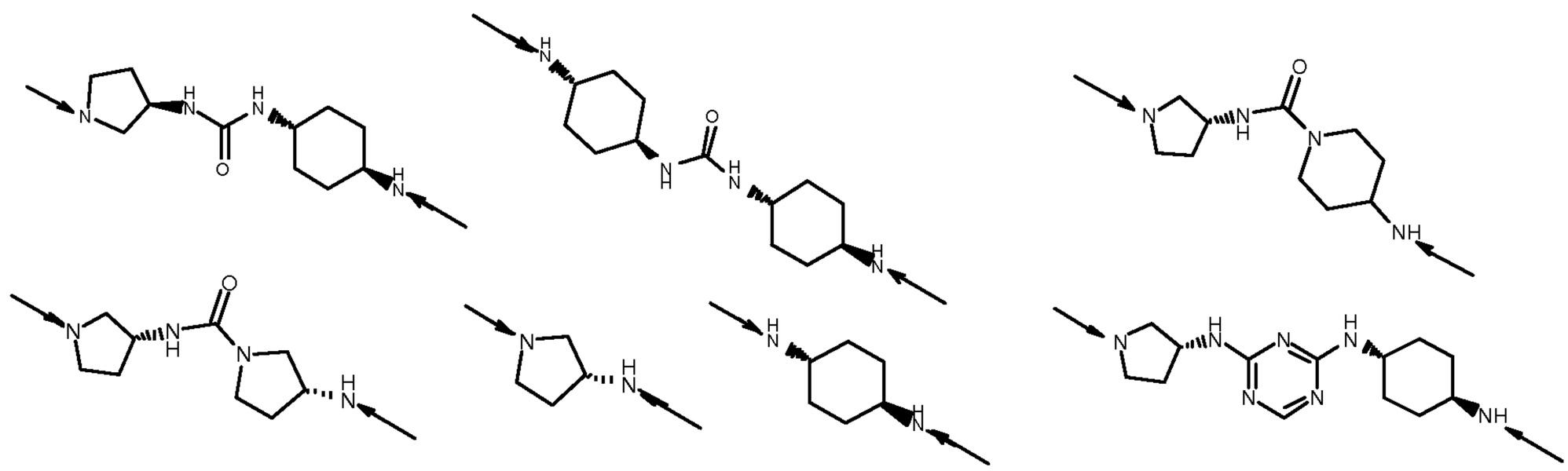


These examples are prepared from Intermediates **YXA2** analogously to examples of formula (III). Intermediates **YXA2** are prepared from Intermediates **YX** in an analogous manner to that used in the preparation of Intermediate **B** by replacing (3*R*)-(+)-(3-Boc-amino)pyrrolidine with the appropriate Boc-protected amine (Boc)-A-H.

Boc-protected amine (Boc)-A-H:

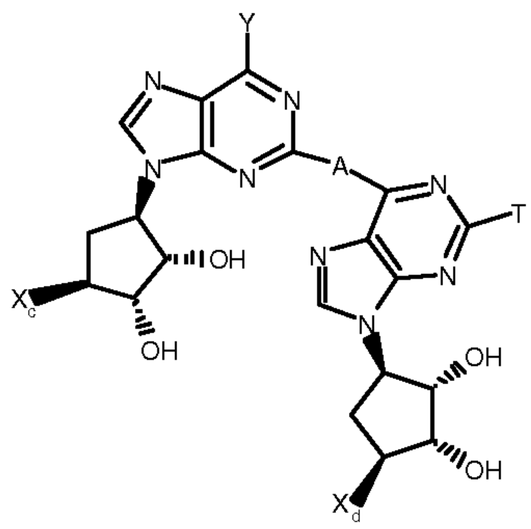


Resulting A Linkers:



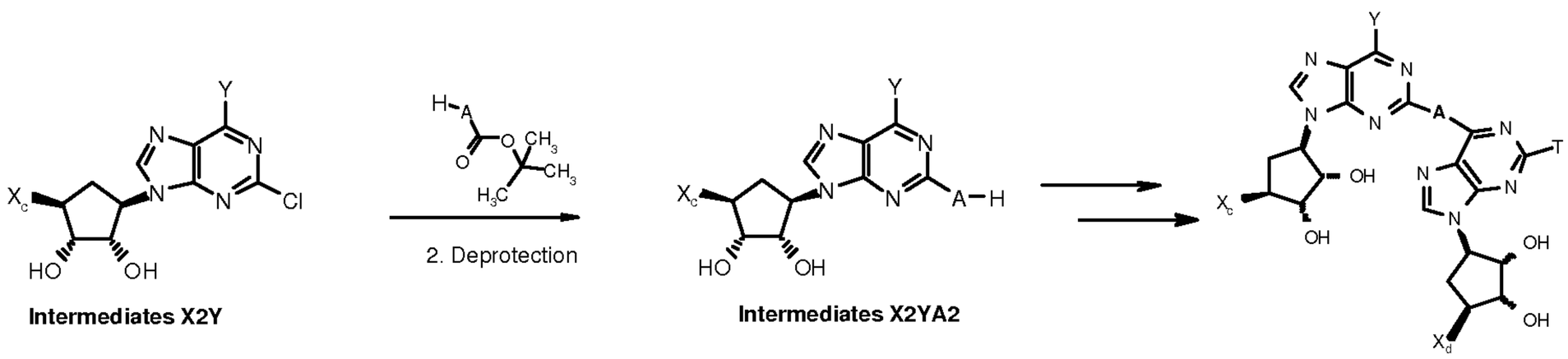
Intermediate **K** is converted to Example **V** in an analogues fashion to Example **I**.

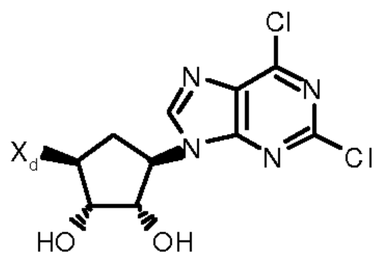
Examples of the formula (VI) are prepared as described below.



(VI)

Scheme 5:





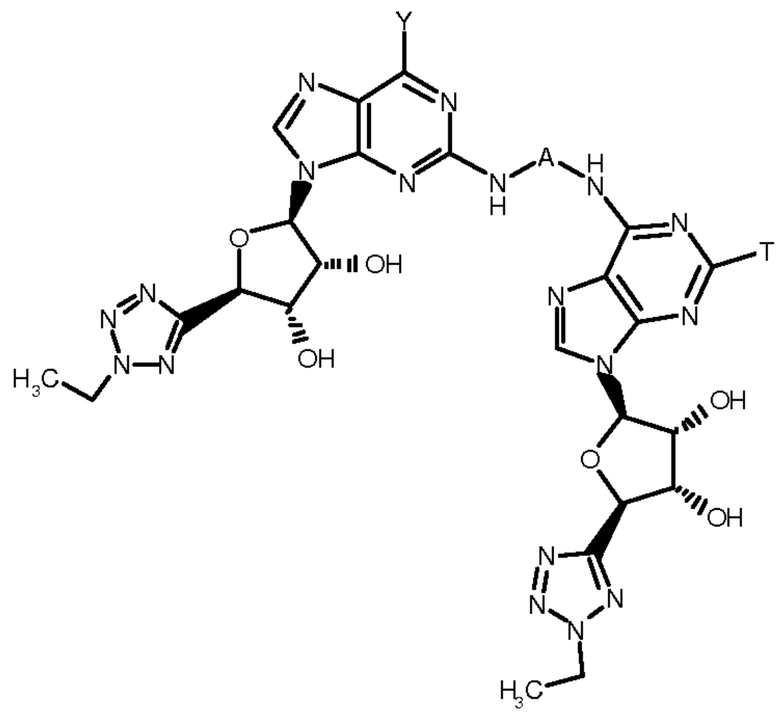
Intermediates X2A

VI

These examples are prepared from Intermediates **X2YA2** analogously to examples of formula (III). Intermediates **X2YA2** are prepared from Intermediates **X2Y** in an analogous manner to that used in the preparation of Intermediate **B** by replacing (3*R*)-(+)-(3-Boc-amino)pyrrolidine with the appropriate Boc-protected amine (Boc)-A-H.

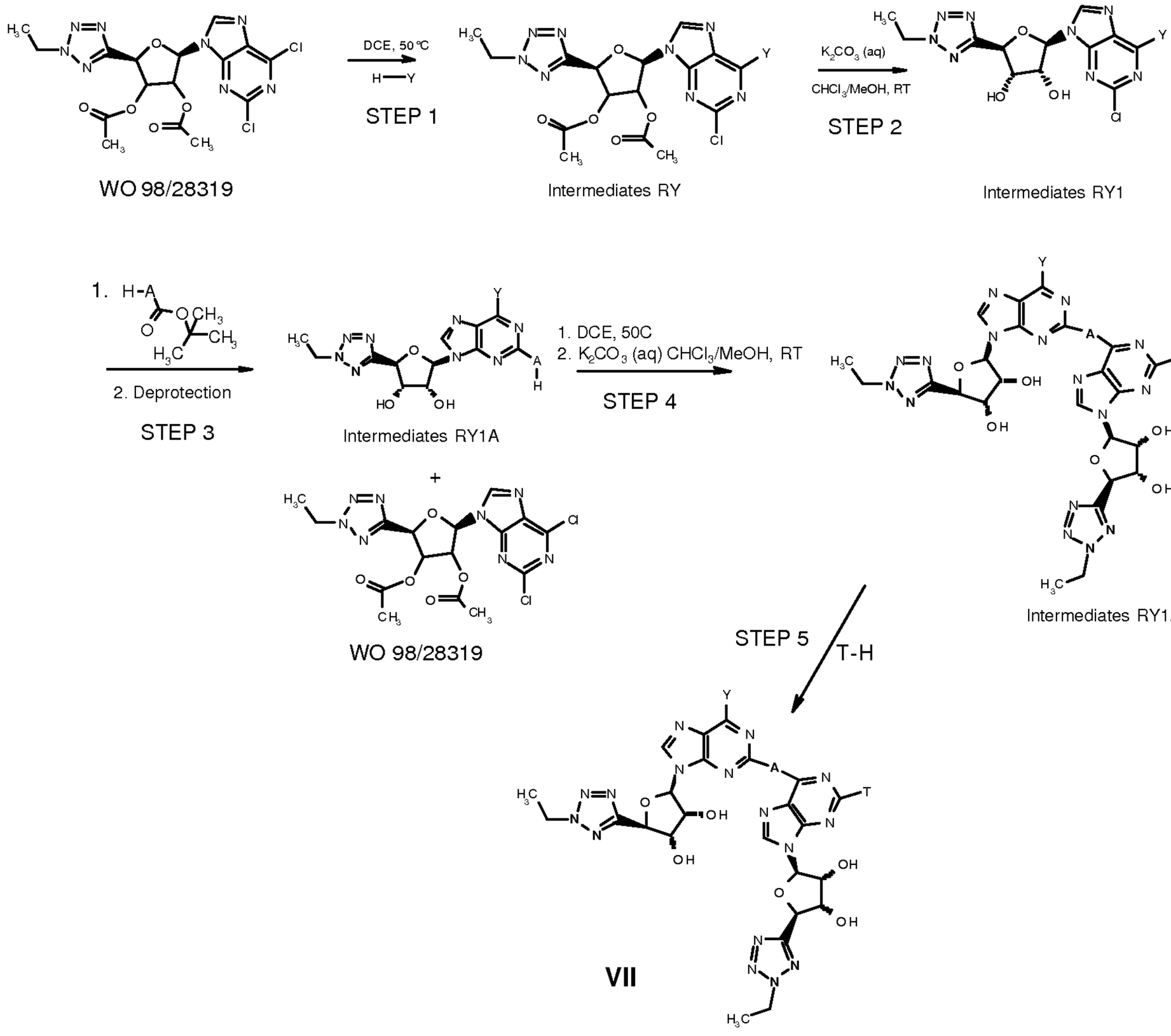
Ribose Examples

Examples of the formula (VII) are prepared as described below.



(VII)

Scheme 6



Step 1:

Reaction of acetic acid (2*R*,5*R*)-4-acetoxy-2-(2,6-dichloro-purin-9-yl)-5-(2-ethyl-2*H*-tetrazol-5-yl)-tetrahydro-furan-3-yl ester (WO 98/28319) in DCE at 50°C with the appropriate amine Y-H in the presence of DIPEA affords Intermediates **RY**.

Step 2:

Intermediates **RY** are deprotected using potassium carbonate in MeOH/chloroform at room temperature to yield Intermediates **RY1**.

Step 3:

Reaction of Intermediates **RY1** individually with the appropriate Boc-protected amine (Boc)-A-H followed by deprotection in an analogous manner to that used in the preparation of Intermediate **B** gives the Intermediates **RY1A**.

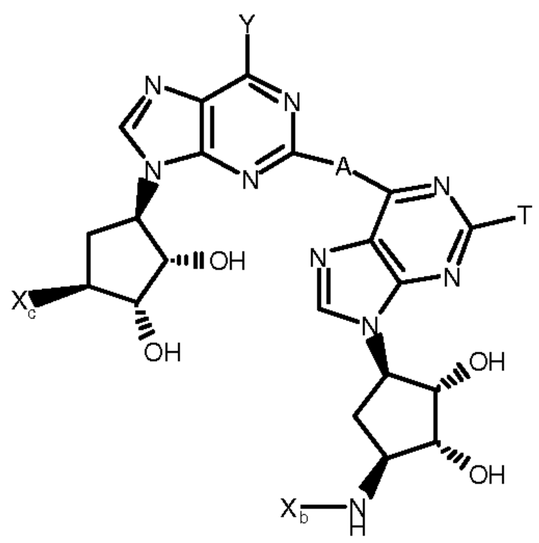
Step 4:

Reaction of Intermediates **RY1A** individually with acetic acid (2*R*,5*R*)-4-acetoxy-2-(2,6-dichloro-purin-9-yl)-5-(2-ethyl-2*H*-tetrazol-5-yl)-tetrahydro-furan-3-yl ester (WO 98/28319) using conditions analogous to those described in *Steps 1* and *2* affords the Intermediates **RY1A2**.

Step 5:

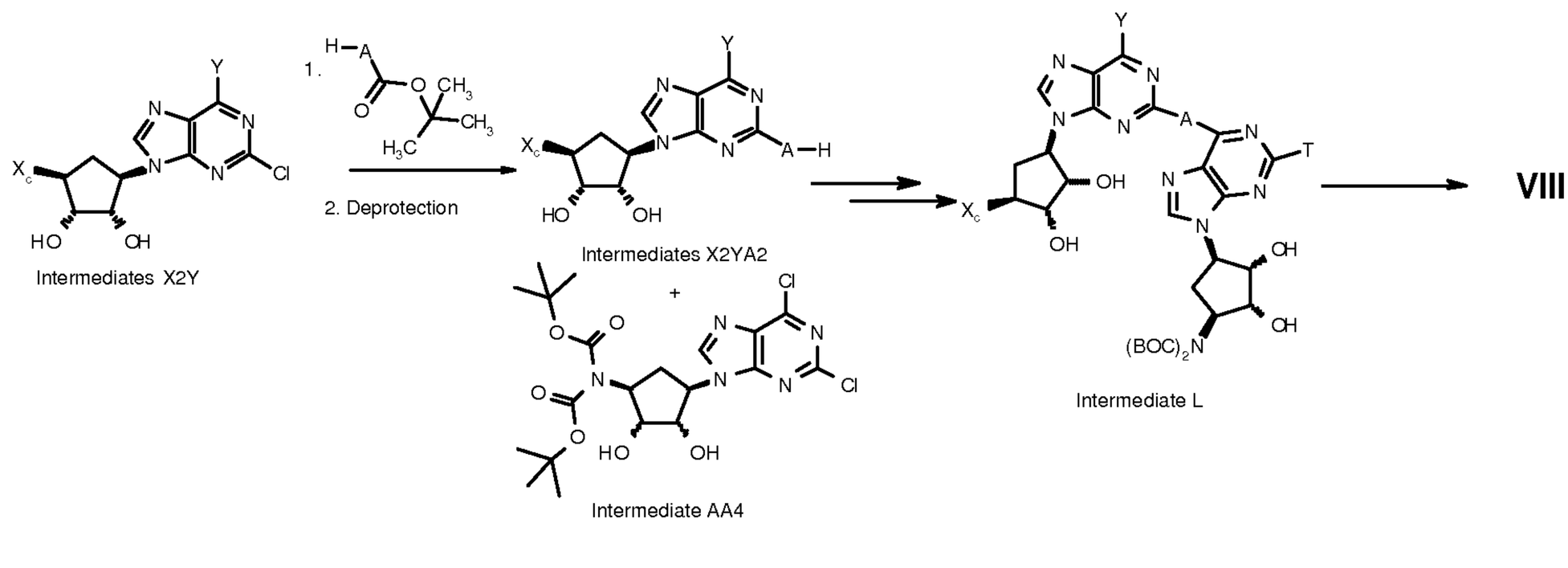
Intermediates **RY1A2** are reacted in acetonitrile/*N*-methyl-pyrrolidone in the presence of sodium iodide, triethylamine, individually with the amines T-H. Heating with microwave radiation at temperatures from 120-220°C gives the series of Examples of formula (VII).

Examples of the formula (VIII) are prepared as described below.



(VIII)

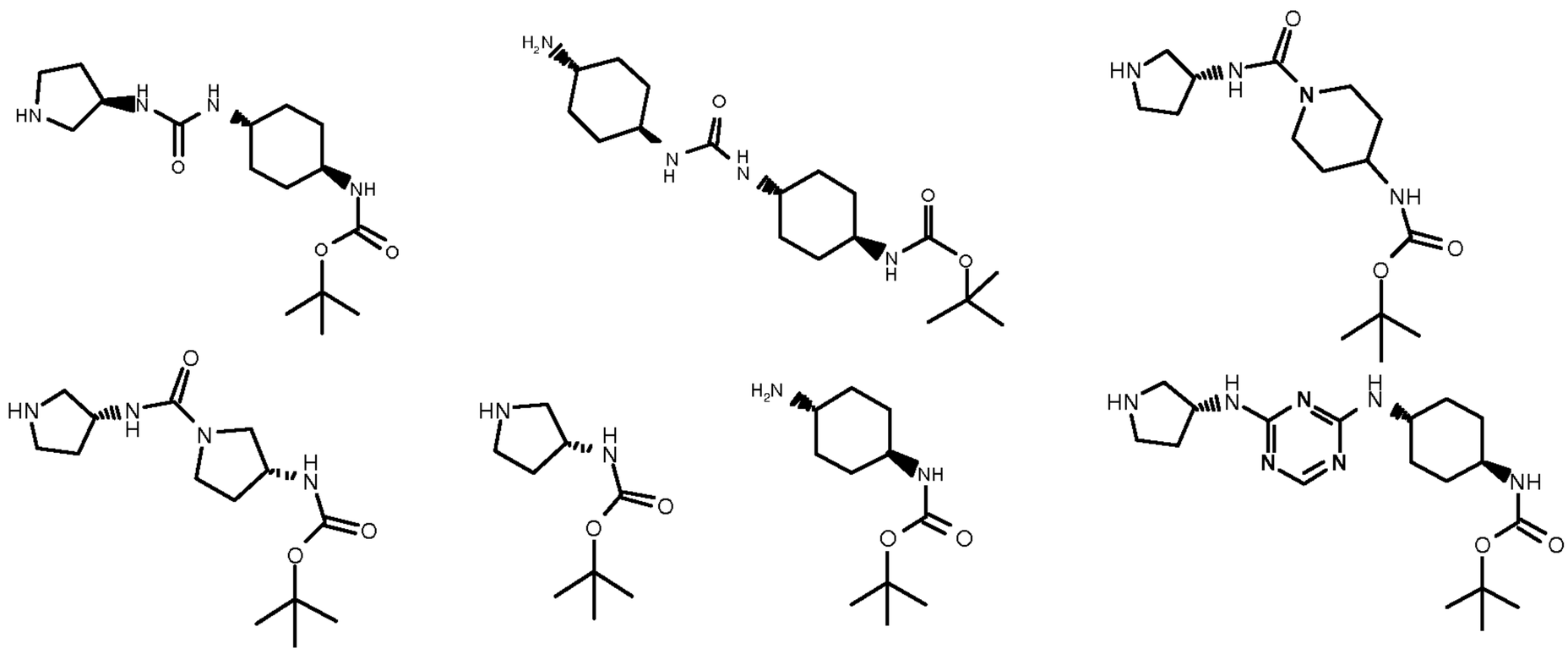
Scheme 4:



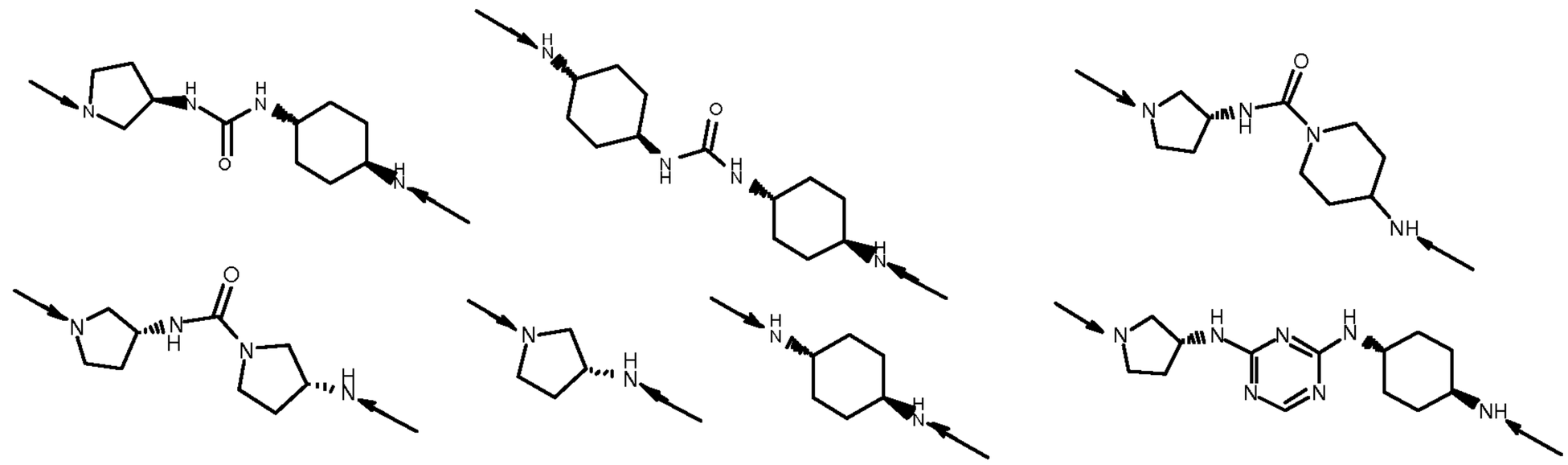
Intermediate AA4

These examples are prepared from Intermediates **X2YA2** analogously to examples of formula (III). Intermediates **X2YA2** are prepared from Intermediates **X2Y** in an analogous manner to that used in the preparation of Intermediate **B** by replacing (3*R*)-(+)-(3-Boc-amino)pyrrolidine with the appropriate Boc-protected amine (Boc)-A-H.

Boc-protected amine (Boc)-A-H:

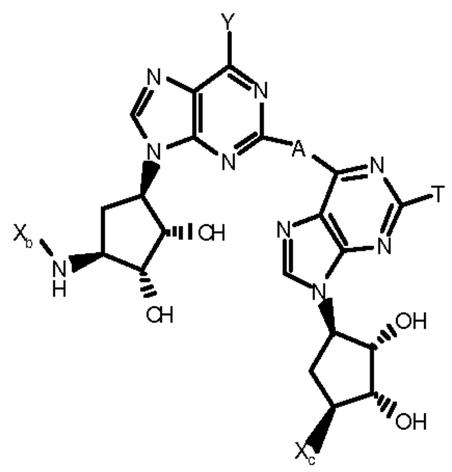


Resulting A Linkers:

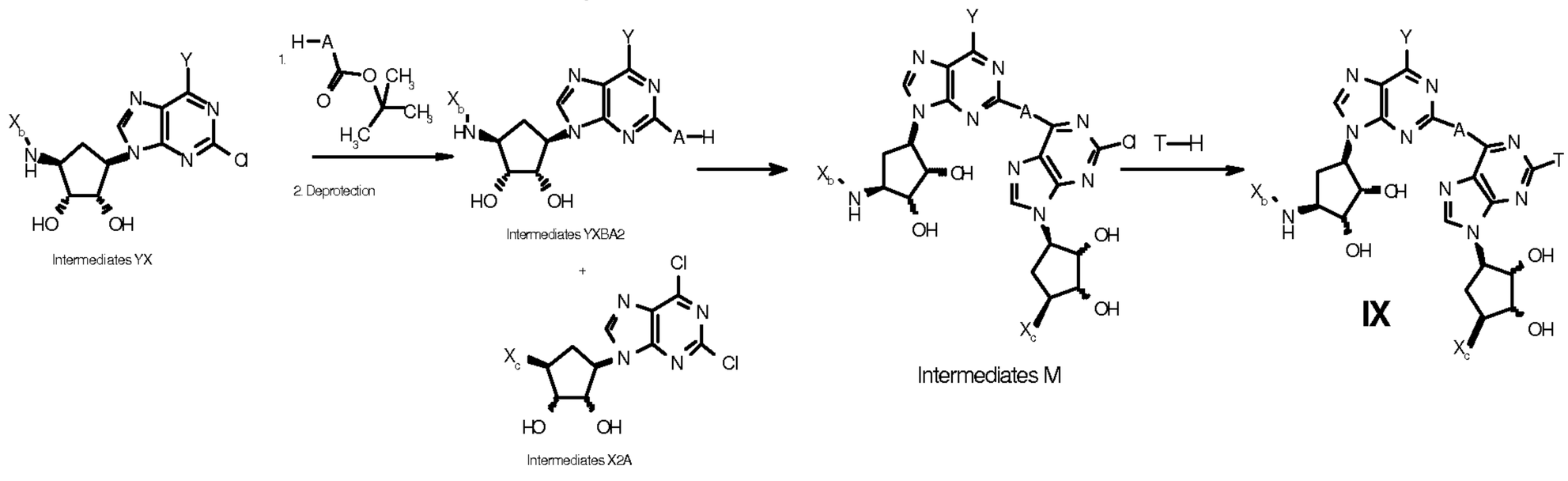


Intermediate **L** is converted to Example **VIII** in an analogues fashion to Example **I**.

Examples of the formula (IX) are prepared as described below.



(IX)



Scheme 5:

These examples are prepared as follows:

Step 1: Intermediates YXBA2 are prepared from Intermediates YX in an analogous manner to that used in the preparation of Intermediate B by replacing (3*R*)-(+)-(3-Boc-amino)pyrrolidine with the appropriate Boc-protected amine (Boc)-A-H.

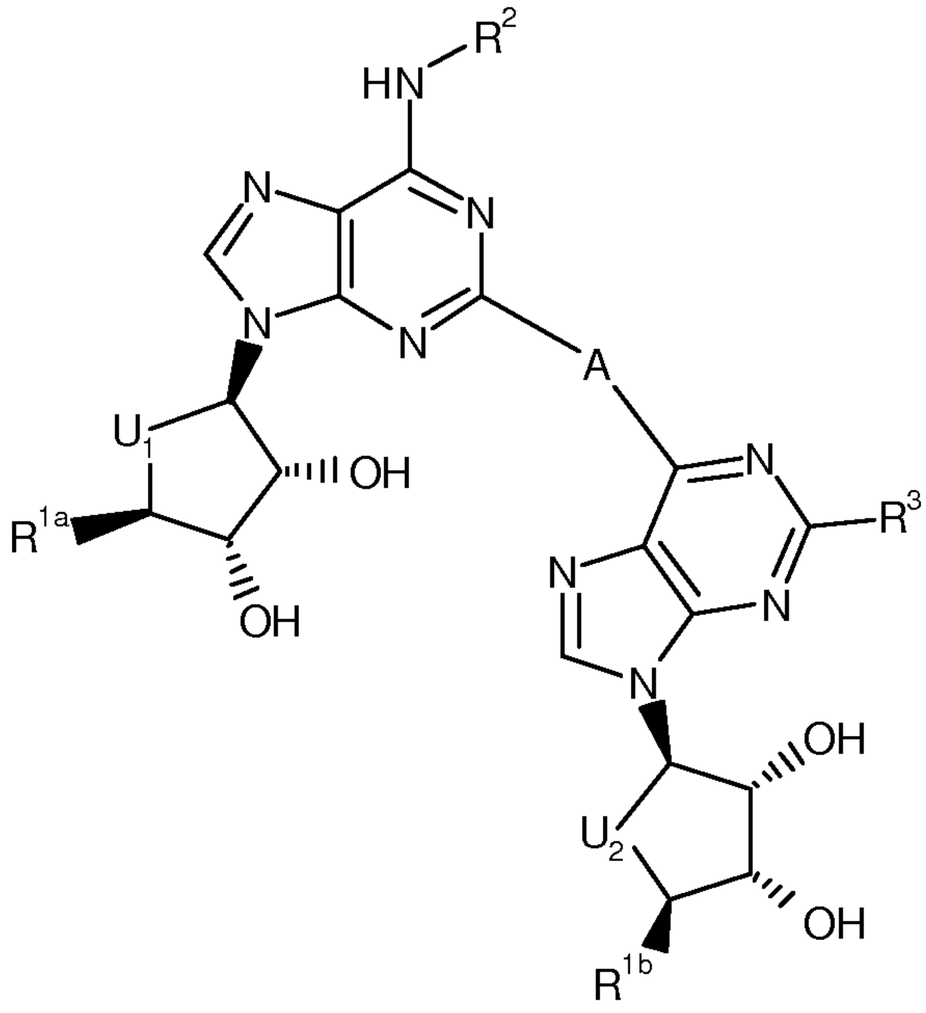
Step 2: Reaction of Intermediates YXBA2 in an analogous manner to that used to prepare [(1*S*,2*R*,3*S*,4*R*)-4-(2-chloro-6-{(*R*)-1-[9-((1*R*,2*S*,3*R*,4*S*)-2,3-dihydroxy-4-propionylamino-cyclopentyl)-6-(2,2-diphenyl-ethylamino)-9*H*-purin-2-yl]-pyrrolidin-3-ylamino}-purin-9-yl)-2,3-dihydroxy-cyclopentyl]-di-carbamic acid tert-butyl ester (Example 1, Step 1), individually using the corresponding Intermediate X2A affords the Intermediates M.

Step 3: Intermediates M are reacted in acetonitrile/*N*-methyl-pyrrolidone in the presence of sodium iodide, triethylamine, individually with the amines T-H. Heating with microwave radiation at temperatures from 120-220°C gives the series of Examples of formula (IX).

Boc-protected amine (Boc)-A-H, resulting A linkers and amines T-H are as described previously.

Claims:

1. A compound of formula (I), or stereoisomers or pharmaceutically acceptable salts thereof,



(I)

wherein

U_1 and U_2 are independently selected from CH_2 and O with the proviso that when U_1 is O then R^{1a} is not a N-bonded substituent, and when U_2 is O then R^{1b} is not a N-bonded substituent;

R^1 and R^{1b} are independently selected from a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, that group being optionally substituted by oxo, O-C_1-C_8-alkyl, C_6-C_{10}-aryl, R^{1c} or by C_1-C_8-alkyl optionally substituted by OH, or

R^1 and R^{1b} are independently selected from -NR^4R^4, -NR^5-C_1-C_8-alkylcarbonyl, -NR^5-C_3-C_8-cycloalkylcarbonyl, -NR^5SO_2-C_1-C_8-alkyl, -NR^5-C_7-C_{14}-aralkylcarbonyl and -$NR^5C(=O)$-$C(=O)$-NR^5-C_1-C_8-alkyl optionally substituted by R^{1c}, or

R^{1a} and R^{1b} are independently selected from NR^4-C_1-C_8-alkyl, $NR^5C(O)C_1$-C_8-hydroxyalkyl, $NR^5CO_2C_1$-C_8-alkyl, and $NR^5CO_2C_2$-C_8-hydroxyalkyl, or

R^{1a} and R^{1b} are independently selected from C_1-C_8-hydroxyalkyl, CH_2-O-C_1-C_8-alkyl, C(O)-O-C_1-C_8-alkyl, $C(O)NR^5R^5$ and C(O)-NH-C_1-C_8-alkyl;

R^{1c} is a 3- or 12-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, said 3- or 12-membered heterocyclic ring being optionally substituted by halo, cyano, oxo, OH, carboxy, amino, nitro, C_1-C_8-alkyl, C_1-C_8-alkylsulfonyl, aminocarbonyl, C_1-C_8-alkylcarbonyl or O-C_1-C_8-alkyl optionally substituted by aminocarbonyl;

R^2 is C_1-C_8-alkyl optionally substituted by OH, halogen C_6-C_{10}-aryl optionally substituted by OH, SO_2R^{10}, SC_1-C_8-alkyl, CN, halogen, O-C_7-C_{14}-aralkyl, or O-C_1-C_8-alkyl, a C_3-C_{15}-carbocyclic group optionally substituted by O-C_7-C_{14} aralkyl, C_3-C_{15}-carbocyclic group, O-C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl or C_1-C_8-alkyl, O-C_1-C_8-alkyl, -SO_2-C_1-C_8-alkyl, a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, that group being optionally substituted by 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, C_7-C_{14}-aralkyl, or C_6-C_{14}-aryl optionally substituted by O-C_7-C_{14}-aralkyl, or

R^2 is C_3-C_{15}-carbocyclic group optionally substituted by O-C_7-C_{14}-aralkyl, C_3-C_{15}-carbocyclic group, O-C_1-C_8-alkyl, or C_1-C_8-alkyl, or

R^2 is a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, that group being optionally substituted by 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, C_7-C_{14}-aralkyl, or C_6-C_{14}-aryl optionally substituted by O-C_7-C_{14}-aralkyl;

R^3 is hydrogen, halo, C_2-C_8-alkenyl, C_2-C_8-alkynyl or C_1-C_8-alkoxycarbonyl, or

R^3 is amino optionally substituted by C_3-C_8-cycloalkyl optionally substituted by amino, hydroxy, C_7-C_{14}-aralkyloxy, -SO_2-C_6-C_{10}-aryl or -NH-C(=O)-NH-R^{3c}, or

R^3 is amino substituted by R^{3a}, -R^{3a}-C_7-C_{14}-aralkyl or a C_5-C_{15}-carbocyclic group optionally substituted by OH, C_1-C_8-alkyl or C_1-C_8-alkoxycarbonyl, or

R^3 is aminocarbonyl optionally substituted by R^{3b}, or

R^3 is C_1-C_8-alkylamino optionally substituted by OH, R^{3b}, amino, di(C_1-C_8-alkyl)amino, -NH-C(=O)-C_1-C_8-alkyl, -NH-SO_2-C_1-C_8-alkyl, -NH-C(=O)-NH-R^{3c}, -NH-C(=O)-NH-C_1-

C_8-alkyl-R^{3b} , a C_5-C_{15}-carbocyclic group or by C_6-C_{10}-aryl optionally substituted by C_6-C_{10}-aryloxy, or

R^3 is C_1-C_8-alkylaminocarbonyl or C_3-C_8-cycloalkylamino-carbonyl optionally substituted by amino, C_1-C_8-alkylamino, di(C_1-C_8-alkyl)amino or -NH-C(=O)-NH-R^{3d}, or

R^3 is a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, that group being optionally substituted by 0-3R^4;

R^{3a} and R^{3b} are each independently a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur; optionally substituted by halo, cyano, oxo, OH, carboxy, nitro, C_1-C_8-alkyl, C_1-C_8-alkylcarbonyl, OH-C_1-C_8-alkyl, C_1-C_8-haloalkyl, amino-C_1-C_8-alkyl, amino(OH)C_1-C_8-alkyl or C_1-C_8-alkoxy optionally substituted by aminocarbonyl;

R^{3c} is a 5- or 6-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by a 5- or 6-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur;

R^{3d} are independently a 5- or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, said 5- or 6-membered heterocyclic ring being optionally substituted by halo, cyano, oxo, OH, carboxy, amino, nitro, C_1-C_8-alkyl, C_1-C_8-alkylsulfonyl, aminocarbonyl, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxy optionally substituted by aminocarbonyl, or a 5- or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, said ring also being optionally substituted by halo, cyano, oxo, OH, carboxy, amino, nitro, C_1-C_8-alkyl, C_1-C_8-alkylsulfonyl, aminocarbonyl, C_1-C_8-alkylcarbonyl, or C_1-C_8-alkoxy optionally substituted by aminocarbonyl;

R^4 is selected from OH, C_1-C_8-alkyl optionally substituted by OH, C_1-C_8-alkoxy, C_7-C_{14}-aralkyl optionally substituted with OH, O-C_1-C_8-alkyl, halogen C_6-C_{10}-aryl, or O-C_6-C_{10}-aryl, C_1-C_8-alkoxy, C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl or -halogen, O-C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl or -halogen, $NR^{4a}R^{4b}$, $NHC(O)R^{4c}$, $NHS(O)_2R^{4d}$, $NHS(O)_2R^{4e}$, $NR^{4f}C(O)NR^{4e}R^{4h}$, $NR^{4f}C(O)NR^{4g}R^{4h}$, $NR^{4i}C(O)OR^{4j}$, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, di(C_1-C_8-alkyl)aminocarbonyl, $COOR^{4k}$, $C(O)R^{4l}$, $NHC(O)R^{4q}$, $NHC(=NR^{4m})N(R^{4n})R^{4o}$, and a 3- to 12-membered heterocyclic group containing at

least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur optionally substituted by $COOR^{4p}$;

R^{4a}, R^{4c}, R^{4f}, R^{4h} and R^{4i} are, independently, H, or C_1-C_8-alkyl;

R^{4b} is H, C_1-C_8-alkyl a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted by 0-3R^5 or C_6-C_{10}-aryl;

R^{4d}, R^{4e}, and R^{4j} are, independently, C_1-C_8-alkyl or a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted by 0-3R^5;

R^{4g} is C_1-C_8-alkyl optionally substituted by a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted with SO_2R^{10}, CN, or 0-3R^5, or

R^{4g} is a C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl, SO_2R^{10} or -halogen, or

R^{4g} is a C_7-C_{14}-aralkyl optionally substituted by OH, O-C_1-C_8-alkyl, halogen, C_6-C_{10}-aryl, SO_2R^{10}, CN, -C(=NH)NH2, or O-C_6-C_{10}-aryl, or

R^{4g} is a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted by 0-3R^5;

R^{4k} is H, C_1-C_8-alkyl, C_6-C_{10}-aryl or a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur;

R^{4l} is C_1-C_8-alkyl, C_6-C_{10}-aryl, NHR^6 or a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur;

R^{4m} is CN;

R^{4n} is H or C_1-C_8-alkyl;

R^{4o} is H, C_1-C_8-alkyl optionally substituted by OH or by a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted with SO_2R^{10}, CN, or 0-3R^5, C_1-C_8-alkoxy, C_7-C_{14}-aralkyl optionally substituted with OH, O-C_1-C_8-alkyl, halogen C_6-C_{10}-aryl, or O-C_6-C_{10}-aryl, C_1-C_8-alkoxy, C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl SO_2R^{10} or -halogen;

R^{4p} is H, C_1-C_8-alkyl or C_7-C_{14}-aralkyl;

R^{4q} is C_6-C_{10}-aryl optionally substituted by OH, $C(=NH)NH_2$, or SO_2NH_2, or a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur optionally substituted by 0-3R^5 or a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted by 0-3R^5;

R^5 is selected from OH, C_1-C_8-alkyl optionally substituted by OH, CN, SO_2R^{10} or halogen, C_7-C_{14}-aralkyl optionally substituted with OH, O-C_1-C_8-alkyl, C_6-C_{10}-aryl, or O-C_6-C_{10}-aryl, C_1-C_8-alkoxy, C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl or -halogen, O-C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl optionally substituted by halogen, $NR^{5a}R^{5b}$, $NHC(O)R^{5c}$, $NHS(O)_2R^{5d}$, $NHS(O)_2R^{5e}$, $NR^{5f}C(O)NR^{5g}R^{5h}$, $NR^{5i}C(O)OR^{5j}$, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, di(C_1-C_8-alkyl)aminocarbonyl, $COOR^{5k}$, $C(O)R^{5l}$, a C(O)-C_6-C_{10}-aryl optionally substituted by OH, -COOH, C_1-C_8-alkyl, O-C_1-C_8-alkyl, -halogen, or SO_2R^{10}, $C(O)NHR^{5m}$ or a 3-12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted by 0-3R^7;

R^{5a}, R^{5b}, R^{5c}, R^{5f}, R^{5h} and R^{5i} are, independently, H, C_1-C_8-alkyl or C_6-C_{10}-aryl;

R^{5d}, R^{5e}, R^{5g}, R^{5j} and R^{5m} are, independently, C_1-C_8-alkyl or a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted by $COOR^8$;

R^{5k} is H, C_1-C_8-alkyl, C_6-C_{10}-aryl or a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur;

R^{5l} is C_1-C_8-alkyl, C_6-C_{10}-aryl or a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted by $COOR^9$;

R^6 is $COOR^{6a}$ or a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted by $COOR^{6b}$;

R^{6a}, R^{6b}, R^7, R^8 and R^9 are selected from H, C_1-C_8-alkyl and C_7-C_{14}-aralkyl; and

R^{10} is C_1-C_8-alkyl optionally substituted by halogen, C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl or -halogen, or $NR^{4a}R^{4b}$;

A is selected from -E-NR^{14}-, -E-NR^{14}-G-NR^{15}-, -E-$NR^{14}C(O)NR^{14}$-G-NR^{15}-, -E-$NR^{14}C(O)$G-NR^{15}-, -E-NR^{14}-G-NR^{14}-E^a-, -$NR^{14}C(O)$-E-$NR^{14}C(O)NR^{14}$-, -NR^{15}-G-NR^{15}-, -NR^{15}-$(CR^{16}R^{17})_n$-NR^{15}-, -NR^{15}-X3-G-X4-NR^{15}-, -$NR^{14}C(O)NR^{14}$-, $NR^{14}C(O)NR^{14}$-J-NR^{15}-, $NR^{14}C(O)$-$(CR^{16}R^{17})_n$-$C(O)NR^{14}$-, and $NR^{14}C(O)NR^{14}$-E-$NR^{14}C(O)NR14^4$-;

E is selected from C_3-C_{15}-carbocyclic group optionally substituted by HO, C_1-C_8-alkyl, C_6-C_{10}-aryl, 3- to 12-membered heterocyclic group, a C_6-C_{10}-aryl optionally substituted by HO, C_1-C_8-alkyl, O- C_1-C_8-alkyl, or halogen, and -E^a-$C(O)NR^{14}$-E^b-$NR^{14}C(O)$-E^a-;

each E^a is independently selected from a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, a C_3-C_{15}-carbocyclic group, and C_6-C_{10}-aryl optionally substituted by HO, C_1-C_8-alkyl, O-C_1-C_8-alkyl, and halogen;

E^b is selected from a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, a C_3-C_{15}-carbocyclic group, and C_6-C_{10}-aryl optionally substituted by HO, C_1-C_8-alkyl, O-C_1-C_8-alkyl, or halogen;

G is selected from selected from C(O), $NR^{14}C(O)$, $C(O)NR^{14}$, C_1-C_8-alkyl optionally substituted by OH, halogen or C_6-C_{10}-aryl, a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur optionally substituted by R^{18}, a C_3-C_{15}-carbocyclic group optionally substituted by HO, C_1-C_8-alkyl, and C_6-C_{10}-aryl optionally substituted by HO, C_1-C_8-alkyl, O-C_1-C_8-alkyl, or halogen;

J is selected from C_6-C_{10}-aryl, SO_2, and C_6-C_{10}-aryl-SO_2-;

X3 and X4 are independently selected from C_1-C_8-alkyl optionally substituted by OH, halogen or C_6-C_{10}-aryl, a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur optionally substituted by R^{18}, a C_3-C_{15}-carbocyclic group, and C_6-C_{10}-aryl;

each R^{14} is independently selected from H, C_1-C_8-alkyl, and C_6-C_{10}-aryl;

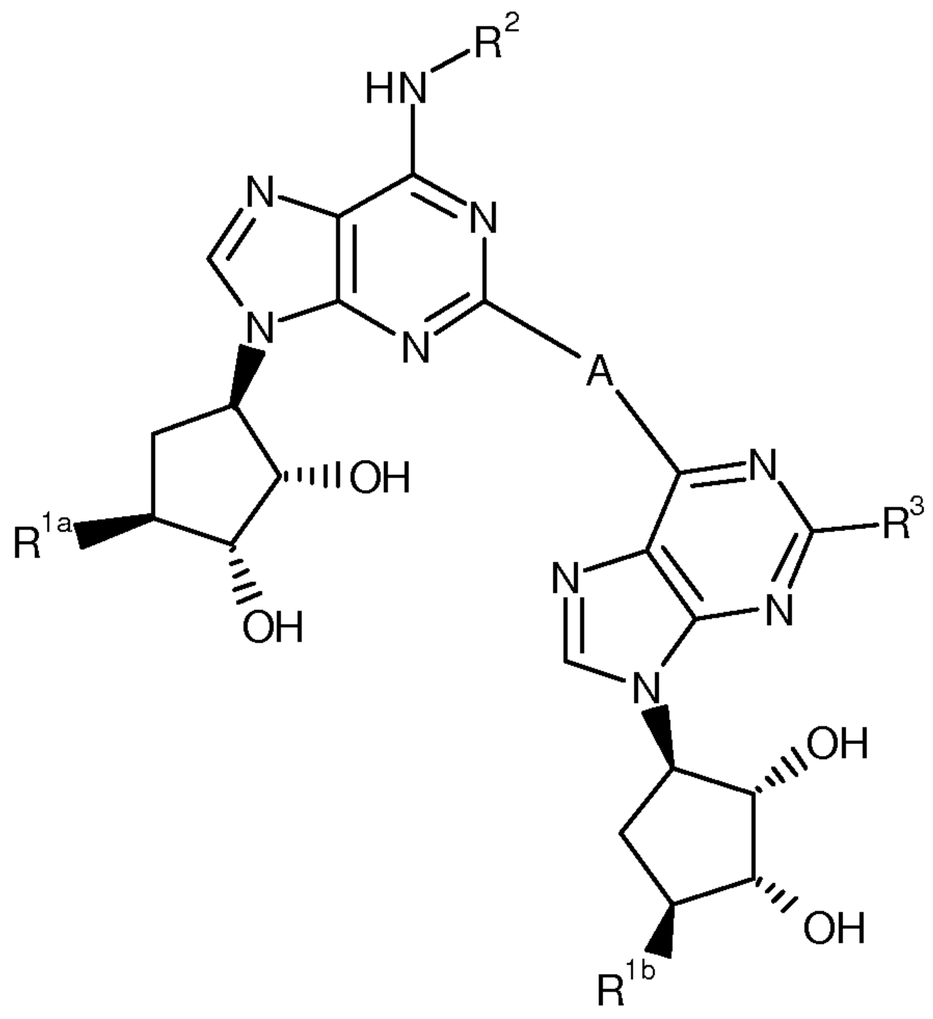
each R^{15} is independently selected from H, -CN, C_1-C_8-alkyl, and C_6-C_{10}-aryl;

each R^{16} and each R^{17} are independently selected from H, halogen, OH, C_1-C_8-alkyl, and C_6-C_{10}-aryl;

R^{18} is 3- or 12-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, said 3- or 12-membered heterocyclic ring being optionally substituted by halo, cyano, oxo, OH, carboxy, amino, nitro, C_1-C_8-alkyl, C_1-C_8-alkylsulfonyl, aminocarbonyl, C_1-C_8-alkylcarbonyl or O-C_1-C_8-alkyl optionally substituted by aminocarbonyl; and

n is an integer selected from 1-8.

2. A compound according to Claim 1 or stereoisomers or pharmaceutically acceptable salts thereof, wherein the compound is of formula (Ia)



(Ia)

,

wherein

R^1 and R^{1b} are independently selected from a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, that group being optionally substituted by oxo, O-C_1-C_8-alkyl, C_6-C_{10}-aryl, R^{1c} or by C_1-C_8-alkyl optionally substituted by OH, or

R^1 and R^{1b} are independently selected from -NR^4R^4, and -NR^5-C_1-C_8-alkylcarbonyl;

R^2 is C_1-C_8-alkyl optionally substituted by OH, halogen C_6-C_{10}-aryl optionally substituted by OH, SC_1-C_8-alkyl, CN, halogen, O-C_7-C_{14}-aralkyl, or O-C_1-C_8-alkyl, a C_3-C_{15}-carbocyclic group optionally substituted by O-C_7-C_{14} aralkyl, C_3-C_{15}-carbocyclic group, O-C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl or C_1-C_8-alkyl, O-C_1-C_8-alkyl, -SO_2-C_1-C_8-alkyl, a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, that group being optionally substituted by 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, C_7-C_{14}-aralkyl, or C_6-C_{14}-aryl optionally substituted by O-C_7-C_{14}-aralkyl, or

R^3 is hydrogen, halo, C_2-C_8-alkenyl, C_2-C_8-alkynyl or C_1-C_8-alkoxycarbonyl, or

R^3 is C_1-C_8-alkylamino optionally substituted by OH, R^{3b}, amino, di(C_1-C_8-alkyl)amino, -NH-C(=O)-C_1-C_8-alkyl, -NH-SO_2-C_1-C_8-alkyl, -NH-C(=O)-NH-R^{3c}, -NH-C(=O)-NH-C_1-C_8-alkyl-R^{3b} , a C_3-C_{15}-carbocyclic group or by C_6-C_{10}-aryl optionally substituted by C_6-C_{10}-aryloxy, or

R^3 is a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, that group being optionally substituted by 0-3R^4;

R^{3a} and R^{3b} are each independently a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur; optionally substituted by halo, cyano, oxo, OH, carboxy, nitro, C_1-C_8-alkyl, C_1-C_8-alkylcarbonyl, OH-C_1-C_8-alkyl, C_1-C_8-haloalkyl, amino-C_1-C_8-alkyl, amino(OH)C_1-C_8-alkyl and C_1-C_8-alkoxy optionally substituted by aminocarbonyl;

R^{3c} is a 5- or 6-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by a 5- or 6-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur;

R^{3d} are independently a 5- or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, said 5- or 6-membered heterocyclic ring being optionally substituted by halo, cyano, oxo, OH, carboxy, amino, nitro, C_1-C_8-alkyl, C_1-C_8-alkylsulfonyl, aminocarbonyl, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxy optionally substituted by aminocarbonyl, or a 5- or 6-membered heterocyclic ring containing at least one ring heteroatom selected from

the group consisting of nitrogen, oxygen and sulfur, said ring also being optionally substituted by halo, cyano, oxo, OH, carboxy, amino, nitro, C_1-C_8-alkyl, C_1-C_8-alkylsulfonyl, aminocarbonyl, C_1-C_8-alkylcarbonyl, or C_1-C_8-alkoxy optionally substituted by aminocarbonyl;

R^4 is selected from OH, C_1-C_8-alkyl optionally substituted by OH, C_1-C_8-alkoxy, C_7-C_{14}-aralkyl optionally substituted with OH, O-C_1-C_8-alkyl, halogen C_6-C_{10}-aryl, or O-C_6-C_{10}-aryl, C_1-C_8-alkoxy, C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl or -halogen, O-C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl or -halogen, and $NR^{4f}C(O)NR^{4g}R^{4h}$;

R^{4f}, R^{4h} are, independently, H, or C_1-C_8-alkyl;

R^{4g} is a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur;

A is selected from -E-NR^{14}-, -E-NR^{14}-G-NR^{15}-, -E-$NR^{14}C(O)NR^{14}$-G-NR^{15}-, -E-$NR^{14}C(O)$G-NR^{15}-, -E-NR^{14}-G-NR^{14}-E^a-, and -NR^{15}-G-NR^{15}-;

E is selected from C_3-C_{15}-carbocyclic group optionally substituted by HO, C_1-C_8-alkyl, C_6-C_{10}-aryl, 3- to 12-membered heterocyclic group, a C_6-C_{10}-aryl optionally substituted by HO, C_1-C_8-alkyl, O-C_1-C_8-alkyl, or halogen, and -E^a-$C(O)NR^{14}$-E^b-$NR^{14}C(O)$-E^a-;

each E^a is independently selected from a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, a C_3-C_{15}-carbocyclic group, and C_6-C_{10}-aryl optionally substituted by HO, C_1-C_8-alkyl, O-C_1-C_8-alkyl, and halogen;

E^b is selected from a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, a C_3-C_{15}-carbocyclic group, and C_6-C_{10}-aryl optionally substituted by HO, C_1-C_8-alkyl, O-C_1-C_8-alkyl, or halogen;

G is selected from selected from C(O), $NR^{14}C(O)$, $C(O)NR^{14}$, C_1-C_8-alkyl optionally substituted by OH, halogen or C_6-C_{10}-aryl, a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur optionally substituted by R^{18}, a C_3-C_{15}-carbocyclic group optionally substituted by HO, C_1-C_8-

alkyl, and C_6-C_{10}-aryl optionally substituted by HO, C_1-C_8-alkyl, O-C_1-C_8-alkyl, or halogen; and

R^{18} is 3- or 12-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, said 3- or 12-membered heterocyclic ring being optionally substituted by halo, cyano, oxo, OH, carboxy, amino, nitro, C_1-C_8-alkyl, C_1-C_8-alkylsulfonyl, aminocarbonyl, C_1-C_8-alkylcarbonyl or O-C_1-C_8-alkyl optionally substituted by aminocarbonyl.

3. A compound according to claim 2, or stereoisomers or pharmaceutically acceptable salts thereof,

wherein

R^1 and R^{1b} are independently selected from a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, that group being optionally substituted by oxo, O-C_1-C_8-alkyl, C_6-C_{10}-aryl, R^{1c} or by C_1-C_8-alkyl optionally substituted by OH, or

R^1 and R^{1b} are independently selected from -NR^4R^4, and -NR^5-C_1-C_8-alkylcarbonyl;

R^2 is C_1-C_8-alkyl optionally substituted by OH, halogen C_6-C_{10}-aryl optionally substituted by OH, SC_1-C_8-alkyl, CN, halogen, O-C_7-C_{14}-aralkyl, or O-C_1-C_8-alkyl, a C_3-C_{15}-carbocyclic group optionally substituted by O-C_7-C_{14} aralkyl, C_3-C_{15}-carbocyclic group, O-C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl or C_1-C_8-alkyl, O-C_1-C_8-alkyl, -SO_2-C_1-C_8-alkyl, a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, that group being optionally substituted by 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, C_7-C_{14}-aralkyl, or C_6-C_{14}-aryl optionally substituted by O-C_7-C_{14}-aralkyl, or

R^3 is hydrogen, halo, C_2-C_8-alkenyl, C_2-C_8-alkynyl or C_1-C_8-alkoxycarbonyl, or

R^3 is C_1-C_8-alkylamino optionally substituted by OH, R^{3b}, amino, di(C_1-C_8-alkyl)amino, -NH-C(=O)-C_1-C_8-alkyl, -NH-SO_2-C_1-C_8-alkyl, -NH-C(=O)-NH-R^{3c}, -NH-C(=O)-NH-C_1-C_8-alkyl-R^{3b} , a C_3-C_{15}-carbocyclic group or by C_6-C_{10}-aryl optionally substituted by C_6-C_{10}-aryloxy, or

R^3 is a 3- to 12-membered heterocyclic group containing from 1-4 ring nitrogen atoms and optionally containing from 1-4 other heteroatoms selected from the group consisting of oxygen and sulfur, that group being optionally substituted by 0-3R^4;

R^{3a} and R^{3b} are each independently a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur; optionally substituted by halo, cyano, oxo, OH, carboxy, nitro, C_1-C_8-alkyl, C_1-C_8-alkylcarbonyl, OH-C_1-C_8-alkyl, C_1-C_8-haloalkyl, amino-C_1-C_8-alkyl, amino(OH)C_1-C_8-alkyl and C_1-C_8-alkoxy optionally substituted by aminocarbonyl;

R^{3c} is a 5- or 6-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by a 5- or 6-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur;

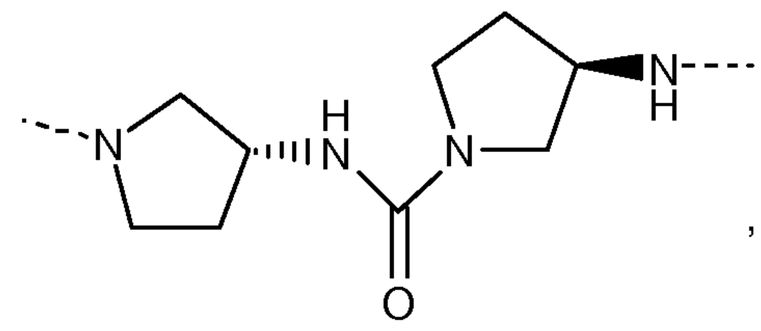
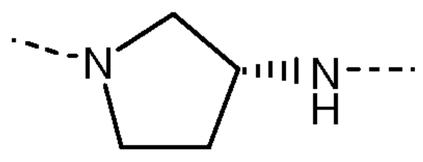
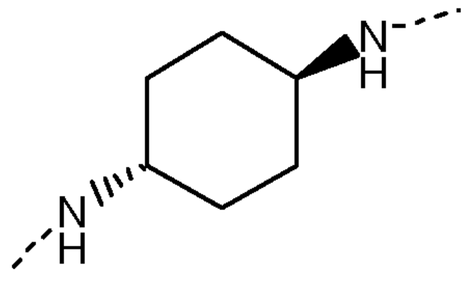
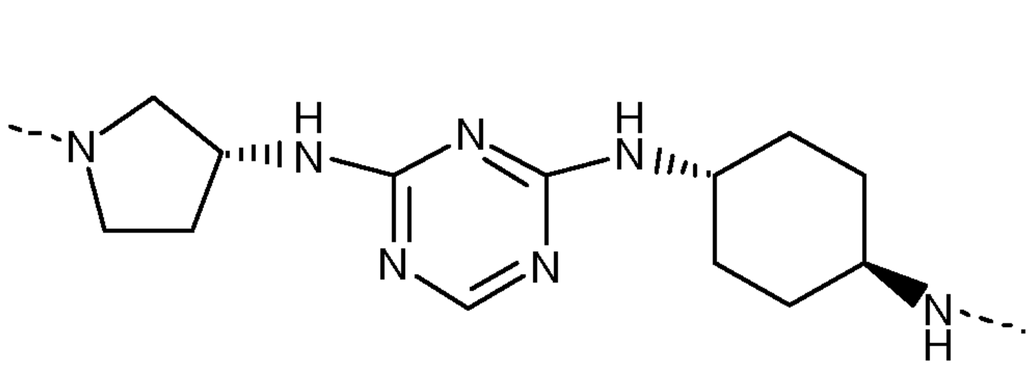
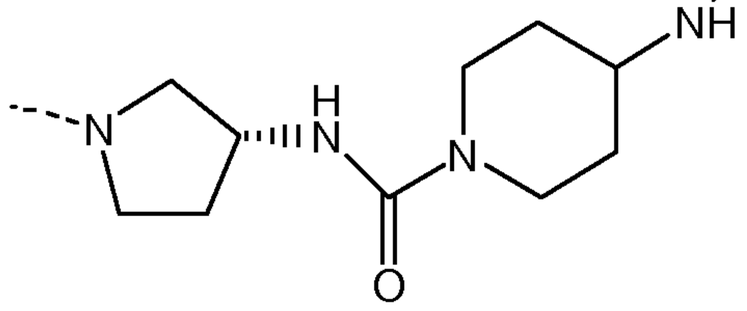
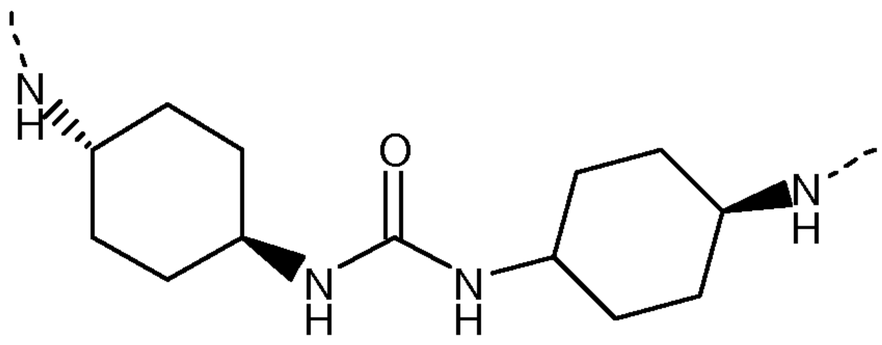
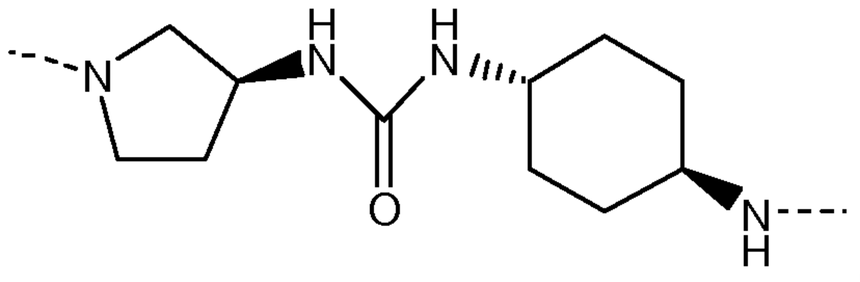
R^{3d} are independently a 5- or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, said 5- or 6-membered heterocyclic ring being optionally substituted by halo, cyano, oxo, OH, carboxy, amino, nitro, C_1-C_8-alkyl, C_1-C_8-alkylsulfonyl, aminocarbonyl, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxy optionally substituted by aminocarbonyl, or a 5- or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, said ring also being optionally substituted by halo, cyano, oxo, OH, carboxy, amino, nitro, C_1-C_8-alkyl, C_1-C_8-alkylsulfonyl, aminocarbonyl, C_1-C_8-alkylcarbonyl, or C_1-C_8-alkoxy optionally substituted by aminocarbonyl;

R^4 is selected from OH, C_1-C_8-alkyl optionally substituted by OH, C_1-C_8-alkoxy, C_7-C_{14}-aralkyl optionally substituted with OH, O-C_1-C_8-alkyl, halogen C_6-C_{10}-aryl, or O-C_6-C_{10}-aryl, C_1-C_8-alkoxy, C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl or -halogen, O-C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl or -halogen, and $NR^{4f}C(O)NR^{4g}R^{4h}$;

R^{4f}, R^{4h} are, independently, H, or C_1-C_8-alkyl;

R^{4g} is a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur; and

A is selected from


,

,

,

,

,

and

.

4. A compound according to Claim 1 or 3 substantially as herein described with reference to any one of the Examples.

5. A compound according to any one of the preceding claims for use as a pharmaceutical.

6. A compound according to any one of Claims 1-4 in combination with an anti-inflammatory, bronchodilatory, anti-histamine or anti-tussive drug substance, said compound and said drug substance being in the same or different pharmaceutical composition.

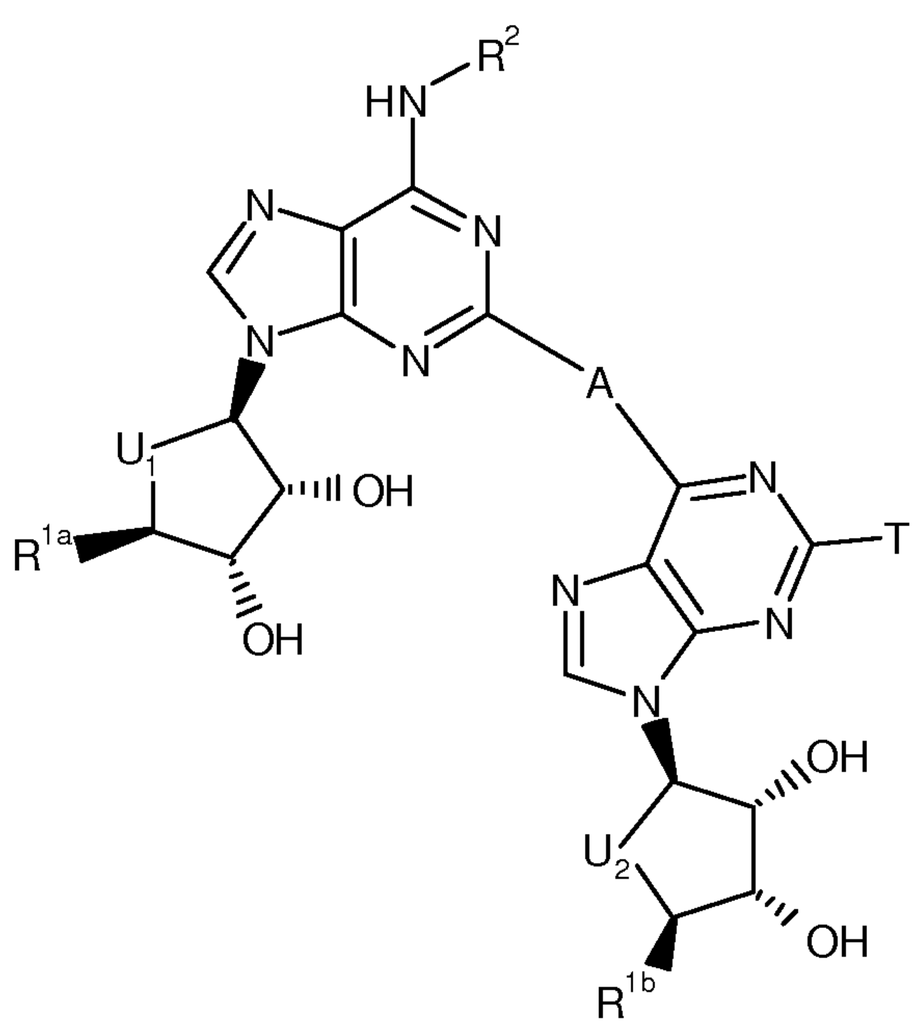
7. A pharmaceutical composition comprising as active ingredient a compound according to any one of Claims 1-4, optionally together with a pharmaceutically acceptable diluent or carrier.

8. Use of a compound according to any one of Claims 1-4 for the manufacture of a medicament for the treatment of a condition mediated by activation of the adenosine A2A receptor.

9. Use of a compound according to any one of Claims 1-4 for the manufacture of a medicament for the treatment of an inflammatory or obstructive airways disease.

10. A process for the preparation of compounds of formula (I) as defined in Claim 1, or stereoisomers or pharmaceutically acceptable salts thereof, which comprises the steps of:

(i) reacting a compound of formula (II)



(II)

,

where

R^{1a}, R^{1b}, R^2, U_1, U_2 are as defined hereinbefore; and

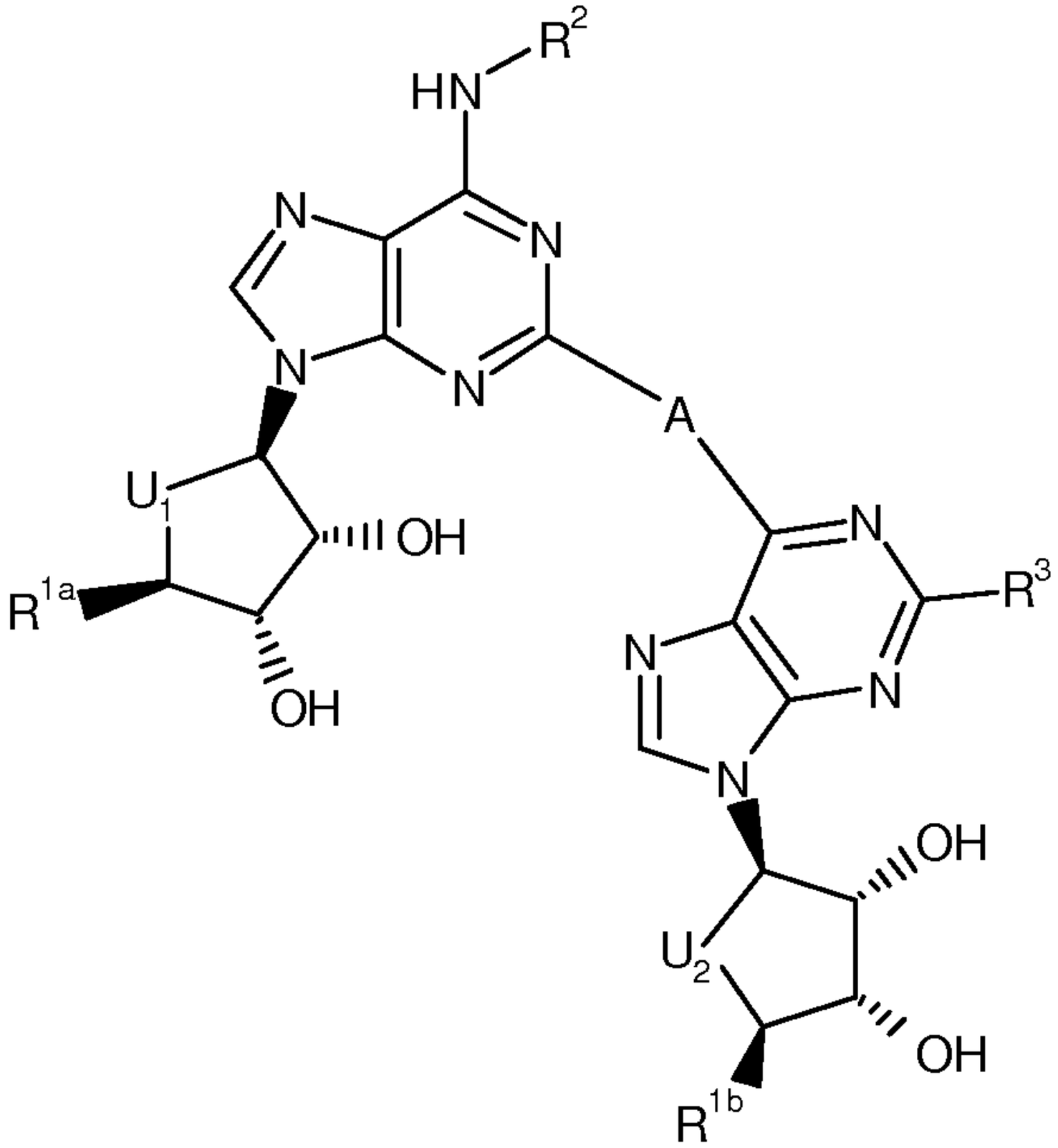
T is a leaving group with a compound of formula (III)

$$H—R^3 \qquad \textbf{(III)}$$

,

where R^3 is as defined in Claim 1; and

(ii) removing any protecting groups and recovering the resultant compound of formula (II) in free or pharmaceutically acceptable salt form.



(I)