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(54) BISADENOSINE COMPOUNDS AS ADENOSINE A2A RECEPTOR AGONISTS

BISADENOSINVERBINDUNGEN ALS ADENOSIN-A2A-REZEPTORAGONISTEN

COMPOSÉS BISADÉNOSINE COMME AGONISTES DU RÉCEPTEUR DE L'ADÉNOSINE A2A

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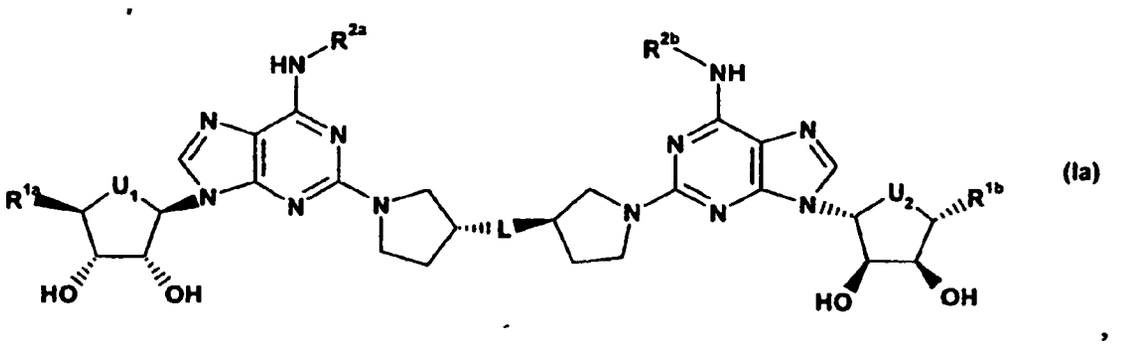
- **KIYOMI KIKUGAWA ET AL: "Platelet aggregation inhibitors. 6. 2-Thioadenosine derivatives" JOURNAL OF MEDICINAL CHEMISTRY, vol. 16, no. 12, 1973, pages 1381-1388, XP002468511**

EP 2 018 388 B9

Description

[0001] This invention relates to organic compounds, their preparation and use as pharmaceuticals.

[0002] An aspect of the invention provides compounds of formula (Ia):



(Ia)

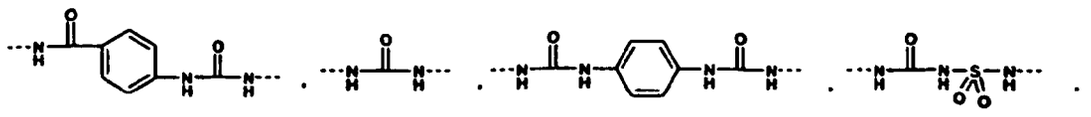
or stereoisomers or pharmaceutically acceptable salts thereof, wherein

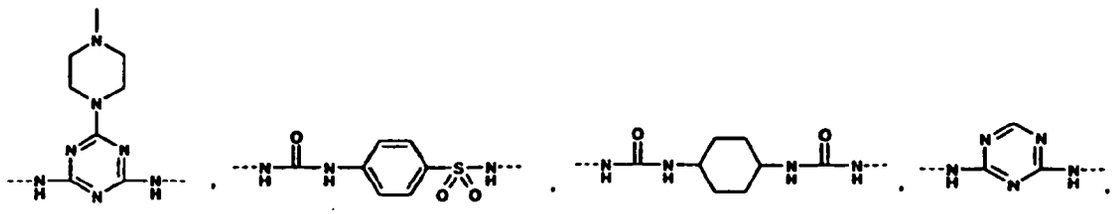
U_1 and U_2	are independently selected from CH_2 and O with the proviso that when U_1 is O then R^{1a} is not a N-bonded substituent, and when U_2 is O then R^{1b} is not a N-bonded substituent;
R^{1a} and R^{1b}	are independently selected from a 3- to 12-membered heterocyclic group containing from 1 to 4 ring nitrogen atoms and optionally containing from 1 to 4 other heteroatoms selected from the group consisting of oxygen and sulfur, that group being optionally substituted by C_1 -C_8-alkyl, or
R^{1a} and R^{1b}	are independently selected from -NH-C_1-C_8-alkylcarbonyl, and -NH-C_3-C_8- cycloalkylcarbonyl, or
R^{1a} and R^{1b}	are independently selected from NH-C_1-C_8-alkyl, NHC(O)C_1-C_8- hydroxyalkyl, $NHCO_2C_1$-C_8-alkyl, and $NHCO_2C_1$-C_8-hydroxyalkyl;
R^{1a} and R^{1b}	are independently selected from C_1-C_8-hydroxyalkyl, and CH_2-O-C_1-C_8-alkyl;
R^{2a} and R^{2b}	are independently selected from hydrogen, C_1-C_8-alkyl optionally substituted by OH, C_3-C_8-carbocyclic group, or C_6-C_{10}-aryl optionally substituted by OH, halogen, or O-C_1-C_8-alkyl, or
R^{2a} and R^{2b}	are independently is C_7-C_{14}-aralkyl optionally substituted by OH, halogen, or CN;
L	is selected from -NHC(O)-W-NHC(O)NH-, -NH-Y-NH-, NHC(O)NH-, NHC(O)NH-Z- NH-, NHC(O)-$(CH_2)_n$-C(O)NH-, and NHC(O)NH-W-NHC(O)NH-;
W	is selected from C_3-C_{15}-carbocyclic group, a C_6-C_{10}-aryl, and -W^a-C(O)NH-W^b- NHC(O)-W^a-;
each W^a	is independently selected from a 3- to 12-membered heterocyclic group containing from 1 to 4 ring nitrogen atoms and optionally containing from 1 to 4 other heteroatoms selected from the group consisting of oxygen and sulfur, a C_3-C_{15}- carbocyclic group optionally substituted by HO, and C_6-C_{10}-aryl optionally substituted by OH;
W^b	is selected from a 3- to 12-membered heterocyclic group containing from I to 4 ring nitrogen atoms and optionally containing from I to 4 other heteroatoms selected from the group consisting of oxygen and sulfur, a C_3-C_{15}-carbocyclic group optionally substituted by OH, and C_6-C_{10}-aryl optionally substituted by OH;
Y	is selected from a 3- to 12-membered heterocyclic group containing from 1 to 4 ring nitrogen atoms and optionally containing from I to 4 other heteroatoms selected from the group consisting of oxygen and sulfur optionally substituted by R^9, a C_3-C_{15}-carbocyclic group optionally substituted by OH, and C_6-C_{10}-aryl optionally substituted by OH;
Z	is selected from C_6-C_{10}-aryl, SO_2, and C_6-C_{10}-aryl-SO_2-;
R^9	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, OH, carboxy, amino, nitro, C_1-C_8-alkyl; and
n	is an integer selected from 1-4.

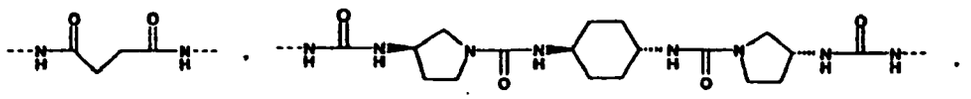
[0003] Another aspect of the invention provides compounds of formula (Ia) or stereoisomers or pharmaceutically acceptable salts thereof,
wherein

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

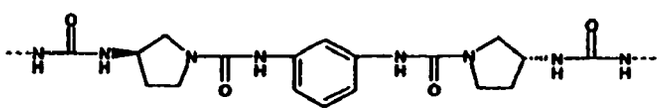
L is selected from:







and



Definitions

[0004] Terms used in the specification have the following meanings:

[0005] "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.

[0006] "Halo" or "halogen", as used herein, may be fluorine, chlorine, bromine or iodine. Preferably halo is chlorine.

[0007] "Hydroxy", as used herein, is OH.

[0008] "C_1-C_8-Alkyl", as used herein, denotes straight chain or branched alkyl having 1 to 8 carbon atoms. Preferably C_1-C_8-alkyl is C_1-C_4-alkyl.

[0009] "C_1-C_8-Alkoxy", or as used herein, denotes straight chain or branched alkoxy having I to 8 carbon atoms (e.g. O-C_1-C_8-alkyl). Preferably, C_1-C_8-alkoxy is C_1-C_4-alkoxy.

[0010] "C_3-C_8-Cycloalkyl", as used herein, denotes cycloalkyl having 3 to 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.

[0011] "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.

[0012] "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.

[0013] "C_6-C_{10}-Aaryl", as used herein, denotes a monovalent carbocyclic aromatic group that contains 6 to 10 carbon atoms and which may be, e.g., a monocyclic group, such as phenyl; or a bicyclic group, such as naphthyl.

[0014] "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.

[0015] "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-cy-

cloalkylaminocarbonyl, respectively.

[0016] "C_3-C_{15}-Carbocyclic group", as used herein, denotes a carbocyclic group having 3 to 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_{15}-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.

[0017] "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.

[0018] "5- or 6-Membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur", as used herein, may be, for example, a saturated or unsaturated heterocyclic group such as furanyl, pyrrolyl, pyrrolidinyl, pyrazolyl, imidazolyl, triazolyl, isotriazolyl, tetrazolyl, thiadiazolyl, isothiazolyl, oxadiazolyl, pyridinyl, piperidinyl, pyrazinyl, oxazolyl, isoxazolyl, pyrazinyl, pyridazinyl, pyrimidinyl, piperazinyl, pyrrolidinyl, morpholinyl, triazinyl, oxazinyl or thiazolyl. Preferred 5- or 6-membered heterocyclic groups include pyrazolyl, imidazolyl, pyrrolidinyl, pyridinyl and piperidinyl. The 5- or 6-membered heterocyclic group can be unsubstituted or substituted. Preferred substituents include halo, cyano, oxo, OH, carboxy, amino, nitro, C_1-C_8-alkyl (optionally substituted by hydroxy), C_1-C_8-alkylsulfonyl, aminocarbonyl, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, and C_1-C_8-alkoxy optionally substituted by aminocarbonyl. Especially preferred substituents include chloro, cyano, carboxy, amino, C_1-C_8-alkoxycarbonyl, C_1-C_4-alkoxy and C_1-C_4-alkyl optionally substituted by OH.

[0019] 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.

[0020] Especially preferred specific compounds of formula (Ia) are those described hereinafter in the Examples.

[0021] 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).

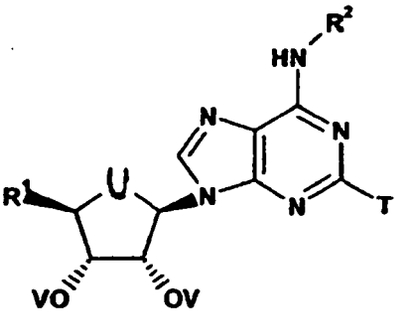
[0022] Tautomers are one of two or more structural isomers that exist in equilibrium and are readily converted from one isomeric form to another.

[0023] 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.

Synthesis

[0024] Another embodiment of the present invention provides a process for the preparation of compounds of formula (Ia) in free or pharmaceutically acceptable salt form, which comprises the steps of:

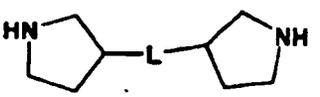
(i) reacting a compound of formula (III):



(III)

wherein

R^1 is equivalent to R^{1a} and R^{1b};
R^2 is equivalent to R^{2a} and R^{2b}; and
U is equivalent to U_1 and U_2, and are as defined in Claim 1;
V is H or a protecting group; and
T is a leaving group, with a compound of formula (V):

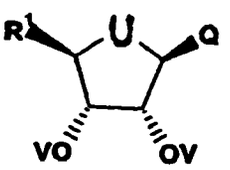


(V)

wherein L is as defined in Claim 1;

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

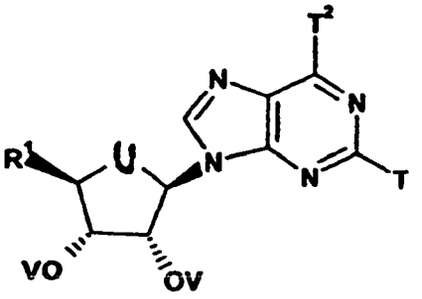
[0025] The compound of formula (III) may be prepared by reacting a compound of formula (VI):



(VI)

wherein

R^1 is equivalent to R^{1a} and R^{1b};
U is equivalent to U_1 and U_2; and
V are as herein before defined; 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)

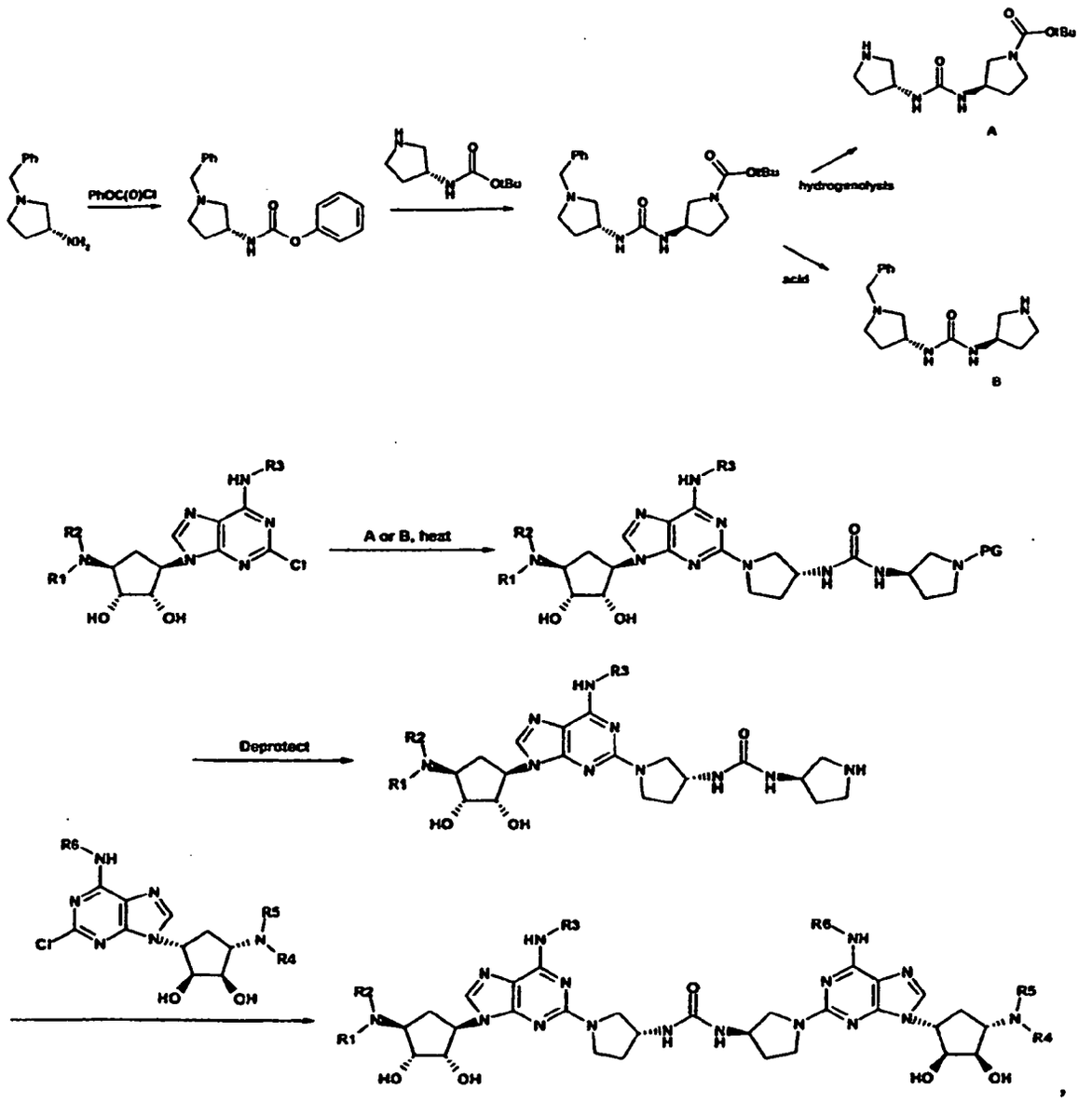
wherein

R^1 is equivalent to R^{1a} and R^{1b};
U is equivalent to U_1 and U_2; and
V are as herein before defined; and
T and T^2 are halogen.

[0026] Compound of formula (VII) can be reacted with R^2NH_2 under conventional conditions to provide compound of formula (III).

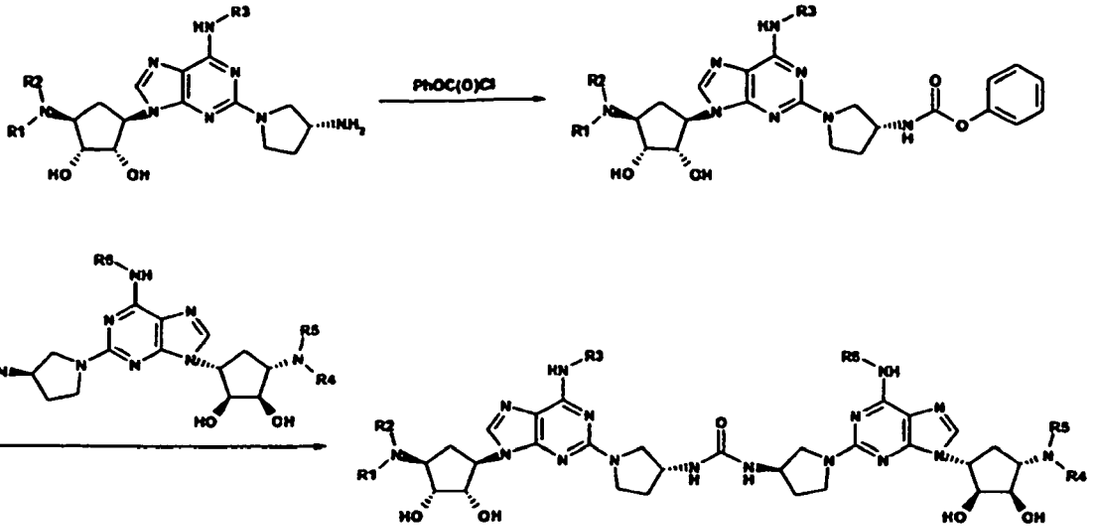
[0027] Alternatively, below are routes to enable the efficient preparation of unsymmetrical adenosine A_{2A} receptor ligands:

[0028] Either through sequential reaction of a differentially protected diamine linker.

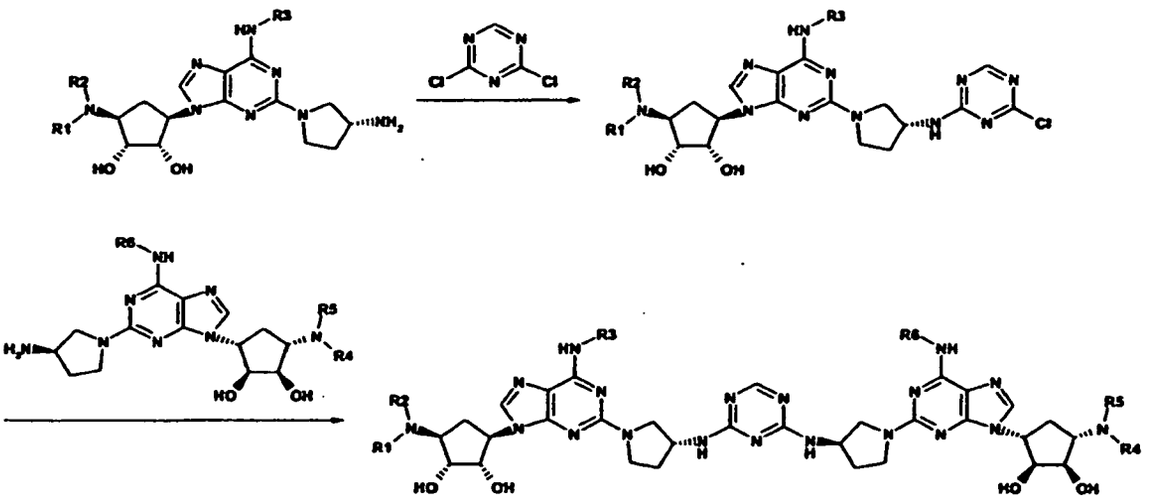


where, PG = the protecting group benzyl or *tert*-butyloxycarbonyl.

[0029] Or alternatively, the central urea linkage can be formed asymmetrically.



[0030] Or the central linkage can be a heterocyclic.



[0031] The compounds of formula (Ia) can be prepared, for example, using the reactions and techniques described below and in the Examples. The compounds of formula (Ia) 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.

[0032] 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 (Ia) into another compound of formula (Ia). 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 T.W. Greene and P.G.M. 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.

[0033] Compounds of formula (Ia), 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 crystallisation. 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 crystallisation or asymmetric synthesis from correspondingly asymmetrically substituted, e.g. optically active, starting materials.

[0034] Compounds of formula (Ia) 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 L.J. Murphree et al in Molecular Pharmacology 61, 455-462 (2002).

[0035] Compounds of the Examples hereinbelow have K_i values below 1.0 μM in the above assay. For example, the compounds of Examples 1, 7, 15 and 19 have K_i values of 0.01, 0.01, 0.07and 0.06 μM, respectively.

[0036] Having regard to their activation of the adenosine A_{2A} receptor, compounds of formula (Ia), 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.

[0037] 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 bronchiectasis, 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.

[0038] 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".)

[0039] 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 to 6 am, i.e. at a time normally substantially distant from any previously administered symptomatic asthma therapy.

[0040] 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

hyper-eosinophilia 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.

[0041] 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.

[0042] 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. haemolytic 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 minal change nephropathy).

[0043] 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.

[0044] 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.

[0045] Agents of the invention are also useful in combination with a protease inhibitor for prevention of organ ischaemia 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.

[0046] Agents of the invention are also useful in promoting wound healing in bronchial epithelial cells as described in AJP-Lung 290: 849-855.

[0047] 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 characterised by elevated intraocular pressure or secretion of ocular aqueous humor, such as glaucoma, ischemic tissue/organ damage from reperfusion, bedsores and as agents for promoting sleep, as agents for treating demyelinating diseases, eg multiple sclerosis and as neuroprotective agents eg, cerebral haemorrhagic injury and spinal cord ischaemi-reperfusion injury.

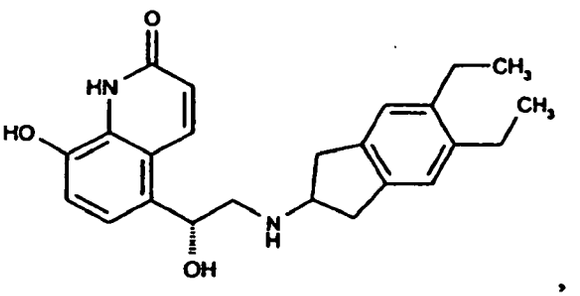
[0048] The effectiveness of an agent of the invention in inhibiting inflammatory conditions, for example in inflammatory airways diseases, may be demonstrated in an animal model, e.g. a mouse or rat model, of airways inflammation or other inflammatory conditions, for example as described by Szarka et al, J. Immunol. Methods 202:49-57 (1997); Renzi et al, Am. Rev. Respir. Dis. 148:932-939 (1993); Tsuyuki et al., J. Clin. Invest. 96:2924-2931 (1995); Cemadas et al. Am. J. Respir. Cell Mol. Biol. 20:1-8 (1999); and Fozard et al., Eur. J. Pharmacol. 438:183-188 (2002).

[0049] 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.

[0050] Accordingly, the invention includes a combination of an agent of the invention as hereinbefore described with an anti-inflammatory, bronchodilatory, antihistamine or antitussive drug substance, said agent of the invention and said drug substance being in the same or different pharmaceutical composition.

[0051] 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 B1IL 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 cilomilast (Ariflo® Glaxo-SmithKline), 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 and WO 05/07908.

[0052] 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.

[0053] 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.

[0054] 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.

[0055] 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)-5H-benzo-cyclohepten-8-yl]carbonyl]amino]phenyl]-methyl]tetrahydro-N,N-dimethyl-2H-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.

[0056] 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 (Ia), in free form, or in the form of a pharmaceutically acceptable salt. In another aspect the invention provides a compound of formula (Ia), 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.

[0057] 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 dennatitis; or rectally, for example in the treatment of inflammatory bowel disease.

[0058] In a further aspect, the invention also provides a pharmaceutical composition comprising a compounds of formula (Ia), 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.

[0059] 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 (Ia) 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 (Ia) either dissolved, or suspended, in a vehicle containing water, a co-solvent, such as ethanol or propylene glycol and a stabiliser, which may be a surfactant.

[0060] The invention includes:

(a) a compound of formula (Ia) 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 compound of formula (Ia) in inhalable form;
(c) a pharmaceutical product comprising a compound of formula (Ia) in inhalable form in association with an inhalation device; and
(d) an inhalation device containing a compound of formula (Ia) in inhalable form.

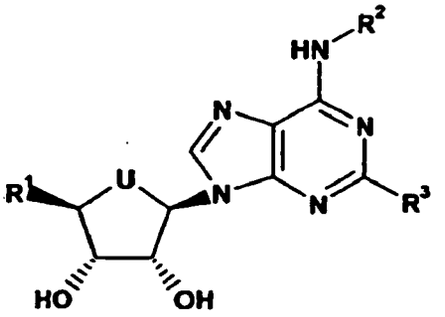
[0061] Dosages of compounds of formula (Ia) employed in practising the present invention will of course vary depending, for example, on the particular condition to be treated, the effect desired and the mode of administration. In general, suitable daily dosages for administration by inhalation are of the order of 0.005-10 mg, while for oral administration suitable daily doses are of the order of 0.05-100 mg.

[0062] The invention is illustrated by the following Examples.

Examples 1-23

Compounds of formula **(I)**:

[0063]



(I)

U is CH_2 except in Examples 10, 13 and 20 where U is O

are shown in the following table. Methods for preparing such compounds are described hereinafter. The table also shows mass spectrometry, MH^+ (ESMS), data. The Examples are trifluoroacetate salts, except for Example 1, which is in parent form and Examples 20-23 which are hydrochloride salts.

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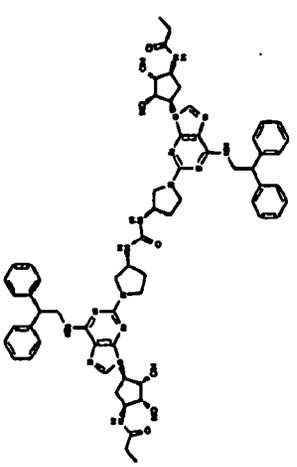
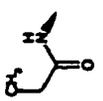
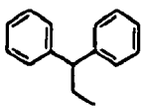
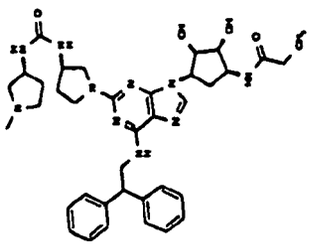
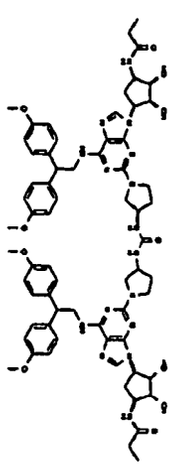
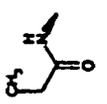
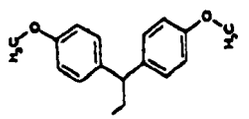
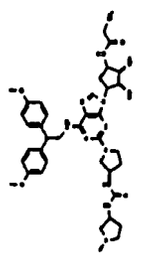
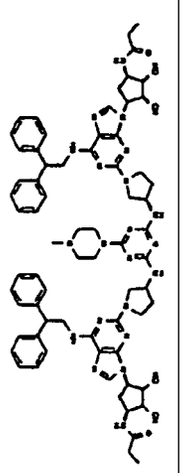
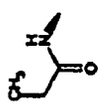
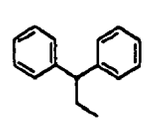
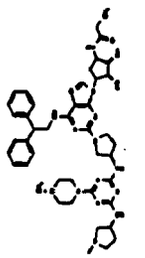
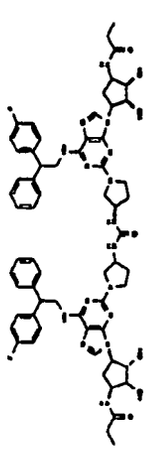
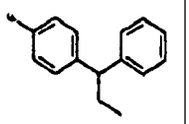
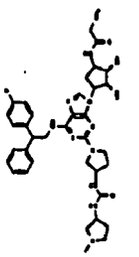
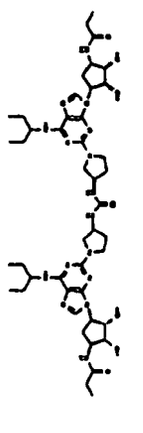
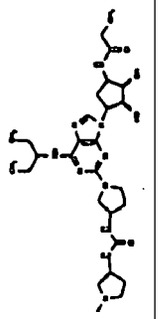
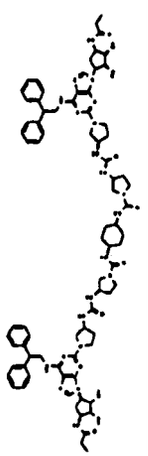
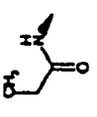
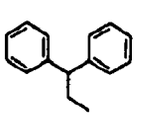
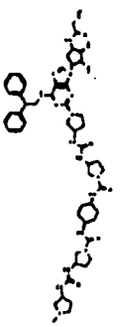
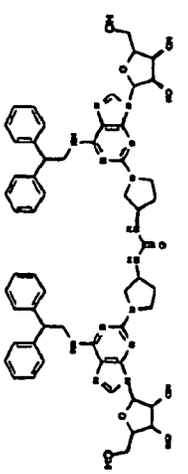
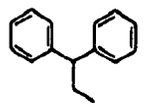
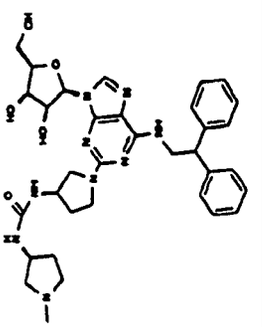
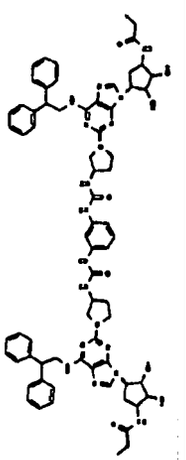
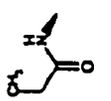
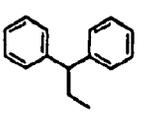
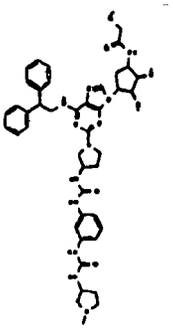
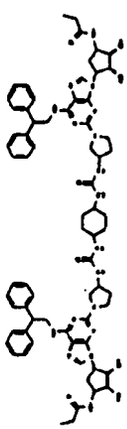
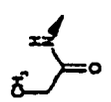
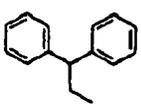
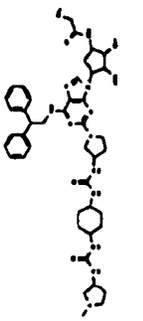
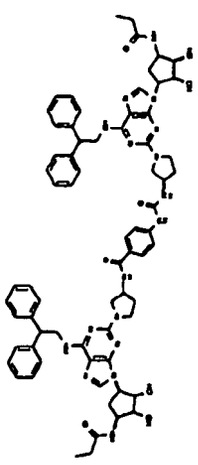
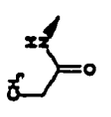
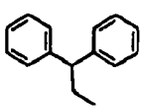
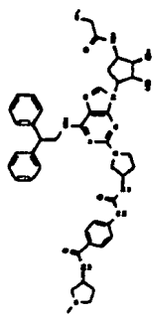
1					585
2					644
3					659
4					603
5					475

(continued)

Ex	Structure	R^1	R^2	R^3	MH^+ (ankers eitherwise described)
6					583
7					539
8					544
9					596
10					1173
11					764

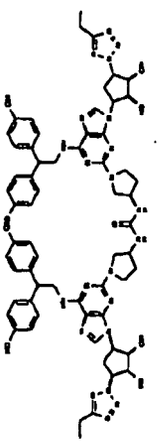
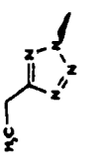
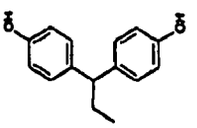
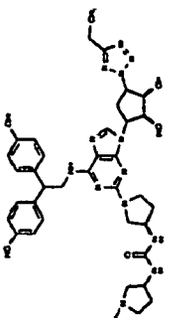
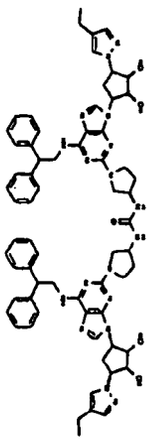
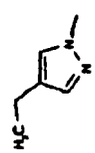
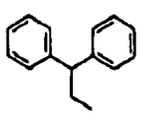
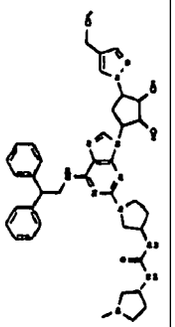
(continued)

Ex	Structure	R^1	R^2	R^3	MH^+ (ankers eitherwise described)
12					767
13					545
14					651
15					655
16					644

(continued)

Ex	Structure	R^1	R^2	R^3	MH^+ (ankers eitherwise described)
17					613
18					662
19					624
20					862 (M+2H)
21					406.32 ($MH^+/3$)

(continued)

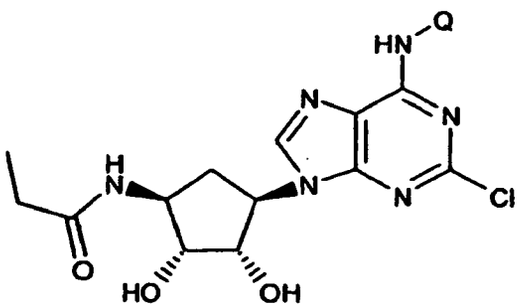
Ex	Structure	R^1	R^2	R^3	MH^+ (ankers eitherwise described)
22					641.81 ($MH^+/2$)
23					607.76 ($MH^+/2$)

Preparation of Intermediates

[0064] Abbreviations used are as follows:

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

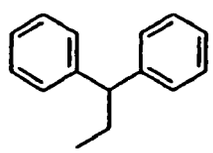
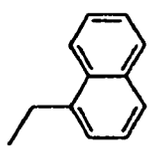
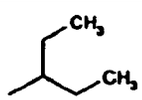
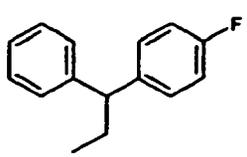
[0065] The following intermediates of formula (A):



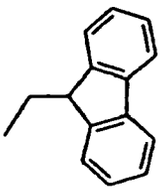
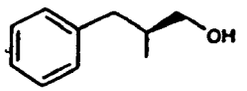
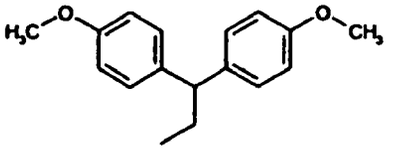
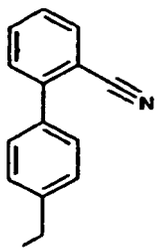
(A)

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

Table 1

Intermediate	Q	M/s MH+
AA		521
AB		481
AC		411
AD		539

(continued)

Intermediate	Q	M/s MH+
AE		519
AF		475
AG		581
AH		532

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

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

[0066] 2,6-Dichloropurine (10 g, 52.90 mmol), (1S,4R)-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 (1S,4R)-4-(2,6-dichloro-purin-9-yl)-cyclopent-2-enyl ester ethyl ester

[0067] (1S,4R)-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 RT. 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 methanol.
^{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, I H), 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-[(1S,4R)-4-(2,6-dichloro-purin-9-yl)-cyclopent-2-enyl]-amine

[0068] Carbonic acid (1S,4R)-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 RT. 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: (1S,2R,3S,5R)-3-(Di-Boc-amino)-5-(2,6-dichloro-purin-9-yl)-cyclopentane-1,2-diol

[0069] A mixture comprising di-Boc-[(1S,4R)-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 RT 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, I H), 2.55 (m, 1H), 1.55 (s, 18H), MS (ES+) *m*/*e* 504 (MH^+).

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

[0070] A solution of (1S,2R,3S,5R)-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 RT. 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-[(1S,2R,3S,4R)-4-(2,6-Dichloro-purin-9-yl)-2,3-dihydroxy-cydopentyl]-propionamide

[0071] A solution of (1S,2R,3S,SR)-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 RT 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-{(1S,2R,3S,4R)-4-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide

[0072] N-[(1S,2R,3S,4R)-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^+).
[0073] Intermediate AA may also be prepared using the following process:

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

[0074] (1S,2R,3S,SR)-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 DCM (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: (1R,2S,3R,5S)-3-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(di-Boc-amino)-cyclopentane-1,2-diol

[0075] The title compound is prepared analogously to (1S,2R,3S,5R)-3-(di-Boc-amino)-5-(2,6-dichloro-purin-9-yl)-cyclopentane-1,2-diol by replacing di-Boc-[(1S,4R)-4-(2,6-dichloro-purin-9-yl)-cyclopent-2-enyl]-amine with {2-chloro-9-[(1R,4S)-4-(di-Boc-amino)-cyclopent-2-enyl]-9H-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).

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

[0076] (1R,2S,3R,5S)-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 RT. 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-{(1S,2R,3S,4R)-4-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide

[0077] (1S,2F,3S,5R)-3-Amino-5-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-cyclopentane-1,2-diol trifluoroacetate (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 RT. 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 re-crystallised 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-((1S,2R,3S,4R)-4-{2-Chloro-6-(naphth-1-ylmethyl)-aminol-purin-9-yl}-2,3-dihydroxy-cyclopentyl)-propionamide trifluoroacetate

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

[0078] The title compound is prepared analogously to di-Boc-[(1S,4R)-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: [(1S,2R,3S,4R)-4-(2,6-Dichloro-purin-9-yl)-2,3-dihydroxy-cyclopentyl]-propionyl-carbamic acid tert-butyl ester:

[0079] A mixture comprising [(1S,4R)-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-butano/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 RT 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 MeOH to afford the title compound. MS (ES+) *m/e* 460 (MH^+).

*StepAB3:*N-((1S,2R,3S,4R)-4-{2-Chloro-6-[(naphth-1-ylmethyl)-amino]-purin-9-yl}-2,3-dihydroxy-cyclopentyl)-propionamide trifluoroacetate:

[0080] A solution comprising [(1S,2R,3S,4R)-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), 1-napthalenemethylamine (0.175 ml, 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 RT for 2 hours, the solvent is removed *in vacuo* to yield the title compound.

Intermediate AC N-{(1S,2R,3S,4R)-4-[2-Chloro-6-(1-ethyl-propylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide

Step *AC1:* {(1S,4R)-4-[2-Chloro-6-(1-ethyl-propylamino)-purin-9-yl]-cyclopent-2-enyl}-propionyl-carbamic acid tert-butyl ester

[0081] [(1S,4R)-4-(2,6-Dichloro-purin-9-yl)-cyclopent-2-enyl]-propionyl-carbamic acid tert-butyl ester (700 mg, 1.64 mmol) is dissolved in THF (15 mL) under an atmosphere of argon. 3-Pentylamine (315 mg, 3.61mmol) is added and the reaction mixture is stirred at 50˚C. The reaction is shown to be complete by LCMS after 18 hours. The reaction mixture is partitioned between DCM (50 mL) and 0.1 M HCl (50 mL). The organic layer is washed with water (20 mL) and brine (20 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); 8.10 (s, 1H), 6.00 (m, 1H), 5.70 (m, 1H), 5.60 (m, 2H), 5.45 (m, 1H), 4.20 (m, 1H), 3.65 (m, 1H), 3.00 (m, 1H), 2.65 (m, 3H), 1.95 (m, 1H), 1.60 (m, 3H), 1.45 (s, 9H), 1.10 (m, 4H), 0.85 (t, 6H), MS (ES+) *m/e* 477 (MH^+).

Step *AC2*: {(1S,2R,3S,4R)-4-[2-Chloro-6-(1-ethyl-propylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionyl-carbamic acid tert-butyl ester

[0082] The title compound is prepared analogously to (1S,2R,3S,5R)-3-(di-Boc-amino)-5-(2,6-dichloro-purin-9-yl)-cyclopentane-1,2-diol by replacing di-Boc-[(1S,4R)-4-(2,6-dichloro-purin-9-yl)-cyclopent-2-enyl]-amine with {(1S,4R)-4-[2-chloro-6-(1-ethyl-propylamino)-purin-9-yl]-cyclopent-2-enyl}-propionyl-carbamic acid tert-butyl ester. Purification is carried out by reverse phase column chromatography (Isolute™ C18, 0-100% acetonitrile in water - 0.1% TFA).
^{1}H NMR (MeOD, 400 MHz); 8.10 (s, 1H), 4.80 (m, 1H), 4.65 (m, 1H), 4.35 (m, 1H), 4.20 (m, 1H), 2.85 (m, 2H), 2.60 (m, 1H), 2.35 (m, 1H), 1.70 (m, 2H), 1.65 (s, 9H), 1.60 (m, 2H), 1.15 (t, 3H), 0.95 (t, 6H).

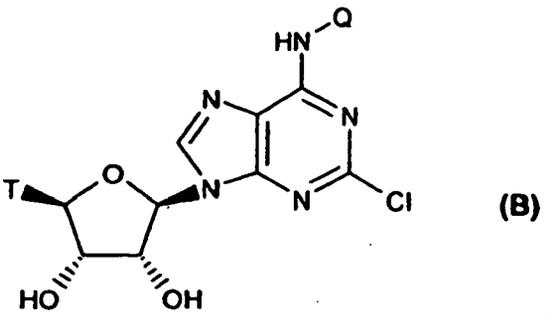
Step *AC3*: N-{(1S,2R,3S,4R)-4-[2-Chloro-6-(1-ethyl-propylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide:

[0083] {(1S,2R,3S,4R)-4-[2-Chloro-6-(1-ethyl-propylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionyl-carbamic acid tert-butyl ester (300 mg, 0.59 mmol) is dissolved in DCM (5 mL). TFA (2 mL) is added and the reaction mixture is stirred at RT. 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 (50 mL) and saturated $NaHCO_3$ (50 mL). The organic layer is washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and the solvent is removed *in vacuo* to give the title compound.
^{1}H NMR (MeOD, 400 MHz); 8.05 (s, 1H), 4.75 (m, 1H), 4.60 (m, 1H), 4.20 (m, 2H), 4.00 (m, 1H), 2.90 (m, 1H), 2.40 (q, 2H), 2.10 (m, 1H), 1.70 (m, 2H), 1.60 (m, 2H), 1.20 (t, 3H), 0.95 (t, 6H), MS (ES+) *m/e* 411 (MH^+).

Intermediate AD-AH

[0084] These compounds namely,
N-((1S,2R,3S,4R)-4-{2-chloro-6-[2-(4-fluoro-phenyl)-2-phenyl-ethylamino]-purin-9-yl}-2,3-dihydroxy-cyclopentyl)-propionamide trifluoroacetate (Intermediate AD),
N-((1S,2R,3S,4R)-4-{2-chloro-6-[(9H-fluoren-9-ylmethyl)-amino]-purin-9-yl -2,3-dihydroxy-cyclopentyl)-propionamide trifluoroacetate (Intermediate AE),
N-{(1S,2R,3S,4R)-4-[2-chloro-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide trifluoroacetate (Intermediate AF),
N-((1S,2R,3S,4R)-4-{6-[2,2-bis-(4-methoxy-phenyl)-ethylamino]-2-chloro-purin-9-yl}-2,3-dihydroxy-cyclopentyl)-propionamide trifluoroacetate (Intermediate AG),
N-((1S,2R,3S,4R)-4- {2-Chloro-6-[(2'-cyano-biphenyl-4-ylmethyl)-amino]-purin-9-yl} -2,3-dihydroxy-cyclopentyl)-propionamide trifluoroacetate (Intermediate AH),
are prepared analogously to Intermediate AB by replacing 1-napthalenemethylamine with the appropriate amine.

[0085] The following intermediates of formula (B):

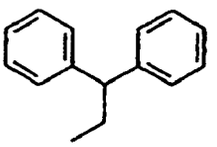
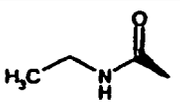
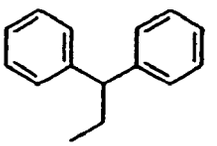
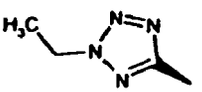


(B)

,

are shown in Table 2 below, their method of preparation being described hereinafter.

Table 2

Intermediate	T	Q	M/s MH+
BA			482
BB			524
BC			368

Intermediate BA (2R,3R,4S,5R)-2-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-ydroxymethyl-tetrahydro-furan-3,4-diol

[0086] The title compound is prepared by the procedure of Di Ayres, Barry Edward; Gregson, Michael; Ewan, George Blanch; Keeling, Suzanne Elaine; Bell, Richard. 'Preparation of aminopurine-β-D-ribofuranuronamide derivatives as antiinflammatories.'(WO 96/02553)

Intermediate BB (2S,3S,4R,5R)-5-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-3,4-dihydroxy-tetrahydro-furan-2-carboxylic acid ethylamide trifluoroacetate

[0087] The title compound is prepared by the procedure of Gregson, Michael; Ayres, Barry Edward; Ewan, George Blanch; Ellis, Frank; Knight, John. 'Preparation of diaminopurinylribofuranuronamide derivatives as antiinflammatories. ' (WO 94/17090)

Intermediate BC (2R,3R,4S,5R)-2-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(2-ethyl-2H-tetrazol-5-yl)-tetrahydro-furan-3,4-diol

[0088] The title compound is prepared by the procedure of 'Preparation of 2-(purin-9-yl)-tetrahydrofuran-3,4-diol nucleosides as anti-inflammatory agents and agonists against adenosine receptors.' Cox, Brian; Keeling, Suzanne Elaine; Allen, David George; Redgrave, Alison Judith; Barker, Michael David; Hobbs, Heather; Roper, Thomas Davis, IV; Geden, Joanna Victoria. (Glaxo Group Ltd., UK). PCT Int. Appl. (1998), 118 pp. WO 98/28319 A1

Intermediate C 1,3-Di-(R)-pyrrolidin-3-yl-urea

Step C1: 1,3-Bis-((R)-1-benzyl-pyrrolidin-3-yl)-urea

[0089] A solution comprising (R)-1-benzyl-pyrrolidin-3-ylamine (5.0 g, 28.4 mmol) in DCM (10 mL) is treated with CDI (2.3 g, 14.2 mmol) and the reaction mixture is stirred at RT for 48 hours. The solvent is removed *in vacuo* and the resulting residue is dissolved in EtOAc. This portion is washed with water followed by brine, dried ($MgSO_4$) and concentrated *in vacuo* to yield the title compound as pale orange solid.

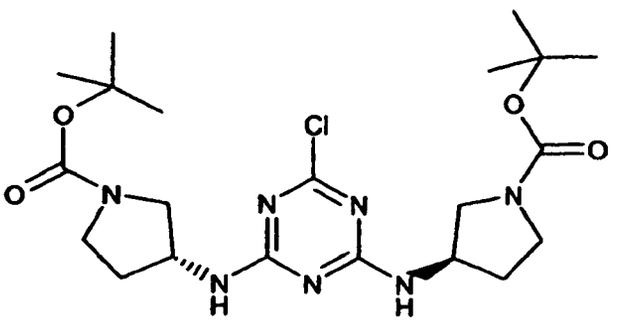
Step C2: 1,3-Di-(R)-pyrrolidin-3-yl-urea

[0090] To a solution of 1,3-bis-((R)-1-benzyl-pyrrolidin-3-yl)-urea (5.34 g, 14.1 mmol) in ethanol (80 mL) under an inert atmosphere of argon is added palladium hydroxide on carbon (1.07 g). The reaction mixture is purged with argon and placed under an atmosphere of hydrogen for two days after which time, the mixture is filtered and the catalyst washed with ethanol. The organic portions are combined and concentrated *in vacuo* to yield the title compound as a white solid.

Intermediate D 6-(4-Methyl-piperazin-1-yl)-N,N'-di-(R)-pyrrolidin-3-yl-[1,3,5] triazine-2,4-diamine trifluoroacetate:

Step D1: Intermediate D1

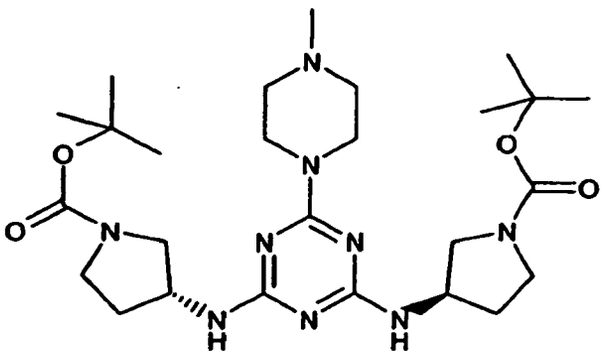
[0091]



[0092] To a cooled (0˚C) solution ofcyanuric chloride (0.1 g, 0.54 mmol) in THF (1 mL) and DIPEA (1 mL) is added dropwise, (R)-3-amino-1-N-Boc-pyrrolidine (0.202 g, 1.08 mmol) in THF (1mL). After stirring at RT for 1 hour, the solvent is removed *in vacuo* and the product is partitioned between DCM and 2 M HCl. The organic portion is separated, washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo* to yield Intermediate D1 which is used in the next step without further purification.

Step D2: Intermediate D2

[0093]

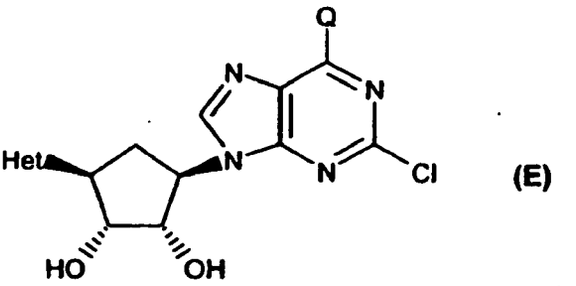


[0094] A reaction mixture comprising Intermediate D1 (0.1 g, 0.21 mmol), methylpiperazine (0.104 g, 1.03 mmol), sodium iodide (0.031 g, 0.21 mmol) in NMP (0.25 ml) and acetonitrile (0.25 mL) is heated using microwave radiation in a Personal Chemistry Emrys™ Optimizer microwave reactor at 160˚C for 30 minutes. Intermediate D2 is obtained after purification by reverse phase column chromatography (Isolute™ C18, 0-100% acetonitrile in water - 0.1% TFA).

Step D3: 6-(4-Methyl-piperazin-1-yl)-N,N-di-(R)-pyrrolidin-3-yl-[1,3,5]triazine-2,4-diamine trifluoroacetate

[0095] A solution of Intermediate D2 (0.1 g, 0.18 mmol) in DCM (2 mL) is treated with TFA (1 mL) and stirred at RT for 2 hours. The solvent is removed *in vacuo* to yield the title product.

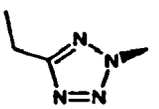
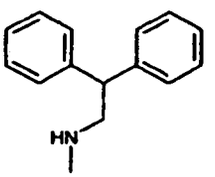
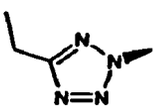
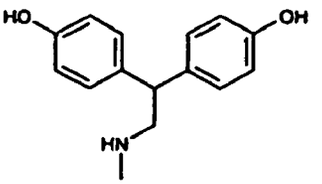
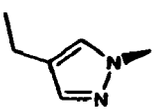
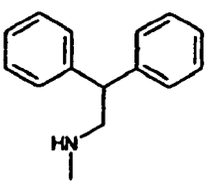
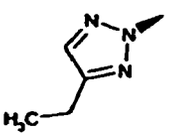
[0096] The following intermediates of formula (E):



(E)

are shown in table 3 below.

Table 3

Intermediate	Het	Q
EA		
EB		
EC		
ED		

Intermediate EA (1R,2S,3R,5S)-3-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(5-ethyl-tetrazol-2-yl)-cyclopentane-1,2-diol

Step EA1: 2,6-Dichloro-9-[(1R,45)-4-(5-ethyl-tetrazol-2-yl)-cyclopent-2-enyl]-9H-purine

[0097] The title compound is prepared analogously to di-Boc-[(1S,4R)-4-(2,6-dichloro-purin-9-yl)-cyclopent-2-enyl]-amine (AA3) by replacing di-t-butyliminodicarboxylate with 5-ethyltetrazole. MS (ES+) *m/e* 351.2(MH^+)

Step EA2: {2-Chloro-9-[(1R,4S)-4-(5-ethyl-tetrazol-2-yl)-cyclopent-2-enyl]-9H-purin-6-yl}-(2,2-diphenyl-ethyl)-amine

[0098] The title compound is prepared analogously to N-{(1S,2R,3S,4R)-4-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide (AA7) by replacing N-[(1S,2R,3S,4R)-4-(2,6-dichloro-purin-9-yl)-2,3-dihydroxy-cyclopentyl]-propionamide (160 mg, 0.44 mmol) with 2,6-dichloro-9-[(1R,4S)-4-(5-ethyl-tetrazol-2-yl)-cyclopent-2-enyl]-9H-purine (EA1). MS (ES+) *m/e* 512.2 (MH^+)

Step EA3: (1R,2S,3R,5S)-3-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(5-ethyltetrazol-2-yl)-cyclopentane-1,2-diol

[0099] The title compound is prepared analogously to (1S,2R,3S,5R)-3-(di-Boc-amino)-5-(2,6-dichloro-purin-9-yl)-cyclopentane-1,2-diol (AA4) by replacing di-Boc-[(1S,4R)4-(2,6-dichloro-purin-9-yl)-cyclopent-2-enyl]-amine with {2-chloro-9-[(1R,4S)-4-(5-ethyl-tetrazol-2-yl)-cyclopent-2-enyl]-9H-purin-6-yl}-(2,2-diphenyl-ethyl)-amine. MS (ES+) *m/e* 546.2 (MH^+)

Intermediate EB (1R,2S,3R,5S)-3-{6-[2,2-Bis-(4-hydroxy-phenyl)ethylamino]-2-chloro-purin-9-yl}-5-(5-ethyl-tetrazol-2-yl)-cyclopentane-1,2-diol

[0100] The title compound is prepared analogously to 1R,2S,3R,5S)-3-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(5-ethyl-teuazol-2-yl)-cyclopentane-1,2-diol (Intermediate EA) by replacing 2,2-diphenylethylamine with 4,4'-(2-aminoethylidene)bisphenol. MS (ES+) *m/e* 578.34 (MH^+)

Intermediate EC (1R,2S,3R,5S)-3-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(4-ethyl-pyrazol-1-yl)-cyclopentane-1,2-diol

[0101] The title compound is prepared analogously to 1R,2S,3R,3S)-3-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(5-ethyl-tetrazol-2-yl)-cyclopentane-1,2-diol (Intermediate EA) by replacing 5-ethyltetrazole with 4-ethyl-1H-pyrazole. MS (ES+) *m/e* 544.23 (MH^+)

Intermediate ED 3-(2,6-Dichloro-purin-9-yl)-5-(4-ethyl-[1,2,3]triazol-1-yl)-cyclopentane-1,2-diol

Step ED1: 2,6-Dichloro-9-[(1R,4S)-4-(4-ethyl-[1,2,3]triazol-1-yl)-cyclopent-2-enyl]-9H-purine

[0102] A mixture comprising triphenylphosphine (0.299 g, 0.874 mmol) and $Pd_2(dba)_3$ (0.267 g, 0.291 mmol) in dry THF (5 mL) under an inert atmosphere of argon is stirred at RT for 10 minutes. This mixture is then added to a pre-stirring mixture of carbonic acid (1S,4R)-4-(2,6-dichloro-purin-9-yl)-cyclopent-2-enyl ester ethyl ester (Intermediate AA2) (2.00 g, 5.83 mmol) and 4-ethyl-2H-[1,2,3]triazole (0.594 g, 6.12 mmol) in THF (15 mL). The resulting mixture is stirred at RT overnight and then concentrated *in vacuo.* The crude product is purified by chromatography on silica eluting with 0-50% EtOAc in iso-hexane to afford the title compound as a white solid. (MH^+) 350).

Step ED2: 3-(2,6-Dichloro-purin-9-yl)-5-(4-ethyl-[1,2,3]triazol-1-yl)-cyclopentane-1,2-diol

[0103] A solution of 2,6-dichloro-9-[(1R,4S)-4-(4-ethyl-[1,2,3]triazol-1-yl)-cyclopent-2-enyl]-9H-purine (1.442 g, 4.12 mmol) in EtOAc (15 mL) and MeCN (15 mL) is treated with a solution of ruthenium trichloride (0.120 g, 0.58 mmol)and sodium periodate (1.32 g, 6.18 mmol) in water (5 mL). The reaction mixture is stirred vigorously for 6 hours and then treated with sodium metabisulfite (saturated aqueous solution, 25 mL) and then stirred overnight. The resulting mixture is partitioned between water and EtOAc and the aqueous portion is extracted with EtOAc. The combined organic portions are washed with water, dried ($MgSO_4$) and concentrated *in vacuo.* The crude product is purified by chromatography on silica eluting with 0-100% EtOAc in iso-hexane to afford the title compound as an oil orange solid. (MH^+ 350).

[0104] Intermediate ED can also be prepared using the following method:

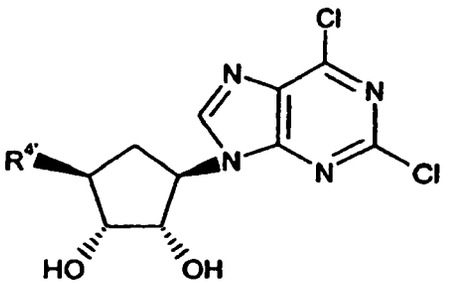
Step ED1': 2,6-Dichloro-9-[(1R,4S)-4-(4-ethyl-[1,2,3]triazol-2-yl)-cyclopent-2-enyl]-9H-purine

[0105] The title compound is prepared analogously to di-Boc-[(1S,4R)-4-(2,6-dichloro-purin-9-yl)-cyclopent-2-enyl]-amine (AA3) by replacing di-t-butyliminodicarboxylate with 4-ethyl-2H-[1,2,3]triazole.

Step ED2': (1R,2S,3R,5S)-3-(2,6-Dichloro-purin-9-yl)-5-(4-ethyl-[1,2,3]triazol-2-yl)-cyclopentane-1,2-diol

[0106] The titled compound is prepared analogously to (1S,2R,3S,5R)-3-(di-Boc-amino)-5-(2,6-dichloro-purin-9-yl)-cyclopentane-1,2-diol (AA4) by replacing di-Boc-[(1S,4R)-4-(2,6-dichloro-purin-9-yl)-cyclopent-2-enyl]-amine with 2,6-dichloro-9-[(1R,4S)-4-(4-ethyl-[1,2,3]triazol-2-yl)-cyclopent-2-enyl]-9H-purine (Step 1).

[0107] The following intermediates of formula (F):

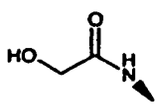
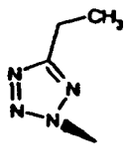
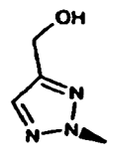


(F)

,

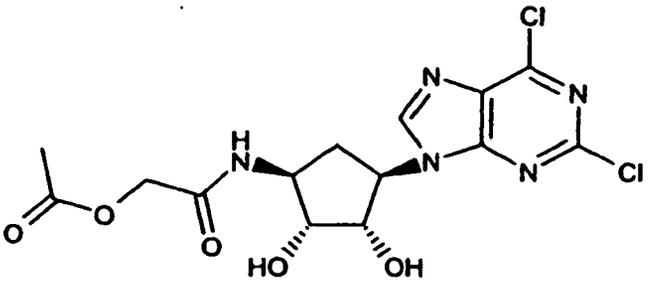
are shown in Table 4 below, their method of preparation being described hereinafter.

Table 4

Intermediate	$R^{4'}$
FA	
FB	
FC	

Intermediate FA Acetic acid [(1S,2R,3S,4R)-4-(2,6-dichloro-purin-9-yl)-2,3-dihydroxy-cyclopentylcarbamoyl]-methyl ester

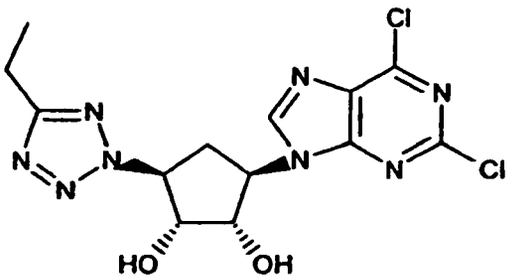
[0108]



[0109] This compound is prepared analogously to Intermediate AA by replacing propionyl chloride in Step AA6 with acetoxyacetyl chloride.

Intermediate FB (1R,2S,3R,5S)-3-(2,6-Dichloro-purin-9-yl)-5-(5-ethyl-tetrazol-2-yl)-cyclopentane-1,2-diol

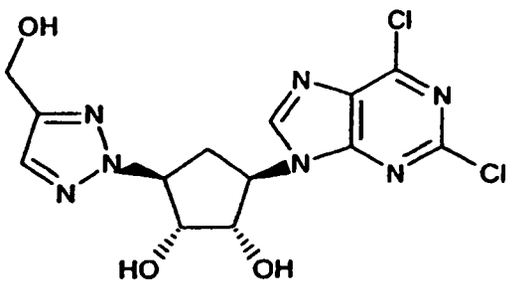
[0110]



[0111] This compound is prepared analogously to (1S,2R,3S,5R)-3-(di-Boc-amino)-5-(2,6-dichloro-purin-9-yl)-cyclopentane-1,2-diol (Step AA4) by replacing di-t-butyliminodicarboxylate (Step AA3) with 5-ethyl-2H-tetrazole.

Intermediate FC (1R,2S,3R,5S)-3-(2,6-Dichloro-purin-9-yl)-5-(4-hydroxymethyl-[1,2,3]triazol-2-yl)-cyclopentane-1,2-diol

[0112]

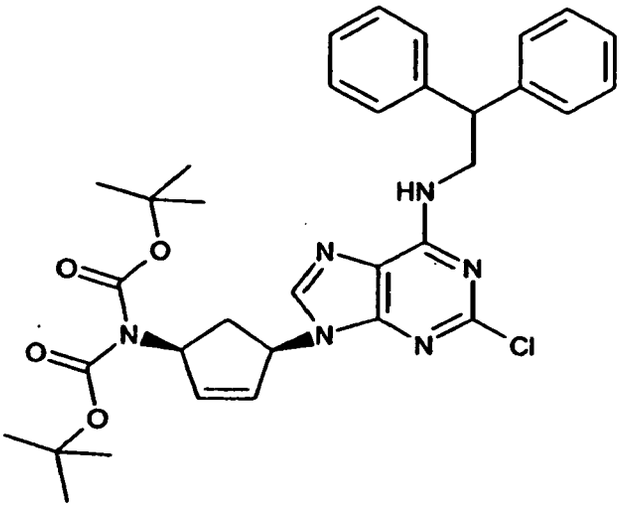


[0113] This compound is prepared analogously to (1S,2R,3S,5R)-3-(di-Boc-amino)-5-(2,6-dichloro-purin-9-yl)-cyclopentane-1,2-diol (Step AA4) by replacing di-t-butyliminodicarboxylate (Step AA3) with (2H-[1,2,3]triazol-4-yl)-methanol.

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

Step GA1:

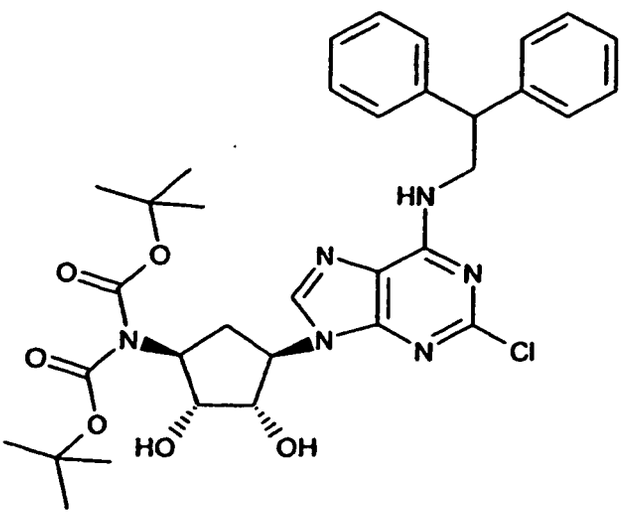
[0114]



[0115] Di-Boc-[(1S,4R)-4-(2,6-dichloro-purin-9-yl)-cyclopent-2-enyl]-amine (Step AA3) (7.0 g, 14.9 mmol), 2,2-diphenylethylamine and DIPEA (2.3 g, 17.9 mmol) are dissolved in dry THF (100 mL) and stirred at 50˚C over night. The reaction mixture is reduced *in vacuo* and the residue is partitioned between DCM and (0.1 M) $HCl_{(aq)}$. The organic portions are washed with water, brine, dried ($MgSO_4$), filtered and reduced *in vacuo* to yield title compound.

Step GA2:

[0116]



[0117] Intermediate GA1 (8.9g, 14mmol) and 4-methylmorpholine 4-oxide (3.3g, 28mmol) are placed in a flask with THF (75 mL). OsO_4 (4% in water) (7.5 mL) is added and the reaction mixture is stirred at RT over night. The reaction mixture is reduced *in vacuo* and the residue is portioned between DCM and (0.1 M) $HCL_{(aq)}$. The organics are washed with water and brine, dried ($MgSO_4$), filtered and reduced *in vacuo.* The title compound is precipitated from MeOH.

Step GA3: (1S,2R,3S,5R)-3-Amino-5-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-cyclopentane-1,2-diol hydrochloride

[0118] Intermediate GA2 (6.8 g, 10 mmol) is dissolved/suspended in (4 M) HCl in dioxane (10 mL) and MeOH (10 mL). The reaction mixture is stirred at RT over night. The solvent is removed *in vacuo* to yield title compound.

Step GA4: Acetic acid {(1S,2R,3S,4R)-4-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl-carbamoyl}-methyl ester

[0119] (1S,2R,3S,5R)-3-Amino-5-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-cyclopentane-1,2-diol hydrochloride (Intermediate GA3) (3.0 g, 5.6 mmol) is dissolved in dry THF (100 mL) and TEA (2.8 g, 28 mmol). Acetoxyacetylchloride (0.76 g, 5.6 mmol) is dissolved in dry THF (4 mL) and is added to the reaction mixture dropwise.

[0120] The solvent is removed *in vacuo* and the residue is partitioned between DCM and $_{(sat)}NaHCO_{3(aq)}$. The organics are washed with water and brine, dried ($MgSO_4$), filtered and reduced *in vacuo* and the title compound is obtained after purification by flash column chromatography (silica, DCM:MeOH 20:1).

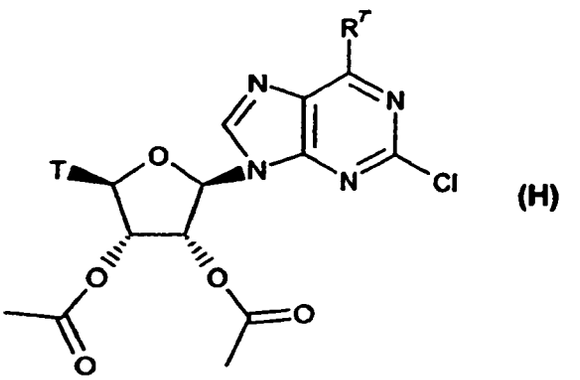
Intermediate GB (1R,2S,3R,5S)-3-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(4-hydroxymethyl-[1,2,3]triazol-2-yl)-cyclopentane-1,2-diol

[0121] (1R,2S,3R,5S)-3-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(4-hydroxymethyl-[1,2,3]triazol-2-yl)-cyclopentane-1,2-diol is prepared analogously to N-{(1S,2R,3S,4R)-4-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide by replacing N-[(1S,2R,3S,4R)-4-(2,6-dichloro-purin-9-yl)-2,3-dihydroxy-cyclopentyl]-propionamide, with (1R,2S,3R,5S)-3-(2,6-dichloro-purin-9-yl)-5-(4-hydroxymethyl-[1,2,3]triazol-2-yl)-cyclopentane-1,2-diol (Intermediate FC).

Intermediate GC N-{(1S,2R,3S,4R)-4-[6-((S)-1-Benzyl-2-hydroxy-ethylamino)-2-chloro-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide

[0122] N- {(1S,2R,3S,4R)-4-[6-((S)-1-Benzyl-2-hydroxy-ethylamino)-2-chloro-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide is prepared analogously to N- {(1S,2R,3S,4R)-4-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide by replacing N-[(1S,2R,3S,4R)-4-(2,6-dichloro-purin-9-yl)-2,3-dihydroxy-cyclopentyl]-propionamide, with acetic acid [(1S,2R,3S,4R)-4-(2,6-dichloro-purin-9-yl)-2,3-dihydroxy-cyclopentylcarbamoyl]-methyl ester (Intermediate FA) and replacing 2,2-diphenylethylamine with (4Z,6Z)-(S)-phenylalinol.

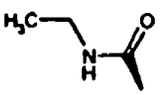
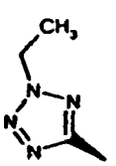
[0123] The following intermediates of formula (H):



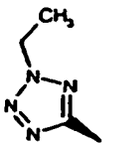
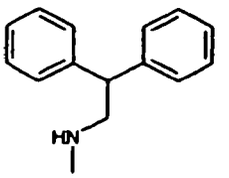
(H)

are shown in Table 5 below, their method of preparation being described hereinafter.

Table 5

Intermediate	T	R^T
HA		-Cl
HB		Cl

(continued)

Intermediate	T	R^T
HC		

Intermediate HA Acetic acid (2S,3S,4R,5R)-4-acetoxy-5-(2,6-dichloro-purin-9-yl)-2-ethylcarbamoyl-tetrahydro-furan-3-yl ester

[0124] The title compound is prepared by the procedure of Vittori, S.; Costanzi, S.; Lambertucci, C.; Volpini, R.; Cristalli, G. Coupling of 2,6-disubstituted purines to ribose-modified sugars. Nucleosides, Nucleotides & Nucleic Acids (2001), 20(4-7), 771-774.

Intermediate HB Acetic acid (2R,3R,4R,5R)-4-acetoxy-5-(2,6-dichloro-purin-9-yl)-2-(2-ethyl-2H-tetrazol-5-yl)-tetrahydro-furan-3-yl ester

[0125] The title compound is prepared by the procedure of Cox, Brian; Keeling, Suzanne Elaine; Allen, David George; Redgrave, Alison Judith; Barker, Michael David; Hobbs, Heather; Roper, Thomas Davis, IV; Geden, Joanna Victoria. Preparation of 2-(purin-9-yl)-tetrahydrofuran-3,4-diol nucleosides as antiinflammatory agents and agonists against adenosine receptors. (WO 98/28319 A1)

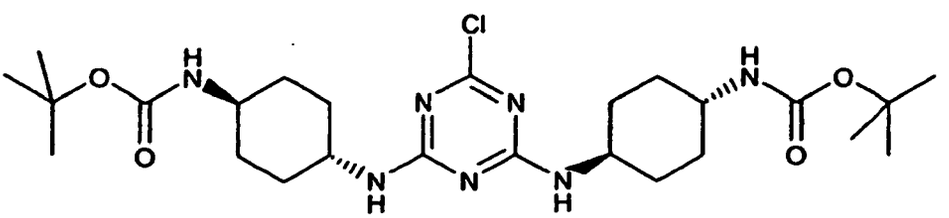
Intermediate HC Acetic acid (2R,3R,4R,5R)-4-acetoxy-5-[2-chloro-(2,2-diphenyl-ethylamino)-purin-9-yl]-2-(2-ethyl-2H-tetrazol-5-yl)-tetrahydro-furan-3-yl ester

[0126] The title compound is prepared by the procedure of Cox, Brian; Keeling, Suzanne Elaine; Allen, David George; Redgrave, Alison Judith; Barker, Michael David; Hobbs, Heather; Roper, Thomas Davis, IV; Geden, Joanna Victoria. Preparation of 2-(purin-9-yl)-tetrahydrofuran-3,4-diol nucleosides as antiinflammatory agents and agonists against adenosine receptors. (WO 98/28319 A 1)

Intermediate IA N,N'-Bis-(4-amino-cyclobexyl)-6-chloro-[1,3,5]triazine-1,4-diamine

Step IA1: Intermediate IA1

[0127]



[0128] To a cooled (0˚C) solution of cyanuric chloride (1 eq.) in THF and DIPEA is added dropwise, (4-ainino-cyclohexyl)-carbamic acid tert-butyl ester (2 eq.) in THF. After stirring at RT for I hour, the solvent is removed *in vacuo* and the product is partitioned between DCM and 2 M HCl. The organic portion is separated, washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo* to yield Intermediate IA1 which is used in the next step without further purification.

Step IA2: N,N'-Bis-(4-amino-cyclohexyl)-6-chloro-[1,3,5]triazine-2,4-diamine trifluoroacetate

[0129] A solution of Intermediate IA1 in DCM is treated with TFA and stirred at RT for 2 hours. The solvent is removed

in vacuo the material is then dissolved in minimal volume of ethanol/saturated aqueous sodium carbonate solution until the pH of the solution is adjusted to pH 9 (ensuring the compound remains in solution). The solution is loaded onto an Isolute™ C18 column and washed through firstly with water and then MeOH. The fractions are combined and concentrated *in vacuo* to yield the title product.

Intermediate IB N,N'-Bis-(4-amino-cyclohexyl)-[1,3,5]triazine-2,4-diamine

[0130] To a solution of N,N'-bis-(4-amino-cyclohexyl)-6-chloro-[1,3,5]triazine-2,4-diamine trifluoroacetate (Intermediate IA) in ethanol under an inert atmosphere of argon is added palladium catalyst on carbon. The reaction mixture is purged with argon and placed under an atmosphere of hydrogen o/n after which time, the mixture is filtered and the catalyst washed with ethanol. The organic portions are combined and concentrated *in vacuo* to yield the title compound.

[0131] N,N'-Bis-(4-amino-cyclohexyl)-[1,3,5]triazine-2,4-diamine (Intermediate IB) may also be prepared using following process:

N,N-Bis-(4-amino-cyclohexyl)-[1,3,5]triazine-2,4-diamine is prepared analogously to N,N'-bis-(4-amino-cyclohexyl)-6-chloro-[1,3,5]triazine-2,4-diamine by replacing cyanuric chloride with 2,4-dichloro-[1,3,5]triazine.

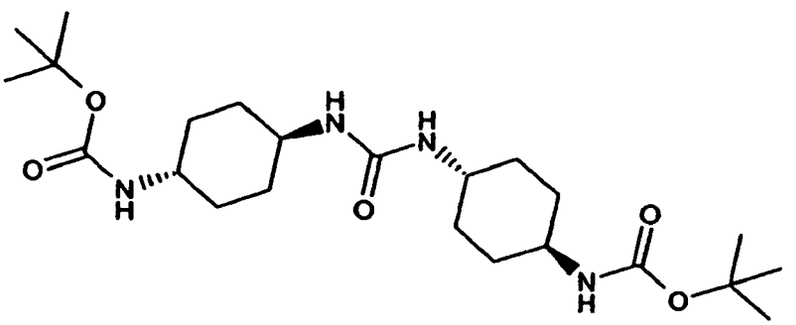
Intermediate IC 1,3-Bis-(4-amino-cyclohexyl)-urea

[0132] (1,3-Bis-(4-amino-cyclohexyl)-urea is prepared analogously to 1,3-di-(R)-pyrrolidin-3-yl-urea (Intermediate C) by replacing (R)-1-benzyl-pyrrolidin-3-ylamine with (4-aminocyclohexyl)-carbamic acid benzyl ester.

[0133] Intermediate IC may also be prepared using following process:

Step IC1:

[0134]



[0135] This compound is prepared analogously to Intermediate C by replacing (R)-1-benzyl-pyrrolidin-3-ylamine with (4-amino-cyclohexyl)-carbamic acid tert-butyl ester.

Step IC2: 1,3-Bis-(4-amino-cyclohexyl)-urea

[0136] This compound is prepared analogously to N,N'-bis-(4-amino-cyclohexyl)-6-chloro-[1,3,5]triazine-2,4-diamine trifluoroacetate (IA2) by replacing Intermediate IA1, with Intermediate IC1.

Intermediate ID Bis-((R)-3-amino-pyrrolidin-1-yl)-methanone

[0137] Bis-((R)-3-amino-pyrrolidin-1-yl)-methanone is prepared analogously to 1,3-bis-(4-amino-cyclohexyl)-urea (Intermediate IC) by replacing 4-amino-cyclohexyl)carbamic acid tert-butyl ester with (R)-pyrrolidin-3-yl-carbamic acid tert-butyl ester.

Intermediate IE Bis-(4-amino-piperidin-1-yl)-methanone

[0138] Bis-(4-amino-piperidin-1-yl)-methanone is prepared analogously to 1,3-bis-(4-aminocyclohexyl)-urea (Intermediate IC), by replacing 4-amino-cyclohexyl)-carbamic acid tert-butyl ester with piperidin-4-yl-carbamic acid tert-butyl

ester.

Intermediate IF (R)-3-Amino-pyrrolidine-I-carboxylic acid (4-amino-cyclohexyl)-amide

StepIF1: (4-tert-Butoxycarbonylamino-cyclohexyl)-carbamic acid phenyl ester

[0139] Phenyl chloroformate (1 eq.) is added dropwise to a solution of pyridine in 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 RT for 1 hour. The reaction mixture is partitioned between (0.2 M) $HCl_{(aq)}$ and DCM. The organics are washed with water (x2), $_{(sat)}NaHCO_{3(aq)}$ and brine. The organics are dried ($MgSO_4$), filtered and reduced *in vacuo* to yield the title compound.

Stew IF2: [(R)-1-(4-tert-Butoxycarbonylwnino-cyclohexylcarbamoyl)-pyrrolidin-3-yl]-carbamic acid tert-butyl ester

[0140] (4-tert-Butoxycarbonylamino-cyclohexyl)-carbamic acid phenyl ester (1 eq.) and (R)-pyrrolidin-3-yl-carbamic acid tert-butyl ester (1 eq.) are dissolved in NMP and heated at 100˚C for 1 hour.

Step IF3: (R)-3-Amino-pyrrolidine-1-carboxylic acid (4-amino-cyclohexyl)-amide

[0141] (R)-3-Amino-pyrrolidine-1-carboxylic acid (4-amino-cyclohexyl)-amide is prepared analogously to N,N'-bis-(4-amino-cyclohexyl)-6-chloro-[1,3,5]triazine-2,4-diamine (Intermediate IA) by replacing Intermediate IA1 with [(R)-1-(4-tert-butoxycarbonytamino-cyclohexylcarbamoyl)-pyrrolidin-3-yl]-carbamic acid tert-butyl ester (IF2)

Intermediate IG 4-Amino-piperidine-1-carboxylic acid (4-amino-cyclohexyl)-amide

[0142] 4-Amino-piperidine-1-carboxylic acid (4-amino-cyclohexyl)-amide is prepared analogously to (R)-3-amino-pyrrolidine-1-carboxylic acid (4-amino-cyclohexyl)-amide (Intermediate IF) by replacing (R)-pyrrolidin-3-yl-carbamic acid tert-butyl ester with piperidin-4-yl-carbamic acid tert-butyl ester.

Intermediate IH (4-Amino-piperidin-1-yl)-((R)-3-amino-pyrrolidin-1-yl)-methanone

[0143] (4-Amino-piperidin-1-yl)-((R)-3-amino-pyrrolidin-1-yl)-methanone is prepared analogously to (R)-3-amino-pyrrolidine-1-carboxylic acid (4-amino-cyclohexyl)-amide (Intermediate IF) by replacing (4-amino-cyclohexyl)-carbamic acid tert-butyl ester with piperidin-4-yl-carbamic acid tert-butyl ester.

Intermediate II 1-(4-Amino-cyclohexyl)-3-(R)-pyrrolidin-3-yl-urea

[0144] 1-(4-Amino-cyclohexyl)-3-(R)-pyrrolidin-3-yl-urea is prepared analogously to (R)-3-amino-pyrrolidine-1-carboxylic acid (4-amino-cyclohexyl)-amide (Intermediate IF) by replacing (R)-pyrrolidin-3-yl-carbamic acid tert-butyl ester with (R)-3-amino-pyrrondine-1-carboxylic acid tert-butyl ester.

Intermediate IJ (R)-3-Amino-pyrrolidine-1-carboxylic acid (R)-pyrrolidin-3-ylamide

[0145] (R)-3-Amino-pyrrolidine-1-carboxylic acid (R)-pyrrolidin-3-ylamide is prepared analogously to (R)-3-amino-pyrrolidine-1-carboxylic acid (4-amino-cyclohexyl)-amide (Intermediate IF) by replacing (4-amino-cyclohexyl)-carbamic acid tert-butyl ester with (R)-3-amino-pyrrolidine-1-carboxylic acid tert-butyl ester.

Intermediate IK 3,4-Bis-(4-amino-cyclohexylamino)-cyclobut-3-ene-1,2-dione

[0146] (4-Amino-cyclohexyl)-carbamic acid tert-butyl ester (2 eq.) and 3,4-dimethoxy-3-cyclobutene-1,2-dione (1 eq.) are dissolved in EtOH and heated at 120˚C for 1 hour in the microwave. The solvent is removed *in vacuo.* The resulting material is dissolved in DCM. TFA is added and the reaction mixture is stirred at RT for 2 hours. The solvent is removed *in vacuo* the material is then dissolved in minimal volume of ethanol/saturated aqueous sodium carbonate solution until the pH of the solution is adjusted to pH 9 (ensuring the compound remains in solution). The solution is loaded onto an Isolute™ C 18 column and washed through firstly with water and then MeOH. The fractions are combined and concentrated *in vacuo* to yield the title product.

Intermediate JA (4-((R)-3-Pyrrolidin-3-ylureido)-cyclohexyl)-carbamic acid tert-butyl ester

Step JA1: (4-[3-((R)-1-Benzyl-pyrrolidin-3-yl)-ureido]-cyclohexyl)-carbamic acid tert-butyl ester

[0147] (4-tert-Butoxycarbonylamino-cyclohexyl)-carbamic acid phenyl ester (1 eq.) and (R)-1-benzyl-pyrrolidin-3-ylamine (1 eq.) are dissolved in NMP and heated at 100˚C for I hour.

Step JA2: [4-((R)-3-Pyrrolidin-3-ylureido)-cyclohexyl]-carbamic acid tert-butyl ester

[0148] 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 for over night. 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 JB [(R)-1-((R)-Pyrrolidin-3-ylcarbamoyl)-pyrrolidin-3-yl]-carbamic acid tert-butyl ester

Step JB1: (R)-3-tert-Butoxycarbonylamino-pyrrolidine-1-carboxylic acid phenyl ester

[0149] Phenyl chloroformate (1 eq.) is added dropwise to a solution of pyridine in DCM. The reaction mixture is cooled to 0˚C and a solution of (R)-pyrrolidin-3-yl-carbamic acid tert-butyl ester (1 eq.) in DCM is added dropwise. The reaction mixture is stirred at RT for 1 hour. The reaction mixture is partitioned between (0.2 M) $HCl_{(aq)}$ and DCM. The organics are washed with water, $_{(sat)}NaHCO_{3(aq)}$ and brine. The organics are dried ($MgSO_4$), filtered and reduced *in vacuo* to yield the title compound.

Step JB2: [(R)-1-((R)-1-Benzyl-pyrrolidin-3-ylcarbamoyl)-pyrrolidin-3-yl]-carbamic acid tert-butyl ester

[0150] (R)-3-tert-Butoxycarbonylamino-pyrrolidine-1-carboxylic acid phenyl ester (1 eq.) and (R)-1-benzyl-pyrrolidin-3-ylamine (1 eq.) are dissolved in NMP and heated at 100˚C for 1 hour.

Step JB3: [(R)-1-((R)-Pyrrolidin-3-ylcarbamoyl)-pyrrolidin-3-yl]-carbamic acid tert-butyl ester

[0151] 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 argon and placed under an atmosphere of hydrogen for over night. 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 JC {4-[3-(4-Amino-cyclohexyl)-ureido]-cyclohexyl}-carbamic acid tert-butyl ester

[0152] {4-[3-(4-Amino-cyclohexyl)-ureido]-cyclohexyl}-carbamic acid tert-butyl ester is prepared analogously to [4-((R)-3-pyrrolidin-3-ylureido)-cyclohexyl]-carbamic acid text-butyl ester, by replacing (R)-1-benzyl-pyrrolidin-3-ylamine, with (4-amino-cyclohexyl)-carbamic acid benzyl ester.

Intermediate K N-{(1S,2R,3S,4R)-4-12-((R)-3-Amino-pyrrolidin-1-yl)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide

Step K1: {(R)-1-[9-((1R,2S,3R,4S)-2,3-Dihydroxy-4-propionylamino-cyclopentyl)-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-carbamic acid tert-butyl ester

[0153] A reaction mixture comprising N-{(1S,2R,3S,4R)-4-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide (Intermediate AA) (2.5 g, 4.80 mmol) and (3R)-(+)-(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™ C 18, 0-20% acetonitrile in water - 0.1 % TFA) yields the title compound.

Step K2: N-{(1S,2R,3S,4R)-4-[2-((R)-3-Ammo-pyrrolidin-1-yl)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide dihydrochloride

[0154] {(R)-1-[9-((1R,2S,3R,4S)-2,3-Dihydroxy-4-propionylamino-cyclopentyl)-6-(2,2-diphenyl-ethylamino)-9H-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 RT for 3 days, the solvent is removed *in vacuo* to yield the title compound as a brown solid. This is used in the next step without further purification.

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

[0155] N-{(1S,2R,3S,4R)-4-[2-((Rp3-Amino-pyrrolidin-1-yl)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide dihydrochloride (ca. 7.7 mmol) is dissolved in minimal volume of a mixture of ethanol/saturated aqueous sodium carbonate solution until the pH of the solution is adjusted to pH 7 (ensuring the compound remains in solution). The solution is loaded onto an Isolute™ C 18 column and washed through firstly with water and then MeOH. The fractions are combined and concentrated *in vacuo* and then further purified by repeating the above process to afford the title compound. LCMS (electiospray): m/z [MH^+] 571

Intermediate LA Acetic acid (2R,3R,4S,5S)-4-acetoxy-2-(2,6-dichloro-purin-9-yl)-5-ethylcarbamoyl-tetrahydro-furan-3-yl ester

[0156] This compound can be prepared by the procedure of Vittori, S.; Costanzi, S.; Lambertucci, C.; Volpini, R.; Cristalli, G. Dipartimento di Scienze Chimiche, University of Camerino, Camerino, Italy. Nucleosides, Nucleotides & Nucleic Acids (2001), 20(4-7), 771-774.

Intermediate LB Acetic acid (2R,3R,4R,5R)-4-acetoxy-2-(2,6-dichloro-purin-9-yl)-5-methoxymethyl-tetrahydro-furan-3-yl ester

[0157] This compound can be prepared by the procedure of van Tilburg, Erica W.; van der Klein, Pieter A.M.; von Frijtag Drabbe Kuenzel, Jacobien K.; de Groote, Miriam; Stannek, Christina; Lorenzen, Anna; IJzerman, Ad P. Division of Medicinal Chemistry, Leiden/Amsterdam Center for Drug Research, Leiden, Neth. Journal of Medicinal Chemistry (2001), 44(18), 2966-2975.

Intermediate LC Acetic acid (2R,3R,4R,5S)-4-acetoxy-2-(2,6-dichloro-purin-9-yl)-5-(3-ethyl-isoxazol-5-yl)-tetrahydro-furan-3-yl ester

[0158] This compound can be prepared by the procedure of Chan, Chuen; Cousins, Richard Peter Charles; Cox, Brian. Preparation and antiinflammatory activity of 2-(purin-9-yl)-tetrahydrofuran-3,4-diol derivatives. (WO 99/38877)

Intermediate LD Acetic acid (2R,3R,4R,SR)-4-acetoxy-2-(2,6-dichloro-purin-9-yl)-5-(2-ethyl-2H-tetrazol-5-yl)-tetrahydro-furan-3-yl ester

[0159] This compound can be prepared by the procedure of Cox, Brian; Keeling, Suzanne Elaine; Allen, David George; Redgrave, Alison Judith; Barker, Michael David; Hobbs, Heather; Roper, Thomas Davis, IV; Geden, Joanna Victoria. (Glaxo Group Ltd., UK). (WO 98/28319)

Intermediate LE Acetic acid (2R,3R,4R,5R)-4-acetoxy-acetoxymethyl-2-(2,6-dichloro-purin-9-yl)-tetrahydro-furan-3-yl ester

[0160] This compound can be prepared by the procedure of Francom, Paula; Robins, Morris J. Nucleic Acid Related Compounds. 118. Nonaqueous Diazotization of Aminopurine Derivatives. Convenient Access to 6-Halo- and 2,6-Dihalopurine Nucleosides and 2'-Deoxynucleosides with Acyl or Silyl Halides. Journal of Organic Chemistry (2003), 68(2), 666-669.

Intermediates NA-NC

[0161] These compounds namely,
[(1S,2R3S,4R)-4-(2,6-Dichloro-purin-9-yl)-2,3-dihydroxy-cyclopentyl]-carbamic acid methyl ester,
N-[(1S,2R,3S,4R)4-(2,6-Dichloro-purin-9-yl)-2,3-dihydroxy-cyclopentyl]-2-hydroxy-acetamide,
Cyclobutanecarboxylic acid [(1S,2R,3S,4R)-4-(2,6-dichloro-purin-9-yl)-2,3-dihydroxycyclopentyl]-amide,
can be prepared analogously to N-[(1S,2R,3S,4R)-4-(2,6-dichloro-purin-9-yl)-2,3-dihydroxycyclopentyl]-propionamide (Intermediate AA6) by replacing propionyl chloride with the appropriate acid chloride or chloroformate.

Intermediates ND-NE

[0162] These compounds namely,
(1R,2S,3R,5S)-3-(2,6-Dichloro-purin-9- yl)-5-(5-ethyl-tetrazol-2-yl)-cyclopentane-1,2-diol and
(1R,2S,3R,5S)-3-(2,6-Dichloro-purin-9-yl)-5-(4-ethyl-pyrazol-1-yl)-cyclopentane-1,2-diol,
can be prepared analogously to Intermediate ED by replacing 4-ethyl-2H-[1,2,3]triazole (Step ED1') with 5-ethyl-2H-tetrazole and 4-ethyl-1H-pyrazole, respectively.

Intermediate MA Sodium nitromalonaldehyde

[0163] Sodium nitromalonaldehyde can be prepared as described by Fanta P.E. Org. Syntheses, Coll. Vol. 4 (1963), pp 844-845.

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

[0164] The title compound can be prepared by dissolving acetic acid {(1S,2R,3S,4R)-4-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl-carbamoyl}-methyl ester (Intermediate GA) in 1.25 M HCl in methanol, stirring at RT until complete, and removing the volatile components under reduced pressure.

Intermediate QB N-{(1S,2R,3S,4R)-4-[6-(2,2-Diphenylethylamino)-2-hydrazino-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide

[0165] The title compound can be prepared by dissolving {(1S,2R,3S,4R)-4-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide (Intermediate QA) in hydrazine monohydrate, and stirring at RT for 72 hours. Sufficient isopropyl alcohol is added to give a final ratio of 20% isopropyl alcohol in hydrazine monohydrate, before the volatile components are removed under reduced pressure, to leave a gummy solid. This is triturated with water, and stirred for 12 hours. The resulting suspension can be filtered, washed with water, and dried, to give a colourless solid, to be used without further purification.

Intermediate QC N-((1S,2R,3S,4R)-4-[2-Hydrazino-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl)-2-hydroxy-acetamide

[0166] The title compound can be prepared from N-{(1S,2R,3S,4R)-4-[2-chloro-6-((S)-1-hydroxymethyl-2-phenylethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide (Intermediate GC), as described for N-{(1S,2R,3S,4R)-4-[6-(2,2-diphenylethylamino)-2-hydrazino-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide (Intermediate QB).

Intermediate QD N-{(1S,2R,3S,4R)-4-[6-(2,2-Diphenyl-ethylamino)-2-(4-nitro-pyrazol-1-yl)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide

Route A

[0167] The title compound can be prepared by dissolving N-{(1S,2R,3S,4R)-4-[6-(2,2-diphenylethylamino)-2-hydrazino-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide (Intermediate QB) in ethanol, adding 1.2 eq. of sodium nitromalonaldehyde (Intermediate MA), and stirring the resulting solution at reflux for 3 hours. Concentration of the solution under reduced pressure, dilution with hexane to give a suspension and filtration would give the product as a colourless solid.

Route B

[0168] The title compound can be prepared by dissolving {(1S,2R,3S,4R)-4-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide (Intermediate QA) in N-methyl-2-pyrrolidinone, followed by potassium carbonate (5 eq.) and 4-nitropyrazole (10 eq.). The mixture is heated by microwave irradiation to 150˚C for 2 hours, then diluted with ethyl acetate and washed consecutively with water (x2) and brine, before drying over magnesium sulphate. Filtration, removal of the volatile components under reduced pressure and purification by flash column chromatography/crystallisation would give the desired product.

Intermediate QE N-{(1S,2R,3S,4R)-2,3-Dihydroxy-4-[6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-2-(4-nitro-pyrazol-1-yl)-purin-9-yl]-cyclopentyl}-2-hydroxy-acetamide

[0169] The title compound can be prepared from N-{(1S,2R,3S,4R)-4-[2-hydrazino-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide (Intermediate QC), as described for N-{(1S,2R,3S,4R)-4-[6-(2,2-diphenyl-ethylamino)-2-(4-nitro-pyrazol-1-yl)-purin-9-yl]-2,3-dihydroxy-cyclopentyl} -2-hydroxy-acetamide (Routes A & B) (Intermediate QD).

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

[0170] The title compound can be prepared by dissolving N-{(1 S,2R,3S,4R)-4-[6-(2,2-diphenylethylamino)-2-(4-nitro-pyrazol-1-yl)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide (Intermediate QD) in methanol and adding a 2:1 by mass mixture of activated carbon and iron (III) chloride (40 mol% with respect to the substrate), followed by a large excess (100-fold with respect to the substrate) ofhydrazine monohydrate. The resulting mixture is stirred at 65˚C for 3 hours, then filtered, before being concentrated under reduced pressure. Trituration of the residue with petroleum ether and subsequent filtration would give the desired product as a colourless solid.

Intermediate QG N-{(1S,2R,3S,4R)-4-[2-(4-Amino-pyrazol-1-yl)-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide

[0171] The title compound can be prepared from N-{(1S,2R,3S,4R)-2,3-dihydroxy-4-[6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-2-(4-nitro-pyrazol-1-yl)-purin-9-yl]-cyclopentyl}-2-hydroxy-acetamide (Intermediate QE), as described for N-{(1S,2R,3S,4R)-4-[2-(4-amino-pyrazol-1-yl)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide (Intermediate QF).

Intermediate QH {1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(2-hydroxy-acetylamino)-cyclopentyl]-6-(2,2-diphenyl-ethylamino)-9H-purin-1-yl]-1H-pyrazol-4-yl}-carbamic acid phenyl ester

[0172] The title compound can be synthesised from N-{(1S,2R,3S,4R)-4-[2-(4-amino-pyrazol-1-yl)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl} -2-hydroxy-acetamide (Intermediate QF) by suspending in sufficient DCM and adding to a solution of phenyl chloroformate (1.1 eq.) in 2:1 pyridine to dichloromethane on ice, to give a final ratio of 1:1 pyridine to DCM. After I hour, the volatile components can be removed under reduced pressure; the residue is taken up in EtOAc and washed with 0.1 M HCl (x2) before drying over magnesium sulphate. Filtration and removal of the solvent under reduced pressure gives the desired product.

Intermediate Q1 {1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(2-hydroxy-acetylamino)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-1H-pyrazol-4-yl}-carbamic acid phenyl ester

[0173] The title compound can be prepared from N-{(1S,2R,3S,4R)-4-[2-(4-amino-pyrazol-1-yl)-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide (Intermediate QG), as described for {1-[9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-(2-hydroxy-acetylamino)-cyclopentyl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl]-1H-pyrazol-4-yl}-carbamic acid phenyl ester(Intermediate QH).

Intermediate RA N-[(1S,2R,3S,4R)-4-(6-{[Bis-(4-methoxy-phenyl)-methyl]-amino}-2-chloro-purin-9-yl)-2,3-dihydroxy-cyclopentyl]-propionamide

[0174] To a solution of N-[(1S,2F,3S,4R)-4-(2,6-dichloro-purin-9-yl)-2,3-dihydroxy-cyclopentyl]-propionamide (Intermediate AA6) (2.6 g, 7.22 mmol) in dry THF (26 mL) was added bis-(4-methoxy-phenyl)-methylamine (3.5 g, 14.44 mmol). The mixture was stirred at 50˚C for 12 hours, then cooled and solvent was removed under reduced pressure. The residue was taken up in chloroform and washed sequentially with 1.5 N HCl, water and saturated aqueous brine solution. The organic phase was dried over anhydrous sodium sulphate and concentrated to give the crude title compound. Purification by flash column chromatography over silica gel (60-120 mesh) using 2% MeOH in chloroform as eluant, gave the pure title compound (2.2 g, 54%). LC-MS (0.1% formic acid, acetonitrile): 567 (M^+)

Intermediate RB Acetic acid [(1S,2R,3S,4R)-4-(6-{[bis-(4-methoxy-phenyl)methyl]-amino}-2-chloro-purin-9-yl)-2,3-dihydroxy-cyclopentylcarbamoyl]-methyl ester

[0175] The title compound can be synthesised analogously to N-[(1S,2R,3S,4R)-4-(6-{[bis-(4-methoxy-phenyl)-methyl]-amino}-2-chloro-purin-9-yl)-2,3-dihydroxy-cyclopentyl]-propionamide (Intermediate RA) by replacing N-[(1S,2R, 35,4R)-4-(2,6-dichloro-purin-9-yl)-2,3-dihydroxy-cyclopentyl]-propionamide (Intermediate AA6) with acetic acid [(1S,2R, 3S,4R)-4-(2,6-dichloro-purin-9-yl)-2,3-dihydroxy-cyclopentylcarbamoyl]-methyl ester (Intermediate FA).

Intermediate RC (1R,2S,3R,5S)-3-(6-{[Bis-(4-methoxy-phenyl)-methyl]-amino}-2-chloro-purin-9-yl)-5-(4-hydroxymethyl-[1,2,3]triazol-2-yl)-cyclopentane-1,2-diol

[0176] The title compound can be synthesised analogously to N-[(1S,2R,3S,4R)-4-(6-{[bis-(4-methoxy-phenyl)-methyl]-amino}-2-chloro-purin-9-yl)-2,3-dihydroxy-cyclopentyl]-propionamide (Intermediate RA) by replacing N-[(1S,2R,3S, 4R)-4-(2,6-dichloro-purin-9-yl)-2,3-dihydroxy-cyclopentyl]-propionamide (Intermediate AA6) with (1R,2S,3R,5S)-3-(2,6-dichloro-purin-9-yl)-5-(4-hydroxymethyl-[1,2,3]triazol-2-yl)-cyclopentane-1,2-diol (Intermediate FC).

Intermediate SA N-{(1S,2R,3S,4R)-2,3-Dihydroxy-4-[6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-2-(4-nitro-imidazol-1-yl)-purin-9-yl]-cyclopentyl}-2-hydroxy-acetamide

[0177] The title compound can be prepared from N-{(1S,2R,3S,4R)-4-[6-((S)-1-benzyl-2-hydroxy-ethylamino)-2-chloro-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide(Intermediate GC) and 4-nitro-imidazole, as described for N-{(1S,2R,3S,4R)-4-[6-(2,2-diphenyl-ethylamino)-2-(4-nitro-pyrazol-1-yl)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide (Intermediate QD).

Intermediate SB N-{(1S,2R,3S,4R)-2,3-Dihydroxy-4-[6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-2,3-nitro-[1,2,4]triazol-1-yl)-purin-9-yl]-cyclopentyl}-2-hydroxy-acetamide

[0178] The title compound can be prepared from N-{(1S,2R,3S,4R)-4-[6-((S)-1-benzyl-2-hydroxy-ethylamino)2-chloro-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide (Intermediate GC) and 3-nitro-1,2,4-triazole, as described for N-{(1S,2R,3S,4R)-4-[6-(2,2-diphenyl-ethylamino)-2-(4-nitro-pyrazol-1-yl)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide (Intermediate QD).

Intermediate SC N-{(1S,2R,3S,4R)-4-[2-(4-Amino-imidazol-1-yl)-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide

[0179] The title compound can be prepared from N-{(1S,2R,3S,4R)-2,3-dihydroxy4-[6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-2-(4-nitro-imidazol-1yl)-purin-9-yl]-cyclopentyl} -2-hydroxy-acetamide (Intermediate SA), as described for N-{(1S,2R,3S,4R)-4-[2-(4-amino-pyrazol-1-yl)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide (Intermediate QF).

Intermediate SD N-1(1S,2R,3S,4R)-4-[2-(3-Amino-[1,2,4]triazol-1-yl)-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyctopentyl}-2-hydroxy-acetamide

[0180] The title compound can be prepared from N-{(1S,2R,3S,4R)-2,3-dihydroxy-4-[6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-2-(3-nitro-[1,2,4]triazol-1-yl)-purin-9-yl]-cyclopentyl}-2-hydroxy-acetamide (intermediate SB), as described for N-{(1S,2R,3S,4R)-4-[2-(4-ainino-pyrazol-1-yl)-6-(2,2-diphenyl-ethylamino)-purin-9-yi]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide (Intermediate QF).

Intermediate SE N-{(1S,2R,3S,4R)-4-[6{[Bis-(4-methoxy-phenylmethyl]-amino}-2-(3-nitro-[1,2,4]triazol-1-yl)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide

[0181] The title compound can be prepared from acetic acid [(1S,2R,3S,4R)-4-(6-{[bis-(4-methoxy-phenylmethyl]-amino}-2-chlor-purin-9-yl)-2,3-dihydroxy-cyclopentylcarbamoyl]-methyl ester (Intermediate RB) and 3-nitro-1,2,4-triazole, as described for N-{(1S,2R,3S,4R)-4-[6-(2,2-diphenyl-ethylamino)-2-(4-nitro-pyrazol-1-yl-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide (Intermediate QD).

Intermediate SF {1-19-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(2-hydroxy-acetylamino)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-1H-imidazol-4-yl}-carbamic acid phenyl ester

[0182] The title compound can be prepared from N-{(1S,2R,3S,4R)-4-[2-(4-amino-imidazol-1-yl)-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide (Intermediate SC), as described for {1-[9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-(2-hydroxy-acetylamino)-cyclopentyl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl]-1H-pyrazol-4-yl}-carbamic acid phenyl ester (Intermediate QH).

Intermediate SG {1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(2-hydroxy-acetylamino)-cyclopentyl)-6-(S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yp-1H-[1,2,4]triazol-3-yl}-carbamic acid phenyl ester

[0183] The title compound can be prepared from N-{(1S,2R,3S,4R)-4-[2-(3-amino-1,2,4)triazol-1-yl)-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide (Intermediate SD), as described for {1-(9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-(2-hydroxy-acetylamino)-cyclopentyl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl]-1H-pyrazol-4-yl}-carbamic acid phenyl ester (Intermediate QH).

Intermediate SH (1-{6-{[Bis-(4-methoxy-phenyl)-methyl]-amino}-9-[(1R,2S,3R,4S)-2,3-dibydroxy-4-(2-hydroxy-acetylamino)-cyclopentyl)-9H-purin-2-yl)-1H-[1,2,41triazol-3-yl)-carbamic acid phenyl ester

[0184] The title compound can be prepared from N-{(1S,2R,3S,4R)-4-[6-{[bis-(4-methoxyphenyl)-methyl]-amino}-2-(3-nitro-[1,2,4]triazol-1-yl)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide (Intermediate SE), as described for {1-[9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-(2-hydroxy-acetylamino)-cyclopentyl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl]-1H-pyrazol-4-yl}-carbamic acid phenyl ester (Intermediate QH).

Intermediate TA (1S,1R,3S,5R)-3-Amino-5-(1-chloro-6-(S)-1-hydroxymethyl-1-phenyl-ethylamino)-purin-9-yl]-cyclopentane-1,2-diol:

Step TA1: {2-Chloro-9-[(1-R,4S)-4-(di-Boc-amino)-cyclopent-2-enyl]-9H-purin-6-yl}-(S)-1 hydroxymethyl-2-phenyl-ethylamino)

[0185] {2-Chloro-9-[(1R,4S-4-(di-Boc-amino)-cyclopent-2-enyl]-9H-purin-6-yl}-((S)-1-hydroxymethyl-2-phenyl-ethyl-amino) is prepared analogously to {2-chloro-9-[(1R,4S)-4-(di-Boc-amino)-cyclopent-2-enyl]-9H-punn-6-yt}-(2,2-diphenyl-ethyl)-amine (Step AAI1) by replacing 2,2-diphenyl ethylamine with (S)-phenylalinol.

Step TA2: (1R,2S,3R,5S)-3-[2-Chloro-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl)-5-(di-Boc-amino)-cyclopentane-1,2-diol

[0186] (1R,2S,3R,5S)-3-[2-Chloro-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-5-(di-Boc-amino)-cyclopentane-1,2-diol is prepared analogously to (1R,2S,3R,5S)-3-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(di-Boc-amino)-cyclopentane-1,2-diol (Step AAI2) by replacing {2-chloro-9-[(1R,4S)-4-(di-Boc-amino)-cyclopent-2-enyl]-9H-purin-6-yl}-(2,2-diphenyl-ethyl)-amine (Step AAI1) with {2-chloro-9-[(1R,4S)-4-(di-Boc-amino)-cyclopent-2-enyl]-9H-purin-6-yl}-((S)-1-hydroxymethyl-2-phenyl-ethylamino) (Step TA1).

Step TA3: (1S,2R,3S,5R)-3-Amino-5-[2-chloro-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-cyclopentane-1,2-diol

[0187] (1S,2R,3S,5R)-3-Amino-5-[2-chloro-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-cyclopentane-1,2-diol is prepared analogously to (1S,2R,3S,5R)-3-amino-5-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-cyclopentane-1,2-diol trifluoroacetate (Step AA13) by replacing 1R,2S,3R,5S)-3-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(di-Boc-amino)-cyctopentanc-1,2-diol (Step AAI2) with (1R,2S,3R,5S)-3-[2-chloro-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-5-(di-Boc-amino)-cyclopentane-1,2-diol (Step TA2).

Intermediate UA ({1S,2R,3S,4R)-4-(2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentylcarbamoyl}-methyl)-carbamic acid benzyl ester

[0188] (1S,2R,3S,5R)-3-Amino-5-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-cyclopentane-1,2-diol trifluoroacetate (Step AAI3) is dissolved in THF. Z-Glycine-N-succinimidyl ester is added and the reaction mixture is stirred at RT over night. The reaction mixture is reduced to yield the title compound.

Intermediate UB ({(1S,2R,3S,4R)-4-(2-Chloro-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentylcarbamoyl}-methyl)-carbamic acid benzyl ester

[0189] ({(1S,2R,3S,4R)-4-[2-Chloro-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentylcarbamoyl}-methyl)-carbamic acid benzyl ester is prepared analogues to ({(1S,2R3S,4R)-4-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentylcarbamoyl}-methyl)-carbamic acid benzyl ester (Intermediate UA) by replacing (1S,2R3S,5R)-3-amino-5-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-cyclopentane-1,2-diol trifluoroacetate (Step AAI3) with (1S,2R,3S,5R)-3-amino-5-[2-chloro-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)purin.9-yl]-cyclopentane-1,2-diol (Intermediate TA).

[0190] These compounds namely,
({(1S,2R,3S,4R)-4-[2-Chloro-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentylcarbamoyl}-methyl)-ethyl-carbamic acid benzyl ester (Intermediate UC),
((S)-1-{(1S,2R,3S,4R)-4-[2-Chloro-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentylcarbamoyl}-2-hydroxy-ethyl)-carbamic acid benzyl ester (Intermediate UD),
((R)-1-{(1S,2R,35,4Rl-4-[2-Chloro-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentylcarbamoyl}-2-hydroxy-ethyl)-carbamic acid benzyl ester (Intermediate UE),
are prepared analogously to ({(1S,2R,3S,4R)-4-[2-chloro-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentylcarbamoyl}-methyl)-carbamic acid benzyl ester (Intermediate UB) by replacing Z-glycine-N-succinimidyl ester with the appropriate succinimidyl ester.

Intermediate VA 3-{(1S,2R,3S,4R-4-[2-Chloro-6-(2,2-diphenyl-ethylamino-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-imidazolidine-2,4-dione

[0191] ({(1S,2R,3S,4R)-4-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentylcarbamoyl}-methyl)-carbamic acid benzyl ester (Intermediate UA) is dissolved in EtOH and purged with argon and Pd/C is added. The reaction mixture is placed under a positive pressure of $H_{2(g)}$ (0.35Barr) at RT over night. The reaction mixture is filtered through celite and reduced *in vacuo.* Intermediate VA is obtained after purification by reverse phase column chromatography (Isolute™ C18, 0-100% acetonitrile in water - 0.1 % TFA).

[0192] These compounds namely,
3-{(1S,2R,3S,4R)-4-[2-Chloro-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-imidazolidine-2,4-dione (Intermediate VB),
3-{(1S,2R,3S,4R)-4-[2-Chloro-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl)-1-ethyl-imidazolidine-2,4-dione (Intermediate VC),
(S)-3-{(1S,2R,3S,4R)-4-[2-Chloro-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-5-hydroxymethyl-imidazolidine-2,4-dione (Intermediate VD),
(R)-3-{(1S,2R,3S,4R)-4-[2-Chloro-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-5-hydroxymethyl-imidazolidine-2,4-dione (Intermediate VE),
are prepared analogously to Intermediate VA by replacing Intermediate UA with the appropriate U Intermediates.

Intermediate VF 3-{(1S,2R,3S,4R)-2,3-Dihydroxy-4-[6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-2-(4-nitro-imidazol-1-yl)-purin-9-yl]-cyclopentyl}-imidazolidine-2,4-dione

[0193] 3-{(1S,2R,3S,4R)-4-[2-Chloro-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-imidazolidine-2,4-dione (Intermediate VB) and 4-nitro-imidazole, as described for N-((1S,2R3S,4R)-4-[6-(2,2-diphenyl-ethylamino)-2-(4-nitro-pyrazol-1-yl)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide (Intermediate QD).

Intermediate VG 3-{(1S,2R,3S,4R)4-[2-(4-Amino-imidazol-1-yl)-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-imidazolidine-2,4-dione

[0194] The title compound can be prepared from 3-{(1S,2R,3S,4R)-2,3-dihydroxy-4-[6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-2-(4-nitro-imidazol-1-yl)-purin-9-yl]-cyclopentyl}-imidazolidine-2,4-dione (Intermediate VF), as described for N-{(1S,2R,3S,4R)-4-[2-(4-amino-pyrazol-1-yl)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl) -2-hydroxy-acetamide (Intermediate QF).

Intermediate WA 9-((1R,4S)-4-Hydroxy-cyclopent-2-enyl)-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purine-2-carboxylic acid methyl ester

[0195] 6-((S)-1-Hydroxymethyl-2-phenyl-ethylamino)-9H-purine-2-carboxylic acid methyl ester (1.05 eq.) is suspended in THF (deoxygenated & dry). NaH (1.05 eq.) is added over 5 minutes and the reaction mixture is stirred at RT over 30 minutes. A solution of acetic acid (1S,3R)-3-hydroxy-cyclopentyl ester (1 eq.), triphenylphosphane (0.15 eq.) and tris (dibenzylideneacetone)dipalladium(0) in THF (deoxygenated & dry) is added to reaction. The reaction mixture is reflux for 6 hours. The reaction mixture is reduce *in vacuo* and columned to give the title compound.

Intermediate WB 9-((1R,4S)-4-Ethoxycarbonyloxy-cyclopent-2-enyl)-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purine-2-carboxylic acid methyl ester

[0196] 9-((1R,4S)4-Hydroxy-cyclopent-2-enyl)-6-((S)-1-hydroxylmethyl-2-phenyl-ethylamino)-9H-purine-2-carboxylic acid methyl ester (Intermediate WA) is dissolved in THF (dry). Pyridine is added and the reaction mixture is cooled to 0˚C. Ethyl chloroformate is added dropwise keeping the temperature below 10˚C. The reaction mixture is warmed to RT and stirred for 2 hours. The reaction mixture is reduced *in vacuo* and portioned between EtOAc and (1 M) $HCl_{(aq)}$. The organics are washed with water, brine, dried ($MgSO_4$) and reduced *in vacuo.* The resulting residue is columned to give the title compound.

Intermediate WC 9-((1R,4S)-4-(Di-Boc-amino)-cyclopent-2-enyl)-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purine-2-carboxylic acid methyl ester

[0197] 9-((1R,4S)-4-Ethoxycarbonyloxy-cyclopent-2-enyl)-6-(S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purine-2-carboxylic acid methyl ester (Intermediate WB) (1 eq.), ditert-butyl iminodicarboxylate (1.1 eq.), triphenylphosphane (0.15 eq.) and TEA are dissolved in THF (deoxygenated & dry). Tris(dibenzylideneacetone)dipalladium$^{(0)}$ (0.05 eq.) is added and the reaction mixture is stirred at 50˚C for I hour. The reaction mixture is removed *in vacuo* and the title compound is obtained by column chromatography.

Intermediate WD 9-((1R,2S,3R,4S)-4-(Di-Boc-amino)-2,3-dihydroxy-cyclopentyl)-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purine-2-carboxylic acid methyl ester

[0198] The title compound is made analogous to (1S,2R,3S,SR)-3-(di-Boc-amino)-5-(2,6-dichloro-purin-9-yl)-cyclopentane-1,2-diol (Step AA4), by replacing di-Boc-[(1S,4R)-4-(2,6-dichloro-purin-9-yl)-cyclopent-2-enyl]-amine (Step AA3) with 9-((1R,4S)-4-(di-Boc-amino)-cyclopent-2-enyl)-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purine-2-carboxylic acid methyl ester (Intermediate WC).

Intermediate WE 9-((1R,2S,3R,4S}-4-Amino-2,3-dihydroxy-cyclopentyl)-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purine-2-carboxylic acid methyl ester

[0199] The title compound is made analogous to (1S,2R,3S,5R)-3-amino-5-(2,6-dichloropurin-9-yl)-cyclopentane-1,2-diol trifluoroacetate (Step AA5), by replacing (1S,2R,3S,SR)-3-(di-Boc-amino)-5-(2,6-dichtoro-purin-9-yl)-cyclopentane-1,2-diol with 9-((1R,2S,3R,4S)-4-(di-Boc-amino)-2,3-dihydroxy-cyctopentyl)-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purine-2-carboxylic acid methyl ester (Intermediate WD).

Intermediate WF 9-[(1R,2S,3R,4S)-4-(2-Acetoxy-acetylamino)-2,3-dihydroxy-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino-9H-purine-2-carboxylic acid methyl ester

[0200] The title compound is made analogous to N-{(1S,2R,3S,4R)-4-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide (Step AAI4), by replacing (1S,2R,3S,5R)-3-amino-5-[2-chloro-6(2,2-diphenyl-ethylamino)-purin-9-yl]-cyclopentane-1,2-diol trifluoroacetate with 9-((1R,2S,3R,4S)-4-amino-2,3-dihydroxy-cyclopentyl)-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purine-2-carboxylic acid methyl ester (Intermediate WE) and replacing propionyl chloride with acetoxyacteyl chloride.

Intermediate WG 9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(2-hydroxy-acetylamino)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purine-2-carboxylic acid (2-amino-ethyl)-amide

[0201] 9-[(1R,2S,3R,4S)-4-(2-Acetoxy-acetylamino)-2,3-dihydroxy-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purine-2-carboxylic acid methyl ester (Intermediate WF) is dissolved in ethylenediamine (>10 eq.). The

reaction mixture is stirred at 90˚C for 1 hour. The reaction mixture is cooled and reduced in *vacuo.* The title compound is obtained by column chromatography.

Intermediate XA (3-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(2-hydroxy-acetylamino)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino-9H-purin-2-yl]-prop-2-ynyl}-carbamic acid tert-butyl ester

[0202] N-{(1S,2R,3S,4R)-4-[6-((S)-1-Benzyl-2-hydroxy-ethylamino)-2-chloro-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide (Intermediate GC) (1 eq.), prop-2-ynylcarbamic acid tert-butyl ester (10 eq.), CuI (0.25 eq.), bis (triphenylphosphine)-palladium (II)chloride (0.25 eq.) and triphenylphosphine (0.5 eq.) are dissolved in diethylamine and DMF. The reaction mixture is heated in a microwave for 1 hour at 120˚C. The title compound is obtained by column chromatography.

Intermediate XB 4-{3-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(2-hydroxy-acetylamino)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-prop-2-ynyl}-piperidine-1-carboxylic acid tert-butyl ester

[0203] The title compound is made analogously to {3-[9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-(2-hydroxy-acetylaminopcy-clopentyl]-6((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-prop-2-ynyl}-carbamic acid tert-butyl ester (Intermediate XA), by replacing prop-2-ynyl-carbamic acid tert-butyl ester with 4-prop-2-ynyl-piperidine-1-carboxylic acid tert-butyl ester.

Intermediate XC ((R)-1-{3-19-1(1R,2S,3R,4S)-2,3-Dihydroxy-4-(2-hydroxy-acetylamino)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl-prop-2-ynyl}-pyrrolidin-3-yl)-carbamic acid tert-butyl ester

[0204] The title compound is made analogously to {3-[9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-(2-hydroxy-acetylamino)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-prop-2-ynyl}-carbamic acid tert-butyl ester (Intermediate XA), by replacing prop-2-ynyl-carbamic acid tert-butyl ester with ((R)-1-But-2-ynyl-pyrrolidin-3-yl)-carbamic acid tert-butyl ester.

Intermediate YA N-{(1S,2R,3S,4R)-4-[2-(3-Amino-prop-1-ynyl)-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl)-2-hydroxy-acetamide

[0205] {3-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(2-hydroxy-acetylamino)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-prop-2-ynyl)-carbamic acid tert-butyl ester (Intermediate XA) is dissolved in 1.25 M HCl in MeOH. After stirring at RT for 3 days, the solvent is removed *in vacuo* to yield the title compound. This is used in the next step without further purification.

Intermediate YB N-{(1S,2R,3S,4R)-2,3-Dihydroxy-4-[6-(S)-1-hydroxymethyl-2-phenyl-ethylamino)-2-(3-piperidin-4-yl-prop-1-ynyl)-purin-9-yl]-cyclopentyl}-2-hydroxy-acetamide

[0206] 4-{3-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(2-hydroxy-acetylamino)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethyl amino)-9H-purin-2-yl]-prop-2-ynyl}-piperidine-1-carboxylic acid tert-butyl ester (Intermediate XB) is dissolved in 1.25 M HCl in MeOH. After stirring at RT for 3 days, the solvent is removed *in vacuo* to yield the title compound. This is used in the next step without further purification.

Intermediate YC N-{(1S,2R,3S,4R)-4-(2-(3-(R)-3-Amino-pyrrolidin-1-yl)-prop-1-ynyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide

[0207] ((R)-1-(3-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(2-hydroxy-acetylamino)-cyclopentyl]-6-((S)-1-hydroxymethyl)-2-phenyl-ethylarmino)-9H-pufin-2-yl]-prop-2-ynyl}-pyrrolidin-3-yl)-carbamic acid tert-butyl ester (Intermediate XC) is dissolved in 1.25 M HCl in MeOH. After stirring at RT for 3 days, the solvent is removed *in vacuo* to yield the title compound. This is used in the next step without further purification.

Intermediate ZA (2-{[9-[(1S,3R,4S)-2,3-Dihydroxy-4-(2-hydroxy-acetylamino)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purine-2-carbonyl]-amino}-ethyl)-carbamic acid phenyl ester

[0208] The title compound can be prepared from 9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-(2-hydroxy-acetylamino)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purine-2-carboxylic acid (2-amino-ethyl)-amide (Intermedi-

ate WG), as described for {1-[9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-(2-hydroxy-acetylamino)-cyclopentyl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl]-1H-pyrazol-4-yl}-carbamic acid phenyl ester (Intermediate QH).

Intermediate ZB {3-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(2-hydroxy-acetylamino)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-prop-2-ynyl}-carbamic acid phenyl ester

[0209] The title compound can be prepared from N-{(1S,2R,3S,4R)-4-[2-(3-amino-prop-1-ynyl)-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide (Intermediate YA), as described for (1-[9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-(2-hydroxy-acetylamino)-cyclopentyl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl]-1H-pyrazol-4-yl}-carbamic acid phenyl ester (Intermediate QH).

Intermediate ZC 4-{3-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(2-hydroxy-acetylamino)-cyclopentyl-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-prop-2-ynyl}-piperidine-1-carboxylic acid phenyl ester

[0210] The title compound can be prepared from N-{(1S,2R,3S,4R)-2,3-dihydroxy-4-[6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-2-(3-piperidin-4-yl-prop-1-ynyl)-purin-9-yl]-cyclopentyl}-2-hydroxy-acetamide (Intermediate YB), as described for {1-[9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-(2-hydroxy-acetylamino)-cyclopentyl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl]-1H-pyrazol-4-yl}-carbamic acid phenyl ester (Intermediate QH).

Intermediate ZD ((R)-1-{3-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(2-hydroxy-acetylamino)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-prop-2-ynyl)-pyrrolidin-3-yl)-carbamic acid phenyl ester

[0211] The title compound can be prepared from N-{(1S,2R,3S,4R)-4-[2-[3-((R)-3-amino-pyrrolidin-1-yl)-prop-1-ynyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide (Intermediate YC), as described for {1-[9-[(1R,25,3R,4S)-2,3-dihydroxy-4-(2-hydroxy-acetylaminoycyciopentyl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl]-1H-pyrazol-4-yl}-carbamic acid phenyl ester (Intermediate QH).

Intermediate ZE {1-[9-[(1R,2S,3R,4S)-4-(2,5-Dioxo-imidazolidin-1-yl)-2,3-dihydroxy-cyclopentyl]-6-((S)-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-1H-imidazol-4-yl}-carbamic acid phenyl ester

[0212] The title compound can be prepared from 3-{(1S,2R,3S,4R)-4-[2-(4-amino-imidazol-1-yl)-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-imidazolidine-2,4-dione (Intermediate VG), as described for {1-[9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-(2-hydroxy-acetylamino)-cyclopentyl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yt]-1H-pyrazol-4-yl}-carbamic acid phenyl ester (Intermediate QH).

Intermediate ZF N-{(1S,2R,3S,4R)-4-(2-((R)-3-Amino-pyrrolidin-1-yl}-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide trifluroacetate

Step1: 2-Benzyloxy-N-{(1S,2R,3S,4R)-4-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-acetamide

[0213] The title compound is prepared analogously to N-{(1S,2R,35,4R)-4-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide (Intermediate AA) by replacing cyclopropanecarboxylic acid propionyl chloride with benzyloxy-acetyl chloride.

Step 2: N-{(1S,2R,3S,4R)-4-[2-((R)-3-Amino-pyrrolidin-1-yl)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-benzyloxy-acetamide trifluoroacetate

[0214] A solution of 2-benzyloxy-N-{(1S,2R,3S,4R)-4-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-acetamide (80 mg, 0.13 mmol) in NMP:MeCN (1 mL of a 1:1 mixture) is treated with sodium iodide (6 mg, 0.04 mmol) followed by (3R)-3-aminopyrrolidine (34 mg, 0.4 mmol). The reaction mixture is heated using microwave radiation in a Personal Chemistry Emrys™ Optimizer microwave reactor at 200˚C. The reaction is shown to be complete by LCMS after 30 minutes. The title compound is obtained after purification by reverse phase column chromatography (Isolute™ C18, 0-100% acetonitrile in water- 0.1% TFA).

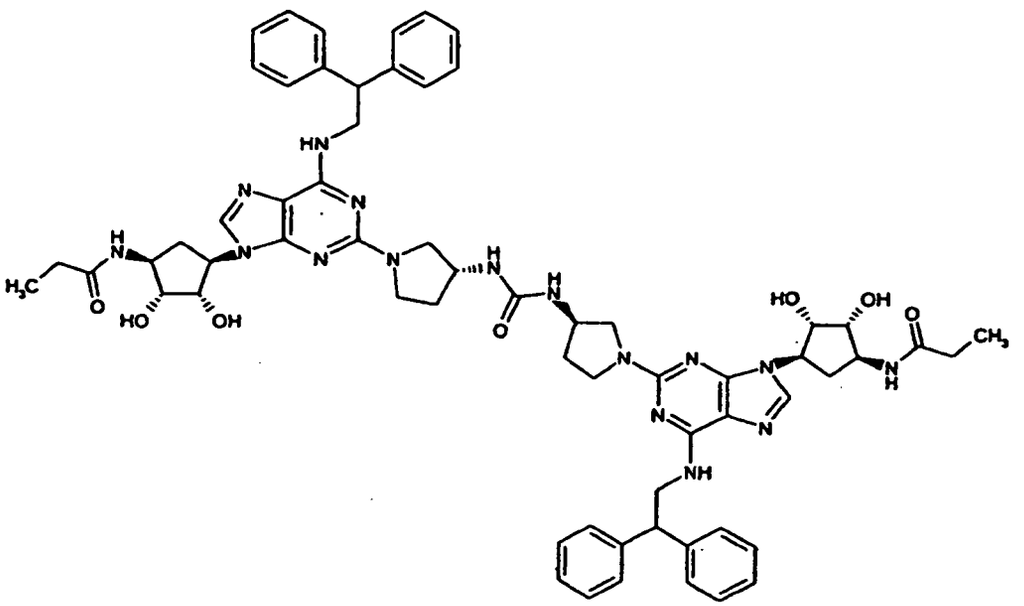
Step 3: N-{(1S,2R,3S,4R}-4-[2-((R)-3-Amino-pyrrolidin-1-yl)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide trifluroacetate

[0215] A solution of N-{(1S,2R,3S,4R}-4-[2-((R)-3-amino-pyrrolidin-1-yl)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-benzyloxy-acetamide trifluoroacetate (0.022 g, 0.03 mmol) in ethanol (2 mL) under an atmosphere of argon is treated with palladium hydroxide on carbon (0.05 g, 20%w/w carbon). The reaction mixture is placed under an atmosphere of hydrogen and stirred at RT for 30 hours and then filtered through celite™. The filtrate is concentrated *in vacuo* and purification of the crude by reverse phase column chromatography (Isolute™ C18, 0-100% acetonitrile in water-0.1% TFA) yields the title product.

Preparation of Specific Examples:

Example 1

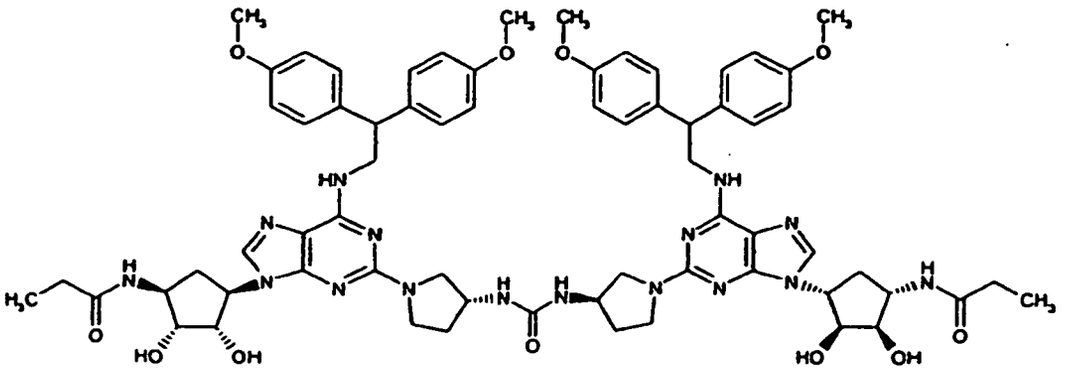
[0216]



[0217] A solution comprising N-{(1S,2R3S,4R)-4-[2-chioro-6-(2,2-diphenyl-ethylaminol)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide (Intermediate AA) (0.25 g, 0.48 mmol) and 1,3-di(R)-pyrrolidin-3-yl-urea (Intermediate C) (0.105 g, 0.53 mmol) in DMSO (0.4 mL) is heated at 110˚C for 3 hours. Purification of the product by reverse phase column chromatography (Isolute™ C18, 0-100% acetonitrile in water - 0.1% TFA) yields Example 1 and N-((1S,2R,3S,4R)-4-{6-(2,2- diphenyl- ethylamino)- 2-[(R)- 3-((R)- 3- pyrrolidin- 3- ylureido)-pyrrolidin- 1- yl]-purin- 9- yl} 2,3- dihydroxy- cyclopentyl)-propionamide.

Example 2

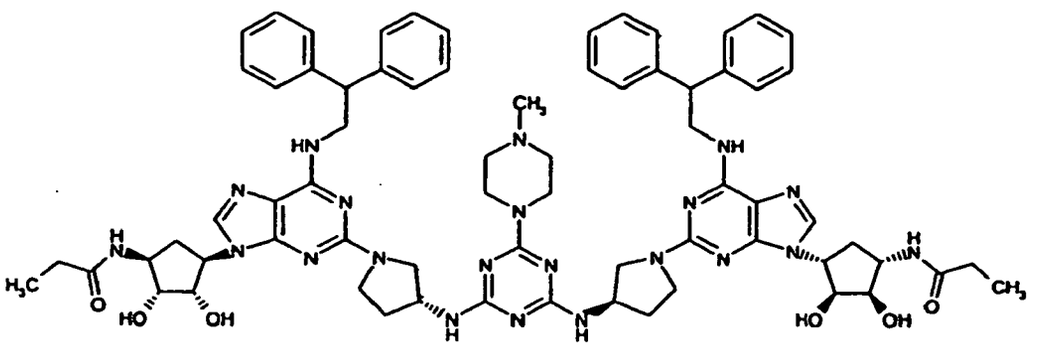
[0218]



[0219] Example 2 is prepared analogously to Example 1 by replacing N-{(1S,2R,3S,4R)-4-(2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide (Intermediate AA) with N-((1S,2R,3S,4R)-4-{6-[2,2-bis-(4-methoxy-phenyl)-ethylamino]-2-chloro-purin-9-yl}-2,3-dihydroxy-cyclopentyl)-propionamide trifluoroacetate (Intermediate AG).

Example 3

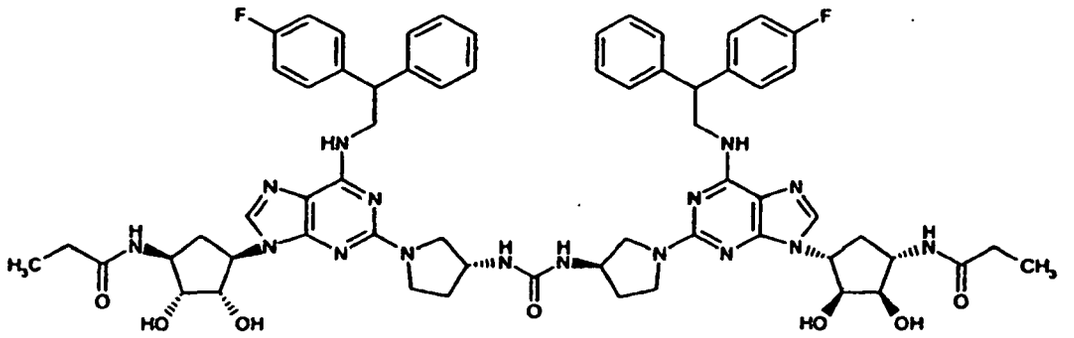
[0220]



[0221] Example 3 is prepared analogously to Example 1 by replacing 1,3-di-(R)-pyrrolidin-3-yl-urea (Intermediate C) with 6-(4-methyl-piperazul-1-yl)-N,N'-di-R-pyrrolidin-3-yl-[1,3,5]triazine-2,4-diamine trifluoroacetate (Intermediate D).

Example 4

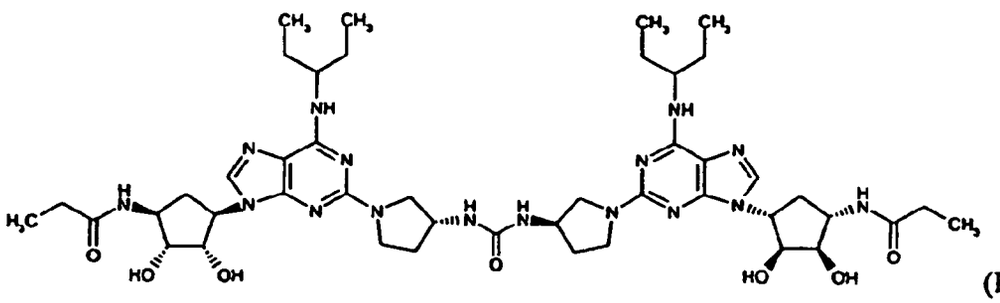
[0222]



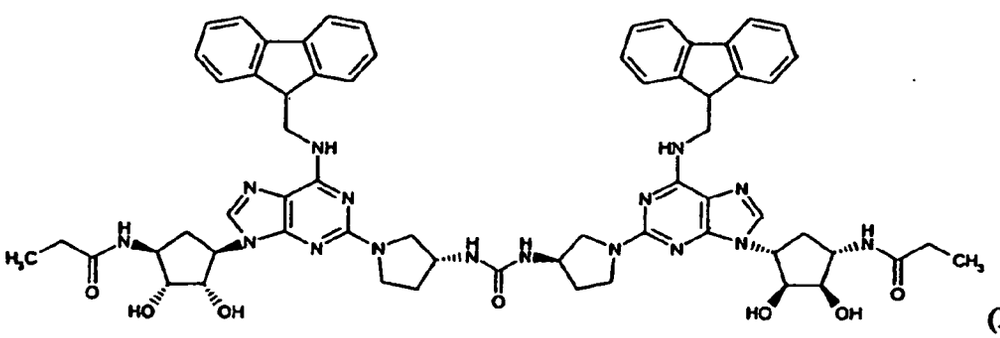
[0223] A reaction mixture comprising N-((1S,2R,3S,4R)-4-{2-chloro-6-[2-(4-fluoro-phenyl)-2-phenyl-ethylamino]-purin-9-yl}-2,3-dihydroxy-cyclopentyl)-propionamide trifluoroacetate (Intermediate AD) (50 mg, 0.08 mmol), 1,3-di-(R)-pyrrolidin-3-yl-urea (Intermediate C) (16 mg, 0.08 mmol), sodium hydrogen carbonate (7 mg, 0.08 mmol) in DMSO (0.1 mL) is heated at 100˚C over night. Purification of the product by reverse phase column chromatography (Isolute™ C18, 0-100% acetonitrile in water-0.1% TFA) yields Example 4.

Examples 5-10

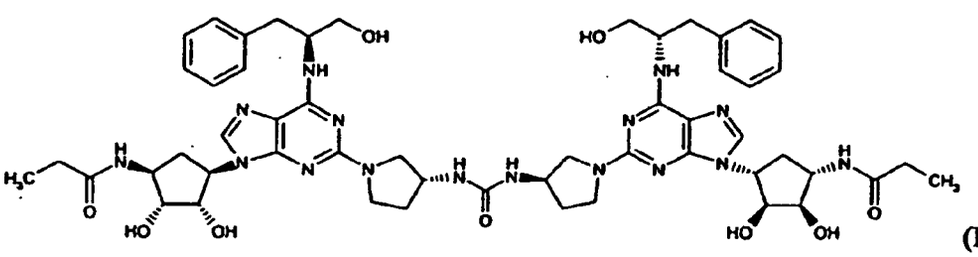
[0224] These compounds,



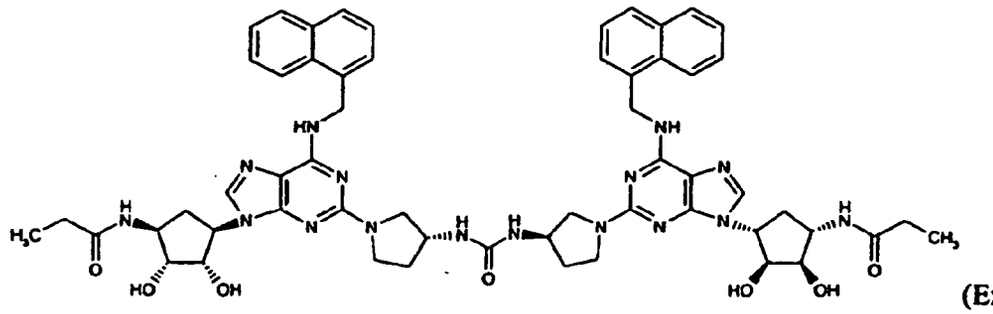
(Example 5),



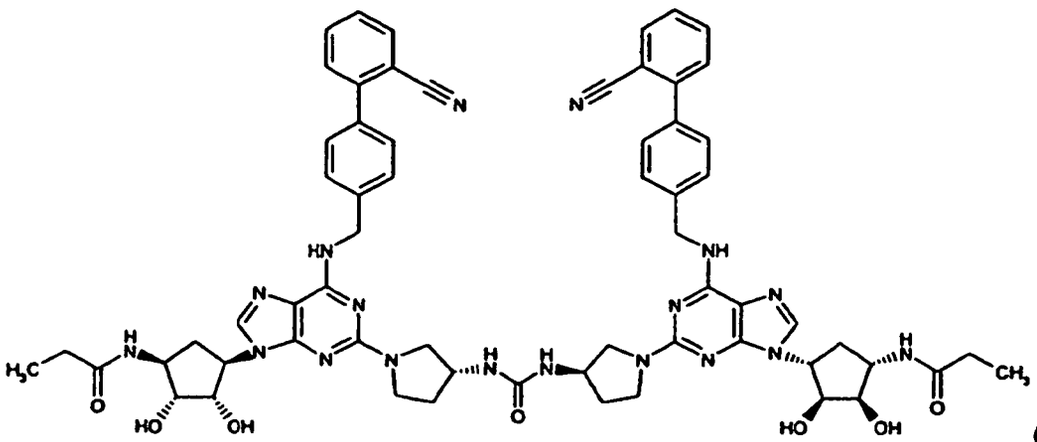
(Example 6),



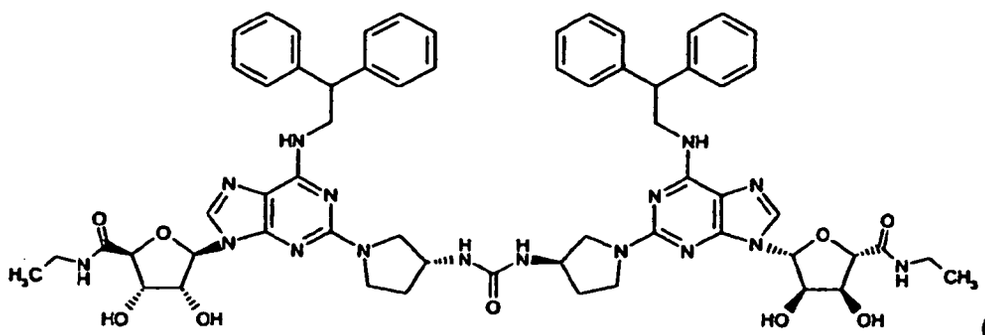
(Example 7),



(Example 8),



(Example 9),

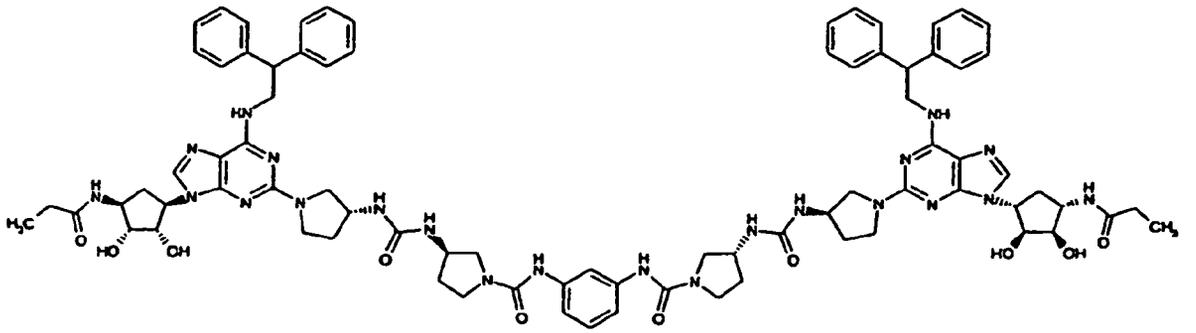


(Example 10),

are prepared analogously to Example 4 by replacing N-((1S,2R,3S,4R)-4-{2-chloro-6-[2-(4-fluoro-phenyl)-2-phenyl-ethylamino]-purin-9-yl}-2,3-dihydroxy-cyclopentyl)-propionamide trifluoroacetate (Intermediate AD) with the appropriate intermediate the preparations of which are described herein.

Example 11

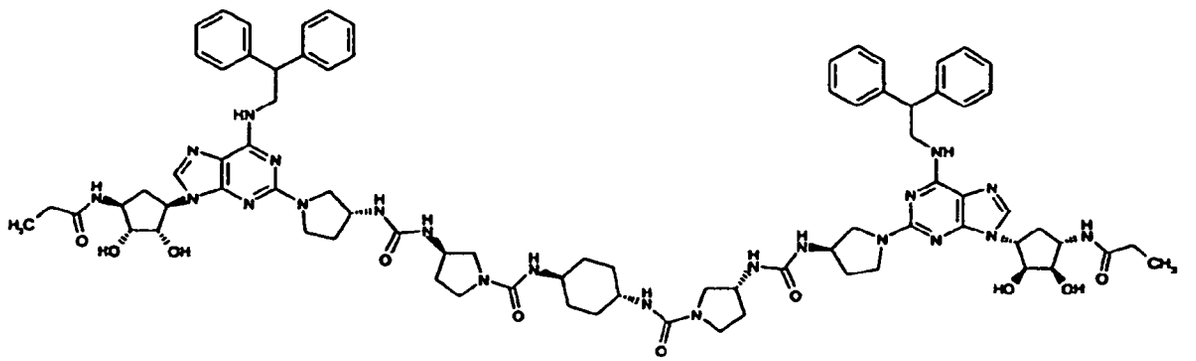
[0225]



[0226] A solution comprising N-((1S,2R,3S,4R)-4-{6-(2,2-diphenyl-ethylamino)-2-[(R)-3-((R)-3-pyrrolidin-3-ylureido)-pyrrolidin-1-yl]-purin-9-yl}-2,3-dihydroxy-cyclopentyl)-propionamide (10 mg, 14.5 μmol) in NMP (0.3 mL) is treated with a solution of 1,3-phenylenediisocyanate (1.2 mg, 7.3 μmol) in NMP (0.2 mL). After 1 hour at RT, the product is purified by reverse phase column chromatography (Isolute™ C18, 0-100% acetonitrile in water- 0.1% TFA) to yield Example 11.

Example 12

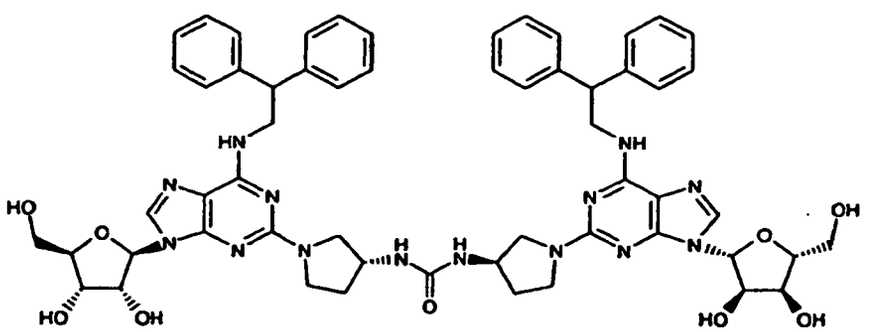
[0227]



[0228] Example 12 is prepared analogously to Example 11 by replacing 1,3-phenylenediisocyanate with trans-1,4-cyclohexylenediisocyanate.

Example 13

[0229]

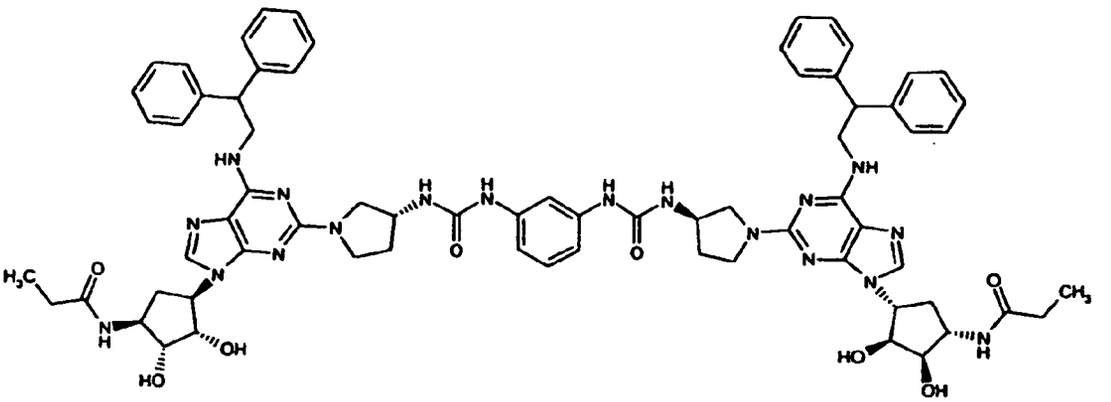


[0230] To a stirred solution of (2R,3R,4S,SR)-2-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-ydroxymethyl-tet-

rahydro-furan-3,4-diol (Intermediate BA) (0.05 g, 0.1 mmol) and sodium iodide (0.016 g, 0.1 mmol) in acetonitrile: NMP (1.0 mL of a 1:1 solution) is added 1,3-di-(R)-pyrrolidin-3-yl-ure (Intermediate C) (0.041 g, 0.2 mmol) and DIPEA (0.05 ml, 0.26 mmol). The reaction mixture is heated to 160˚C for 30 minutes in a microwave. Purification by reverse phase column chromatography (Isolute™ C18, 0-100% acetonitrile in water - 0.1% TFA) affords Example 13 and 1-{(5)-1-[9-((2R3R,4S,5R)-3,4-dihydroxy-5-hydroxymethyl-tetrahydro-furan-2-yl)-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-3-(R)-pyrrolidin-3-yl-urea trifluoroacetate.

Example 14

[0231]



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

[0232] A reaction mixture comprising N-{(1S,2R,3S,4R)-4-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide (Intermediate AA) (2.5 g, 4.80 mmol) and (3R)-(+)-(3-Boc-amino)pyrrolidine (2.5 g, 13.6 mmol) in DMSO (8 mL) is heated at 100˚C over night. Purification of the product by reverse phase column chromatography (Isolute™ C18, 0-20% acetonitrile in water - 0.1% TFA) yields the title compound.

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

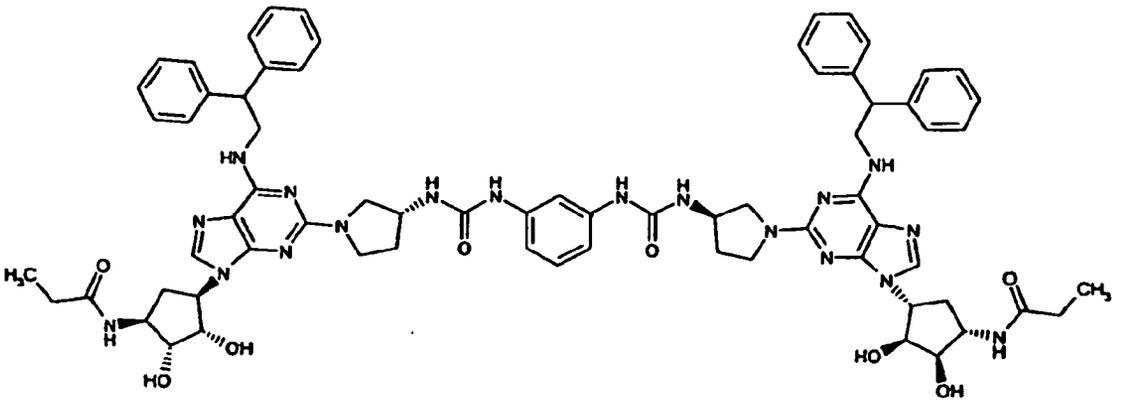
[0233] {(R)-1-[9-((1R,2S,3R,4S)-2,3-Dihydroxy-4-propionylamino-cyclopentyl)-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-carbamic acid tert-butyl ester (ca 4.80 mmol) is dissolved in 1.25 M HCl in MeOH (60 mL). After stirring at RT for 3 days, the solvent is removed *in vacuo* to yield the title compound as a brown solid. This is used in the next step without further purification.

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

[0234] N-{(1S,2R,3S,4R)-4-[2-((R)-3-Amino-pyrrolidin-1-yl)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide dihydrochloride (ca. 7.7 mmol) is dissolved in minimal volume of a mixture of ethanol/saturated aqueous sodium carbonate solution until the pH of the solution is adjusted to pH 7 (ensuring the compound remains in solution). The solution is loaded onto an Isolute™ C18 column and washed through firstly with water and then MeOH. The fractions are combined and concentrated *in vacuo* and then further purified by repeating the above process to afford the title compound. LCMS (electrospray): m/z [MH^+] 571

Step 4:

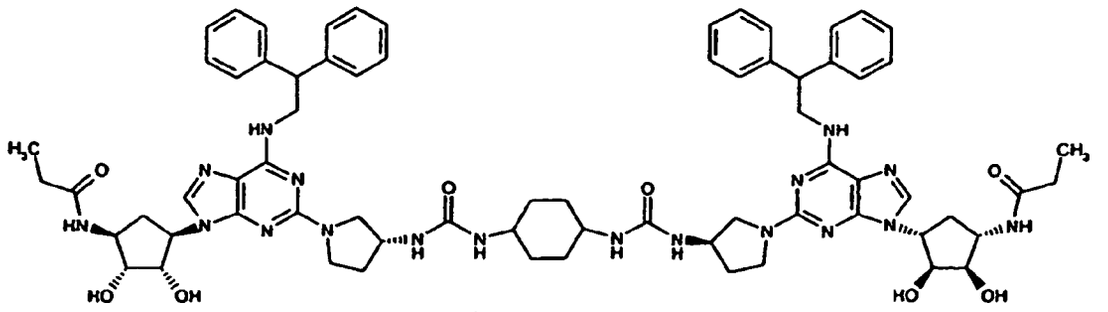
[0235]



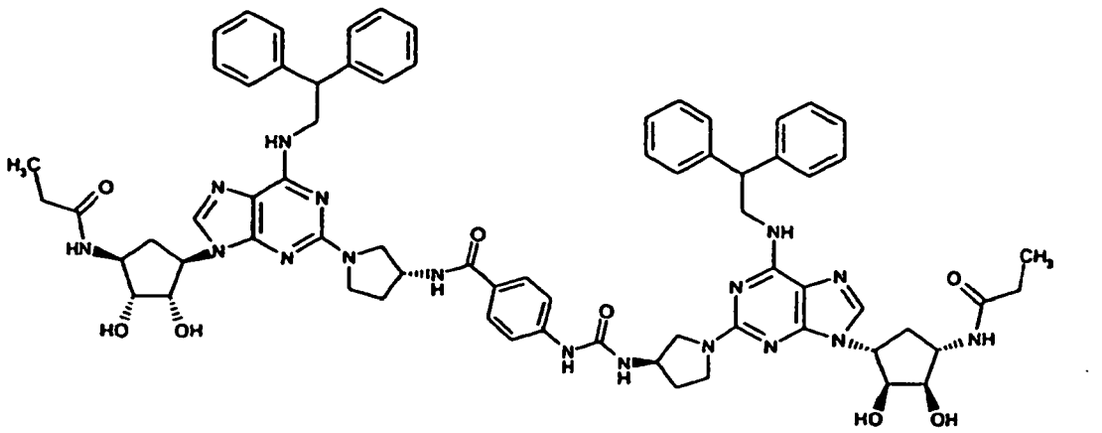
[0236] A solution comprising N-{(1S,2R,3S,4R)-4-(2-((R)-3-amino-pynrolidin-1-yl)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide (10 mg, 17.5 μmol) in dry THF (0.3 mL) is treated with 1,3-diisocyanatobenzene (1.4 mg, 8.8 μmlol) and stirred at RT for 3 days. Purification of the product by reverse phase column chromatography (Isolute™ C18, 0-100% acetonitrile in water - 0.1 % TFA) affords Example 14.

Examples 15 and 16

[0237] These compounds,



(Example 15) and

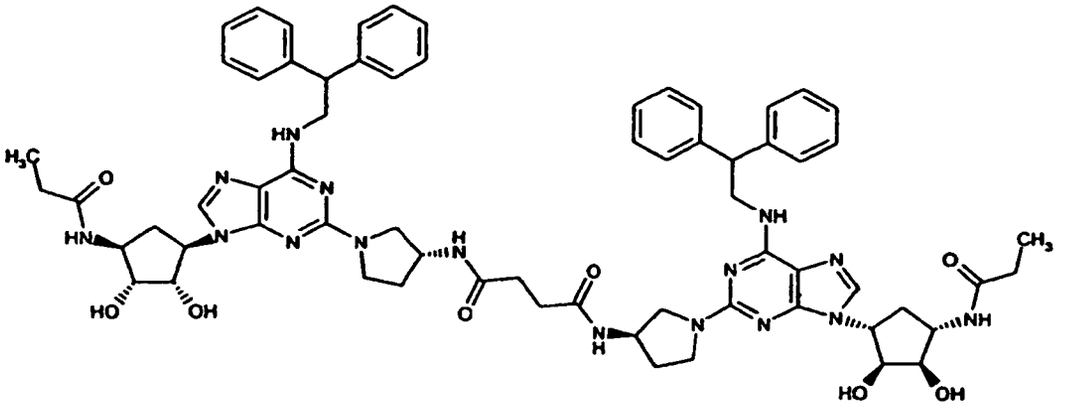


(Example 16),

are prepared analogously to Example 14 by replacing 1,3-diisocyanatobenzene with the appropriate acid chloride/ isocyanate.

Example 17

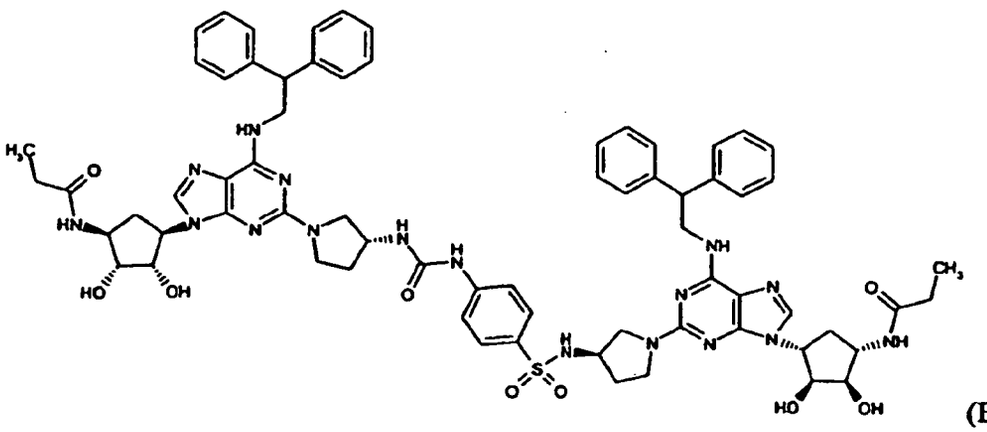
[0238]



[0239] To a solution of {(1S,2R,3S,4R)-4-[2-((R)-3-amino-pyrrolidinl-yl)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide (10 mg, 17.5 μmol) and TEA (7 mg, 0.07 mmol) in dry THF (0.3 mL) is added butanedioyl chloride (1.93 μL, 0.018 mmol) and the reaction mixture is allowed to stand at RT for 18 hours. The solvent is removed *in vacuo* and purification of the crude product by reverse phase column chromatography (Isolute™ C18, 0-100% acetonitrile in water- 0.1% TFA) affords Example 17.

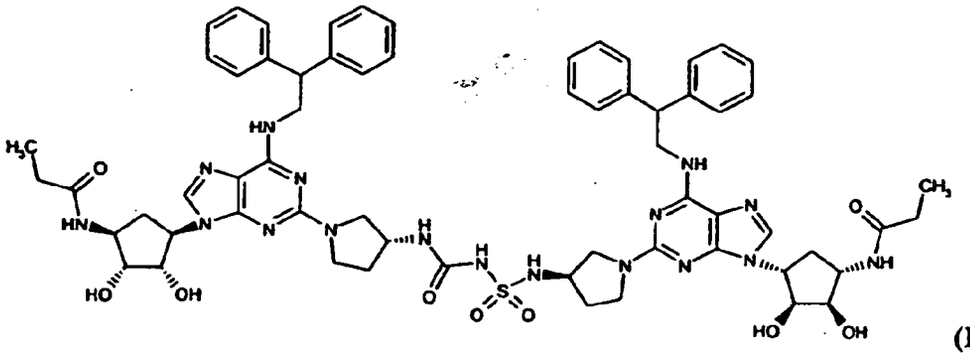
Examples 18 and 19

[0240] These compounds,



(Example 18)

and

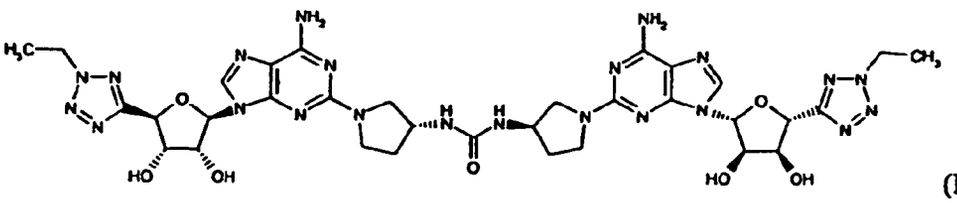


(Example 19),

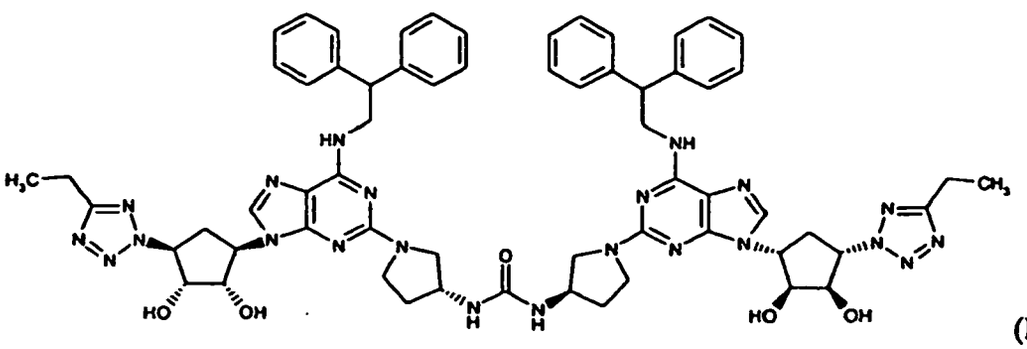
are prepared analogously to Example 17 by replacing butanedioyl chloride with the appropriate sulphonyl chloride isocyanate.

Examples 20 and 23

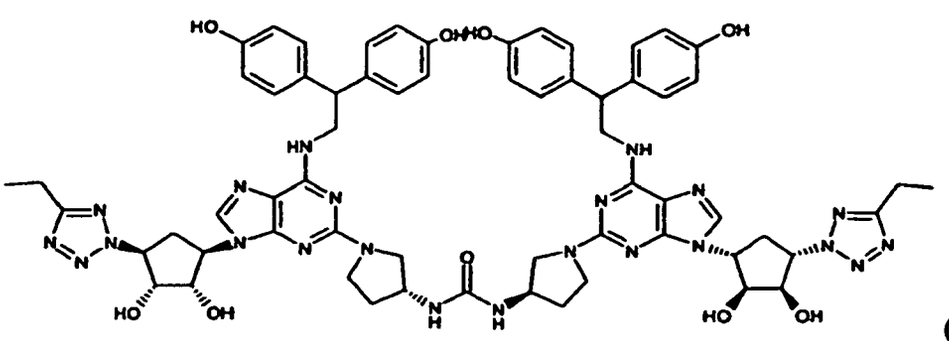
[0241] These compounds,



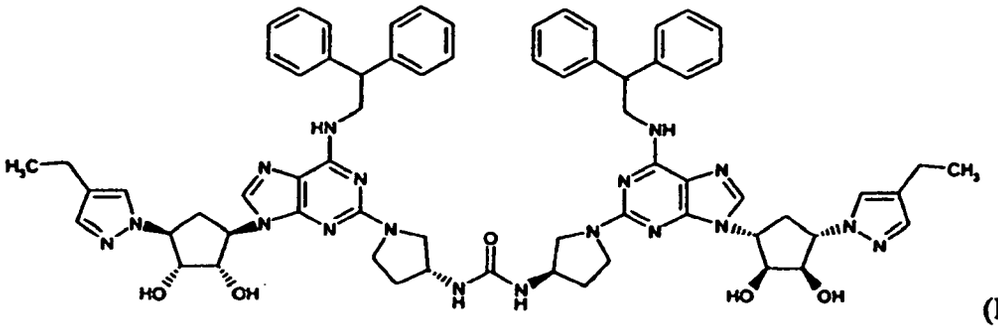
(Example 20),



(Example 21),



(Example 22) and

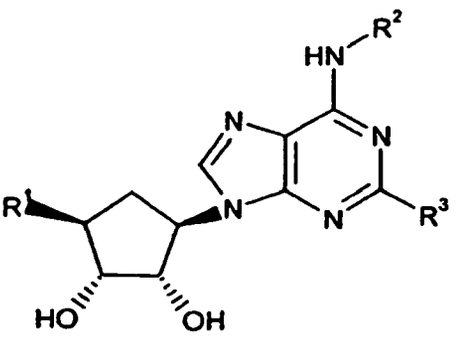


(Example 23),

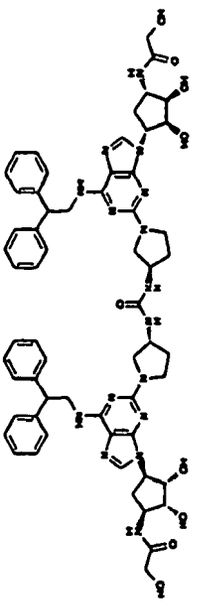
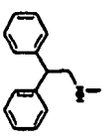
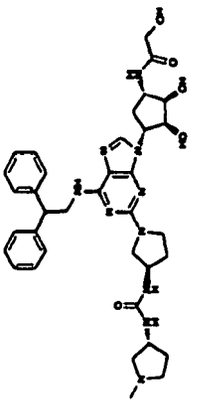
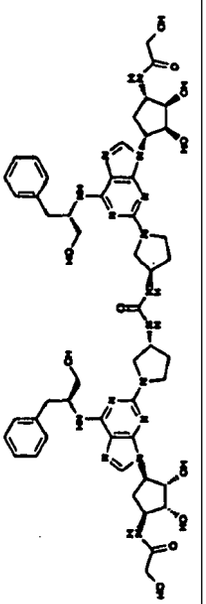
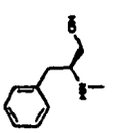
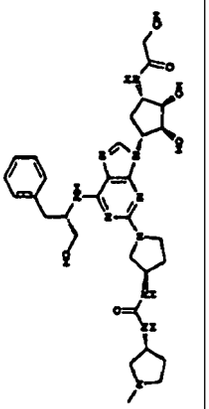
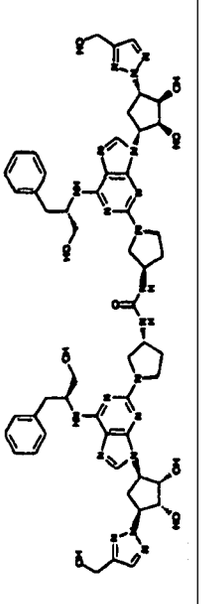
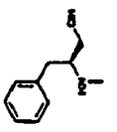
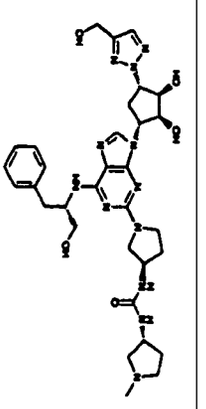
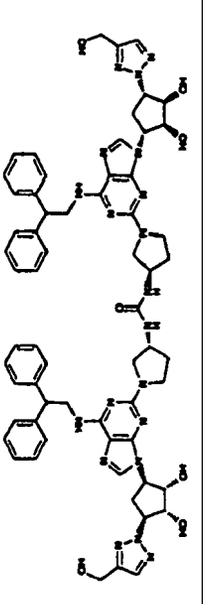
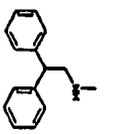
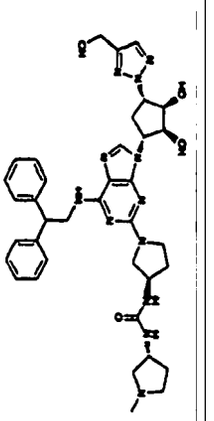
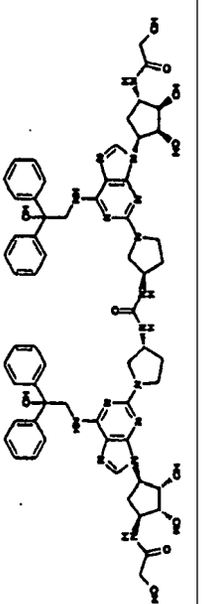
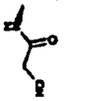
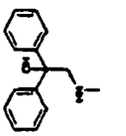
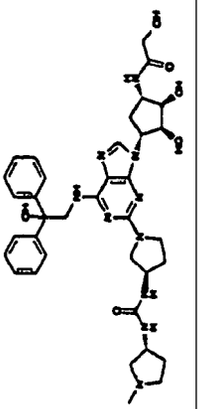
are prepared analogously to Example 1 by replacing N-{(1S,2R,3S,4R)-4-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide (Intermediate A) with the appropriate intermediate, the preparations of which are described herein.

Examples 181-186

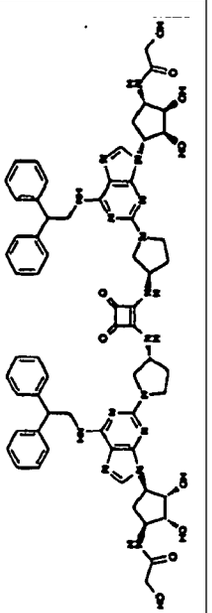
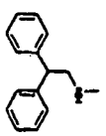
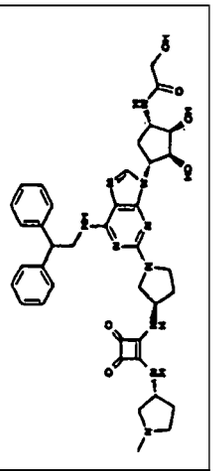
[0242] Compounds of formula (X3) are shown in the following table. Methods of preparing such compounds are described hereinafter.



(X3)

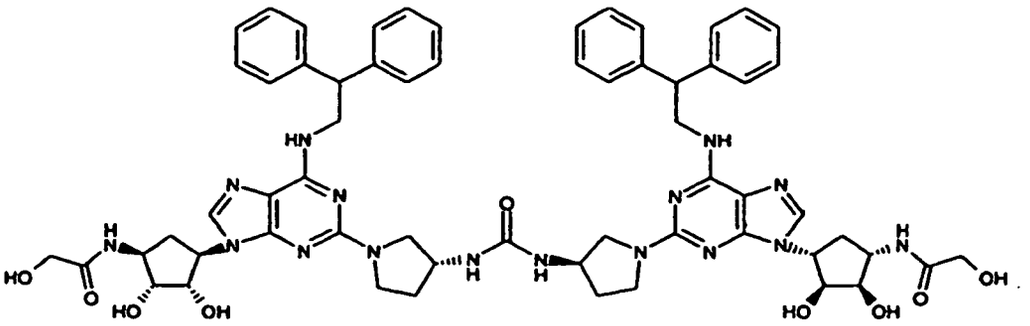
Ex	Structure	R^1	R^2	R^3
181				
182				
183				
184				
185				

(continued)

Ex	Structure	R^1	R^2	R^3
186				

Example 181

[0243]



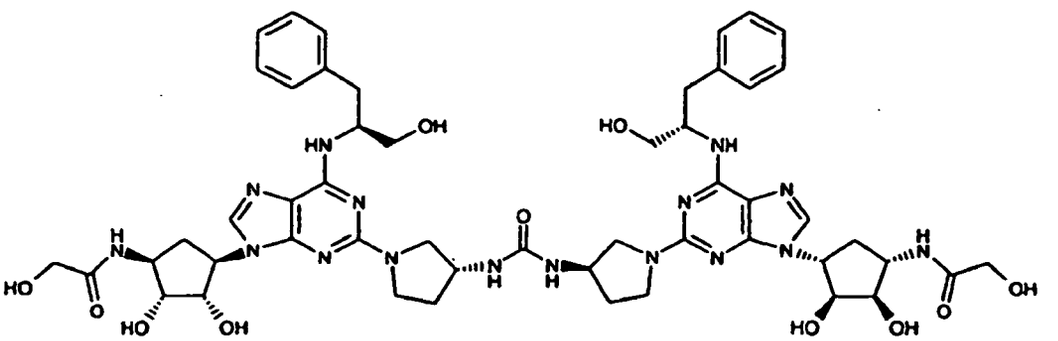
[0244] A solution of N-{(1S,2R,3S,4R)-4-[2-((R)-3-amino-pyrrolidin-1-yl)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide trifluroacetate (Intermediate ZF) (150 mg, 0.26 mmol) in NMP (3 mL) is treated with TEA (139 μL, 1 mmol) followed by phenyl chloroformate (45 mg, 0.29 mmol). The resulting mixture is stirred at RT for 20 minutes and then treated with N-{(1S,2R,3S,4R)-4-[2-((R)-3-amino-pyrrolidin-1-yl)-6-(2,2-diphenyl-ethyl-amino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl)-2-hydroxy-acetamide trifluroacetate (Intermediate ZF) (150 mg, 0.26 mmol). After heating at 100˚C over night, the mixture is treated with EtOH (10 mL) and the resulting precipitate is collected by filtration. Purification of this solid by reverse phase column chromatography (Isolute™ C18, 0-100% acetonitrile in water- 0.3% NH_3) affords the desired product as a solid. $[M/2]H^+$ 586.43

[0245] Examples 181-186 can be prepared analogously to Example 4 by replacing N-((1S,2R,3S,4R)-4-{2-chloro-6-[2-(4-fluoro-phenyl-2-phenyl-ethylamino]-purin-9-yl}-2,3-dihydroxy-cyclopentyl)-propionamide trifluoroacetate (Intermediate AD) with the appropriate Intermediate the preparations of which are described herein.

[0246] For example:

Example 182

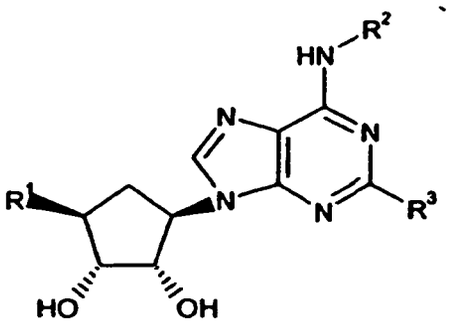
[0247]



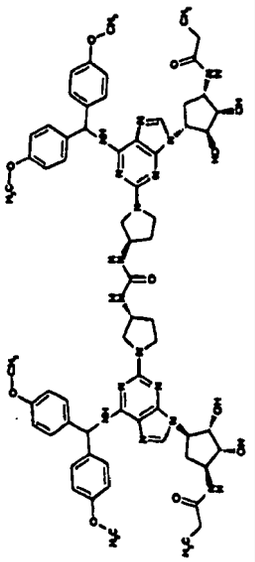
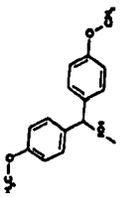
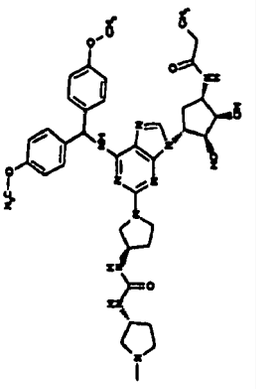
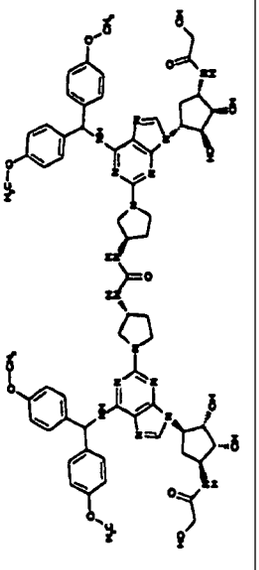
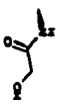
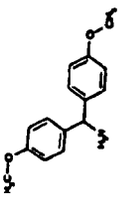
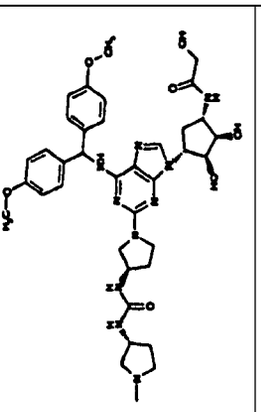
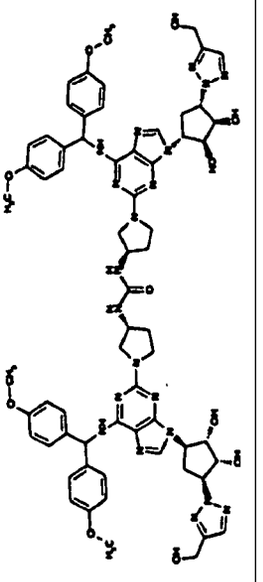
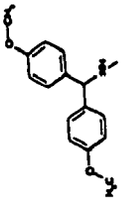
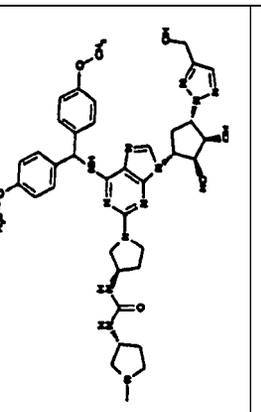
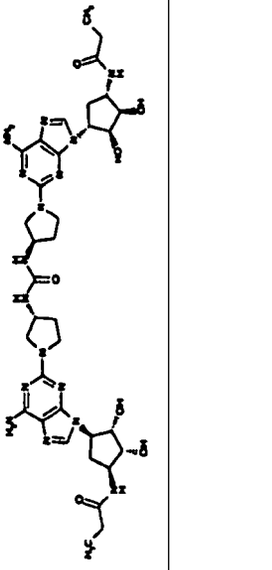
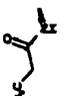
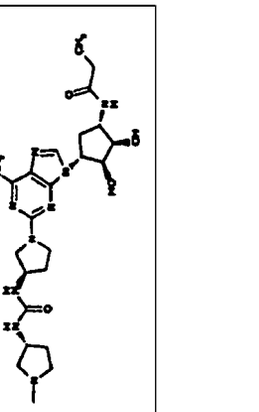
[0248] This compound is prepared analogously to Example 4 by replacing N-((1S,2R,3S,4R)-4-{2-chloro-6-[2-(4-fluoro-phenyl)-2-phenyl-ethylamino]-purin-9-yl}-2,3-dihydroxy-cyclopentyl)-propionamide trifluoroacetate(Intermediate AD) with N-{(1S,2R,3S,4R)-4-[6-((S)-1-benzyl-2-hydroxy-ethylamino)-2-chloro-punrin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-hydroxy-acetamide (Intermediate GC). $[M/2]H^+$ 540.49

Examples 191-204

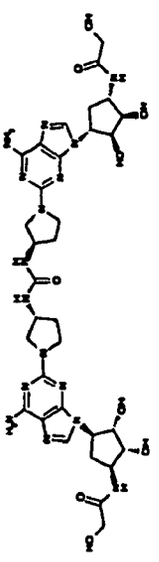
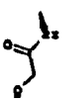
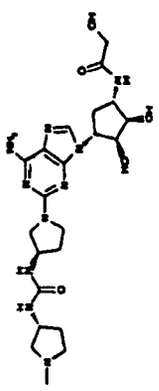
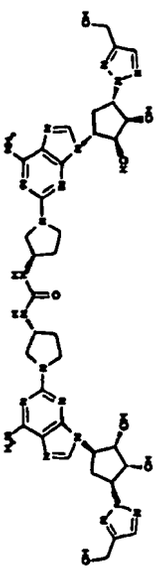
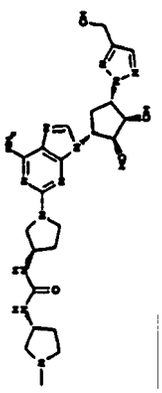
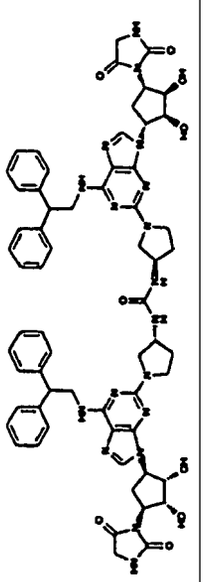
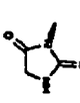
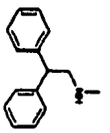
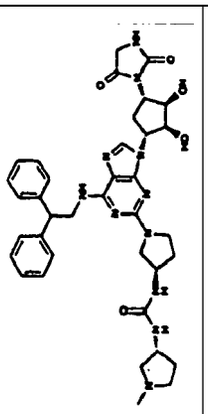
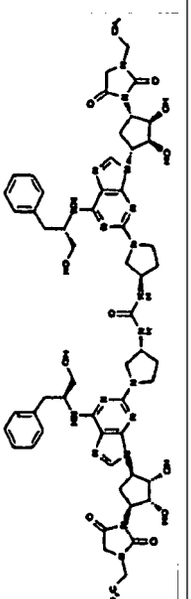
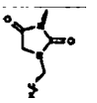
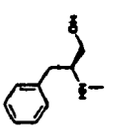
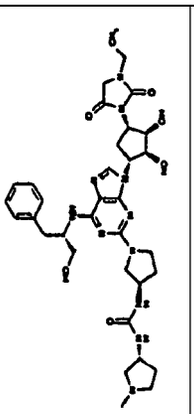
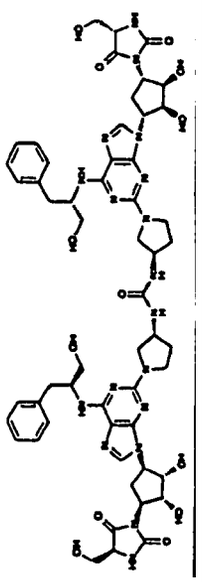
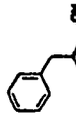
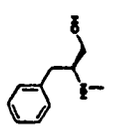
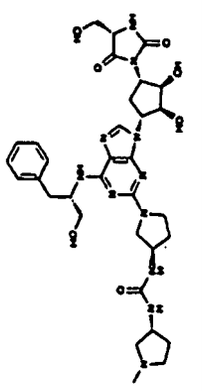
[0249] Compounds of formula (X4) are shown in the following table. Methods of preparing such compounds are described hereinafter.



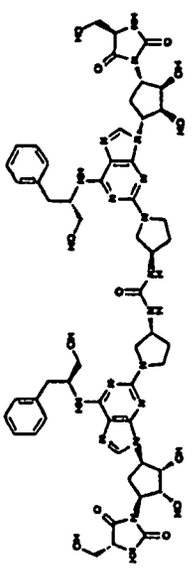
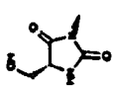
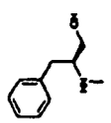
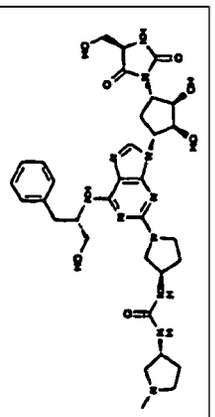
(X4)

Ex	Structure	R^1	R^2	R^3
191				
192				
193				
194				

(continued)

Ex	Structure	R^1	R^2	R^3
195				
196				
201				
202				
203				

(continued)

Ex	Structure	R1	R2	R3
204				

Example 191 1,3-Bis-{1-(R)-[(1S,2R,3S,4R)-6-([bis-(4-methoxyphenyl)-methyl)-amino}-9-(2,3-dihydroxy-4-propionamido-cyclopentyl)-9H-purin-2-yl]-pyrrolidin-3-yl}-urea

[0250] The title compound can be prepared analogously to Example 1 by replacing N-{(1S,2R,3S,4R)-4-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide (Intermediate AA) with (1R,2S,3R,5S)-3-(6-([bis-(4-methoxyphenyl)-methyl]-amino)-2-chloro-purin-9-yl)-5-(4-hydroxymethyl-[1,2,3]triazol-2-yl)-cyclopentane-1,2-diol (Intermediate RA).

Example 192 1,3-Bis-{1-(R)-[(1S,2R,3S,4R)-6-{[bis-(4-methoxyphenyl-methyl]-amino)-9-(2,3-dihydroxy-4-(2-acetoxyacetamido)-cyclopentyl)-9H-purin-2-yl]-pyrrolidin-3-yl}-urea

[0251] The title compound can be prepared analogously to Example 1 by replacing N-{(1S,2R,3S,4R)-4-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide (Intermediate AA) with acetic acid [(1S, 2R, 3S, 4R)- 4-(6- { [bis-(4- methoxy- phenyl)-methyl]-amino}- 2- chloro- purin- 9- yl)- 2,3- dihydroxy- cyclopentylcarbamoyl)-methyl ester (Intermediate RB).

Example193 1,3-Bis-{1-(R)-[(1S,2R,3S,4R)-6-{[bis-(4-methoxyphenyl)-methyl]-amino}-9-(2,3-dibydroxy-4-(4-hydroxymethyl-[1,2,3]triazol-2-yl-cyclopentyl)-9H-purin-2-yl]-pyrrolidin-3-yl}-urea

[0252] The title compound can be prepared analogously to Example 1 by replacing N-{(1S,2R,3S,4R)-4-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide (Intermediate AA) with (1R,2S,3R,5S)-3-(6-{[bis-{4-methoxyphenyl)-methyl]-amino}-2-chloro-purin-9-yl)-5-(4-hydroxymethyl-[1,2,3]triazol-2-yl)-cyclopentane-1,2-diol. (Intermediate RC).

Example 194 1,3-Bis-(1-(R)-[(1S,2R,3S,4R)-6-amino-9-(2,3-dihydroxy-4-propionamido-cyclopentyl)-9H-purin-2-yl]-pyrrolidin-3-yl}-urea (Paper)

[0253] The title compound can be prepared by dissolving Example 191 1,3-bis-{1-(R)-[(1S,2R,3S,4R)-6-{[bis-(4-methoxyphenyl)-methyl]-amino}-9-(2,3-dihydroxy-4-propionamido-cyclopentyl)-9H-purin-2-yl]-pyrrolidin-3-yl}-urea in DCM, chilling on ice/water to 0˚C, and adding trifluoroacetic acid to 33% concentration with stirring. Once complete, volatile components are removed under reduced pressure, and the crude product purified.

Example 195 1,3-Bis-{1-(R)..[(1S,2R,3S,4R)-6-amino-9-(2,3-dihydroxy-4-(2-hydroxyacetamido)-cyclopentyl)-9H-purin-2-yl]-pyrrolidin-3-yl}-urea

[0254] The title compound can be prepared analogously to Example 194 1,3-bis-{1-(R) [(1S,2R,3S,4R-6-amino-9-(2,3-dihydroxy-4-propionamido-cyclopentyl)-9H-purin-2-yl]-pyrrolidin-3-yl}-urea.

Example 196 1,3-Bis-{1-(R)-[(1S,2R,3S,4R)6-amino-9-(2,3-dihydroxy-4-(4-hydroxymethyl-11,2,3]triazol-2-yl)-cyclopentyl)-9H-purin-2-yl]-pyrrolidin-3-yl)-urea

[0255] The title compound can be prepared analogously to Example 194 1,3-bis-(1-(R)-[(1S,2R,3S,4R)-6-amino-9-(2,3-dihydroxy-4-propionamido-cyclopentyl)-9H-purin-2-yl]-pyrrolidin-3-yl}-urea.

Example 201

[0256] The title compound is prepared analogues to Example 1 by replacing N-{(1S,2P,3S,4R)-4-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide (Intermediate AA) with 3-{(1S,2R,3S,4R)-4-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-imidazolidine-2,4-dione (Intermediate VA).

Example 202 1,3-Bis-1(R)-1-19-1(1R,2S,3R,4S)-4-(3-ethyl-2,5-dioxo-imidazolidin-1-yl)-2,3-dihydroxy-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl)-urea

[0257] The title compound is prepared analogues to Example I by replacing N-{(1S,2R,3S,4R)-4-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl)-2,3-dihydroxy-cyclopentyl}-propionamide (Intermediate AA) with 3-{(1S,2R,3S,4R)-4-[2-chloro-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-1-ethyl-imidazolidine-2,4-dione (Intermediate VC).

Example 203 1,3-Bis-{(R)1-[9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-((S)-4-hydroxymethyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9-purin-2-yl]-pyrrolidin-3-yl}-urea

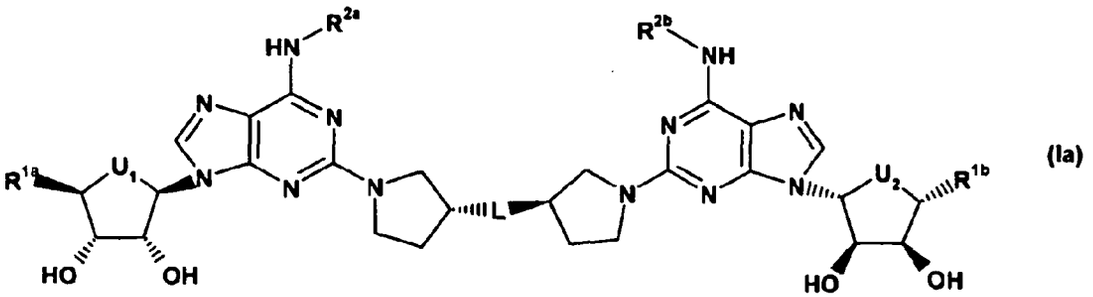
[0258] The title compound is prepared analogues to Example 1by replacing N-{(1S,2R,3S,4R)-4-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide (Intermediate AA) with (S)-3-{(1S,2R,3S,4R)-4-[2-chloro-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-5-hydroxymethyl-imidazolidine-2,4-dione (Intermediate VD).

Example 204 1,3-Bis-((R)-1-19-[(1R,2S,3R,4S)-2,3-dihydroxy-4-((R)-4-hydroxymethyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-urea

[0259] The title compound is prepared analogues to Example 1 by replacing N-{(1S,2R,3S,4R)-4-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide (Intermediate AA) with (R)-3-{(1S,2R,3S,4R)-4-[2-chloro-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl)-2,3-dihydroxy-cyclopentyl}-5-hydroxymethyl-imidazolidine-2,4-dione (Intermediate VE).

Claims

1. A compound, or stereoisomers or pharmaceutically acceptable salts thereof, wherein the compound is of formula (Ia):



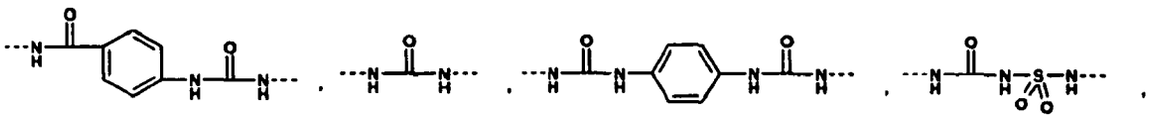
(Ia)

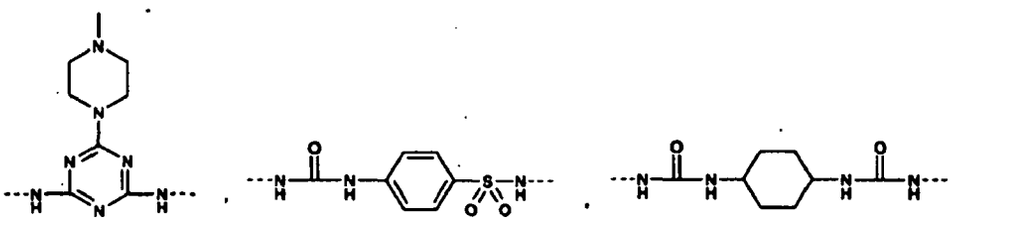
wherein

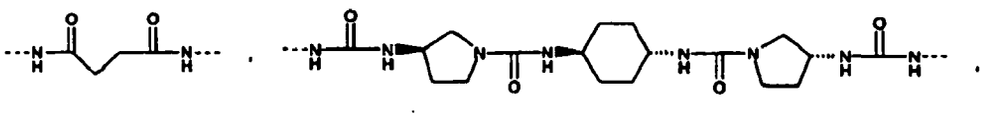
U_1, and U_2 are independently selected from CH_2 and O with the proviso that when U_1 is O then R^{1a} is not a N-bonded substituent, and when U_2 is O then R^{1b} is not a N-bonded substituent;
R^{1a} and R^{1b} are independently selected from a 3- to 12-membered heterocyclic group containing from 1 to 4 ring nitrogen atoms and optionally containing from 1 to 4 other heteroatoms selected from the group consisting of oxygen and sulfur, that group being optionally substituted by C_1-C_8-alkyl, or
R^{1a} and R^{1b} are independently selected from -NH-C_1-C_8-alkylcarbonyl, and -NH-C_3-C_8- cycloalkylcarbonyl, or
R^{1a} and R^{1b} are independently selected from NH-C_1-C_8-alkyl, NHC(O)C_1-C_8- hydroxyalkyl, $NHCO_2C_1$-C_8-alkyl, and $NHCO_2C_1$-C_8-hydroxyalkyl, or
R^{1a} and R^{1b} are independently selected from C_1-C_8-hydroxyalkyl, and CH_2-O-C_1-C_8-alkyl;
R^{2a} and R^{2b} are independently selected from hydrogen, C_1-C_8-alkyl optionally substituted by OH, C_3-C_{15}-carbocyclic group, or C_6-C_{10}-aryl optionally substituted by OH, halogen, or O-C_1-C_8-alkyl, or
R^{2a} and R^{2b} are independently is C_7-C_{18}aralkyl optionally substituted by OH, halogen, or CN;
L is selected from -NHC(O)-W-NHC(O)NH-, -NH-Y-NH-, NHC(O)NH-, NHC(O)NH-Z- NH-, NHC(0)-$(CH_2)_n$-C(O)NH-, and NHC(O)NH-W-NHC(O)NH-;
W is selected from C_3-C_{15}-carbocyclic group, a C_6-C_{10}-aryl, and -W^a-C(O)NH-W^b- NHC(O)-W^b-;
each W^a is independently selected from a 3- to 12-membered heterocyclic group containing from 1 to 4 ring nitrogen atoms and optionally containing from 1 to 4 other heteroatoms selected from the group consisting of oxygen and sulfur, a C_3-C_{15}- carbocyclic group optionally substituted by HO, and C_6-C_{10}-aryl optionally substituted by OH;
W^b is selected from a 3- to 12-membered heterocyclic group containing from 1 to 4 ring nitrogen atoms and optionally containing from 1 to 4 other heteroatoms selected from the group consisting of oxygen and sulfur, a C_3-C_{15}-carbocyclic group optionally substituted by OH, and C_6-C_{10}-aryl optionally substituted by OH;
Y is selected from a 3- to 12-membered heterocyclic group containing from 1 to 4 ring nitrogen atoms and

optionally containing from 1 to 4 other heteroatoms selected from the group consisting of oxygen and sulfur optionally substituted by R^9, a C_3-C_{15}-carbocyclic group optionally substituted by OH, and C_6-C_{10}-aryl optionally substituted by OH;
Z is selected from C_6-C_{10}-aryl, SO_2, and C_6-C_{10}-aryl-SO_2-; R^9 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, OH, carboxy, amino, nitro, C_1-C_8-alkyl; and
n is an integer selected from 1-4.

2. A compound according to Claim I or stereoisomers or pharmaceutically acceptable salts thereof, wherein L is selected from







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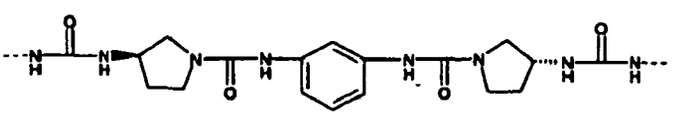
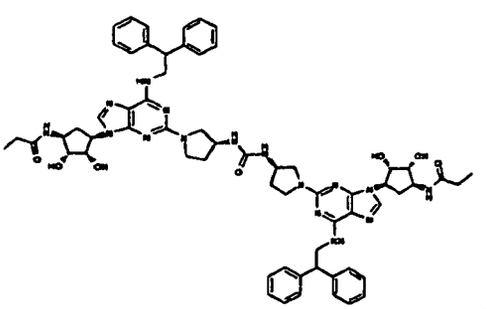
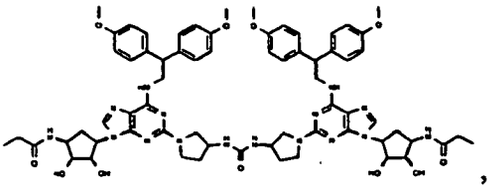
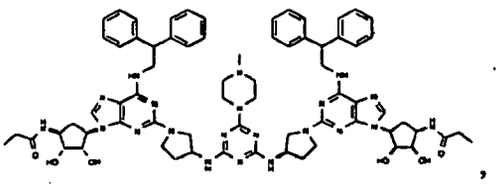
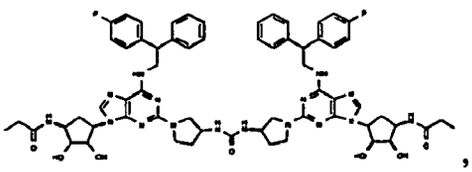


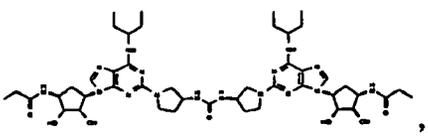
3. A compound according to Claim 1 or Claim 2 wherein said compound is selected from

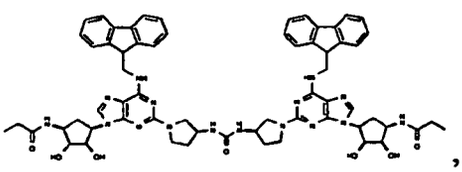


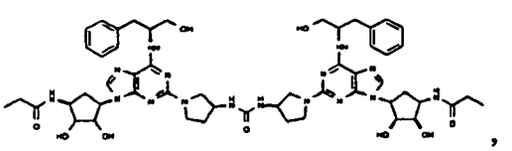


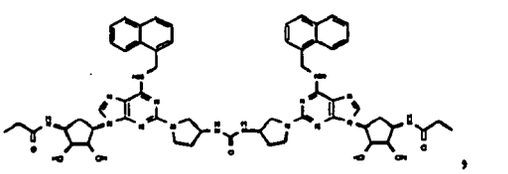


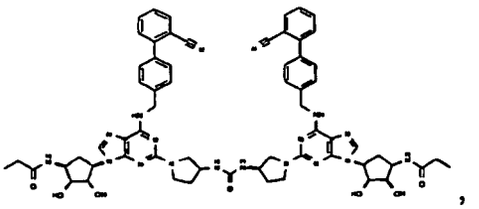


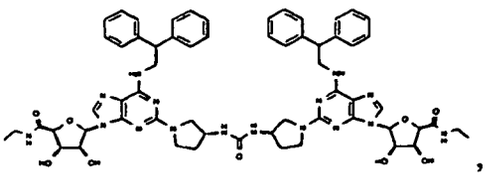


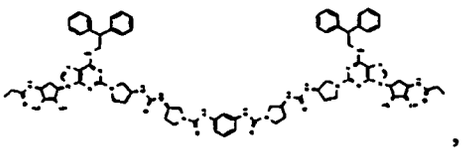


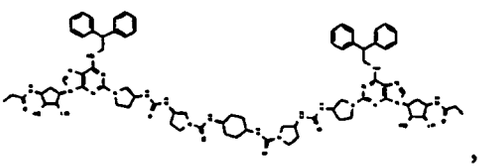


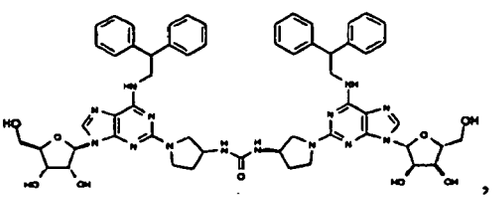


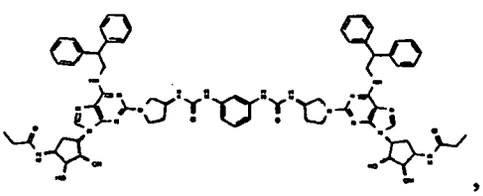


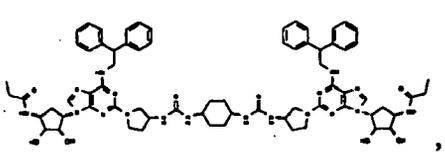


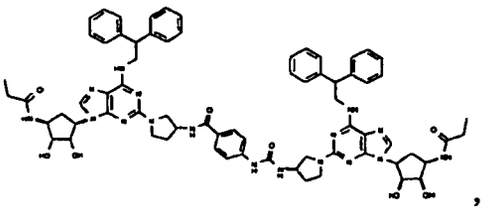












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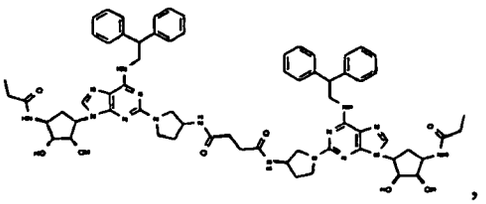

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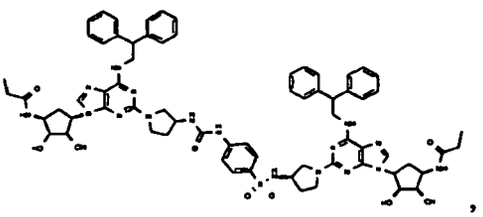

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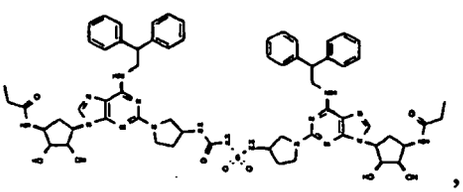

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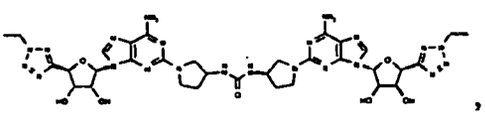

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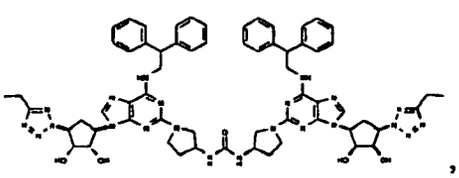

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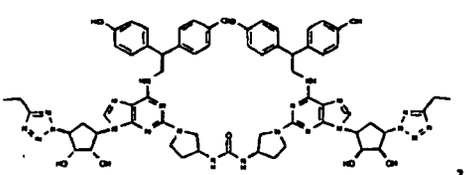

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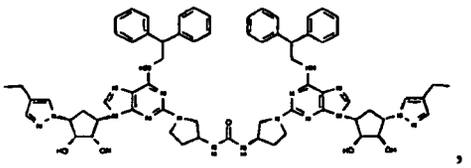
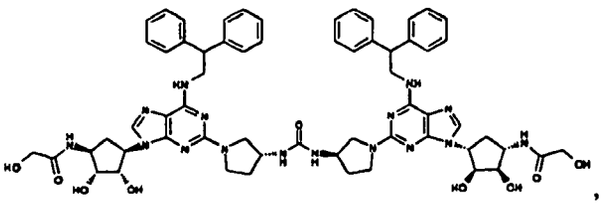
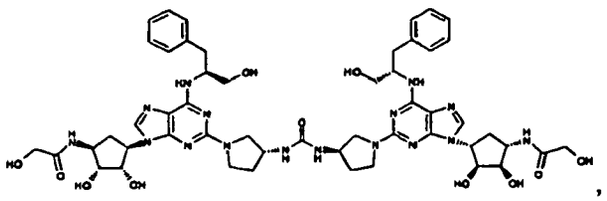
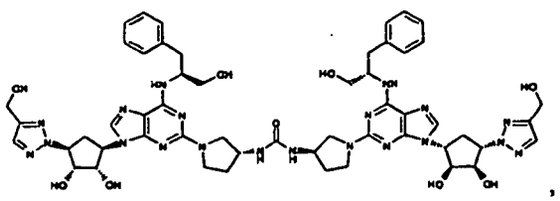
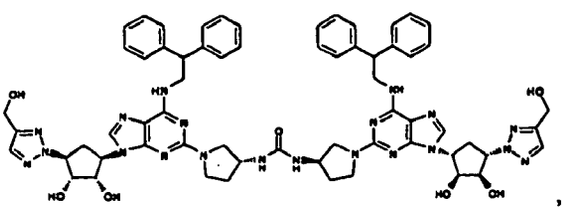
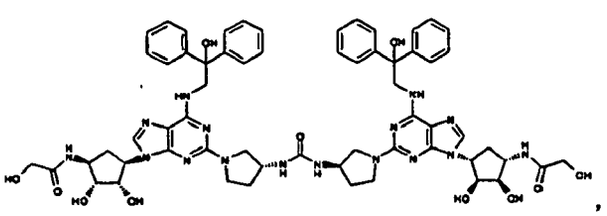


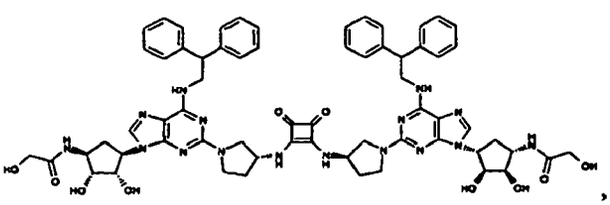


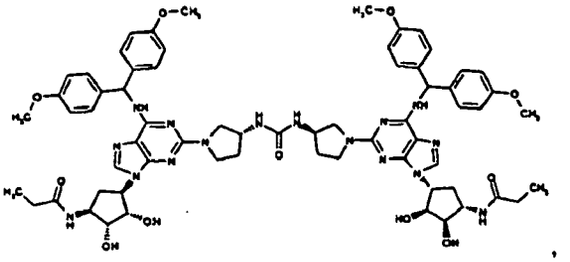


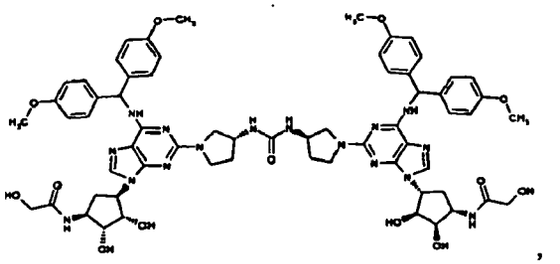


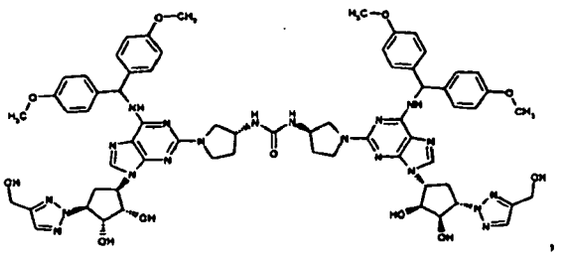


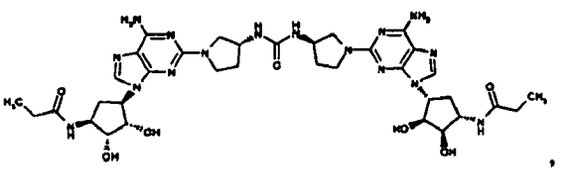


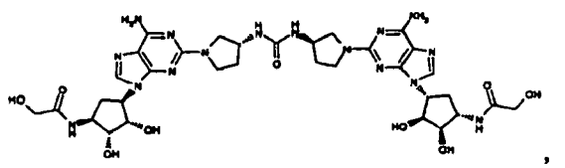


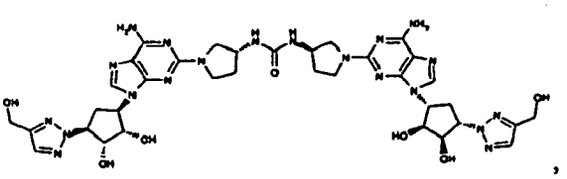


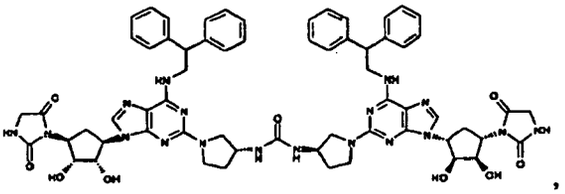


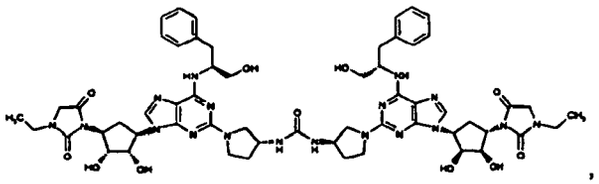


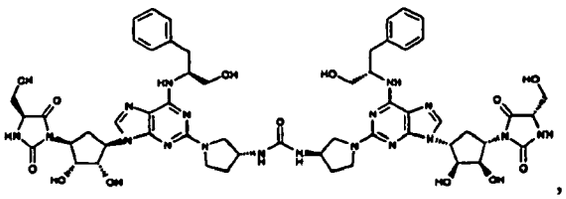




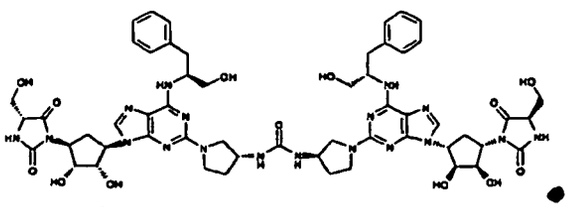








and



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

5. A compound according to any one of Claims 1-3 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.

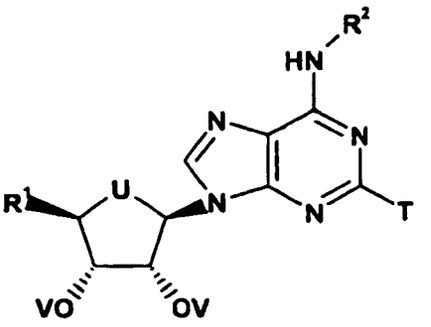
6. A pharmaceutical composition comprising as active ingredient a compound according to any one of Claims 1-3, optionally together with a pharmaceutically acceptable diluent or carrier.

7. A compound according to any one of Claims 1-3 for use in the treatment of a condition mediated by activation of the adenosine A2A receptor

8. A compound according to any one of Claims 1-3 for use in the treatment of an inflammatory or obstructive airways disease.

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

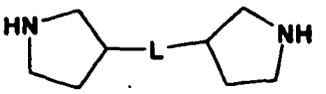
(i) reacting a compound of formula (III):



(III)

wherein

R^1 is equivalent to R^{1a} and R^{1b};
R^2 is equivalent to R^{2a} and R^{2b}; and
U is equivalent to U_1 and U_2, and are as defined in Claim 1;
V is H or a protecting group; and
T is a leaving group, with a compound of formula (V):



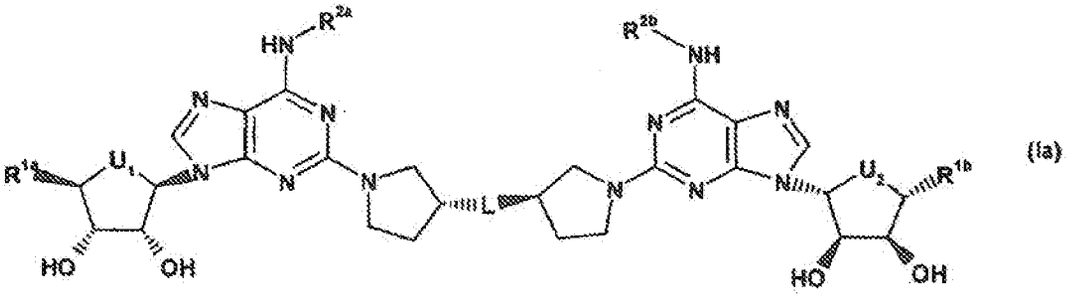
(V)

wherein L is as defined in Claim 1;

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

Patentansprüche

1. Verbindung oder Stereoisomere oder pharmazeutisch unbedenkliche Salze davon, wobei die Verbindung die Formel (Ia):



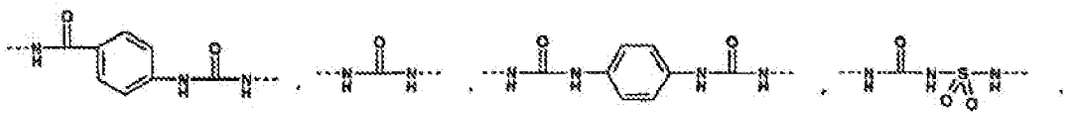
(Ia)

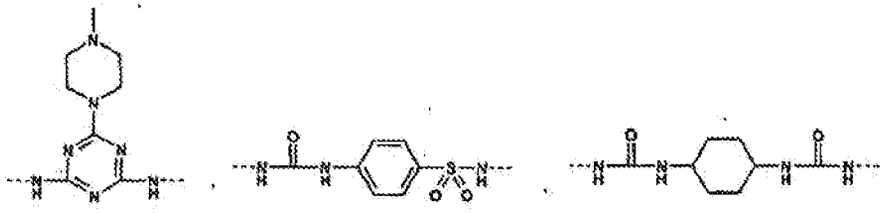
aufweist, worin

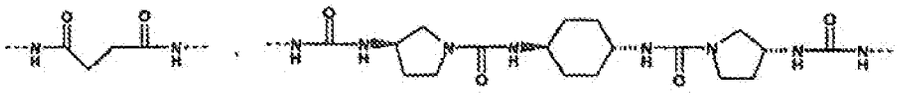
U_1 und U_2 unabhängig voneinander unter CH_2 und O ausgewählt sind, mit der Maßgabe, faß dann, wenn U_1 für O steht, R^{1a} nicht für einen N-gebundenes Substituenten steht, und denn, wenn U_2 für O steht. R^{1b} nicht

für einen N-gebundenes Substituenten steht;
R^{1a} und R^{1b} unabhängig voneinander unter einer 3-bis 12-gliedrigen heterocyclischen Gruppe mit 1 bis 4 Ringstickstoffatomen und gegebenenfalls 1. bis 4 anderen Heteroatomen aus der Gruppe bestehend aus Sauerstoff und Schwefel ausgewählt sind, wobei die Gruppe gegebenenfalls durch C_1-C_8-Alkyl substituiert sein kann, oder
R^{1a} und R^{1b} unabhängig voneinander unter -NH-C_1-C_8-Alkylcarbonyl und -NH-C_3-C_8-cycloalkylcarbonyl ausgewählt sind, oder
R^{1a} und R^{1b} unabhängig voneinander unter NH-C_1-C_8-Alkyl, NHC(O)-C_1-C_8-Hydroxyalkyl, $NHCO_2$-C_1-C_8-Alkyl und $NHCO_2$-C_1-C_8-Hydroxyalkyl ausgewählt sind, oder R^{1a} und R^{1b} unabhängig voneinander unter C_1-C_8-Hydroxyalkyl und CH_2-O-C_1-C_8-Alkyl ausgewählt sind;
R^{2a} und R^{2b} unabhängig voneinander unter Wasserstoff, gegebenenfalls durch OH substituiertem C_1-C_8-Alkyl, einer C_3-C_{15}-carbocyclischen Gruppe oder gegebenenfalls durch OH, Halogen oder O-C_1-C_8-Alkyl substituiertem C_6-C_{10}-Aryl ausgewählt sind, oder
R^{2a} und R^{2b} unabhängig voneinander für gegebenenfalls durch OH, Halogen oder CN substituiertes C_7-C_{14}-Aralkyl stehen;
L unter -NHC(O)-W-NHC(O)NH-, -NH-Y-NH-, NHC(O)NH-, NHC(O)NH-Z-NH-, NHC(O)-$(CH_2)_n$-C(O)NH - und NHC(O)NH-W-NHC(O)NH- ausgewählt ist;
W unter einer C_3-C_{15}-carbocyclischen Gruppe, C_6-C_{10}-Aryl und -W^a-C(O)NH-W^b-NHC(O)-W^a- ausgewählt ist;
jedes W^a unabhängig voneinander unter einer 3- bis 12-gliedrigen heterocyclischen Gruppe mit 1 bis 4 Ringstickstoffatomen und gegebenenfalls 1 bis 4 anderen Heteroatomen aus der Gruppe bestehend aus Sauerstoff und Schwefel , einer gegebenenfalls durch HO substituierten C_3-C_{15}-carbocyclischen Gruppe und gegebenenfalls durch OH substituiertem C_6-C_{10}-Aryl, ausgewählt ist;
W^b unter einer 3- bis 12-gliedrigen heterocyclischen Gruppe mit 1 bis 4 Ringstickstoffatomen und gegebenenfalls 1 bis 4 anderen Heteroatomen aus der Gruppe bestehend aus Sauerstoff und Schwefel, einer gegebenenfalls durch OH substituierten C_3-C_{15}-carbocyclischen Gruppe und gegebenenfalls durch OH substituiertem C_6-C_{10}-Aryl ausgewählt ist;
Y unter einer 3- bis 12-gliedrigen heterocyclischen Gruppe mit 1 bis 4 Ringstickstoffatomen und gegebenenfalls 1 bis 4 anderen Heteroatomen aus der Gruppe bestehend aus Sauerstoff und Schwefel, die gegebenenfalls durch R^9 substituiert ist, einer gegebenenfalls durch OH substituierten C_3-C_{15}-carbocyclischen Gruppe und gegebenenfalls durch OH substituiertemC_6-C_{10}-Aryl ausgewählt ist;
z unter C_6-C_{10}-Aryl, SO_2 und C_6-C_{10}-Aryl-SO_2-ausgewählt ist;
R^9 für einen 3 - oder 12 - gliedrigen heterocyclischen Ring mit mindestens einem Ringheteroatom aus der Gruppe bestehend aus Stickstoff, Sauerstoff und Schwefel steht, wobei der 3- oder 12-gliedrige heterocyclische Ring gegebenenfalls durch Halogen, Cyano, OH, Carboxy, Amino, Nitro, C_1-C_8-Alkyl substituiert ist; und
n für eine ganze Zahl im Bereich von 1-4 steht.

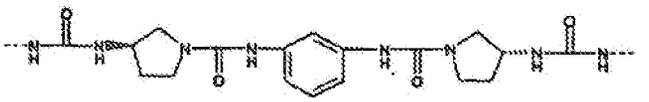
2. Verbindung nach Anspruch 1 oder Stereoisontere oder pharmazeutisch unbedenkliche Salze davon, worin L unter





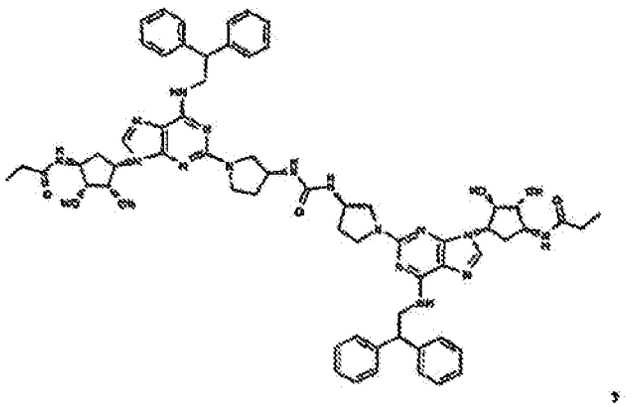


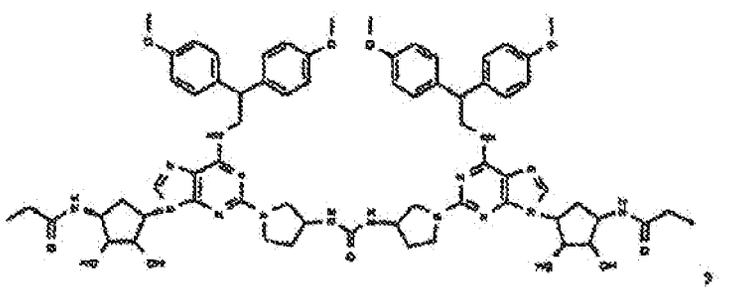
und

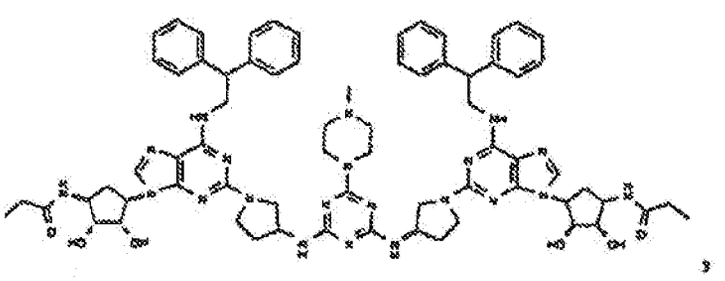


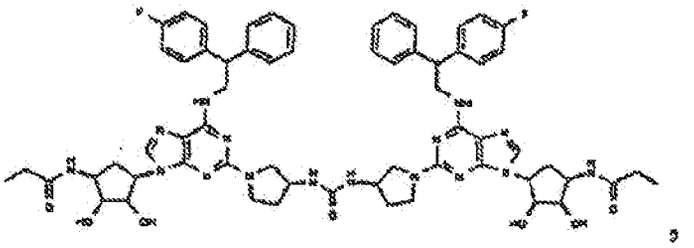
ausgewählt ist,

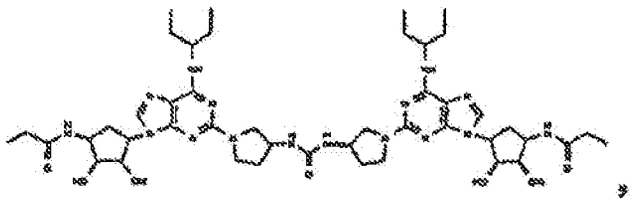
3. Verbindung nach Anspruch 1 oder Anspruch 2, wobei die Verbindung unter

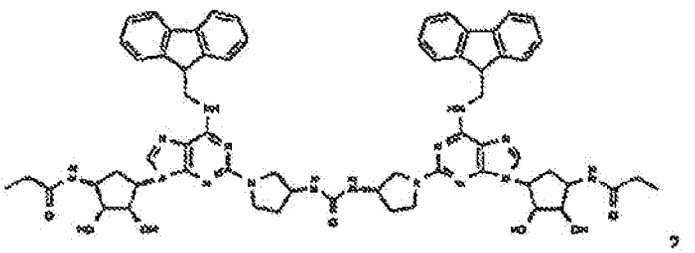


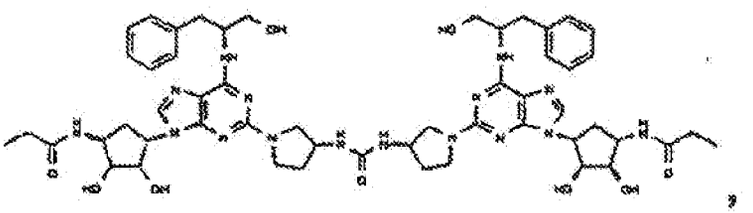


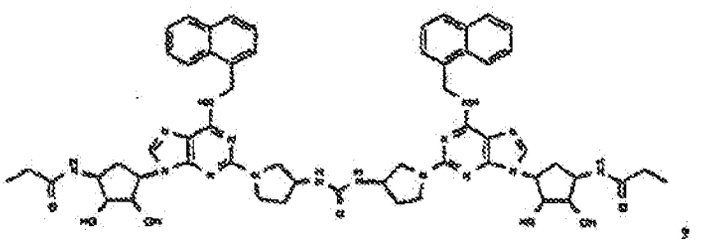


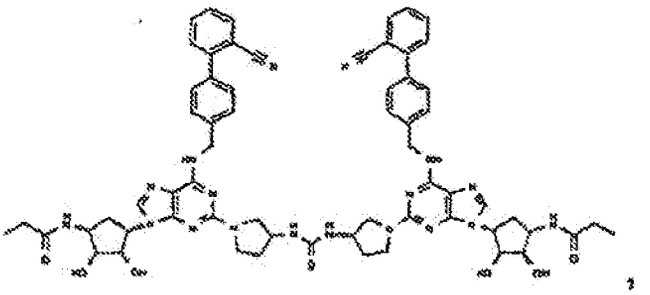


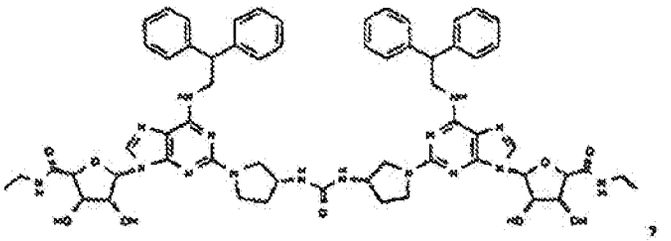


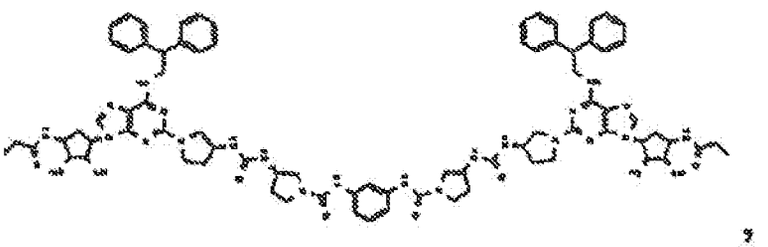


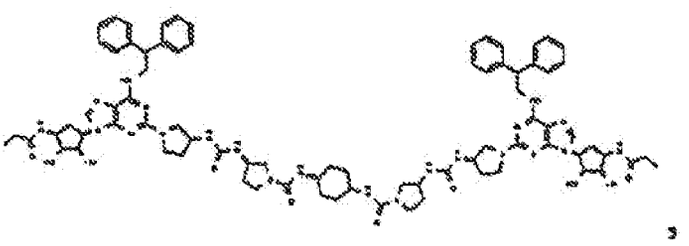


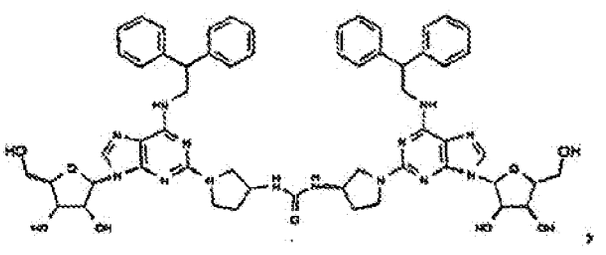


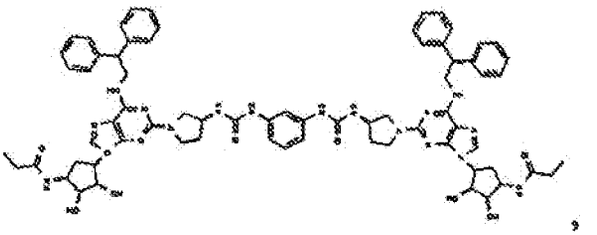


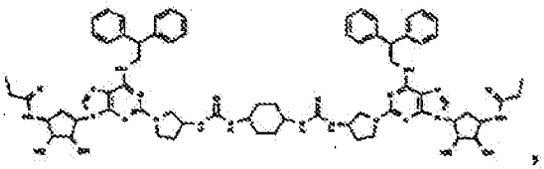


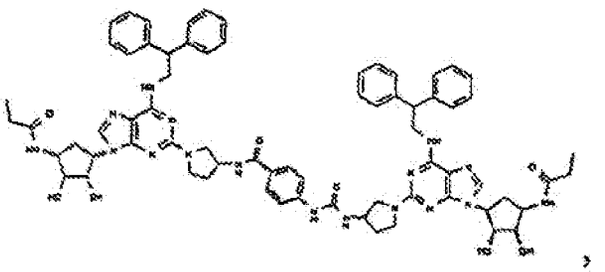


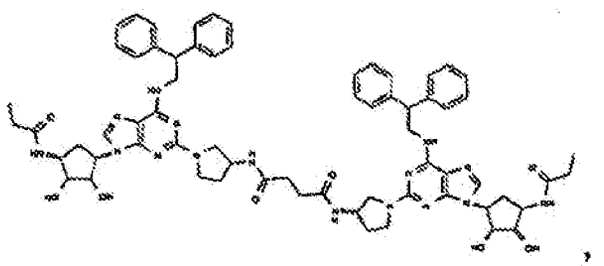


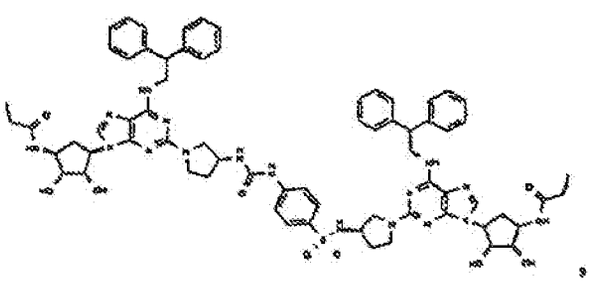


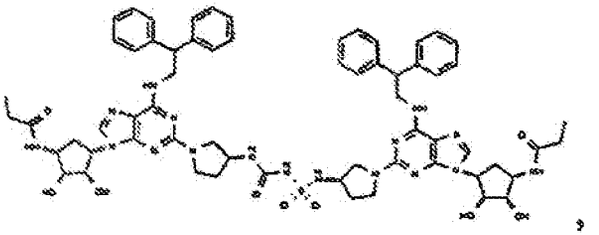


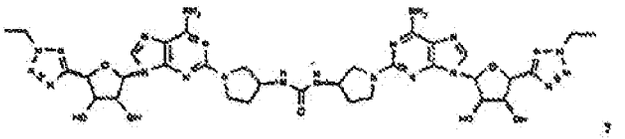


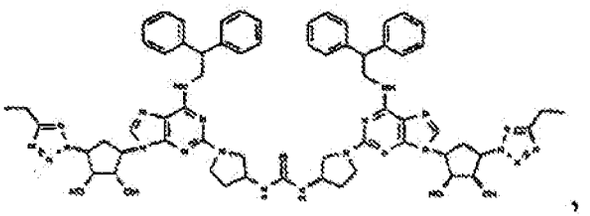


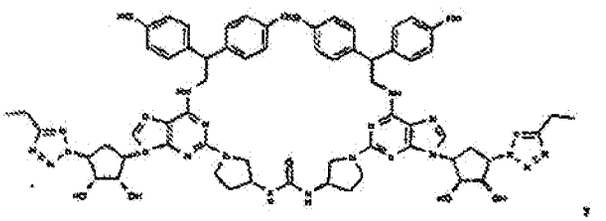


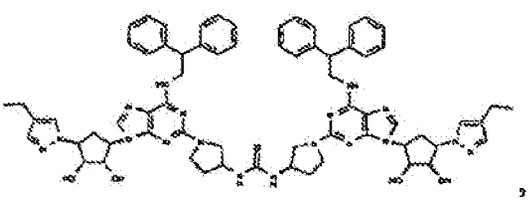


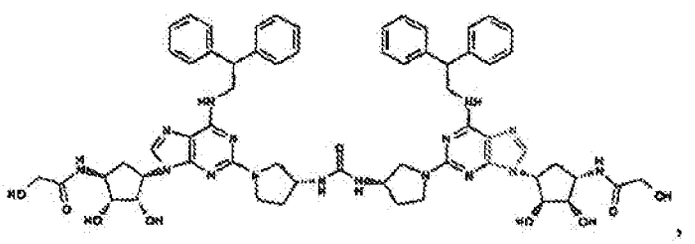


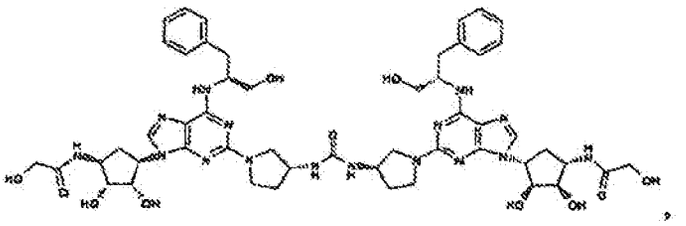


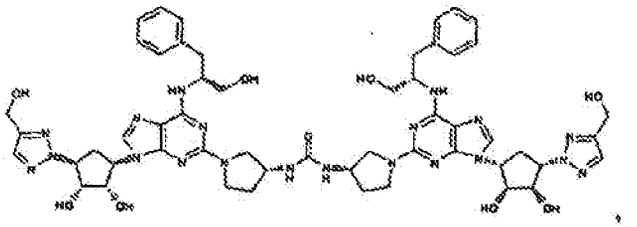


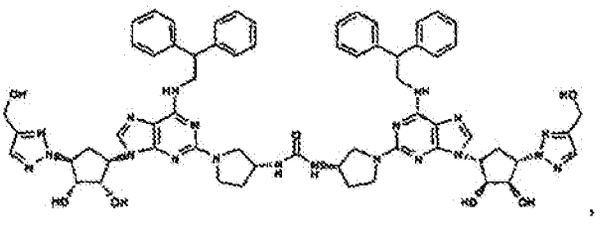


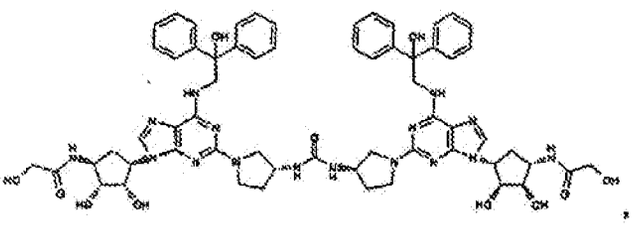


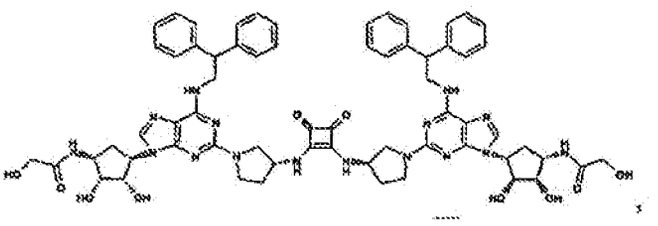


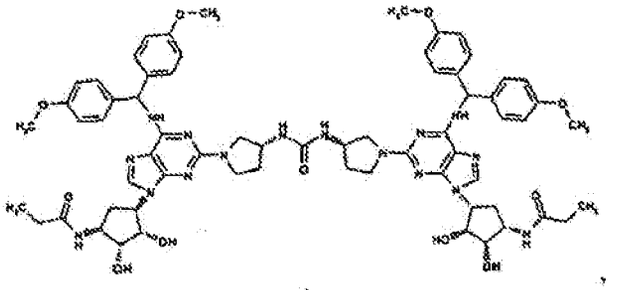


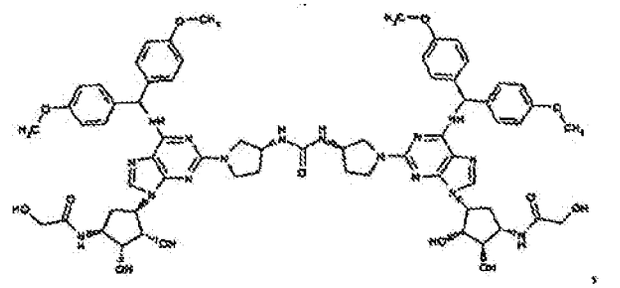


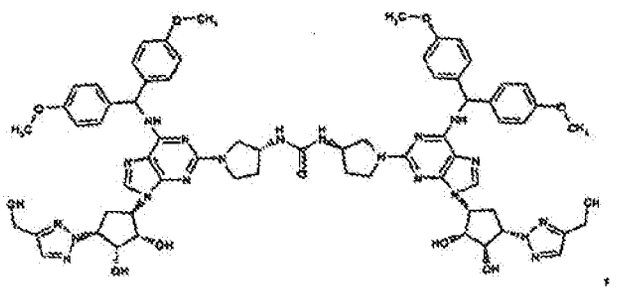


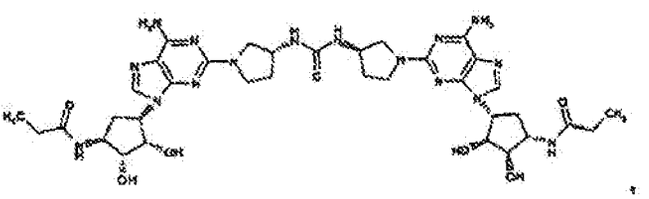


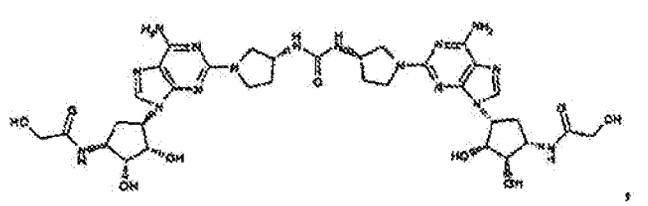


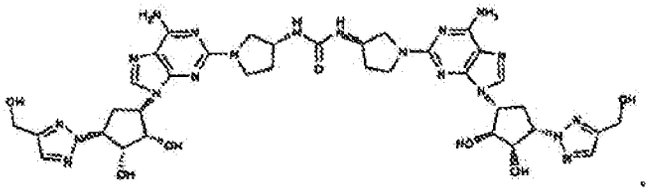


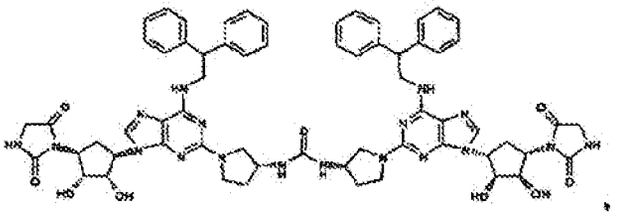


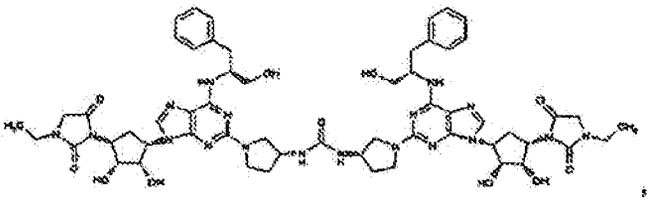


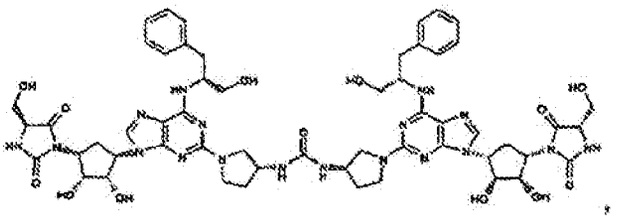












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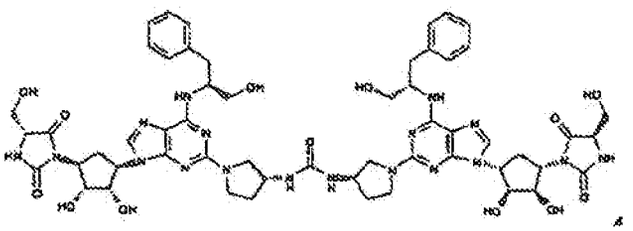


ausgewählt ist.

4. Verbindung nach einem der vorhergehenden Ansprüche zur Verwindung als Pharmazeutikum.

5. Verbindung nach einem der Ansprüche 1-3 in Kombination mit einem entzündungshemmenden oder bronchodilatorischen Arzneistoff oder einem Arzneistoff mit Antihistaminwirkung order antitussiver Wirkung, wobei die Werbindung und der Arzneistoff in der gleichen pharmazeutischen Zusammensetzung oder in verschiedenen pharmazeutischen Zusammensetzungen vorliegen.

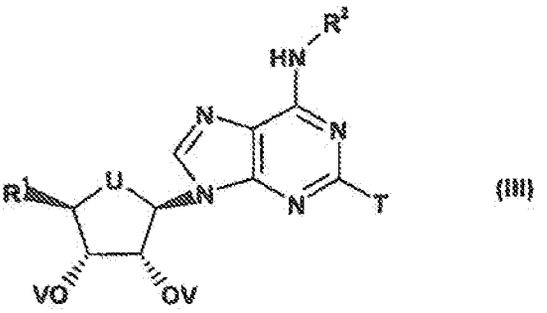
6. Pharmazeutische Zusammensetzung, die als Wirkstoff eine Verbindung nach einem der Ansprüche 1-3 umfaßt, gegebenenfalls zusammen mit einem pharmazeutisch unbedenklichen Verdünnungsmittel oder Träger.

7. Werbindung nach einem der Ansprüche 1-3 zur Verwendung bei der Behandlung eines durch Aktivierung des Adenosin-A2A-Rezeptors vermittelten Leidens.

8. Verbindung nach einem der Ansprüche 1-3 zur Verwendung bei der Behandlung einer entzündlichen oder obstruktiven Atemwegserkrankung.

9. Verfahren zur Herstellung von Verbindungen der Formel (Ia) gemäß Anspruch 1. oder Stereoisomeren oder pharmazeutisch unbedenklichen Salzen davon, bei dem man:

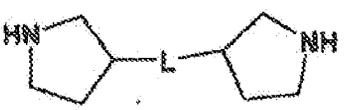
(i) eine Verbindung der Formel (III):



(III)

worin

R^1 zu R^{1a} und R^{1b} äquivalent ist,
R^1 zu R^{2a} und R^{2b} äquivalent ist; und
U zu U_1 und U_2 äquivalent ist, wobei diese Variablen wie in Anspruch 1 definiert sind;
V für H oder eine Schutzgruppe steht und
T für eine abgangsgruppe steht, mit einer Verbindung der Formel (V):



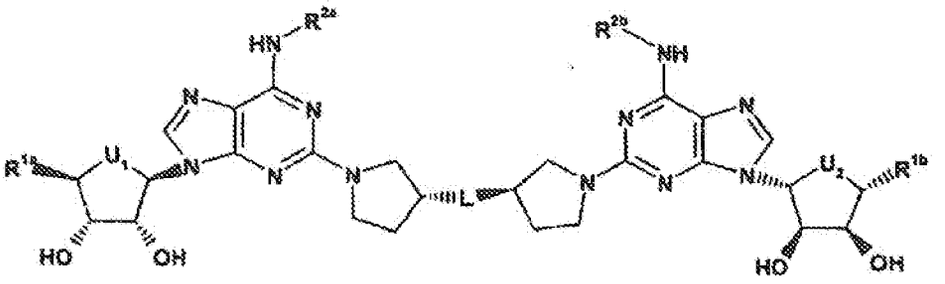
(V)

worin L wie in Anspruch 1 definiert ist, umsetzt und

(ii) jegliche Schutzgruppen abspaltet und die erhaltene Verbindung der Formel (Ia) in freier Form oder in Form eines pharmazeutisch unbedenklichen Salzes erhält.

Revendications

1. composé, ou stéréo-isomères ou sels pharmaceutiquement acceptables de celui-ci, **caractérisé en ce que** le composé est de formule (Ia) :

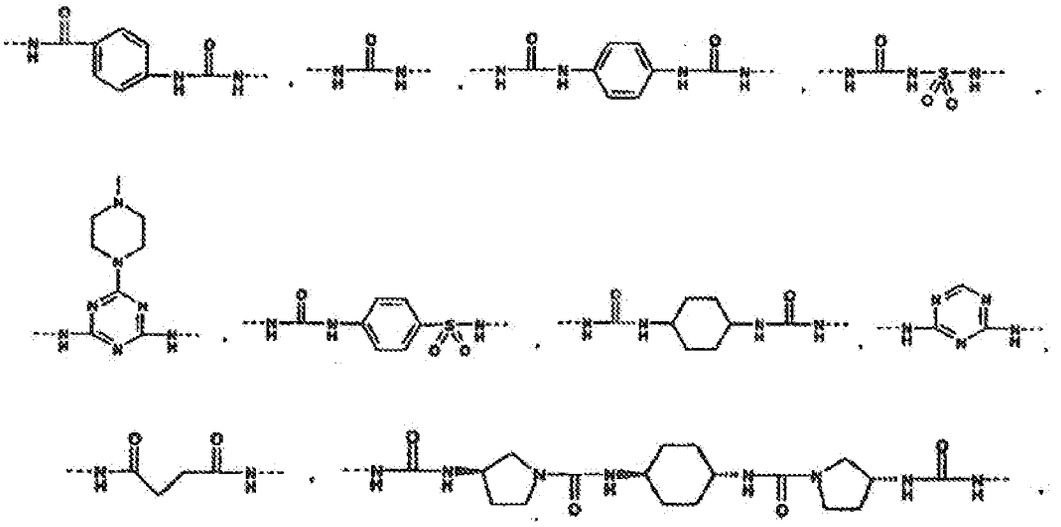


(Ia)

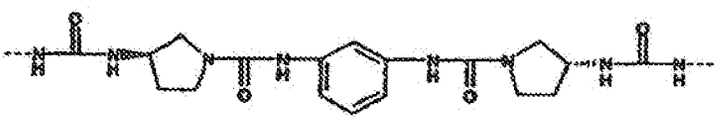
dans laquelle

U_1 et U_2 sont indépendamment choisis parmi CH_2 et O à condition que lorsque U_1 est O alors R^{1a} n'est pas un substituant lié à N, et lorsque U_2 est O alors R^{1b} n'est pas un substituant lié à N ;
R^{1a}, et R^{1b} sont indépendamment choisis parmi un groupe hétérocyclique de 3 à 12 chaînons contenant de 1 à 4 atomes d'azote Cycliques et contenant facultativement de 1 à 4 autres hétéroatomes choisis dans le groupe constitué de l'oxygène et du soufre, ce groupe étant facultativement substitué par un alkyle en C_1-C_8, ou R^{1a} et R^{1b} sont indépendamment choisis parmi -NH-(alkyle en C_1-C_8) carbonyle et -NH-(cycloalkyle en C_3-C_8) carbonyle, ou
R^{1a} et R^{1b} sont indépendamment choisis parmi NH-(alkyle en C_1-C_8) , NHC(O)-(hydroxyalkyle en C_1-C_8), $NHCO_3$-(alkyle en C_1-C_8) et $NHCO_2$- (hydroxyalkyle en C_1-C_8), ou
R^{1a} et R^{1b} sont indépendamment choisis parmi un hydroxyalkyle en C_1-C_8, et CH_2-O- (alkyle en C_1-C_8) ;
R^{2a} et R^{2b} sont indépendamment choisis parmi un hydrogène, un alkyle en C_1-C_8 facultativement substitué par OH, un groupe carbocyclique en C_3-C_{15}, ou un aryle en C_6-C_{10} facultativement substitué par OH, un halogène ou O-(alkyle en C_1-C_8), ou
R^{2a} et R^{2b} sont indépendamment un aralkyle en C_7-C_{14} facultativement substitué par OH, un halogène, ou CN ; L est choisi parmi -NHC(O)-W-NHC(O)NH-, -NH-Y-NH-, MHC(O)NH-, NHC(O)NH-Z-NH-, NHC(O)-$(CH_2)_n$-C(O)NH-, et NHC(O)NH-W-NHC(O)NH- ;
W est choisi parmi un groupe carbocyclique en C_3-C_{15}, un aryle en C_6-C_{10}, et W^a-C(O)NH-W^b-NHC(O)-W^a- ;
chaque W^3 est indépendamment choisi parmi un groupe hétérocyclique de 3 à 12 chaînons contenant de 1 à 4 atomes d'azote cycliques et contenant facultativement de 1 à 4 autres hétéroatomes choisis dans le groupe constitué de l'oxygène et du soufre, un groupe carbocyclique en C_3-C_{15} facultativement substitué par HO, et un aryle en C_6-C_{10} facultativement substitué par OH ;
W^b est choisi parmi un groupe hétérocyclique de 3 à 12 chaînons contenant de 1 à 4 atomes d'azote cycliques et contenant facultativement de 1 à 4 autres hétéroatomes choisis dans le groupe constitué de l'oxygène et du soufre, un groupe carbocyclique en C_3-C_{15} facultativement substitué par OH, et un aryle en C_6-C_{10} facultativement substitué par OH ;
Y est choisi parmi un groupe hétérocyclique de 3 à 12 chaînons contenant de 1 à 4 atomes d'azote cycliques et contenant facultativement de 1 à 4 autres hétéroatomes choisis dans le groupe constitué de l'oxygène et du soufre facultativement substitué par R^9, l'oxygène et du soufre facultativement substitué par R^9, un groupe carbocyclique en C_3-C_{15} facultativement substitué par OH, et un aryle en C_6-C_{10} facultativement substitué par OH ;
Z est choisi parmi un aryle en C_6-C_{10}, SO_2, et un (aryle en C_6-C_{10})-SO_2- ;
R^9 est un cycle hétérocyclique de 3 à 12 chaînons contenant au moins un hétéroatome cyclique choisi dans le groupe constitué de l'azote, l'oxygène et le soufre, ledit cycle hétérocyclique de 3 à 12 chaînons étant facultativement substitué par un halogène, un cyano, OH, un carboxy, un amino, un nitro, un alkyle en C_1-C_8 ; et n est un entier choisi de 1 à 4.

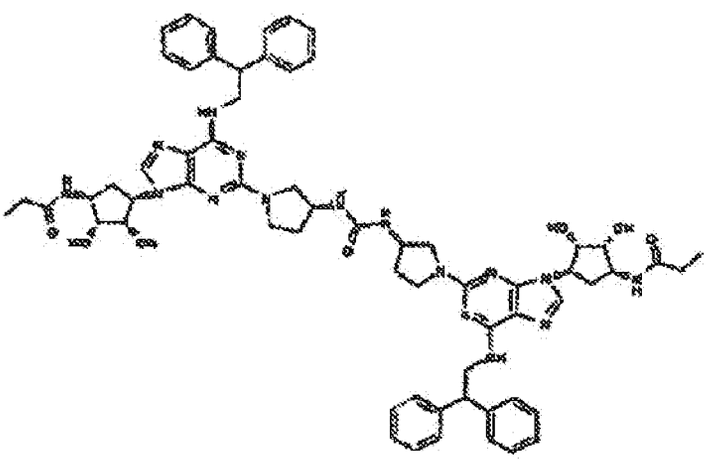
2. Composé selon la revendication 1 ou des stéréo-isomères ou des sels pharmaceutiquement acceptables de celui-ci, dans lequel
L est choisi parmi :

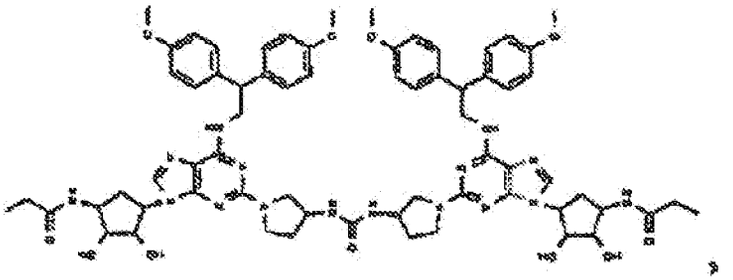


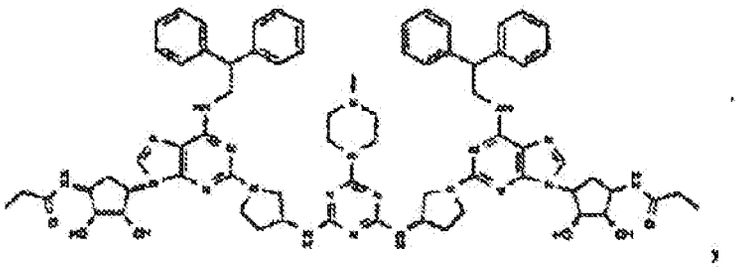
et

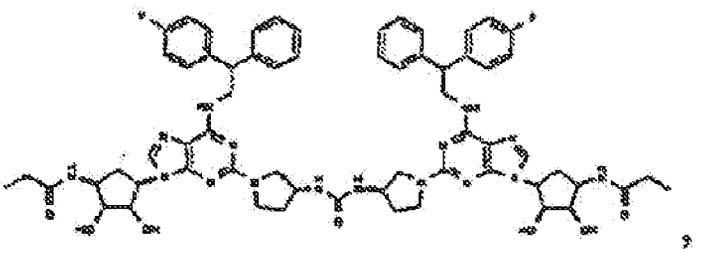


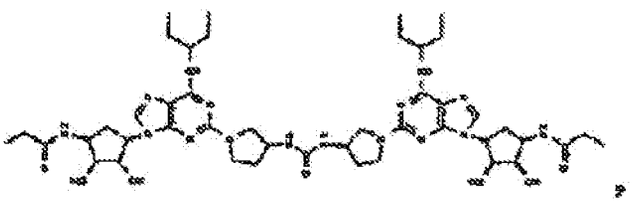
3. Composé selon la revendication 1 ou la revendication 2 **caractérisé en ce que** ledit composé est choisi parmi

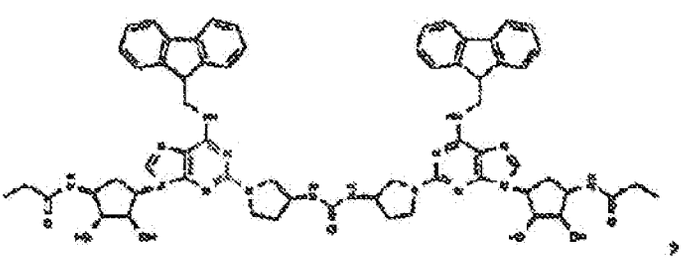


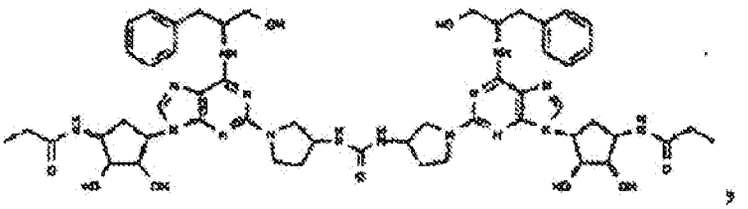


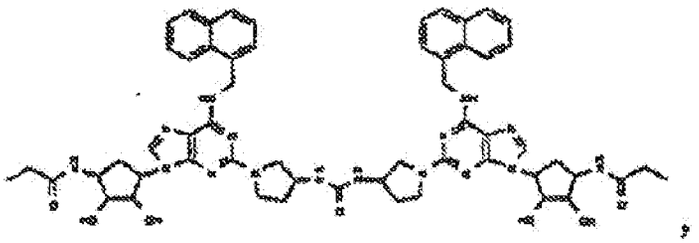


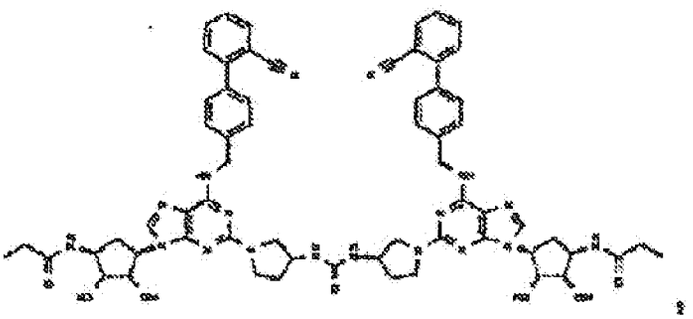


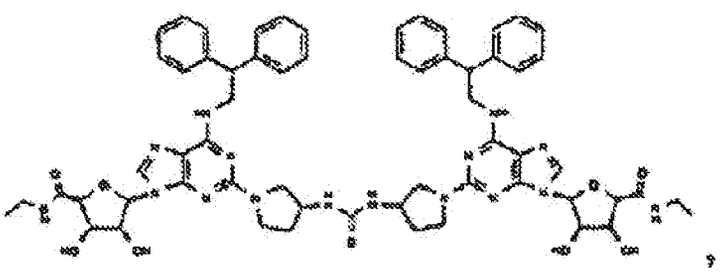


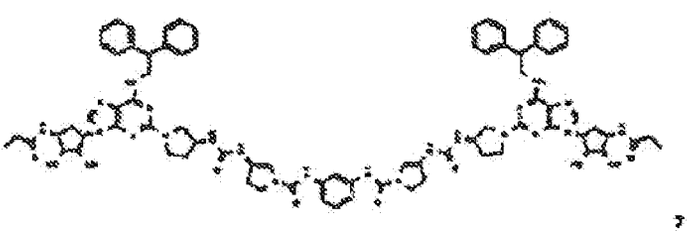


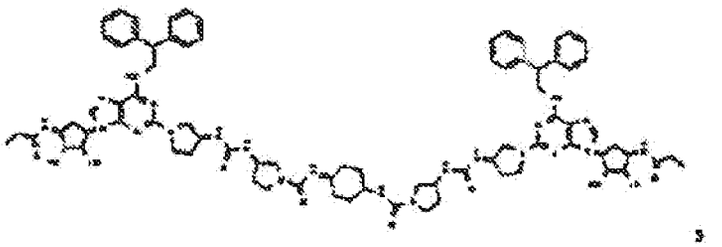


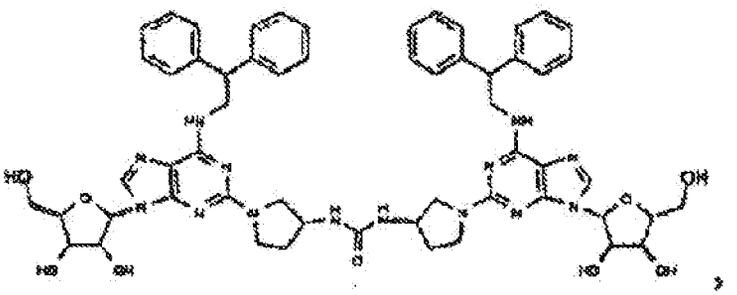


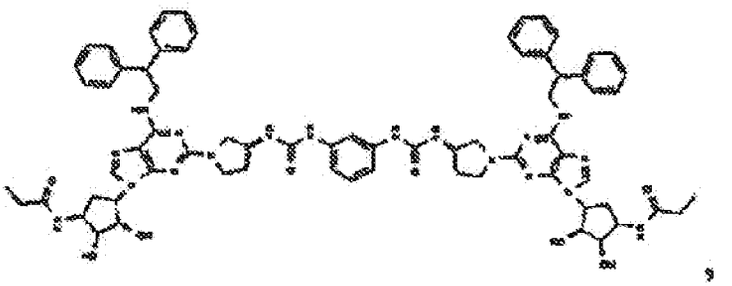


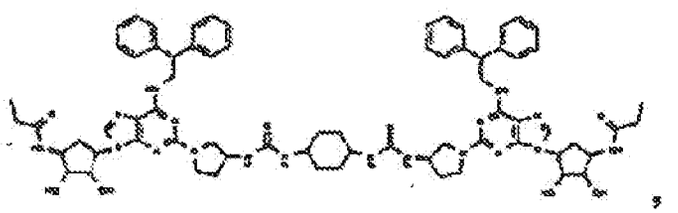


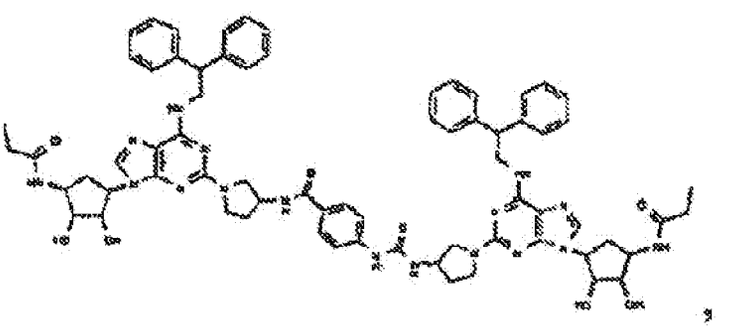


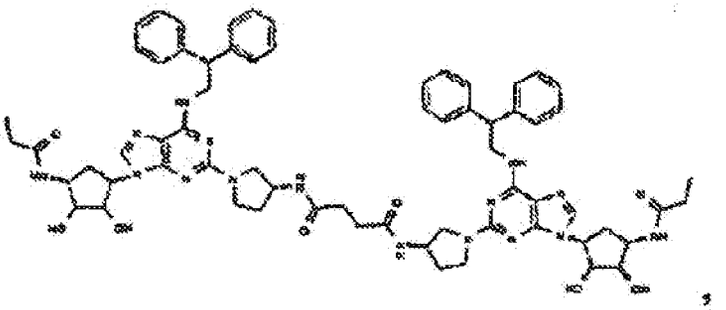


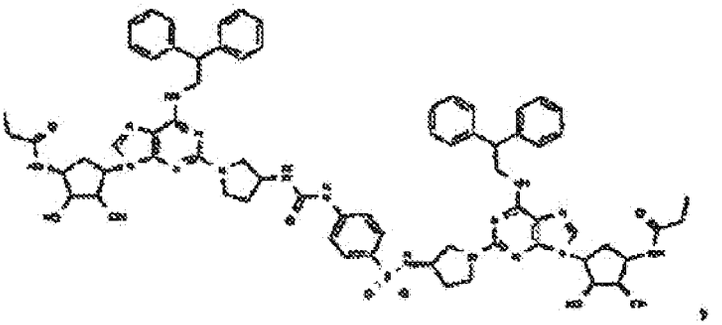


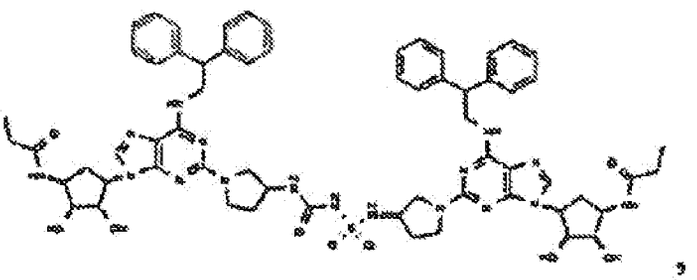


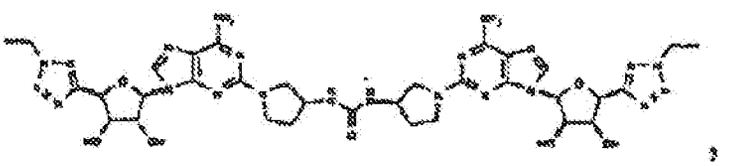


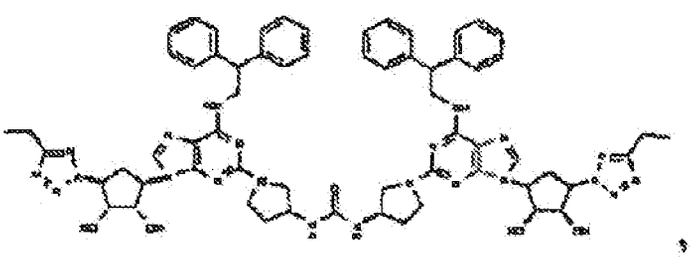


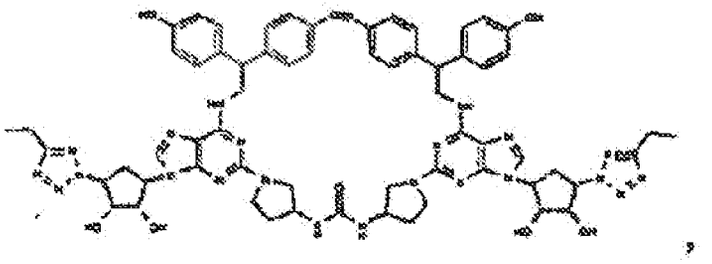


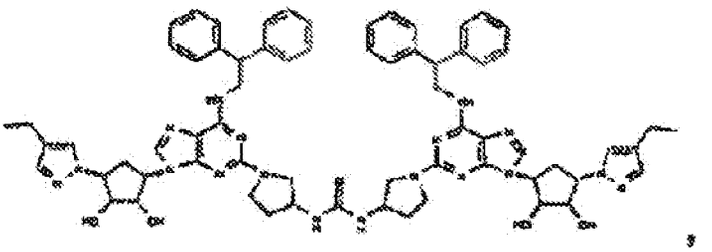


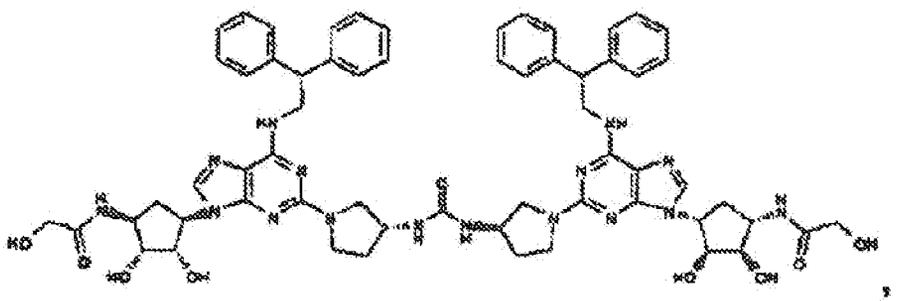


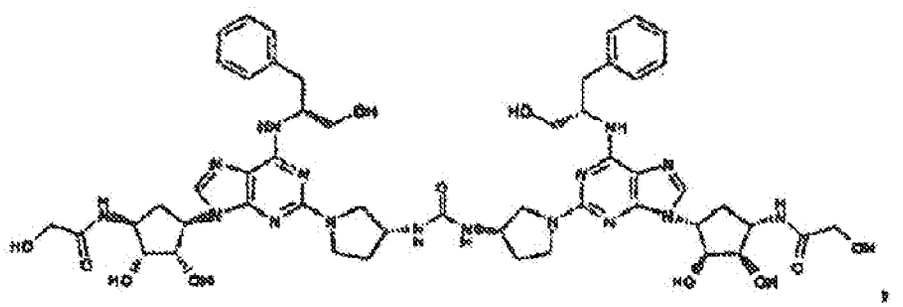


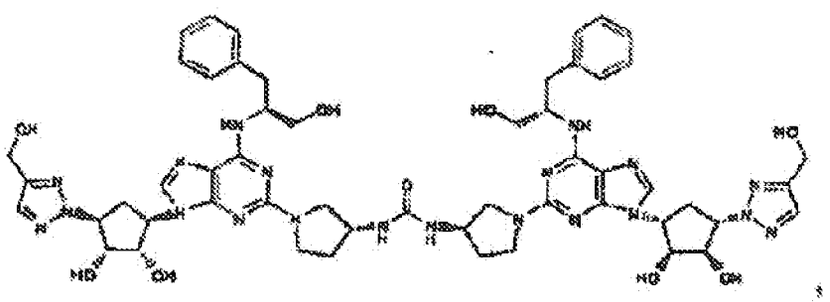


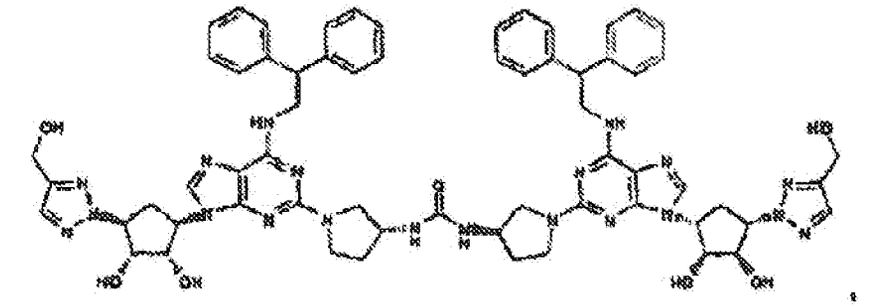


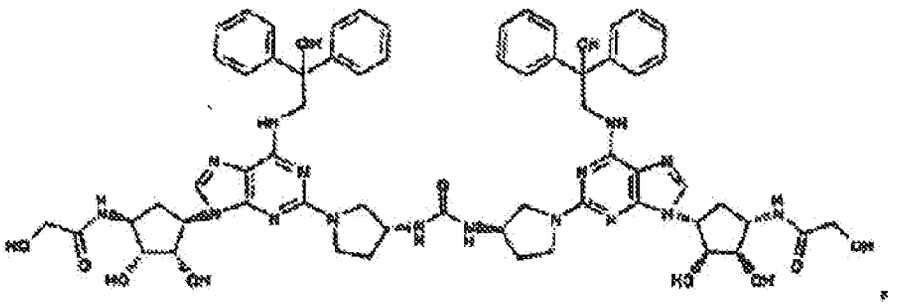


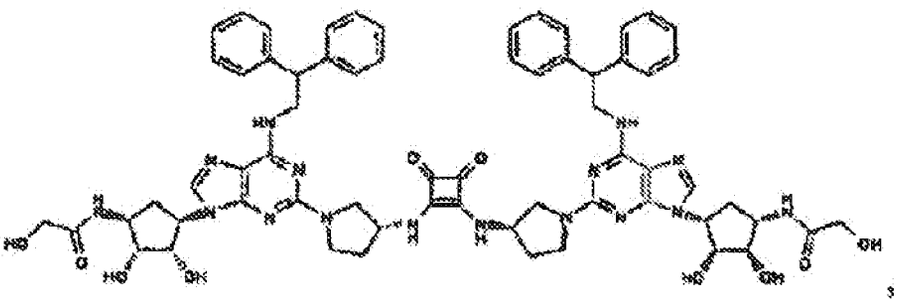


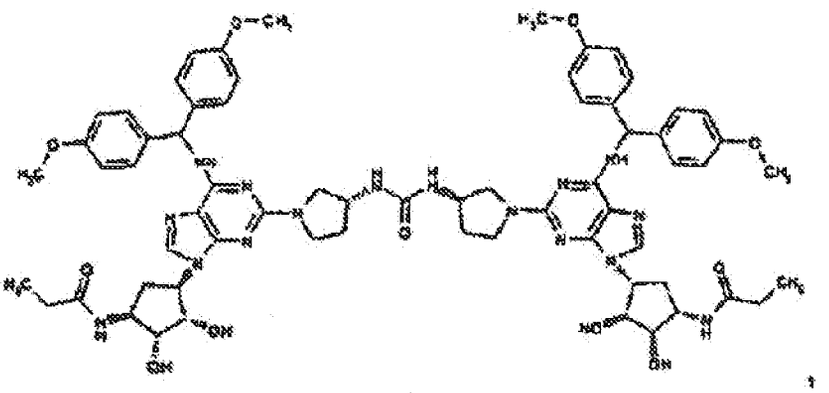


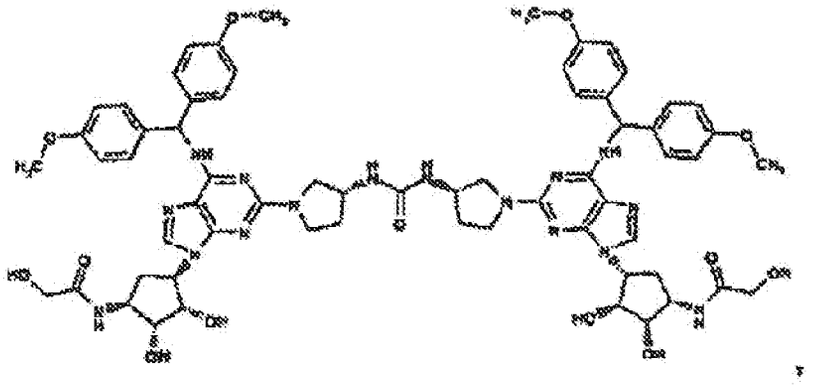


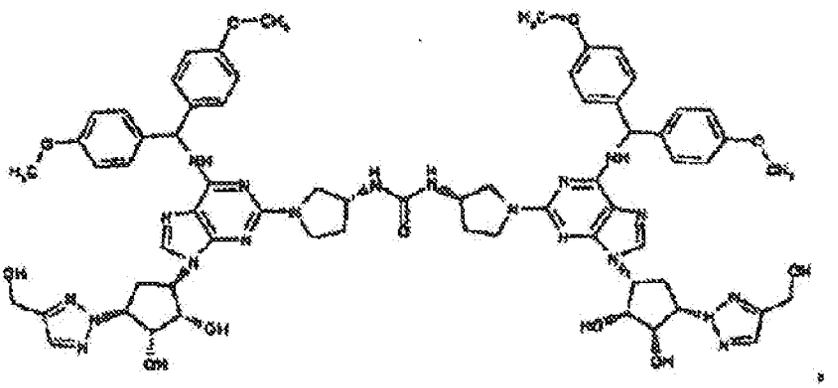


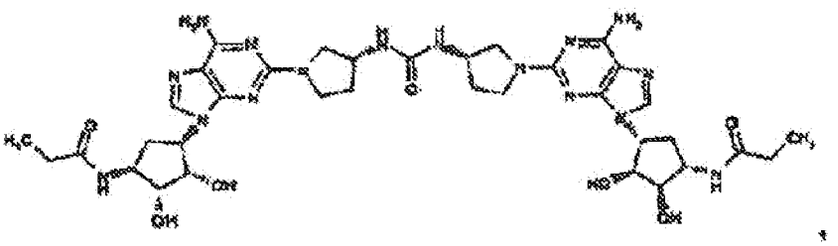


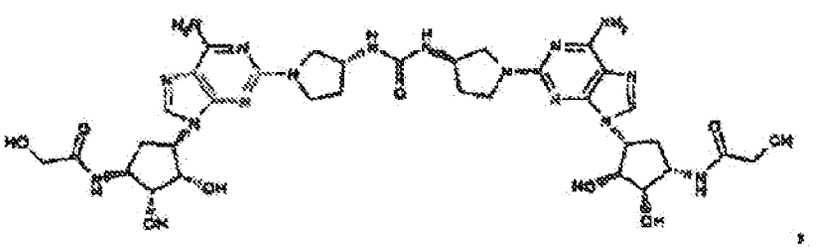


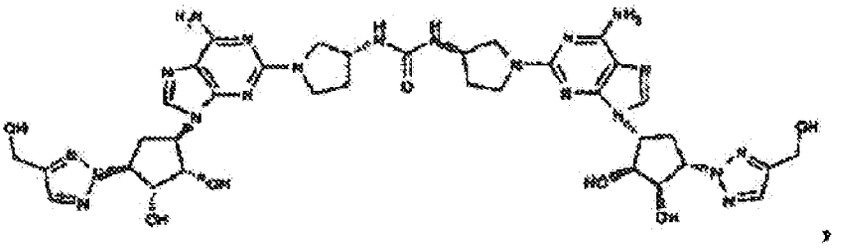


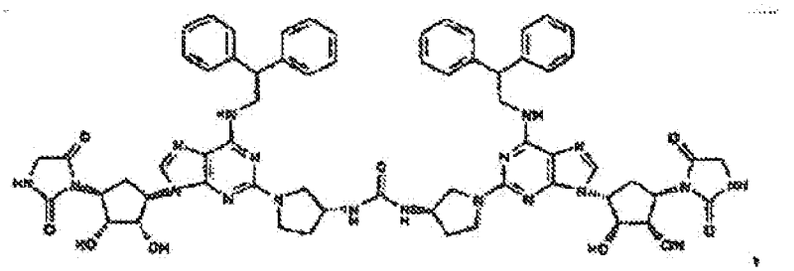


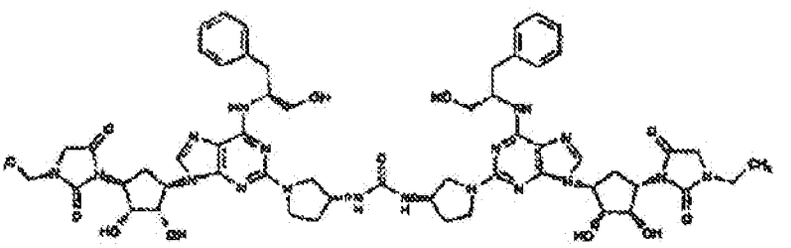


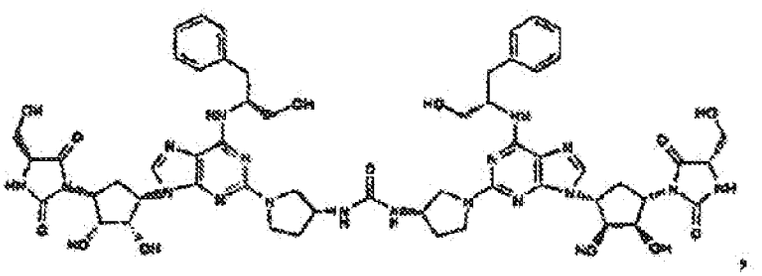












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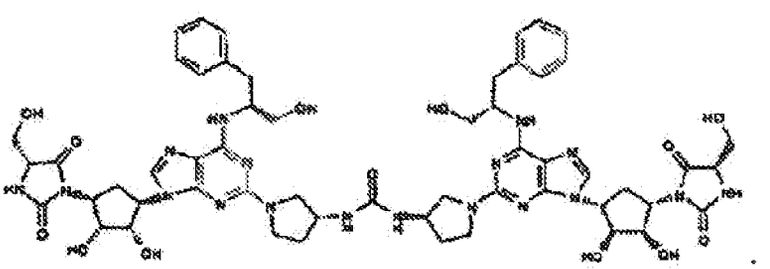


4. Composé selon l'une quelconque des revendications précédentes pour utilisation en tant qu'agent pharmaceutique.

5. Composé selon l'une quelconque des revendications 1 à 3 en combinaison avec une substance pharmaceutique anti-inflammatoire, bronchodilatatrice, antihistaminique ou antitussive, ledit composé et ladite substance pharmaceutique étant dans la même composition pharmaceutique ou dans des compositions pharmaceutiques différentes.

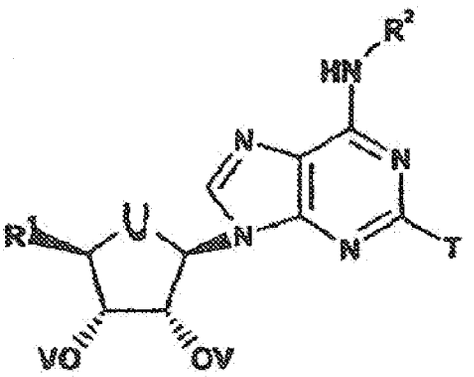
6. Composition pharmaceutique comprenant en tant que principe actif un composé selon l'une quelconque des revendications 1 à 3, facultativement conjointement avec un diluant ou véhicule pharmaceutiquement acceptable.

7. Composé selon l'une quelconque des revendications 1 à 3 pour utilisation dans le traitement d'une pathologie véhiculée par activation du récepteur d'adénosine A2A.

8. Composé selon l'une quelconque des revendications 1 à 3 pour utilisation dans le traitement d'une maladie inflammatoire ou obstructive des voies respiratoires.

9. Procédé pour la préparation de composés de formule (Ia) comme défini dans la revendications, ou des stéréoisomères ou sels pharmaceutiquement acceptables de ceux-ci, qui comprend les étapes consistant à :

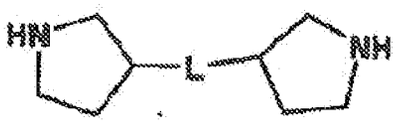
(i) faire réagir un composé de formule (III) :



(III)

dans lequel

R^1 est équivalent à R^{1a} et R^{1b};
R^2 est équivalent à R^{2a} et R^{2b}; et
U est équivalent à U_1 et U_2, et sont comme défini dans la revendication 1 ;
V est H ou un groupe protecteur ; et
T est un groupe parant, avec un composé de formule (V) :



(V),

dans lequel L est comme défini dans la revendication 1 ;

et
(ii) éliminer les éventuels groupes protecteurs et récupérer le composé de formule (Ia) résultant sous forme libre ou de sel pharmaceutiquement acceptable.

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